eman ta zabal zazu
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Kimika Organikoa eta Ez-organikoa Saila
Departamento de Química Orgánica e Inorgánica

New palladium catalysts for cross-coupling, cycloisomerization, cascade and multicomponent reactions

MEMORIA PRESENTADA POR

Aimar García Martín

PARA OPTAR AL GRADO DE DOCTOR CON MENCIÓN “DOCTOR INTERNACIONAL”

Leioa, Junio 2021

Part of the results of this dissertation have been reported in the following publication:

"Design and Development of a Cyclic Decapeptide Scaffold with Suitable Properties for Bioavailability and Oral Exposure"

Fouché, M.; Schäfer, M.; Berghausen, J.; Desrayaud, S.; Blatter, M.; Piéchon, P.; Dix, I.; Garcia Martin, A. and Roth, H. J.

ChemMedChem **2016**, *11*, 1048–1059

DOI: 10.1002/cmdc.201600082

Moreover, the following contributions have been presented to conferences and symposia:

"α-Arilación de enolatos de cetona más eficiente y en agua"
Astarloa, I.; San Martín, R.; Herrero, M. T.; Domínguez, E.; Urgoitia, G.; García, A.
XXXVII Reunión Bienal Real Sociedad Española de Química
Donostia-San Sebastián (Spain) May 26–30, 2019 (Oral communication)

"Palladium-catalyzed hydro-oxycarbonylation leading to alkylidene lactones"
García, A.; Conde, N.; SanMartin, R.; Herrero, M. T.; Urgoitia, G.; Domínguez, E.
VI Jornadas investigación Facultad de Ciencia y Tecnología UPV/EHU
Leioa (Spain) March 14–15, 2018 (Oral communication)

"Enaminoketone derivatives as key intermediates for the synthesis of 4-quinolones"
Álvaro, A.; SanMartin, R.; Herrero, M. T.; Astarloa, I.; García, A.; Llorente, G.; Urgoitia, G.; Domínguez, E.
MOL2NET 2017, International Conference on Multidisciplinary Sciences, 3rd Edition
Leioa (Spain) December 20th, 2017 (On-line communication)

"A more efficient catalyst for the cycloisomerization of alkynoic acids"
Conde, N.; SanMartin, R.; Herrero, M. T.; Urgoitia, G.; Astarloa, I.; García, A.; Llorente, G.; E. Domínguez
MOL2NET 2017, International Conference on Multidisciplinary Sciences, 3rd Edition
Leioa (Spain) December 20th, 2017 (On-line communication)

"A highly active catalyst system for the aerobic oxidation of alcohols and methylene compounds"
Urgoitia, G.; Maiztegi, A.; San Martin, R.; Herrero, M. T.; Domínguez, E.; Astarloa, I.; García, A.
11th Spanish-Italian Symposium on Organic Chemistry (SISOC XI)
Donostia-San Sebastián July 13–15, 2019 (Poster communication)

“Cross-coupling reactions in water catalyzed by a palladium phosphinite complex”
García, A.
V Jornadas investigación Facultad de Ciencia y Tecnología UPV/EHU
Leioa (Spain) April 6–7, 2016 (Oral communication)

“Reacciones de acoplamiento cruzado en presencia de un complejo no simétrico de paladio (II)”
García, A.
2º Workshop UFI-QOSyC Jóvenes investigadores UPV/EHU
Vitoria-Gasteiz (Spain) October 16th, 2015 (Oral communication)

“Suzuki Biaryl Coupling in the presence of a New Non-Symmetric Palladium Pincer-Complex”
García, A.; Astarloa, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E.
I International Symposium on Synthesis and Catalysis (ISySyCat I)
Évora (Portugal) September 2–4, 2015 (Poster communication)

“Un nuevo acceso al núcleo indolo[1,2-c]quinazolínico de la Hinckdentina A”
Diaz de Sarralde, J.; Herrero, M. T.; SanMartin, R.; García, A.; Astarloa, I.; Domínguez, E.
XXXIV Reunión Bienal Real Sociedad Española de Química
Santander (Spain) September 15–18, 2013 (Poster communication)

“Novel cesium carbonate-catalyzed cascade reaction: an elegant approach to complex nitrogen heterocycles”
Díaz de Sarralde, J.; SanMartin, R.; Herrero, M.T.; García, A.; Domínguez, E.
XXXIV Reunión Bienal Real Sociedad Española de Química
Santander (Spain) September 15–18, 2013 (Poster communication)

“A new nonsymmetric pincer-type palladium complex. Synthesis and activity in cross-coupling reactions”

García, A.; SanMartin, R.; Herrero, M.T.; Domínguez; E.

XXXIV Reunión Bienal Real Sociedad Española de Química

Santander (Spain) September 15–18, 2013 (Poster communication)

“A straightforward access to pyrazolo(benzo)thienoquinolines”

Hernández; S.; Perea; M.; Churruca; F.; SanMartin, R.; Conde, N.; Herrero, M.T.; García, A.; Astarloa, I.; Domínguez, E.

European Symposium on Organic Chemistry (ESOC 2013)

Marsella (France) July 7–12, 2013 (Poster communication)

Internship during PhD:

Internship as a research trainee (2014) at Novartis Pharma AG (Fabrikstrasse 2, 4056 Basel, Switzerland) in the Novartis Institutes for Biomedical Research-Global Discovery Chemistry-Macrocycles group (NIBR-GDC-Macrocycles) in order to develop Synthetic Chemistry skills during a 9-month period (April 1st–December 31st) under the supervision of Dr. Hans-Jörg Roth (Head of Macrocycles) and Dr. Marianne Fouchè (Postdoctoral Research Associate).

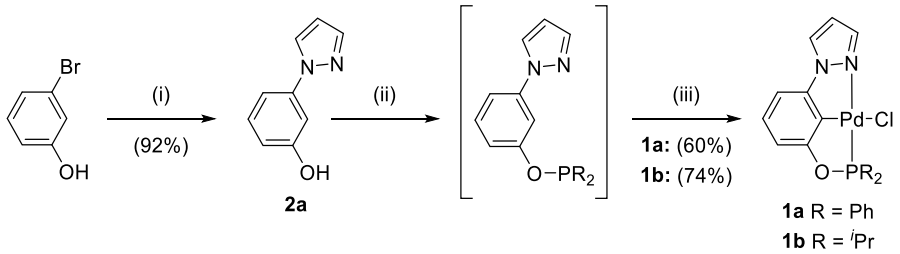
The contents of this internship work will be commented in the 3rd chapter of the present work.

Note:

The bibliographic references of this Doctoral Thesis are collected at the end of each page, and they are chapter-independent. In several cases, the references have been repeated for the convenience of the reader.

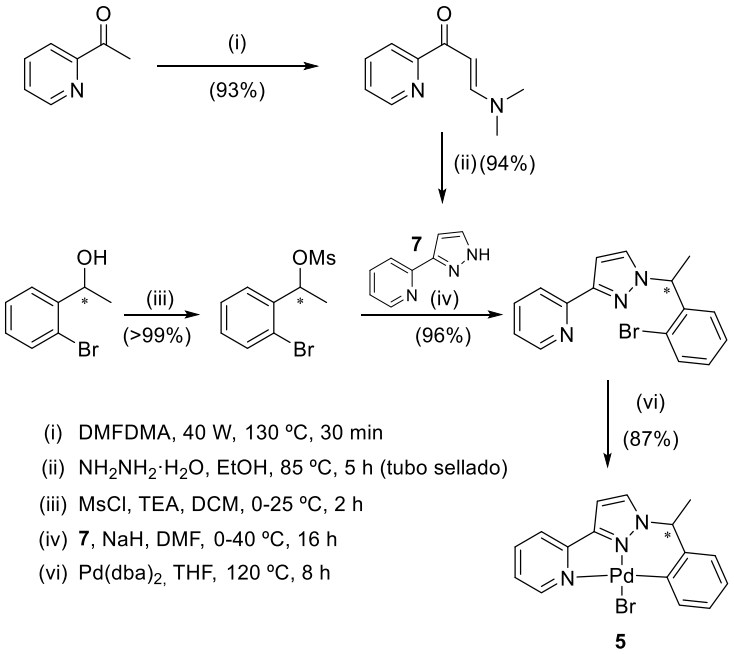
El trabajo de investigación recopilado en la presente memoria se ha centrado en el desarrollo de nuevos catalizadores de paladio tipo pincer de paladio, así como en el estudio catalítico de los mismos en el acoplamiento biarílico de Suzuki-Miyaura y la cicloisomerización de ácidos alquinoicos en medio acuoso. Asimismo, también se ha llevado a cabo el estudio de reacciones en "cascada" y multicomponente catalizadas por paladio, partiendo de enaminocetonas como *building-blocks* para la obtención de poliheterociclos fusionados de diversa complejidad.

De este modo, en el primer capítulo se describen las síntesis de tres complejos de paladio no-simétricos tipo PCN y NNC. Los complejos que integran la unidad de fosfinito se obtuvieron a través de una secuencia sintética de dos etapas. La primera se basó en la *N*-arilación del 1*H*-pirazol co-catalizada por cobre y hierro, para proporcionar el intermedio sintético clave **2a**. Dicho fenol se sometió a una reacción secuencial de fosfinación y posterior paladación mediante coordinación y activación del enlace *C-H* aromático, para obtener así los complejos **1**. La estructura de los nuevos paladaciclos se confirmó de manera inequívoca mediante difractometría de rayos X.



(i): 1*H*-pirazol, CuI, $Fe(acac)_3$, Cs_2CO_3, DMF, 120 ºC (tubo sellado), 24 h
(ii): R_2PCl (**4a**, R = Ph/**4b**, R = ^{i}Pr), Et_3N, THF, Ar, 25 ºC, 2 h
(iii): $Pd(COD)Cl_2$, PhMe, Ar, 120 ºC (tubo sellado), 20 h

Por otro lado, el complejo pincer de paladio NNC **5** se obtuvo con un excelente rendimiento global mediante una síntesis convergente. Por un lado, se obtuvo el intermedio pirazólico clave (**7**) mediante una secuencia de aminometilenación y posterior intercambio amínico/heterociclación. Paralelamente, se formó el metanosulfonato de 1-(2-bromofenil)etilo, el cual a continuación se hizo reaccionar con la 2-(1*H*-pirazol-3-il)piridina previamente sintetizada. En última instancia, la paladación del preligando resultante mediante coordinación/adición oxidante proporcionó el complejo deseado **5**, cuya estructura se elucidó de nuevo mediante difractometría de rayos X.



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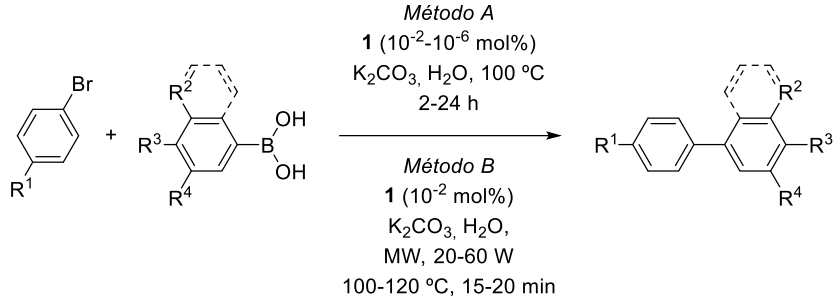
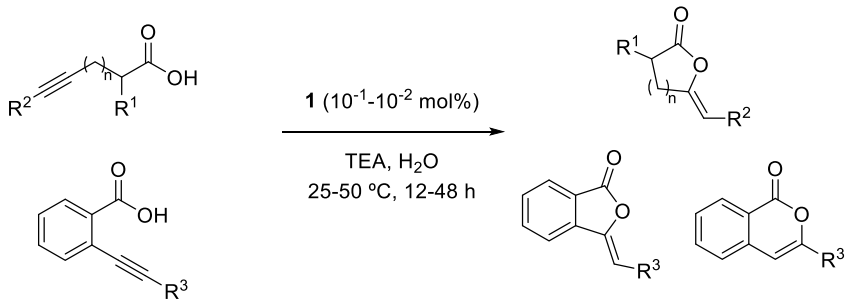
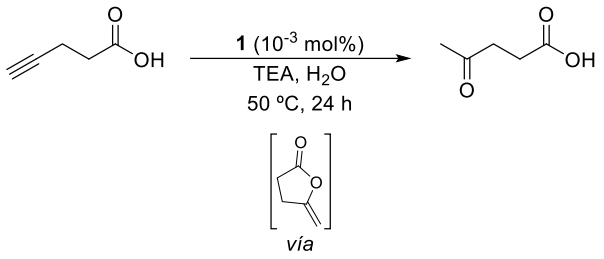
Una vez sintetizados los complejos **1**, se evaluó su perfil catalítico llevando a cabo con éxito diversos acoplamientos biarílicos en medio acuoso, y empleando cargas catalíticas muy bajas, de hasta 10^{-6} mol% de catalizador. Asimismo, se consiguió minimizar el tiempo requerido para esta transformación a tan solo 15–20

minutos, empleando la irradiación con microondas como método alternativo a la activación térmica convencional.

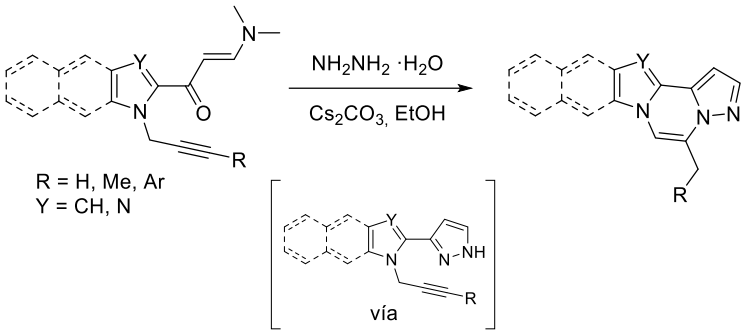


Además, los complejos de paladio **1** demostraron una alta eficiencia en la cicloisomerización de ácidos alquinoicos a sus correspondientes alquilidenlactonas a cargas catalíticas (10^{-1}–10^{-2} mol%) y temperaturas (25–50 ºC) relativamente bajas. De este modo se ha logrado poner a punto el método de cicloisomerización de tales sustratos con la mejor relación sustrato:catalizador en medio acuoso hasta la fecha. Aparte de esto, una ligera variación de las condiciones de reacción propició la obtención del ácido levulínico a partir del ácido 4-pentinoico.

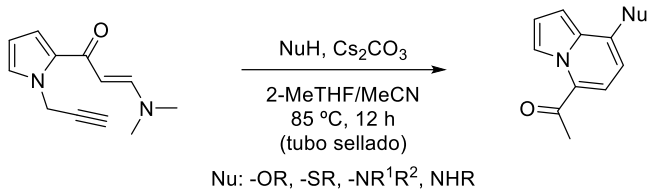




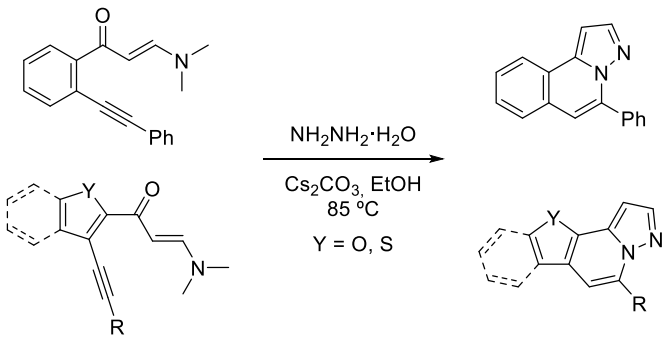
Por otro lado, en el segundo capítulo se muestra la síntesis de poliheterociclos nitrogenados en base a dos estrategias que parten de enaminocetonas como sustrato clave: reacciones en cascada, y reacciones multicomponente. Para la primera estrategia se sintetizaron una serie de enaminonas derivadas de *N*-propargilpirrol y *N*-propargilbenzimidazol, las cuales se hicieron reaccionar con hidrazina en medio básico para proporcionar los correspondientes pirazolopirazinoheterociclos. Esta transformación puede explicarse a través de una reacción en cascada de intercambio amínico/heterociclación/hidroaminación.



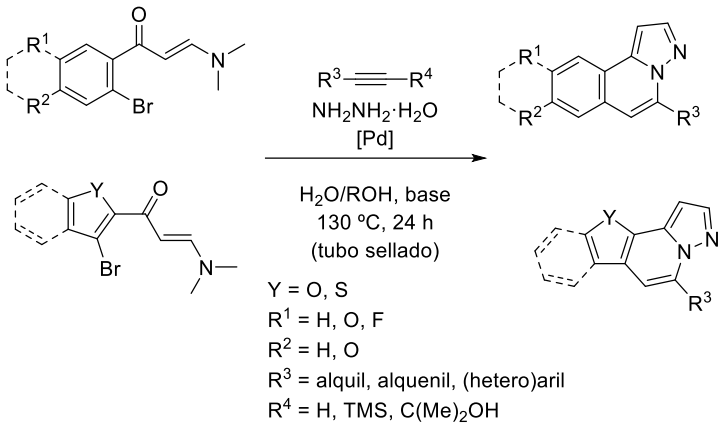
En este contexto, se ha accedido de manera directa a 5-acetil-8-alcoxi/tioxi/amino-indolizinas mediante una reacción en cascada a partir de enaminocetonas análogas, que podría implicar una hidratación de alquino o aleno/formación de enolato/anelación/condensación con nucleófilo.



Dicho proceso en cascada de intercambio amínico/heterociclación/hidroaminación pudo promoverse también en una serie de enaminocetonas derivadas de 1-acetil-2-alquinil(hetero)arenos, proporcionando con éxito diferentes pirazoloisoquinolinas, furopirazolopiridinas, pirazolotienopiridinas y benzotienopirazolopiridinas.



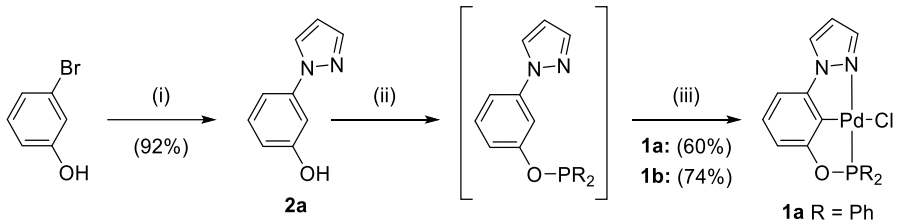
Además, se estudió la posibilidad de acceso a estos últimos sistemas poliheterocíclicos a través de una reacción multicomponente. Para ello se sintetizaron una serie de 2-bromo(hetero)aril enaminonas y se hicieron reaccionar con hidrazina y diversos alquinos, en presencia de una fuente de paladio en medio acuoso o alcohólico, obteniéndose de ese modo las pirazolo(hetero)arenopiridinas correspondientes.



Por último, en el tercer capítulo se muestra parte del trabajo llevado a cabo bajo la supervisión de los doctores Marianne Fouché y Hans-Jörg Roth, en el grupo *Macrocycles* de la sección General Discovery Chemistry de Novartis Institutes for Biomedical Research (NIBR-GDC) en Novartis Pharma AG, Basilea, Suiza. El trabajo consistió en la síntesis de diversos ciclodecapeptidos, cuya estructura específica no se mostrará por motivos de confidencialidad.

Memoria honetan bildutako ikerketa lana pintzer motatako paladio katalizatzaileen garapenean, eta azken hauek ingurune urtsuko Suzuki-Miyaura koplamendu biarilikoan zein azido alkinoikoen hidroxikarbonilazioan erakutsitako aktibitate katalitikoaren azterketan oinarritu da. Halaber, enaminozetonak *building-block* gisa erabilita, kaskada eta multikonponente erreakzioen bidezko konplexutasun desberdineko poliheterozikloen sintesia aztertu egin da.

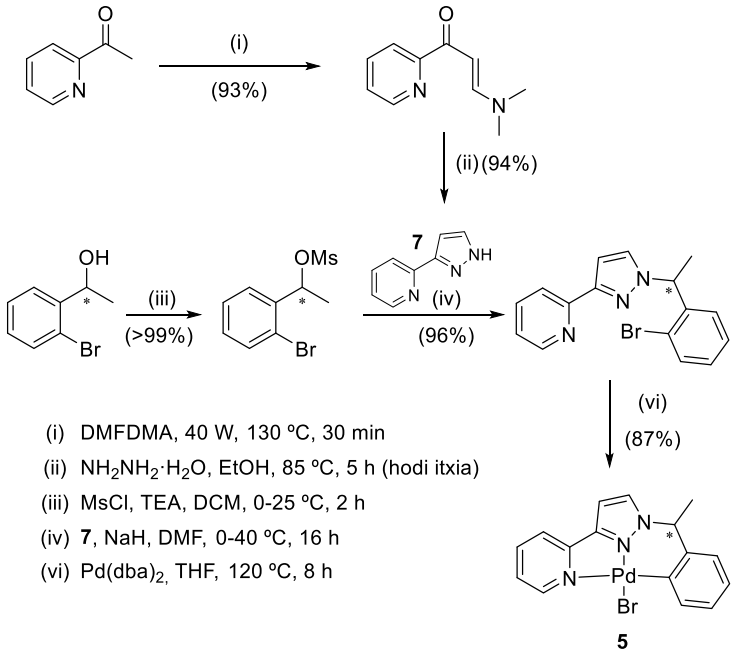
Honela, lehenengo kapituluan PCN eta NNC motatako hiru paladio(II) konplexu ez-simetriko berrien sintesiak deskribatzen dira. Fosfinito unitatedun konplexuak bi etapatan lortu ziren. Lehengoa, kobreak eta burdinak katalizaturiko 1*H*-pirazolaren *N*-arilazioan oinarritu zen, **2a** tartekari sintetikoa eskuratzeko. Modu sekuentzialean bideratutako fosforilazioaz eta paladazioaz **1** konplexuak eskuratu ziren. X-Izpien difraktometriaren bitartez egiaztatu zen paladaziklo hauen egitura.



(i): 1*H*-pirazol, CuI, $Fe(acac)_3$, Cs_2CO_3, DMF, 120 ºC (hodi itxia), 24 h
(ii): R_2PCl (**4a**, R = Ph/**4b**, R = ^{i}Pr), Et_3N, THF, Ar, 25 ºC, 2 h
(iii): $Pd(COD)Cl_2$, PhMe, Ar, 120 ºC (hodi itxia), 20 h

5 Izeneko NNC paladio konplexua sintesi konbergente baten bidez lortu zen. Alde batetik, pirazoldun tartekari sintetikoa (**7**), aminometilenazioz eta lortutako enaminonaren gaineko elkartrukaketa aminiko/heteroziklazio sekuentziaren

ostean eskuratu zen. Aldi berean, 1-(2-bromofenil)etil metanosulfonatoa prestatu eta 2-(1*H*-pirazol-3-il)piridina-rekin erreakzionarazi zen. Honela, lortutako aurre-ligandoa paladioarekin erreakzionatzerakoan, koordinazio/adizio oxidatzailearen bitartez; nahi genuen **5** zenbakidun konplexua lortu zen. Beraren egitura X-izpien difraktometriaren bitartez egiaztatu zen.



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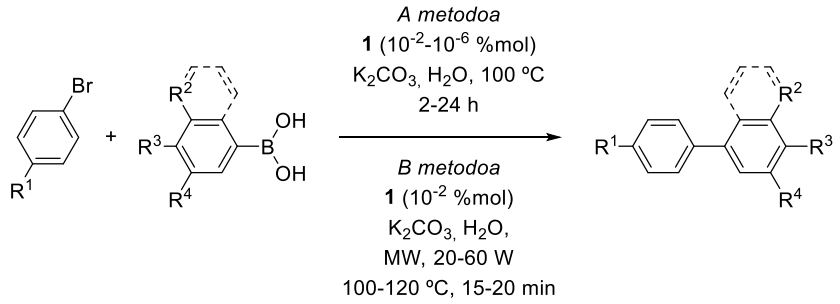
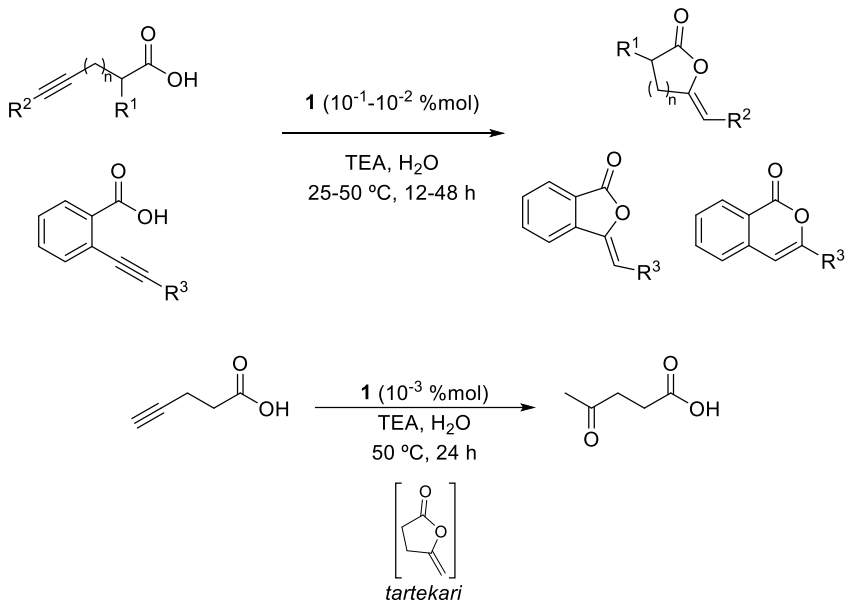
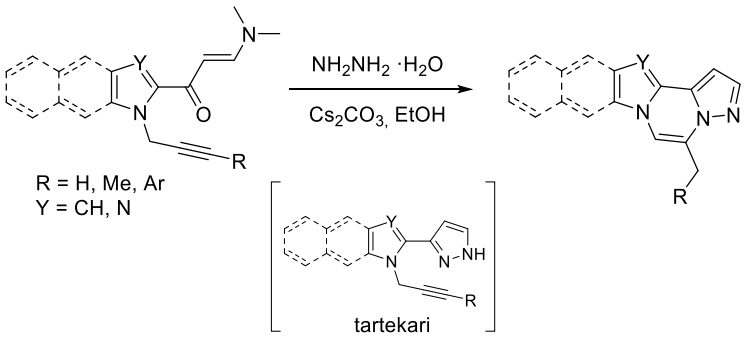
Behin **1** konplexuak sintetizatu zirela, euren eraginkortasun katalitikoa ingurune urtsuan probatu egin zen, 10^{-6} %mol-eko karga katalitikoz zenbait akoplamendu biarilikoak lortu zirelarik. Gainera, erreakzio denbora-tartea 15–20 minututara jaistea lortu zen mikrouhinen irradiazioa beroketa metodo gisa erabilita.



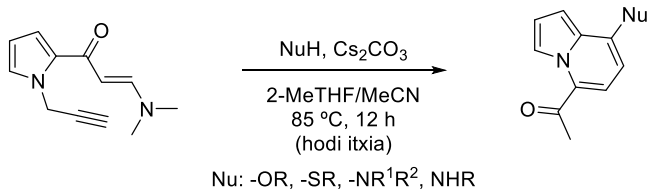
Honetaz aparte, **1** paladio konplexuek azido alkinoikoen zikloisomerizazioan efizientzia katalitiko altua aurkeztu zuten, zegozkien alkilidenlaktonak erlatiboki baxuak diren karga katalitikotan (10^{-1}–10^{-2} %mol) zein tenperaturatan (25–50 ºC) lortzeko gai izan zirelarik. Hauxe, lorpen nabarmena eta adierazteko modukoa izan zen, izan ere, egunerarte ingurune urtsuan gauzatutako sustrato:katalizatzaile erlazio handieneko zikloisomerizazioa baita. Bestalde, erreakzio baldintzen gutxieneko aldaketa batek, azido lebulinikoa eskuratzea ahalbidetu zuen, azido 4-pentinoiko abiapuntu gisa hartuta.



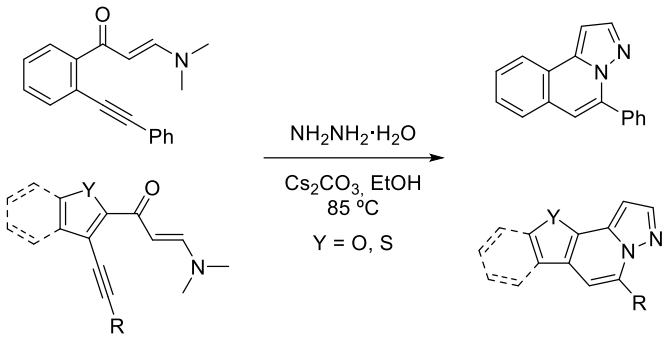
Bigarren kapituluan, enaminozetona ezberdinak sustrato klabe moduan erabilita, nitrogenodun poliheterozikloak eskuratzeko erabili diren bi estrategietan sakontzen da, hots, kaskada eta multikonponente erreakzioetan. Lehenengoan, *N*-propargilatutako pirrol eta bentzimidazolen enaminonak, base eta hidrazinaren presentzian erreakzionatu ziren pirazoloheterozikloetara iristeko. Kaskada erreakzio honetan, hidrazinak enaminonaren gaineko elkartrukaketa aminiko/heteroziklazioa eragiten du pirazoldun tartekaria eratuz, zeinak propargil taldearen gaineko hidroaminazio formal bat ematen duen.



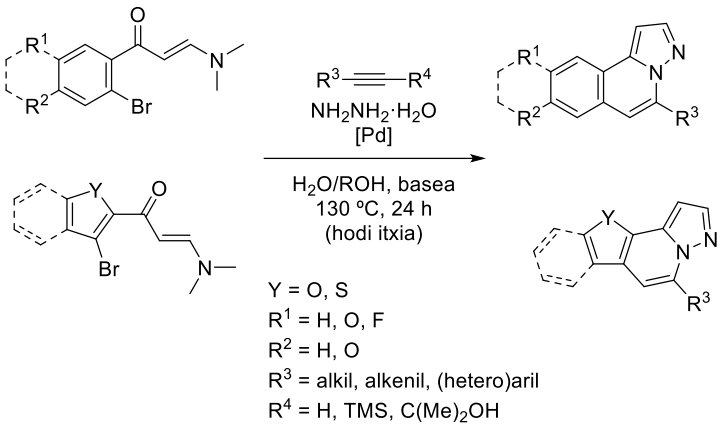
Gainera, 5-azetil-8-alkoxi/tioxi/amino-indolizinak eskuratzeko erreakzioa aurkitu da. Eraldaketa hau, alkino edo alenoaren hidratazioa/enolato eraketa/anelazioa/nukleozale batek eragindako kondentsazio baten erreakzio sekuentzia gisa azaldu genezake.



Bestalde, 2-alkinil(hetero)arenoetatik eratorritako enaminozetonak elkartrukaketa aminiko/heteroziklazio/hidroaminazio baldintzetan erreakzionaraztean dagozkien pirazoloisokinolina, furopirazolopiridina, pirazolotienopiridina eta bentzotienopirazolopiridina heterozikloak etekin bikainekin lortu ziren.



Aipatutakoaz gain, eta azkenengo eraldaketari lotuta, erreakzioa osagai anitzezko (multikonponente) eran egiteko aukera aztertu zen. Horretarako, zenbait 2-bromo(hetero)aril enaminonak prestatu eta gero, hidrazina eta azetileno ezberdinekin erreakzionarazi ziren ingurune alkoholiko zein urtsuan paladio iturri desberdinen presentzian, honela lehen aipatutako pirazolo(hetero)arenopiridinak eskuratu zirelarik.



Y = O, S
R^1 = H, O, F
R^2 = H, O
R^3 = alkil, alkenil, (hetero)aril
R^4 = H, TMS, $C(Me)_2OH$

Azkenik, hirugarren kapituluan Marianne Fouché eta Hans-Jörg Roth doktoreen gainbegiratzepean *Macrocycles* taldean (Novartis Institutes for Biomedical Research-eko General Discovery Chemistry sailean, Novartis Pharma AG, Basilea, Suitza) egindako lanaren zati bat azalduko da. Lan hau hainbat

ziklodekapeptidoen sintesian oinarritu zen. Hala ere, peptido horien egitura zehatzak ez dira testuan adieraziko konfidentzialtasun hitzarmena dela eta.

Å²	Square angstroms
Ac	Acetyl
acac	acetylacetonate
Ar	Aryl or argon
ASTM	American Society for Testing and Materials
ATR	Attenuated Total Reflectance
AUC	Area under the curve
$AUC_{i.v.}$	Area under the curve for intravenously administered drug
$AUC_{p.o.}$	Area under the curve for orally administered drug
Bn	Benzyl
Boc	*Tert*-butyloxycarbonyl
bs	Broad singlet
Bu	Butyl
c	Concentration
CCD	Charge-coupled device
CH_{arom}	C-H bonded aromatic carbon
COD	1,5-Cyclooctadiene
col.	Collaborator(s)
conc.	Concentrated
cont.	Continuation
COX-2	Cyclooxygenase-2
CPP	Cell permeable peptide
Cy	Cyclohexyl
d	Doublet
D	Deuterium
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
dd	Double doublet
DEC	Diethyl carbonate
Dipp	2,6-Diisopropylphenyl

$D_{i.v.}$	Intravenously administered dose
DMA	*N,N*-Dimethylacetamide
DMAP	*N,N*-Dimethylaminopyridine
DMF	Dimethylformamide
DMFDMA	Dimethylformamide dimethyl acetal
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
$D_{p.o.}$	Orally administered dose
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DtBPF	1,1'-Bis(di-*tert*-butylphosphino)ferrocene
e.g.	Exempli gratia
EC	Ethylene carbonate
ee	Enantiomeric excess
EI	Electron impact
EMEA	European Medicines Agency
equiv.	Equivalent(s)
ESI	Electrospray ionization
Et	Ethyl
et al.	Et alii
ETG	Ethylene glycol
EWG	Electron-withdrawing
F_{abs}	Absolute bioavailability
FDA	Food and Drug Administration
FTIR-ATR	Fourier Transform Infrared-Attenuated Total Reflectance
g	Gram(s)
GC	Gas chromatography
Glyc.	Glycerol
h	Hour(s)/heptaplet
HetAr	Heteroaryl
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	Hertz(s)
ICH	International Agency on Harmonisation

ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
i. e.	Id est
^{i}Pr	*Iso*-propyl
IR	Infrared
i.v.	Intravenous administration
J	Scalar coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
K	Kelvin
K_{as}	Association (Binding) constant
$k_{cycloisom.}$	Rate of cycloisomerization
k_{free}	Reaction-rate constant for free base
$k_{hydrolysis}$	Rate of hydrolysis
KHMDS	Potassium hexamethyldisilazide
$k_{ion-pair}$	Reaction-rate constant for ion-pair
L	Ligand
LG	Leaving group
Lit.	Literature
m	Multiplet
M	Molar
MDCK	Madin-Darby Canine Kidney cells
Me	Methyl
Mes	Mesityl
mg	Miligram(s)
min	Minute(s)
mL	Mililiter(s)
mmol	Milimole
m.p.	Melting point
MS	Mass Spectrometry or molecular sieves
Ms	Methanesulfonyl
MW	Microwave
^{n}Bu	*n*-Butyl
NHC	*N*-heterocyclic carbene
^{n}Hex	*n*-Hexyl

nm	Nanometer(s)
NMP	*N*-Methylpyrrolidone
NMR	Nuclear Magnetic Resonance
^{n}Pr	*n*-Propyl
Nu	Nucleophile
^{o}C	Celsius degrees
PCC	Pyridinium chlorochromate
Pd/C	Palladium on activated charcoal
PDC	Pyridinium dichromate
PDE	Permitted Daily Exposure
PE	Petroleum ether
PEG	Poly(ethylene glycol)
PG	Protecting group
Ph	Phenyl
PIFA	[Bis(trifluoroacetoxy)iodo]benzene
pK_a	Inverse of the acid-dissociation constant
pK_{aH}	Inverse of the acid-dissociation constant of the acid conjugate
p.o.	Per oral administration
ppm	Parts per million
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
PVPy	Poly(vinylpyridine)
Py	Pyridine
q	Quadruplet, quaternary
qC_{arom}	Quaternary aromatic carbon
QTOF	Quadrupole-Time of Flight
r.t.	Room temperature
rac	Racemic
s	Singlet
SDS	Sodium dodecylsulfate
SN	Nucleophilic substitution
t	Time, triplet
T	Temperature
TBAB	Tetrabutylammonium bromide

TBAF	Tetrabutylammonium fluoride
TBAHSO4	Tetrabutylammonium hydrogensulfate
TBAOH	Tetrabutylammonium hydroxide
TBDMS	*Tert*-butyldimethylsilyl
^{t}Bu	*Tert*-butyl
td	Triple doublet
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFE	2,2,2-Trifluoroethanol
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	1,1,4,4-Tetramethylethylenediamine
TMS	Trimethylsilyl or tetramethylsilane
Ts	*Para*-toluenesulfonyl
UPLC	Ultra Performance Liquid Chromatography
UV	Ultraviolet
vs	*Versus*
W	Watt(s)
α	Specific optical rotation
δ	Chemical shift
Δ	Heating
λ	Wavelenght
λ_{exc}	Excitation wavelenght
µL	Microliter(s)
Φ_f	Fluorescence quantum yield

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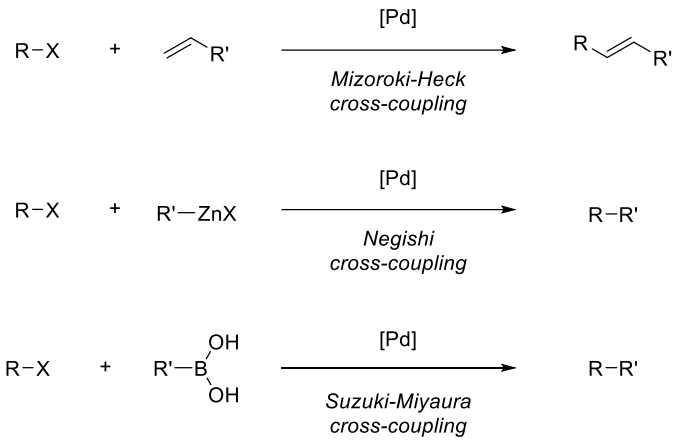
1

Palladium pincer complexes: catalysis in aqueous media

1 INTRODUCTION

1.1 Palladium in catalysis

The use of palladium as catalyst experienced an apogee when its application in cross-coupling reactions was discovered. Actually, this finding entailed a huge revolution for organic synthesis since it provided a brand-new and very versatile tool for C-C bond construction. Such was the impact of these investigations that Richard F. Heck,[1] Ei-ichi Negishi[2] and Akira Suzuki[3] received the 2010 Nobel Prize in Chemistry[4] for their contribution to "palladium cross-coupling reactions in organic synthesis" (Scheme 1.1).



Scheme 1.1 General depiction of Mizoroki-Heck, Negishi, and Suzuki-Miyaura couplings.

Thus, the initial studies in the 70's on palladium catalyzed cross-coupling reactions established the foundations for the development of new cross-coupling

[1] Heck, K. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320–2322.
[2] King, A. O.; Okukado, N.; Negishi, E. I. *J. Chem. Soc. Chem. Commun.* **1977**, *0*, 683–684.
[3] a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440. b) Miyaura, N.; Suzuki, A. *J. Chem. Soc. Chem. Commun.* **1979**, *0*, 866–867.
[4] For Nobel Lectures, see: a) Negishi, E. I. *Angew. Chem. Int. Ed.* **2011**, *50*, 6738–6764. b) Suzuki, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 6723–6733.

reactions such as Sonogashira,[5] Hiyama[6], Buchwald-Hartwig[7] and α-arylation of carbonyl compounds to name but a few examples. As a consequence, these transformations put palladium in the spotlight of scientific community, and led to the evolution of new synthetic transformations with this metal as the keystone.

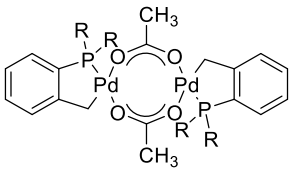
Besides, in the second half of the 20th century, the increasing social awareness about environment pushed chemists to achieve some commitments regarding environmental sustainability. Among these commitments, the development of more efficient synthetic methodologies gained importance. Indeed, the use of high atom-efficient processes, as well as the use of catalysts and toxic waste minimization were prioritized in order to lower the environmental impact derived from chemical industry. In this regard, in 1991 Paul Anastas coined the term "*Green Chemistry"* or "*Sustainable Chemistry"* and settled the basis for a sustainable development in chemical industry.[8]

Therefore, the former employment of large amounts of palladium was replaced by more efficient catalytic systems. In this field, the discovery of phosphines as potent ligands in combination with the palladium species made a huge difference. These bulky and strongly σ-donating ligands enhanced dramatically the catalytic activity of the metal complexes, thereby facilitating catalyst-loading minimization. Furthermore, the use of ligands enabled catalyst modulation, *e.g.* stereoelectronic tuning, as well as changes driving to stability and solubility enhancement, so that catalyst reactivity and behavior could be adjusted to reaction requirements. In this way, ligand design gained relevance, which triggered off the synthesis of a wide range of tailor-made ligands or metal complexes. In addition, this possibility to customize the ligands enabled the design of chiral catalytic systems that would allow carrying out stereoselective reactions. One of the first steps towards improved

[5] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.
[6] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918–920.
[7] a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1995**, *34*, 1348–1350. b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
[8] *Green Chemistry Theory and Practice*; Anastas, P. T. and Warner, J. C. Eds.; Oxford University Press, New York, **1998.**

palladium catalysts was the synthesis of palladacycles, firstly obtained by Cope *et al.* in the 60's.[9]

These palladacyclic complexes shared improved stabilities and activities in comparison with their non-chelated counterparts. For instance, Herrmann *et al.* reported a higher catalytic activity in Heck coupling reaction by using the now called Herrmann's catalyst (Figure 1.1).[10a] As shown, the use of metallacycles provided enhanced activity that eased the use of lower catalyst-loadings and together with their improved stability, enabled catalyst recycling in some cases.[10b]



R= *o*-tolyl, mesityl

Figure 1.1 Herrmann's cyclopalladated catalyst.

Besides, it was in the 70's when Moulton and Shaw reported the first terdentate metallacycles bearing a symmetric bis(phosphino)aryl chelate moiety (Figure 1.2).[11] In those cyclometallated complexes, the coordination of the ligand was accomplished by a six-electron donation to the metal core, *i.e.* two electrons by a metal-carbon σ-bond and the remaining four provided by two neutral electron-donor groups. In 1989, van Koten named those complexes "pincer-complexes" due to their resemblance to the gripping tool consisting of two grasping jaws working on a pivot.[12] Interestingly, these tridentate ligands endowed the complex with an unusually high stability against temperature, air and moisture.[11]

[9] For information about first palladacycles, read: a) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272–3273. b) Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909–913.
[10] a) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **2007**, *3*, 1357–1364. b) Pandiri, H.; Soni, V.; Gonnade, R. G.; Punji, B. *New J. Chem.* **2017**, *41*, 3543–3554.
[11] Moulton, C. J.; Shaw, B. L *J. Chem. Soc. Dalt. Trans.* **1976**, *0*, 1020–1024.
[12] van Koten, G. *Pure Appl. Chem.* **1989**, *61*, 1681–1694.

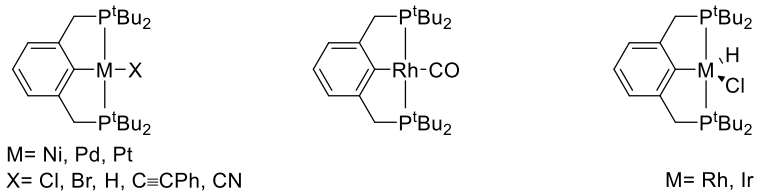


Figure 1.2 Terdentate metallacycles synthesized by Moulton and Shaw.

Nowadays, the term pincer has widened its meaning and the requirement of having C-M bonds has been omitted for pincer complexes so that any metal core coordinated to a terdentate ligand by a six-electron donation can be called “pincer complex”.[13] They are classified according to the coordinating atoms of the terdentate ligand.

Likewise, regarding the nomenclature, pincer complexes are named according to the binding-sites of the ligand to the metal, that is, the donating groups. As depicted in Figure 1.3 but not limited to that structure**,** the most common coordinating atoms on the binding sites are carbon, phosphorus, nitrogen, sulphur and selenium. More precisely, the phosphorus atom from phosphines and carbenic carbon from *N*-heterocyclic carbenes (NHC). Therefore, the latter atoms together with R^1 and R^2 substituents in the pincer-ligand, endow the complex with additional features. In this way, the electronic nature of the ligand moiety may enable electronic modulation of the metal core, whereas its steric volume can control the access of the substrate to the catalytic site or even reaction stereoselectivity might be handled.

[13] For some examples of pincer complexes lacking C-M bonds , read: a) Spiegelberg, B.; Dell’Acqua, A.; Xia, T.; Spannenberg, A.; Tin, S.; Hinze, S.; de Vries, J. G. *Chem. Eur. J.* **2019**, *25*, 7820–7825. b) Shi, R.; Zhang, Z.; Hu, X. *Acc. Chem. Res.* **2019**, *52*, 1471–1483. c) Murphy, L. J.; Hollenhorst, H.; McDonald, R.; Ferguson, M.; Lumsden, M. D.; Turculet, L. *Organometallics* **2017**, *36*, 3709–3720.

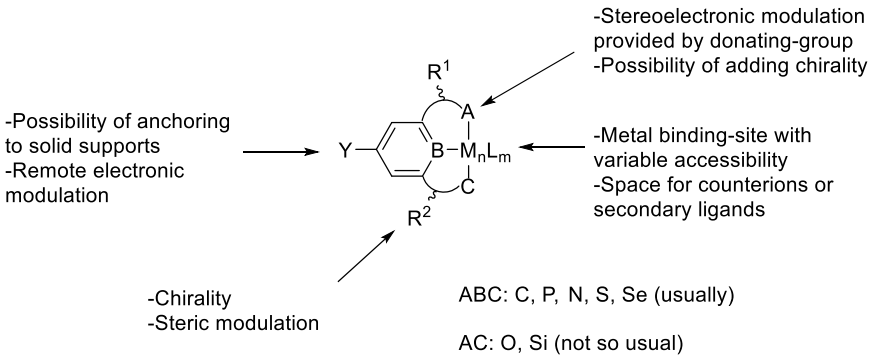


Figure 1.3 General structure of a pincer complex bearing a (hetero)aromatic core and modifiable sites.

In this context, another factor to take into account is the size of rings formed upon ligand to metal coordination. In addition to the common five-membered rings, important changes in catalytic activities have been observed when larger ring-sizes are present (Figure 1.4).[14,15]

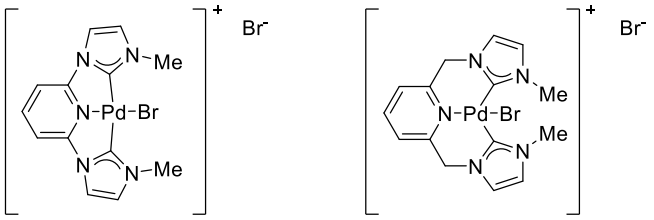


Figure 1.4 CNC palladium pincer-complexes with different ring-sizes.

Besides, pincer-complexes of a plethora of metals can be found in literature, Fe, Co, Ni, Cu, Pt, Rh, Ru, Ir or Pd among others. As it may be deduced, the metal-core is a determinant factor in the catalytic reactivity of the complex, as well as its geometry, which is usually square-planar for those metal cores with d^8 configuration

[14] For additional information about these pincer complexes and differences between their catalytic activities, read: a) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201–202. b) Gründemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. O*rganometallics* **2001**, *20*, 5485–5488.

[15] For another example where ring-size determines reactivity, see: Wang, Z.; Eberhard, M. R.; Jensen, C. M.; Matsukawa, S.; Yamamoto, Y. *J. Organomet. Chem.* **2003**, *681*, 189–195.

(Pd^{II}, Ni^{II}, Pt^{II}, Rh^{I} or Ir^{I}) and square pyramidal for those metal centers with d^6 (Ru^{II}, Rh^{III}, Ir^{III}) configuration.

Despite palladium pincer complexes were firstly synthesized in 1976,[11] their use in catalysis was scarce until 90's. Nevertheless, due to their enhanced thermal stability, the use of high reaction temperatures without catalyst decomposition is allowed when using pincer complexes as catalysts. Together with their thermal stability, the shield provided by the terdentate ligand contributes for a higher air and moisture tolerance and makes them easy to handle and store.[11] Moreover, their stability has led, in some cases, to their implementation as catalysts in aqueous, as well as in oxidative reaction media.[16]

Besides, the pincer ligand itself plays an important role in catalytic selectivity. As mentioned above, there is only one free coordination site available for catalytic interaction in square planar Pd(II) pincer complexes. Accordingly, side-products derived from undesired ligand-exchange processes can be restricted. In pincer complexes comprising a Pd-C bond, the reduction of palladium ion to Pd(0) normally results in an irreversible cleavage of the latter bond, which ultimately leads to catalyst decomposition. In those cases, the pincer complex itself does not play a role as catalyst but as a precatalyst, thus acting as a reservoir of often highly active colloidal Pd(0) species, such as Pd(0) nanoparticles or clusters, that are released to the reaction medium upon catalyst degradation.[17]

1.2 Pincer complexes

A number of palladium pincer complexes have been reported in literature and associated to several applications, such as molecule-sensing[18] and molecular

[16] For examples about pincer-catalyzed reactions in aqueous or oxidative media, see: a) Gu, S.; Chen, W. *Organometallics* **2009**, *28*, 909–914. b) Urgoitia, G.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Environ. Chem. Lett.* **2017**, *15*, 157–164.
[17] For studies about degradation of palladium pincer complexes to highly active Pd(0) particles, see: a) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139–10140. b) Eberhard, M. R. *Org. Lett.* **2004**, *6*, 2125–2128. c) Sommer, W. J.; Yu, K.; Sears, J. S.; Ji, Y.; Zheng, X.; Davis, R. J.; Sherrill, C. D.; Jones, C. W.; Week, M. *Organometallics* **2005**, *24*, 4351–4361.
[18] Zhao, Y.; Swager, T. M. *J. Am. Chem. Soc.* **2015**, *137*, 3221–3224.

switches[19] or even as potential cytotoxic[20] and anticancer compounds.[21] However, their main role has been as metal catalysts in synthetic chemistry owing to their ability for C-H and C-heteroatom activation for an array of substrates.

Pincer complexes can be easily classified into two groups: symmetric (or palindromic, Figure 1.5), when the side arms are equal; and non-symmetric (or non-palindromic), when the side arms are unequal.

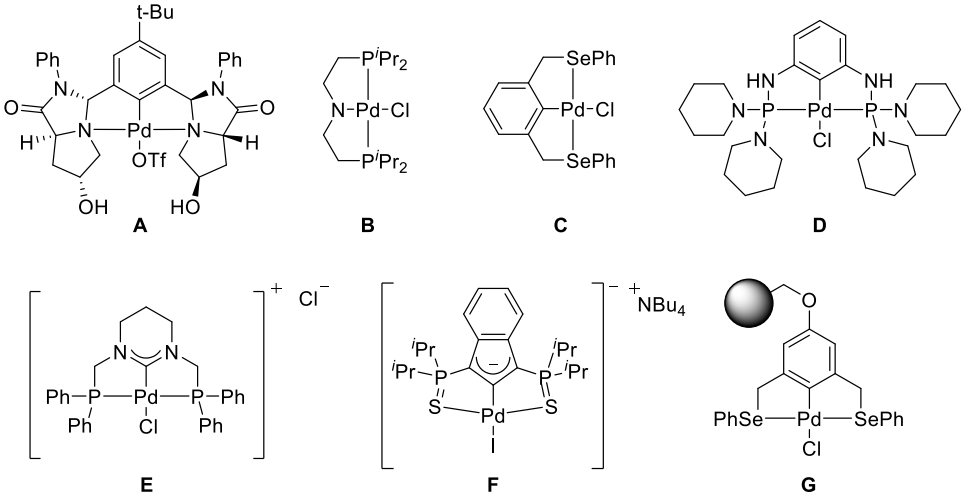
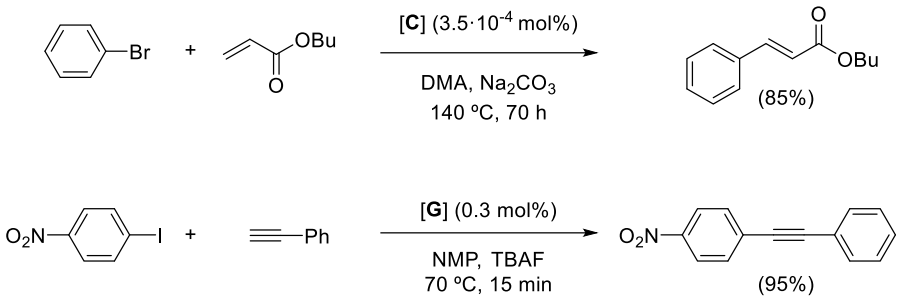


Figure 1.5 Some examples of symmetric palladium pincer complexes.

Among the examples of symmetric pincers depicted in Figure 1.5, we have chiral pincer complex **A**,[22] employed in catalytic asymmetric Michael addition; or bis(*iso*-propylphosphino) complex **B**[23] with a saturated backbone, or SeCSe pincer

[19] Wang, Q. Q.; Ara Begum, R.; Day, V. W.; Bowman-James, K. *Inorg. Chem.* **2012**, *51*, 760–762.
[20] Hung, F. F.; Wu, S. X.; To, W. P.; Kwong, W. L.; Guan, X.; Lu, W.; Low, K. H.; Che, C. M. *Chem. - An Asian J.* **2017**, *12*, 145–158.
[21] Lee, J. Y.; Lee, J. Y.; Chang, Y. Y.; Hu, C. H.; Wang, N. M.; Lee, H. M. *Organometallics* **2015**, *34*, 4359–4368.
[22] Takenaka, K.; Uozumi, Y. *Org. Lett.* **2004**, *6*, 1833–1835.
[23] Marziale, A. N.; Herdtweck, E.; Eppinger, J.; Schneider, S. *Inorg. Chem.* **2009**, *48*, 3699–3709.

complex **C**[24], and its polystyrene supported analogue **G**[25], which has been used in cross-coupling reactions[24a,b,d,25] (Scheme 1.2) and in Petasis reaction,[24c] as well.



Scheme 1.2 Cross-coupling reactions in the presence of complexes **C** and **G**.

For their part, bis(aminophosphine) bearing catalyst **D**[26] and *N*-heterocyclic carbene-decorated palladacycle **E**[27] have been recently used for carbonylative Sonogashira and Suzuki couplings, and in *N*-arylation processes, respectively. Finally, carbenic SCS pincer complex **F**[28] presented excellent performance in cycloisomerization reactions of alkynamide and alkynoic acid derivatives (Scheme 1.3).

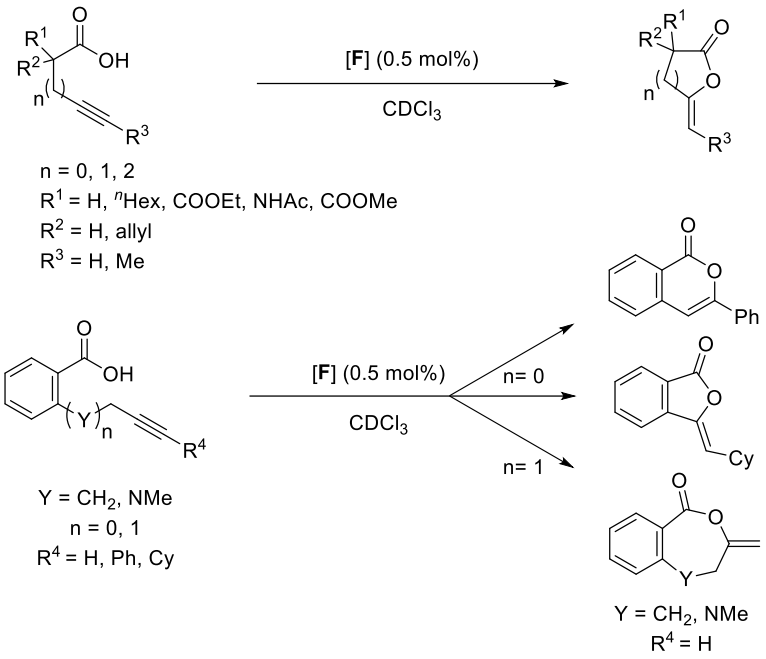
[24] For synthesis and applications of pincer catalyst **C**, read: a) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997–2999. b) Wallner, O. A.; Szabó, K. J. *J. Org. Chem.* **2005**, *70*, 9215–9221. c) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723–13731. d) Sigeev, A. S.; Peregudov, A. S.; Cheprakov, A. V.; Beletskaya, I. P. *Adv. Synth. Catal.* **2015**, *357*, 417–429.

[25] Mohammadi, E.; Movassagh, B. *New J. Chem.* **2018**, *42*, 11471–11479.

[26] For synthesis and applications of pincer catalyst **D**, see: a) Bolliger, J. L.; Blacque, O.; Frech, C. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 6514–6517. b) Bolliger, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2009**, *351*, 891–902. c) Gautam, P.; Tiwari, N. J.; Bhanage, B. M. *ACS Omega* **2019**, *4*, 1560–1574.

[27] Subramaniyan, V.; Dutta, B.; Govindaraj, A.; Mani, G. *Dalt. Trans.* **2019**, *48*, 7203–7210.

[28] For the synthesis and catalytic activity of palladacycle **F**, refer to: a) Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2013**, *3*, 2930–2934. b) Espinosa-Jalapa, N. Á.; Ke, D.; Nebra, N.; Le Goanvic, L.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2014**, *4*, 3605–3611. c) Ke, D.; Espinosa, N. Á.; Mallet-Ladeira, S.; Monot, J.; Martin-Vaca, B.; Bourissou, D. *Adv. Synth. Catal.* **2016**, *358*, 2324–2331.



Scheme 1.3 Cycloisomerizations reported by Bourissou and co-workers.

Although palindromic pincer complexes present catalytic activities that, in some cases, go beyond what other catalysts have achieved, sometimes their symmetry is, in turn, their Achilles' heel because it can reduce reactivity. Moreover, stable non-palyndromic pincer complexes can be found in the literature (Figure 1.6), presenting an evolved catalytic performance in comparison with their symmetric counterparts presumably owing to a certain fluxionality and hemilability.

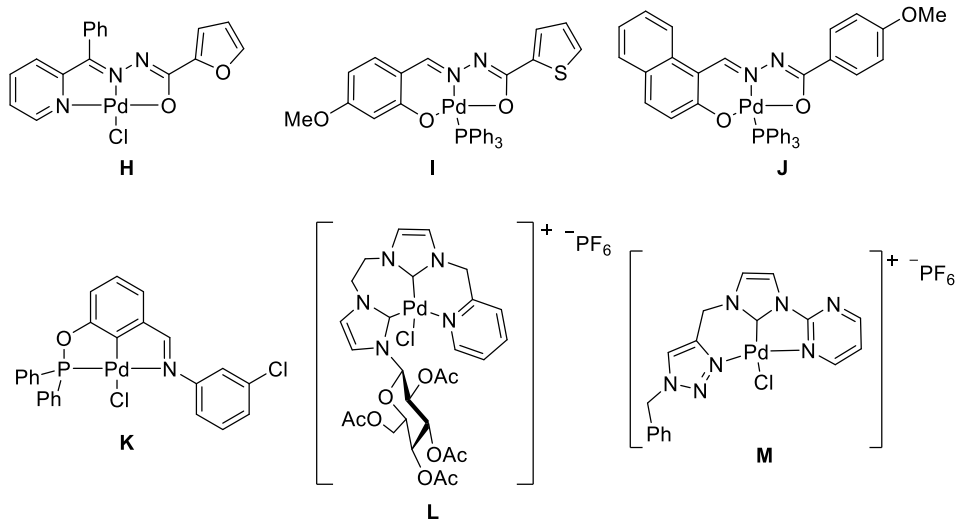
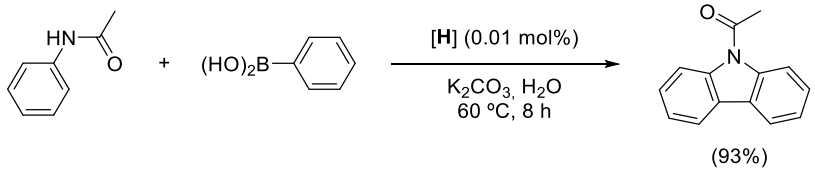


Figure 1.6 Some examples of non-symmetric palladium pincer complexes.

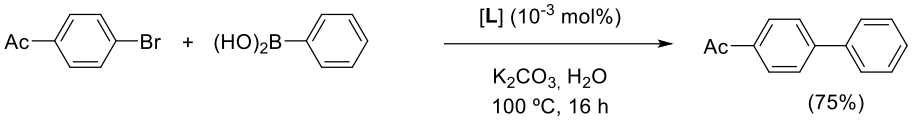
To mention a few examples, we can find a group of palladacycles designed by Nallasamy and col. for catalysis in aqueous media. Among them, palladacycle **H**,[29] employed in a tandem C-H/N-H activation leading to carbazoles (Scheme 1.4), ONO analogous pincer complex **I**,[30] applied to fluorenone synthesis, and **J**,[31] used in the arylation of oxindoles, should be highlighted.



Scheme 1.4 "On water" C-H/N-H activation in the presence of complex **H**.

[29] Vignesh, A.; Kaminsky, W.; Nallasamy, D. *Green Chem*. **2016**, *18*, 3295–3301.
[30] Vignesh, A.; Kaminsky, W.; Nallasamy, D. *ChemCatChem* **2016**, *8*, 3207–3212.
[31] Vignesh, A.; Kaminsky, W.; Nallasamy, D. *ChemCatChem* **2017**, *9*, 910–914.

In addition, complex **K**[32] was reported to promote Suzuki and Sonogashira couplings in EtOH and MeOH, respectively. Glycosylated biscarbene catalyst **L**[33] and NNN complex **M**[34] have been successfully applied in aqueous Suzuki-Miyaura coupling affording good yields with catalyst-loadings down to 10^{-3} mol% (Scheme 1.5).



Scheme 1.5 Suzuki-cross coupling reaction performed using by complex **L** in aqueous media as reported by Nishioka and col.

Pincer-complexes have demonstrated their valuable catalytic performance in aqueous media. This feature is highly appreciated due to the benefits the use of water provides regarding security and sustainability issues. An aqueous reaction environment procures a more secure working-framework given the absence of toxicity and flammability in comparison with common organic solvents. Additionally, in many cases the use of water notably eases the purification process owing to a low solubility of the organic reaction products in the reaction media, which might allow the separation by just a simple filtration. This could be useful in cases where the catalyst itself is negligibly soluble in water, which might expedite catalyst separation thus minimizing the metal content in final product, a determining issue in pharmaceutical industry.

1.3 Background of the research group

Our research group has gathered extensive experience in both pincer-complex design and synthesis together with organometallic catalysis in sustainable media, including water. In the next figure are compiled all the synthesized pincer complexes within the research group (Figure 1.7).

[32] Zhang, B. S.; Wang, C.; Gong, J. F.; Song, M. P *J. Organomet. Chem.* **2009**, *694*, 2555–2561.
[33] Imanaka, Y.; Shiomoto, N.; Tamaki, M.; Maeda, Y.; Nakajima, H.; Nishioka, T. *Bull. Chem. Soc. Jpn.* **2017**, *90*, 59–67.
[34] Gu, S.; Xu, H.; Zhang, N.; Chen, W. *Chem. Asian J.* **2010**, *5*, 1677–1686.

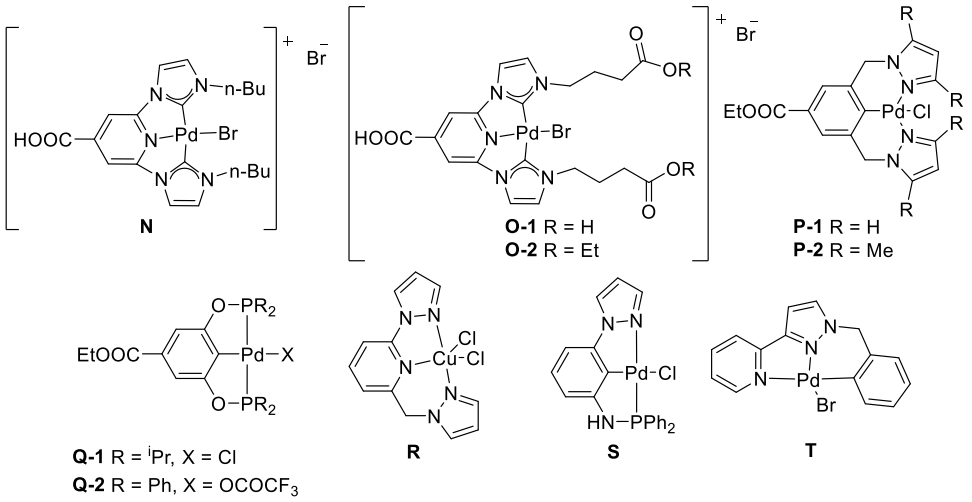
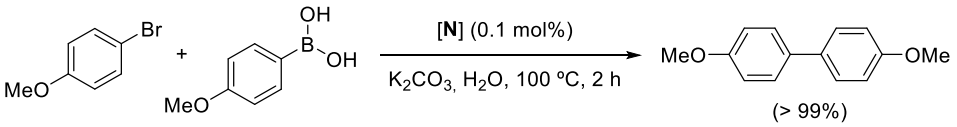


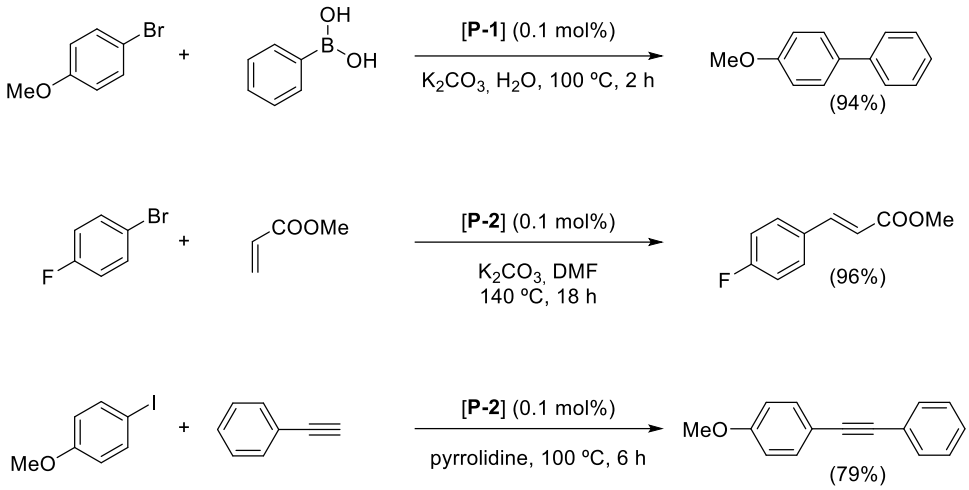
Figure 1.7 Pincer complexes synthesized by our research group.

The symmetric bis(carbene) chelates **N**[35] (Scheme 1.6) and **O**,[36,37,38] bis(pyrazole) decorated complexes **P**[39] (Scheme 1.7) and bis(phosphinite) complexes **Q**[40,41] were successfully employed in different cross-coupling reactions demonstrating excellent catalytic activities.[42] Moreover, catalysts **Q** demonstrated high efficiency in ketone α-arylation[40] reactions as well as in aerobic oxidations.[41]

[35] Churruca, F.; SanMartin, R.; Inés, B.; Tellitu, I.; Domínguez, E. *Adv. Synth. Catal.* **2006**, *348*, 1836–1840.
[36] Inés, B.; SanMartin, R.; Moure, M. J.; Domínguez, E. *Adv. Synth. Catal.* **2009**, *351*, 2124–2132.
[37] SanMartin, R.; Inés, B.; Moure, M. J.; Herrero, M. T.; Moreno, I.; Domínguez, E. *Arkivoc* **2011**, *2011*, 191–199.
[38] SanMartin, R.; Inés, B.; Moure, M. J.; Herrero, M. T.; Domínguez, E. *Helv. Chim. Acta* **2012**, *95*, 955–962.
[39] Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Synlett* **2005**, *2005*, 3116–3120.
[40] Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron Lett.* **2006**, *47*, 3233–3237.
[41] Urgoitia, G.; Galdón, G.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Environ. Chem. Lett.* **2018**, *16*, 1101–1108.
[42] Moreno, I.; SanMartin, R.; Inés, B.; Churruca, F.; Domínguez, E. *Inorg. Chim. Acta* **2010**, *363*, 1903–1911.



Scheme 1.6 Aqueous Suzuki cross-couplings in the presence of pincer complex **N**.



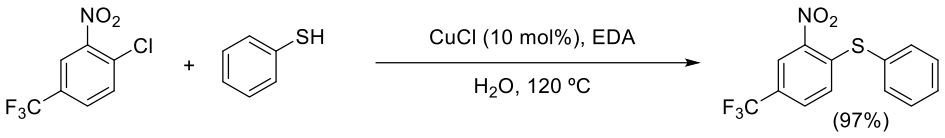
Scheme 1.7 Pincer complexes **P** as advantageous Pd sources for Suzuki, Heck and Sonogashira coupling reactions.

Besides, copper complex **R** was employed for the efficient heteroannulation between *O*-halophenols and alkynes leading to 2-arylbenzofurans in low catalyst loadings.[43] On the other hand, phosphinoamide pincer **S** demonstrated high catalytic activity in cross-coupling reactions in aqueous media.[44] Moreover, pincer **S** enabled intramolecular direct arylation with as small catalyst amounts as 0.05 mol%.[45] NNC complex **T** was applied to the ynoic acid hydroxycarbonylation reaction, providing the highest substrate:catalyst ratio ($1:10^{-4}$) so far.[46]

As mentioned before, our group has an extensive background on the development of more sustainable processes, based, in many cases, on the use of

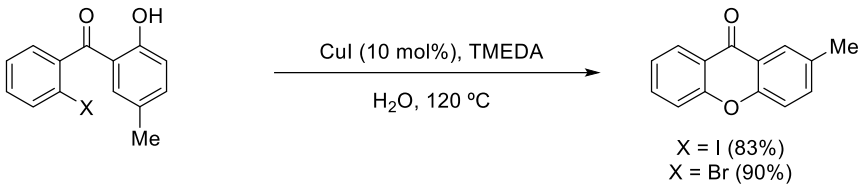
[43] Moure, M. J.; SanMartin, R.; Domínguez, E. *Adv. Synth. Catal.* **2014**, *356*, 2070–2080.
[44] Inés, B.; SanMartin, R.; Churruca, F.; Domínguez, E.; Urtiaga, M. K.; Arriortua, M. I. *Organometallics* **2008**, *27*, 2833–2839.
[45] Conde, N.; Churruca, F.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Adv. Synth. Catal.* **2015**, *357*, 1525–1531.
[46] Conde, N.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Adv. Synth. Catal.* **2016**, *358*, 3283–3292.

environmentally benign reaction media. In addition to the already mentioned aqueous cross-couplings or oxidations in polyol solvents, copper-catalyzed *S*-, *N*- and *O*-arylation reactions performed on water should be also pointed out. [47,48,49]



Scheme 1.8 Copper-catalyzed intramolecular *S*-arylation in water.

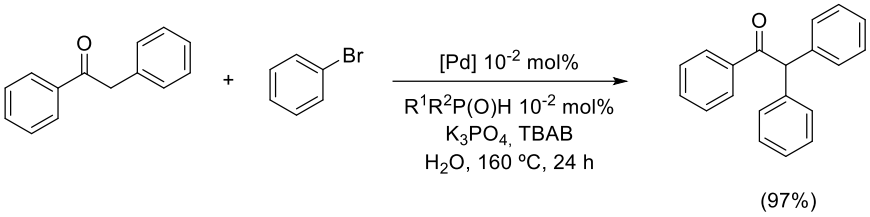
In this regard, several protocols were designed, which allowed the access to different heterocyclic scaffolds such as benzofuroindoles,[49] xanthones[50,51] and benzoimidazolones.[52]



Scheme 1.9 Copper-catalyzed intramolecular *O*-arylation on water: access to xanthones.

The treatment of (hetero)aryl mercaptans with ammonium hydroxide in water under aerobic conditions enabled the formation of the corresponding disulfides.[53] Recently, the combination of catalytic amounts (0.01 mol%) of commercially available palladium(II) acetate with diphenylphosphine oxide enabled the on-water α-arylation of ketone enolates (Scheme 1.10).[54]

[47] Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100–5105.
[48] Herrero, M. T.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2009**, *65*, 1500–1503.
[49] Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Green Chem.* **2007**, *9*, 219–220.
[50] Barbero, N.; SanMartin, R.; Domínguez, E. *Green Chem.* **2009**, *11*, 830–836.
[51] Barbero, N.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2009**, *65*, 5729–5732.
[52] Barbero, N.; Carril, M.; SanMartin, R.; Domínguez, E. *Tetrahedron* **2008**, *64*, 7283–7288.
[53] Carril, M.; SanMartin, R.; Domínguez, E.; Tellitu, I. *Green Chem.* **2007**, *9*, 315–317.
[54] Astarloa, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Adv. Synth. Catal.* **2018**, *360*, 1711–1718.



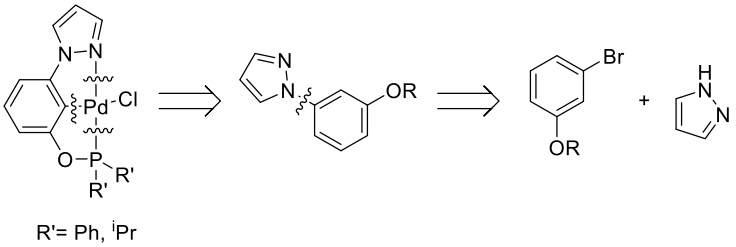
Scheme 1.10 Ketone α-arylation in water catalyzed by the $Pd(OAc)_2/Ph_2POH$ system.

Our expertise in the development of advantageous catalytic systems amenable to aqueous reaction conditions led us to envisage the synthesis of three new palladium pincer complexes and their application to two relevant organic transformations in water: Suzuki-Miyaura biaryl coupling and cycloisomerization of alkynoic acids.

2 AIMS AND OBJECTIVES

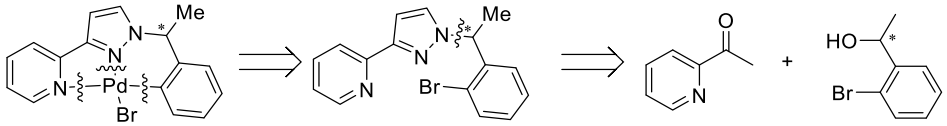
Considering the advantages provided by the use of pincer complexes as catalysts in several reactions, as well as our expertise in the development of this kind of metal complexes along with their use as catalysts or pre-catalysts in more sustainable reaction media, we formulated the following objectives:

- The synthesis of two novel non-symmetric palladium PCN pincer complexes, by a short sequence starting from commercially available, cheap pyrazole and 3-bromophenol.



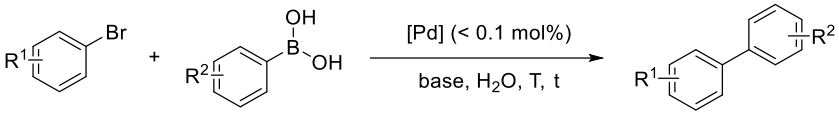
Scheme 1.11 Retrosynthetic design for Pd(II) complexes bearing PCN pincer ligands.

- The preparation of a non-symmetric chiral NNC-Pd(II) complex by palladation of 2-[1-(2-bromobenzyl)pyrazol-3-yl]pyridine precursor, easily accessible from 2-acetylpyridine and 2-bromophenylethanol.

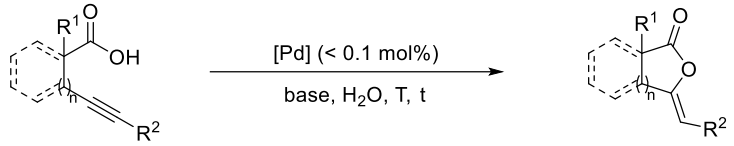


Scheme 1.12 Retrosynthetic scheme for the construction of a new palladium NNC pincer complex.

- The application of the aforementioned palladacycles in Suzuki-Miyaura cross-coupling and ynoic acid cycloisomerization reactions, giving priority to the employment of sustainable reaction media (water) and to the minimization of catalyst loadings ([Pd] < 10^{-1} mol%).



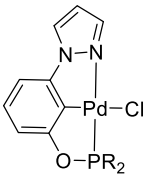
Scheme 1.13 General scheme for Suzuki biaryl coupling in water.



Scheme 1.14 General scheme for the cycloisomerization of alkynoic acids in water.

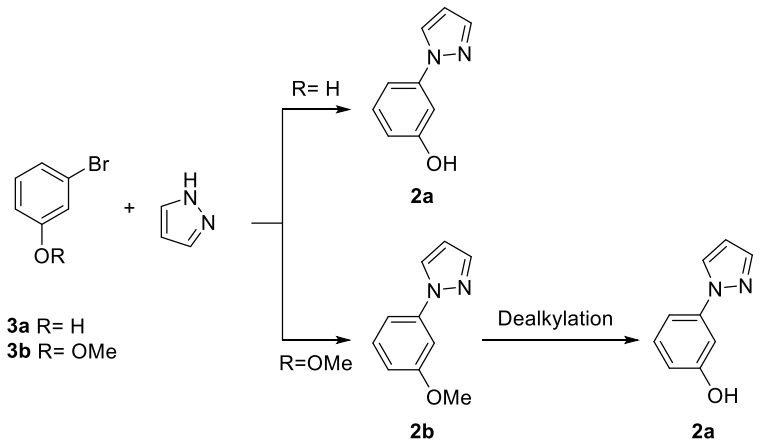
3 RESULTS AND DISCUSSION

3.1 Synthesis of non-symmetric PCN palladium pincer complexes 1



R^1= Ph **1a**
R^2= ^{i}Pr **1b**

The proposed synthetic route for the synthesis of palladacycles **1a-b** required the formation of 3-(1*H*-pyrazol-1-yl)phenol intermediate **2a**. However, no *N*-arylation process starting from 3-bromophenol (**3a**) and 1*H*-pyrazole had been described at the time, probably due to the risk of concomitant *O*-arylation processes. Therefore we planned two alternative ways to reach target intermediate **2a**. One was the direct *N*-arylation of 1*H*-pyrazole with 3-bromophenol. The other route would be the theoretically more feasible *N*-arylation employing 3-bromoanisole (**3b**) followed by a demethylation step (Scheme 1.15).

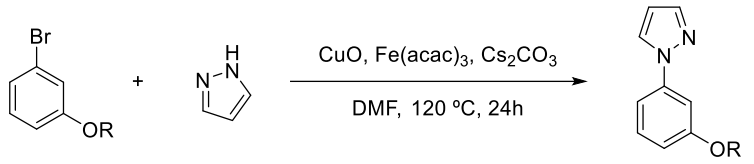


Scheme 1.15 Proposed synthetic routes to **2a**.

In the initial assays for the *N*-arylation reaction, Taillefer's work on copper and iron co-catalyzed *N*-arylation processes was taken into account.[55] In this regard, we performed several experiments for the *N*-arylation of 1*H*-pyrazole employing either 3-bromoanisole or 3-bromophenol in the presence of copper(II) oxide and iron(III) acetylacetonate as catalysts.

[55] Taillefer, M.; Xia, N.; Ouali, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 934–936.

Table 1.1 Synthesis of arylpyrazoles **2**.



3a, R= H
3b, R= OMe

2a, R= H
2b, R= OMe

Entry	(i)[a]	Yield[b] (%)
1	1 mmol **3b**, 1 mL DMF	96
2	1 mmol **3a**, 1 mL DMF	92
3	3 mmol **3a**, 3.2 mL DMF	72
4	6 mmol **3a**, 6.5 mL DMF	54
5	6 mmol **3a**, 6.5 mL DMF (acidic work-up)	60
6	6 mmol **3a**, 6.5 mL DMF (basic work-up)	67

[a] Reactions carried out with **3a/3b** (X mmol), 1*H*-pyrazole (1.5 equiv.), CuO (0.1 equiv.), $Fe(acac)_3$ (0.3 equiv.), Cs_2CO_3 (2 equiv.) and DMF at 120 ºC for 24 h.[b] Isolated yield.

As shown in Table 1.1, both reactions, the one starting from 3-bromoanisole as well as the one employing 3-bromophenol, proceeded smoothly affording the desired products **2b** and **2a** with an excellent yield (entries 1 and 2). Interestingly, the direct access to **2a** turned out to be a more straightforward approach, and no *O*-arylation product was detected.

Unfortunately, we observed a yield-decreasing trend while scaling-up the reaction (entries 2, 3 and 4). Despite this problem, we succeeded in improving slightly the yields just modifying the work-up process described in the bibliography. In the latter, reaction crude had to be diluted with DCM, filtered through celite and further washed with large amounts of water in order to remove DMF. Finally, the aqueous layer had to be extracted with DCM to afford the desired product with little amounts of DMF. When we performed the reaction at higher scale following the procedure described in the literature, we got the desired pyrazole in a 54% yield (entry 4).

Faced with this problem, we noticed that the phenol present in the target product could be susceptible of being stuck in the aqueous layer as a phenoxide. Hence a change in work-up was proposed. We decided to acidify the filtrate with an aqueous 1.0 M HCl solution to pH= 3-4 to ensure protonation of the hypothetic phenoxide and then the literature process was followed, obtaining the desired product in a 60% yield (entry 5).

As no important improvement was achieved, the opposite work-up procedure was carried out (the initial filtrate was basified with aqueous 1.0 M NaOH solution to pH = 11–12, followed by extraction with DCM, acidification to pH 3–4 and extraction with DCM) to provide the desired product in a 67% yield (entry 6).

In spite of the slight improvements achieved (entries 4, 5 and 6), it was decided that the best solution would be to set several parallel low-scale reactions (1 mmol) in order to avoid the problems occurred during scale-up process.

Besides, the structure for **2a** was unequivocally confirmed by different analytical methods as ^{1}H- and ^{13}C-NMR, GC-MS and single-crystal X-Ray diffractometry.

In ^{1}H-NMR the signals related to pyrazole protons could be observed at 6.34, 7.56 and 7.99 ppm, whereas ^{13}C-NMR showed pyrazole-core carbons at 111.1, 131.6 and 144.5 ppm, respectively.

Moreover, the X-ray diffractometry analysis of a single crystal obtained after recrystallization of **2a** in DCM confirmed the structure of this key intermediate, which crystallized in the monoclinic system ($P_{21/n}$ space-group) with a single molecule in the asymmetric unit.[56] Concerning the structure, the most relevant

[56] For additional information about crystallographic data: cell-unit parameters, bond-lengths, angles etc., look into experimental section.

bond-lengths and -angles correlate with those of similar derivatives found in the literature.[57]

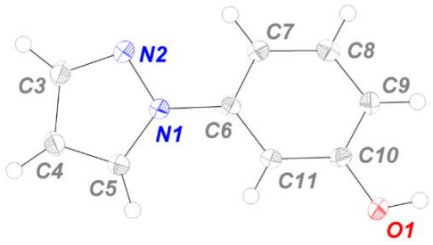


Figure 1.8 ORTEP diagram of 3-(*1H*-pyrazole-1-yl)phenol **2a** with thermal ellipsoids given at 50% probability level.

Table 1. 2 A selection of bond-lengths, bond-angles and torsion angles for compound **2a**.

Bond-length (Å)			
N(1)-C(6)	1.4273	O-C(10)	1.3609
C(6)-C(11)	1.3859	N(1)-N(2)	1.3573
Bond-angle (º)			
N(2)-N(1)-C(6)		120.9	
O-C(10)-C(11)		116.6	
Torsion-angle (º)			
N(2)-N(1)-C(6)-C(11)	141.5	N(2)-N(1)-C(6)-C(7)	-38.5

Moreover, as shown in (Figure 1.9), the analysis revealed a possible H-bond between the phenolic hydrogen and the pyrazole free nitrogen (N2) that shapes to some extent the packing in the crystal lattice of **2a**.

[57] For additional information about bond-lengths in similar derivatives, read: a) Catalán, J.; Fabero, F.; Soledad Guijarro, M.; Claramunt, R. M.; Dolores Santa María, M.; de la Concepción, M.; Hernández Cano, F.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1990**, *112*, 747–759.

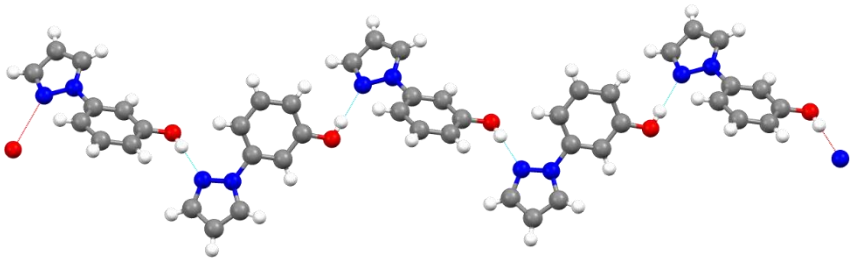


Figure 1.9 Possible H-bonds in compound **2a.**

Once phenol **2a** was obtained, we explored a tandem *O*-phosphination/palladation in order to access to target pincer complex **1**, using our expertise in phosphinite formation and palladium insertion *via* C-H activation/cyclometalation mechanism.[58] In this regard, different trials that combined a phosphination of the phenolic alcohol followed by palladation with $Pd(COD)Cl_2$ were carried out (Table 1.3).

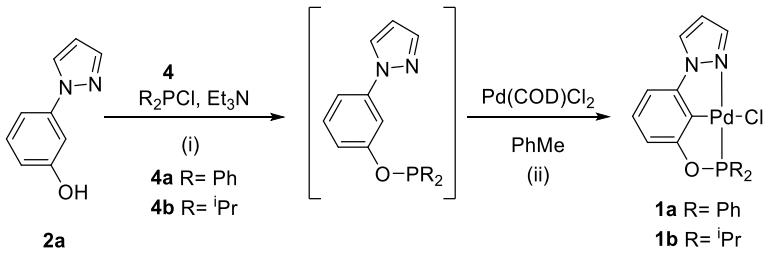
In a preliminary test, **2a** was reacted with chlorodiphenylphosphine (**4a**) in the presence of triethylamine in dry and degassed toluene at 130 ºC for 20 h, after which isolation of the reaction intermediate (phosphinite) was tried (entry 1). For that purpose, the reaction was concentrated *in vacuo* and further analyzed by ^{31}P-NMR, which confirmed the formation of the phosphinite proligand. Nevertheless, a second analysis of the same sample after 5 minutes, demonstrated the instability of the aforementioned compound, since degradation could be observed.[59] Even then, we continued with the metallation process and heated the reaction to 120 ºC in the presence of $Pd(COD)Cl_2$. In spite of the poor yield, we were able to isolate a product whose ^{31}P-NMR spectrum data ($\delta_{^{31}P}$) agreed with that of a phosphinite palladacycle previously synthesized in our research group.[40]

[58] Baber, R. A.; Bedford, R. B.; Betham, M.; Blake, M. E.; Coles, S. J.; Haddow, M. F.; Hursthouse, M. B.; Orpen, A. G.; Pilarski, L. T.; Pringle, P. G.; Wingad, R. L. *Chem. Commun.* **2006**, *0*, 3880–3882. For previous work of our group on the preparation of palladacycles by related strategies, see refs. 40 and 44.

[59] In the second analysis, a noticeable decrease of the ^{31}P-NMR signal intensity was observed together with the appearance of several new signals.

Taking into account the instability of the intermediate, in the next experiment the intermediate isolation step was avoided and thereby a slightly better yield was achieved (entry 2).

Table 1.3 Reaction conditions for the sequential *O*-phosphination/palladation leading to complexes **1**.



2a

1a R= Ph
1b R= ^{i}Pr

Entry	(i)[a]	(ii)[b]	Yield (%)[c]
1	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe,120 ºC[d]	12
2	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe,120 ºC[d]	20
3	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe,120 ºC, 24 h[d]	<1
4	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe, 120 ºC, 2 h[d]	<1
5	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe,115 ºC[d], [f]	33
6	**4a**, Et_3N, PhMe	$Pd(COD)Cl_2$, PhMe,120 ºC[g]	58
7	**4a**, Et_3N, THF[e]	$Pd(COD)Cl_2$, PhMe,120 ºC[g]	60
8	**4b**, Et_3N, THF[e]	$Pd(COD)Cl_2$, PhMe,120 ºC[g]	74

[a] Reactions carried out with R_2PCl (1.1 equiv.), TEA (1.1 equiv.) in PhMe (16 mL/mmol phenol) under Ar in a sealed-tube at 130 ºC for 20 h. [b] Reactions were performed with $Pd(COD)Cl_2$ (1.1 equiv.), PhMe (24 mL/mmol) under Ar in heavy walled sealed-tube without intermediate isolation, except in specified cases, at the specified temperature for 20 h. [c] Isolated overall yield from **2a**, after flash column chromatography. [d] Syringe transfer. [f] Performed in a round-bottom flask. [e] Reactions carried out with **2a**, chlorophosphine **4** (1.1 equiv.), TEA (1.1 equiv.) in THF (13 mL/mmol) under Ar in a round-bottom flask at 25 ºC for 2 h. [g] Double-tipped needle transfer.

In every case, vanishing of the signal of chlorodiphenylphosphine and appearance of the corresponding phosphinite signal was observed by ^{31}P-NMR analyses of reaction samples, thus proving to some extent that the phosphination conditions were adequate. Therefore, more experiments were performed to optimize the metalation step. Longer reaction times (entry 3) resulted in the visible

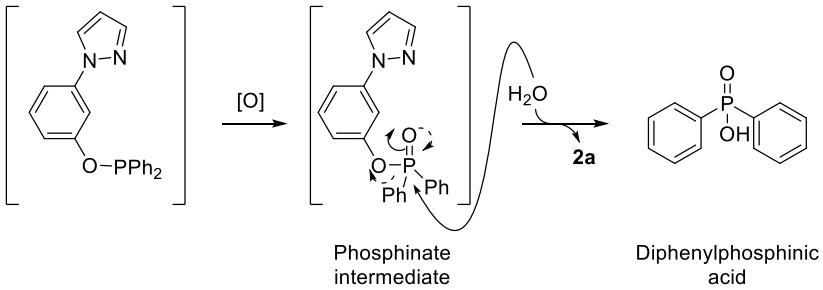
formation of palladium black. Similar negligible results were also obtained when a shorter reaction time (2 h) was tried (entry 4).[60]

Reaction pressure was then reduced to atmospheric (reflux, entry 5) on the suspicion that a higher pressure (sealed tube) might promote degradation of the labile phosphine intermediate. At that stage, we succeeded in improving the yield to 33%.

Shortly after, we managed to isolate a recurrent side-product with a characteristic ^{31}P-NMR signal at δ_{31P} = 31 ppm. Comparison with literature values and X-Ray diffractometry revealed its structure, that of diphenylphosphinic acid. We also found some examples in literature that showed the degradation of phosphinites to the corresponding phosphinic acids by the action of oxidants and moisture (Scheme 1.16).[61]

This result gave us a clue about what could be happening in the reaction. Taking into account that the reaction was being performed under rigorous anhydrous (freshly distilled chlorodiphenylphosphine and Et_3N, as well as freshly distilled and sodium dried PhMe) and inert media (Ar), the only weak spot in the procedure should be the filtration step. In such step, the readily formed proligand (intermediate) was added under Ar *via* syringe to a celite plug in order to remove by filtration the $Et_3N{\cdot}HCl$ formed in the phosphination step. Therefore, we decided to perform the transfer by means of a double-tipped needle, thus minimizing the contact with external agents. It resulted in a significant improvement in the yield (entry 6).

[60] With that in mind, longer reaction time was tested (entry 3) which resulted in palladium black precipitation and a further analysis of the crude revealed the presence of a main impurity at 31 ppm (^{31}P-NMR). As in previous experiments, a color change was observed at about 2 h from the setting up of the reaction, so we tried to carry out the reaction in shorter reaction times. These attempts concluded with similar results, that is, poor conversion to target complex and degradation side-products.
[61] Hong, H. J.; Lee, J.; Bae, A. R.; Um, I. H. *Bull. Korean Chem. Soc.* **2013**, *34*, 2001–2005.



Scheme 1.16 A proposal to explain the formation of diphenylphosphinc acid in the phosphination-palladation sequence.

Encouraged by the latter result, we tried to shorten the reaction time by switching the solvent of the phosphination step to THF. This step was successfully performed in 2 h at r.t., and it was also confirmed that the use of 3Å MS-predried solvents was enough to accomplish the reaction so that sodium-dried solvents could be avoided (entry 7).

Metallacycle **1a** was fully characterized and the ^{31}P-NMR experiment showed a remarkable deshielding of the signal (from 112 ppm in the proligand to 156 ppm in the complex) due to metal coordination. Furthermore, a single crystal of the target complex was obtained upon crystallization from a diethyl ether/chloroform mixture, thus allowing us to confirm its structure by X-ray diffractometry.

In such analysis, it was found that crystallization of **1a** takes place in the orthorhombic $P_{na}2_1$ space group, with the asymmetric unit formed by a single molecule of **1a**. Regarding the most relevant bond-lengths, Pd-N2, Pd-C11 and Pd-P5 (2.109 Å, 1.962 Å and 2.210 Å, respectively) were in accordance to those of the PCN complex previously synthesized in our group.[44] On the other hand, the palladium atom adopted a distorted square-planar configuration defined by the phosphorus atom in the phosphinite, the central aromatic carbon, the coordinating nitrogen present in the pyrazole and the chloride anion, as could be deduced from

torsion angles Pd-P-O-C10, C6-N1-N2-Pd and Cl-Pd-N2-C3 (6.23º, 1.62º and 9.00º, respectively).[62]

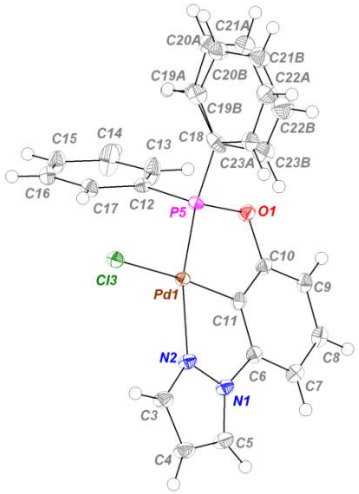


Figure 1.10 ORTEP diagram of complex **1a** with thermal ellipsoids given at 50% probability level. Molecule showing employed nomenclature and the orientational disorder observed for one of the phenyl groups.

Following the same synthetic procedure as for complex **1a**, the use of $^{i}Pr_2PCl$ (**5b**) provided palladacycle **1b** with an even higher yield (74%, Table 1.3, entry 8).

Metallacycle **1b** was fully characterized and the ^{31}P-NMR experiment showed a similar shift to lower field due to metal coordination (from 150 ppm in the phosphinite ligand to 205 ppm in the complex). The same solvent mixture (diethyl ether/chloroform) was used to crystalize it. X-Ray diffractometry confirmed its structure, featuring same point- and space-groups (orthorhombic $Pna2_1$), Pd-N2, Pd-C11 and Pd-P1 coordinating bond lengths (2.10 Å, 1.96 Å and 2.22 Å respectively), and a similar distorted square planar geometry (Figure 1.11).[62]

[62] For additional data about cell-unit parameters, bond-lengths, angles etc. see the experimental section.

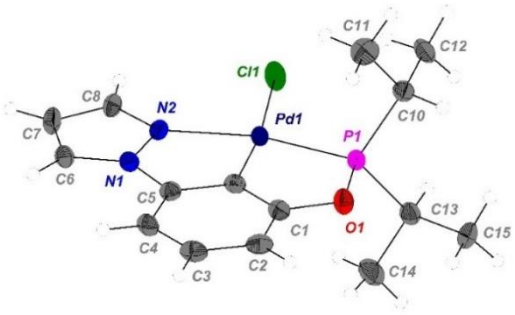
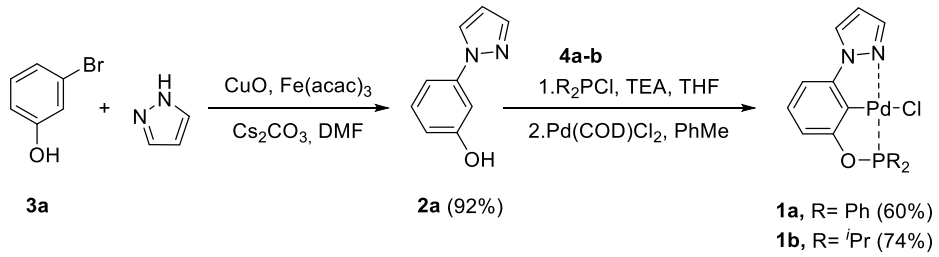


Figure 1.11 ORTEP diagram of complex **1b** with thermal ellipsoids given at 50% probability level.

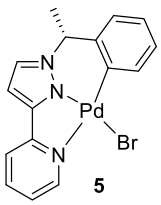
In summary, a short synthetic route based on an initial *N*-arylation reaction followed by a carefully performed tandem phosphorylation/palladation has led to two new phosphinite-based Pd(II) pincer complexes (**1a-b**) with good overall yields (55-68%, Scheme 1.17).



Scheme 1.17 Synthesis of palladacycles **1a** and **1b**.

3.2 Synthesis of a novel non-symmetric chiral NNC pincer complex 5

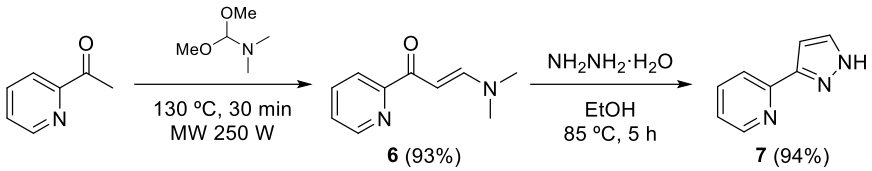
As mentioned in the introduction section, the remarkable performance of NNC-type palladium pincer catalyst **T** (Figure 1.7, page 14)[46] and the increasing interest in the synthesis of asymmetric pincer complexes encouraged us to design the preparation of a chiral NNC-type palladium pincer **5**.



5

The sequence started from commercially available 2-acetylpyridine. A microwave-assisted aminomethylenation reaction with dimethylformamide dimethyl

acetal was performed[63,64] to get enaminoketone **6**, which upon treatment with hydrazine provided 2-(1*H*-pyrazole-3-yl)pyridine **7** in excellent yield (Scheme 1.18).[65]



Scheme 1.18 Two-step approach to derivative **7**.

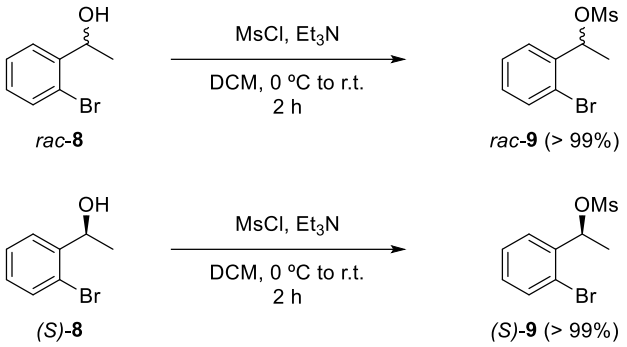
In parallel, based on the protocol reported by Lambert,[66] we prepared the mesylates of *rac*-1-(2bromophenyl)ethan-1-ol (*rac*-**8**) and (*S*)-1-(2-bromophenyl)ethan-1-ol (**8**), by treating the carbinols with methanesulfonyl chloride in the presence of TEA. Methanesulfonates **9** were obtained quantitatively (Scheme 1.19).

[63] For some examples of aminomethylenation reactions carried out by our group, see: a) Domínguez, E.; Martínez de Marigorta, E.; Olivera, R.; SanMartín, R. *Synlett* **1995**, *1995*, 955–956. b) Domínguez, E.; Ibeas, E.; Martínez de Marigorta, E.; Palacios, J. K.; SanMartín, R. *J. Org. Chem.* **1996**, *61*, 5435–5439. c) Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021–3037. d) Hernández, S.; Moreno, I.; SanMartin, R.; Gómez, G.; Herrero, M. T.; Domínguez, E. *J. Org. Chem.* **2010**, *75*, 434–441. e) Hernández, S.; Moreno, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Org. Biomol. Chem.* **2011**, *9*, 2251–2257.

[64] For aminomethylenation assisted by microwave irradiation, see: a) Al-Zaydi, K. M.; Borik, R. M. *Molecules* **2007**, *12*, 2061–2079. b) El-Apasery, M. A.; Al-Mousawi, S. M.; Elnagdi, M. H. *Eur. J. Chem.* **2011**, *2*, 168–172. c) Jadhav, R. K.; Karale, B. K.; Randhavane, P. V; Nikumbh, A. B.; Kakde, K. P. *Int. J. Chem. Pharm. Sci.* **2018**, *7*, 144–147.

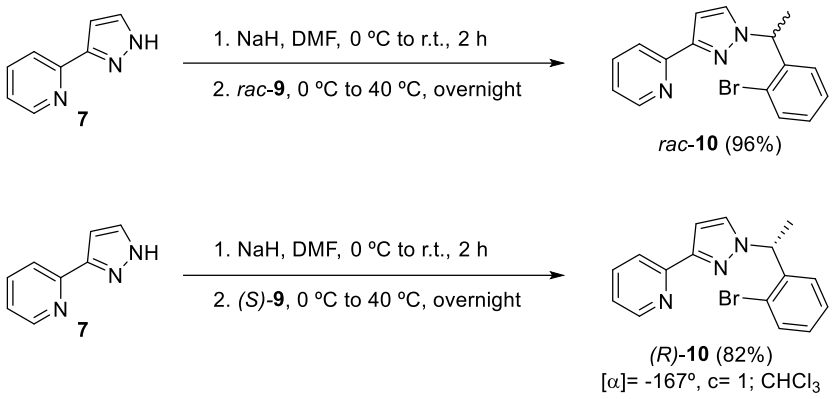
[65] For the preparation of pyrazoles from enaminoketones and hydrazine, see: Pleier, A.-K.; Glas, H.; Grosche, M.; Sirsch, P.; Thiel, W. R. *Synthesis* **2001**, *2001*, 55–62.

[66] Nacsa, E. D.; Lambert, T. H. *Org. Lett.* **2013**, *15*, 38–41.



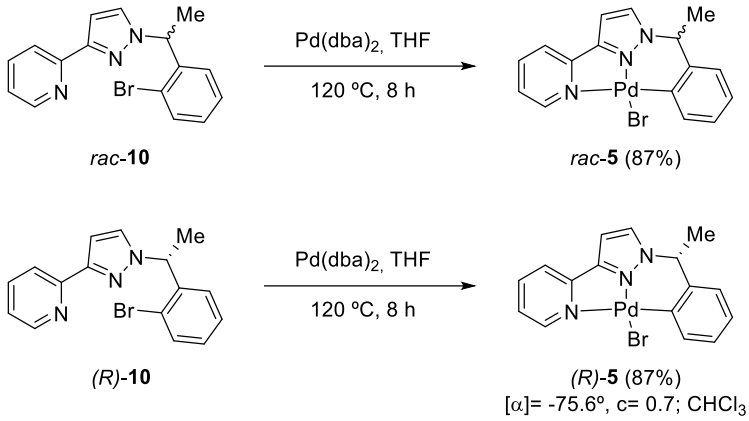
Scheme 1.19 Sulfonylation of racemic and (*S*)-1-(2-bromophenyl)ethan-1-ol **8**.

After deprotonation of pyridylpyrazole **7** with sodium hydride to the corresponding pyrazolide, mesylates **9** were added and reaction was continued to afford the proligands *rac*-**10** and *(R)*-**10** in good to excellent yields.



Scheme 1.20 Synthesis of proligands **10**.

Finally, pincer-complexes **5** were prepared by subjecting the proligands **10** to the oxidative addition/coordination conditions previously reported in the group,[46] that is, $Pd(dba)_2$ in THF at 120 ºC for 8 h, whereby the desired racemic and enantioenriched NNC-type palladium pincer complexes **5** were obtained in good yield (Scheme 1.21).



Scheme 1.21 Palladation of proligands **10** in presence of $Pd(dba)_2$ to afford palladacycles **5**.

After isolation, crystallization experiments were carried out to get single crystals from *rac*-**5** and *(R)*-**5**. The former crystallized easily in a couple of days in an acetone:petroleum ether mixture. Nonetheless, a change in the crystallization solvent (DCM:PhMe) was required along with a different crystallization technique (liquid-liquid diffusion) in order to obtain a productive crystallization from (*R*)-**5**. A further analysis by X-Ray diffractometry of the latter single crystal revealed a monoclinic spatial group ($P2_1/c$) corresponding to an enantiomeric mixture. However, we measured the specific rotation ([α] = -75.6º, c = 0.7, $CHCl_3$) thus confirming the absence of a racemate which was observed when *rac*-**5** was analyzed ([α] = 0, c = 0.7, $CHCl_3$). After this, and observing the differences in crystallization processes, we hypothesized about the possibility of the presence of a slight amount of the opposite enantiomer, *(S)*-**5**, and that both enantiomers might have co-crystallized giving rise to a racemic single-crystal.[67] However, further assays and analyses (*e.g.* chiral HPLC) should be made in order to confirm this proposal.

The crystallographic analysis also showed an asymmetric unit formed by a molecule of **5**. Pd-N1, Pd-N7 and Pd-C14 bond lengths (2.19 Å, 1.97 Å and 2.01 Å,

[67] For a comprehensive report on the crystallization (symmetry, space-groups, etc.) of chiral molecules, see: Flack, H.D. *Helv. Chim. Acta* **2003**, *86*, 905–921.

respectively) were similar to those of the NNC complex previously synthesized in our group.[46] The palladium atom adopted a distorted square-planar configuration in its binding position defined by the pyridine nitrogen atom, the central pyrazole nitrogen, the anionic carbon from phenyl moiety and the bromide anion, as could be deduced from torsion angle N7-Pd-N1-C6, N7-Pd-C14-C15 and Br-Pd-N1-C2 values (-7.66º, -15.26º and 4.42º).

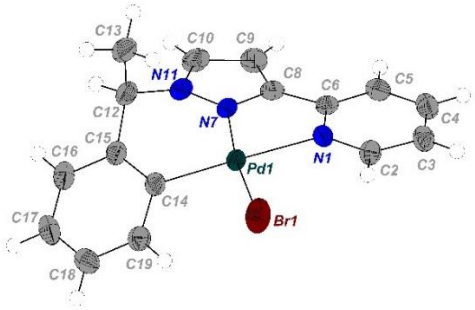


Figure 1. 12 ORTEP diagram of complex **5** with thermal ellipsoids given at 50% probability level. Molecule showing employed nomenclature.

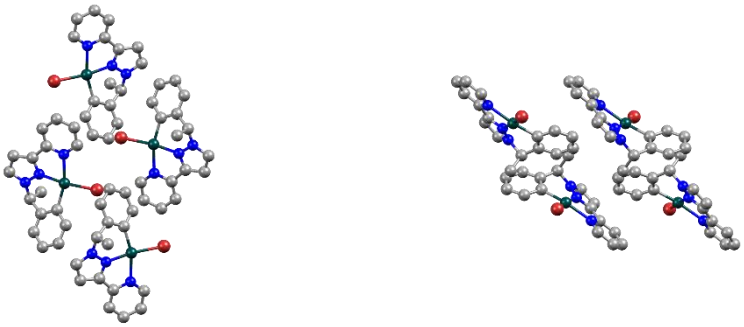


Figure 1.13 Perspective view of the crystal packing along the a (left) and b (right) axes. Hydrogen atoms have been removed for clarity.

3.3 Aqueous Suzuki-Miyaura biaryl coupling in the presence of palladacycles 1

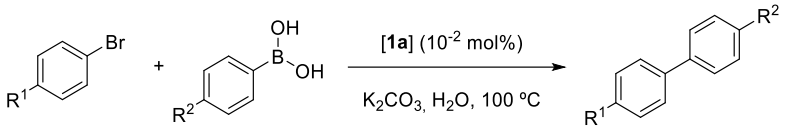
The catalytic performance of phosphinite complex **1a-b** was explored by using them as palladium sources for the Suzuki cross-coupling of a number of arylboronic

acid and haloarene derivatives. As mentioned before, preference was given not only to the use of sustainable reaction media but also to the minimization of catalyst amounts. In addition to classical heating, we also studied the possibility of performing the desired couplings by microwave irradiation in order to shorten reaction times and to increase the energetic efficiency of the process. Thereupon, the most remarkable results will be outlined.

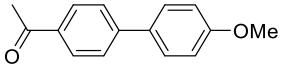
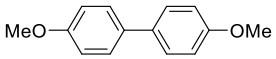
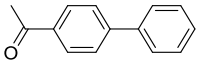
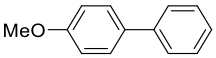
3.3.1 Suzuki cross-coupling under conventional heating

Based on the expertise gained by our research group, we decided to perform the model reaction, the coupling between 4-bromoacetophenone **11a** and 4-methoxyphenylboronic acid **12a**, under conditions akin to those optimized for the coupling using non-symmetric phosphinoamino complex **S** (page 14),[44] just replacing **S** with our new phosphinite complex **1a** as the palladium source. In this regard, we carried out the reaction using a 10^{-2} mol% of palladacycle **1a** and potassium carbonate as base in water at 100 ºC for 2 h (Table 1.4). The aforementioned coupling was achieved quantitatively in just 2 h. At this catalyst loading the reaction took place with excellent results not only with **12a** but also with less reactive phenylboronic acid (**12b**, entry 3). Moreover, 4-bromoanisole **11b**, a substrate theoretically deactivated for the oxidative addition step, was also successfully coupled (entries 2 and 4). Encouraged by these results we envisioned the use of even smaller amounts of complex **1a** (10^{-4}–10^{-6} mol%, Table 1.5).

Table 1.4 Suzuki-Miyaura cross-couplings in the presence of a 10^{-2} mol% of complex **1a**.[a]



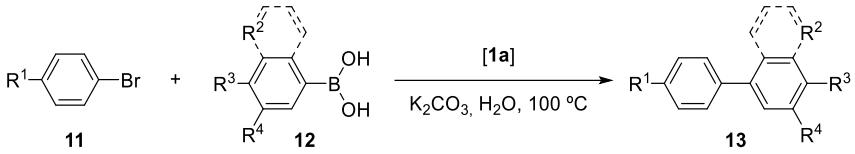
11 **12** **13**

Entry	**11**	**12**	**13**	Yield (%)[b]
1	**11a**, R^1 = -Ac	**12a**, R^2 = -OMe	 **13a**	>99
2	**11b**, R^1 = -OMe	**12a**, R^2 = -OMe	 **13b**	>99
3	**11a**, R^1 = -Ac	**12b**, R^2 = -H	 **13c**	93
4	**11b**, R^1 = -OMe	**12b**, R^2 = -H	 **13d**	86

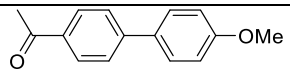
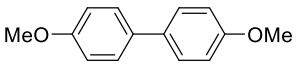
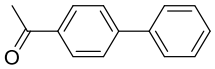
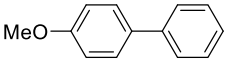
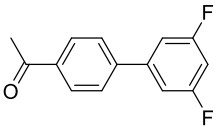
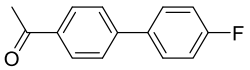
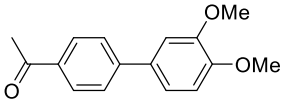
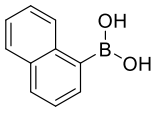
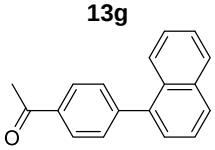
[a] Reactions carried out in a sealed-tube with **11** (0.15 mmol), **12** (1.5 equiv.), K_2CO_3 (2.0 equiv.) and **1a** (10^{-2} mol%) in water (0.3 mL) at 100 ºC for 2 h. [b] Yield determined by ^{1}H-NMR employing 3,4,5-trichloropyridine as internal standard.

4'-Bromoacetophenone (**11a**) was smoothly coupled to phenylboronic acids **12a** and **12b** and 1-naphthylboronic acid **12f** with a 10^{-4} mol% of complex **1a** in 12 h (Table 1.5, entries 1, 3 and 8). In addition, we were pleased to verify that similar results could be obtained using as low as 10^{-6} mol% of **1a**, except for 4-methoxyphenylboronic acid, whose yield dropped to 67% (entry 1).

Table 1.5 Suzuki-Miyaura biaryl coupling in the presence of a 10^{-4}–10^{-6} mol% of complex **1a**.[a]



11 **12** **13**

Entry	**11**	**12**	**13**	Yield[b] (%) 10^{-4} mol%	Yield[b] (%) 10^{-6} mol%
1	**11a** R^1 = -Ac	**12a** R^2 = -OMe	 **13a**	98 (24)[c]	67
2	**11b** R^1 = -OMe	**12a** R^2 = -OMe	 **13b**	trace[c]	trace
3	**11a** R^1 = -Ac	**12b** R^2 = -H	 **13c**	91 (>99)[c]	97
4	**11b** R^1 = -OMe	**12b** R^2 = -H	 **13d**	7 (31)[c]	trace
5	**11a** R^1 = -Ac	**12c** R^2, R^4 = -F R^3 = -H	 **13e**	57	trace
6	**11a** R^1 = -Ac	**12d** R^2, R^4 = -H R^3 = -F	 **13f**	42	52
7	**11a** R^1 = -Ac	**12e** R^2, R^3 = -OMe R^4 = -H	 **13g**	33	95
8	**11a** R^1 = -Ac	 **12f**	 **13h**	96	92

[a] Reactions carried out in sealed-tube with **11** (0.15 mmol), **12** (1.5 equiv.), K_2CO_3 (2.0 equiv.) and **1a** (as indicated, 10^{-4}-10^{-6} mol%) in water (0.3 mL) at 100 ºC for 12 h. [b] Yield determined by ^{1}H-NMR employing 3,4,5-trichloropyridine as internal standard. [c] The ^{1}H-NMR yield observed when TBAB (1.0 equiv.) was used as additive is displayed in brackets.

Unexpectedly, the use of 3,4-dimethoxyphenylboronic acid **12e** gave poor yield when a 10^{-4} mol% of **1a** was used, but a noteworthy improvement (from 33 to 95%) was observed by a decrease of the catalyst amount to 10^{-6} mol%. The latter results along with the observed dark reaction when a 10^{-4} mol% of **1a** was employed might account for the formation of Pd(0) aggregates and subsequent palladium black, inactive to furnish biaryl **13g**. On the contrary, a lower catalyst loading might have prevented aggregate formation, thus allowing the complex itself or Pd(0) nanoparticles to catalyze the reaction.[68]

In the case of bromoanisole **11b** (entries 2 and 4), a decrease in the yield was observed (entry 4) when catalytic loading was set below 0.01 mol%. Such was the effect that the reaction did not take place when 4-methoxyphenylboronic acid was used as coupling partner (entry 2). These results may be explained on the basis of the electronics of the bromoarene (**11b**). Indeed, the strong electron-donating group (-OMe) of **11b** increases the electron-density in the ring as well as in the C-Br bond, thus hampering the oxidative addition step required for the coupling.

The use of fluorinated boronic acids (entries 5 and 6) rendered moderate yields from a 10^{-4} mol% of **1a**. As it may be expected, an electron-withdrawing effect tends to reduce the electron density of the boronic acid and thereby its nucleophilicity, thus hindering the transmetalation step. In fact, the yield was lower when 3,5-difluorophenylboronic acid (**12c**) was used instead of 4-fluorophenylboronic acid (**12d**) for the same catalyst loading (10^{-4} mol%, entries 5-6).

Besides, in some experiments TBAB was tested as additive. The beneficial effect of TBAB and other tetraalkylammonium salts is widely known for cross-coupling reactions improving notably the reaction outcome. Generally, their use is linked to chloroarenic substrates or biphasic reaction media. The real task of those salts remains unclear, although different theories have been postulated. One of

[68] For a discussion on the topic, see: Van Leeuwen, P. W. N. M. *Appl. Catal. A Gen.* **2001**, *212*, 61–81.

them considers that these agents stimulate the metal-ligand exchange due to the enhanced ionic-strength induced by halide ions, whereas others concentrate on their ability to stabilize the catalyst taking into account their phase-transfer ability in biphasic systems.[69] However, in our case, the use of TBAB did not provide clear results (entries 1–4).

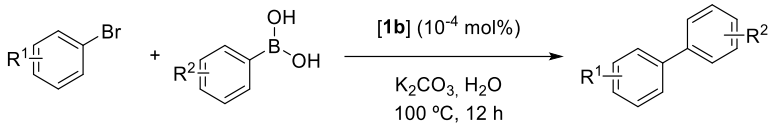
Briefly, when catalyst amounts were diminished the yields also fell. However, in several cases excellent (entries 3, 7 and 8) and good yields (entries 1 and 6) were achieved even with infinitesimal catalyst-loadings (10^{-6} mol%). Besides, the use of TBAB did not provide significant improvement.

In order to test to some extent the catalytic performance of palladacycle **1b**, some experiments were carried out at a 10^{-4} mol% level, as shown in Table 1.6. In general, pincer complex **1b** exhibited an improved catalytic activity in comparison with that of complex **1a** (Table 1.5, entries 2, 4 *vs* Table 1.6 entries 1–2; Table 1.5, entries 5–7 *vs* Table 1.6, entries 3–5). This enhanced activity was observed even when non-activated 4-bromoanisole (**11b**) was assayed. Whereas **1a** provided traces of the product (**13b**), a 69% yield was achieved with complex **1b** (entry 2). Despite further research should be undertaken in order to clarify the origin of this marked catalytic performance, it might be attributed to a more electron-rich palladium-core that would ease Pd(II)-Pd(0) reduction, thus boosting the formation of catalytically active species.

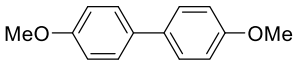
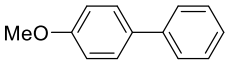
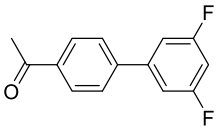
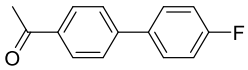
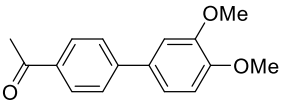
As a conclusion, several Suzuki cross-coupling reactions have been carried out with very small amounts of the new PCN pincer complexes **1a-b** (down to 10^{-6} mol%) in water, achieving good to excellent yields.

[69] For additional information check: a) Lysén, M.; Köhler, K. *Synlett* **2005**, *2005*, 1671–1674. b) Lysén, M.; Köhler, K. *Synthesis*, **2006**, *2006*, 692–698. c) Soomro, S. S.; Röhlich, C.; Köhler, K. *Adv. Synth. Catal.* **2011**, *353*, 767–775.

Table 1.6 Suzuki-Miyaura biaryl coupling in the presence of a 10^{-4} mol% of complex **1b**.[a]



11 **12** **13**

Entry	**11**	**12**	**13**	Yield (%)[b]
1	**11b** R^1 = -OMe	**12a** R^2 = -OMe	 **13b**	69
2	**11b** R^1 = -OMe	**12b** R^2 = -H	 **13d**	48
3	**11a** R^1 = -Ac	**12c** R^2, R^4 = -F R^3 = -H	 **13e**	>99
4	**11a** R^1 = -Ac	**12d** R^2, R^4 = -H R^3 = -F	 **12g**	98
5	**11a** R^1 = -Ac	**12e** R^2, R^3 = -OMe R^4 = -H	 **13g**	>99

[a] Reactions carried out in sealed-tube with **11** (0.15 mmol), **12** (1.3 equiv.), K_2CO_3 (2.0 equiv.) and **1b** (10^{-4} mol%) in water (0.3 mL) at 100 ºC for 12 h. [b] Isolated yield.

3.3.2 MW-assisted Suzuki cross-coupling

It is well known that many microwave-assisted reactions exhibit an accelerated kinetics. This occurs owing to the difference in the way the heating process takes place. On the one hand, in traditional heating the effect proceeds *via* convection, that is, heat is driven from an external heating source to the substance but firstly, it has overcome some barriers, *i.e.* walls of the vessel. This energy transfer is slow

and makes the process relatively inefficient since it depends on the thermal conductivities of the materials involved.[70,71]

On the other hand, microwave irradiation, as an electromagnetic energy source (the walls of the reaction vessel are completely "transparent"), will allow for a more efficient and faster heating, as a result of the molecules' dipole rotation when trying to orientate themselves to the rapidly changing electric field. This effect, in cases where ionic species are present, adds to the so-called ionic induction process in which the electric field promotes ionic motion because of the constant reorientation of the ions to fit the changing electric field. This last effect generates instant superheating nuclei that evolve to the rest of the reaction achieving the target temperature very quickly. Briefly, as a consequence of the rapid heating process the reactants reach activation-energy faster, thus increasing the reaction-rate.[72,73]

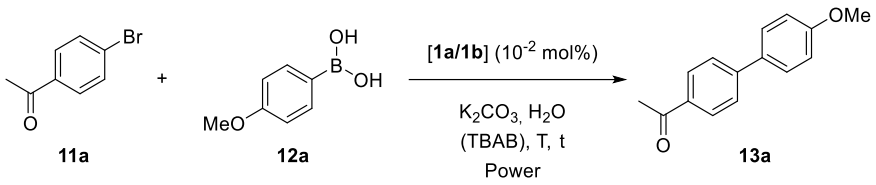
Encouraged by the excellent results obtained by the Suzuki coupling performed under conventional heating, and as an attempt to achieve a further optimization of the process, we decided to explore microwave irradiation.[74] The same model reaction was chosen for a number of optimization assays, summarized in Table 1.7.

First, two temperatures were assayed considering the addition or absence of TBAB as a reaction additive (entries 1-4). When carrying the reaction at 120 ºC in the absence of TBAB (entry 1) the desired product was obtained in an excellent yield, whereas the presence of TBAB (entry 2) turned to be deleterious. The addition of TBAB at lower temperatures (entry 3) remained equally ineffective. However, we were pleased to confirm that the outcome in the absence of that

[70] Henary, M.; Kananda, C.; Rotolo, L.; Savino, B.; Owens, E. A.; Cravotto, G. *RSC Adv*. **2020**, *10,* 14170–14197.
[71] Nain, S.; Singh, R.; Ravichandran, S. *Adv. J. Chem. A* **2019**, *2*, 94–104.
[72] Lidström, P., Tierney, J., Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
[73] *Microwave synthesis: Chemistry at the speed of light* Hayes, L. B.; CEM publishing**,** Matheews, **2002.**
[74] For additional information on MW-assisted Suzuki couplings, read: a) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 888–892. b) Leadbeater, N. E.; Marco, M. *J. Org. Chem.* **2003**, *68*, 5660–5667. c) Bedford, R. B.; Butts, C. P.; Hurst, T. E.; Lidström, P. *Adv. Synth. Catal.* **2004**, *346*, 1627–1630.

additive was even better at 100 ºC than at a higher temperature, thus obtaining the product quantitatively (entry 4). Besides, the shortening of the reaction time turned out to be detrimental for the reaction (entries 5-7). Although the reaction yields were visibly affected, we proved that the catalyst was able to provide a 50% yield of target biaryl **13a** in just 5 min (entry 7).

Table 1.7 Screening of reaction conditions for Suzuki-Miyaura cross-coupling assisted by microwave irradiation.[a]



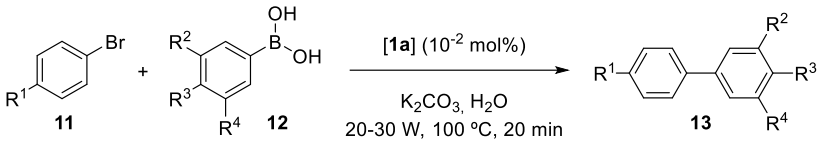
Entry	TBAB (equiv.)	**1**	T (ºC)	t (min)	Yield (%)[b]
1	-	**1a**	120	20	91
2	1.0	**1a**	120	20	76
3	1.0	**1a**	100	20	75
4	-	**1a**	100	20	99
5	-	**1a**	100	15	71
6	-	**1a**	100	10	60
7	-	**1a**	100	5	50
8	-	**1b**	100	20	90
9[c]	-	**1b**	120	15	99

[a] Reactions carried out with **11a** (0.15 mmol), **12a** (1.3 equiv.), complex **1** (0.01 mol%), K_2CO_3 (2.0 equiv.), water (0.3 mL) and TBAB (1.0 equiv., when specified) in a microwave sealed-tube heated to the corresponding temperature and time (Power: 20–30 W). [b] Yield determined by ^{1}H-NMR employing 3,4,5-trichloropyridine as internal standard. [c] Power: 60 W, cooling.

As a result, we decided to set the parameters tested in entry 4 as the optimized ones for complex **1a**, and then we tried to adapt those conditions for **1b**. On account of the lower yield achieved (entry 8), we performed the reaction heating to 120 ºC while cooling under microwave irradiation at 60 W. This provided a full conversion to the desired product (entry 9) and therefore those conditions were chosen as optimal for catalyst **1b**. Unfortunately, the minimization of catalyst loadings down to 10^{-4}–10^{-6} mol% did not work and the substrates were recovered.

With the optimized reaction conditions in hand, we investigated the reaction scope employing both novel pincer complexes **1a-b**. The corresponding results are displayed in Table 1.8 and Table 1.9 for catalysts **1a** and **1b**, respectively.

Table 1.8 Microwave-assisted Suzuki biaryl coupling in the presence of palladacycle **1a**: substrate scope. [a]



Entry	R^1	R^2	R^3	R^4	Yield (%)[b]
1	-Ac	-H	-OMe	-H	99
2	-Ac	-H	-H	-H	91
3	-Ac	-F	-H	-F	70
4	-Ac	-H	-F	-H	83
5	-Ac	-OMe	-OMe	-H	90
6	-H	-H	-OMe	-H	20
7	-H	-F	-H	-F	60
8	-H	-H	-F	-H	99
9	-H	-OMe	-OMe	-H	35
10	-OMe	-H	-OMe	-H	19
11	-OMe	-H	-H	-H	74
12	-OMe	-F	-H	-F	56
13	-OMe	-H	-F	-H	99

[a] Reactions carried out with **11** (0.15 mmol), **12** (1.3 equiv.), K_2CO_3 (2.0 equiv.), complex **1a** (10^{-2} mol%) in water (0.3 mL) heating to 100 ºC under microwave irradiation (20-30 W) for 20 min. [b] Yield determined by ^{1}H-NMR employing 3,4,5-trichloropyridine as internal standard.

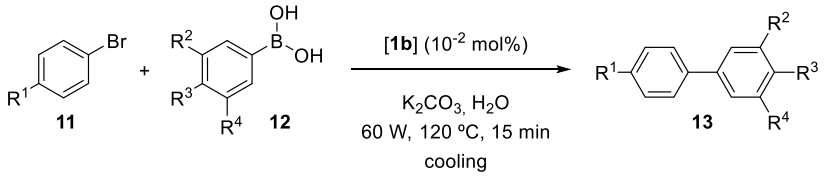
When the relatively electron-poor 4-bromoacetophenone (**11a**) was employed (entries 1-5) good to excellent yields were afforded regardless of the nature of the coupling partner, albeit a slight decrease was observed when electronically handicapped fluoroarylboronic acids were involved (entries 3 and 4).

When bromobenzene was submitted to the same conditions (entries 6-9) reaction yields fell notably even when electron-rich arylboronic acids were employed (entries 6 and 9). Surprisingly, 3,5-difluoro- and 4-fluorophenylboronic

acids (**12c** and **12d**, respectively) provided good to excellent results (entries 7 and 8).

Finally, we were glad to see that the results obtained with 4-bromoanisole were good, taking into account the short reaction times employed for the transformation (entries 10-13) with a relatively deactivated substrate. However, poor yields were obtained from 4-methoxyphenylboronic acid (entry 10), whereas fluorinated arylboronic acids provided moderate to excellent yields (entries 12 and 13). In view of these results, it is clear that a more elaborate explanation that goes beyond the simple electronic characteristics of the coupling partners is required to rationalize the observed yields.[75]

Table 1.9 Microwave-assisted Suzuki biaryl coupling in the presence of palladacycle **1b**: Substrate scope. [a]



Entry	R^1	R^2	R^3	R^4	Yield (%)[b]
1	-Ac	-H	-OMe	-H	99
2	-Ac	-H	-H	-H	88
3	-Ac	-F	-H	-F	89
4	-Ac	-H	-F	-H	91
5	-Ac	-OMe	-OMe	H	96
6	-H	-H	-OMe	-H	29
7	-H	-F	-H	-F	40
8	-H	-H	-F	-H	92
9	-H	-OMe	-OMe	-H	14

[a] Reactions carried out with **11** (0.15 mmol), **12** (1.3 equiv.), K_2CO_3 (2.0 equiv.), pincer catalyst **1b** (10^{-2} mol%) in water (0.3 mL) heating to 120 ºC under microwave irradiation (60 W) under cooling for 15 min. [b] Isolated yield.

As shown in the table above (Table 1.9), palladacycle **1b** exhibited a comparable activity in the microwave-assisted Suzuki coupling of several

[75] Pagett, A. B.; Lloyd-Jones, G. C. *Org. React.* **2019**, *100*, 547–619.

arylboronic acids and bromoarenes in water, providing in some cases even better yields than complex **1a** over shorter reaction times (entries 3–6).

In summary, palladacycles **1** turned out to be suitable palladium sources for the Suzuki-Miyaura biaryl coupling carried out in water. Moreover, microwave irradiation enhanced the reaction rate and, in some cases, provided even better results. The convenience of such low catalyst amounts (0.01 mol%), sustainable solvent (water), short reaction times (15 min) and energy efficiency (60 W/15 min) should be pointed out.

3.4 Cycloisomerization of alkynoic acids catalyzed by complexes 1

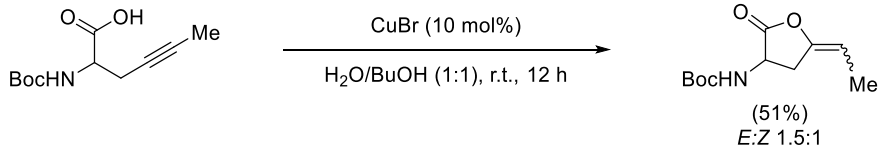
3.4.1 Cycloisomerization of alkynoic acids in water

The hydroxycarbonylation of acetylenic acids has gathered much attention as a highly atom-economic process for the formation of valuable alkylidene lactones. As a result, several research groups have devoted their research to the discovery of new catalytic systems that enable the synthesis of the latter lactone cores as efficiently as possible.[76,77] In the way to do so, catalyst loading minimization and environmentally bening reaction media have become priorities for a more sustainable approach.[78]

In 2007, Mindt *et al.* reported the first alkynoic acid hydroxycarbonylation in aqueous media employing a relatively high amount of cuprous bromide (10 mol%) in a butanol:water (1:1) mixture (Scheme 1.22), but the procedure was limited to six substrates.[79] A few years later Alemán *et al.* found that the anticancer agent *cis*-

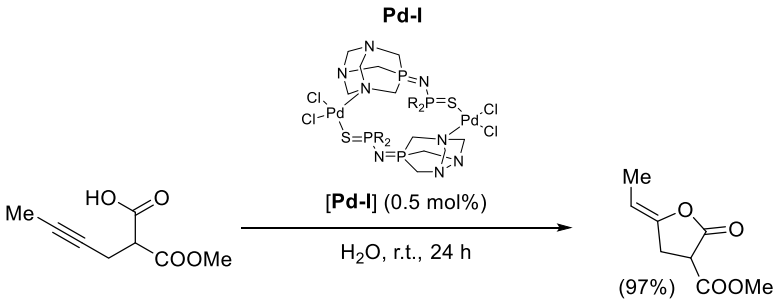
[76] For the properties and uses of alkylidene lactones, see: a) Liu, F.; Negishi, E. I. *J. Org. Chem.* **1997**, *62*, 8591–8594. b) Raju, R.; Garcia, R.; Müller, R. *J. Antibiot*. **2014**, *67*, 725–726. c) Zhao, W.; Lorenz, N.; Jung, K.; Sieber, S. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 1187–1191.
[77] For some examples of hydroxycarbonylation of alkynoic acis, see: a) Leconte, N.; Du Moulinet D'Hardemare, A.; Philouze, C.; Thomas, F. *Chem. Commun.* **2018**, *54*, 8241–8244. b) Gutiérrez-Blanco, A.; Peris, E.; Poyatos, M. *Organometallics* **2018**, *37*, 4070–4076.
[78] For the use of more sustainable media and catalytic systems, see: a) Mancuso, R.; Pomelli, C. S.; Chiappetta, P.; Gioia, K. F.; Maner, A.; Marino, N.; Veltri, L.; Chiappe, C.; Gabriele, B. *J. Org. Chem.* **2018**, *83*, 6673–6680. b) Eriksson, K.; Verho, O.; Nyholm, L.; Oscarsson, S.; Bäckvall, J. E. *Eur. J. Org. Chem.* **2015**, *2015*, 2250–2255.
[79] Mindt, T. L.; Schibli, R. *J. Org. Chem.* **2007**, *72*, 10247–10250.

$PtCl_2(NHMe_2)_2$ triggered the same transformation at room temperature and in neat water in just 12 h employing a 1 mol%.[80] However, the reaction scope was mostly limited to α-alkoxycarbonylated acetylenic acids and failed to cyclize longer ynoic acids than 4-pentynoic acid derivatives.



Scheme 1.22 Copper(I) bromide-catalyzed alkynoic acid cycloisomerization in aqueous mixture.

In the same year, García-Álvarez *et al.* utilized a dimeric palladium catalyst (**Pd-I**) to carry out these reactions, obtaining good outcomes even when non-terminal alkynes were used. Moreover, they were able to recycle the catalytic system up to 5 cycles at the expense of slightly longer reaction times (Scheme 1.23). However, the reaction scope remained limited to α-methoxycarbonylated ynoic acids.[81]

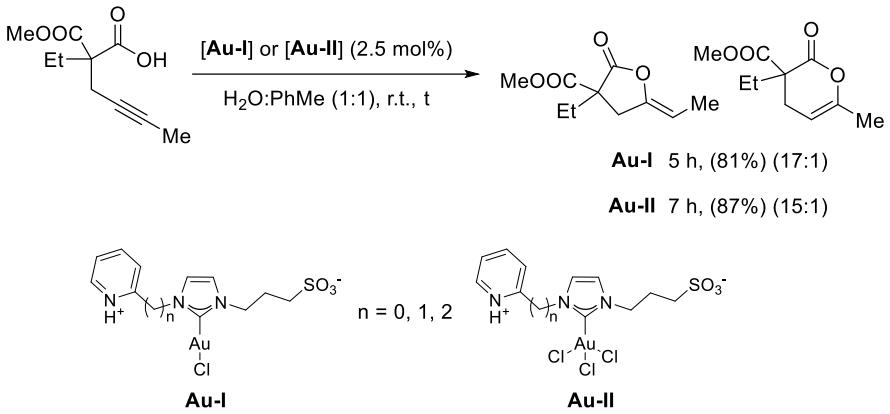


Scheme 1.23 Cycloisomerization of ynoic acid catalyzed by a palladium iminophosphorane complex reported by Vidal and co-workers.

Then, Cadierno and col. reported the use of sulfonate decorated and thereby, water-soluble Au(I) and Au(III) NHC complexes for the intramolecular hydroxycarbonylation of several alkynoic acids in a biphasic PhMe:H_2O (1:1)

[80] Alemán, J.; Del Solar, V.; Navarro-Ranninger, C. *Chem. Commun.* **2010**, *46*, 454–456.
[81] García-Álvarez, J.; Díez, J.; Vidal, C. *Green Chem.* **2012**, *14*, 3190–3196.

mixture. Catalyst amount was set at 0.1 mol%, although it had to be increased up to 2.5 mol % in cases where non-terminal alkynes were used (Scheme 1.24).[82]



Scheme 1.24 Gold-catalyzed alkynoic acid cycloisomerization in a toluene:water mixture reported by Cadierno's group.

Following with gold catalysts, Krause and col.,[83] and Pleixats and co-workers[84] described the use of two carbenic Au(I) catalysts for ynoic acid hydrocarbonylations, **Au-III** and **Au-IV** respectively (Figure 1.14). The former complex was employed at a 2.5 mol% level for the cycloisomerization of α-substituted 4-pentynoic acids, performed in an aqueous triethylammonium acetate solution. 4-Pentynoic acid was cycloisomerized in a toluene:water (1:1) mixture at room temperature in the presence of a 2.5 mol% water-soluble **Au-IV**. The latter complex presented an advantageous recycling ability that allowed the reutilization of the catalyst up to 6 cycles without a remarkable activity loss. However, its main drawback was the poor regioselectivity observed when non-terminal alkynes were employed.[84]

[82] Tomás-Mendivil, E.; Toullec, P. Y.; Borge, J.; Conejero, S.; Michelet, V.; Cadierno, V. *ACS Catal.* **2013**, *3*, 3086–3098.
[83] Belger, K.; Krause, N. *Org. Biomol. Chem.* **2015**, *13*, 8556–8560.
[84] Ferré, M.; Cattoën, X.; Wong Chi Man, M.; Pleixats, R. *ChemCatChem* **2016**, *8*, 2824–2831.

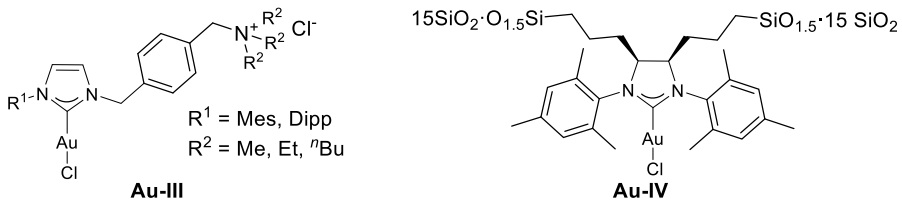
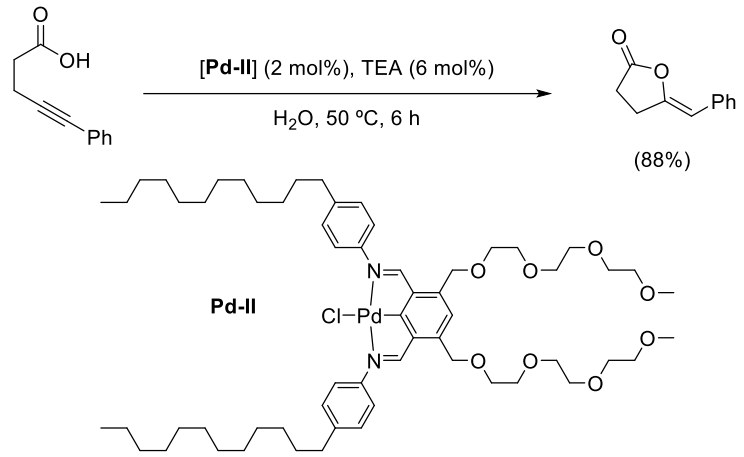


Figure 1.14 Water-soluble NHC-Au(I) complexes employed by for ynoic acid cycloisomerization.

Returning to the subject of palladium, Uozumi's group described an amphiphilic NCN palladium pincer complex employed for the cycloisomerization of 5-aryl-4-pentynoic acids in water.[85] Complex **Pd-II**, due to its polar and non-polar tails, was able to form vesicles in aqueous media that enabled a rapid catalytic activity owing to the closeness of the hydrophobic area containing the substrate to the catalyst's palladium core. In this protocol, a catalyst loading of 2 mol% was required and good to excellent yields were achieved (Scheme 1.25). Recently, a report by Saavedra *et al.* showed the activity of a palladium(II) oxide-impregnated magnetite, as a magnetically separable and recyclable heterogeneous catalyst for the alkynoic acid cycloisomerization in water along with alkylidene lactone hydrolysis as a way to prepare γ-ketoacids. In this work, a low catalyst loading (0.13 mol%) was featured.[86]

In summary, an increasing numer of methodologies have been reported for the cycloisomerization of alkynoic acids. However, processes in aqueous reaction media remain scarce and mostly limited to relatively high catalyst loadings (> 1 mol%). Limited substrate scope, water and organic solvent mixtures,[80,82] complex catalysts[81] and temperatures above r.t. are also common in this field.

[85] Hamasaka, G.; Uozumi, Y. *Chem. Commun.* **2014**, *50*, 14516–14518.
[86] Saavedra, B.; Pérez, J. M.; Rodríguez-Álvarez, M. J.; García-Álvarez, J.; Ramón, D. J. *Green Chem.* **2018**, *20*, 2151–2157.



Scheme 1.25 Amphiphilic NCN palladium pincer complex for the cycloisomerization of 5-aryl-4-pentynoic acids in water.

3.4.2 Optimization of reaction parameters: 4-pentynoic acid

As commented before, most of the publications on metal-catalyzed cycloisomerization of alkynoic acids are based on the use of Au and Pt catalysts. Moreover, catalyst loadings range from 0.1 to 2.5 mol%, and the reaction scope is relatively narrow. Therefore, we envisaged the use of PCN-type palladium pincer complexes **1a-b** as catalysts to carry out such cycloisomerizations in aqueous media. The catalyst amount was set at 10^{-2} mol% for the initial experiments. A summary of the screening results is shown in Table 1.10.

Complex **1a** was chosen as a promising palladium source, and 4-pentynoic acid (**14a**) as model substrate. In order to use such a relatively small catalyst amount, stock solutions of **1a** were prepared in water-miscible solvents due to the fact that **1a** was insoluble in water. Palladacycle **1a** was dissolved in methanol, acetone and *N,N*-dimethylformamide and from those solutions, a small volume was added to the reaction mixtures so that the organic solvent proportion could be considered negligible.

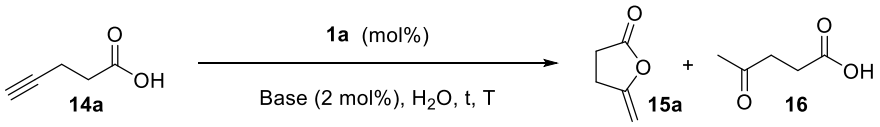
Once the solutions were ready, an array of initial experiments were carried out using TEA (Table 1.10, entries 1–3) or NaOH (entries 4–6) as base. To our delight,

the yields[87] were excellent in all cases (entries 1-6). Trace amounts of 2-oxopentanoic acid **16**, presumable formed by hydrolysis of furanone **15a** were detected. Taking into account that the stock solution solvent had no remarkable impact in the reaction outcome, DMF was chosen for its excellent performance and good solubilizing properties that allowed a negligible proportion of this co-solvent (<1%). Besides, the observed reactivity was similar when employing either TEA or NaOH, and thereby the weaker base was selected.

Encouraged by these results, we tried unsuccessfully to decrease the catalyst amount to 10^{-3} mol%. Indeed, low conversion rates were observed (entries 7 and 8) even over longer reaction times (entries 9 and 10). Higher temperatures (50 ºC) promoted higher conversion rates, but in this case ketoacid **16** was the main product, generated in almost quantitative yields (entries 11-12). Considering the reaction outcome and the mildness of the slightly basic conditions employed, the reaction conditions displayed in entry 2 appeared to be optimal. Interestingly, a blank experiment in the absence of TEA showed a relatively high conversion but a lower selectivity towards the lactone (entry 13), and no conversion was observed in the absence of **1a** complex catalyst. Finally, the reaction time was shortened to half (12 h) with similar results (entry 15).

[87] Due to the volatile nature of alkylidene lactone **15a**, ^{1}H-NMR yields were determined employing 3,4,5-trichloropyridine as internal standard.

Table 1.10. Cycloisomerization of 4-pentynoic acid in the presence of **1a**. Optimization experiments.[a]



Entry	Base	T (ºC)	t (h)	Solvent	**1a** (mol%)	**15a** (%)[b]	**16** (%)[b]
1	Et_3N	25	24	H_2O (MeOH 8%)	10^{-2}	93	0
2	Et_3N	25	24	H_2O (DMF 0.8%)	10^{-2}	97	1
3	Et_3N	25	24	H_2O (acetone 4%)	10^{-2}	96	2
4	NaOH	25	24	H_2O (MeOH 8%)	10^{-2}	93	3
5	NaOH	25	24	H_2O (DMF 0.8%)	10^{-2}	95	3
6	NaOH	25	24	H_2O (acetone 4%)	10^{-2}	93	2
7	Et_3N	25	24	H_2O (DMF 0.08%)	10^{-3}	14	3
8	NaOH	25	24	H_2O (DMF 0.08%)	10^{-3}	16	4
9	Et_3N	25	72	H_2O (DMF 0.08%)	10^{-3}	35	7
10	NaOH	25	72	H_2O (DMF 0.08%)	10^{-3}	34	6
11	Et_3N	50	72	H_2O (DMF 0.08%)	10^{-3}	0	98
12	Et_3N	50	24	H_2O (DMF 0.08%)	10^{-3}	14	79
13	-	25	24	H_2O (DMF 0.8%)	10^{-2}	76	10
14	Et_3N	25	24	H_2O	-	0	0
15	Et_3N	25	12	H_2O (DMF 0.8%)	10^{-2}	94	

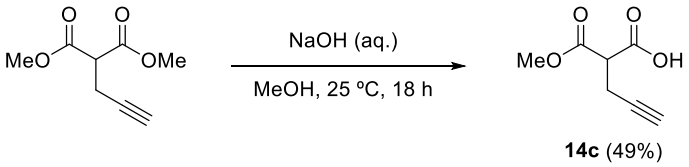
[a] Reaction conditions: **14a** (0.5 mmol), H_2O (0.5 mL). [b] ^{1}H-NMR yield employing 3,4,5-trichloropyridine as internal standard.

3.4.3 Substrate syntheses

Once the initial screening was performed, several alkynoic acids were prepared in order to increase the number of substrates that would be subjected to the optimized reaction conditions.

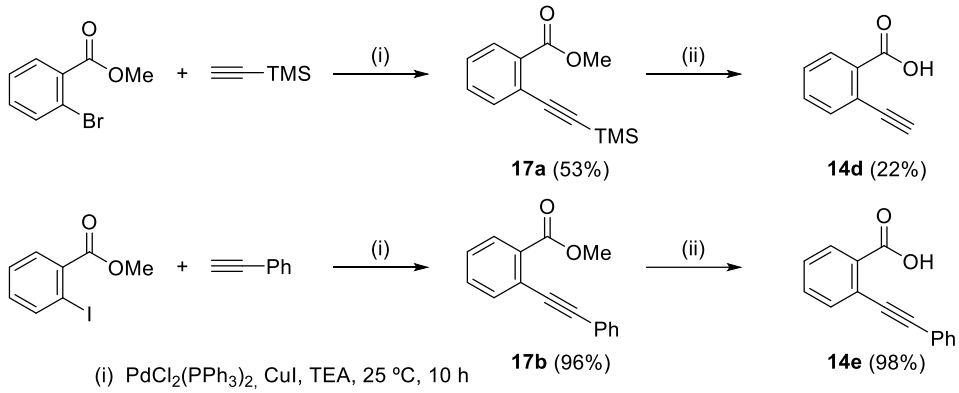
Thus, the synthesis of 2-(methoxycarbonyl)-4-pentynoic acid (**14c**) was carried out by the selective monohydrolysis at room temperature of the

commercially available dimethyl 2-propargylmalonate, as published by Alemán and col. (Scheme 1.26).[88]



Scheme 1.26 Synthesis of 2-(methoxycarbonyl)pent-4-ynoic acid **14c** *via* selective monohydrolysis.

2-Ethynylbenzoic acid (**14d**) was prepared from methyl 2-bromobenzoate, following the two-step sequence reported by Hashmi *et al.*[89] The ester was reacted with trimethysilylacetylene in the presence of $PdCl_2(PPh_3)_2$ and CuI in dry and degassed TEA under common Sonogashira cross-coupling conditions. The alkynylated ester **17a** underwent hydrolysis and desilylation in an alkaline methanol solution at 0 ºC to provide the corresponding benzoic acid **14d**. In the same way, the synthesis of 2-(phenylethyn-1-yl)benzoic acid **14e** involved Sonogashira coupling with phenylacetylene followed by alkaline hydrolysis (Scheme 1.27).

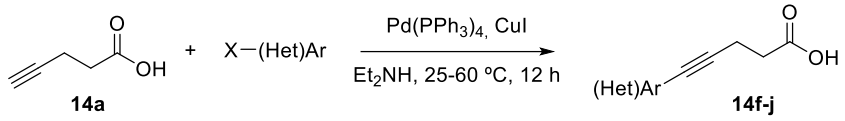


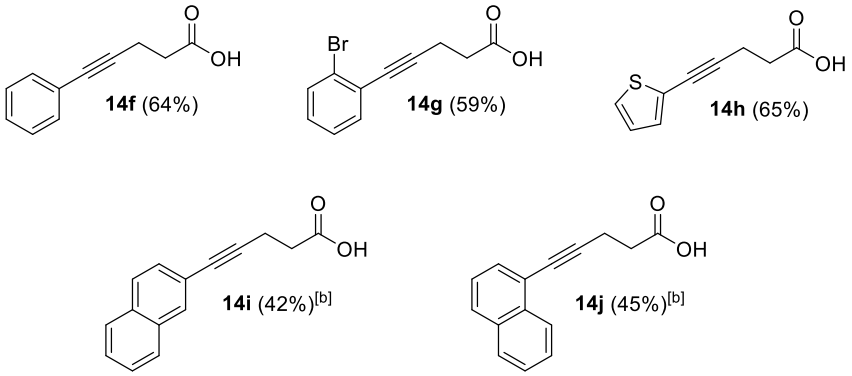
Scheme 1.27 Two-step synthesis of 2-alkynylbenzoic acids **14d-e**.

[88] Alemán, J.; Del Solar, V.; Martín-Santos, C.; Cubo, L.; Ranninger, C. N. *J. Org. Chem.* **2011**, *76*, 7287–7293.
[89] Hashmi, A. S. K.; Lothschütz, C.; Döpp, R.; Ackermann, M.; De Buck Becker, J.; Rudolph, M.; Scholz, C.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 133–147.

Besides, 5-(hetero)aryl-4-pentynoic acids **14f-h** were synthesized according to the methodology published by Wu *et al.*[90] Hence, a $Pd(PPh_3)_4$/CuI co-catalyzed Sonogashira cross-coupling reaction between 4-pentynoic acid and several iodoarenes in diethylamine at r.t. enabled the synthesis of the latter acetylenic acids. Analogously, 5-(naphthalen-1-yl)-4-pentynoic and 5-(naphthalen-2-yl)-4-pentynoic acids **14i-j** were synthesized from 4-pentynoic acid and 1- and 2-bromonaphthalene, respectively, employing the same methodology but heating the reaction at 60 ºC (Table 1.11).

Table 1.11 Synthesis of 5-(hetero)aryl-4-pentynoic acids **14f-j**.[a]

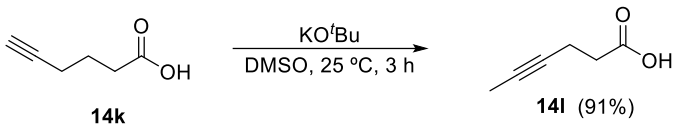




[a] **14a**, (hetero)aryl halide (1.2 equiv.), $Pd(PPh_3)_4$ (6 mol%), CuI (12 mol%), Et_2NH (1.7 mL/mmol) at 25 ºC for 12 h. [b] 60 ºC.

4-Hexynoic acid **14l** was prepared following the isomerization procedure established by Nolan's group,[91] thus treating 5-hexynoic acid **14k** with potassium *tert*-butoxide in DMSO at r.t. (Scheme 1.28).

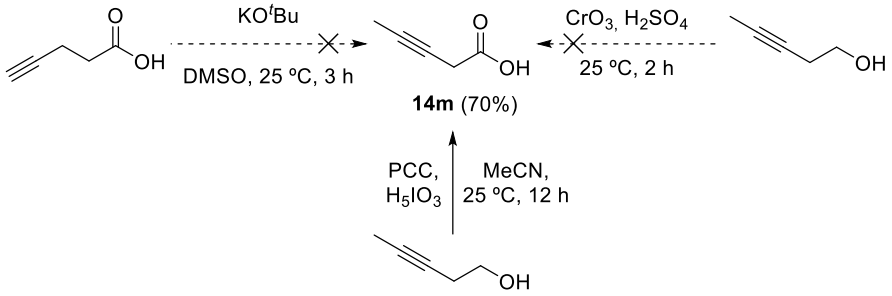
[90] Wu, H.; He, Y. P.; Gong, L. Z. *Adv. Synth. Catal.* **2012**, *354*, 975–980.
[91] Gasperini, D.; Maggi, L.; Dupuy, S.; Veenboer, R. M. P.; Cordes, D. B.; Slawin, A. M. Z.; Nolan, S. P. *Adv. Synth. Catal.* **2016**, *358*, 3857–3862.



14k **14l** (91%)

Scheme 1.28 Potassium *tert*-butoxide-mediated alkyne isomerization.

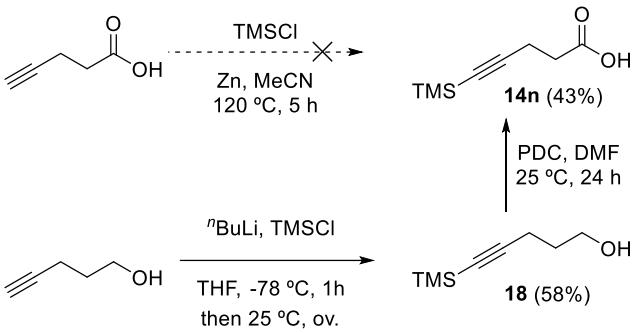
Encouraged by this result, the same method was attempted in order to transform 4-pentynoic acid into 3-pentynoic acid. Unfortunately, instead of the desired product, 2,4-pentadienoic acid was obtained. Alternatively, the Jones oxidation of 4-pentyn-1-ol was also carried out but with negligible results. Finally, following the work by Gorske *et al.,*[92] 4-pentyn-1-ol was treated with a mixture of PCC and periodic acid, providing target 3-pentynoic acid **14m** with good yield (70%, Scheme 1.29).



Scheme 1.29 Synthetic pathways to 3-pentynoic acid, **14m**.

A direct silylation[93] of 4-pentynoic acid **14a** with chlorotrimethylsilane in the presence of Zn was attempted in order to prepare 5-trimethylsilyl-4-pentynoic acid **14n**. Upon its failure, an alternative sequence was envisaged. 4-Pentyn-1-ol was deprotonated with ^{n}BuLi at -78 ºC and the resulting acetylide reacted with chlorotrimethylsilane to afford the corresponding alcohol **18** that upon oxidation with PDC in DMF[94] furnished the desired silylated alkynoic acid **14n** (Scheme 1.30).

[92] Gorske, B. C.; Mbofana, C. T.; Miller, S. J. *Org. Lett.* **2009**, *11*, 4318–4321.
[93] For a direct silylation of acetylene derivatives using chlorotrimethylsilane and zinc, see: Sugita, H.; Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1995**, *36*, 2769–2772.
[94] Harris, M. R.; Konev, M. O.; Jarvo, E. R. *J. Am. Chem. Soc.* **2014**, *136*, 7825–7828.



Scheme 1.30 Synthetic route to 5-trimethylsilyl-4-pentynoic acid **14n**.

3.4.4 Reaction scope

With a set of structurally derived alkynoic acids **14** in hand, the scope of the cycloisomerization reaction was explored. The optimized conditions were applied, although slight modifications were necessary in some cases. Some of the required adjustments (changes in the amount of base, temperature, and the assistance of sonication) were due to the low solubility of alkynoic acids **14** in water. The results are displayed in Table 1.12.

4-Pentynoic acid (**14a**) and α-substituted 4-pentynoic acid derivatives **14b-c** were cyclized to the corresponding alkylidene lactones **15a-c** in excellent yields by catalysts **1a** and **1b** (entries 1, 4–5). Unlike all the other alkynoic acids, we noticed that 2-methoxycarbonyl-4-pentynoic acid (**14c**) underwent cycloisomerization in the absence of catalyst upon standing at r.t. for a few days.

Regarding 5-(hetero)aryl-4-pentynoic acids (entries 6-9), different results were obtained. To begin with, 5-phenyl-4-pentynoic acid (**14f**, entry 6) and 5-(2-naphthyl)-4-pentynoic acid (**14i**, entry 8) were successfully cyclized in good to excellent yields, with either pincer complex **1a** or **1b**. Longer reaction times were needed in order to achieve good yields, and in the case of the latter acid (**14i**) a higher temperature was required. For the 2-thienyl-decorated acid **14h**, both the temperature and the catalyst loading were increased to achieve similar yields (entry 7). By the way, it should be pointed out that alkylidene lactones were prepared in

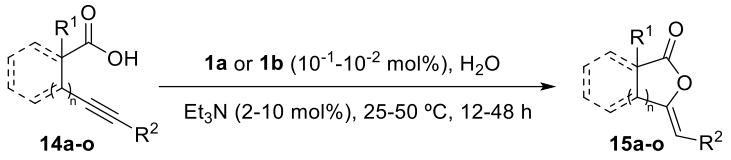
good yields and with the highest substrate:catalyst ratio so far for alkynoic acid cycloisomerization in water. Besides, a remarkably high steric congestion might be behind the failure from 5-(naphth-1-yl)-4-pentynoic acid **14j** (entry 9). The only report on cycloisomerization of this particularly bulky substrate required a 2 mol% of a vesicular palladium catalyst at 50 ºC.[85] In this regard, a poor solubility in water of 5-(2-bromophen-1-yl)-4-pentynoic acid **14g** (entry 10) and a possible palladation at the brominated position might account for the failed cyclization. To the best of our knowledge, the cycloisomerization of derivative **14g** has not been described so far. Attempts to effect cyclization of **14g** and **14j** by increasing the reaction temperature to 50 ºC resulted in the formation of complex mixtures in which the products derived from hydrolysis of enol lactone intermediates were detected.

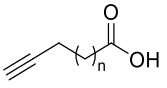
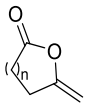
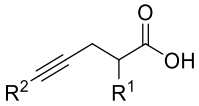
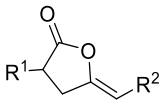
In this context of solubility issues, despite the fact that *o*-ethynylbenzoic acid (**14d**, entry 12) needed an extra amount of base (entry 12) and assistance of ultrasound irradiation in order to improve solubility, the desired isobenzofuranone (**15d**) was isolated in good yield. Although the cyclization took place in the case of 2-(phenylethyn-1-yl)benzoic acid (**14e,** entry 13), it required a higher temperature (50 ºC) which probably induced a lack of regioselectivity (a mixture of isobenzofuranone **15e** and isochromanone **15e'**). This problem was partially solved using pincer complex **1b**, which showed a higher preference for the exo-product (**15e**).

Although cycloisomerization also worked for internal alkynes, terminally alkylated (**14l-m**, entries 14–15) or silylated (**14n**, entry 11) acetylenic acids provided poorer conversions. In these examples, catalyst loadings had to be raised up to 0.1 mol% and even in those cases conversions were not good with the exception of 4-hexynoic acid (**14l**, entry 14) where better conversions were achieved although at the cost of relatively poor regioselectivities. Interestingly, 5-trimethylsilyl-4-pentynoic acid **14n** was cyclized without the loss of the silyl moiety (**15n**, entry 11). Furthermore, to the best of our knowledge, it was the first time this compound was synthesized in the literature. A hydroxylated analogue of **15n** (4-

hydroxy-3,3,4-trimethyl-5-methylenedihydrofuran-2(3*H*)-one) had been previously synthesized in aqueous media but a higher reaction temperature (100 ºC) and copper catalyst-loading (5 mol%) were required.[95]

Table 1.12 Ynoic acid cycloisomerization in aqueous media catalyzed by pincer complexes **1**.[a]

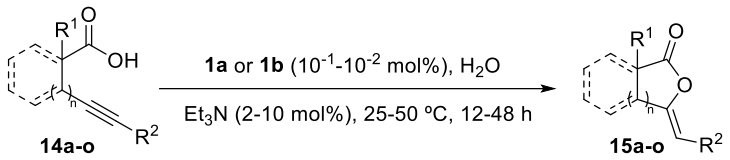


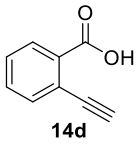
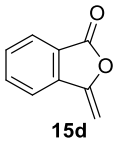
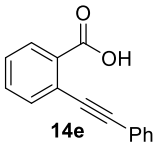
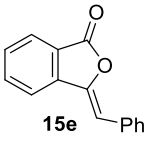
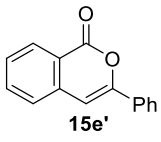
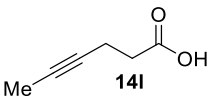
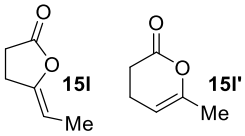
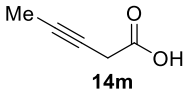
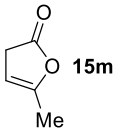
Entry	14	15	Yield (%)[b]	
			1a	**1b**
				
1[c],[d]	**14a**, n=1	**15a**, n=1	94	96
2[e],[f]	**14k**, n= 2	**15k**, n= 2	79	85
3	**14o**, n= 3	**15o**, n= 3	-	-
				
4[c]	**14b** R^1= n-hex R^2= H	**15b** R^1= n-hex R^2= H	89[i]	99[i]
5[c],[d]	**14c** R^1= COOMe R^2= H	**15c** R^1= COOMe R^2= H	93	94
6[f]	**14f** R^1= H R^2= Ph	**15f** R^1= H R^2= Ph	91[i]	99[i]
7[e],[h]	**14h** R^1= H R^2= 2-thienyl	**15h** R^1= H R^2= 2-thienyl	91[i]	80[i]
8[h],[j]	**14i** R^1= H R^2= 2-naphthyl	**15i** R^1= H R^2= 2-naphthyl	82[i]	80[i]
9	**14j** R^1= H R^2= 1-naphthyl	**15j** R^1= H R^2= 1-naphthyl	traces	traces
10	**14g** R^1= H R^2= 2-BrC_6H_4	**15g** R^1= H R^2= 2-BrC_6H_4	-	-
11[e],[j]	**14n** R^1= H R^2= TMS	**15n** R^1= H R^2= TMS	50	20

[a] **14a-o**, TEA (10 mol%), complex **1a/1b** (10^{-2} mol%), H_2O (1 mL/mmol) at r.t. for 24 h. [b] ^{1}H-NMR yield employing 3,4,5-trichloropyridine as internal standard. [c] 2 mol% TEA. [d] 12 h. [e] 10^{-1} mol% of **1**. [f] 40 h. [g] 18 h. [h] 50 ºC. [i] Isolated yield. [j] 48 h.

[95] López-Reyes, M. E.; Toscano, R. A.; López-Cortés, J. G.; Alvarez-Toledano, C. *Asian J. Org. Chem.* **2015**, *4*, 545–551.

Table 1.12 Ynoic acid cycloisomerization in aqueous media catalyzed by pincer complexes **1.**[a] *(cont.)*



Entry	14a	15a	Yield (%)[b] 1a	Yield (%)[b] 1b
12[g],[k]	 **14d**	 **15d**	85[i]	90[i]
13[h]	 **14e** Ph	 **15e** Ph  **15e'** Ph	90[i] 48:42	90[i] 76:14
14[e],[f]	 Me **14l**	 **15l** Me **15l'** Me	86 69:17	64 54:10
15[e],[d],[h]	 Me **14m**	 **15m** Me	38	46

[a] Reaction conditions: **14a-o**, TEA (10 mol%), complex **1a**/**1b** (10^{-2} mol%), H_2O (1 mL/mmol) at r.t. for 24 h. [b] ^{1}H-NMR yield employing 3,4,5-trichloropyridine as internal standard. [c] 2 mol% TEA. [d] 12 h. [e] 10^{-1} mol% of **1**.[f] 40 h. [g] 18 h. [h] 50 ºC. [i] Isolated yield. [j] 48 h. [k] Ultrasound assisted (25 ºC).

Moreover, 6-membered alkylidene lactone **15k** was successfully synthesized from 5-hexynoic acid (**14k**, entry 2) after increasing the catalyst loading to 0.1 mol% and lengthening the reaction time to 40 h. Unfortunately, unlike 5-hexynoic acid **14k** (entry 2), 6-heptynoic acid **14o** did not undergo cyclization and the starting material was recovered untouched (entry 3). To the best of our knowledge, the hydroxycarbonylation of **14k** and **14o** often requires more demanding reaction conditions, *i.e.* higher temperatures (> 80 ºC), extended reaction times (> 24 h) and

typically higher catalyst loadings (5 mol%)[28b] or complex cluster catalysts.[96] In the case of **14o**, the use of other transition-metal catalysts such as Au,[91] Ru,[97] Pt[28c] in non-aqueous environments or even more toxic complexes such as $Hg(OTf)_2$[98] are required.

As a summary, several structurally divergent ynoic acids were successfully cyclized to the corresponding enol lactones at a 0.01 mol% catalyst loading. Although in some cases higher amounts of complexes **1** were needed and regioselectivity issues have emerged, the results are good for reactions carried out in water and at low catalyst loadings. In fact, these results represent the smallest catalyst amounts for these transformations in aqueous media so far. Both complexes **1a-b** showed a good catalytic performance with a similar catalytic activity, although in some cases they behaved in a complementary way.

In addition, the tendency of some enol lactones to undergo hydrolysis leading to ketoacids was also observed. Further studies will reveal the full potential of this side reaction, already explored by some groups[86] to get access to such valuable ketones.

3.4.5 Mechanistic studies: kinetic curve and poisoning assays

In order to shed light onto the reaction mechanism a kinetic study of the cycloisomerization of pentynoic acid **14a** with a 10^{-3} mol% of **1a** complex at 50 ºC was carried out. In addition to the cycloisomerization to alkylidene lactone **15a**, it would also show the formation of ketoacid **16**. For that purpose, a number of reactions were set up for different reaction times, and after quenching, the reaction mixtures were analysed by ^{1}H-NMR.

[96] Wakabayashi, T.; Ishii, Y.; Ishikawa, K.; Hidai, M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2123–2124.
[97] Barik, C. K.; Tessensohn, M. E.; Webster, R. D.; Leong, W. K. *J. Organomet. Chem.* **2019**, *889*, 40–44.
[98] For mercury-catalyzed cycloisomerization reaction, see: a) Imagawa, H.; Kinoshita, A.; Fukuyama, T.; Yamamoto, H.; Nishizawa, M. *Tetrahedron Lett.* **2006**, *47*, 4729–4731. b) Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, M. *Synlett* **2006**, *2006*, 639–641.

Conversion rates were easily determined due to the cleanliness of the reaction. 3,4,5-Trichloropyridine was used as internal standard for ^{1}H-NMR, which also allowed the determination of the amounts of the three components of the mixture: starting alkynoic acid **14a**, cycloisomerization product **15a**, and alkyne hydration product **16**. Figures 1.18 and 1.19 show the conversion rate of **14a** *vs* time and the cycloisomerization *vs* formal hydration of **14a** as a function of time, respectively.

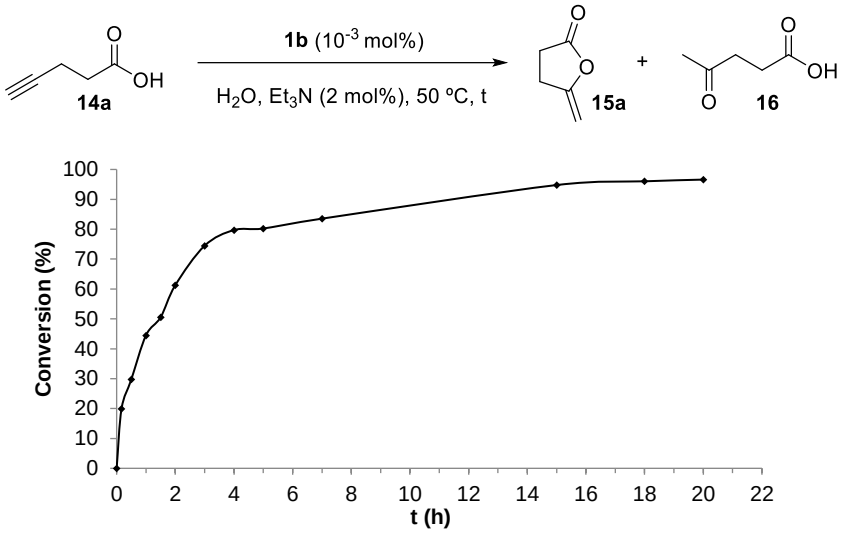


Figure 1.15 Conversion of **14a** *vs* time.

As observed in the kinetic plot (Figure 1.15), the reaction start-up was quite fast (20% conversion in just 10 min) so neither induction-time nor sigmoidal shape were observed for the kinetic curve, thereby providing evidence in support of the participation of complex **1a** as a homogeneous catalyst.[99]

[99] The presence of induction-time and sigmoidal shaped kinetic curves are often related to the participation of heterogeneous species and, in particular, of palladium nanoparticles. For a review on the parameters to be addressed in the determination of heterogeneous species check: a) Bayram, E.; Linehan, J. C.; Fulton, J. L.; Roberts, J. A. S.; Szymczak, N. K.; Smurthwaite, T. D.; Ozkar, S.; Balasubramanian, M.; Finke, R. G. *J. Am. Chem. Soc.* **2011**, *133*, 18889–18902.

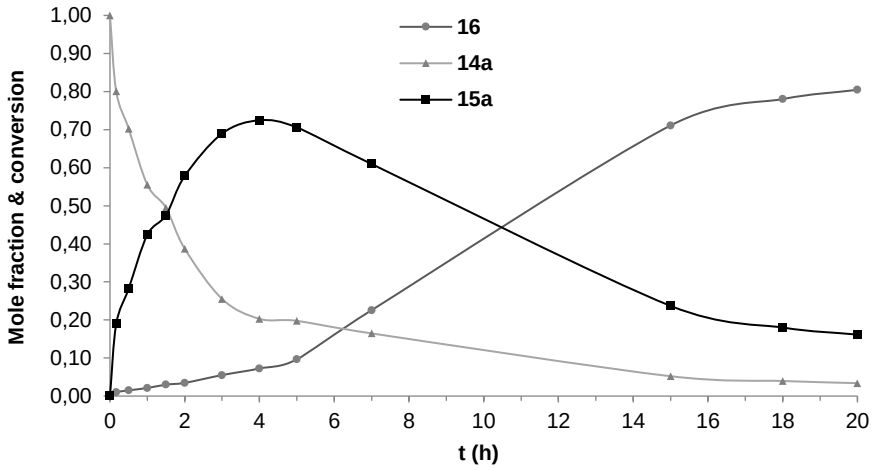


Figure 1.16 Cycloisomerization *vs* hydration of 4-pentynoic acid **14a** as a function of the reaction time.

As shown in Figure 1.16, after a quick and selective cycloisomerization (after 10 min. a 20% conversion to furanone **15a** was observed), the reaction evolved to a 72% of the lactone at its summit after 4 h, while the proportion of ketoacid **16** was steadily increasing (7% at 4 h). From that point, the decrease of lactone **15a** is inversely proportional to the increase of ketoacid **16**. After 20 h, most of the starting alkyne **14a** is consumed and only a 20% of the lactone **15a** is left, with an 80% of ketoacid **16**. Hence, it is easily deducible that the ketone formation arises from lactone hydrolysis by the action of the aqueous reaction medium, as later will be discussed.

Apart from this kinetic study, additional tests were carried out in order to elucidate the nature of our catalytic system. In 2003, Widegren and Finke reported an interesting guideline that gathered literature information to ease the process of discrimination between a homogeneous and heterogeneous catalytic process.[100a] Among these tests, we can find the use of several additives or poisons which,

[100] a) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem*. **2003**, *198*, 317–341. b) Phan, N. T. S.; Van der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679.

added in different proportions, could distinguish the nature of the catalyst depending on their effect in the reaction outcome.

In this regard, it is well known that, in contrast with homogeneous catalysts, in heterogeneous catalysts (*e.g.* nanoparticles, clusters or aggregates) the active sites are only partially exposed, limited to the surface, and therefore the addition of substoichiometric amounts (per catalyst atom) of poison may be enough to diminish or even inactivate their catalytic activity.

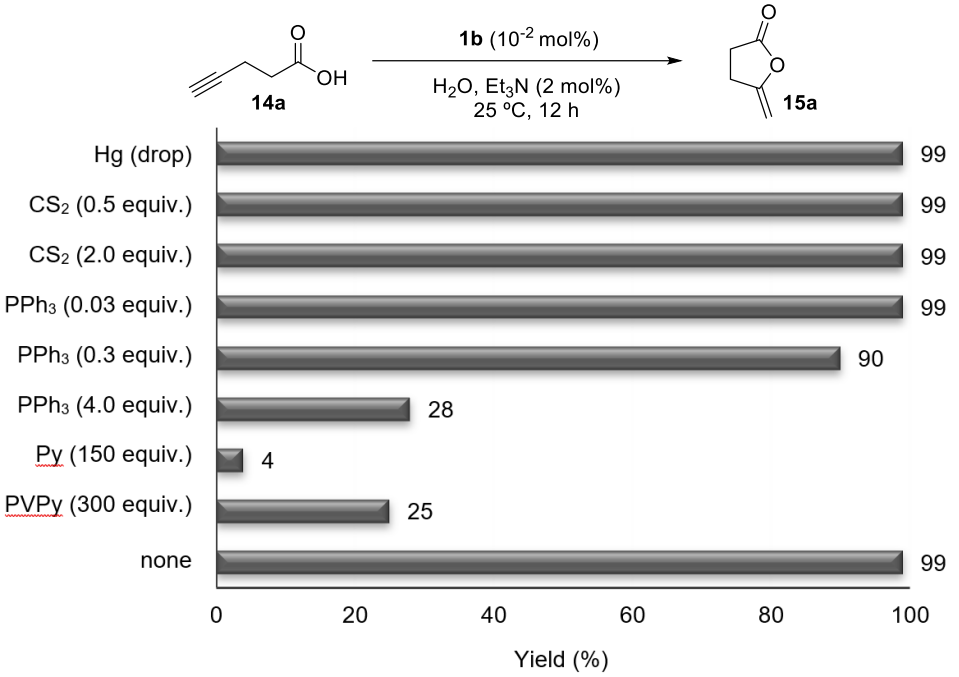
Besides, it is acknowledged the ability of mercury [Hg(0)] to poison heterogeneous catalytic systems either by amalgamation with metal heterogeneous particles or by adsorption onto metal surfaces.[101] Hence, not surprisingly, it is a widely utilized test for heterogeneous catalyst detection, particularly for palladium (Hg-drop test). A complete inhibition usually accounts for the presence of heterogeneous catalytic species, whereas a regular activity may indicate the presence of homogeneous catalysis.[102]

Finally, the comparison of the results after the addition of overstoichiometric portions of pyridine and poly(4-vinylpyridine), hereinafter PVPy, may provide evidence on the participation of palladium nanoparticles. In this regard, if a sharp decrease in conversion is noticed when PVPy is employed in comparison to that observed with pyridine, it may account to metal(0) particle formation and thereby to a heterogeneous system.[103] According to these studies in literature, we performed the poisoning assays whose results are outlined in the table below (Table 1.13). These results should be analysed considering that our cycloisomerization reaction

[101] a) Campbell, K. C.; Hislop, J. S. *J. Catal.* **1969**, *13*, 12–19. b) Jatta, S.; Dutta, B.; Bera, R.; Koner, S. *Inorg. Chem.* **2008**, *47*, 5512-5520. c) Demel, J.; Lamac, J.; Cejka, J.; Stepnicka, P. *ChemSusChem* **2009**, *2*, 442–451.
[102] For specific information on the use of the mercury drop-test, see: a) Whitesides, G. M.; Hackett, M.; Brainard, R. L.; Lavalleye, J. P. P. M.; Sowinski, A. F.; Izumi, A. N.; Moore, S. S.; Brown, D. W.; Staudt, E. M. *Organometallics* **1985**, *4*, 1819–1830. b) Anton, D. R.; Crabtree, R. H. *Organometallics* **1983**, *2*, 855–859.
[103] Yu, K.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161–171.

is taking place as an "on water" process, and all the poisoning experiments were devised for a monophasic system.

Table 1.13 Poisoning assays for ynoic acid cycloisomerization in the presence of **1b**.[a]

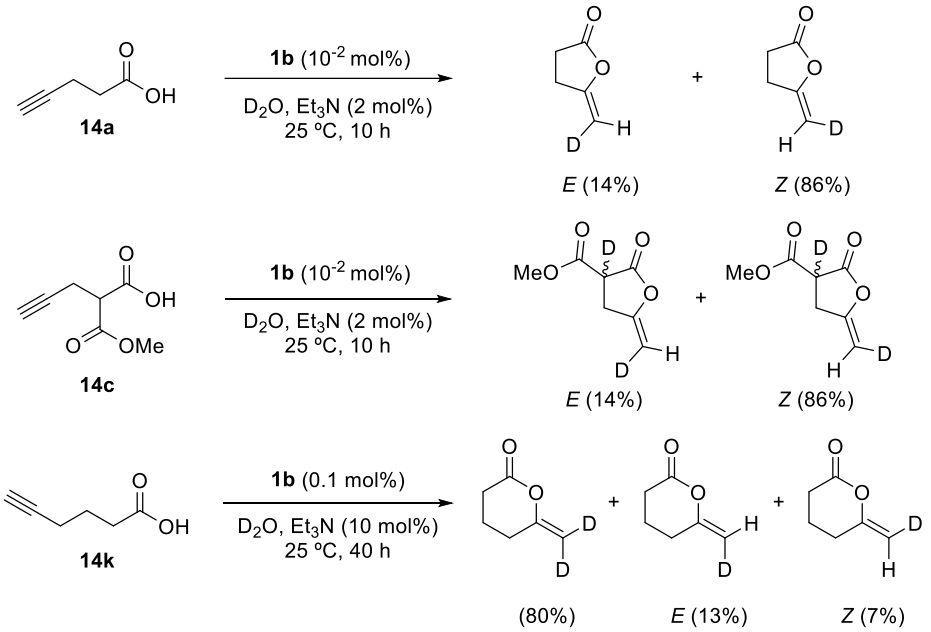


[a] Reaction conditions: **14a** (0.25 mmol), Et_3N (0.02 equiv.), **1b** (10^{-2} mol%), H_2O (1 mL/mmol), 25 ºC, 12 h. [b] ^{1}H-NMR yield employing 1,3,5-trichloropyridine as internal standard.

When mercury-drop test was performed, the catalytic activity remained unaffected. Additionally, the use of substoichiometric amounts of both additives, CS_2 and PPh_3, did not disturb the catalytic performance. These results evidence the absence of "naked" Pd(0) species catalyzing the reaction. An overstoichiometric amount of CS_2 did not halt the reaction, whereas a detrimental effect was noticed when employing a large excess of PPh_3. This fact might evince the participation of homogeneous and stable ("ligand-protected") palladium species that only get spoilt in the presence of a large poison/competitive ligand excess. Similarly, a large excess of pyridine and PVPy undermined the regular performance of the catalyst. Anyway, the negative Hg-drop test, the fact that no changes in the catalytic performance were observed under substoichiometric amounts of poisoning agents,

and the lack of induction time and sigmoidal shaped curve derived from kinetic studies strongly suggest the intermediacy of a homogeneous catalytic system.

Additionally, some deuteration tests were performed in deuterium oxide to check if the isotopic distribution could provide further information on the reaction mechanism (Scheme 1.31).[104]

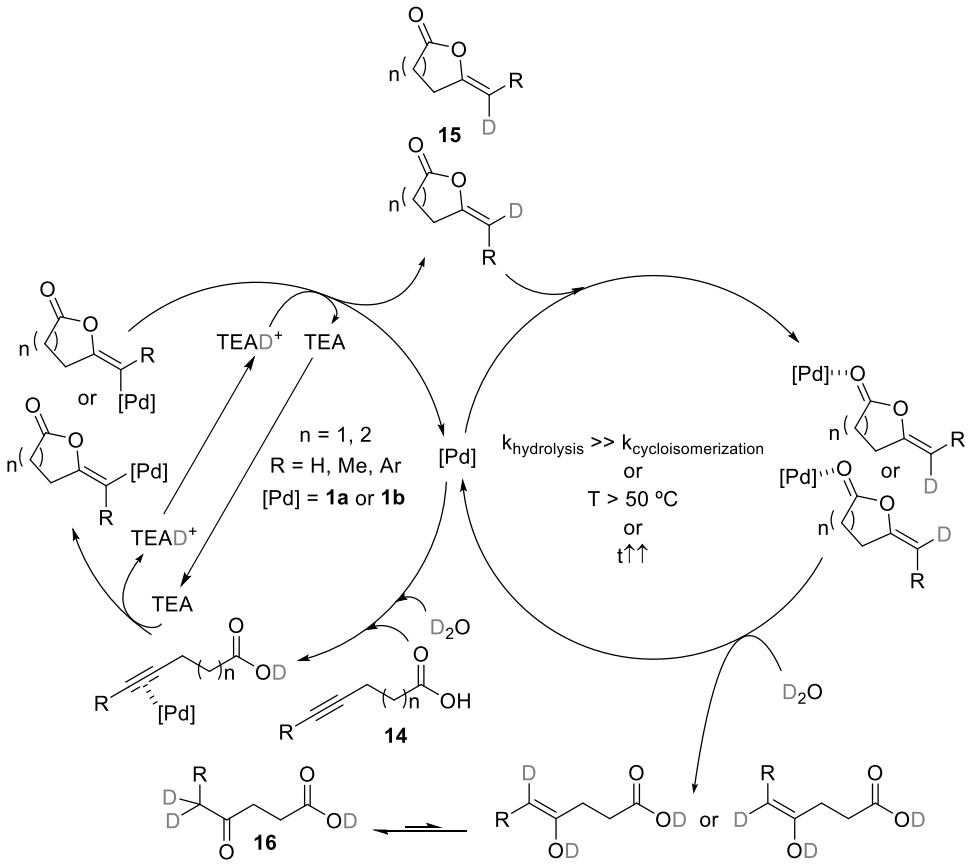


Scheme 1.31 Deuteration tests performed over some substrates.

As observed in the first two examples, there was a preference towards the formation of the *Z*-diastereoisomer. Furthermore, in the case of the 2-methoxycarbonyl-4-pentynoic acid **14c** an additional deuteration was observed, due to a proton-deuterium exchange at the acidic α-position. Finally, the cycloisomerization of the 5-hexynoic acid **14k** revealed the formation of three different products. Two of them corresponded to both diastereoisomers, *Z* and *E,*

[104] a) For the use of isotopic marking in the elucidation of reaction mechanisms, see: Lloyd-Jones, G. C.; Muñoz, M. P. *J. Label. Compd. Radiopharm.* **2007**, *50*, 1072–1087. b) Deuteration experiments were carried out in the cycloisomerization of 4-pentynoic acid, see: Ogata, K.; Sasano, D.; Yokoi, T.; Isozaki, K.; Seike, H.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2012**, *41*, 498–500.

in low proportion, whereas the third product was the dideuterated olefin. This was explained based on the lower reaction-rate, in comparison with that of the previous reactions from **14a** and **14c**, which might have allowed a proton-deuterium exchange in the acetylenic position *prior* to the hydroxycarbonylation reaction. In view of the obtained results, we postulated the mechanism depicted in Scheme 1.32:



Scheme 1.32 Postulated mechanism for the hydroxycarbonylation of alkynoic acids and the hydrolysis of alkylidene lactones catalyzed by pincer complexes **1**.

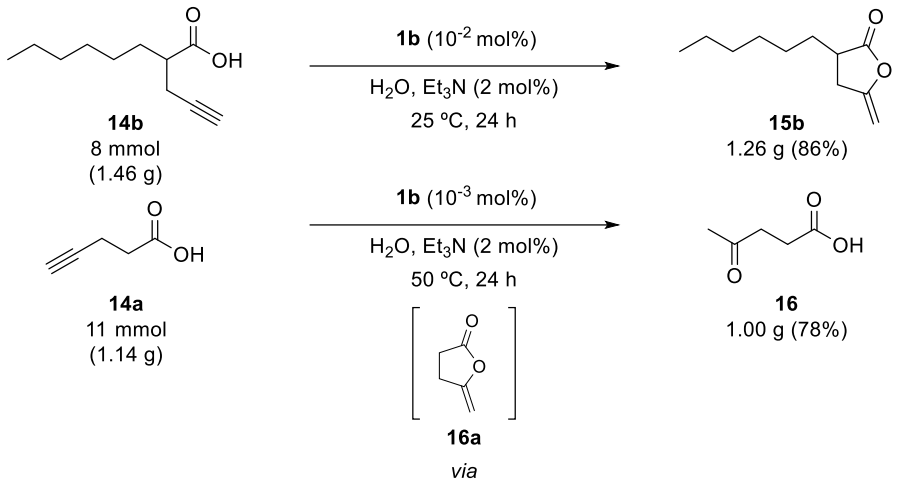
In this mechanism, we hypothesize about the role of palladium catalysts **1a**-**1b** as activating agents for the acetylenic bond, and upon deprotonation by TEA, promoters of the corresponding cycloisomerization reaction. Subsequently, the so-

formed alkenylpalladium species might suffer a protonolysis, triggered by the relatively acidic triethylammonium ions, leading to the alkylidenelactones **15**. Besides, as observed experimentally for some highly reactive alkynoic acids, longer reaction times or higher temperatures (over 50 ºC) may lead to ketoacid formation (**16**). To explain those results, we postulate that the same palladium catalyst could work as an oxophile Lewis acid, thus activating the lactone moiety, which, as a consequence of its increased electrophilicity, might undergo a hydrolysis or lactone opening reaction. The resulting enol would thereby tautomerize to generate ketoacid **16**.

Besides, considering the potential of the cyclosiomerization reaction as well as the subsequent hydrolysis leading to ketoacid, we decided to study the scalability of both reactions (Scheme 1.33). Regarding the cycloisomerization reaction, 1.26 g of 2-hexyl-4-pentynoic acid **14b** were cyclized to afford the desired furanone **15b** in 86% yield. Although a bit lower, it is still a good yield considering the catalyst loading, the reaction media and time investment. In addition, taking advantage of the information extracted from the kinetic studies (Figure 1.16), 1.1 g of 4-pentynoic acid **14a** were reacted under optimized conditions for such a cascade cycloisomerization/hydrolysis (10^{-3} mol% of complex **1b**, 50 ºC), providing levulinic acid **16** in good yield (78%, Scheme 1.33). To the best of our knowledge, these results represent the lowest catalyst loading employed for alkynoic acid cycloisomerization and alkylidene lactone hydrolysis in aqueous media.

Finally, we hypothesized that the use of such low amount of palladacycles **1** along with the use of aqueous media would reduce metal contamination levels in final products. In this regard, ICP-MS analyses were performed to determine the palladium content present in samples of alkylidene lactone **15b** and ketoacid **16**.

The analyses revealed a low palladium content, with a value of 0.5 ppm in both samples and therefore safe for oral and parenteral administration.[105,106]



Scheme 1.33 Scale-up of the syntheses of lactone **15b** and ketoacid **16**.

In summary, catalysts **1a** and **1b** have shown a good performance in the cycloisomerization of alkynoic acids in aqueous media, thus providing an advantageous access (substrate:catalyst ratio $1:10^{-2}$, T < 50 ºC) to enol lactones. In some cases the use of ultrasounds proved to be instrumental to solve solubility issues. Finally, catalyst **1b** enabled the access to levulinic acid (**16**) *via* hydrolysis of intermediate alkylidene lactone **15a** using an even lower catalyst amount (10^{-3} mol%). As a result of the low catalyst loading required, palladium content in final products was found to be extremely low, as determined by ICP-MS. Finally, based on the results from the kinetic plot, poisoning assays and deuteration tests a plausible mechanism has been proposed.

[105] International Conference on Harmonisation, Elemental impurities. ICH Q3D (R1) Guideline. EMA/CHMP/ICH/353369/2013

[106] Considering that PDE values of palladium for oral and parenteral administration are defined as 100 and 10 µg/day intake, respectively, the maximum palladium content in the drug should be of 10 and 1 ppm for oral and parenteral administered drugs, respectively. Assuming a worst case of a ≤10 g/day drug intake defined in ICH Q3D (R1) guideline. See ref. 105. See also: Kielhorn, J.; Melber, C.; Keller, D.; Mangelsdorf, I. *Int J. Hyg. Environ. Health.* **2002**, 205, 417–432.

4 EXPERIMENTAL PROCEDURES

4.1 General methods and materials

All reagents were purchased and used as received except when indicated. Anhydrous solvents and reagents were dried and purified according to standard procedures.[107] All air- or moisture-sensitive reactions were carried out under argon atmosphere. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) at 20ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.00 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). Melting points (m.p.) were determined in a capillary tube using a Gallenkamp melting point apparatus and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). IR spectra were recorded on a JASCO FTIR-4100 ATR infrared spectrophotometer, and only strong absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a Büchi or Heidolph rotary evaporator. In the cases where sonication was required to enhance solubility, a Ultrasons 20 ultrasonic bath was used. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions. HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI). Other electrospray Ionization Mass Spectra (ESI-MS) were measured employing an Acquity UPLC-Mass Spectrometer QTOF from Waters. ICP-MS measurements were carried out on a Thermo Elemental X7 series equipped with an ASX-520 autosampler. Reactions carried out under microwave irradiation were performed using a CEM Discover 1-

[107] a) Armarego, W. L. F.; "*Purification of Laboratory Chemicals"*, 8th Ed., Elsevier, **2017**, Oxford, UK; b) Williams, B. G.; Lawton, M. S. *J. Org. Chem.* **2010**, *75*, 8351–8354.

300W system equipped with a built-in pressure measurement sensor and a vertically focused IR temperature measurement sensor. X-ray diagrams of the obtained single crystals were performed in an Agilent SuperNova Cu-diffractometer, equipped with an Atlas model CCD detector at 100 K, using a liquid-nitrogen cooled Cryostream 700 system from Agilent cryosystems. All the hydrogen atoms have been located in the residual density map and have been refined using SHELXL97's *riding* model.[108]

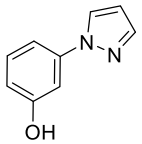
4.2 Synthesis of non-symmetric pincer complexes 1a and 1b

4.2.1 General procedure for the synthesis of 3-(1H-pyrazol-1-yl)arenes 2.

A dry screw-capped tube containing a magnetic stirrer was charged with 1*H*-pyrazole (104.2 mg, 1.5 mmol), CuO (8.1 mg, 0.1 mmol), $Fe(acac)_3$ (109.2 mg, 0.3 mmol), Cs_2CO_3 (654.9 mg, 2.0 mmol) and dry and degassed DMF (1.0 mL) under argon. This mixture was stirred at r.t. for 15 min. Then, the 3-bromoarene (1 mmol) was added and the reaction was heated to 120 ºC for 24 h. After allowing to cool to room temperature, the mixture was diluted with DCM (10 mL) and filtered through a plug of celite. The resulting filtrate was washed with H_2O (2 × 30 mL) and the aqueous phase was re-extracted with DCM (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered and concentrated *in vacuo* to afford a brownish oil. Purification of this residue by flash column chromatography (hexanes:EtOAc) furnished the desired product **2**.

- **3-(1*H*-Pyrazol-1-yl)phenol (2a)**. From 3-bromophenol (176.5 mg, 1 mmol). Isolated as an off-white powder (147.4 mg, 92%) after purification by flash column chromatography (hexanes: EtOAc 9:1 to hexanes:EtOAc 7:3). Recrystallization from DCM provided single crystals suitable for X-ray diffractometry.

[108] Sheldrick, G. M. *Acta Crystallogr.* **2008**, *64*, 112–122.

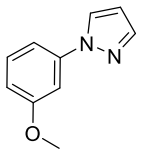


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 2.1, 1.8 Hz, 1H, C*H*$_{pyrazole}$), 7.73 (dd, *J* = 1.8 Hz, 1H, C*H*$_{pyrazole}$), 7.33–7.28 (m, 2H, C*H*$_{phenol}$), 7.18 (d, *J* = 8.1 Hz, 1H, C*H*$_{phenol}$), 6.77 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H, C*H*$_{phenol}$), 6.47 (dd, *J* = 2.1, 1.8 Hz, 1H, C*H*$_{pyrazole}$).

^{13}C-NMR (75 MHz, MeOD) δ 162.3 (q*C*$_{arom}$), 145.0 (q*C*$_{arom}$), 144.5 (*C*H$_{pyrazole}$), 134.0 (*C*H$_{arom}$), 131.6 (*C*H$_{arom}$), 117.4 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 111.1 (*C*H$_{arom}$), 110.4 (*C*H$_{arom}$).

m.p.: 117–120°C (DCM). *Lit*.[109] 120–122 ºC (PE:EtOAc)

3-(1*H*-Pyrazol-1-yl)anisole (2b).[110] From 3-bromoanisole (191.0 mg, 1 mmol). Isolated as a yellowish oil (167.2 mg, 96%) after purification by flash column chromatography (DCM:hexanes 4:6).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 1.9 Hz, 1H, C*H*$_{pyrazole}$), 7.69 (d, *J* = 1.4 Hz, 1H, C*H*$_{anisole}$), 7.36–7.26 (m, 2H, C*H*$_{anisole}$ + C*H*$_{pyrazole}$), 7.20 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H, C*H*$_{anisole}$), 6.79 (ddd, *J* = 8.1, 2.5, 1.1 Hz, 1H, C*H*$_{anisole}$), 6.41 (t, *J* = 2.8, 1.9 Hz, 1H, C*H*$_{pyrazole}$), 3.81 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.5 (q*C*$_{arom}$), 141.3 (q*C*$_{arom}$), 141.0 (*C*H$_{pyrazole}$), 130.2 (*C*H$_{pyrazole}$), 126.9 (*C*H$_{arom}$), 112.4 (*C*H$_{arom}$), 111.1 (*C*H$_{arom}$), 107.6 (*C*H$_{arom}$), 105.1 (*C*H$_{arom}$), 55.5 (C*H*$_{3,\ OMe}$).

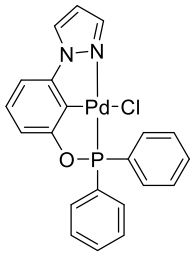
4.2.2 Synthesis of palladium pincer complex 1a, method A

3-(1*H*-Pyrazole-1-yl)phenol **2a** (100.0 mg, 0.62 mmol) was added to a dry heavy-walled screw-capped tube equipped with a magnetic stir bar under argon. Then, dry and degassed toluene (5.0 mL, solvent still) was added, and to the

[109] Wang, Y.; Zhang, Y.; Yang, B.; Zhang, A.; Yao, Q. *Org. Biomol. Chem.* **2015**, *13*, 4101–4114.
[110] Lee, H. W.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2009**, *50*, 5868–5871.

resulting suspension dry and degassed TEA (96 µL, 0.69 mmol) was added dropwise. A solution of freshly distilled and degassed chlorodiphenylphosphine (126 µL, 0.69 mmol) in dry and degassed toluene (5.0 mL, solvent still) was added to the mixture, and after argon flushing, the tube was tightly sealed and heated to 130 ºC for 20 h. After allowing to cool the reaction to r.t., the suspension was transferred *via* syringe to a plug of celite and filtered through it, under argon, into a heavy-walled screw-capped tube containing a suspension of $Pd(COD)Cl_2$ (198.0 mg, 0.69 mmol) in dry toluene (5.0 mL). The tube was tightly sealed and the mixture was heated to 120 ºC for 20 h, after which the reaction was concentrated *in vacuo* to yield a viscous yellow solid. This residue was purified by flash column chromatography (hexanes:EtOAc 6:4), affording complex **1a** as an off-white powder (100.9 mg, 33%).

Chloro-[2-(*1H*-pyrazole-κN2)-6-(diphenylphosphinito-κP)-phenyl-κC1]-Pd(II) (1a).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95–8.12 (m, 5H, C*H*$_{phenyl}$ + C*H*$_{pyrazole}$), 7.93 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.42–7.58 (m, 6H, 6C*H*$_{phenyl}$), 7.11 (td, *J* = 8.0, 1.3 Hz, 1H, C*H*$_{phenyl}$), 6.9 (d, *J* = 7.8 Hz, 1H, C*H*$_{phenyl}$), 6.81 (d, *J* = 8.1 Hz, 1H, C*H*$_{phenyl}$), 6.48 (q, *J* = 2.4 Hz, 1H, C*H*$_{pyrazole}$).

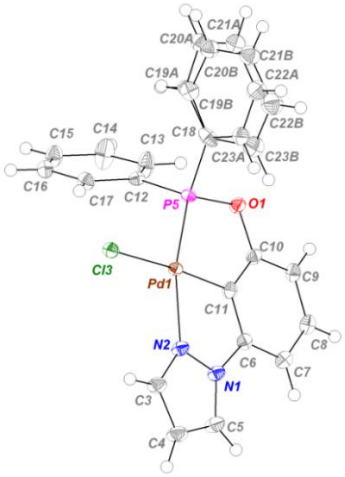
^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.2 (d, *J* = 8.8 Hz, q*C*$_{arom}$), 143.3 (q*C*$_{arom}$), 140.2 (d, *J* = 3.3 Hz, *C*H$_{arom}$), 135.5 (d, *J* = 2.2 Hz, q*C*$_{arom}$), 133.1 (q*C*$_{arom}$), 132.2–132.6 (m, *C*H$_{arom}$), 131.7 (d, *J* = 15.4 Hz, *C*H$_{arom}$), 129.0 (d, *J*= 12.1 Hz, *C*H$_{arom}$), 127.7 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 110.0 (d, *J* = 16.5 Hz, *C*H$_{arom}$), 107.1 (d, *J* = 4.4 Hz, *C*H$_{arom}$), 106.5 (*C*H$_{arom}$).

^{31}P-NMR ($CDCl_3$) δ 156.4

m.p.: 265–269 °C (DCM)

IR (ATR) (cm^{-1}) 3089, 3042, 2955, 2917, 2848, 1580

HRMS-ESI (m/z): $[M\text{-}Cl]^+$ calc. for $C_{21}H_{16}N_2OPPd$: 449.0035, found: 449.0032



Crystallographic data (1a):

Crystal system	monoclinic	Space group	P21/n
a (Å)	9.5169(5)	α (°)	90
b (Å)	7.4242(3)	β (°)	95.565(4)
c (Å)	11.0643(6)	γ (°)	90
V (Å^3)	778.07(7)	Z	4 (Z' = 1)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
Pd-N2	2.109	Pd-C11	1.962
Pd-P	2.210	Pd-Cl	2.378

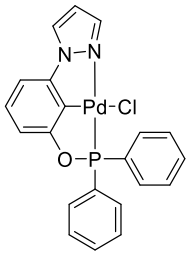
Selected angles (º)	
Atoms	Angle (Å)
N2-Pd-C11	79.21
C11-Pd-P	79.51
Cl-Pd-P	105.65
Cl-Pd-N2	95.74
N2-N1-C6	115.97
N1-C6-C11	114.71
C11-C10-O	117.19
C10-O-P	112.75

Selected torsion-angles (º)	
Atoms	Angle (Å)
Pd-P-O-C10	6.23
C6-N1-N2-Pd	1.62
Cl-Pd-N2-C3	9.00
C6-N1-N2-C3	176.64
O-P-C12-C13	-14.69
Cl-Pd-P-O	173.62
Cl-Pd-P-C12	-73.03
Cl-Pd-N2-N1	-178.64

4.2.3 Synthesis of palladium pincer complexes 1a and 1b, method B

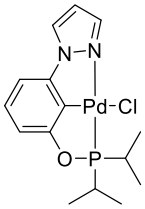
3-(1*H*-Pyrazole-1-yl)phenol **2a** (100.0 mg, 0.62 mmol) was added to a dry round-bottomed flask equipped with a magnetic stir bar under argon. Then, dry and degassed THF (5.0 mL, solvent still) was added followed by the dropwise addition of dry and degassed TEA (96 µL, 0.69 mmol) at 0 ºC. The corresponding chlorophosphine (0.69 mmol) was added dropwise and the reaction was flushed with argon and stirred for 2 h at room temperature.[111] The solvent was removed *in vacuo* and the white residue was resuspended in dry and degassed PhMe (10.0 mL) and briefly sonicated. The so-obtained fine suspension was transferred *via* double-tipped needle to a plug of celite and filtered through it, under argon, into a heavy-walled screw-capped tube containing a suspension of $Pd(COD)Cl_2$ (198.0 mg, 0.69 mmol) in dry toluene (5.0 mL). The tube was tightly sealed and the mixture was heated to 120 ºC for 20 h, after which the reaction was concentrated *in vacuo* to yield a viscous yellow solid. This residue was purified by flash column chromatography (hexanes:EtOAc), affording the corresponding complex **1**.

Chloro-[2-(*1H*-pyrazole-κN2)-6-(diphenylphosphinito-κP)-phenyl-κC1]-Pd(II) (1a). General method B was employed with Ph_2PCl (126 µL, 0.69 mmol) and the crude was purified by flash column chromatography (hexanes:EtOAc 6:4) affording the desired palladacycle **1a** as an off-white powder (180.6 mg, 60%).



[111] Balakrishna, M. S.; Panda, R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, *178*, 1391–1396.

Chloro-[2-(*1H*-pyrazole-κN2)-6-(diisopropylphosphinito-κP)-phenyl-κC1]-Pd(II) (1b). General method B was employed with $^{i}Pr_2PCl$ (114 µL, 0.69 mmol) and the crude was purified by flash column chromatography (hexanes:EtOAc 1:1) affording the desired palladacycle **1b** as an off-white powder (194.1 mg, 74%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 2H, C*H*$_{pyrazole}$), 7.11 (t, *J* = 7.9 Hz, 1H, C*H*$_{phenyl}$), 6.88 (d, *J* = 8.1 Hz, 1H, C*H*$_{phenyl}$), 6.7 (d, *J* = 8.1 Hz, 1H, C*H*$_{phenyl}$), 6.51 (q, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 2.63–2.38 (m, 2H, C*H*$_{iPr}$), 1.55–1.43 (m, 3H, C*H*$_{3,\ iPr}$), 1.43–1.39 (m, 3H, C*H*$_{3,\ iPr}$), 1.39–1.34 (m, 3H, C*H*$_{3,\ iPr}$), 1.34–1.29 (m, 3H, C*H*$_{3,\ iPr}$).

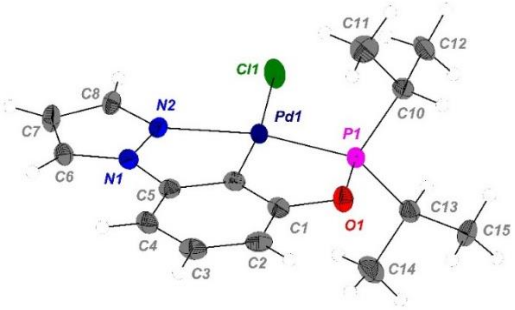
^{13}C-NMR (75 MHz, $CDCl_3$) δ 164.7 (d, *J* = 5.1 Hz, q*C*$_{arom}$), 143.6 (q*C*$_{arom}$), 139.8 (d, *J* = 2.1 Hz, *C*H$_{pyrazole}$), 134.3 (q*C*$_{arom}$), 127.2 (*C*H$_{pyrazole}$), 126.1 (*C*H$_{arom}$), 109.1 (d, *J* = 15.1 Hz, *C*H$_{arom}$), 107.0 (d, *J* = 4.0 Hz, *C*H$_{pyrazole}$), 106.0 (*C*H$_{arom}$), 29.3 (d, *J* = 26.2 Hz, *C*H$_{iPr}$), 17.3 (d, *J* = 5.7 Hz, *C*H$_{3,\ iPr}$), 16.8 (*C*H$_{3,\ iPr}$).

^{31}P-NMR ($CDCl_3$) δ 204.7

m.p.: 183–187 °C (DCM)

IR (ATR) (cm^{-1}) 3091, 2964, 2926, 2871, 1577

HRMS-ESI (m/z): $[M\text{-}Cl]^+$ calc. for $C_{15}H_{20}N_2OPPd$: 381.0348, found: 381.0345



Crystallographic data (1b):

Crystal system	orthorhombic	Space group	$Pna2_1$
a (Å)	11.06293(10)	α (°)	90
b (Å)	13.49862(11)	β (°)	90
c (Å)	11.19390(10)	γ (°)	90
V ($Å^3$)	1671.63	Z	4 (Z' = 0)

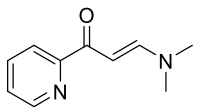
Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
Pd-N2	2.101	Pd-C9	1.958
Pd-P	2.219	Pd-Cl	2.101

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
N2-Pd-C9	79.21	Pd-P-O-C1	-0.31
C9-Pd-P	79.84	C9-N1-N2-Pd	1.47
Cl-Pd-P	107.60	Cl-Pd-N2-C8	-0.08
Cl-Pd-N2	93.34	C5-N1-N2-C8	-179.24
N2-N1-C5	116.05	O-P-C10-C11	-61.64
N1-C5-C9	114.54	Cl-Pd-P-O	179.67
C9-C1-O	117.00	Cl-Pd-P-C10	62.12
C1-O-P	113.35	Cl-Pd-N2-N1	178.84

4.3 Synthesis of non-symmetric chiral NNC palladium complex 5

4.3.1 (E)-3-(Dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one (6).

2-Acetylpyridine (230 µL, 2.01 mmol) and DMFDMA (305 µL, 2.21 mmol) were charged in a microwave tube equipped with a magnetic stir bar. The reaction was argon flushed, sealed and heated by microwave irradiation (40 W) to 130ºC for 30 min under a cooling flow. The resulting brown oil was dissolved in DCM (10 mL) dispersed in silica gel (1.5 g) and submitted to flash chromatography (EtOAc 100%) to afford enaminone **6** as a yellow powder, which darkened upon standing (327.3 mg, 93%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.51 (dq, *J* = 4.8, 0.9 Hz, 1H, C*H*$_{pyridine}$), 8.02 (dt, *J* = 7.9, 0.9 Hz, 1H, C*H*$_{pyridine}$), 7.79 (d, *J* = 12.7 Hz, 1H, C*H*$_{enaminone}$), 7.68 (td, *J* = 7.7, 1.7 Hz, 1H, C*H*$_{pyridine}$), 7.24 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1H, C*H*$_{pyridine}$), 6.34 (d, *J* = 12.7 Hz, 1H, C*H*$_{enaminone}$), 3.03 (s, 3H, C*H*$_{3,\ NMe}$), 2.85 (s, 3H, C*H*$_{3,\ NMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 186.7 (*C*=O), 156.1 (q*C*$_{arom}$), 154.6 (*C*H$_{enaminone}$), 148.1 (*C*H$_{arom}$), 136.6 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 121.8 (*C*H$_{arom}$), 91.0 (*C*H$_{enaminone}$), 45.0 (*C*H$_{3,\ NMe}$), 37.3 (*C*H$_{3,\ NMe}$).

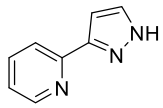
m.p.: 126–128 °C (EtOAc). *Lit.*[112] 124–126 ºC (hexane)

4.3.2 2-(1H-Pyrazol-3-yl)pyridine (7).

In heavy-walled screw-capped tube enaminone **6** (1.05 g, 5.96 mmol) was dissolved in EtOH (6.0 mL) and heated to 85 ºC with excess of hydrazine monohydrate (440 µL, 8.94 mmol) for 5 h. After cooling to r.t., the solvent was removed by rotary evaporation. The remaining dark orange oil was redissolved in EtOH and the solution was dried with $MgSO_4$, gravity filtered and evaporated *in*

[112] Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Rosa, F. A.; Marzari, M. R. B.; Zanatta, N.; Bonacorso, H. G. *Catal. Commun.* **2008**, *9*, 1375–1378.

vacuo to provide an off-white solid that was recrystallized from EtOAc to afford pyrazole **7**[113] as off-white needle-like crystals (810.7 mg, 94%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.20 (bs, 1H, N*H*), 8.63 (dt, *J* = 4.9, 1.4 Hz, 1H, C$H_{pyridine}$), 7.77–7.72 (m, 2H, C$H_{pyridine}$), 7.66 (d, *J* = 2.0 Hz, 1H, C$H_{pyrazole}$), 7.25–7.18 (m, 1H, C$H_{pyridine}$), 6.80 (d, *J* = 2.1 Hz, 1H, C$H_{pyrazole}$)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 150.0 (qC_{arom}), 149.1 (CH_{arom}), 146.2 (qC_{arom}), 136.6 (CH_{arom}), 135.2 ($CH_{pyrazole}$), 122.3 (CH_{arom}), 119.9 (CH_{arom}), 103.28 ($CH_{pyrazole}$).

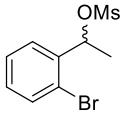
m.p. 126–129 ºC (EtOAc). *Lit*.[113] 108 °C (acetone)

*4.3.3 Synthesis of (***rac)- and (*S)-1-(2-bromophenyl)ethyl methanesulfonates 9.***

To a solution of (*rac*)- or *(S)*-1-(2-bromophenyl)ethan-1-ol **8** (100.5 mg, 0.5 mmol) in dry DCM (3 mL) at 0 ºC, TEA (140 µL, 1.1 mmol) was added dropwise under argon. The mixture was cooled to 0 ºC and methanesulfonyl chloride (63 µL, 0.75 mmol) was added dropwise. The stirring was continued for 2 h at r.t., then quenched with water (20 mL) and the phases were separated. The resulting aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and dried under reduced pressure to yield a colorless oil as crude (139.0 mg, >99%). Analysis of the crude by ^{1}H-NMR confirmed a conversion of >99%. Due to its lability, the product was used in the next step without further purification.

[113] Pleier, A. K.; Glas, H.; Grosche, M.; Sirsch, P.; Thiel, W. R. *Synthesis* **2001**, *1*, 55–62.

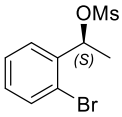
(*rac*)-1-(2-Bromophenyl)ethyl methanesulfonate, *(rac)*-9. Isolated as a colorless oil (139.0 mg, >99%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 7.7, 4.2, 1.5 Hz, 2H, C*H*$_{phenyl}$), 7.38 (td, *J* = 7.7, 1.5 Hz, 1H, C*H*$_{phenyl}$), 7.20 (td, *J* = 7.7, 1.5 Hz, 1H, C*H*$_{phenyl}$), 6.09 (q, *J* = 6.5 Hz, 1H, C*H*-OMs), 2.86 (s, 3H, C*H*$_{3, OMs}$), 1.68 (d, *J* = 6.5 Hz, 3H, C*H*$_{3, Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 139.2 (q*C*$_{arom}$), 132.9 (*C*H$_{arom}$), 130.1 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 121.1 (q*C*$_{arom\text{-}Br}$), 79.3 (*C*H-OMs), 38.6 (*C*H$_{3, OMs}$), 23.0 (*C*H$_{3, Me}$).

(*S*)-1-(2-Bromophenyl)ethyl methanesulfonate, *(S)*-9. Isolated as a colorless oil (139.1 mg, >99%).



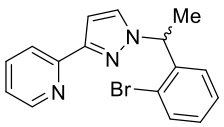
$[\alpha]_D^{20}$= 166.91º (c = 1, $CHCl_3$)

4.3.4 Synthesis of NNC proligand 10.

To a solution of pyrazole **7** (88 mg, 0.6 mmol) in freshly distilled dry DMF (2.5 mL), sodium hydride (60 % dispersion in mineral oil, 32 mg, 0.8 mmol) was added and the mixture was cooled to 0 ºC under argon. The mixture was allowed to warm to r.t. and stirred for 2 h. Then, the obtained suspension was cooled again to 0 ºC and a solution of **(*rac*)-9** or **(*S*)-9** (140 mg, 0.5 mmol) in freshly distilled dry DMF (2.5 mL) was added dropwise under inert atmosphere. After the addition, the reaction was allowed to warm to r.t., heated to 40 ºC and stirred overnight at the same temperature. The mixture was diluted with Et_2O (30 mL) and washed with water (5 x 10 mL) to remove DMF. The resulting aqueous layer was further extracted with Et_2O (3 x 10 mL). The organic layers were combined, dried over

anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide a yellowish oil. This residue was purified by flash column chromatography (PE:EtOAc 8:2), thus affording proligand **10** as a colorless oil.

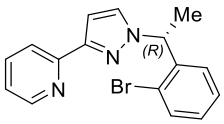
- **(*rac*)-2-[1-[1-(2-Bromophenyl)ethyl]-1*H*-pyrazol-3-yl]pyridine, *(rac)*-10**. Isolated as a colorless oil (158.0 mg, 96%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.61 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H, C*H*$_{pyridine}$), 7.99 (dt, *J* = 8.0, 1.1 Hz, 1H, C*H*$_{pyridine}$), 7.68 (td, *J* = 7.8, 1.8 Hz, 1H, C*H*$_{pyridine}$), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H, C*H*$_{pyridine}$), 7.52 (d, *J* = 2.4 Hz, 1H, C*H*$_{pyrazole}$), 7.25–7.00 (m, 4H, C*H*$_{arom}$), 6.93 (d, *J* = 2.4 Hz, 1H, C*H*$_{pyrazole}$), 5.97 (q, *J* = 7.0 Hz, 1H, C*H*-Me), 1.93 (d, *J* = 7.0 Hz, 3H, C*H*$_{3,\ Me}$).

^{13}C NMR (75 MHz, CDCl3) δ 152.5 (q*C*$_{arom}$), 151.7 (q*C*$_{arom}$), 149.3 (*C*H$_{arom}$), 141.4 (q*C*$_{arom}$), 136.5 (*C*H$_{arom}$), 133.0 (*C*H$_{arom}$), 130.2 (*C*H$_{pyrazole}$), 129.2 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 122.5 (*C*H$_{arom}$), 122.3 (q*C*$_{arom\text{-}Br}$), 120.3 (*C*H$_{arom}$), 104.4 (*C*H$_{arom}$), 60.6 (*C*H-Me), 20.6 (*C*H$_{3,\ Me}$).

- **(*R*)-2-[1-[1-(2-Bromophenyl)ethyl]-1*H*-pyrazol-3-yl]pyridine, *(R)*-10**. Isolated as a colorless oil (135.0 mg, 82%).

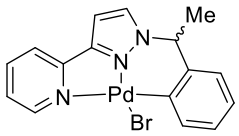


$[\alpha]_D^{20}$= - 167.0º (c = 1, $CHCl_3$)

4.3.5 Synthesis of NNC chiral palladium complex 5.

In a round bottom flask proligand **10** (302.0 mg, 0.92 mmol) was dissolved in dry and degassed THF (22 mL) under argon atmosphere after which $Pd(dba)_2$ (582.0 mg, 1.0 mmol) was added. The reaction mixture was heated to 120 ºC for 8 hours. After cooling, the mixture was filtered through a plug of celite and the filtrate was subsequently evaporated under reduced pressure to provide a yellow oil that was further purified by flash column chromatography (PE:EtOAc 1:1 to EtOAc), thus affording complex **5** as a yellow powder (348.0 mg, 87 %).

2-[1-[1-(Phenyl-κC2)ethyl]-1*H*-pyrazol-3-yl-κN2]pyridine-κN-palladium(II) bromide, *(rac)*-5.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (d, *J* = 5.5 Hz, 1H, C*H*$_{pyridine}$), 8.47 (d, *J* = 7.5 Hz, 1H, C*H*$_{pyridine}$), 7.91 (t, *J* = 7.5 Hz, 1H, C*H*$_{pyridine}$), 7.75–7.67 (m, 2H, C*H*$_{pyridine}$ + C*H*$_{pyrazole}$), 7.41 (t, *J* = 6.6 Hz, 1H, C*H*$_{arom}$), 7.12–6.88 (m, 3H, C*H*$_{arom}$), 6.79 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 5.58 (q, *J* = 6.9 Hz, 1H, C*H*-Me), 1.79 (d, *J* = 6.9 Hz, 3H, C*H*$_{3,\ Me}$).

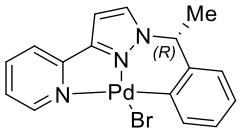
^{13}C-NMR (75 MHz, $CDCl_3$) δ 151.5 (*C*H$_{arom}$), 151.1 (q*C*$_{arom}$), 149.5 (q*C*$_{arom}$), 143.5 (*C*H$_{arom}$), 139.0 (*C*H$_{arom}$), 138.3 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 130.5 (*C*H$_{arom}$), 127.5 (*C*H$_{arom}$), 126.4 (*C*H$_{arom}$), 124.8 (*C*H$_{arom}$), 124.7 (*C*H$_{arom}$), 120.3 (*C*H$_{arom}$), 105.0 (*C*H$_{arom}$), 69.2 (*C*H-Me), 29.3 (*C*H$_{3,\ Me}$).

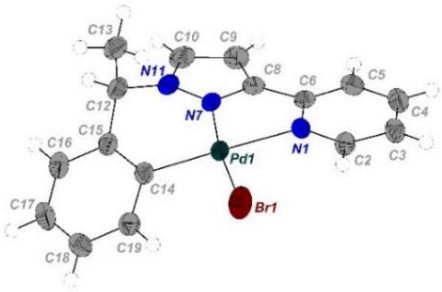
m.p.: 150–153°C (PE:EtOAc)

IR (ATR) (cm^{-1}) 3145, 3106, 3054, 2878, 1609, 1441

HRMS-ESI (m/z): $[M]^+$ calc. for $C_{16}H_{14}BrN_3$: 432.9406, found: 432.9401

2-[1-[1-(Phenyl-κC2)ethyl]-1*H*-pyrazol-3-yl-κN2]pyridine-κN-palladium(II) bromide, *(R)*-5.





$[\alpha]_D^{20}$= - 75.6º (c = 0.7, $CHCl_3$)

Crystallographic data (5):

Crystal system	monoclinic	Space group	$P2_1/c$
a (Å)	10.37481(13)	α (°)	90
b (Å)	9.43440(11)	β (°)	103.7914(13)
c (Å)	15.7685(2)	γ (°)	90
V ($Å^3$)	1498.93	Z	4 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
Pd-N1	2.192	Pd-C14	2.007
Pd-N7	1.974	Pd-Br	2.414

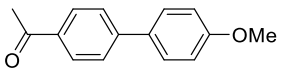
Selected angles (º)	
Atoms	Angle (Å)
N1-Pd-N7	76.76
N7-Pd-C14	90.30
C14-Pd-Br	97.11
Br-Pd-N1	96.60
Pd-C14-C15	121.81
C15-C12-C13	112.11
Pd-N7-N11	131.44
C6-N1-Pd	112.63

Selected torsion-angles (º)	
Atoms	Angle (Å)
N7-Pd-N1-C6	-7.66
N7-Pd-C14-C15	-15.26
Br-Pd-N1-C2	4.42
Br-Pd-C14-C15	161.85
N1-C6-C8-N7	1.71
C15-C12-N11-N7	-52.10
C14-C15-C12-C13	-72.16
N7-N11-C12-C13	72.42

4.4 General procedure for the on-water Suzuki cross-coupling between arylboronic acids and aryl bromides catalyzed by palladacycles *1a* and *1b* under conventional heating

To a screw-capped tube containing a magnetic stir bar, the aryl bromide (0.15 mmol), potassium carbonate (41.5 mg, 0.30 mmol), the boronic acid (0.23 mmol), degassed water (0.15 mL) and the corresponding solution of pincer complexes **1** (0.15 mL of a 10^{-4} M stock solution of 1 in DMF:H_2O 1:412 for **1a**/DMF:H_2O 1:479 for **1b**, $15 \cdot 10^{-6}$ mmol; or 0.15 mL of a 10^{-6} M stock solution of **1** in DMF:H_2O 1:41200 for **1a**/DMF:H_2O 1:47900 for **1b**, $15 \cdot 10^{-8}$ mmol; or 0.15 mL of a 10^{-8} M stock solution of **1** in DMF:H_2O 1:4120000 for **1a**/DMF:H_2O 1:4790000 for **1b**, $15 \cdot 10^{-10}$ mmol) were added. The tube was purged with argon and sealed, after which the mixture was heated to 100 ºC for 2 h (when $15 \cdot 10^{-6}$ mmol of **1** were used) or for 12 h (when $15 \cdot 10^{-8}$–$15 \cdot 10^{-10}$ mmol of **1** where used). Then, the reaction was allowed to cool to r.t. and an aqueous 10% Na_2CO_3 solution (5 mL) was added, after which the mixture was extracted with DCM (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered and concentrated *in vacuo* to provide the corresponding biaryl. The latter product was dissolved in $CDCl_3$ and the reaction yield was determined by ^{1}H-NMR employing 3,4,5-trichloropyridine as internal standard in the case of catalyst **1a**. For those reactions carried out in the presence of complex **1b**, the crudes were purified by flash column chromatography.

1-(4'-Methoxybiphenyl-4-yl)ethanone (13a). Obtained as a white powder (99%, using complex **1a**).

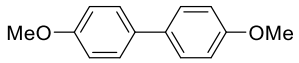


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H, C*H*$_{acetophenone}$), 7.65 (d, *J* = 8.5 Hz, 2H, C*H*$_{acetophenone}$), 7.58 (d, *J* = 8.5 Hz, 2H, C*H*$_{anisole}$), 7.00 (d, *J* = 8.5 Hz, 2H, C*H*$_{anisole}$), 3.87 (s, 3H, C*H*$_{3,\ OMe}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.7 (*C*=O), 159.9 (q*C*$_{arom}$), 145.3 (q*C*$_{arom}$), 135.3 (q*C*$_{arom}$), 132.2 (q*C*$_{arom}$), 128.9 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 114.4 (*C*H$_{arom}$), 55.4 (*C*H$_{3,\ OMe}$), 26.6 (*C*H$_{3,\ Ac}$)

m.p.: 145–147 ºC (DCM). *Lit*.[114] 154–155 °C (EtOAc)

♁ **4,4'-Dimethoxyibiphenyl (13b).** Obtained as a white powder (99% using complex **1a**; 22.2 mg, 69% using complex **1b**).

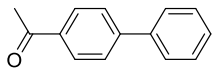


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 9.0 Hz, 4H, C*H*$_{anisole}$), 7.00 (d, *J* = 9.0 Hz, 4H, C*H*$_{anisole}$), 3.89 (s, 6H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.0 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 128.1 (*C*H$_{arom}$), 114.5 (*C*H$_{arom}$), 55.7 (*C*H$_{3,\ OMe}$).

m.p.: 174–176 ºC (DCM). *Lit*.[115] 177–178 °C (EtOH)

♁ **1-Biphenyl-4-yl-ethanone (13c).** Obtained as a white powder (29.1 mg, 99% using complex **1a** and TBAB (49.3 mg ,0.15 mmol)).



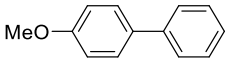
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H, C*H*$_{arom}$), 7.69 (d, *J* = 4.0 Hz, 2H, C*H*$_{arom}$), 7.63 (t, *J* = 4.5 Hz, 2H, C*H*$_{arom}$), 7.48 (t, *J* = 7.5 Hz, 2H, C*H*$_{arom}$), 7.40 (t, *J* = 7.0 Hz, 1H, CH$_{arom}$), 2.64 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.8 (*C*=O), 145.8 (q*C*$_{arom}$), 139.9 (q*C*$_{arom}$), 135.8 (q*C*$_{arom}$), 128.9 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 26.7 (*C*H$_{3,\ Ac}$).

m.p.: 117–119 ºC (DCM). *Lit*.[116] 121–122 °C (hexane)

[114] Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122–6125.
[115] Nising, C. F.; Schmid, U. K.; Nieger, M.; Bräse, S. *J. Org. Chem.* **2004**, *69*, 6830–6833
[116] Fairlamb, I. J.S.; Kapdi, A. R.; Lee, A. F. *Org. Lett.* **2004**, *6*, 4435-4438

4-Methoxybiphenyl (13d). Obtained as a white powder (86% using complex **1a**; 13.2 mg, 48% using complex **1b**).

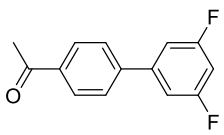


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (q, *J* = 6.7 Hz, 4H, C*H*$_{arom}$), 7.42 (t, *J* = 7.7 Hz, 2H, C*H*$_{arom}$), 7.28 (t, *J* = 14.8 Hz, 1H, C*H*$_{arom}$), 6.98 (d, *J* = 4.3 Hz, 2H, C*H*$_{arom}$), 3.85 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.2 (q*C*$_{arom}$), 140.8 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 128.7 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 126.8 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 114.2 (*C*H$_{arom}$), 55.4 (*C*H$_{3,\ OMe}$).

m.p.: 87–89 ºC (DCM). *Lit*.[116] 91–93 °C (EtOAc)

1-(3',5'-Difluorobiphenyl-4-yl)ethanone (13e).[117] Obtained as a white powder (57% using complex **1a**; 34.4 mg, 99% using complex **1b**).



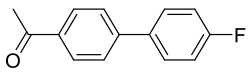
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02–8.05 (d, *J* = 8.6 Hz, 2H, C*H*$_{acetophenone}$), 7.62–7.65 (d, *J* = 8.6 Hz, 2H, C*H*$_{acetophenone}$), 7.05–7.14 (m, 2H, C*H*$_{arom}$), 6.84 (tt, *J* =9.0,1.9 Hz, 1H, C*H*$_{arom}$), 2.62 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.4 (*C*=O), 164.6 (d, $^{1}J_{CF}$ = 245.0 Hz, q*C*$_{arom\text{-}F}$), 143.4 (q*C*$_{arom}$), 143.1 (q*C*$_{arom}$), 136.8 (dd, $^{3}J_{CF}$ = 10 Hz, q*C*$_{arom}$), 129.0 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 110.2 (*C*H$_{arom}$), 103.4 (dd, $^{2}J_{CF}$ = 26 Hz, *C*H$_{arom}$), 26.6 (*C*H$_{3,\ Ac}$).

m.p.: 88–91 ºC (DCM)

[117] Marziale, A. N.; Jantke, D.; Faul, S. H.; Reiner, T.; Herdtweck, E.; Eppinger, J. *Green Chem.* **2011**, *13*, 169–177.

1-(4'-Fluorobiphenyl-4-yl)ethanone (13f). Obtained as a white powder (52% using complex **1a**; 31.5 mg, 98% using complex **1b**).

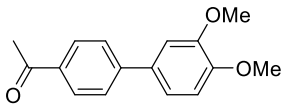


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H, C*H*$_{acetophenone}$), 7.64 (d, *J* = 8.0 Hz, 2H, C*H*$_{acetophenone}$), 7.60–7.58 (m, 2H, C*H*$_{arom}$), 7.17 (t, *J* = 8.4 Hz, 2H, C*H*$_{arom}$), 2.65 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.7 (*C*=O), 164.2 (d, $^{1}J_{CF}$ = 245 Hz, q*C*$_{arom\text{-}F}$), 144.7 (q*C*$_{arom}$), 135.9 (d, $^{4}J_{CF}$ = 4.2 Hz, q*C*$_{arom}$), 135.8 (q*C*$_{arom}$), 129.0 (d, $^{3}J_{CF}$ = 8.0 Hz, *C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 116.0 (d, $^{2}J_{CF}$ = 22 Hz, *C*H$_{arom}$), 26.7 (*C*H$_{3,\ Ac}$).

m.p.: 98–100 ºC (DCM). *Lit*.[118] 102–103 °C (AcOEt)

1-(3',4'-Dimethoxybiphenyl-4-yl)ethanone (13g).[119] Obtained as a white powder (95% using complex **1a**; 38.0 mg, 99% using complex **1b**).



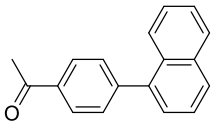
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92–8.03 (m, 2H, *C*H$_{acetophenone}$), 7.58–7.67 (m, 2H, *C*H$_{acetophenone}$), 7.17 (dd, *J* = 8.3, 2.1 Hz, 1H, *C*H$_{arom}$), 7.11 (d, *J* = 2.1 Hz, 1H, *C*H$_{arom}$), 6.93 (d, *J* = 8.3 Hz, 1H, *C*H$_{arom}$), 3.94 (s, 3H, *C*H$_{3,\ OMe}$), 3.90 (s, 3H, *C*H$_{3,\ OMe}$), 2.60 (s, 3H, *C*H$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.7 (*C*=O), 149.4 (q*C*$_{arom}$), 149.3 (q*C*$_{arom}$), 145.5 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 132.7 (qC$_{arom}$), 128.9 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 119.8 (*C*H$_{arom}$), 111.5 (*C*H$_{arom}$), 110.3 (*C*H$_{arom}$), 56.0 (*C*H$_{3,\ OMe}$), 26.6 (*C*H$_{3,\ Ac}$).

m.p.: 153–155 ºC (DCM)

[118] Li, J. H.; Liu, W. J.; Xie, Y. X. *J. Org. Chem.* **2005**, *70*, 5409–5412.
[119] Leung, F. K.-C.; Ishiwari, F.; Shoji, Y.; Nishikawa, T.; Takeda, R.; Nagata, Y.; Suginome, M.; Uozumi, Y.; Yamada, Y. M. A.; Fukushima, T *ACS Omega* **2017**, *2*, 1930–1937.

1-[4-(Naphthalen-1-yl)phenyl]ethanone (13h).[120] Obtained as a white powder (96% using complex **1a**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09–8.21 (m, 2H, C*H*$_{arom}$), 7.43–7.87 (m, 9H, C*H*$_{arom}$), 2.67 (s, 3H, C*H*$_{3,\ Ac}$).

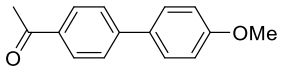
^{13}C-NMR (75 MHz, $CDCl_3$) δ 197.8 (*C*=O), 145.7 (q*C*$_{arom}$), 139.0 (q*C*$_{arom}$), 136.0 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 131.2 (q*C*$_{arom}$), 130.3 (CH$_{arom}$), 128.4 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 126.9 (*C*H$_{arom}$), 126.3 (*C*H$_{arom}$), 126.0 (*C*H$_{arom}$), 125.5 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 26.7 (*C*H$_{3,\ Ac}$).

4.5 General procedure for microwave-assisted Suzuki cross-coupling between arylboronic acids and aryl bromides in water catalyzed by palladacycles 1a and 1b.

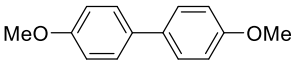
A microwave sealed tube was charged with a magnetic stirring bar, bromide (0.15 mmol), potassium carbonate (41.5 mmol, 0.30 mmol), the boronic acid (0.23 mmol), degassed water (0.15 mL) and the corresponding solution of pincer complexes **1** (0.15 mL of a 10^{-4} M stock solution of 1 in DMF:H_2O 1:412 for **1a**/DMF:H_2O 1:479 for **1b**, $15 \cdot 10^{-6}$ mmol). The tube was Ar purged, sealed and heated to 100 ºC, at 40 W, for 20 min for catalyst **1a** or heated to 120 ºC, at 60 W under cooling flow for 15 min for catalyst **1b**. Then, the reaction was allowed to cool to r.t. and an aqueous 10% Na_2CO_3 solution (5 mL) was added, after which the mixture was extracted with DCM (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, gravity filtered and concentrated *in vacuo* to provide the corresponding biaryl. The latter product was dissolved in $CDCl_3$ and the reaction yield was determined by 1H-NMR employing 3,4,5-trichloropyridine as internal standard in the case of catalyst **1a**. For those reactions carried out in the presence of complex **1b**, the crudes were purified by flash column chromatography.

[120] Chen, G.-J.; Huang, J.; Gao, L.-X.; Han, F.-S. *Chem. Eur. J.* **2011**,*17*, 4038–4042.

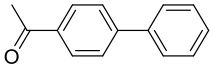
- **1-(4'-Methoxybiphenyl-4-yl)ethanone (13a)**.[114] Obtained as a white powder (99% using complex **1a**; 33.6 mg, 99% using complex **1b**).



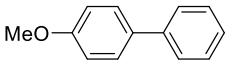
- **4,4'-Dimethoxyibiphenyl (13b).**[115] Obtained as a white powder (19% using complex **1a**).



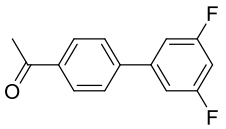
- **1-Biphenyl-4-yl-ethanone (13c).**[116] Obtained as a white powder (91% using complex **1a**; 25.9 mg, 88% using complex **1b**).



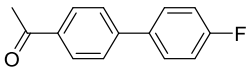
- **4-Methoxybiphenyl (13d).**[116] Obtained as a white powder (74% using complex **1a**; 8.0 mg, 29% using complex **1b**).



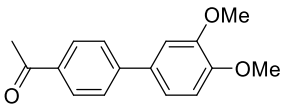
- **1-(3',5'-Difluorobiphenyl-4-yl)ethanone (13e).**[117] Obtained as a white powder (70% using complex **1a**; 30.9 mg, 89% using complex **1b**).



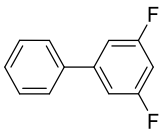
- **1-(4'-Fluorobiphenyl-4-yl)ethanone (13f).**[118] Obtained as a white powder (83% using complex **1a**; 29.2 mg, 91% using complex **1b**).



1-(3',4'-Dimethoxybiphenyl-4-yl)ethanone (13g).[119] Obtained as a white powder (90% using complex **1a**; 36.9 mg, 96% using complex **1b**).



3,5-Difluorobiphenyl (13i). Obtained as a white powder (60% using complex **1a**; 11.4 mg, 40% using complex **1b**).

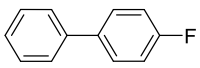


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.2 Hz, 2H, C*H*$_{phenyl}$), 7.47 (t, *J* = 7.2 Hz, 2H, C*H*$_{phenyl}$), 7.41 (t, *J* = 7.2 Hz, 1H, C*H*$_{phenyl}$), 7.14 (dd, *J* = 8.8, 2.4 Hz, 2H, C*H*$_{arom}$), 6.76 (tt, *J* = 8.8, 2.0 Hz, 1H, C*H*$_{arom}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.5 (dd, $^{1}J_{CF}$ = 247, 13 Hz, qC$_{arom-F}$), 144.6 (t, $^{3}J_{CF}$ = 10 Hz, q*C*$_{arom}$), 139.2 (q*C*$_{arom}$), 129.2 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 110.1 (dd, $^{2}J_{CF}$ =18, 6 Hz, *C*H$_{arom}$), 102.5 (t, $^{1}J_{CF}$ = 100 Hz, *C*H$_{arom}$).

m.p.: 59–60 ºC (DCM). *Lit.*[121] 56–58 °C (AcOEt)

4-Fluorobiphenyl (13j). Obtained as a white powder (99% using complex **1a**; 23.8 mg, 92% using complex **1b**).



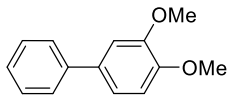
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50–7.62 (m, 4H, C*H*$_{arom}$ + C*H*$_{phenyl}$), 7.44 (t, *J* = 7.1 Hz, 2H, C*H*$_{phenyl}$), 7.34 (t, *J* = 7.4 Hz, 1H, C*H*$_{phenyl}$), 7.13 (t, *J* = 8.6 Hz, 2H, C*H*$_{arom}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.4 (d, $^{1}J_{CF}$= 246.3, qC$_{arom-F}$), 140.2 (q*C*$_{arom}$), 137.3 (d, *J* = 3.3, q*C*$_{arom}$), 128.8 (*C*H$_{arom}$), 128.6 (d, $^{3}J_{CF}$ = 8.0, *C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 127.0 (*C*H$_{arom}$), 115.6 (d, $^{2}J_{CF}$ = 21.3, *C*H$_{arom}$).

[121] Demir, A., S.; Findik, H.; Saygili, N.; Subasi, N. T. *Tetrahedron* **2010**, *66,* 1308–1312.

m.p.: 71–73 ºC (DCM). *Lit*.[122] 73–74 °C (hexane)

3,4-Dimethoxybiphenyl (13k). Obtained as a white powder (35% using complex **1a**; 4.5 mg, 14% using complex **1b**).

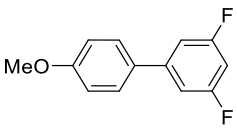


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H, C*H*$_{phenyl}$), 7.43 (t, *J* = 7.5 Hz, 2H, C*H*$_{phenyl}$), 7.32 (t, *J* = 7.5 Hz, 1H, C*H*$_{phenyl}$), 7.16 (dd, *J* = 8.2, 2.1 Hz, 1H, C*H*$_{arom}$), 7.12 (d, *J* = 2.1Hz, 1H, C*H*$_{arom}$), 6.95 (d, *J* = 8.2 Hz, 1H, C*H*$_{arom}$), 3.96 (s, 3H, C*H*$_{3,\ OMe}$), 3.93 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 149.2 (q*C*$_{arom}$), 148.7 (q*C*$_{arom}$), 141.2 (q*C*$_{arom}$), 134.4 (q*C*$_{arom}$), 128.9 (*C*H$_{arom}$), 127.0 (*C*H$_{arom}$), 127.0 (*C*H$_{arom}$), 119.5 (*C*H$_{arom}$), 111.5 (*C*H$_{arom}$), 110.5 (*C*H$_{arom}$), 56.1 (*C*H$_{3,\ OMe}$), 56.1 (*C*H$_{3,\ OMe}$).

m.p.: 62–64 ºC (DCM). *Lit*.[123] 66–67 °C (Hexane:EtOAc)

3,5-Difluoro-4'-methoxybiphenyl (13l). Obtained as a white powder (56% using complex **1a**).



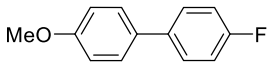
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42–7.60 (m, 2H, C*H*$_{anisole}$), 6.92–7.01 (m, 2H, C*H*$_{anisole}$), 6.74–6.82 (m, 2H, C*H*$_{arom}$), 6.65–6.74 (m, 1H, C*H*$_{arom}$), 3.85 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.4 (d, $^{1}J_{CF}$ = 246.0 Hz, q*C*$_{arom\text{-}F}$), 163.2 (d, $^{1}J_{CF}$ = 245.3 Hz, q*C*$_{arom\text{-}F}$), 160.0 (q*C*$_{arom}$), 144.1 (d, $^{3}J_{CF}$ = 9.5 Hz, q*C*$_{arom}$), 131.3 (d, $^{4}J_{CF}$ = 2.6 Hz, q*C*$_{anisole}$), 128.1 (*C*H$_{arom}$), 114.4 (*C*H$_{arom}$), 109.6-109.1 (m, *C*H$_{arom}$), 101.8 (d, $^{2}J_{CF}$ = 25.5 Hz, *C*H$_{arom}$), 55.4 (*C*H$_{3,\ OMe}$).

m.p.: 72–74 ºC (DCM). *Lit.*[124] 74–75 °C (AcOEt)

[122] Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661–1664.
[123] Lau, K. C. Y.; He, H. S.; Chiu, P.; Troy, P. H. *J. Comb. Chem.* **2004**, *6*, 955–960.
[124] Yamada, S.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 2215–2218.

4-Fluoro-4'-methoxybiphenyl (13m).[125] Obtained as a white powder (99% using complex **1a**).



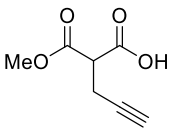
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42–7.57 (m, 4H, C*H*$_{arom}$), 7.04–7.15 (m, 2H, C*H*$_{arom}$), 6.91–7.01 (m, 2H, C*H*$_{arom}$), 3.85 (s, 3H, C*H*$_{3,\ OMe}$)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 245.6 Hz, q*C*$_{arom\text{-}F}$), 159.1 (q*C*$_{arom}$), 136.9 (d, ^4J = 3.3 Hz, q*C*$_{arom}$), 132.8 (q*C*$_{arom}$), 128.2 (d, $^3J_{CF}$ = 8.0 Hz, *C*H$_{arom}$), 128.0 (*C*H$_{arom}$), 115.5 (d, $^2J_{CF}$ = 21.4 Hz, *C*H$_{arom}$), 114.2 (*C*H$_{arom}$), 55.3 (*C*H$_{3,\ OMe}$).

4.6 Synthesis of alkynoic acids

4.6.1 Method A. Monohydrolysis of dimethyl propargylmalonate

2-(Methoxycarbonyl)-4-pentynoic acid (14c). To a solution of dimethyl propargylmalonate (0.35 mL, 2.2 mmol) in methanol (5 mL), NaOH (96 mg, 2.4 mmol) was added. The mixture was stirred at room temperature for 18 hours. Then, a saturated aqueous solution of $NaHCO_3$ (10 mL) were added, and the mixture was extracted with EtOAc (3 × 10 mL). The aqueous phase was acidified to pH = 1 with concentrated hydrochloric acid and extracted with DCM (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, providing alkynoic acid **14c** as a white powder (168.2 mg, 49%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.99 (bs, 1H, OH), 3.80 (s, 3H, C*H*$_{3,\ OMe}$), 3.65 (t, *J* = 7.5 Hz, 1H, C*H*$_{malonate}$), 2.81 (ddd, *J* = 7.7, 2.6, 1.4 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.05 (t, *J* = 2.6 Hz, 1H, C*H*$_{acetylene}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.4 (*C*OOH), 168.0 (*C*OOMe), 79.4 (-C≡*C*H), 70.8 (-*C*≡CH), 53.0 (*C*H$_{3,\ OMe}$), 50.1 (*C*H$_{malonate}$), 18.4 (CH$_{2,\ propargyl}$).

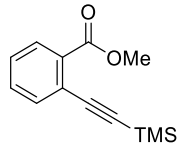
m.p.: 68–70 °C (DCM). *Lit.*[46] 68–71 ºC ($CHCl_3$)

[125] Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364–9370.

4.6.2 Method B. General procedure for the alkynylation of methyl 2-halobenzoate

Under an atmosphere of argon the aryl halide (1.5 mmol) and acetylene derivative (1.8 mmol) were dissolved in freshly distilled and degassed TEA (6 mL) at room temperature. Then, $(Ph_3P)_2PdCl_2$ (21.0 mg, 0.03 mmol) and CuI (11.4 mg, 0.03 mmol) were added sequentially and stirring at room temperature, under argon, was continued overnight. Then, the mixture was dissolved in DCM (30 mL) and the solution was filtered through a plug of silica, and then the solvent was removed under reduced pressure. This work-up procedure (solution in DCM, filtration through silica) was repeated two times to remove triethylamine completely. The residue was purified by flash column chromatography (PE:EtOAc) to afford the desired ynoic acid ester **17**.

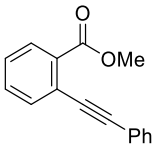
Methyl 2-[(trimethylsilyl)ethynyl]benzoate (17a).[46] The general procedure was followed and methyl 2-[(trimethylsilyl)ethynyl]benzoate was obtained an orange oil (264.6 mg, 76%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.7, 1.2 Hz, 1H, C*H*$_{phenyl}$), 7.52 (dd, *J* = 7.6, 1.0 Hz, 1H, C*H*$_{phenyl}$), 7.39–7.31 (m, 2H, C*H*$_{phenyl}$), 3.88 (s, 3H, C*H*$_{3,\ OMe}$), 0.25 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.9 (*C*=O), 134.5 (*C*H$_{arom}$), 132.6 (q*C*$_{arom}$), 131.4 (*C*H$_{arom}$), 130.2 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 123.2 (q*C*$_{arom}$), 103.3 (-*C*≡C-TMS), 99.7 (-C≡*C*-TMS), 52.0 (*C*H$_{3,\ OMe}$), -0.1 (-Si(*C*H$_3$)$_3$).

Methyl 2-phenylethynylbenzoate (17b).[126] The general procedure was followed and methyl 2-phenylethynylbenzoate was obtained as a yellow oil (152.8 mg, 96%).

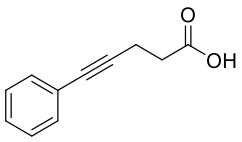


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.5 Hz, 1H, C*H*$_{phenyl}$), 7.63–7.56 (m, 3H, C*H*$_{phenyl}$), 7.46–7.40 (m, 1H, C*H*$_{phenyl}$), 7.36–7.30 (m, 4H, C*H*$_{phenyl}$), 3.92 (s, 3H, *CH*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.4 (*C*=O), 133.8 (*C*H$_{arom}$), 131.6 (*C*H$_{arom}$), 131.5 (*C*H$_{arom}$), 130.3 (q*C*$_{arom}$), 128.3 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 127.7 (q*C*$_{arom}$), 123.5 (q*C*$_{arom}$), 123.1 (*C*H$_{arom}$), 94.2 (-*C*≡C-Ph), 88.1 (-C≡*C*-Ph), 52.0 (O*C*H$_3$).

4.6.3 Method C. General procedure for the (hetero)arylation of 4-pentynoic acid

5-Phenylpent-4-ynoic acid (14f). Typical procedure. A solution of iodobenzene (266 µL, 2.33 mmol), $Pd(PPh_3)_4$ (135.9 mg, 0.12 mmol) and CuI (45.2 mg, 0.23 mmol) in Et_2NH (1.9 mL) was stirred for 10 mins. To the resulting mixture, a solution of 4-pentynoic acid **14a** (200 mg, 1.94 mmol) in Et_2NH (1.4 mL) was added and the reaction was then stirred at r.t. for 12 h under an argon atmosphere. Then, the reaction was diluted with water (20 mL). The aqueous layer was extracted with EtOAc (4 × 20 mL), basified with a 2.0 M NaOH solution (30 mL) and re-extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes:EtOAc 1:1) to provide alkynoic acid **14f** as an off-white powder (259.0, 64%).



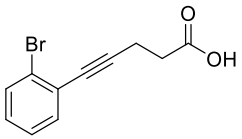
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38–7.45 (m, 2H, C*H*$_{phenyl}$), 7.23–7.35 (m, 3H, C*H*$_{phenyl}$), 2.66–2.80 (m, 4H, C*H*$_2$).

[126] Jithunsa, M.; Ueda, M.; Miyata, O. *Org. Lett.* **2011**, *13*, 518–521.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.7 (*C*=O), 131.6 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 127.9 (*C*H$_{arom}$), 123.4 (q*C*$_{arom}$), 87.6 (-*C*≡C-Ph), 81.4 (-C≡*C*-Ph), 33.2 (*C*H$_2$-COOH), 15.1 (*C*H$_2$-alkyne).

m.p.: 98–101 °C (Et_2O). *Lit.*[127] 98–99 ºC (Et_2O)

♁ **5-(2-Bromophenyl)pent-4-ynoic acid (14g).** The same procedure was followed starting from **14a** (147.2 mg, 1.5 mmol) and 1-bromo-2-iodobenzene (520 mg, 1.80 mmol) to obtain 5-(2-bromophenyl)pent-4-ynoic acid as a white powder after flash chromatography (hexanes:EtOAc 1:1) (223.0 mg, 59%).

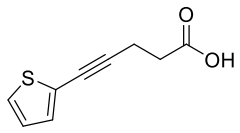


^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.62 (s, 1H, O*H*), 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H, C*H*$_{arom}$), 7.42 (dd, *J* = 7.6, 1.8 Hz, 1H, C*H*$_{arom}$), 7.22 (td, *J* = 7.6, 1.3 Hz, 1H, C*H*$_{arom}$), 7.12 (td, *J* = 7.7, 1.8 Hz, 1H, C*H*$_{arom}$), 2.88–2.67 (m, 4H, C*H*$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.5 (*C*=O), 133.4 (*C*H$_{arom}$), 132.4 (*C*H$_{arom}$), 129.1 (*C*H$_{arom}$), 127.0 (*C*H$_{arom}$), 125.6 (q*C*$_{arom}$), 125.5 (q*C*$_{arom\text{-}Br}$), 92.7 (-*C*≡C-Ar), 80.2 (-C≡*C*-Ar), 33.4 (*C*H$_2$-COOH), 15.4 (*C*H$_2$-alkyne).

m.p.: 89–92 °C (Et_2O). *Lit.*[128] 87–91 ºC ($CHCl_3$:hexane)

♁ **5-(Thiophen-2-yl)pent-4-ynoic acid (14h).** The same procedure was followed starting from **14a** (147.2 mg, 1.5 mmol) and 2-iodothiophene (203 µL, 1.80 mmol) to obtain 5-(thiophen-2-yl)pent-4-ynoic acid as a white powder after flash chromatography (hexanes:EtOAc 1:1) (175.5 mg, 65%).



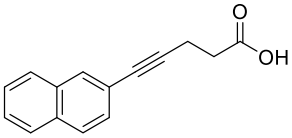
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.14 (d, *J* = 3.2 Hz, 1H, C*H*$_{thiophene}$), 6.94 (dd, *J* = 5.1, 3.2 Hz, 1H, C*H*$_{thiophene}$), 2.65–2.80 (m, 4H, C*H*$_2$).

[127] Wu, H.; He, Y.; Gong, L. *Adv. Synth. Catal.* **2012**, *354*, 975.
[128] Djuric, S. W. *Furyl, phenylene and thienyl leukotriene B4 analogues.* EP 319900 A2, September 29, 1993.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.1 (*C*=O), 131.4 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 126.3 (*C*H$_{arom}$), 123.3 (q*C*$_{arom}$), 91.6 (-*C*≡C-thiophene), 74.5 (-C≡*C*-thiophene), 33.1 (*C*H$_2$-COOH), 15.2 (*C*H$_2$-alkyne).

m.p.: 82–84 °C (Et_2O). *Lit.*[129] 83–85 ºC (hexanes)

5-(Naphthalen-2-yl)pent-4-ynoic acid (14i). A similar procedure was followed reacting **14a** (147.2 mg, 1.5 mmol) and 2-bromonaphthalene (380 mg, 1.80 mmol) at 60 ºC for 12 h. Flash chromatography purification (hexanes:EtOAc 1:1) provided 5-(naphthalen-2-yl)pent-4-ynoic acid as a white powder (141.2 mg, 42%).



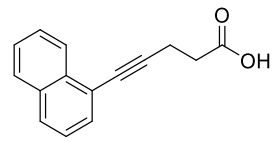
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.5 Hz, 1H, C*H*$_{naphthyl}$), 7.82–7.68 (m, 3H, C*H*$_{naphthyl}$), 7.54–7.37 (m, 3H, C*H*$_{naphthyl}$), 3.00–2.64 (m, 4H, CH_2).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.8 (*C*=O), 132.9 (q*C*$_{arom}$), 132.6 (q*C*$_{arom}$), 131.3 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 127.8 (*C*H$_{arom}$), 127.7 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 126.4 (*C*H$_{arom}$), 120.7 (q*C*$_{arom}$), 87.9 (-*C*≡C-Ar), 81.7 (-C≡*C*-Ar), 33.3 (*C*H$_2$-COOH), 15.2 (*C*H$_2$-alkyne).

m.p.: 134–137 °C (Et_2O)

5-(Naphthalen-1-yl)pent-4-ynoic acid (14j). A similar procedure was followed reacting **14a** (147.2 mg, 1.5 mmol) and 1-bromonaphthalene (380 mg, 1.80 mmol) at 60 ºC for 12 h. Flash chromatography purification (hexanes:EtOAc 1:1) provided 5-(naphthalen-1-yl)pent-4-ynoic acid as a white powder (151.3 mg, 45%).

[129] Tellitu, I.; Serna, S.; Herrero, M.T.; Moreno, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem*. **2007**, *72*, 1526–1529.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 7.9 Hz, 1H, C*H*$_{naphthyl}$), 7.41–7.89 (m, 6H, C*H*$_{naphthyl}$), 2.85–2.95 (m, 4H, C*H*$_2$).

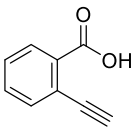
^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.5 (*C*=O), 133.3 (q*C*$_{arom}$), 133.0 (q*C*$_{arom}$), 130.1 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 126.5 (*C*H$_{arom}$), 126.2 (*C*H$_{arom}$), 126.0 (*C*H$_{arom}$), 125.0 (*C*H$_{arom}$), 120.9 (-*C*≡C-Ar), 92.5 (-C≡*C*-Ar), 79.4 (q*C*$_{arom}$), 33.5 (*C*H$_2$-COOH), 15.3 (*C*H$_2$-alkyne).

m.p.: 78–81 °C (Et_2O). *Lit*.[129] 82–84 ºC (hexanes)

4.6.4 General procedure for the hydrolysis/desilylation of methyl 2-alkynylbenzoates 17

To a solution of the corresponding methyl ester **17** (1 mmol) in MeOH (6.5 mL) at 0 ºC, a solution of potassium hydroxide (560 mg, 10 mmol) in water (3 mL) was added. The mixture was stirred for 2 hours at room temperature. After decantation the aqueous layer was acidified with aqueous HCl 1M to pH = 3. The aqueous phase was extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvents were removed *in vacuo*. Purification by flash column chromatography provided alkynoic acids.

2-Ethynylbenzoic acid (14d).[130] The general procedure was followed and methyl 2-ethynylbenzoic acid was obtained as a white powder (32.1 mg, 22%).



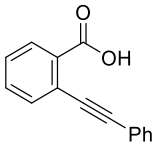
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.7,1.4 Hz, 1H, C*H*$_{phenyl}$), 7.67 (dd, *J* = 7.7, 1.4 Hz, 1H, C*H*$_{phenyl}$), 7.54 (td, *J* = 7.7, 1.4 Hz, 1H, C*H*$_{phenyl}$), 7.45 (td, *J* = 7.7, 1.4 Hz, 1H, C*H*$_{phenyl}$), 3.46 (s, 1H, -C≡C*H*).

[130] Marchal, E.; Uria, P.; Legouin, B.; Toupet, L.; van de Weghe, P. *Tetrahedron* **2007**, *63*, 9979–9990.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.0 (*C*=O), 152.1 (q*C*$_{arom}$), 138.9 (q*C*$_{arom}$), 134.4 (*C*H$_{arom}$), 130.4 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 120.9 (*C*H$_{arom}$), 90.4 (-*C*≡CH), 89.8 (-C≡*C*H).

m.p.: 125–128 °C ($CHCl_3$). *Lit.*[130] 121–123 ºC (Et_2O:pentane)

2-(Phenylethynyl)benzoic acid (14e).[130] The general procedure was followed and 2-(phenylethynyl)benzoic acid was obtained as a white powder (217.6 mg, 98%).



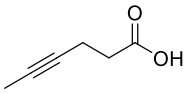
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.9 Hz, 1H, C*H*$_{phenyl}$), 7.17–7.65 (m, 8H, C*H*$_{phenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.4 (*C*=O), 134.2 (*C*H$_{arom}$), 132.6 (*C*H$_{arom}$), 131.7, (*C*H$_{arom}$), 131.4 (*C*H$_{arom}$), 130.5 (q*C*$_{arom}$), 128.6 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 128.0 (*C*H$_{arom}$), 124.4 (q*C*$_{arom}$), 123.1 (q*C*$_{arom}$), 95.4 (-*C*≡C-Ph), 88.0 (-C≡*C*-Ph).

m.p.: 124–127 °C (Et_2O). *Lit*. 127–129 ºC (DCM:MeOH)

4.6.5 Synthesis of hex-4-ynoic acid (14l)[91] *via alkyne isomerization*

Hex-5-ynoic acid (560.7 mg, 5 mmol) and KO^{t}Bu (1.122 g, 10 mmol) were dissolved in DMSO (20 mL). The reaction was stirred at r.t. for 3 h, then the reaction was quenched with an aqueous 2M HCl (10 mL) solution and extracted with Et_2O (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo* to afford hex-4-ynoic acid **14l** as a colorless oil (510.2 mg, 91%), which was used without further purification.



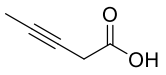
^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.53 (ddd, *J* = 7.8, 6.7, 1.1 Hz, 2H, C*H*$_2$-COOH), 2.42 (ddqt, *J* = 7.6, 6.3, 2.5, 1.1 Hz, 2H, C*H*$_2$-alkyne), 1.74 (t, *J* = 2.5 Hz, 3H, C*H*$_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 178.1 (*C*=O), 76.5 (-*C*≡C-Me), 76.2 (-C≡*C*-Ph), 33.3 (CH_2-COOH), 14.0 (CH_2-alkyne), 3.0 ($CH_{3,\ Me}$).

m.p.: 97–99 °C (Et_2O). *Lit.*[131] 102–103 ºC (H_2O:MeOH)

4.6.6 Synthesis of pent-3-ynoic acid (14m).[132]

To a stirred suspension of periodic acid (1.01 g, 4.4 mmol) in MeCN (15 mL) was added 4-pentyn-1-ol (192 µL, 2 mmol) and PCC (8.8 mg, 0.04 mmol) at 0 ºC. The temperature was gradually raised to 25 ºC and stirring was continued for further 12 h. Upon completion, disappearance of the alcohol was monitored by TLC, and the reaction mixture was diluted with EtOAc (50 mL) and washed once with H_2O (25 mL) followed by brine (25 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* and the crude was purified by silica column chromatography (DCM:MeOH 97:3) providing pent-3-ynoic acid **14m** as a white powder (137.2 mg, 70%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 10.35 (br s, 1H, OH), 3.32 (q, *J* = 2.6 Hz, 2H, C*H*$_2$), 1.84 (t, *J* = 2.6 Hz, 3H, C*H*$_3$)

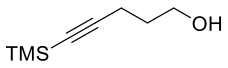
^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.2 (*C*=O), 80.0 (-*C*≡C-Me), 69.7 (-C≡*C*-Me), 25.8 (*C*H_2), 3.5 (*C*$H_{3,\ Me}$).

m.p.: 78–82 °C ($CHCl_3$). *Lit.*[133] 102–104 ºC (pentane)

[131] Starostin, E. K.; Ignatenko, A. V.; Lapitskaya, M. A.; Pivnitsky, K. K.; Nikishin, G. I. *Russ. Chem. Bull.* **2001**, *50*, 833–837.
[132] Gorske, B. C.; Mbofana, C. T.; Miller, S. *J. Org. Lett.* **2009**, *11*, 4318–4321.
[133] Qiu, J. C.; Pradhan, P. P.; Blanck, N. B.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2012**, *14*, 350–353.

4.6.7 Synthesis of 5-trimethylsilyl-4-pentynoic acid 14n

5-(Trimethylsilyl)pent-4-yn-1-ol (18c).[134] To a magnetically stirred solution of 4-pentyn-1-ol (2 g, 23.8 mmol) in THF (50 mL) was added ^{n}BuLi (31.25 mL of a 1.6 M solution in hexane, 50.0 mmol) at -78 °C under argon atmosphere. Stirring was continued for 1 h at the same temperature, then TMSCl (6.05 mL, 47.6 mmol) was added at -78 °C, and the mixture was stirred for 1 h before being quenched with an aqueous 1 M HCl (23.8 mL, 23.8 mmol) solution. The mixture was then diluted with water (50 mL), and extracted with EtOAc (2 × 20 mL). Evaporation of solvents *in vacuo* gave a residue that was purified by flash column chromatography (hexanes:EtOAc 7:3) to provide pure compound **18c** as a colorless oil (2.37 g, 58%).

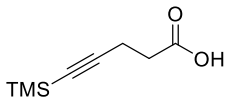


^{1}H-NMR (300 MHz, $CDCl_3$) δ 3.77 (t, *J* = 6.0 Hz, 2H, C*H*$_2$-OH), 2.36 (t, *J* = 6.8 Hz, 2H, C*H*$_2$-alkyne), 1.78 (q, *J* = 6.8, 6.0 Hz, 2H, -CH$_2$C*H*$_2$CH$_2$OH), 0.15 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 106.6 (*C*H$_2$-OH), 84.7 (-*C*≡C-TMS), 61.0 (-C≡*C*-TMS), 31.1 (CH$_2$*C*H$_2$CH$_2$OH), 16.2 (*C*H$_2$-alkyne), -0.1 (-Si(*C*H$_3$)$_3$).

5-(Trimethylsilyl)pent-4-ynoic acid (14n).[135] 5-(Trimethylsilyl)pent-4-yn-1-ol (5.0 g, 32 mmol) and pyridinium dichromate (30.0 g, 80 mmol) were dissolved in DMF (50 mL). The resulting black solution was stirred for 24 h at room temperature. The reaction mixture was diluted with water (200 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with aqueous 1 M HCl (2 × 100 mL), brine (100 mL), then dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under the reduced pressure and the so-obtained residue was purified by flash column chromatography (PE:EtOAc 7:3) to give alkynoic acid **14n** as a white powder (2.33 g, 43%).

[134] Pabbaraja, S.; Gantasala, N.; Ydhyam, S.; Namballa, H. K.; Gundeboina, S.; Lambu, M.R.; Meena, S.; Datta, D. *Tetrahedron Lett.* **2018**, *59*, 2570–2576.
[135] Ledin, P. A.; Friscourt, F.; Guo, J.; Boons, G. J. *Chem. Eur. J.* **2011**, *17*, 839–846.



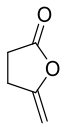
^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.51–2.64 (m, 4H, C*H*$_2$), 0.14 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.8 (*C*=O), 104.5 (*C*H$_2$-acetylene), 85.7 (-*C*≡C-TMS), 33.3 (-C≡*C*-TMS), 15.5 (*C*H$_2$-C=O), -0.01 (-Si(*C*H$_3$)$_3$).

4.7 General procedure for the cycloisomerization of alkynoic acids in the presence of complexes 1

The alkynoic acid **14** (1 mmol), TEA (0.6 mL of a 0.03 M solution in H_2O, 0.02 mmol or 0.6 mL of a 0.17 M solution in H_2O, 0.1 mmol) and palladacycle **1** (0.4 mL of a $2.5\cdot10^{-3}$ M solution in DMF:H_2O 1:164 for **1a**, 0.4 mL of a $2.5\cdot10^{-3}$ M solution in DMF:H_2O 1:191 for **1b**, 10^{-3} mmol / 0.4 mL of a $2.5\cdot10^{-4}$ M solution in DMF:H_2O 1:1640 for **1a**, or 0.4 mL of a $2.5\cdot10^{-4}$ M solution in DMF:H_2O 1:1910 for **1b**, 10^{-4} mmol) were placed in a screw-capped tube. Then, the tube was argon flushed and tightly closed, after which the reaction was stirred for 24 h at a room temperature. The reaction mixture was extracted with $CDCl_3$ (2 × 0.5 mL) and dried over anhydrous Na_2SO_4. After filtration, the resulting lactone **15** was analyzed by NMR employing 3,4,5-trichloropyridine as internal standard when volatile, or concentrated *in vacuo* and purified to provide the corresponding lactone **15**.

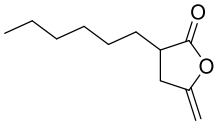
5-Methylenedihydrofuran-2(3*H*)-one (15a).[46] Product obtained from **14a** employing TEA (0.6 mL of a 0.03 M stock solution in H_2O, 0.02 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5\cdot10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 12 h at r.t. Yield was determined by NMR (94% for catalyst **1a**; 96% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 4.2, 2.0 Hz, 1H, C*H*$_{methylene}$), 4.31 (dd, *J* = 4.2, 2.0 Hz, 1H, =C*H*$_2$), 2.93–2.83 (m, 2H, C*H*$_2$-C=O), 2.72–2.63 (m, 2H, C*H*$_2$-C=CH$_2$)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.0 (*C*=O), 155.6 (*C*=CH$_2$), 88.7 (=*C*H$_2$), 28.0 (*C*H$_2$-C=O), 25.1 (*C*H$_2$-C=CH$_2$).

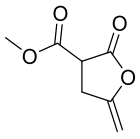
3-Hexyl-5-methylenedihydrofuran-2(3*H*)-one (15b).[46] Product obtained from **14b** employing TEA (0.6 mL of a 0.03 M stock solution in H_2O, 0.02 mmol), catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 24 h at r.t. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford **15b** as a colorless oil (162.0 mg, 89% for catalyst **1a**; 180.3 mg, 99% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.71 (dd, *J* = 3.9, 2.0 Hz, 1H, =C*H*$_2$), 4.30 (dd, *J* = 3.9, 2.0 Hz, 1H, =C*H*$_2$), 2.99 (dd, *J* = 15.9, 9.6 Hz, 1H, C*H*$_{furanone}$), 2.74 (ddd, *J* = 14.1, 8.7, 4.9 Hz, 1H, C*H*$_{furanone}$), 2.54 (ddt, *J* = 15.9, 7.7, 2.1 Hz, 1H, C*H*$_{furanone}$), 1.94–1.77 (m, 1H, C*H*$_{hexyl}$), 1.59–1.44 (m, 1H, C*H*$_{hexyl}$), 1.43–1.21 (m, 8H, 4C*H*$_{2,\ hexyl}$), 0.88 (t, *J* = 6.6 Hz, 3H, C*H*$_{3,\ hexyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.2 (*C*=O), 154.5 (-*C*=*C*H$_2$), 88.6 (=*C*H$_2$), 39.9 (*C*H$_{furanone}$), 31.6 (CH$_{2,\ hexyl}$), 31.5 (CH$_{2,\ hexyl}$), 30.9 (*C*H$_{furanone}$), 28.9 (*C*H$_{2,\ hexyl}$), 26.9 (CH$_{2,\ hexyl}$), 22.5 (CH$_{2,\ hexyl}$), 14.0 (CH$_{3,\ hexyl}$).

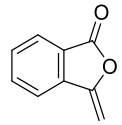
Methyl 5-methylene-2-oxotetrahydrofuran-3-carboxylate (15c).[46] Product obtained from **14c** employing TEA (0.6 mL of a 0.03 M stock solution in H_2O, 0.02 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 12 h at r.t. Yield was determined by NMR (93% for catalyst **1a**; 94% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.82 (dd, *J* = 4.5, 2.3 Hz, 1H, =C*H*$_2$), 4.41 (dd, *J* = 4.4, 1.8 Hz, 1H, =C*H*$_2$), 3.83 (s, 3H, C*H*$_{3,\ OMe}$), 3.76 (dd, *J* = 10.4, 7.6 Hz, 1H, C*H*COOMe), 3.31 (ddt, *J* = 16.6, 7.6, 2.1 Hz, 1H, C*H*$_{furanone}$), 3.09 (ddt, *J* = 16.6, 10.4, 1.6 Hz, 1H, C*H*$_{furanone}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.5 (*C*OOMe), 167.3 (*C*=O), 153.1 (*C*=*C*H$_2$), 89.9 (=*C*H$_2$), 53.4 (q*C*$_{OMe}$), 46.2 (*C*H$_{furanone}$), 29.3 (*C*H$_{2,\ furanone}$).

3-Methyleneisobenzofuran-1(3*H*)-one (15d).[46] Product obtained from **14d** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 18 h under sonication at r.t. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford **15d** as a white powder (124.0 mg, 85% for catalyst **1a**; 131.5 mg, 90% for catalyst **1b**).

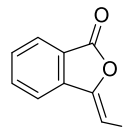


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.90 (t, *J* = 7.5 Hz, 1H, C*H*$_{arom}$), 7.85 (t, *J* = 7.5 Hz, 1H, C*H*$_{arom}$), 7.79 (td, *J* = 7.5, 1.1 Hz, 1H, C*H*$_{arom}$), 7.64 (td, *J* = 7.4, 1.0 Hz, 1H, C*H*$_{arom}$), 5.40 (d, *J* =3.0 Hz, 1H, =C*H*$_2$), 5.22 (d, *J* = 3.0 Hz, 1H, =C*H*$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 166.9 (*C*=O), 152.0 (*C*=*C*H$_2$), 138.9 (q*C*$_{arom}$), 134.6 (*C*H$_{arom}$), 130.4 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 120.7 (q*C*$_{arom}$), 90.4 (=*C*H$_2$).

m.p.: 51–52 °C (DCM). *Lit*.[46] 50–53 ºC ($CHCl_3$)

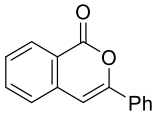
(*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-one (15e).[46] Product obtained from **14e** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 24 h at 50 ºC. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford a mixture of **15e** and **15e'** as a white powder [200.0 mg, 90% (48:42, **15e**:**15e´**) for catalyst **1a**; 199.8 mg, 90% (76:14, **15e**:**15e´**) for catalyst **1b**]. Regioisomeric ratio was determined by NMR.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63–7.89 (m, 5H, C*H*$_{arom}$), 7.23–7.51 (m, 4H, C*H*$_{arom}$), 6.36 (s, 1H, =C*H*).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 167.3 (*C*=O), 144.8 (*C*=*C*H$_2$), 140.8 (q*C*$_{arom}$), 134.7 (q*C*$_{arom}$), 133.3 (*C*H$_{arom}$), 130.3 (*C*H$_{arom}$), 129.9 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 125.7 (*C*H$_{arom}$), 123.5 (q*C*$_{arom}$), 112.0 (*C*H$_{arom}$), 107.2 (=*C*H).

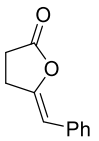
3-Phenyl-1*H*-isochromen-1-one (15e´).[46] Product obtained from **14e** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 24 h at 50 ºC. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford a mixture of **15e** and **15e'** as a white powder [200.0 mg, 90% (48:42, **15e**:**15e´**) for catalyst **1a**; 199.8 mg, 90% (76:14, **15e**:**15e´**) for catalyst **1b**]. Regioisomeric ratio was determined by NMR.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 7.8 Hz, 1H, C*H*$_{arom}$), 7.88 (dd, *J* = 7.8, 1.8 Hz, 2H, C*H*$_{phenyl}$), 7.71 (t, *J* = 7.8 Hz, 1H, C*H*$_{arom}$), 7.41–7.52 (m, 5H, C*H*$_{arom}$), 6.95 (s, 1H, C*H*$_{pyranone}$).

^{13}C-NMR (75 MHz, $CDCl_3$ δ 162.2 (*C*=O), 153.7 (q*C*$_{arom}$), 137.5 (q*C*$_{arom}$), 134.8 (*C*H$_{arom}$), 132.0 (q*C*$_{arom}$), 129.9 (*C*H$_{arom}$), 129.7 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 125.9 (*C*H$_{arom}$), 125.2 (*C*H$_{arom}$), 120.6 (q*C*$_{arom}$), 101.8 (*C*H$_{pyranone}$).

(*Z*)-5-Benzylidenedihydrofuran-2(3*H*)-one (15f).[46] Product obtained from **14f** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 40 h at r.t. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford **15f** as a white powder (158.2 mg, 91% for catalyst **1a**; 172.4 mg, 99% for catalyst **1b**).



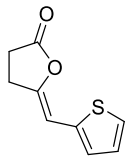
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.55 (d, *J* =7.4 Hz, 2H, C*H*$_{phenyl}$), 7.33 (t, *J* = 7.5Hz, 2H, C*H*$_{phenyl}$), 7.21 (t, *J* = 7.3 Hz, 1H, C*H*$_{phenyl}$), 5.55 (s, 1H, =C*H*), 3.12–2.93 (m, 2H, C*H*$_2$-C=O), 2.81–2.62 (m, 2H, C*H*$_2$-C=CHPh).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.9 (*C*=O), 148.1 (*C*=*C*H$_2$), 133.9 (q*C*$_{arom}$), 128.5 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 104.9 (=*C*H), 27.0 (*C*H$_2$-C=O), 26.3 (*C*H$_2$-C=CHPh).

m.p.: 88–91 °C ($CHCl_3$). *Lit.*[136] 94.2–95.7 ºC (PE:EtOAc)

- **(*Z*)-5-(Thiophen-2-ylmethylene)dihydrofuran-2(3*H*)-one (15h)**.[137]

Product obtained from **14h** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 24 h at 50 ºC. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford **15h** as a white powder (164.0 mg, 91% for catalyst **1a**; 144.1 mg, 80% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.08 (d, *J* = 4.2 Hz, 1H, C*H*$_{thiophene}$), 6.99 (dd, *J* = 4.2, 5.0 Hz, 1H, C*H*$_{thiophene}$), 5.84−5.86 (m, 1H, =C*H*), 3.00−3.05 (m, 2H, C*H*$_2$-C=O), 2.73−2.78 (m, 2H, C*H*$_2$-C=CHHetAr).

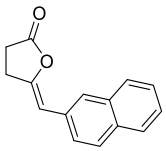
^{13}C-NMR (75 MHz, $CDCl_3$) δ 174.2 (*C*=O), 146.6 (*C*=*C*H_2), 136.5 (q*C*$_{arom}$), 126.8 (*C*H$_{arom}$), 125.7 (*C*H$_{arom}$), 125.1 (*C*H$_{arom}$), 99.0 (=*C*H), 27.3 (*C*H_2-C=O), 25.5 (*C*H_2-C=CHHetAr).

m.p.: 92–94 °C (Et_2O) *Lit*.[137] 96.5–97.5 ºC ($CHCl_3$)

- **(*Z*)-5-(Naphthalen-2-ylmethylene)dihydrofuran-2(3*H*)-one (15i).**

Product obtained from **14i** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-4}$ M stock solution in DMF:H_2O, 10^{-4} mmol) after 48 h at 50 ºC. The product was purified by flash column chromatography (PE:EtOAc 6:4) to afford **15i** as a white powder (183.7 mg, 82% for catalyst **1a**; 179.3 mg, 80% for catalyst **1b**).

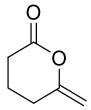
[136] Yu, L.; Wu, Y.; Cao, H.; Zhang, X.; Shi, X.; Luan, J.; Chen, T.; Pan, Y.; Xu, Q. *Green Chem.* **2014**, *16*, 287–293.
[137] Hamasaka, G.; Uozumi, Y. *Chem. Commun.* **2014**, *50*, 14516–14518.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.08–7.98 (m, 1H, C*H*$_{naphthyl}$), 7.94–7.85 (m, 1H, C*H*$_{naphthyl}$), 7.87–7.80 (m, 1H, C*H*$_{naphthyl}$), 7.80–7.70 (m, 1H, C*H*$_{naphthyl}$), 7.55–7.42 (m, 3H, C*H*$_{naphthyl}$), 6.24 (t, *J* = 1.9 Hz, 1H, =C*H*), 3.24–3.11 (m, 2H, C*H*$_2$-C=O), 2.85–2.72 (m, 2H, C*H*$_2$-C=CHAr).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.0 (*C*=O), 149.6 (*C*=*C*H$_2$), 133.8 (q*C*$_{arom}$), 131.2 (q*C*$_{arom}$), 130.0 (q*C*$_{arom}$), 128.9 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 126.1 (*C*H$_{arom}$), 125.8 (*C*H$_{arom}$), 125.7 (*C*H$_{arom}$), 123.7 (*C*H$_{arom}$), 101.4 (=*C*H), 27.4 (*C*H$_2$-C=O), 26.6 (*C*H$_2$-C=CHAr).

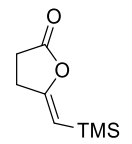
- **6-Methylenetetrahydro-2*H*-pyran-2-one (15k)**.[46] Product obtained from **14k** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 40 h at r.t. Yield was determined by NMR (79% for catalyst **1a**; 85% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.64 (s, 1H, =C*H*$_2$), 4.29 (s, 1H, =C*H*$_2$), 2.63 (t, *J* = 6.8 Hz, 2H, C*H*$_2$-C=O), 2.48 (t, *J* = 6.5 Hz, 2H, C*H*$_2$), 1.93–1.81 (m, 2H, C*H*$_2$-C=CH$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 168.1 (*C*=O), 155.3 (*C*=CH$_2$), 93.7 (=*C*H$_2$), 30.3 (*C*H$_2$-C=CH$_2$), 26.7 (*C*H$_2$-C=O), 18.6 (*C*H$_2$).

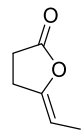
- **(*Z*)-5-[(Trimethylsilyl)methylene]dihydrofuran-2(3*H*)-one (15n)**. Product obtained from **14n** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 48 h at r.t. Yield was determined by NMR (50% for catalyst **1a**; 20% for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.60–4.50 (m, 1H, =C*H*), 2.94–2.80 (m, 2H, CH_2-C=O), 2.68–2.60 (m, 2H, CH_2-C=CHTMS), 0.13 (s, 9H, 3C$H_{3,\ TMS}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.5 (*C*=O), 160.4 (q$C_{furanone}$), 100.5 (=*C*H), 28.2 (*C*H_2-C=O), 27.6 (*C*H_2-C=CHTMS), -0.3 (-Si(*C*H_3)$_3$).

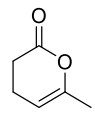
- **(*Z*)-5-Ethylidenedihydrofuran-2(3*H*)-one (15l)**.[77a] Product obtained from **14l** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5\cdot10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 40 h at r.t. Yield and regioisomeric ratio were determined by NMR [86% (69:17, **15l**:**15l´**) for catalyst **1a**; 64% (54:10, **15l**:**15l´**) for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.61 (tq, *J* = 6.8, 2.0, 1.6 Hz, 1H, =C*H*), 2.83–2.77 (m, 2H, CH_2-C=O), 2.65–2.61(m, 2H, CH_2-C=CHMe), 1.67 (dt, *J* = 6.8, 1.6, 2.0 Hz, 3H, C$H_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 175.3 (*C*=O), 148.4 (*C*=*C*H_2), 99.4 (=*C*H), 28.2 (*C*H_2-C=O), 25.1 (*C*H_2-C=CHMe),10.5 (*C*$H_{3,\ Me}$).

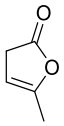
- **6-Methyl-3,4-dihydro-2*H*-pyran-2-one (15l´).**[138] Product obtained from **14l** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5\cdot10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 40 h at r.t. Yield and regioisomeric ratio were determined by NMR [86% (69:17, **16l**:**16l´**) for catalyst **1a**; 64% (54:10, **16l**:**16l´**) for catalyst **1b**).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.00 (m, 1H, C$H_{pyranone}$), 2.61–2.55 (m, 2H, CH_2-C=O), 2.31–2.26 (m, 2H, CH_2-C=CHMe), 1.89–1.88 (m, 3H, C$H_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 169.3 (*C*=O), 150.2 (C=*C*OPh), 99.9 (*C*H$_{pyranone}$), 28.5 (*C*H_2-C=O), 18.9 (*C*H_2-C=CHMe), 18.8 (*C*$H_{3,\ Me}$).

5-Methylfuran-2(3*H*)-one (15m).[126] Product obtained from **14m** employing TEA (0.6 mL of a 0.17 M stock solution in H_2O, 0.1 mmol) and catalyst **1a/1b** (0.4 mL of a $2.5 \cdot 10^{-3}$ M stock solution in DMF:H_2O, 10^{-3} mmol) after 12 h at 50 ºC. Yield determined by NMR (38% for catalyst **1a**; 46% for catalyst **1b**).

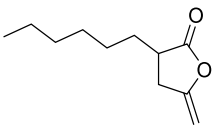


^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.11 (td, *J* = 3.3, 2.0 Hz, 1H, C*H*$_{furanone}$), 3.20–3.09 (m, 2H, C*H*$_{2,\ furanone}$), 1.99 (d, *J* = 2.0, 3H, C*H*$_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.9 (*C*=O), 153.3 (*C*H=*C*OMe), 99.0 (*C*H$_{furanone}$), 34.1 (*C*H$_{2,\ furanone}$), 14.0 (*C*H$_{3,\ Me}$).

4.8 Scale-up of cycloisomerization reaction of 2-(prop-2-yn-1-yl)octanoic acid (14b) in the presence of complex 1b

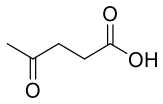
2-(Prop-2-yn-1-yl)octanoic acid **14b** (1.64 mL, 8 mmol), TEA (23 µL, 0.16 mmol), palladacycle **1b** (4.0 mL of a $2.0 \cdot 10^{-4}$ M stock solution in DMF:H_2O 1:239, $8 \cdot 10^{-4}$ mmol) and H_2O (4 mL) were placed in a screw-capped tube. Then, the tube was argon flushed and tightly closed, after which the reaction was stirred for 24 h at room temperature. The reaction mixture was extracted with DCM (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The so-obtained oily residue was purified by flash column chromatography (PE:EtOAc 8:2) to provide lactone **15b**[46] as a colorless oil (1.26 g, 86%).



4.9 Procedure for cycloisomerization/lactone hydrolysis reaction of pent-4-ynoic acid (14a) in the presence of complex 1b

Pent-4-ynoic acid **14b** (100 mg, 1 mmol), TEA (0.6 mL of an aqueous 0.03M solution, 0.02 mmol), palladacycle **1b** (0.4 mL of a $2.5 \cdot 10^{-5}$ M solution in DMF:H_2O

1:1910 for **1b**, 10^{-5} mmol) were placed in a screw-capped tube. Then, the tube was argon flushed and tightly closed, after which the reaction was heated to 50 ºC for 24 h. The reaction mixture was extracted with $CDCl_3$ (2 × 0.5 mL) and dried over anhydrous Na_2SO_4. After filtration, the resulting ketoacid **16**[138] was analyzed by NMR employing 3,4,5-trichloropyridine as internal standard (80%).

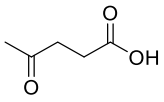


^{1}H-NMR (300 MHz, Chloroform-d) δ 9.25 (s, 1H, O*H*), 2.77 (t, *J* = 6.4 Hz, 2H, C*H*$_2$-COOH), 2.64 (t, *J* = 6.4 Hz, 2H, C*H*$_2$-CO), 2.21 (s, 3H, C*H*$_{3,\ OAc}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 206.8 (*C*=O), 178.4 (*C*OOH), 37.8 (*C*H$_2$-COOH), 29.9 (*C*H$_2$-CO), 27.9 (*C*H$_{3,\ OAc}$).

4.10 Scale-up of cascade reaction of cycloisomerization/lactone hydrolysis reaction of pent-4-ynoic acid (14a) in the presence of complex 1b.

Pent-4-ynoic acid **14a** (1.10 g, 11 mmol), TEA (31 µL, 0.22 mmol), palladacycle **1b** (0.5 mL of a $2.2 \cdot 10^{-4}$ M solution in DMF:H_2O 1:219, $1.1 \cdot 10^{-4}$ mmol) and H_2O (10.5 mL) were placed in a screw-capped tube. Then, the tube was argon flushed and tightly closed, after which the reaction was heated to 50 ºC for 24 h. The reaction mixture was extracted with DCM (3 × 5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The so-obtained oily residue was purified by flash column chromatography (PE:EtOAc 6:4) to provide levulinic acid (**16**) as a colorless oil (998.5 g, 78%).



[138] Yu, H.; Ru, S.; Dai, G.; Zhai, Y.; Lin, H.; Han, S.; Wei, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 3867–3871.

II

Enaminoketones as privileged substrates for cascade and multicomponent reactions

1 INTRODUCTION

1.1 Enaminones: amine exchange/heteroannulation as a tool for heterocycle construction

β-Enaminoketones can be acyclic or cyclic (Figure 2.1) and present interesting electronic features. In fact, their synthetic interest lies in their singularity since, in such a reduce moiety, three nucleophilic and two electrophilic sites are present (Figure 2.2).

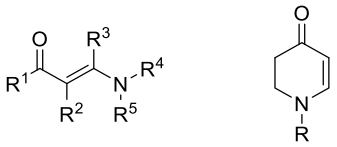


Figure 2.1 General structure of acyclic and cyclic β-enaminoketones.

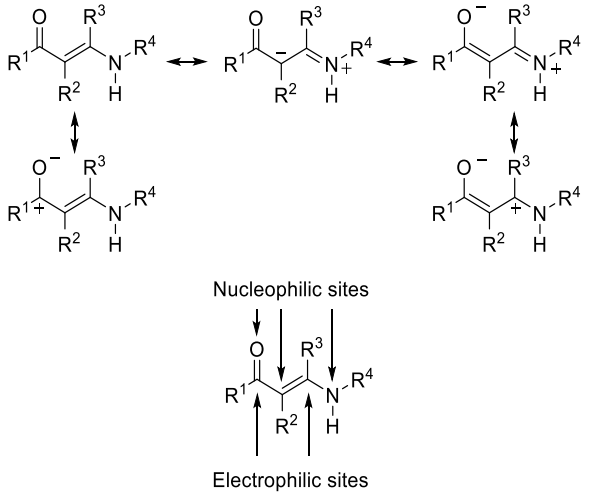
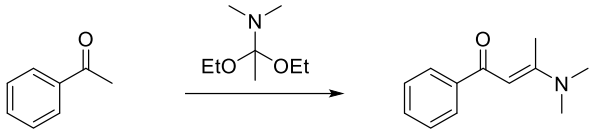


Figure 2.2 Resonant structures and electron-rich and -deficient sites in enaminones.

Concerning enaminoketone synthesis, there are several methodologies to access this moiety, such as ketone aminomethylenation reaction,[1] condensation reactions between 1,3-dicarbonyl compounds and amines,[2] amine or alkyl azide

[1] Cruz, M. C.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377–2380.
[2] Mousavi, S. R.; Sereshti, H.; Nodeh, H. R.; Foroumadi, A. *Appl. Organometal. Chem.* **2019**, *33*, e4644.

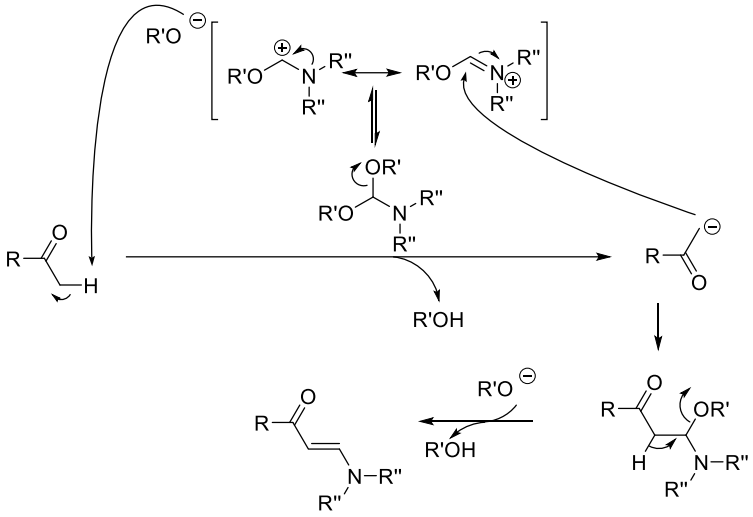
addition to enones,[3,4] ynone hydroamination[5] and some transition-metal catalyzed processes, among others.[6] Aminomethylenation of ketones is probably the most used approach to enaminones on account of the easy-to-handle reactants required and the convenient reaction conditions. Already in 1961, Meerwein and co-workers explored the use of amide dialkyl acetals or ketals as aminomethylenation agents, thus performing the first documented α-functionalization of acetophenone and other ketones with dimethylacetamide diethyl ketal (Scheme 2.1).[7]



Scheme 2.1 Aminomethylenation of acetophenone carried out by Meerwein and co-workers.[7]

The authors proposed the release of alkoxide from the amide dialkyl ketal to explain the formation of the ketone enolate that, after reacting with the aforementioned ketal and upon elimination of alcohol provides the enaminone (Scheme 2.2).

[3] Seko, S.; Miyake, K. *Synth. Commun.* **1999**, *29*, 2487–2492.
[4] Xie, Y. Y.; Wang, Y. C.; Qu, H. E.; Tan, X. C.; Wang, H. S.; Pan, Y. M. *Adv. Synth. Catal.* **2014**, *356*, 3347–3355.
[5] Zeng, R.; Sheng, H.; Rao, B.; Feng, Y.; Wang, H.; Sun, Y.; Chen, M.; Zhu, M. *Chem. Res. Chinese Univ.* **2015**, *31*, 212–217.
[6] Zhu, Z.; Tang, X.; Li, J.; Li, X.; Wu, W.; Deng, G.; Jiang, H. *Chem. Commun.* **2017**, *53*, 3228–3231.
[7] Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1–39.



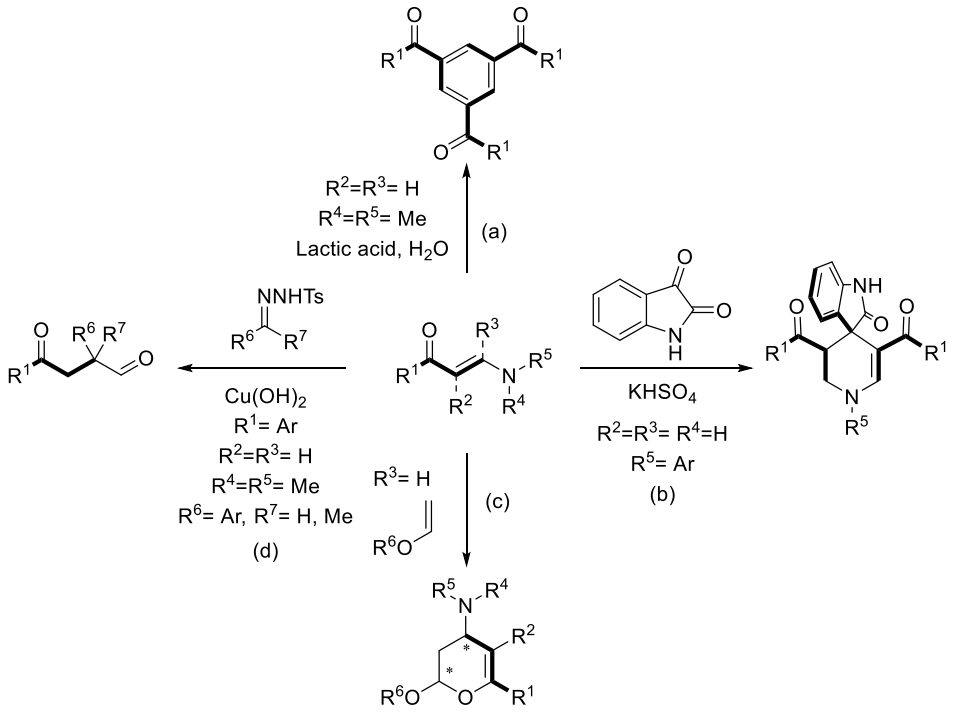
Scheme 2.2 Mechanism for aminomethylation of ketones with amide dialkyl acetals as proposed by Meerwein and co-workers.

As previously commented, 2-aminovinyl ketones are versatile substrates for a number of transformations. A brief summary of some reactions involving the use of these substrates is depicted in Scheme 2.3.

A well-known transformation where enaminones take part is the acid catalyzed cyclotrimerization (a),[8] which constitutes a straightforward access to 1,3,5-triacylbenzenes, which are very useful precursors for the synthesis of complex dendrimers[9] or even supramolecular hosts such as cyclophanes.[10] Furthermore, there are other interesting reactions in literature such as the cyclization between enaminones and isatins (b) to provide strained spirooxindoles,[11] or the preparation of 3-aminosugars (c) carried out by Tietze and co-workers.[12] Recently, a novel approach to 1,4-ketoaldehydes based on an *in-situ* generated transient

[8] Wan, J. P.; Lin, Y.; Hu, K.; Liu, Y. *RSC Adv.* **2014**, *4*, 20499–20505.
[9] Matsuda, K.; Nakamura, N.; Inoue, K.; Koga, N.; Iwamura, H. *Chem. Eur. J.* **1996**, *2*, 259–264.
[10] Pigge, F. C.; Ghasedi, F.; Rath, N. P. *J. Org. Chem.* **2002**, *67*, 4547–4552.
[11] Xu, H.; Zhou, B.; Zhou, P.; Zhou, J.; Shen, Y.; Yu, F. C.; Lu, L. L. *Chem. Commun*., **2016**, *52*, 8002–8005.
[12] Tietze, L. F.; Voß, E. *Tetrahedron Lett.* **1986**, *27*, 6181–6184.

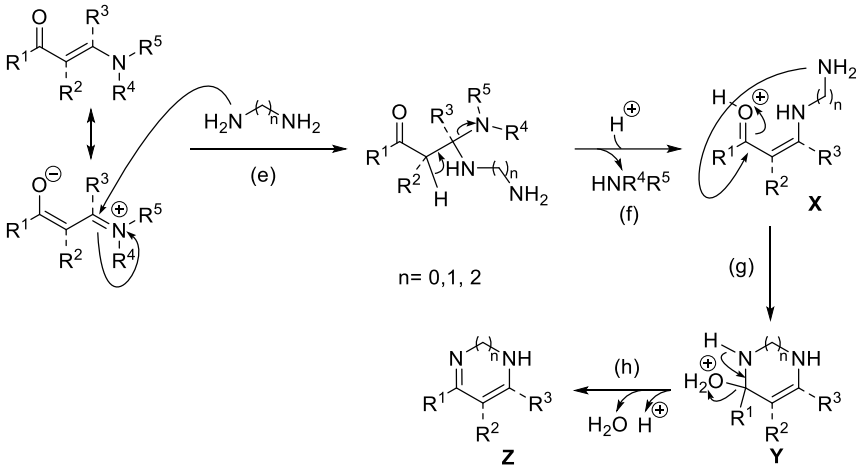
cyclopropane derivative starting from enaminoketones and tosylhydrazones (d), has been published.[13]



Scheme 2.3 Some reactions involving the use of enaminoketones.

Apart from the transformations displayed in Scheme 2.3, there is a wide range of heterocycle-forming reactions with dinucleophiles that proceed *via* an amine-exchange or -displacement + cyclocondensation cascade reaction. This kind of reactions follow a general mechanism depicted below (diamines used as example).

[13] Ni, M.; Zhang, J.; Liang, X.; Jiang, Y.; Loh, T. P. *Chem. Commun.* **2017**, *53*, 12286–12289.

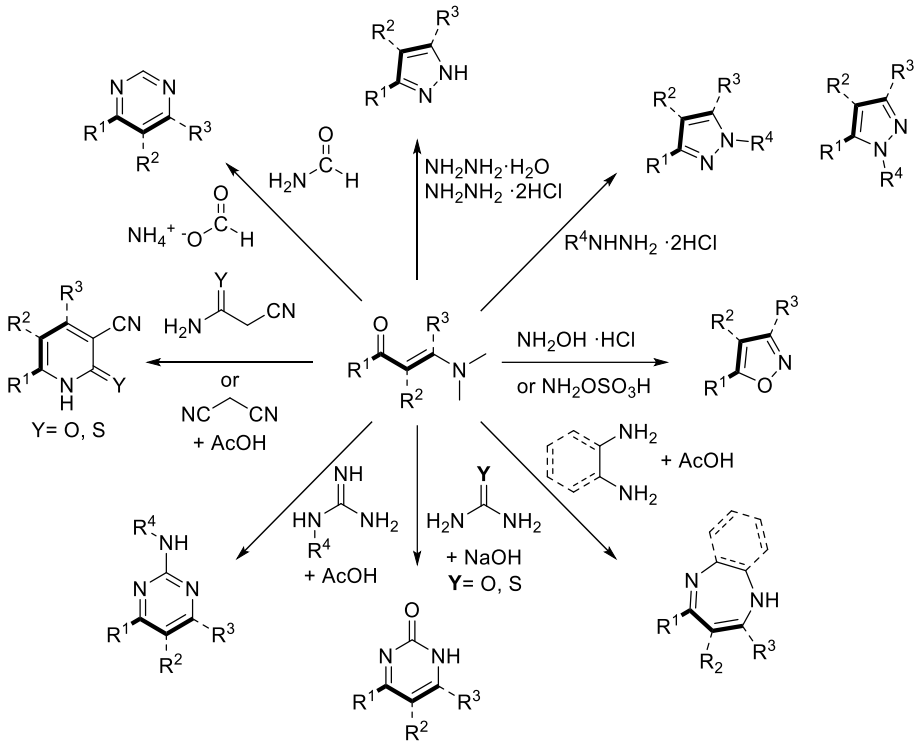


Scheme 2.4 Amine exchange/heterocyclization between enaminones and diamines.

As displayed in Scheme 2.4, a nucleophilic attack at the β-position of the enaminoketone (e) followed by elimination of the corresponding dialkylamine (f) generates a new enaminone intermediate **X**. Then, intramolecular addition to the carbonyl carbon by the remaining amine nucleophile takes place (g), and the so-formed hemiaminal **Y** undergoes dehydration (h) to yield heterocyclic product **Z**. It must be taken into account that depending on the employed nucleophile an acidic catalysis may be needed in order to promote the cyclocondensation step.[14,15] In view of the simplicity of these reactions, it is reasonable to think that they are often used to afford different heterocycles by merely changing the dinucleophile. The synthetic potential of these transformations is outlined in the portfolio displayed in Scheme 2.5:

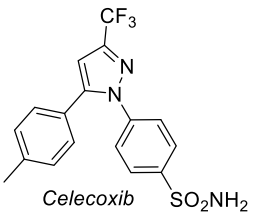
[14] For information about enaminone-based heterocycle construction in acidic media, see: a) Alnajjar, A. A.; Abdelkhalik, M. M.; Al-Enezi, A.; Elnagdi, M. H. *Molecules* **2009**, *14*, 68–77. b) Mohamed, K. S.; El-Sayed, E. H. *Heterocycles* **2018**, *96*, 1897–1909. c) Ribeiro, C. J. A.; Kankanala, J.; Xie, J.; Williams, J.; Aihara, H.; Wang, Z. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 257–261.

[15] For more information on amine exchange in enaminoketones, see: Olivera, R.; SanMartin, R.; Domínguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398–6411.



Scheme 2.5 Synthesis of some heterocycles starting from 2-aminovinyl ketones.

As shown in the Scheme above, enaminoketones offer a straightforward access to a wide number of heterocyclic moieties. For example, the reaction between enaminones and hydrazines leads to pyrazoles,[16] which are present in several drugs such as the well-known



[16] For some examples on the synthesis of pyrazoles from enaminoketones, and applications of these valuable heterocycles, see: a) Masaret, G. S.; Farghaly, T. A. *Curr. Org. Synth.* **2018**, *15*, 126–136. b) Bartual-Murgui, C.; Vela, S.; Roubeau, O.; Aromí, G. *Dalton Trans.* **2016**, *45*, 14058–14062. c) Cumming, J. G.; Debreczeni, J.; Edfeldt, F.; Evertsson, E.; Harrison, M.; Holdgate, G. A.; James, M. J.; Lamont, S. G.; Oldham, K.; Sullivan, J. E.; Wells, S. L. *J. Med. Chem.* **2015**, *58*, 278–293. d) Kunitomo, J.; Yoshikawa, M.; Fushimi, M.; Kawada, A.; Quinn, J. F.; Oki, H.; Kokubo, H.; Kondo, M.; Nakashima, K.; Kamiguchi, N.; Suzuki, K.; Kimura, H.; Taniguchi, T. *J. Med. Chem.* **2014**, *57*, 9627–9643.

cyclooxygenase-2 (COX-2) inhibitor *Celecoxib,* used in the treatment of inflammation of osteoarthritis and rheumatoid arthritis, among other ailments.[17]

Isoxazole is another readily accessible heterocycle coming up from the reaction between aminovinyl ketones and hydroxylamine or (aminooxy)sulfonic acid.[18] The use of other dinucleophiles and related species, such as 1,2-diamines, (thio)ureas, guanidines, cyano(thio)acetamide or formamide + ammonium acetate gives access to (benzo)diazepines,[19] pyrimidine-2-thiones[20] or pyridine-2-ones[21], 2-aminopyrimidines,[22] pyridine-2-thiones[23] or pyridin-2-ones[24] and pyrimidines,[25] respectively.

1.2 Alkyne hydrofunctionalization reactions

In general, hydrofunctionalization reactions can be described as the addition of H-X, where X is any atom except H, to any C-C or C-heteroatom multiple bond.[26] Although this kind of reactions is not new (*e.g.* hydroboration,[27]

[17] Talley, J.; Penning, T. D.; Collins, P. W.; Rogier, D. J. Jr.; Malecha, J. W.; Miyashiro, J. M.; Bertenshaw, S. R.; Khanna, I. K.; Granets, M. J.; Rogers, R. S.; Carter, J. S.; Docter, S. H.; Yu, S., *Substituted pyrazolyl benzenesulfonamides for the treatment of inflammation*. WO 1995/015316, June 8, 1995.

[18] For the synthesis of isoxazoles from enaminones, see: a) Huang, Z.; Matsubara, O.; Jia, S.; Tokunaga, E.; Shibata, N. *Org. Lett.* **2017**, *19*, 934–937. b) RamaRao, R. J.; Rao, A. K. S. B.; Sreenivas, N.; Kumar, B. S.; Murthy, Y. L. N. *J. Korean Chem. Soc.* **2011**, *55*, 243–250. d) Rosa, F. A.; Machado, P.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **2008**, *45*, 879–885.

[19] Moskalenko, A. I.; Boeva, A. V.; Boev, V. I. *Russ. J. Gen. Chem.* **2011**, *81*, 521–528.

[20] Zhou, Y.; Dun, Y.; Fu, H.; Wang, L.; Pan, X.; Yang, X.; Fang, H. *Chem. Biol. Drug Des.* **2017**, *90*, 936–942.

[21] Feng, G. S.; Chen, M. W.; Shi, L.; Zhou, Y. G. *Angew. Chem. Int. Ed.* **2018**, *57*, 5853–5857.

[22] Zhao, H.; Hu, X.; Cao, K.; Zhang, Y.; Zhao, K.; Tang, C.; Feng, B. *Eur. J. Med. Chem.* **2018**, *157*, 935–945.

[23] Ma, F.; Liu, J.; Zhou, T.; Lei, M.; Chen, J.; Wang, X.; Zhang, Y.; Shen, X.; Hu, L. *Eur. J. Med. Chem.* **2018**, *152*, 307–317.

[24] Alberola, A.; Calvo, L. A.; Ortega, A. G.; Ruíz, M. C. S.; Yustos, P.; Granda, S. G.; García-Rodríguez, E. *J. Org. Chem.* **1999**, *64*, 9493–9498.

[25] Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021–3037.

[26] Ananikov, V.; Tanaka, M. *Topics in Organometallic Chemistry: Hydrofunctionalization.* Springer Verlag: Berlin, **2013**.

[27] For additional information about initial hydroboration reactions by 1979 Novel prize laureate Prof. Herbert C. Brown, read: a) Brown, H. C.; Subba Rao, B. C *J. Org. Chem.* **1957**, *22*, 1136–1137. b) Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1957**, *22*, 1137–1138. c) Brown, H. C. *Tetrahedron* **1961**, *12*, 117–138.

hydrohalogenation[28]…), their inherent atom economy has attracted the interest of the scientific community and fostered the development of novel and more efficient transformations.[29] In this section, H-X additions to alkynes will be discussed. In this regard, terms such as: hydrosilylation, for silanes;[30] hydroboration, for boranes;[31] hydroalkoxylation, for alcohols (Scheme 2.6);[32] hydrophosphination, for phosphines;[33] hydroarylation, for arenes;[34] hydroamidation, for amides[35] and hydroamination, for amines (Scheme 2.7),[36] *inter alia,* are ubiquitously found in literature.

[28] For information about classic hydrohalogenation reactions, check: a) Cristol, S. J.; Caple, R. Bridged *J. Org. Chem.* **1966**, *31*, 2741–2748. b) Stille, J. K.; Sonnenberg, F. M.; Kinstle, T. H. *J. Am. Chem. Soc.* **1966**, *88*, 4922–4925. c) Brown, H. C.; Liu, K. T. *J. Am. Chem. Soc.* **1975**, *97*, 600–610. d) Kropp, P. J.; Daus, K. A.; Crawford, S. D.; Tubergen, M. W.; Kepler, K. D.; Craig, S. L.; Wilson, V. P. *J. Am. Chem. Soc.* **1990**, *112*, 7433–7434.

[29] For some reviews on new hydrofunctionalization methodologies, see: a) Hopkinson, M. N.; Tlahuext-Aca, A.; Glorius, F. *Acc. Chem. Res.* **2016**, *49*, 2261–2272. b) Xiao, L.-J.; Ye, M.-C.; Zhou, Q.-L. *Synlett* **2018**, *29*, A-I. c) Ai, W.; Zhong, R.; Liu, X.; Liu, Q. *Chem. Rev.* **2019**, *119,* 2876–2953.

[30] For some examples on hydrosilylation of alkynes, see: a) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2005**, *127*, 17644–17655. b) Sridevi, V. S.; Wai, Y. F.; Weng, K. L. *Organometallics* **2007**, *26*, 1157–1160. c) Mo, Z.; Xiao, J.; Gao, Y.; Deng, L. *J. Am. Chem. Soc.* **2014**, *136*, 17414–17417.

[31] For recent hydroboration examples, read: a) Wu, Y.; Shan, C.; Ying, J.; Su, J.; Zhu, J.; Liu, L. L.; Zhao, Y. *Green Chem.* **2017**, *19*, 4169–4175. b) Mandal, S.; Verma, P. K.; Geetharani, K. *Chem. Commun.* **2018**, *54*, 13690–13693. c) Mamidala, R.; Pandey, V. K.; Rit, A. *Chem. Commun.* **2019**, *55*, 989–992.

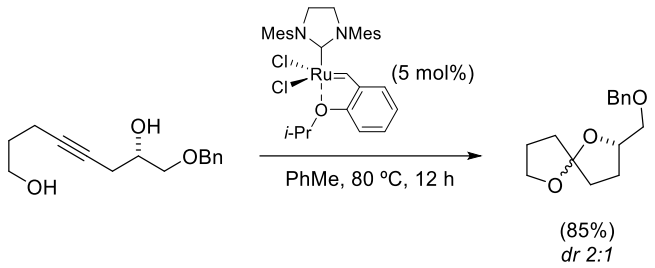
[32] For recent examples of alkyne hydroalkoxylation, see: a) Shibuya, M.; Okamoto, M.; Fujita, S.; Abe, M.; Yamamoto, Y. *ACS Catal.* **2018**, *8*, 4189–4193. b) Alonso-Marañón, L.; Martínez, M. M.; Sarandeses, L. A.; Gómez-Bengoa, E.; Pérez Sestelo, J. *J. Org. Chem.* **2018**, *83*, 7970–7980. c) Iio, K.; Sachimori, S.; Watanabe, T.; Fuwa, H. *Org. Lett.* **2018**, *20*, 7851–7855. d) Jean, A.; Rouden, J.; Maddaluno, J.; De Paolis, M.; Blanchet, J. *Tetrahedron Lett.* **2019**, *60*, 534–537.

[33] For examples on hydrophosphination of acetylenes, see: a) King, A. K.; Gallagher, K. J.; Mahon, M. F.; Webster, R. L. *Chem. Eur. J.* **2017**, *23*, 9039–9043. b) Ackley, B. J.; Pagano, J. K.; Waterman, R. *Chem. Commun.* **2018**, *54*, 2774–2776. c) Coles, N. T.; Mahon, M. F.; Webster, R. L. *Chem. Commun.* **2018**, *54*, 10443–10446.

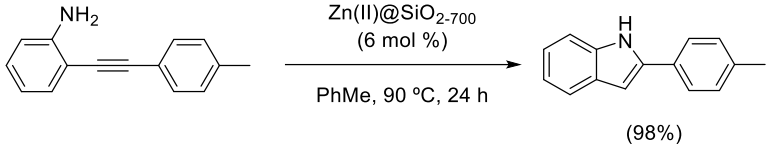
[34] Hydroarylation of alkynes is described in: a) Wang, Z.; Zhu, L.; Zhong, K.; Qu, L.-B.; Bai, R.; Lan, Y. *ChemCatChem* **2018**, *10*, 5280–5286. b) Selmani, S.; Vanderzwet, L.; Kukor, A.; Schipper, D. *Synlett* **2018**, *29*, 2552–2556. c) Blons, C.; Mallet-Ladeira, S.; Amgoune, A.; Bourissou, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 11732–11736.

[35] For alkyne hydroamidation, read: a) Panda, N.; Mothkuri, R. *J. Org. Chem.* **2012**, *77*, 9407–9412. b) Nayak, S.; Ghosh, N.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 2996–2999. c) Pathare, R. S.; Sharma, S.; Elagandhula, S.; Saini, V.; Sawant, D. M.; Yadav, M.; Sharon, A.; Khan, S.; Pardasani, R. T. *Eur. J. Org. Chem.* **2016**, *2016*, 5579–5587. d) Tao, Y.; Gilbertson, S. R. *Chem. Commun.* **2018**, *54*, 11292–11295.

[36] For some examples on alkyne hydroaminations, see: a) Dagar, A.; Guin, S.; Samanta, S. *Asian J. Org. Chem.* **2018**, *7*, 123–127. b) Rode, N. D.; Arcadi, A.; Chiarini, M.; Marinelli, F.; Portalone, G. *Adv. Synth. Catal.* **2017**, *359*, 3371–3377. c) Lui, E. K. J.; Brandt, J. W.; Schafer, L. L. *J. Am. Chem. Soc.* **2018**, *140*, 4973–4976. d) Cook, A. K.; Copéret, C. *Organometallics* **2018**, *37*, 1342–1345. e) Jillella, R.; Oh, C. H. *RSC Adv.* **2018**, *8*, 22122–22126.

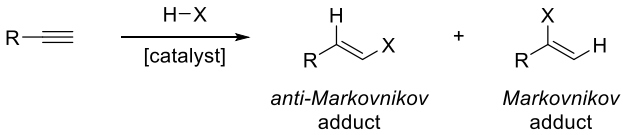


Scheme 2.6 Fuwa and co-workers published spiroketal formation *via* a cascade alkyne/alkene hydroalkoxylation.[32c]



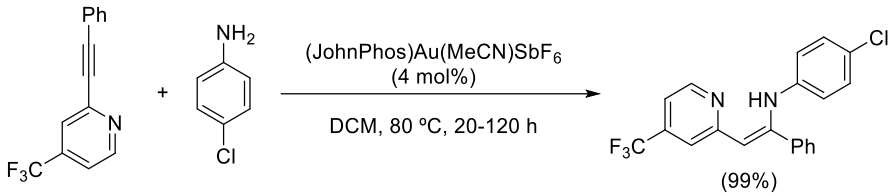
Scheme 2.7 Silica-supported Zn(II)-catalyzed intramolecular hydroamination of *o*-alkynylaniline by Copéret and collaborators.[36d]

As expected, when those additions occur over non-symmetric alkynes (including terminal acetylenes), two adducts (Scheme 2.8) may form, *i.e.* Markovnikov and anti-Markovnikov products, concretely. Therefore, regioselectivity problems may happen and hence, new regioselective protocols are increasingly published (*e.g.* Scheme 2.9).[37]



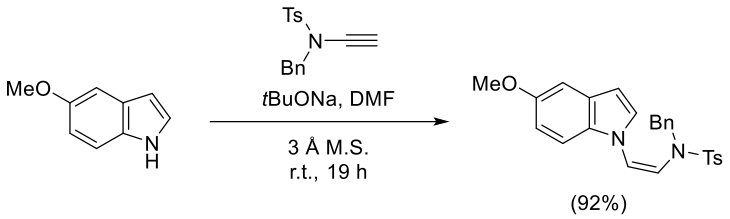
Scheme 2.8 Possible regioisomer formation during alkyne hydrofunctionalization reactions.

[37] For examples on regioselective hydroamination processes, read: a) Yim, J.C.-H.; Schafer, L. L. *Eur. J. Org. Chem.* **2014**, *2014*, 6825–6840. b) Manan, R. S.; Zhao, P. *Nat. Commun.* **2016**, *7*, 11506. c) Cacchi, S.; Fabrizi, G.; Fochetti, A.; Ghirga, F.; Goggiamani, A.; Iazzetti, A. *Org. Biomol. Chem.* **2019**, *17*, 527–532.



Scheme 2.9 Gold(I)-catalyzed regio- and stereoselective hydroamination of *o*-alkynylpyridines published by Cacchi *et al*.[37c]

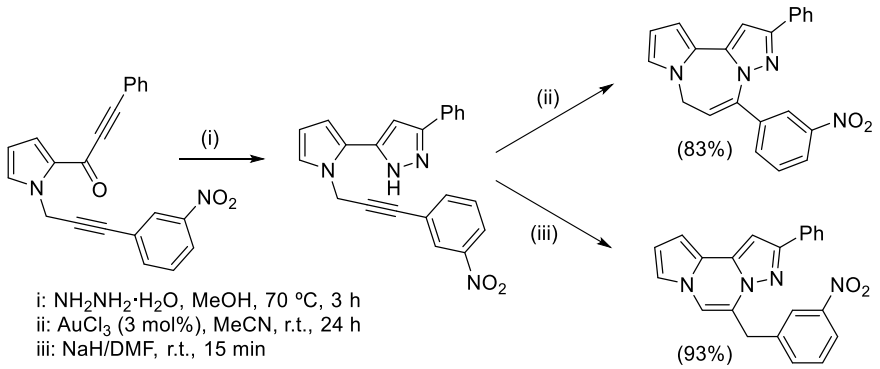
Alkyne hydroamination reactions have been carried out employing very different catalysts (transition-metals as Lewis acids, or organic[38] (Scheme 2.10) and inorganic bases).[39] This kind of transformations gains relevance when the nucleophile is an *N*-heterocycle, thus giving access to *N*-vinylated heterocycles.[38b-40]



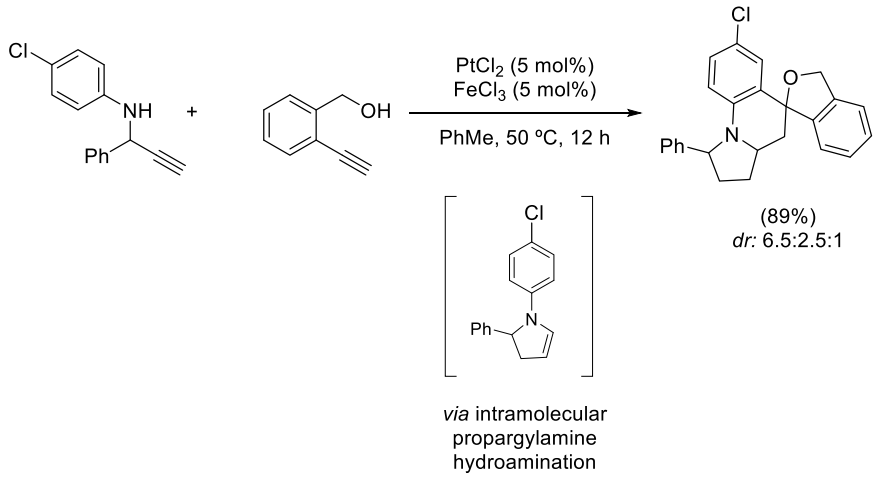
Scheme 2.10 Sodium *tert*-butoxide-promoted hydroamination of ynamides by Dodd and col.[38b]

These hydroamination reactions become even more interesting when involved in ring-closing steps[41] (Scheme 2.11) or in cascade processes[42] leading to complex heterocycles (Scheme 2.12).

[38] For some examples on organic base-promoted hydroaminations, see: a) Imahori, T.; Hori, C.; Kondo, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090–1092. b) Hentz, A.; Retailleau, P.; Gandon, V.; Cariou, K.; Dodd, R. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8333–8337.
[39] For some examples on inorganic base promoted hydroamination, read: a) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193–6195. b) Lu, L.; Yan, H.; Liu, D.; Rong, G.; Mao, J. *Chem. Asian J.* **2014**, *9*, 75–78.
[40] For a complete review on base mediated hydroamination, read: Patel, M.; Saunthwal, R. K.; Verma, A. K. *Acc. Chem. Res.* **2017**, *50*, 240–254.
[41] Hydroamination as a ring-closing tool, read: a) Basceken, S.; Balci, M. *J. Org. Chem.* **2015**, *80*, 3806–3814. b) Basceken, S.; Kaya, S.; Balci, M *J. Org. Chem.* **2015**, *80*, 12552–12561. c) Aslanoglu, F.; Basceken, S.; Balci, M. *Tetrahedron Lett.* **2019**, *60*, 449–451.
[42] For some recent cascade reactions involving hydroamination steps, refer to: a) Wang, H.; Wang, C.; Huang, K.; Liu, L.; Chang, W.; Li, J. *Org. Lett.* **2016**, *18*, 2367–2370. b) Wang, L.; Liu, L.; Chang, W.; Li, J. *J. Org. Chem.* **2018**, *83*, 7799–7813. c) Mishra, M.; Twardy, D.; Ellstrom, C.; Wheeler, K. A.; Dembinski, R.; Török, B. *Green Chem.* **2019**, *21*, 99–108.



Scheme 2.11 Two-step access to pyrazolopyrrolopyrazines and pyrazolopyrrolodiazepines published by Balci and co-workers.[41a]

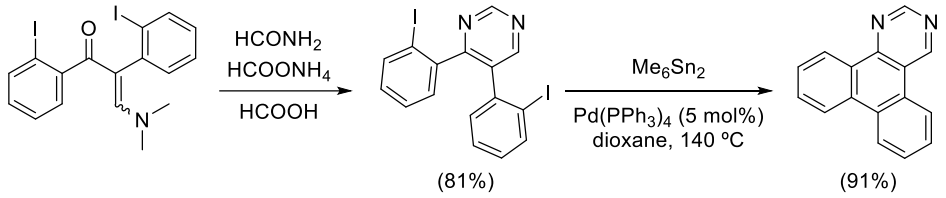


Scheme 2.12 Cascade alkyne hydroamination/hydroalkoxylation/pseudo-Povarov cyclization published by Wang et al.

1.3 Background of the research group

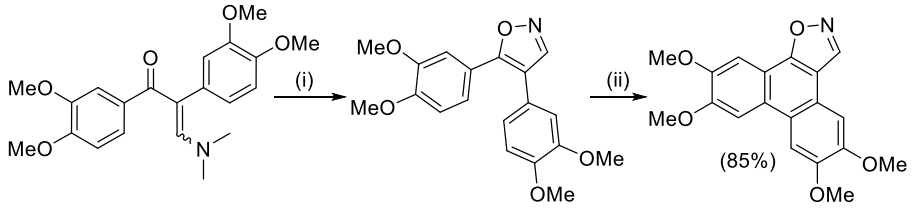
Our group has a long track record of applying amine-exchange reactions from enaminoketones to the synthesis of heterocycles, as well as of developing new alkyne hydrofunctionalization procedures. 4,5-Diarylpyrimidines were readily

prepared from enaminones derived from deoxybenzoins,[43] and then coupled to synthesize phenanthropyrimidines (Scheme 2.13).[44]



Scheme 2.13 Diarylpyrimidines and phenanthropyrimidines from enaminoketones.[44a]

Moreover, our group was able to synthesize not just 4,5-diarylisoxazoles[15,45] but also 4,5-diarylpyrazoles,[46] and upon intramolecular oxidative coupling phenanthroisoxazoles[47] and 1-aryl-1*H*-dibenzoindazoles were obtained, respectively (Scheme 2.14).[46,47]



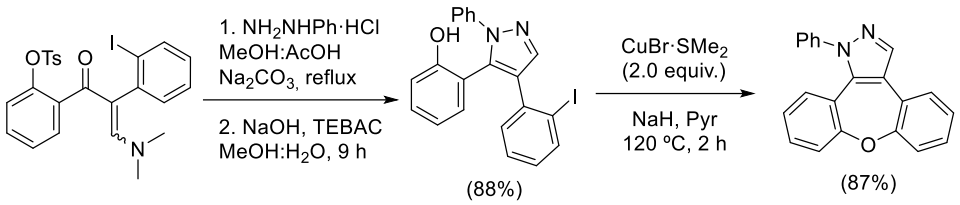
(i) $NH_2OH{\cdot}HCl$, MeOH:AcOH, Na_2CO_3, reflux

(ii) PIFA, $BF_3{\cdot}Et_2O$, DCM, -40 ºC

Scheme 2.14 Two-step approach to phenanthro[9,10-*d*]isoxazoles.

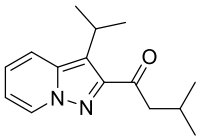
Two alternative, straightforward routes leading to dibenzooxepinopyrazoles were also devised by our group, using this time Ullmann ether condensation[48] and intramolecular Buchwald-Hartwig *O*-arylation reactions (Scheme 2.15).[49]

[43] Domínguez, E.; Martínez de Marigorta, E.; Olivera, R.; SanMartín, R. *Synlett* **1995**, *1995*, 955–956.
[44] a) Olivera, R., Pascual, S., Herrero, M., SanMartin, R., Domínguez, E. *Tetrahedron Lett*. **1998**, *39*, 7155–7158. b) Olivera, R.; SanMartin, R.; Pascual, S.; Herrero, M.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479–3480.
[45] For information about diarylisoxazole synthesis and structure, read: a) Domínguez, E.; Ibeas, E.; De Marigorta, E. M.; Palacios, J. K.; SanMartín, R *J. Org. Chem.* **1996**, *61*, 5435–5439. b) Sanmartin, R.; Olivera, R.; Domínguez, E.; Solans, X.; Font-bardia, M.; Urtiaga, M. K. *Cryst. Res. Technol.* **1997**, *32*, 1015–1020.
[46] Olivera, R.; SanMartin, R.; Dominguez, E. A *J. Org. Chem.* **2000**, *65*, 7010–7019.
[47] Olivera, R.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Tetrahedron* **2002**, *58*, 3021–3037.
[48] Olivera, R.; SanMartin, R.; Domínguez, E. *Tetrahedron Lett.* **2000**, *41*, 4353–4356.
[49] Olivera, R.; Sanmartin, R.; Domínguez, E. A *Tetrahedron Lett.* **2000**, *41*, 4357–4360.

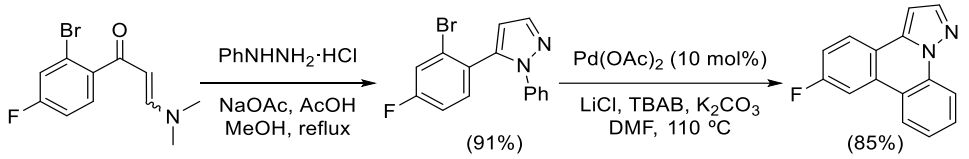


Scheme 2.15 Synthetic route leading to dibenzo[2,3:6,7]oxepino[4,5-*c*]pyrazoles by means of intramolecular ether formation.

On the other hand, acetophenone-derived enaminones were the key for the access to diarylisoxazoles and pyrazolophenanthridines[50,51] (Scheme 2.16) akin to currently marketed drugs such as *Celecoxib* or *Ibudilast.*[52]



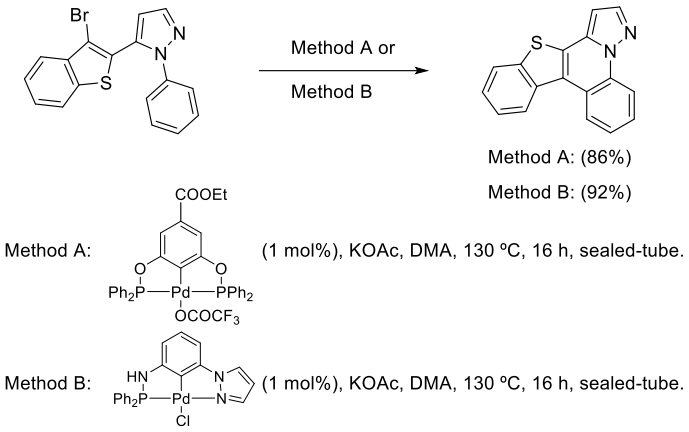
Ibudilast



Scheme 2.16 Synthesis of pyrazolo[1,5-*f*]phenanthridines.

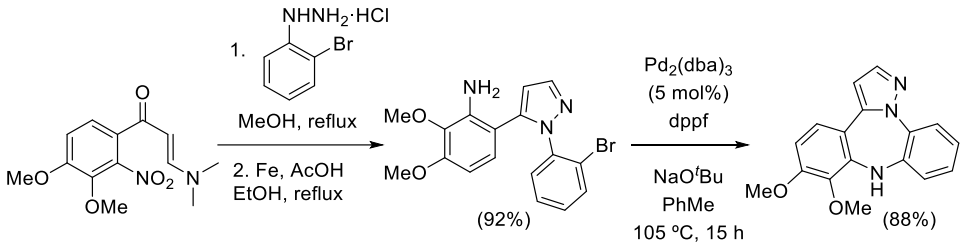
An analogous strategy was adopted to transform 3-halo(benzo)thienyl methyl ketones into (benzo)thienopyrazoloquinolines (Scheme 2.17). In this case, in addition to Jeffrey´s ligand free conditions, a bis(phosphinite) PCP palladium pincer complex and a non-symmetric PCN palladacycle were employed as advantageous palladium sources for the final direct arylation step.[53]

[50] Hernández, S.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett.* **2003**, *5*, 1095–1098.
[51] Hernández, S.; Moreno, I.; SanMartin, R.; Gómez, G.; Herrero, M. T.; Domínguez, E. *J. Org. Chem.* **2010**, *75*, 434–441.
[52] For additional information on Ibudilast, read: a) Irikura, T. T.; Hayashi, M. A.; Koshirae, K.; Kudo, Y.; Hatayama, J. K.; Hetsugi, E. U. *Blood vessel dilating 3-acy-2-alkylpyrazolo[1,5-a]pyridines.* DE 2315801, October 11, 1973. b) Fox, R. J.; Coffey, C. S.; Conwit, R.; Cudkowicz, M. E.; Gleason, T.; Goodman, A.; Klawiter, E. C.; Matsuda, K.; McGovern, M.; Naismith, R. T.; *et al. N. Engl. J. Med.* **2018**, *379*, 846–855. c) Baldassari, L. E.; Fox, R. J. *Drugs*., **2018**, *78*, 1549–1566.
[53] Churruca, F.; Hernández, S.; Perea, M.; SanMartin, R.; Domínguez, E. *Chem. Commun.* **2013**, *49*, 1413–1415.



Scheme 2.17 Route to (benzo)thieno[2,3-*c*]pyrazolo[1,5-*a*]quinolines.

Enaminones derived from *o*-nitroacetophenones were starting materials for the synthesis of dibenzopyrazolodiazepines. In this regard, a palladium-catalyzed intramolecular *N*-arylation served to cyclize *o*-amino-*o'*-bromodiarylpyrazole intermediates (Scheme 2.18).[54]

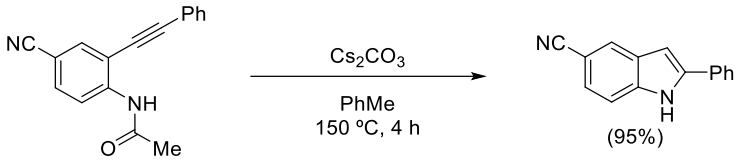


Scheme 2.18 Access to dibenzo[*b,f*]pyrazolo[1,5-*d*][1,4]diazepines by Hernández *et al.*

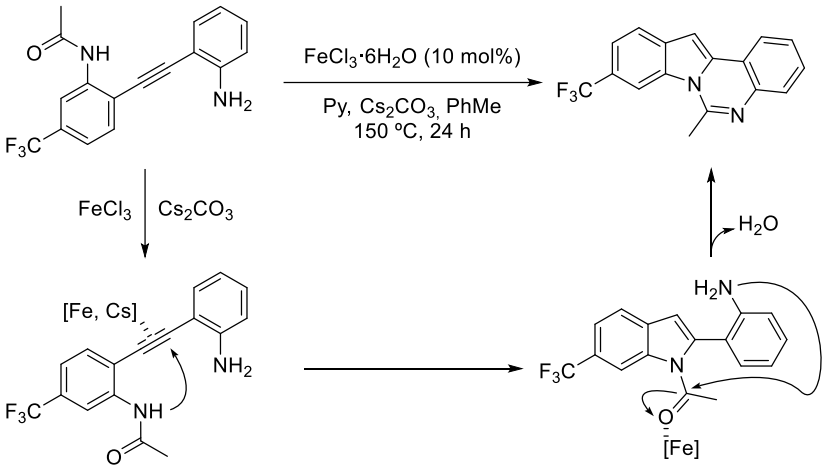
Besides, as mentioned before, our group has gained experience in alkyne hydrofunctionalization reactions, especially in alkyne hydroamidation, hydrophenoxylation and some cascade reactions involving them.[55,56] Indeed, a cesium carbonate-promoted hydroamidation provided an easy access to *N*-

[54] Hernández, S.; Moreno, I.; SanMartin, R.; Herrero, M. T.; Domínguez, E. *Org. Biomol. Chem.* **2011**, *9*, 2251–2257.
[55] Herrero, M. T.; De Sarralde, J. D.; Sanmartin, R.; Bravo, L.; Domínguez, E. *Adv. Synth. Catal.* **2012**, *354*, 3054–3064.
[56] Moure, M. J.; SanMartin, R.; Domínguez, E *Adv. Synth. Catal.* **2014**, *356*, 2070–2080.

alkenylamides and C2-substituted indoles (Scheme 2.19). In the same paper, a cooperative catalytic system combining Cs_2CO_3 and $FeCl_3 \cdot 6H_2O$ enabled a cascade alkyne hydroamidation/heteroannulation leading to the indolo[1,2-*c*]quinazoline core (Scheme 2.20).[55]

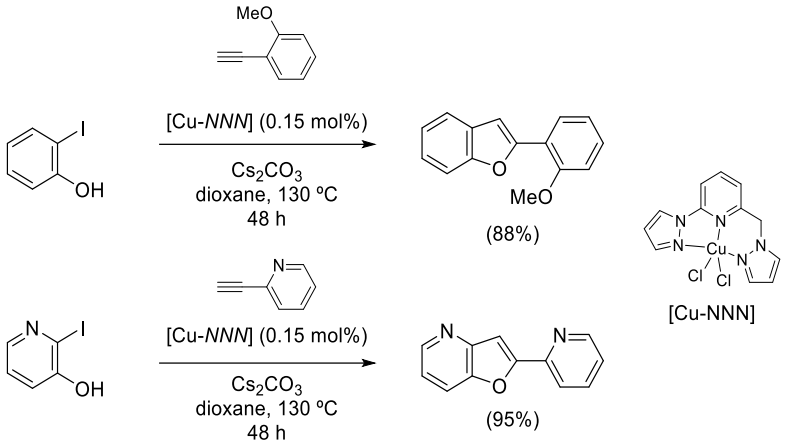


Scheme 2.19 Intramolecular hydroamidation of alkynes by Herrero *et al*.



Scheme 2.20 Cascade hydroamidation/heteroannulation to indolo[1,2-*c*]quinazolines.

A novel copper NNN-type pincer catalyst for the heteroannulation between alkynes and *o*-halophenols was also presented by our group. Regarding the reaction mechanism, two alternative pathways involving either initial Sonogashira/Castro-Stephens coupling or hydroalkoxylation steps were proposed (Scheme 2.21).[56]



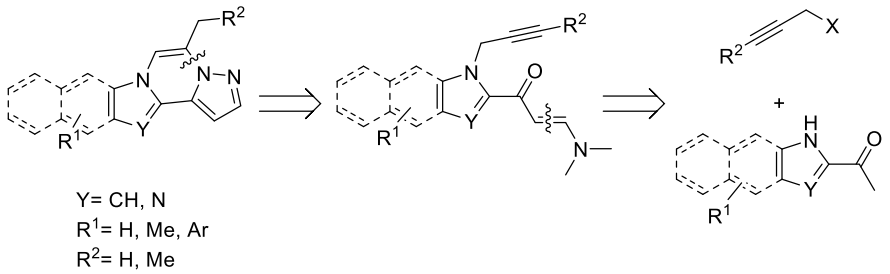
Scheme 2.21 One-pot access to C2-substituted benzo[*b*]furans and furo[3,2-*b*]pyridines by Moure *et al*.

Taking into account our group's background in the synthesis of enaminoketones and their use for the preparation of heterocycles, as well as in alkyne hydrofunctionalization reactions together with cascade processes, we envisaged the possibility of merging this knowledge for new transformations involving a one-pot amine-exchange/heteroannulation/alkyne hydroamination process.

2 AIMS AND OBJECTIVES

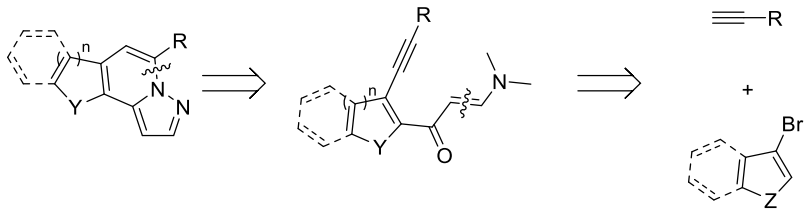
In view of the synthetic possibilities provided by enaminoketones and by hydrofunctionalization reactions, we propose:

- The access to several of pyrazolo-fused *N*-heterocyclic cores *via* a cascade reaction based on amine-exchange + heteroannulation + alkyne hydroamination processes (Scheme 2.22 and Scheme 2.23):



Y= CH, N
R^1= H, Me, Ar
R^2= H, Me

Scheme 2.22 Retrosynthetic analysis of fused pyrazolopyrazine derivatives.

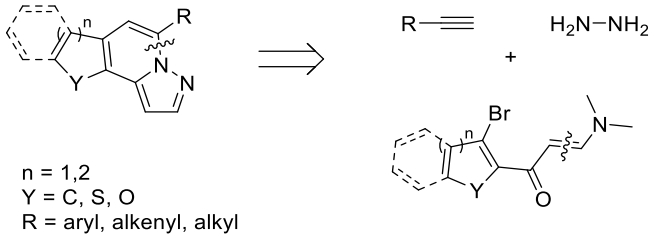


n= 1,2
Y= CH, S, O
R= aryl, alkenyl, alkyl

Z= O, S

Scheme 2.23 Retrosynthetic analysis of pyrazoloheterocycles.

- A multicomponent reaction using suitably functionalized enaminoketones, alkynes and hydrazine that would lead to similar pyrazoloheterocycles (Scheme 2.24).



n = 1,2
Y = C, S, O
R = aryl, alkenyl, alkyl

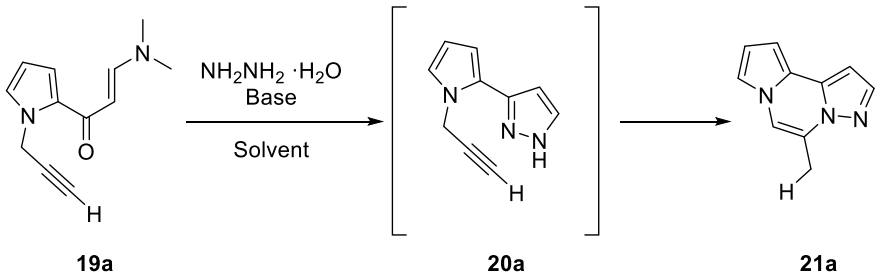
Scheme 2.24 Alternative retrosynthetic analysis of pyrazoloheterocycles.

3 RESULTS AND DISCUSSION

3.1 Initial hypothesis and substrate preparation

As previously mentioned (page 121), Balci and col. reported a two-step strategy for the synthesis of 5-sustituted pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazines. In that work, a previously prepared alkynone underwent a hydroamination + cyclocondensation reaction in the presence of hydrazine hydrate to afford the corresponding pyrazole. Upon purification, the latter compound was treated with a strong base (NaH) so that base-promoted hydroamination took place leading to the *6-endo-dig* cyclization product. Besides, when the same pyrazolyl pyrrol intermediate was treated with $AuCl_3$ (3 mol%), a gold-catalyzed hydroamination provided the 7-*endo-dig* cyclization product (Scheme 2.11, page 121).

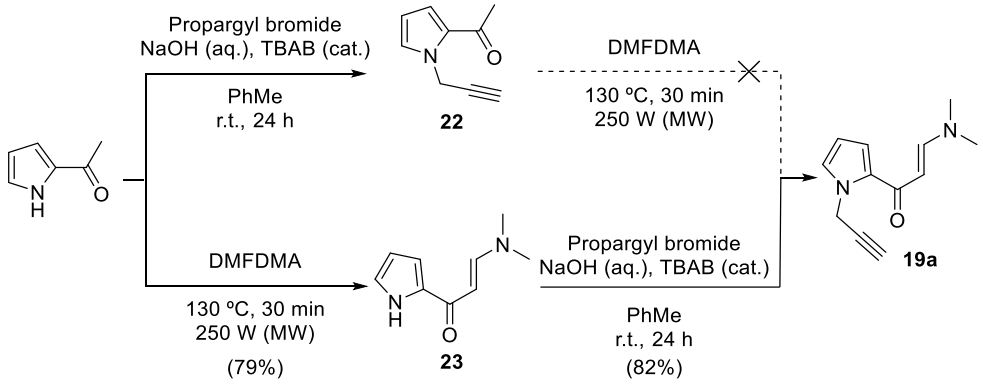
Following the aims outlined in the previous section (page 127), we decided to attempt a one-pot approach to 5-methylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine **21a** by reacting *N*-propargylated enaminoketone **19a** with hydrazine. A cascade amine-exchange/heterocyclization/intramolecular hydroamination based on the formation of a pyrazolyl intermediate akin to **20a** was intended to take place (Scheme 2.25).



Scheme 2.25 Proposed cascade reaction from enaminoketone **19a**.

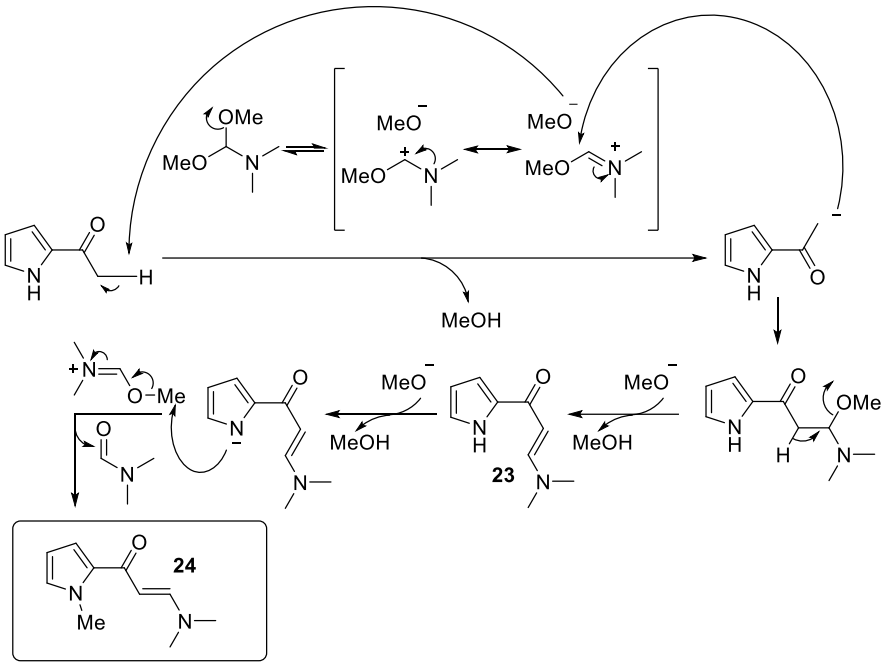
To begin with, two alternative routes were proposed to prepare key substrate **19a**: either i) propargylation of 2-acetylpyrrole followed by an aminomethylenation reaction, or ii) just the other way round.

As shown in Scheme 2.26, the propargylation of 2-acetylpyrrole with propargyl bromide proceeded smoothly (**22**), yet the subsequent aminomethylenation reaction ended in product degradation. Hence, the first synthetic route was discarded. On the other hand, aminomethylenation of 2-acetylpyrrole with dimethylformamide dimethyl acetal (DMFDMA) was achieved with good yield (**23**, 79%) under microwave irradiation after reducing the amount of the *N*-methylated side-product **24**. Indeed, *N*-alkylation of heterocycles with Vilsmeier-Haack reagents has been already described,[57] and the presence of this undesired side-product was minimized by optimization of the DMFDMA amount. A tentative mechanism to explain the formation of **24** under reaction conditions is displayed in Scheme 2.27. Enaminoketone **23** was propargylated to render target *N*-propargyl enaminoketone **19a** in excellent yield when carrying out the reaction under phase transfer conditions. Briefly, the compound **19a** was easily obtained by a two-step sequence in an overall yield of 65% (Scheme 2.26).



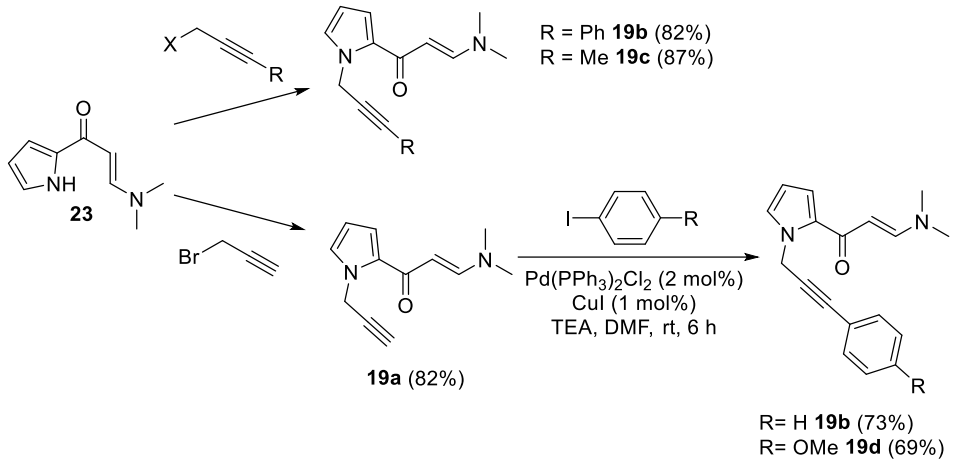
Scheme 2.26 Synthesis of *N*-propargyl pyrrolyl enaminone **19a**.

[57] Loidreau, Y.; Melissen, S.; Levacher, V.; Logé, C.; Graton, J.; Le Questel, J. Y.; Besson, T. *Org. Biomol. Chem.* **2012**, *10*, 4916–4925.



Scheme 2.27 A proposal to explain the formation of by-product **24**.

In conjunction with the initial screening of reaction conditions for the planned cascade reaction, the synthesis of two analogues of **19a** was devised following the same method (initial aminomethylenation of 2-acetylpyrrole followed by propargylation with 3-haloprop-1-ynes other than propargyl bromide). As shown in Scheme 2.28, enaminoketones **19b-c** were prepared with good yields. In addition, *N*-phenylpropargylated enaminone **19b** and *p*-methoxyphenyl propargyl derivative **19d** were also prepared by Sonogashira coupling of terminal alkyne **19a** with iodobenzene and *p*-methoxybromobenzene, respectively.

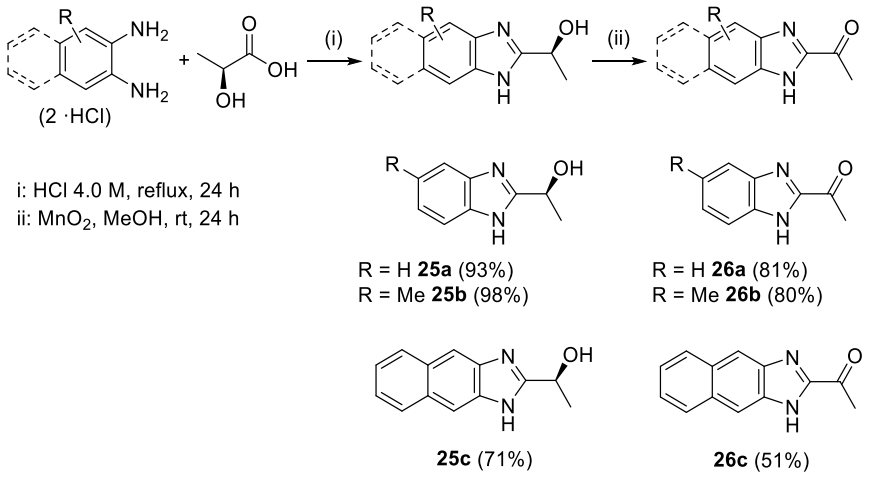


Scheme 2.28 Synthesis of *N*-propargylated enaminones **19**.

All the knowledge acquired from the synthesis of pyrrol derivatives **19** came in handy for the preparation of other propargylated or alkynylated enaminoketones, which could be substrates susceptible to similar transformations. In this regard, considering the similarity between the pyrrole and imidazole frameworks, a closely related approach to *N*-propargylated enaminones derived from 2-acetylbenzimidazoles was devised. The synthesis began with the condensation of commercially available *o*-arylidenediamines and (*L*)-lactic acid[58] followed by oxidation of the corresponding carbinols **25a-c** with activated MnO_2 to obtain the desired ketones **26a-c** (Scheme 2.29).[59]

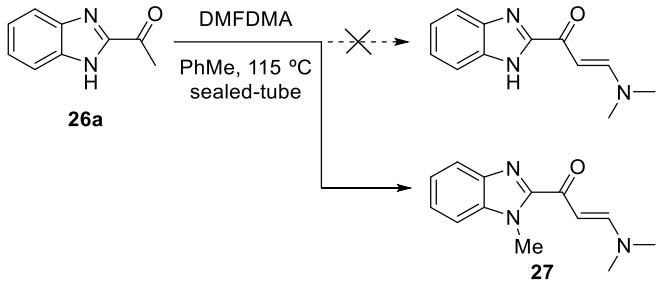
[58] For the preparation of benzimidazoles from phenylene diamine and lactic acid, see: Hayes, M. E.; Wallace, G. A.; Grongsaard, P.; Bischoff, A.; George, D. M.; Miao, W.; McPherson, M. J.; Stoffel, R. H.; Green, D. W.; Roth, G. P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1573–1576. b) Hsu, M. H.; Hsu, S. M.; Kuo, Y. C.; Liu, C. Y.; Hsieh, C. Y.; Twu, Y. C.; Wang, C. K.; Wang, Y. H.; Liao, Y. J. *RSC Adv.* **2017**, *7*, 16253–16263.

[59] Mild oxidation of benzyl alcohol by means of activated manganese dioxide is a well-known procedure. See for example: a) Varma, R. S.; Saini, R. K.; Dahiya, R. *Tetrahedron Lett.* **1997**, *38*, 7823–7824. b) Lai, T. K.; Banerji, J.; Chatterjee, A.; Basak, B. *Indian J. Chem. Sect. B Org. Med. Chem.* **2005**, *44*, 1309–1311. c) Potapov, V. A.; Yaroshenko, T. I.; Panov, V. A.; Musalov, M. V.; Khabibulina, A. G.; Musalova, M. V.; Amosova, S. V. *Russ. J. Org. Chem.* **2016**, *52*, 1733–1737.



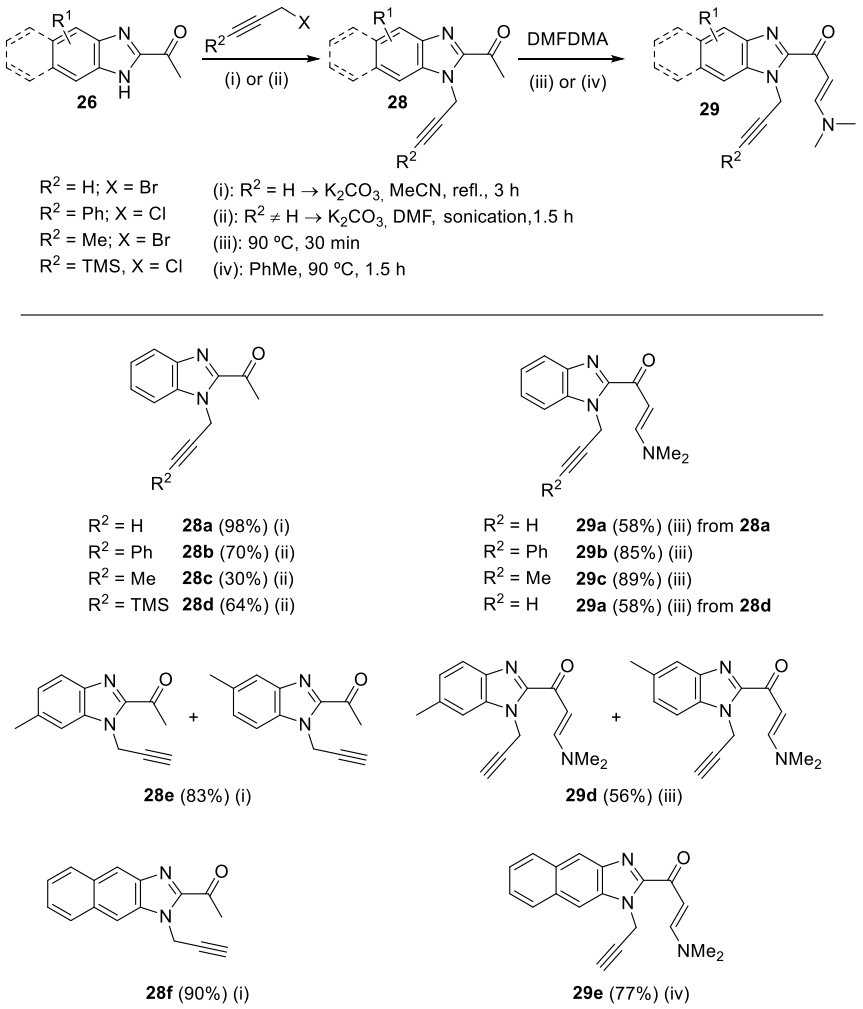
Scheme 2.29 Preparation of 2-benzimidazoyl ethanones **26**.

In contrast with pyrrole derivatives **19**, where we were obliged to carry out the aminomethylenation prior to the propargylation step, reaction of 2-benzimidazoyl ethanone **26a** with DMFDMA provided almost completely *N*-methylated enaminoketone **27** (Scheme 2.30), probably owing to a side reaction analogous to that leading to enaminone **24** (Scheme 2.27).



Scheme 2.30 Formation of by-product **27**.

Therefore, in order to prepare several *N*-propargylated enaminoketones **29** derived from 2-acetylbenzimidazoles **26**, an initial propargylation with propargyl halides followed by aminomethylenation with DMFDMA was carried out (Scheme 2.31).

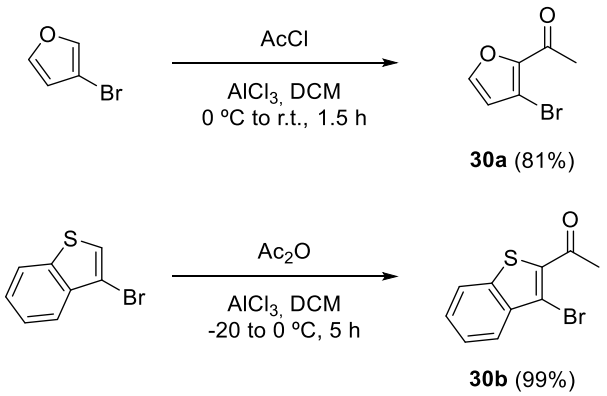


Scheme 2.31 *N*-Propargylation and aminomethylenation leading to enaminoketones **29**.

Depending on the propargyl halide employed, different conditions [(i) or (ii)] were required to obtain propargyl ketones **28** with good yields. In this regard, the formation of a mixture of regioisomers **28e** by propargylation of 5-methylbenzimidazolylethanone **26b** cannot be ignored. This expected result is due to the tautomeric equilibrium of *N*-H benzimidazoles. Anyway, we decided to continue the route and thus react *N*-propargylated ketones **28** with DMFDMA. In most cases, heating with neat DMFDMA provided enaminones **29** with moderate

to good yields. However, aminomethylenation of naphthoimidazole derivative **28f** required the addition of toluene as solvent (**29e**, 77%, Scheme 2.31). It should be also pointed out the desilylation process observed in the transformation **28d**→**29a**. The latter enaminone was obtained with the same yield from *N*-propargyl derivative **28a** and from trimethylsilylpropargyl derivative **28d** (58%).[60]

In addition to the preparation of the *N*-propargylated heterocyclic enaminoketones **19** and **29**, we envisaged that other enaminones derived from 2-alkynyl(hetero)aryl methyl ketones might serve as substrates for the aimed cascade amine exchange/heterocyclization/intramolecular hydroamination reaction. Therefore, after preparing 2-acetyl-3-bromofuran and -benzothiophen derivatives **30a** and **30b** respectively by a simple Friedel-Crafts acylation with acetyl chloride and acetic anhydride (Scheme 2.32), these two ketones and other commercially available 2-bromo(hetero)aryl methyl ketones were subjected to Sonogashira cross-coupling conditions, thus providing the 2-alkynyl(hetero)aryl methyl ketones **31** displayed in Table 2.1.



30a (81%)

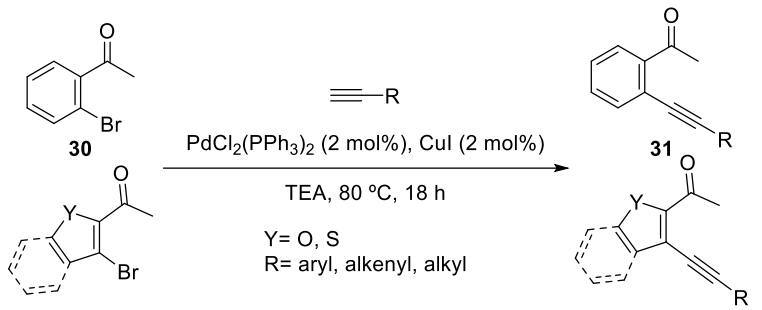
30b (99%)

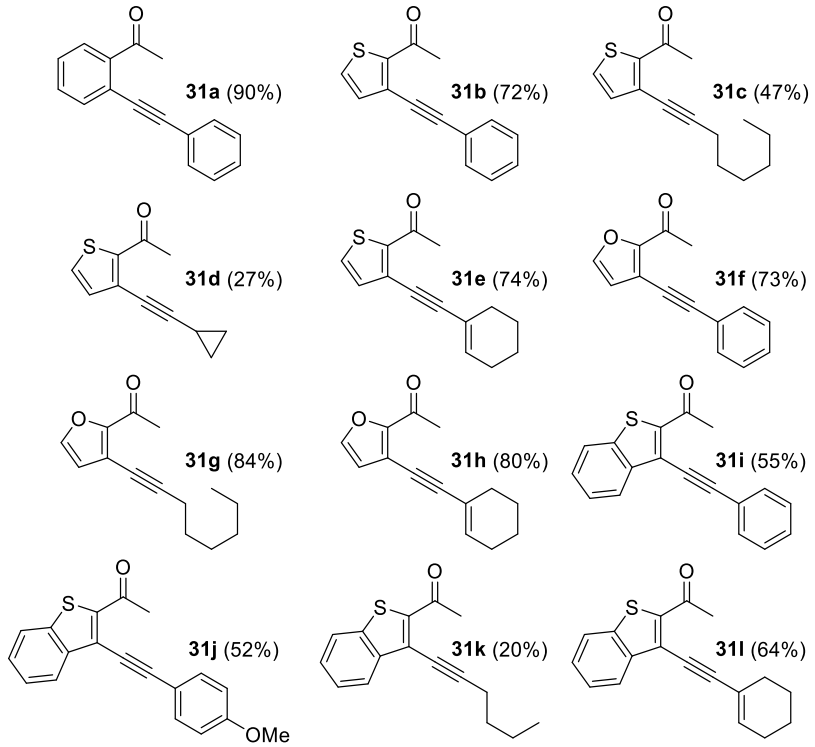
Scheme 2.32 Friedel-Crafts acylation of 3-bromofuran and 3-bromobenzo[*b*]thiophene.

[60] As far as we know, there are only two examples in literature of deprotection of silylated alkynes during aminomethylenation processes: a) Richard, J. A.; Chen, D. Y.-K. *Eur. J. Org. Chem.* **2012**, *2012*, 484–487. b) Kaura, M.; Hrdlicka, P. J. *Org. Biomol. Chem.* **2015**, *13*, 7236–7247.

Except for the formation of 3-octynylated derivatives **31c** and **31g**, the coupling with alkylacetylenes provided lower yields in comparison with arylacetylenes, probably due to a poor resolution between the alkynylation product and the substrate, which hampered the purification process.

Table 2.1 Synthesis of 2-alkynyl(hetero)aryl methyl ketones **30**.[a]





[a] Reactions were carried out with ketone **30** (2 mmol), alkyne (1.5 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (2 mol%) and TEA (3 mL/mmol) under Ar at 80 ºC for 24 h.

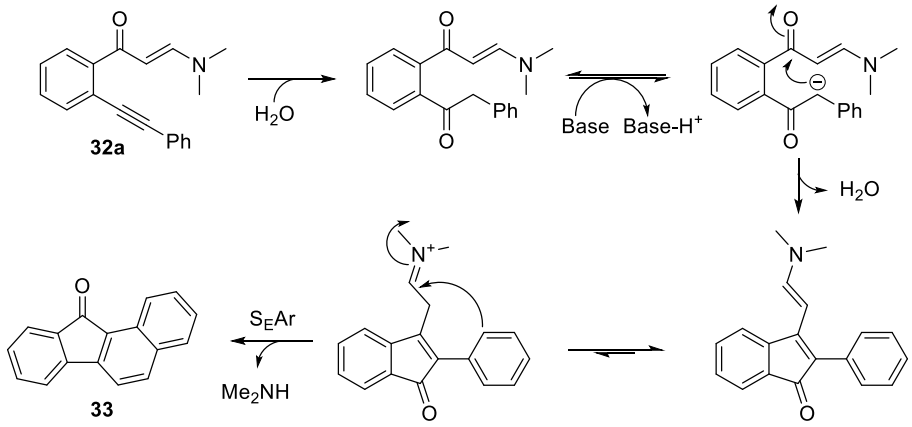
The next step, the synthesis of enaminoketones **32** by aminomethylenation of methyl ketones **31** with DMFDMA, was carried out using a variation of the previously optimized protocols. However, caution was required with temperature and reaction times since heating above 120 ºC for longer than 24 h led to the formation of indenone derivatives. Indeed, 11*H*-benzo[*a*]fluorenone **33** was obtained along with other complex side-products when the aminomethylation of **31a** was carried out at 140 ºC for 24h.

The formation of benzofluorenones has been already described, not for *o*-alkynyl enaminoketones but for *o*-alkynyl ynones.[61] However, the products obtained from alkynones present a different regioisomerism (benzo[*b*]- and benzo[*c*]fluorenones), except in some cases where the benzofluorenone scaffold appeared as a regioisomeric mixture.[62] It has been postulated that these reactions from alkynones proceed *via* cyclic allenes that rearrange intramolecularly by a dehydro Diels-Alder that evolve to generate benzofluorenones.[61,62]

In our case, we propose that hydration under basic conditions of the alkyne moiety would induce an intramolecular aldol reaction followed by an intramolecular electrophilic aromatic substitution on an iminium ion intermediate (Scheme 2.33).

[61] For an example on the use of *o*-alkynyl ynones for the construction of benzo[*b*]- and benzo[*c*]fluorenones, see: a) Rodríguez, D.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **2002**, *43*, 2717–2720. b) González-Cantalapiedra, E.; De Frutos, Ó.; Atienza, C.; Mateo, C.; Echavarren, A.; M. *Eur. J. Org. Chem.* **2006**, *2006*, 1430–1443. c) Rodríguez, D.; Martínez-Esperón, M. F.; Navarro-Vázquez, A.; Castedo, L.; Domínguez, D.; Saá, C. *J. Org. Chem.* **2007**, *69*, 3842–3848.

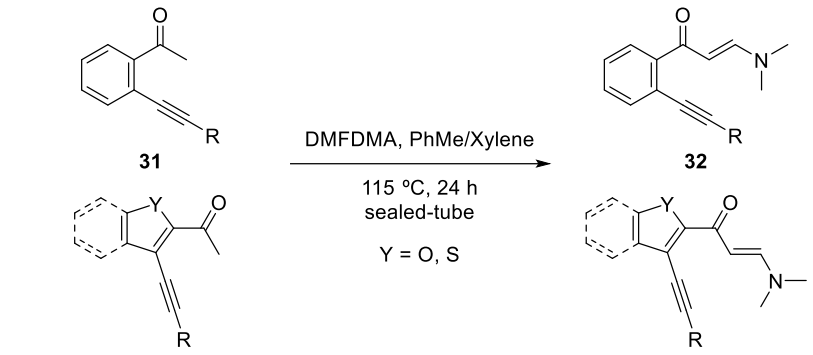
[62] Atienza, C.; Mateo, C.; De Frutos, Ó.; Echavarren, A.; M. *Org. Lett.* **2001**, *3*, 153–155.

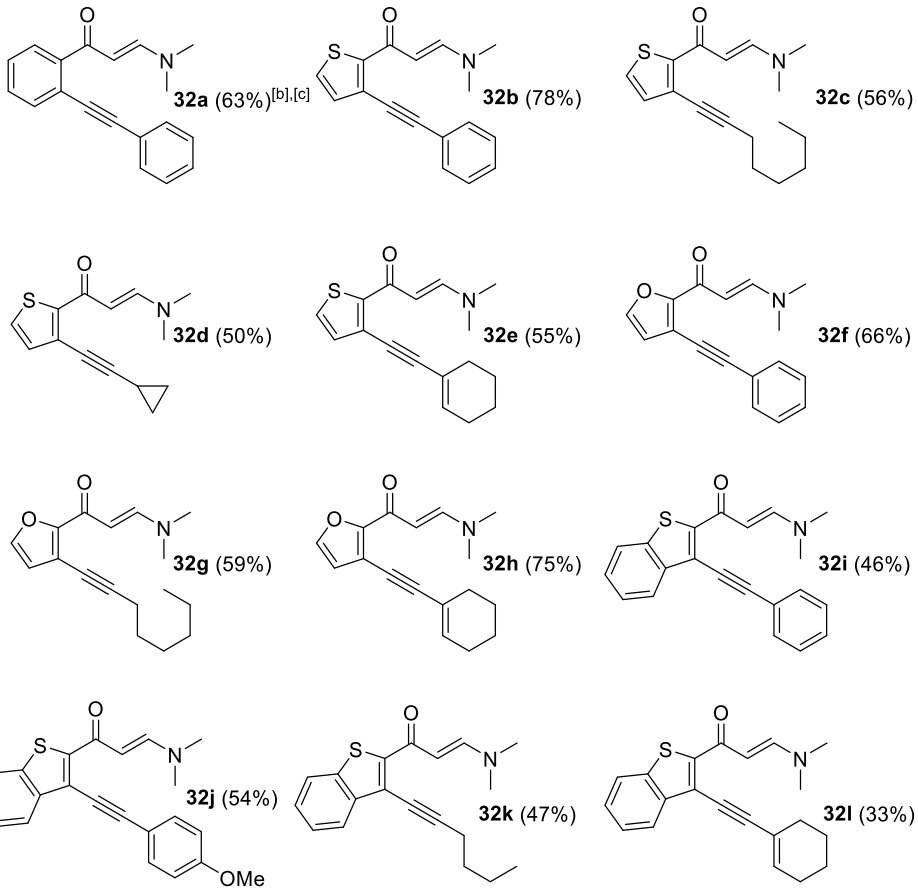


Scheme 2.33 Postulated mechanism for the formation of benzo[*a*]fluorenone **33**.

By means of the optimized conditions for this functionality-sensitive aminomethylenation reaction (DMFDMA, PhMe, 115 ºC, sealed tube, 24 h) enaminoketones **33** were prepared with moderate to good yields (Table 2.2), thus adding quite a few substrates on which to explore the target cascade transformation.

Table 2.2 Aminomethylenation of 2-alkynyl(hetero)aryl methyl ketones.[a]





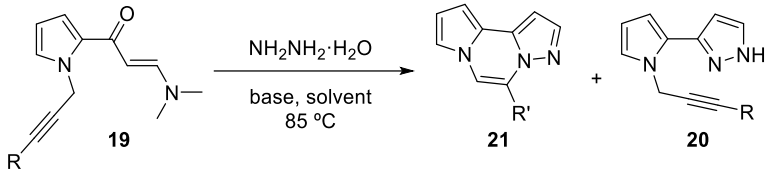
[a] Reactions performed with ketone **31** (X mmol), DMFDMA (1.5 equiv.), PhMe (1.5 mL/mmol) in a sealed tube heated to 115 ºC for 24 h. [b] Xylene was used as solvent. [c] 140 ºC,18 h.

3.2 One-pot amine exchange/heteroannulation/hydroamination

As outlined in section 3.1, *N*-propargylated enaminoketone **19a** was chosen as model substrate for the screening of reaction conditions. On the basis of amine exchange/heterocyclization conditions previously optimized by our group for the synthesis of pyrazoles, the effect of several reaction parameters such as the amount of hydrazine, solvent and base was evaluated. Table 2.3 summarizes the results from these initial experiments, including those performed with a similar substrate, *N*-phenylpropargyl derivative **19b**.

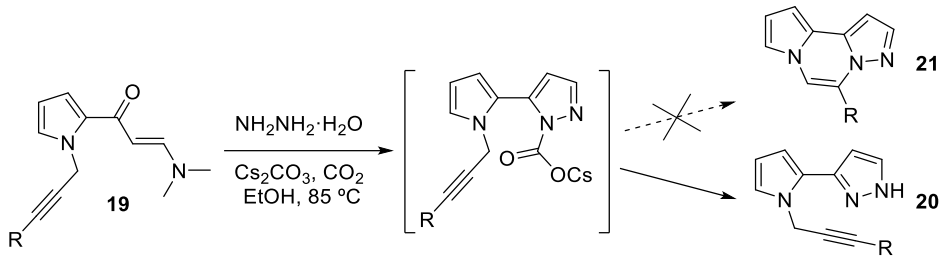
To our delight, in our first attempt (entry 1), we noticed that the addition of Cs_2CO_3 promoted the intramolecular hydroamination to provide pyrazolopyrazine **21a** with an excellent yield. A ten-fold decrease in the amount of hydrazine still afforded the target tricycle, although with inferior yield (entry 2). Interestingly, the alleged pyrazole intermediate **20a** was the only product isolated when *N,N*-dimethylaminopyridine (DMAP) was the base employed (entry 3). The following experiments were performed to check the effect of an inert atmosphere and to minimize the required amounts of the reagents employed (entries 4-8). Further optimization involved shortening of the reaction time (entry 9). As mentioned before, a parallel study was carried out with **19b**, providing similar results (entries 14-17). In both cases (**19a** and **19b**) the change from argon atmosphere to CO_2 led to the isolation of *N*-propargyl derivative **20**. In order to explain this curious behaviour, we propose that the formation of a labile carbamate intermediate under reaction conditions would hinder the hydroamination step (Scheme 2.34).

Table 2.3 Screening reactions for one-pot reaction amine exchange/heteroannulation/hydroamination reaction.[a]



Entry	R	$NH_2NH_2{\cdot}H_2O$ (equiv.)	Base (equiv.)	Solvent	Atmos.	t (h)	**21** (%)[b]	**20** (%)[b]
1	H	15	Cs_2CO_3 (3.0)	EtOH	air	12	**21a** (96) (R'=CH_3)	
2	H	1.5	Cs_2CO_3 (3.0)	EtOH	air	12	**21a** (81) (R'=CH_3)	
3	H	1.5	DMAP (3.0)	EtOH	air	12		**20a** (79)
4	H	10	Cs_2CO_3 (3.0)	EtOH	argon	12	**21a** (97) (R'=CH_3)	
5	H	5	Cs_2CO_3 (3.0)	EtOH	argon	12	**21a** (94) (R'=CH_3)	
6	H	5	Cs_2CO_3 (1.5)	EtOH	argon	12	**21a** (96) (R'=CH_3)	
7	H	5	Cs_2CO_3 (1.0)	EtOH	argon	12	**21a** (98) (R'=CH_3)	
8	H	5	Cs_2CO_3 (0.5)	EtOH	argon	12	**21a** (87) (R'=CH_3)	
9	H	5	Cs_2CO_3 (1.0)	EtOH	argon	5	**21a** (95) (R'=CH_3)	
10	H	5	DBU (3.0)	EtOH	argon	5	**21a** (98) (R'=CH_3)	
11	H	5	Cs_2CO_3 (1.0)	EtOH	CO_2	5		**20a** (75)
12	H	5	Cs_2CO_3 (1.0)	H_2O	argon	5	**21a** (89) (R'=CH_3)	
13[c]	H	5	Cs_2CO_3 (1.0)	H_2O	argon	5	**21a** (87) (R'=CH_3)	
14	Ph	1.5	Cs_2CO_3 (3.0)	EtOH	air	12	**21b** (48) (R'=Bn)	
15	Ph	1.5	DMAP (3.0)	EtOH	air	12		**20b** (64)
16	Ph	10	Cs_2CO_3 (3.0)	EtOH	argon	12	**21b** (57) (R'=Bn)	
17	Ph	5	Cs_2CO_3 (1.0)	EtOH	argon	5	**21b** (87) (R'=Bn)	
18	Ph	5	DBU (3.0)	EtOH	argon	5	**21b** (64) (R'=Bn)	
19	Ph	5	Cs_2CO_3 (1.0)	H_2O	argon	5	**21b** (21) (R'=Bn)	
20[c]	Ph	5	Cs_2CO_3 (1.0)	H_2O	argon	5	**21b** (20) (R'=Bn)	

[a]Reaction conditions: Enaminoketone **19** (0.5 mmol), base (0.5–3.0 equiv.), hydrazine (1.5–15 equiv.), solvent (1.5 mL/mmol) under the specified atmosphere in a sealed tube at 85 ºC. [b] Isolated yield. [c] The reaction was carried out at 100 ºC.



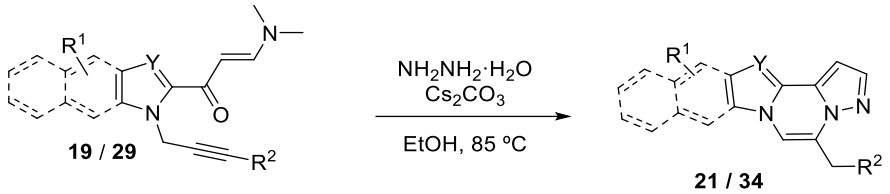
Scheme 2.34 A possible explanation for the results obtained when using a CO_2 atmosphere.

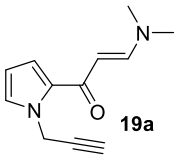
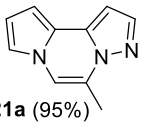
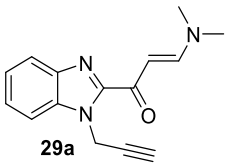
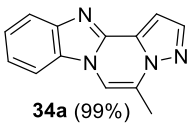
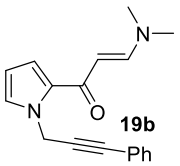
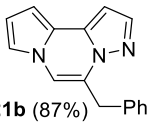
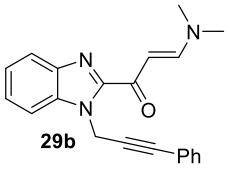
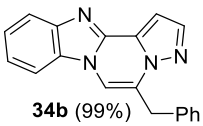
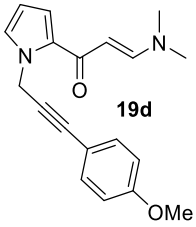
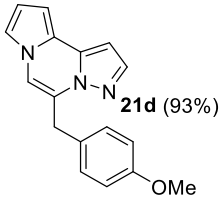
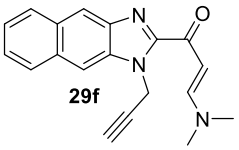
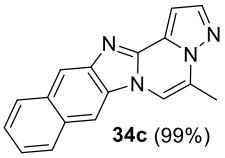
A relatively strong organic base such as DBU was able to promote the whole cascade reaction, including the hydroamination step, although 3 equivalents were required (entries 10 and 18). Water proved to be a valid solvent for the reaction at the same temperature (heating to 100 ºC did not improve the yields) although on account of the better yields obtained in ethanol (*e.g*. entry 9 vs 12 and entry 17 *vs* entry 19) and the availability and sustainability of this alcohol,[63] we chose it as the optimal solvent for the reaction. Moreover, inexpensive ethanol 96% worked as well as absolute ethanol. The optimized conditions (entry 9 or entry 17) for this unprecedented cascade amine exchange/heterocyclization/hydroamination were then applied to a number of *N*-propargylated pyrrolyl and -benzimidazolyl derivatives **19** and **29**, providing the results displayed in Table 2.4.

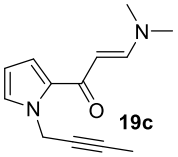
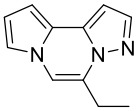
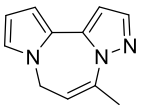
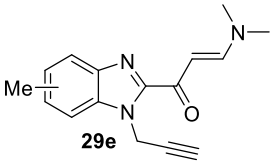
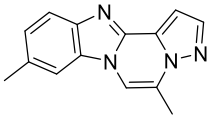
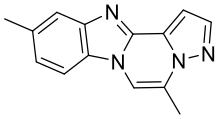
Excellent yields were achieved in most cases. However, when 2-butyn-1-yl derivative **19c** was used, a mixture of 6-*endo* (**21c**) and 7-*endo* (**35**) regioisomers were obtained. This behaviour could be related to the participation of allene intermediates, as will be discussed in Scheme 2.37 (page 149).

[63] For information about sustainability of ethanol, see: a) Prat, D.; Hayler, J.; Wells, A. *Green Chem.* **2014**, *16*, 4546–4551. b) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879–3890.

Table 2.4 Cascade amine exchange/heteroannulation/hydroamination of enaminoketones derived from *N*-propargylpyrrole and -benzimidazole derivatives.[a]

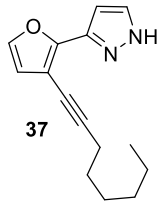


Substrate	Product (%)[b]	Substrate	Product (%)[b]
 **19a**	 **21a** (95%)	 **29a**	 **34a** (99%)
 **19b** Ph	 **21b** (87%) Ph	 **29b** Ph	 **34b** (99%) Ph
 **19d** OMe	 **21d** (93%) OMe	 **29f**	 **34c** (99%)

Substrate	Product (%)[b]	
 **19c**	 **21c** (34%)	 **35** (54%)
 **29e**	 **34d** (99%)[c]	 **34d'**

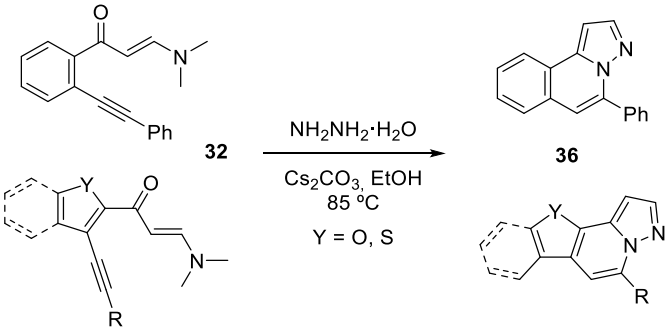
[a]Reaction conditions: Enaminone **19**/**29** (0.5 mmol), hydrazine hydrate (5.0 equiv.), Cs_2CO_3 (1.0 equiv.), EtOH 96% (1.5 mL/mmol), Ar, 85 ºC, 5 h. [b] Isolated yield. [c] Inseparable mixture.

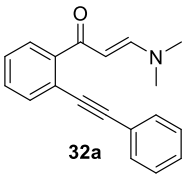
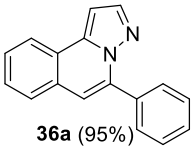
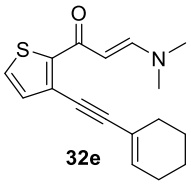
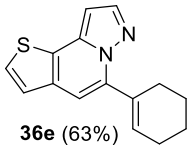
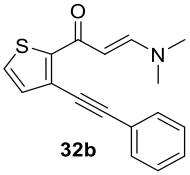
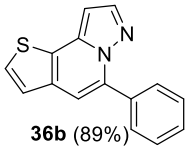
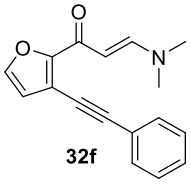
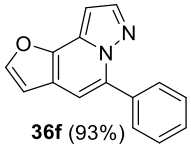
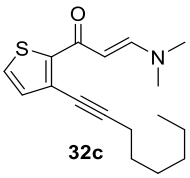
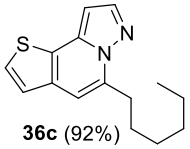
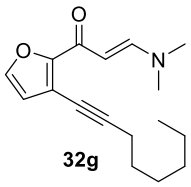
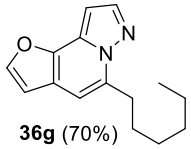
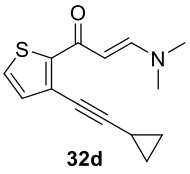
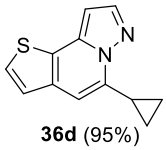
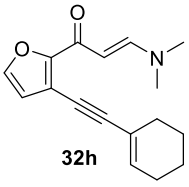
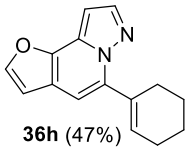
Following with the exploration of the scope of this unreported cascade process, a series of 2-alkynylaryl- or 2-alkynylheteroaryl enaminones **32** were reacted with hydrazine under the optimized reaction conditions (Table 2.5). The reactions took place smoothly to provide good to excellent yields in most cases. Indeed, pyrazoloisoquinoline **36a**, pyrazolothienopyridine **36b**, furopyrazolopyridine **36f** and benzothienopyrazolopyridines **36i-j** were prepared with excellent yields, all of them bearing a 5-aryl moiety. In other words, arylalkynyl substrates **32a,b,f** and **32i-j** underwent the cascade reaction selectively to the corresponding tri- or tetracycles (Table 2.5). Unlike *N*-methylpropargyl derivative **19c** (Table 2.4), the reactions from arylalkynyl compounds evolved regioselectively to the desired 6-*endo* product without a trace of the 5-*exo* isomer. Interestingly, in the case of **32g**, although the reaction took place with an almost quantitative conversion rate, furopyrazolopyridine **36g** was isolated with a 70% yield, and 2-(3-pyrazolyl)-3-(1-octynyl)furan **37** was obtained with a 23% yield, thus providing again strong evidence of the participation of such pyrazole intermediates. Moderate to good yields were achieved from the enaminones bearing the 2-(cyclohex-1-en-1-yl)ethyn-1-yl moiety (**32e**, **32h** and **32l**).



37

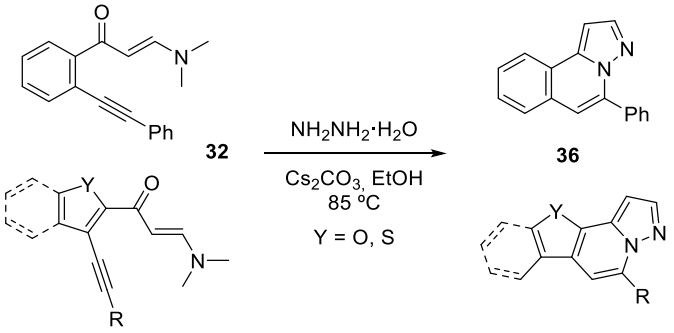
Table 2.5 Cascade amine exchange/heterocyclization/hydroamination of 2-alkynyl(hetero)aryl enaminones **32**.[a]

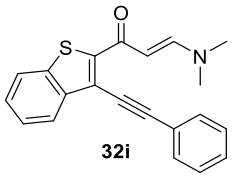
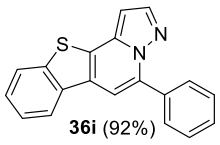
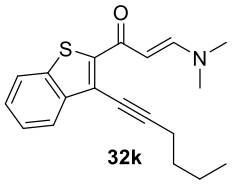
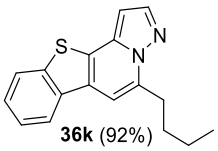
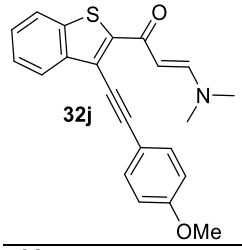
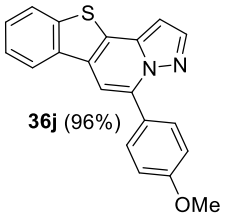
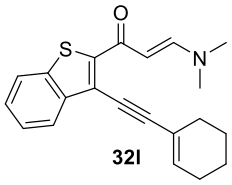
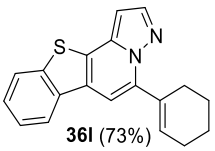


Substrate	Product (%)[b]	Substrate	Product (%)[b]
 **32a**	 **36a** (95%)	 **32e**	 **36e** (63%)
 **32b**	 **36b** (89%)	 **32f**	 **36f** (93%)
 **32c**	 **36c** (92%)	 **32g**	 **36g** (70%)
 **32d**	 **36d** (95%)	 **32h**	 **36h** (47%)

[a] Reaction conditions: enaminone **32** (0.5 mmol), hydrazine hydrate (5.0 equiv.), Cs_2CO_3 (1.0 equiv.), EtOH 96% (1.5 mL/mmol), Ar, 85 °C, 5 h. [b] Isolated yield.

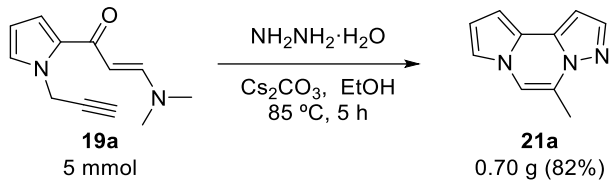
Table 2.5 Cascade amine exchange/heterocyclization/hydroamination of 2-alkynyl(hetero)aryl enaminones **32**.[a] *(cont.)*



Substrate	Product (%)[b]	Substrate	Product (%)[b]
 **32i**	 **36i** (92%)	 **32k**	 **36k** (92%)
 **32j**	 **36j** (96%)	 **32l**	 **36l** (73%)

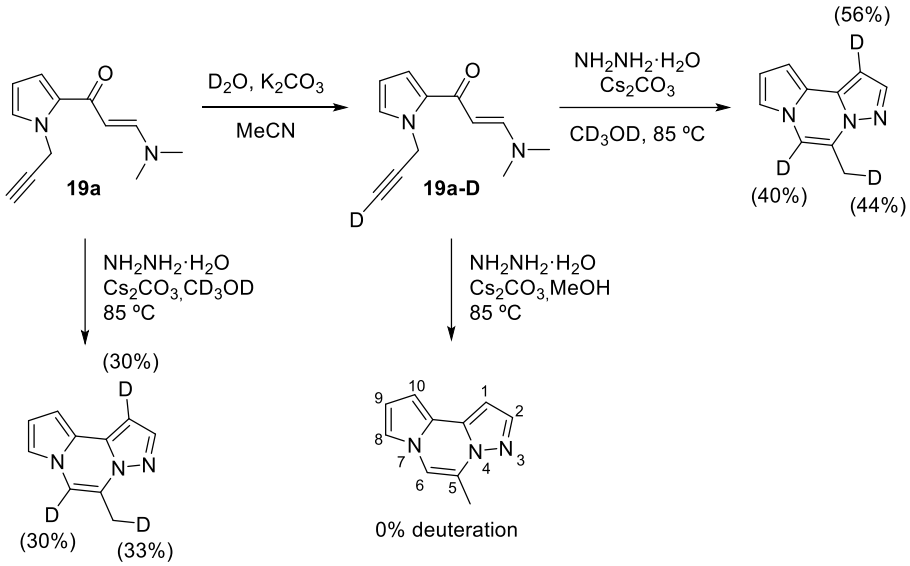
[a] Reaction conditions: enaminone **32** (0.5 mmol), hydrazine hydrate (5.0 equiv.), Cs_2CO_3 (1.0 equiv.), EtOH 96% (1.5 mL/mmol), Ar, 85 ºC, 5 h. [b] Isolated yield.

In order to explore the scalability of the presented method, 1.01 g of enaminoketone **19a** was reacted with hydrazine under the optimized conditions, providing the corresponding pyrazolopyrrolopyrazine **21a** with an 82% yield (Scheme 2.35).



Scheme 2.35 Scale-up of the cascade reaction from enaminoketone **19a**.

Along with the collected experimental data during the screening and substrate scope stages, additional deuteration tests were performed to gather useful information to understand the reaction mechanism. After a selective deuteration of pyrrole derivative **19a** by a procedure described by Bew and col.,[64] the so-formed alkyne **19a-D** along with **19a** were subjected to the reaction conditions[65] displayed in Scheme 2.36.



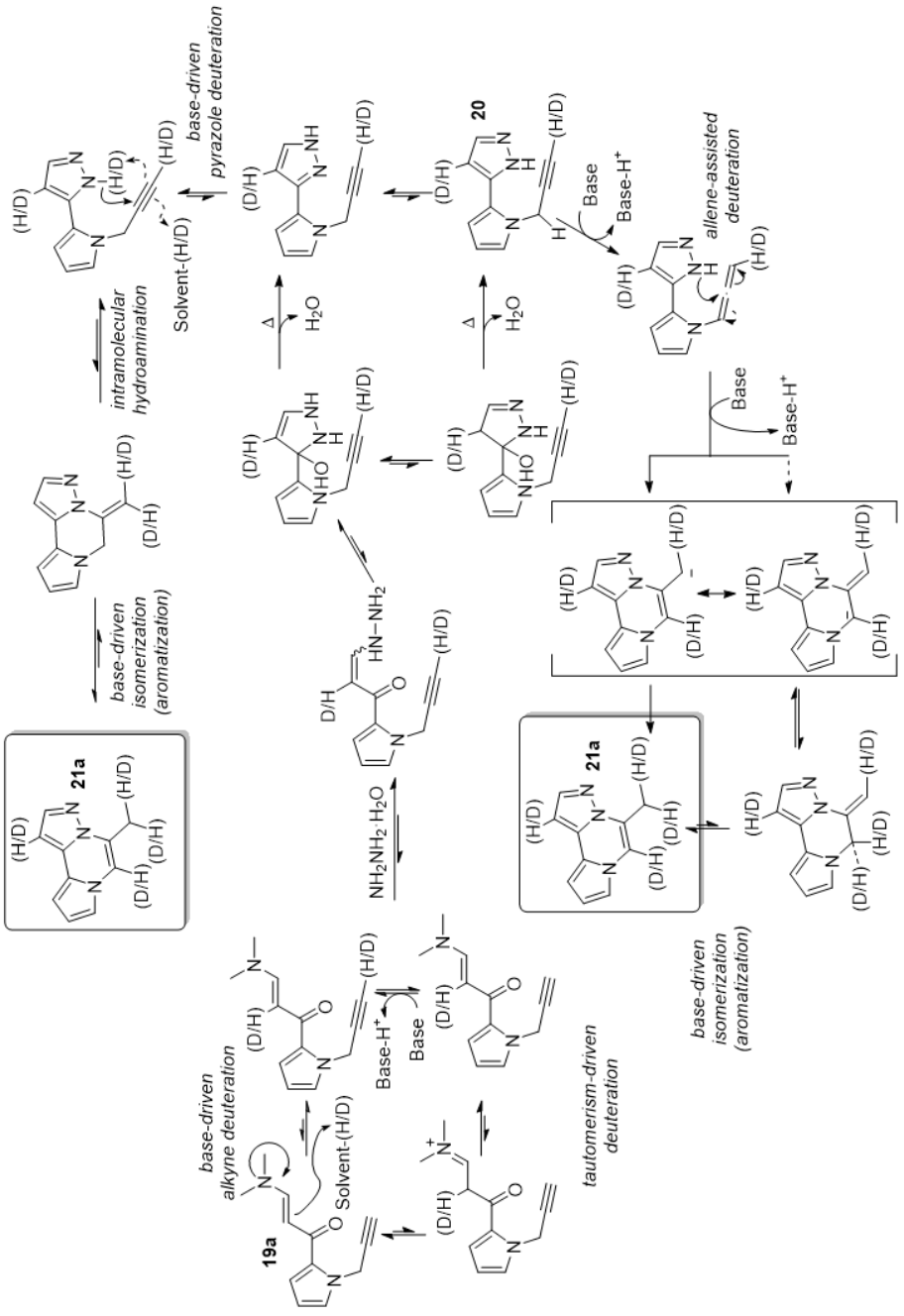
Scheme 2.36 Deuteration labelling experiments. Displayed percentages indicate deuteration degree.

[64] Bew, S. P.; Hiatt-Gipson, G. D.; Lovell, J. A.; Poullain, C. *Org. Lett.* **2012**, *14*, 456–459.

[65] These experiments were carried out using methanol-d_4 and methanol owing to convenience reasons (availability, lower price).

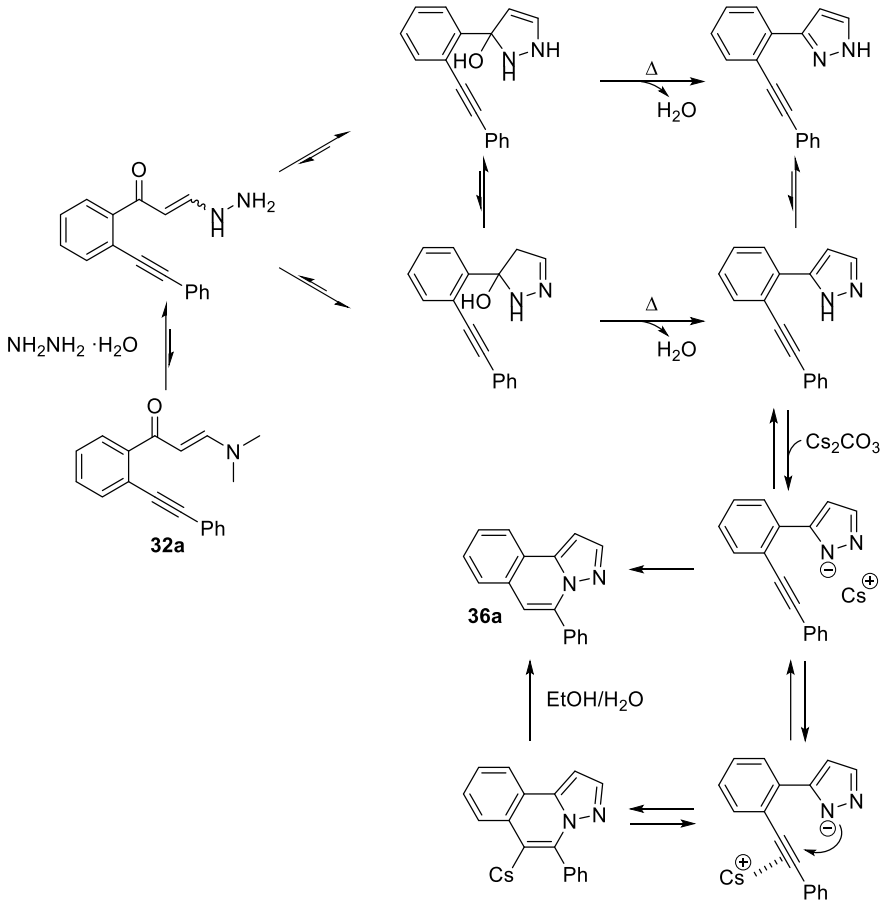
With regard to the reaction of **19a** in CD_3OD, the partial labelling observed at C-1 position can be associated to a proton-deuterium exchange due to the initial iminium-enamine equilibrium prior to the amine exchange/heterocyclization (see Scheme 2.4 on page 115 for further details). The partial isotopic labelling observed at C-6 and at 5-Me provides evidence for the participation of transient allene species as well as a proton-deuterium exchange at the terminal position of the acetylene. This latter exchange was proved by reacting **19a-D** in methanol, as only non-deuterated pyrazolopyrrolopyrazine was isolated. Reactions of **19a-D** in methanol-d_4 provided a higher degree of deuteration at the aforementioned C-1, C-6 and 5-Me positions.

Considering the latter labelling results and our own experience with amine-exchange/heterocyclization reactions, we postulated a mechanism involving several equilibria where proton-deuterium exchange could take place. An initial amine-exchange process followed by heterocyclization would lead to a hydroxydihydropyrazole intermediate, which upon dehydration would generate pyrazole **20**. Then, two different pathways were considered. In the first one, a base-promoted pyrazole deuteration would take place followed by an intramolecular hydroamination (or deuteroamination) to attain the exocyclic olefin that, in the end, would undergo an aromatization process towards **21a** promoted by the base. In the second pathway, base-induced allene formation and pyrazole N-H deprotonation would promote a nucleophilic attack at the central allene carbon. In that way, two olefinic intermediates could be formed (endocyclic and exocyclic). The former would provide directly tricycle **21a** after protonation (or deuteration), whereas the latter would need to undergo a base-driven aromatization process to get the pyrazolopyrrolopyrazine product (Scheme 2.37).



Scheme 2.37 A mechanistic proposal for the cascade amine-exchange/heterocyclization/hydroamination leading to pyrazolopyrrolopyrazine **21a.**

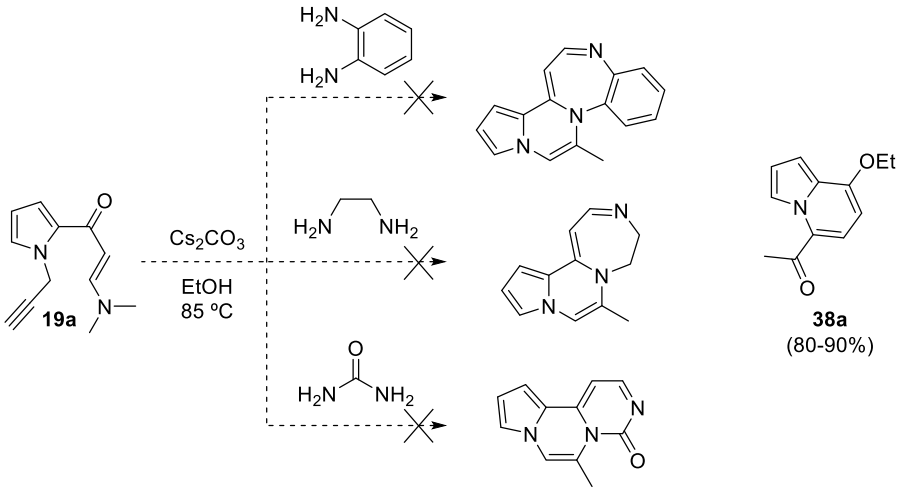
Analogously to what has been explained for pyrrole and benzimidazole derivatives, in the case of *o*-alkynylarylenaminones an initial amine exchange/heterocyclization would generate hydroxypyrazoline and pyrazole intermediates that would undergo deprotonation under basic conditions, and the final intramolecular step would lead to the pyrazoloisoquinoline core (Scheme 2.38).



Scheme 2.38 General mechanistic postulation for cascade amine-exchange-heteroannulation-hydroamination of *o*-alkynyl derived enaminones.

3.2.1 A new route to indolizines

With the aim of broadening the reaction scope, other nitrogen dinucleophiles were tested as possible candidates for the presented cascade reaction. However, when *o*-phenylenediamine, ethylenediamine and urea were reacted with enaminone **19a**, instead of the initially expected diazepine and pyrimidine derivatives, 1-(8-ethoxyindazolizin-5-yl)ethan-1-one **38a** was isolated in variable amounts (Scheme 2.39).



Scheme 2.39 Reaction of enaminone **19a** with dinucleophiles other than hydrazyne.

The structure of the latter indolizine **38a** was confirmed by X-diffractometry, revealing an asymmetric unit comprising two identical molecules (orthorhombic Pnma space group). As a result of the completely planar system (C8A-N1A-C1A-C2A, N1A-C1A-C9A-C10A and C3A-C4A-O2A-C11A torsion angle values were 180º, 180º and 0º, respectively), a clear π-stacking interaction (Figure 2.3 and Figure 2.4) was observed in the crystal packing.[66]

Compound **38a** presented a shiny yellow color that turned into a bright green glow upon UV-lamp irradiation (365 nm). The analysis of the fluorescence emission

[66] For extended information on crystallographic data, check the experimental section.

of this indolizine revealed a quantum yield of 47% [Φ_f (10^{-5} M in acetone, λ_{exc}= 405 nm) = 0.47].

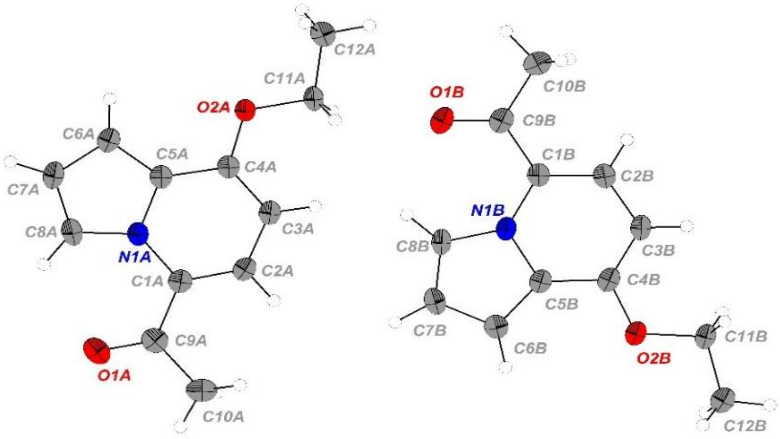


Figure 2.3 ORTEP diagram of complex **38a** with thermal ellipsoids given at 50% probability level.

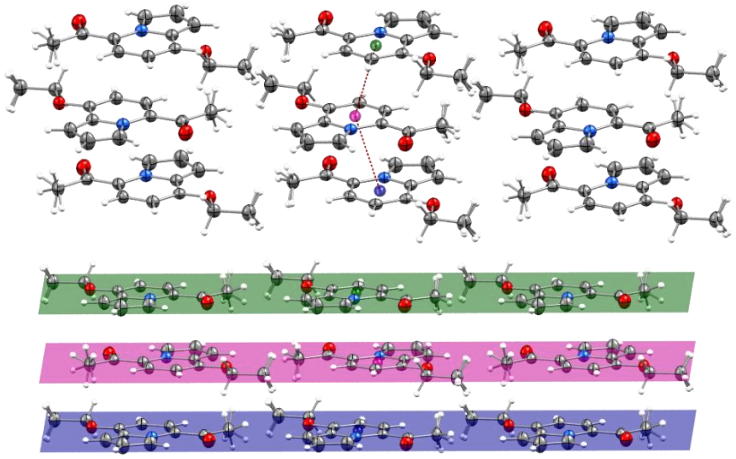
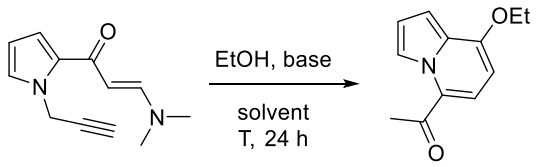


Figure 2.4 Detail of π-stacking interaction displaying ring centroids, up and representation of the planes formed by the layers, down.

In view of this unexpected result, a number of experiments were carried out in order to optimize the synthesis of **38a** (Table 2.6). From the very beginning, it became clear that the source of the 8-ethoxy group was the solvent employed (EtOH), as no indolizine derivative was isolated from reactions in the absence of alcohol.

Table 2.6 Screening for reaction conditions for the cascade formation of 8-ethoxy-5-acetylindolizine **38a**.[a]

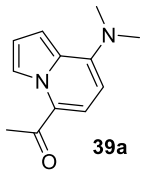


19a **38a**

Entry	Solvent	EtOH (equiv.)	Base (1.0 equiv.)	T/ ºC	**38a** (%)[b]
1	EtOH	-	Cs_2CO_3	85	93
2	EtOH	-	K_2CO_3	85	33
3	EtOH	-	Na_2CO_3	85	7
4	EtOH	-	$NaHCO_3$	85	7
5	EtOH	-	DBU	85	33
6	EtOH	-	DABCO	85	8
7	EtOH	-	KOH	85	44
8	EtOH	-	CsOH	85	40
9	EtOH	-	CsF	85	8
10	EtOH	-	CsCl	85	5
11	MeCN	3.0	Cs_2CO_3	85	66
12	PhMe	3.0	Cs_2CO_3	85	86
13[c]	PhMe	3.0	Cs_2CO_3	85	68
14[d]	PhMe	3.0	Cs_2CO_3	85	80
15[e]	PhMe	3.0	Cs_2CO_3	85	50
16	2-MeTHF	3.0	Cs_2CO_3	85	92
17	DEC	3.0	Cs_2CO_3	85	34
18	EC	3.0	Cs_2CO_3	85	8
19	1,3-dioxolane	3.0	Cs_2CO_3	85	74
20	2-MeTHF	3.0	Cs_2CO_3	100	82
21	2-MeTHF	3.0	Cs_2CO_3	130	81
22	2-MeTHF	1.0	Cs_2CO_3	85	30
23	2-MeTHF	2.0	Cs_2CO_3	85	67
24	2-MeTHF	4.0	Cs_2CO_3	85	88
25[f]	2-MeTHF	3.0	Cs_2CO_3	85	92

[a] Reactions conditions: Enaminone **19a** (0.5 mmol), EtOH (X equiv.), base (1.0 equiv.) solvent (1.5 mL/mmol), Ar, sealed tube, T, 24 h. [b] Isolated yield. [c] Dry PhMe and absolute ethanol were employed. [d] Cs_2CO_3 (1.5 equiv.). [e] Cs_2CO_3 (0.5 equiv.). [f] Reaction time: 12 h.

In addition, the purification of **38a** was often hampered by the presence of certain amounts (1–15%) of 1-(8-(dimethylamino)indolizin-5-yl)ethan-1-one **39a**. As shown in Table 2.6, different bases were initially tested, and remarkably higher yields were achieved with cesium carbonate (entry 1 *vs* entries 2–10). With regard to the carbonate bases and even other organic and inorganic bases, these results could be related to the so-called "cesium-effect" which some authors have associated with a higher solubility of the base due to the bigger size of the cationic counter-ion so that the "free" or "naked" amount of the anionic base present in the reaction media is larger. However, some researchers believe in a real and specific effect inherent to cesium itself.[55,67]



39a

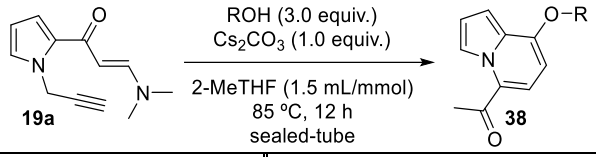
Other solvents were also tried for the reaction, thus decreasing ethanol to slightly over-stoichiometric amounts (3.0 equiv.). Several variations of the base loading were also combined with the above solvents (entries 11–19). As a result, we observed that the reaction outcome was not related to the polarity or dielectric constant of the solvent,[68] and it was also noticed that the absence of water had a detrimental effect on the reaction (the use of absolute ethanol or dry toluene led to significantly inferior results, entry 13), so a little amount of water was clearly beneficial. 2-Methyltetrahydrofurane (2-MeTHF), a convenient biogenic solvent derived from renewable sources such as furfural or levulinic acid and increasingly used as a more sustainable reaction media for a wide range of chemical and

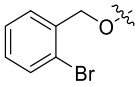
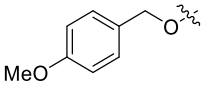
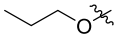
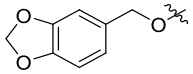
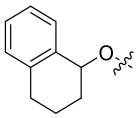
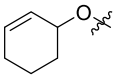
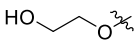
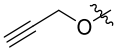
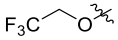
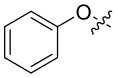
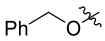
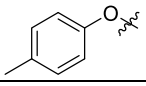
[67] It is well-known that for a given base ($Base^-M^+$) the bigger the counter-ion size (M^+) the bigger the base dissociation (lower K_{as}), as the bond is weaker due to a longer bond-length. Moreover, the higher the ion-pairing ($Base^-M^+$) the slower the base activity since the readily available "free-base" amount would be lower. Furthermore, bearing in mind that reactions from ion-pairs are more hindered than from dissociated base ($k_{ion\text{-}pair} << k_{free}$) and that higher solvent dielectric constants lead to lower ion-pairing, it is easily deduced that the most appropriate solvents for "free-base" obtention should be the polar aprotic ones provided they possess the highest dielectric constants. As a matter of fact, cesium carbonate is the only alkali carbonate soluble in ethanol, being ionic radius of cesium 1.61, while ionic radii of potassium and sodium are 1.52 and 1.16, respectively. See: Galli, C. *Org. Prep. Proced. Int.* **1992**, *24*, 285–307.

[68] Dielectric constants of some of the solvents assayed: EtOH (22.4), DEC (2.8), 2-MeTHF (6.2), 1,3-dioxolane (7.1), MeCN (37.5). The values were determined at 20 ºC except for 2-MeTHF (25 ºC).

enzymatic synthetic processes,[69] was chosen as the best candidate on account of the excellent result achieved (entry 16). Further optimization involved changing the temperature as well as the amount of ethanol and the reaction time (entries 20–25). The optimized conditions (entry 25) were then applied to a number of alcohols and enaminoketone **19a**, obtaining the indolizine derivatives displayed in Table 2.7.

Table 2.7 8-Alkoxy- and 8-aryloxy-5-acetylindolizines **38** synthesized from enaminone **19a**.[a]

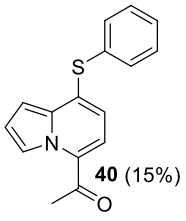


Entry	RO-	**38** (%)[b]	Entry	RO-	**38** (%)[b]
1		**38a** (92)	9		**38i** (98)
2		**38b** (93)	10		**38j** (81)
3		**38c** (81)	11		**38k** (60)
4		**38d** (60)	12		**38l** (78)
5		**38e** (40)	13		**38m** (42)
6[c]		**38f** (52)	14		**38n** (24)
7		**38g** (76)	15[d]		**38o** (25)
8		**38h** (91)	16[d]		**38p** (61)

[a] Reactions conditions: enaminoketone **19a** (0.5 mmol), ROH (3.0 equiv.), Cs_2CO_3 (1.0 equiv.), 2-MeTHF (1.5 mL/mmol), Ar, sealed tube, 85 ºC, 12 h.[b] Isolated yield. [c] ROH used as solvent. [d] 4.0 equiv. of Cs_2CO_3 were used.

[69] For a review, see: (a) Alcántara, A. R.; Domínguez de María, P. *Curr. Green. Chem.* **2018**, *5*, 86–103. See also: (b) Smolén, M.; Kezdiorek, M.; Grela, K. *Catal. Commun.* **2014**, *44*, 80–84.

Primary aliphatic alcohols provided good to excellent yields (entries 1-3 and 7-11). A moderate yield (52%) was obtained for ethylene glycol and a poor yield was observed for propargyl alcohol. Double interactions might be responsible of the former result, while acetilyde formation could be the reason for the latter. Secondary aliphatic alcohols afforded the corresponding indolizine derivatives with inferior but still acceptable yields (entries 5, 12-13) and even sterically hindered *tert*-butanol performed fairly well. With regard to phenols, the amount of base had to be increased probably because of their higher acidity (pKa values of phenol, *p*-cresol and *p*-nitrophenol are 9.98, 10.14 and 7.15, respectively)[70] that led to a consumption of the base. It seems that the more electron rich phenol employed, the higher yield was obtained, or at least that conclusion can be drawn by comparing the yields observed from phenol (entry 15), *p*-cresol (entry 16) and the complete failure (< 5%) from *p*-nitrophenol. A high acidity of the nucleophile could be partially behind the low yield (15%) obtained from thiophenol under the same reaction conditions to give **40**. Methyl 3-mercaptopropanoate failed to provide the corresponding indolizine.



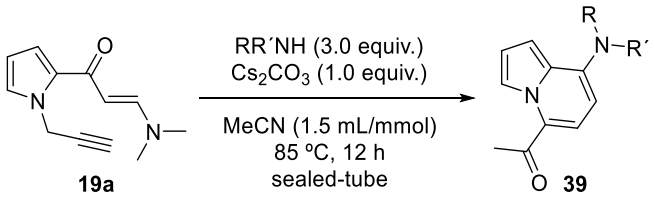
40 (15%)

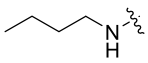
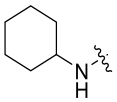
Regarding amines as nucleophiles, no clear trend relating nucleophility, basicity or steric hindrance of the amine to the reaction outcome could be found. In order to get moderate yields, the solvent had to be changed to the more polar aprotic MeCN. As shown in Table 2.8, the reaction performed in the absence of any exogenous nucleophile provided the already detected dimethylamino-derived indolizine **39a**, formed by the action of the dimethylamine released during the reaction (entry 1). Negligible results (< 5 %) were obtained by adding sterically more hindered secondary amines such as diisopropylamine or diethylamine. However, cyclic piperidine and morpholine provided the corresponding indolizines with moderate yields (entries 2-3). The use of primary amines such as butylamine and cyclopropylamine did not improve the yields, but rather the opposite (entries 4-5).

[70]Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421–6427.

However, it was another primary amine, cyclohexylamine, the one that provided the highest yield of all the 8-alkylaminoindolizines prepared by this method (entry 6). Table 2.8 shows as a footnote the nucleophilicity and pK_{aH} values of some of amines assayed.[71]

Table 2.8 8-Amino-5-acetylindolizines **39** synthesized from enaminone **19a**.[a]

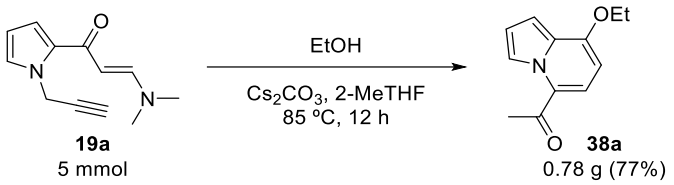


Entry	RR'N-	**39** (%)[b]	Entry	RR´N-	**39** (%)[b]
1[c]		**39a** (49)	4		**39d** (21)
2		**39b** (49)	5		**39e** (14)
3		**39c** (45)	6		**39f** (53)

[a] Reactions conditions: enaminoketone **19a** (0.5 mmol), amine (3.0 equiv.), Cs_2CO_3 (1.0 equiv.), MeCN (1.5 mL/mmol), Ar, sealed tube, 85 ºC, 12 h.[b] Isolated yield. [c] No nucleophile (amine) added. Nucleophility values of some of the amines employed: Me_2NH (17.12), Et_2NH (15.10), $^nBuNH_2$ (15.27), morpholine (15.65), piperidine (17.35). pK_{aH} values of some amines employed: Me_2NH (10.64), Et_2NH (10.98), $^nBuNH_2$ (10.59), morpholine (8.36), piperidine (11.22), cyclohexylamine (10.64).

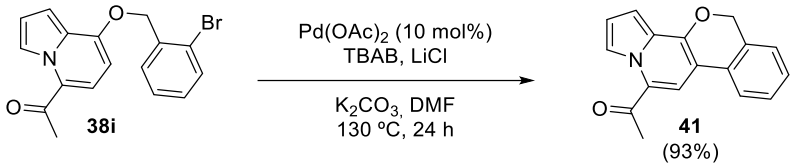
Before dealing with the reaction mechanism, it should be pointed out that the reaction with ethanol leading to 8-ethoxy-5-acetylindolizine **38a** was carried out on a 1.01 g scale and the yield obtained was a more than acceptable 77% (Scheme 2.40).

[71] Hall, H. K. Jr *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444.



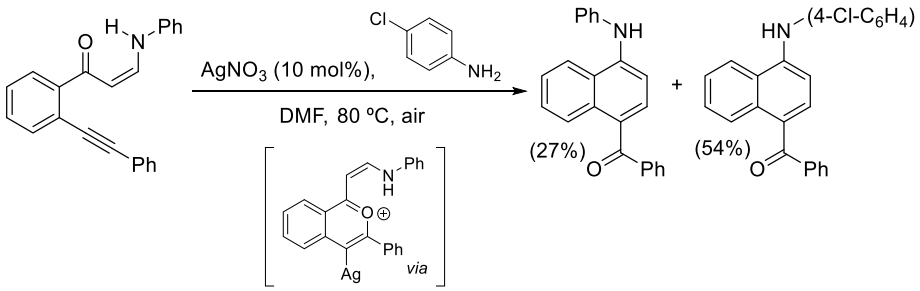
Scheme 2.40 Scale-up of the cascade reaction from enaminoketone **19a**.

Additionally, we were able to cyclize 8-alkoxyindolizine **38i** under ligand-free intramolecular direct arylation conditions previously employed in our research group, thus affording the desired isochromenoindolizine **41** in excellent yield (Scheme 2.41).[53]



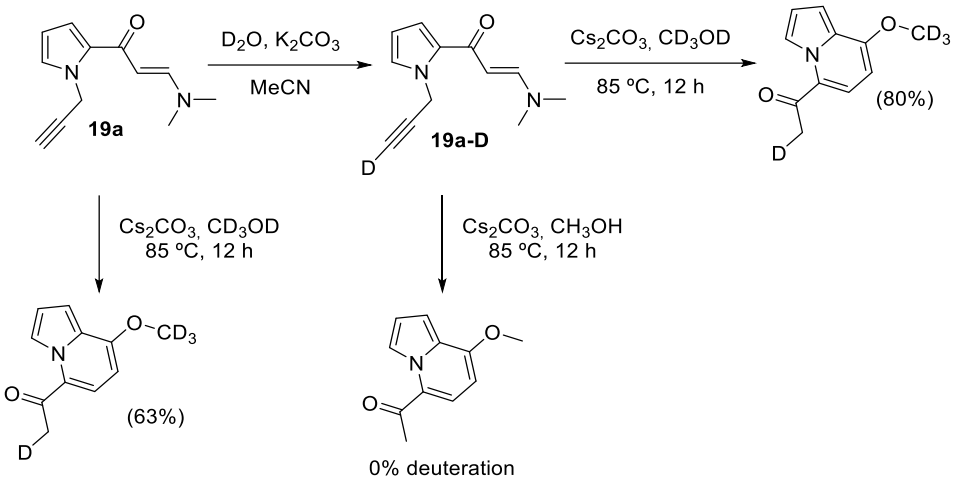
Scheme 2.41 Cyclization of indolizine **38i** to isochromenoindolizine **41**.

A search in the literature revealed that a related transformation from alkynylenaminones catalyzed by Lewis acid had been proposed to occur through a pyrylium-type intermediate (Scheme 2.42).[72]



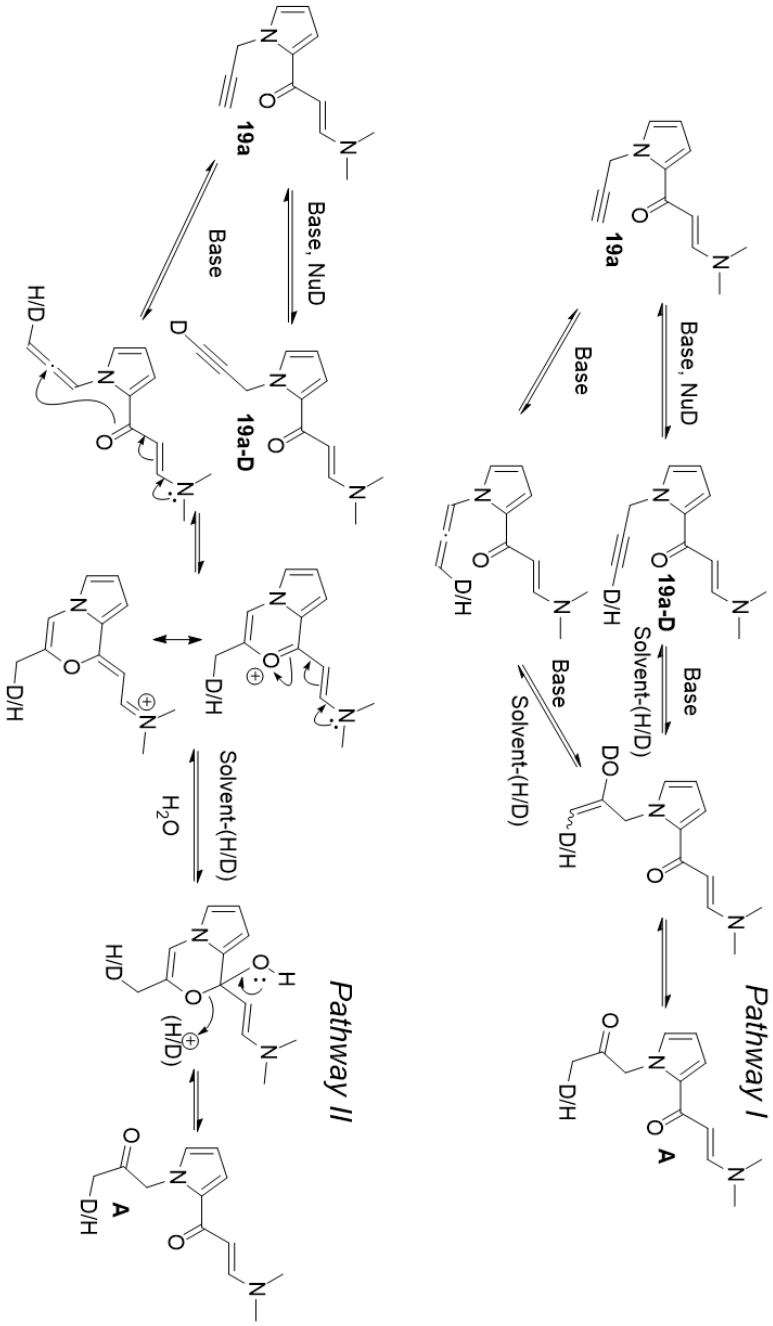
Scheme 2.42 Tandem formation of α-naphthylamines from *o*-alkynyl enaminones.

[72] Zhang, F.; Qin, Z.; Kong, L.; Zhao, Y.; Liu, Y.; Li, Y. *Org. Lett.* **2016**, *18*, 5150–5153.

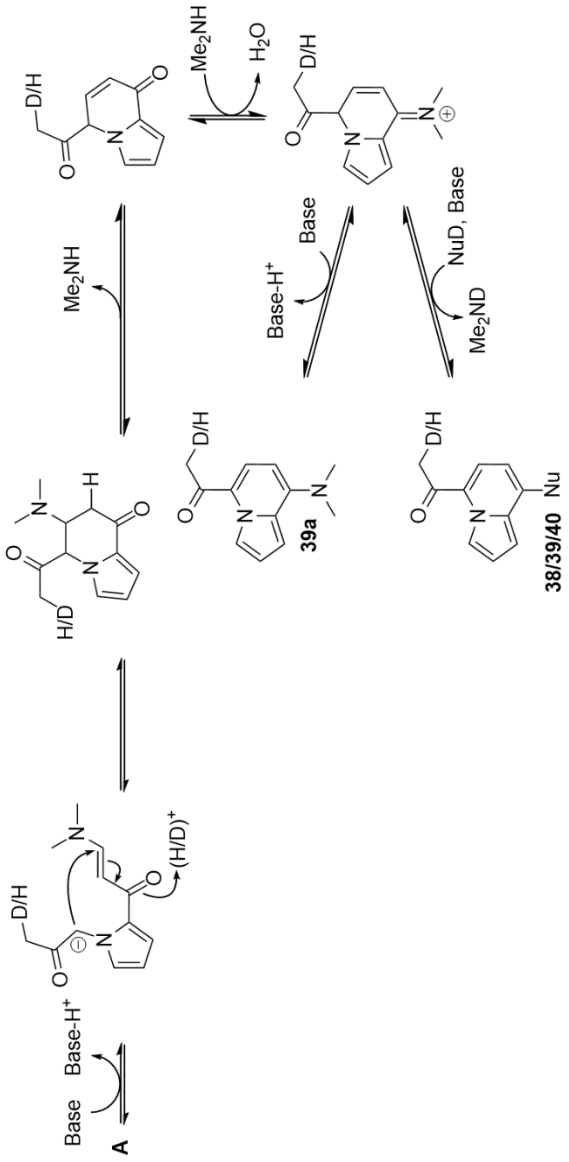


Scheme 2.43 Deuteration labelling experiments preformed on indolizine formation. Displayed percentages indicate deuteration degree.

Initial deuteration labelling experiments performed on enaminones **19a** and **19a-D** (for the procedure for the selective deuteration of **19a**, see Scheme 2.36, page 147) provided strong evidence on the origin of the 8-methoxy substituent, as well as for a proton-deuterium exchange at the alkyne terminal position or α-position of the acetyl group (Scheme 2.43). These results, in addition to the above precedents on a pyrylium-type intermediate associated to a related reaction, led us to propose a tentative mechanism displayed in Scheme 2.44. We soon realized that two alternative pathways could be postulated, one derived from a base-induced hydration of the *N*-propargyl or *N*-allenyl moiety (Pathway I), and the other from the participation of an oxazinium intermediate (Pathway II). After formation of common intermediate **A**, amine-exchange or displacement with the so-formed ketone enolate would promote cyclization to provide a cyclohexenone and the corresponding dimethyliminium ion by condensation with the released dimethylamine (Scheme 2.45). Depending on the aromatization rate, 8-dimethylaminoindolizine derivative **39a** or 8-alkoxyindolizine **38** would be the main product.

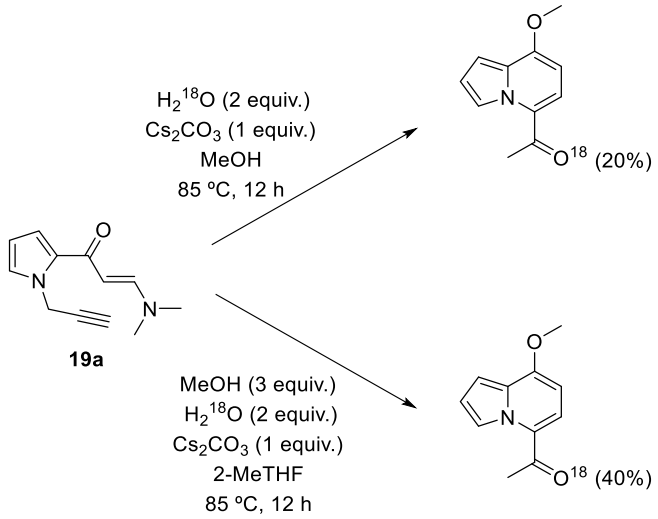


Scheme 2.44 Postulated mechanism for the formation of intermediate **A** from **19a**. Some steps have been summarized for more clarity.



Scheme 2.45 Postulated mechanism for the formation of derivatives **38–40** and **39a** from intermediate **A**. Some steps have been summarized for more clarity.

In order to discern between Pathway I and II, isotopically labeled water ($H_2{}^{18}O$) was added to the reactions between **19a** and MeOH (Scheme 2.46). In both cases (MeOH and 2-MeTHF as solvent) isotopically enriched (^{18}O) **38b** was obtained, and the isotopic content was measured by GC-MS. In Pathway II, the acetyl oxygen in intermediate **A** derived from the initial enaminoketone moiety, whereas in Pathway I that acetyl comes from the nucleophilic attack by water. Therefore, our isotopic labelling experiment provides strong evidence in favour of a mechanism based on Pathway I. However, as both the ^{18}O-labelled and the ^{16}O products were isolated,[73] Pathway II cannot be discarded.

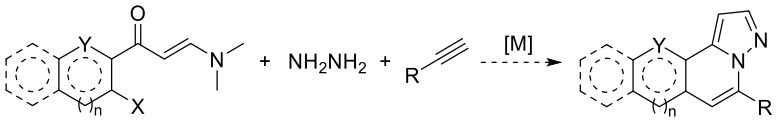


Scheme 2.46 Isolation of ^{18}O-labelled 5-acetylindolizines when $H_2{}^{18}O$ was added. Displayed percentages indicate ^{18}O-labelling degree.

[73] Although questionable, MeOH and Cs_2CO_3 could be the sources of $H_2{}^{16}O$.

3.3 Multicomponent reaction of *o*-halo(hetero)arylenaminones, hydrazine and alkynes

Encouraged by the excellent results obtained from the cascade reaction, we envisaged a multicomponent reaction comprising an *ortho*-halo(hetero)aryl enaminoketone, hydrazine and alkynes in the presence of a palladium catalyst, so that some of the products obtained in the above section (pyrazoloisoquinolines, pyrazolothienopyridines and furopyrazolopyridines, *inter alia*) could be accessed directly from the aforementioned substrates (Scheme 2.47).



42
Y = C, N, O, S
X = halogen
n = 0,1

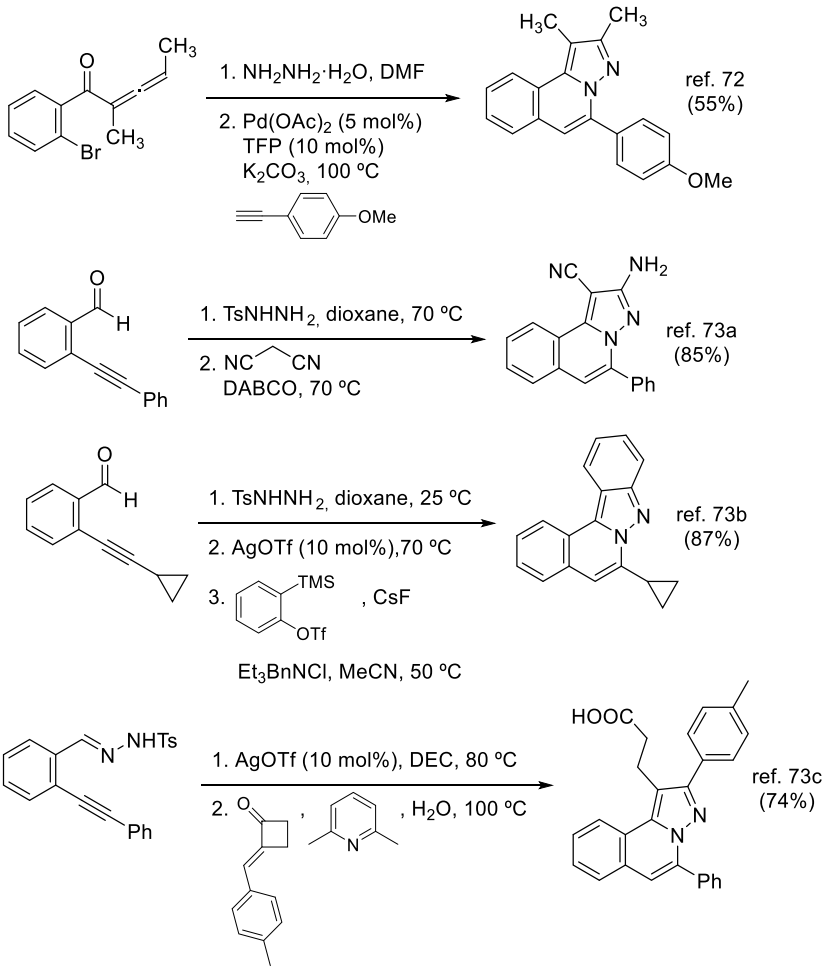
36

Scheme 2.47 Multicomponent approach to pyrazolo-fused heterocycles.

A search of the literature revealed that other groups had published the preparation of structurally related pyrazoloisoquinoles. Synthetically more challenging allenyl ketones, *o*-alkynylbenzaldehydes and *o*-alkynylhydrazides were the starting materials, and although the authors claimed that their approaches were based on genuine multicomponent reactions, in all cases a consecutive or sequential one-pot protocol was required, since reactants were added in separate steps (Scheme 2.48).[74,75]

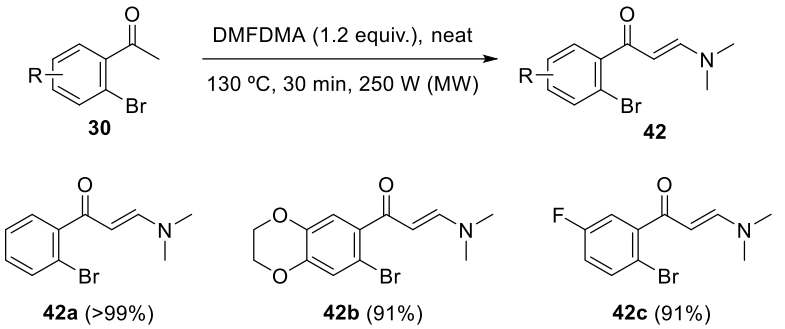
[74] Fan, X.; Yan, M.; Wang, Y.; Zhang, X. *J. Org. Chem.* **2015**, *80*, 10536–10547.

[75] For examples about synthesis of pyrazoloisoquinolines *via N*-isoquinolinium tosylamides check: a) Yu, X.; Yang, Q.; Lou, H.; Peng, Y.; Wu, J. *Org. Biomol. Chem.* **2011**, *9*, 7033–7037. b) Yang, J.; Yu, X.; Wu, J. *Synthesis* **2014**, *46*, 1362–1366. c) Pan, X.; Wang, H.; Xia, H. G.; Wu, J. *RSC Adv.* **2015**, *5*, 85225–85228.



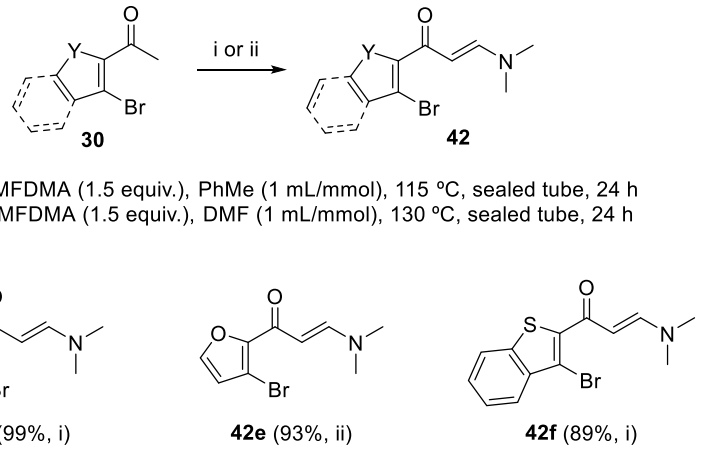
Scheme 2.48 Consecutive approach to the pyrazoloisoquinoline core.[a]
[a] Note: the reagents were added in the order specified by a one-pot multistep reaction.

(*E*)-1-(2-Bromophenyl)-3-(dimethylamino)prop-2-en-1-one **42a** was chosen as model substrate. This enaminoketone was prepared quantitatively from a commercially available *o*-bromoacetophenone by a microwave-assisted solventless aminomethylenation reaction (Scheme 2.49). It should be pointed out that we devised this protocol based on microwave irradiation. Further investigations will be required to expand the scope of the method.



Scheme 2.49 Microwave-assisted aminomethylenation of methyl ketones **30.**

This microwave-assisted procedure was also useful to prepare enaminones **42b-c** with good yields. Other heteroaromatic enaminoketones **42d-f** were prepared by conventional heating under the conditions displayed in Scheme 2.50.



Scheme 2.50 Preparation of heteroarylenaminones **42d-f**.

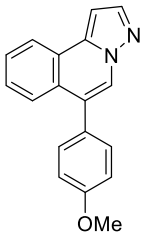
As mentioned before, enaminone **42a** was chosen as model substrate. A screening of reaction conditions (palladium sources, ligand, additives, solvents, etc.) was then carried out in order to get target pyrazoloisoquinoline **36a**. The initial assays were analyzed by GC-MS, and after noticing that better results were obtained when using water or alcohols as solvents, the experiments summarized in Table 2.9 were carried out in order to optimize other variables such as palladium source, catalyst loading, temperature, amount of reagents, bases, and additives.

From the results of the preliminary screening it became clear that $Pd(PPh_3)_4$ and $Pd(OAc)_2$ showed better performances than other candidates such as $Pd(dba)_2$ (entry 5), Pd/C (entry 6) or even palladium pincer complexes.[76] Hence, we decided to develop two alternative catalytic systems, one based on $Pd(PPh_3)_4$ and the other on $Pd(OAc)_2$. Optimization of the former led us to change from ethanol as solvent to water, but poor yields were achieved until substoichiometric amounts of a phase-transfer agent (TBAB) were added (entry 4 *vs* entries 1-3). After some changes in the temperature and the loading of TBAB, a five-fold decrease of catalyst and TBAB content was achieved (entry 11 *vs* 4, 7-10). However, we soon realized that slight modifications of the main protocol had to be performed in order to get comparable yields from other alkynes (*e.g.* 4-fluorophenylacetylene or *p*-anisylacetylene). Lower amounts of hydrazine and the replacement of TBAB with tetrabutylammonium bisulfate ($TBAHSO_4$) was required. Interestingly, Cs_2CO_3, K_2CO_3 and K_3PO_4 provided exactly the same result (entries 17–19), and the product was obtained using bases as different as KOH (entry 20, pKa= 15.6), DBU (entry 21, pka≈ 12) and KOAc (entry 22, pKa= 4.76), although providing poorer yields. In this regard, the reaction outcome did not seem to be directly related to basicity, although both an increase and a decrease in base equivalents (entries 23–25) had a negative effect on the reaction.

Entries 26–45 of Table 2.9 show some optimization assays performed on the catalyst system based on $Pd(OAc)_2$, taking *p*-anisylacetylene as model substrate. After trying with several monodentate ligands such as PPh_3 (entries 26–27), $PPh_2(O)H$ (entries 28–29), $P(OPh)_3$ (entry 30) and $P(OMe)_3$ (entry 31), dppf was chosen as the best candidate (entries 32–33), providing a moderate yield when 1.0 equivalent of ligand in relation to palladium (entry 32 *vs* 28–31 and 33) was added. In view of the performance of $Pd(OAc)_2$ at 1 mol% catalyst loading, it was decided to check its catalytic activity in ethanol, a solvent that had provided excellent results

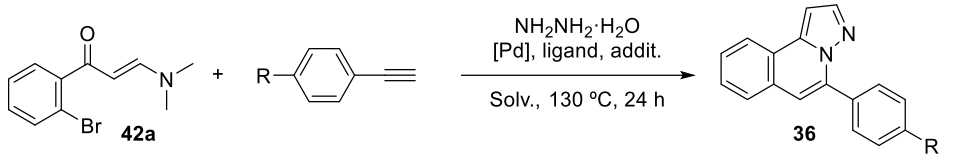
[76] Previously mentioned palladium pincer complexes **S**, **T** and **1a** were tested but they did not exhibit any catalytic profile in this reaction with the exception of palladacycle **S**, which provided dehalogenated intermediate 3-phenyl-1*H*-pyrazole.

in the cascade process (entries 34–35, see Table 2.5 for comparison). Surprisingly, in this case, unlike in water, a more saturated palladium sphere drove to slightly better results (entry 35 *vs* 34), and a change to Cs_2CO_3 as base provoked a marked decrease in yield (entry 44). Bearing in mind that the reaction was likely to proceed better in alcoholic media, (entry 35 *vs* 32) a wide range of alcohols were tested as possible solvent candidates (entries 37–43). MeOH (entry 37) demonstrated the highest performance and even surpassed that of the EtOH (entry 35), whereas the remaining alcohols provided lower yet similar yields (entries 38-41) except for PEG-400 (entry 43). As a curiosity, from the reaction in ^{n}PrOH (entry 39) we were able to isolate a side-product, previously detected in all the reactions, which upon analysis turned out to be the 6-arylregioisomer **43**.



43

Table 2.9 Optimization of reaction conditions for the multicomponent preparation of pyrazoloisoquinolines **36**.[a]



Entry	[Pd] (mol%)	NH_2NH_2 (equiv.)	R (equiv.)	Base (equiv.)	Ligand/add. (mol%)	Solv.	**36** (%)[c]
1[c]	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	KOH (2)	-	EtOH	70
2[c]	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	-	EtOH	67
3	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	-	H_2O	40
4	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (50)	H_2O	90
5	$Pd(dba)_2$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	PPh_3 (4.0), TBAB (50)	H_2O	60
6	Pd/C (5)	5.0	H (1.5)	Cs_2CO_3 (2)	PPh_3 (4.0), TBAB (50)	H_2O	57
7[d]	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (50)	H_2O	34
8[e]	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (50)	H_2O	90
9	$Pd(PPh_3)_4$ (5)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (100)	H_2O	80
10	$Pd(PPh_3)_4$ (1)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (50)	H_2O	90
11	$Pd(PPh_3)_4$ (1)	5.0	H (1.5)	Cs_2CO_3 (2)	TBAB (10)	H_2O	90
12	$Pd(PPh_3)_4$ (1)	5.0	F (1.5)	Cs_2CO_3 (2)	TBAB (10)	H_2O	32
13	$Pd(PPh_3)_4$ (1)	1.2	F (1.5)	Cs_2CO_3 (2)	TBAB (10)	H_2O	40
14	$Pd(PPh_3)_4$ (1)	1.2	F (1.3)	Cs_2CO_3 (2)	TBAB (10)	H_2O	40
15	$Pd(PPh_3)_4$ (1)	1.2	F (1.3)	Cs_2CO_3 (2)	TBAOH (10)	H_2O	36
16	$Pd(PPh_3)_4$ (1)	1.2	F (1.3)	Cs_2CO_3 (2)	$TBAHSO_4$ (10)	H_2O	50
17	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	Cs_2CO_3 (2)	$TBAHSO_4$ (10)	H_2O	72
18	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	K_2CO_3 (2)	$TBAHSO_4$ (10)	H_2O	72
19	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	K_3PO_4 (2)	$TBAHSO_4$ (10)	H_2O	72
20	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	KOH (2)	$TBAHSO_4$ (10)	H_2O	65
21	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	DBU (2)	$TBAHSO_4$ (10)	H_2O	63
22	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	KOAc (2)	$TBAHSO_4$ (10)	H_2O	54

[a] Reactions carried out with enaminoketone **42a** (0.5 mmol), hydrazine hydrate (X equiv.), alkyne (X equiv.), palladium source (X mol%), ligand (X mol%), additive (X equiv.) and solvent (1.5 mL/mmol), 130 ºC, 24 h, in a sealed-tube. [b] Isolated yields. [c] 120 ºC. [d] 100 ºC. [e] 150 ºC.

Table 2.9 Optimization of reaction conditions for the multicomponent preparation of pyrazoloisoquinolines **36**.[a] (*cont.*)

Entry	[Pd] (mol%)	NH_2NH_2 (equiv.)	R (equiv.)	Base (equiv.)	Ligand/add. (mol%)	Solv.	**36** (%)[c]
23	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	K_2CO_3 (3)	$TBAHSO_4$ (10)	H_2O	51
24	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	KOH (3)	$TBAHSO_4$ (10)	H_2O	46
25	$Pd(PPh_3)_4$ (1)	1.2	OMe (1.3)	K_2CO_3 (1)	$TBAHSO_4$ (10)	H_2O	31
26	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	PPh_3 (2.0), $TBAHSO_4$ (10)	H_2O	48
27	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	PPh_3 (4.0), $TBAHSO_4$ (10)	H_2O	46
28	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	$PPh_2(O)H$ (2.0), $TBAHSO_4$ (10)	H_2O	-
29	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	$PPh_2(O)H$ (4.0), $TBAHSO_4$ (10)	H_2O	-
30	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	$P(OPh)_3$ (4.0), $TBAHSO_4$ (10)	H_2O	-
31	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	$P(OMe)_3$ (4.0), $TBAHSO_4$ (10)	H_2O	-
32	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (1.0), $TBAHSO_4$ (10)	H_2O	60
33	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0), $TBAHSO_4$ (10)	H_2O	48
34	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (1.0)	EtOH	70
35	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	EtOH	76
36	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	Cs_2CO_3 (2)	dppf (2.0)	EtOH	44
37	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	MeOH	85
38	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	^{i}PrOH	39
39	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	PrOH	39
40	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	^{n}BuOH	38
41	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	^{t}BuOH	33
42	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	Glyc.	37
43	$Pd(OAc)_2$ (1)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	PEG-400	17
44	$Pd(OAc)_2$ (0.5)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	EtOH	23
45	$Pd(OAc)_2$ (2)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	EtOH	78
46	Pd/C (1.0)	1.2	OMe (1.3)	KOH (2)	dppf (2.0)	EtOH	68

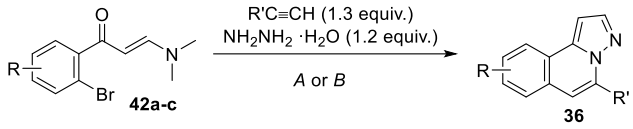
[a] Reactions carried out with enaminoketone **42a** (0.5 mmol), hydrazine hydrate (X equiv.), alkyne (X equiv.), palladium source (X mol%), ligand (X mol%), additive (X equiv.) and solvent (1.5 mL/mmol), 130 ºC, 24 h, in a sealed-tube. [b] Isolated yields.

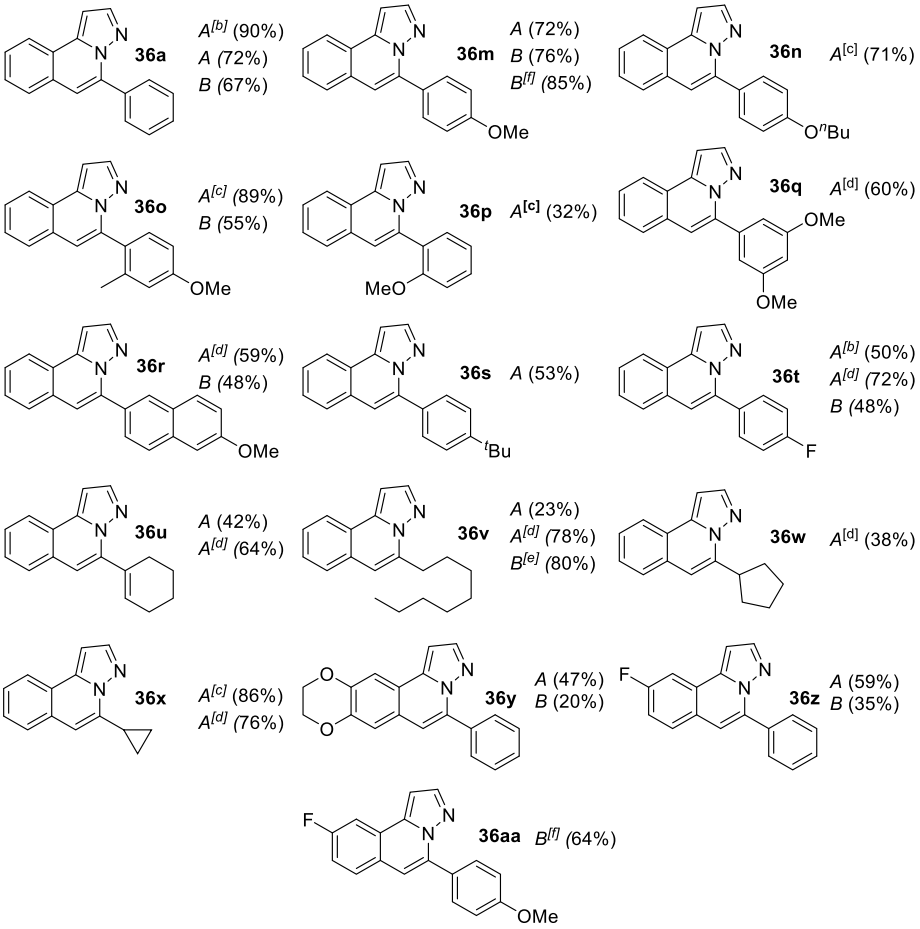
In spite of the promising result obtained in methanol, we decided to carry on the reactions in ethanol since it presents a lower toxicity and hence it is a better prospective candidate for industrial applications.[63,77] Anyway, MeOH was kept in reserve for cases where EtOH was not effective enough. Finally, although a lower yield was achieved, we succeeded in performing the reaction employing Pd/C (entry 46) a cheaper and easy-to-handle palladium source. Once the catalysts were tuned, they were applied to a number of arylenaminoketones **42** and aliphatic and aromatic alkynes to provide the results displayed in Table 2.10.

Moderate to good yields were obtained for all the pyrazoloisoquinolines **36** synthesized by this multicomponent cascade reaction regardless of the aliphatic, olefinic or aromatic nature of the alkyne employed or of the substitution pattern at the 2-bromoarylenaminone **42**. As predicted, both catalyst systems *A* and *B* provided alternative means for the access to target tri- and tetracycles **36**, although in some cases (*e.g.* sterically hindered 2-methoxyphenylacetylene to generate **36p** or olefinic 1-ethynylcyclohex-1-ene to form **36u**) the reaction yields were noticeably lower or the catalyst amount had to be increased to get acceptable results. The good results for a multicomponent reaction performed in aqueous media should be pointed out, considering that the change to alcoholic media did not provide remarkable improvements in many cases. Interestingly, catalyst performance was sometimes enhanced by changing the base, as for derivatives **36a, 36o** or **36x**.

[77] For a guide on sustainable reaction media, refer to: a) Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. *Green Chem.* **2011**, *13*, 854–862. b) Prat, D.; Pardigon, O.; Flemming, H. W.; Letestu, S.; Ducandas, V.; Isnard, P.; Guntrum, E.; Senac, T.; Ruisseau, S.; Cruciani, P.; et al. *Org. Process Res. Dev.* **2013**, *17*, 1517–1525. c) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. *Green Chem.* **2016**, *18*, 3879–3890.

Table 2.10 Multicomponent reaction from arylenaminones and terminal acetylenes. Substrate scope.[a]





[a] Method A: Enaminoketone **42a-c** (0.5 mmol), alkyne (1.3 equiv.), $NH_2NH_2{\cdot}H_2O$ (1.2 equiv.), $Pd(PPh_3)_4$ (1 mol%), K_2CO_3 (2 equiv.), $TBAHSO_4$ (10 mol%), H_2O (1.5 mL/mmol of **42**), 130 ºC, sealed tube, 24 h. Isolated yield. Method B: Enaminoketone **42a-c** (0.5 mmol), alkyne (1.3 equiv.), $NH_2NH_2{\cdot}H_2O$ (1.2 equiv.), $Pd(OAc)_2$ (1 mol %), dppf (2 mol %), KOH (2 equiv.), EtOH 96% (1.5 mL/mmol of **42**), 130 ºC, sealed tube, 24 h. Isolated yield. [b] Cs_2CO_3 (2 equiv.) was used as a base. [c] KOH (2 equiv.) was used as a base. [d] $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 equiv.), TBAB (10 mol%), 14 h. [e] $Pd(OAc)_2$ (2 mol%), dppf (4 mol %). [f] MeOH (1.5 mL/mmol) was used as solvent.

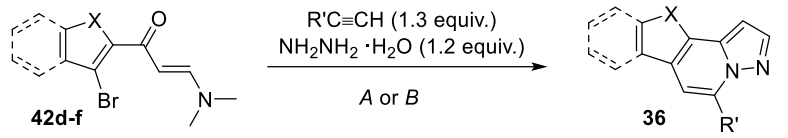
Previously prepared heteroarylenaminones **42d-f** were also reacted under the same reaction conditions (Table 2.11). In this regard, the catalyst system of choice was highly dependent on the starting heterocycle. Thus, benzothiophene derivatives provided better results when reacted using *Method A*, that is, in water as solvent. As with pyrazoloisoquinolines, slight modifications such as changing of the base, increasing the amount of the ligand or the palladium source were also carried out in order to improve the yields. Except for 5-cyclohexenyl derivatives **36l** and **36ah**, all the other pyrazolothienopyridines, furopyrazolopyridines and benzothienopyrazolopyridines derived from **42d-f** were regioselectively obtained in a single step with more than acceptable yields. Interestingly, when, in order to add such a low amount of the palladium source, $Pd(OAc)_2$ was added in solution (DMF), the already mentioned C-6 regioisomer (**43**) was detected in some cases. However, no trace of this regioisomer was observed when solid $Pd(OAc)_2$ was added to the reaction mixture. This behaviour could be related to the participation of competing different mechanisms depending on the palladium species involved.

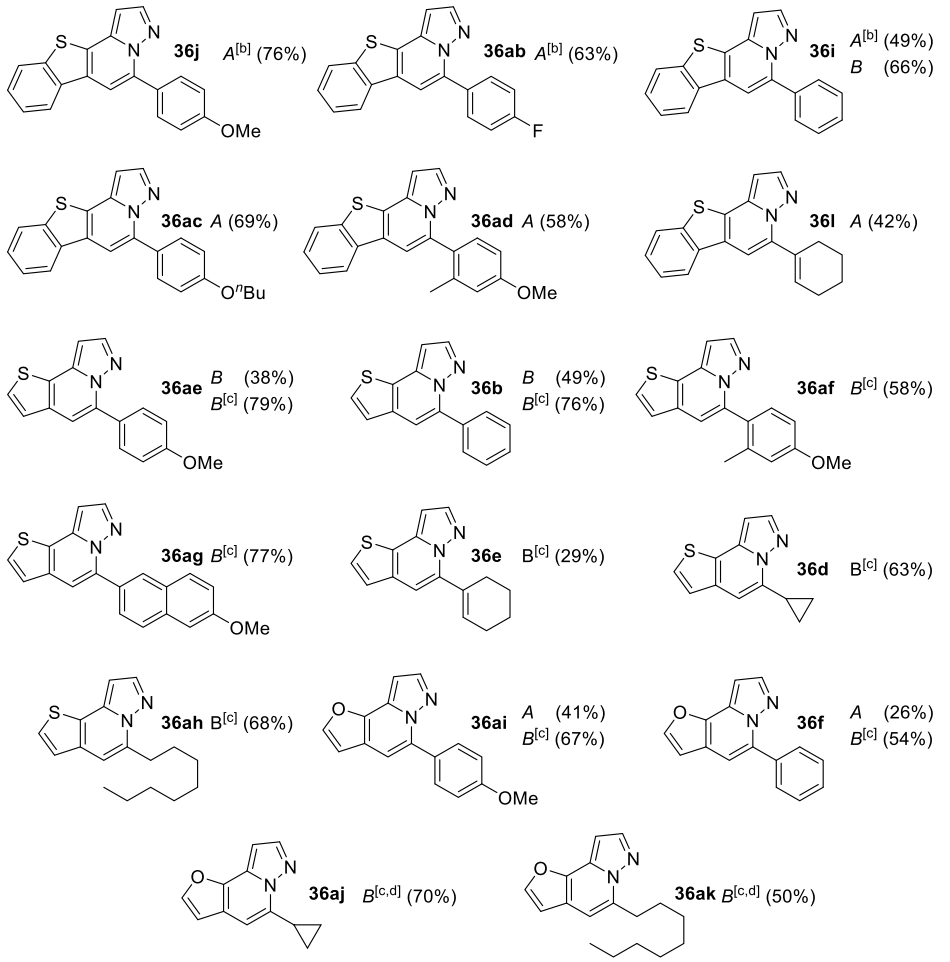
Many of the polyheterocycles prepared by this novel multicomponent reaction have been firstly synthesized in the present work. However, some pyrazoloisoquinolines have shown a remarkable biological activity[78] as well as appealing optoelectronic properties as organic light-emitting devices.[79]

[78] For information about bioactive pyrazoloisoquinolines, see: a) Chen, Z.; Wu, J. *Org. Lett.* **2010**, *12*, 4856–4859. b) Dore, A.; Asproni, B.; Scampuddu, A.; Pinna, G. A.; Christoffersen, C. T.; Langgård, M.; Kehler, J. *Eur. J. Med. Chem.* **2014**, *84*, 181–193.

[79] For information about pyrazoloisoquinolines as light-emitting devices, see: a) Kim, D. J.; Kim, M. J.; Ha, Y. S.; Eum, S. J.; Lee, J. D.; Lee, J. A.; Park, G. Y.; Lee, J. H.; An, Y. H.; Kim, Y. W. *Preparation of pyrazole-based compounds as organic light-emitting device materials.* WO 2014112728, July 24, 2014. b) Jung, S. J; Kim, K. Y.; Hong, J. M.; Eum, S. J.; Lee, J. D.; Jung, J. H.; Kim, M. J.; No, Y. S. *Polycyclic compounds containing pyrazole moiety as organic light-emitting device material*. WO 2015034140, March 12, 2015.

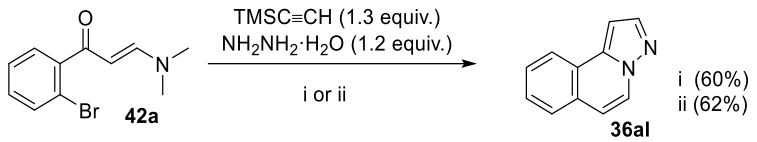
Table 2.11 Multicomponent reaction from heteroarylenaminones and terminal acetylenes. Substrate scope.[a]





[a] Method A: Enaminoketone **42d-f** (0.5 mmol), alkyne (1.3 equiv.), $NH_2NH_2{\cdot}H_2O$ (1.2 equiv.), $Pd(PPh_3)_4$ (1 mol%), K_2CO_3 (2 equiv.), $TBAHSO_4$ (10 mol%), H_2O (1.5 mL/mmol of **42**), 130 ºC, sealed tube, 24 h. Isolated yield. Method B: Enaminoketone **42d-f** (0.5 mmol), alkyne (1.3 equiv.), $NH_2NH_2{\cdot}H_2O$ (1.2 equiv.), $Pd(OAc)_2$ (1 mol %), dppf (2 mol %), KOH (2 equiv.), EtOH 96% (1.5 mL/mmol of **42**), 130 ºC, sealed tube, 24 h. Isolated yield. [b] Cs_2CO_3 (2 equiv.) was used as a base and TBAB (10 mol%) as additive. [c] $Pd(OAc)_2$ (2 mol %), dppf (4 mol %). [d] MeOH (1.5 mL/mmol) was used as solvent.

After the preparation of all these polyheterocyclic compounds, we wondered if a simple pyrazolo[5,1-*a*]isoquinoline without any substituent at C-5 could be also prepared by our methodology. Trying to avoid the use of highly flammable acetylene, two experiments employing trimethylsilylacetylene were carried out by slight modifications of *Methods A* and *B*. Good yields were obtained in both cases (60% and 62% respectively), and more interestingly, both implied an *in-situ* desilylation or deprotection of the alkyne reagent. In fact, this base-induced desilylation was visually evident. Indeed, bubbles from acetylene gas evolution were observed upon the addition of the silylated onto the reaction mixture (Scheme 2.51).



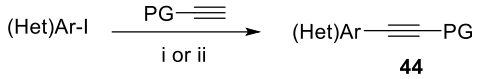
i : $Pd(PPh_3)_4$ (5 mol%), Cs_2CO_3 (2 equiv.), TBAB (10 mol%), H_2O (1.5 mL/mmol), 130 ºC, sealed tube, 14 h
ii : $Pd(OAc)_2$ (2 mol%), dppf (4 mol%), KOH (2 equiv.), EtOH 96% (1.5 mL/mmol), 130 ºC, sealed tube, 24 h

Scheme 2.51 Multicomponent reaction with trimethylsilylacetylene to form pyrazoloisoquinoline **36al**.

Therefore, we envisaged the possibility of using protected alkynes in our multicomponent reaction. The use of protected alkyne reagents has attracted much attention due to the problems associated to the use of alkyne reagents under strong basic media or oxidizing conditions.[80] With that aim in mind, a number of aryl- and heteroaryl alkynes protected as trimethysilylacetylenes or 2-methyl-3-butyn-2-ol derivatives were prepared by Sonogashira coupling of (hetero)aryl iodides with TMS-acetylene and 2-methyl-3-butyn-2-ol (Table 2.12).

[80] For information about protected alkynes as substrates, see: a) Caporale, A.; Tartaggia, S.; Castellin, A.; De Lucchi, O. *Beilstein J. Org. Chem.* **2014**, *10*, 384-393. b) Sun, F.; Gu, Z. *Org. Lett.* **2015**, *17*, 2222–2225. c) Ladouceur, S.; Soliman, A. M.; Zysman-Colman, E. *Synthesis* **2011**, *2011*, 3604–3611.

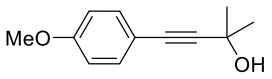
Table 2.12 Synthesis of protected (hetero)arylalkynes **44** by Sonogashira cross-coupling.[a]



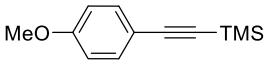
44

PG = -TMS, -CMe_2OH

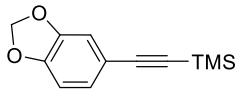
i : $PdCl_2(PPh_3)_4$ (2 mol%), CuI (4 mol%), TEA, reflux
ii : $PdCl_2(PPh_3)_4$ (3 mol%), CuI (6 mol%), TEA, DMF, 50 ºC.



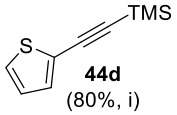
44a
(90%, i)



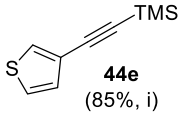
44b
(95%, i)



44c
(90%, ii)



44d
(80%, i)



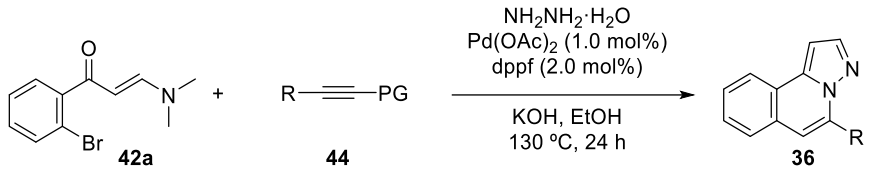
44e
(85%, i)

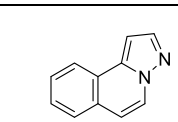
[a] (i) Reaction conditions: PG-acetylene (1.5 equiv.), $PdCl_2(PPh_3)_2$ (2 mol%), CuI (4 mol%), TEA (3.3 mL/mmol of ArI), reflux, 0.5 h. (ii) Reaction conditions: PG-acetylene (1.1 equiv.), $PdCl_2(PPh_3)_2$ (3 mol%), CuI (6 mol%), TEA (3.6 mL/mmol of ArI), DMF (1.7 mL/mmol of ArI), 50 ºC, 5 h.

After preparing these protected alkynes, we attempted a further expansion of the scope of our multicomponent reaction so that this cascade process would include *in-situ* deprotection (desilylation or base-induced release of acetone) and 5-(hetero)arylpyrazoloisoquinolines **36** could be also prepared from such protected alkynes. As shown in Table 2.13, enaminoketone **42a** was reacted with the above alkynes using our *Method B* ($Pd(OAc)_2$-dppf-EtOH) with an increased amount of base in order to facilitate the concomitant base-induced deprotection.

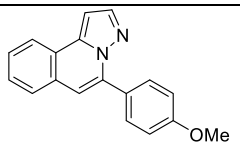
To our delight, protected *p*-methoxyphenylacetylenes **44a-b** provided comparable yields to that obtained with the *free* acetylene. Good yields were also obtained from the other TMS-alkynes derived from the Sonogashira coupling, with the exception of (thien-3-ylethynyl)trimethylsilane. Commercially available (cyclopropylethynyl)-trimethylsilane also provided the corresponding pyrazoloisoquinoline **36x** with a good yield, slightly inferior to the one from cyclopropylacetylene (see **36x** in Table 2.10). It is important to highlight that in all the reactions involving -TMS or -$C(CH_3)_2OH$ acetylenes no trace of the C-6 regioisomer was detected.

Table 2.13 Multicomponent reactions with protected alkynes.[a]

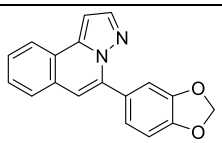




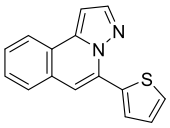
36al (62%)[b] PG = TMS
(60%)[c] PG = TMS



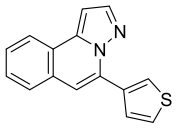
36m (76%) PG = TMS
(72%) PG = -C(CH3)2OH
(76%) PG = H
(37%)[d] PG = H



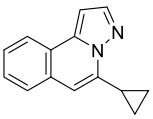
36am (60%) PG = TMS



36an (64%) PG = TMS



36ao (17%) PG = TMS



36x (75%) PG = TMS

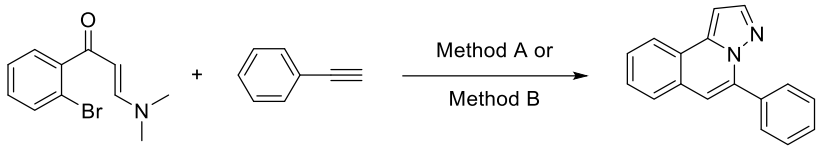
[a] Reactions conditions: Enaminone **42a** (0.5 mmol), protected alkyne **44** (1.3 equiv.), hydrazine hydrate (1.2 equiv.), $Pd(OAc)_2$ (1 mol%), dppf (2 mol%), KOH (4.0 equiv.) and EtOH 96% (1.5 mL/mmol **42a**), Ar, sealed-tube, 130 ºC, 24 h. Isolated yields. [b] $Pd(OAc)_2$ (2 mol%), dppf (4 mol%), KOH (2.0 equiv.). [c] Enaminone **42a** (0.5 mmol), protected alkyne **44** (1.3 equiv.), hydrazine hydrate (1.2 equiv.), $Pd(PPh_3)_4$ (5 mol%), TBAB (10 mol%), Cs_2CO_3 (2.0 equiv.), H_2O (1.5 mL/mmol **42a**), Ar, sealed-tube, 130 ºC, 14 h. Isolated yields. [d] KOH (2.0 equiv.) was used as a base.

In addition, we decided to check the scalability of the multicomponent reaction. For this purpose, we carried out the reaction leading to pyrazoloisoquinoline **36a** from 1.27 g of enaminoketone **42a** (Scheme 2.52). Although the yield decreased slightly, the "on-water" reaction allowed the access to 5-phenylpyrazoloisoquinoline **36a** in a 60% yield in 24 h. To our delight, the reaction in alcoholic medium worked even better than on small scale, thus affording the desired tricycle **36a** in a 77% yield.

Furthermore, ICP-MS analyses were performed to determine the palladium content in samples of pyrazoloisoquinoline **36a** obtained following both synthetic

methodologies, *i.e. Method A* and *Method B*. Surprisingly, the palladium content in **36a** synthesized by *Method A* turned out to be as high as 46 ppm, whereas metal content of **36a** obtained through *Method B* was notably lower (2.40 ppm). Therefore, considering that PDE[81] values of palladium for oral and parenteral administration are defined as 100 and 10 µg/day intake, respectively, the maximum palladium content in the drug should be of 10 and 1 ppm for oral and parenteral administered drugs, respectively.[82] In this regard, *Method B* afforded a product compatible for oral administration. It is worth mentioning that modified *Method A*, employing Pd/C (1 mol%) and dppf (2 mol%) instead of $Pd(PPh_3)_4$, provided a product with low metal content (0.89 ppm) which may comply with the regulations established for both oral and parenteral drug administration.

Besides, the implementation of an effective work-up or a final product crystallization step might contribute to minimize palladium content in the product, thus enabling its use directly for a drug formulation.



42a
1.27 g
5 mmol

36a
A: 0.73 g, (60%)
B: 0.95 g, (77%)

Method A: $Pd(PPh_3)_4$ (1 mol%), $NH_2NH_2{\cdot}H_2O$, K_2CO_3, $TBAHSO_4$, H_2O, 130 ºC, 24 h
Method B: $Pd(OAc)_2$ (1 mol%), dppf (2 mol%), $NH_2NH_2{\cdot}H_2O$, KOH, EtOH 96º, 130 ºC, 24 h

Scheme 2.52 Scale-up of the multicomponent reaction leading to pyrazoloisoquinoline **36a**.

The structure of some of the multicomponent cascade products was additionally confirmed by X-ray diffractometry. Thienopyrazolopyridine **36b** and 4-butyloxyphenyl-decorated pyrazoloisoquinoline **36n** (Figure 2.5) crystallized in the

[81] International Conference on Harmonisation, Elemental impurities. ICH Q3D (R1) Guideline. EMA/CHMP/ICH/353369/2013
[82] The calculation was performed assuming a worst case of ≤ 10 g/day drug intake, following ICH Q3D (R1) Guideline.

monoclinic $P2_1$ space-group. Planarity of the tricyclic moieties was easily proven by examining the N2-N1-C9-C8, C8-C7-C4-S1 or C2-C3-C4-S1 torsion angle values for **36b** (175.6º, 177.5º and 4.7º, respectively) and N2-N1-C5-C15, C15-C14-C9-C10 or C10-C9-C8-C7 for **36n** (- 175.3º, 178.7º and - 3.5º, respectively). The derivation from co-planarity for the 5-phenyl group of **36b** (*e.g.* C8-C9-C10-C11 torsion angle of - 48º) was probably related to packing of the crystal lattice. Although there was no reliable evidence of π-stacking interactions (centroid···centroid = 4.569 Å),[83] an orderly layout of the tricyclic systems is clearly visible when analyzing several views of the crystal packing (*e.g.* Figure 2.6).

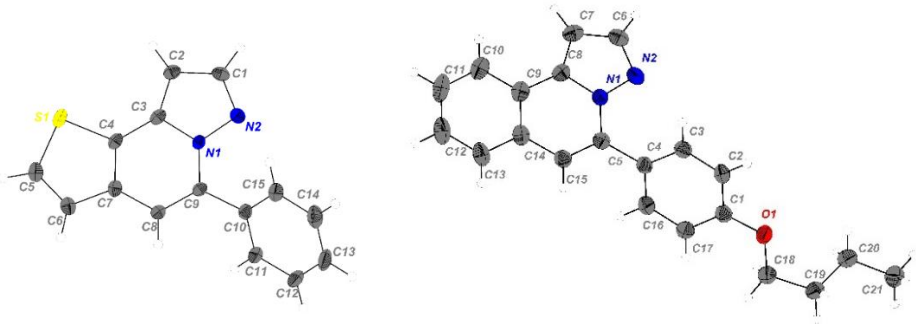


Figure 2.5 ORTEP diagrams of thienopyrazolopyridine **36b** (left) and pyrazoloisoquinoline **36n** (right) with thermal ellipsoids given at 50% probability level. Molecules showing employed nomenclature.

[83] There are studies that support that the distance between ring centroids for π-π interactions should not exceed 3.8 Å: Janiak, C. *J. Chem. Soc. Dalt. Trans.* **2000**, *21*, 3885–3896.

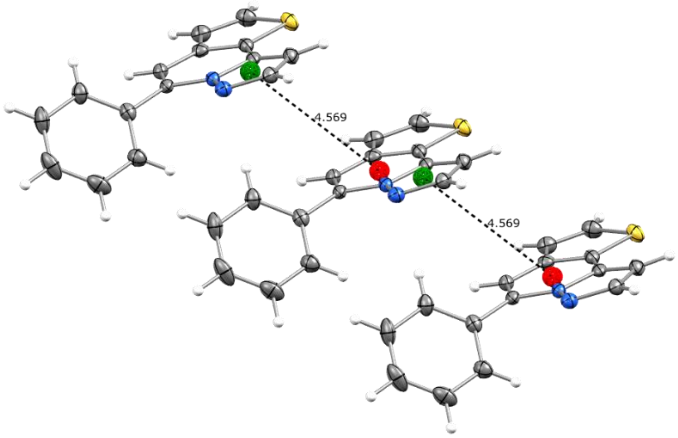


Figure 2.6 Distance between centroids in **36b**.

In a similar way, 4-butyloxyphenyl moiety present in **36n** suffers a deviation from planarity as proven by the C15-C5-C4-C16 (53.7º) torsion angle. This may account, to some extent as in the previous case, for the zig-zag T-shaped π-stacking (C7···ring centroid = 3.514 Å) observed (Figure 2.7).

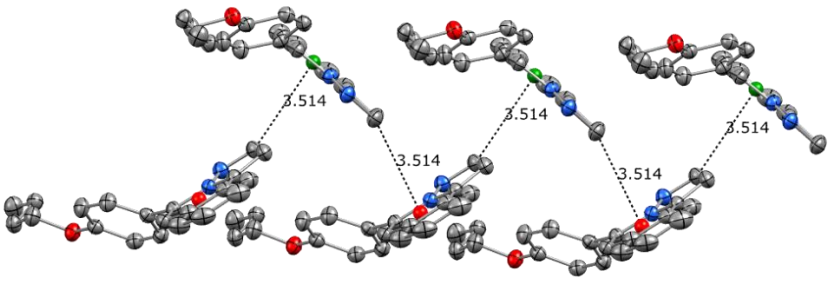


Figure 2.7 Zig-zag T-shaped π-stacking (protons are omitted for clarity).

Similarly, heterocycles **36i** and **36m**, crystallized in the monoclinic crystal-system with a $P2_1/c$ space-group with only a molecule present in the asymmetric-unit (Figure 2.8). Planarity of the tetracyclic and tricyclic moieties present in **36i** and **36m** was confirmed observing some torsion angle values such as N2-N1-C13-C12 (-177.6º) and N2-N1-C11-C10 (179.3º), for **36i** and **36m** respectively. In addition,

as in the previous examples, a deviation from co-planarity was observed for the aryl substituent (see for example C12-C13-C14-C15 = 44.4º, for **36i** and C10-C11-C12-C13 = 56.6º, for **36m**). Both geometric effects might contribute to the energy minimization promoted by orthogonally placed antiparallel sandwich-type π-stacking interactions in **36i** (centroid···centroid = 3.720 Å) and stair-like π-π interactions (C10···H13 and C11···H1 2.872 Å and 2.849 Å, respectively) in **36m** that stabilize the crystal-systems (Figure 2.9 and Figure 2.10).

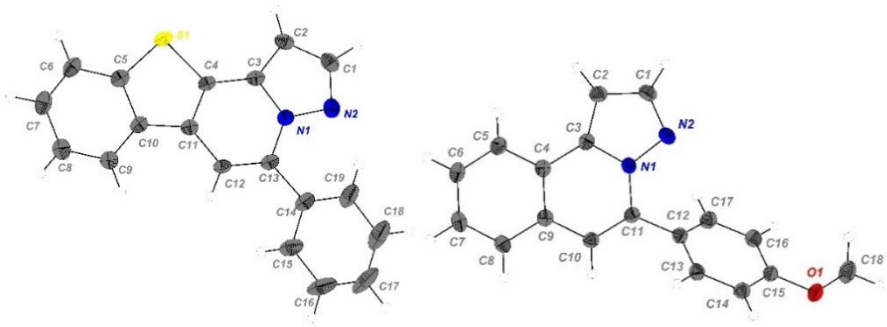


Figure 2.8 ORTEP diagram of benzothienopyrazolopyridine **36i** (left) and pyrazoloisoquinoline **36m** (right) with thermal ellipsoids given at 50% probability level. Molecules showing employed nomenclature.

Interestingly, the presence of a benzo-fused ring in **36i** provoked a slight elongation of the C5-C10 bond (1.408 Å) in comparison to its analogous tricycle **36b** (Figure 2.5, C5-C6 = 1.355 Å) owing to conjugation.

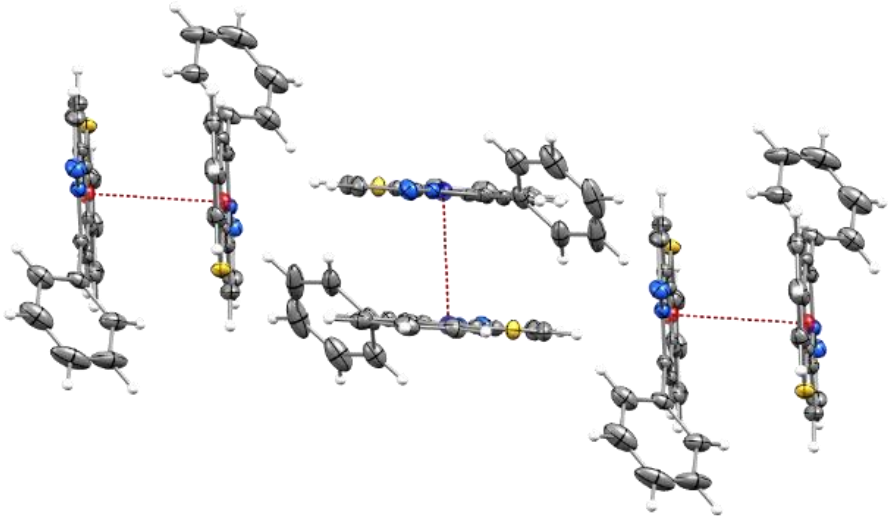


Figure 2.9 Detail of π-π-stacking interaction in **36i.**

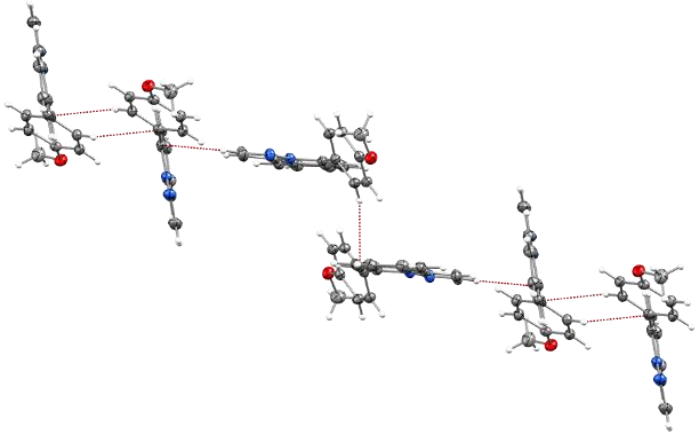


Figure 2.10 Detail of π-π-stacking interaction in **36m** (down).

Finally, unlike previously analyzed structures, pyrazoloisoquinoline **36p** crystallized in the orthorhombic $Pna2_1$ space-group with two molecules in the asymmetric unit (Figure 2.11). Planarity of the tricyclic system was again confirmed by examining torsion angle values such as N2-N1-C11-C10 = - 179.4º.

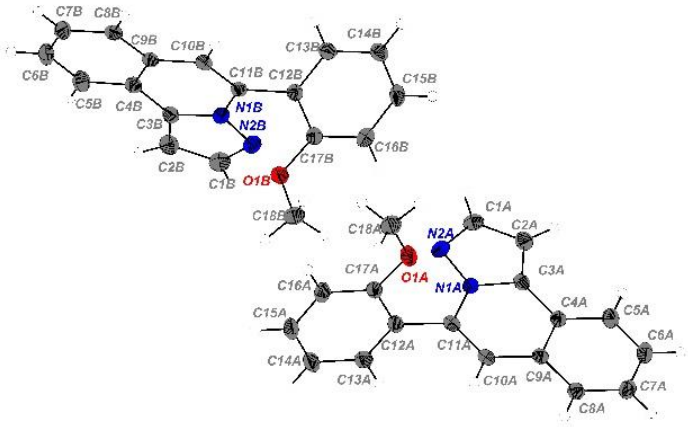


Figure 2.11 ORTEP diagram of pyrazoloisoquinoline **36p** with thermal ellipsoids given at 50% probability level. Molecule showing employed nomenclature.

Moreover, due to the steric hindrance arising from the *o*-methoxy group present on the aryl substituent, the latter adopts a nearly orthogonal conformation as displayed by the C10-C11-C12-C17 torsion angles (99.2º). Additionally, the crystal-system presents not only antiparallel π-π interactions (centroid···centroid = 3.662 Å), but also what seems to be π-alkyl interactions (C18···2-anisyl centroid = 3.438 Å) between the methyl group in the methoxy moiety and the 2-anisyl ring (Figure 2.12).

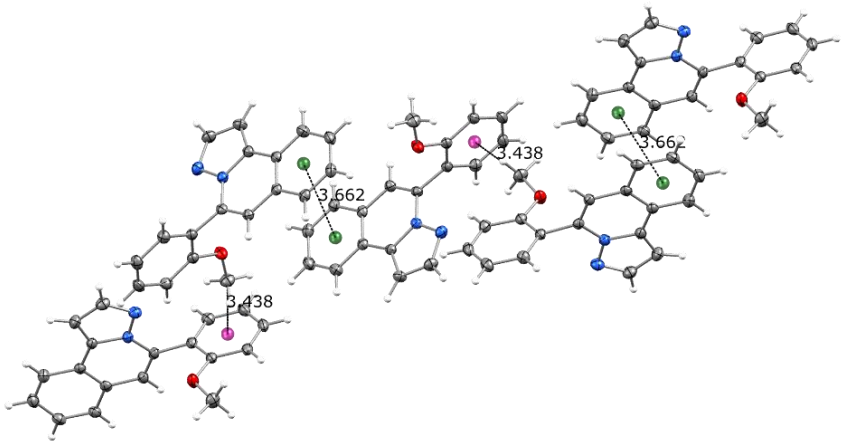


Figure 2.12 Detail of the antiparallel π-π (green centroids) and π-alkyl (pink centroids) interactions present in **36p**.

3.3.1 Mechanistic insights into the multicomponent cascade reaction from o-halo(hetero)arylenaminones, alkynes and hydrazine.

A number of experiments were carried out (kinetic curve, poisoning assays and isotopic labelling) in order to clarify the reaction mechanism. Regarding the kinetic study, it was performed in order to know if the catalyst system was homogeneous or heterogeneous. Due to the difficulties to perform an accurate analysis of the reaction crude, the reactions were worked up and purified to get the isolated yield at different reaction times. The so-obtained kinetic plot (Figure 2.13) showed neither induction-time nor a sigmoidal shape, so the kinetic analysis pointed *a priori* to a homogeneous catalytic system.[84]

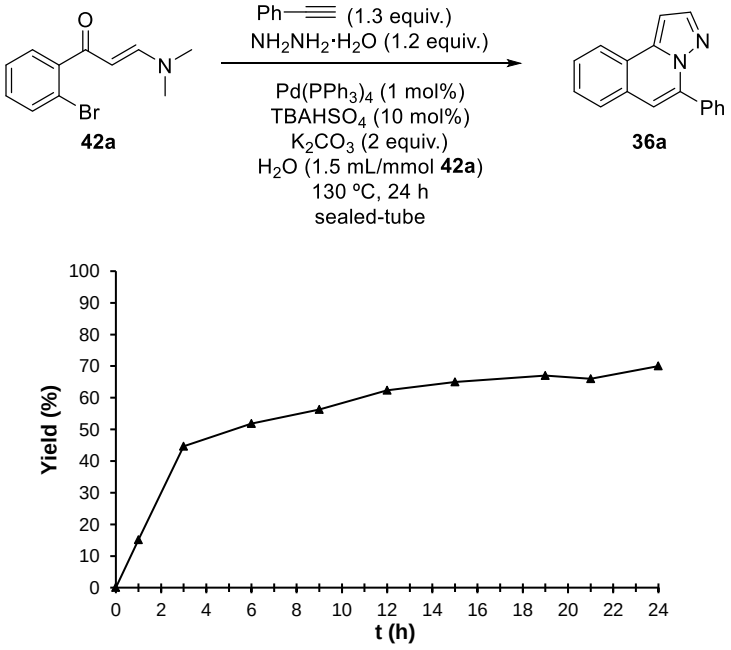


Figure 2.13 Isolated yield of pyrazoloisoquinoline **36a** *vs* time. For reaction conditions, see *Method A.*

[84] The presence of induction-time and sigmoidal shaped kinetic curves are often related to the participation of heterogeneous species. For a deeper review on the parameters to be addressed in the determination of heterogeneous species, check: Bayram, E.; Balasubramanian, M.; Finke, R. G. *J. Am. Chem. Soc.* **2011**, *133*, 18889–18902.

Poisoning tests[85] were also performed with the aim of defining the catalyst-type as a homogeneous or heterogeneous system. Safe for the mercury drop-test, all the other results provided evidence in favour of the participation of homogeneous catalytic species. Thus, there is no substantial decrease in the yields when comparing the addition of substoichiometric and overstoichiometric amounts of the poisoning additive (*e.g.* CS_2 or PPh_3). Moreover, there is no striking difference between the results from the addition of pyridine and polyvinylpyridine (PVPy). Moreover, both catalytic systems (*Method A* and *B*) behaved the same or the same trend was observed for both. This is somehow surprising, since the addition of $Pd(OAc)_2$ to the reaction mixture (*Method B*) provoked the quick noticeable formation of a black precipitate that looked like palladium black.

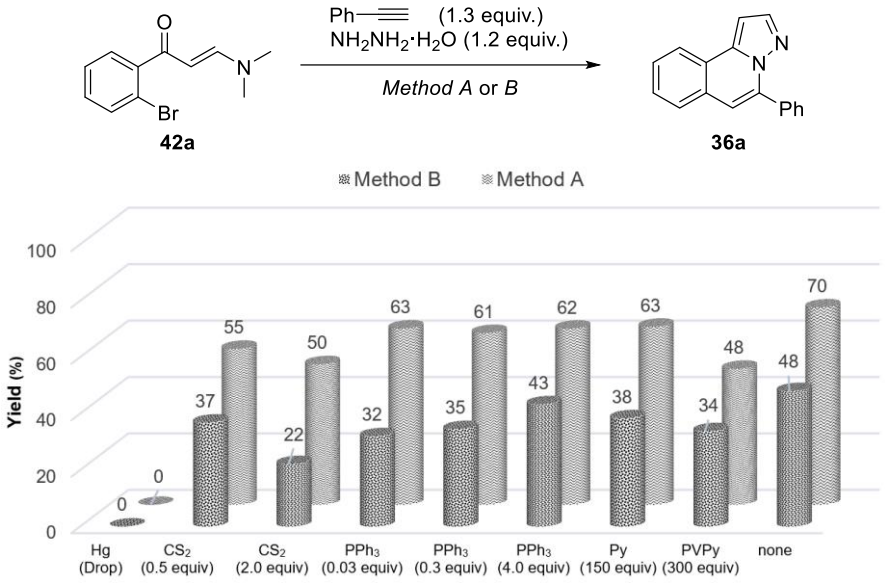


Figure 2.14 Plot of the yields observed from several poisoning assays. See Table 2.10 for more details on *Method A* and *B*.[86]

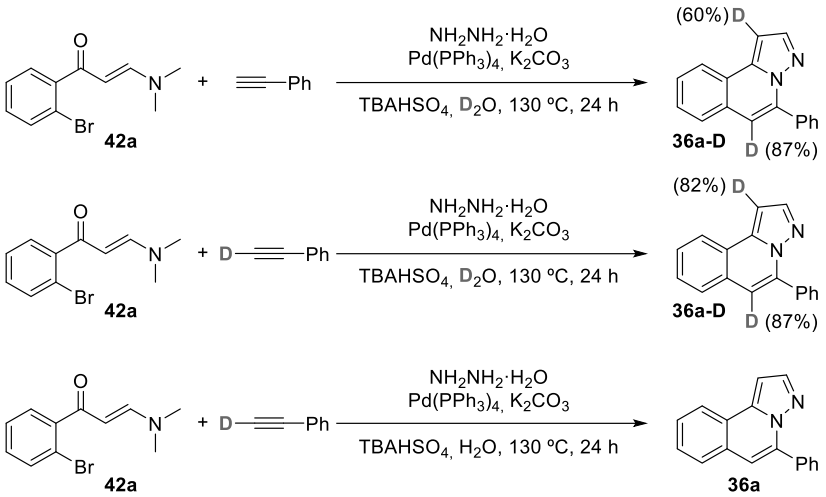
[85] Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A. Chem.* **2003**, *198*, 317–341.

[86] These poisoning assays were performed at a very small scale (0.3 mmol of enaminone **43a**) and subsequently, stock solutions of $Pd(OAc)_2$ in DMF were used. As mentioned before, the use of such solution led to a substantial decrease (Δ% ~ 20%) in the yield, as well as to the detection of the C-6 regioisomer. Anyway, we decided to include these results that, in our opinion, follow the same trend observed for *Method A*.

With regard to the mercury drop-test, false positive results have been previously reported in palladacycle-catalyzed Suzuki reactions.[87] Recently, Hg has been reported to have the ability to undergo transmetalation with nitrogen-bearing palladacycles, thus inactivating the catalyst and leading to a wrong conclusion.[88] Moreover, it should be pointed out that these poisoning assays, including the Hg drop-test, were designed for monophasic systems and thereby, this might lead to ambiguous results given we are examining an "on-water" process when dealing with Method A.[84,85]

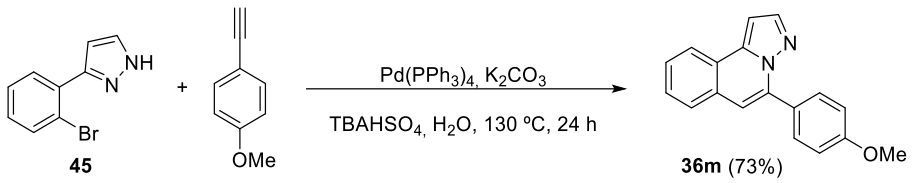
Isotopically labelled substrates and solvents were also subjected to the optimized reaction conditions (*Method A*) in order to gain knowledge on the reaction mechanism through proton-transfer processes. As shown in Scheme 2.53, deuteration at C-6 and C-1 was observed when D_2O was used as solvent as well as when deuterium oxide was combined with (ethynyl-*d*)benzene. Deuteration degree at C-1 increased from 60% to 82% in the latter case. However, no deuterated position was observed when the aforementioned deuterated phenylacetylene was used with water instead of with D_2O. Deuteration at C-1 can be associated to an iminium-enamine tautomeric equilibrium, while deuteration at C-6 might account for a "deuterolysis/protonolysis" of the final palladium intermediate.

[87] Gorunova, O. N.; Livantsov, M. V.; Grishin, Y. K.; Ilyin, M. M.; Kochetkov, K. A.; Churakov, A. V.; Kuz'Mina, L. G.; Khrustalev, V. N.; Dunina, V. V. *J. Organomet. Chem.* **2013**, *737*, 59–63.
[88] Gorunova, O. N.; Novitskiy, I. M.; Grishin, Y. K.; Gloriozov, I. P.; Roznyatovsky, V. A.; Khrustalev, V. N.; Kochetkov, K. A.; Dunina, V. V. *Organometallics* **2018**, *37*, 2842–2858.



Scheme 2.53 Isotopically labelled alkyne and solvent in multicomponent cascade reaction. Displayed percentages indicate deuteration degree.

In order to confirm the intermediacy of pyrazole intermediates, *i.d.*, the participation of amine exchange/heterocyclization processes, readily available[89] 5-(2-bromophenyl)-1*H*-pyrazole **45** was treated with *p*-methoxyphenylacetylene under the optimized reaction conditions (*Method A*), and pyrazoloisoquinoline **36m** was obtained with a 73% yield (Scheme 2.54).



Scheme 2.54 Reaction of 5-(2-bromophenyl)-1*H*-pyrazole with *p*-anisylacetylene (*Method A*).

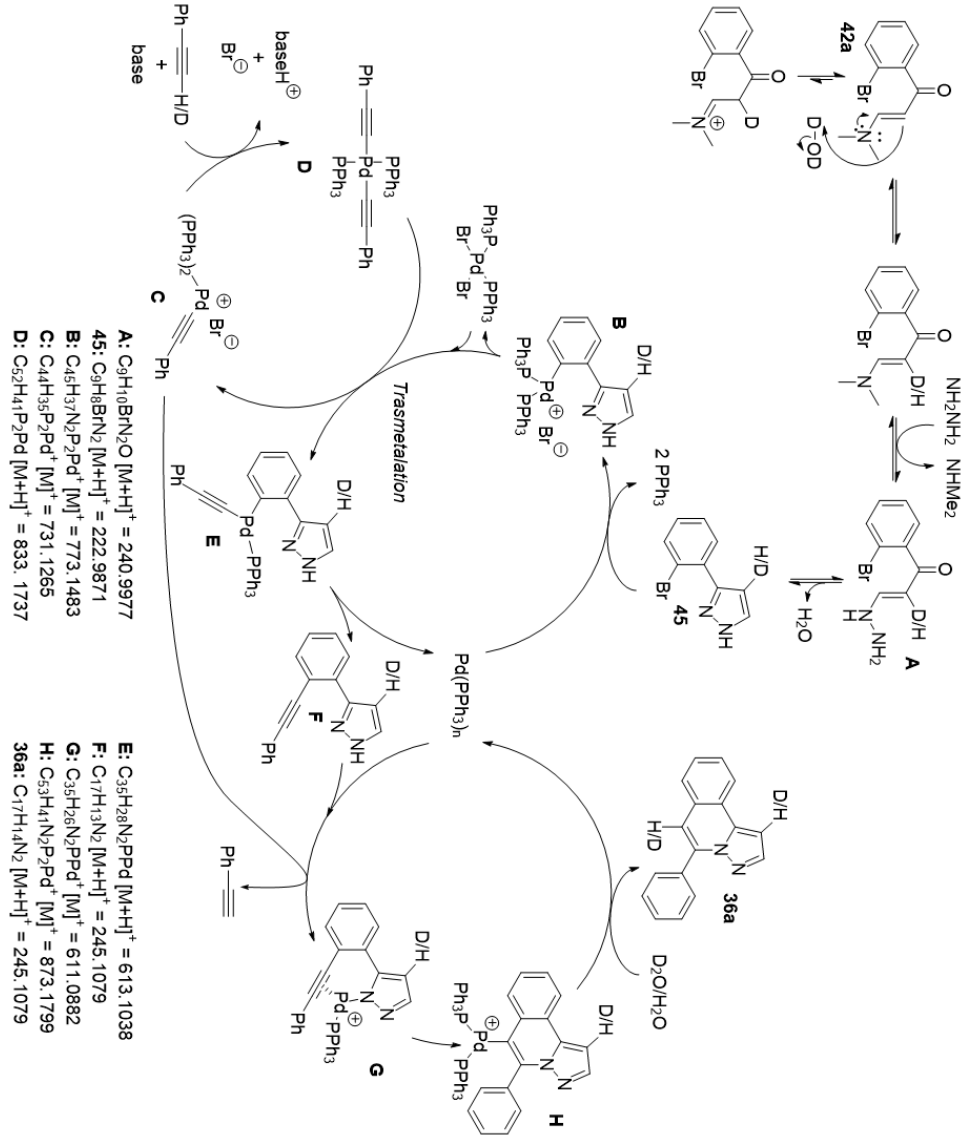
With all these experimental results at hand, the mechanism depicted in Scheme 2.55 was proposed. Rapid hydrogen/deuterium exchange at the α-position of the starting enaminoketone *via* a dimethyliminium intermediate would explain the deuteration observed at C-1. After amine-exchange with hydrazine, the resulting

[89] The corresponding pyrazole was prepared in a 93% yield by reaction of enaminoketone **42a** with hydrazine hydrate in ethanol 96º for 5 h. This reaction had not been previously described for that product.

intermediate **A** would cyclize by condensation with the carbonyl moiety and dehydration/aromatization would render 5-(2-bromophenyl)-1*H*-pyrazole **45**, which in the presence of the palladium(0) source would undergo oxidative addition to intermediate **B**. This step would start the two interconnected Pd^{0}/Pd^{II} catalytic cycles recently accepted to explain the mechanism of copper-free Sonogashira coupling.[90]

Thus, base-induced deprotonation would favour the formation of monoacetylide and diacetylide palladium complexes **C** and **D**, which also requires the participation of transient $(Ph_3P)_2PdBr_2$ (formed by homocoupling of **B**).[90] Key transmetalation between **B** and diacetylide **D** would generate intermediate **E**, which upon reductive elimination would release *o*-alkynylphenylpyrazole **F**. Deprotonation of the latter by monoacetylide **C** may provide palladacycle **G**, ready for the intramolecular amination of the *o*-alkynyl moiety that would lead to palladated pyrazoloisoquinoline intermediate **H**. Protonolysis/deuterolysis with the solvent would render final product **36a**, which depending on the last step would show isotopic labelling at C-6 or not. In addition to the above confirmed 5-(2-bromophenyl)-1*H*-pyrazole **45**, all the proposed intermediates **A**-**H** were detected by UPLC-MS (ESI) from the reaction crude.

[90] For more information concerning revised mechanism for copper-free Sonogashira cross-couplings, see: Gazvoda, M.; Virant, M.; Pinter, B.; Košmrlj, J. *Nat. Commun.* **2018**, *9*, 4814.



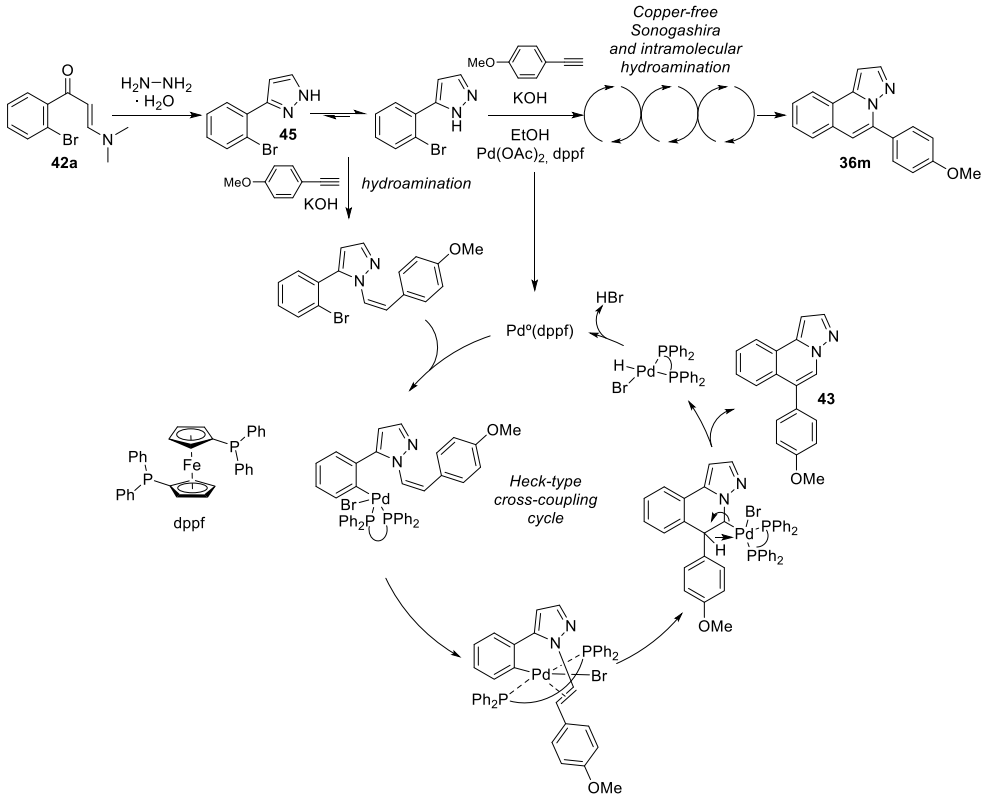
Scheme 2.55 Postulated mechanism for the palladium-catalyzed multicomponent reaction of *o*-bromo(hetero)arylenaminones, hydrazine and alkynes. Some steps have been omitted for more clarity.

On account of the latter tentative proposal, we also hypothesized that the formation of 6-arylpyrazoloisoquinoline **43**, an already mentioned side-product only detected when *Method B* was used (to be precise, when DMF stock solution of $Pd(OAc)_2$ was employed), could be related to a competing intermolecular hydroamination undergone by 5-(2-bromoaryl)-1*H*-pyrazole **45**. Instead of the aforementioned copper-free Sonogashira coupling and subsequent palladium-catalyzed cyclization, alkyne hydroamination by pyrazole **45** would generate an enamine intermediate which might undergo an intramolecular Heck-type coupling leading to 6-(4-methoxyphenyl)pyrazoloisoquinoline **43** (Scheme 2.56). This latter Heck reaction was likely aided by the bite-angle (99º for dppf)[91] provided by the diphosphine.

In summary, a new multicomponent approach to 5-aryl-pyrazoloisoquinolines, -(benzo)thienopyrazolopyridines and -furopyrazolopyridines has been developed. This new process is based on the reaction between *o*-halo(hetero)arylenaminones, hydrazine and alkynes. Considering the state-of-the-art for palladium-catalyzed reactions, relatively low catalyst loadings for two alternative catalytic systems have been implemented, both based on the use of sustainable reaction media. Competitive yields are obtained by this straightforward approach, thus overcoming the difficulty inherent to multicomponent strategies.

In addition, an alternative and in some cases complementary approach to the above polyheterocyclic compounds and related structures has been devised using a cascade amine exchange/heteroannulation/hydroamination of enaminoketones. The exploration of this process from *N*-propargylated enaminoketones derived from pyrrole has resulted in a new entry to indolizine derivatives.

[91] Birkholz, M. N.; Freixa, Z.; Van Leeuwen, P. W. N. M. *Chem. Soc. Rev*. **2009**, 38, 1099–1118.



Scheme 2.56 Proposed mechanism for the formation of C-6 regioisomer **43**.

4 EXPERIMENTAL PROCEDURES

4.1 General methods and materials

All reagents were purchased and used as received except when indicated. Anhydrous solvents and reagents were dried and purified according to standard procedures.[92] All air- or moisture-sensitive reactions were carried out under argon atmosphere. The glassware was oven dried (140 ºC) overnight and purged with argon prior to use. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.5 MHz for ^{13}C) at 20ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.00 for ^{13}C). Coupling constants, *J*, are reported in hertz (Hz). Melting points (m.p.) were determined in a capillary tube using a Gallenkamp melting point apparatus and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). IR spectra were recorded on a JASCO FTIR-4100 ATR infrared spectrophotometer, and only strong absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Evaporation of solvents was accomplished with a Büchi or Heidolph rotary evaporator. In the cases where sonication was required to enhance solubility, a Ultrasons 20 ultrasonic bath was used. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions. HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI). Other electrospray Ionization Mass Spectra (ESI-MS) were measured employing an Acquity UPLC-Mass Spectrometer QTOF from Waters. ICP-MS measurements were carried out on a Thermo Elemental X7 series equipped with an ASX-520 autosampler. Reactions carried out under microwave irradiation were performed using a CEM Discover 1-

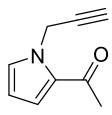
[92] a) Armarego, W. L. F.; "*Purification of Laboratory Chemicals"*, 8th Ed., Elsevier, **2017**, Oxford, UK; b) Williams, B. G.; Lawton, M. S. *J. Org. Chem.* **2010**, *75*, 8351–8354.

300W system equipped with a built-in pressure measurement sensor and a vertically focused IR temperature measurement sensor. X-ray diagrams of the obtained single crystals were performed in an Agilent SuperNova Cu-diffractometer, equipped with an Atlas model CCD detector at 100 K, using a liquid-nitrogen cooled Cryostream 700 system from Agilent cryosystems. All the hydrogen atoms have been located in the residual density map and have been refined using SHELXL97's *riding* model.[93]

4.2 Cascade amine exchange/heteroannulation/hydroamination reaction

4.2.1 Propargylation of pyrrole derivatives

1-[1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl]ethan-1-one (22).[94] **Typical procedure.** A round-bottom flask containing a magnetic stirrer was charged with 2-acetylpyrrole (500 mg, 4.58 mmol), TBAB (75.4 mg, 0.23 mmol) and toluene (48.5 mL). Then, an aqueous NaOH 50% w/w (5.5 mL) solution was added, followed by slow addition of propargyl bromide (0.66mL, 6.0 mmol), and the reaction was stirred at r.t. for 12 h. After that, the reaction mixture was diluted with toluene (50 mL) and washed with water (2 × 100 mL), after which the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent purification of the residue by flash column chromatography (PE:EtOAc 8:2) furnished the desired product **22** as a brownish powder (566.5 mg, 84%).



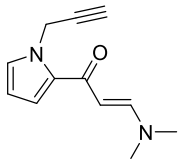
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 2.6, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.99 (dd, *J* = 4.1, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.19 (dd, *J* = 4.1, 2.6 Hz, 1H, C*H*$_{pyrrole}$), 5.22 (d, *J* = 2.6 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.44 (s, 3H, C*H*$_{3,\ Ac}$), 2.42 (t, *J* = 2.6 Hz, 1H, C*H*$_{alkyne}$).

[93] Sheldrick, G. M. *Acta Crystallogr.* **2008**, *64*, 112–122.
[94] Abbiati, G.; Casoni, A.; Canevari, V.; Nava, D.; Rossi, E. *Org. Lett.* **2006**, *8*, 4839–4842.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 188.7 (*C*=O), 130.1 (q*C*$_{arom}$), 129.3 (*C*H$_{arom}$), 120.6 (*C*H$_{arom}$), 108.7 (*C*H$_{arom}$), 78.3 (q*C*$_{alkyne}$), 74.0 (*C*H$_{alkyne}$), 38.9 (*C*H$_{2,\ propargyl}$), 27.2 (*C*H$_{3,\ Ac}$).

m.p.: 109–111 ºC (EtOAc). *Lit.*[94] 111–114 ºC (PhMe)

♁ ***(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl)-1*H*-pyrrol-2-yl]prop-2-en-1-one (19a).** The typical procedure was followed employing enaminone **23** (500 mg, 3.04 mmol) and propargyl bromide (0.44 mL, 4.0 mmol). The product was isolated after purification (PE:EtOAc 7:3) as a yellow powder (505.2 mg, 82%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.66 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.08 (dd, *J* = 2.7, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.83 (dd, *J* = 4.0, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.16 (dd, *J* = 4.0, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 5.59 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 5.34 (d, *J* = 2.6 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.98 (s, 6H, N(C*H*$_3$)$_2$), 2.38 (t, *J* = 2.6 Hz, 1H, C*H*$_{alkyne}$).

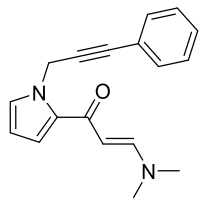
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.7 (*C*=O), 152.4 (*C*H$_{enaminone}$), 131.9 (q*C*$_{arom}$), 127.1 (*C*H$_{arom}$), 115.8 (*C*H$_{arom}$), 108.0 (*C*H$_{arom}$), 93.4 (*C*H$_{enaminone}$), 79.3 (q*C*$_{alkyne}$), 73.2 (*C*H$_{alkyne}$), 38.6 (*C*H$_{2,\ propargyl}$).

m.p.: 113–116 ºC (EtOAc)

HRMS (*m/z*): [M$^+$] calc. for $C_{12}H_{14}N_2O$: 202.1106; found: 202.1105

IR (ATR) (cm^{-1}): 3102, 2931, 2912, 1631, 1555

♁ ***(E)*-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl]-1*H*-pyrrol-2-yl)prop-2-en-1-one (19b).** The typical procedure was followed employing enaminone **23** (500 mg, 3.04 mmol) and 3-phenylpropargyl chloride (0.56 mL, 4.0 mmol). The product was isolated after purification (PE:EtOAc 7:3) as a yellow powder (694.4 mg, 82%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.44 (dd, *J* = 6.7, 3.0 Hz, 2H, C*H*$_{phenyl}$), 7.37–7.24(m, 3H, C*H*$_{phenyl}$), 7.22 (t, *J* = 2.2 Hz, 1H, C*H*$_{pyrrole}$), 6.85 (dd, *J* = 4.0, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.17 (dd, *J* = 3.9, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 5.61 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 5.58 (s, 2H, C*H*$_2$, $_{propargyl}$), 2.95 (s, 6H, N(C*H*$_3$)$_2$).

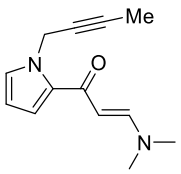
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.7 (*C*=O), 152.2 (*C*H$_{enaminone}$), 131.8 (q*C*$_{arom}$), 131.8 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 127.0 (*C*H$_{arom}$), 122.8 (q*C*$_{arom}$), 115.7 (*C*H$_{arom}$), 107.8 (*C*H$_{arom}$), 93.4 (*C*H$_{enaminone}$), 85.1 (q*C*$_{alkyne}$), 84.6 (q*C*$_{alkyne}$), 39.2 (*C*H$_2$, $_{propargyl}$).

m.p.: 77–80 ºC (EtOAc)

HRMS (*m/z*): [M$^+$] calc. for $C_{18}H_{18}N_2O$: 278.1419; found: 278.1422

IR (ATR) (cm^{-1}): 3110, 2920, 2910, 1630, 1554

- ***(E)*-1-[1-(But-2-yn-1-yl)-1*H*-pyrrol-2-yl]-3-(dimethylamino)prop-2-en-1-one (19c).** The typical procedure was followed employing enaminone **23** (500 mg, 3.04 mmol) and 1-bromobut-2-yne (0.35 mL, 4.0 mmol). The product was isolated after purification (PE:EtOAc 7:3) as a brown powder (572.7 mg, 87%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.12 (t, *J* = 2.2 Hz, 1H, C*H*$_{pyrrole}$), 6.82 (dd, *J* = 3.9, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.14 (dd, *J* = 3.9, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 5.59 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 5.26 (q, *J* = 2.5 Hz, 2H, C*H*$_2$, $_{propargyl}$), 2.97 (bs, 6H, 2C*H*$_{3,\ NMe}$), 1.84 (t, *J* = 2.5 Hz, 3H, C*H*$_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.8 (*C*=O), 152.2 (*C*H$_{enaminone}$), 131.8 (q*C*$_{arom}$), 127.1 (*C*H$_{arom}$), 115.7 (*C*H$_{arom}$), 107.7 (*C*H$_{arom}$), 93.5 (*C*H$_{enaminone}$), 81.1 (q*C*$_{alkyne}$), 74.6 (q*C*$_{alkyne}$), 39.1 (*C*H$_2$, $_{propargyl}$), 3.8 (*C*H$_3$, $_{Me}$).

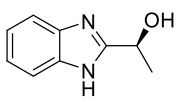
m.p.: 81–84 ºC (EtOAc)

HRMS (*m/z)*: [M^+] calc. for $C_{13}H_{16}N_2O$: 216.1263; found: 216.1262

IR (ATR) (cm^{-1}): 3102, 2931, 2912, 1629

4.2.2 Synthesis of 1-(imidazol-2-yl)ethan-1-ol derivatives 25

♁ ***(S)*-1-(1*H*-Benzo[*d*]imidazol-2-yl)ethan-1-ol (25a).**[95] **Typical procedure.** *o*-Phenylenediamine (2.17 g, 20 mmol) was refluxed with (*L*)-lactic acid (1.67 mL, 20 mmol) in the presence of a 4.0 M aqueous HCl solution (10 mL) for 24 h. Then, the reaction was cooled to r.t. and basified with 28-30% NH_4OH or aqueous NaOH 4.0 M solution upon which the product precipitated (pH ≈ 8). After vacuum filtration, the product was washed with H_2O (2 × 20 mL) affording benzimidazole **25a** as an off-white powder (3.02 g, 93%).

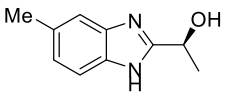


^{1}H-NMR (300 MHz, MeOD) δ 7.53 (dd, *J* = 6.0, 3.2 Hz, 2H, C*H*$_{benzimidazole}$), 7.20 (dd, *J* = 6.0, 3.2 Hz, 2H, C*H*$_{benzimidazole}$), 5.06 (q, *J* = 6.6 Hz, 1H, -C*H*OH), 1.61 (d, *J* = 6.6 Hz, 3H, C*H*$_3$).

^{13}C-NMR (75 MHz, MeOD) δ 159.8 (q*C*$_{arom}$), 138.3 (q*C*$_{arom}$), 123.3 (*C*H$_{arom}$), 115.8 (*C*H$_{arom}$), 65.5 (*C*HOH), 23.2 (-CHOH*C*H$_3$).

m.p.: 171–174 ºC (H_2O). *Lit.*[95] 180–182 ºC (EtOH)

♁ ***(S)*-1-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethan-1-ol (25b).** The mixture was obtained as a yellow powder (3.42 g, 98%) starting from 3,4-diaminotoluene (2.52 g, 20 mmol).



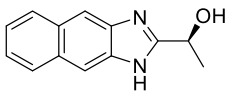
^{1}H-NMR (300 MHz, MeOD) δ 7.41 (d, *J* = 8.2 Hz, 1H, C*H*$_{benzimidazole}$), 7.33 (bs, 1H, C*H*$_{benzimidazole}$), 7.06 (dd, *J* = 8.2, 0.9 Hz, 1H, C*H*$_{benzimidazole}$), 5.04 (q, *J* = 6.5 Hz, 1H, -C*H*OH), 3.05 (s, 3H, C*H*$_3$), 1.62 (d, *J* = 6.5 Hz, 3H, -CHOHC*H*$_3$).

[95] Rao, K. G.; Chakraborty, Dipankar *Int. J. Pharm. Sci. Drug Res.* **2014**, *6,* 67–69.

^{13}C-NMR (75 MHz, MeOD) δ 159.4 (q*C*$_{arom}$), 138.9 (q*C*$_{arom}$), 133.5 (q*C*$_{arom}$), 125.0 (*C*H$_{arom}$), 115.6 (*C*H$_{arom}$), 115.2 (*C*H$_{arom}$), 65.4 (*C*HOH), 23.1 (*C*H$_3$), 21.7 (*C*H$_3$).

m.p.: 164–166 ºC (H$_2$O). *Lit.*[96] 160–162 ºC (EtOH)

(*S*)-1-(1*H*-Naphtho[2,3-*d*]imidazol-2-yl)ethan-1-ol (25c). The product was obtained as a yellow powder (0.60 g, 71%) starting from 1,2-diaminonaphthalene (0.63 g, 4 mmol).



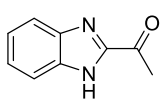
^{1}H-NMR (300 MHz, MeOD) δ 8.27–7.73 (m, 4H, C*H*$_{naphthimidazole}$), 7.37 (dd, *J* = 6.5, 3.2 Hz, 2H, C*H*$_{naphthimidazole}$), 5.12 (q, *J* = 6.7 Hz, 1H, -C*H*OH), 1.67 (d, *J* = 6.7 Hz, 3H, -CHOHC*H*$_3$).

^{13}C-NMR (75 MHz, MeOD) δ 164.4 (q*C*$_{arom}$), 138.8 (q*C*$_{arom}$), 132.0 (q*C*$_{arom}$), 128.9 (*C*H$_{arom}$), 125.1 (*C*H$_{arom}$), 111.9 (*C*H$_{arom}$), 65.5 (*C*HOH), 23.0 (-CHOH*C*H$_3$).

m.p.: 236–239 ºC (H$_2$O). *Lit.*[97] 244–246 ºC (EtOH)

4.2.3 Oxidation to 2-acetylbenzimidazole derivatives 26.

1-(1*H*-Benzo[*d*]imidazol-2-yl)ethan-1-one (26a). Typical procedure. A round-bottom flask equipped with a magnetic stirrer was charged with alcohol **25a** (1.61 g, 10 mmol), MnO_2 (13.0 g, 150 mmol) and MeOH (50 mL) and the mixture was stirred overnight at r.t. The reaction was suspended in silica gel, concentrated and purified by flash column chromatography (EtOAc) to provide ketone **26a** as an off-white powder (1.28 g, 81%).



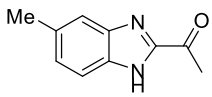
^{1}H-NMR (300 MHz, CDCl$_3$) δ 10.84 (bs, 1H, N*H*), 7.89 (m,1H, C*H*$_{benzimidazole}$), 7.55 (m, 1H, C*H*$_{benzimidazole}$), 7.39 (m, 2H, C*H*$_{benzimidazole}$), 2.84 (s, 3H, C*H*$_{3,\ Ac}$).

[96] Reddy, V. M.; Reddy, K. R. *Chem. Pharm. Bull.* **2010**, *58*, 953–956.
[97] Zellner, H.; Zellner, G.; Köppl, F.; Dirnberger, J. *Monatsh. Chem.* **1967**, *98*, 643–665.

^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.3 (*C*=O), 147.9 (q*C*$_{arom}$), 143.5 (q*C*$_{arom}$), 134.1 (q*C*$_{arom}$), 126.3 (*C*H$_{arom}$), 124.1 (*C*H$_{arom}$), 121.9 (*C*H$_{arom}$), 112.4 (*C*H$_{arom}$), 26.2 (*C*H$_{3,\ Ac}$).

m.p.: 187–190 ºC (EtOAc). *Lit*.[98]189–191 ºC (EtOH)

♁ **1-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethan-1-one (26b).**[98] The mixture was obtained as a yellow powder (1.39 g, 80%) starting from alcohol **25b** (1.76 g, 10 mmol).

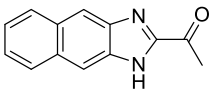


^{1}H-NMR (300 MHz, $CDCl_3$) δ 11.23 (bs, 1H, N*H*), 7.65 (m, 1H, C*H*$_{benzimidazole}$), 7.48 (m, 1H, C*H*$_{benzimidazole}$), 7.24 (m, 1H, C*H*$_{benzimidazole}$), 2.82 (s, 3H, C*H*$_{3,\ Ac}$), 2.50 (s, 3H, C*H*$_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*=O), 144.8 (q*C*$_{arom}$), 141.9 (q*C*$_{arom}$), 136.3 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 128.5 (*C*H$_{arom}$), 126.4 (*C*H$_{arom}$) 121.5 (*C*H$_{arom}$), 110.6 (*C*H$_{arom}$), 28.2 (*C*H$_{3,\ Ac}$), 21.8 (*C*H$_{3,\ Me}$).

m.p.: 194–198 ºC (EtOAc). *Lit*.[99] 195–197 ºC (EtOAc)

♁ **1-(1*H*-Naphtho[2,3-*d*]imidazol-2-yl)ethan-1-one (26c).** The product was obtained as a yellow powder (0.29 g, 51%) starting from alcohol **25c** (0.57 g, 2.7 mmol), MnO_2 (3.52 g, 40.5 mmol) and MeOH (13.5 mL).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.99 (bs, 1H, N*H*), 8.45 (s, 1H, C*H*$_{naphthimidazole}$), 8.14–7.84 (m, 3H, C*H*$_{naphthimidazole}$), 7.63–7.34 (m, 2H, C*H*$_{naphthimidazole}$), 2.89 (s, 3H, C*H*$_{3,\ Ac}$).

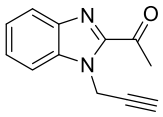
[98] Reddy, V. M.; Reddy, K. R. *Chin. Chem. Lett.* **2010**, *21*, 1145–1148.
[99] Shivakumar, B.; Madawali, I. M.; Hugar, S.; Kalyane, N. V. *Am. J. Pharm.Tech. Res.* **2018**, *8,* 155–164.

^{13}C-NMR (75 MHz, CDCl3) δ 192.3 (*C*=O), 150.8 (q*C*$_{arom}$), 143.6 (q*C*$_{arom}$), 138.9 (q*C*$_{arom}$), 132.8 (q*C*$_{arom}$), 129.0 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 125.8 (*C*H$_{arom}$), 124.2 (*C*H$_{arom}$), 119.9 (*C*H$_{arom}$), 107.9 (*C*H$_{arom}$), 26.2 (CH$_{3,\ Ac}$). (missing peaks due to coalescence)

m.p.: 205–208 ºC (EtOAc). *Lit.*[97] 225 ºC (^{i}PrOH:H$_2$O)

4.2.4 Propargylation of benzimidazole derivatives 28

1-[1-(Prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one (28a). **Typical procedure (Method A)**.[100] A round-bottom flask equipped with a magnetic stirrer was charged with ketone **26a** (0.16 g, 1.0 mmol), propargyl bromide (0.12 mL, 1.1 mmol), potassium carbonate (0.15 g, 1.1 mmol) and dry MeCN (1.0 mL) and the mixture was refluxed for 3 h under argon. The reaction was diluted with EtOAc (10 mL) and washed with H$_2$O (2 × 5 mL). The resulting organic layer was dried over anhydrous sodium sulfate, filtered and further concentrated under reduced pressure. The residue was purified by flash-column chromatography (PE:EtOAc 7:3) to afford the propargylated derivative **28a** as a yellowish powder (0.19 g, 98%). This reaction was also carried out on a higher scale (5 mmol), providing 1.78 g of derivative **28a** (92%).



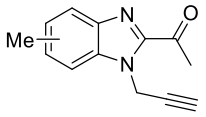
^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.07–7.77 (m, 1H, C*H*$_{benzimidazole}$), 7.74–7.53 (m, 1H, C*H*$_{benzimidazole}$), 7.53–7.42 (m, 1H, C*H*$_{benzimidazole}$), 7.42–7.29 (m, 1H, C*H*$_{benzimidazole}$), 5.48 (d, *J* = 2.4 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.84 (s, 3H, C*H*$_{3,\ Ac}$), 2.32 (t, *J* = 2.4 Hz, 1H, C*H*$_{alkyne}$).

^{13}C-NMR (75 MHz, CDCl$_3$) δ 193.4 (*C*=O), 144.8 (q*C*$_{arom}$), 141.7 (q*C*$_{arom}$), 135.9 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 124.2 (*C*H$_{arom}$), 122.2 (*C*H$_{arom}$), 111.1 (*C*H$_{arom}$), 77.3 (q*C*$_{arom}$), 73.3 (*C*H$_{alkyne}$), 34.8 (*C*H$_{2,\ propargyl}$), 28.1 (*C*H$_{3,\ Ac}$).

m.p.: 117–119 ºC (DCM). *Lit.*[100] 112–113 ºC (hexane:Et$_2$O)

[100] Bognár, B.; Kálai, T.; Hideg, K. *Synthesis* **2008**, *2008*, 2439–2445.

♁ **1-[5-Methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one:1-[6-methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one (1:1) (28e).** This mixture was obtained as a yellowish powder (0.89 g, 83%) starting from ketone mixture **26b** (0.87 g, 5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.5 Hz, 1H, C*H*$_{benzimidazole}$), 7.71–7.64 (m, 1H, C*H*$_{benzimidazole}$), 7.47 (d, *J* = 8.5 Hz, 1H, C*H*$_{benzimidazole}$), 7.38–7.33 (m, 1H, C*H*$_{benzimidazole}$), 7.33–7.28 (m, 1H, C*H*$_{benzimidazole}$), 7.25–7.17 (m, 1H, C*H*$_{benzimidazole}$), 5.49 (d, *J* = 2.6 Hz, 2H, C*H*$_{2,\ propargyl}$), 5.48 (d, *J* = 2.6 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.84 (s, 3H, C*H*$_{3,\ Ac}$), 2.84 (s, 3H, C*H*$_{3,\ Ac}$), 2.55 (s, 3H, C*H*$_{3,\ Me}$), 2.51 (s, 3H, C*H*$_{3,\ Me}$), 2.31 (q, *J* = 2.5 Hz, 2H, 2C*H*$_{alkyne}$).

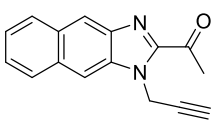
^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*=O), 193.3 (*C*=O), 144.8 (q*C*$_{arom}$), 144.6 (q*C*$_{arom}$), 141.9 (q*C*$_{arom}$), 139.9 (q*C*$_{arom}$), 137.3 (q*C*$_{arom}$), 136.3 (q*C*$_{arom}$), 134.3 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 128.5 (*C*H$_{arom}$), 126.4 (*C*H$_{arom}$), 121.7 (*C*H$_{arom}$), 121.5 (*C*H$_{arom}$), 110.6 (*C*H$_{arom}$), 110.6 (*C*H$_{arom}$), 77.4 (q*C*$_{alkyne}$), 77.4 (q*C*$_{alkyne}$), 73.3 (*C*H$_{alkyne}$), 73.2 (*C*H$_{alkyne}$), 34.9 (*C*H$_{2,\ propargyl}$), 34.8 (*C*H$_{2,\ propargyl}$), 28.2 (*C*H$_{3,\ Ac}$), 28.1 (*C*H$_{3,\ Ac}$), 22.4 (*C*H$_{3,\ Me}$), 21.8 (*C*H$_{3,\ Me}$).

m.p.: 100–104 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{13}H_{12}N_2O$: 212.0950; found: 212.0952

IR (ATR) (cm^{-1}): 3277, 3239, 3189, 2999, 2923, 2117, 1684

♁ **1-[1-(Prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]ethan-1-one (28f).** The product was obtained as a yellow powder (0.26 g, 90%) starting from ketone **26c** (0.24 g, 1.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.44 (s, 1H, C*H*$_{naphthimidazole}$), 8.09–7.91 (m, 3H, C*H*$_{naphthimidazole}$), 7.55–7.38 (m, 2H, C*H*$_{naphthimidazole}$), 5.58 (d, *J* = 2.5 Hz, 2H, C*H*$_{2,\ propargyl}$), 2.93 (s, 3H, C*H*$_{3,\ Ac}$), 2.34 (t, *J* = 2.5 Hz, 1H, C*H*$_{alkyne}$).

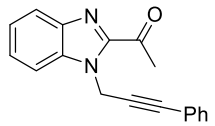
^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*=O), 147.4 (q*C*$_{arom}$), 140.5 (q*C*$_{arom}$), 135.5 (q*C*$_{arom}$), 132.6 (q*C*$_{arom}$), 131.4(q*C*$_{arom}$), 129.0 (*C*H$_{arom}$), 127.9 (*C*H$_{arom}$), 126.0 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 119.8 (*C*H$_{arom}$), 107.2 (*C*H$_{arom}$), 77.3 (q*C*$_{alkyne}$), 73.5 (*C*H$_{alkyne}$), 35.0 (*C*H$_{2,\ propargyl}$), 28.6 (*C*H$_{3,\ Ac}$).

m.p.: 147–149 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{12}N_2O$: 248.0950; found: 248.0952

IR (ATR) (cm^{-1}): 3303, 1685

- **1-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one (28b)**. **Typical procedure (Method B)**.[101] A round-bottom flask containing a magnetic stirrer was charged with ketone **26a** (160.2 mg, 1.0 mmol), 3-phenylpropargyl chloride (0.21 mL, 1.5 mmol), potassium carbonate (113.6 mg, 1.0 mmmol) and dry DMF (3.0 mL) and the mixture was sonicated for 1.5 h under argon. The reaction was diluted with EtOAc (30 mL) and washed with H_2O (3 × 10 mL). The resulting organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash-column chromatography (PE:EtOAc 7:3) to provide derivative **28b** as a yellowish powder (192.1 mg, 70%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.2 Hz, 1H, C*H*$_{benzimidazole}$), 7.68 (d, *J* = 8.2 Hz, 1H, C*H*$_{benzimidazole}$), 7.49 (td, *J* = 7.6, 1.5 Hz, 1H, C*H*$_{benzimidazole}$), 7.42 (td, *J* = 7.6, 1.5 Hz, 1H, C*H*$_{benzimidazole}$), 7.41–7.32 (m, 2H, C*H*$_{phenyl}$), 7.32–7.19 (m, 3H, C*H*$_{phenyl}$), 5.74 (s, 2H, C*H*$_{2,\ propargyl}$), 2.88 (s, 3H, C*H*$_{3,\ Ac}$).

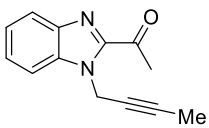
^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.5 (*C*=O), 144.9 (q*C*$_{arom}$), 141.7 (q*C*$_{arom}$), 136.2 (q*C*$_{arom}$), 131.9 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 126.5 (*C*H$_{arom}$), 124.2

[101] Da Silva, G. B.; Guimarães, B. M.; Assis, S. P. O.; Lima, V. L. M.; De Oliveira, R. N. *J. Braz. Chem. Soc.* **2013**, *24*, 914–921.

(CH_{arom}), 122.2 (qC_{arom}), 122.1 (CH_{arom}), 111.4 (CH_{arom}), 85.0 (qC_{alkyne}), 82.7 (qC_{alkyne}), 35.7 ($CH_{2,\ propargyl}$), 28.3 ($CH_{3,\ Ac}$).

m.p.: 98–101 ºC (DCM). *Lit.*[100] 84–85 (hexane:Et_2O)

♁ **1-[1-(But-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one (28c)**. The product was obtained after purification (PE:EtOAc 7:3) as a yellowish powder (62.8 mg, 30%) employing 1-bromobut-2-yne (0.13 mL, 1.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (ddd, *J* = 8.2, 1.2, 0.8 Hz, 1H, C$H_{benzimidazole}$), 7.57 (dt, *J* = 8.2, 1.2 Hz, 1H, C$H_{benzimidazole}$), 7.44 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, C$H_{benzimidazole}$), 7.36 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, C$H_{benzimidazole}$), 5.41 (q, *J* = 2.4 Hz, 2H, C$H_{2,\ propargyl}$), 2.83 (s, 3H, C$H_{3,\ Ac}$), 1.74 (t, *J* = 2.4 Hz, 3H, C$H_{3,\ alkyne}$).

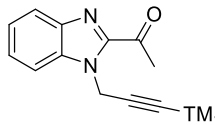
^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.4 (*C*=O), 145.0 (qC_{arom}), 141.7 (qC_{arom}), 136.1 (qC_{arom}), 126.3 (CH_{arom}), 124.0 (CH_{arom}), 122.0 (CH_{arom}), 111.3 (CH_{arom}), 81.1 (qC_{alkyne}), 72.9 (qC_{alkyne}), 35.3 ($CH_{2,\ propargyl}$), 28.2 ($CH_{3,\ Ac}$), 3.6 ($CH_{3,\ alkyne}$).

m.p.: 111–113 ºC (DCM)

HRMS (*m/z*): [M^+] calc. for $C_{13}H_{12}N_2O$: 212.0950; found: 212.0955

IR (ATR) (cm^{-1}): 3051, 2992, 2853, 1681

♁ **1-[1-[3-(Trimethylsilyl)prop-2-yn-1-yl]-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one (28d).** The product was obtained after purification (PE:EtOAc 1:1) as a yellowish powder (174.1 mg, 64%) employing 3-trimethylsilylpropargyl bromide (0.21 mL, 1.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96–7.87 (m, 1H, C$H_{benzimidazole}$), 7.67–7.59 (m, 1H, C$H_{benzimidazole}$), 7.53–7.44 (m, 1H, C$H_{benzimidazole}$), 7.44–7.35 (m, 1H, C$H_{benzimidazole}$), 5.53 (s, 2H, C$H_{2,\ propargyl}$), 2.86 (s, 3H, C$H_{3,\ Ac}$), 0.11 (s, 9H, Si(CH_3)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 193.7 (*C*=O), 145.1 (q*C*$_{arom}$), 141.9 (q*C*$_{arom}$), 136.4 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 124.3 (*C*H$_{arom}$), 122.3 (*C*H$_{arom}$), 111.8 (*C*H$_{arom}$), 98.7 (q*C*$_{alkyne}$), 90.7 (q*C*$_{alkyne}$), 36.1 (*C*H$_{2,\ propargyl}$), 28.5 (*C*H$_{3,\ Ac}$), 0.0 (Si(*C*H$_3$)$_3$).

m.p.: 74–76 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{18}N_2OSi$: 270.1188; found: 270.1186

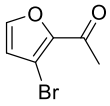
IR (ATR) (cm^{-1}): 3049, 2987, 2901, 1683

4.2.5 Acetylation of 3-bromofuran.

An argon-flushed flask was charged with CH_2Cl_2 (15 mL) and cooled to 0 ºC, after which $AlCl_3$ (1.36 g, 10.2 mmol) was added in one portion and the suspension was stirred at 0 °C for 15 min. Then, a solution of acetyl chloride (0.75 mL, 11 mmol) in CH_2Cl_2 (15 mL) was added over 5 min and the mixture was stirred at 0 °C for 30 min. Finally, a solution of 3-bromofuran (0.31 mL, 3.45 mmol) in CH_2Cl_2 (15 mL) was slowly added still at 0 ºC, and it was stirred for additional 20 min, after which the mixture was allowed to warm to r.t. After cooling again to 0 ºC, water (50 mL) was slowly added, and then it was partitioned in CH_2Cl_2 (150 mL) and water (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (200 mL) and brine (200 mL). Then, it was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide furan derivative **30a**[102] as a brownish powder (0.53 g, 81%). The so-obtained product was pure enough to proceed without further purifications.

[102] Pelly, S. C.; Parkinson, C. J.; Van Otterlo, W. A. L.; De Koning, C. B. *J. Org. Chem.* **2005**, *70*, 10474–10481.

♁ **1-(3-Bromofuran-2-yl)ethan-1-one (30a).** Isolated as a brownish powder (0.53 g, 81%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 1.7 Hz, 1H, C*H*$_{furan}$), 6.63 (d, *J* = 1.7, Hz, 1H, C*H*$_{furan}$), 2.55 (3H, s, C*H*$_{3,\ Ac}$)

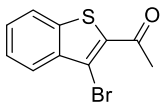
^{13}C-NMR (75 MHz, $CDCl_3$) δ 186.4 (*C*=O), 148.3 (q*C*$_{arom}$), 145.3 (*C*H$_{arom}$), 117.4 (*C*H$_{arom}$), 106.9 (q*C*$_{arom}$-Br), 27.4 (*C*H$_{3,\ Ac}$).

m.p.: 39–42 ºC (DCM). *Lit.*[103] 43.5–44.0 ºC (heptane)

4.2.6 Acetylation of 3-bromobenzo[b]thiophene.

3-Bromobenzo[*b*]thiophene (1.46 mL, 10.6 mmol) was dissolved in dry DCM (80 mL) under Ar and cooled to -20 ºC, upon which acetic anhydride (3.06 mL, 31.8 mmol) was added. Finally, aluminum trichloride (8.65 g, 63.6 mmol) was added in portions while at -20 ºC and the reaction was further stirred at that temperature for additional 5 h. The mixture was then poured into ice-water and extracted with DCM (3 × 100 mL). The resulting organic layer was treated with a saturated aqueous $NaHCO_3$ solution (100 mL), dried over anhydrous Na_2SO_4, filtered and rotary evaporated, yielding the acetylated product as an off-white solid (2.68 g, >99%). The product was used in the next step without further purification.

♁ **1-(3-Bromobenzo[*b*]thiophen-2-yl)ethan-1-one (30b).** Isolated as an off-white powder (2.68 g, 99%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03–7.94 (m, 1H, C*H*$_{benzothiophene}$), 7.88–7.80 (m, 1H, C*H*$_{benzothiophene}$), 7.58–7.45 (m, 2H, C*H*$_{benzothiophene}$), 2.84 (s, 3H, C*H*$_{3,\ Ac}$).

[103] Gol'dfarb, Ya. L.; Marakatkina, M. A.; Belen'kii, L. I., M. *Khim. Geterotsikl. Soedin.* **1970**, *1*, 132–133.

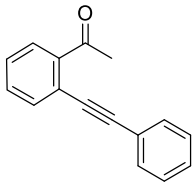
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.9 (*C*=O), 139.6 (q*C*$_{arom}$), 139.3 (q*C*$_{arom}$), 139.1 (q*C*$_{arom}$), 128.5 (*C*H$_{arom}$), 125.9 (*C*H$_{arom}$), 125.9 (*C*H$_{arom}$), 122.9 (*C*H$_{arom}$), 112.3 (q*C*$_{arom}$-Br), 30.8 (*C*H$_{3,\ Ac}$).

m.p.: 103–105 ºC (DCM) *Lit.*[104] 99.5-100 ºC (DCM:hexane)

4.2.7 General procedure for the alkynylation of acetyl bromo(hetero)arenes 30

In a round-bottom flask containing a magnetic stirrer and equipped with a condenser, brominated (hetero)arene **30** (2 mmol), $PdCl_2(PPh_3)_2$ (28.4 mg, 0.04 mmol), CuI (7.7 mg, 0.04 mmol) and degassed triethylamine (14.0 mL) were added at room temperature under Ar. Then, the corresponding acetylene (2.2 mmol) was added dropwise and heated to 80 ºC for 18 h. After cooling, it was diluted with Et_2O (25 mL) and gravity filtered to remove triethylammonium bromide. The filtrate was then concentrated *in vacuo* and the residue was purified by flash column chromatography to provide the corresponding alkynylated (hetero)arene **31**.

1-[2-(Phenylethynyl)phenyl]ethan-1-one (31a).[105] The product was isolated (PE:EtOAc 95:5) as an orangish oil (396.2 mg, 90%), after reacting 2'-bromoacetophenone (0.27 mL, 2 mmol) and phenylacetylene (0.25 mL, 2.2 mmol).

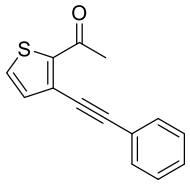


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.7, 1.5 Hz, 1H, C*H*$_{arom}$), 7.68–7.60 (m, 1H, C*H*$_{arom}$), 7.59–7.52 (m, 2H, C*H*$_{arom}$), 7.52–7.44 (m, 1H, C*H*$_{arom}$), 7.41 (dd, *J* = 7.7, 1.5 Hz, 1H, C*H*$_{arom}$), 7.39–7.32 (m, 3H, C*H*$_{arom}$), 2.80 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 200.5 (*C*=O), 140.9 (q*C*$_{arom}$), 134.0 (*C*H$_{arom}$), 131.6 (*C*H$_{arom}$), 131.4 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 123.0 (q*C*$_{arom}$), 121.8 (q*C*$_{arom}$), 95.2 (-*C*≡C-Ph), 88.6 (-C≡*C*-Ph), 30.1 (*C*H$_{3,\ Ac}$).

[104] Muratake, H., Hayakawa, A., Natsume, M. *Chem. Pharm. Bull.*, **2000**, *48*, 1558–1566.
[105] Kim, M.; Kang, H.; Park, K. H. *Catal. Commun.* **2015**, *72*, 150–155.

1-[3-(Phenylethynyl)thiophen-2-yl]ethan-1-one (31b). The product was isolated (PE:EtOAc 9:1) as an orange-brownish powder (325.7 mg, 72%), after reacting 2-acetyl-3-bromothiophene (422.8 mg, 2 mmol) and phenylacetylene (0.25 mL, 2.2 mmol).

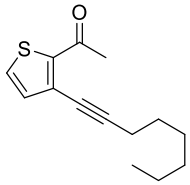


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60–7.49 (m, 3H, C*H*$_{thiophene}$ + C*H*$_{phenyl}$), 7.45–7.34 (m, 3H, C*H*$_{phenyl}$), 7.30–7.20 (m, 1H, C*H*$_{thiophene}$), 2.83 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (C=O), 145.8 (q*C*$_{arom}$), 132.9 (*C*H$_{arom}$), 132.0 (*C*H$_{arom}$), 131.6 (CH$_{arom}$), 129.3 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 125.5 (q*C*$_{arom}$), 122.5 (q*C*$_{arom}$), 96.8 (-C≡*C*-Ph), 84.7 (-*C*≡C-Ph), 29.1 (*C*H$_{3,\ Ac}$).

m.p.: 49–53 ºC (DCM). *Lit.*[106] 45.5–46.8 ºC (hexane:EtOAc)

1-[3-(Oct-1-yn-1-yl)thiophen-2-yl]ethan-1-one (31c). The product was isolated (PE:DCM 1:1) as an orange-brownish oil (220.4 mg, 47%), after reacting 2-acetyl-3-bromothiophene (422.8 mg, 2 mmol) and 1-octyne (0.33 mL, 2.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.09 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 2.73 (s, 3H, C*H*$_{3,\ Ac}$), 2.55–2.42 (m, 2H, C*H*$_{2,\ hexyl}$), 1.71–1.55 (m, 2H, C*H*$_{2,\ hexyl}$), 1.53–1.40 (m, 2H, C*H*$_{2,\ hexyl}$), 1.39–1.25 (m, 4H, C*H*$_{2,\ hexyl}$), 0.96–0.85 (m, 3H, C*H*$_{3,\ hexyl}$).

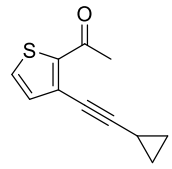
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.5 (C=O), 145.1 (q*C*$_{arom}$), 133.3 (*C*H$_{arom}$), 131.8 (*C*H$_{arom}$), 126.7 (q*C*$_{arom}$), 99.1 (-C≡*C*-hexyl), 76.2 (-*C*≡C-hexyl), 31.4 (*C*H$_{2,\ hexyl}$), 28.9 (*C*H$_{3,\ Ac}$), 28.8 (*C*H$_{2,\ hexyl}$), 28.5 (*C*H$_{2,\ hexyl}$), 22.7 (*C*H$_{2,\ hexyl}$), 19.9 (*C*H$_{2,\ hexyl}$), 14.2 (*C*H$_{3,\ hexyl}$).

HRMS (*m/z*): [M$^+$] calc. for $C_{14}H_{18}OS$: 234.1078; found: 234.1080

[106] Domaradzki, M. E.; Long, Y.; She, Z.; Liu, X.; Zhang, G.; Chen, Y. *J. Org. Chem.* **2015**, *80*, 11360–11368.

IR (ATR) (cm^{-1}): 3098, 2956, 2858, 1710, 1662

1-[3-(Cyclopropylethynyl)thiophen-2-yl]ethan-1-one (31d). The product was isolated (PE:DCM 1:1) as an orange-brownish oil (102.0 mg, 27%), after reacting 2-acetyl-3-bromothiophene (422.8 mg, 2 mmol) and cyclopropylacetylene (0.19 mL, 2.2 mmol).

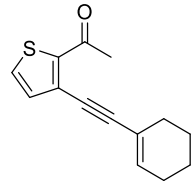


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.03 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 2.65 (s, 3H, C*H*$_{3,\ Ac}$), 1.56–1.37 (m, 1H, C*H*$_{cyclopropyl}$), 1.00–0.85 (m, 2H, C*H*$_{2,\ cyclopropyl}$), 0.85–0.70 (m, 2H, C*H*$_{2,\ cyclopropyl}$).

HRMS (*m/z)*: [M^+] calc. for $C_{11}H_{10}OS$: 190.0452; found: 190.0451

IR (ATR) (cm^{-1}): 3098, 2222, 1695, 1658

1-[3-(Cyclohex-1-en-1-ylethynyl)thiophen-2-yl]ethan-1-one (31e). The product was isolated (PE:DCM 1:1) as an brownish oil (342.1 mg, 74%), after reacting 2-acetyl-3-bromothiophene (422.8 mg, 2 mmol) and 1-ethynylcyclohexene (0.26 mL, 2.2 mmol).



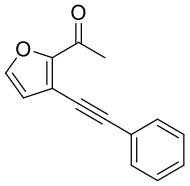
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.2, 1.2 Hz, 1H, C*H*$_{thiophene}$), 7.11 (dd, *J* = 5.2, 1.2 Hz, 1H, C*H*$_{thiophene}$), 6.35–6.19 (m, 1H, C*H*$_{cyclohexenyl}$), 2.74 (s, 3H, $CH_{3,\ Ac}$), 2.35–2.02 (m, 4H, C*H*$_{2,\ cyclohexenyl}$), 1.77–1.55 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (C=O), 144.9 (q*C*$_{arom}$), 136.9 (*C*H$_{arom}$), 132.7 (*C*H$_{arom}$), 131.7 (*C*H$_{arom}$), 126.1 (q*C*$_{arom}$), 120.4 (q*C*$_{arom}$), 98.9 (-C≡*C*-cyclohexenyl), 82.3 (-*C*≡C-cyclohexenyl), 28.9 ($CH_{3,\ Ac}$), 28.7 ($CH_{2,\ cyclohexenyl}$), 25.9 ($CH_{2,\ cyclohexenyl}$), 22.2 (*C*H$_{2,\ cyclohexenyl}$), 21.4 ($CH_{2,\ cyclohexenyl}$).

HRMS (*m/z)*: [M^+] calc. for $C_{14}H_{14}OS$: 230.0765; found: 230.0760

IR (ATR) (cm^{-1}): 3102, 2937, 2197, 1654

1-[3-(Phenylethynyl)furan-2-yl]ethan-1-one (31f). The product was isolated (PE:EtOAc 9:1) as an orange-brownish powder (306.3 mg, 73%), after reacting 2-acetyl-3-bromofuran (378.0 mg, 2 mmol) and phenylacetylene (0.25 mL, 2.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60–7.49 (m, 3H, C*H*$_{furan}$ + C*H*$_{phenyl}$), 7.43–7.32 (m, 3H, C*H*$_{phenyl}$), 6.64 (d, *J* = 1.8 Hz, 1H, C*H*$_{furan}$), 2.66 (s, 3H, C*H*$_{3,\ Ac}$).

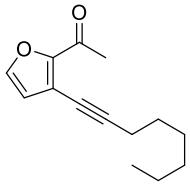
^{13}C-NMR (75 MHz, $CDCl_3$) δ 186.0 (*C*=O), 152.8 (q*C*$_{arom}$), 145.7 (*C*H$_{arom}$), 131.7 (*C*H$_{arom}$), 129.3 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 122.4 (q*C*$_{arom}$), 115.7 (*C*H$_{arom}$), 114.6 (q*C*$_{arom}$), 97.8 (-C≡*C*-Ph), 81.0 (-*C*≡C-Ph), 27.7 (*C*H$_{3,\ Ac}$).

m.p.: 68–71 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{14}H_{10}O_2$: 210.0681; found: 210.0684

IR (ATR) (cm^{-1}): 2935, 1670

1-[3-(Oct-1-yn-1-yl)furan-2-yl]ethan-1-one (31g). The product was isolated (PE:DCM 1:1) as a brownish oil (367.1 mg, 84%), after reacting 2-acetyl-3-bromofuran (378.0 mg, 2 mmol) and 1-octyne (0.33 mL, 2.2 mmol).



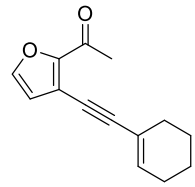
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 1.6 Hz, 1H, C*H*$_{furan}$), 6.51 (d, *J* = 1.6 Hz, 1H, C*H*$_{furan}$), 2.58 (s, 3H, C*H*$_{3,\ Ac}$), 2.46 (td, *J* = 7.2, 1.3 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.62 (p, *J* = 7.2 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.44 (p, *J* = 6.8 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.38–1.20 (m, 4H, C*H*$_{2,\ hexyl}$), 0.98–0.75 (m, 3H, C*H*$_{3,\ hexyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 186.1 (*C*=O), 152.6 (q*C*$_{arom}$), 145.6 (*C*H$_{arom}$), 116.1 (*C*H$_{arom}$), 115.6 (q*C*$_{arom}$), 100.2 (-C≡*C*-hexyl), 72.4 (-*C*≡C-hexyl), 31.4 (*C*H$_{2,\ hexyl}$), 28.8 (*C*H$_{2,\ hexyl}$), 28.5 (*C*H$_{3,\ Ac}$), 27.6 (*C*H$_{2,\ hexyl}$), 22.6 (*C*H$_{2,\ hexyl}$), 19.9 (*C*H$_{2,\ hexyl}$), 14.2(*C*H$_{3,\ hexyl}$).

HRMS (*m/z*): [M$^+$] calc. for $C_{14}H_{18}O_2$: 218.1307; found: 218.1303

IR (ATR) (cm^{-1}): 2954, 2858, 1762, 1673

1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]ethan-1-one (31h). The product was isolated (PE:DCM 1:1) as an orange oil (344.7 mg, 80%), after reacting 2-acetyl-3-bromofuran (378.0 mg, 2 mmol) and 1-ethynylcyclohexene (0.26 mL, 2.2 mmol).



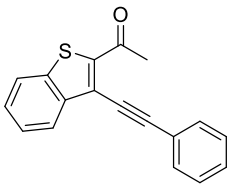
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 1.0 Hz, 1H, C*H*$_{furan}$), 6.52 (d, *J* = 1.0 Hz, 1H, C*H*$_{furan}$), 6.34–6.14 (m, 1H, C*H*$_{cyclohexenyl}$), 2.58 (s, 3H, C*H*$_{3,\ Ac}$), 2.29–2.05 (m, 4H, C*H*$_{2,\ cyclohexenyl}$), 1.73–1.55 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 186.0 (*C*=O), 152.4 (q*C*$_{arom}$), 145.7 (*C*H$_{arom}$), 137.3 (*C*H$_{arom}$), 120.4 (q*C*$_{arom}$), 115.6 (*C*H$_{arom}$), 115.5 (q*C*$_{arom}$), 100.1 (-C≡*C*-cyclohexenyl), 78.6 (-*C*≡C-cyclohexenyl), 28.8 (*C*H$_{2,\ cyclohexenyl}$), 27.6 (*C*H$_{3,\ Ac}$), 25.9 (*C*H$_{2,\ cyclohexenyl}$), 22.2 (*C*H$_{2,\ cyclohexenyl}$), 21.4 (*C*H$_{2,\ cyclohexenyl}$).

HRMS (*m/z)*: [M^+] calc. for $C_{14}H_{14}O_2$: 214.0994; found: 214.0998

IR (ATR) (cm^{-1}): 3126, 2931, 2860, 1667

1-[3-(Phenylethynyl)benzo[*b*]thiophen-2-yl]ethan-1-one (31i). The product was isolated (PE:DCM 7:3) as a yellow powder (303.7 mg, 55%), after reacting 2-acetyl-3-bromobenzo[*b*]thiophene (510.3 mg, 2 mmol) and phenylacetylene (0.25 mL, 2.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.13–8.02 (m, 1H, C*H*$_{benzothiophene}$), 7.83–7.75 (m, 1H, C*H*$_{benzothiophene}$), 7.68–7.58 (m, 2H, C*H*$_{benzothiophene}$), 7.53–7.36 (m, 5H, C*H*$_{phenyl}$), 2.91 (s, 3H, C*H*$_{3,\ Ac}$).

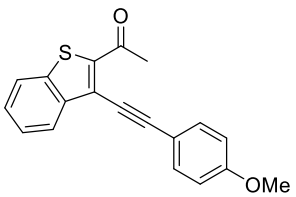
^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.4 (*C*=O), 145.6 (q*C*$_{arom}$), 140.5 (q*C*$_{arom}$), 140.2 (q*C*$_{arom}$), 131.7 (*C*H$_{arom}$), 129.5 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 122.8 (*C*H$_{arom}$), 122.3 (q*C*$_{arom}$), 121.6 (q*C*$_{arom}$), 100.3 (-C≡*C*-Ph), 83.3 (-*C*≡C-Ph), 29.4 (*C*H$_{3,\ Ac}$).

m.p.: 133–136 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{18}H_{12}OS$: 276.0609; found: 276.0611

IR (ATR) (cm^{-1}): 3286, 3058, 2202, 1654

1-[3-[(4-Methoxyphenyl)ethynyl]benzo[*b*]thiophen-2-yl]ethan-1-one (31j). The product was isolated (PE:DCM 1:1) as a yellowish powder (318.2 mg, 52%), after reacting 2-acetyl-3-bromobenzo[*b*]thiophene (510.3 mg, 2 mmol) and 4-ethynylanisole (0.29 mL, 2.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–8.06 (m, 1H, C*H*$_{benzothiophene}$), 7.90–7.79 (m, 1H, C*H*$_{benzothiophene}$), 7.64–7.55 (m, 2H, C*H*$_{anisole}$), 7.55–7.44 (m, 2H, C*H*$_{benzothiophene}$), 7.00–6.92 (m, 2H, C*H*$_{anisole}$), 3.87 (s, 3H, C*H*$_{3,\ OMe}$), 2.95 (s, 3H, C*H*$_{3,\ Ac}$).

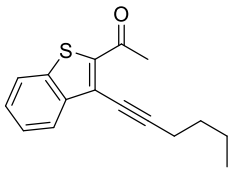
^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.7 (*C*=O), 160.7 (q*C*$_{arom}$), 145.0 (q*C*$_{arom}$), 140.7 (q*C*$_{arom}$), 140.4 (q*C*$_{arom}$), 133.4 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 125.5 (*C*H$_{arom}$), 125.4 (*C*H$_{arom}$), 123.0 (*C*H$_{arom}$), 122.3 (q*C*$_{arom}$), 114.5 (*C*H$_{arom}$), 114.5 (q*C*$_{arom}$), 100.8 (-C≡*C*-anisole), 82.5 (-*C*≡C-anisole), 55.6 (*C*H$_{3,\ OMe}$), 29.6 (*C*H$_{3,\ Ac}$).

m.p.: 112–115 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{19}H_{14}O_2S$: 306.0715; found: 306.0714

IR (ATR) (cm^{-1}): 3056, 2837, 2198, 1658

1-[3-(Hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]ethan-1-one (31k). The product was isolated (PE:DCM 1:1) as a brownish oil (104.3 mg, 20%), after reacting 2-acetyl-3-bromobenzo[*b*]thiophene (510.3 mg, 2 mmol) and 1-hexyne (0.26 mL, 2.2 mmol).



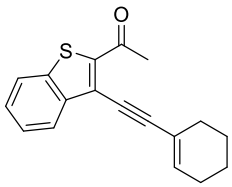
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06–7.95 (m, 1H, C*H*$_{benzothiophene}$), 7.89–7.75 (m, 1H, C*H*$_{benzothiophene}$), 7.56–7.37 (m, 2H, C*H*$_{benzothiophene}$), 2.86 (s, 3H, C*H*$_{3,\ Ac}$), 2.63 (t, *J* = 7.0 Hz, 2H, C*H*$_{2,\ butyl}$), 1.79–1.66 (m, 2H, C*H*$_{2,\ butyl}$), 1.65–1.46 (m, 2H, C*H*$_{2,\ butyl}$), 1.00 (t, *J* = 7.3 Hz, 3H, C*H*$_{3,\ butyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.9 (*C*=O), 145.1 (q*C*$_{arom}$), 141.1 (q*C*$_{arom}$), 140.3 (q*C*$_{arom}$), 128.0 (*C*H$_{arom}$), 125.4 (*C*H$_{arom}$), 125.2 (*C*H$_{arom}$), 122.9 (*C*H$_{arom}$), 122.8 (q*C*$_{arom}$), 102.8 (-C≡*C*-butyl), 75.0 (-*C*≡C-butyl), 30.8 (*C*H$_{2,\ butyl}$), 29.5 (*C*H$_{3,\ Ac}$), 22.3 (*C*H$_{2,\ butyl}$), 19.8 (*C*H$_{2,\ butyl}$), 13.7 (*C*H$_{3,\ butyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{16}OS$: 256.0922; found: 256.0925

IR (ATR) (cm^{-1}): 3061, 2959, 2871, 2202, 1714, 1667

1-[3-(Cyclohex-1-en-1-ylethynyl)benzo[*b*]thiophen-2-yl]ethan-1-one (31l). The product was isolated (PE:DCM 1:1) as a brownish oil (359.1 mg, 64%), after reacting 2-acetyl-3-bromobenzo[*b*]thiophene (510.3 mg, 2 mmol) and 1-ethynylcyclohexene (0.26 mL, 2.2 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.09–7.93 (m, 1H, C*H*$_{benzothiophene}$), 7.89–7.73 (m, 1H, C*H*$_{benzothiophene}$), 7.57–7.37 (m, 2H, C*H*$_{benzothiophene}$), 6.41 (tt, *J* = 4.0, 1.8 Hz, 1H, C*H*$_{cyclohexenyl}$), 2.87 (s, 3H, CH$_{3,\ Ac}$), 2.40–2.27 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.27–2.15 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.84–1.61 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

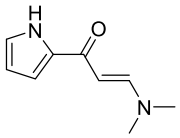
^{13}C-NMR (75 MHz, $CDCl_3$) δ 192.8 (*C*=O), 144.8 (q*C*$_{arom}$), 140.7 (q*C*$_{arom}$), 140.3 (q*C*$_{arom}$), 137.7 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 125.4 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 122.9 (*C*H$_{arom}$), 122.6 (q*C*$_{arom}$), 120.6 (q*C*$_{arom}$), 102.8 (-C≡*C*-cyclohexenyl), 81.1 (-*C*≡C-cyclohexenyl), 29.6 (*C*H$_{3,\ Ac}$), 29.0 (*C*H$_{2,\ cyclohexenyl}$), 26.1 (*C*H$_{2,\ cyclohexenyl}$), 22.3 (*C*H$_{2,\ cyclohexenyl}$), 21.5 (*C*H$_{2,\ cyclohexenyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{18}H_{16}OS$: 280.0922; found: 280.0923

IR (ATR) (cm^{-1}): 3058, 2926, 2190, 1650

4.2.8 Aminomethylenation of (hetero)aryl methyl ketones

***(E)*-3-(Dimethylamino)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (23). Typical procedure (Method A).** A microwave tube containing a magnetic stirrer was charged with 2-acetylpyrrole (109.1 mg, 1.0 mmol) and dimethylformamide dimethyl acetal (150 µl, 1.1 mmol) and the mixture was heated to 130 ºC under 250 W for 30 min. Then, the mixture was dissolved in DCM (10 mL) and transferred to a round bottom flask. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash-column chromatography (100% EtOAc) affording enaminoketone **23** as a yellow powder (129.7 mg, 79%).

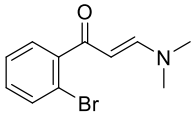


^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.72 (bs, 1H, N*H*), 7.74 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 6.93 (dt, *J* = 2.6, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 6.76 (ddt, *J* = 3.7, 2.6, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 6.24 (dt, *J* = 3.7, 2.6 Hz, 1H, C*H*$_{pyrrole}$), 5.57 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 3.00 (s, 6H, N(C*H*$_3$)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.1 (*C*=O), 152.5 (*C*H$_{enaminone}$), 133.8 (q*C*$_{arom}$), 122.0 (*C*H$_{arom}$), 111.8 (*C*H$_{arom}$), 110.0 (*C*H$_{arom}$), 91.7 (*C*H$_{enaminone}$), 44.4 (*C*H$_{3,\ NMe}$), 37.6 (*C*H$_{3,\ NMe}$)

m.p.: 163–167 ºC (EtOAc). *Lit.*[107] 162 ºC (hexane)

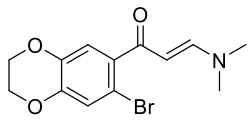
♁ ***(E)*-3-(Dimethylamino)-1-(1*H*-pyrrol-2-yl)prop-2-en-1-one (42a).** The product was isolated as an orange syrup (505.4 mg, >99%), after reacting 2'-bromoacetophenone (0.28 mL, 2 mmol) and DMFDMA (0.33 mL, 2.4 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.9 Hz, 1H, C*H*$_{arom}$), 7.40–7.27 (m, 1H, C*H*$_{arom}$), 7.24–7.14 (m, 1H, C*H*$_{arom}$), 5.32 (d, *J* = 12.7 Hz, 1H, C*H*$_{enaminone}$), 3.08 (bs, 3H, C*H*$_{3,\ NMe}$), 2.88 (bs, 3H, C*H*$_{3,\ NMe}$). (Missing second C*H*$_{enaminone}$ peak due to coalescence

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 155.2 (*C*H$_{enaminone}$), 142.8 (q*C*$_{arom}$), 132.5 (*C*H$_{arom}$), 129.4 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 118.7 (q*C*$_{arom}$-Br), 96.2 (*C*H$_{enaminone}$), 44.6 (*C*H$_{3,\ NMe}$), 36.7 (*C*H$_{3,\ NMe}$).

♁ ***(E)*-1-(7-Bromo-2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-3-(dimethylamino)prop-2-en-1-one (42b).** The product was isolated as an orange syrup (711.2 mg, 91%), after reacting 1-(7-bromo-2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one (0.66 g, 2.5 mmol) and DMFDMA (0.59 mL, 4.3 mmol).



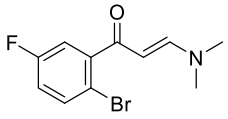
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.69–7.07 (bs, 1H, C*H*$_{enaminone}$), 7.07–6.87 (m, 1H, C*H*$_{arom}$), 6.87–6.68 (m, 1H, C*H*$_{arom}$), 5.19 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 4.39–3.91 (m, 4H, OC*H*$_2$C*H*$_2$O), 2.99 (s, 3H, C*H*$_{3,\ NMe}$), 2.77 (s, 3H, C*H*$_{3,\ NMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.4 (C=O), 155.7 (*C*H$_{enaminone}$), 144.6 (q*C*$_{arom}$), 142.7 (q*C*$_{arom}$), 121.7 (*C*H$_{arom}$), 117.8 (*C*H$_{arom}$), 110.3 (q*C*$_{arom}$-Br), 97.1 (*C*H$_{enaminone}$), 64.6 (-O*C*H$_2$CH$_2$O-), 64.4 (-OCH$_2$*C*H$_2$O-), 45.2 (*C*H$_{3,\ NMe}$), 37.4 (*C*H$_{3,\ NMe}$).

HRMS (*m/z*): [M$^+$] calc. for $C_{13}H_{14}BrNO_3$: 311.0157; found: 311.0162

[107] Kantevari, S.; Patpi, S. R.; Addla, D.; Putapatri, S. R.; Sridhar, B.; Yogeeswari, P.; Sriram, D. *ACS Comb. Sci.* **2011**, *13*, 427–435.

♁ ***(E)*-1-(2-Bromo-5-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one (42c).** The product was isolated as a yellowish powder (616.2 mg, 91%), after reacting 2'-bromo-5'-fluoroacetophenone (0.54 g, 2.5 mmol) and DMFDMA (0.41 mL, 3.0 mmol).



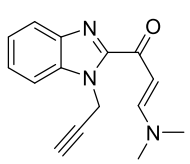
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.61–7.43 (m, 1H, C*H*$_{arom}$), 7.16–7.00 (m, 1H, C*H*$_{arom}$), 7.00–6.82 (m, 1H, C*H*$_{arom}$), 5.28 (d, *J* = 12.7 Hz, 1H, C*H*$_{enaminone}$), 3.11 (s, 3H, C*H*$_{3,\ NMe}$), 2.89 (s, 3H, C*H*$_{3,\ NMe}$). (Missing second C*H*$_{enaminone}$ peak due to coalescence)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 189.5 (*C*=O), 161.79 (d, $^{1}J_{CF}$ = 248.6 Hz, q*C*$_{arom}$-F), 156.2 (*C*H$_{enaminone}$), 145.4 (q*C*$_{arom}$), 134.6 (d, $^{3}J_{CF}$ = 7.7 Hz, *C*H$_{arom}$), 117.2 (d, $^{2}J_{CF}$ = 22.5 Hz, *C*H$_{arom}$), 116.0 (d, $^{2}J_{CF}$ = 23.4 Hz, *C*H$_{arom}$), 113.6 (q*C*$_{arom}$-Br), 97.5 (*C*H$_{enaminone}$), 45.4 (*C*H$_{3,\ NMe}$), 37.4 (*C*H$_{3,\ NMe}$). (Missing second *C*H$_{enaminone}$ peak due to coalescence)

m.p.: 103–106 ºC (EtOAc). *Lit.*[108] 107.8–108.6 (hexane)

♁ ***(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one (29a). Typical procedure (Method B).** A screw-capped tube equipped with a magnetic stirrer was charged with propargylated ketone **28a** (0.5 mmol) and DMFDMA (0.5 mL) and the mixture was heated to 90 ºC for 15 min. Then, the mixture was dissolved in DCM (10 mL) and transferred to a round bottom flask. The mixture was concentrated *in vacuo* and the resulting residue was purified by flash-column chromatography (PE:EtOAc 1:1 → EtOAc→ EtOAc:MeOH 9:1) affording enaminoketone **29a** as a light yellow powder (74.2 mg, 58%).

[108] Ajeesh Kumar, A. K.; Bodke, Y. D.; Lakra, P. S.; Sambasivam, G.; Bhat, K. G. *Med. Chem. Res.* **2017**, *26*, 714–744.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02–7.80 (m, 2H, C*H*$_{benzimidazole}$ + C*H*$_{enaminone}$), 7.65–7.52 (m, 1H, C*H*$_{benzimidazole}$), 7.48–7.30 (m, 2H, C*H*$_{benzimidazole}$), 6.42 (bs, 1H, C*H*$_{enaminone}$), 5.66 (bs, 2H, C*H*$_{2,\ propargyl}$), 3.18 (s, 3H, C*H*$_{3,\ NMe}$), 3.01 (s, 3H, C*H*$_{3,\ NMe}$), 2.30 (bs, 1H, -C≡C*H*).

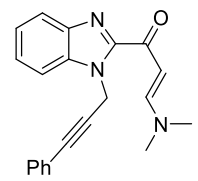
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.5 (*C*=O), 154.8 (*C*H$_{enaminone}$), 147.9 (q*C*$_{arom}$), 141.7 (q*C*$_{arom}$), 135.9 (q*C*$_{arom}$) 124.8 (*C*H$_{arom}$), 123.5 (*C*H$_{arom}$), 121.1 (*C*H$_{arom}$), 110.8 (*C*H$_{arom}$), 94.1 (*C*H$_{enaminone}$), 78.2 (-*C*≡CH), 72.8 (-C≡*C*H), 45.5 (*C*H$_{3,\ NMe}$), 37.8 (*C*H$_{3,\ NMe}$), 34.8 (*C*H$_{2,\ propargyl}$).

m.p.: 159–161 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{15}N_3O$: 253.1215; found: 253.1214

IR (ATR) (cm^{-1}): 3152, 2959, 2926, 1634, 1556

♁ ***(E)*-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one (29b).** The product was isolated (PE:EtOAc 1:1 → EtOAc → EtOAc:MeOH 9:1) as a light yellow-brownish powder (288.2 mg, 85%), after reacting ketone **28b** (0.283 g, 1.03 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98–7.86 (m, 2H, C*H*$_{benzimidazole}$ + C*H*$_{enaminone}$), 7.69 (m, 1H, C*H*$_{benzimidazole}$), 7.46–7.33 (m, 4H, C*H*$_{benzimidazole}$ + C*H*$_{phenyl}$), 7.29–7.20 (m, 3H, C*H*$_{phenyl}$), 6.48 (s, 1H, C*H*$_{enaminone}$), 5.93 (s, 2H, C*H*$_{2,\ propargyl}$), 3.20 (s, 3H, C*H*$_{3,\ NMe}$), 3.05 (s, 3H, C*H*$_{3,\ NMe}$).

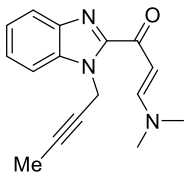
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.0 (*C*=O), 154.9 (*C*H$_{enaminone}$), 147.7 (q*C*$_{arom}$), 141.1 (q*C*$_{arom}$),135.9 (q*C*$_{arom}$), 131.9 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 125.0 (*C*H$_{arom}$), 123.7 (*C*H$_{arom}$), 122.5 (q*C*$_{arom}$), 120.9 (*C*H$_{arom}$), 111.2 (*C*H$_{arom}$), 94.5 (*C*H$_{enaminone}$), 84.7 (q*C*$_{alkyne}$), 83.4 (q*C*$_{alkyne}$), 45.6 (*C*H$_{3,\ NMe}$), 38.0 (*C*H$_{3,\ NMe}$), 35.7 (*C*H$_{2,\ propargyl}$).

m.p.: 149–150 ºC (DCM)

HRMS (*m/z*): [M⁺] calc. for $C_{21}H_{19}N_3O$: 329.1528; found: 329.1529

IR (ATR) (cm^{-1}): 3068, 2916, 1632, 1549

♁ ***(E)*-1-[1-(But-2-yn-1-yl)-1*H*-benzo*[d]*imidazol-2-yl]-3-(dimethylamino)prop -2-en-1-one (29c).** The product was isolated (PE:EtOAc 1:1 → EtOAc → EtOAc:MeOH 9:1) as a light yellow-brownish powder (188.9 mg, 89%), after reacting ketone **28c** (168.2 mg, 0.79 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 11.7 Hz, 1H, C*H*$_{enaminone}$), 7.84 (m, 1H, C*H*$_{imidazole}$), 7.57 (m, 1H, C*H*$_{imidazole}$), 7.42–7.28 (m, 2H, C*H*$_{imidazole}$), 6.40 (bs, 1H, C*H*$_{enaminone}$), 5.57 (q, *J* = 2.5 Hz, 2H, C*H*$_{2,\ propargyl}$), 3.16 (s, 3H, C*H*$_{3,\ NMe}$), 3.00 (s, 3H, C*H*$_{3,\ NMe}$), 1.74 (t, *J* = 2.4 Hz, 3H, -C≡C-C*H*$_3$).

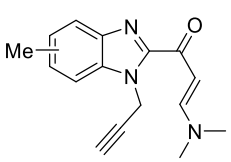
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.6 (*C*=O), 154.6 (*C*H$_{enaminone}$), 148.0 (q*C*$_{arom}$), 141.6 (q*C*$_{arom}$), 136.0 (q*C*$_{arom}$), 124.6 (*C*H$_{arom}$), 123.3 (*C*H$_{arom}$), 121.0 (*C*H$_{arom}$), 111.0 (*C*H$_{arom}$), 94.3 (*C*H$_{enaminone}$), 80.5 (q*C*$_{alkyne}$), 73.6 (q*C*$_{alkyne}$), 45.5 (*C*H$_{3,\ NMe}$), 37.8 (*C*H$_{3,\ NMe}$), 35.2 (*C*H$_{2,\ propargyl}$), 3.7 (-C≡C-*C*H$_3$).

m.p.: 155–157 ºC (DCM)

HRMS (*m/z*): [M⁺] calc. for $C_{16}H_{17}N_3O$: 267.1372; found: 267.1375

IR (ATR) (cm^{-1}): 2942, 2915, 1634, 1555

♁ ***(E)*-3-(Dimethylamino)-1-[5-methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one : *(E)*-3-(dimethylamino)-1-[6-methyl-1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one (1:1) (29d).** The product was isolated (PE:EtOAc 1:1 → EtOAc → EtOAc:MeOH 9:1) as a light yellow powder (300.1 mg, 56%), after reacting ketone **28e** (424.0 mg, 2.0 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 12.5 Hz, 2H, C*H*$_{enaminone}$), 7.65 (d, *J* = 8.3 Hz, 1H, C*H*$_{imidazole}$), 7.56 (bs, 1H, C*H*$_{imidazole}$), 7.38 (d, *J* = 8.4 Hz, 1H, C*H*$_{imidazole}$), 7.27 (bs, 1H, C*H*$_{imidazole}$), 7.16 (dd, *J* = 8.3, 1.1 Hz, 1H, C*H*$_{imidazole}$), 7.10 (dd, *J* = 8.3, 1.1 Hz, 1H, C*H*$_{imidazole}$), 6.33 (bs, 2H, C*H*$_{enaminone}$), 5.73–5.41 (m, 4H, C*H*$_{2, propargyl}$), 3.12 (bs, 6H, -N(C*H*$_3$)$_2$), 2.95 (bs, 6H, -N(C*H*$_3$)$_2$), 2.47 (s, 3H, C*H*$_{3, Me}$), 2.43 (s, 3H, C*H*$_{3, Me}$), 2.27–2.16 (m, 2H, -C≡C*H*).

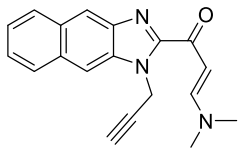
^{13}C-NMR (75 MHz, $CDCl_3$) δ 179.9 (*C*=O), 179.7 (*C*=O), 154.9 (*C*H$_{enaminone}$), 154.8 (*C*H$_{enaminone}$), 147.3 (q*C*$_{arom}$), 147.3 (q*C*$_{arom}$), 139.4 (q*C*$_{arom}$), 139.3 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 133.7 (q*C*$_{arom}$), 133.7 (q*C*$_{arom}$), 126.9 (*C*H$_{arom}$), 125.7 (*C*H$_{arom}$), 120.5 (*C*H$_{arom}$), 120.5 (*C*H$_{arom}$), 120.3 (*C*H$_{arom}$), 120.3 (*C*H$_{arom}$), 110.5 (*C*H$_{arom}$), 94.4 (*C*H$_{enaminone}$), 94.3 (*C*H$_{enaminone}$), 78.2 (q*C*$_{alkyne}$), 78.0 (q*C*$_{alkyne}$), 72.9 (*C*H$_{alkyne}$), 72.8 (*C*H$_{alkyne}$), 45.6 (*C*H$_{3, NMe}$), 45.5 (*C*H$_{3, NMe}$), 38.0 (*C*H$_{3, NMe}$), 37.9 (*C*H$_{3, NMe}$), 34.9 (*C*H$_{2, propargyl}$), 34.8 (*C*H$_{2, propargyl}$), 22.2 (*C*H$_{3, Me}$), 21.8 (*C*H$_{3, Me}$).

m.p.: 188–191 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{17}N_3O$: 267.1372; found: 267.1370

IR (ATR) (cm^{-1}): 3140, 2901, 1635, 1554

- ***(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]prop-2-en-1-one (29e).** The product was isolated (PE:EtOAc 1:1 → EtOAc → EtOAc:MeOH 9:1) as a light yellow-brownish powder (235.0 mg, 77%), after reacting ketone **28f** (0.248 g, 1.0 mmol) with DMFDMA (0.5 mL) in dry PhMe (1.0 mL) for 90 min.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.36 (bs, 1H, C*H*$_{enaminone}$), 8.10–7.86 (m, 4H, C*H*$_{naphthimidazole}$), 7.52–7.36 (m, 2H, C*H*$_{naphthimidazole}$), 6.50 (s, 1H, C*H*$_{enaminone}$), 5.73 (d, *J* = 2.4 Hz, 2H, C*H*$_{2, propargyl}$), 3.20 (s, 3H, C*H*$_{3, NMe}$), 3.05 (s, 3H, C*H*$_{3, NMe}$), 2.32 (t, *J* = 2.4 Hz, 1H, C*H*$_{alkyne}$).

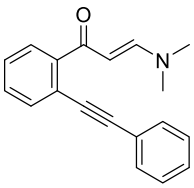
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.2 (*C*=O), 155.0 (*C*H$_{enaminone}$), 151.3 (q*C*$_{arom}$), 141.5 (q*C*$_{arom}$), 136.1 (q*C*$_{arom}$), 131.7 (q*C*$_{arom}$), 131.1 (q*C*$_{arom}$), 128.7 (*C*H$_{arom}$), 127.8 (*C*H$_{arom}$), 125.1 (*C*H$_{arom}$), 123.9 (*C*H$_{arom}$), 118.4 (*C*H$_{arom}$), 106.6 (*C*H$_{arom}$), 94.3 (*C*H$_{enaminone}$), 78.2 (-*C*≡CH), 72.8 (-C≡*C*H), 45.6 (*C*H$_{3,\ NMe}$), 37.9 (*C*H$_{3,\ NMe}$), 34.9 (*C*H$_{2,\ propargyl}$).

m.p.: 223–225 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{17}N_3O$: 303.1372; found: 303.1373

IR (ATR) (cm^{-1}): 3167, 2921, 1637, 1555

♁ ***(E)*-3-(dimethylamino)-1-[2-(phenylethynyl)phenyl]prop-2-en-1-one (32a). Typical procedure (Method C).** A screw-capped tube equipped with a magnetic stirrer was loaded with ketone **31a** (110.0 mg, 0.5 mmol), DMFDMA (0.08 mL) and dry xylene (0.6 mL) under Ar atmosphere. The reaction was then heated to 140 ºC for 18 h. The reaction was allowed to cool to r.t., after which the solvent was evaporated and the residue was purified by flash column chromatography (100% EtOAc) yielding enaminoketone **32a** as a yellow powder (86.4 mg, 63%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.67–7.49 (m, 3H, C*H*$_{arom}$ + C*H*$_{enaminone}$), 7.49–7.40 (m, 2H, C*H*$_{arom}$), 7.39–7.23 (m, 5H, C*H*$_{arom}$), 5.68 (d, *J* = 12.6 Hz, 1H, C*H*$_{enaminone}$), 3.02 (s, 3H, C*H*$_{3,\ NMe}$), 2.76 (s, 3H, C*H*$_{3,\ NMe}$).

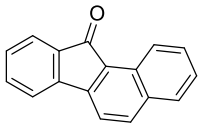
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (*C*=O), 154.3 (*C*H$_{enaminone}$), 144.5 (q*C*$_{arom}$), 132.8 (*C*H$_{arom}$), 131.4 (*C*H$_{arom}$), 129.0 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 128.3 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 123.4 (q*C*$_{arom}$), 120.5 (q*C*$_{arom}$), 97.1 (*C*H$_{enaminone}$), 93.6 (-C≡*C*-Ph), 88.9 (-*C*≡C-Ph), 44.9 (*C*H$_{3,\ NMe}$), 37.0 (*C*H$_{3,\ NMe}$).

m.p.: 126–130 ºC (EtOAc)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{17}NO$: 275.1310; found: 275.1311

IR (ATR) (cm^{-1}): 3045, 2910, 1543

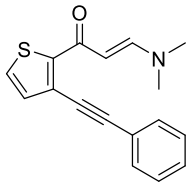
11*H*-Benzo[*a*]fluoren-11-one (33).[109] This product was isolated as an orange powder (103.2 mg, 90%) from the same substrates when the reaction time was lengthened to 24 h. Needle-like crystals were easily obtained by slow evaporation of a solution of this ketone in DCM.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.5 Hz, 1H, C*H*$_{arom}$), 7.94 (d, *J* = 8.2 Hz, 1H, C*H*$_{arom}$), 7.75 (d, *J* = 8.2 Hz, 1H, C*H*$_{arom}$), 7.65–7.51 (m, 3H, C*H*$_{arom}$), 7.49–7.34 (m, 3H, C*H*$_{arom}$), 7.24 (td, *J* = 7.1, 1.9 Hz, 1H, C*H*$_{arom}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 195.4 (*C*=O), 146.2 (q*C*$_{arom}$), 143.9 (q*C*$_{arom}$), 135.9 (*C*H$_{arom}$), 134.7 (*C*H$_{arom}$), 134.5 (q*C*$_{arom}$), 134.3 (q*C*$_{arom}$), 130.2 (q*C*$_{arom}$), 129.5 (*C*H$_{arom}$), 129.3 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 126.9 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 124.4 (*C*H$_{arom}$), 123.9 (*C*H$_{arom}$), 120.0 (*C*H$_{arom}$), 118.2 (*C*H$_{arom}$).

***(E)*-3-(Dimethylamino)-1-[3-(phenylethynyl)thiophen-2-yl]prop-2-en-1-one (32b). Typical procedure (Method D).** A screw-capped sealed tube equipped with a magnetic stirrer was loaded with ketone **31b** (226.3 mg, 1.0 mmol), DMFDMA (0.20 mL, 1.5 mmol) and dry PhMe (1.2 mL) under Ar atmosphere. The reaction was then heated to 115 ºC for 24 h. The reaction was allowed to cool to r.t., the solvent was evaporated and the product was directly submitted to flash column chromatography (EtOAc) yielding the enaminoketone **32b** as a brownish powder (218.8 mg, 78%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.59–7.48 (m, 2H, C*H*$_{phenyl}$), 7.40 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.39–7.31 (m, 3H, C*H*$_{phenyl}$), 7.19 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 6.45 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 3.14 (bs, 3H, C*H*$_{3,\ NMe}$), 2.83 (bs, 3H, C*H*$_{3,\ NMe}$).

[109] Large, B.; Gigant, N.; Joseph, D.; Clavier, G.; Prim, D. *Eur. J. Org. Chem.* **2019**, *2019*, 1835–1841.

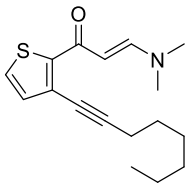
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.5 (*C*=O), 154.5 (*C*H$_{enaminone}$), 149.8 (q*C*$_{arom}$), 132.5 (*C*H$_{arom}$), 131.6 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 123.2 (q*C*$_{arom}$), 120.9 (q*C*$_{arom}$), 94.8 (*C*H$_{enaminone}$), 93.3 (q*C*$_{alkyne}$), 85.7 (q*C*$_{alkyne}$), 45.2 (*C*H$_{3,\ NMe}$), 37.5 (*C*H$_{3,\ NMe}$).

m.p.: 91–93 ºC (EtOAc)

HRMS (*m/z*): [M$^+$] calc. for $C_{17}H_{15}NOS$: 281.0874; found: 281.0879

IR (ATR) (cm^{-1}): 3002, 2234, 1640

♁ ***(E)*-3-(Dimethylamino)-1-[3-(oct-1-yn-1-yl)thiophen-2-yl]prop-2-en-1-one (32c).** The product was isolated (EtOAc) as a a brownish powder (151.9 mg, 56%), starting from ketone **31c** (220.0 mg, 0.94 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.31 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.04 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 6.42 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 3.13 (bs, 3H, C*H*$_{3,\ NMe}$), 2.91 (bs, 3H, C*H*$_{3,\ NMe}$), 2.44 (t, *J* = 7.1 Hz, 2H, C*H*$_{2,\ octyl}$), 1.71–1.52 (m, 2H, C*H*$_{2,\ octyl}$), 1.51–1.19 (m, 6H, C*H*$_{2,\ octyl}$), 1.01–0.77 (m, 3H, C*H*$_{3,\ octyl}$).

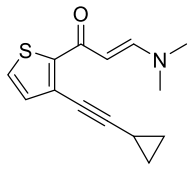
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.6 (*C*=O), 154.2 (*C*H$_{enaminone}$), 148.6 (q*C*$_{arom}$), 132.9 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 121.9 (q*C*$_{arom}$), 96.4 (q*C*$_{alkyne}$), 93.3 (*C*H$_{enaminone}$), 76.9 (q*C*$_{alkyne}$), 45.1 (*C*H$_{3,\ NMe}$), 37.4 (*C*H$_{3,\ NMe}$), 31.5 (*C*H$_{2,\ octyl}$), 28.9 (*C*H$_{2,\ octyl}$), 22.6 (*C*H$_{2,\ octyl}$), 19.9 (*C*H$_{2,\ octyl}$), 14.1 (*C*H$_{3,\ octyl}$).

m.p.: 100–105 ºC (EtOAc)

HRMS (*m/z*): [M$^+$] calc. for $C_{17}H_{23}NOS$: 289.1500; found: 289.1503

IR (ATR) (cm^{-1}): 3020, 2250, 1642

***(E)*-1-[3-(Cyclopropylethynyl)thiophen-2-yl]-3-(dimethylamino)prop-2-en-1-one (32d).** The product was isolated (EtOAc) as a brownish powder (66.6 mg, 50%), starting from ketone **31d** (102.0 mg, 0.54 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.29 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.00 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 6.39 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 3.12 (bs, 3H, C*H*$_{3,\ NMe}$), 2.92 (bs, 3H, C*H*$_{3,\ NMe}$), 1.48 (tt, *J* = 8.2, 5.1 Hz, 1H, C*H*$_{cyclopropyl}$), 0.95–0.84 (m, 2H, C*H*$_{cyclopropyl}$), 0.84–0.72 (m, 2H, C*H*$_{cyclopropyl}$).

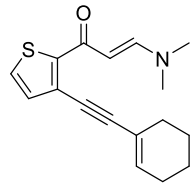
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.5 (*C*=O), 154.2 (*C*H$_{enaminone}$), 148.9 (q*C*$_{arom}$), 132.8 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 121.7 (q*C*$_{arom}$), 99.3 (-C≡*C*-cyclopropyl), 93.2 (*C*H$_{enaminone}$), 72.2 (-*C*≡C-cyclopropyl), 45.1 (*C*H$_{3,\ NMe}$), 37.4 (*C*H$_{3,\ NMe}$), 29.7(*C*H$_{2,\ cyclopropyl}$), 8.8 (*C*H$_{2,\ cyclopropyl}$), 0.5 (*C*H$_{cyclopropyl}$).

m.p.: 108–113 ºC (DCM)

HRMS (*m/z*): [M^+] calc. for $C_{14}H_{15}NOS$: 245.0874; found: 245.0875

IR (ATR) (cm^{-1}): 3095, 2853, 2226, 1641, 1552

***(E)*-1-[3-(Cyclohex-1-en-1-ylethynyl)thiophen-2-yl]-3-(dimethylamino)prop-2-en-1-one (32e).** The product was isolated (EtOAc) as a brownish powder (166.9 mg, 55%), starting from ketone **31e** (244.2 mg, 1.06 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.34 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.07 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 6.40 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 6.22 (tt, *J* = 4.0, 1.8 Hz, 1H, C*H*$_{cyclohexenyl}$), 3.15 (s, 3H, C*H*$_{3,\ NMe}$), 2.92 (s, 3H, C*H*$_{3,\ NMe}$), 2.33–2.19 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.19–2.08 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.73–1.53 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

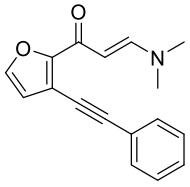
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.6 (*C*=O), 154.4 (*C*H$_{enaminone}$), 148.8 (q*C*$_{arom}$), 136.0 (*C*H$_{arom}$), 132.7 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 121.6 (q*C*$_{arom}$), 120.9 (q*C*$_{arom}$), 96.9 (-C≡*C*-cyclohexenyl), 93.4 (*C*H$_{enaminone}$), 83.1 (-*C*≡C-cyclohexenyl), 45.2 (*C*H$_{3,\ NMe}$), 37.5 (*C*H$_{3,\ NMe}$), 29.3 (*C*H$_{2,\ cyclohexenyl}$), 26.0 (*C*H$_{2,\ cyclohexenyl}$), 22.4 (*C*H$_{2,\ cyclohexenyl}$), 21.6 (*C*H$_{2,\ cyclohexenyl}$).

m.p.: 120–123 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{19}NOS$: 285.1187; found: 285.1186

IR (ATR) (cm^{-1}): 3066, 2931, 1642, 1537

♁ ***(E)*-3-(Dimethylamino)-1-[3-(phenylethynyl)furan-2-yl]prop-2-en-1-one (32f).** The product was isolated (PE:EtOAc 9:1) as an orange powder (87.1 mg, 66%) after reacting ketone **31f** (105.1 mg, 0.5 mmol) for 12 h.



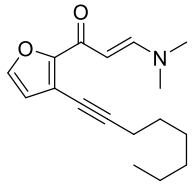
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02–7.74 (m, 1H, C*H*$_{enaminone}$), 7.58–7.49 (m, 2H, C*H*$_{phenyl}$), 7.51–7.41 (m, 1H, C*H*$_{furan}$), 7.38–7.28 (m, 3H, C*H*$_{phenyl}$), 6.67–6.50 (m, 1H, C*H*$_{furan}$), 6.21–6.01 (m, 1H, C*H*$_{enaminone}$), 3.13 (s, 3H, C*H*$_{3,\ NMe}$), 2.86 (s, 3H, C*H*$_{3,\ NMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.2 (*C*=O), 154.8 (q*C*$_{arom}$), 153.9 (*C*H$_{enaminone}$), 143.5 (*C*H$_{arom}$), 131.5 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 123.0 (q*C*$_{arom}$), 115.1 (*C*H$_{arom}$), 109.9 (q*C*$_{arom}$), 95.7 (-C≡*C*-Ph), 92.9 (*C*H$_{enaminone}$), 82.3 (-*C*≡C-Ph), 45.0 (*C*H$_{3,\ NMe}$), 37.3 (*C*H$_{3,\ NMe}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1100

IR (ATR) (cm^{-1}): 2980, 2842, 1724, 1662

***(E)*-3-(Dimethylamino)-1-[3-(oct-1-yn-1-yl)furan-2-yl]prop-2-en-1-one (32g).** The product was isolated (EtOAc) as a dark brown powder (225.2 mg, 59%), starting from ketone **31g** (305.3 mg, 1.40 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.41 (d, *J* = 1.8 Hz, 1H, C*H*$_{furan}$), 6.46 (d, *J* = 1.8 Hz, 1H, C*H*$_{furan}$), 6.09 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 3.14 (s, 3H, C*H*$_{3, NMe}$), 2.91 (s, 3H, C*H*$_{3, NMe}$), 2.45 (t, *J* = 7.2 Hz, 2H, C*H*$_{2, hexyl}$), 1.69–1.52 (m, 2H, C*H*$_{2, hexyl}$), 1.52–1.37 (m, 2H, C*H*$_{2, hexyl}$), 1.37–1.16 (m, 4H, 2C*H*$_{2, hexyl}$), 0.89 (t, *J* = 6.9 Hz, 3H, C*H*$_{3, hexyl}$).

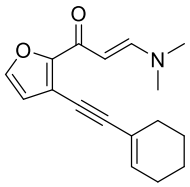
^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.6 (*C*=O), 154.4 (q*C*$_{arom}$), 153.9 (*C*H$_{enaminone}$), 143.5 (*C*H$_{arom}$), 115.7 (*C*H$_{arom}$), 111.0 (q*C*$_{arom}$), 97.7 (-C≡*C*-hexyl), 93.2 (*C*H$_{enaminone}$), 73.4 (-*C*≡C-hexyl), 45.1 (*C*H$_{3, NMe}$), 37.4 (*C*H$_{3, NMe}$), 31.5 (*C*H$_{2, hexyl}$), 28.9 (*C*H$_{2, hexyl}$), 28.9 (*C*H$_{2, hexyl}$), 22.7 (*C*H$_{2, hexyl}$), 20.0 (*C*H$_{2, hexyl}$), 14.2 (*C*H$_{3, hexyl}$).

m.p.: 35–37 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{23}NO_2$: 273.1729; found: 273.1729

IR (ATR) (cm^{-1}): 3131, 2953, 2855, 1726, 1664, 1577

***(E)*-1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]-3-(dimethylamino)prop-2-en-1-one (32h).** The product was isolated (EtOAc) as a brownish powder (300.1 mg, 75%), starting from ketone **31h** (316.8 mg, 1.48 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 12.4 Hz, 1H, C*H*$_{enaminone}$), 7.43 (d, *J* = 1.8 Hz, 1H, C*H*$_{furan}$), 6.49 (d, *J* = 1.8 Hz, 1H, C*H*$_{furan}$), 6.23 (tt, *J* = 3.9, 1.8 Hz, 1H, C*H*$_{cyclohexenyl}$), 6.09 (d, *J* = 12.4 Hz, 1H, C*H*$_{enaminone}$), 3.14 (s, 3H, C*H*$_{3, NMe}$), 2.91 (s, 3H, C*H*$_{3, NMe}$), 2.31–2.18 (m, 2H, C*H*$_{2, cyclohexenyl}$), 2.18–2.06 (m, 2H, C*H*$_{2, cyclohexenyl}$), 1.76–1.48 (m, 4H, C*H*$_{2, cyclohexenyl}$).

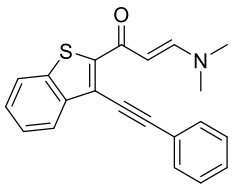
^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.5 (*C*=O), 154.3 (q*C*$_{arom}$), 153.9 (*C*H$_{enaminone}$), 143.7 (*C*H$_{arom}$), 136.1 (*C*H$_{arom}$), 120.9 (q*C*$_{arom}$), 115.4 (*C*H$_{arom}$), 110.7 (q*C*$_{arom}$), 98.0 (-C≡*C*-cyclohexenyl), 93.2 (*C*H$_{enaminone}$), 79.7 (-*C*≡C-cyclohexenyl), 45.1 (*C*H$_{3,\ NMe}$), 37.5 (*C*H$_{3,\ NMe}$), 29.2 (*C*H$_{2,\ cyclohexenyl}$), 25.9 (*C*H$_{2,\ cyclohexenyl}$), 22.4 (*C*H$_{2,\ cyclohexenyl}$), 21.6 (*C*H$_{2,\ cyclohexenyl}$).

m.p.: 109–112 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{19}NO_2$: 269.1416; found: 269.1415

IR (ATR) (cm^{-1}): 3098, 2928, 1630, 1560, 1541

♁ ***(E)*-3-(Dimethylamino)-1-[3-(phenylethynyl)benzo*[b]*thiophen-2-yl]prop-2-en-1-one (32i).** The product was isolated (EtOAc) as a brownish powder (208.7 mg, 46%), starting from ketone **31i** (380.9 mg, 1.37 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26–7.30 (m, 10H, C*H*$_{arom.}$ + C*H*$_{enaminone}$), 6.62 (d, *J* = 11.1 Hz, 1H, C*H*$_{enaminone}$), 3.15 (s, 3H, C*H*$_{3,\ NMe}$), 2.88 (s, 3H, C*H*$_{3,\ NMe}$).

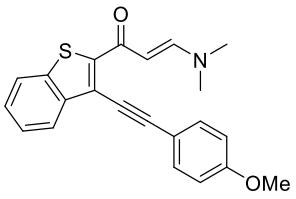
^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.1 (*C*=O), 154.6 (*C*H$_{enaminone}$), 150.4 (q*C*$_{arom}$), 141.2 (q*C*$_{arom}$), 139.4 (q*C*$_{arom}$), 131.7 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 124.9 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 123.0 (q*C*$_{arom}$), 122.7 (*C*H$_{arom}$), 116.6 (q*C*$_{arom}$), 98.2 (-C≡*C*-Ph), 94.0 (*C*H$_{enaminone}$), 84.2 (-*C*≡C-Ph), 45.2 (*C*H$_{3,\ NMe}$), 37.6 (*C*H$_{3,\ NMe}$).

m.p.: 159–161 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{21}H_{17}NOS$: 331.1031; found: 331.1034

IR (ATR) (cm^{-1}): 3061, 2923, 1629, 1532

♁ ***(E)*-3-(Dimethylamino)-1-[3-[(4-methoxyphenyl]ethynyl]benzo*[b]*thiophen-2-yl)prop-2-en-1-one (32j).** The product was isolated (EtOAc) as an orange powder (62.1 mg, 54%), starting from ketone **31j** (96.6 mg, 0.32 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15–8.00 (m, 1H, C*H*$_{benzothiophene}$), 7.91 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.87–7.77 (m, 1H, C*H*$_{benzothiophene}$), 7.64–7.50 (m, 2H, C*H*$_{anisole}$), 7.50–7.33 (m, 2H, C*H*$_{benzothiophene}$), 7.04–6.81 (m, 2H, C*H*$_{anisole}$), 6.63 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 3.84 (s, 3H, C*H*$_{3,\ OMe}$), 3.15 (s, 3H, C*H*$_{3,\ NMe}$), 2.88 (s, 3H, C*H*$_{3,\ NMe}$).

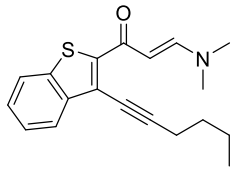
^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.1 (*C*=O), 160.1 (q*C*$_{arom}$), 154.4 (*C*H$_{enaminone}$), 149.6 (q*C*$_{arom}$), 141.2 (q*C*$_{arom}$), 139.3 (q*C*$_{arom}$), 133.1 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 124.7 (*C*H$_{arom}$), 124.4 (*C*H$_{arom}$), 122.6 (*C*H$_{arom}$), 117.0 (q*C*$_{arom}$), 115.0 (q*C*$_{arom}$), 114.2 (*C*H$_{arom}$), 98.4 (-C≡*C*-anisole), 93.9 (*C*H$_{enaminone}$), 82.9 (-*C*≡C-anisole), 55.4 (*C*H$_{3,\ OMe}$), 45.1 (*C*H$_{3,\ NMe}$), 37.5 (*C*H$_{3,\ NMe}$).

m.p.: 165–170 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{22}H_{19}NO_2S$: 361.1137; found: 361.1142

IR (ATR) (cm^{-1}): 3056, 2938, 1627, 1530

- ***(E)*-3-(Dimethylamino)-1-[3-(hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]prop-2-en-1-one (32k).** The product was isolated (EtOAc) as a brownish gum (60.2 mg, 47%), starting from ketone **31k** (104.0 mg, 0.41 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97–7.91 (m, 1H, C*H*$_{benzothiophene}$), 7.89 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.82–7.74 (m, 1H, C*H*$_{benzothiophene}$), 7.45–7.33 (m, 2H, C*H*$_{benzothiophene}$), 6.59 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 3.15 (s, 3H, C*H*$_{3,NMe}$), 2.94 (s, 3H, C*H*$_{3,NMe}$), 2.60 (t, *J* = 7.1 Hz, 2H, C*H*$_{2,butyl}$), 1.78–1.62 (m, 2H, C*H*$_{2,butyl}$), 1.62–1.46 (m, 2H, C*H*$_{2,butyl}$), 0.97 (t, *J* = 7.3 Hz, 3H, C*H*$_{3,butyl}$).

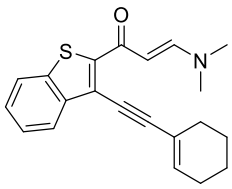
^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.3 (*C*=O), 154.4 (*C*H$_{enaminone}$), 149.1 (q*C*$_{arom}$), 141.7 (q*C*$_{arom}$), 139.3 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 124.5 (C*H*$_{benzo[b]thiophene}$), 122.6 (*C*H$_{arom}$), 117.6 (q*C*$_{arom}$), 100.0 (-C≡*C*-butyl), 94.0 (*C*H$_{enaminone}$), 75.5 (-*C*≡C-

butyl), 45.2 (*C*$H_{3,NMe}$), 37.5 (*C*$H_{3,NMe}$), 31.1 (*C*$H_{2,butyl}$), 22.3 (*C*$H_{2,butyl}$), 19.8 (*C*$H_{2,butyl}$), 13.7 (*C*$H_{3,butyl}$).

HRMS (*m/z)*: [M^+] calc. for $C_{19}H_{21}NOS$: 311.1344; found: 311.1346

IR (ATR) (cm^{-1}): 3107, 2928, 2860, 1625, 1533

♁ ***(E)*-1-[3-(Cyclohex-1-en-1-ylethynyl)benzo[*b*]thiophen-2-yl]-3-(dimethylamino)prop-2-en-1-one (32l).** The product was isolated (EtOAc) as an orange powder (192.7, 33%), starting from ketone **31l** (359.0 mg, 1.28 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (ddd, *J* = 6.0, 3.2, 0.8 Hz, 1H, C*H*$_{benzothiophene}$), 7.90 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 7.80 (ddd, *J* = 6.0, 3.2, 0.8 Hz, 1H, C*H*$_{benzothiophene}$), 7.41 (dd, *J* = 6.0, 3.2 Hz, 2H, C*H*$_{benzothiophene}$), 6.57 (d, *J* = 12.3 Hz, 1H, C*H*$_{enaminone}$), 6.34 (tt, *J* = 4.0, 1.8 Hz, 1H, C*H*$_{cyclohexenyl}$), 3.18 (s, 3H, C*H*$_{3,\ NMe}$), 2.98 (s, 3H, C*H*$_{3,\ NMe}$), 2.41–2.30 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.24–2.15 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.78–1.60 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.4 (*C*=O), 154.5 (*C*H$_{enaminone}$), 149.3 (q*C*$_{arom}$), 141.5 (q*C*$_{arom}$), 139.5 (q*C*$_{arom}$), 136.4 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 124.7 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 122.7 (*C*H$_{arom}$), 121.0 (q*C*$_{arom}$), 117.3 (q*C*$_{arom}$), 100.5 (-C≡*C*-cyclohexenyl), 94.1 (*C*H$_{enaminone}$), 81.8 (-*C*≡C-cyclohexenyl), 45.3 (*C*$H_{3,\ NMe}$), 37.6 (*C*$H_{3,\ NMe}$), 29.5 (*C*$H_{2,\ cyclohexenyl}$), 26.1 (*C*$H_{2,\ cyclohexenyl}$), 22.4 (*C*$H_{2,\ cyclohexenyl}$), 21.6 (*C*$H_{2,\ cyclohexenyl}$).

m.p.: 137–139 ºC (DCM)

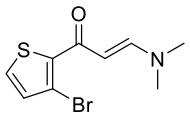
HRMS (*m/z)*: [M^+] calc. for $C_{21}H_{21}NOS$: 335.1344; found: 335.1342

IR (ATR) (cm^{-1}): 3063, 2935, 2856, 1621, 1531

General procedure for the aminomethylenation of 2-bromoheteroaryl methyl ketones (Method E).

A screw-capped tube equipped with a magnetic stirrer was loaded with the corresponding methyl ketone (2.0 mmol), DMFDMA (0.36 mL, 3.0 mmol) and dry DMF or PhMe (3.0 mL) under Ar atmosphere. The reaction was then heated to 115 ºC for 18 h, allowed to cool to r.t., and then the solvent was evaporated *in* vacuo. The residue was purified by flash column chromatography (EtOAc) yielding the desired enaminoketone **42**.

(*E*)-1-(3-Bromothiophen-2-yl)-3-(dimethylamino)prop-2-en-1-one (42d). The product was isolated as a yellow powder (515.3 mg, >99%) after carrying out the reaction in PhMe and purification using EtOAc as eluent.

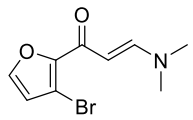


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 12.2 Hz, 1H, C*H*$_{enaminone}$), 7.35 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 7.01 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 6.00 (d, *J* = 12.2 Hz, 1H, C*H*$_{enaminone}$), 3.15 (s, 3H, C*H*$_{3, NMe}$), 2.93 (s, 3H, C*H*$_{3, NMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.1 (*C*=O), 154.5 (*C*H$_{enaminone}$), 141.8 (q*C*$_{arom}$), 132.8 (*C*H$_{arom}$), 129.0 (*C*H$_{arom}$), 109.9 (q*C*$_{arom}$-Br), 93.7 (*C*H$_{enaminone}$), 45.3 (*C*H$_{3, NMe}$), 37.6 (*C*H$_{3, NMe}$).

m.p.: 64–65 ºC (EtOAc). *Lit.*[53] 56–58 ºC (pentane)

(*E*)-1-(3-Bromofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one (42e). The product was isolated as a yellow-brownish powder (453.8 mg, 93%) after carrying out the reaction in DMF and purification using EtOAc as eluent.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 12.4 Hz, 1H, C*H*$_{enaminone}$), 7.40 (d, *J* = 1.9 Hz, 1H, C*H*$_{furan}$), 6.54 (d, *J* = 1.9 Hz, 1H, C*H*$_{furan}$), 5.82 (d, *J* = 12.4 Hz, 1H, C*H*$_{enaminone}$), 3.14 (s, 3H, C*H*$_{3, NMe}$), 2.92 (s, 3H, C*H*$_{3, NMe}$).

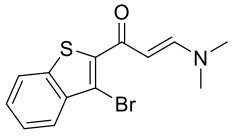
^{13}C-NMR (75 MHz, $CDCl_3$) δ 176.9 (*C*=O), 154.0 (*C*H$_{enaminone}$), 149.5 (q*C*$_{arom}$), 143.5 (*C*H$_{arom}$), 116.9 (*C*H$_{arom}$), 103.5 (q*C*$_{arom}$-Br), 92.5 (*C*H$_{enaminone}$), 45.2 (*C*H$_{3,\ NMe}$), 37.5 (*C*H$_{3,\ NMe}$).

m.p.: 117–121 ºC (EtOAc)

HRMS (*m/z)*: [M$^+$] calc. for $C_9H_{10}BrNO_2$: 242.9895; found: 242.9892

IR (ATR) (cm^{-1}): 3075, 1640, 1578, 1543

(*E*)-1-(3-bromobenzo[*b*]thiophen-2-yl)-3-(dimethylamino)prop-2-en-1-one (42f). The product was isolated as a fluffy orange powder (552.3 mg, 89%) after carrying out the reaction in PhMe and purification using EtOAc as eluent.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.97–7.89 (m, 1H, C*H*$_{arom}$), 7.86 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.82–7.74 (m, 1H, C*H*$_{arom}$), 7.56–7.35 (m, 2H, C*H*$_{arom}$), 6.09 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 3.16 (s, 3H, C*H*$_{3,\ NMe}$), 2.96 (s, 3H, C*H*$_{3,\ NMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 181.0 (*C*=O), 154.9 (*C*H$_{enaminone}$), 141.5 (q*C*$_{arom}$), 139.4 (q*C*$_{arom}$), 138.5 (q*C*$_{arom}$), 126.9 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 124.7 (*C*H$_{arom}$), 122.6 (*C*H$_{arom}$), 107.2 (q*C*$_{arom}$-Br), 94.9 (*C*H$_{enaminone}$), 45.4 (*C*H$_{3,\ NMe}$), 37.7 (*C*H$_{3,\ NMe}$).

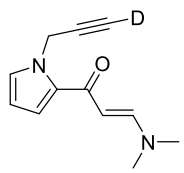
m.p.: 140–143 ºC (EtOAc). *Lit.*[53] 137–139 ºC (Et_2O)

4.2.9 Deuteration of terminal alkyne

A round-bottom flask equipped with a magnetic stirrer was charged with enaminoketone **19a** (404.5 mg, 2 mmol), potassium carbonate (418.8 mg, 3 mmol) and dry acetonitrile (4.0 mL) under argon atmosphere. The mixture was stirred at r.t. for 30 min and then, D_2O (1.0 mL, 55.6 mmol) was added and the reaction was further stirred for 1 h. The mixture was then extracted with DCM (2 × 5 mL) and the combined organic layers were dried with anhydrous sodium sulfate and evaporated

under reduced pressure to afford deuterated alkyne **19a-D** as a yellow powder (402.2 mg, >99%, 95% deuteration).

***(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl-3-*d*)-1*H*-pyrrol-2-yl]prop-2-en-1-one (19a-D).** The product was isolated as a yellow powder (402.2 mg, >99%, 95% deuteration).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.06 (dd, *J* = 2.6, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.82 (dd, *J* = 4.0, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.14 (dd, *J* = 4.0, 2.6 Hz, 1H, C*H*$_{pyrrole}$), 5.58 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 5.32 (s, 2H, C*H*$_{2,\ propargyl}$), 2.96 (bs, 6H, -N(C*H*$_3$)$_2$).

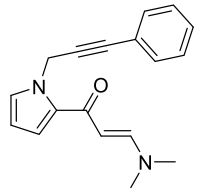
^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.6 (*C*=O), 152.3 (*C*H$_{enaminone}$), 131.8 (q*C*$_{arom}$), 127.1 (*C*H$_{arom}$), 115.7 (*C*H$_{arom}$), 108.0 (*C*H$_{arom}$), 93.3 (*C*H$_{enaminone}$), 78.9 (t, $^{2}J_{CD}$ = 7.6 Hz, q*C*$_{alkyne}$), 73.2 (t, $^{1}J_{CD}$ = 19.8 Hz, *C*D$_{alkyne}$), 38.6 (-N(*C*H$_3$)$_2$).

m.p.: 119–121 ºC (DCM)

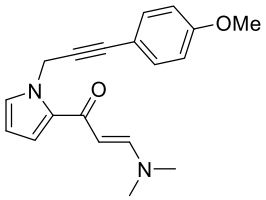
4.2.10 General procedure for the arylation of terminal propargyl compound 19a via Sonogashira cross-coupling

A round-bottom flask equipped with a magnetic stirrer was charged with enaminone **19a** (121.4 mg, 0.6 mmol), $PdCl_2(PPh_3)_2$ (7.1 mg, 0.01 mmol), CuI (1.0 mg, 0.005 mmol), deoxygenated triethylamine (1.1 mL) and deoxygenated DMF (3.3 mL) under argon atmosphere. Then, the corresponding iodoarene (0.5 mmol) was added and the reaction was stirred at r.t. for 6 h. After that, the reaction mixture was diluted with EtOAc (30 mL) and washed with water (2 × 15 mL). Then, the organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent purification of the residue by flash column chromatography (PE:EtOAc) yielded the desired product.

♁ ***(E)*-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl)-1*H*-pyrrol-2-yl]prop-2-en-1-one (19b).** The product was isolated (PE:EtOAc 8:2) as an orangish powder (100.9 mg, 73%), starting from iodobenzene (0.057 mL, 0.5 mmol).



♁ ***(E)*-3-(Dimethylamino)-1-[1-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-1*H*-pyrrol-2-yl]prop-2-en-1-one (19d).** The product was isolated (PE:EtOAc 7:3) as a brown gum (106.2 mg, 69%), starting from iodoanisole (119.4 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 7.38 (d, *J* = 8.6 Hz, 2H, C*H*$_{anisole}$), 7.24 (t, *J* = 2.2 Hz, 1H, C*H*$_{pyrrole}$), 6.89–6.84 (m, 1H, C*H*$_{pyrrole}$), 6.82 (d, *J* = 8.6 Hz, 2H, C*H*$_{anisole}$), 6.16 (t, *J* = 3.3 Hz, 1H, C*H*$_{pyrrole}$), 5.61 (d, *J* = 12.5 Hz, 1H, C*H*$_{enaminone}$), 5.55 (s, 2H, C*H*$_{2,\ propargyl}$), 3.80 (s, 3H, C*H*$_{3,\ OMe}$), 2.99 (bs, 6H, N(C*H*$_3$)$_2$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 180.9 (*C*=O), 159.8 (q*C*$_{arom}$), 152.3 (*C*H$_{enaminone}$), 133.4 (*C*H$_{arom}$), 131.9 (q*C*$_{arom}$), 127.1 (*C*H$_{arom}$), 115.8 (*C*H$_{arom}$), 115.0 (q*C*$_{arom}$), 114.0 (*C*H$_{arom}$), 107.8 (*C*H$_{arom}$), 93.6 (*C*H$_{enaminone}$), 85.2 (q*C*$_{alkyne}$), 83.2 (q*C*$_{alkyne}$), 55.4 (*C*H$_{3,\ OMe}$), 39.4 (*C*H$_2$, propargyl). (N(*C*H$_3$)$_2$ signals missing due to coalescence)

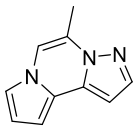
HRMS (*m/z*): [M$^+$] calc. for $C_{19}H_{20}N_2O_2$: 308.1525; found: 308.1526

IR (ATR) (cm^{-1}): 3080, 2907, 1630, 1556

4.3 General procedure for the one-pot amine exchange/heteroannulation/alkyne hydroamination

A screw-capped tube containing a magnetic stirrer was charged with the alkyne-bearing enaminoketone (0.5 mmol), hydrazine hydrate (0.123 mL, 2.5 mmol), cesium carbonate (167.3 mg, 0.5 mmol) and ethanol 96% (0.75 mL) under Ar. Then, the reaction was heated to 85 ºC for 5 h. After cooling to r.t., the reaction was concentrated *in vacuo,* the residue was redissolved in CH_2Cl_2 (10 mL) and filtered to remove cesium carbonate. Then, the filtrate was concentrated under reduced pressure and the residue purified by silica gel flash column chromatography (PE:EtOAc) to afford the desired product.

5-Methylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine (21a). The product was isolated (PE:EtOAc 8:2) as an off-white powder (81.3 mg, 95%), starting from enaminone **19a** (101.1 mg, 0.5 mmol).

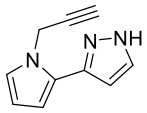


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.06 (dd, *J* = 2.7, 1.3 Hz, 1H, C*H*$_{pyrrole}$), 7.03 (d, *J* = 1.1 Hz, 1H, C*H*$_{pyrazine}$), 6.65 (ddd, *J* = 3.9, 1.3, 0.8 Hz, 1H, C*H*$_{pyrrole}$), 6.61 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.58 (dd, *J* = 3.9, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 2.53 (d, *J* = 1.1 Hz, 3H, C*H*$_{3,\ Me}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.9 (*C*H$_{pyrazole}$), 133.1 (q*C*$_{arom}$), 122.4 (q*C*$_{arom}$), 122.0 (q*C*$_{arom}$), 115.2 (*C*H$_{arom}$), 111.9 (*C*H$_{arom}$), 109.9 (*C*H$_{arom}$), 101.8 (*C*H$_{arom}$), 97.4 (*C*H$_{pyrazole}$), 14.8 (*C*H$_{3,\ Me}$).

m.p.: 81–83 ºC (DCM). *Lit.*[41] (oil)

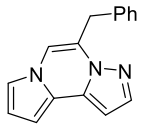
3-[1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole (20a).[41a] The product was isolated (PE:EtOAc 6:4) as a yellowish oil (67.4 mg, 79%), reacting enaminone **19a** (101.1 mg, 0.5 mmol) with hydrazine hydrate (93 µL, 0.75 mmol) and DMAP (76.6 mg, 1.5 mmol) in EtOH (0.75 mL) for 12 h in air atmosphere.



^{1}H-NMR (300 MHz, CDCl3) δ 10.19 (bs, 1H, N*H*), 7.55 (d, *J* = 2.2 Hz, 1H, C$H_{pyrazole}$), 6.95 (dd, *J* = 2.8, 1.8 Hz, 1H, C$H_{pyrrole}$), 6.48 (d, *J* = 2.2 Hz, 1H, C$H_{pyrazole}$), 6.44 (dd, *J* = 3.7, 1.8 Hz, 1H, C$H_{pyrrole}$), 6.26 (dd, *J* = 3.7, 2.8 Hz, 1H, C$H_{pyrrole}$), 4.97 (d, *J* = 2.5 Hz, 2H, C$H_{2,\ propargyl}$), 2.39 (t, *J* = 2.5 Hz, 1H, -C≡C*H*).

^{13}C-NMR (75 MHz, CDCl$_3$) δ 142.3 (q*C*$_{arom}$), 132.3 (*C*H$_{pyrazole}$), 125.4 (q*C*$_{arom}$), 122.8 (*C*H$_{arom}$), 109.8 (*C*H$_{arom}$), 108.9 (*C*H$_{arom}$), 104.4 (*C*H$_{pyrazole}$), 79.2 (-C≡*C*H), 73.4 (-C≡*C*H), 37.5 (*C*H$_{2,\ propargyl}$).

5-Benzylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine (21b). The product was isolated (PE:EtOAc 8:2) as an off-white powder (107.3 mg, 87%), starting from enaminone **19b** (139.2 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.84 (d, *J* = 2.1 Hz, 1H, C$H_{pyrazole}$), 7.49–7.27 (m, 5H, CH_{phenyl}), 7.02 (dd, *J* = 2.7, 1.3 Hz, 1H, C$H_{pyrrole}$), 6.75 (t, *J* = 1.0 Hz, 1H, C$H_{pyrazine}$), 6.68 (dt, *J* = 3.7, 1.3 Hz, 1H, C$H_{pyrrole}$), 6.65 (d, *J* = 2.1 Hz, 1H, C$H_{pyrazole}$), 6.59 (dd, *J* = 3.7, 2.7 Hz, 1H, C$H_{pyrrole}$), 4.35 (d, *J* = 1.0 Hz, 2H, C$H_{2,\ benzyl}$).

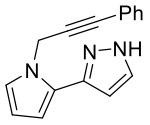
^{13}C-NMR (75 MHz, CDCl$_3$) δ 140.8 (*C*H$_{pyrazole}$), 136.4 (q*C*$_{arom}$), 133.1 (q*C*$_{arom}$), 129.7 (*C*H$_{arom}$), 128.8 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 125.7 (q*C*$_{arom}$), 122.2 (q*C*$_{arom}$), 115.6 (*C*H$_{arom}$), 112.1 (*C*H$_{arom}$), 111.1 (*C*H$_{arom}$), 101.9 (*C*H$_{arom}$), 97.5 (*C*H$_{pyrazole}$), 34.5 (*C*H$_{2,\ benzyl}$).

m.p.: 73–76 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{16}H_{13}N_3$: 247.1109; found: 247.1110

IR (ATR) (cm^{-1}): 3093, 2918, 2849, 1590, 1515

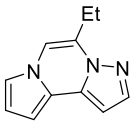
3-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole (20b). The product was isolated (PE:EtOAc 6:4) as a yellowish oil (79.0 mg, 64%), reacting enaminone **19b** (139.2 mg, 0.5 mmol) with hydrazine hydrate (93 µL, 0.75 mmol) and DMAP (76.6 mg, 1.5 mmol) in EtOH (0.75 mL) for 12 h in air atmosphere.



^{1}H-NMR (300 MHz, CDCl3) δ 9.96 (bs, 1H, N*H*), 7.57 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.48–7.36 (m, 2H, C*H*$_{phenyl}$), 7.36–7.27 (m, 3H, C*H*$_{phenyl}$), 7.04 (dd, *J* = 2.8, 1.8 Hz, 1H, C*H*$_{pyrrole}$), 6.52 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 6.46 (dd, *J* = 3.6, 1.8 Hz, 1H, C*H*$_{pyrrole}$), 6.27 (dd, *J* = 3.6, 2.8 Hz, 1H, C*H*$_{pyrrole}$), 5.20 (s, 2H, C*H*$_{2,\ propargyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.0 (q*C*$_{arom}$), 132.9 (*C*H$_{pyrazole}$), 131.9 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 125.2 (q*C*$_{arom}$), 123.0 (*C*H$_{arom}$), 122.5 (q*C*$_{arom}$), 109.7 (*C*H$_{arom}$), 108.7 (*C*H$_{arom}$), 104.5 (*C*H$_{pyrazole}$), 85.2 (q*C*$_{alkyne}$), 84.4 (q*C*$_{alkyne}$), 38.4 (*C*H$_{2,\ propargyl}$).

5-Ethylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine (21c). The product was isolated (PE:EtOAc 8:2) as a brownish oil (31.7 mg, 34%), starting from enaminone **19c** (108.1 mg, 0.5 mmol).



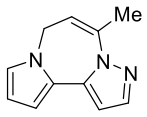
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.0 Hz, 1H, C*H*$_{pyrazole}$), 7.12 (dd, *J* = 2.7, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 7.12–7.04 (m, 1H, C*H*$_{pyazine}$), 6.66 (ddd, *J* = 3.8, 1.4, 0.8 Hz, 1H, C*H*$_{pyrrole}$), 6.63–6.57 (m, 2H, C*H*$_{pyrazole}$ + C*H*$_{pyrrole}$), 3.02 (qd, *J* = 7.4, 1.2 Hz, 2H, C*H*$_{2,\ Et}$), 1.40 (t, *J* = 7.4 Hz, 3H, C*H*$_{3,\ Et}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.8 (*C*H$_{pyrazole}$), 133.2 (q*C*$_{arom}$), 127.4 (q*C*$_{arom}$), 122.4 (q*C*$_{arom}$), 115.4 (*C*H$_{arom}$), 112.0 (*C*H$_{arom}$), 109.0 (*C*H$_{arom}$), 101.8 (*C*H$_{arom}$), 97.3 (*C*H$_{arom}$), 22.0 (*C*H$_{2,\ Et}$), 11.8 (*C*H$_{3,\ Et}$).

HRMS (*m/z*): [M^+] calc. for $C_{11}H_{11}N_3$: 185.0953; found: 185.0952

IR (ATR) (cm^{-1}): 3105, 2920, 1591, 1515

♁ **5-Methyl-7*H*-pyrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]diazepine (35).** The product was isolated (PE:EtOAc 8:2) as an off-white powder (50.3 mg, 54%), starting from enaminone **19c** (108.1 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 1.9 Hz, 1H, C*H*$_{pyrazole}$), 6.68 (dd, *J* = 2.6, 1.7 Hz, 1H, C*H*$_{pyrrole}$), 6.49–6.44 (m, 2H, C*H*$_{pyrazole}$ + C*H*$_{pyrrole}$), 6.20 (dd, *J* = 3.7, 2.6 Hz, 1H, C*H*$_{pyrrole}$), 5.59 (tq, *J* = 7.2, 0.9 Hz, 1H, C*H*$_{diazepine}$), 4.39 (dq, *J* = 7.2, 0.4 Hz, 2H, C*H*$_{2,\ diazepine}$), 2.36–2.29 (m, 3H, C*H*$_{3,\ Me}$).

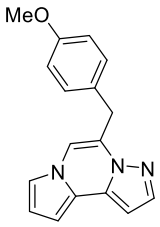
^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.7 (q*C*$_{arom}$), 140.4 (*C*H$_{pyrazole}$), 138.0 (q*C*$_{arom}$), 123.5 (q*C*$_{arom}$), 121.9 (*C*H$_{arom}$), 110.1 (*C*H$_{arom}$), 109.5 (*C*H$_{arom}$), 108.8 (*C*H$_{arom}$), 104.9 (*C*H$_{pyrazole}$), 43.8 (*C*H$_{2,\ diazepine}$), 21.2 (*C*H$_{3,\ Me}$).

m.p.: 135–138 ºC (DCM)

HRMS (*m/z*): [M^+] calc. for $C_{11}H_{11}N_3$: 185.0953; found: 185.0955

IR (ATR) (cm^{-1}): 3105, 2926, 1673, 1585, 1502

♁ **5-(4-Methoxybenzyl)pyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine (21d).** The product was isolated (PE:EtOAc 7:3) as a brownish powder (128.7 mg, 93%), starting from enaminone **19d** (154.2 mg, 0.5 mmol).



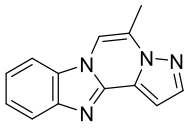
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.29 (d, *J* = 8.6 Hz, 2H, C*H*$_{anisole}$), 7.07–6.98 (m, 1H, C*H*$_{pyrrole}$), 6.91 (d, *J* = 8.6 Hz, 2H, C*H*$_{anisole}$), 6.72 (s, 1H, C*H*$_{pyrazine}$), 6.69–6.65 (m, 1H, C*H*$_{pyrrole}$), 6.63 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.61–6.55 (m, 1H, C*H*$_{pyrrole}$), 4.28 (s, 2H, C*H*$_{2,\ benzyl}$), 3.83 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6 (q*C*$_{arom}$), 140.7 (*C*H$_{pyrazole}$), 132.9 (q*C*$_{arom}$), 130.5 (*C*H$_{arom}$), 128.2 (q*C*$_{arom}$), 126.0 (q*C*$_{arom}$), 122.1 (q*C*$_{arom}$), 115.5 (*C*H$_{arom}$), 114.1 (*C*H$_{arom}$), 111.9 (*C*H$_{arom}$), 110.8 (*C*H$_{arom}$), 101.7 (*C*H$_{arom}$), 97.3 (*C*H$_{pyrazole}$), 55.2 (*C*H$_{3, OMe}$), 33.5 (*C*H$_{2, benzyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{15}N_3O$: 277.1215; found: 277.1217

IR (ATR) (cm^{-1}): 3125, 2834, 1611, 1587, 1511

5-Methylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine (34a). The product was isolated (EtOAc) as an off-white powder (111.7 mg, >99%), starting from enaminone **29a** (126.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.97 (dt, *J* = 8.1, 0.7 Hz, 1H, C*H*$_{benzimidazole}$), 7.76 (dt, *J* = 8.1, 0.8 Hz, 1H, C*H*$_{benzimidazole}$), 7.56 (q, *J* = 1.3 Hz, 1H, C*H*$_{pyrazine}$), 7.50 (td, *J* = 7.8, 7.2, 1.6 Hz, 1H, C*H*$_{benzimidazole}$), 7.47–7.40 (m, 2H, C*H*$_{benzimidazole}$ + C*H*$_{pyrazole}$), 2.75 (d, *J* = 1.3 Hz, 3H, C*H*$_{3, Me}$).

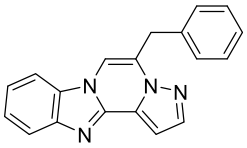
^{13}C-NMR (75 MHz, $CDCl_3$) δ 142.7 (q*C*$_{arom}$), 141.9 (*C*H$_{pyrazole}$), 140.2 (q*C*$_{arom}$), 130.3 (q*C*$_{arom}$), 129.3 (q*C*$_{arom}$), 125.2 (*C*H$_{arom}$), 124.2 (q*C*$_{arom}$), 123.3 (*C*H$_{arom}$), 120.0 (*C*H$_{arom}$), 110.0 (*C*H$_{arom}$), 106.6 (*C*H$_{arom}$), 103.3 (*C*H$_{pyrazole}$), 15.1 (*C*H$_{3, Me}$).

m.p.: 183–186 (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{13}H_{10}N_4$: 222.0905; found: 222.0906

IR (ATR) (cm^{-1}): 3106, 3048, 2925, 1501

5-Benzylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine (34b). The product was isolated (EtOAc) as a yellowish powder (148.1 mg, >99%), starting from enaminone **29b** (164.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.85 (dt, *J* = 8.2, 0.9 Hz, 1H, C*H*$_{benzimidazole}$), 7.42 (dt, *J* = 8.2, 0.9 Hz, 1H, C*H*$_{benzimidazole}$), 7.39–7.28 (m, 6H, 5C*H*$_{arom}$ + C*H*$_{benzimidazole}$), 7.27 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.21 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H, C*H*$_{benzimidazole}$), 7.03 (t, *J* = 1.1 Hz, 1H, C*H*$_{pyrazine}$), 4.36 (d, *J* = 1.1 Hz, 2H, C*H*$_{2,\ benzyl}$).

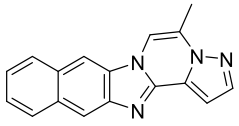
^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.6 (q*C*$_{arom}$), 141.5 (*C*H$_{pyrazole}$), 140.3 (q*C*$_{arom}$), 135.7 (q*C*$_{arom}$), 130.6 (*C*H$_{arom}$), 129.5 (q*C*$_{arom}$), 129.4 (*C*H$_{arom}$), 128.9 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 127.2 (q*C*$_{arom}$), 124.8 (*C*H$_{arom}$), 122.8 (*C*H$_{arom}$), 120.1 (*C*H$_{arom}$), 109.8 (*C*H$_{arom}$), 107.6 (*C*H$_{arom}$), 102.6 (*C*H$_{pyrazole}$), 34.5 (*C*H$_{2,\ benzyl}$).

m.p.: 132–135 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{14}N_4$: 298.1218; found: 298.1221

IR (ATR) (cm^{-1}): 3477, 3193, 3023, 2917, 1507

5-Methylnaphtho[2',3':4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine (34c). The product was isolated (EtOAc) as an off-white powder (136.0 mg, >99%), starting from enaminone **29f** (151.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H, C*H*$_{arom}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 8.03–7.94 (m, 1H, C*H*$_{naphthimidazole}$), 7.93 (s, 1H, C*H*$_{naphthimidazole}$), 7.92–7.85 (m, 1H, C*H*$_{naphthimidazole}$), 7.48–7.38 (m, 3H, C*H*$_{naphthimidazole}$), 7.37 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 2.67 (s, 3H, C*H*$_{3,\ Me}$).

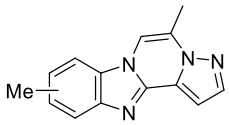
^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.5 (q*C*$_{arom}$), 143.1 (q*C*$_{arom}$), 141.6 (*C*H$_{pyrazole}$), 131.6 (q*C*$_{arom}$), 130.3 (q*C*$_{arom}$), 130.1 (q*C*$_{arom}$), 130.0 (q*C*$_{arom}$), 128.4 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 124.8 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 123.0 (*C*H$_{arom}$), 116.8 (*C*H$_{arom}$), 107.0 (*C*H$_{arom}$), 106.1 (*C*H$_{arom}$), 103.8 (*C*H$_{pyrazole}$), 15.0 (*C*H$_{3,\ Me}$).

m.p.: 241–244 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{12}N4$: 272.1062; found: 272.1067

IR (ATR) (cm^{-1}): 3142, 3049, 3003, 2925, 1514

♁ **5,10-*Dimethylbenzo[4,5]imidazo[1,2-a*]pyrazolo[5,1-*c*]pyrazine and 5,9-*dimethylbenzo[4,5]imidazo[1,2-a*]pyrazolo[5,1-*c*]pyrazine (34d & 34d').** The product was isolated (EtOAc) as an off-white powder (118.0 mg, >99%), starting from enaminones **29d** (133.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02–7.97 (m, 2H, C*H*$_{pyrazole}$), 7.78 (d, *J* = 8.3 Hz, 1H, C*H*$_{benzimidazole}$), 7.71–7.65 (m, 1H, C*H*$_{pyrazine}$), 7.53 (d, *J* = 8.3 Hz, 1H, C*H*$_{benzimidazole}$), 7.45–7.43 (m, 1H, C*H*$_{pyrazine}$), 7.43–7.35 (m, 2H, C*H*$_{benzimidazole}$), 7.31 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.29 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.25 (dd, *J* = 8.3, 1.4 Hz, 1H, C*H*$_{benzimidazole}$), 7.17 (dd, *J* = 8.3, 1.4 Hz, 1H, C*H*$_{benzimidazole}$), 2.68 (t, *J* = 1.4 Hz, 6H, C*H*$_{3,\ pyrazine}$), 2.53 (s, 6H, C*H*$_{3,\ Me}$).

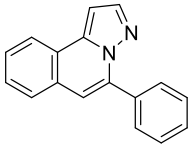
^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.9 (q*C*$_{arom}$), 141.8 (q*C*$_{arom}$), 141.5 (CH$_{pyrazole}$), 141.5 (CH$_{pyrazole}$), 140.5 (q*C*$_{arom}$), 140.2 (q*C*$_{arom}$), 134.8 (q*C*$_{arom}$), 133.2 (q*C*$_{arom}$), 130.9 (q*C*$_{arom}$), 130.8 (q*C*$_{arom}$), 129.6 (q*C*$_{arom}$), 127.6 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 123.4 (*C*H$_{arom}$), 119.8 (*C*H$_{arom}$), 119.7 (*C*H$_{arom}$), 109.6 (*C*H$_{arom}$), 109.3 (*C*H$_{arom}$), 106.7 (*C*H$_{arom}$), 106.6 (*C*H$_{arom}$), 102.4 (*C*H$_{pyrazole}$), 102.4 (*C*H$_{pyrazole}$), 22.0 (*C*H$_{3,\ Me}$), 21.9 (*C*H$_{3,\ Me}$), 15.0 (*C*H$_{3,\ Me}$).

m.p.: 163–166 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{14}H_{12}N_4$: 236.1062; found: 236.1060

IR (ATR) (cm^{-1}): 3429, 3364, 3090, 2922, 2860, 1508

♁ **5-Phenylpyrazolo[5,1-*a*]isoquinoline (36a).** The product was isolated (PE:EtOAc 8:2) as an off-white powder (116.2 mg, 95%), starting from enaminone **32a** (137.7 mg, 0.5 mmol).

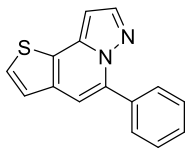


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18–8.07 (m, 1H, C*H*$_{isoquinoline}$), 8.03 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.96–7.87 (m, 2H, C*H*$_{isoquinoline}$), 7.79–7.68 (m, 1H, C*H*$_{isoquinoline}$), 7.64–7.46 (m, 5H, C*H*$_{phenyl}$), 7.10 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.05 (s, 1H, C*H*$_{pyridine}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.0 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 138.7 (q*C*$_{arom}$), 134.0 (q*C*$_{arom}$), 129.6 (*C*H$_{arom}$), 129.4 (*C*H$_{arom}$), 129.3 (q*C*$_{arom}$), 128.5 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 127.5 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 124.2 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 112.7 (*C*H$_{arom}$), 98.0 (*C*H$_{pyrazole}$).

m.p.: 141–143 ºC (DCM). *Lit.*[110] 145.2–146.0 (PE:EtOAc)

♁ **5-Phenylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36b).** The product was isolated (PE:EtOAc 8:2) as a white powder (111.0 mg, 89%), starting from enaminone **32b** (140.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.6 Hz, 1H, C*H*$_{pyrazole}$), 7.94–7.83 (m, 2H, C*H*$_{thiophene}$ + C*H*$_{phenyl}$), 7.65–7.43 (m, 4H, C*H*$_{phenyl}$), 7.35 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.17 (s, 1H, C*H*$_{pyridine}$), 6.78 (d, *J* = 1.6 Hz, 1H, C*H*$_{pyrazole}$).

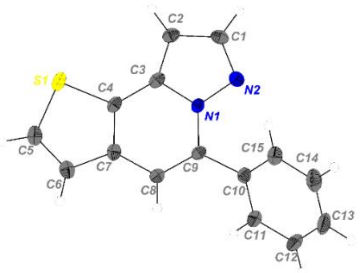
^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.5 (*C*H$_{pyrazole}$), 137.9 (q*C*$_{arom}$), 136.8 (q*C*$_{arom}$), 134.9 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 129.5 (*C*H$_{arom}$), 129.3 (*C*H$_{arom}$), 128.5 (*C*H$_{arom}$), 127.4 (q*C*$_{arom}$), 126.7 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 108.6 (*C*H$_{pyridine}$), 95.9 (*C*H$_{pyrazole}$).

[110] Pan, X.; Luo, Y.; Wu, J. *J. Org. Chem.* **2013**, *78*, 5756–5760.

m.p.: 115–118 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{10}N_2S$: 250.0565; found: 250.0562

IR (ATR) (cm^{-1}): 3102, 2925, 1624, 1545



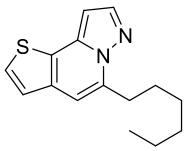
Crystallographic data (36b):

Crystal system	monoclinic	Space group	$P2_1$
a (Å)	6.22355(12)	α (°)	90
b (Å)	8.67880(16)	β (°)	105.675(2)
c (Å)	11.4663(2)	γ (°)	90
V (Å^3)	596.296	Z	2 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1-C9	1.392	C5-C6	1.355
C8-C9	1.362	C9-C10	1.485

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
N2-N1-C9	124.10	N2-N1-C9-C8	175.59
C9-C10-C11	119.31	C8-C7-C4-S1	177.56
C4-S1-C5	90.91	C2-C3-C4-S1	4.76
C8-C9-N1	117.85	C8-C9-C10-C11	- 48.03
C1-C2-C3	104.65	N1-C9-C10-C15	- 51.01
C3-C4-S1	126.80	S1-C4-C7-C6	- 0.61
C6-C7-C8	129.39	C7-C8-C9-N1	1.89
C7-C8-C9	121.36	C1-C2-C3-C4	178.12

5-Hexylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36c). The product was isolated (PE:EtOAc 8:2) as a brownish oil (118.9 mg, 92%), starting from enaminone **32c** (144.7 mg, 0.5 mmol).



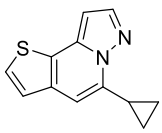
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 7.48 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 7.31 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 7.00 (s, 1H, C*H*$_{pyridine}$), 6.72 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 3.20 (t, *J* = 7.7 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.96–1.83 (m, 2H, C*H*$_{2,\ hexyl}$), 1.59–1.45 (m, 2H, C*H*$_{2,\ hexyl}$), 1.42–1.31 (m, 4H, C*H*$_{2,\ hexyl}$), 0.90 (t, J = 6.9 Hz, 3H, C*H*$_{3,\ hexyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.8 (*C*H$_{pyrazole}$), 138.9 (q*C*$_{arom}$), 136.5 (q*C*$_{arom}$), 135.2 (q*C*$_{arom}$), 126.7 (*C*H$_{arom}$), 124.3 (*C*H$_{arom}$), 106.1 (*C*H$_{arom}$), 95.9 (*C*H$_{pyrazole}$), 31.8 (*C*H$_{2,\ hexyl}$), 31.4 (*C*H$_{2,\ hexyl}$), 29.3 (*C*H$_{2,\ hexyl}$), 26.9 (*C*H$_{2,\ hexyl}$), 22.8 (*C*H$_{2,\ hexyl}$), 14.2 (*C*H$_{3,\ hexyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{18}N_2S$: 258.1191; found: 258.1189

IR (ATR) (cm^{-1}): 3112, 3061, 2846, 1626, 1546

5-Cyclopropylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36d). The product was isolated (PE:EtOAc 7:3) as a yellowish powder (102.0 mg, 95%), starting from enaminone **32d** (122.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 7.45 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.26 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 6.82 (s, 1H, C*H*$_{pyridine}$), 6.73 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 2.68 (td, *J* = 8.1, 4.1 Hz, 1H, C*H*$_{cyclopropyl}$), 1.28–1.13 (m, 2H, C*H*$_{cyclopropyl}$), 0.96–0.81 (m, 2H, C*H*$_{cyclopropyl}$).

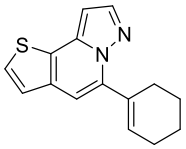
^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.4 (*C*H$_{pyrazole}$), 140.2 (q*C*$_{arom}$), 136.3 (q*C*$_{arom}$), 134.8 (q*C*$_{arom}$), 126.4 (*C*H$_{arom}$), 126.1 (q*C*$_{arom}$), 124.3 (*C*H$_{arom}$), 103.3 (*C*H$_{arom}$), 95.9 (*C*H$_{pyrazole}$), 11.8 (*C*H$_{cyclopropyl}$), 7.0 (*C*H$_{2,\ cyclopropyl}$).

m.p.: 83–85 ºC (EtOAc)

HRMS (*m/z)*: [M⁺] calc. for $C_{12}H_{10}N_2S$: 214.0565; found: 214.0563

IR (ATR) (cm^{-1}): 3121, 3075, 2921, 2851, 1627, 1547

5-(Cyclohex-1-en-1-yl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36e). The product was isolated (PE:EtOAc 8:2) as a yellowish powder (79.6 mg, 63%), starting from enaminone **32e** (142.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.46 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 7.29 (d, *J* = 5.2 Hz, 1H, C*H*$_{thiophene}$), 7.00 (s, 1H, C*H*$_{pyridine}$), 6.69 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 6.28 (tt, *J* = 3.8, 1.7 Hz, 1H, C*H*$_{cyclohexenyl}$), 2.72–2.55 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.39–2.22 (m, 2*H*, C*H*$_{2,\ cyclohexenyl}$), 1.98–1.70 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

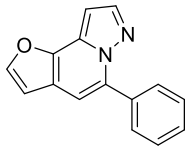
^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.3 (*C*H$_{pyrazole}$), 140.8 (q*C*$_{arom}$), 136.5 (q*C*$_{arom}$), 135.1 (q*C*$_{arom}$), 134.0 (q*C*$_{arom}$), 130.5 (*C*H$_{arom}$), 126.8 (q*C*$_{arom}$), 126.4 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 106.6 (*C*H$_{arom}$), 95.5 (*C*H$_{pyrazole}$), 27.4 (*C*H$_{2,\ cyclohexenyl}$), 25.7 (*C*H$_{2,\ cyclohexenyl}$), 22.7 (*C*H$_{2,\ cyclohexenyl}$), 22.1 (*C*H$_{2,\ cyclohexenyl}$).

m.p.: 73–75 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{15}H_{14}N_2S$: 254.0878; found: 254.0877

IR (ATR) (cm^{-1}): 3117, 2961, 2928, 2867, 2828, 1622, 1541

5-Phenylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36f). The product was isolated (PE:EtOAc 9:1) as an off-white powder (109.1 mg, 93%), starting from enaminone **32f** (132.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.89–7.80 (m, 2H, C*H*$_{phenyl}$), 7.72 (d, *J* = 2.0 Hz, 1H, C*H*$_{furan}$), 7.60–7.42 (m, 3H, C*H*$_{phenyl}$), 7.00 (s, 1H, C*H*$_{pyridine}$), 6.88–6.79 (m, 2H, C*H*$_{furan}$ + C*H*$_{pyrazole}$).

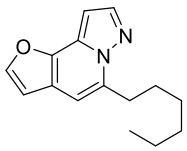
^{13}C-NMR (75 MHz, $CDCl_3$) δ 145.1 (*C*H$_{arom}$), 144.4 (q*C*$_{arom}$), 141.2 (*C*H$_{pyrazole}$), 137.3 (q*C*$_{arom}$), 134.5 (q*C*$_{arom}$), 131.8 (q*C*$_{arom}$), 129.6 (*C*H$_{arom}$), 129.2 (*C*H$_{arom}$), 128.5 (*C*H$_{arom}$), 120.6 (q*C*$_{arom}$), 107.6 (*C*H$_{arom}$), 106.2 (*C*H$_{arom}$), 93.6 (*C*H$_{pyrazole}$).

m.p.: 108–110 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{15}H_{10}N_2O$: 234.0793 found: 234.0791

IR (ATR) (cm^{-1}): 3124, 2961, 2926, 1657, 1561

5-Hexylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36g). The product was isolated (PE:EtOAc 9:1) as a dark brown powder (84.8 mg, 70%), starting from enaminone **32g** (136.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (bs, 1H, C*H*$_{pyrazole}$), 7.66 (bs, 1H, C*H*$_{furan}$), 6.79 (s, 1H, C*H*$_{pyridine}$), 6.78–6.69 (m, 2H, C*H*$_{furan}$ + C*H*$_{pyrazole}$), 3.17 (t, *J* = 7.6 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.86 (p, *J* = 7.6 Hz, 2H, C*H*$_{2,\ hexyl}$), 1.61–1.42 (m, 2H, C*H*$_{2,\ hexyl}$), 1.42–1.28 (m, 4H, C*H*$_{2,\ hexyl}$), 0.90 (t, *J* = 6.8 Hz, 3H, C*H*$_{3,\ hexyl}$).

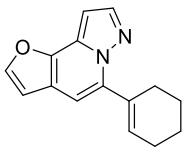
^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.7 (*C*H$_{arom}$), 143.7 (q*C*$_{arom}$), 140.8 (*C*H$_{pyrazole}$), 138.1 (q*C*$_{arom}$), 131.3 (q*C*$_{arom}$), 120.4 (q*C*$_{arom}$), 107.3 (*C*H$_{arom}$), 103.0 (*C*H$_{arom}$), 93.4 (*C*H$_{pyrazole}$), 31.8 (*C*H$_{2,\ hexyl}$), 31.5 (*C*H$_{2,\ hexyl}$), 29.2 (*C*H$_{2,\ hexyl}$), 26.8 (*C*H$_{2,\ hexyl}$), 22.7 (*C*H$_{2,\ hexyl}$), 14.2 (*C*H$_{3,\ hexyl}$).

m.p.: 35–37 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{18}N_2O$: 242.1419; found: 242.1417

IR (ATR) (cm^{-1}): 3100, 2954, 2931, 2858, 1660, 1568

5-(Cyclohex-1-en-1-yl)furo[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36h). The product was isolated (PE:EtOAc 8:2) as a yellowish powder (56.0 mg, 47%), starting from enaminone **32h** (134.7 mg, 0.5 mmol).



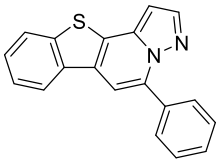
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H, C*H*$_{pyrazole}$), 7.76–7.62 (m, 1H, C*H*$_{furan}$), 6.82 (s, 1H, C*H*$_{pyridine}$), 6.80–6.71 (m, 2H, C*H*$_{pyrazole}$ + C*H*$_{furan}$), 6.34–6.09 (m, 1H, C*H*$_{cyclohexenyl}$), 2.73–2.52 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.45–2.17 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.96–1.69 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.8 (*C*H$_{arom}$), 144.1 (q*C*$_{arom}$), 141.0 (*C*H$_{pyrazole}$), 140.2 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 131.5 (q*C*$_{arom}$), 130.3 (*C*H$_{arom}$), 120.6 (q*C*$_{arom}$), 107.5 (*C*H$_{arom}$), 104.1 (*C*H$_{arom}$), 93.1 (*C*H$_{pyrazole}$), 27.3 (*C*H$_{2,\ cyclohexenyl}$), 25.7 (*C*H$_{2,\ cyclohexenyl}$), 22.7 (*C*H$_{2,\ cyclohexenyl}$), 22.1 (*C*H$_{2,\ cyclohexenyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1108

IR (ATR) (cm^{-1}): 3147, 2928, 2856, 1653, 1562

5-Phenylbenzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36i). The product was isolated (PE:EtOAc 8:2) as an off-white powder (137.9 mg, 92%), starting from enaminone **32i** (165.7 mg, 0.5 mmol).



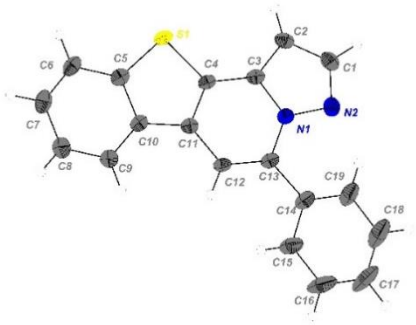
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15–8.08 (m, 1H, C*H*$_{benzothiophene}$), 8.07 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 8.01–7.88 (m, 3H, C*H*$_{benzothiophene}$ + C*H*$_{phenyl}$), 7.63–7.43 (m, 6H, C*H*$_{benzothiophene}$ + C*H*$_{phenyl}$ + C*H*$_{pyridine}$), 6.82 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.9 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 138.3 (q*C*$_{arom}$), 136.9 (q*C*$_{arom}$), 135.5 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 130.2 (q*C*$_{arom}$), 129.6 (*C*H$_{arom}$), 129.5 (*C*H$_{arom}$), 128.7 (*C*H$_{arom}$), 127.2 (q*C*$_{arom}$), 126.6 (*C*H$_{arom}$), 125.2 (*C*H$_{arom}$), 123.3 (*C*H$_{arom}$), 122.0 (*C*H$_{arom}$), 106.5 (*C*H$_{arom}$), 96.9 (*C*H$_{pyrazole}$).

m.p.: 138–142 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{12}N_2S$: 300.0721; found: 300.0720

IR (ATR) (cm^{-1}): 3147, 2924, 2854, 1624, 1542



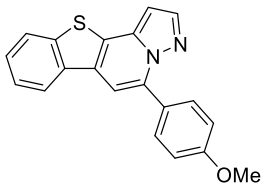
Crystallographic data (36i):

Crystal system	Monoclinic	Space group	$P2_1/c$
a (Å)	13.4844(14)	α (°)	90
b (Å)	8.4865(4)	β (°)	106.850(10)
c (Å)	13.5825(12)	γ (°)	90
V (Å^3)	1487.59	Z	4 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1-C13	1.392	C12-C13	1.365
C13-C14	1.481	C5-C10	1.408

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
N2-N1-C13	124.56	N2-N1-C13-C12	- 177.67
C13-C14-C15	118.31	C12-C13-C14-C15	44.49
C12-C13-N1	117.76	C11-C12-C13-N1	0.31
C4-S1-C5	90.76	C5-C10-C11-C12	177.42
C10-C11-C12	129.24	C2-C3-C4-S1	- 2.01
C1-N2-N1	103.71	C3-C2-C1-N2	- 0.49

5-(4-Methoxyphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36j). The product was isolated (PE:EtOAc 7:3) as a yellowish powder (152.0 mg, 96%), starting from enaminone **32j** (180.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14–8.07 (m, 1H, C*H*$_{benzothiophene}$), 8.06 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 7.98–7.92 (m, 1H, C*H*$_{benzothiophene}$), 7.92–7.85 (m, 2H, C*H*$_{anisole}$), 7.55–7.45 (m, 2H, C*H*$_{benzothiophene}$), 7.44 (s, 1H, C*H*$_{pyridine}$), 7.16–7.04 (m, 2H, C*H*$_{anisole}$), 6.81 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 3.91 (s, 3H, C*H*$_{3,\ OMe}$).

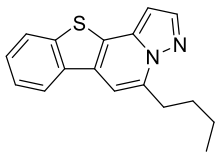
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.5 (q*C*$_{arom}$), 141.7 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 138.1 (q*C*$_{arom}$), 136.9 (q*C*$_{arom}$), 135.5 (q*C*$_{arom}$), 130.9 (*C*H$_{arom}$), 130.2 (q*C*$_{arom}$), 126.7 (q*C*$_{arom}$), 126.6 (*C*H$_{arom}$), 126.5 (q*C*$_{arom}$), 125.1 (*C*H$_{arom}$), 123.2 (*C*H$_{arom}$), 121.9 (*C*H$_{arom}$), 114.1 (*C*H$_{arom}$), 105.9 (*C*H$_{arom}$), 96.8 (*C*H$_{pyrazole}$), 55.6 (*C*H$_{3,\ OMe}$).

m.p.: 153–155 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{20}H_{14}N_2OS$: 330.0827; found: 330.0828

IR (ATR) (cm^{-1}): 3047, 2835, 1610, 1542, 1513

5-Butylbenzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36k). The product was isolated (PE:EtOAc 7:3) as a yellow oil (128.2 mg, 92%), starting from enaminone **32k** (155.7 mg, 0.5 mmol).



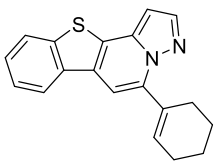
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14–8.08 (m, 1H, C*H*$_{benzothiophene}$), 8.07 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.96–7.90 (m, 1H, C*H*$_{benzothiophene}$), 7.57–7.41 (m, 2H, C*H*$_{benzothiophene}$), 7.28 (s, 1H, C*H*$_{pyridine}$), 6.76 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 3.35–3.22 (m, 2H, C*H*$_{2,\ butyl}$), 2.06–1.88 (m, 2H, C*H*$_{2,\ butyl}$), 1.56 (h, *J* = 7.4 Hz, 2H, C*H*$_{2,\ butyl}$), 1.03 (t, *J* = 7.4 Hz, 3H, C*H*$_{3,\ butyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.2 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 139.4 (q*C*$_{arom}$), 136.5 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 130.2 (q*C*$_{arom}$), 126.5 (*C*H$_{arom}$), 125.8 (q*C*$_{arom}$), 125.0 (*C*H$_{arom}$), 123.2 (*C*H$_{arom}$), 122.0 (*C*H$_{arom}$), 103.9 (*C*H$_{arom}$), 96.8 (*C*H$_{pyrazole}$), 31.3 (*C*H$_{2,\ butyl}$), 29.1 (*C*H$_{2,\ butyl}$), 22.8 (*C*H$_{2,\ butyl}$), 14.1 (*C*H$_{3,\ butyl}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{16}N_2S$: 280.1034; found: 280.1035

IR (ATR) (cm^{-1}): 3060, 2948, 2867, 1629, 1546

- **5-(Cyclohex-1-en-1-yl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36l).** The product was isolated (PE:EtOAc 7:3) as an off-white powder (111.0 mg, 73%), starting from enaminone **32l** (167.7 mg, 0.5 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15–8.08 (m, 1H, C*H*$_{benzothiophene}$), 8.05 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.97–7.88 (m, 1H, C*H*$_{benzothiophene}$), 7.57–7.43 (m, 2H, C*H*$_{benzothiophene}$), 7.32 (s, 1H, C*H*$_{pyridine}$), 6.75 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 6.38 (tt, *J* = 3.8, 1.7 Hz, 1H, C*H*$_{cyclohexenyl}$), 2.78–2.60 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.45–2.25 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.99–1.74 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.5 (*C*H$_{pyrazole}$), 140.9 (q*C*$_{arom}$), 139.5 (q*C*$_{arom}$), 136.5 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 130.8 (q*C*$_{arom}$), 130.1 (*C*H$_{arom}$), 126.3 (q*C*$_{arom}$), 126.2 (*C*H$_{arom}$), 124.9 (*C*H$_{arom}$), 123.0 (*C*H$_{arom}$), 121.7 (*C*H$_{arom}$), 104.4 (*C*H$_{arom}$), 96.2 (*C*H$_{pyrazole}$), 27.3 (*C*H$_{2,\ cyclohexenyl}$), 25.7 (*C*H$_{2,\ cyclohexenyl}$), 22.6 (*C*H$_{2,\ cyclohexenyl}$), 22.1 (*C*H$_{2,\ cyclohexenyl}$).

m.p.: 148–150 ºC (DCM)

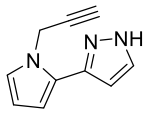
HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{16}N_2S$: 304.1034; found: 304.1031

IR (ATR) (cm^{-1}): 2923, 2858, 2830, 1619, 1539

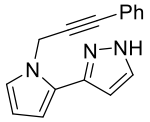
4.3.1 Effect of CO_2 in the one-pot reaction

A screw-capped tube containing a magnetic stirrer was charged with enaminoketone **19** (0.5 mmol), hydrazine hydrate (0.123 mL, 2.5 mmol), cesium carbonate (167.3 mg, 0.5 mmol) and ethanol 96% (0.75 mL) under Ar. Then, Ar-CO_2 gas exchange was performed flushing the reaction with CO_2 and performing vacuum-CO_2 flush cycles at cryogenic temperatures (liquid nitrogen) to promote CO_2 solubility in the reaction medium. The vessel was then sealed, and the reaction was heated to 85 ºC for 24 h. After cooling to r.t., the reaction was concentrated *in vacuo,* the residue was redissolved in CH_2Cl_2 (10 mL) and filtered to remove cesium carbonate. Then, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (PE:EtOAc 6:4) to obtain pyrazole **20** as a colorless oil.

- **3-[1-(Prop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole (20a).**[41a] The product was isolated as a yellowish oil (64.0 mg, 75%) starting from enaminone **19a** (101.1 mg, 0.5 mmol).

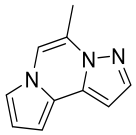


- **3-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole (20b).** The product was isolated as a yellowish oil (85.5 mg, 69%) starting from enaminone **19b** (139.2 mg, 0.5 mmol).



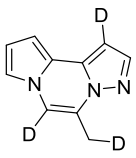
4.3.2 Scale-up of cascade reaction to obtain 21a

A heavy-walled reaction tube containing a magnetic stirrer was charged with the enaminoketone **19a** (1.01 g, 5 mmol), hydrazine hydrate (1.22 mL, 25 mmol), cesium carbonate (1.64 g, 5 mmol) and ethanol 96% (7.5 mL) under Ar. Then, the reaction was heated to 85 ºC for 5 h. After cooling to r.t., the reaction was concentrated *in vacuo,* the residue was redissolved in CH_2Cl_2 (25 mL) and filtered to remove cesium carbonate. Then, the filtrate was concentrated under reduced pressure and the residue was subsequently purified by flash chromatography (PE:EtOAc 8:2) to obtain pyrazolopyrrolopyrazine **21a** as an off-white powder (0.70 g, 82%).



4.3.3 Deuteration tests

A screw-capped tube containing a magnetic stirrer was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol) or enaminoketone **19a-D** (101.6 mg, 0.5 mmol), hydrazine hydrate (0.123 mL, 2.5 mmol), cesium carbonate (167.3 mg, 0.5 mmol) and CD_3OD (0.75 mL) under Ar. The vessel was then sealed, and the reaction was heated to 85 ºC for 5 h. After cooling to r.t., the reaction was concentrated *in vacuo,* the residue was redissolved in CH_2Cl_2 (10 mL) and filtered to remove cesium carbonate. Then, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel flash column chromatography (PE:EtOAc 8:2) to obtain the deuterated pyrazolopyrrolopyrazine.

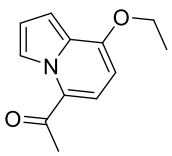


4.4 General procedure for the indolizine formation

4.4.1 General procedure for the formation of indolizines from alcohols and thiols. Method A

A screw-capped sealed tube was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol), Cs_2CO_3 (163.7 mg, 0.5 mmol), alcohol/thiol (1.5 mmol) and 2-MeTHF (0.75 mL). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The mixture was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether:ethyl acetate) to afford the desired product.

1-(8-Ethoxyindolizin-5-yl)ethan-1-one (38a). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (93.2 mg, 92%), employing EtOH (0.088 mL, 1.5 mmol) as the nucleophile.



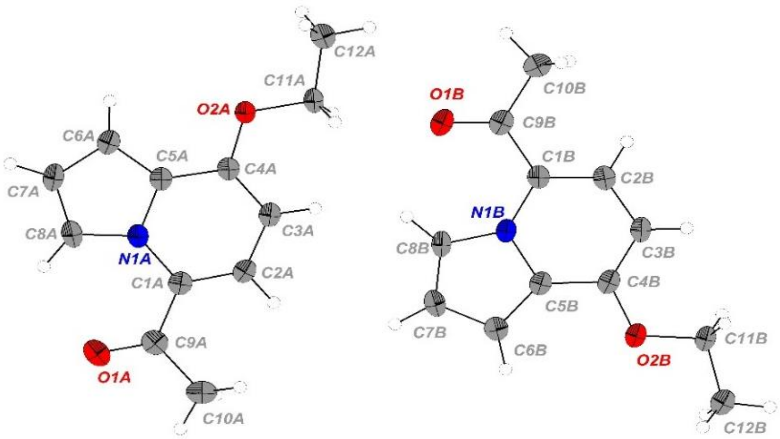
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 2.7, 1.6 Hz, 1H, C*H*$_{pyrrole}$), 7.51 (d, *J* = 8.0 Hz, 1H, C*H*$_{2,\ pyridine}$), 6.86–6.81 (m, 2H, C*H*$_{pyrrole}$), 6.07 (d, *J* = 8.0 Hz, 1H, C*H*$_{2,\ pyridine}$), 4.26 (q, *J* = 7.0 Hz, 2H, C*H*$_{2,\ OEt}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$), 1.53 (t, *J* = 7.0 Hz, 3H, C*H*$_{3,\ OEt}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.8 (*C*=O), 155.7 (q*C*$_{arom}$), 128.0 (q*C*$_{arom}$), 125.5 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 119.0 (*C*H$_{arom}$), 113.8 (*C*H$_{arom}$), 100.5 (*C*H$_{arom}$), 93.0 (*C*H$_{arom}$), 64.3 (*C*H$_{2,\ OEt}$), 26.9 (*C*H$_{3,\ Ac}$), 14.7 (*C*H$_{3,\ OEt}$).

m.p.: 125–126 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{12}H_{13}NO_2$: 203.0946; found: 203.0947

IR (ATR) (cm^{-1}): 2976, 1641



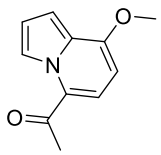
Crystallographic data (38a):

Crystal system	Orthorhombic	Space group	Pnma
a (Å)	15.7457(2)	α (°)	90
b (Å)	6.65960(10)	β (°)	90
c (Å)	19.7161(2)	γ (°)	90
V (Å^3)	2067.43	Z	8 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1A-C5A	1.406	O1A-C9A	1.227
N1A-C1A	1.405	O2A-C4A	1.354

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
N1A-C1A-C9A	120.06	C8A-N1A-C1A-C2A	180.00
N1B-C1B-C9B	119.94	C8B-N1B-C1B-C2B	180.00
C4A-C5A-C6A	132.87	N1A-C1A-C9A-C10A	180.00
C4B-C5B-C6B	132.96	N1B-C1B-C9B-C10B	180.00
O2A-C4A-C5A	114.15	C3A-C4A-O2A-C11A	0.00
O2B-C4B-C5B	112.96	C3B-C4B-O2B-C11B	0.00

1-(8-Methoxyindolizin-5-yl)ethan-1-one (38b). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (89.8 mg, 93%), employing MeOH (0.061 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.02 (dd, *J* = 2.5, 1.8 Hz, 1H, C*H*$_{pyrrole}$), 7.52 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.88–6.75 (m, 2H, C*H*$_{pyrrole}$), 6.09 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 4.02 (s, 3H, C*H*$_{3,\ OMe}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$).

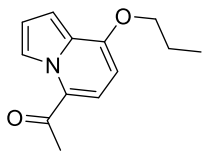
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 156.3 (q*C*$_{arom}$), 127.8 (q*C*$_{arom}$), 125.7 (q*C*$_{arom}$), 123.5 (*C*H$_{arom}$), 119.0 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 100.4 (*C*H$_{arom}$), 92.5 (*C*H$_{arom}$), 55.9 (*C*H$_{3,\ OMe}$), 26.9 (*C*H$_{3,\ Ac}$).

m.p.: 104–106 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0792

IR (ATR) (cm^{-1}): 1648

1-(8-Propoxyindolizin-5-yl)ethan-1-one (38c). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (88.0 mg, 81%), employing ^{n}PrOH (0.112 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.03 (dd, *J* = 2.5, 1.8 Hz, 1H, C*H*$_{pyrrole}$), 7.50 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.95–6.71 (m, 2H, C*H*$_{pyrrole}$), 6.06 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 4.14 (t, *J* = 7.0 Hz, 2H, C*H*$_{2,\ OPr}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$), 1.93 (q, *J* = 7.0 Hz, 2H, C*H*$_{2,\ OPr}$), 1.11 (t, *J* = 7.0 Hz, 3H, C*H*$_{3,\ OPr}$).

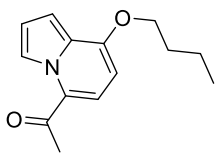
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.8 (*C*=O), 155.8 (q*C*$_{arom}$), 128.0 (q*C*$_{arom}$), 125.4 (q*C*$_{arom}$), 123.8 (*C*H$_{arom}$), 118.9 (*C*H$_{arom}$), 113.8 (*C*H$_{arom}$), 100.4 (*C*H$_{arom}$), 93.1 (*C*H$_{arom}$), 70.1 (O*C*H$_2$CH$_2$CH$_3$), 26.9 (*C*H$_{3,\ Ac}$), 22.5 (OCH$_2$*C*H$_2$CH$_3$), 10.7 (*C*H$_{3,\ OPr}$).

m.p.: 97–98 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1107

IR (ATR) (cm^{-1}): 1643

♁ **1-(8-Butoxyindolizin-5-yl)ethan-1-one (38d).** The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (69.2 mg, 60%), employing ^{n}BuOH (0.137 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.08–8.95 (m, 1H, C$H_{pyrrole}$), 7.47 (d, *J* = 8.0 Hz, 1H, C$H_{pyridine}$), 7.08–6.66 (m, 2H, C$H_{pyrrole}$), 6.04 (d, *J* = 8.0 Hz, 1H, C$H_{pyridine}$), 4.48–3.90 (m, 2H, C$H_{2,\ OBu}$), 2.61 (s, 3H, C$H_{3,\ Ac}$), 2.07–1.77 (m, 2H, C$H_{2,\ OBu}$), 1.56 (q, *J* = 7.5 Hz, 2H, C$H_{2,\ OBu}$), 1.02 (t, *J* = 7.5 Hz, 3H, C$H_{3,\ OBu}$).

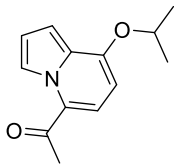
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.7 (*C*=O), 155.8 (q*C*$_{arom}$), 128.0 (q*C*$_{arom}$), 125.3 (q*C*$_{arom}$), 123.8 (*C*H$_{arom}$), 118.9 (*C*H$_{arom}$), 113.7 (*C*H$_{arom}$), 100.4 (*C*H$_{arom}$), 93.1 (*C*H$_{arom}$), 68.4 ($OCH_2CH_2CH_2CH_3$), 31.1 ($OCH_2CH_2CH_2CH_3$), 26.9 (*C*$H_{3,\ Ac}$), 19.4 ($OCH_2CH_2CH_2CH_3$), 13.9 (*C*$H_{3,\ OBu}$).

m.p.: 64–65 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{14}H_{17}NO_2$: 231.1259; found: 231.1261

IR (ATR) (cm^{-1}): 2954, 2928, 1643

♁ **1-(8-*Iso*-propoxyindolizin-5-yl)ethan-1-one (38e).** The product was isolated (PE:EtOAc 8:2) as a brownish powder (43.1 mg, 40%), employing ^{i}PrOH (0.115 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.12–8.93 (m, 1H, C$H_{pyrrole}$), 7.54 (d, *J* = 8.1 Hz, 1H, C$H_{pyridine}$), 6.93–6.74 (m, 2H, C$H_{pyrrole}$), 6.09 (d, *J* = 8.1 Hz, 1H, C$H_{pyridine}$), 4.80 (p, *J* = 6.1 Hz, 1H, C$H_{O\textit{i}Pr}$), 2.63 (s, 3H, C$H_{3,\ Ac}$), 1.46 (d, *J* = 6.1 Hz, 6H, 2C$H_{3,\ O\textit{i}Pr}$).

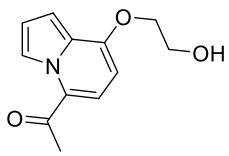
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.7 (*C*=O), 154.8 (q*C*$_{arom}$), 128.1 (q*C*$_{arom}$), 125.4 (q*C*$_{arom}$), 123.9 (*C*H$_{arom}$), 119.0 (*C*H$_{arom}$), 113.8 (*C*H$_{arom}$), 100.7 (*C*H$_{arom}$), 93.8 (*C*H$_{arom}$), 71.1 (*C*H$_{OiPr}$), 26.9 (*C*H$_{3,\ Ac}$), 22.1 (*C*H$_{3,\ OiPr}$).

m.p.: 65–67 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{13}H_{15}NO_2$: 217.1103; found: 217.1105

IR (ATR) (cm^{-1}): 3179, 2980, 2935, 1646

♁ **1-[8-(2-Hydroxyethoxy)indolizin-5-yl]ethan-1-one (38f).** The product was isolated (PE:EtOAc 1:1) as a bright yellow powder (56.8 mg, 52%), employing ethylene glycol (0.75 mL) as the nucleophile and solvent.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.13–8.89 (m, 1H, C*H*$_{pyrrole}$), 7.52 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 6.84 (s, 2H, C*H*$_{pyrrole}$), 6.12 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 4.32 (t, *J* = 4.8, 2H, C*H*$_{2,\ ETG}$), 4.08 (t, *J* = 4.8, 2H, C*H*$_{2,\ ETG}$), 2.64 (s, 3H, C*H*$_{3,\ Ac}$), 1.73 (bs, 1H, O*H*).

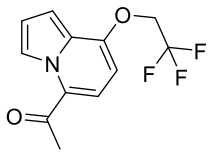
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.0 (*C*=O), 155.2 (q*C*$_{arom}$), 127.8 (q*C*$_{arom}$), 125.9 (q*C*$_{arom}$), 123.3 (*C*H$_{arom}$), 119.2 (*C*H$_{arom}$), 114.1 (*C*H$_{arom}$), 100.5 (*C*H$_{arom}$), 93.4 (*C*H$_{arom}$), 70.0 (O*C*H$_2$CH$_2$OH), 61.4 (OCH$_2$*C*H$_2$OH), 27.0 (*C*H$_{3,\ Ac}$).

m.p.: 117–119 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{12}H_{13}NO_3$: 219.0895; found: 219.0891

IR (ATR) (cm^{-1}): 3338, 2920, 1647

♁ **1-[8-(2,2,2-Trifluoroethoxy)indolizin-5-yl]ethan-1-one (38g).** The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (97.6 mg, 76%), employing 2,2,2-trifluoroethanol (0.110 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.08–9.00 (m, 1H, C*H*$_{pyrrole}$), 7.50 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 6.95–6.83 (m, 2H, C*H*$_{pyrrole}$), 6.08 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 4.56 (q, *J* = 7.9 Hz, 2H, C*H*$_{2,\ TFE}$), 2.66 (s, 3H, C*H*$_{3,\ Ac}$).

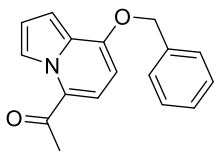
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (*C*=O), 153.5 (q*C*$_{arom}$), 127.3 (q*C*$_{arom}$), 126.8 (q*C*$_{arom}$), 122.3 (*C*H$_{arom}$), 119.5 (*C*H$_{arom}$), 114.7 (*C*H$_{arom}$), 101.1 (*C*H$_{arom}$), 93.4 (*C*H$_{arom}$), 65.68 (q, $^{2}J_{CF}$ = 36.7 Hz, -O*C*H$_2$CF$_3$), 27.1 (*C*H$_{3,\ Ac}$).

m.p.: 145–147 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{12}H_{10}F_3NO_2$: 257.0664; found: 257.0666

IR (ATR) (cm^{-1}): 3188, 3114, 2931, 1646

1-[8-(Benzyloxy)indolizin-5-yl]ethan-1-one (38h). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (120.8 mg, 91%), employing benzyl alcohol (0.157 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.04 (dd, *J* = 2.7, 1.6 Hz, 1H, C*H*$_{pyrrole}$), 7.54–7.27 (m, 6H, C*H*$_{pyridine\ +}$ C*H*$_{phenyl}$), 6.91 (dd, *J* = 4.1, 1.6 Hz, 1H, C*H*$_{pyrrole}$), 6.85 (dd, *J* = 4.1, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 6.15 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 5.30 (s, 2H, -OC*H*$_2$Ph), 2.63 (s, 3H, C*H*$_{3,\ Ac}$).

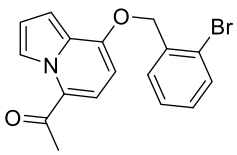
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 155.2 (q*C*$_{arom}$), 136.1 (q*C*$_{arom}$), 128.8 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 128.0 (q*C*$_{arom}$), 127.3 (*C*H$_{arom}$), 125.7 (q*C*$_{arom}$), 123.4 (*C*H$_{arom}$), 119.1 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 100.7 (*C*H$_{arom}$), 93.8 (*C*H$_{arom}$), 70.3 (-O*C*H$_2$Ph), 26.9 (*C*H$_{3,\ Ac}$).

m.p.: 124–127 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1107

IR (ATR) (cm^{-1}): 3042, 2959, 2921, 1643

1-[8-[(2-Bromobenzyl)oxy]indolizin-5-yl]ethan-1-one (38i). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (168.4 mg, 98%), employing *o*-bromobenzyl alcohol (283.1 mg, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H, C*H*$_{pyrrole}$), 7.67–7.54 (m, 2H, C*H*$_{arom}$), 7.50 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 7.35 (t, *J* = 7.5 Hz, 1H, C*H*$_{arom}$), 7.22 (t, *J* = 7.5 Hz, 1H, C*H*$_{arom}$), 6.94 (d, *J* = 4.1 Hz, 1H, C*H*$_{pyrrole}$), 6.87 (t, *J* = 2.7 Hz, 1H, C*H*$_{pyrrole}$), 6.14 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 5.36 (s, 2H, -OC*H*$_2$Ar), 2.63 (s, 3H, C*H*$_{3,\ Ac}$).

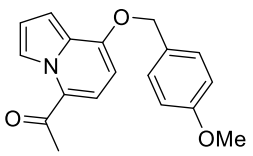
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 154.8 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 132.9 (*C*H$_{arom}$), 129.7 (*C*H$_{arom}$), 128.7 (q*C*$_{arom}$), 127.9 (*C*H$_{arom}$), 125.9 (q*C*$_{arom}$-Br), 123.3 (*C*H$_{arom}$), 122.2 (q*C*$_{arom}$), 119.2 (*C*H$_{arom}$), 114.1 (*C*H$_{arom}$), 100.7 (*C*H$_{arom}$), 93.9 (*C*H$_{arom}$), 69.6 (-O*C*H$_2$Ar), 27.0 (*C*H$_{3,\ Ac}$).

m.p.: 132–134 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{14}BrNO_2$: 343.0209; found: 343.0219

IR (ATR) (cm^{-1}): 2963, 2926, 1642

1-[8-[(4-Methoxybenzyl)oxy]indolizin-5-yl]ethan-1-one (38j). The product was isolated (PE:EtOAc 7:3) as a bright yellow powder (116.4 mg, 81%), employing *p*-methoxybenzyl alcohol (0.190 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.11–8.95 (m, 1H, C*H*$_{pyrrole}$), 7.51 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 7.46–7.35 (m, 2H, C*H*$_{anisole}$), 7.02–6.91 (m, 2H, C*H*$_{anisole}$), 6.91–6.78 (m, 2H, C*H*$_{pyrrole}$), 6.16 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 5.22 (s, 2H, -OC*H*$_2$Ar$_{,\ benzyl}$), 3.83 (s, 3H, C*H*$_{3,\ OMe}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$).

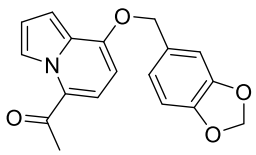
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 159.8 (q*C*$_{arom}$), 155.4 (q*C*$_{arom}$), 129.2 (*C*H$_{arom}$), 128.1 (q*C*$_{arom}$), 125.7 (q*C*$_{arom}$), 123.5 (*C*H$_{arom}$), 119.0 (*C*H$_{arom}$), 114.2 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$) , 100.7 (*C*H$_{arom}$), 93.8 (*C*H$_{arom}$), 70.3 (-O*C*H$_2$Ar), 55.5 (CH$_{3, OMe}$), 27.0 (*C*H$_{3, Ac}$).

m.p.: 150–153 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{18}H_{17}NO_3$: 295.1208; found: 292.1212

IR (ATR) (cm^{-1}): 2959, 2926, 2843, 1643

- **1-[8-(Benzo[*d*][*1,3*]dioxol-5-ylmethoxy)indolizin-5-yl]ethan-1-one (38k).** The product was isolated (PE:EtOAc 7:3) as a bright yellow powder (92.5 mg, 60%), employing piperonyl alcohol (209.2 mg, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.11–8.94 (m, 1H, C*H*$_{pyrrole}$), 7.50 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 7.04–6.75 (m, 5H, C*H*$_{pyrrole\ +}$ C*H*$_{piperonyl}$), 6.14 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 5.99 (s, 2H, -OC*H*$_2$O-), 5.18 (s, 2H, -OC*H*$_2$Ar), 2.63 (s, 3H, C*H*$_{3, Ac}$).

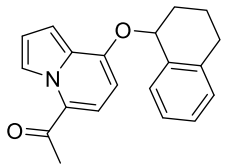
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 155.2 (q*C*$_{arom}$), 148.2 (q*C*$_{arom}$), 147.8 (q*C*$_{arom}$), 129.8 (q*C*$_{arom}$), 128.0 (q*C*$_{arom}$), 125.8 (q*C*$_{arom}$), 123.4 (*C*H$_{arom}$), 121.3 (*C*H$_{arom}$), 119.1 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 108.5 (*C*H$_{arom}$), 108.3 (*C*H$_{arom}$), 101.4 (-O*C*H$_2$O-), 100.7 (*C*H$_{arom}$), 93.8 (*C*H$_{arom}$), 70.4 (-O*C*H$_2$Ar), 27.0 (*C*H$_{3, Ac}$).

m.p.: 181–183 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{18}H_{15}NO_4$: 309.1001; found: 309.1004

IR (ATR) (cm^{-1}): 2888, 1643

1-[8-[(1,2,3,4-Tetrahydronaphthalen-1-yl)oxy]indolizin-5-yl]ethan-1-one (38l). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (119.2 mg, 78%), employing α-tetralol (0.216 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.06–8.84 (m, 1H, C*H*$_{pyrrole}$), 7.46 (d, *J* = 8.2 Hz, 1H, C*H*$_{pyridine}$), 7.37–7.24 (m, 1H, C*H*$_{arom}$), 7.24–7.00 (m, 3H, C*H*$_{arom}$), 6.72 (s, 2H, C*H*$_{pyrrole}$), 6.20 (d, *J* = 8.2 Hz, 1H, C*H*$_{pyridine}$), 5.54 (t, *J* = 4.6 Hz, 1H, -C*H*OC-), 2.98–2.78 (m, 1H, C*H*$_{tetralol}$), 2.78–2.63 (m, 1H, C*H*$_{tetralol}$), 2.55 (s, 3H, C*H*$_{3,\ Ac}$), 2.23–1.86 (m, 3H, C*H*$_{tetralol}$), 1.86–1.66 (m, 1H, C*H*$_{tetralol}$).

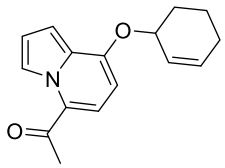
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.7 (*C*=O), 155.1 (q*C*$_{arom}$), 137.9 (q*C*$_{arom}$), 134.8 (q*C*$_{arom}$), 129.4 (*C*H$_{arom}$), 129.2 (*C*H$_{arom}$), 128.6 (q*C*$_{arom}$), 128.3 (*C*H$_{arom}$), 126.3 (*C*H$_{arom}$), 125.4 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 119.1 (*C*H$_{arom}$), 113.9 (*C*H$_{arom}$), 101.1 (*C*H$_{arom}$), 94.2 (*C*H$_{arom}$), 74.7 (O*C*H$_{tetralol}$), 29.1 (*C*H$_{2,\ tetralol}$), 28.5 (*C*H$_{2,\ tetralol}$), 26.9 (CH$_{3,\ Ac}$), 19.3 (*C*H$_{2,\ tetralol}$).

m.p.: 143–145 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1418

IR (ATR) (cm^{-1}): 3188, 3049, 2942, 1646

1-[8-(Cyclohex-2-en-1-yloxy)indolizin-5-yl]ethan-1-one (38m). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (53.3 mg, 42%), employing 2-cyclohexen-1-ol (0.155 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.16–8.91 (m, 1H, C*H*$_{pyrrole}$), 7.52 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.97–6.68 (m, 2H, C*H*$_{pyrrole}$), 6.13 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.09–5.99 (m, 1H, C*H*$_{cyclohexene}$), 5.99–5.86 (m, 1H, C*H*$_{cyclohexene}$), 5.14–4.92 (m, 1H, -C*H*OC-), 2.63 (s, 3H, C*H*$_{3,\ Ac}$), 2.25–1.98 (m, 4H, C*H*$_{cyclohexene}$), 1.98–1.64 (m, 2H, C*H*$_{cyclohexene}$).

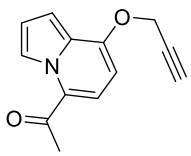
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.7 (*C*=O), 154.8 (q*C*$_{arom}$), 133.3 (*C*H$_{arom}$), 128.5 (q*C*$_{arom}$), 125.3 (*C*H$_{arom}$), 125.2 (q*C*$_{arom}$), 123.8 (*C*H$_{arom}$), 119.0 (*C*H$_{arom}$), 113.8 (*C*H$_{arom}$), 100.8 (*C*H$_{arom}$), 94.0 (*C*H$_{arom}$), 71.7 (O*C*H$_{cyclohexene}$), 28.5 (*C*H$_2$, $_{cyclohexene}$), 26.9 (*C*H$_{3,\ Ac}$), 25.2 (*C*H$_2$, $_{cyclohexene}$), 19.1 (*C*H$_2$, $_{cyclohexene}$).

m.p.: 100–103 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{17}NO_2$: 255.1259; found: 255.1254

IR (ATR) (cm^{-1}): 2963, 2948, 2854, 1648

1-[8-(Prop-2-yn-1-yloxy)indolizin-5-yl]ethan-1-one (38n). The product was isolated (PE:EtOAc 8:2) as a bright brown gel (22.6 mg, 24%), employing propargyl alcohol (0.089 mL, 1.5 mmol) as the nucleophile.



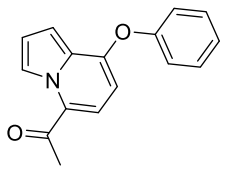
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.03 (t, *J* = 2.1 Hz, 1H, C*H*$_{pyrrole}$), 7.53 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.93–6.76 (m, 2H, 2C*H*$_{pyrrole}$), 6.23 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 4.91 (d, *J* = 2.4 Hz, 2H, -OC*H*$_2$C≡CH), 2.65 (s, 3H, C*H*$_{3,\ Ac}$), 2.60 (t, *J* = 2.4 Hz, 1H, -C≡C*H*).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.0 (*C*=O), 154.0 (q*C*$_{arom}$), 127.7 (q*C*$_{arom}$), 126.1 (q*C*$_{arom}$), 123.0 (*C*H$_{arom}$), 119.1 (*C*H$_{arom}$), 114.2 (*C*H$_{arom}$), 100.7 (*C*H$_{arom}$), 93.9 (*C*H$_{arom}$), 77.5 (-OCH$_2$*C*≡CH), 76.8 (-OCH$_2$C≡*C*H), 56.3 (-O*C*H$_2$C≡CH), 27.0 (*C*H$_{3,\ Ac}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{13}H_{11}NO_2$: 213.0790; found: 213.0792

IR (ATR) (cm^{-1}): 3105, 1649

1-(8-Phenoxyindolizin-5-yl)ethan-1-one (38o). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (31.1 mg, 25%), employing phenol (144.1 mg, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.10 (dd, *J* = 2.8, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 7.50–7.40 (m, 3H, C*H*$_{pyridine\ +}$ C*H*$_{phenyl}$), 7.35–7.13 (m, 3H, C*H*$_{phenyl}$), 7.01–6.86 (m, 2H, C*H*$_{pyrrole}$), 5.96 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 2.64 (s, 3H, C*H*$_{3,\ Ac}$).

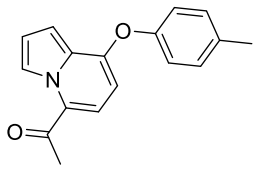
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.1 (*C*=O), 155.1 (q*C*$_{arom}$), 154.7 (q*C*$_{arom}$), 130.2 (*C*H$_{arom}$), 128.3 (q*C*$_{arom}$), 126.3 (q*C*$_{arom}$), 125.4 (*C*H$_{arom}$), 122.8 (*C*H$_{arom}$), 120.9 (*C*H$_{arom}$), 119.4 (*C*H$_{arom}$), 114.7 (*C*H$_{arom}$), 100.9 (*C*H$_{arom}$), 97.8 (*C*H$_{arom}$), 27.1 (*C*H$_{3,\ Ac}$).

m.p.: 84–86 ºC (DCM)

HRMS (*m/z*): [M$^+$] calc. for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0944

IR (ATR) (cm^{-1}): 3049, 1650

1-[8-(*p*-Tolyloxy)indolizin-5-yl]ethan-1-one (38p). The product was isolated (PE:EtOAc 8:2) as a bright yellow powder (81.0 mg, 61%), employing *p*-cresol (165.2 mg, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.51–8.76 (m, 1H, C*H*$_{pyrrole}$), 7.44 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 7.39–7.18 (m, 2H, C*H*$_{tolyl}$), 7.18–7.03 (m, 2H, C*H*$_{tolyl}$), 7.03–6.81 (m, 2H, C*H*$_{pyrrole}$), 5.93 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 2.63 (s, 3H, C*H*$_{3,\ Ac}$), 2.40 (s, 3H, C*H*$_{3,\ Me}$).

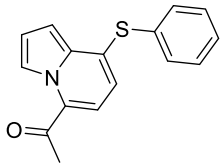
^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.0 (*C*=O), 155.5 (q*C*$_{arom}$), 152.3 (q*C*$_{arom}$), 135.2 (q*C*$_{arom}$), 130.6 (*C*H$_{arom}$), 128.2 (q*C*$_{arom}$), 126.1 (q*C*$_{arom}$), 123.0 (*C*H$_{arom}$), 120.9 (*C*H$_{arom}$), 119.3 (*C*H$_{arom}$), 114.6 (*C*H$_{arom}$), 100.9 (*C*H$_{arom}$), 97.3 (*C*H$_{arom}$), 27.0 (*C*H$_{3,\ Ac}$), 21.0 (*C*H$_{3,\ Me}$).

m.p.: 99–101 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{15}NO_2$: 265.1103; found: 265.1105

IR (ATR) (cm^{-1}): 3053, 1648

1-[8-(Phenylthio)indolizin-5-yl]ethan-1-one (40). The product was isolated (PE:EtOAc 8:2) as a brownish oil (19.6 mg, 15%), employing benzenethiol (0.157 mL, 1.5 mmol) as the nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 2.8, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 7.66–7.27 (m, 6H, C*H*$_{phenyl}$ + C*H*$_{pyridine}$), 6.95 (dd, *J* = 4.2, 2.8 Hz, 1H, C*H*$_{pyrrole}$), 6.88 (dd, *J* = 4.2, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 6.25 (d, *J* = 7.6 Hz, 1H, C*H*$_{pyridine}$), 2.63 (s, 3H, C*H*$_{3,Ac}$).

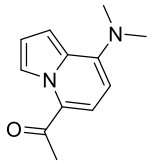
HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{13}NOS$: 267.0718; found: 267.0716

IR (ATR) (cm^{-1}): 3059, 2922, 2854, 1654

4.4.2 General procedure for the formation of indolizines from amines. Method B

A screw capped sealed tube was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol), Cs_2CO_3 (163.7 mg, 0.5 mmol), amine (1.5 mmol) and MeCN (0.75 mL). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The reaction was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether:ethyl acetate) to afford the desired product.

1-[8-(Dimethylamino)indolizin-5-yl]ethan-1-one (39a). The product was isolated (PE:EtOAc 7:3) as a yellow oil (49.7 mg, 49%), in the absence of ani additional amine nucleophile.



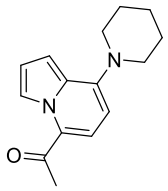
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.17 (dd, *J* = 2.8, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 7.51 (d, *J* = 8.3 Hz, 1H, C*H*$_{pyridine}$), 6.84 (dd, *J* = 4.2, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 6.79 (dd, *J* = 4.2, 2.8 Hz, 1H, C*H*$_{pyrrole}$), 5.91 (d, *J* = 8.3 Hz, 1H, C*H*$_{pyridine}$), 3.23 (s, 6H, -N(C*H*$_3$)$_2$), 2.60 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 149.0 (q*C*$_{arom}$), 129.0 (q*C*$_{arom}$), 125.5 (q*C*$_{arom}$), 124.9 (*C*H$_{arom}$), 118.8 (*C*H$_{arom}$), 112.7 (*C*H$_{arom}$), 103.8 (*C*H$_{arom}$), 96.8 (*C*H$_{arom}$), 42.6 (-N(*C*H$_3$)$_2$), 26.8 (*C*H$_{3,\ Ac}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{12}H_{14}N_2O$: 202.1106; found: 202.1107

IR (ATR) (cm^{-1}): 3003, 2361, 1739, 1634

1-[8-(Piperidin-1-yl)indolizin-5-yl]ethan-1-one (39b). The product was isolated (PE:EtOAc 7:3) as a yellow gum (59.2 mg, 49%), employing piperidine (150 µL, 1.5 mmol) as the amine nucleophile.



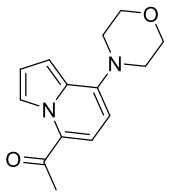
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, *J* = 2.8, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 7.51 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 6.82 (dd, *J* = 4.2, 2.8 Hz, 1H, C*H*$_{pyrrole}$), 6.68 (dd, *J* = 4.2, 1.4 Hz, 1H, CH$_{pyrrole}$), 6.20 (d, *J* = 8.0 Hz, 1H, C*H*$_{pyridine}$), 3.40 (t, *J* = 5.4 Hz, 4H, 2CH$_{2,\ piperidine}$), 2.62 (s, 3H, C*H*$_{3,\ Ac}$), 1.92–1.64 (m, 6H, 3C*H*$_{2,\ piperidine}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.4 (*C*=O), 149.8 (q*C*$_{arom}$), 129.0 (q*C*$_{arom}$), 125.0 (q*C*$_{arom}$), 123.9 (*C*H$_{arom}$), 118.5 (*C*H$_{arom}$), 113.3 (*C*H$_{arom}$), 102.1 (*C*H$_{arom}$), 100.0 (*C*H$_{pyridine}$), 52.1 (*C*H$_{2,\ piperidine}$), 26.9 (*C*H$_{3,\ Ac}$), 26.1 (*C*H$_{2,\ piperidine}$), 24.8 (*C*H$_{2,\ piperidine}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{18}N_2O$: 242.1419; found: 242.1410

IR (ATR) (cm^{-1}): 3256, 2924, 1632

1-(8-Morpholinoindolizin-5-yl)ethan-1-one (39c). The product was isolated (PE:EtOAc 7:3) as a yellow gum (55.0 mg, 45%), employing morpholine (133 µL, 1.5 mmol) as the amine nucleophile.



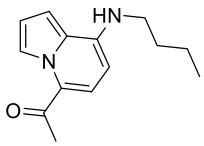
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, *J* = 2.7, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 7.52 (d, *J* = 7.9 Hz, 1H, C*H*$_{pyridine}$), 6.85 (dd, *J* = 4.2, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 6.74–6.56 (dd, *J* = 4.2, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 6.18 (d, *J* = 7.9 Hz, 1H, C*H*$_{pyridine}$), 4.02–3.88 (m, 4H, C*H*$_{2,\ morpholine}$), 3.45–3.29 (m, 4H, C*H*$_{2,\ morpholine}$), 2.64 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.9 (*C*=O), 149.0 (q*C*$_{arom}$), 129.0 (q*C*$_{arom}$), 125.9 (q*C*$_{arom}$), 123.2 (*C*H$_{arom}$), 118.6 (*C*H$_{arom}$), 113.7 (*C*H$_{arom}$), 101.8 (*C*H$_{arom}$), 100.2 (*C*H$_{arom}$), 67.0 (*C*H$_{2,\ morpholine}$), 51.3 (*C*H$_{2,\ morpholine}$), 27.0 (*C*H$_{3,\ Ac}$).

HRMS (*m/z*): [M^+] calc. for $C_{14}H_{16}N_2O_2$: 244.1212; found: 244.1219

IR (ATR) (cm^{-1}): 3028, 1738

1-[8-(Butylamino)indolizin-5-yl]ethan-1-one (39d). The product was isolated (PE:EtOAc 7:3) as a yellow oil (24.3 mg, 21%), employing butylamine (150 µL, 1.5 mmol) as the amine nucleophile.



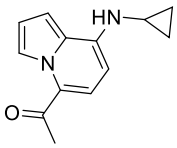
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.35–8.84 (m, 1H, C*H*$_{pyrrole}$), 7.55 (d, *J* = 8.2 Hz, 1H, C*H*$_{pyridine}$), 6.85–6.71 (m, 1H, C*H*$_{pyrrole}$), 6.69–6.49 (m, 1H, C*H*$_{pyrrole}$), 5.86 (d, *J* = 8.2 Hz, 1H, C*H*$_{pyridine}$), 4.04 (s-br, 1H, N*H*), 3.35 (t, *J* = 7.2 Hz, 2H, C*H*$_{3,\ butyl}$), 2.59 (s, 3H, C*H*$_{3,\ Ac}$), 1.72 (p, *J* = 7.8, 7.4 Hz, 2H, C*H*$_{2,\ butyl}$), 1.49 (p, *J* = 7.4 Hz, 2H, C*H*$_{2,\ butyl}$), 1.00 (dd, *J* = 8.5, 6.2 Hz, 3H, C*H*$_{3,\ butyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 189.4 (*C*=O), 144.2 (q*C*$_{arom}$), 125.9 (q*C*$_{arom}$), 125.7 (*C*H$_{arom}$), 122.5 (q*C*$_{arom}$), 119.6 (*C*H$_{arom}$), 112.7 (*C*H$_{arom}$), 97.5 (*C*H$_{arom}$), 91.3 (*C*H$_{arom}$), 43.0 (*C*H$_{2,\ butyl}$), 31.5 (*C*H$_{2,\ butyl}$), 26.6 (*C*H$_{3,\ Ac}$), 20.4 (*C*H$_{2,\ butyl}$), 14.0 (*C*H$_{3,\ butyl}$).

HRMS (*m/z*): [M$^+$] calc. for $C_{14}H_{18}N_2O$: 230.1419; found: 230.1421

IR (ATR) (cm^{-1}): 3349, 3133, 2948, 2928, 2862, 1611

1-[8-(Cyclopropylamino)indolizin-5-yl]ethan-1-one (39e). The product was isolated (PE:EtOAc 7:3) as a yellow gum (15.0 mg, 14%), employing cyclopropylamine (106 µL, 1.5 mmol) as the amine nucleophile.



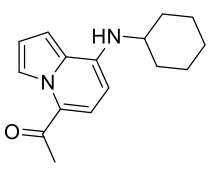
^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.10 (dd, *J* = 2.7, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 7.59 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.76 (dd, *J* = 4.2, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 6.49 (dd, *J* = 4.2, 1.4 Hz, 1H, C*H*$_{pyrrole}$), 6.26 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 5.07 (bs, 1H, N*H*), 2.67 (tt, *J* = 6.8, 3.7 Hz, 1H, C*H*$_{cyclopropyl}$), 2.61 (s, 3H, C*H*$_{3,\ Ac}$), 0.96–0.84 (m, 2H, C*H*$_{cyclopropyl}$), 0.74–0.63 (m, 2H, C*H*$_{cyclopropyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 189.8 (*C*=O), 144.8 (q*C*$_{arom}$), 125.8 (q*C*$_{arom}$), 125.4 (*C*H$_{arom}$), 123.1 (q*C*$_{arom}$), 119.5 (*C*H$_{arom}$), 112.9 (*C*H$_{arom}$), 97.4 (*C*H$_{arom}$), 93.1 (*C*H$_{arom}$), 26.6 (*C*H$_{3,\ Ac}$), 24.7 (*C*H$_{cyclopropyl}$), 7.8 (*C*H$_{2,\ cyclopropyl}$).

HRMS (*m/z*): [M$^+$] calc. for $C_{13}H_{14}N_2O$: 214.1106; found: 214.1109

IR (ATR) (cm^{-1}): 3028, 1940, 1739, 1630

1-[8-(cyclohexylamino)indolizin-5-yl]ethan-1-one (39f). The product was isolated (PE:EtOAc 7:3) as a yellow gum (68.1 mg, 53%), employing cyclohexylamine (173 µL, 1.5 mmol) as the amine nucleophile.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.07 (dd, *J* = 2.9, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 7.50 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 6.82 (dd, *J* = 4.2, 2.9 Hz, 1H, C*H*$_{pyrrole}$), 6.67 (dd, *J* = 4.2, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 6.13 (d, *J* = 8.1 Hz, 1H, C*H*$_{pyridine}$), 3.46–3.29 (m, 4H, C*H*$_{2,\ cyclohexane}$), 2.62 (s, 3H, C*H*$_{3,\ Ac}$), 1.89–1.62 (m, 7H, C*H*$_{2,\ cyclohexane}$ + N*H*).

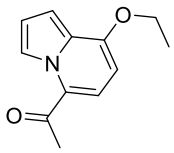
^{13}C-NMR (75 MHz, $CDCl_3$) δ 190.4 (*C*=O), 150.1 (q*C*$_{arom}$), 129.1 (q*C*$_{arom}$), 124.9 (q*C*$_{arom}$), 123.9 (*C*H$_{arom}$), 118.4 (*C*H$_{arom}$), 113.2 (*C*H$_{arom}$), 102.1 (*C*H$_{arom}$), 99.9 (*C*H$_{arom}$), 52.1 (*C*H$_{2,\ cyclohexane}$), 26.9 (*C*H$_{3,\ Ac}$), 26.2 (*C*H$_{2,\ cyclohexane}$), 24.8 (*C*H$_{2,\ cyclohexane}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{20}N_2O$: 256.1576; found: 256.1578

IR (ATR) (cm^{-1}): 3320, 3115, 2928, 1629

4.4.3 Scale-up of the reaction leading to indolizine 38a

A heavy-walled reaction tube was charged with enaminoketone **19a** (1.01 g, 5 mmol), Cs_2CO_3 (1.64 g, 5 mmol), EtOH (0.88 mL,15 mmol) and 2-MeTHF (7.5 mL). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The mixture was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:EtOAc 8:2) to obtain indolizine **38a** as a yellow powder (0.78 g, 77%).

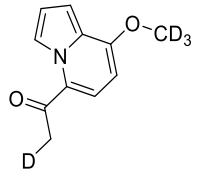


4.4.4 Deuteration and ^{18}O labelling tests

4.4.4.1 Deuterated indolizine 38b

A screw-capped sealed tube was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol) or enaminoketone **19a-D** (101.6 mg, 0.5 mmol), Cs_2CO_3 (163.7 mg, 0.5 mmol) and CD_3OD or MeOH (0.75 mL). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The mixture was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The

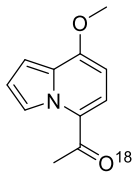
residue was purified by flash column chromatography (PE:EtOAc 8:2) to provide the deuterated indolizine.



4.4.4.2 ^{18}O-labelled indolizine 38b

Method A (MeOH as solvent and nucleophile). A screw-capped sealed tube was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol), Cs_2CO_3 (163.7 mg, 0.5 mmol), dry MeOH (0.75 mL) and $H_2{}^{18}O$ (18 µL, 1.0 mmol). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The mixture was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:EtOAc 8:2) to provide the ^{18}O-enriched indolizine.

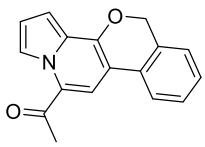
Method B (2-MeTHF as solvent and MeOH as nucleophile). A screw-capped sealed tube was charged with enaminoketone **19a** (101.1 mg, 0.5 mmol), Cs_2CO_3 (163.7 mg, 0.5 mmol), dry MeOH (0.061 mL, 1.5 mmol), $H_2{}^{18}O$ (18 µL, 1.0 mmol) and dry 2-MeTHF (0.75 mL). The tube was flushed with Ar, sealed and heated to 85 ºC for 12 h. The mixture was allowed to cool to r.t., diluted with DCM (15 mL), gravity filtered to remove solid particles and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:EtOAc 8:2) to provide the ^{18}O-enriched indolizine.



4.5 Intramolecular direct arylation leading to isochromenoindolizine 42

A screw-capped tube was charged with the indolizine **38i** (172.1 mg, 0.5 mmol), K_2CO_3 (345.5 mg, 2.5 mmol), TBAB (162.8 mg, 0.5 mmol), LiCl (32.1 mg, 0.75 mmol), $Pd(OAc)_2$ (11.6 mg, 0.05 mmol) and distilled DMF (2.5 mL). The tube was flushed with Ar, sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with DCM (10 mL), filtered to remove inorganic salts and further washed with water (5 mL). The resulting organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo*. The so-obtained residue was purified by flash column chromatography (PE:EtOAc 9:1) providing indolizine **41** as an off-white powder (122.2 mg, 93%)

- **1-(5*H*-Isochromeno[4,3-*g*]indolizin-11-yl)ethan-1-one (41).** The product was isolated as an off-white powder (122.2 mg, 93%).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 2.7, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 7.85 (s, 1H, C*H*$_{pyridine}$), 7.55–7.47 (m, 1H, C*H*$_{arom}$), 7.33 (td, *J* = 7.4, 1.4 Hz, 1H, C*H*$_{arom}$), 7.19 (td, *J* = 7.4, 1.2 Hz, 1H, C*H*$_{aorm}$), 7.13–7.05 (m, 1H, C*H*$_{arom}$), 6.82 (dd, *J* = 4.2, 1.5 Hz, 1H, C*H*$_{pyrrole}$), 6.79 (dd, *J* = 4.2, 2.7 Hz, 1H, C*H*$_{pyrrole}$), 5.29 (s, 2H, -OC*H*$_2$Ar), 2.68 (s, 3H, C*H*$_{3,\ Ac}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 191.2 (*C*=O), 150.8 (q*C*$_{arom}$), 129.0 (*C*H$_{arom}$), 128.8 (q*C*$_{arom}$), 128.6 (q*C*$_{arom}$), 127.3 (q*C*$_{arom}$), 127.1 (*C*H$_{arom}$), 126.3 (q*C*$_{arom}$), 125.0 (CH$_{arom}$), 120.5 (*C*H$_{arom}$), 120.2 (*C*H$_{arom}$), 117.6 (*C*H$_{arom}$), 115.1 (*C*H$_{arom}$), 106.2 (q*C*$_{arom}$), 101.8 (*C*H$_{arom}$), 69.4 (-O*C*H$_2$Ar), 27.2 (*C*H$_{3,\ Ac}$).

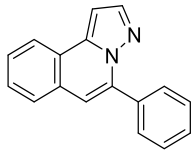
m.p.: 173–178 ºC (EtOAc)

4.6 Multicomponent reactions

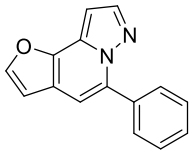
4.6.1 Method A. Multicomponent reactions in water. General procedure

A screw-capped tube was charged with the enaminoketone (0.5 mmol), K_2CO_3 (140 mg, 1.0 mmol) or Cs_2CO_3 (327 mg, 1.0 mmol) or KOH (62 mg, 1.0 mmol), ^{n}Bu$_4$NHSO$_4$ (17.1 mg, 0.05 mmol) or TBAB (16.5 mg, 0.05 mmol), Pd(PPh$_3$)$_4$ (5.7 mg, 0.005 mmol or 28.9 mg, 0.025 mmol) and distilled H_2O (0.75 mL). The tube was flushed with Ar and further charged with the alkyne (0.65 mmol) and $NH_2NH_2 \cdot H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 14–24 h. The reaction was allowed to cool to r.t. and diluted with water (15 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM) to provide the desired product.

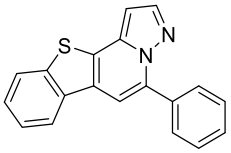
♁ **5-Phenylpyrazolo[5,1-*a*]isoquinoline (36a).** The product was isolated (PE:DCM 4:6) as an off-white powder [(Cs_2CO_3: 110.0 mg, 90%) or (K_2CO_3: 87.6 mg, 72%)], starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol), ^{n}Bu$_4$NHSO$_4$ (17.1 mg, 0.05 mmol) and Pd(PPh$_3$)$_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



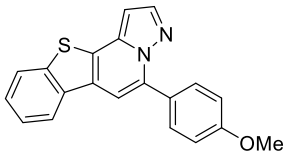
- **5-Phenylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36f).** The product was isolated (PE:DCM 7:3 to 1:1) as an off-white powder (30.2 mg, 26%), starting from enaminoketone **42e** (122.0 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



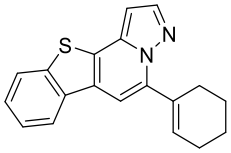
- **5-Phenylbenzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36i).** The product was isolated (PE:DCM 3:7 to 1:1) as an off-white powder (74.3 mg, 49%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



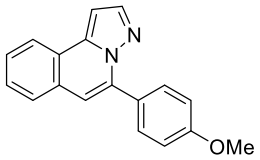
- **5-(4-Methoxyphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36j).** The product was isolated (PE:DCM 1:1 to 4:6) as a yellowish powder (125.3 mg, 76%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), *p*-ethynylanisole (0.087 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



5-(Cyclohex-1-en-1-yl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36l). The product was isolated (PE:DCM 1:1 to 4:6) as an off-white powder (64.1 mg, 42%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), 1-ethynylcyclohexene (0.077 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



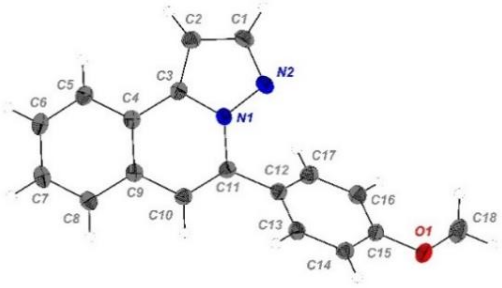
5-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36m). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (98.7 mg, 72%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), *p*-ethynylanisole (0.087 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–8.06 (m, 1H, C*H*$_{isoquinoline}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.92–7.80 (m, 2H, C*H*$_{anisole}$), 7.78–7.68 (m, 1H, C*H*$_{isoquinoline}$), 7.62–7.48 (m, 2H, C*H*$_{isoquinoline}$), 7.09 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.09–7.04 (m, 2H, C*H*$_{anisole}$), 7.07–7.02 (s, 1H, C*H*$_{pyridine}$), 3.90 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.5 (q*C*$_{arom}$), 140.8 (*C*H$_{pyrazole}$), 139.4 (q*C*$_{arom}$), 138.4 (q*C*$_{arom}$), 130.9 (*C*H$_{arom}$), 129.4 (q*C*$_{arom}$), 128.0 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 126.3 (q*C*$_{arom}$), 124.0 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 113.9 (*C*H$_{arom}$), 112.0 (*C*H$_{arom}$), 97.9 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ OMe}$).

m.p.: 158–160 ºC (DCM). *Lit.*[110] 138.5–139.2 ºC (PE:EtOAc)



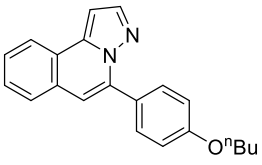
Crystallographic data (36m):

Crystal system	Monoclinic	Space group	$P2_1/c$
a (Å)	7.70427(16)	α (°)	90
b (Å)	20.6031(3)	β (°)	114.120(2)
c (Å)	9.32885(19)	γ (°)	90
V ($Å^3$)	1351.5	Z	4 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1-C11	1.401	C9-C10	1.442
C11-C12	1.482	C10-C11	1.353

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
N1-C11-C10	117.49	C10-C11-C12-C13	56.6
C11-C12-C13	120.30	N2-N1-C11-C10	179.29
C4-C9-C10	119.51	N1-C3-C4-C5	179.45
C1-C2-C3	104.78	C3-C4-C9-C8	175.52
C5-C4-C9	119.95	C8-C9-C10-C11	- 176.34
N1-C3-C4	119.15	C2-C3-C4-C5	0.07

5-(4-Butoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36n). The product was isolated (PE:DCM 1:9 to 0:1) as an off-white powder (112.3 mg, 71%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), *p*-butoxyphenylacetylene (116.8 mg, 0.65 mmol), KOH (62 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



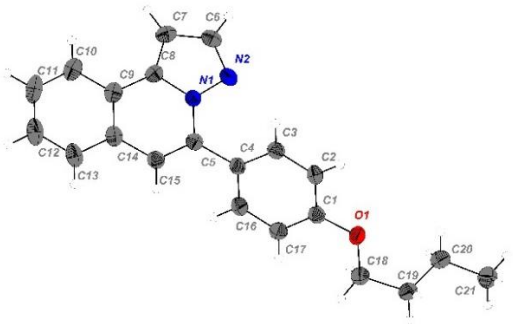
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.16–8.06 (m, 1H, C*H*$_{isoquinoline}$), 8.03 (d, *J* = 2.0 Hz, 1H, C*H*$_{pyrazole}$), 7.92–7.81 (m, 2H, C*H*$_{arom}$), 7.76–7.66 (m, 1H, C*H*$_{isoquinoline}$), 7.59–7.47 (m, 2H, C*H*$_{isoquinoline}$), 7.07 (d, *J* = 2.0 Hz, 1H, C*H*$_{pyrazole}$), 7.08–7.04 (m, 2H, C*H*$_{arom}$), 7.01 (s, 1H, C*H*$_{pyridine}$), 4.06 (t, *J* = 6.5 Hz, 2H, C*H*$_{2,\ OBu}$), 1.92–1.76 (m, 2H, C*H*$_{2,\ OBu}$), 1.65–1.48 (m, 2H, C*H*$_{2,\ OBu}$), 1.03 (t, *J* = 7.4 Hz, 3H, C*H*$_{3,\ OBu}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.1 (q*C*$_{arom}$), 140.8 (*C*H$_{pyrazole}$), 139.4 (q*C*$_{arom}$), 138.5 (q*C*$_{arom}$), 130.8 (*C*H$_{arom}$), 129.4 (q*C*$_{arom}$), 127.9 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 126.0 (q*C*$_{arom}$), 123.9 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 114.5, 111.9, 97.8 (*C*H$_{pyrazole}$), 67.9 (*C*H$_{2,\ OBu}$), 31.4 (*C*H$_{2,\ OBu}$), 19.4 (*C*H$_{2,\ OBu}$), 13.9 (*C*H$_{3,\ OBu}$).

m.p.: 96–98 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{21}H_{20}N_2O$: 316.1576; found: 316.1577

IR (ATR) (cm^{-1}): 2959, 2927, 2871, 1605, 1508



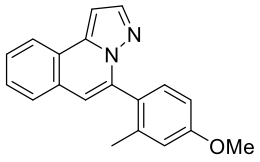
Crystallographic data (36n):

Crystal system	Monoclinic	Space group	$P2_1$
a (Å)	9.5960(5)	α (°)	90
b (Å)	7.4051(3)	β (°)	111.068(6)
c (Å)	12.7875(7)	γ (°)	90
V (Å^3)	847.931	Z	2 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1-C5	1.399	C5-C15	1.347
C4-C5	1.484	C14-C15	1.443

Selected angles (º)		Selected torsion-angles (º)	
Atoms	Angle (Å)	Atoms	Angle (Å)
C5-N1-C8	123.16	N2-N1-C5-C15	-175.27
C4-C5-N1	118.12	C15-C14-C9-C10	178.67
C5-C15-C14	122.65	C10-C9-C8-C7	-3.36
C5-C4-C16	118.71	C15-C5-C4-C16	53.6
C1-O1-C18	117.31	C17-C1-O1-C18	1.15
N1-N2-C6	103.51	C13-C14-C15-C5	-179.26

5-(4-Methoxy-2-methylphenyl)pyrazolo[5,1-*a*]isoquinoline (36o). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (128.1 mg, 89%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-ethynyl-4-methoxy-2-methylbenzene (95.0 mg, 0.65 mmol), KOH (62 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22–8.09 (m, 1H, C*H*$_{isoquinoline}$), 7.99 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.81–7.68 (m, 1H, C*H*$_{isoquinoline}$), 7.67–7.48 (m, 2H, C*H*$_{isoquinoline}$), 7.39 (d, *J* = 8.3 Hz, 1H, C*H*$_{arom}$), 7.09 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.95 (s, 1H, C*H*$_{pyridine}$), 6.94–6.82 (m, 2H, C*H*$_{arom}$), 3.88 (s, 3H, C*H*$_{3,\ OMe}$), 2.16 (s, 3H, C*H*$_{3,\ Me}$).

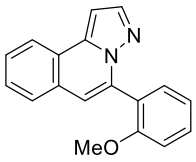
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.4 (q*C*$_{arom}$), 141.3 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 138.9 (q*C*$_{arom}$), 138.4 (q*C*$_{arom}$), 131.4 (*C*H$_{arom}$), 129.2 (q*C*$_{arom}$), 127.9 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 126.5 (q*C*$_{arom}$), 124.2 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 115.9 (*C*H$_{arom}$), 112.9 (*C*H$_{arom}$), 111.3 (*C*H$_{arom}$), 97.8 (*C*H$_{pyrazole}$), 55.4 (*C*H$_{3,\ OMe}$), 20.1 (*C*H$_{3,\ Me}$).

m.p.: 144–146 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{16}N_2O$: 288.1263; found: 288.1262

IR (ATR) (cm^{-1}): 3130, 2998, 1608

5-(2-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36p). The product was isolated (PE:DCM 2:8 to 0:1) as a yellowish powder (43.6 mg, 32%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 2-ethynylanisole (0.087 mL, 0.65 mmol) , KOH (62 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



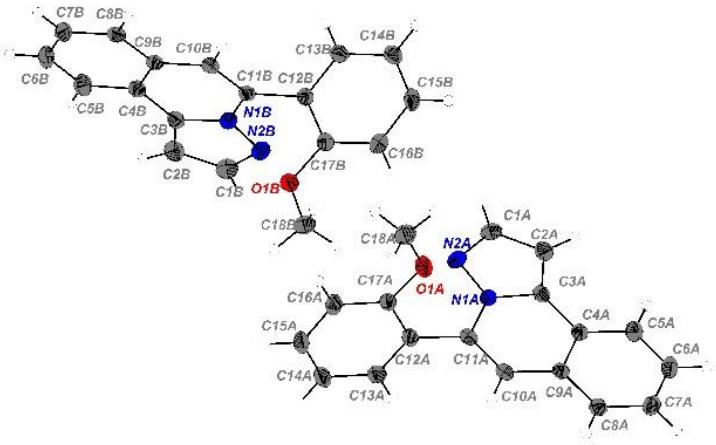
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22–8.08 (m, 1H, C*H*$_{isoquinoline}$), 7.97 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.82–7.68 (m, 1H, C*H*$_{isoquinoline}$), 7.65–7.44 (m, 4H, C*H*$_{isoquinoline}$ + C*H*$_{anisole}$), 7.17–7.08 (m, 2H, C*H*$_{anisole}$), 7.08 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.02 (s, 1H, C*H*$_{pyridine}$), 3.77 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.0 (q*C*$_{arom}$), 140.9 (*C*H$_{pyrazole}$), 138.9 (q*C*$_{arom}$), 136.2 (q*C*$_{arom}$), 131.4 (*C*H$_{arom}$), 131.0 (*C*H$_{arom}$), 129.2 (q*C*$_{arom}$), 127.8 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 124.4 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 123.5 (q*C*$_{arom}$), 120.8 (*C*H$_{arom}$), 113.2 (*C*H$_{arom}$), 111.6 (*C*H$_{arom}$), 97.6 (*C*H$_{pyrazole}$), 55.9 (*C*H$_{3,\ OMe}$).

m.p.: 158–160 ºC (DCM)

HRMS (*m/z)*: [M^+] calc. for $C_{18}H_{14}N_2O$: 274.1106; found: 274.1105

IR (ATR) (cm^{-1}): 3135, 3058, 2994, 2842, 1641, 1544



Crystallographic data (36p):

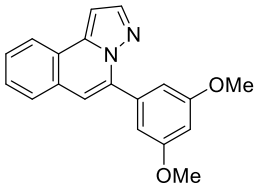
Crystal system	orthorhombic	Space group	$Pna2_1$
a (Å)	14.28404(12)	α (°)	90
b (Å)	7.45292(8)	β (°)	90
c (Å)	25.7571(2)	γ (°)	90
V ($Å^3$)	2742.04	Z	8 (Z' = 0)

Selected bond-lengths			
Atoms	Distance (Å)	Atoms	Distance (Å)
N1A-C11A	1.393	N1B-C11B	1.396
C11A-C12A	1.482	C11B-C12B	1.490

Selected angles (º)	
Atoms	Angle (Å)
N1A-C11A-C10A	117.38
N1B-C11B-C10B	117.70
C10A-C11A-C12A	124.59
C10B-C11B-C12B	124.08
C2A-C3A-C4A	135.08
C2B-C3B-C4B	135.02
C1A-N2A-N1A	103.68

Selected torsion-angles (º)	
Atoms	Angle (Å)
C10A-C11A-C12A-C17A	99.44
C10B-C11B-C12B-C17B	99.13
N2A-N1A-C11A-C10A	-179.51
N2B-N1B-C11B-C10B	-179.16
C2A-C3A-C4A-C5A	-0.19
C2B-C3B-C4B-C5B	-1.18
C5A-C4A-C9A-C10A	-178.18

5-(3,5-Dimethoxyphenyl)pyrazolo[5,1-a]isoquinoline (36q). The product was isolated (PE:DCM 2:8 to 0:1) as a yellow syrup (91.4 mg, 60%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-ethynyl-3,5-dimethoxybenzene (107.6 mg, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



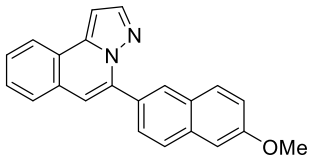
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–8.06 (m, 1H, C*H*$_{isoquinoline}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.78–7.69 (m, 1H, C*H*$_{isoquinoline}$), 7.62–7.47 (m, 2H, C*H*$_{isoquinoline}$), 7.09 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.07–7.03 (m, 3H, C*H*$_{arom}$ + C*H*$_{pyridine}$), 6.62 (t, *J* = 2.3 Hz, 1H, C*H*$_{arom}$), 3.86 (s, 6H, 2C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.8 (q*C*$_{arom}$), 141.0 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 138.5 (q*C*$_{arom}$), 135.7 (q*C*$_{arom}$), 129.2 (q*C*$_{arom}$), 128.1 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 124.2 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 112.6 (*C*H$_{arom}$), 107.8 (*C*H$_{arom}$), 101.7 (*C*H$_{arom}$), 97.9 (*C*H$_{pyrazole}$), 55.6 (*C*H$_{3,\ OMe}$).

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{16}N_2O_2$: 304.1212; found: 304.1213

IR (ATR) (cm^{-1}): 3001, 2957, 2934, 2837, 1589, 1542

5-(6-Methoxynaphthalen-2-yl)pyrazolo[5,1-a]isoquinoline (36r). The product was isolated (PE:DCM 1:9 to 0:1) as a yellowish powder (95.7 mg, 59%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 2-ethynyl-6-methoxynaphthalene (122.1 mg, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H, C*H*$_{naphthalene}$), 8.20–8.10 (m, 1H, C*H*$_{isoquinoline}$), 8.03 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.99 (dd, *J* = 8.5, 1.8 Hz, 1H, C*H*$_{naphthalene}$), 7.88 (d, *J* = 8.6 Hz, 1H, C*H*$_{naphthalene}$), 7.84 (d, *J* = 9.7 Hz, 1H, C*H*$_{naphthalene}$), 7.81–7.72 (m, 1H, C*H*$_{isoquinoline}$), 7.64–7.51 (m, 2H, C*H*$_{isoquinoline}$), 7.25–7.17 (m, 2H, 2C*H*$_{naphthalene}$), 7.15 (s, 1H, C*H*$_{pyridine}$), 7.12 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 3.97 (s, 3H, C*H*$_{3,\ OMe}$).

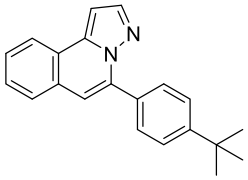
^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6 (q*C*$_{arom}$), 141.0 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 138.8 (q*C*$_{arom}$), 135.2 (q*C*$_{arom}$), 130.2 (*C*H$_{arom}$), 129.5 (q*C*$_{arom}$), 129.3 (q*C*$_{arom}$), 128.8 (q*C*$_{arom}$), 128.8 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 127.5 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 126.8 (*C*H$_{arom}$), 124.2 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 119.3 (*C*H$_{arom}$), 112.8 (*C*H$_{arom}$), 105.9 (*C*H$_{naphthalene}$), 98.0 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ OMe}$).

m.p.: 183–186 ºC (DCM)

HRMS (*m/z*): [M^+] calc. for $C_{22}H_{16}N_2O$: 324.1263; found: 324.1265

IR (ATR) (cm^{-1}): 3017, 1633, 1626, 1604, 1542, 1484, 1436

5-[4-(*Tert*-butyl)phenyl]pyrazolo[5,1-*a*]isoquinoline (36s). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white powder (79.7 mg, 53%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 4-*tert*-butylphenylacetylene (0.122 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



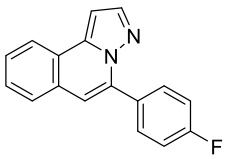
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.19–8.08 (m, 1H, C*H*$_{isoquinoline}$), 8.03 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.92–7.80 (m, 2H, C*H*$_{arom}$), 7.79–7.68 (m, 1H, C*H*$_{isoquinoline}$), 7.64–7.48 (m, 4H, C*H*$_{isoquinoline}$ + C*H*$_{arom}$), 7.10 (d, *J* = 2.1 Hz, 1H, CH$_{pyrazole}$), 7.06 (s, 1H, C*H*$_{pyridine}$), 1.41 (s, 9H, -C(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 152.4 (q*C*$_{arom}$), 140.9 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 138.7 (q*C*$_{arom}$), 131.0 (q*C*$_{arom}$), 129.4 (q*C*$_{arom}$), 129.2 (*C*H$_{arom}$), 128.0 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 125.5 (*C*H$_{arom}$), 124.1 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 112.4 (*C*H$_{arom}$), 97.9 (*C*H$_{pyrazole}$), 34.9 (-*C*(CH$_3$)$_3$), 31.4 (-C(*C*H$_3$)$_3$).

m.p.: 145–147 ºC (DCM). *Lit.*[110] 96.1–97.1 ºC (PE:EtOAc)

IR (ATR) (cm^{-1}): 3053, 2967, 2955, 2904, 2868, 1631, 1542

5-(4-Fluorophenyl)pyrazolo[5,1-*a*]isoquinoline (36t). The product was isolated (PE:DCM 4:6 to 2:8) as a yellowish powder (65.4 mg, 50%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), *p*-fluorophenylacetylene (0.076 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h. The product was also obtained as a yellowish powder (93.9 mg, 72%) starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), *p*-fluorophenylacetylene (0.076 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.20–8.07 (m, 1H, C*H*$_{isoquinoline}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.89 (dd, *J* = 8.6, 5.5 Hz, 2H, C*H*$_{arom}$), 7.82–7.69 (m, 1H, C*H*$_{isoquinoline}$), 7.60–7.52 (m, 2H, C*H*$_{isoquinoline}$), 7.23 (td, *J* = 8.6, 1.8 Hz, 2H, C*H*$_{arom}$), 7.10 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.03 (s, 1H, C*H*$_{pyridine}$).

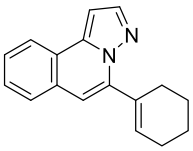
^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.4 (d, $^1J_{CF}$ = 249.2 Hz, q*C*$_{arom-F}$), 141.0 (*C*H$_{pyrazole}$), 139.5 (q*C*$_{arom}$), 137.6 (q*C*$_{arom}$), 131.5 (d, $^3J_{CF}$ = 8.3 Hz, *C*H$_{arom}$), 130.0 (d, $^4J_{CF}$ = 3.6 Hz, q*C*$_{arom}$), 129.2 (q*C*$_{arom}$), 128.2 (*C*H$_{arom}$), 127.6 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 124.2 (q*C*$_{arom}$), 123.7 (*C*H$_{arom}$), 115.6 (d, $^2J_{CF}$ = 21.6 Hz, *C*H$_{arom}$), 112.6 (*C*H$_{arom}$), 98.1 (*C*H$_{pyrazole}$).

m.p.: 177–179 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{11}FN_2$: 262.0906; found: 262.0907

IR (ATR) (cm^{-1}): 3058, 2954, 1609, 1542

5-(Cyclohex-1-en-1-yl)pyrazolo[5,1-*a*]isoquinoline (36u). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white powder (52.0 mg, 42%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-ethynylcyclohexene (0.077 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), ^{n}Bu$_4$NHSO$_4$ (17.1 mg, 0.05 mmol) and Pd(PPh$_3$)$_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h. The product was also obtained as an off-white powder (79.3 mg, 64%) starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-ethynylcyclohexene (0.077 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and Pd(PPh$_3$)$_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.15–8.03 (m, 1H, C*H*$_{isoquinoline}$), 8.00 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.75–7.61 (m, 1H, C*H*$_{isoquinoline}$), 7.57–7.43 (m, 2H, C*H*$_{isoquinoline}$), 7.02 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.88 (s, 1H, C*H*$_{pyridine}$), 6.35 (m, 1H, C*H*$_{cyclohexenyl}$), 2.66 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 2.43–2.24 (m, 2H, C*H*$_{2,\ cyclohexenyl}$), 1.84 (m, 4H, C*H*$_{2,\ cyclohexenyl}$).

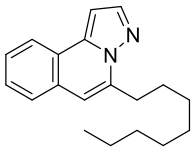
^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.4 (q*C*$_{arom}$), 140.7 (*C*H$_{pyrazole}$), 139.1 (q*C*$_{arom}$), 133.7 (q*C*$_{arom}$), 130.6 (*C*H$_{arom}$), 129.5 (q*C*$_{arom}$), 127.8 (*C*H$_{arom}$), 126.9 (*C*H$_{arom}$), 126.9 (*C*H$_{arom}$), 123.9 (q*C*$_{arom}$), 123.5 (*C*H$_{arom}$), 110.4 (*C*H$_{arom}$), 97.4 (*C*H$_{pyrazole}$), 27.6 (*C*H$_{2,\ cyclohexenyl}$), 25.7 (*C*H$_{2,\ cyclohexenyl}$), 22.7 (*C*H$_{2,\ cyclohexenyl}$), 22.1 (*C*H$_{2,\ cyclohexenyl}$).

m.p.: 104–107 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{17}H_{16}N_2$: 248.1313; found: 248.1315

IR (ATR) (cm^{-1}): 3126, 2927, 2858, 1633, 1540

5-Octylpyrazolo[5,1-*a*]isoquinoline (36v). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white low melting-point powder (32.3 mg, 23%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-decyne (0.120 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h. The product was also obtained as an off-white low melting-point powder (108.9 mg, 78%) starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), 1-decyne (0.120 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.11–8.04 (m, 1H, C*H*$_{isoquinoline}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.73–7.59 (m, 1H, C*H*$_{isoquinoline}$), 7.57–7.44 (m, 2H, C*H*$_{isoquinoline}$), 7.03 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.82 (s, 1H, C*H*$_{pyridine}$), 3.28–3.08 (m, 2H, C*H*$_{2,\ octyl}$), 2.00–1.82 (td, *J* = 7.5, 0.7 Hz, 2H, C*H*$_{2,\ octyl}$), 1.60–1.22 (m, 10H, C*H*$_{2,\ octyl}$), 1.00–0.81 (t, *J* = 6.7 Hz, 3H, C*H*$_{3,\ octyl}$).

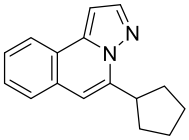
^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.6 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 138.9 (q*C*$_{arom}$), 129.3 (q*C*$_{arom}$), 127.8 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 123.7 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 109.6 (*C*H$_{arom}$), 97.7 (*C*H$_{pyrazole}$), 32.0 (*C*H$_{2,\ octyl}$), 31.1 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.4 (*C*H$_{2,\ octyl}$), 27.0 (*C*H$_{2,\ octyl}$), 22.8 (*C*H$_{2,\ octyl}$), 14.2 (*C*H$_{3,\ octyl}$).

m.p.: 49–51 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{19}H_{24}N_2$: 280.1939; found: 280.1941

IR (ATR) (cm^{-1}): 3058, 2954, 2924, 2853, 1640, 1541

5-Cyclopentylpyrazolo[5,1-*a*]isoquinoline (36w). The product was isolated (PE:DCM 4:6 to 2:8) as brownish oil (45.0 mg, 38%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), cyclopentylacetylene (0.079 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–8.04 (m, 1H, C*H*$_{isoquinoline}$), 8.02 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.76–7.60 (m, 1H, C*H*$_{isoquinoline}$), 7.58–7.41 (m, 2H, C*H*$_{isoquinoline}$), 7.04 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.89 (s, 1H, C*H*$_{pyridine}$), 4.08–3.83 (m, 1H, C*H*$_{cyclopentyl}$), 2.50–2.25 (m, 2H, C*H*$_{cyclopentyl}$), 1.97–1.75 (m, 6H, C*H*$_{cyclopentyl}$).

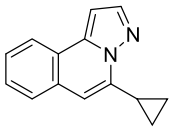
^{13}C-NMR (75 MHz, $CDCl_3$) δ 143.3 (q*C*$_{arom}$), 140.4 (*C*H$_{pyrazole}$), 139.0 (q*C*$_{arom}$), 129.3 (q*C*$_{arom}$), 127.8 (*C*H$_{arom}$), 126.7 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 123.5 (*C*H$_{arom}$), 123.5 (q*C*$_{arom}$), 107.1 (*C*H$_{arom}$), 97.6 (*C*H$_{pyrazole}$), 40.3 (*C*H$_{cyclopentyl}$), 31.5 (*C*H$_{2,\ cyclopentyl}$), 25.2 (*C*H$_{2,\ cyclopentyl}$).

HRMS (*m/z)*: [M^+] calc. for $C_{16}H_{16}N_2$: 236.1313; found: 236.1317

IR (ATR) (cm^{-1}): 2952, 2869, 1641, 1542, 1435

5-Cyclopropylpyrazolo[5,1-*a*]isoquinoline (36x).[111] The product was isolated (PE:DCM 2:8 to 0:1) as a yellowish powder (89.6 mg, 86%), starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), cyclopropylacetylene (0.057 mL, 0.65 mmol), KOH (62 mg, 1.0 mmol), ^{n}Bu$_4$NHSO$_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h. The product was also obtained as a yellowish powder (79.0 mg, 76%) starting from enaminoketone **42a** (127.1 mg, 0.5 mmol), cyclopropylacetylene (0.057 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol). Reaction time: 14 h.

[111] Ye, C.; Yu, X.; Qiu, G.; Wu, J. *RSC Adv.* **2012**, *2*, 5961–5963.

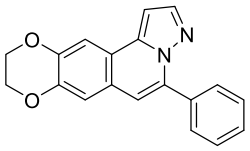


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.06 (m, 2H, C*H*$_{isoquinoline}$ + C*H*$_{pyrazole}$), 7.68–7.56 (m, 1H, C*H*$_{isoquinoline}$), 7.55–7.40 (m, 2H, C*H*$_{isoquinoline}$), 7.05 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.64 (s, 1H, C*H*$_{pyridine}$), 2.82–2.57 (m, 1H, C*H*$_{cyclopropyl}$), 1.25–1.16 (m, 2H, C*H*$_{cyclopropyl}$), 0.98–0.86 (m, 2H, C*H*$_{cyclopropyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.9 (q*C*$_{arom}$), 140.7 (*C*H$_{pyrazole}$), 138.8 (q*C*$_{arom}$), 129.2 (q*C*$_{arom}$), 127.8 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 123.5 (*C*H$_{arom}$), 123.4 (q*C*$_{arom}$), 106.9 (*C*H$_{arom}$), 97.9 (*C*H$_{pyrazole}$), 11.5 (*C*H$_{cyclopropyl}$), 7.1 (*C*H$_{2,\ cyclopropyl}$).

m.p.: 64–67 ºC (DCM)

- **5-Phenyl-9,10-dihydro-[1,4]dioxino[2,3-*g*]pyrazolo[5,1-*a*]isoquinoline (36y).** The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (71.6 mg, 47%), starting from enaminoketone **42b** (156.1 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.90–7.83 (m, 2H, C*H*$_{phenyl}$), 7.55 (s, 1H, C*H*$_{isoquinoline}$), 7.55–7.42 (m, 3H, C*H*$_{phenyl}$), 7.19 (s, 1H, C*H*$_{isoquinoline}$), 6.90 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 6.89 (s, 1H, C*H*$_{pyridine}$), 4.37 (s, 4H, C*H*$_{2,}$ -OC*H*$_2$C*H*$_2$O-).

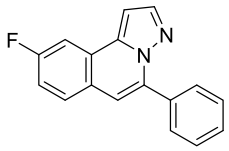
^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.7 (q*C*$_{arom}$), 144.3 (q*C*$_{arom}$), 140.7 (*C*H$_{pyrazole}$), 138.9 (q*C*$_{arom}$), 137.2 (q*C*$_{arom}$), 134.2 (q*C*$_{arom}$), 129.5 (*C*H$_{arom}$), 129.2 (*C*H$_{arom}$), 128.4 (*C*H$_{arom}$), 124.5 (q*C*$_{arom}$), 119.2 (q*C*$_{arom}$), 113.8 (*C*H$_{arom}$), 111.9 (*C*H$_{arom}$), 110.7 (*C*H$_{arom}$), 97.1 (*C*H$_{pyrazole}$), 64.6 (-O*C*H$_2$CH$_2$O-), 64.6 (-OCH$_2$*C*H$_2$O-).

m.p.: 152–155 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{19}H_{14}N_2O_2$: 302.1055; found: 302.1056

IR (ATR) (cm^{-1}): 3055, 2924, 1637, 1548, 1490

9-Fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline (36z). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white powder (77.8 mg, 59%), starting from enaminoketone **42c** (136.1 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.92–7.84 (m, 2H, C*H*$_{isoquinoline}$), 7.80–7.69 (m, 2H, C*H*$_{phenyl}$), 7.61–7.43 (m, 3H, C*H*$_{phenyl}$), 7.29 (td, *J* = 8.6, 2.5 Hz, 1H, C*H*$_{isoquinoline}$), 7.06 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.04 (s, 1H, C*H*$_{pyridine}$).

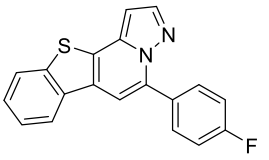
^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.8 (d, $^1J_{CF}$ = 247.7 Hz, q*C*$_{arom-F}$), 141.0 (*C*H$_{pyrazole}$), 138.8 (d, $^3J_{CF}$ = 4.1 Hz, q*C*$_{arom}$), 138.1 (d, $^4J_{CF}$ = 2.7 Hz, q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 129.5 (*C*H$_{arom}$), 129.5 (*C*H$_{arom}$), 128.6 (*C*H$_{arom}$), 125.9 (d, $^4J_{CF}$ = 2.1 Hz, qC$_{arom}$), 125.5 (d, $^3J_{CF}$ = 9.7 Hz, q*C*$_{arom}$), 116.9 (d, $^2J_{CF}$ = 23.5 Hz, *C*H$_{arom}$), 112.0 (*C*H$_{arom}$), 109.0 (d, $^2J_{CF}$ = 22.8 Hz, *C*H$_{arom}$), 98.6 (*C*H$_{pyrazole}$).

m.p.: 136–139 ºC (DCM)

HRMS (*m/z)*: [M^+] calc. for $C_{17}H_{11}FN_2$: 262.0906; found: 262.0907

IR (ATR) (cm^{-1}): 3033, 2916, 2848, 1611, 1547, 1489

5-(4-Fluorophenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ab). The product was isolated (PE:DCM 3:7 to 1:1) as a yellowish powder (100.5 mg, 63%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), *p*-fluorophenylacetylene (0.076 mL, 0.65 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.17–8.08 (m, 1H, C*H*$_{benzothiopene}$), 8.06 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 8.01–7.89 (m, 3H, C*H*$_{benzothiopene}$ + C*H*$_{arom}$), 7.59–7.47 (m, 2H, C*H*$_{benzothiopene}$), 7.46 (s, 1H, C*H*$_{pyridine}$), 7.33–7.20 (m, 2H, C*H*$_{arom}$), 6.83 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$).

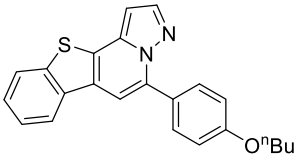
^{13}C-NMR (75 MHz, $CDCl_3$) δ 163.4 (d, $^{1}J_{CF}$ = 249.8 Hz, q*C*$_{arom-F}$), 141.9 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 137.2 (q*C*$_{arom}$), 136.9 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 131.6 (d, $^{3}J_{CF}$ = 8.6 Hz, *C*H$_{arom}$), 130.2 (q*C*$_{arom}$), 130.1 (q*C*$_{arom}$), 126.7 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 123.3 (*C*H$_{arom}$), 122.0 (*C*H$_{arom}$), 115.8 (d, $^{2}J_{CF}$ = 21.8 Hz, *C*H$_{arom}$), 106.5 (*C*H$_{arom}$), 97.1 (*C*H$_{pyrazole}$).

m.p.: 140–142 ºC (DCM)

HRMS (*m/z)*: [M^{+}] calc. for $C_{19}H_{11}FN_2S$: 318.0627; found: 318.0628

IR (ATR) (cm^{-1}): 3050, 2920, 1606, 1548

- **5-(4-Butoxyphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ac).** The product was isolated (PE:DCM 1:1 to 4:6) as an off-white powder (128.5 mg, 69%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), *p*-butoxyphenylacetylene (116.8 mg, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^{n}Bu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14–7.99 (m, 2H, C*H*$_{pyrazole}$ + C*H*$_{benzothiopene}$), 7.97–7.80 (m, 3H, C*H*$_{benzothiopene}$ + C*H*$_{arom}$), 7.53–7.34 (m, 3H, C*H*$_{benzothiopene}$ + C*H*$_{pyridine}$), 7.16–7.00 (m, 2H, C*H*$_{arom}$), 6.78 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 4.07 (t, *J* = 6.4 Hz, 2H, C*H*$_{2,\ butyl}$), 1.98–1.67 (m, 2H, C*H*$_{2,\ butyl}$), 1.67–1.39 (m, 2H, C*H*$_{2,\ butyl}$), 1.03 (t, *J* = 7.4 Hz, 3H, C*H*$_{3,\ butyl}$).

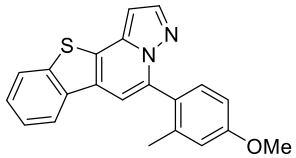
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.1 (q*C*$_{arom}$), 141.6 (*C*H$_{pyrazole}$), 139.6 (q*C*$_{arom}$), 138.0 (q*C*$_{arom}$), 136.8 (q*C*$_{arom}$), 135.4 (q*C*$_{arom}$), 130.8 (*C*H$_{arom}$), 130.1 (q*C*$_{arom}$), 126.5 (q*C*$_{arom}$), 126.4 (*C*H$_{arom}$), 126.1 (q*C*$_{arom}$), 125.0 (*C*H$_{arom}$), 123.1 (*C*H$_{arom}$), 121.8 (*C*H$_{arom}$), 114.5 (*C*H$_{arom}$), 105.8 (*C*H$_{arom}$), 96.7 (*C*H$_{pyrazole}$), 67.9 (*C*H$_{2,\ butyl}$), 31.3 (*C*H$_{2,\ butyl}$), 19.3 (*C*H$_{2,\ butyl}$), 14.0 (*C*H$_{3,\ butyl}$).

m.p.: 168–171ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{23}H_{20}N_2OS$: 372.1296; found: 372.1299

IR (ATR) (cm^{-1}): 3099, 2923, 1604, 1545

5-(4-Methoxy-2-methylphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ad). The product was isolated (PE:DCM 1:1 to 4:6) as an off-white powder (99.7 mg, 58%), starting from enaminoketone **42f** (155.1 mg, 0.5 mmol), 1-ethynyl-4-methoxy-2-methylbenzene (95.1 mg, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), ^{n}Bu$_4$NHSO$_4$ (17.1 mg, 0.05 mmol) and Pd(PPh$_3$)$_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.14–8.05 (m, 1H, C*H*$_{benzothiopene}$), 8.03 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 8.00–7.92 (m, 1H, C*H*$_{benzothiopene}$), 7.57–7.46 (m, 2H, C*H*$_{benzothiopene}$), 7.40 (d, *J* = 8.3 Hz, 1H, C*H*$_{arom}$), 7.38 (s, 1H C*H*$_{pyridine}$), 6.98–6.87 (m, 2H, C*H*$_{arom}$), 6.81 (d, *J* = 2.3 Hz, 1H, C*H*$_{pyrazole}$), 3.89 (s, 3H, C*H*$_{3,\ OMe}$), 2.15 (s, 3H, C*H*$_{3,\ Me}$).

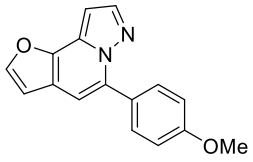
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.6 (q*C*$_{arom}$), 142.2 (*C*H$_{pyrazole}$), 139.7 (q*C*$_{arom}$), 139.6 (q*C*$_{arom}$), 138.1 (q*C*$_{arom}$), 136.4 (q*C*$_{arom}$), 135.5 (q*C*$_{arom}$), 131.5 (*C*H$_{arom}$), 130.0 (q*C*$_{arom}$), 127.1 (q*C*$_{arom}$), 126.7 (q*C*$_{arom}$), 126.6 (*C*H$_{arom}$), 125.2 (*C*H$_{arom}$), 123.3 (*C*H$_{arom}$), 122.0 (*C*H$_{arom}$), 116.0 (*C*H$_{arom}$), 111.5 (*C*H$_{arom}$), 106.8 (*C*H$_{arom}$), 96.7 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ OMe}$), 20.1 (*C*H$_{3,\ Me}$).

m.p: 176–179 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{21}H_{16}N_2OS$: 344.0983; found: 344.0983

IR (ATR) (cm^{-1}): 3070, 2916, 2838, 1605, 1546

5-(4-Methoxyphenyl)furo[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ai). The product was isolated (PE:DCM 1:1 to 4:6) as an off-white powder (54.2 mg, 41%), starting from enaminoketone **42e** (122.0 mg, 0.5 mmol), *p*-ethynylanisole (0.086 mL, 0.65 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol). Reaction time: 24 h.



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.82–7.74 (m, 2H, C*H*$_{anisole}$), 7.71 (d, *J* = 2.0 Hz, 1H, C*H*$_{furan}$), 7.10–7.01 (m, 2H, C*H*$_{anisole}$), 6.96 (s, 1H, C*H*$_{pyridine}$), 6.82 (d, *J* = 2.2 Hz, 2H, C*H*$_{pyrazole}$ + C*H*$_{furan}$), 3.88 (s, 3H, C*H*$_{3,\ OMe}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.3 (q*C*$_{arom}$), 145.0 (*C*H$_{arom}$), 144.1 (q*C*$_{arom}$), 141.1 (*C*H$_{arom}$), 137.1 (q*C*$_{arom}$), 131.8 (q*C*$_{arom}$), 130.9 (*C*H$_{arom}$), 126.8 (q*C*$_{arom}$), 120.7 (q*C*$_{arom}$), 114.0 (*C*H$_{arom}$), 107.5 (*C*H$_{arom}$), 105.6 (*C*H$_{arom}$), 93.5 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ anisole}$).

m.p: 106–108 ºC (DCM)

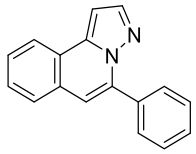
HRMS (*m/z)*: [M$^+$] calc. for $C_{16}H_{12}N_2O_2$: 264.0898; found: 264.0896

IR (ATR) (cm^{-1}): 3135, 3115, 1658, 1611, 1514, 1483

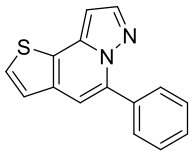
4.6.2 Method B. Multicomponent reaction in alcoholic media. General procedure

A screw-capped tube was charged with the enaminoketone (0.5 mmol), KOH (62.3 mg, 1.0 mmol), dppf (5.7 mg, 0.01 mmol or 11.4 mg, 0.02 mmol) and the corresponding alcohol (0.75 mL). The tube was flushed with Ar and further charged with $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol or 2.3 mg, 0.01 mmol), the alkyne (0.65 mmol) and $NH_2NH_2 \cdot H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t., diluted with DCM (15 mL) and gravity filtered to remove solid particles. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (PE:DCM) to provide the desired heterocycle.

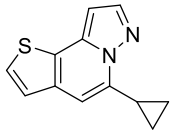
- **5-Phenylpyrazolo[5,1-*a*]isoquinoline (36a).** The product was isolated (PE:DCM 4:6) as an off-white powder (164.3 mg, 67%), by reacting enaminoketone **42a** (254.1 mg, 1.0 mmol) and phenylacetylene (0.146 mL, 1.3 mmol) in EtOH (1.5 mL) in the presence of $Pd(OAc)_2$ (2.31, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



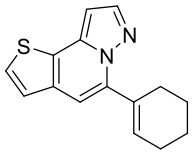
- **5-Phenylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36b).** The product was isolated (PE:DCM 4:6) as an off-white powder (95.5 mg, 76%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and phenylacetylene (0.073 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol). The product was also obtained as an off-white powder (61.2 mg, 49%) starting from enaminoketone **42d** (130.1 mg, 0.5 mmol), phenylacetylene (0.073 mL, 0.65 mmol) and KOH (62 mg, 1.0 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



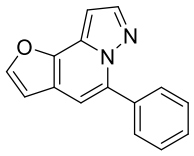
5-Cyclopropylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36d). The product was isolated (PE:DCM 2:8 to 0:1) as a yellowish powder (67.6 mg, 63%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and cyclopropylacetylene (0.057 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



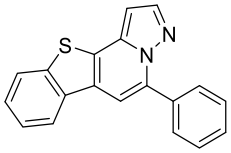
5-(Cyclohex-1-en-1-yl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36e). The product was isolated (PE:DCM 4:6 to 2:8) as a yellowish powder (31.0 mg, 29%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and 1-ethynylcyclohexene (0.077 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



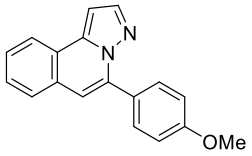
5-Phenylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36f). The product was isolated (PE:DCM 4:6) as an off-white powder (63.2 mg, 54%), by reacting enaminoketone **42e** (122.0 mg, 0.5 mmol) and phenylacetylene (0.073 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



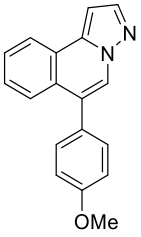
5-Phenylbenzo[4,5]thieno[2,3-c]pyrazolo[1,5-a]pyridine (36i). The product was isolated (PE:DCM 3:7 to 1:1) as an off-white powder (99.0 mg, 66%), by reacting enaminoketone **42f** (155.1 mg, 0.5 mmol) and phenylacetylene (0.073 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



5-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36m). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (EtOH: 104.4 mg, 76%; or MeOH: 116.6 mg, 85%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and *p*-ethynylanisole (0.086 mL, 0.65 mmol) in alcohol (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



6-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (43). The product was isolated (PE:DCM 2:8 to 0:1) as an yellowish oil (17.7 mg, 13%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and *p*-ethynylanisole (0.086 mL, 0.65 mmol) in ^{n}PrOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).

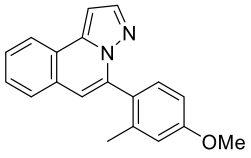


^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 1H, C*H*$_{pyridine}$), 8.17 (d, *J* = 8.0 Hz, 1H, C*H*$_{isoquinoline}$), 7.99 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.72 (d, *J* = 8.0 Hz, 1H, C*H*$_{isoquinoline}$), 7.65–7.52 (m, 1H, C*H*$_{isoquinoline}$), 7.55–7.43 (m, 1H, C*H*$_{isoquinoline}$), 7.43 (d, *J* = 8.5 Hz, 2H, C*H*$_{anisole}$), 7.05 (d, *J* = 8.5 Hz, 2H, C*H*$_{anisole}$), 7.02 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 3.90 (s, 3H, C*H*$_{3,\ OMe}$).

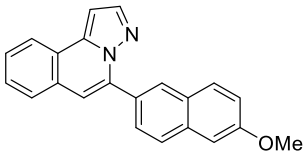
^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.6 (q*C*$_{arom}$), 141.3 (*C*H$_{pyrazole}$), 138.0 (q*C*$_{arom}$), 131.5 (*C*H$_{arom}$), 129.1 (q*C*$_{arom}$), 128.7 (q*C*$_{arom}$), 127.9 (*C*H$_{arom}$), 127.7 (*C*H$_{arom}$), 126.2 (*C*H$_{arom}$), 125.4 (*C*H$_{arom}$), 125.3 (q*C*$_{arom}$), 124.8 (q*C*$_{arom}$), 124.1 (*C*H$_{arom}$), 114.2 (*C*H$_{arom}$), 97.5 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ OMe}$).

HRMS (*m/z*): [M^{+}] calc. for $C_{18}H_{14}N_2O$: 274.1106; found: 274.1104

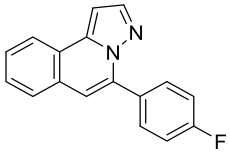
- **5-(4-Methoxy-2-methylphenyl)pyrazolo[5,1-*a*]isoquinoline (36o).** The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (79.1 mg, 55%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and 1-ethynyl-4-methoxy-2-methylbenzene (95 mg, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



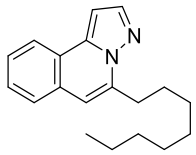
- **5-(6-Methoxynaphthalen-2-yl)pyrazolo[5,1-a]isoquinoline (36r).** The product was isolated (PE:DCM 1:9 to 0:1) as a yellowish powder (77.7 mg, 48%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and 1-ethynyl-4-methoxy-2-methylbenzene (130.1 mg, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



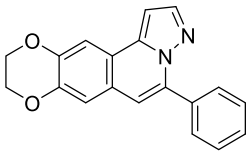
5-(4-Fluorophenyl)pyrazolo[5,1-a]isoquinoline (36t). The product was isolated (PE:DCM 4:6 to 2:8) as a yellowish powder (63.0 mg, 48%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and *p*-fluorophenylacetylene (0.076 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



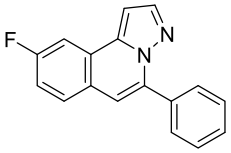
5-Octylpyrazolo[5,1-*a*]isoquinoline (36v). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white low melting-point powder (112.1 mg, 80%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and 1-decyne (0.120 mL, 0.65 mmol), in EtOH (0.75 mL) in the presence of Pd(OAc)2 (2.3 mg, 0.01 mmol) and dppf (11.2 mg, 0.02 mmol)



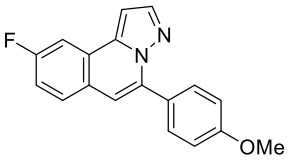
5-Phenyl-9,10-dihydro-[1,4]dioxino[2,3-*g*]pyrazolo[5,1-*a*]isoquinoline (36y). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (30.2 mg, 20%), by reacting enaminoketone **42b** (156.1 mg, 0.5 mmol) and phenylacetylene (0.073 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



9-Fluoro-5-phenylpyrazolo[5,1-a]isoquinoline (36z). The product was isolated (PE:DCM 4:6 to 2:8) as an off-white powder (46.1 mg, 35%), by reacting enaminoketone **42c** (136.1 mg, 0.5 mmol) and phenylacetylene (0.073 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



9-Fluoro-5-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36aa). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (93.5 mg, 64%), by reacting enaminoketone **42c** (127.1 mg, 0.5 mmol) and *p*-ethynylanisole (0.086 mL, 0.65 mmol) in MeOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.88–7.79 (m, 2H, C*H*$_{anisole}$), 7.78–7.66 (m, 2H, C*H*$_{isoquinoline}$), 7.28 (td, *J* = 8.6, 2.6 Hz, 1H, C*H*$_{isoquinoline}$), 7.09–7.03 (m, 2H, C*H*$_{anisole}$), 7.05 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.00 (s, 1H, C*H*$_{pyridine}$), 3.89 (s, 3H, C*H*$_{3,\ OMe}$).

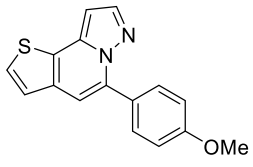
^{13}C-NMR (75 MHz, $CDCl_3$) δ 161.7 (d, $^1J_{CF}$ = 247.2 Hz, q*C*$_{arom\text{-}F}$), 160.5 (q*C*$_{arom}$), 140.9 (*C*H$_{pyrazole}$), 138.8 (d, $^4J_{CF}$ = 4.4 Hz, q*C*$_{arom}$), 137.87 (d, $^4J_{CF}$ = 2.8 Hz, q*C*$_{arom}$), 130.9 (*C*H$_{arom}$), 129.4 (d, $^3J_{CF}$ = 8.8 Hz, *C*H$_{arom}$), 126.1 (q*C*$_{arom}$), 126.0 (d, $^4J_{CF}$ = 2.0 Hz, q*C*$_{arom}$), 125.3 (d, $^3J_{CF}$ = 9.3 Hz, q*C*$_{arom}$), 116.8 (d, $^2J_{CF}$ = 23.1 Hz, *C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 111.4 (*C*H$_{arom}$), 109.0 (d, $^2J_{CF}$ = 23.1 Hz, *C*H$_{arom}$), 98.5 (*C*H$_{pyrazole}$), 55.6 (*C*H$_{3,\ OMe}$).

m.p.: 147–150 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{18}H_{13}FN_2O$: 292.1012; found: 292.1013

IR (ATR) (cm^{-1}): 2966, 2935, 2839, 1614, 1509, 1491

5-(4-Methoxyphenyl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36ae). The product was isolated (PE:DCM 2:8 to 1:9) as an off-white powder (92.6 mg, 79%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and *p*-ethynylanisole (0.086 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol). The product was also obtained as an off-white powder (44.1 mg, 38%) starting from enaminoketone **42d** (130.1 mg, 0.5 mmol), *p*-ethynylanisole (0.086 mL, 0.65 mmol) and KOH (62 mg, 1.0 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (50 µL of a 0.107 M stock solution in DMF, 0.005 mmol) and dppf (5.7 mg, 0.01 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.83 (d, *J* = 8.2 Hz, 2H, C*H*$_{anisole}$), 7.50 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.35 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.14 (s, 1H, C*H*$_{pyridine}$), 7.06 (d, *J* = 8.2 Hz, 2H, C*H*$_{anisole}$), 6.76 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 3.89 (s, 3H, CH$_{3,\ OMe}$).

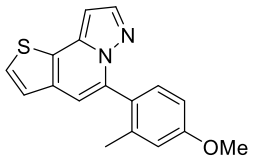
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.4 (q*C*$_{arom}$), 141.4 (*C*H$_{pyrazole}$), 137.7 (q*C*$_{arom}$), 136.8 (q*C*$_{arom}$), 135.0 (q*C*$_{arom}$), 130.9 (*C*H$_{arom}$), 127.0 (q*C*$_{arom}$), 126.6 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 124.5 (*C*H$_{arom}$), 114.0 (*C*H$_{arom}$), 108.0 (*C*H$_{arom}$), 95.9 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ anisole}$).

m.p.: 87–88 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{16}H_{12}N_2OS$: 280.0670; found: 280.0673

IR (ATR) (cm^{-1}): 3068, 2963, 2928, 1629, 1606, 1547, 1506

- **5-(4-Methoxy-2-methylphenyl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36af).** The product was isolated (PE:DCM 2:8 to 1:9) as an off-white powder (85.3 mg, 58%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and 1-ethynyl-4-methoxy-2-methylbenzene (95 mg, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.59–7.49 (m, 1H, C*H*$_{thiophene}$), 7.40–7.29 (m, 2H, C*H*$_{thiophene}$ + C*H*$_{arom}$), 7.06 (s, 1H, C*H*$_{pyridine}$), 6.95–6.81 (m, 2H, C*H*$_{arom}$), 6.75 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 3.87 (s, 3H, C*H*$_{3,\ OMe}$), 2.12 (s, 3H, C*H*$_{3,\ Me}$).

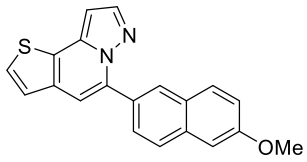
^{13}C-NMR (75 MHz, $CDCl_3$) δ 160.5 (q*C*$_{arom}$), 141.8 (*C*H$_{pyrazole}$), 139.6 (q*C*$_{arom}$), 137.7 (q*C*$_{arom}$), 136.4 (q*C*$_{arom}$), 134.8 (q*C*$_{arom}$), 131.4 (*C*H$_{arom}$), 127.4 (q*C*$_{arom}$), 126.7 (q*C*$_{arom}$), 126.7 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 115.9 (*C*H$_{arom}$), 111.4 (*C*H$_{arom}$), 108.9 (*C*H$_{arom}$), 95.8 (*C*H$_{pyrazole}$), 55.4 (*C*H$_{3,\ OMe}$), 20.0 (*C*H$_{3,\ Me}$).

m.p.: 143–147 ºC (DCM)

HRMS (*m/z)*: [M⁺] calc. for $C_{17}H_{14}N_2OS$: 294.0827; found: 294.0825

IR (ATR) (cm^{-1}): 3100, 2933, 1607, 1548

5-(6-Methoxynaphthalen-2-yl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36ag). The product was isolated (PE:DCM 1:9 to 0:1) as a yellowish powder (127.2 mg, 77%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and 1-ethynyl-4-methoxy-2-methylbenzene (130.1 mg, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H, C*H*$_{naphthalene}$), 8.03 (s, 1H, C*H*$_{naphthalene}$), 7.97 (d, *J* = 8.5 Hz, 1H, C*H*$_{naphthalene}$), 7.92–7.78 (m, 2H, C*H*$_{naphthalene}$ + C*H*$_{pyrazole}$), 7.53 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.38 (d, *J* = 5.1 Hz, 1H, C*H*$_{thiophene}$), 7.27 (s, 1H, C*H*$_{pyridine}$), 7.25–7.16 (m, 2H, C*H*$_{naphthalene}$), 6.80 (d, *J* = 1.2 Hz, 1H, C*H*$_{pyrazole}$), 3.96 (s, 3H, C*H*$_{3,\ OMe}$).

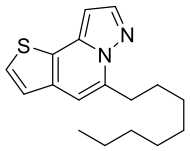
^{13}C-NMR (75 MHz, $CDCl_3$) δ 158.6 (q*C*$_{arom}$), 141.5 (*C*H$_{pyrazole}$), 138.1 (q*C*$_{arom}$), 136.9 (q*C*$_{arom}$), 135.1 (q*C*$_{arom}$), 130.1 (*C*H$_{arom}$), 129.5 (q*C*$_{arom}$), 128.8 (*C*H$_{arom}$) (q*C*$_{arom}$), 128.8 (*C*H$_{arom}$), 127.5 (*C*H$_{arom}$), 127.4 (q*C*$_{arom}$), 126.8 (*C*H$_{arom}$), 126.8 (*C*H$_{arom}$), 124.6 (*C*H$_{arom}$), 119.3 (*C*H$_{arom}$), 108.8 (*C*H$_{arom}$), 105.9 (*C*H$_{arom}$), 96.0 (*C*H$_{pyrazole}$), 55.5 (*C*H$_{3,\ OMe}$).

m.p.: 172–174 ºC (DCM)

HRMS (*m/z)*: [M^+] calc. for $C_{20}H_{14}N_2OS$: 330.0827; found: 330.0825

IR (ATR) (cm^{-1}): 3096, 1629, 1604, 1544, 1485

5-Octylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine (36ah). The product was isolated (PE:DCM 4:6 to 2:8) as a yellowish oil (97.4 mg, 68%), by reacting enaminoketone **42d** (130.1 mg, 0.5 mmol) and 1-decyne (0.120 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



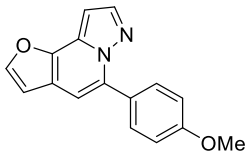
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.48 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 7.30 (d, *J* = 5.0 Hz, 1H, C*H*$_{thiophene}$), 6.99 (s, 1H, C*H*$_{pyridine}$), 6.71 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 3.19 (t, *J* = 7.7 Hz, 2H, C*H*$_{2,\ octyl}$), 1.89 (p, *J* = 7.7 Hz, 2H, C*H*$_{2,\ octyl}$), 1.56–1.43 (m, 2H, C*H*$_{2,\ octyl}$), 1.43–1.15 (m, 8H, C*H*$_{2,\ octyl}$), 0.98–0.76 (m, 3H, C*H*$_{3,\ octyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.1 (*C*H$_{pyrazole}$), 139.0 (q*C*$_{arom}$), 136.4 (q*C*$_{arom}$), 134.9 (q*C*$_{arom}$), 126.4 (*C*H$_{arom}$), 126.2 (q*C*$_{arom}$), 124.3 (*C*H$_{arom}$), 105.8 (*C*H$_{arom}$), 95.8 (*C*H$_{pyrazole}$), 32.0 (*C*H$_{2,\ octyl}$), 31.4 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.4 (*C*H$_{2,\ octyl}$), 26.9 (*C*H$_{2,\ octyl}$), 22.8 (*C*H$_{2,\ octyl}$), 14.2 (*C*H$_{3,\ octyl}$).

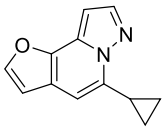
HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{22}N_2S$: 286.1504; found: 286.1502

IR (ATR) (cm^{-1}): 2952, 2923, 2854, 1631, 1548

5-(4-Methoxyphenyl)furo[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ai). The product was isolated (PE:DCM 2:8 to 1:9) as an off-white powder (88.6 mg, 67%), by reacting enaminoketone **42e** (122.0 mg, 0.5 mmol) and *p*-ethynylanisole (0.086 mL, 0.65 mmol) in EtOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



5-Cyclopropylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36aj). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (69.4 mg, 70%), by reacting enaminoketone **42e** (122.0 mg, 0.5 mmol) and cyclopropylacetylene (0.057 mL, 0.65 mmol) in MeOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, C*H*$_{pyrazole}$), 7.63 (bs, 1H, C*H*$_{furan}$), 6.77 (bs, 1H, C*H*$_{furan}$), 6.70 (s, 1H), 6.62 (s, 1H, C*H*$_{pyrazole}$), 2.63 (tt, *J* = 8.1, 4.1 Hz, 1H, C*H*$_{cyclopropyl}$), 1.22–1.09 (m, 2H, C*H*$_{cyclopropyl}$), 0.88–0.77 (m, 2H, C*H*$_{cyclopropyl}$).

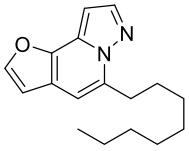
^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.7 (*C*H$_{arom}$), 143.5 (q*C*$_{arom}$), 141.0 (*C*H$_{pyrazole}$), 139.2 (q*C*$_{arom}$), 131.2 (q*C*$_{arom}$), 107.2 (*C*H$_{arom}$), 100.8 (*C*H$_{arom}$), 93.5 (CH$_{pyrazole}$), 12.0 (*C*H$_{cyclopropyl}$), 6.8 (*C*H$_{2,\ cyclopropyl}$).

m.p.: 78–81 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{12}H_{10}N_2O$: 198.0793; found: 198.0794

IR (ATR) (cm^{-1}): 3109, 3008, 2963, 2926, 1658, 1567, 1487

5-Octylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine (36ak). The product was isolated (PE:DCM 4:6 to 2:8) as a low melting off-white powder (67.7 mg, 50%), by reacting enaminoketone **42e** (122.0 mg, 0.5 mmol) and 1-decyne (0.120 mL, 0.65 mmol) in MeOH (0.75 mL) in the presence of $Pd(OAc)_2$ (2.3 mg, 0.01 mmol) and dppf (11.4 mg, 0.02 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H, C*H*$_{pyrazole}$), 7.66 (bs, 1H, C*H*$_{furan}$), 6.78 (s, 1H, C*H*$_{pyridine}$), 6.77–6.72 (m, 2H, C*H*$_{pyrazole}$ + C*H*$_{furan}$), 3.16 (t, *J* = 7.7 Hz, 2H, C*H*$_{2,\ octyl}$), 1.86 (p, *J* = 7.7 Hz, 2H, C*H*$_{2,\ octyl}$), 1.60–1.41 (m, 2H, C*H*$_{2,\ octyl}$), 1.41–1.16 (m, 8H, C*H*$_{2,\ octyl}$), 0.88 (t, *J* = 6.3 Hz, 3H, C*H*$_{3,\ octyl}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 144.6 (*C*H$_{arom}$), 143.7 (q*C*$_{arom}$), 140.8 (*C*H$_{pyrazole}$), 138.1 (q*C*$_{arom}$), 131.3 (q*C*$_{arom}$), 120.4 (q*C*$_{arom}$), 107.3 (*C*H$_{arom}$), 103.0 (*C*H$_{arom}$), 93.3 (*C*H$_{pyrazole}$), 32.0 (*C*H$_{2,\ octyl}$), 31.5 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.6 (*C*H$_{2,\ octyl}$), 29.4 (*C*H$_{2,\ octyl}$), 26.8 (*C*H$_{2,\ octyl}$), 22.8 (*C*H$_{2,\ octyl}$), 14.2 (*C*H$_{3,\ octyl}$).

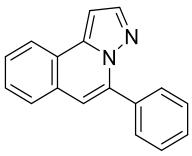
m.p.: 30–33 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{17}H_{22}N_2O$: 270.1732; found: 270.1743

IR (ATR) (cm^{-1}): 2954, 2925, 2851, 1660, 1567, 1486

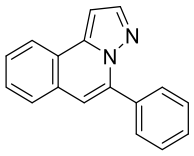
4.6.3 Scale up of the multicomponent reaction: Method A

A heavy-walled reaction tube was charged with the enaminoketone **42a** (1.27 g, 5 mmol), K_2CO_3 (1.40 g, 10 mmol), $^nBu_4NHSO_4$ (171 mg, 0.5 mmol), $Pd(PPh_3)_4$ (58.3 mg, 0.05 mmol) and distilled H_2O (7.5 mL). The tube was flushed with Ar and further charged with phenylacetylene (0.73 mL, 6.5 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.30 mL, 6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with water (25 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM 4:6) to provide tricycle **36a** as an off-white powder (0.73 g, 60%).



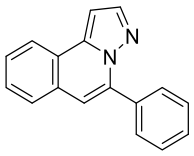
4.6.4 Scale up of the multicomponent reaction: modified Method A

A heavy-walled reaction tube was charged with the enaminoketone **42a** (1.27 g, 5 mmol), K_2CO_3 (1.40 g, 10 mmol), $^nBu_4NHSO_4$ (171 mg, 0.5 mmol), Pd/C (53.2 mg, 0.05 mmol), dppf (57.0 mg, 0.1 mmol) and distilled H_2O (7.5 mL). The tube was flushed with Ar and further charged with phenylacetylene (0.73 mL, 6.5 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.30 mL, 6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with water (25 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM 4:6) to provide tricycle **36a** as an off-white powder (0.61 g, 50%).



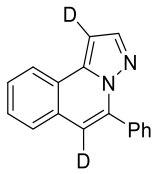
4.6.5 Scale up of the multicomponent reaction: Method B

A heavy-walled reaction tube was charged with the enaminoketone **42a** (1.27 g, 5 mmol), KOH (0.62 g, 10 mmol), dppf (57 mg, 0.1 mmol) and EtOH 96% (7.5 mL). The tube was flushed with Ar and further charged with $Pd(OAc)_2$ (11.5 mg, 0.05 mmol), phenylacetylene (0.73 mL, 6.5 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.30 mL, 6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t., diluted with DCM (25 mL) and gravity filtered to remove solid particles. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (PE:DCM 4:6) to provide tricycle **36a** as an off-white powder (0.95 g, 77%).



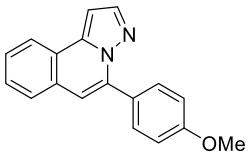
4.6.6 Deuteration tests

A screw-capped tube was charged with enaminoketone **42a** (127.1 mg, 0.5 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol), $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol) and distilled H_2O (0.75 mL) or D_2O (0.75 mL). The tube was flushed with Ar and further charged with the phenylacetylene (0.073 mL, 0.65 mmol) or phenylacetylene-*d* (0.072 mL, 0.6 mmol) and $NH_2NH_2{\cdot}H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with water (15 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM 4:6) to provide the deuterated pyrazoloisoquinoline.



4.6.7 Synthesis of pyrazoloisoquinoline 36m from pyrazole derivative 45

A screw-capped tube was charged with pyrazole **45** (111.5 mg, 0.5 mmol), K_2CO_3 (140 mg, 1.0 mmol), $^nBu_4NHSO_4$ (17.1 mg, 0.05 mmol), $Pd(PPh_3)_4$ (5.7 mg, 0.005 mmol) and distilled H_2O (0.75 mL). The tube was flushed with Ar and further charged with the 4-methoxyphenylacetylene (0.086 mL, 0.65 mmol) after which it was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with water (15 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM 4:6) to provide pyrazoloisoquinoline **36a** as an off-white powder (100.5 mg, 73%).

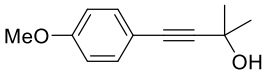


4.7 Multicomponent reaction employing protected alkynes

4.7.1 Preparation of protected alkynes

4-(4-Methoxyphenyl)-2-methylbut-3-yn-2-ol (44a). Typical procedure. In a round-bottom flask containing a magnetic stirrer and equipped with a condenser, 4-iodoanisole (478.0 mg, 2 mmol), $PdCl_2(PPh_3)_2$ (50. mg, 0.04 mmol), CuI (16.0 mg, 0.04 mmol) and freshly distilled, degassed triethylamine (7.0 mL) were added under Ar. Then, 2-methyl-3-butyn-2-ol (0.30 mL, 3.0 mmol) was added dropwise and the mixture was heated to 80 ºC for 0.5 h. After cooling to r.t., the mixture was diluted with Et_2O (25 mL) and gravity filtered to remove

triethylammonium iodide. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (PE:EtOAc 9:1) to provide alkyne **44a** as a yellowish powder (342.0 mg, 90%).

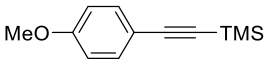


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J*= 8.6 Hz, 2H, C*H*$_{anisole}$), 6.85 (d, *J*= 8.6 Hz, 2H, C*H*$_{anisole}$), 3.81 (s, 3H, C*H*$_{3,\ OMe}$), 3.30 (bs, 1H, O*H*), 1.64 (s, 6H, C*H*$_{3,\ Me}$)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.5 (q*C*$_{arom}$), 133.1 (*C*H$_{arom}$), 114.9 (q*C*$_{arom}$), 113.9 (*C*H$_{arom}$), 92.5 (-C≡*C*-C(CH$_3$)$_2$OH), 82.0 (-*C*≡C-C(CH$_3$)$_2$OH), 65.6 (-*C*(CH$_3$)$_2$OH), 55.3 (*C*H$_{3,\ OMe}$), 31.6 (*C*H$_{3,\ Me}$).

m.p.: 50–52 ºC (PE:EtOAc). *Lit.*[112]47–49 ºC (ligroin)

♁ **[(4-Methoxyphenyl)ethynyl]trimethylsilane (44b).**[113] The product was isolated (PE:EtOAc 1:0 to PE:EtOAc 9:1) as a yellowish oil (388.0 mg, 95%), starting from *p*-iodoanisole (478.0 mg, 2.0 mmol) and trimethylsilylacetylene (0.42 mL, 3.0 mmol).

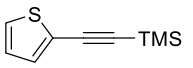


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.4 Hz, 2H, C*H*$_{anisole}$), 6.82 (d, *J* = 8.4 Hz, 2H, C*H*$_{anisole}$), 3.80 (s, 3H, C*H*$_{3,\ OMe}$), 0.24 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.9 (q*C*$_{arom}$), 133.6 (*C*H$_{arom}$), 115.4 (q*C*$_{arom}$), 113.9 (*C*H$_{arom}$), 105.3 (q*C*$_{alkyne}$), 92.6 (q*C*$_{alkyne}$), 55.4 (*C*H$_{3,\ OMe}$), 0.2 (-Si(*C*H$_3$)$_3$).

[112] Heller, C.; Pucher, N.; Seidl, B.; Kalinyaprak-Icten, K.; Ullrich, G.; Kuna, L.; Satzinger, V.; Schmidt, V.; Lichtenegger, H. C.; Stampfl, J.; Liska, R. *J. Polym. Sci. Part A Polym. Chem.* **2007**, *45*, 3280–3291.
[113] Adjabeng, G.; Brenstrum, T.; Frampton, C. S.; Robertson, A. J.; Hillhouse, J.; McNulty, J.; Capretta, A. *J. Org. Chem.* **2004**, *69*, 5082–5086.

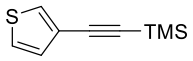
Trimethyl(thiophen-2-ylethynyl)silane (44d).[114] The product was isolated (PE:EtOAc 1:0 to PE:EtOAc 9:1) as a yellowish oil (288.1 mg, 80%), starting from 2-iodothiophene (0.21 mL, 2.0 mmol) and trimethylsilylacetylene (0.42 mL, 3.0 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.25–7.21(m, 2H, C*H*$_{thiophene}$), 6.98–6.92 (m, 1H, C*H*$_{thiophene}$), 0.25 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 132.6 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 126.8 (*C*H$_{arom}$), 123.2 (q*C*$_{arom}$), 98.7 (q*C*$_{alkyne}$), 97.5 (q*C*$_{alkyne}$), -0.1 (-Si(*C*H$_3$)$_3$).

Trimethyl(thiophen-3-ylethynyl)silane (44e).[114] The product was isolated (PE:EtOAc 1:0 to PE:EtOAc 9:1) as a brownish oil (306.2 mg, 85%), starting from 3-iodothiophene (0.21 mL, 2.0 mmol) and trimethylsilylacetylene (0.42 mL, 3.0 mmol).

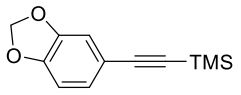


^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 3.0, 1.2 Hz, 1H, C*H*$_{thiophene}$), 7.23 (dd, *J* = 5.0, 3.0 Hz, 1H, C*H*$_{thiophene}$), 7.14 (dd, *J* = 5.0, 1.2 Hz, 1H, C*H*$_{thiophene}$), 0.27 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 130.2 (*C*H$_{arom}$), 129.7 (*C*H$_{arom}$), 125.3 (*C*H$_{arom}$), 122.5 (q*C*$_{arom}$), 100.1 (q*C*$_{alkyne}$), 94.0 (q*C*$_{alkyne}$), 0.1 (-Si(*C*H$_3$)$_3$).

[114] Weingand, V.; Wurm, T.; Vethacke, V.; Dietl, M. C.; Ehjeij, D.; Rudolph, M.; Rominger, F.; Xie, J.; Hashmi, A. S. K. *Chem. Eur. J.* **2018**, *24*, 3725–3728.

(Benzo[*d*][1,3]dioxol-5-ylethynyl)trimethylsilane (44c). Typical procedure. In a round-bottom flask containing a magnetic stirrer and equipped with a condenser, 4-iodo-1,2-(methylenedioxy)benzene (506.0 mg, 2 mmol), $PdCl_2(PPh_3)_4$ (74.0 mg, 0.06 mmol), CuI (23.0 mg, 0.12 mmol), freshly distilled, degassed triethylamine (7.2 mL) and freshly distilled and degassed DMF (3.4 mL) were added under Ar. Then, trimethylsilylacetylene (0.42 mL, 3.0 mmol) was added dropwise and the mixture was heated to 50 ºC for 5 h. After cooling to r.t., the mixture was diluted with Et_2O (25 mL) and gravity filtered to remove triethylammonium iodide. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (PE→ PE:EtOAc 9:1) to provide alkyne **44c** as an off-white powder (393.2 mg, 90%).



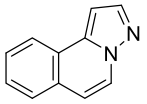
^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 8.1, 0.6 Hz, 1H, C*H*$_{piperonyl}$), 6.91 (d, *J* = 0.6 Hz, 1H, C*H*$_{piperonyl}$), 6.73 (d, *J* = 8.1 Hz, 1H, C*H*$_{piperonyl}$), 5.96 (s, 2H, -OC*H*$_2$O-), 0.23 (s, 9H, -Si(C*H*$_3$)$_3$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.1 (q*C*$_{arom}$), 147.4 (q*C*$_{arom}$), 126.8 (*C*H$_{arom}$), 116.5 (q*C*$_{arom}$), 112.0 (*C*H$_{arom}$), 108.4 (*C*H$_{arom}$), 105.1 (q*C*$_{alkyne}$), 101.4 (-O*C*H$_2$O-), 92.4 (q*C*$_{alkyne}$), 0.1 (-Si(*C*H$_3$)$_3$).

m.p.: 54–56 ºC (DCM)

4.7.2 First approach for the multicomponent reaction employing protected alkynes: trimethylsilyl acetylene

Pyrazolo[5,1-*a*]isoquinoline (36al).[115] **Method A.** A screw-capped tube was charged with the enaminoketone **42a** (127.1 mg, 0.5 mmol), Cs_2CO_3 (327 mg, 1.0 mmol), TBAB (16.5 mg, 0.05 mmol), $Pd(PPh_3)_4$ (28.9 mg, 0.025 mmol) and distilled H_2O (0.75 mL). The tube was flushed with Ar and further charged with the ethynyltrimethylsilane (0.092 mL, 0.65 mmol) and $NH_2NH_2 \cdot H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t. and diluted with water (15 mL) after which it was decanted and concentrated *in vacuo*. The residue was purified by flash column chromatography (PE:DCM 6:4) to provide the desired pyrazoloisoquinoline **36al** as an off-white powder (50.2 mg, 60%).



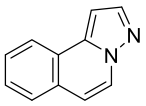
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.4 Hz, 1H, C*H*$_{isoquinoline}$), 8.14–8.04 (m, 1H, C*H*$_{isoquinoline}$), 7.97 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.78–7.64 (m, 1H, C*H*$_{isoquinoline}$), 7.63–7.44 (m, 2H, C*H*$_{isoquinoline}$), 7.05–6.89 (m, 2H, C*H*$_{isoquinoline}$ + C*H*$_{pyrazole}$).

^{13}C-NMR (75 MHz, $CDCl_3$) δ 141.3 (*C*H$_{pyrazole}$), 138.5 (q*C*$_{arom}$), 128.9 (q*C*$_{arom}$), 128.0 (*C*H$_{arom}$), 127.8 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 126.6 (*C*H$_{arom}$), 124.7 (q*C*$_{arom}$), 123.8 (*C*H$_{arom}$), 112.2 (*C*H$_{arom}$), 97.6 (*C*H$_{pyrazole}$).

m.p.: 65–67 ºC (DCM). *Lit.*[116] 62 ºC (distilled)

[115] Kobayashi, M.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 7019–7021.
[116] Huisgen, R.; Grashey, R.; Krischke, R. *Justus Liebigs Ann. Chem.* **1977**, *1977*, 506–527.

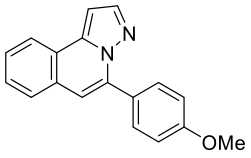
Pyrazolo[5,1-*a*]isoquinoline (36al).[115] **Method B.** A screw-capped tube was charged with the enaminoketone **42a** (127.1 mg, 0.5 mmol), KOH (62.3 mg, 1.0 mmol), dppf (11.4 mg, 0.02 mmol) and EtOH 96% (0.75 mL). The tube was flushed with Ar and further charged with $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), ethynyltrimethylsilane (0.092 mL, 0.65 mmol) and $NH_2NH_2 \cdot H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 24 h. The reaction was allowed to cool to r.t., diluted with DCM (15 mL) and gravity filtered to remove solid particles. The filtrate was concentrated under reduced pressure and the residue purified by flash column chromatography (PE:DCM 6:4) to provide isoquinoline **36al** as an off-white powder (52.0 mg, 62%).



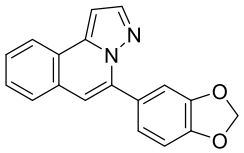
4.7.3 General procedure for the multicomponent reaction employing protected alkynes

A screw-capped tube was charged with enaminone **42a** (127.1 mg, 0.5 mmol), KOH (124.7 mg, 2.0 mmol), dppf (5.7 mg, 0.01 mmol) and EtOH 96% (0.75 mL). The tube was flushed with Ar and further charged with $Pd(OAc)_2$ (50 µL of a 0.107M stock solution in DMF, 0.005 mmol), the corresponding alkyne (0.65 mmol) and $NH_2NH_2 \cdot H_2O$ (0.030 mL, 0.6 mmol). The tube was sealed and heated to 130 ºC for 24 h. After cooling to r.t., the mixture was diluted with DCM (15 mL) and gravity filtered to remove solid particles. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (PE:DCM) to provide the desired heterocycle.

5-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline (36m). The product was isolated (PE:DCM 2:8 to 0:1) as an off-white powder (from **44a*:*** 98.8 mg, 72%; or **44b:** 104.3 mg, 76%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and alkyne **44a** (123.7 mg, 0.65 mmol) or **44b** (132.8 mg, 0.65 mmol). The product was also isolated (PE:DCM 2:8 to 0:1) as an off-white powder (50.6 mg, 37%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and alkyne **44b** (132.8 mg, 0.65 mmol) in the presence of less KOH (62 mg, 1.0 mmol).



5-(Benzo[*d*][1,3]dioxol-5-yl)pyrazolo[5,1-*a*]isoquinoline (36am). The product was isolated (PE:DCM 1:9) as an off-white powder (86.5 mg, 60%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and alkyne **44c** (141.9 mg, 0.65 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.18–8.06 (m, 1H, C*H*$_{isoquinoline}$), 8.01 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.77–7.66 (m, 1H, C*H*$_{isoquinoline}$), 7.60–7.49 (m, 2H, C*H*$_{isoquinoline}$), 7.42 (d, *J* = 1.8 Hz, 1H, C*H*$_{piperonyl}$), 7.35 (dd, *J* = 8.1, 1.8 Hz, 1H, C*H*$_{piperonyl}$), 7.08 (d, *J* = 2.1 Hz, 1H, C*H*$_{pyrazole}$), 7.01 (s, 1H, C*H*$_{pyridine}$), 6.96 (d, *J* = 8.1 Hz, 1H, C*H*$_{piperonyl}$), 6.05 (s, 2H, -OC*H*$_2$O-).

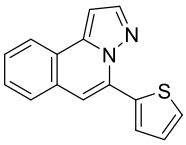
^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.6 (q*C*$_{arom}$), 147.6 (q*C*$_{arom}$), 140.9 (*C*H$_{pyrazole}$), 139.4 (q*C*$_{arom}$), 138.2 (q*C*$_{arom}$), 129.3 (q*C*$_{arom}$), 128.0 (*C*H$_{arom}$), 127.7 (q*C*$_{arom}$), 127.3 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 124.0 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 123.6 (*C*H$_{arom}$), 112.3 (*C*H$_{arom}$), 110.2 (*C*H$_{arom}$), 108.4 (*C*H$_{arom}$), 101.5 (-O*C*H$_2$O-), 98.0 (*C*H$_{pyrazole}$).

m.p.: 120–122 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{18}H_{12}N_2O_2$: 288.0899; found: 288.0898

IR (ATR) (cm^{-1}): 2898, 1638, 1604, 1544, 1497

5-(Thiophen-2-yl)pyrazolo[5,1-*a*]isoquinoline (36an). The product was isolated (PE:DCM 2:8) as an off-white powder (80.1 mg, 64%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and alkyne **44d** (117.2 mg, 0.65 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.16–8.11 (m, 1H, C*H*$_{isoquinoline}$), 8.10 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 8.08 (dt, *J* = 3.8, 1.0 Hz, 1H, C*H*$_{thiophene}$), 7.85–7.69 (m, 1H, C*H*$_{isoquinoline}$), 7.64–7.48 (m, 3H, C*H*$_{isoquinoline}$ + C*H*$_{thiophene}$), 7.42 (s, 1H, C*H*$_{pyridine}$), 7.21 (dd, *J* = 5.1, 3.8 Hz, 1H, C*H*$_{thiophene}$), 7.12 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$).

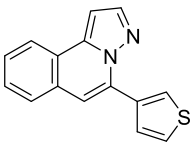
^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.6 (*C*H$_{pyrazole}$), 139.4 (q*C*$_{arom}$), 134.4 (q*C*$_{arom}$), 132.4 (q*C*$_{arom}$), 129.0 (q*C*$_{arom}$), 128.6 (*C*H$_{arom}$), 128.2 (*C*H$_{arom}$), 128.1 (*C*H$_{arom}$), 127.5 (*C*H$_{arom}$), 127.3 (*C*H$_{arom}$), 127.1 (*C*H$_{arom}$), 123.7 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 110.7 (*C*H$_{arom}$), 98.1 (*C*H$_{pyrazole}$).

m.p.: 90–93 ºC (DCM)

HRMS (*m/z)*: [M^+] calc. for $C_{15}H_{10}N_2S$: 250.0565; found: 250.0564

IR (ATR) (cm^{-1}): 3104, 2918, 2830, 1630, 1544, 1440

5-(Thiophen-3-yl)pyrazolo[5,1-*a*]isoquinoline (36ao). The product was isolated (PE:DCM 2:8) as an off-white powder (21.3 mg, 17%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and alkyne **44e** (117.2 mg, 0.65 mmol).



^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 3.1, 1.2 Hz, 1H, C*H*$_{thiophene}$), 8.16–8.08 (m, 1H, C*H*$_{isoquinoline}$), 8.06 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$), 7.82–7.68 (m, 2H, C*H*$_{isoquinoline}$ + C*H*$_{thiophene}$), 7.61–7.49 (m, 2H, C*H*$_{isoquinoline}$), 7.46 (dd, *J* = 5.1, 3.1 Hz, 1H, C*H*$_{thiophene}$), 7.25 (s, 1H, C*H*$_{pyridine}$), 7.10 (d, *J* = 2.2 Hz, 1H, C*H*$_{pyrazole}$).

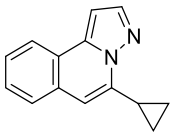
^{13}C-NMR (75 MHz, $CDCl_3$) δ 140.8 (*C*H$_{pyrazole}$), 139.6 (q*C*$_{arom}$), 133.8 (q*C*$_{arom}$), 133.6 (q*C*$_{arom}$), 129.1 (q*C*$_{arom}$), 128.0 (*C*H$_{arom}$), 127.4 (*C*H$_{arom}$), 127.2 (*C*H$_{arom}$), 126.9 (*C*H$_{arom}$), 125.4 (*C*H$_{arom}$), 123.9 (q*C*$_{arom}$), 123.6 (*C*H$_{arom}$), 111.6 (*C*H$_{arom}$), 97.9 (*C*H$_{pyrazole}$).

m.p.: 88–90 ºC (DCM)

HRMS (*m/z)*: [M$^+$] calc. for $C_{15}H_{10}N_2S$: 250.0565; found: 250.0567

IR (ATR) (cm^{-1}): 3144, 3104, 2918, 2851, 1628, 1543, 1438

5-Cyclopropylpyrazolo[5,1-*a*]isoquinoline (36x). The product was isolated (PE:DCM 2:8 to 0:1) as a yellowish powder (78.1 mg, 75%), by reacting enaminoketone **42a** (127.1 mg, 0.5 mmol) and (cyclopropylethynyl)trimethylsilane (92.7 mg, 0.65 mmol).



III

Study on bioavailable cyclopeptides

1 INTRODUCTION

1.1 Peptides as drugs

Peptide drugs have attracted much attention since the first isolation and commercialization of the peptide hormone insulin in the early 1920s.[1] Since then, advances in protein purification, DNA recombination and synthetic techniques have facilitated the access to other bioactive peptide scaffolds.

1.1.1 Application of peptide drugs

Protein-protein interactions are the heart of protein function and cellular organization. Biological signaling requires that protein complexes are generated and activated at the right time and place, and that this formation is both transient and reversible in order to control the effect of hormones or other signaling interactions. As many proteins exhibit their biological activity through their interaction with other proteins, molecules that can interfere in those interactions may become a new class of drugs. Provided the complexity of protein surfaces and the frequently unknown nature of the protein-protein interactions, it is difficult to design drugs with a specific interference effect. Moreover, protein complexes are held together by their contact interfaces, whose size range from 300 to 4800 Å^2. The design and synthesis of small molecules capable of interfering in such contact interfaces is a difficult and demanding, yet not unattainable, venture that is currently being studied.[2]

In addition to small molecules, peptides have emerged as privileged candidates for protein-protein interaction disruption. These medium-size compounds present some advantages with respect to small molecules, since their larger structure allows them for a more selective, specific, and potent interaction

[1] Rosenfeld, L. *Clin. Chem.* **2002**, *48*, 2270–2288
[2] Nero, T. L.; Morton, C. J.; Holien, J. K.; Wielens, J.; Parker, M. W. *Nat. Rev. Cancer* **2014**, *14*, 248–262.

with the receptor. However, they present some limitations in comparison with the small molecules that will be briefly discussed on the next section.

In the last decades, the improvement of synthetic techniques has allowed for a tailored modulation of pharmacokinetic properties through amino acid or backbone modification that elongates peptide's half-life or improves its physicochemical properties.[3] Besides, peptide drugs have shown diverse therapeutic effects against a plethora of illnesses and disorders. For example, the synthetic peptide *Bivalirudin* (Figure 3.1), after intravenous administration, acts as a potent and highly specific direct thrombin inhibitor that is able to overcome some limitations associated to some indirect thrombin inhibitors such as heparin.[4]

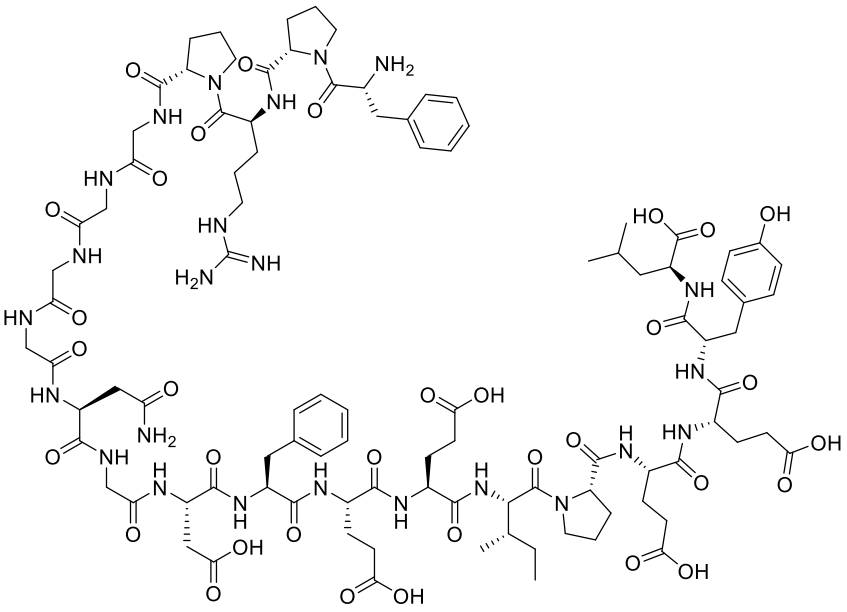


Figure 3.1 Structure of *Bivalirudin*.

[3] Lau, J. L.; Dunn, M. K. *Bioorg. Med. Chem.* **2018**, *26*, 2700–2707.
[4] Anand, S. X.; Kim, M. C.; Kamran, M.; Sharma, S. K.; Kini, A. S.; Fareed, J.; Hoppensteadt, D. A.; Carbon, F.; Cavusoglu, E.; Varon, D.; Viles-Gonzalez, J. F.; Badimon, J. J.; Marmur, J. D. *Am. J. Cardiol.* **2007**, *100*, 417–424.

In 2003, *Bortezomib* (Figure 3.2, left) was approved by the FDA for the treatment of multiple myeloma and mantle cell lymphoma. It is a synthetic *N*-protected dipeptide in which the *C*-terminus was substituted by a boronic acid.[5] This drug is administered intravenously and it acts as proteasome 26S inhibitor which triggers cancerous cell apoptosis.[6] In 2015, FDA approved the commercialization of *Ixazomib* (Figure 3.2, right), an orally administered *Bortezomib* analogue developed by Takeda Pharmaceuticals also for the treatment of multiple myeloma.[7]

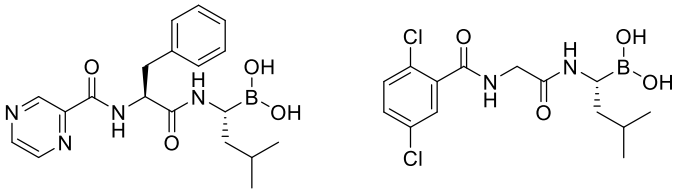


Figure 3.2 Structures of *Bortezomib*, left and *Ixazomib*, right.

As a last example, we have *Gramicidin S*,[8] a natural cyclodecapeptide produced by the gram-positive *Bacillus brevis,* that has been employed since World War II as a topically administered antibiotic against some gram-positive and gram-negative bacteria, as well as some fungi.[9]

[5] Larkin, M. *Lancet* **1999**, *354*, 1915.
[6] Bonvini, P.; Zorzi, E.; Basso, G.; Rosolen, A. *Leukemia* **2007**, *21,* 838–842.
[7] Raab, M. S.; Podar, K.; Breitkreutz, I.; Richardson, P. G.; Anderson, K. C. *Lancet* **2009**, *374,* 324–339.
[8] Gause, G. F.; Brazhnikova, M. G. *Nature* **1944**, *154,* 703.
[9] Gall, Y. M.; Konashev, M. B. *Hist. Philos. Life Sci.* **2001**, *23*, 137–150.

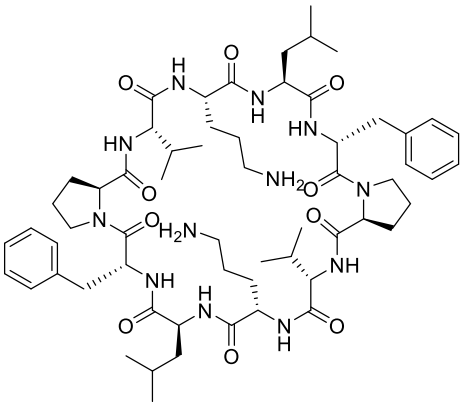


Figure 3.3 Structure of *Gramicidin S.*

1.1.2 Limitations of peptide drugs and efforts on overcoming them

Despite the broad applications of peptide drugs, they still present two major drawbacks: *in vivo* metabolic instability and poor membrane permeability.[10] Enzymatic peptide degradation limits drug's half-life in serum, thus reducing drug's bioavailable concentration. As a result of this instability, regular dosing may be needed in order to maintain the drug at a clinically effective concentration. Besides, in contrast with small molecules, which usually present a hydrophobic nature that allows them to permeate through plasma cell membrane, the typical highly hydrophilic nature of peptide drugs along with their fluctuating conformations hinder significantly cell membrane permeation and therefore the access to intracellular targets is jeopardized.[11] Therefore, treatments employing peptide drugs are usually limited to intravenous administration so the drug can access systemic circulation. However, there are alternatives such as the membrane protein-facilitated intracellular peptide uptake, in which some short sequence peptides called cell

[10] In reference to passive cell membrane permeation, *i.e.* the translocation across the cell membrane without the need for an intracellular transporter. In this kind of permeation the substance diffuses through the lipid bilayer according to Fick's first law of diffusion, from regions of high concentration (extracellular) to regions of low concentration (intracellular) across a concentration gradient. For additional information read: Gautier, A.; Hinner, M. J "*Site-Specific Protein Labeling: Methods and Protocols"* Humana Press, **2019**, New York, USA.
[11] Fosgerau, K.; Hoffmann, T. *Drug Discov. Today* **2015**, *20*, 122–128.

permeable peptides (hereinafter, CPPs) form conjugates with the membrane-impermeable peptide, thus enabling peptide uptake. However, this technique is still under study.[12] Taking into account those limitations, much effort has been focused on overcoming these limitations.

In addition, diverse strategies have been developed to bridge the gap of proteolytic instability. One of those strategies focuses on peptide termini protection since it is well-known that metabolic degradation can possibly occur in both *C*- and *N*- termini of a peptide. Additionally, there are examples in literature which conclude that different amino acid residues will result in different degradation grades. Therefore, if termini modification (*e.g.* amino acid residue variation, *N*-terminal acylation or *C*-terminal amidation) can be carried out while maintaining target affinity and specificity, such modification can improve *in vivo* stability and therefore enhance bioavailability.[13]

On the other hand, non-chemical methods have also been employed. One of these methods is based on the identification of critical amino acid residues essential for peptide bioactivity. There are different strategies to carry out this identification employing molecular biology tools, among them one of the most employed procedures being the iterative and combinatorial truncation of amino acid residues of the peptide backbone to determine the crucial motif in charge of the peptide activity. Another methodology is the one called “alanine scanning”, in which amino acid residues of a given peptide are individually substituted by alanine employing site-directed mutagenesis in order to find out the contribution of each residue to peptide activity.[14] This amino acid is chosen mainly due to its small size and its lack of charge which impedes the interaction with adjacent residue’s side chains. Apart from those methods, there are more complex *in silico* procedures based on

[12] Trabulo, S.; Cardoso, A. L.; Mano, M.; de Lima, M. C. P. *Pharmaceuticals* **2010**, *3,* 961–993.
[13] Lee, A. C. L.; Harris, J. L.; Khanna, K. K.; Hong, J. H. *Int. J. Mol. Sci.* **2019**, *20,* 2383.
[14] a) Weiss, G.A.; Watanabe, C.K.; Zhong, A.; Goddard, A.; Sidhu, S.S. *Proc. Natl. Acad. Sci. USA* **2000**, 97, 8950–8954. b) Morrison, K. L.; Weiss, G. A. *Curr. Opin. Chem. Biol.* **2001**, *5,* 302–307.

structure-activity relationship studies that help in identifying metabolically-labile residues within a peptide backbone.

In this regard, information extracted from the previously mentioned non-chemical techniques represent a valuable starting point for a potential modification of backbone amino acid. Getting back to chemical methods, there are examples in which the substitution of an amino acid residue by its enantiomer provides an enhanced proteolytic stability since the proteases are not able to recognize its reversed conformation.[15] In that sense, modifications such as substitutions by synthetic α- and/or β-amino acids in the backbone have also proved to be effective in improving metabolic stability. Apart from these variations, strategies such as *N*- or α-methylation have also been used to ameliorate both stability and peptide solubility.[16]

Finally, peptide cyclization has also been proven effective to achieve this objective owing to the limited access of proteases. Depending on how this cycle is formed, head-to-tail or between side-chains, different properties can be achieved. On the first one, the cyclization involves the reaction between *C*- and *N*-termini resulting in both protection of the termini and conformational restriction. On the other hand, the reaction between side-chains lead to conformational restriction. This conformational rigidity plays an important role in passive membrane permeation since it, somehow, limits the entropic penalty of passing through the lipid bilayer.[17]

As mentioned before, proteolytic instability leads to poor bioavailability, albeit this is not the only factor to take into account. Apart from that, aqueous drug solubility plays an essential role in drug's bioavailability. Drugs with good aqueous solubility present enhanced bioavailability since their effective serum concentration

[15] Weinstock, M.T.; Francis, J.N.; Redman, J.S.; Kay, M.S. *Biopolymers* **2012**, *98*, 431–442.
[16] Werner, H.M.; Cabalteja, C.C.; Horne, W.S. *ChemBioChem* **2016**, *17*, 712–718.
[17] a) Kluskens, L.D.; Nelemans, S.A.; Rink, R.; de Vries, L.; Meter-Arkema, A.; Wang, Y.; Walther, T.; Kuipers, A.; Moll, G.N.; Haas, M. *J. Pharm. Exp*. **2009**, *328*, 849–854. b) Decoene, K.W.; Vannecke, W.; Passioura, T.; Suga, H.; Madder, A. *Biomedicines* **2018**, *6*, 99.

is easily maintained. At first glance, taking all these factors into account and due to their features, cyclic peptides seem to be better candidates for orally administered peptide drugs than their linear counterparts.

1.2 Cyclopeptide drugs

1.2.1 Natural cyclopeptides

Improved natural product isolation techniques have led to the isolation of an increasing number of naturally occurring cyclic peptides. One of the most well-known natural cyclopeptides is *Cyclosporin A* (Figure 3.4, left), which was firstly isolated in the early 1970's from the fungus *Tolypocladium inflatum*, found in soil samples from Norway and Wisconsin by researchers from Sandoz (now Novartis). This peptide came into medical use as immunosuppressant for the treatment of organ transplantation rejection in 1983 and it appears on the World Health Organization's List of Essential Medicines.[18] Additionally, this drug has been approved for the treatment of rheumatoid arthritis, psoriasis, severe atopic dermatitis and acute severe ulcerative colitis, *inter alia.* This cyclopeptide is composed by 11 amino acids, among which there is a D-amino acid and a rare butenyl-methyl-*L*-threonine. Additionally, the structure of *Cyclosporin* is stabilized by three intramolecular H-bonds that grant a relatively fixed conformation and improved *in vivo* stability. Therefore, this peptide has an enhanced cell membrane permeability and allows for oral administration.

[18] Laupacis, A.; Keown, P. A.; Ulan, R. A.; McKenzie, N.; Stiller, C. R. *Can. Med. Assoc. J.* **1982**, *126*, 1041–1046.

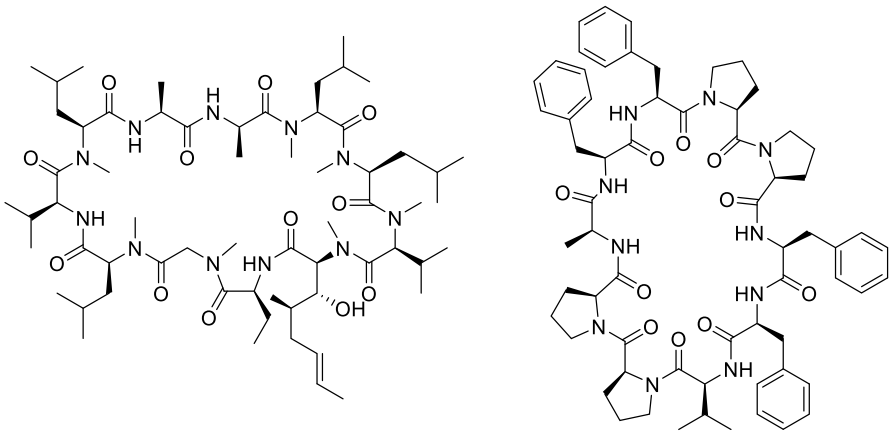


Figure 3.4 Structure of Cyclosporin A, left and Antamanide, right.

Another example is the *Antamanide* (Figure 3.4, right), a cyclodecapeptide isolated from the well-known poisonous fungus *Amanita phalloides,* which protects against phalloidin poisoning and exhibits potential activity for edema treatment.[19] Besides, *Viomycin*, a natural cyclopeptide extracted from *Streptomyces puniceus* actinobacteria, is employed as an intravenous antibiotic which exhibits anti-tuberculosis properties.[20] Moreover, *Sanguinamide A*, isolated from *Hexabranchus sanguineus* sea slug[21] has shown some oral bioavailability in rats.[22]

[19] Wieland, T.; Faulstich, H.; Fiume, L. *Crit. Rev. Biochem. Mol. Biol.* **1978**, *5*, 185–260.
[20] Bartz, Q. R.; Ehrlich, J.; Mold, J. D.; Penner, M. A.; Smith, R. M. *Am. Rev. Tuberc.* **1951**, *63*, 4–6.
[21] Dalisay, D. S.; Rogers, E. W.; Edison, A. S.; Molinski, T. F. *J. Nat. Prod.* **2009**, *72*, 732–738.
[22] Nielsen, D. S.; Hoang, H. N.; Lohman, R. J.; Diness, F.; Fairlie, D. P. *Org. Lett.* **2012**, *14*, 5720–5723.

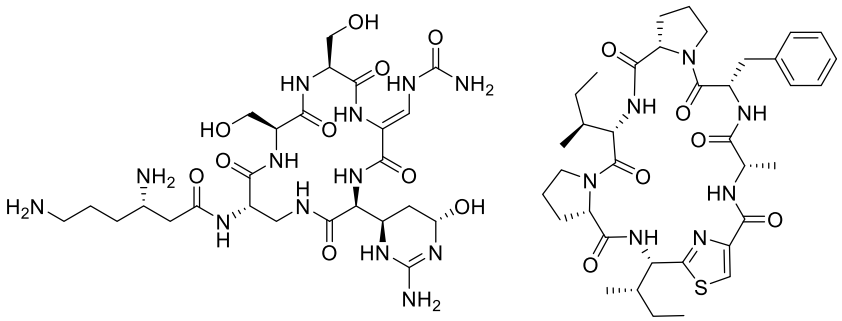


Figure 3.5 Structure of *Viomycin*, left and *Sanguinamide A*, right.

1.2.2 On the way to orally administered cyclopeptide drugs

In the last years, cyclopeptides have emerged as an interesting alternative for linear peptides due to their increased metabolic stability, restricted conformation and reduced polarity by eliminating charged termini. The previous features together with a higher propensity for internal hydrogen bonding, confer on these macrocycles improved drug-like properties.[23] Typical cyclic peptide backbone is comprised from 5 to 14 amino acids, which represents a size large enough to ensure a correct contact area with the receptor. Therefore, they are prone to exhibit high selectivity and, in addition, their potential ability for multiple H-bonding can lead to strong binding affinity with large and flat receptor surfaces not easily accessible[24] by small molecules, thus making them valuable candidates for the

[23] a) Witek, J.; Wang, S.; Schroeder, B.; Lingwood, R.; Dounas, A.; Roth, H. J.; Fouché, M.; Blatter, M.; Lemke, O.; Keller, B.; Riniker, S. *J. Chem. Inf. Model.* **2019**, *59*, 294–308. b) Rezai, T.; Yu, B.; Millhauser, G. L.; Jacobson, M. P.; Lokey, R. S. *J. Am. Chem. Soc.* **2006**, *128*, 2510–2511. c) Thansandote, P.; Harris, R. M.; Dexter, H. L.; Simpson, G. L.; Pal, S.; Upton, R. J.; Valko, K. *Bioorg. Med. Chem.* **2015**, *23*, 322–327. d) Pauletti, G. M.; Gangwar, S.; Siahaan, T. J.; Jeffrey Aubé; T. Borchardt, R. *Adv. Drug Deliv. Rev.* **1997**, *27*, 235–256.

[24] a) Cai, M.; Marelli, U. K.; Bao, J.; Beck, J. G.; Opperer, F.; Rechenmacher, F.; McLeod, K. R.; Zingsheim, M. R.; Doedens, L.; Kessler, H.; Hruby, V. J. *J. Med. Chem.* **2015**, *58*, 6359–6367. b) Henchey, L. K.; Porter, J. R.; Ghosh, I.; Arora, P. S. *ChemBioChem* **2010**, *11*, 2104–2107. c) Fairlie, D. P.; Tyndall, J. D. A.; Reid, R. C.; Wong, A. K.; Abbenante, G.; Scanlon, M. J.; March, D. R.; Bergman, D. A.; Chai, C. L. L.; Burkett, B. A. *J. Med. Chem.* **2000**, *43*, 1271–1281. d) March, D. R.; Abbenante, G.; Bergman, D. A.; Brinkworth, R. I.; Wickramasinghe, W.; Begun, J.; Martin, J. L.; Fairlie, D. P. *J. Am. Chem. Soc.* **1996**, *118*, 3375–3379.

modulation of protein-protein interactions.[25] In addition, their well-defined structure provides them a relatively predictable metabolism, which along with their target selectivity give rise to a reliable pharmacotoxicologic profile with little or nearly absent off-target toxicity.[26]

In spite of these desirable characteristics, cyclic peptides exhibit some drawbacks such as poor membrane permeability, and metabolic stability leading to high clearance[27]. Those factors limit oral bioavailability and hence scarce oral exposure levels are usually observed. Therefore, in general and with the exception of *Cyclosporin*, the use of cyclopeptides has been relegated to extracellular targets and intravenous dosing.[28]

Despite efforts to overcome these limitations on cyclopeptide lead or hit development, most of these investigations have been focused on readouts from biochemical or affinity assays. In those lead optimization processes; the minimal backbone modification frequently implies a deleterious impact on target selectivity or/and potency leading to a tedious optimization process. In this work, it was decided to incorporate oral exposure and bioavailability assays in the lead optimization studies in order to achieve a family of cyclopeptides with enhanced oral bioavailability and membrane permeation, to access intracellular targets by oral administration.

[25] a) Bhat, A.; Roberts, L. R.; Dwyer, J. J. *Eur. J. Med. Chem.* **2015**, *94*, 471–479. b) Hennemann, H.; Wirths, S.; Carl, C. *Eur. J. Med. Chem.* **2015**, *94*, 489–496. c) Henchey, L. K.; Porter, J. R.; Ghosh, I.; Arora, P. S. *ChemBioChem* **2010**, *11*, 2104–2107. d) Meyer, S. C.; Gaj, T.; Ghosh, I. *Chem. Biol. Drug Des.* **2006**, *68*, 3–10. d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Mol. Divers.* **2000**, 5, 289–304.
[26] Bose, P. P.; Chatterjee, U.; Hubatsch, I.; Artursson, P.; Govender, T.; Kruger, H. G.; Bergh, M.; Johansson, J.; Arvidsson, P. I. *Bioorg. Med. Chem.* **2010**, *18*, 5896–5902.
[27] Clearance is a term coined in pharmacology and refers to the pharmacokinetic measurement that relates the concentration of a drug measured in the body to its rate of elimination and is expressed as a volume per time (L/ h or mL/min). For additional information read: a) Toutain, P. L.; Bousquet-Mélou, A. *J. Vet. Pharmacol. Ther.* **2004**; *27*, 415–425. b) Rowland, M; Tozer, T. M. "*Clinical pharmacokinetics and pharmacodynamics: concepts and applications"*, 5th Ed., Lippincott Williams and Wilkins, **2019**, Baltimore, USA.
[28] a) Di, L. *AAPS J.* **2015**, *17*, 134–143. b) Diao, L.; Meibohm, B. *Clin. Pharmacokinet*. **2013**, 855–868. c) Craik, D. J.; Fairlie, D. P.; Liras, S.; Price, D. *Chem. Biol. Drug Des.* **2013**, *81*, 136–147. d) Schreiber, S. L.; Crabtree, G. R. *Immunol. Today*. **1992**, *13*, 136–142.

On the other hand, some parameters, such as intramolecular H-bonding and *N*-methylation of solvent exposed amides, have proved to be convenient to improve passive permeability in small cyclopeptides (*e.g.* cyclopenta- and cyclohexapeptides) as demonstrated by Lokey *et al.* and Kessler and co-workers.[29,30] In this sense, hexapeptides might have an appropriate size if the target contains a deep pocket for ligand binding, whereas in targets where large flat regions for protein-protein interactions are present, their size could be a truly limiting factor for high affinity.[31,32] For that purpose, in this work the investigation of bigger cyclic peptide decamers is proposed on the belief that their bigger size could contribute for the latter interactions. Furthermore, cyclodecapeptides are also similar in size to orally available *Cyclosporine* so this precedent was a good starting-point in the way to develop a decamer scaffold with enhanced permeability and bioavailability properties.

[29] a) Bockus, A. T.; Schwochert, J. A.; Pye, C. R.; Townsend, C. E.; Sok, V.; Bednarek, M. A.; Lokey, R. S. *J. Med. Chem.* **2015**, *58*, 7409–7418. b) Nielsen, D. S.; Hoang, H. N.; Lohman, R. J.; Hill, T. A.; Lucke, A. J.; Craik, D. J.; Edmonds, D. J.; Griffith, D. A.; Rotter, C. J.; Ruggeri, R. B.; Price, D. A.; Liras, S.; Fairlie, D. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 12059–12063.
[30] a) Beck, J. G.; Chatterjee, J.; Laufer, B.; Kiran, M. U.; Frank, A. O.; Neubauer, S.; Ovadia, O.; Greenberg, S.; Gilon, C.; Hoffman, A.; Kessler, H. *J. Am. Chem. Soc.* **2012**, *134*, 12125–12133.
[31] a) Hennemann, H.; Wirths, S.; Carl, C. *Eur. J. Med. Chem.* **2015**, *94*, 489–496. b) De Veer, S. J.; Wang, C. K.; Harris, J. M.; Craik, D. J.; Swedberg, J. E. *J. Med. Chem.* **2015**, *58*, 8257–8268.
[32] a) Villar, E. A.; Beglov, D.; Chennamadhavuni, S.; Porco, J. A.; Kozakov, D.; Vajda, S.; Whitty, A. *Nat. Chem. Biol.* **2014**, *10*, 723–731. b) Kuntz, I. D.; Chen, K.; Sharp, K. A.; Kollman, P. A. *Proc. Natl. Acad. Sci.* **1999**, *96*, 9997–10002.

2 AIMS AND OBJECTIVES

In view of the promising properties of some cyclopeptides found in the literature, the following aims were defined:

- To carry out the synthesis of a number of cyclodecapeptides
- To study the pharmacokinetic and pharmacodynamic profiles of these novel macrocycles
- To find a rationale that would serve as a starting-point for future construction of orally bioavailable cyclopeptides

- During my stay, I was in charge of the synthesis of several of those cyclodecapeptides (Figure 3.6).

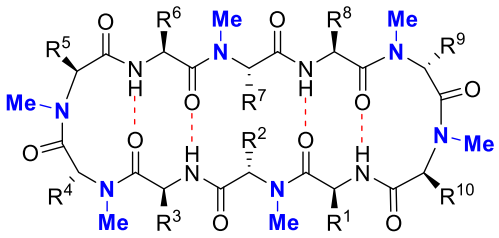


Figure 3.6 Tentative template for cyclodecapeptides.

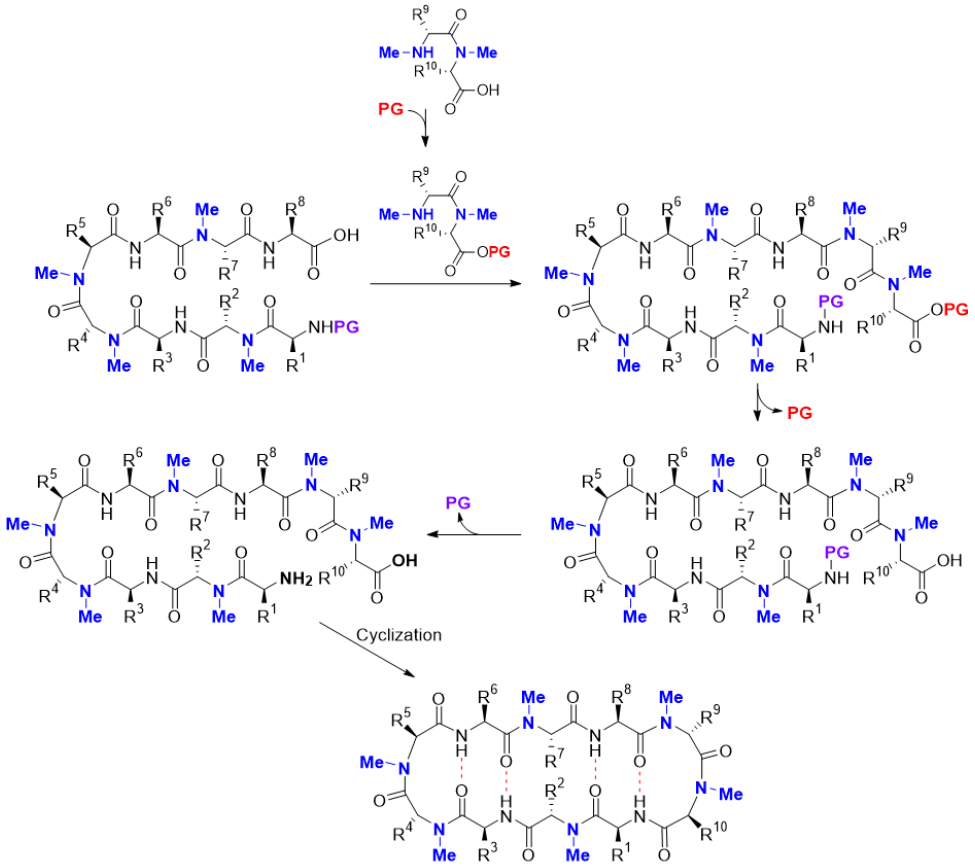
3 RESULTS AND DISCUSSION

3.1 Synthesis of cyclodecapeptides

Part of the ongoing research on cyclopeptides carried out by Novartis[33] was based on the preparation of a series of cyclodecapeptides with enhanced membrane permeability and improved proteolytic stability that could lead to orally bioavailable macrocyclic peptides. Additionally, a thorough study about the effects of backbone modification on peptide properties was being undertaken in the way to establish a comprehensive structure-properties relationship. First, based on previous studies, the group had established a "cyclodecapeptide template design" focusing on the selection of the correct *N*-methylated pattern[34] in order to foster intramolecular H-bonding that might enable conformational restriction, thus easing passive membrane permeation (Figure 3.6).

Therefore, a fragment-based synthesis was carried out in order to obtain the desired oligopeptides (Scheme 3.1). For that purpose, a series of peptide coupling/functional group deprotection steps were performed in order to get the corresponding cyclopeptide. A thorough study was undertaken to find the optimal reaction conditions, *i.e.* reaction solvent or solvent mixture, temperature and more importantly, the most efficient peptide coupling agent system; so as to avoid amino acid epimerization. In this regard, the final intramolecular macrolactamization proved to be a critical step.

[33] Due to the confidential nature of the research carried out at Novartis, only some general structures and limited information will be displayed. For more details, see: Fouché, M.; Schäfer, M.; Berghausen, J.; Desrayaud, S.; Blatter, M.; Piéchon, P.; Dix, I.; García Martín, A.; Roth, H. J. *ChemMedChem* **2016**, *11*, 1048–1059.
[34] N-methyl units have been highlighted in blue for clarity.



Scheme 3.1 Fragment-based synthesis of cyclodecapeptides.

3.2 Solubility and permeability studies

Once the peptides were synthesized, they were submitted to a series of solubility, pharmacokinetic and pharmacodynamic tests to evaluate their properties and behavior in both, *in vitro* and *in vivo* assays. First, clog *P*[35] values were computationally predicted in order to take a glimpse at their hydrophobicity/hydrophilicity level. Furthermore, equilibrium solubility of each

[35] clog *P* is a calculated value of the ratio of partition of a molecule into a hydrophobic (normally 1-octanol, which simulates a lipidic media) and hydrophilic (water), and it provides an idea of the hydrophobic/hydrophilic nature of the assayed molecule. For more information, see: Comer, J.; Tam, K. *Pharmacokinetic Optimization in Drug Research*, **2007**; 275–304.

molecule was determined by high-throughput screening adding a solution of the candidate into a buffer solution, which simulated physiological medium, and shaking it. After the shaking process, the concentration of the supernatant solution was determined by LC-MS/MS, thus getting the solubility of each macrocycle. Besides, *in vitro* apparent cell membrane permeability of each candidate was determined with MDCK cell line assay.[36]

3.3 Pharmacokinetic studies

An important pharmacokinetic parameter to be assessed in drug candidates is the study of their oxidative metabolic stability and proteolytic stability. Since cytochrome P450 mediated oxidation and peptide proteolysis are two of the main ways for peptide elimination, the *in vitro* clearance of the synthesized peptides was measured in two different ways: *via* rat hepatic microsomes,[37] to check for their resistance towards oxidative stress; and *via* rat plasma exposure, to evaluate their proteolytic stability.

Finally, for the *in vivo* experiments male Sprague-Dawley rats were employed as model. In this regard, each cyclopeptide candidate was intravenously and orally administered to 3–4 rats and drug concentration was measured in blood samples taken at scheduled times. With those results, drug exposures of both i.v. and p.o. administrations were determined as the AUC. Then, with this data absolute bioavailability (F_{abs}) was determined as follows:

$$F_{abs}\,(\%) = \frac{AUC_{p.o.} \cdot D_{i.v}}{AUC_{i.v.} \cdot D_{p.o.}} \times 100$$

Finally, the research group succeeded in obtaining a single crystal of a synthesized cyclopeptide, which was analyzed by X-ray diffractometry, thus

[36] MDCK (Madin-Darby canine kidney) cells belong to an epithelial cell line from kidney. Their low protein transporter expression and metabolic activity confer them unique features in order to assess permeability of drug candidates. Volpe, D. A. *Future Med. Chem.* **2011**, 2063–2077.
[37] Hepatic microsomes are in charge of the oxidative metabolism of molecules (*e.g.* peptides*)*, carried out by cytochrome P450 in the liver. See: Delaforge, M.; Bouillé, G.; Jaouen, M.; Jankowski, C. K.; Lamouroux, C.; Bensoussan, C. *Peptides* **2001**, *22*, 557–565.

unequivocally confirming the existence of four transannular H-bond interactions as in the designed template (Figure 3.7).

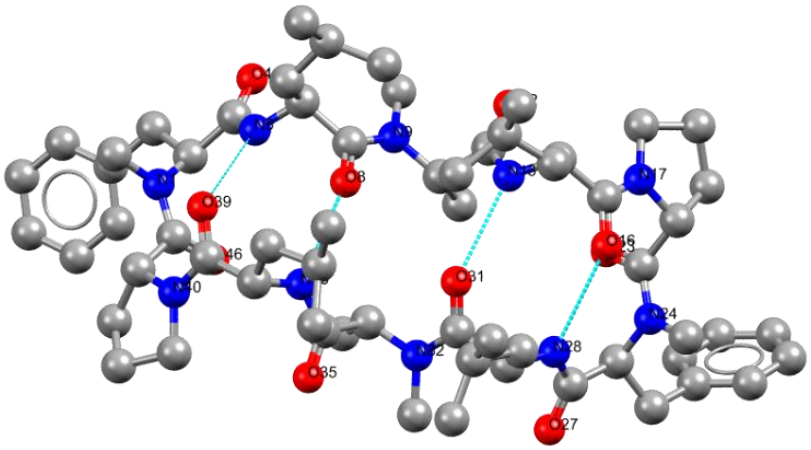


Figure 3.7 X-ray structure of a cyclopeptide candidate showing transannular H-bonds with dotted lines. Protons have been omitted for clarity.

CONCLUSIONS

CONCLUSIONS

- Phosphinite-based PCN palladium(II) pincer complexes can be prepared from 3-pyrazolylphenol by a one-pot sequential phosphination/palladation, reaching overall yields of 55–68%. In addition, the sequence of *N*-benzylation/oxidative addition gives access to an asymmetric NNC palladium(II) pincer complex.

- Aqueous Suzuki biaryl coupling is efficiently carried out under classical thermal and microwave-assisted conditions in the presence of very small amounts of PCN pincer complexes.

- Alkylidene lactones can be prepared in moderate to excellent yields by the cycloisomerization of alkynoic acids in water at low temperatures (r.t.–50 ºC) by using PCN palladium pincer complexes. These exceptionally active catalysts feature the highest substrate:catalyst ratio for such cycloisomerization reactions so far. In addition, an even smaller amount of catalyst promotes the transformation of 4-pentynoic acid into levulinic acid. These aqueous and extremely efficient conditions allow the isolation of products with minimal metal content.

- On account of a series of mechanistic experiments, it can be concluded that the aqueous Suzuki-Miyaura biaryl couplings and cycloisomerizations performed in the presence of PCN pincer complexes take place through homogeneous catalytic conditions.

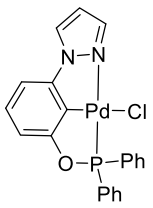
- A novel amine-exchange/heteroannulation/hydroamination cascade reaction involving *N*-propargyl-pyrrole and -benzimidazole derived enaminoketones provides pyrazolopyrrolopirazine and benzimidazo-pyrazolopyrazine fused *N*-heterocycles in excellent yields. In addition, this reaction, performed using a mild base (Cs_2CO_3) and a sustainable solvent (EtOH), gives access to other polyheterocyclic scaffolds such as pyrazoloisoquinolines, pyrazolo(benzo)-thienopyridines and furopyrazolopyridines.

- *N*-propargylpyrrole derived enaminones undergo a cascade alkyne or allene hydration/enolate formation/annulation/condensation in the presence of nucleophiles the provide 5-acetyl-8-alkoxy-/amino/thioxy-indolizines.

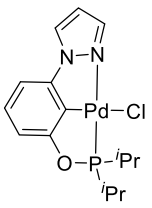
- A palladium-catalyzed multicomponent reaction of enaminoketones, alkynes and hydrazine provides a straightforward access to pyrazoloisoquinolines, pyrazolo(benzo)thienopyridines and furopyrazolopyridines. The reaction is performed in aqueous and alcoholic media.

- From the results of kinetic curves, poisoning assays, UPLC-MS of reaction crude, ^{2}H- and ^{18}O-labelling experiments, etc., rational proposals can be made to understand the mechanism of the above cascade and multicomponent reactions.

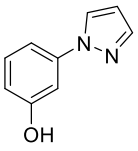
SUMMARY OF COMPOUNDS



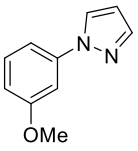
1a



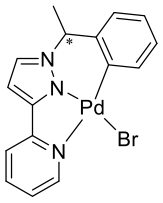
1b



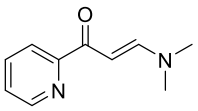
2a



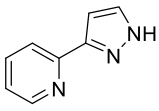
2b



***rac*-5**
(*R*)-5



6



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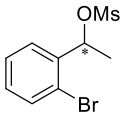

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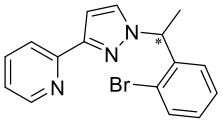

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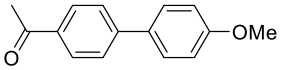

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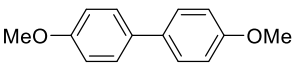

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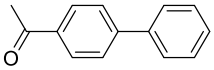

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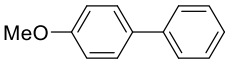

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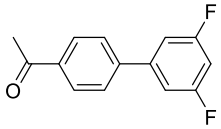

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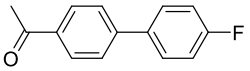

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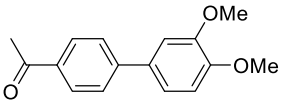

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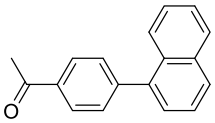

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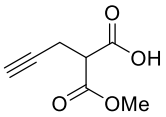

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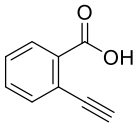

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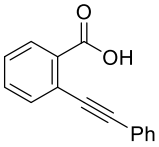

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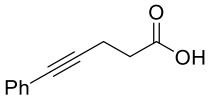

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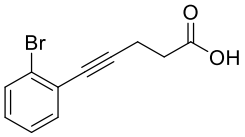

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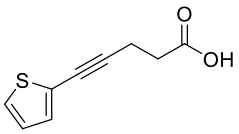

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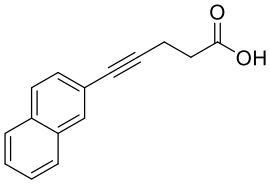

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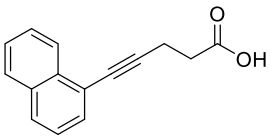

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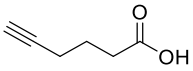

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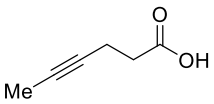

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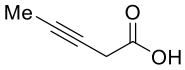

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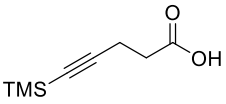

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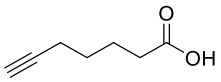

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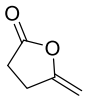

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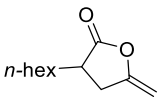

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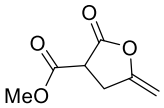

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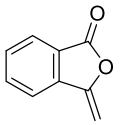

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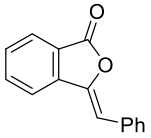

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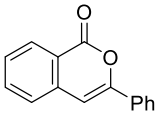

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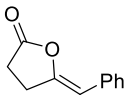

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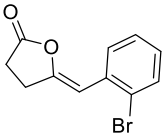

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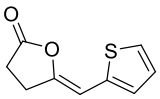

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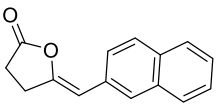

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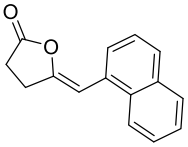

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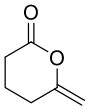

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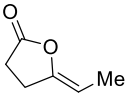

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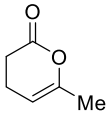

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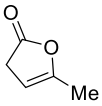

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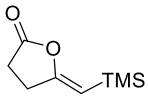

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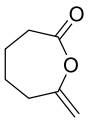

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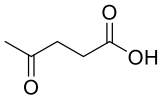

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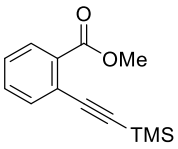

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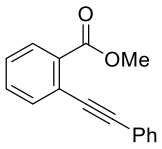

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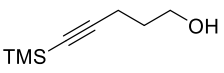

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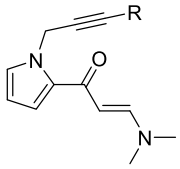

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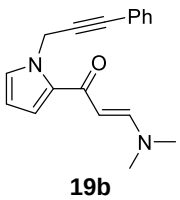
R = D, **19a-D**



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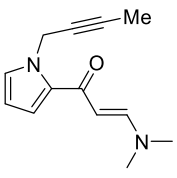

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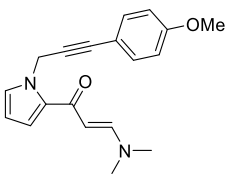

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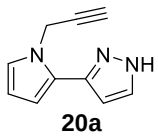

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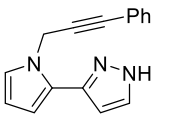
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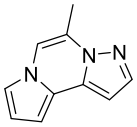
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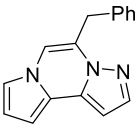
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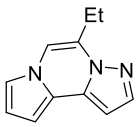
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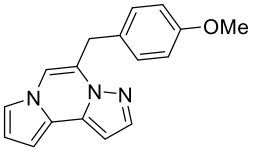
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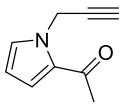
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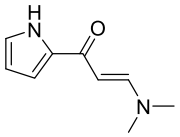
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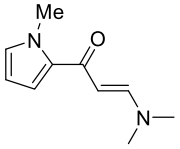
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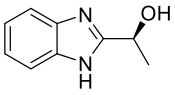
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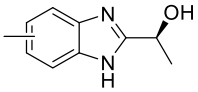
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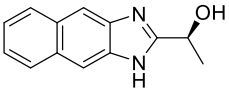
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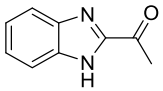
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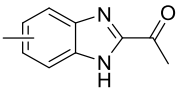
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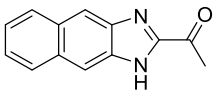
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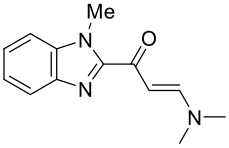
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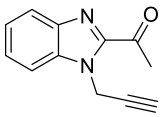
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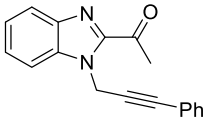
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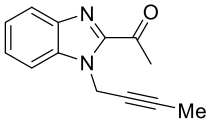
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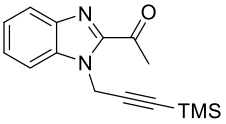
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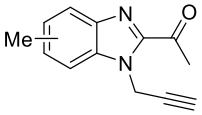
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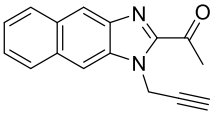
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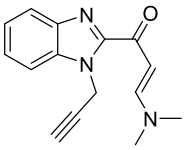
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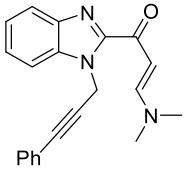
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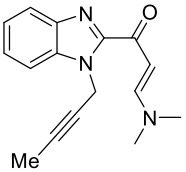
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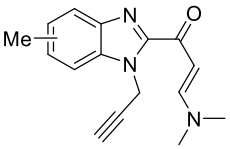
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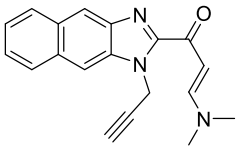
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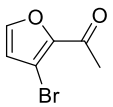
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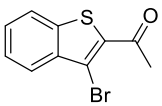
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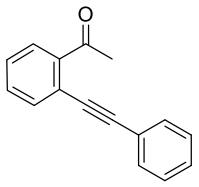

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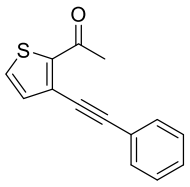

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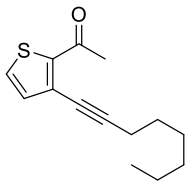

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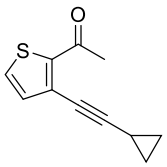

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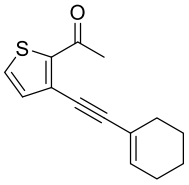

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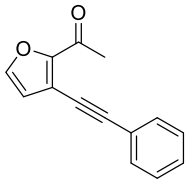

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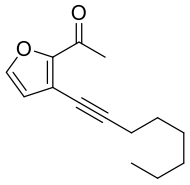

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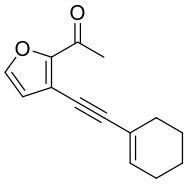

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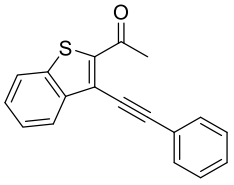

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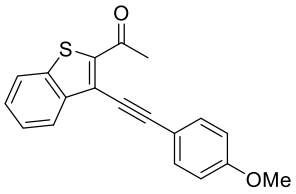

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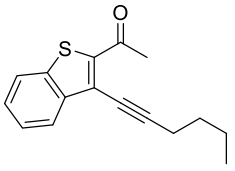

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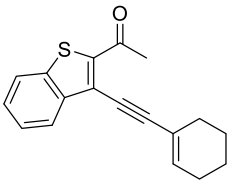

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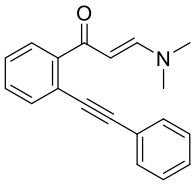

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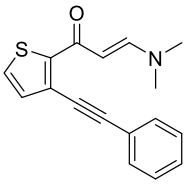

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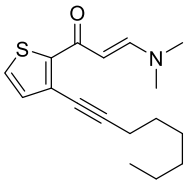

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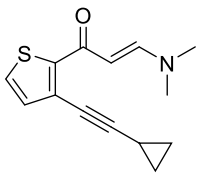

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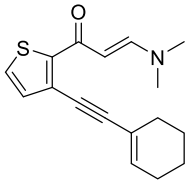

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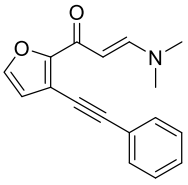

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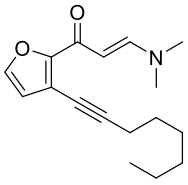

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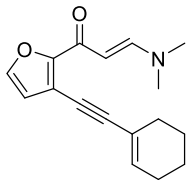

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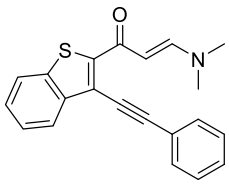

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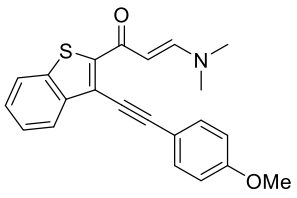

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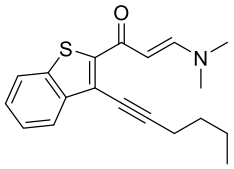

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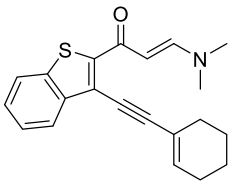

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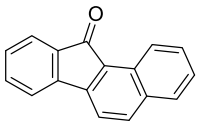

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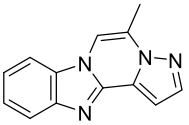

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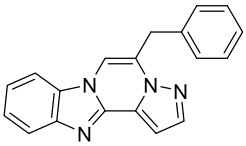

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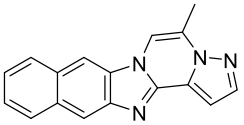

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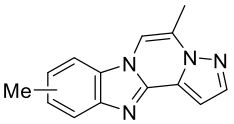

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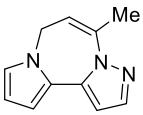

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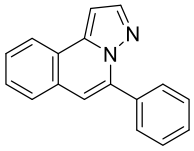

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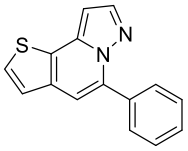

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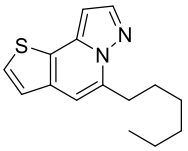

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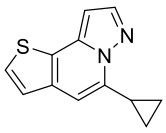

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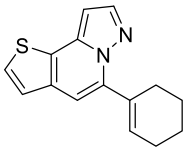

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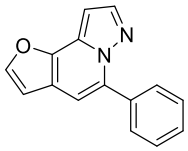

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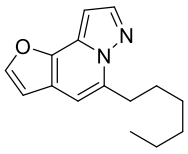

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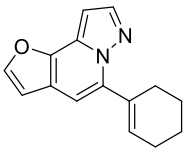

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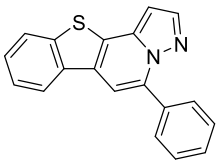

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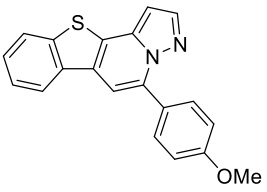

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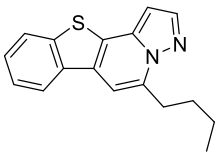

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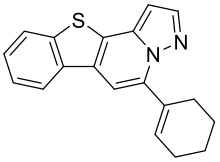

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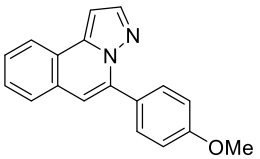

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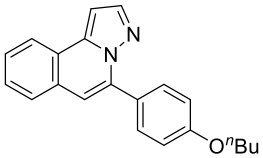

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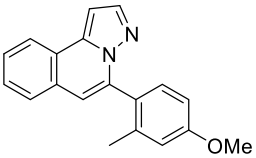

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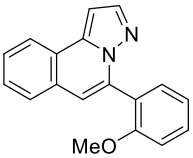

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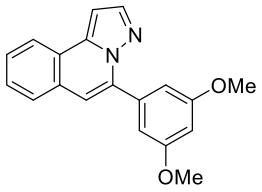

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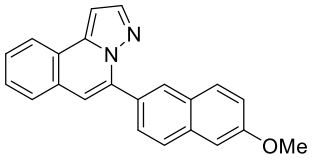

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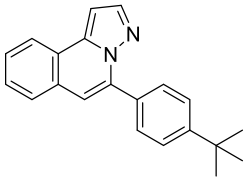

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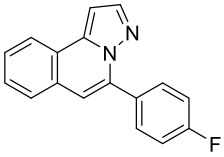

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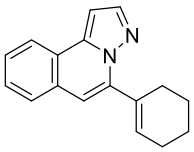

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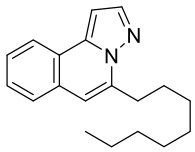

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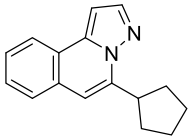

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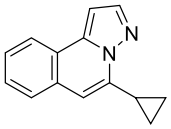

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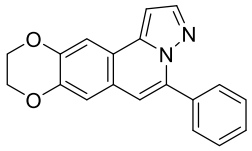

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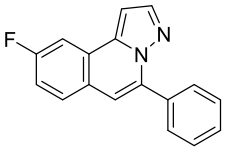

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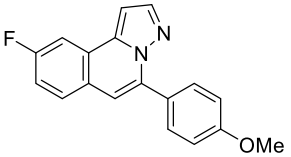

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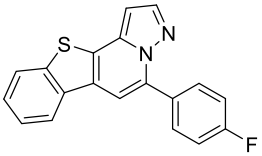

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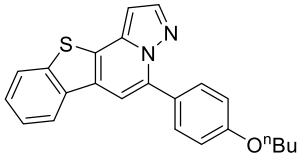

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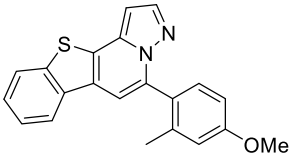

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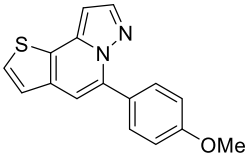

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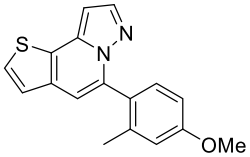

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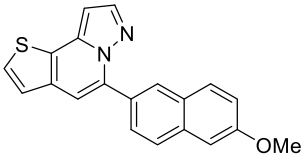

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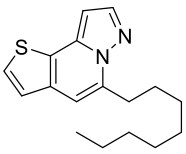

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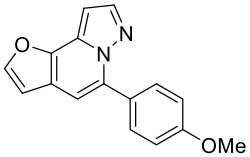

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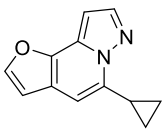

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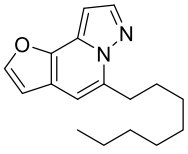

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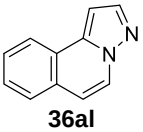

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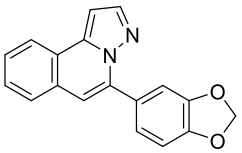

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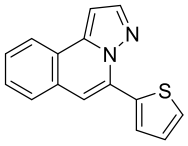

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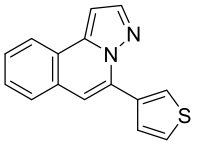

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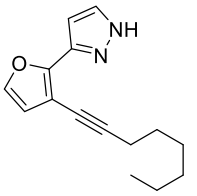

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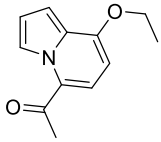

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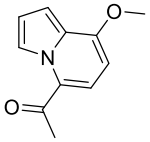

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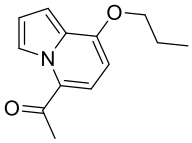

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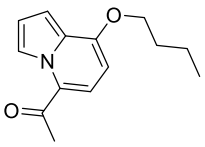

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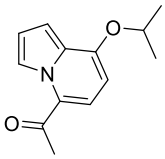

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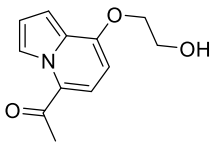

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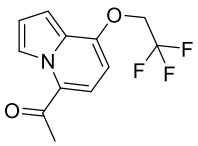

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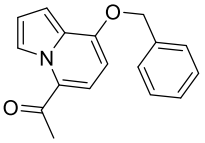

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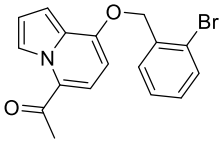

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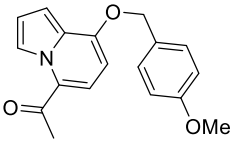

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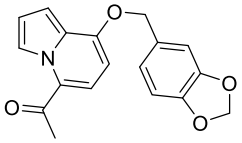

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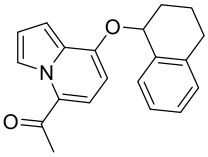

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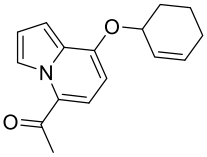

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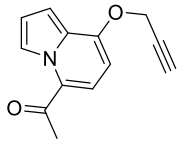

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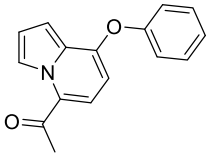

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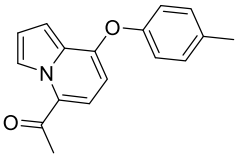

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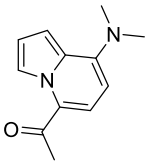

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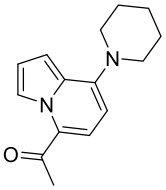

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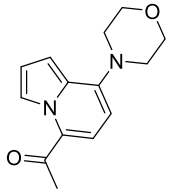

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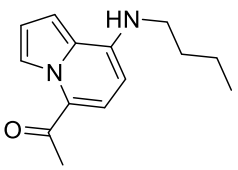

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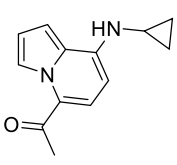

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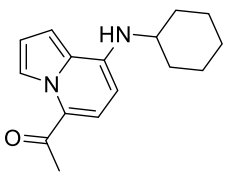

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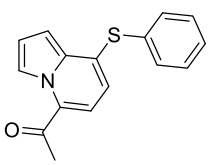

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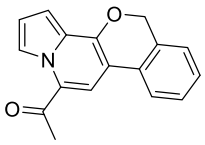

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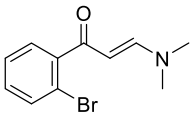

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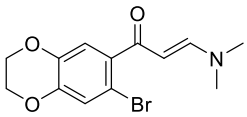

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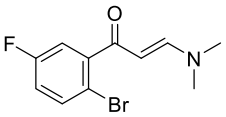

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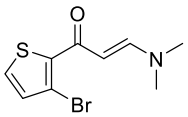

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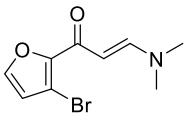

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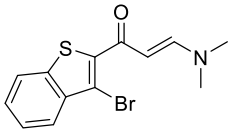

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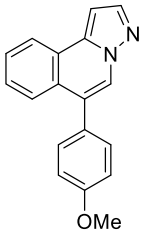

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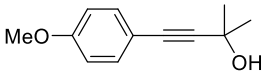

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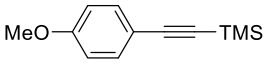

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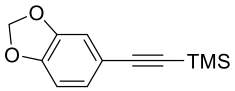

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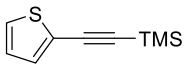

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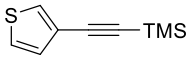

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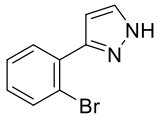


45a

APPENDIX

SELECTION OF REPRESENTATIVE SPECTRA

2a: 3-(1*H*-Pyrazol-1-yl)phenol

1a: Chloro-[2-(1*H*-pyrazole-κ*N*2)-6-(diphenylphosphinito-κ*P*)-phenyl-κ*C*1]-Pd(II)

1b: Chloro-[2-(1*H*-pyrazole-κ*N*2)-6-(diisopropylphosphinito-κ*P*)-phenyl-κ*C*1]-Pd(II)

6: (*E*)-3-(Dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one

9: 1-(2-Bromophenyl)ethyl methanesulfonate

10: 2-[1-[1-(2-Bromophenyl)ethyl]-1*H*-pyrazol-3-yl]pyridine

5: 2-[1-[1-(Phenyl-κC2)ethyl]-1*H*-pyrazol-3-yl-κN2]pyridine-κN-palladium(II) bromide

13a: 1-(4'-Methoxybiphenyl-4-yl)ethenone

13c: 1-Biphenyl-4-yl-ethanone

14c: 2-(Methoxycarbonyl)-4-pentynoic acid

14d: 2-Ethynylbenzoic acid

14g: 5-(2-Bromophenyl)pent-4-ynoic acid

14h: 5-(Thiophen-2-yl)pent-4-ynoic acid

14i: 5-(Naphthalen-2-yl)pent-4-ynoic acid

15b: 3-Hexyl-5-methylenedihydrofuran-2(3*H*)-one

15d: 3-Methyleneisobenzofuran-1(3*H*)-one

15e & 15e': (*Z*)-3-Benzylideneisobenzofuran-1(3*H*)-one & 3-Phenyl-1*H*-isochromen-1-one

15f: (*Z*)-5-Benzylidenedihydrofuran-2(3*H*)-one

15h: (*Z*)-5-(Thiophen-2-ylmethylene)dihydrofuran-2(3*H*)-one

15i: (*Z*)-5-(Naphthalen-2-ylmethylene)dihydrofuran-2(3*H*)-one

15k: 6-Methylenetetrahydro-2*H*-pyran-2-one

15n: (*Z*)-5-[(Trimethylsilyl)methylene]dihydrofuran-2(3*H*)-one

17a: Methyl 2-[(trimethylsilyl)ethynyl]benzoate

19a-D: *(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl-3-*d*)-1*H*-pyrrol-2-yl]prop-2-en-1-one

19b: *(E)*-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl]-1*H*-pyrrol-2-yl)prop-2-en-1-one

20b: 3-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole

21b: 5-Benzylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine

21c: 5-Ethylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine

25b: *(S)*-1-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethan-1-ol

26c: 1-(1*H*-Naphtho[2,3-*d*]imidazol-2-yl)ethan-1-one

28b: 1-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one

28f: 1-[1-(Prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]ethan-1-one

29b: *(E)*-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one

29e: *(E)*-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]prop-2-en-1-one

31b: 1-[3-(Phenylethynyl)thiophen-2-yl]ethan-1-one

31h: 1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]ethan-1-one

31k: 1-[3-(Hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]ethan-1-one

32a: *(E)*-3-(dimethylamino)-1-[2-(phenylethynyl)phenyl]prop-2-en-1-one

32d: *(E)*-1-[3-(Cyclopropylethynyl)thiophen-2-yl]-3-(dimethylamino)prop-2-en-1-one

32h: *(E)*-1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]-3-(dimethylamino)prop-2-en-1-one

32k: *(E)*-3-(Dimethylamino)-1-[3-(hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]prop-2-en-1-one

33: 11*H*-Benzo[*a*]fluoren-11-one

34b: 5-Benzylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine

34d & **34d'**: 5,10-Dimethylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine & 5,9-dimethylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine

35: 5-Methyl-7*H*-pyrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]diazepine

36a: 5-Phenylpyrazolo[5,1-*a*]isoquinoline

36d: 5-Cyclopropylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine

36h: 5-(Cyclohex-1-en-1-yl)furo[2,3-*c*]pyrazolo[1,5-*a*]pyridine

36y: 5-Phenyl-9,10-dihydro-[1,4]dioxino[2,3-*g*]pyrazolo[5,1-*a*]isoquinoline

36aa: 9-Fluoro-5-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline

36ac: 5-(4-Butoxyphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine

36ag: 5-(6-Methoxynaphthalen-2-yl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine

36ak: 5-Octylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine

36am: 5-(Benzo[*d*][1,3]dioxol-5-yl)pyrazolo[5,1-*a*]isoquinoline

36ao: 5-(Thiophen-3-yl)pyrazolo[5,1-*a*]isoquinoline

38f: 1-[8-(2-Hydroxyethoxy)indolizin-5-yl]ethan-1-one

38g: 1-[8-(2,2,2-Trifluoroethoxy)indolizin-5-yl]ethan-1-one

38i: 1-[8-[(2-Bromobenzyl)oxy]indolizin-5-yl]ethan-1-one

39b: 1-[8-(Piperidin-1-yl)indolizin-5-yl]ethan-1-one

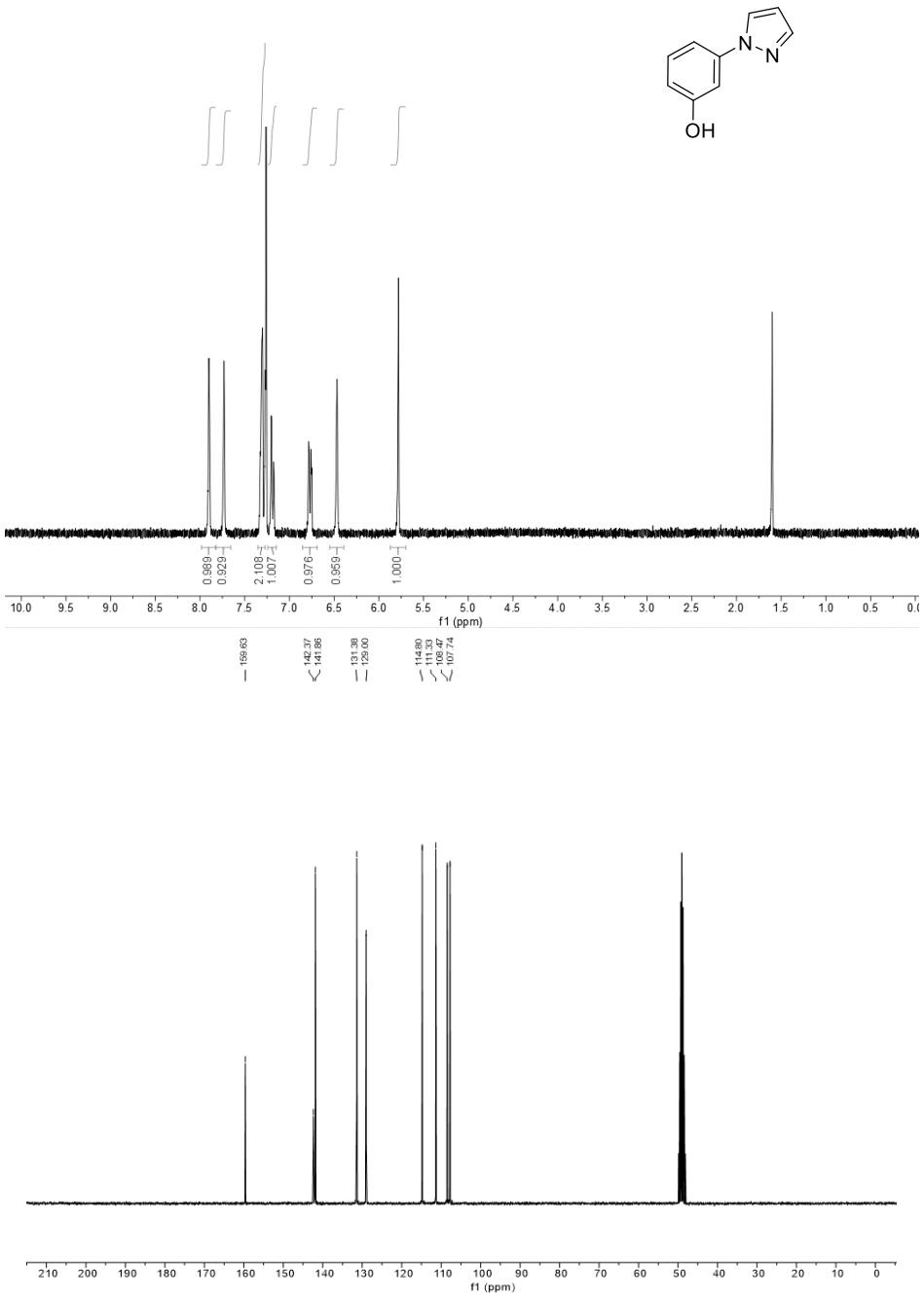
41: 1-(5*H*-isochromeno[4,3-*g*]indolizin-11-yl)ethan-1-one

42c: *(E)*-1-(2-Bromo-5-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one

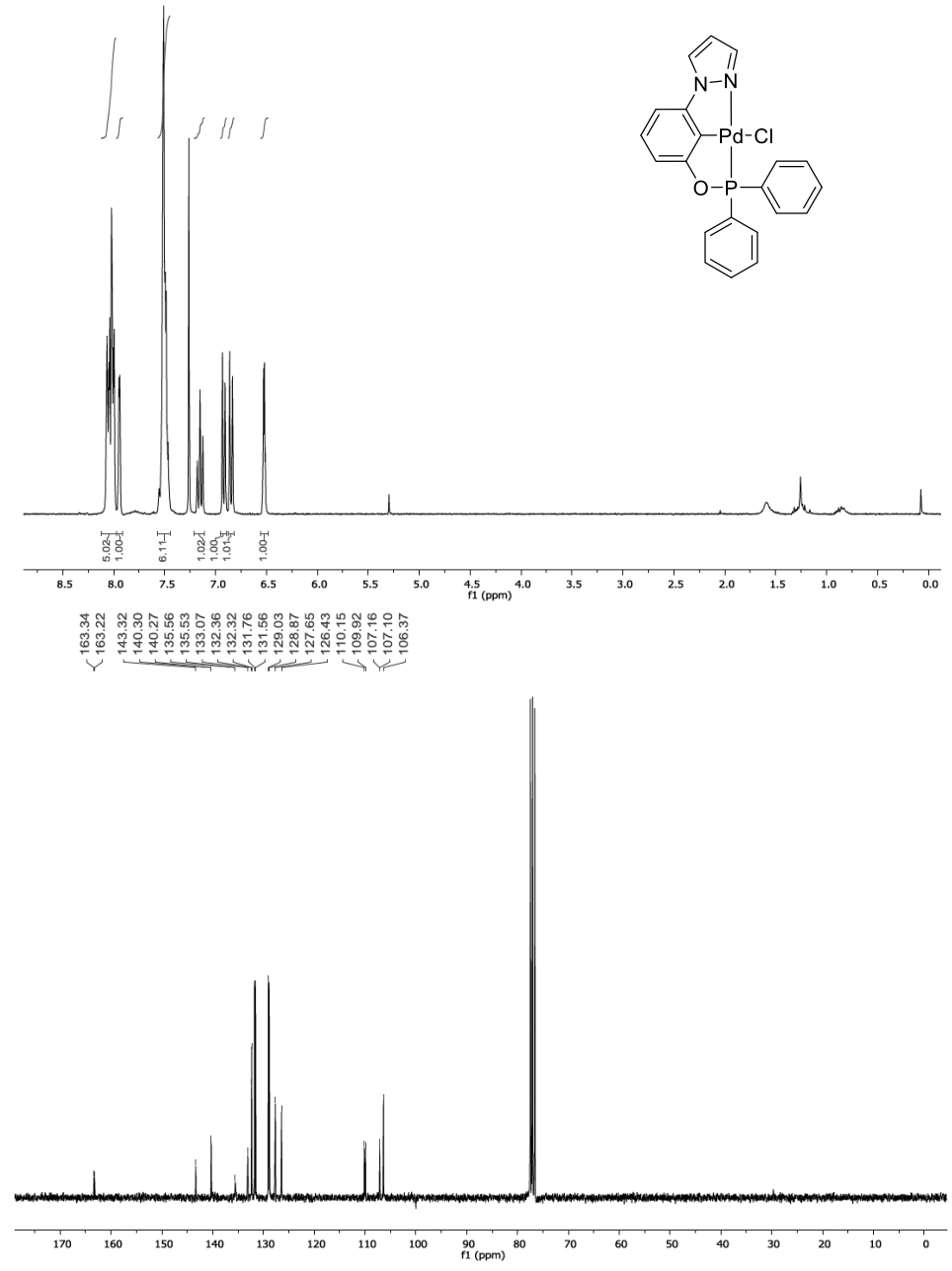
42e: (*E*)-1-(3-Bromofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one

43: 6-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline

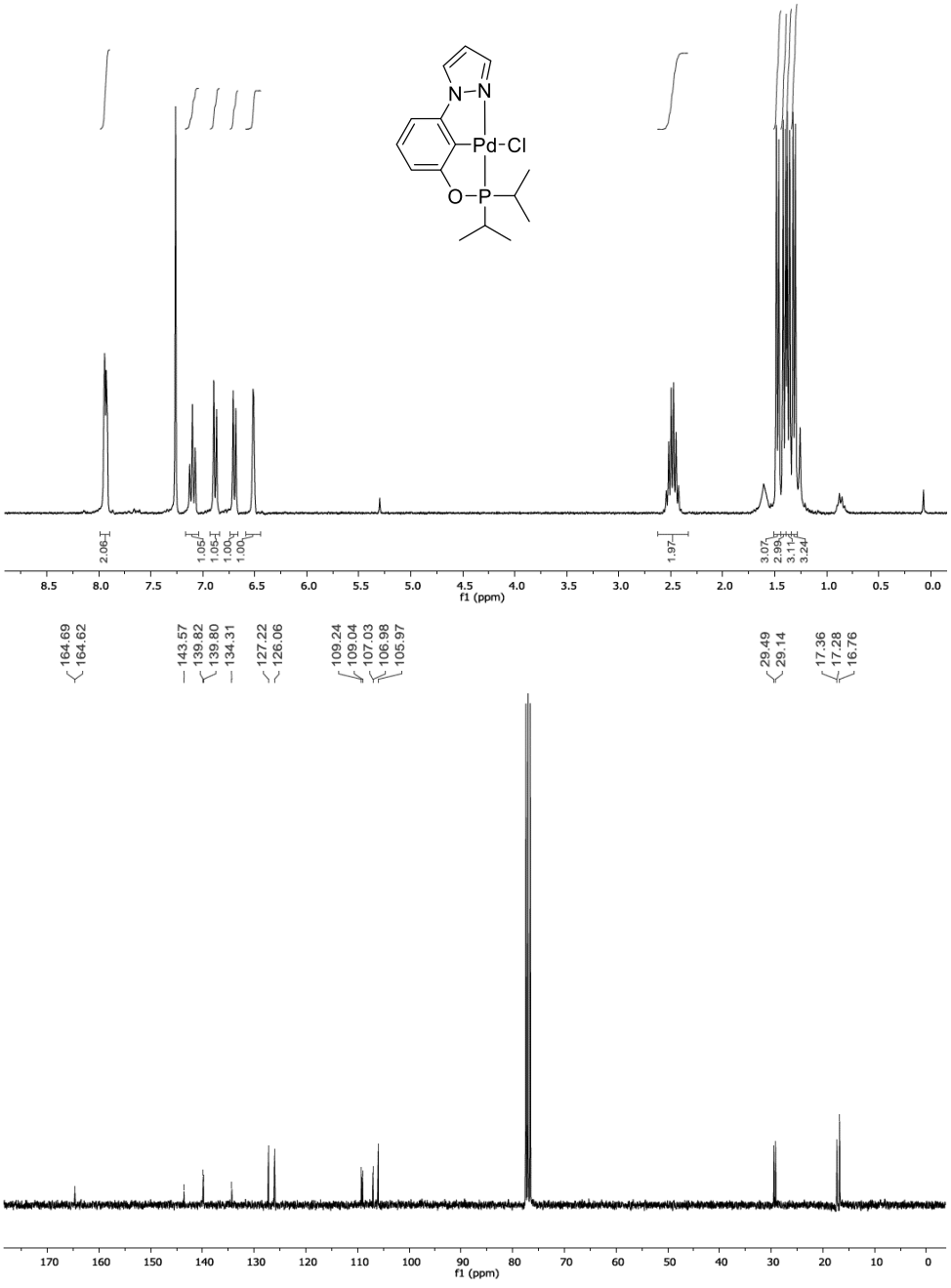
2a: 3-(1*H*-Pyrazol-1-yl)phenol



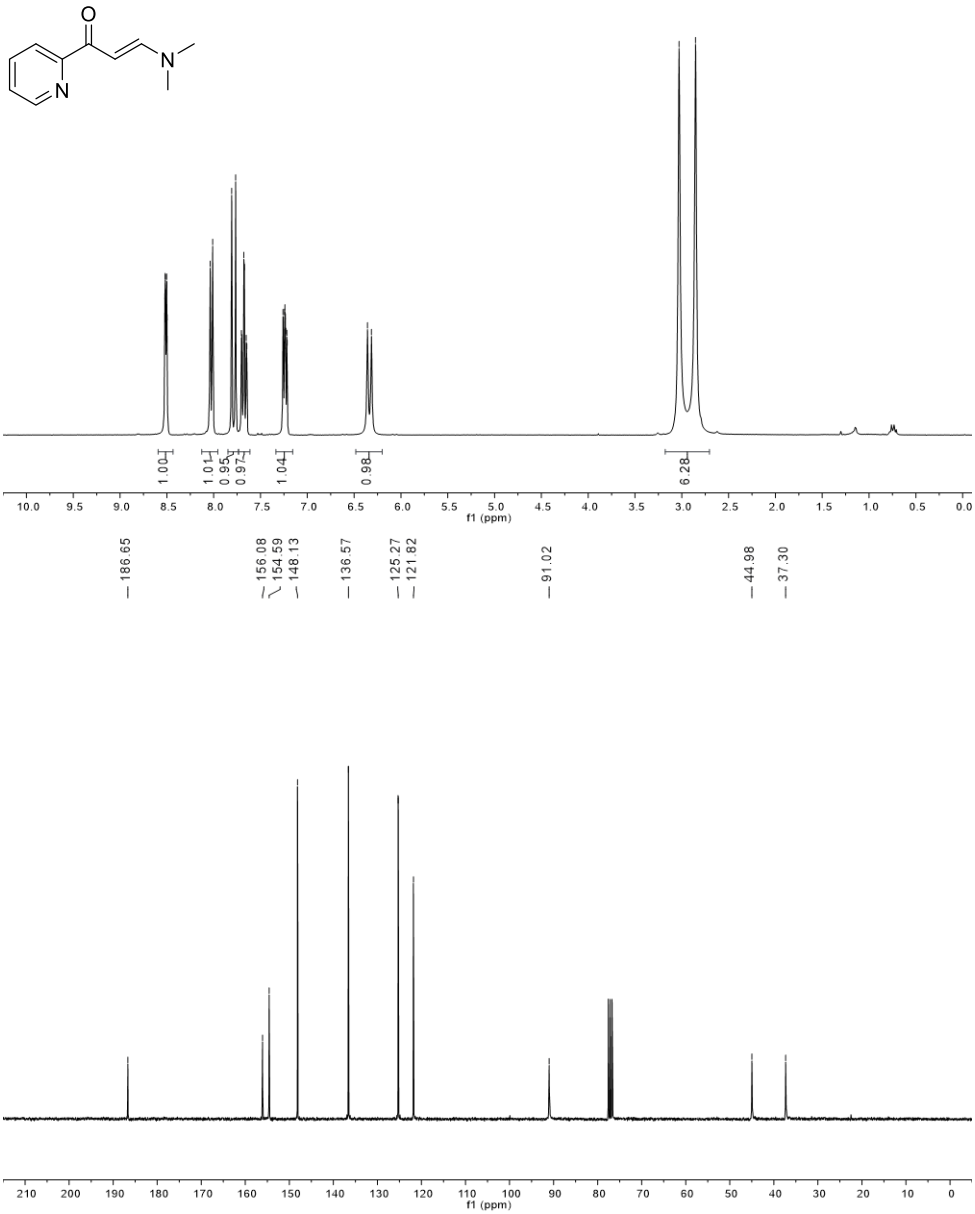
1a: Chloro-[2-(1*H*-pyrazole-κ*N*2)-6-(diphenylphosphinito-κ*P*)-phenyl-κ*C*1]-Pd(II)



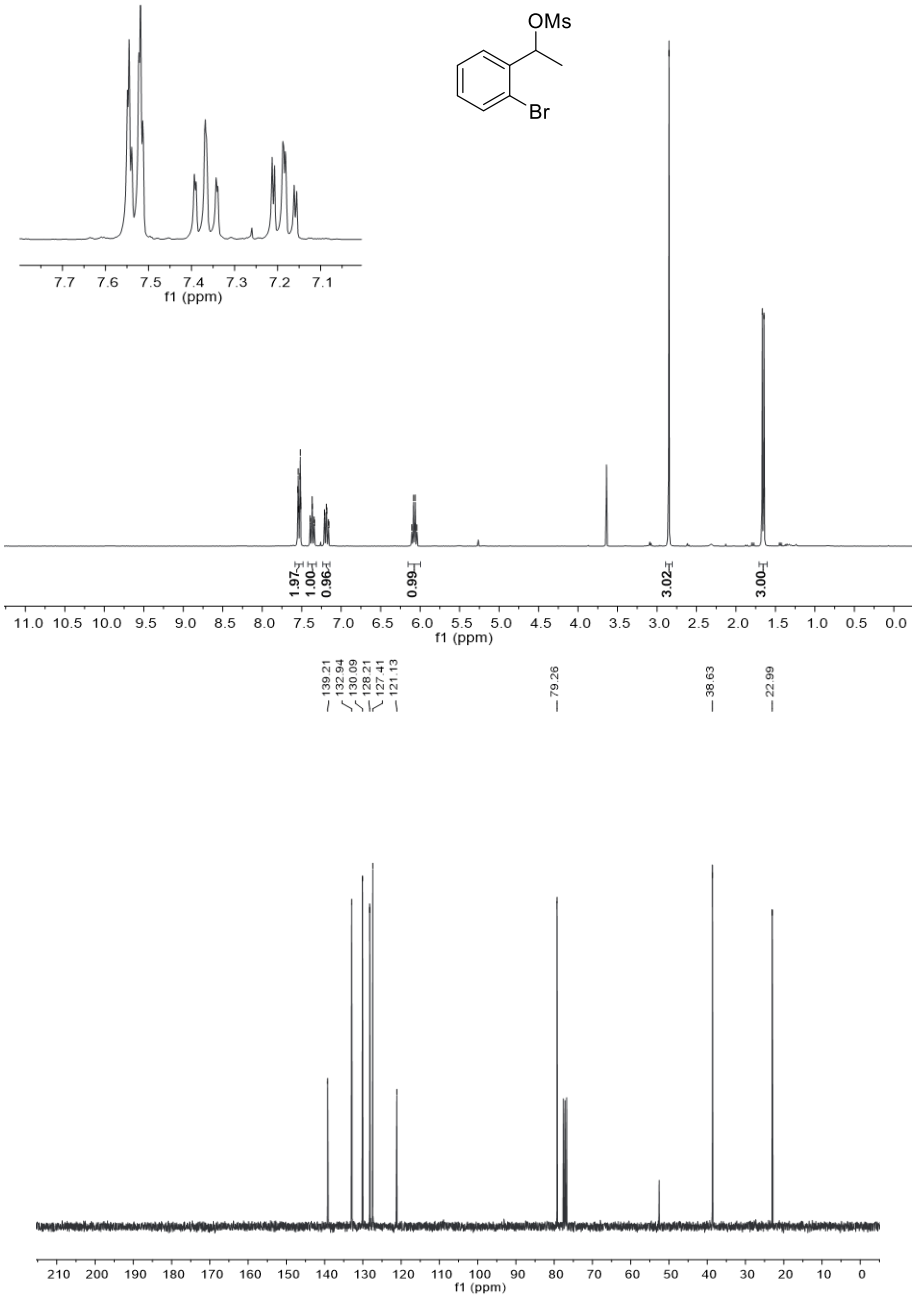
1b: Chloro-[2-(1*H*-pyrazole-κ*N*2)-6-(diisopropylphosphinito-κ*P*)-phenyl-κ*C*1]-Pd(II)



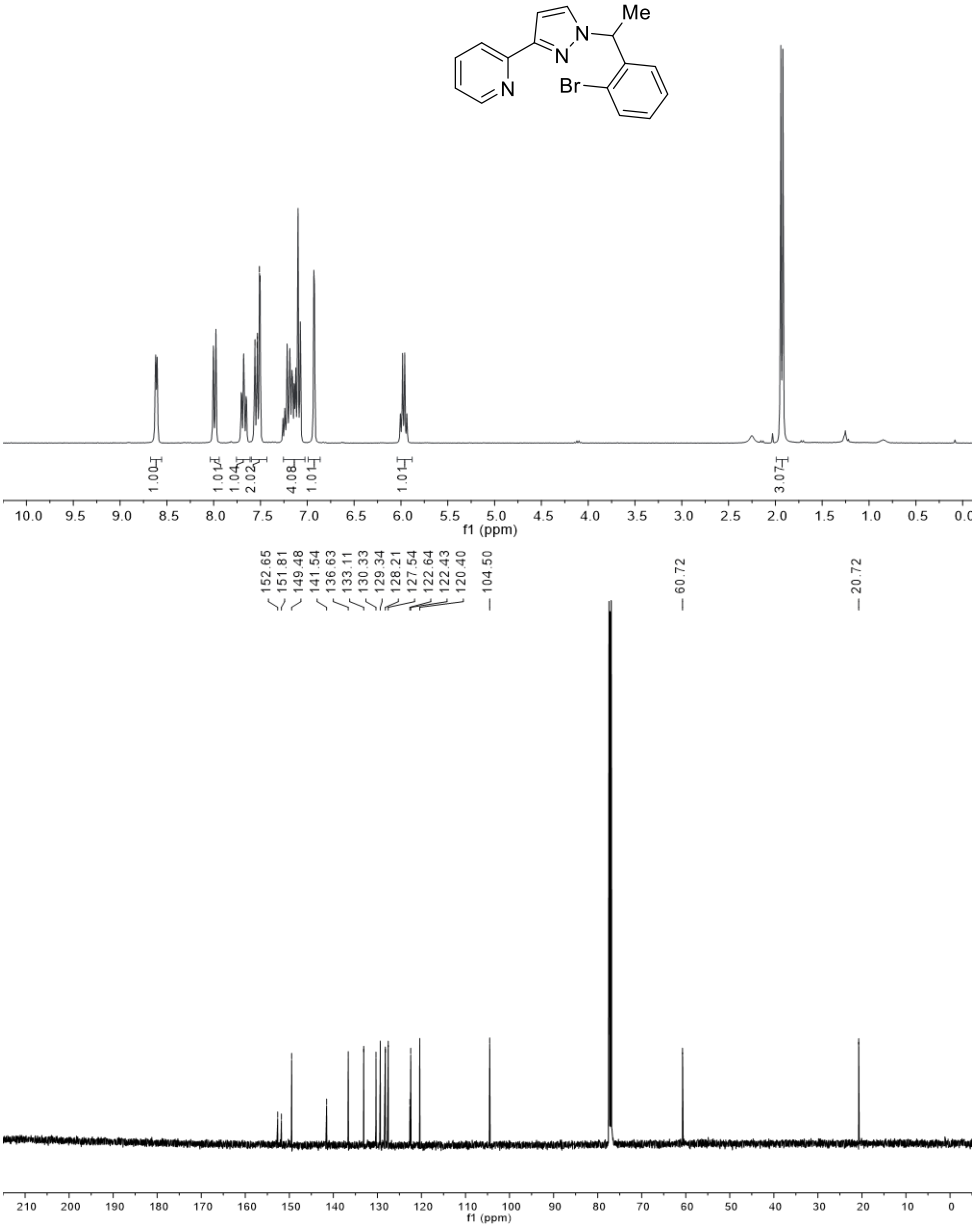
6: (*E*)-3-(Dimethylamino)-1-(pyridin-2-yl)prop-2-en-1-one



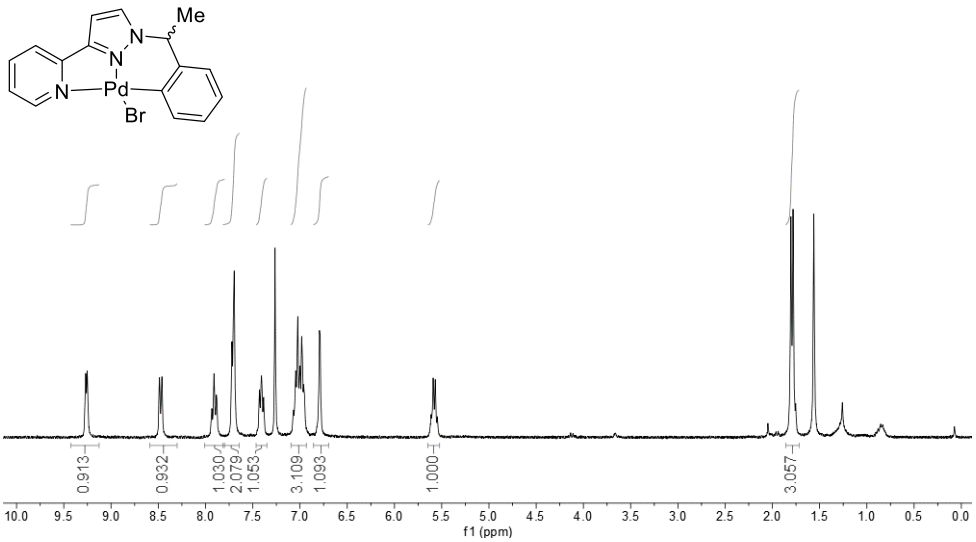
9: 1-(2-Bromophenyl)ethyl methanesulfonate

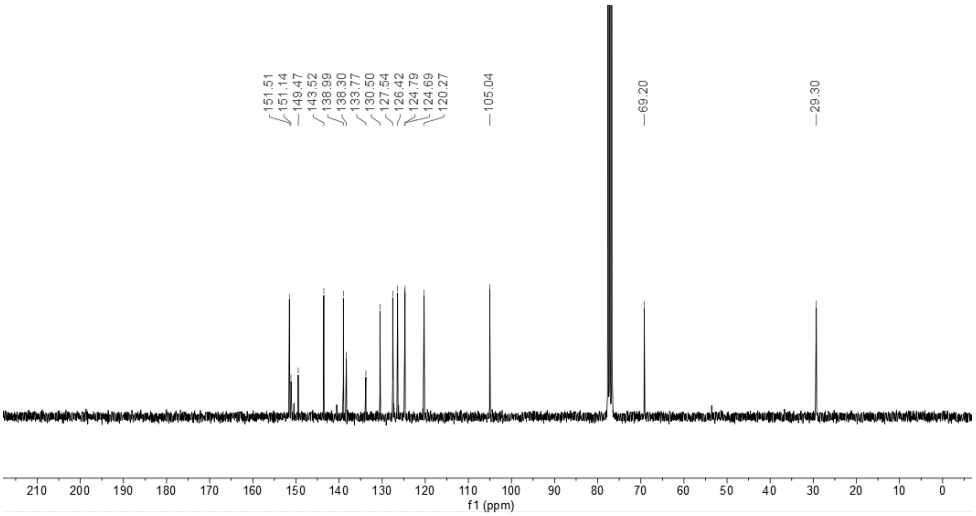


10: 2-[1-[1-(2-Bromophenyl)ethyl]-1*H*-pyrazol-3-yl]pyridine

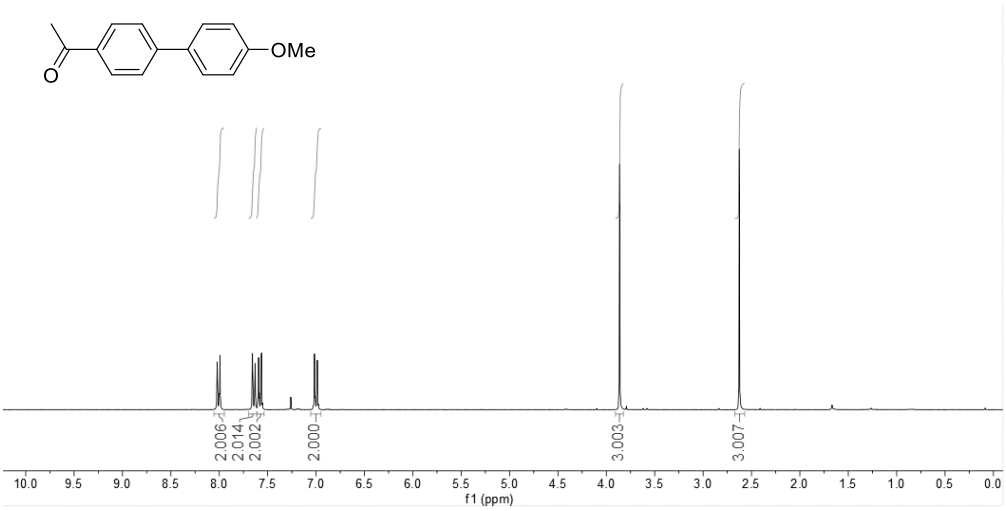


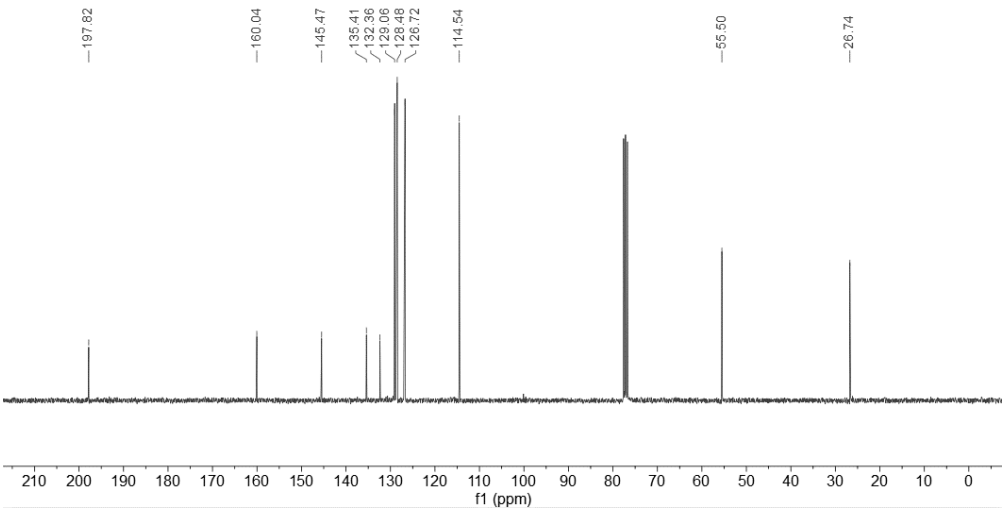
5: 2-[1-[1-(Phenyl-κ*C*2)ethyl]-1*H*-pyrazol-3-yl-κ*N*2]pyridine-κ*N*-palladium(II) bromide



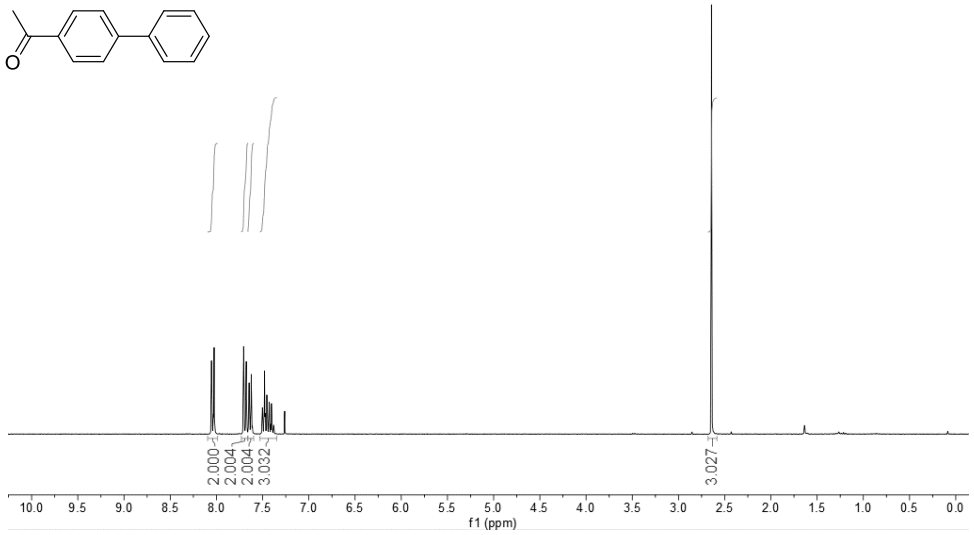


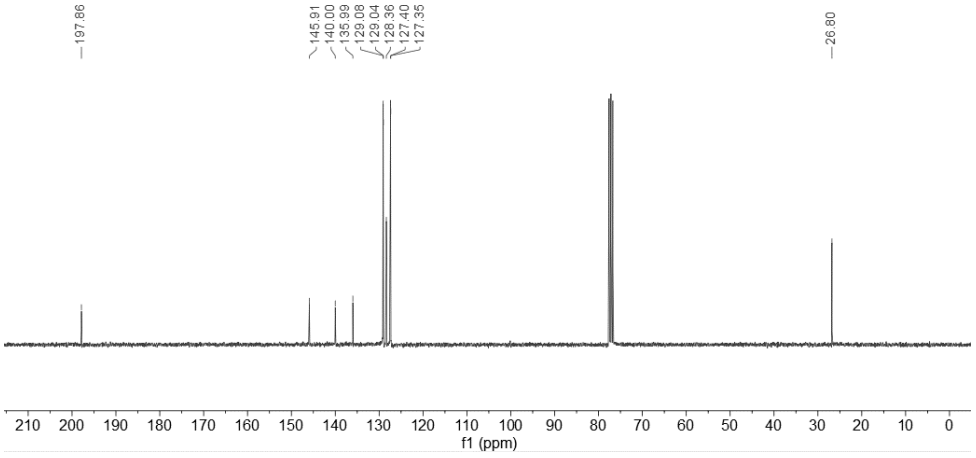
13a: 1-(4'-Methoxybiphenyl-4-yl)ethenone



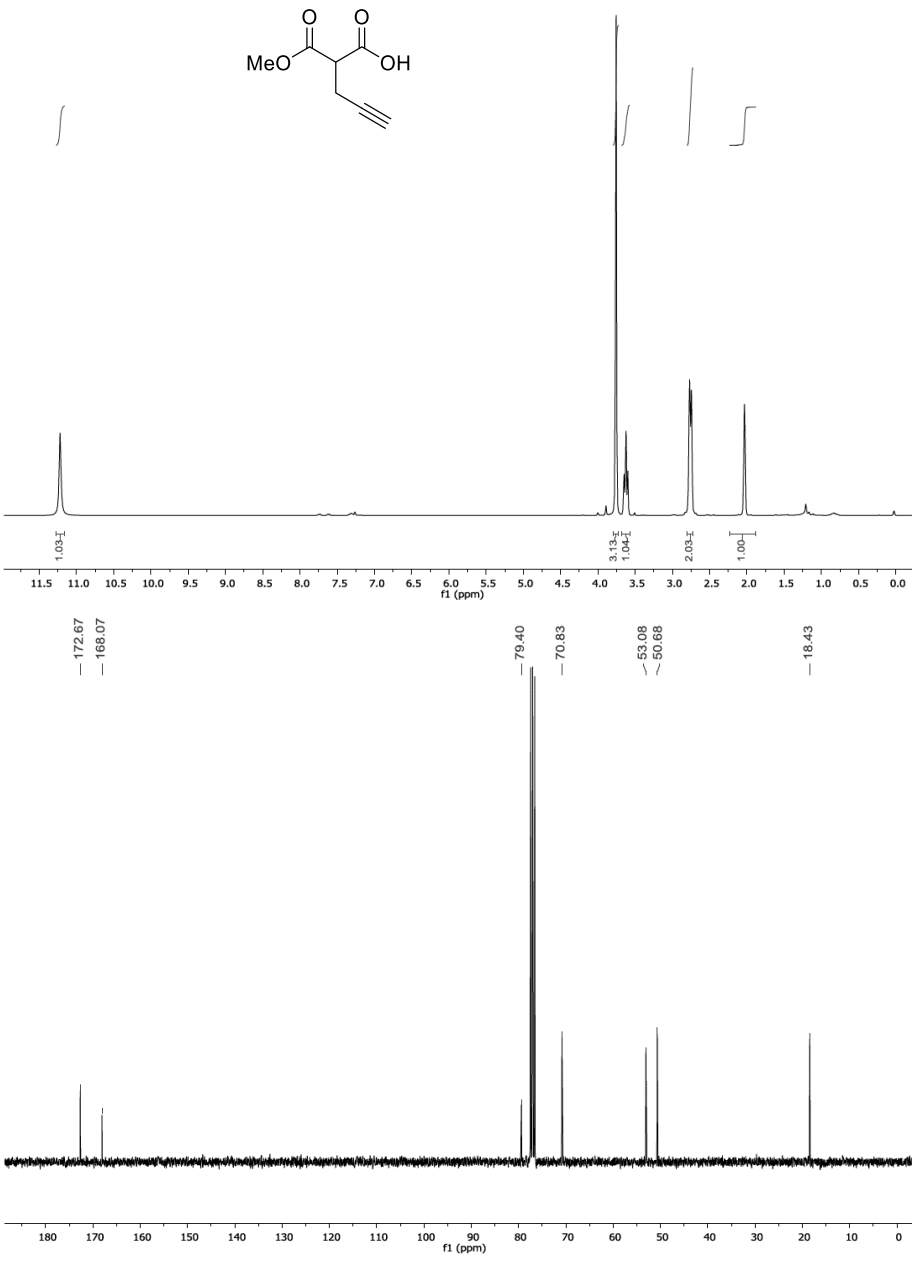


13c: 1-Biphenyl-4-yl-ethanone

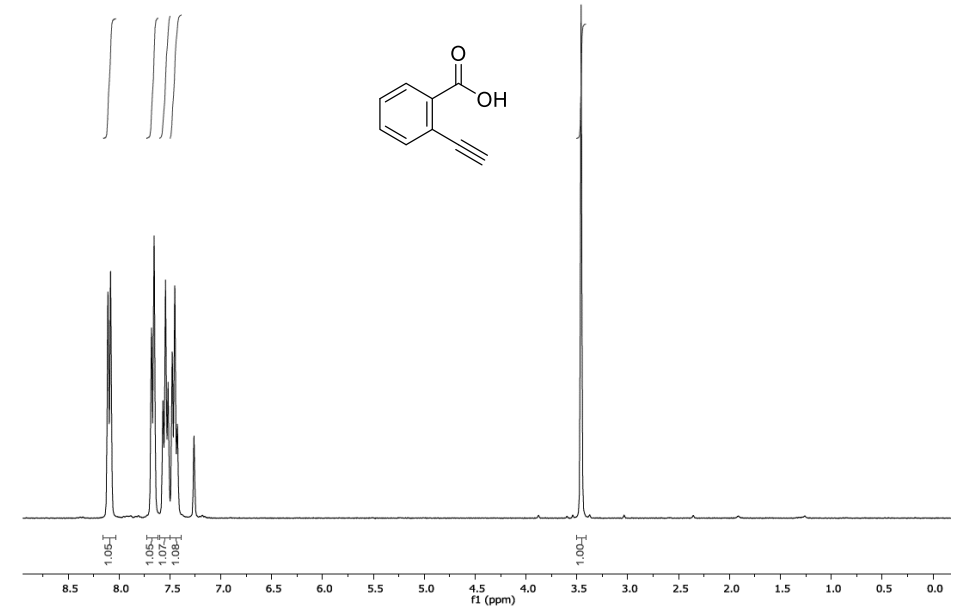


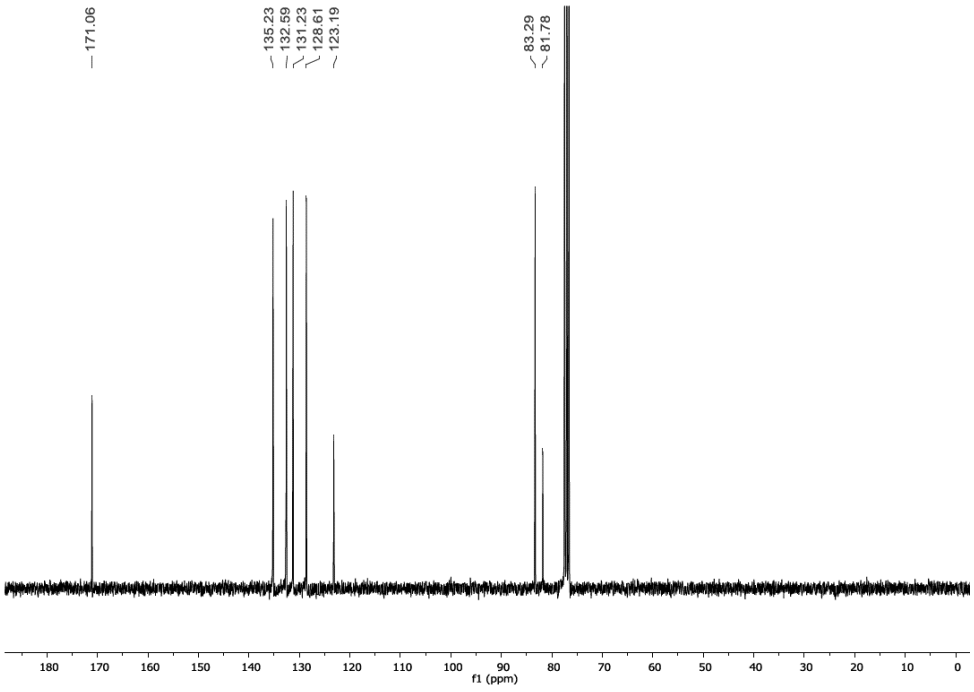


14c: 2-(Methoxycarbonyl)-4-pentynoic acid

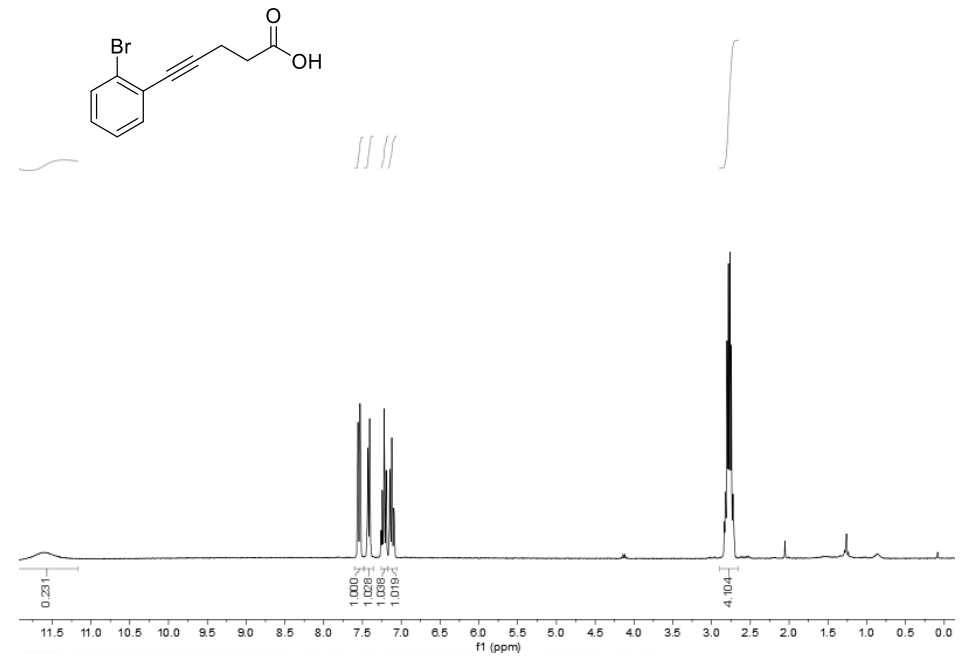


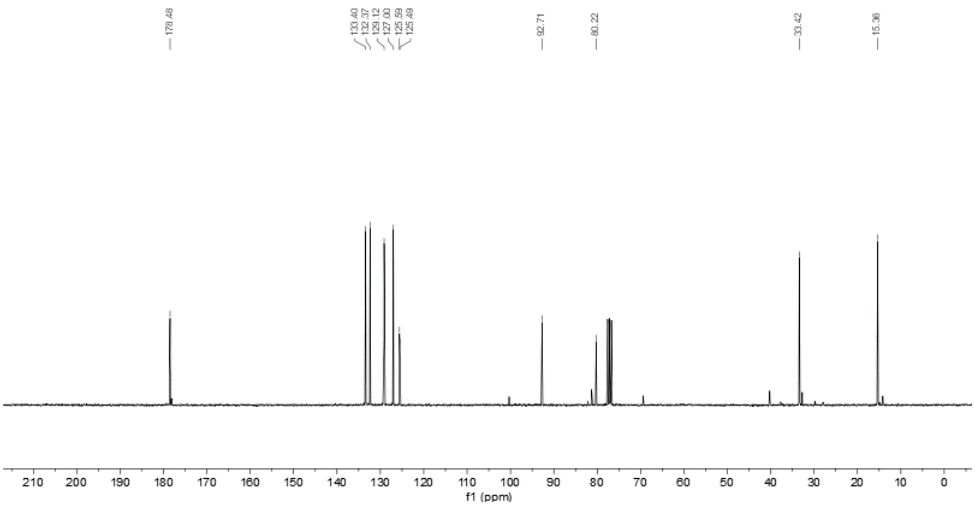
14d: 2-Ethynylbenzoic acid



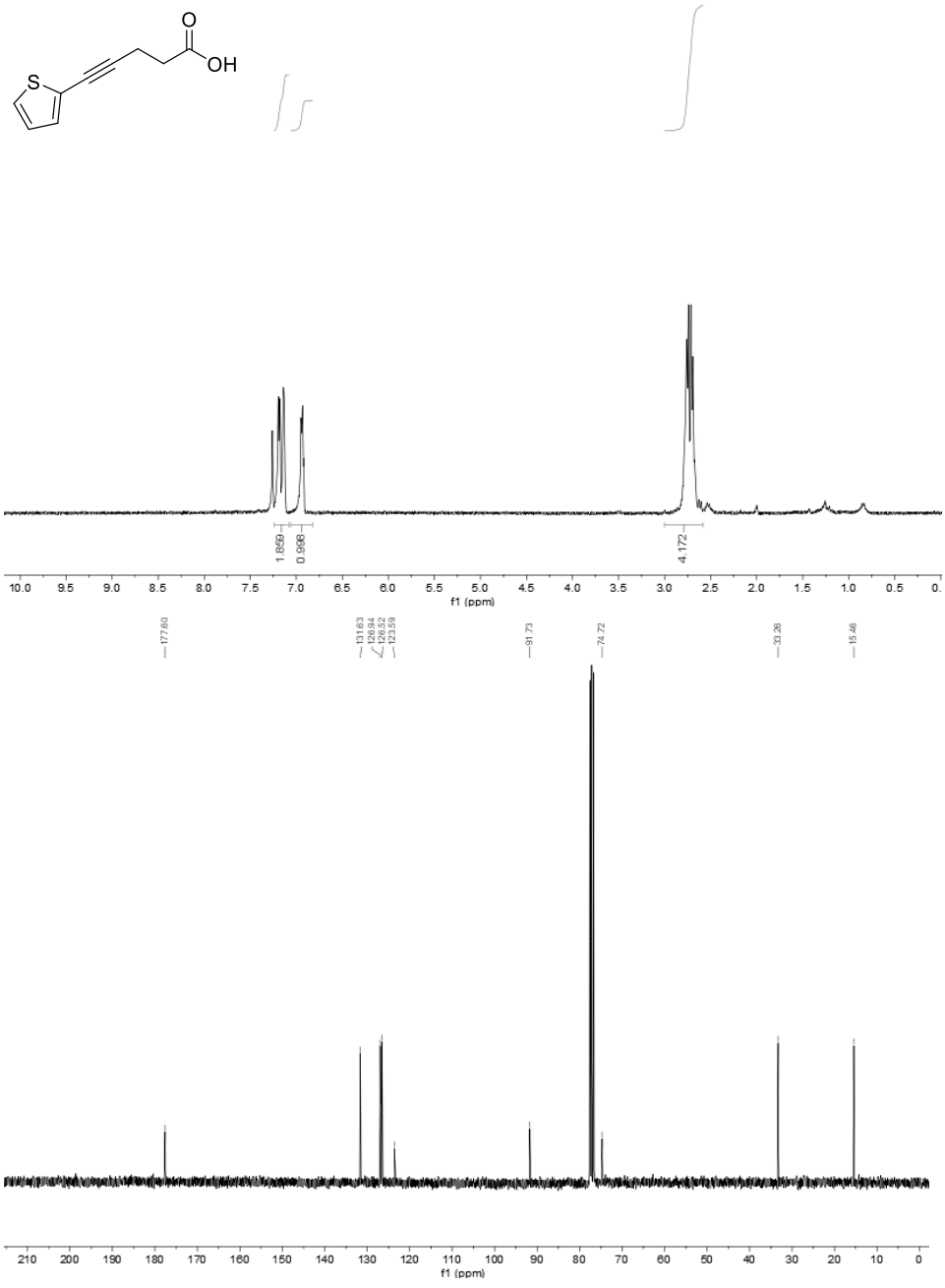


14g: 5-(2-Bromophenyl)pent-4-ynoic acid

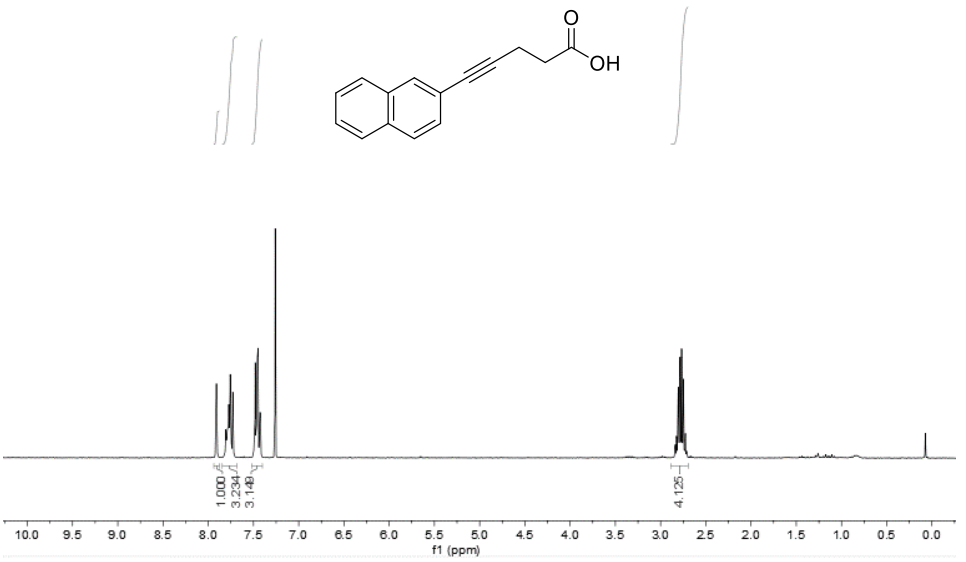


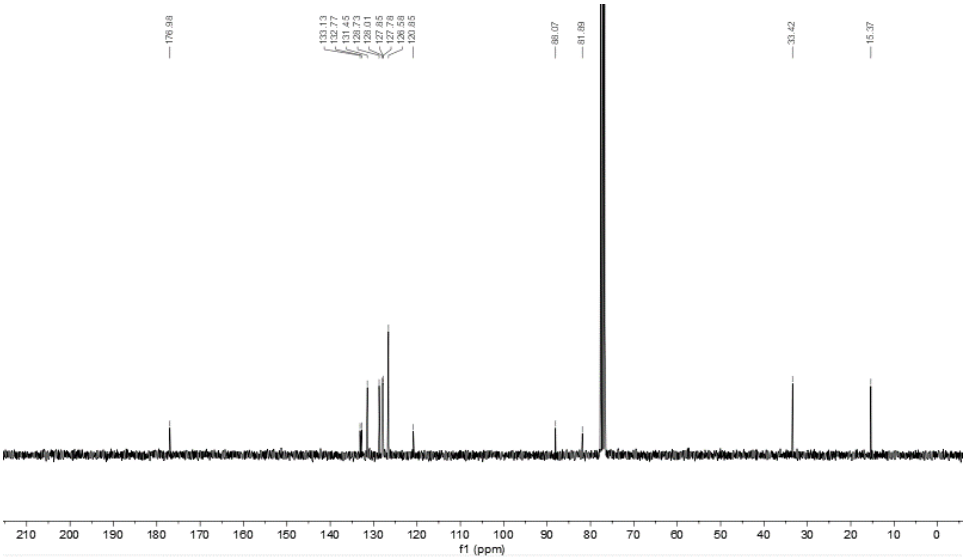


14h: 5-(Thiophen-2-yl)pent-4-ynoic acid

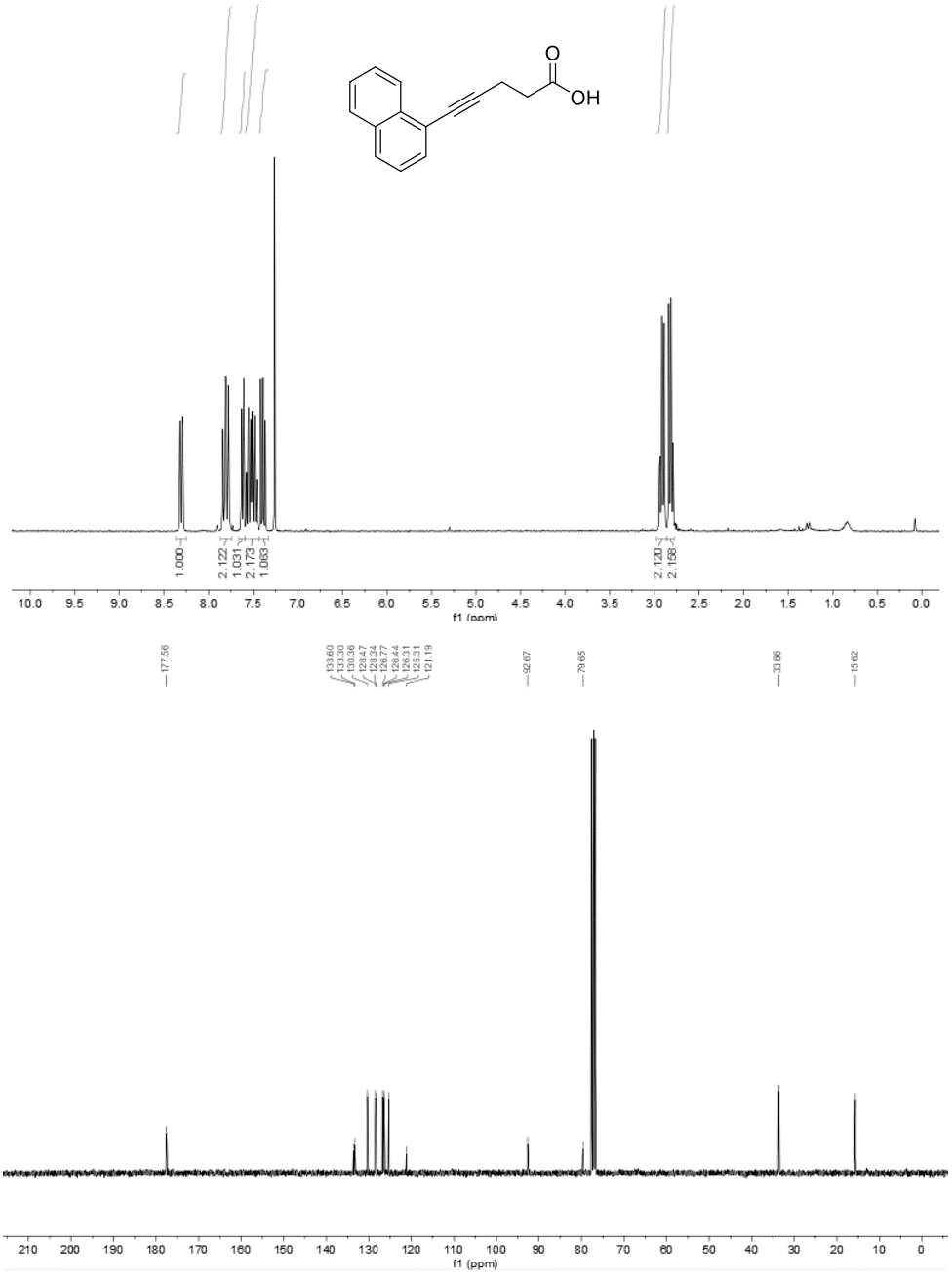


14i: 5-(Naphthalen-2-yl)pent-4-ynoic acid

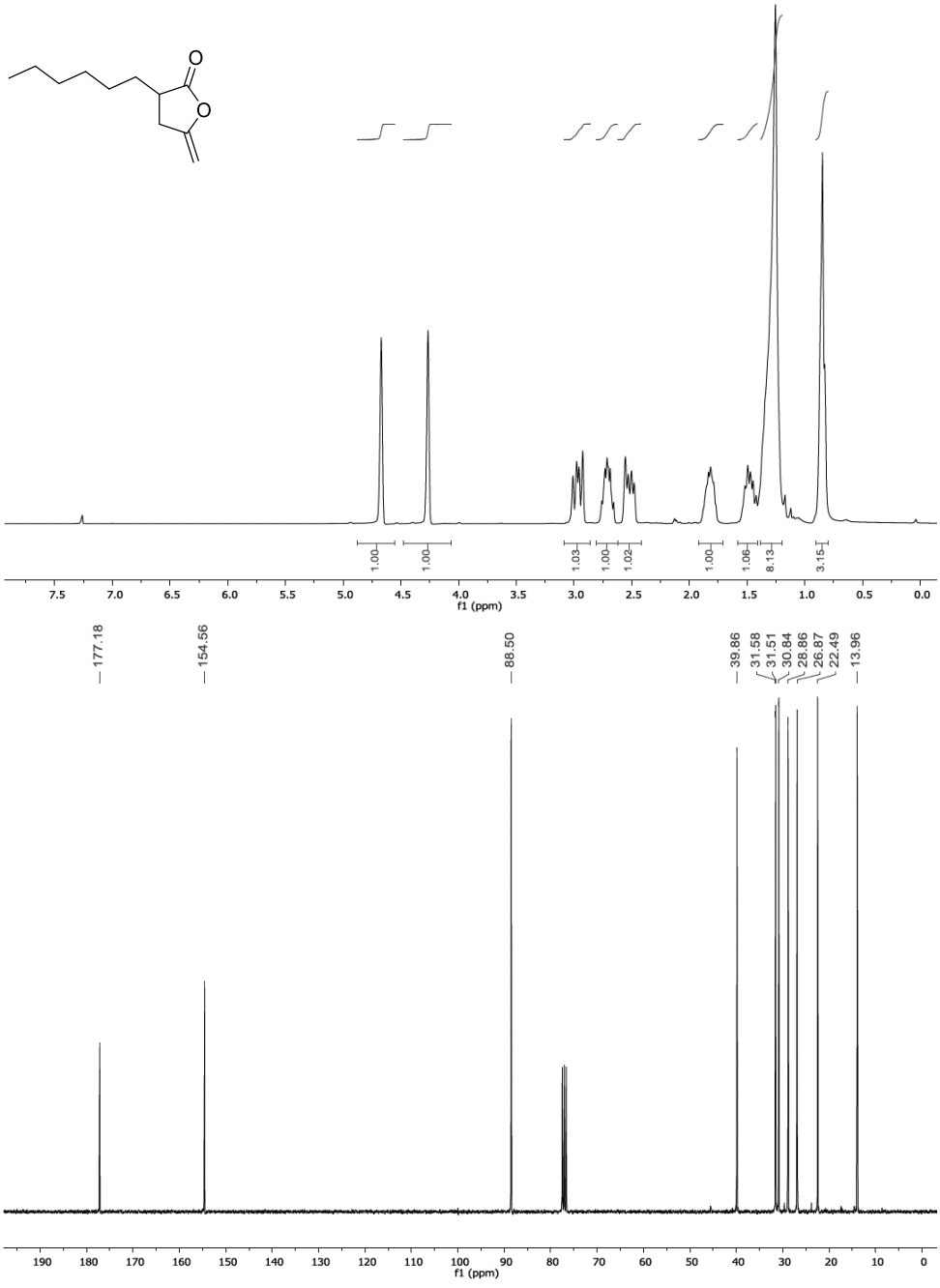




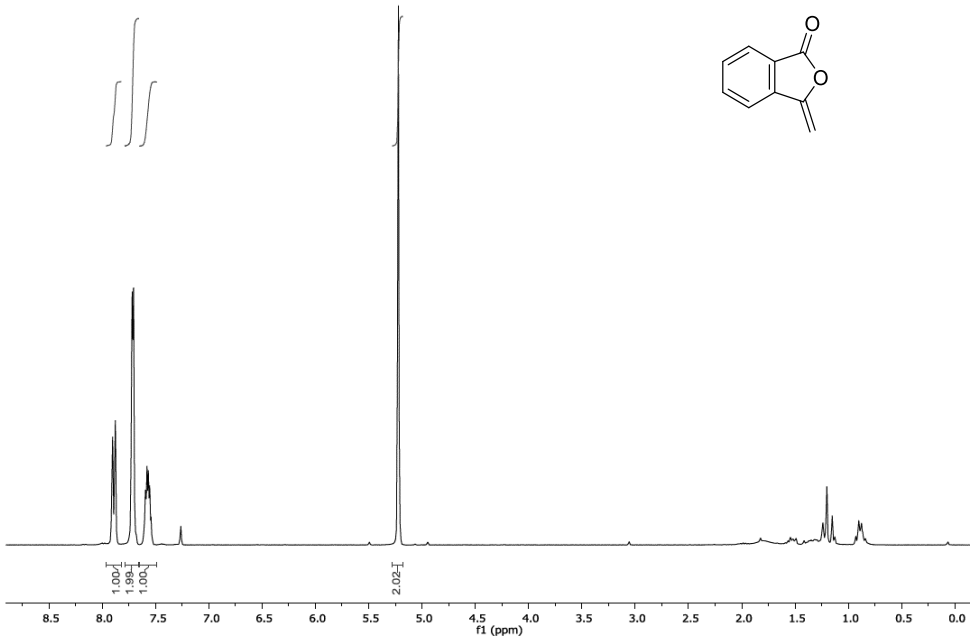
14j: 5-(Naphthalen-1-yl)pent-4-ynoic acid

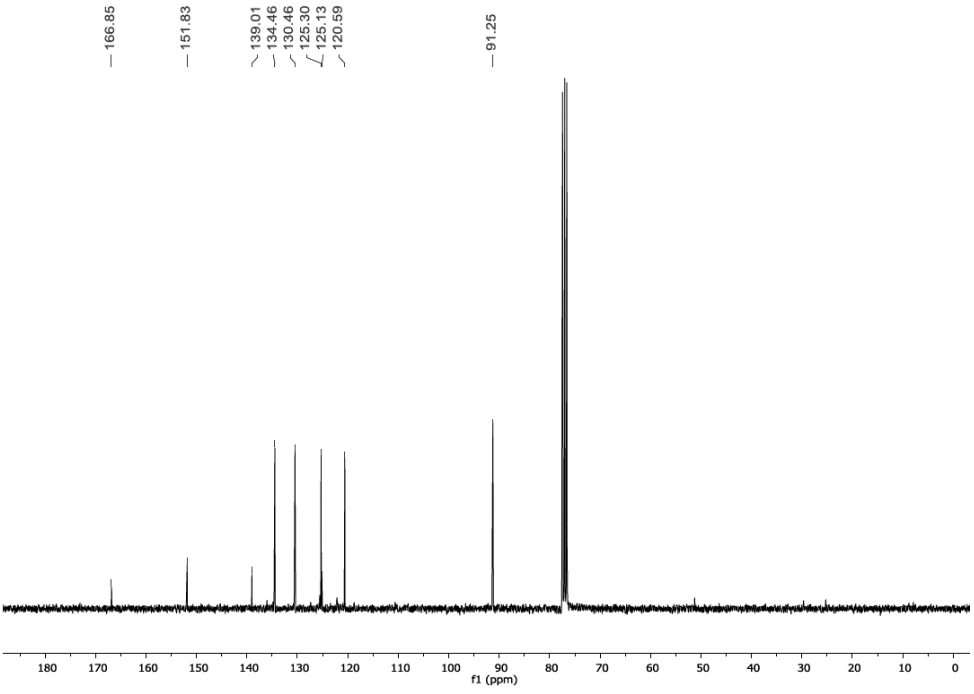


15b: 3-Hexyl-5-methylenedihydrofuran-2(3*H*)-one

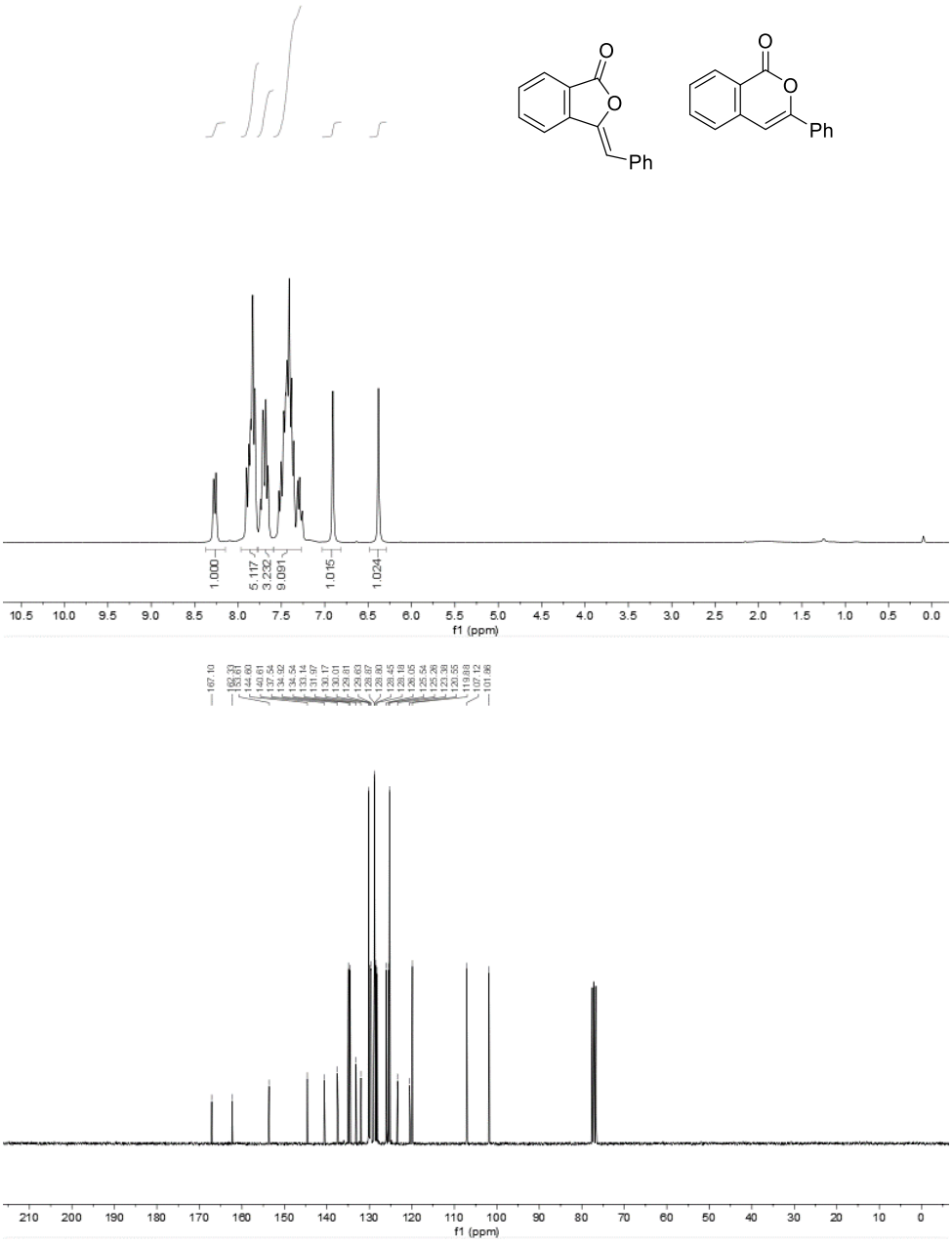


15d: 3-Methyleneisobenzofuran-1(3*H*)-one

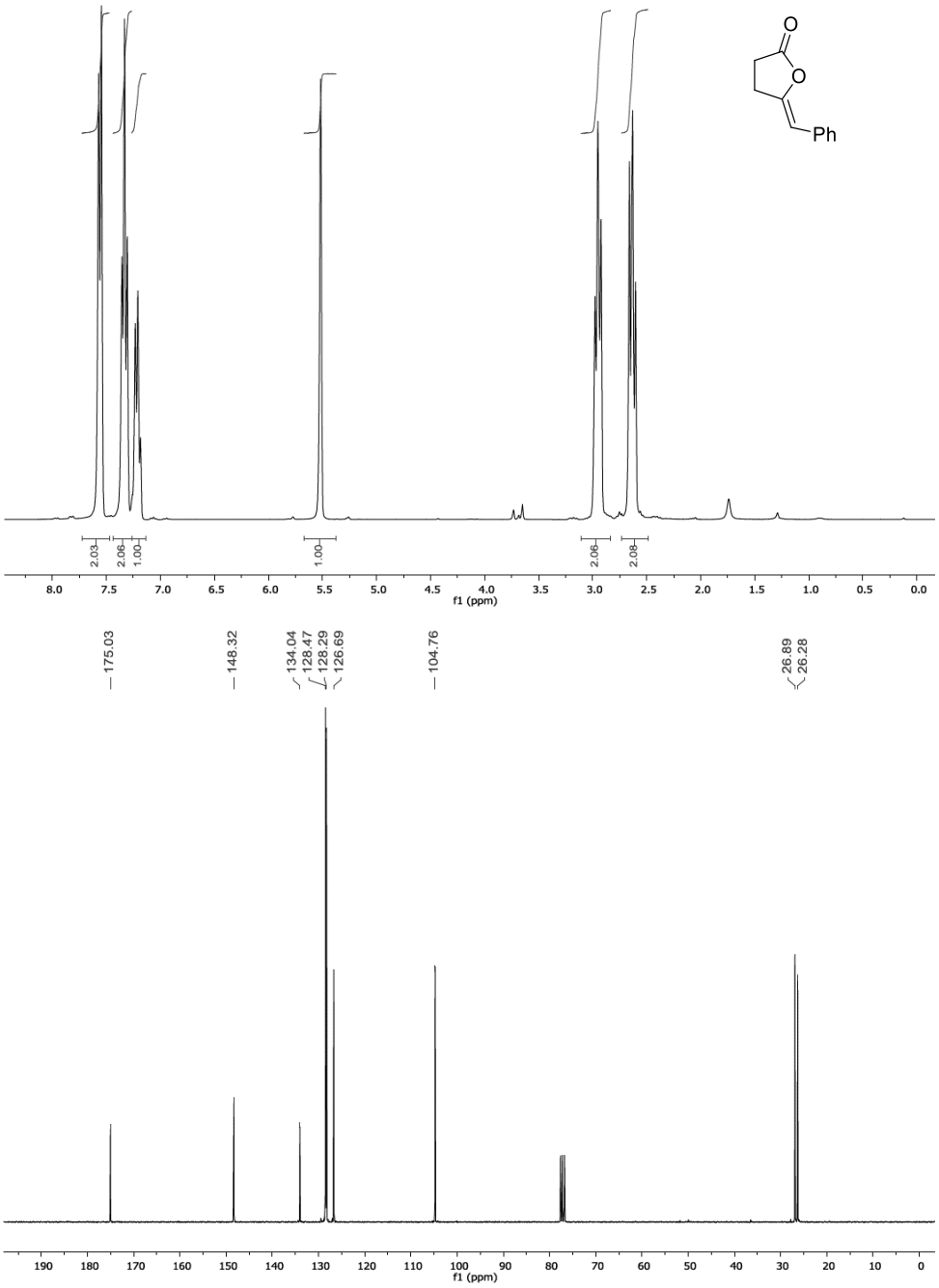




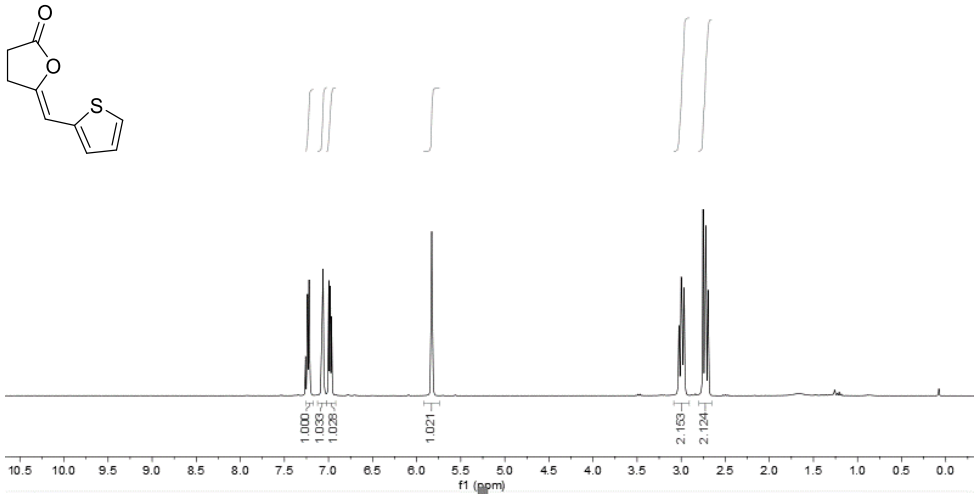
15e & 15e': (*Z*)-3-Benzylideneisobenzofuran-1(3H)-one & 3-Phenyl-1H-isochromen-1-one (15e´)

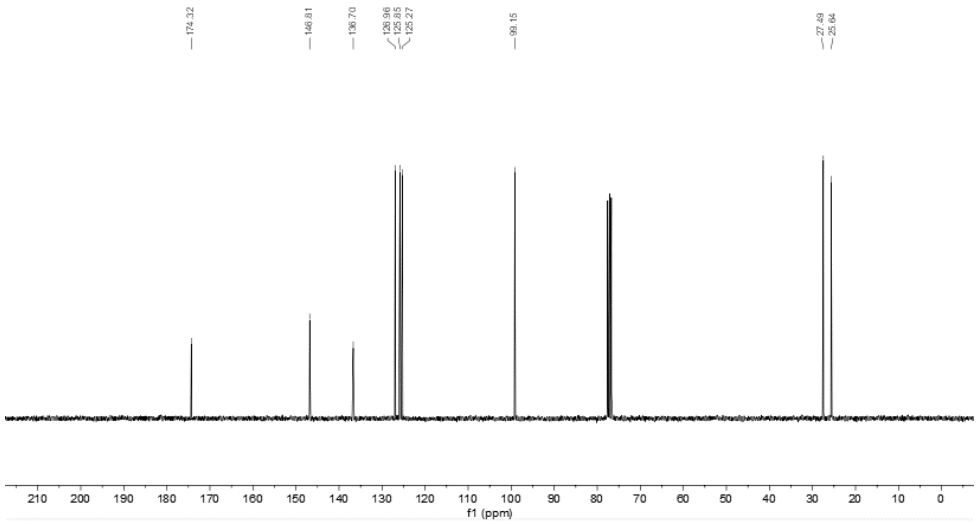


15f: (*Z*)-5-Benzylidenedihydrofuran-2(3*H*)-one

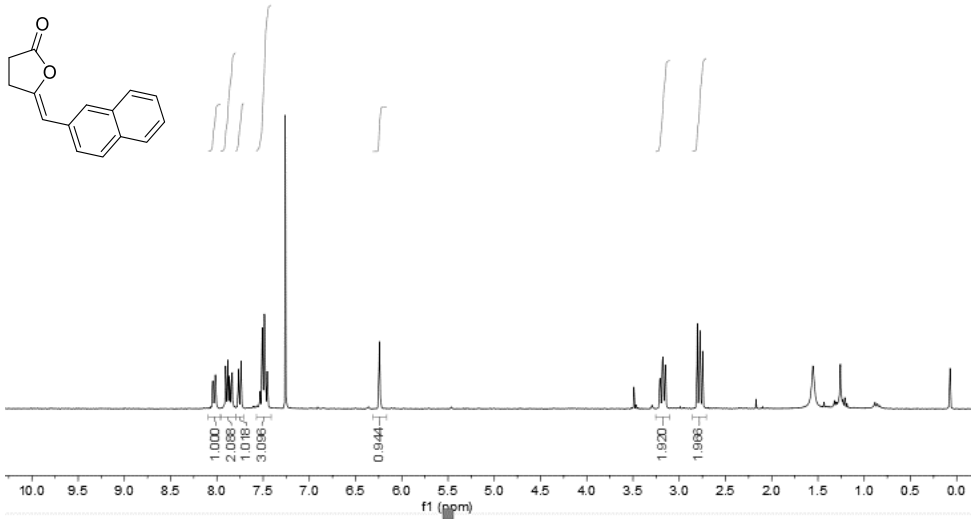


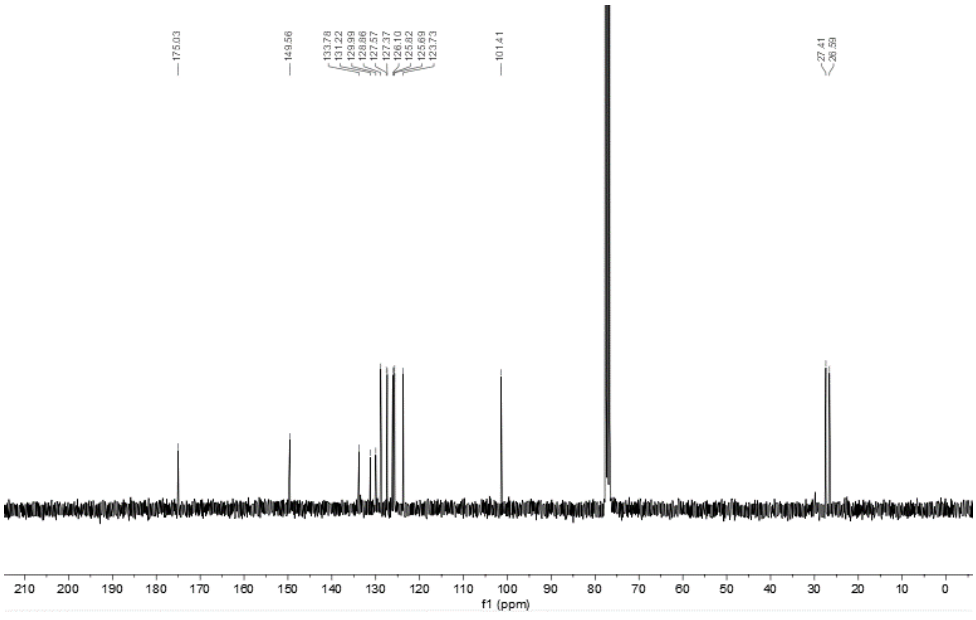
15h: (*Z*)-5-(Thiophen-2-ylmethylene)dihydrofuran-2(3H)-one



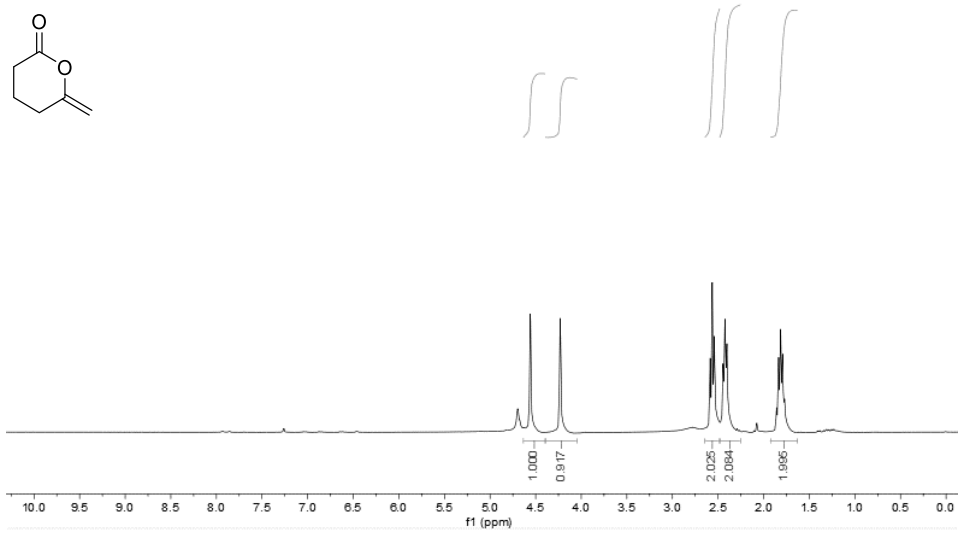


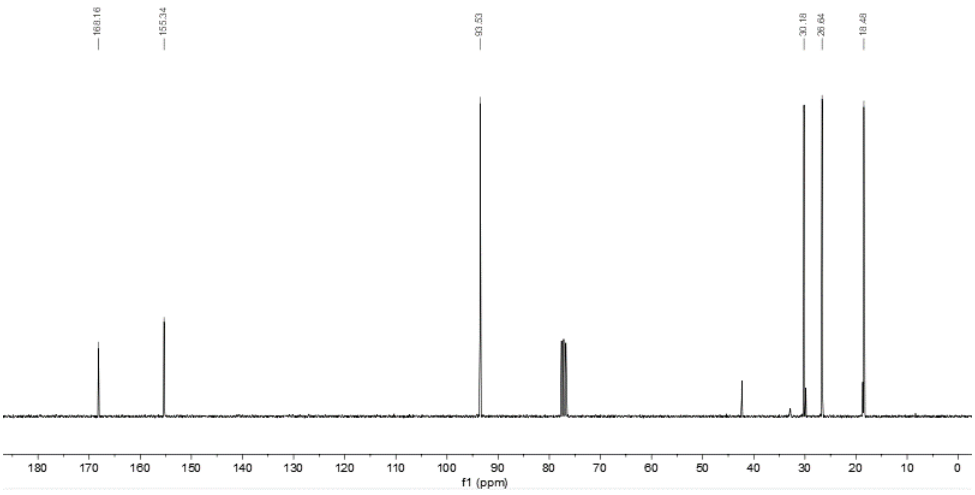
15i: (*Z*)-5-(Naphthalen-2-ylmethylene)dihydrofuran-2(3*H*)-one



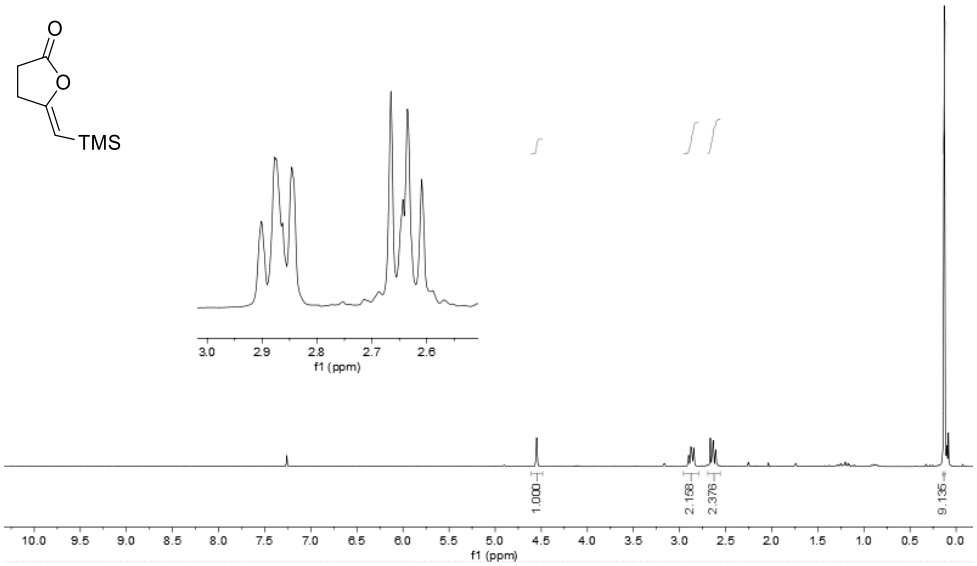


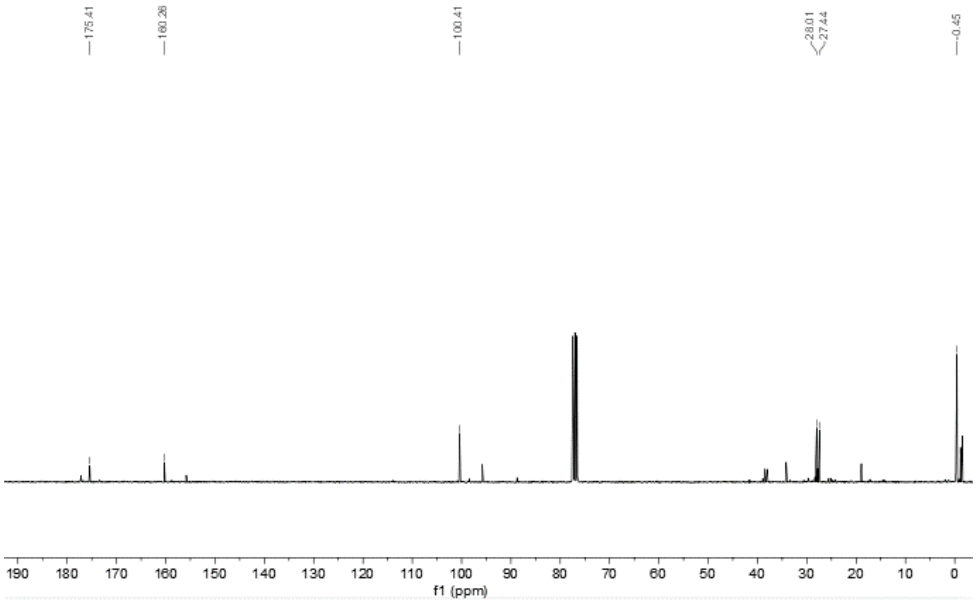
15k: 6-Methylenetetrahydro-2*H*-pyran-2-one



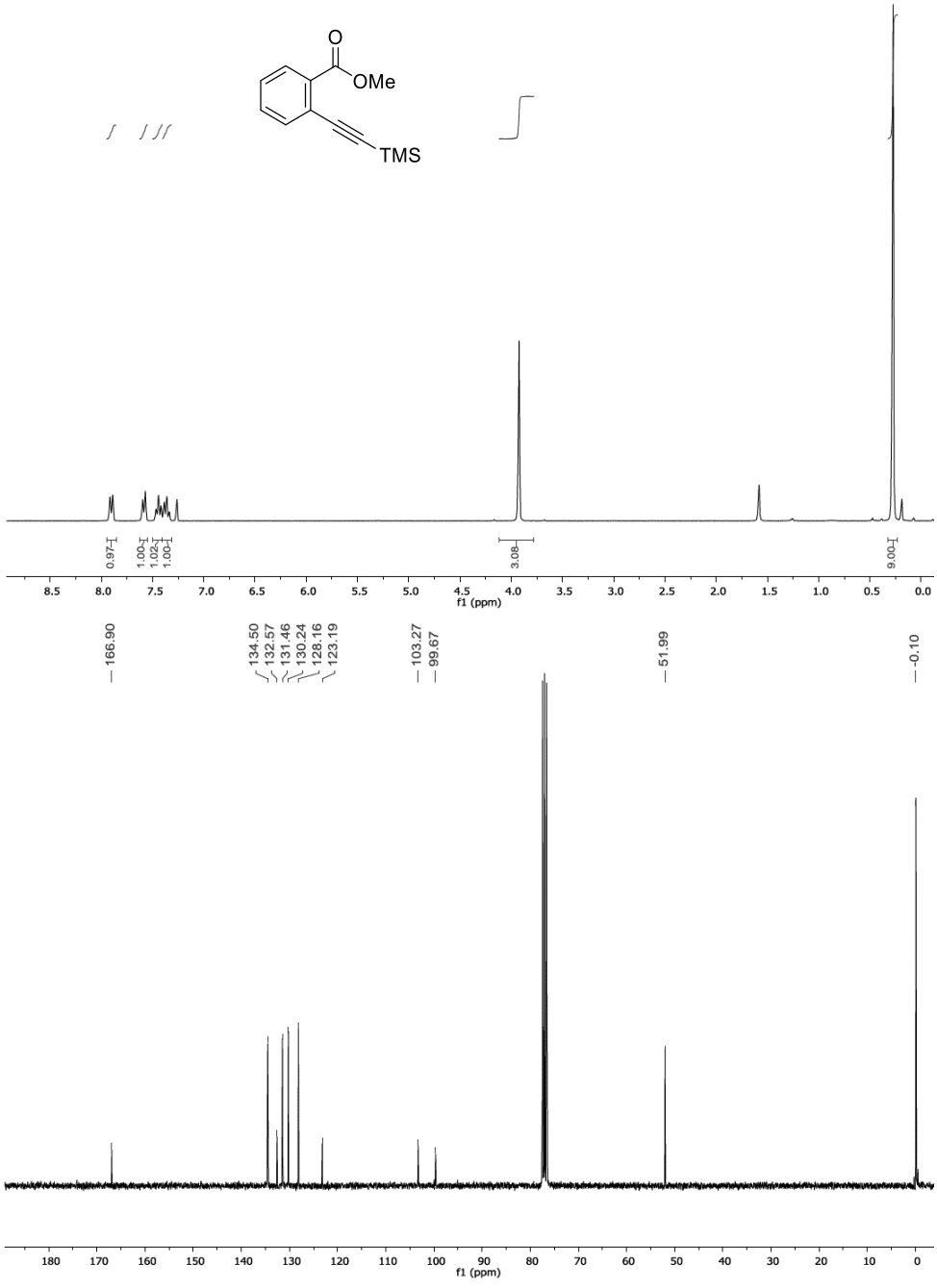


15n: (*Z*)-5-[(Trimethylsilyl)methylene]dihydrofuran-2(3*H*)-one

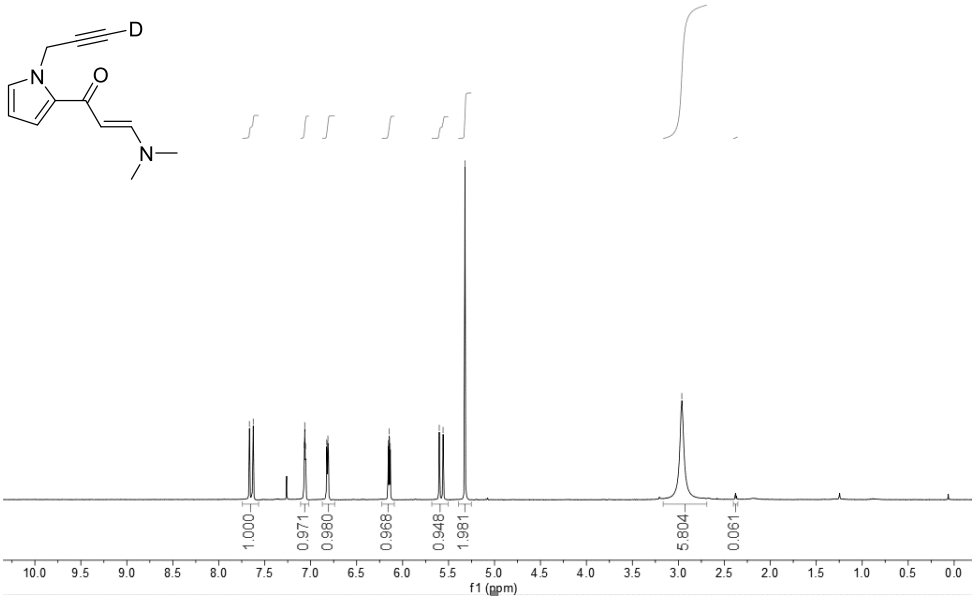


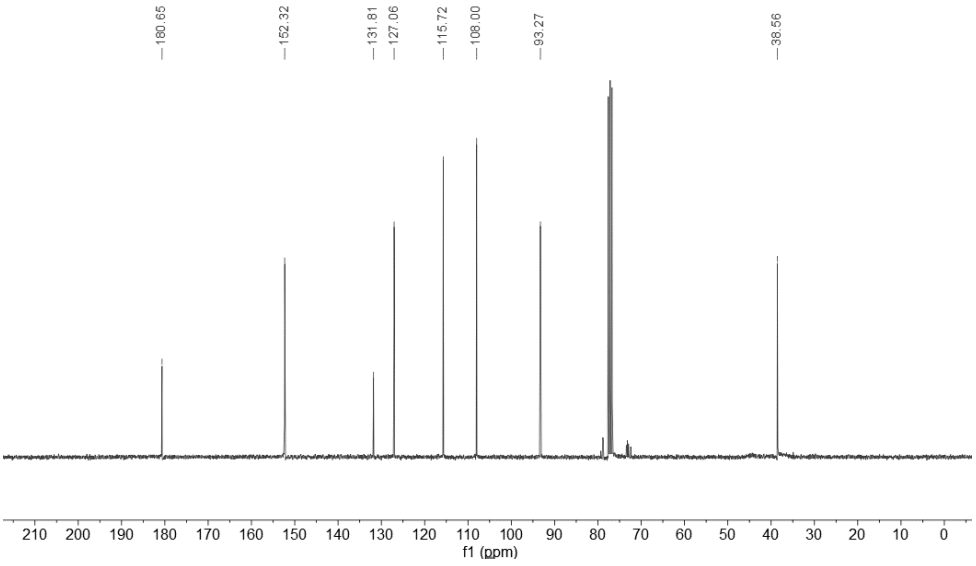


17a: Methyl 2-[(trimethylsilyl)ethynyl]benzoate

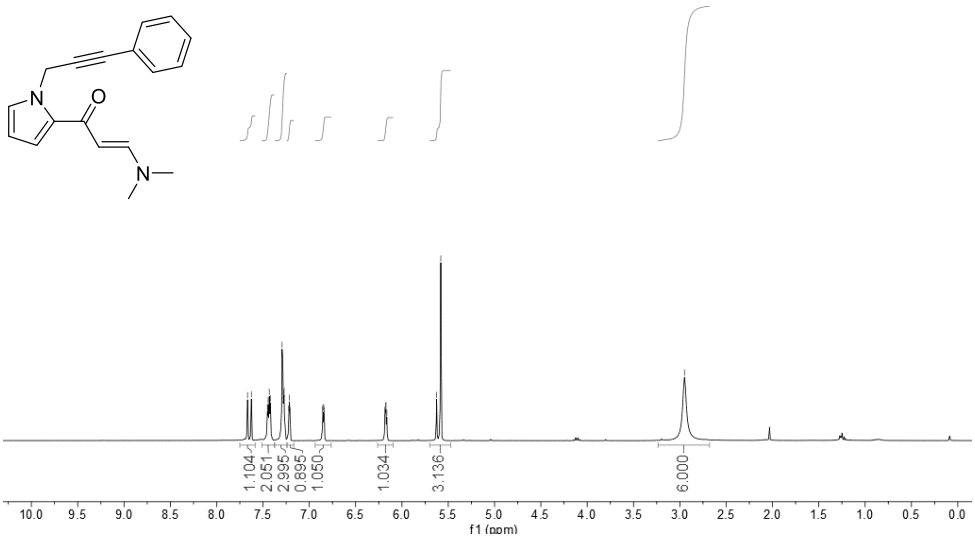


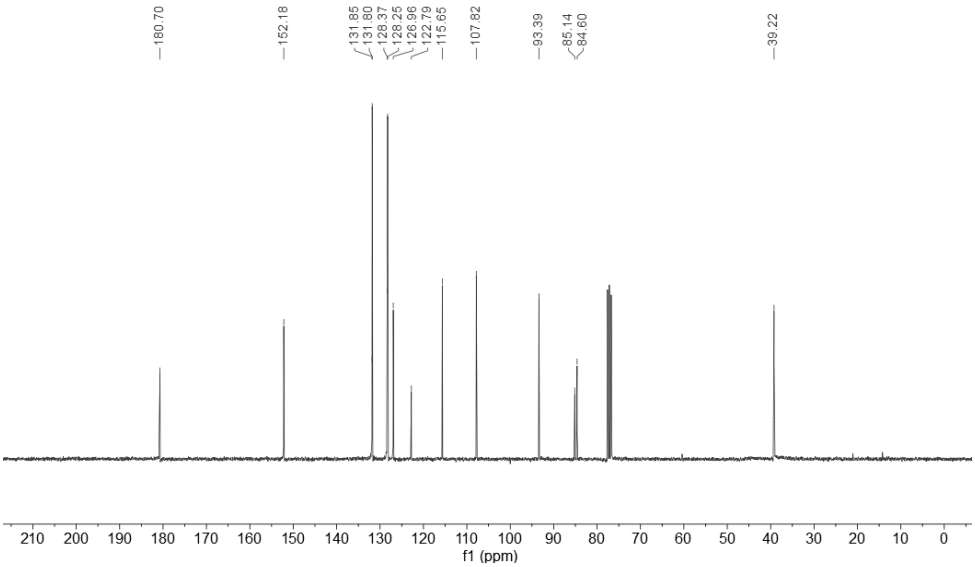
19a-D: (*E*)-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl-3-*d*)-1*H*-pyrrol-2-yl]prop-2-en-1-one



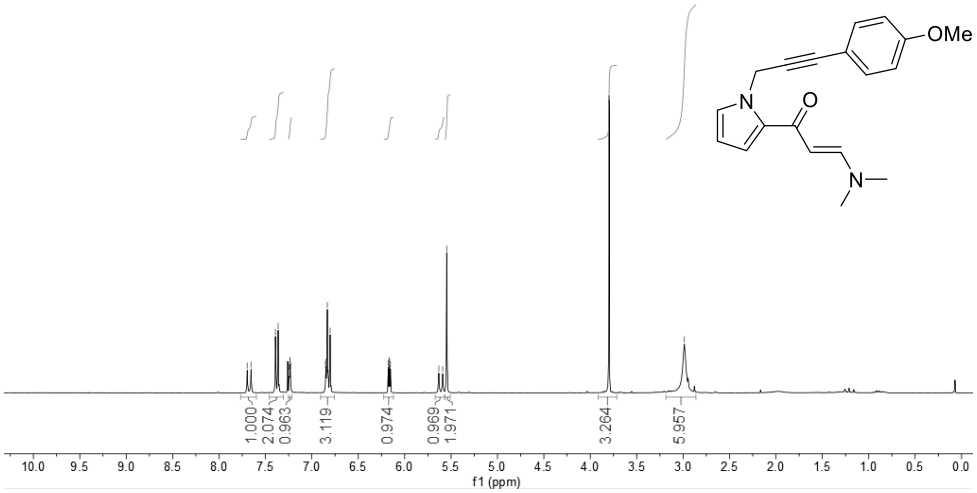


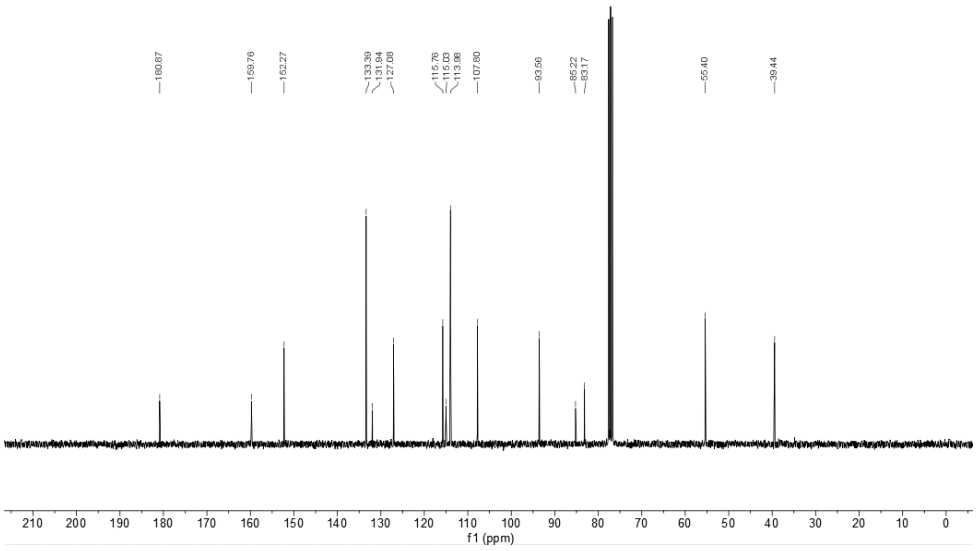
19b: (*E*)-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl]-1*H*-pyrrol-2-yl)prop-2-en-1-one



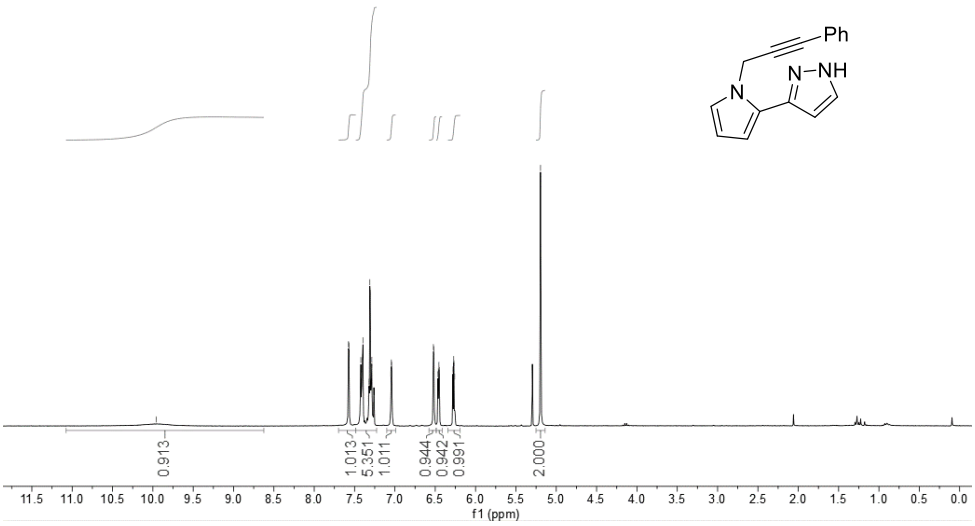


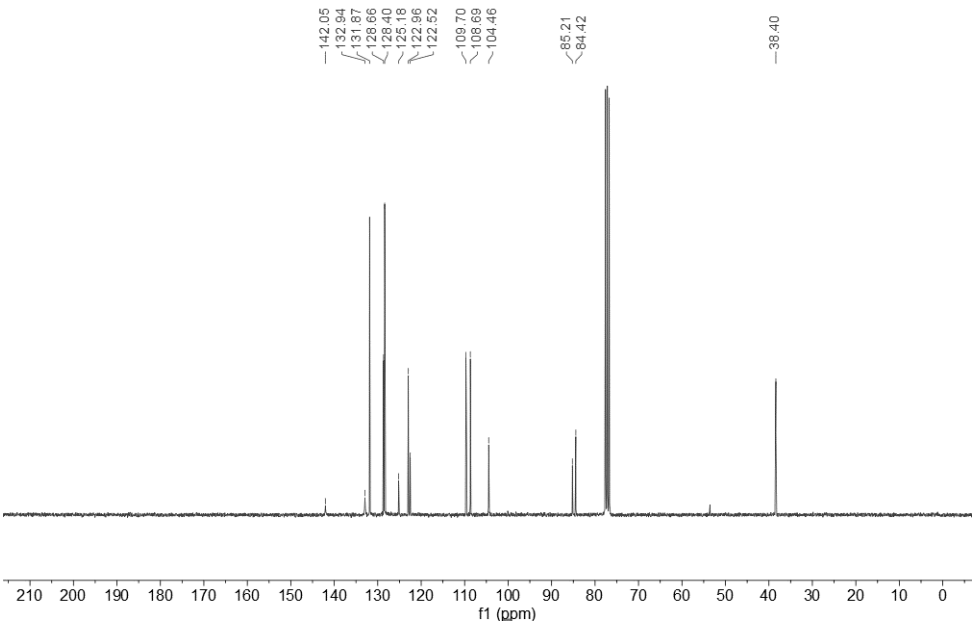
19d: (*E*)-3-(Dimethylamino)-1-[1-[3-(4-methoxyphenyl)prop-2-yn-1-yl]-1*H*-pyrrol-2-yl]prop-2-en-1-one



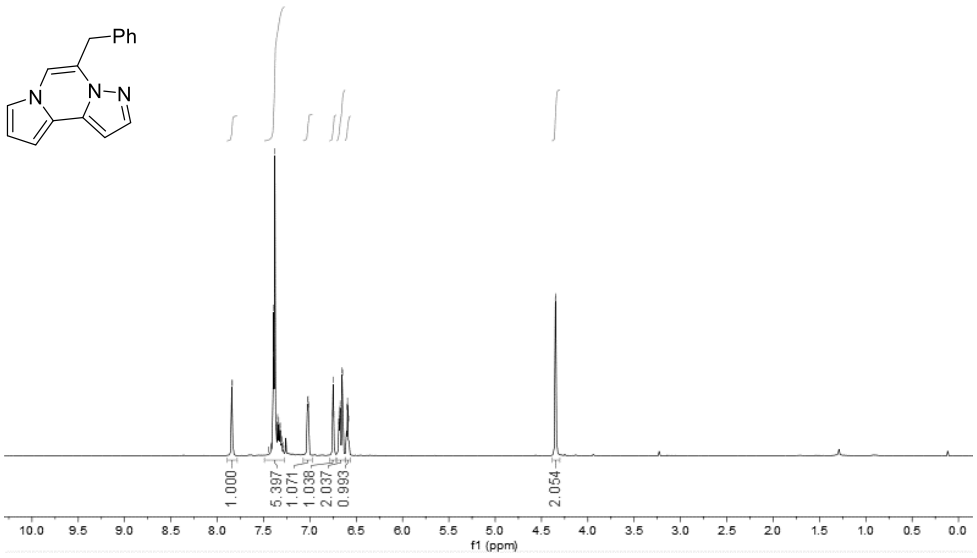


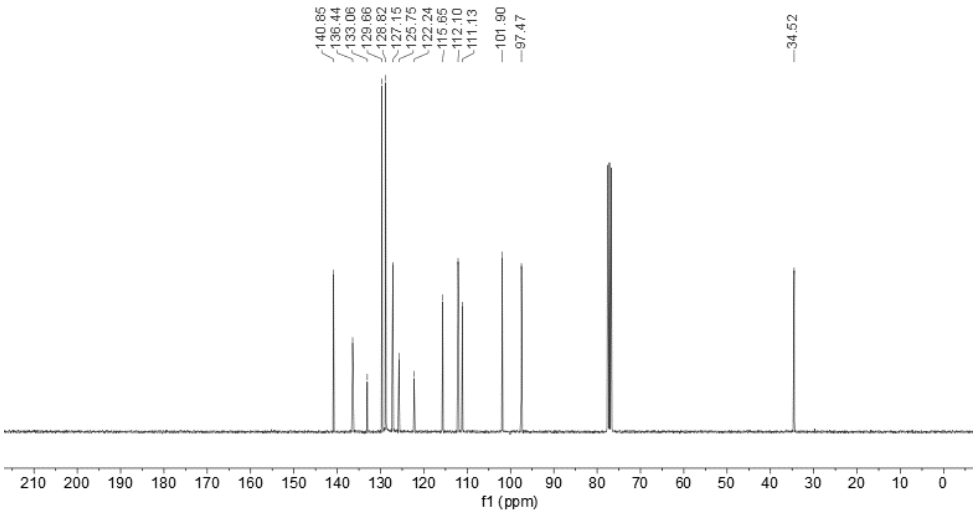
20b: 3-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-pyrrol-2-yl]-1*H*-pyrazole



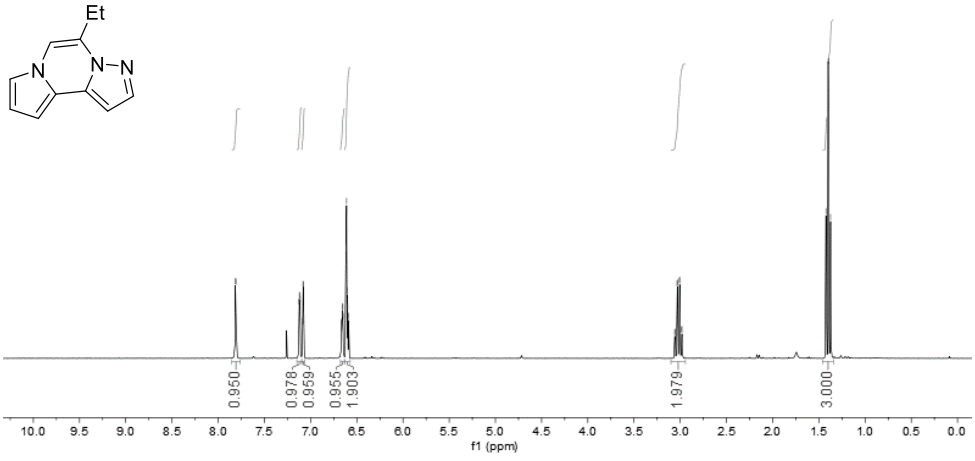


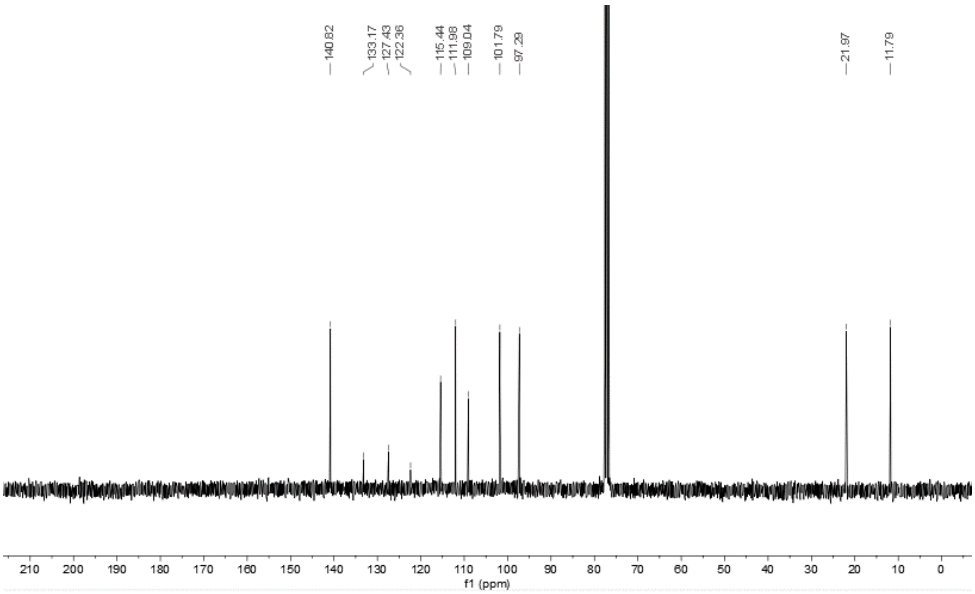
21b: 5-Benzylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine



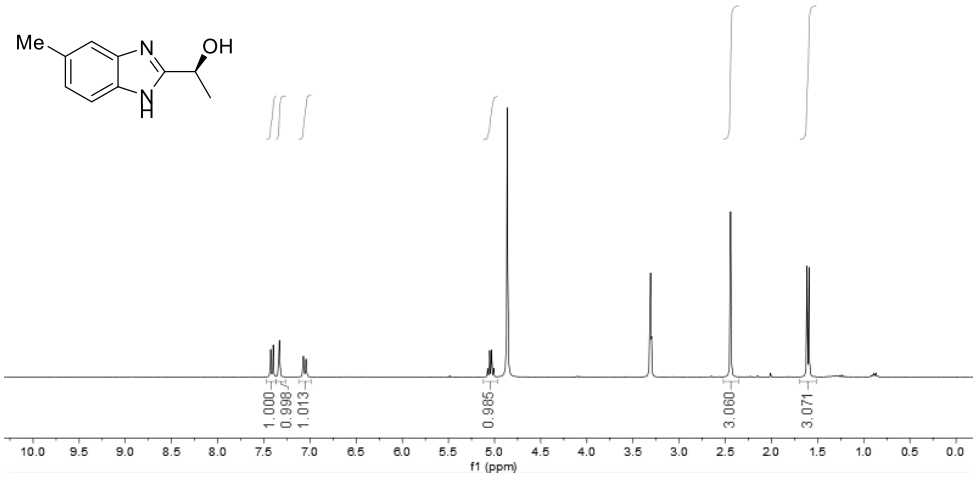


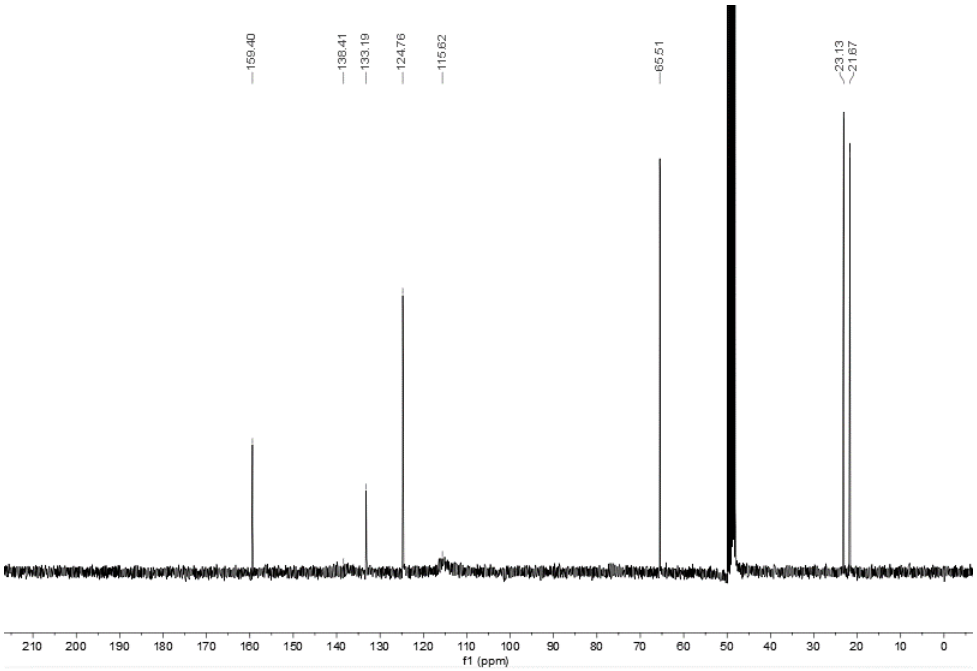
21c: 5-Ethylpyrazolo[1,5-*a*]pyrrolo[2,1-*c*]pyrazine



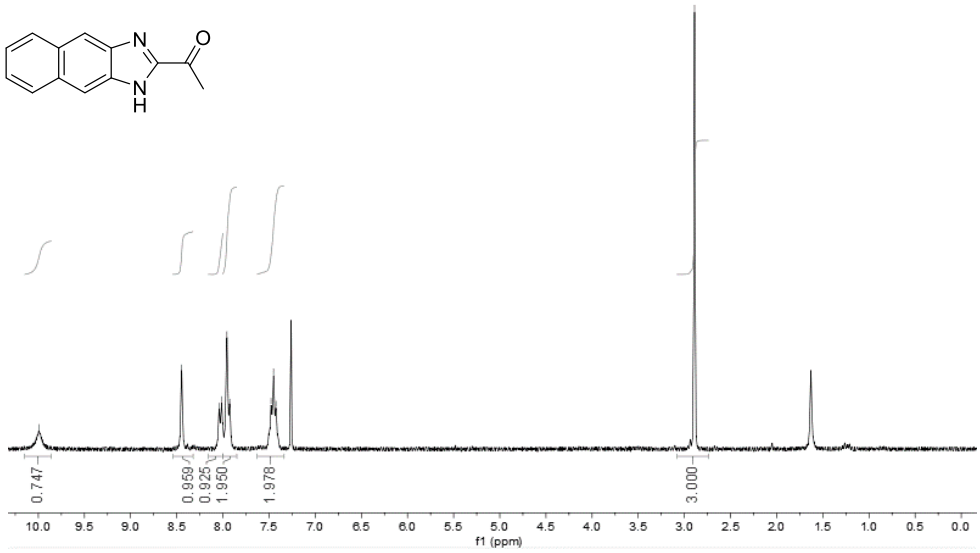


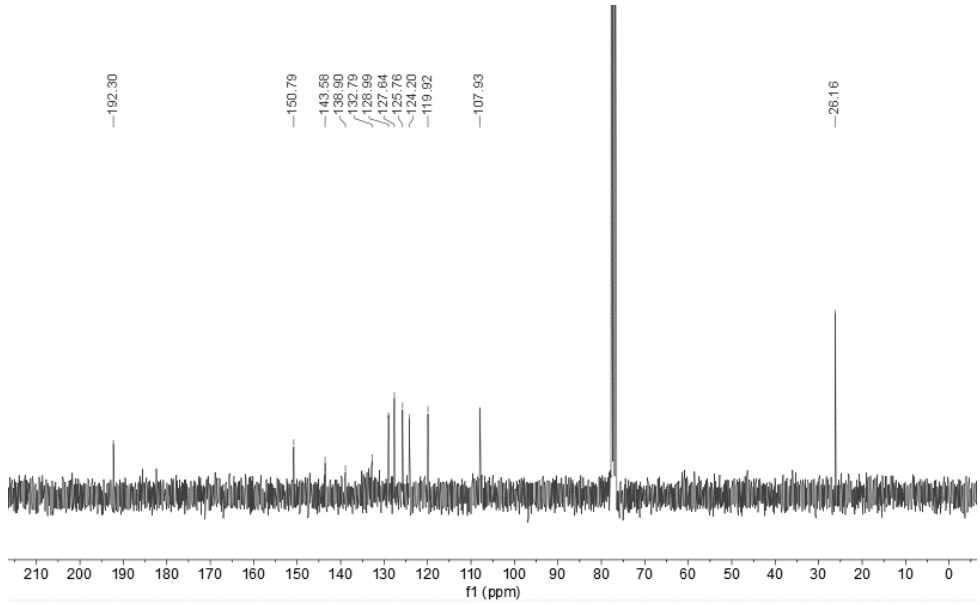
25b: (*S*)-1-(5-Methyl-1*H*-benzo[*d*]imidazol-2-yl)ethan-1-ol



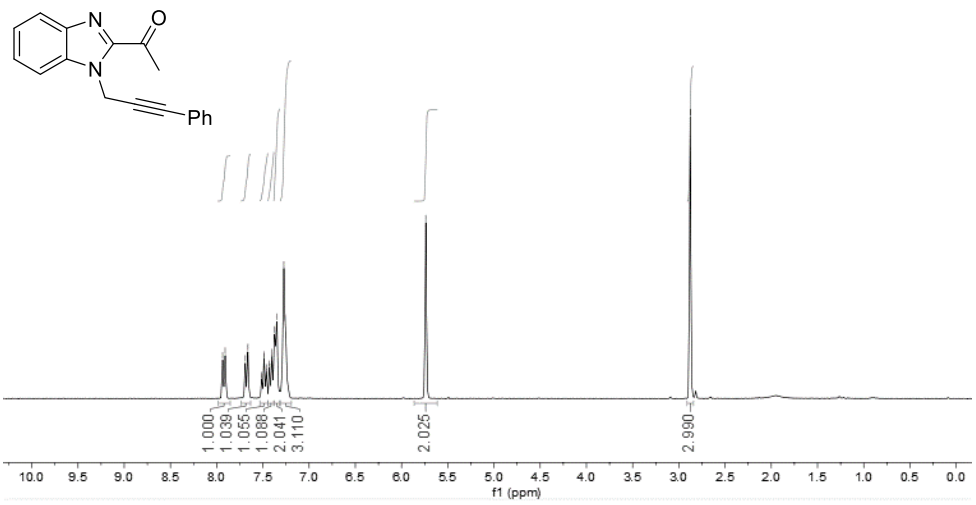


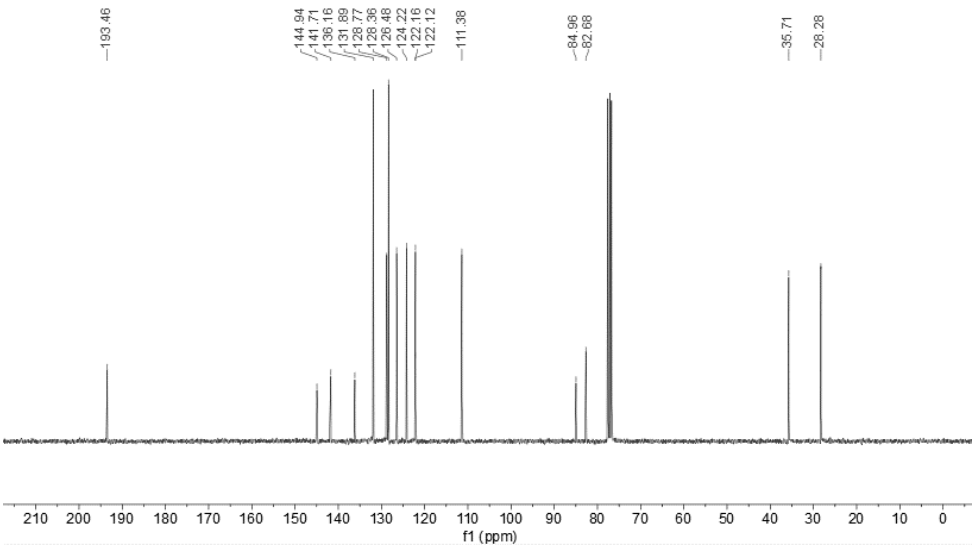
26c: 1-(1*H*-Naphtho[2,3-*d*]imidazol-2-yl)ethan-1-one



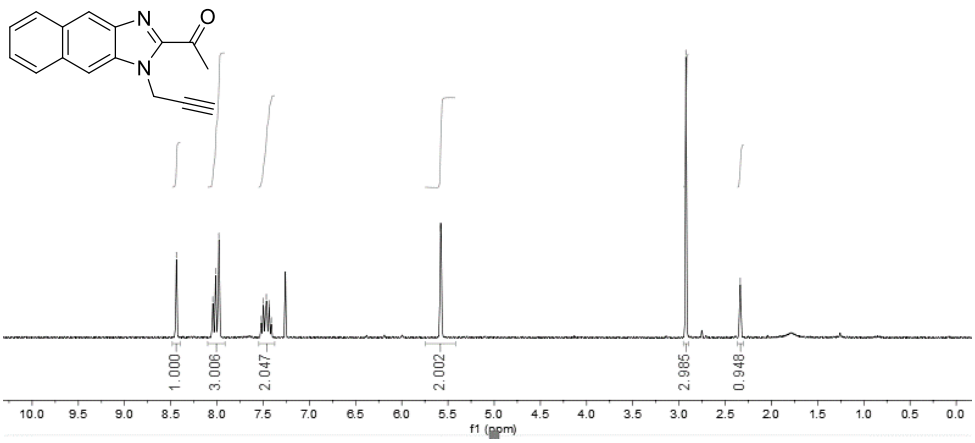


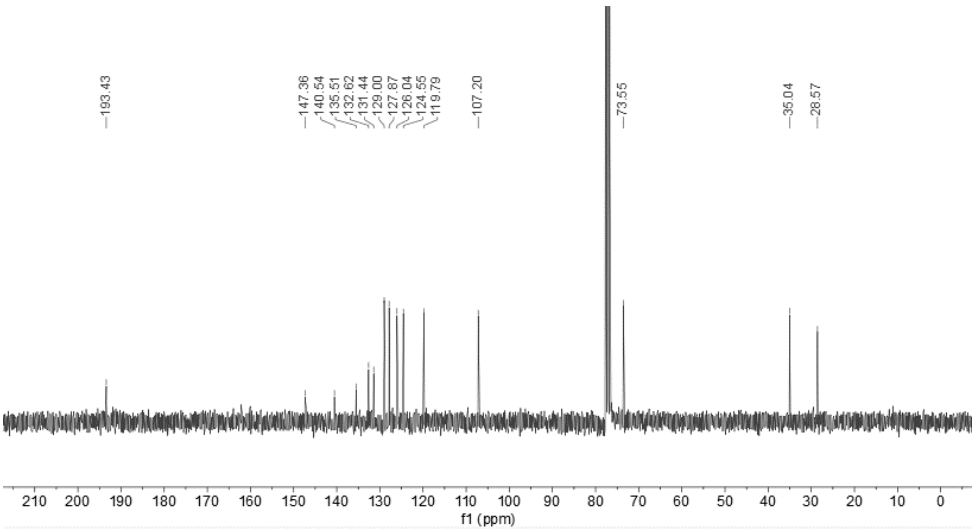
28b: 1-[1-(3-Phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]ethan-1-one



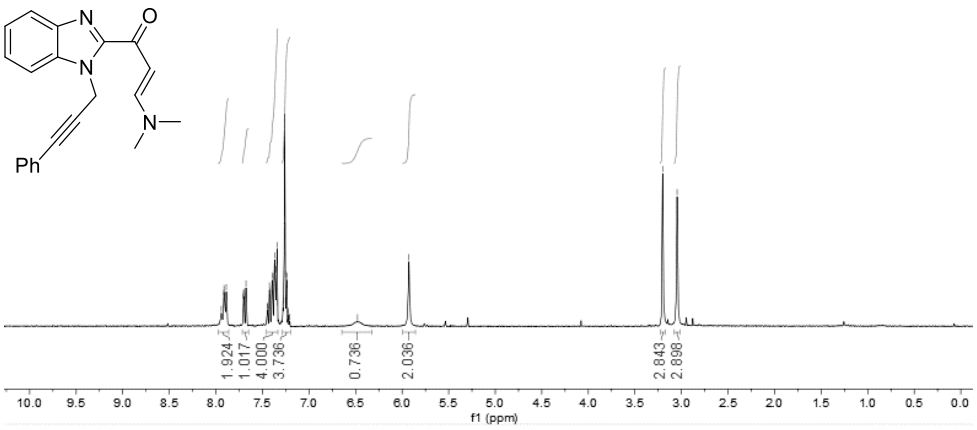


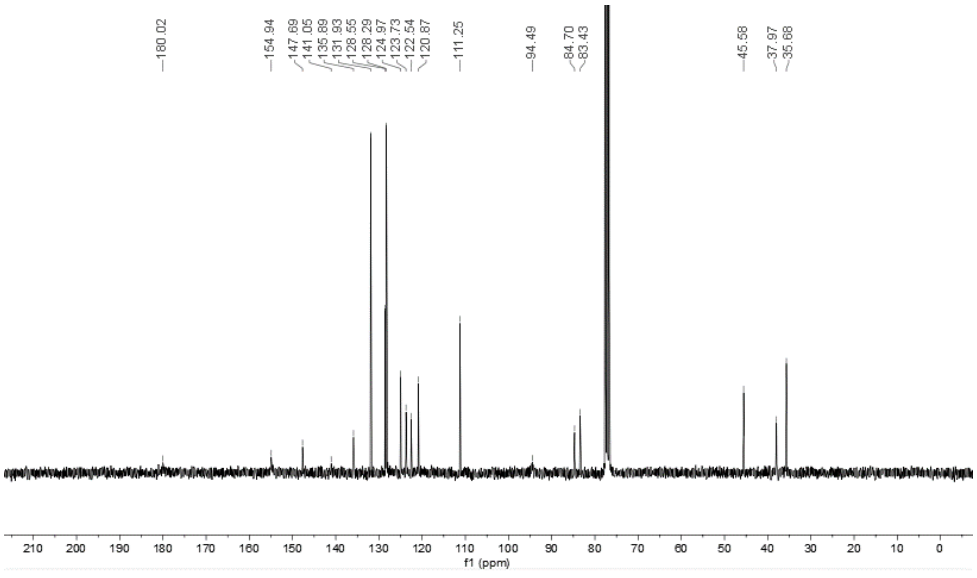
28f: 1-[1-(Prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]ethan-1-one



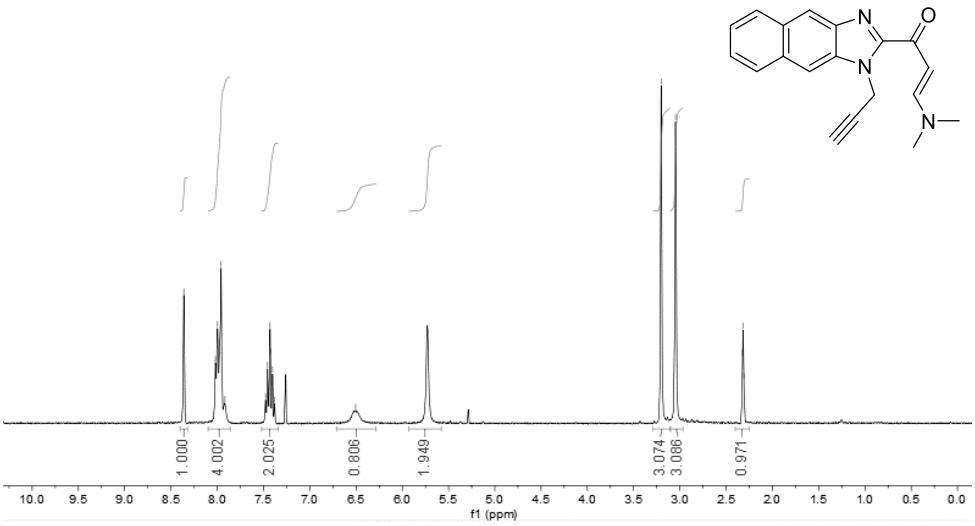


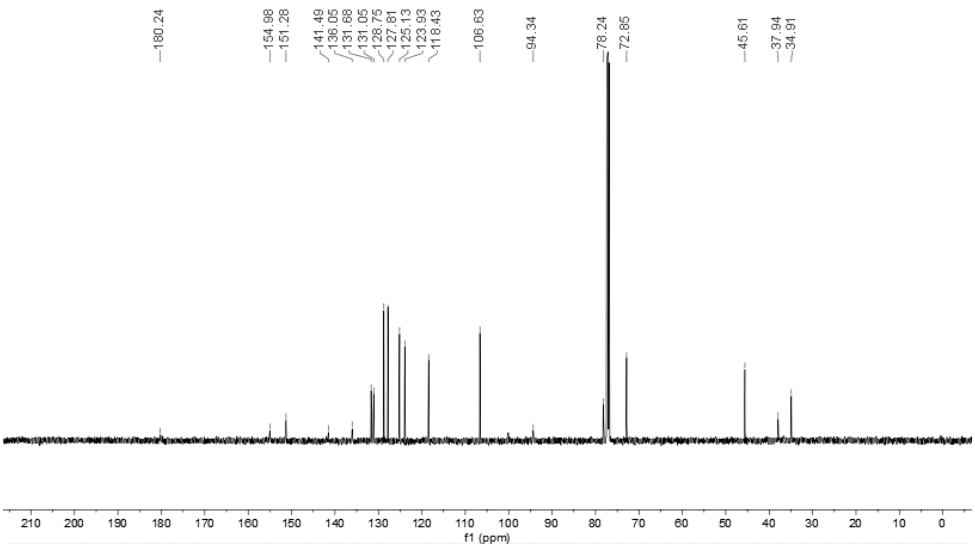
29b: (*E*)-3-(Dimethylamino)-1-[1-(3-phenylprop-2-yn-1-yl)-1*H*-benzo[*d*]imidazol-2-yl]prop-2-en-1-one



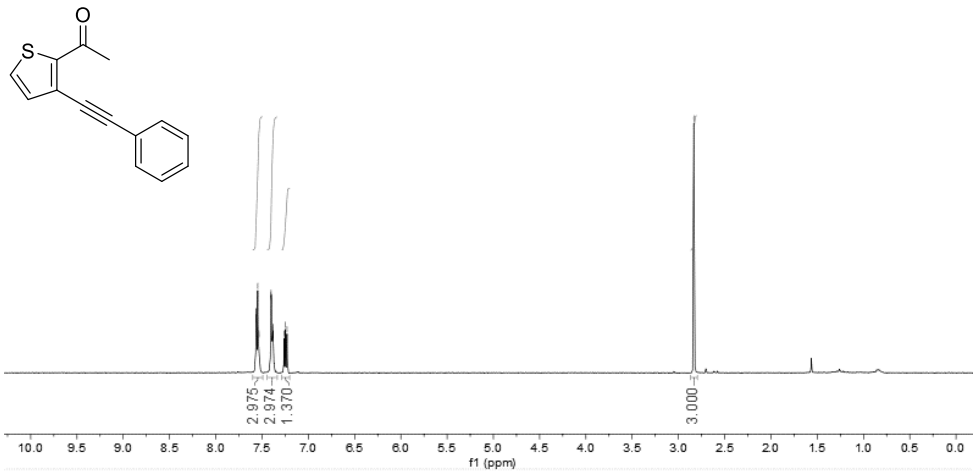


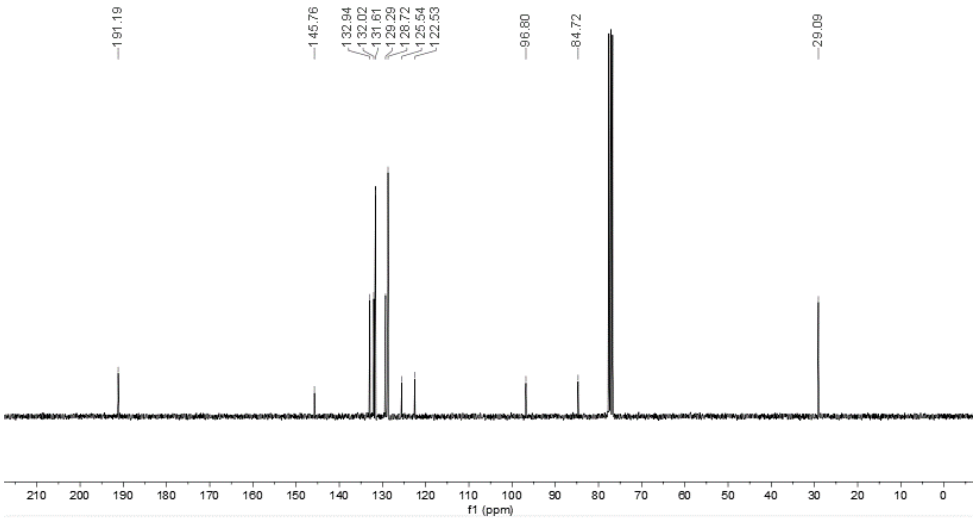
29e: (*E*)-3-(Dimethylamino)-1-[1-(prop-2-yn-1-yl)-1*H*-naphtho[2,3-*d*]imidazol-2-yl]prop-2-en-1-one



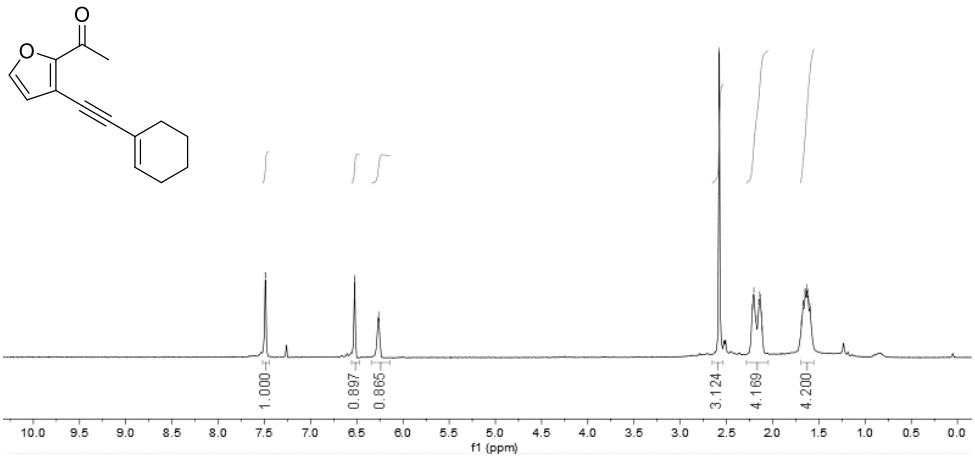


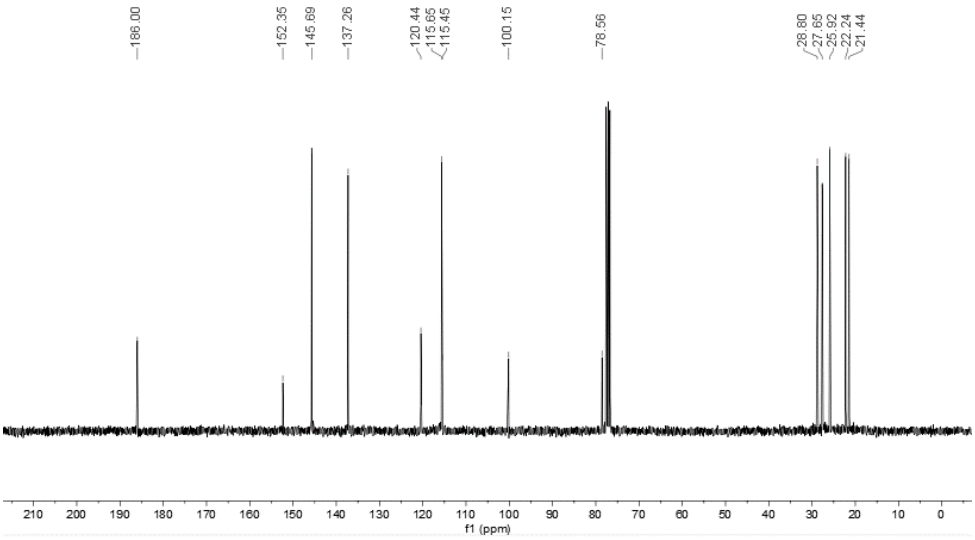
31b: 1-[3-(Phenylethynyl)thiophen-2-yl]ethan-1-one



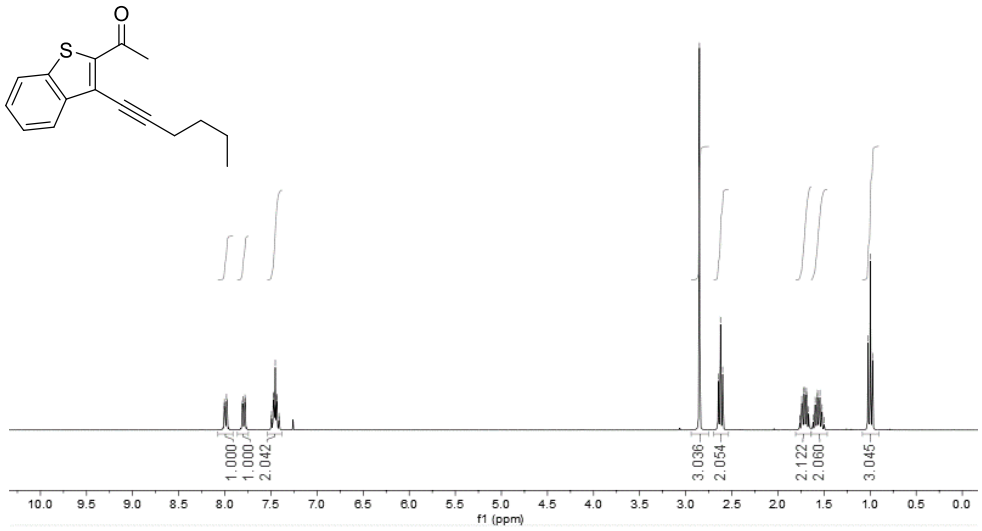


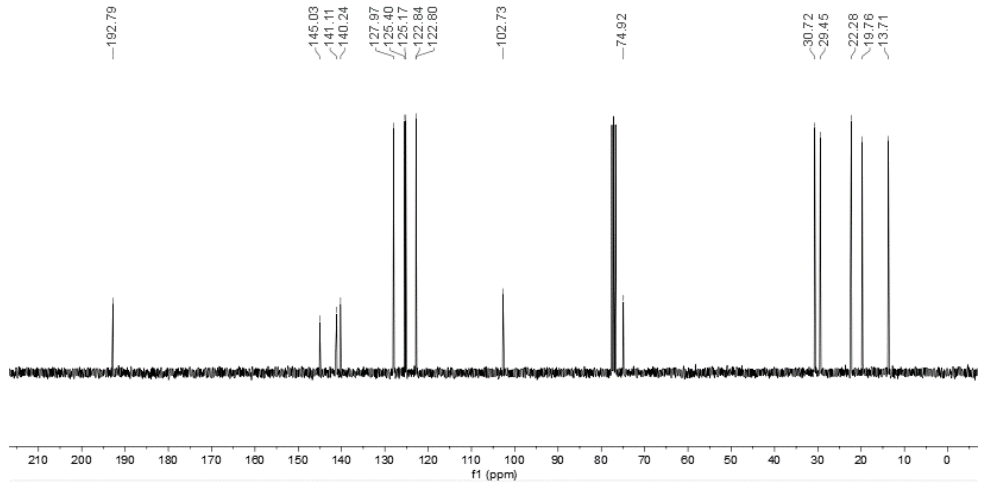
31h: 1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]ethan-1-one



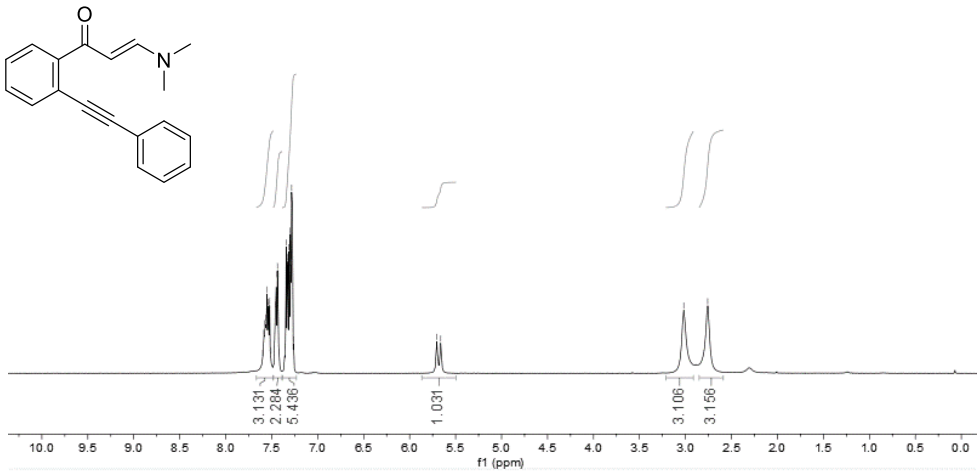


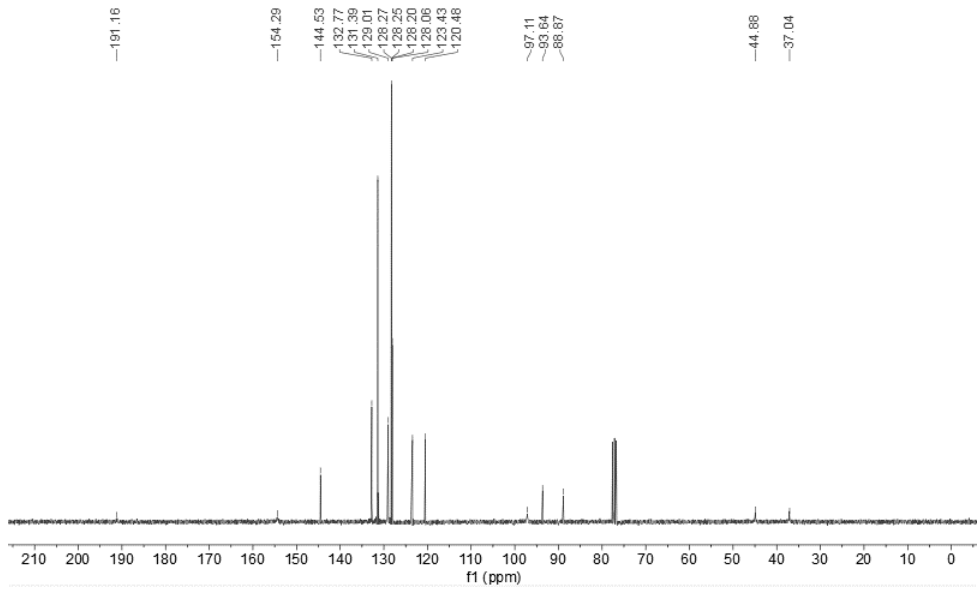
31k: 1-[3-(Hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]ethan-1-one



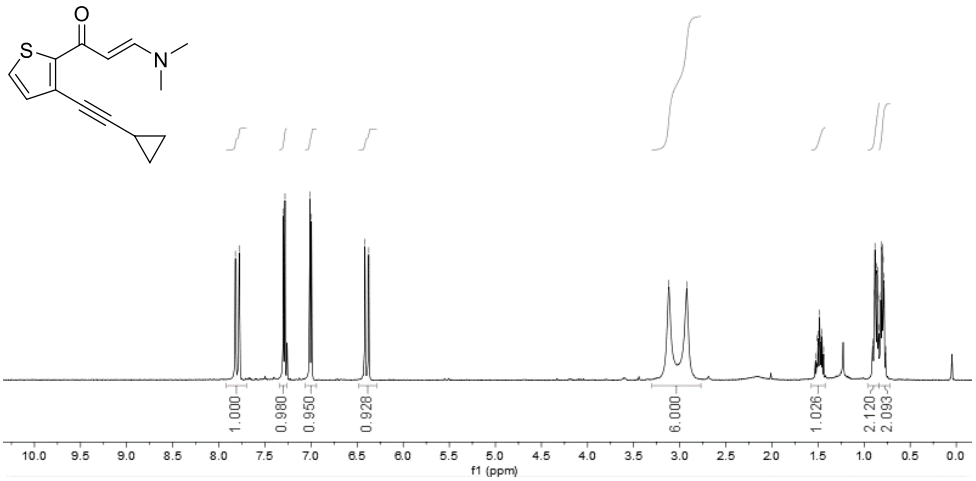


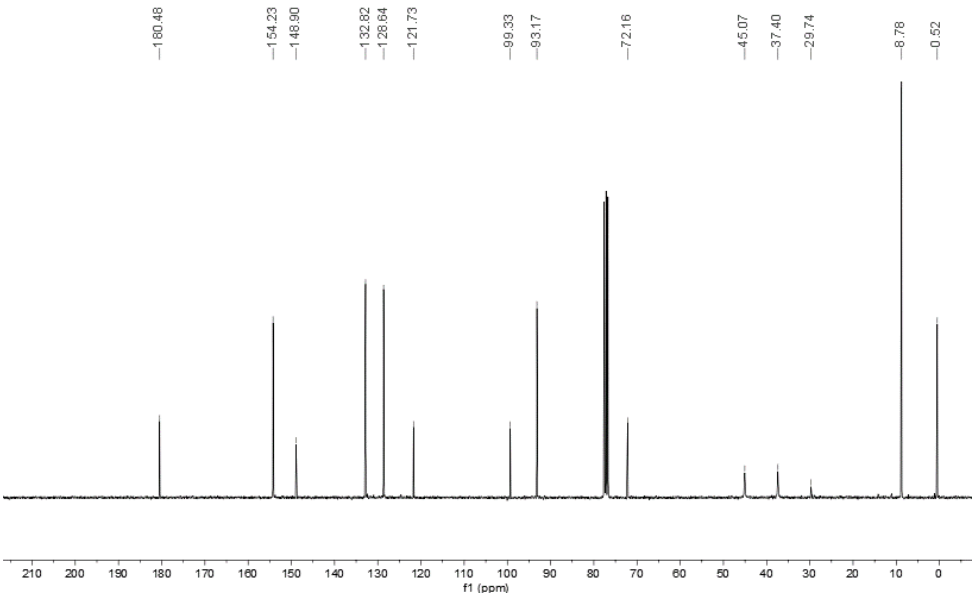
32a: (*E*)-3-(dimethylamino)-1-[2-(phenylethynyl)phenyl]prop-2-en-1-one



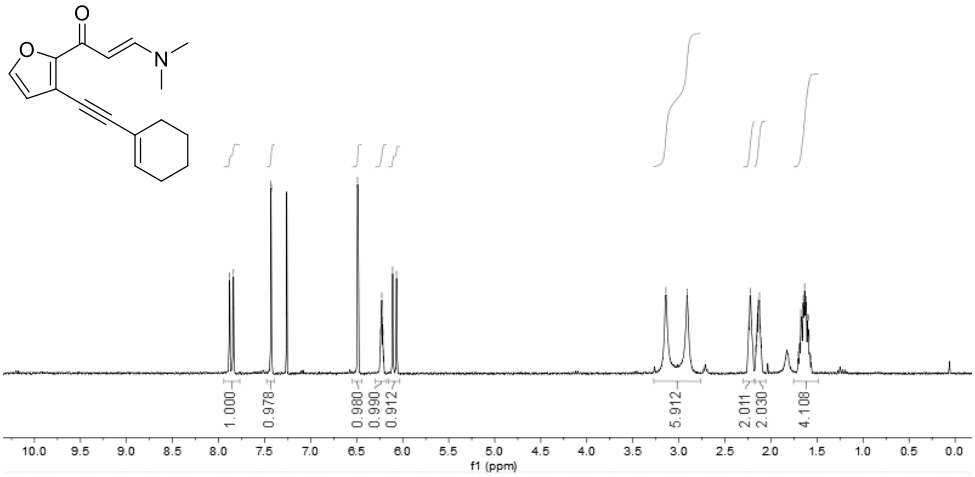


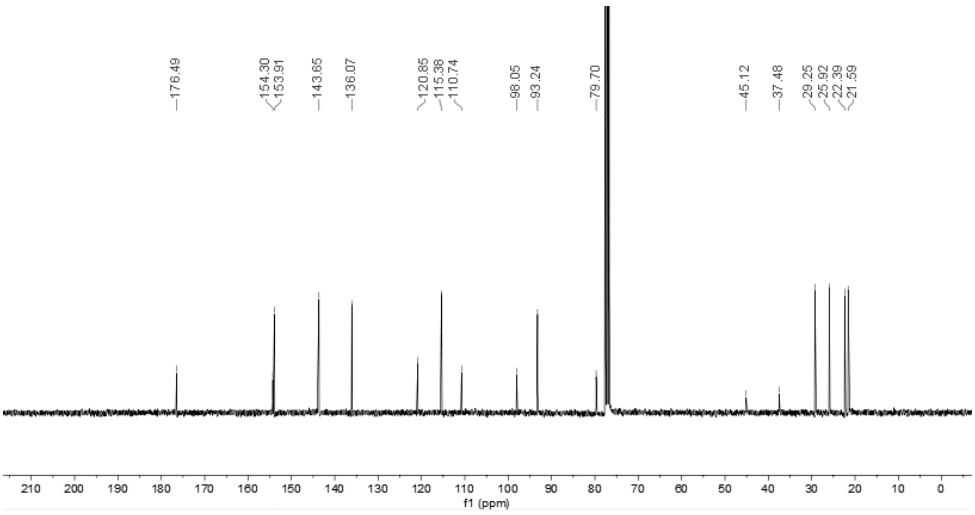
32d: (*E*)-1-[3-(Cyclopropylethynyl)thiophen-2-yl]-3-(dimethylamino)prop-2-en-1-one



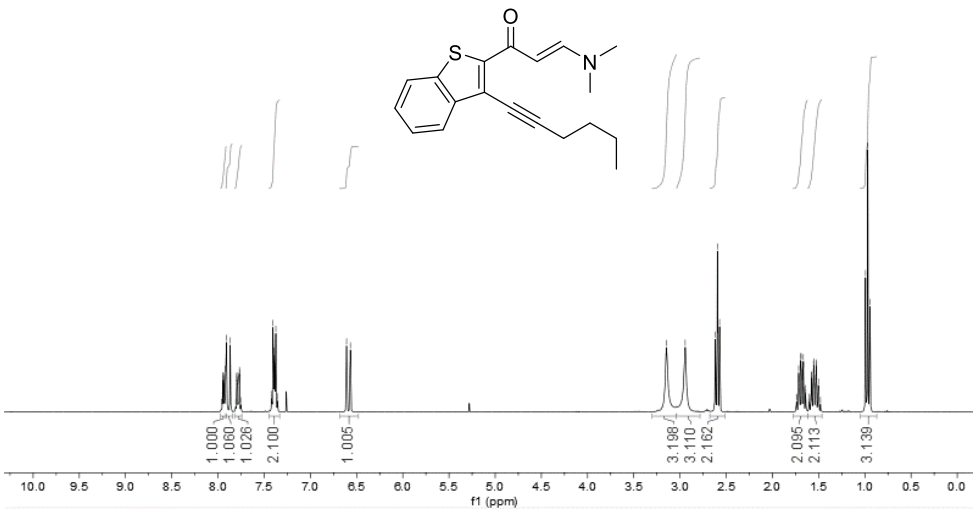


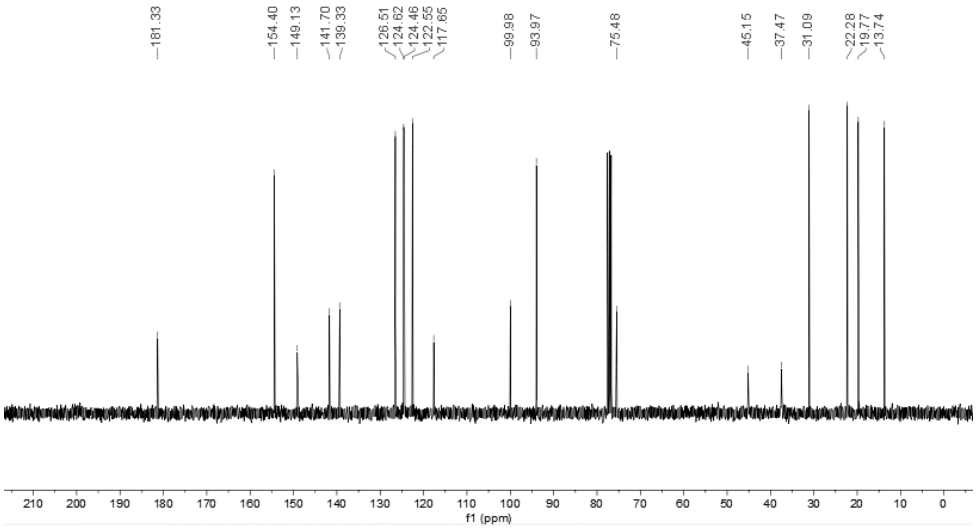
32h: (*E*)-1-[3-(Cyclohex-1-en-1-ylethynyl)furan-2-yl]-3-(dimethylamino)prop-2-en-1-one



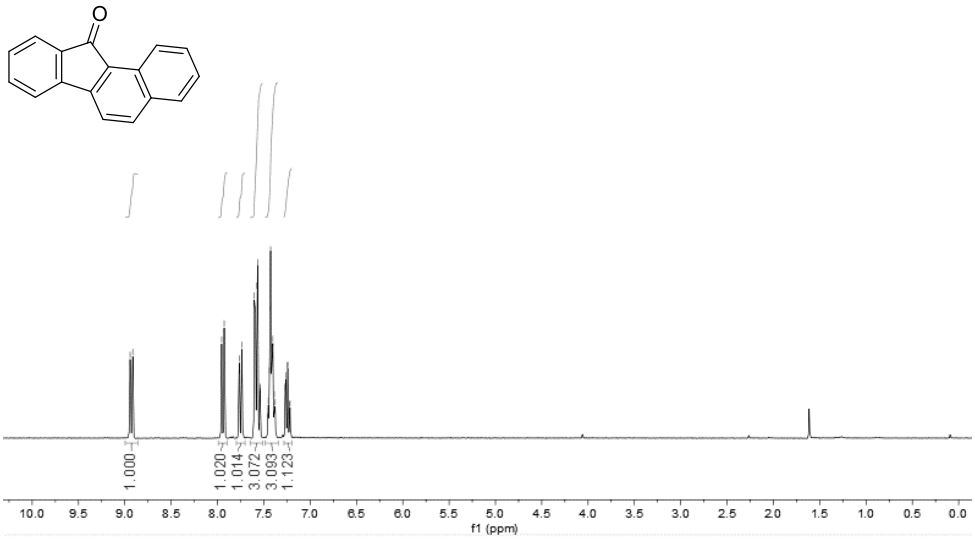


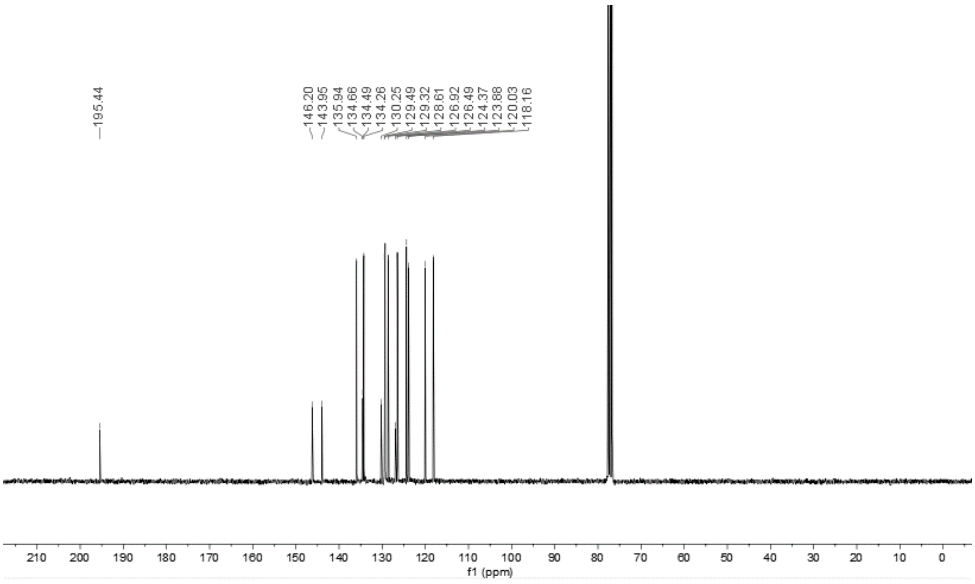
32k: (E)-3-(Dimethylamino)-1-[3-(hex-1-yn-1-yl)benzo[*b*]thiophen-2-yl]prop-2-en-1-one



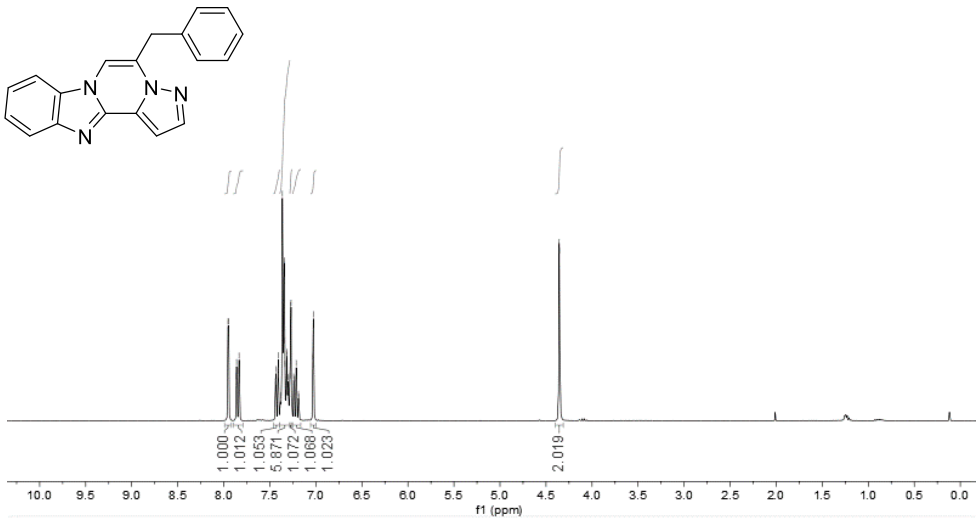


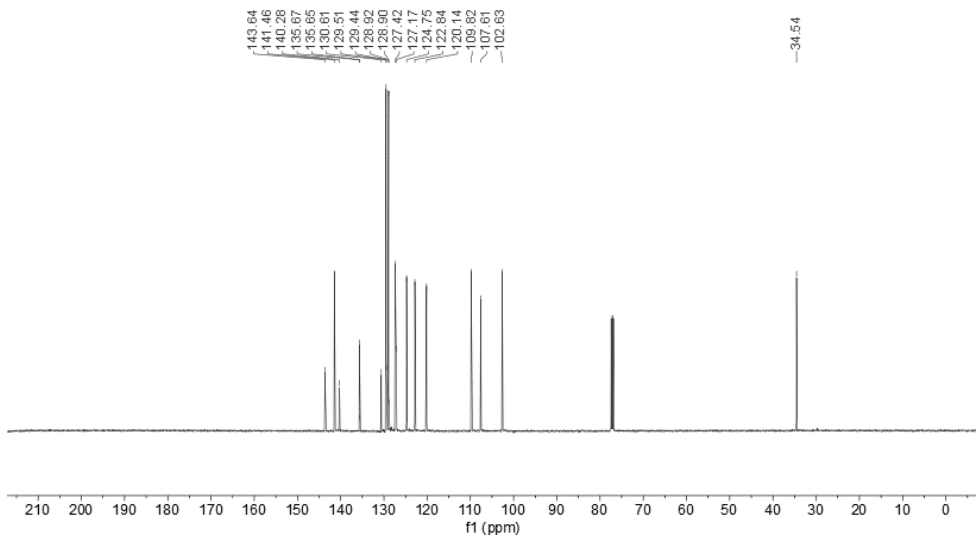
33: 11*H*-Benzo[*a*]fluoren-11-one



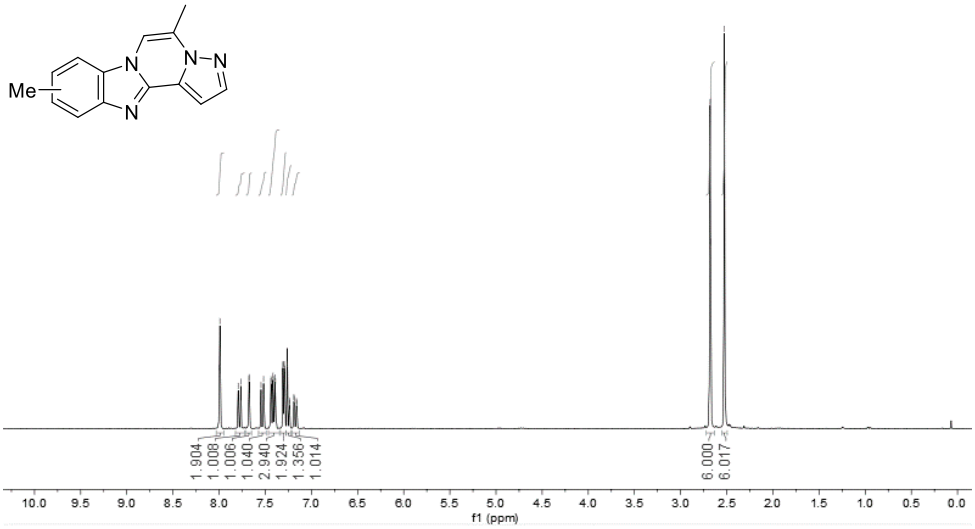


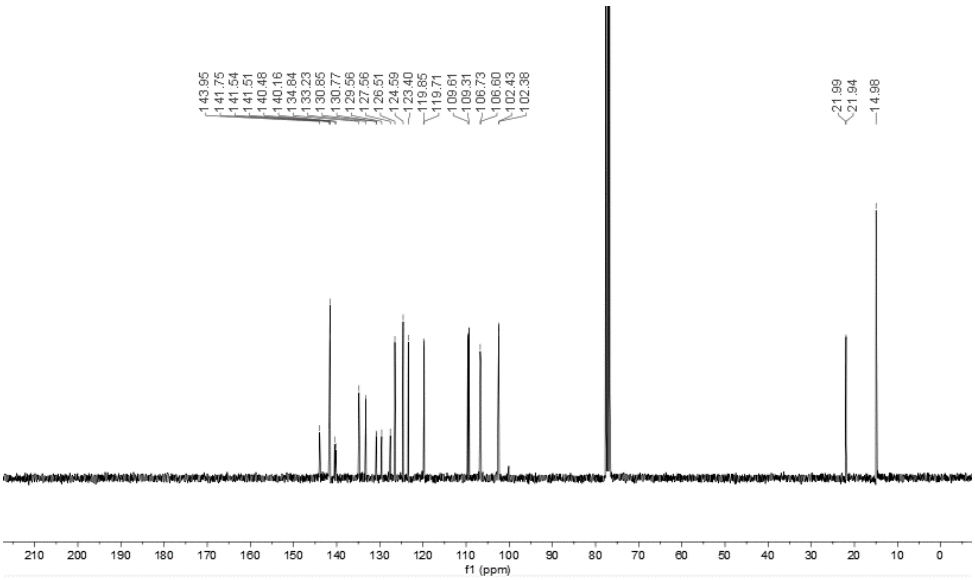
34b: 5-Benzylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine



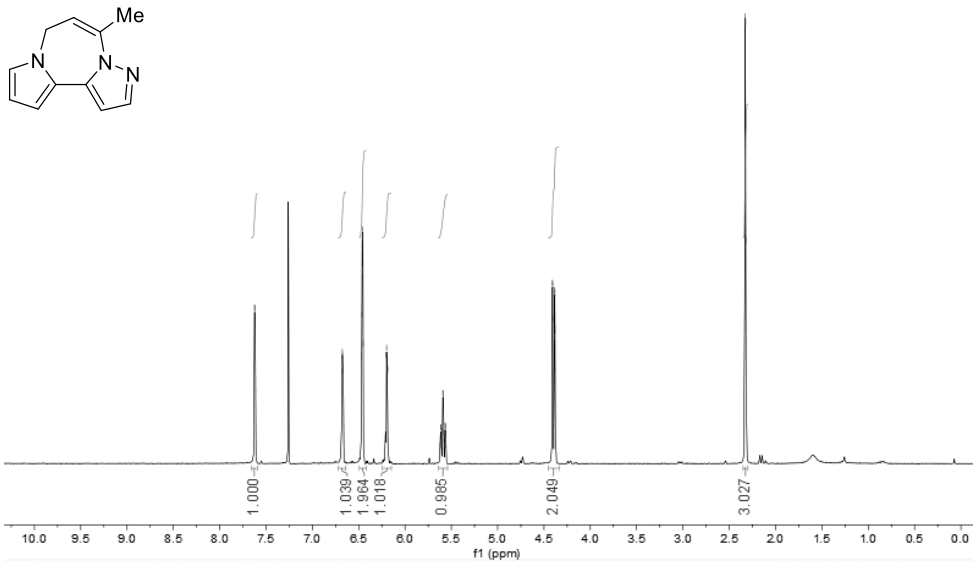


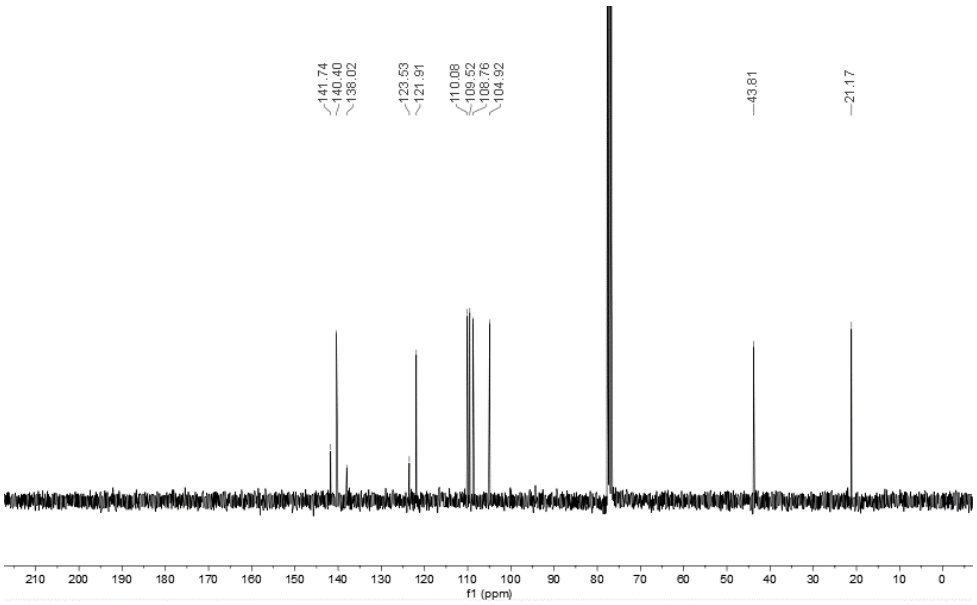
34d & 34d': 5,10-Dimethylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine & 5,9-dimethylbenzo[4,5]imidazo[1,2-*a*]pyrazolo[5,1-*c*]pyrazine



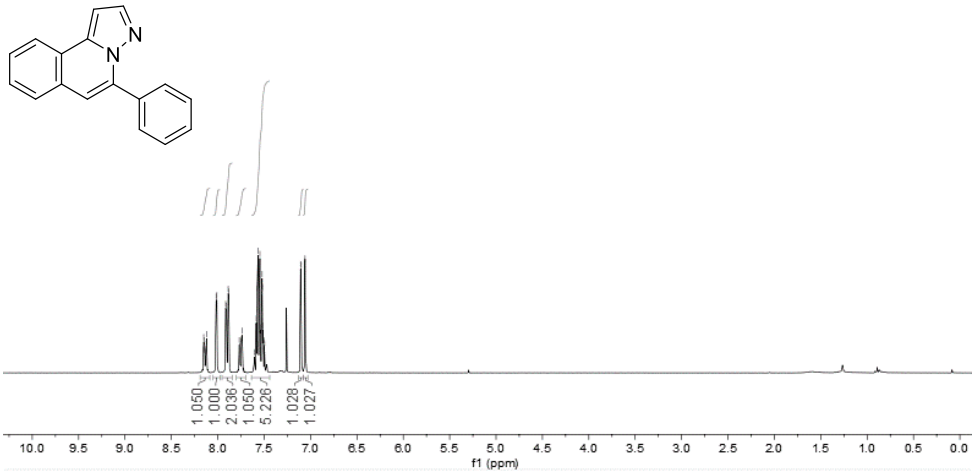


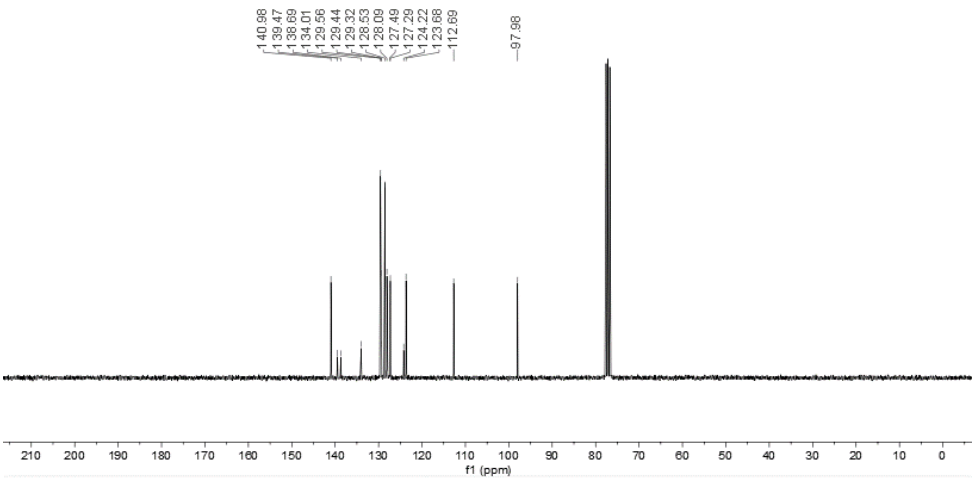
35: 5-Methyl-7*H*-pyrazolo[1,5-*a*]pyrrolo[2,1-*c*][1,4]diazepine



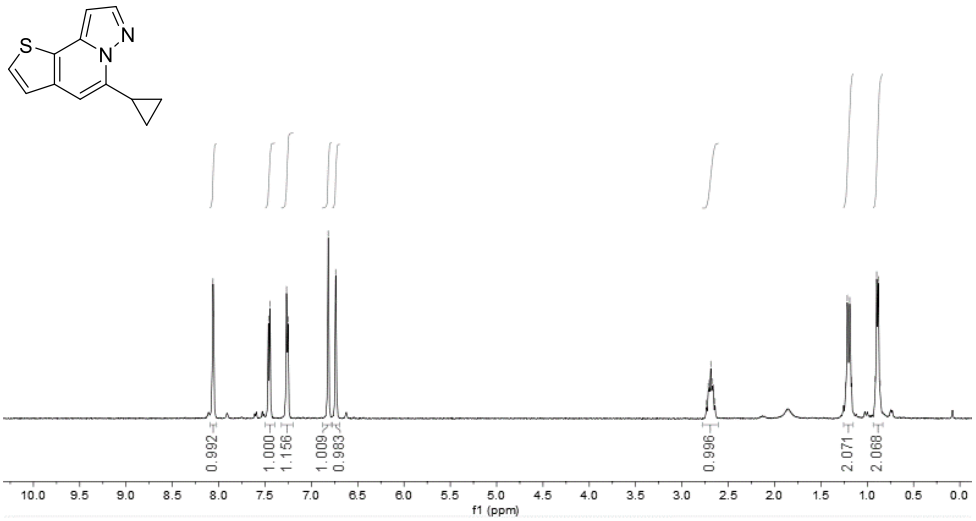


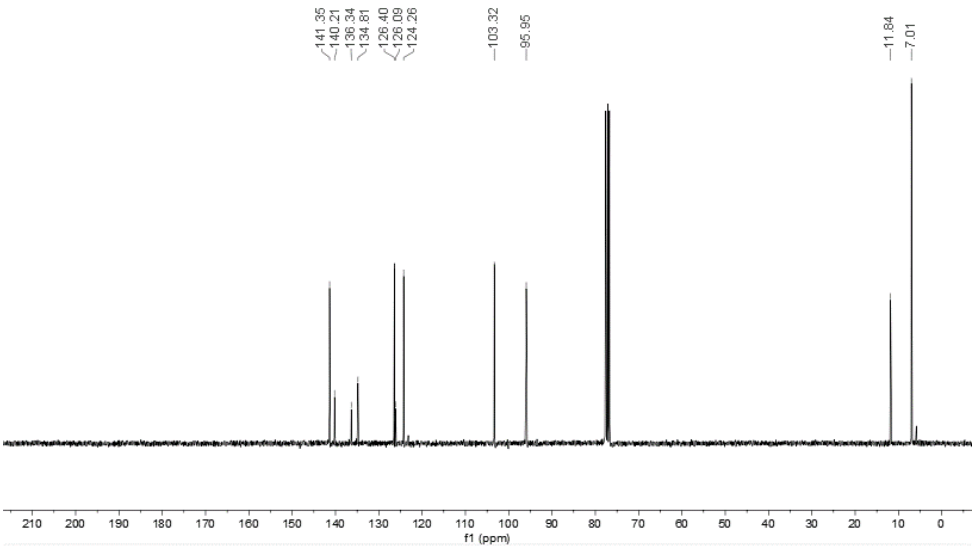
36a: 5-Phenylpyrazolo[5,1-*a*]isoquinoline



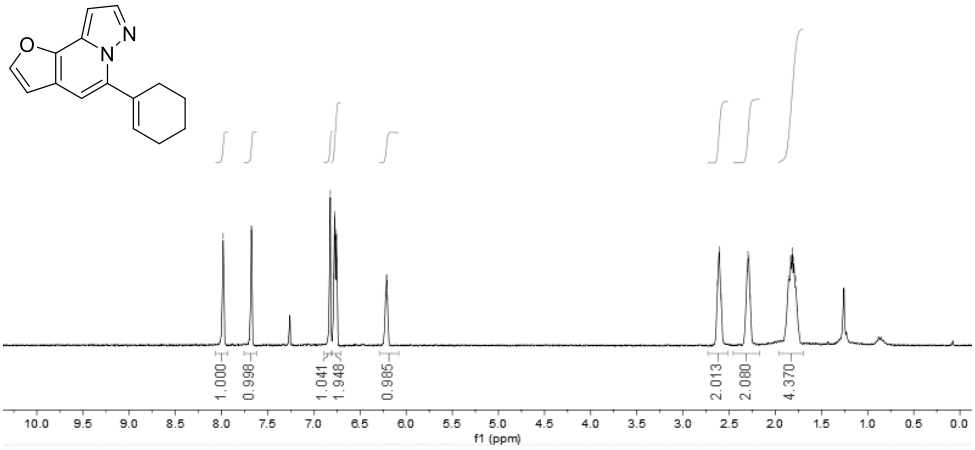


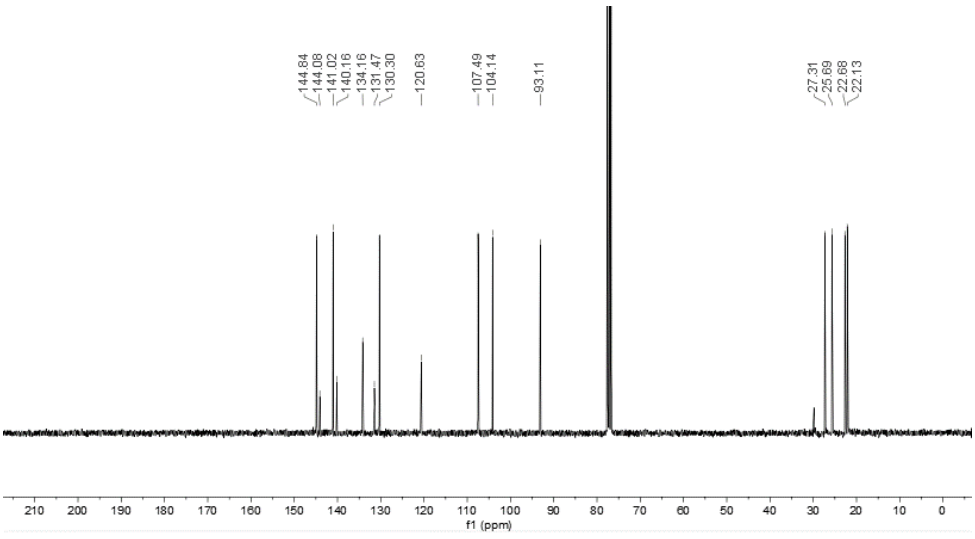
36d: 5-Cyclopropylpyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine



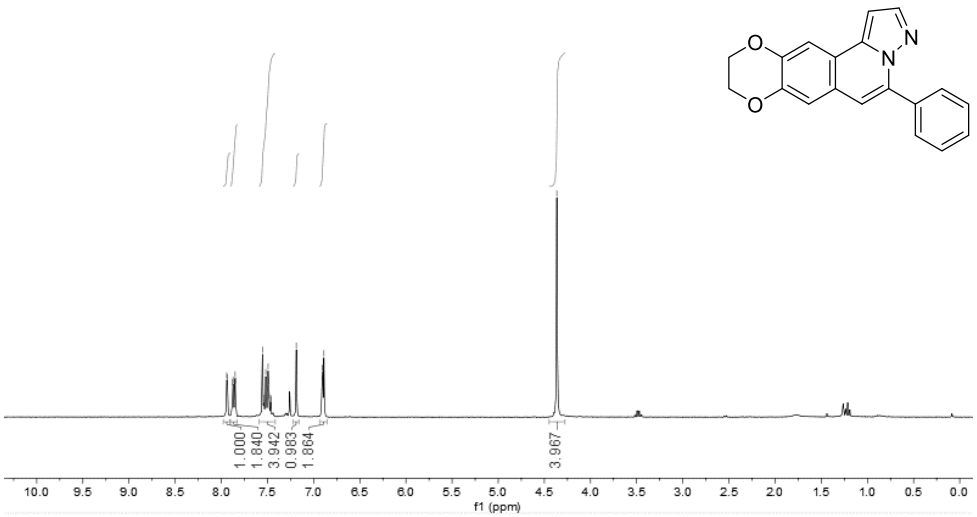


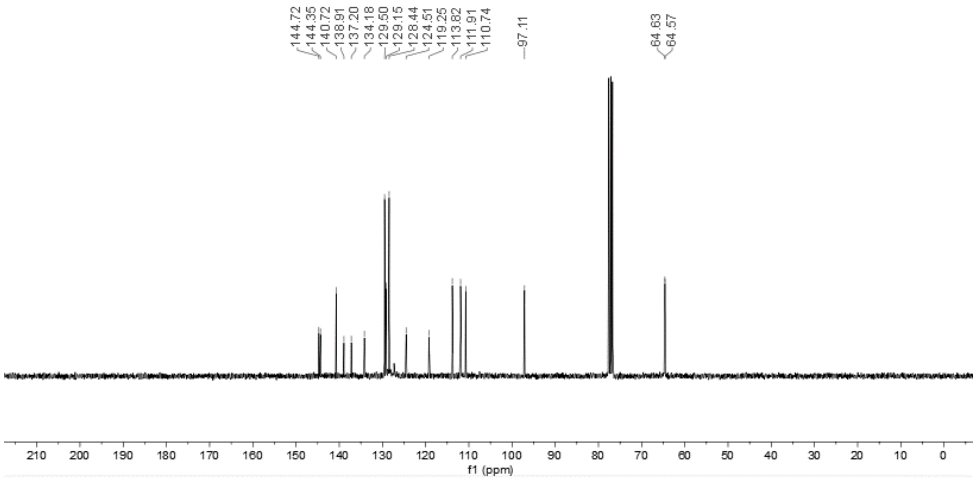
36h: 5-(Cyclohex-1-en-1-yl)furo[2,3-*c*]pyrazolo[1,5-*a*]pyridine



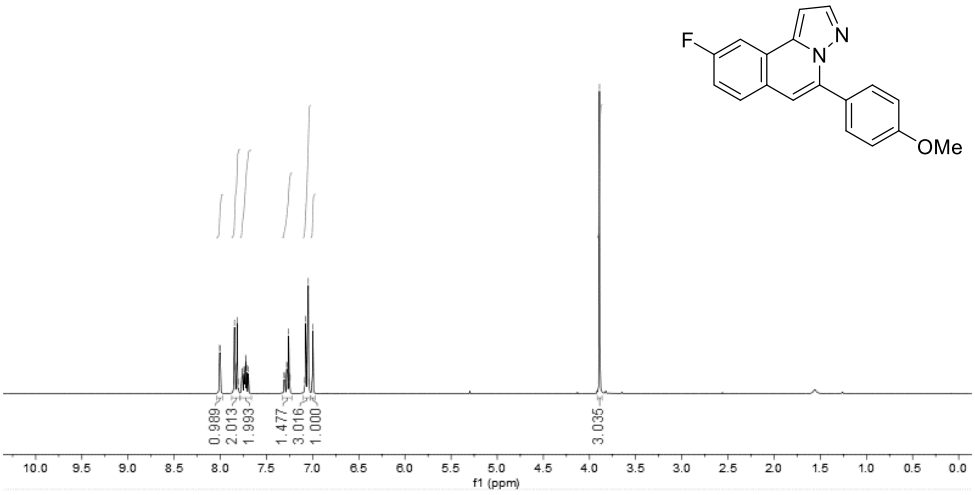


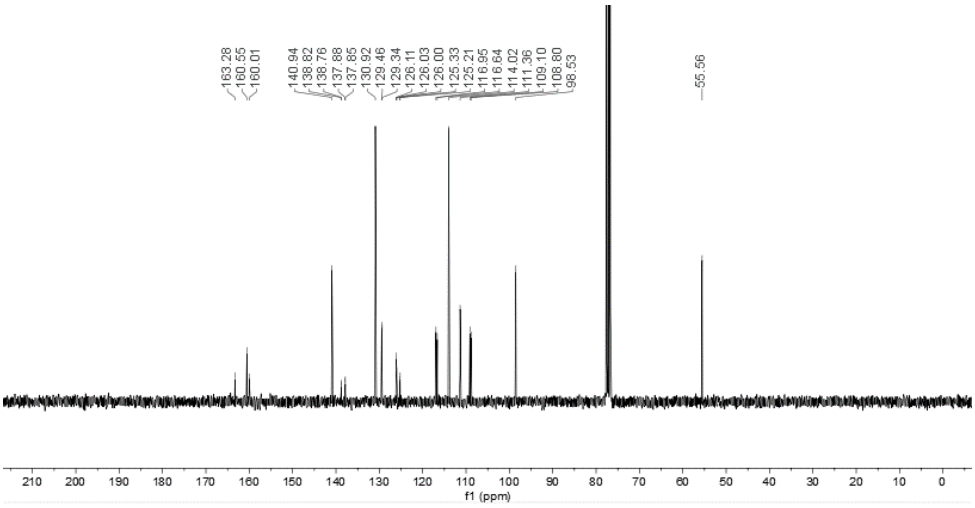
36y: 5-Phenyl-9,10-dihydro-[1,4]dioxino[2,3-*g*]pyrazolo[5,1-*a*]isoquinoline



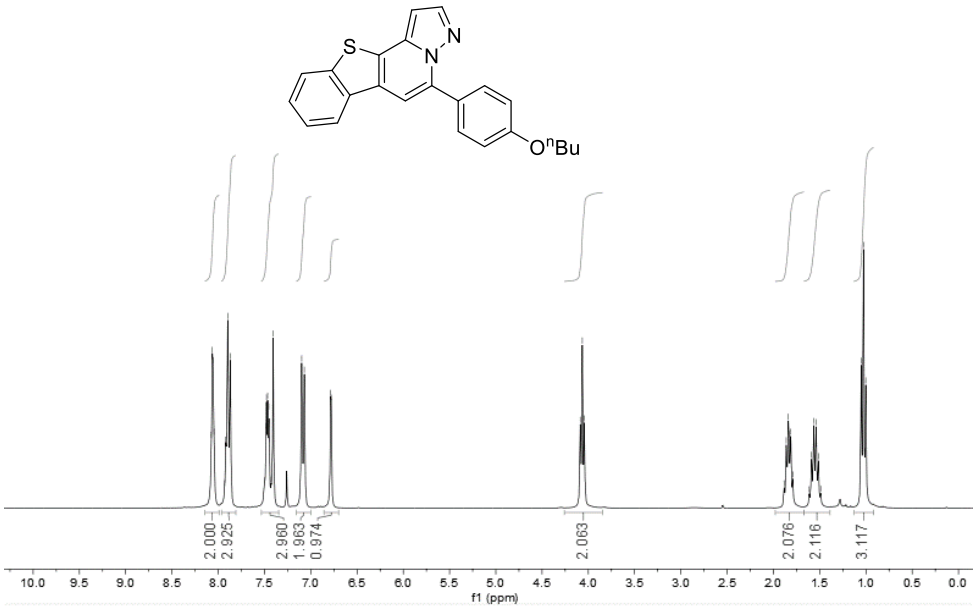


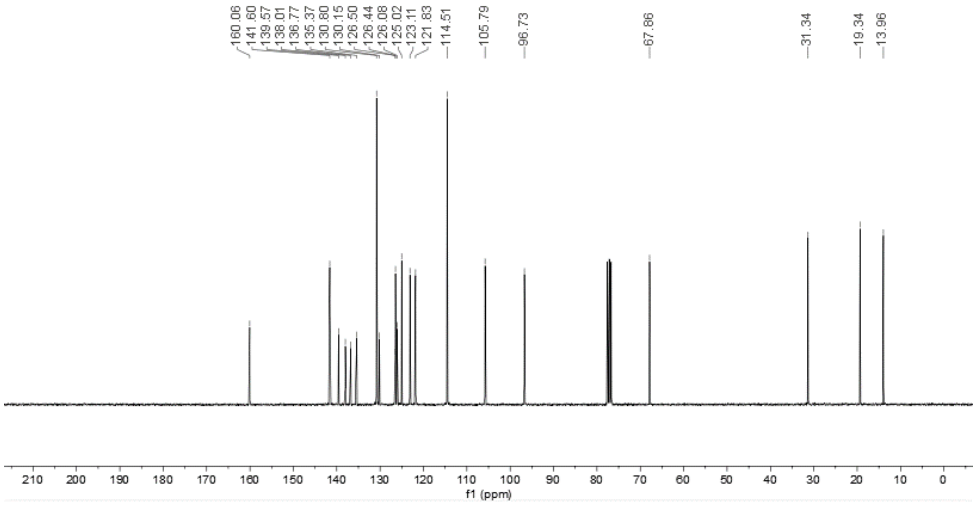
36aa: 9-Fluoro-5-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline



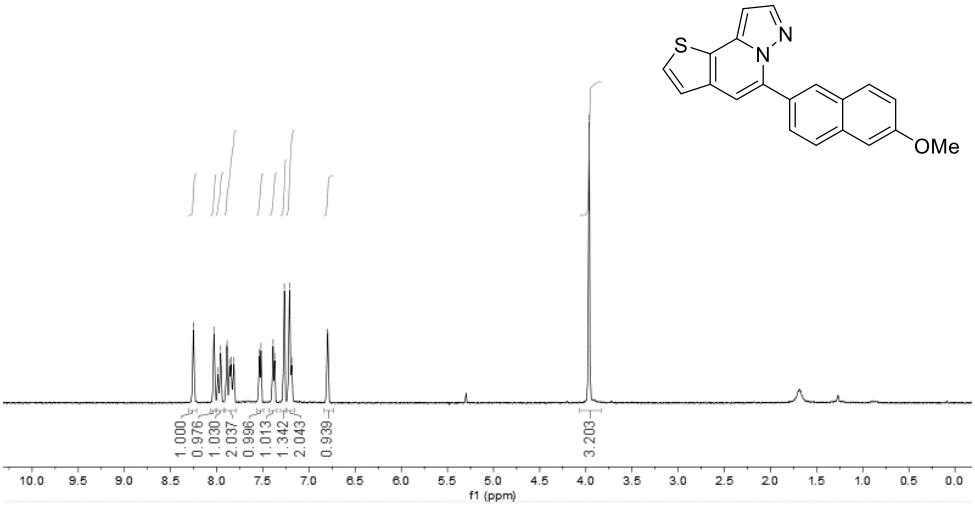


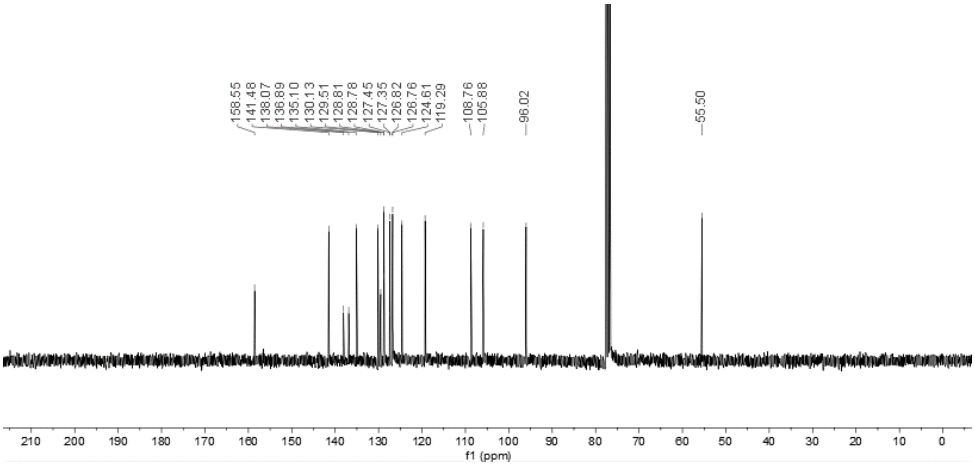
36ac: 5-(4-Butoxyphenyl)benzo[4,5]thieno[2,3-*c*]pyrazolo[1,5-*a*]pyridine



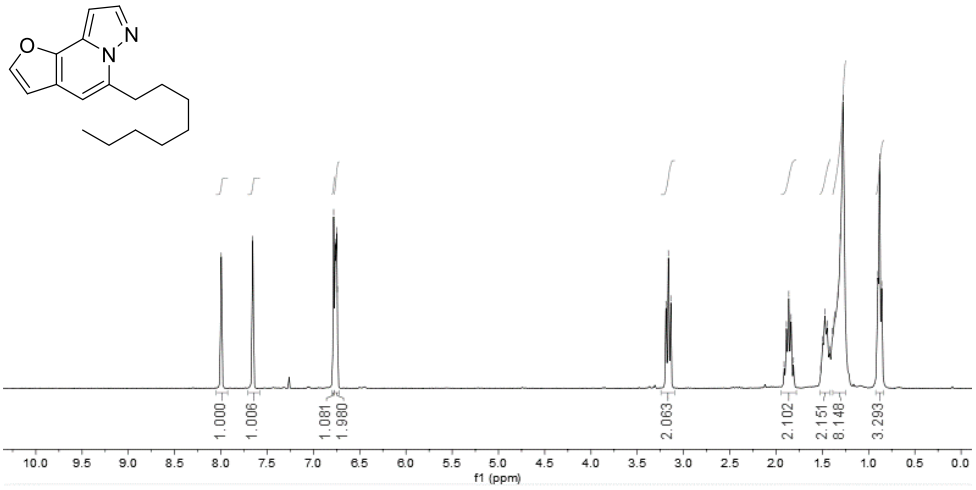


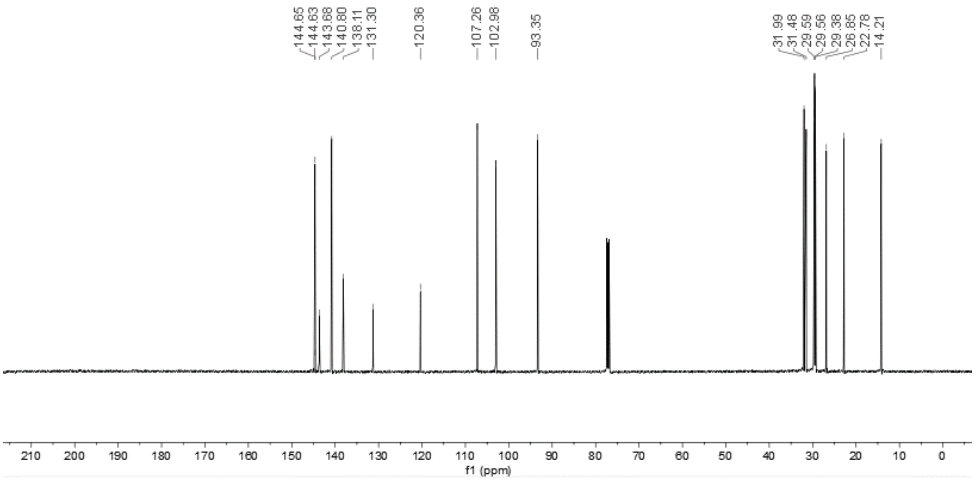
36ag: 5-(6-Methoxynaphthalen-2-yl)pyrazolo[1,5-*a*]thieno[2,3-*c*]pyridine



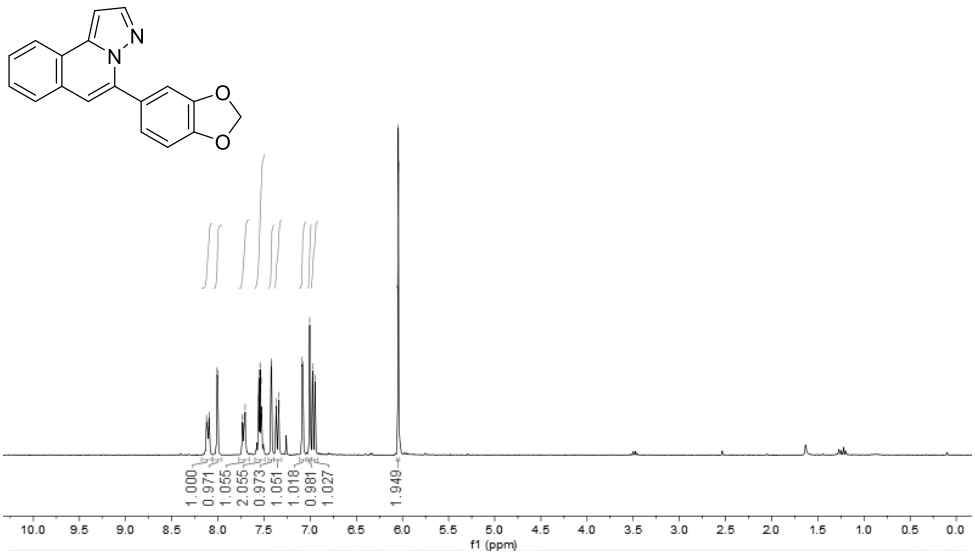


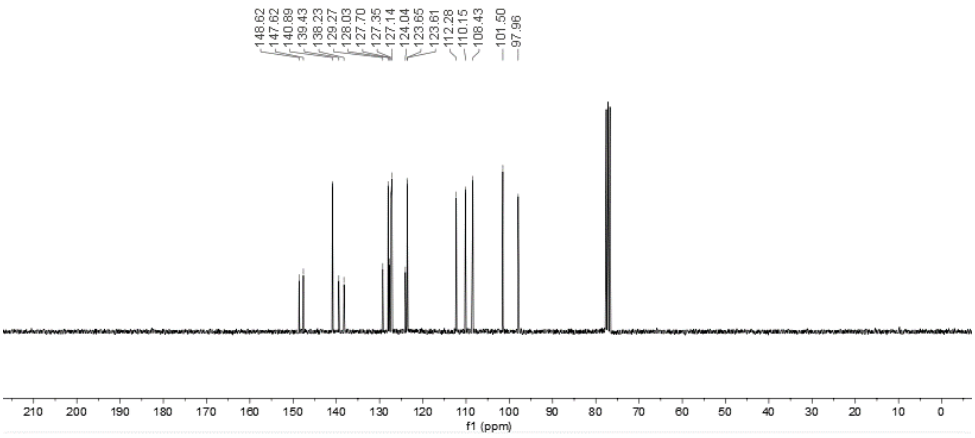
36ak: 5-Octylfuro[2,3-*c*]pyrazolo[1,5-*a*]pyridine



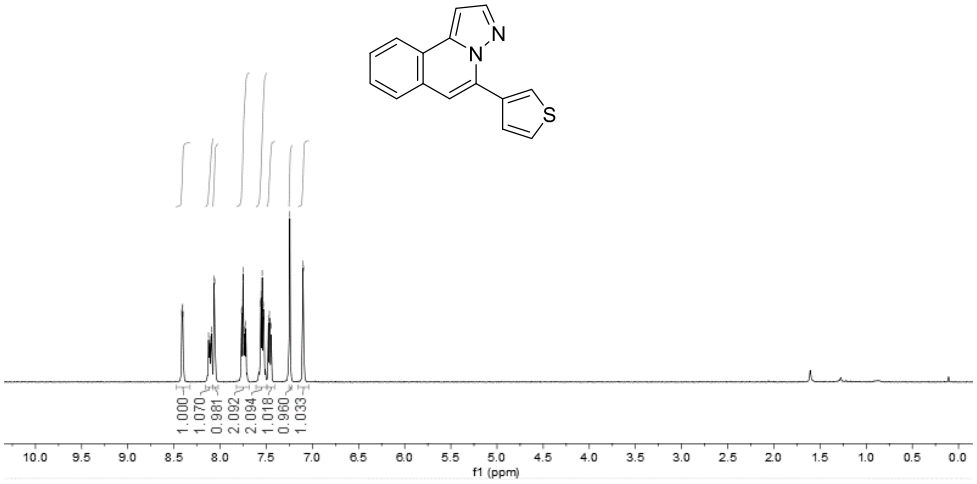


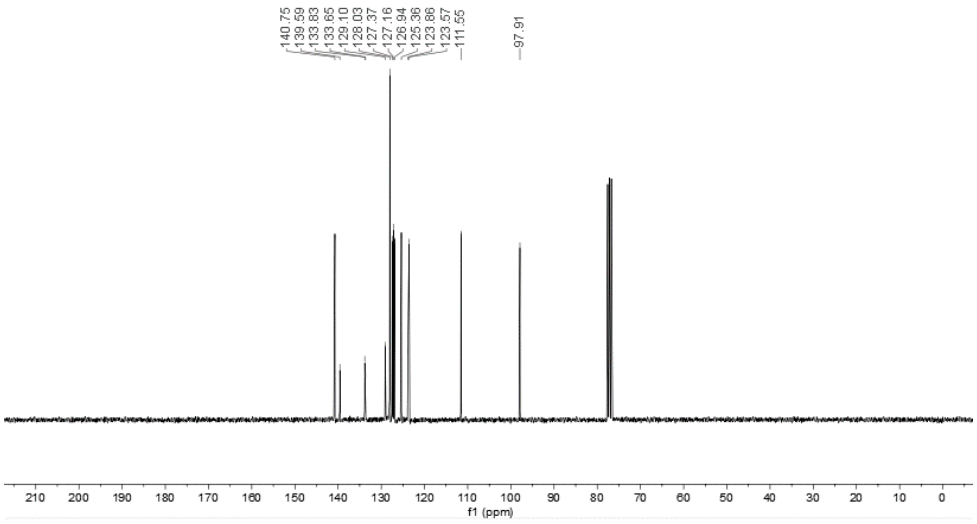
36am: 5-(Benzo[*d*][1,3]dioxol-5-yl)pyrazolo[5,1-*a*]isoquinoline



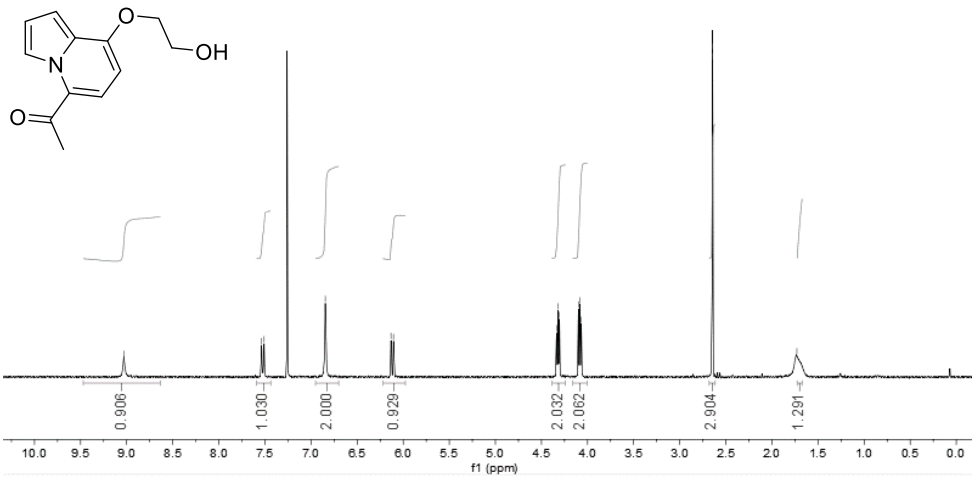


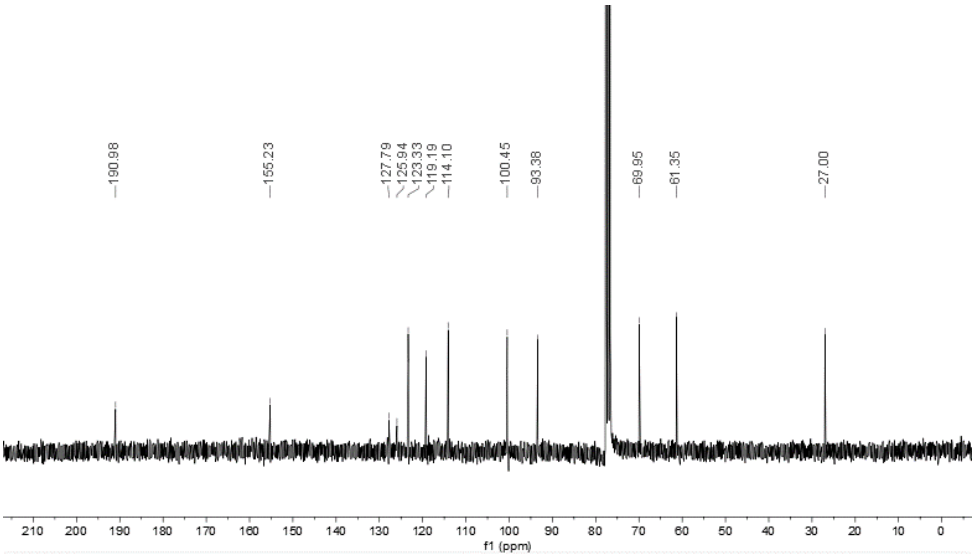
36ao: 5-(Thiophen-3-yl)pyrazolo[5,1-*a*]isoquinoline



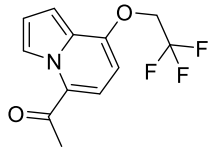


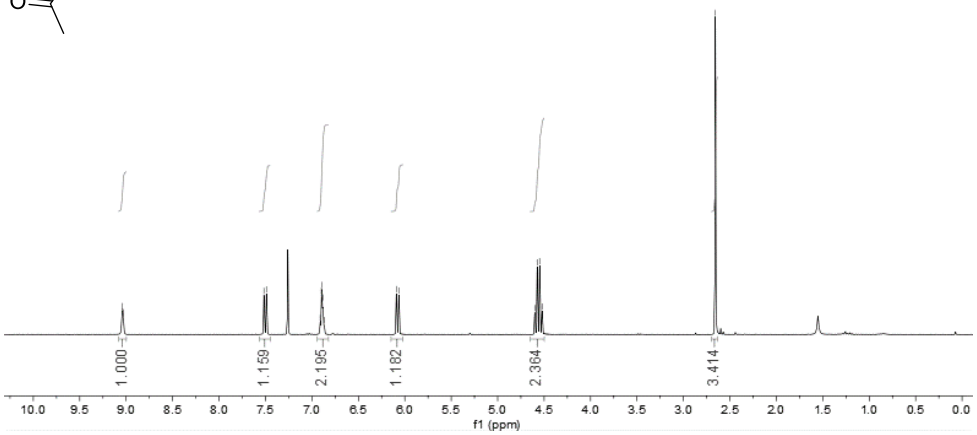
38f: 1-[8-(2-Hydroxyethoxy)indolizin-5-yl]ethan-1-one

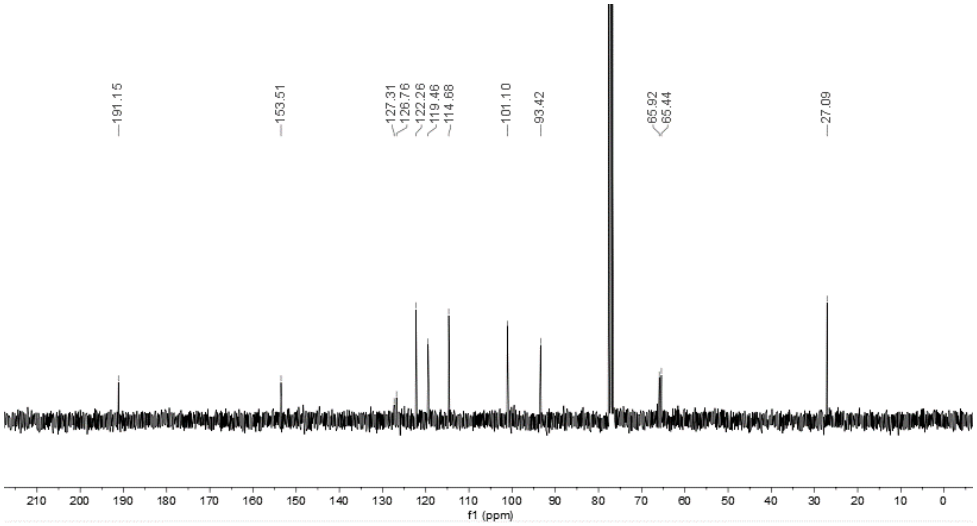




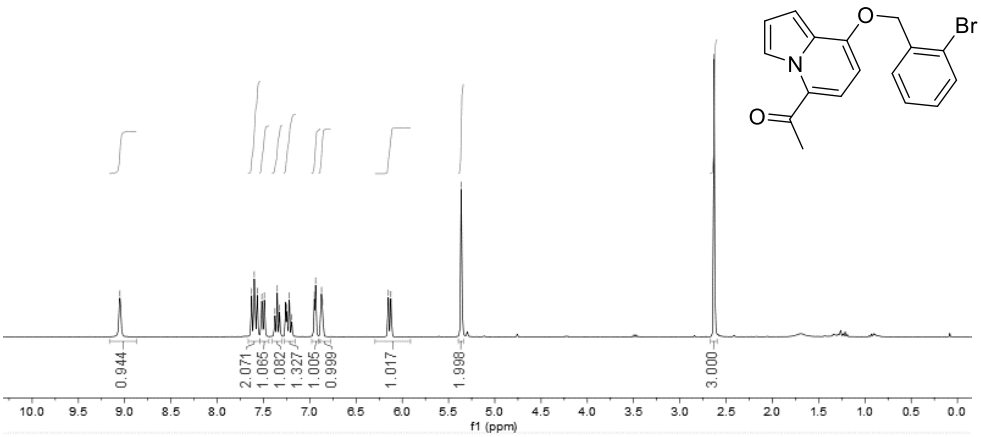
38g: 1-[8-(2,2,2-Trifluoroethoxy)indolizin-5-yl]ethan-1-one

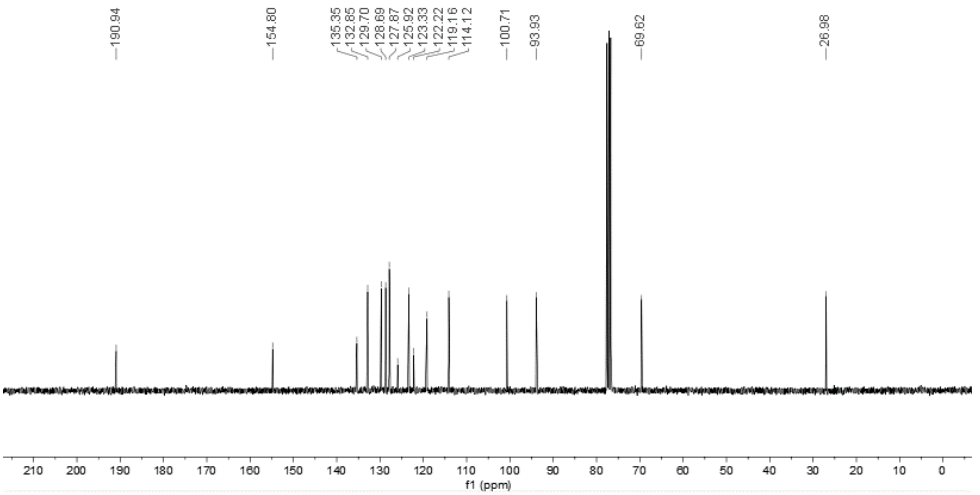




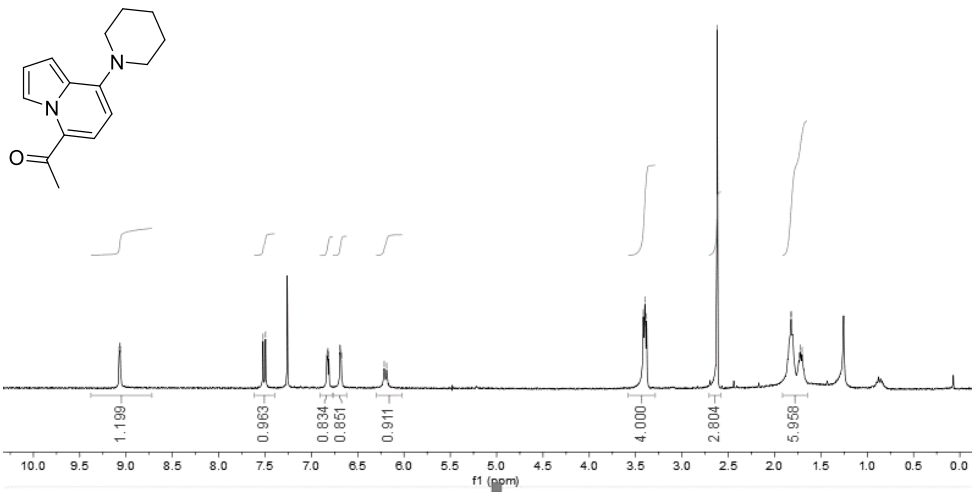


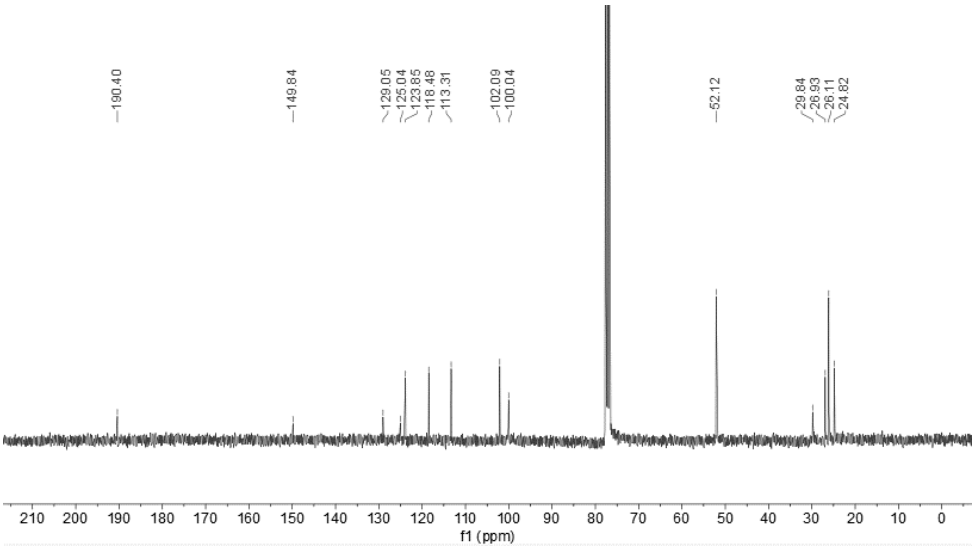
38i: 1-[8-[(2-Bromobenzyl)oxy]indolizin-5-yl]ethan-1-one



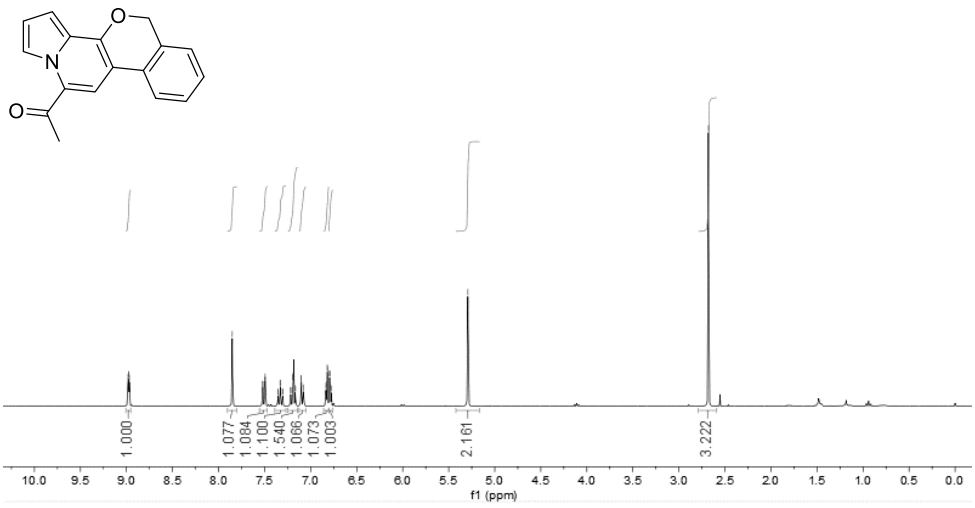


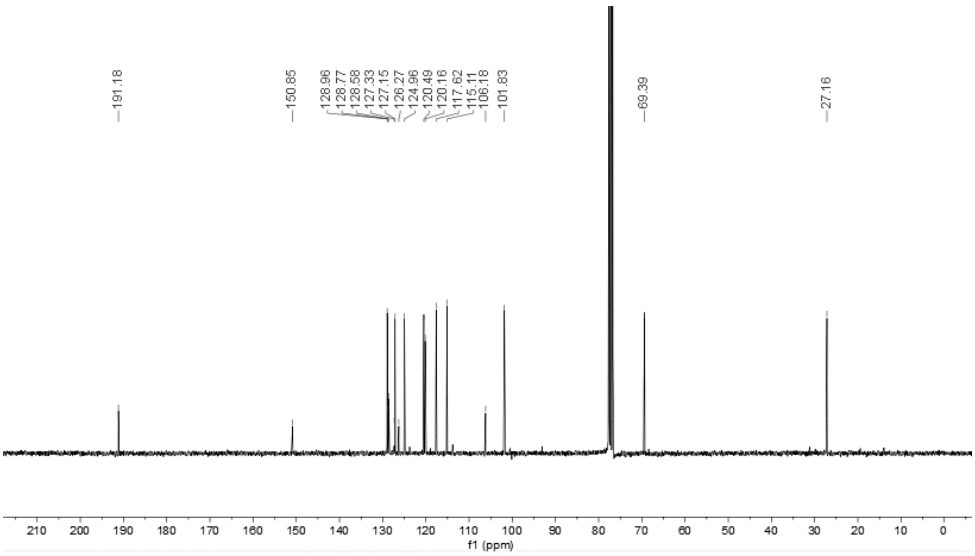
39b: 1-[8-(Piperidin-1-yl)indolizin-5-yl]ethan-1-one



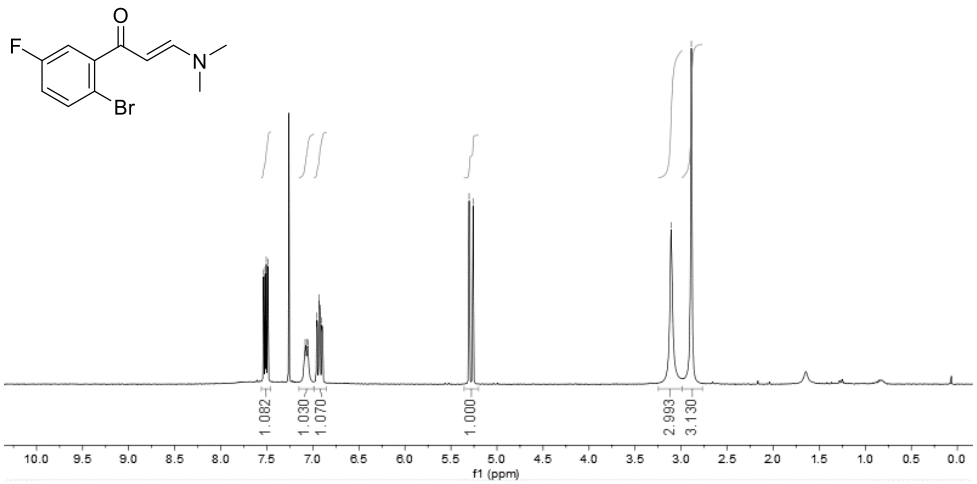


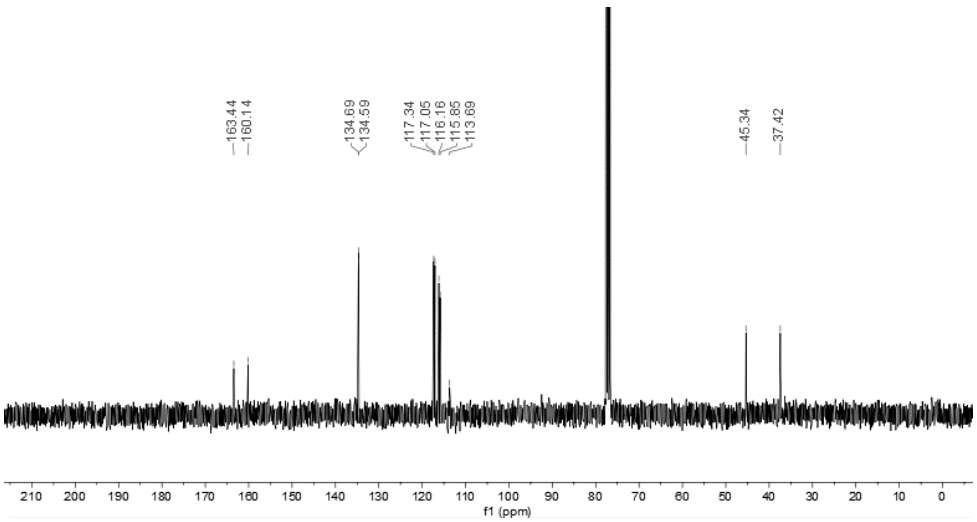
41: 1-(5*H*-isochromeno[4,3-*g*]indolizin-11-yl)ethan-1-one



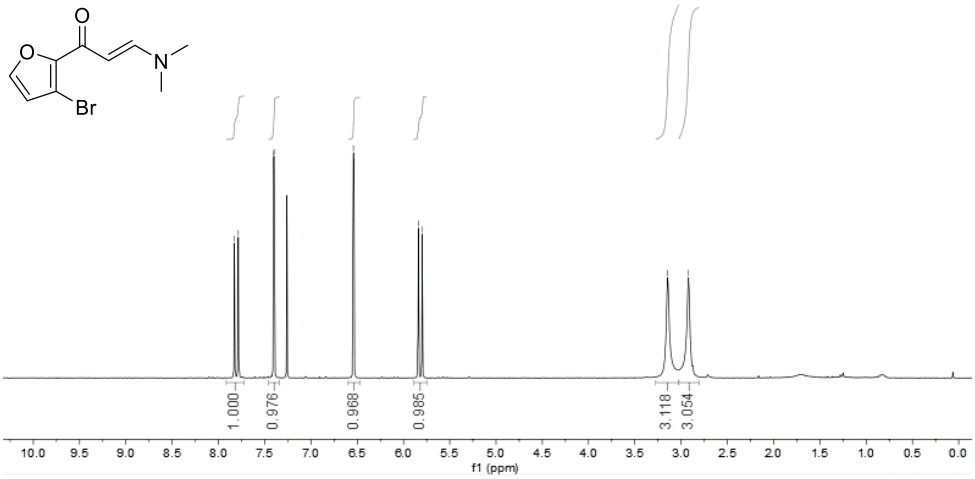


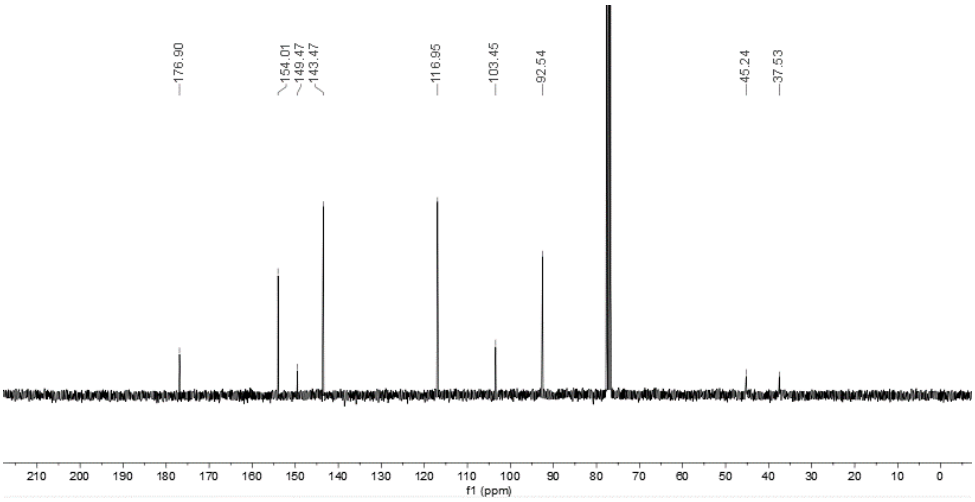
42c: (*E*)-1-(2-Bromo-5-fluorophenyl)-3-(dimethylamino)prop-2-en-1-one





42e: (*E*)-1-(3-Bromofuran-2-yl)-3-(dimethylamino)prop-2-en-1-one





43: 6-(4-Methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline