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Activación de aldehídos α,β-insaturados mediante aminocatálisis en procesos enantioselectivos. Cicloadiciones (3+2) y reacciones en cascada Michael/Henry

MEMORIA PRESENTADA POR

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Resumen

En el trabajo de investigación que se recoge en esta memoria se ha estudiado la activación de enales mediante catálisis vía ión iminio en diferentes transformaciones.

Primeramente se ha optimizado la reacción de cicloadición 1,3-dipolar entre iluros de azometino estables y aldehídos α,β-insaturados catalizada por un derivado de imidazolidinona quiral. Empleando esta reacción se han conseguido sintetizar una amplia gama de pirrroloisoquinolinas y pirroloftalazinas altamente sustituidas con buenos rendimientos y altos valores de diastereo y enantioselectividad. Asimismo se ha realizado un estudio mecanístico basado en datos computacionales y experimentales que nos ha permitido proponer que la reacción de cicloadición (3+2) estudiada transcurre a través de un proceso en cascada consistente en una secuencia de reacción Michael-Mannich, en el que la activación del aldehído α,β-insaturado vía formación de una sal de iminio, por condensación con el catalizador, juega un papel fundamental, ya que ejerce el deseado control estereoquímico.

Por otro lado se ha desarrollado una metodología para llevar a cabo una reacción de adición de Michael/Henry en cascada seguida de deshidratación en la que se accede a nitrociclohexadienos de manera estereocontrolada, partiendo de sustratos sencillos (2-nitrometilacrilatos y aldehídos α,β-insaturados), mediante activación vía ión iminio con un catalizador derivado de prolinol.

Laburpena

Jarraian aurkezten den ikerkuntza lanean ioi iminioaren bidezko enalen aktibazio katalitikoa hainbat eraldaketa kimikoetan aztertu egin da.

Hasteko, azometino iluro egonkorren eta ordezkapen ezberdina duten aldehido α,β-asegabeen arteko (3+2) zikloadizio organokatalitiko enantioselektiboa lortzeko metodologia orokor bat garatu da. Honen bidez ordezkapen anitzeko pirroloisokinolina eta pirroloftalazina ugari lortu dira, etekin altuekin eta diastereo- eta enantiokontrol bikainarekin. Era berean, datu konputazional eta esperimentaletan oinarrituriko ikerketa bat burutu da, zeinek ikasitako (3+2) zikloadizio erreakzioa etapaka gertatzen den mekanismo baten bitartez igarotzen dela proposatzeko moduan gaudelarik. Mekanismo hau Michael adizio-Mannich prozesu sekuentzial batean datza, zeinetan katalizatzailearen kondentsazioari esker gertatzen den iminio gatz baten eraketak eragiten duen aldehido α,β-asegabearen aktibazioak ezinbesteko papera betetzen duen, nahi genuen esterokontrola eragiten duelarik.

Bestalde, 2-nitrometilakrilato eta aldehido α,β-asegabeen arteko Michael adizio/Henry domino erreakzio eta jarraian gertatzen den deshidratazio prozesu bat aurrera eraman da. Prolinatik eratorritako amina sekundario bat erabili delarik, zeinen papera iminio gatz baten eraketa itzulgarriaren bitartez dipolarofiloa aktibatzea duen, eraldaketa enantio altuarekin lortu da, nitroziklohexadieno kiralak sintetizatzen direlarik.

Summary

During the research that it is summarized in the present memory, the activation of enals *via* iminium ion catalysis in different transformations has been studied.

Firstly, a 1,3-dipolar cycloaddition between stable azomethine ylides and α,β-unsaturated aldehydes catalyzed by a chiral imidazolidinone derivative has been optimized. Employing this methodology we have synthesized a large range of densely substituted pyrroloisoquinolines and pyrrolophthalazines with good yields and high values of diastereo- and enantioselectivity. Moreover, a mechanistic study has been carried out based on DFT calculations and experimental data which have allowed us to propose that the (3+2) cycloaddition reaction follows a sequential Michael addition/Mannich cyclization pathway. The formation of the iminium ion as a result of the condensation between the α,β-unsaturated aldehyde and the catalyst plays an essential role, regarding both reactivity and stereoselectivity.

On the other hand we have developed a methodology to carry out a cascade Michael/Henry reaction followed by a sequential dehydration. Starting from simple substrates (2-nitromethylacrilates and α,β-unsaturated aldehydes) and employing a prolinol-derivative catalyst a series of quiral nitrocyclohexadienes have been synthesized.

Abreviaturas, símbolos y acrónimos

Å	Amstrong
Ac	Acetilo
Aminocat.*	Aminocatalizador quiral
Ar	Arilo
Bn	Bencilo
Boc	*terc*-Butiloxicarbonilo
^{n}Bu	*n*-Butilo
^{t}Bu	*terc*-Butilo
^{o}C	Grado centígrado
Cat.*	Catalizador quiral
col.	Colaboradores
COSY	Espectroscopia de correlación
δ	Desplazamiento químico
DEPT	Ampliación sin distorsión por transferencia de polarización
dm	Decímetro
DMF	*N*,*N*-Dimetilformamida
DMSO	Dimetilsulfóxido
E	Electrófilo
e.e.	Exceso enantiomérico
EM	Espectrometría de masas
EMAR	Espectrometría de masas de alta resolución
equiv.	Equivalente
Et	Etilo
eV	Electrón voltio
EWG	Grupo electronatractor
FTIR	Espectroscopia de infrarrojos por transformada de Fourier
GC-MS	Cromatografía de gases-espectrometría de masas
HA	Ácido de Brønsted
HOMO	Orbital molecular ocupado de mayor energía
HPLC	Cromatografía líquida de alta resolución

HSQC	Correlación heteronuclear de cuanto sencillo
Hz	Hercio
IE	Impacto electrónico
IQ	Ionización química
J	Constante de acoplamiento
K	Grados Kelvin
LUMO	Orbital molecular desocupado de menor energía
m	Metro
mm	Milímetro
μm	Micrómetro
nm	Nanómetro
Me	Metilo
MHz	Megahercio
M.S.	Tamiz molecular
m/z	Relación masa/carga
NOESY	Espectroscopia de efecto nuclear Overhauser
Nu	Nucleófilo
OFBA	Ácido *o*-fluorobenzoico
Oxid.	Oxidante
P.f.	Punto de fusión
Ph	Fenilo
ppm	Partes por millón
^{i}Pr	*iso*-Propilo
^{n}Pr	*n*-Propilo
R	Alquilo
r.d.	Rendimiento diastereomérico
Rdto.	Rendimiento
RMN	Resonancia magnética nuclear
t.a.	Temperatura ambiente
TBS	*terc*-Butil dimetilsilil
TES	Trietilsililo
TFE	Trifluoroetanol

TfOH	Ácido trifluorometanosulfónico
TIPBA	Ácido 2,4,6-tri-*iso*-propil bencenosulfónico
TOF	Tiempo de vuelo
Ts	Tosilo
UV	Ultravioleta
λ	Longitud de onda

Abbreviations, symbols and acronyms

Å	Amstrong
Ac	Acetyl
Ar	Aryl
BINAM	1,1′-Binaphthalenyl-2,2′-diamine
BINOL	1,1′-Binaphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bs	Broad singlet
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
^{o}C	Degree centigrade
C_{arom}	Aromatic carbon
Cat.*	Chiral catalyst
cm	Centimeter
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
d_{ap}	Apparent doublet
DBU	1,5-Diazabicyclo[5.4.0]undec-5-ene
dd	Double doublet
ddd	Double doublet of doublets
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereomeric ratio
dt	Double triplet
E	Electrophile
e.e.	Enantiomeric excess
EI	Electronic impact
equiv.	Equivalent
Et	Ethyl
et al.	And others

EWG	Electron withdrawing group
ΔG^{react}	Change in Gibbs free energy of the reaction
$\Delta G^{\pm}$	Change in Gibbs free energy of the transition state
g	Gram
HRMS	High resolution mass spectrometry
HPLC	High performance liquid chromatography
Hz	Hertz
IR	Infrared
J	Coupling constant
Kcal	Kilocalorie
Lit.	Literature
m	Multiplet
$\mathbf{M^+}$	Molecular ion
Me	Methyl
mg	Miligram
MHz	Megahertz
min	Minute
mL	Mililitre
μL	Microlitre
mmol	Milimol
M.p.	Melting point
m/z	Mass/charge relation
n.d.	Not determined
NMR	Nuclear Magnetic Resonance
n.O.e.	Nuclear Overhauser effect
Nu	Nucleophile
Organocat.*	Chiral organocatalyst
Ph	Phenyl
^{i}**Pr**	*iso*-Propyl
^{n}**Pr**	*n*-Propyl
R	Alkyl
rt	Room temperature

s	Singlet
sat.	Saturated solution
Solv.	Solvent
t	Triplet
T	Temperature
t_{ap}	Apparent triplet
TBS	t*ert*-Butyl dimethylsilyl
TBAF	Tetrabutylammonium fluoride
TCNEO	Tetracyanoethylene oxide
td	Triplet of doublets
TFA	Trifluoroacetic acid
TfOH	Sulfonic acid
THF	Tetrahydrofuran
t.l.c	Thin layer chomatography
TMS	Trymethylsilyl
t_R	Retention time
TS	Transition state

Nota:

Las referencias bibliográficas de la presente memoria se recogen a pie de página y son independientes en cada uno de los capítulos, por lo que en los casos en que se ha considerado oportuno, han sido repetidas para comodidad del lector.

Índice

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1

Introducción

1. Síntesis asimétrica

El concepto de quiralidad y el adjetivo "quiral" han interesado e inspirado a los científicos de todo el mundo desde hace más de un siglo.[1] A nivel molecular la quiralidad se define como la propiedad que presentan ciertas moléculas de poseer una imagen especular no superponible, denominadas moléculas enantiomorfas o enantiómeros, propiedad que hace que dichas moléculas difieran en su respuesta ante la luz polarizada como consecuencia de la diferente disposición espacial de sus átomos o grupos de átomos. Así, cuando la luz polarizada pasa a través de una disolución de una sustancia quiral, se produce una rotación en el plano de polarización denominándose a estas sustancias compuestos ópticamente activos. Más pronunciadas son las diferentes propiedades biológicas que, en muchos casos, presentan los enantiómeros cuando interactúan con sus receptores biológicos, altamente estereoespecíficos y, por tanto, capaces de reconocer una molécula en una única disposición espacial.[2]

La importancia de la quiralidad en varios campos de la química, ciencias de materiales y ciencias de la vida ha llevado a un importante esfuerzo de la comunidad científica en su empeño por diseñar metodologías para conseguir moléculas quirales de forma enantipura que satisfagan la demanda de la industria alimentaria, agroquímica y farmacéutica, entre otras. Así, el acceso estereocontrolado a moléculas quirales se puede llevar a cabo de tres modos: por

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[1] Para una revisión del origen y evolución de la quiralidad ver: (a) Cintas, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 4016. (b) Riehl, J. P. *Mirror-Image Asymmetry. An Introduction to The Origin and Consequences of Chirality.* John Wiley & Sons: New York, **2010**. (c) Gal, J. *Chirality* **2011**, *23*, 1.

[2] (a) Francotte, E.; Lidner, W. *Chirality in Drug Research.* Wiley-VCH: Weinhein, **2006**. (b) Lin, G.-Q.; You, Q.-D.; Cheng, J.-F. *Chiral Drugs: Chemistry and Biologycal Action.* John Wiley & Sons: New Jersey, **2011**. (c) Nilos, M. G.; Gan, J.; Schlenk, D. *Effects of Chirality on Toxicity. General, Applied and Systems Toxicology.* John Wiley & Sons, **2011**. (d) Mori, K. *Chirality* **2011**, *23*, 449.

resolución de racematos, manipulando materiales de partida quirales o mediante síntesis asimétrica.[3]

La resolución de racematos consiste en la separación mediante métodos físicos o químicos de los enantiómeros que forman la mezcla racémica. La separación suele realizarse generalmente por cristalización, resolución cromatográfica, formación de sales diastereoméricas o resolución cinética.

Otra forma de conseguir compuestos ópticamente activos consiste en derivatizar compuestos de partida quirales. La metodología más empleada es la estrategia del *chiral pool*, basada en la utilización de compuestos quirales accesibles y asequibles que se modifican a través de procesos estereocontrolados con el fin de conseguir la molécula quiral objetivo, de manera que en el producto final quede incorporado en parte o en su totalidad el sustrato quiral. El mayor inconveniente de esta metodología lo encontramos en la dificultad que conlleva el hecho de encontrar las moléculas adecuadas que puedan ser precursoras del compuesto deseado y la frecuente imposibilidad de disponer de ambas formas enantioméricas.

Finalmente, la síntesis asimétrica consiste en la obtención de las moléculas quirales objetivo desde materiales de partida proquirales (Esquema 1.1). El diseño de una síntesis asimétrica puede basarse tanto en los sustratos (inducción interna), en los reactivos (inducción externa), como en ambos (doble inducción). Así, en el primer caso se lleva a cabo la transformación deseada diastereoselectivamente mediante el uso de auxiliares quirales, compuestos quirales que se unen covalentemente al sustrato de partida aquiral transformándolo en quiral. El

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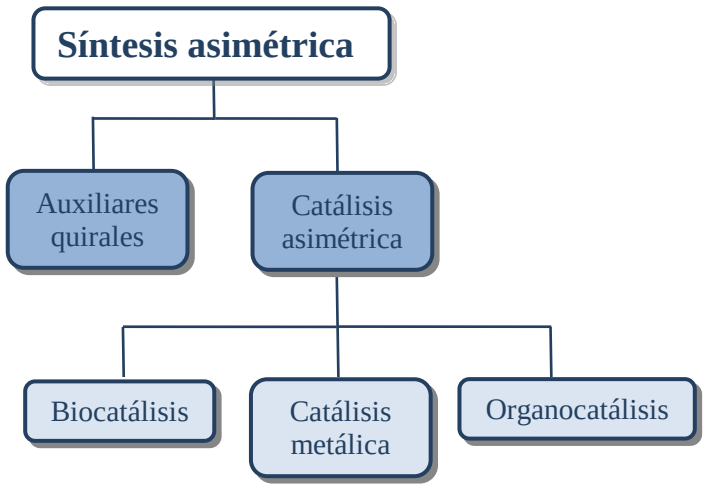
[3] Seebach, D.; Hungerbüler, E. *Syntheses of Enantiomerically Pure Compounds (EPC-Syntheses) in Modern Synthetic Methods* R. Scheffold, Ed., Salle & Sauerländer: Frankfurt, **1980**.

auxiliar quiral, una vez cumplida su función, se retira de la molécula, de manera que el proceso global puede considerarse enantioselectivo. La inducción asimétrica para la obtención de un compuesto quiral desde un sustrato aquiral puede provenir de un reactivo externo quiral que, de modo estequiométrico o subestequiométrico, controle la formación del nuevo o los nuevos centros estereogénicos en el producto final. Con respecto a la utilización de cantidades subestequiométricas de una sustancia enantiopura capaz de promover una reacción a través de un proceso asimétrico catalítico, existen tres metodologías: biocatálisis, catálisis metálica y organocatálisis.



Esquema 1. 1

En la catálisis enzimática o biocatálisis[4] se utilizan enzimas para realizar la transformación química deseada emulando el papel de las mismas cuando intervienen en las reacciones de los procesos biológicos, donde tiene lugar un

[4] Illanes, A. *Enzyme Biocatalysis. Principles and Applications.* Springer, **2008**.

reconocimiento preciso entre las molécula. Las características más destacadas de los enzimas son su poder catalítico y alta especificidad, siendo capaces de sintetizar un compuesto enantiopuro de un modo muy eficiente. Si bien su alta especificidad resulta una limitación en muchos casos en términos de generalidad y versatilidad sintética, el desarrollo de biotransformaciones cada vez más eficaces ha permitido emplear esta metodología en la producción de numerosas sustancias quirales a escala industrial.[5]

En la catálisis metálica asimétrica la especie catalítica es un complejo basado en un centro metálico, generalmente un metal de transición en el que reside la actividad catalítica, que se rodea de ligandos orgánicos quirales responsables del estereocontrol, pudiendo ser también éstos partícipes de la reactividad.[6] Los principios en los que se fundamentan las metodologías basadas en la catálisis metálica son: a) la activación de electrófilos poco reactivos por coordinación a un ácido de Lewis quiral, b) la formación de compuestos organometálicos quirales y c) la combinación de ambas.[7] El desarrollo de la catálisis asimétrica como metodología sintética fue motivo del Premio Nobel en 2001[8] a W.S. Knowles, R. Noyori y K. B. Sharpless por su larga y exitosa trayectoria investigadora en este campo, los dos primeros en reacciones de hidrogenación y el último en reacciones de oxidación. La catálisis organometálica asimétrica ha mostrado ser muy útil en la industria para la producción de compuestos enantiopuros al igual que la biocatálisis. Ambos tipos de catálisis han sido también combinados con éxito en

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[5] (a) Chin, T. H. *Handbook of Industrial Biocatalysis*. CRC Press: Florida, **2005**. (b) Blaze, H. U.; Smidt, E. *Asymmetric Catalysis and Industrial Scale. Challenges, Approach and Solutions.* Wiley-VCH: Weinheim, **2010**.

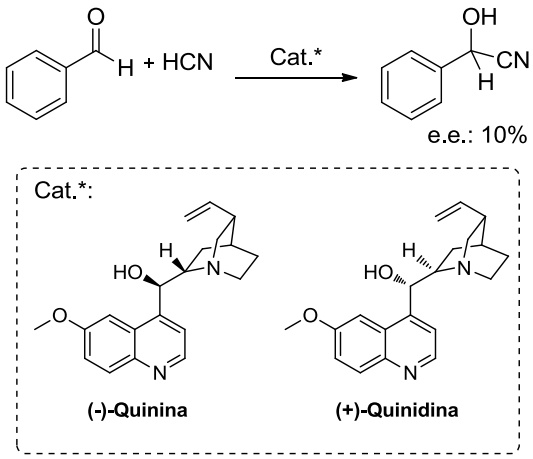
[6] Berrisford, D. J.; Carsten, B.; Sharpless, K. B. *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1059.

[7] Ma, J. A.; Chahard, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4566.

[8] Ahlberg, P. *Nobel Lectures in Chemistry (2001-2005).* World Scientific Publishing Company: London, **2008**.

procesos de resolución cinética dinámica para la obtención de compuestos quirales.[9]

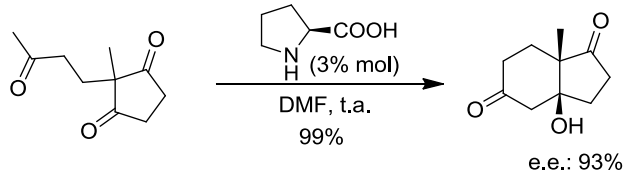
Finalmente, la organocatálisis asimétrica se fundamenta en la aceleración de una reacción química mediante una molécula orgánica enantiopura, de bajo peso molecular, que no contiene átomos metálicos en su estructura. La existencia de este tipo de proceso catalítico se conoce desde hace ya más de un siglo, cuando en 1912 Bredig[10] realizó la adición de HCN a benzaldehído catalizada por los alcaloides (-)-quinina y (+)-quinidina obteniendo, con un discreto exceso enantiomérico de apenas 10%, las correspondientes D-(-) y L-(+)-cianhidrinas, indicativo de la participación del alcaloide en el ciclo catalítico (Esquema 1.2).



Esquema 1. 2

[9] Pàmies, O.; Bäckvall, J.-E. *Chem. Rev*. **2003**, *103*, 3247.
[10] Bredig, G.; Fiske, P.S. *Biochem Z.* **1912**, *46*, 7.

Otro hito importante lo constituyó la transformación conocida como reacción de Hajos-Parrish-Eder-Sauer-Wiecher (Esquema 1.3),[11] que se fundamenta en la química estequiométrica de enaminas de Stork y describe, por primera vez, la formación reversible de una enamina como paso clave de un ciclo catalítico.



Esquema 1. 3

No obstante, tan sólo se llevan realizando trabajos de investigación de modo sistemático en este campo desde hace poco más de una década, a raíz de los trabajos consistentes en la activación de aldehídos mediante aminas secundarias quirales publicados en el año 2000, de modo independiente, por dos grupos de investigación.[12] Así, MacMillan y col. diseñaron un catalizador quiral derivado de imidazolidinona empleándolo con éxito en la primera reacción de Diels-Alder organocatalítica de ciclohexadienos con acroleína. Esta amina secundaria preparada *ad hoc* es capaz de activar el sustrato cabonílico por formación de un ión iminio intermedio (Esquema 1.4a). Por su parte, List, Lerner y Barbas III llevaron a cabo la primera reacción aldólica intermolecular organocatalítica mediada por L-prolina entre acetona y un amplio rango de aldehídos, vía formación de la correspondiente enamina, (Esquema 1.4b).

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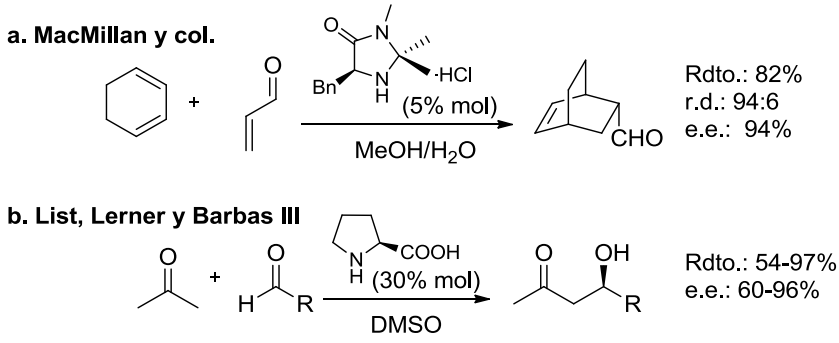
[11] (a) Eder, U.; Sauer, G.; Wiecher, R. *Angew. Chem. Int. Ed. Engl.* **1971**, *10,* 496. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

[12] (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. J. *J. Am. Chem. Soc.* **2000**, *122*, 4243. (b) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.



Esquema 1. 4

Desde entonces, este área de trabajo ha crecido de un modo tan espectacular que hoy en día es ya considerado como el tercer pilar de la catálisis asimétrica junto con la catálisis metálica y la biocatálisis. El auge experimentado por la organocatálisis se debe, sin duda, a las ventajas que ofrece en cuanto a simplicidad operacional, derivado de la estabilidad de los organocatalizadores frente al oxígeno y a la humedad ambiental, que permite una manipulación sencilla de la reacción sin equipos costosos ni sofisticados. Asimismo existe un gran número de organocatalizadores que son comerciales o fácilmente sintetizables. Otra ventaja asociada a la metodología es el hecho de poder llevar a cabo las reacciones con una mínima cantidad de disolvente o sin él, lo que junto con la ausencia de metales reduce considerablemente el impacto medioambiental.

2. Modos de activación en organocatálisis: aminocatálisis

Los organocatalizadores han sido clasificados típicamente en base al tipo de unión catalizador-sustrato; así, se pueden diferenciar dos grandes bloques: la catálisis covalente y no covalente (Figura 1.1).[13]

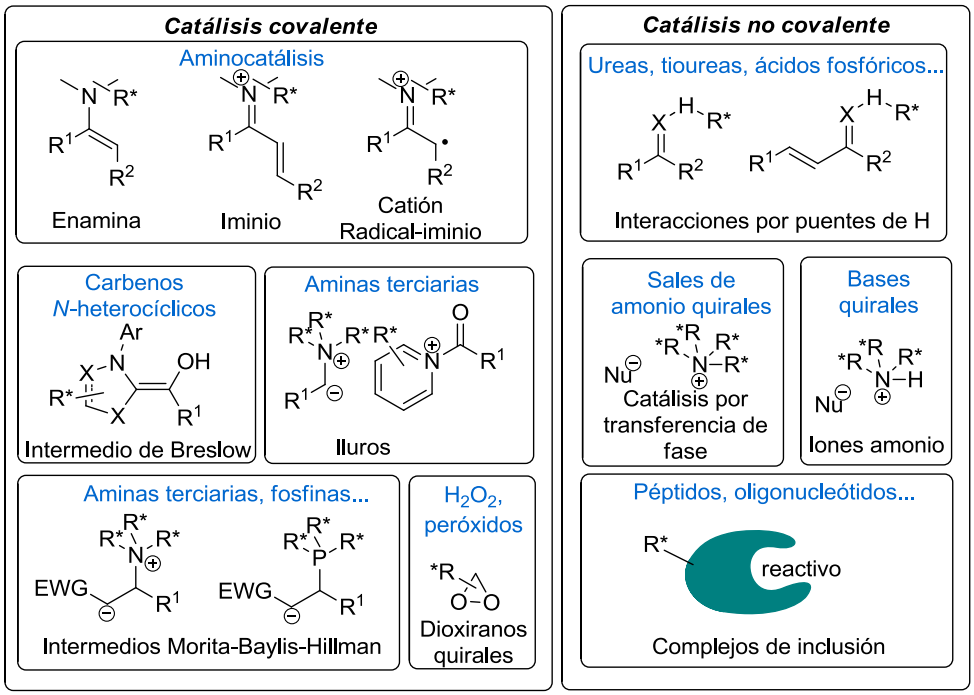


Figura 1. 1

La activación covalente requiere que el sustrato y el catalizador se unan covalentemente mediante una reacción reversible ya que, una vez cumplida su función, el catalizador deberá ser fácilmente separado del sustrato. En este apartado se encuentra la aminocatálisis, que se basa en la formación de

[13] Dalko, P.I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

intermedios activados de tipo azometino tales como enaminas, sales de iminio o cationes radical-iminio.[14] También hallamos el uso de carbenos *N*-heterocíclicos que forman intermedios de adición conocidos como intermedios de Breslow, el uso de aminas terciarias o fosfinas que actúan como bases de Lewis,[15] y los oxiranos quirales utilizados en reacciones de oxidación.[16]

En cuanto a los catalizadores que no se unen al sustrato de forma covalente, la interacción más común es la unión mediante puentes de hidrógeno; en este ámbito podemos enmarcar los trabajos relacionados con catalizadores de tipo urea, tiourea y ácidos fosfóricos[17] con los que se están consiguiendo muy buenos resultados. La interacción sustrato-catalizador también se puede basar en la formación de pares de iones quirales, bien en la catálisis de transferencia de fase, que implica el uso

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[14] (a) Melchiorre, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1360. (b) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465. (c) Renaud, P.; Leong, P. *Science* **2008**, *322*, 55. (d) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (e) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun*. **2007**, 3123. (f) Bertelsen, S.; Nielsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7356. (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev*. **2007**, *107*, 5471. (h) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.

[15] (a) Mansilla, J.; Saá, J. M. *Molecules* **2010**, *15*, 709. (b) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1. (c) Krishna, P. R.; Sachwani, R.; Reddy, P. S. *Synlett* **2008**, 2897. (d) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606. (e) Marion, N.; Diez-Gonzalez, S.; Nolan, S. P. *Angew. Chem. Int. Ed*. **2007**, *46*, 2988. (f) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (g) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905. (h) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614.

[16] (a) Wong O. A.; Shi, Y. *Top. Curr. Chem*. **2010**, *291*, 201. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (d) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (e) Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847.

[17] (a) Takemoto, Y. *Chem. Pharm. Bull*. **2010**, *58*, 593. (b) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (c) Yu, X. H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 516. (d) Connon, S. J. *Chem. Commun,* **2008**, 2499. (e) Miyabe, H.; Takemoto, Y. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 785. (f) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5173. (g) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520. (h) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418. (i) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289.

de sales de amonio o fosfonio quirales como catalizadores,[18] o bien mediante el empleo de aminas terciarias quirales que se utilizan como bases en la activación de un nucleófilo por desprotonación.[19] Finalmente, podemos incluir en este grupo las moléculas como éteres corona, ciclodextrinas etc.[20] que, formando un complejo anfitrión-huésped, activan el sustrato

Dado que en el presente trabajo de investigación se lleva a cabo la funcionalización de compuestos carbonílicos mediante activación con aminas secundarias, a continuación se realiza un resumen de los antecedentes descritos en este tipo de catálisis, la aminocatálisis asimétrica.

La aminocatálisis es una subárea de la organocatálisis asimétrica basada en la utilización de aminas quirales primarias y secundarias como catalizadores en reacciones de compuestos carbonílicos. El fundamento de la activación aminocatalítica emula el mecanismo de activación de los compuestos carbonílicos con ácidos de Lewis en el que tiene lugar una unión reversible de un ácido de Lewis a un sistema π aislado o conjugado, dando como resultado una redistribución electrónica alrededor del centro metálico. La condensación reversible de una amina secundaria con un compuesto carbonílico conduce a un

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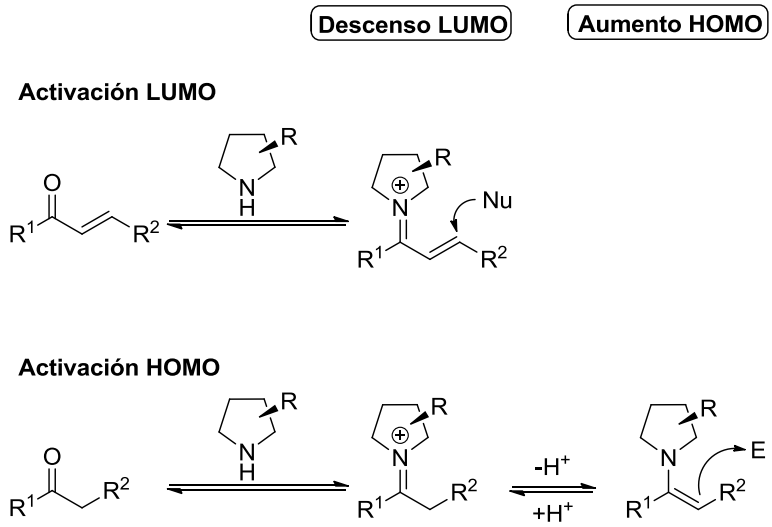
[18] (a) Jew, S.; Park, H. *Chem. Commun*. **2009**, 7090. (b) Hashimoto, T.; Maruoka, T. *Chem. Rev.* **2007**, *107*, 5656. (c) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, 40, 77. (d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed*. **2007**, *46*, 4222. (e) O´Donnell, M. J. *Acc. Chem. Res*. **2004**, *37*, 506. (f) Lygo, B.; Anderws, B. *Acc. Chem. Res*. **2004**, *37*, 518. (g) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (h) Martyres, D. *Synlett* **1999**, 1508. (i) Nelson, A. *Angew. Chem. Int. Ed*. **1999**, *38*, 1583.

[19] (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (b) Shen, J.; Tan, C. H. *Org. Biomol. Chem*. **2008**, *6*, 3229.

[20] (a) Rapi, Z.; Szabó, T.; Keglevich., G.; Sozöllösy, A.; Drahos, L.; Bakó, P. *Tetrahedron: Asymmetry* **2011**, *22*, 1189. (b) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures.* Wiley-VCH: Weinheim, **2007**. (c) Colby, E. A.; Davie, S. M.; Mennen, Y. X.; Miller, S. J. *Chem. Soc. Rev*. **2007**, *107*, 5759. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (e) Takahashi, K.; Hattori, K. *J. Inclus. Phenom. Mol.* **1994**, *17*, 1.

ión iminio intermedio que tiene como consecuencia un descenso de la energía del LUMO del sistema, un comportamiento similar al provocado por un ácido de Lewis. En sistemas conjugados la redistribución electrónica resultante de la formación del ión iminio facilita la adición conjugada del nucleófilo y las reacciones pericíclicas. En sistemas π aislados el descenso del LUMO aumenta la acidez del protón en α facilitando la formación de una enamina, elevando la energía de su HOMO (Esquema 1.5).



Esquema 1. 5

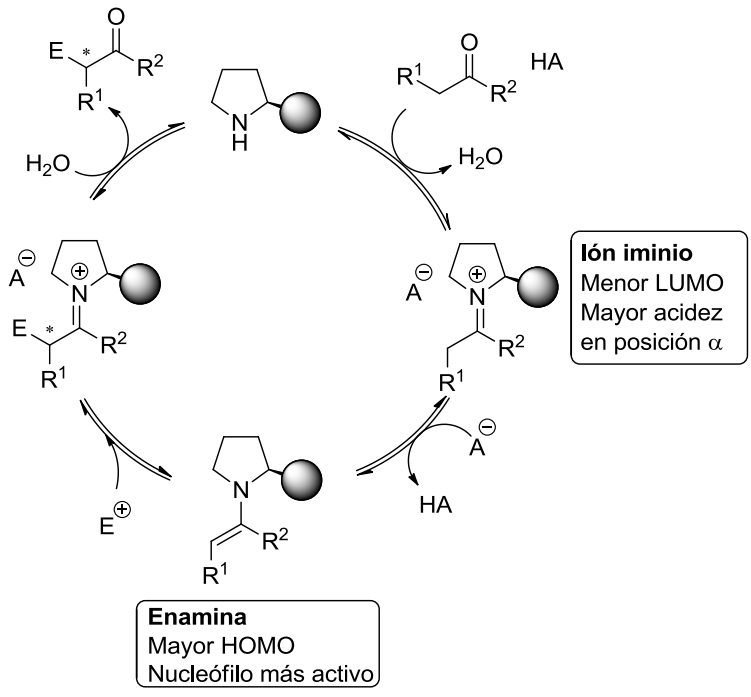
Estos patrones de activación dan como resultado cuatro posibles modos de funcionalización de compuestos carbonílicos según se activen aldehídos o cetonas no conjugados o α,β-insaturados. Empleando compuestos carbonílicos no conjugados es posible llevar a cabo funcionalizaciones electrófilas o nucleófilas en α; si se emplean compuestos carbonílicos α,β-insaturados pueden realizarse

funcionalizaciones con nucleófilos en posición β o con electrófilos en posición γ, en este caso, a través de intermedios de tipo dienamina.

2.1. Activación vía enamina

- Funcionalización en posición α

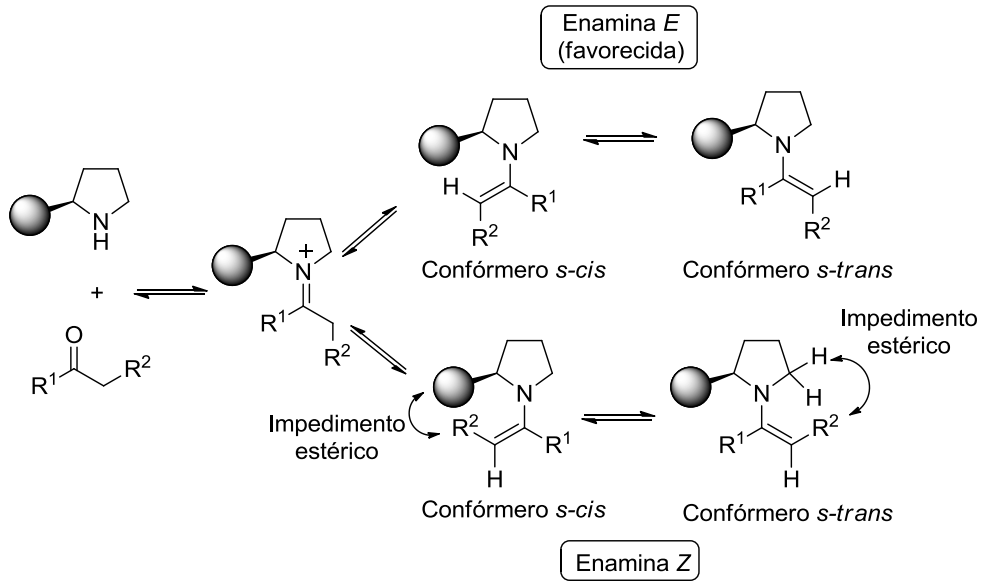
La activación vía enamina permite la funcionalización en posición α de aldehídos y cetonas enolizables con una amplia gama de electrófilos. El ciclo catalítico propuesto para la reacción está representado en el Esquema 1.6. Una condensación inicial entre el compuesto carbonílico y la amina promovida por un ácido (un disolvente prótico, un ácido externo añadido o una parte ácida presente en el catalizador), lleva a la formación de un ión iminio intermedio en equilibrio con la enamina correspondiente. La reacción de ésta con un electrófilo y la hidrólisis del ión iminio resultante libera el producto deseado, regenerando el catalizador. La principal característica de esta metodología es la transformación del aldehído proquiral en una enamina quiral, más nucleófila como consecuencia del aumento de energía del HOMO asociada al proceso.



Esquema 1. 6

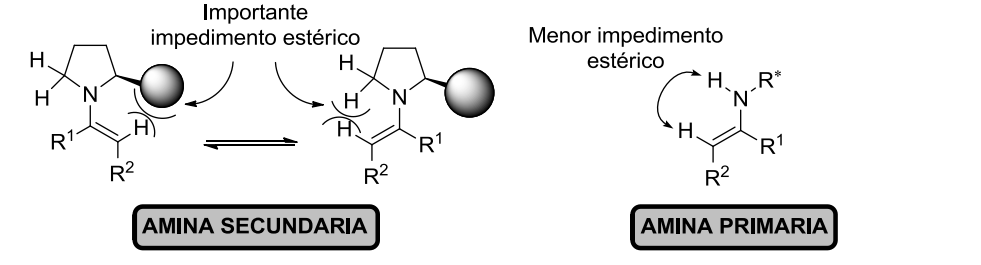
En este contexto, controlar la geometría de la enamina intermedia formada es fundamental para conseguir el control estereoquímico deseado. La condensación de una amina secundaria con un aldehído o cetona conduce a dos posibles diastereoisómeros que pueden tener configuración *Z* o *E*, dependiendo de la naturaleza del compuesto carbonílico y de la amina secundaria. En general, se consiguen mejores resultados cuando se emplean aldehídos como dadores de Michael que cuando se utilizan cetonas. Los aldehídos condensan más rápido con la amina secundaria y el control de la conformación de la enamina formada es más sencillo debido a la preferente conformación s-*trans* y a la mayor diferencia de tamaño entre los sustituyentes de la enamina (R^1 = H). Por otro lado, la baja actividad catalítica observada al utilizar aminas secundarias para activar cetonas,

derivada principalmente de la inherente dificultad asociada a la formación de las enaminas intermedias estéricamente congestionadas, se suma al problema del control de la geometría. Este problema se ve reducido al utilizar cetonas simétricamente sustituidas debido a la equivalencia química de los dos posibles regioisómeros. Sin embargo el uso de cetonas no simétricas en las que en el sustituyente R^1 se encuentran agrupaciones de diferente tamaño y naturaleza, supone que este inconveniente se agrave, resultando la adecuada elección del sustrato transcendental para el diseño de una metodología aminocatalítica efectiva (Esquema 1.7).



Esquema 1. 7

Una solución para solventar este problema podemos encontrarla en el uso de aminas primarias como catalizadores, las cuales han demostrado su efectividad en reacciones de Michael, mediante activación vía enamina.[21] La reacción de condensación entre la cetona y la amina primaria resulta estéricamente más favorable, formando la correspondiente imina, que está en equilibrio con la correspondiente enamina. Además, el control de la geometría del intermedio resulta más sencillo debido a la mayor diferencia de tamaño entre los sustituyentes coplanares a través del enlace N-C=C (Esquema 1.8).

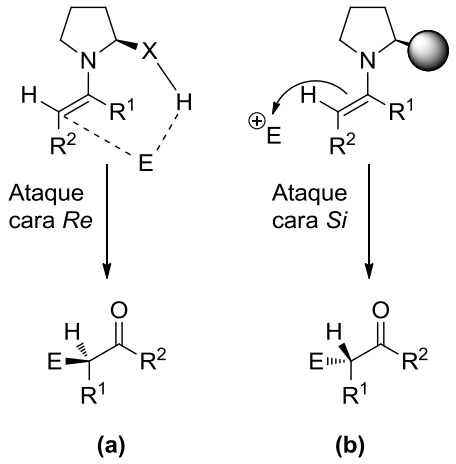


Esquema 1. 8

La estereodiferenciación ejercida por el catalizador quiral viene determinada por el tipo de sustituyente presente en el centro estereogénico del aminocatalizador. La presencia de grupos que puedan participar en enlaces de hidrógeno con el reactivo electrófilo (ácidos carboxílicos, amidas...), asiste el ataque del nucleófilo a través de un intermedio cíclico, dirigiendo por tanto el ataque del sustrato por la cara de la enamina en la que se sitúa el este sustituyente (Esquema 1.9a). Si, en cambio, el sustituyente es voluminoso, una de las caras

[21] (a) Chen, Y.-C. *Synlett* **2008**, 1919. (b) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (c) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (c) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. Angew. Chem. Int. Ed. 2008, 47, 6138.

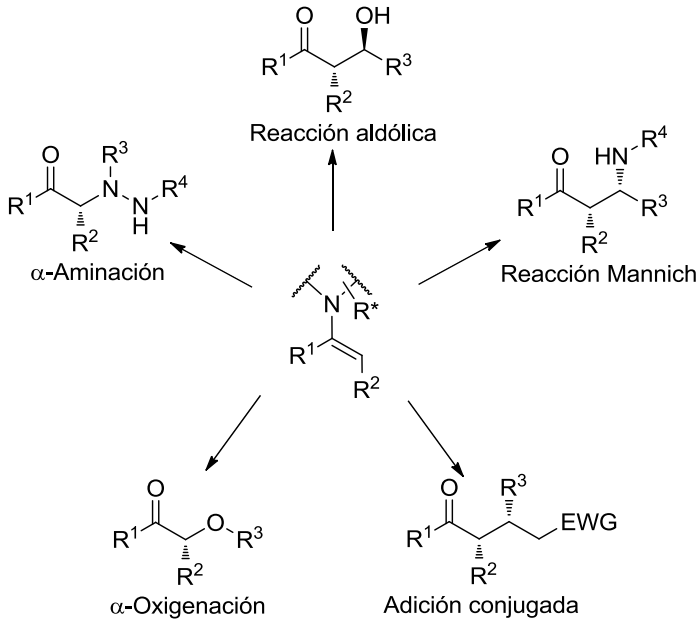
diastereotópicas de la enamina estará impedida por razones puramente estéricas, forzando que el ataque al electrófilo tenga lugar por la cara opuesta (Esquema 1.9b).



Esquema 1. 9

La activación vía enamina ha sido aplicada a un gran número de reacciones de adición;[22] las transformaciones más comunes en las que se ha utilizado esta metodología quedan resumidas en el Esquema 1.10.

[22] Pihko, P. M.; Majander, I.; Erkkilä, A. *Top. Curr. Chem*. **2010**, *291*, 29.



Esquema 1. 10

En 2007 la activación vía enamina derivó en un nuevo modelo de activación en organocatálisis, la activación vía SOMO, tras los trabajos descritos por MacMillan y col.[23] basados en la formación de intermedios iminio catión-radical consecuencia de la oxidación de la enamina[24] generada por condensación del aldehído y la amina quiral. Este catión-radical posee tres electrones π y un único orbital molecular ocupado individualmente (SOMO), más activo que el aldehído de partida (Esquema 1.11).

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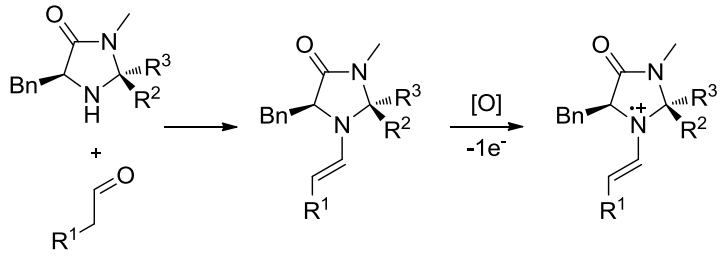
[23] Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

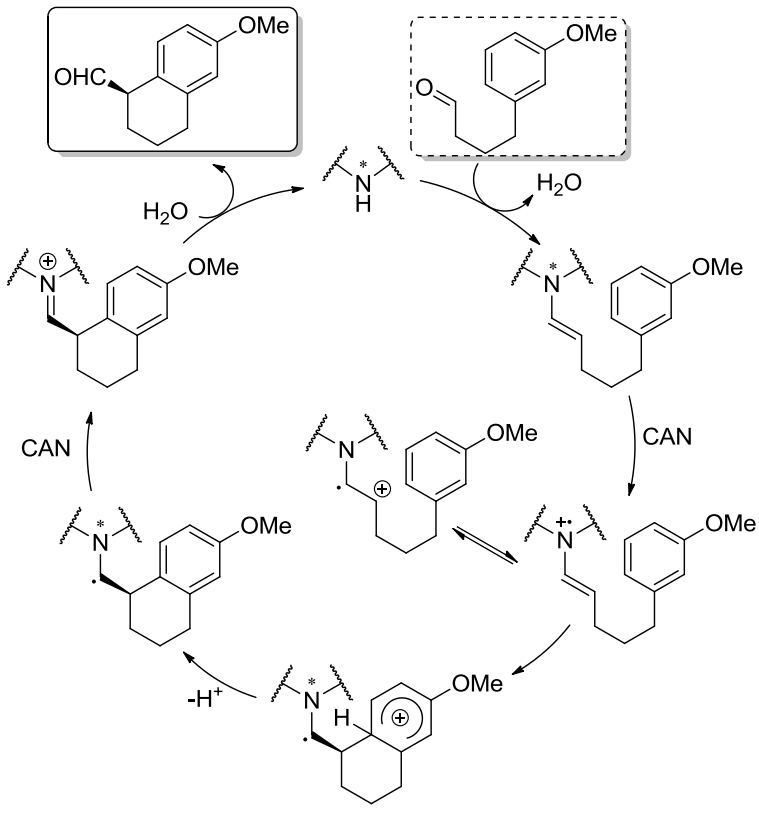
[24] Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632.



Esquema 1. 11

El interés de estas investigaciones pioneras en activación SOMO ha sido avalado por diversos trabajos entre los que cabe destacar el llevado a cabo por el grupo de investigación de Nicolau[25] en el que este tipo de activación promueve una reacción de α-arilación tipo Friedel-Crafts intramolecular en la que un derivado de imidazolidinona controla la estereoselectividad del proceso y el responsable de la transferencia del electrón es el amonio de cerio y nitrato (CAN) obteniéndose un amplio rango de bi- y triciclos altamente sustituidos de manera muy eficiente y con excelentes excesos enantioméricos (Esquema 1.12).

[25] Nicolau, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086.



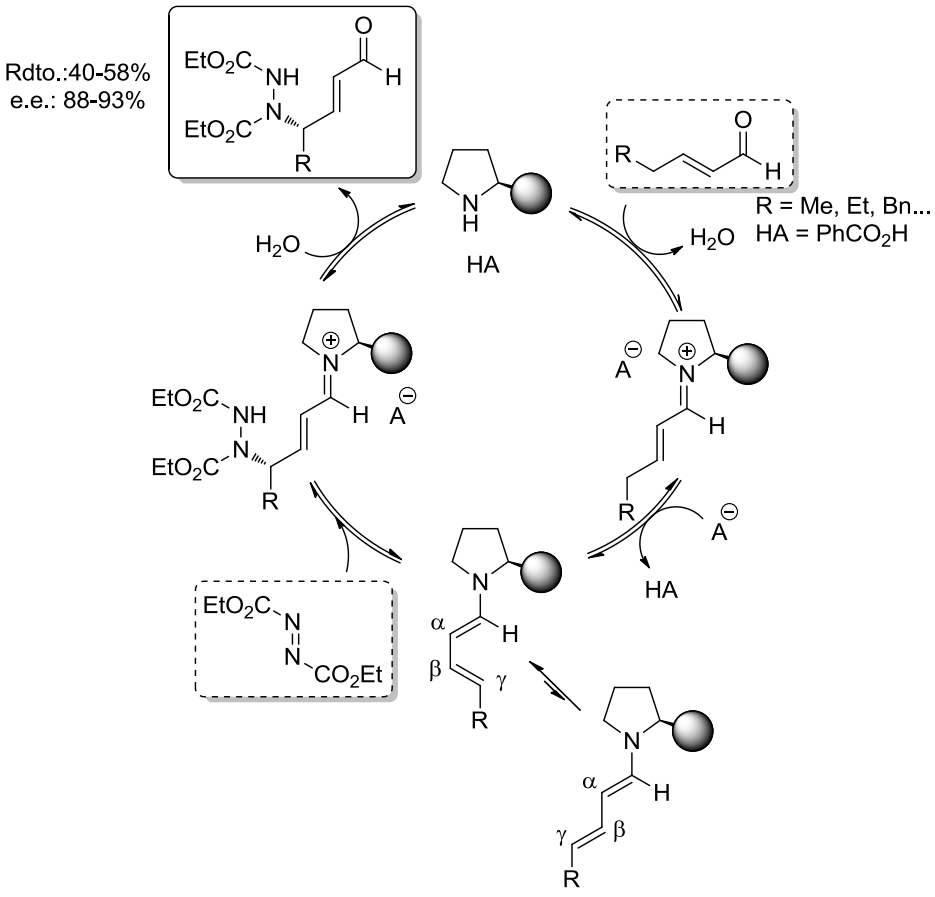
Esquema 1. 12

- Funcionalización en posición γ

Recientemente se ha dado un paso más en la activación vía enamina explorando las posibilidades que un enlace conjugado adicional puede ofrecer empleando la denominada catálisis vía dienamina.[26] En 2006, Jørgensen y col.[27] publicaron la γ-aminación organocatalítica enantioselectiva de aldehídos α,β-insaturados con azodicarboxilato de dietilo como fuente de nitrógeno electrófilo. En ese trabajo los autores propusieron que el empleo de cantidades catalíticas de una amina secundaria podía invertir la reactividad normal del aldehído α,β-insaturado a través de un intermedio de tipo dienamina (Esquema 1.13). Así, el ión iminio resultante de la condensación entre el compuesto carbonílico α,β-insaturado y el aminocatalizador evoluciona hacia una dienamina susceptible de reaccionar con el electrófilo en posición γ.

[26] Ramachay, D. B; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865.

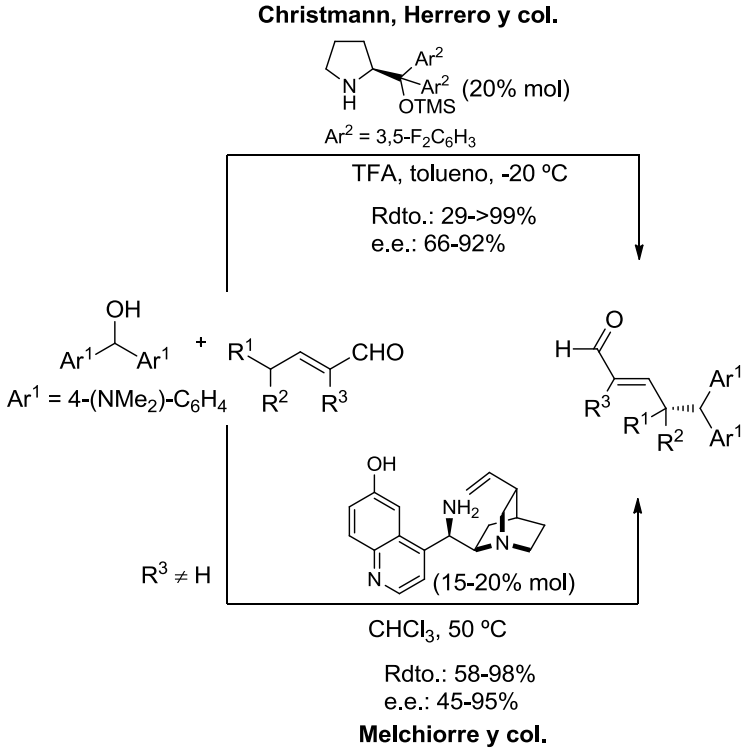
[27] Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 12973.



Esquema 1. 13

Este tipo de activación ha abierto una nueva dimensión en el campo de la aminocatálisis enantioselectiva, inspirando numerosos trabajos de investigación. A modo de ejemplo cabe mencionar el trabajo Christmann y col.[28] en el que haciendo uso de esta estrategia llevan a cabo la alquilación de aldehídos α,β-insaturados con carbocationes estabilizados a modo de electrófilos, obteniendo

buenos rendimientos y excesos enantioméricos, aunque no una completa regioselectividad debido a la competencia de la posible alquilación en posición α. Es por ello que una buena solución se encuentra en el bloqueo de esa posición tal y como lo describe Melchiorre[29] en un trabajo en el que realizan γ-alquilaciones regioselectivamente sobre aldehídos α,β-insaturados α-sustituidos promovidas por un derivado de quinidina mediante activación dienamina (Esquema 1.14).

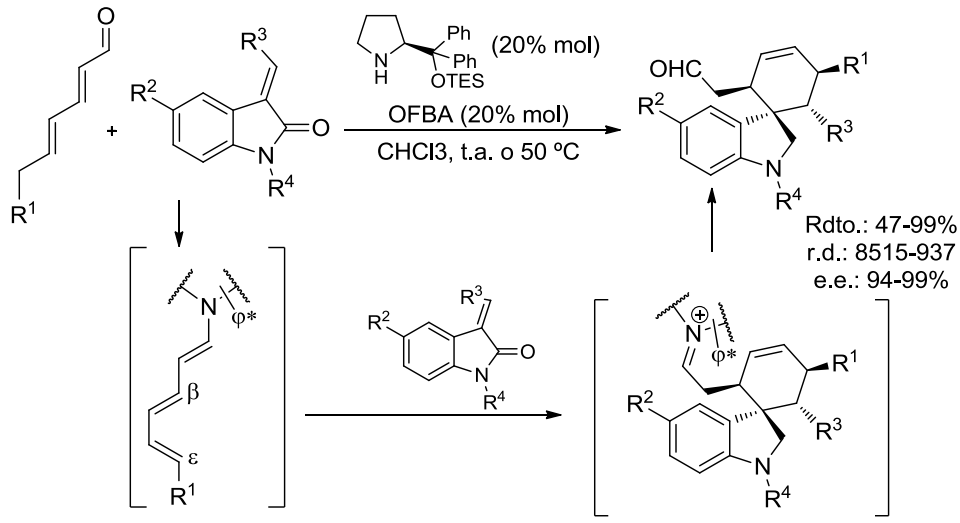


Esquema 1. 14

[28] Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70.

[29] Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 9685.

Recientemente se ha descrito incluso la habilidad del catalizador para transferir su información quiral hasta la posición ε, a seis átomos de distancia del punto de unión al carbono carbonílico, mediante intermedios trienamina.[30] La viabilidad de este tipo de activación surgió de los trabajos de colaboración de Chen y Jørgensen[31] extendiendo el sistema conjugado con 2,4-dienales. Posteriormente se ha extendido a 2,4-dienonas empleando como catalizadores aminas primarias basadas en cincona (Esquema 1.15).[32] La aplicabilidad de esta nueva estrategia a la síntesis de moléculas complejas está aún por determinar pero es, sin duda, prometedora.



Esquema 1. 15

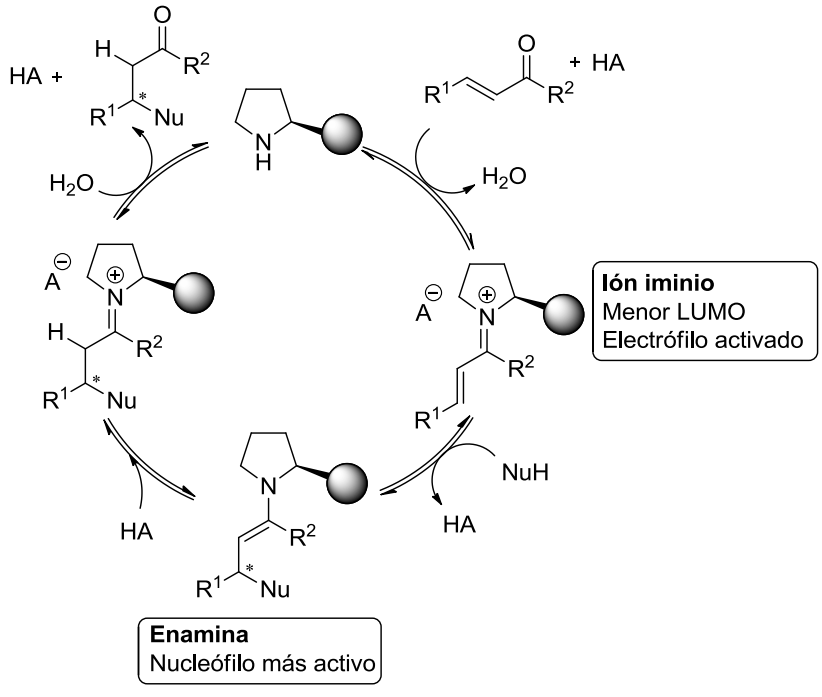
[30] Para revisión ver: Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 5290.

[31] (a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (b) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032. (c) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 8638.

[32] Xiong, X.-F.; Zhou, J.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2012**, 51, 4401.

2.2. Activación vía ión iminio

A diferencia de la catálisis vía enamina el concepto de la catálisis vía iminio, desarrollado por primera vez por MacMillan en el año 2000 en reacciones enantioselectivas de cicloadición Diels-Alder,[12a] se basa en el descenso de la energía del LUMO en el compuesto carbonílico α,β-insaturado asociada a la formación de un ión iminio por condensación con la amina quiral que actúa como catalizador, favoreciendo así el ataque del nucleófilo. A continuación este intermedio sufre el ataque del nucleófilo en posición β, conduciendo a una enamina, en equilibrio tautomérico con el correspondiente ión iminio que se hidroliza para dar el producto deseado liberando el catalizador (Esquema 1.16).



Esquema 1. 16

La estereodiferenciación vendrá determinada por la aproximación del nucleófilo a una u otra de las caras diastereotópicas del ión iminio intermedio. Como en el caso de la activación vía enamina, la estereodiscriminación vendrá gobernada por la información quiral proveniente del aminocatalizador, siendo un factor clave la geometría *E* o *Z* del ión iminio intermedio a la hora de obtener elevada enantioselecitividad. Así, la existencia de sustituyentes voluminosos en el centro estereogénico de la amina favorece la formación del ión iminio de geometría *E*, menos impedido en el caso de enales. Más problemático es el control de la geometría en el caso de enonas α,β-insaturadas, ya que el hecho de que los sustituyentes del carbono carbonílico sean de tamaño similar conduce a mezclas de isómeros *Z*/*E*. Sin embargo, el empleo de catalizadores bifuncionales que incorporen un elemento estereodirector determina el agrupamiento más reactivo del ión iminio intermedio en el paso de adición conjugada (Figura 1.2).

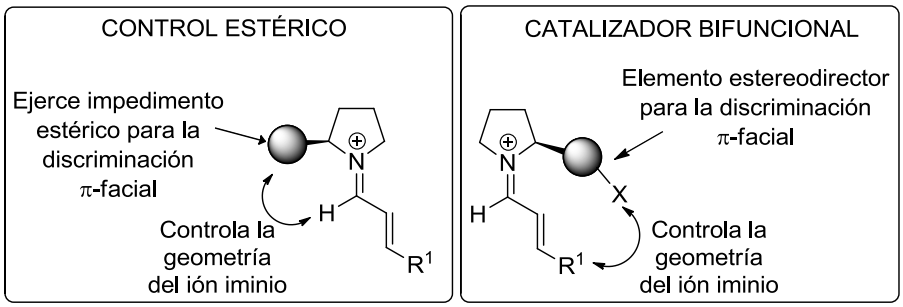
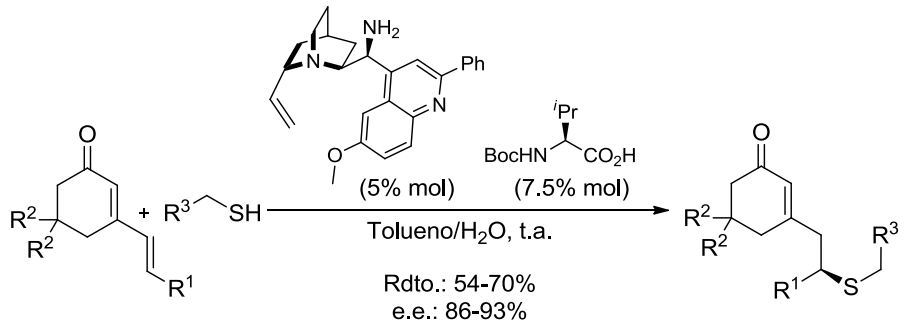


Figura 1. 2

Recientemente Melchiorre y col.[33] han publicado la posibilidad de extender la catálisis vía ión iminio a adiciones conjugadas vinílogas. Así, el efecto de la bajada de energía de LUMO debida a la formación del ión iminio intermedio imínico se hace extensible a diferentes puntos a través de la conjugación del sistema π en compuestos carbonílicos α,β,γ,δ-insaturados, pudiendo ser controlada la adición conjugada en posición δ. Con esta idea, llevaron a cabo la adición 1,6 estereocontrolada de alquiltioles a dienonas cíclicas empleando aminocatalizadores derivados de cincona (Esquema 1.17).



Esquema 1. 17

Para finalizar, hay que destacar que la combinación secuencial de los modos de activación comentados, vía enamina e ión iminio, da como resultado la posibilidad de llevar a cabo reacciones en cascada aumentando considerablemente la complejidad molecular con procesos operacionalmente muy simples, con mínimo coste e impacto medioambiental. Es por ello que este campo ha experimentado un desarrollo exponencial en los últimos años.

[33] Tian, X.; Liu, Y.; Melchiorre, P *Angew. Chem. Int. Ed.* **2012**, *51*, 6439.

3. Antecedentes del grupo de investigación en organocatálisis asimétrica

Nuestro grupo de investigación tiene una dilatada trayectoria en síntesis estereocontrolada. Si bien en los inicios se trabajó con auxiliares quirales,[34] la ambición de plantear nuevos retos que se adaptaran al curso de la evolución de la síntesis asimétrica, hizo que el esfuerzo se centrara en las metodologías organocatalíticas y más concretamente en aminocatálisis asimétrica.

Así se comenzó explorando la activación vía enamina en adiciones Michael al dimetilacetal de β-nitroacroleína empleando derivados de prolinol como catalizadores, consiguiéndose valores de rendimiento, diastereo- y enantioselectividad prometedoras. La investigación se completó con la transformación de las funcionalidades presentes en los aductos obtenidos hacia la síntesis de pirrolidinas polisustituidas enantioenriquecidas (Esquema 1.18).[35]

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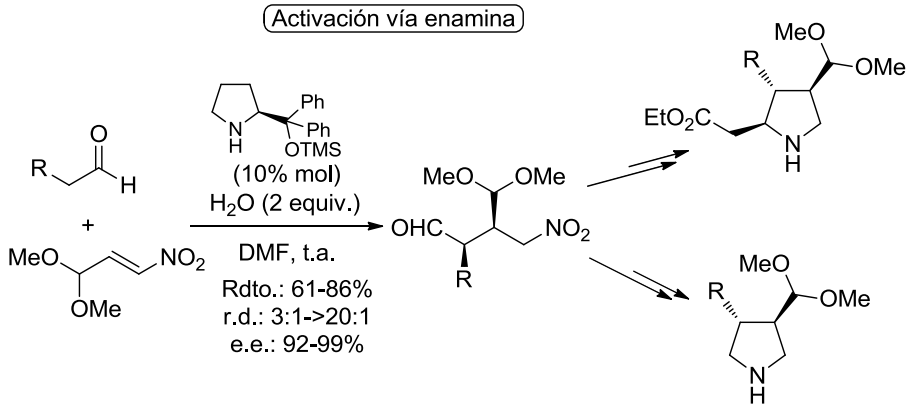
[34] Sobre la utilización de seudoefedrina como auxiliar quiral ver por ejemplo: (a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404. (b) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790. (c) Vicario, J. L.; Rodríguez, M.; Badía, D.; Carrillo, L.; Reyes, E. *Org. Lett*. **2004**, *6*, 3171. (d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588. (e) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2001**, *66*, 9030. (f) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2001**, *66*, 5801. (g) Anakabe, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Yoldi, V. *Eur. J. Org. Chem*. **2001**, 4343. (h) Vicario, J. L.; Badía, D.; Domínguez, E.; Rodríguez, M.; Carrillo, L. *J. Org. Chem*. **2000**, *65*, 3754.

[35] (a) Ruiz, N.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Eur. J.* **2008**, *14*, 9357. (b) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett*. **2006**, *8*, 61.

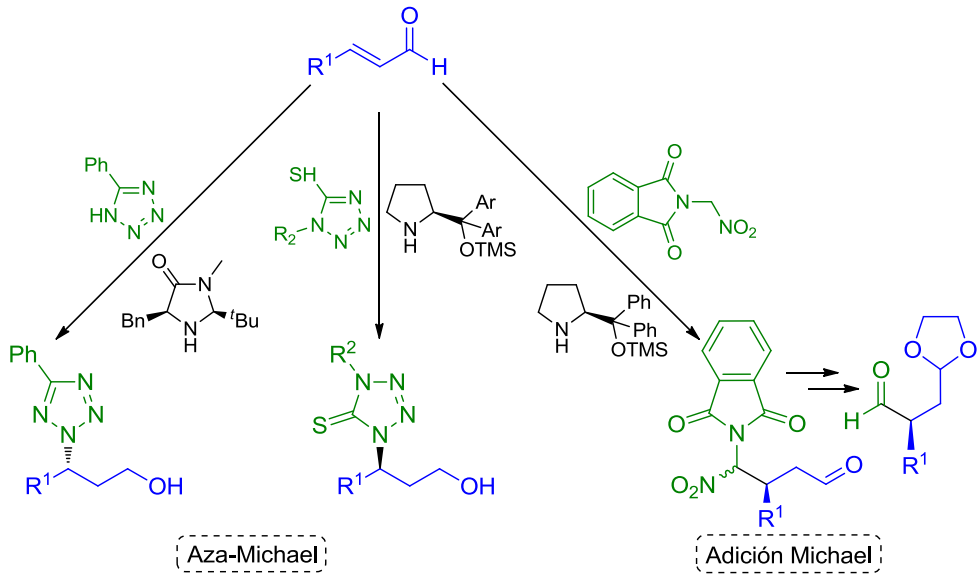


Esquema 1. 18

Paralelamente se iniciaron trabajos de investigación con aldehídos α,β-insaturados mediante activación organocatalítica vía ión iminio poniéndose a punto reacciones aza-Michael con heterociclos nitrogenados[36] y de adición conjugada de equivalentes *umpolung* de formilo.[37] En estos trabajos, además, ha quedado patente la versatilidad de los aductos obtenidos, en ocasiones altamente funcionalizados, mediante derivatización a otros compuestos de interés (Esquema 1.19).

[36] (a) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509.

[37] Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.



Esquema 1. 19

Asimismo se han llevado a cabo cicloadiciones 1,3-dipolares organocatalíticas enantioselectivas. El primer acercamiento a esta reacción, entre iluros de azometino y aldehídos α,β-insaturados tuvo lugar en 2007,[38] cuando se desarrolló un novedoso trabajo sobre la formación diastereo- y enantioselectiva de pirrolidinas altamente sustituidas utilizando la catálisis vía ion iminio. La cicloadición (3+2) organocatalítica resultó de gran valor sintético ya que permitía acceder a heterociclos nitrogenados de cinco miembros polisustituidos de una manera muy eficaz (Esquema 1.20). Este pionero trabajo fue aplicado a la preparación de productos de alto valor sintético.[39]

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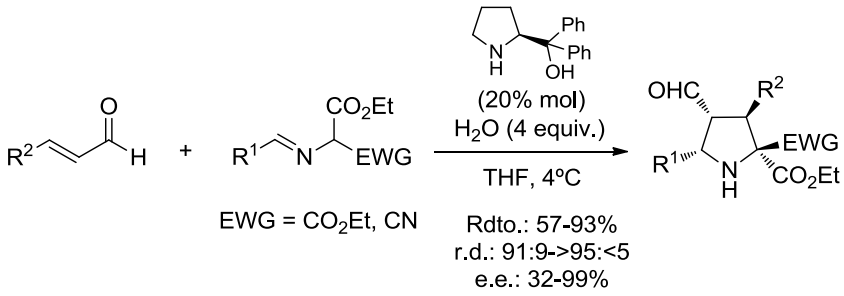
[38] (a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Catal.* **2011**, *353*, 3307. (b) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. Destacado en *Synfacts* **2007**, 813.

[39] Iza, A.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E.; Martínez, J. I. *Org. Biomol. Chem*. **2010**, *8*, 2238.

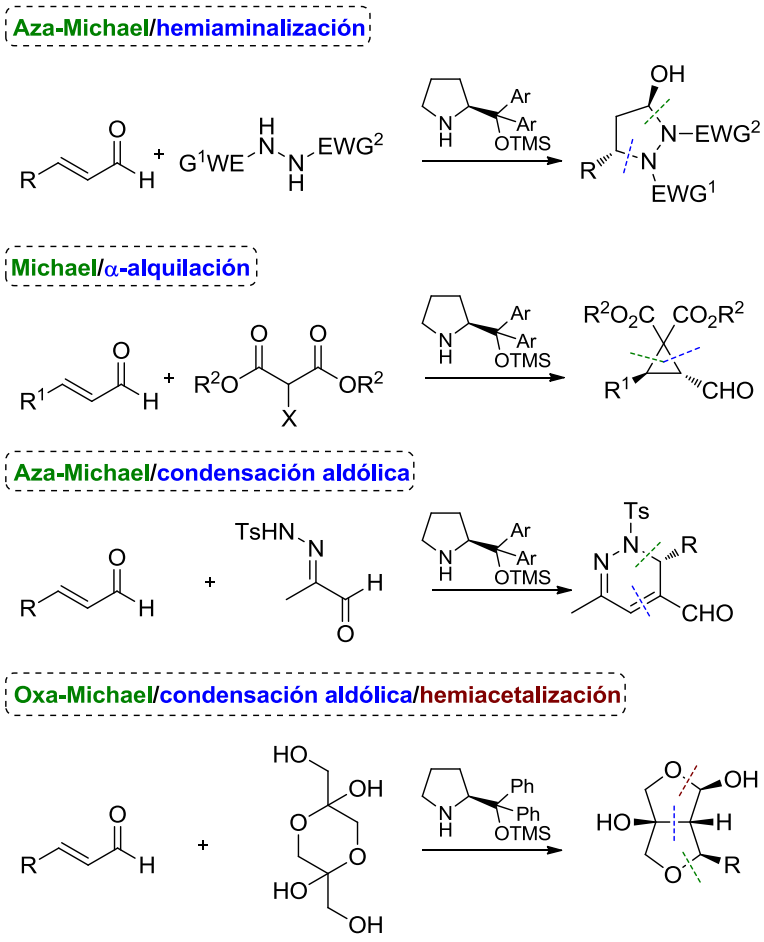


Esquema 1. 20

Más adelante el trabajo se complementó con un estudio exhaustivo del mecanismo de la reacción de cicloadición, avalado por cálculos computacionales, llegándose a la conclusión de que transcurría en una secuencia en cascada Michael/Mannich, siendo el primer paso de adición conjugada el paso determinante de la velocidad de reacción.[38a,40]

Las posibilidades que ofrece la utilización de aminocatalizadores en procesos dominó o cascada abre, sin duda, un amplio espectro de posibilidades como herramienta en química orgánica para la creación de complejidad molecular con el mínimo esfuerzo sintético. Este campo de trabajo también ha sido explorado con éxito en nuestro grupo de investigación en procesos iniciados por reacciones de adición conjugada mediante activación vía iminio. Como se puede ver en el Esquema 1.21 se han llevado a cabo procesos en cascada organocatalíticos combinando distintos tipos de activación, obteniendo una diversa variedad de productos de elevado potencial sintético de manera estereocontrolada.

[40] Reboredo, S.; Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L.; de Cózar, A.; Cossío, F. P. *Chem. Eur. J*. **2012**, 18, 7179.



Esquema 1. 21

Así se ha accedido a heterociclos de tipo pirazolidina por una secuencia en cascada aza-Michael/hemiaminalización entre enales e hidrazidas *N,N′*-disustituidas con elevada regio- y enantioselectividad.[41] La combinación secuencial de activación vía iminio/enamina se ha empleado también para la

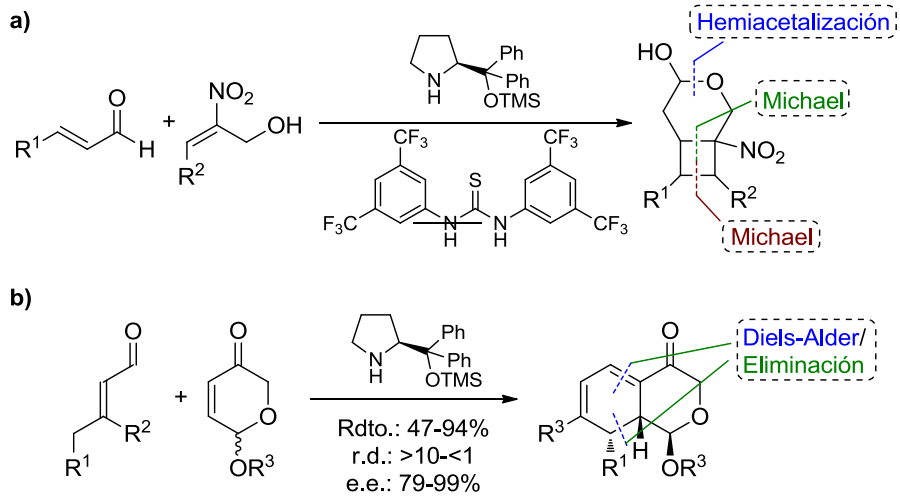
[41] Fernández, M.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 317.

síntesis de sistemas cíclicos y heterocíclicos quirales polifuncionalizados tales como ciclopropanos, por un proceso tándem adición conjugada/α-alquilación en medio acuoso,[42] dihidropiridazinas mediante una secuencia aza-Michael/condensación aldólica[43] y compuestos con estructura de furofuranos por una cadena de reacciones oxa-Michael/aldólica/hemiacetalización[44] que implica la formación de dos nuevos enlaces C-O y un nuevo enlace C-C y la generación simultánea de cuatro centros estereogénicos.

Cabe destacar los trabajos que se han llevado a cabo últimamente referentes a la catálisis vía dienamina. Así, se ha descrito una metodología para la síntesis enantio- y diastereocontolada de ciclobutanos por reacción directa de aldehídos α,β-insaturados y α-hidroximetilnitroestirenos empleando una amina secundaria quiral y una tiourea aquiral como pareja catalítica (Esquema 1.22a).[45] El éxito de la reacción recae en la activación dual del enal y el nitroalqueno por los catalizadores: la amina activa el enal vía dienamina y la tiourea activa el nitroalqueno mediante enlaces de hidrógeno. La reacción en cascada implica una secuencia de activación dienamina/iminio siendo una muestra más del potencial que ofrece la combinación de los diferentes modos de activación catalítica. Asimismo se ha desarrollado una metodología para la obtención de tetrahidro-1H-isocromanos entre 5-aciloxidihidropiranonas y aldehídos α,β-insaturados enolizables. La activación del enal por condensación con una amina secundaria a través de un intermedio tipo dienamina promueve una reacción en cascada Diels-Alder/eliminación dando como resultado la formación de tetrahidroisocromanos

[42] Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701.
[43] Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L, Badía, D. *Chem. Commun.* **2012**, *48*, 2092.
[44] Reyes, E.; Talavera, G.; Vicario, J. L.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701. Destacado en *Synfacts* **2009**, *9*, 1032.
[45] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104.

con muy buenos resultados tras un proceso de resolución cinética dinámica (Esquema 1.22b).[46]



Esquema 1. 22

Para finalizar haremos mención a un reciente trabajo en el que se ha explorado el potencial sintético de hidrazonas provistas de grupos dadores y aceptores en reacciones diazaénicas con aldehídos α,β-insaturados en condiciones de catálisis vía iminio. El estudio ha permitido acceder a ácidos carboxílicos γ-hidrazono sustituidos mediante una secuencia en cascada adición conjugada/oxidación/desplazamiento [1,3]-H. Es preciso resaltar, además, que la metodología puesta a punto resulta útil para la síntesis de α-ceto-1,5-diésteres β-sustituidos tras la posibilidad de transformar la hidrazona en un grupo carbonilo (Esquema 1.23).[47]

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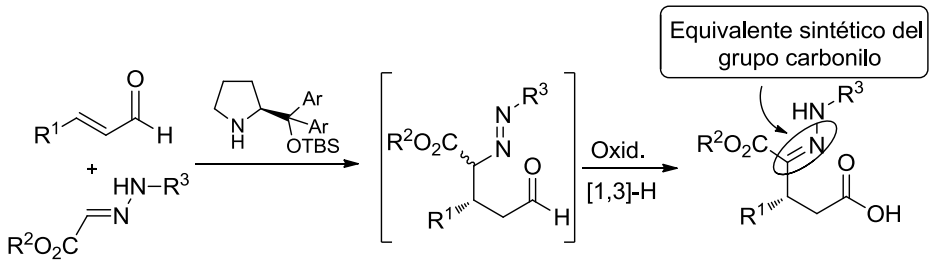
[46] Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.

[47] Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E.; Carrillo, L. *J. Am. Chem. Soc*. **2012**, *134*, 114872.


Equivalente sintético del grupo carbonilo
Ar
Ar
OTBS
Oxid.
[1,3]-H
OH

Esquema 1. 23

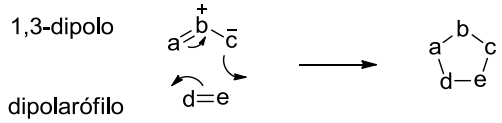
2

2

Cicloadición (3+2) organocatalítica enantioselectiva: Síntesis de pirroloisoquinolinas y pirroloftalazinas

1. Introducción

La cicloadición (3+2) o 1,3-dipolar consiste en la reacción entre un 1,3-dipolo y un sustrato insaturado para la formación de un ciclo de cinco eslabones. Esta metodología ha sido ampliamente empleada en química orgánica para la formación de heterociclos funcionalizados y es también muy útil para la generación simultánea de varios estereocentros si se establecen condiciones para controlar el curso estereoquímico del proceso.[1] En la reacción participan cuatro electrones π del dipolo y dos electrones π del compuesto dipolarófilo, en un proceso [4π + 2π] favorecido por las reglas de Woodward-Hoffman (Esquema 2.1).



Esquema 2. 1

En base a la teoría de orbitales frontera, la cicloadición 1,3-dipolar transcurre a través de la interacción de los orbitales HOMO y LUMO.[2] Dependiendo de las energías relativas de los orbitales de cada reactivo, la interacción puede darse entre el orbital HOMO del dipolo y el LUMO del dipolarófilo o viceversa. Además la sustitución y la estructura de ambos también juegan un papel importante, ya que los sustituyentes electronatractores de cualquiera de los

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[1] Algunos artículos de revisión: (a) Pellissier, H. *Tetrahedron* **2012**, *68*, 2197. (b) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (c) Hashimoto, T.; Maruoka, K. *1,3-Dipolar Cycloaddition*. Ma, S. (Ed) *Handbook of Cyclization Reaction.* Wiley-VCH: Weinheim, **2010**. (d) Kissane, M.; Maguire, A. *Chem. Soc. Rev*. **2010**, *39*, 845. (e) Nájera, C.; Sansano, J. M.; Yus, M. *J. Braz. Chem. Soc.* **2010**, *21*, 377. (f) Pineiro, M.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2009**, 5287. (g) Nájera, C.; Sansano, J. M. *Org. Biomol. Chem.* **2009**, *7*, 4567. (h) Stanley, L. M.; Sibi, M. P. *Chem. Rev*. **2008**, 2887. (i) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (j) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (k) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863.

[2] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions.* Wiley-Interscience: London, **1976**.

reactivos disminuyen la energía tanto del orbital HOMO como del LUMO; por el contrario, sustituyentes con carácter electrondador la aumentan. En el caso de sustituyentes conjugados, éstos hacen ascender la energía del orbital HOMO, pero disminuir la del LUMO. En base a la clasificación de Sustmann[3] existen tres tipos de interacción dependiendo de los sustituyentes de los reactivos. En la de **Tipo I**, el LUMO del dipolarófilo interactúa con el HOMO del dipolo, lo que ocurre especialmente cuando hay sustituyentes electrondeficientes en el dipolarófilo. En la interacción **Tipo II** cualquiera de los orbitales HOMO o LUMO del dipolo o dipolarófilo puede participar en la reacción ya que la diferencia de energía entre ellos es muy pequeña. Finalmente, nos encontramos con la interacción de **Tipo III**, donde la reacción tiene lugar entre el LUMO del dipolo y el HOMO del dipolarófilo, común para los dipolarófilos con sustituyentes electrondadores (Figura 2.1).

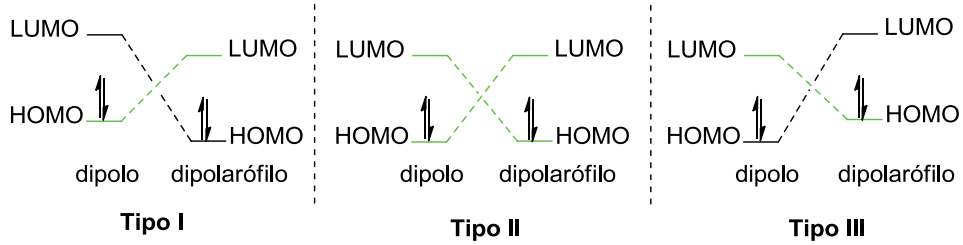

Figura 2. 1

Además de la pequeña diferencia energética necesaria entre los orbitales frontera, se ha de tener en cuenta el solapamiento entre los orbitales para que la reacción sea favorable. Esto permite prever la regioselectividad del proceso en función de la naturaleza electrónica del dipolo y del dipolarófilo, pudiendo así

[3] Sustmann, R. *Tetrahedron Lett.* **1971**, *12*, 2717.

diseñar los reactivos con los sustituyentes adecuados para la obtención de la regioselectividad buscada.

Si bien fue el prestigioso químico americano Smith[4] quien describió originalmente las adiciones 1,3 cíclicas, fue Huisgen[5] quien realizó los trabajos más exhaustivos, por lo que a menudo, ciertas cicloadiciones (3+2) llevan su nombre. Desde su descubrimiento las propuestas mecanísticas no han estado exentas de polémica. Así, Huisgen aseguraba que la reacción transcurría de forma sincrónica y concertada,[6] mientras que Firestone proponía un mecanismo dirradicalario por pasos.[7] El argumento principal de esta discusión era la estereoquímica del producto final: Huisgen alegaba que el hecho de que se conserve la relación geométrica de los reactivos en el producto tenía que deberse a su condición de reacción concertada; Firestone rebatía explicando que la diastereoselectividad de la cicloadición ocurría porque la energía necesaria para girar el enlace en el intermedio dirradicalario es mayor que la energía de activación para promover el cierre del anillo. En la actualidad la visión más extendida es que, cuando la reacción tiene lugar de forma concertada, ésta suele ocurrir de forma no sincrónica, de modo que uno de los enlaces σ se va creando antes que el otro.[8] No obstante, que el mecanismo sea concertado o por etapas

4 Smith, L. I. *Chem. Rev*. **1938**, *23*, 193.

5 Huisgen, R. *Angew. Chem. Int. Ed.* **1963**, *2*, 565.

6 (a) Huisgen, R. *J. Org. Chem.* **1968**, *41*, 403. (b) Huisgen, R. *J. Org. Chem.* **1968**, *33*, 2291.

7 (a) Firestone, R. A. *Tetrahedron* **1977**, *33*, 3009. (b) Firestone, R. A. *J. Org. Chem.* **1972**, *37*, 2181. (c) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285.

8 (a) Neumann, F.; Lambert, C.; Scheyler, P. v. R. *J. Am. Chem. Soc*. **1998**, *120*, 3357. (b) Yoshioka, Y.; Yamaki, D.; Kiribayashi, S.; Tsunesada, T.; Nishino, M.; Yamaguchi, K.; Saito, I. *Electron. J. Theor. Chem.* **1997**, *2*, 218. (c) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res*. **1995**, *28*, 81. (d) Lluch, J. M.; Bertrán, J. *Tetrahedron* **1979**, *35*, 2601.

depende de la estructura y naturaleza de los sustituyentes tanto del dipolo como del dipolarófilo.[9]

Los compuestos 1,3-dipolares que se emplean en este tipo de transformaciones pueden dividirse en dos bloques dependiendo de su estructura: de tipo anión alílico y de tipo anión propargílico/alenílico. Los 1,3-dipolos de tipo alílico poseen cuatro electrones en tres orbitales p_z paralelos, perpendiculares a su vez al plano del dipolo y el átomo central de estos dipolos pertenece frecuentemente a los grupos V y VI. Así, como ejemplo representativo encontramos nitronas, iluros de azometino, iluros, iminas de carbonilo o iminas de azometino entre otros. Los dipolos propargílicos/alenílicos son lineales, debido a la presencia de un doble enlace ortogonal al sistema π deslocalizado. En este tipo de dipolos el átomo central sólo puede ser del grupo V, ya que únicamente estos elementos pueden soportar una carga positiva en un estado tetravalente. Como aniones tipo propargilo/alenilo se han utilizado, entre otros, óxidos de nitrilo, iminas de nitrilo, iluros de nitrilo, diazoalcanos o azidas (Figura 2.2).

[9] Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.

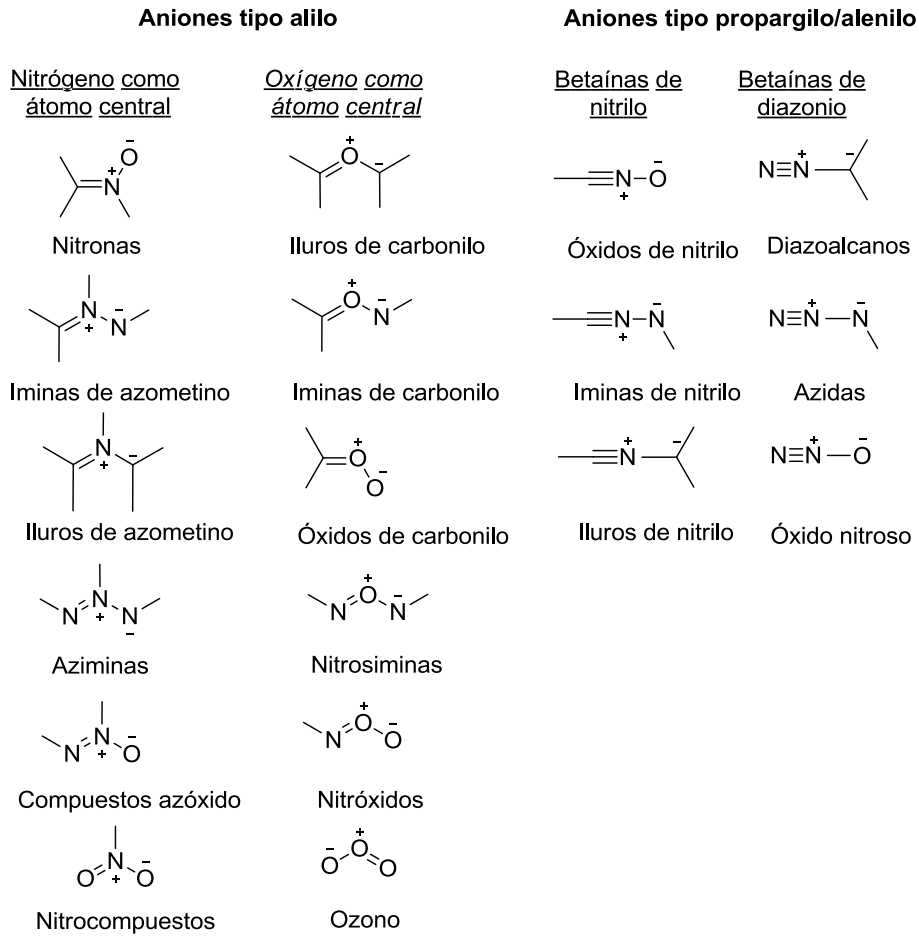

Figura 2. 2

En cuanto al dipolarófilo, cualquier compuesto que contenga una insaturación puede participar como tal en la reacción de cicloadición. Esto incluye la situación más común, que supone el empleo de alquenos o alquinos, pero también contempla la posibilidad de utilizar compuestos que contienen funcionalidades heterotómicas como aldehídos, cetonas, iminas, hidrazonas etc. donde además la insaturación puede estar aislada o conjugada.

Cuando la reacción de cicloadición 1,3-dipolar es concertada, no es sólo regioselectiva sino que también es estereoselectiva[2,5] y estereoespecífica, manteniéndose la estereoquímica del dipolo y del dipolarófilo en el producto final.

En lo que se refiere a la disposición relativa entre los sustituyentes provenientes del dipolo y los del dipolarófilo se debe tener en cuenta que existe la posibilidad de obtener dos diastereoisómeros denominados *endo* y *exo* que difieren en la configuración relativa de los sustituyentes del dipolarófilo con respecto al dipolo.[10] Generalmente, las interacciones orbitálicas secundarias existentes entre el sustituyente del dipolarófilo, típicamente un grupo electronatractor, y el sistema π formado por el 1,3-dipolo, se traducen en una situación que favorece el estado de transición que conduce a la formación del diastereoisómero *endo*. En los casos en los que se observa la formación preferente del isómero *exo*, el origen del cambio de la diastereoselectividad se suele basar en efectos de tipo estérico, aunque otros factores tales como efectos del disolvente, enlaces de hidrógeno o incluso interacciones electrostáticas pueden también intervenir a favor de la formación preferente de uno u otro diastereoisómero.

Finalmente, para lograr un control total en la configuración absoluta de los nuevos estereocentros creados en la reacción de cicloadición, la condición establecida para la obtención de un único estereoisómero viene dada por la capacidad para bloquear de manera eficaz una de las caras estereotópicas del dipolo o del dipolarófilo. Para que esto suceda, son dos los puntos sobre los que se puede incidir, lo que nos permite clasificar los métodos disponibles para llevar a cabo reacciones de cicloadición (3+2) estereocontroladas en dos tipos. En primer lugar, pueden emplearse dipolos o dipolarófilos quirales, dando lugar en este caso

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[10] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*. Verlag Chemie: Weinheim, **1970**.

a procesos diastereoselectivos. Por otro lado, el empleo de un catalizador quiral puede ser el responsable de la diferenciación facial, siendo en estos casos procesos enantioselectivos.

1.1. Cicloadición 1,3-dipolar organocatalítica

La estereoselectividad y especificidad inherente a la cicloadición 1,3-dipolar confiere a esta reacción unas características privilegiadas con vistas a la aplicación en el área de la síntesis orgánica asimétrica. Por ello han sido muchos los grupos interesados en desarrollar metodologías que permitieran acceder a ciclos de cinco miembros altamente sustituidos de manera diastereo- y enantioselectiva. En procesos catalíticos han sido empleados tanto catalizadores metálicos como organocatalizadores quirales para dar acceso a las ciclos deseados. Por ser el tema que nos ocupa pasaremos a continuación a realizar un breve repaso por los estudios que se han llevado a cabo en reacciones (3+2) organocatalíticas utilizando diferentes tipos de dipolos.

- Cicloadiciones (3+2) organocatalíticas asimétricas con nitronas como 1,3-dipolos

Las reacciones de cicloadición (3+2) con nitronas han sido ampliamente estudiadas en síntesis asimétrica. Una de las razones de ello puede ser que, a diferencia de la mayoría de los dipolos, las nitronas suelen ser compuestos estables que no requieren de formación *in situ*. Además, un valor añadido al empleo de nitronas es la gran variedad de compuestos nitrogenados con tres centros estereogénicos contiguos a los que es posible acceder desde la

isoxazolidinona formada en el proceso de ciclación, tales como aminoalcoholes, aminoácidos, aza-azúcares o alcaloides.

En los últimos años, paralelamente al auge de la organocatálisis, se han desarrollado versiones asimétricas organocatalíticas de la cicloadición 1,3-dipolar con nitronas.[11] En el año 2000 MacMillan y col.[12] presentaron la primera cicloadición 1,3-dipolar enantioselectiva organocatalítica con nitronas y aldehídos α,β-insaturados. La estrategia empleada se fundamenta en el descenso de energía LUMO del dipolarófilo asociado a la formación reversible de un ión iminio α,β-insaturado que permite llevar a cabo la reacción empleando cantidades catalíticas de una amina quiral. En concreto, empleando la imidazolidinona mostrada en el Esquema 2.2, una variedad de aldehídos α,β-insaturados se hicieron reaccionar con una amplia serie de nitronas proporcionando las correspondientes isoxazolidinonas con excelente rendimiento y estereocontrol. La diastereoselectividad y el sentido de la inducción asimétrica observada son consistentes con la formación de un ión iminio intermedio de geometría *E* de modo que la cicloadición tiene lugar por la cara menos impedida del dipolarófilo.

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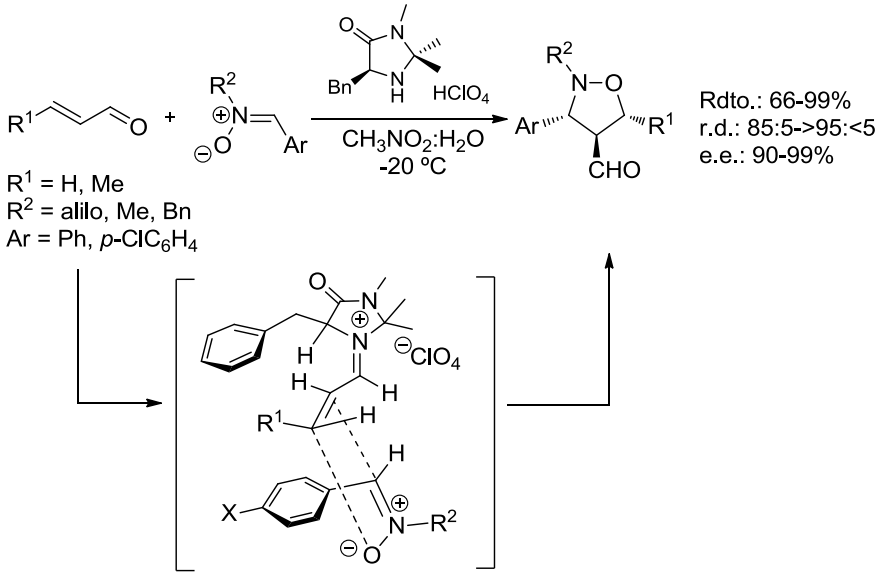
[11] Hong, C.-H. *Enantiocatalyzed Cycloadditions*. Mahrwald, R. (Ed.) *Enantioselective Organocatalyzed Reactions II. Asymmetric C-C Bond Formation Processes*. Springer Dordrecht Heidelberg London: New York, **2011**.

[12] Jen, W. S.; Weiner, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.



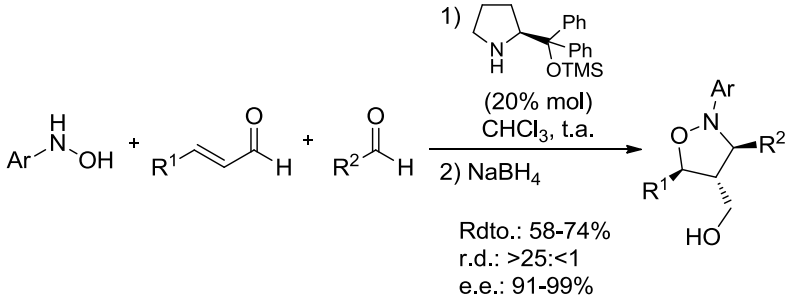
Esquema 2. 2

También en el contexto de la aminocatálisis cabe destacar el uso de derivados de difenilprolinol como catalizadores en este tipo de transformaciones. Así Karlsson y Högberg[13] describieron una cicloadición 1,3-dipolar enantioselectiva de nitronas a 1-cicloalquen-1-carbaldehídos promovida por sales de pirrolidinio quirales, obteniendo la isoxazolidina bicíclica *exo*, con muy buenos valores de rendimiento y diastereoselectividad, aunque con enantioselectividad de moderada a baja. Córdova y col.[14] llevaron a cabo un proceso *one pot* en el que el dipolo se genera *in situ* desde la correspondiente *N*-arilhidroxilamina y reacciona con un aldehído α,β-insaturado proporcionando, tras reducción del grupo formilo, la

[13] (a) Karlsson, S.; Höegberg, H.-E. *Eur. J. Org. Chem*. **2003**, 2782. (b) Karlsson, S.; Höegberg, H.-E. *Tetrahedron: Asymmetry* **2002**, *13*, 923.

[14] (a) Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5701. Ver también (b)Vesely, J.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem. Eur. J.* **2008**, *14*, 2693.

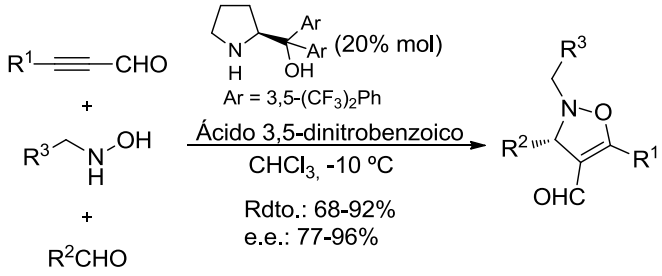
correspondiente isoxazolidina con buen rendimiento y estereoselectividad (Esquema 2.3).



Esquema 2. 3

Recientemente Sun y col.[15] han implementado un protocolo para llevar a cabo la cicloadición entre aldehídos acetilénicos y nitronas mediante activación vía iminio. La metodología emplea α,α-bis(3,5-ditrifluorometilfenil)prolinol como catalizador y ácido 3,5-dinitrobenzoico como aditivo para favorecer la formación del ión iminio en una operación *one pot* formando el dipolo *in situ*. La estrategia permite el acceso a 4-isoxazolinas quirales bajo condiciones suaves de reacción con buenos rendimientos y elevada enantioselectividad (Esquema 2.4).

[15] Cai, X.; Wang, C.; Sun, J. *Adv. Synth. Catal.* **2012**, *354*, 359.



Esquema 2. 4

Cabe destacar el trabajo de Zhong y col.[16] en el que desarrollaron una síntesis *one pot* altamente estereoselectiva de isoxazolidinas, con control de cinco centros estereogénicos, mediante una secuencia dominó Michael/formación de nitrona/cicloadición (3+2) entre 7-oxohept-2-enoato, una nitroolefina y fenilhidroxilamina catalizada por α,α-difenilprolinoltrimetilsilil éter empleando ácido acético como aditivo (Esquema 2.5). Además la aplicabilidad sintética de los aductos obtenidos se evidencia mediante su transformación en los correspondientes α-hidroxi-γ-aminoácidos. Los mismos autores extendieron esta metodología a la síntesis de indoles con cuatro centros estereogénicos empleando como dipolarófilo bis(fenilsulfonil)eteno con excelentes rendimientos y excesos enantioméricos (superiores al 99%).[17] Asimismo con una estrategia similar han aplicado una secuencia en cascada adición de Michael/formación de nitrona/cicloadición entre enoatos de nitroolefinas, aldehídos e hidroxilaminas en medio acuoso promovida por el mismo catalizador.[18]

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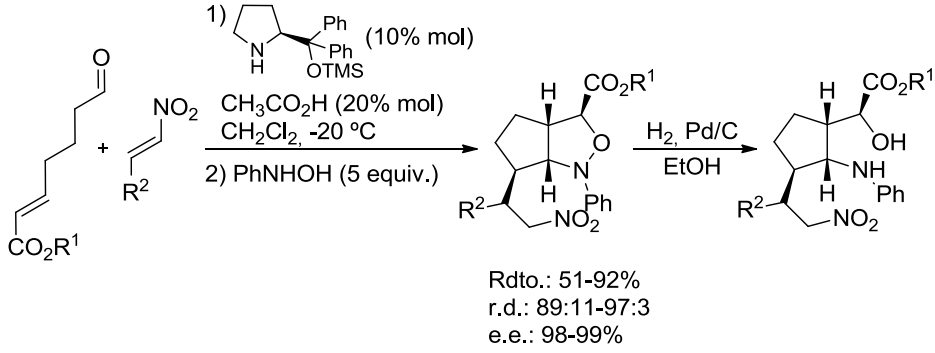
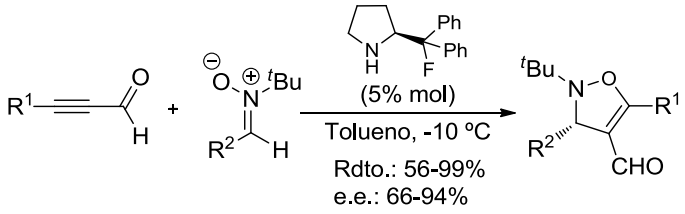
[16] Zhu, D.; Lu, M.; Dai, L.; Zhong, G. *Angew. Chem. Int. Ed*. **2009**, *48*, 6089.
[17] Chua, P. J.; Tan, B.; Yang, L.; Zeng, X.; Zhu, D.; Zhong, G. *Chem. Comm*. **2010**, *46*, 7611.
[18] Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem. Eur. J.* **2010**, *16*, 3842.



Esquema 2. 5

Es destacable un reciente trabajo de Alemán y col.[19] que propone una cicloadición 1,3-dipolar de nitronas con alquinales mediada por fluorodifenilmetilpirrolidinas dando acceso a 4-isoxazolinas con excelentes valores de rendimiento y enantioselectividad. Cabe acentuar la baja carga de catalizador necesaria que ilustra la eficiencia de la transformación (Esquema 2.6).



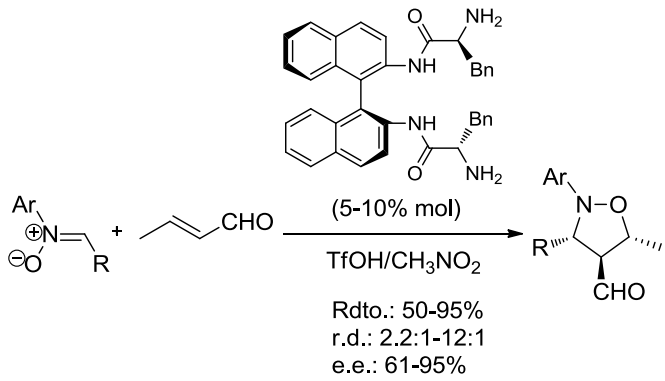
Esquema 2. 6

En este contexto cabe destacar, por último, el trabajo de Jurczak[20] en el que se utilizan diamidas híbridas derivadas de (*S*)-BINAM y α-aminoácidos para promover el proceso de cicloadición de nitronas aromáticas a crotonaldehído vía

[19] Alemán, J.; Fraile, A.; Marzo, L.; Ruano, J. L. G.; Izquierdo, C.; Díaz-Tendero, S. *Adv. Synth. Catal.* **2012**, *354*, 1665.

[20] Weselinski, Ł.; Stepniak, P.; Jurczak, J. *Synlett* **2009**, 2261.

formación de ión iminio (Esquema 2.7). Los resultados óptimos se obtienen con el catalizador basado en L-fenilalanina y ácido trifluorometanosulfónico como aditivo proporcionando los cicloaductos como diastereoisómeros *endo* (valores superiores al 76%) y excesos enantioméricos de hasta 95%. Hay que apuntar, no obstante, que estos resultados no mejoran los obtenidos para las mismas reacciones promovidas por derivados de prolina. Este catalizador ha sido posteriormente empleado por los mismos autores con nitronas derivadas de glioxilato con buenos resultados.[21]

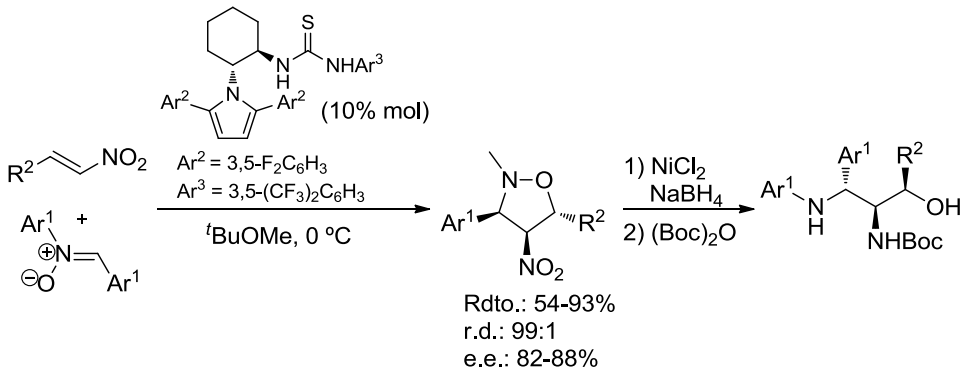


Esquema 2. 7

La capacidad de los ácidos de Brønsted para activar el dipolarófilo mediante la formación de puentes de hidrógeno tiene varios ejemplos representativos en reacciones 1,3-dipolares con nitronas. Así, por ejemplo, Chen y col.[22] describieron en 2008 la primera cicloadición 1,3-dipolar asimétrica organocatalítica de nitronas a β-alquilnitroolefinas promovida por un catalizador tipo tiourea-pirrol derivado de (*R,R*)-1,2-diaminociclohexano que actúa interaccionando selectivamente con el

[21] Weselinski, Ł.; Słik, E.; Jurczak, J. *Tetrahedron Lett.* **2011**, *52*, 381.
[22] Du, W.; Liu, Y.-K.; Yue, L.; Chen, Y.-C. *Synlett* **2008**, 2997.

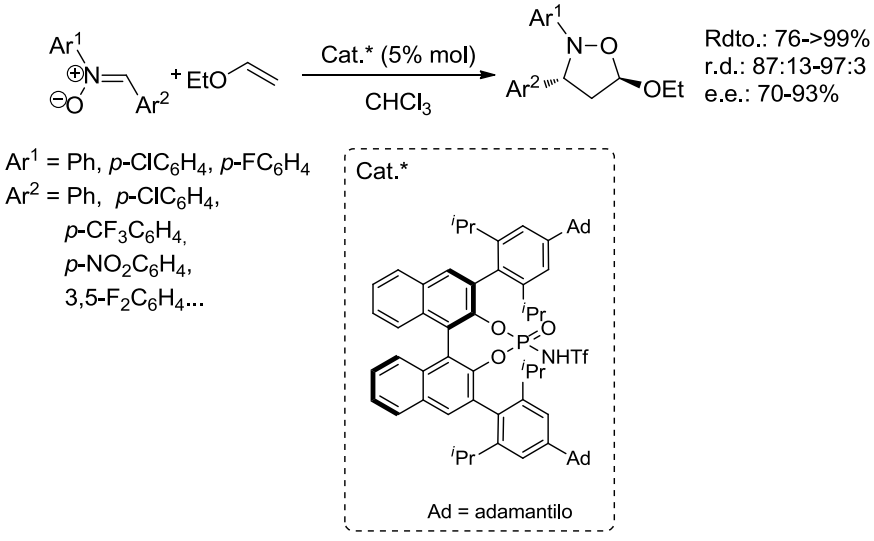
grupo nitro de la olefina. De modo general, el empleo de un 10% de catalizador en *terc*-butilmetil éter como disolvente proporciona la correspondiente isoxazolidina quiral con buen rendimiento, enantioselectividad de moderada a buena y excelente diastereoselectividad para un amplio rango de sustratos. Cabe mencionar, además, la transformación de los aductos a derivados de 2,3-diaminopropanol enantiopuros con tres estereocentros contiguos (Esquema 2.8).



Esquema 2. 8

En el mismo año en un estudio del grupo de Yamamoto[23] se describió la cicloadición de demanda electrónica inversa entre nitronas y etilviniléteres promovida por una *N*-triflifosforamida derivada de BINOL, capaz de activar la nitrona por interacciones vía enlace de hidrógeno. Con tan sólo un 5% de catalizador es posible llevar a cabo la reacción en una hora proporcionando los correspondientes cicloaductos *endo* con excelentes rendimientos, diastereoselectividades y elevada enantioselectividad (Esquema 2.9).

[23] Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2411.



Esquema 2. 9

La selectividad *endo* de la cicloadición es opuesta a la observada para la misma reacción catalizada por complejos de aluminio.[24] Estos resultados ponen de manifiesto la utilidad de la catálisis mediada por ácidos de Brønsted en síntesis asimétrica, complementaria a la catálisis por ácidos de Lewis.[25] Cabe destacar, además, que la presencia de sustituyentes alquilo voluminosos en posición *para* de los grupos arilo de la estructura del esqueleto de BINOL parece ser crucial para conseguir buena selectividad, lo que sin duda es un factor importante a considerar en el diseño de estos ácidos de Brønsted.

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[24] Simonsen, K. B.; Bayón, P.; Hazell, R. G.; Gothelf, V.; Jørgensen, K. A. *J. Am. Chem. Soc*. **1999**, *121*, 3845.

[25] Nakashima, D.; Yamamoto, H. *Org. Lett.* **2007**, *7*, 1251.

- Cicloadiciones (3+2) organocatalíticas asimétricas con iluros de azometino como 1,3-dipolos

Las versiones asimétricas de la cicloadición 1,3-dipolar que emplean iluros de azometino como 1,3-dipolos, constituyen un área de interés en química orgánica sintética como metodología para el acceso a pirrolidinas de manera regio y estereocontrolada,[26] siendo escasas las aproximaciones organocatalíticas que se han descrito en este contexto, en gran parte debido a la inestabilidad propia de los iluros de azometino que hace necesaria su preparación *in situ* en la mayoría de los casos.

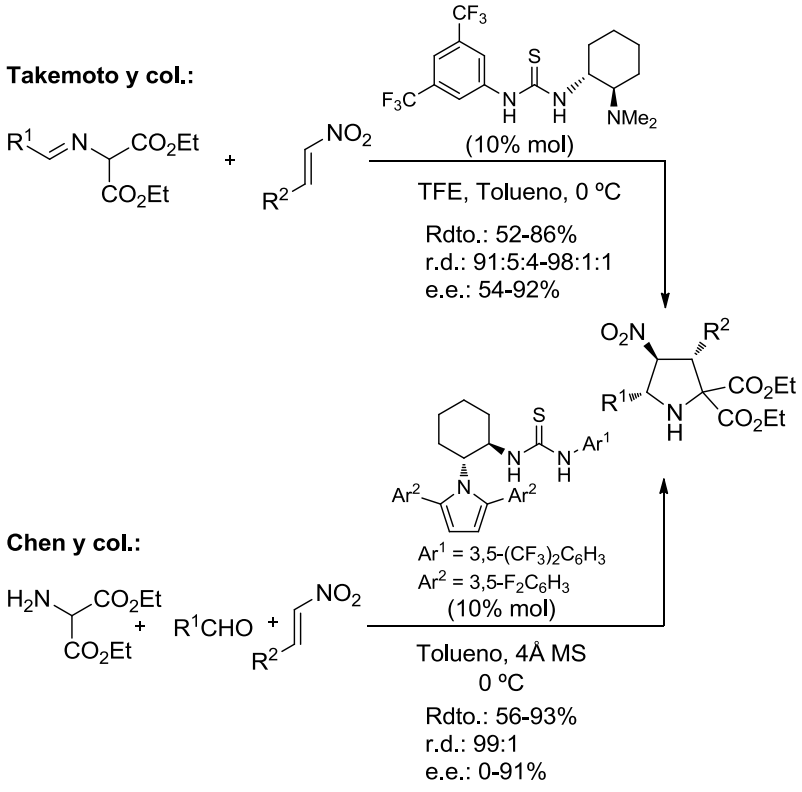
Así, nuestro grupo de investigación dio a conocer el primer ejemplo de cicloadición (3+2) enantioselectiva entre iluros de azometino y aldehídos α,β-insaturados, promovida por derivados de prolinol con excelentes resultados, como ya se ha comentado en el apartado referente a los antecedentes en el capítulo anterior. Poco después Córdova y col.[27] describieron una reacción con dipolos y dipolarófilos análogos a los empleados en nuestro grupo con la novedad de llevar a cabo un proceso multicomponente promovido por (*S*)-α,α-difenilprolinoltrimetilsilil éter.

La primera reacción organocatalítica de la que se tiene constancia entre iluros de azometino y nitroalquenos catalizada por un derivado de tiourea fue publicado en 2008 por Gong y col.[28] aunque con enantioselectividad moderada y limitado a iluros derivados de imina de benzofenona. Poco después quedó patente la eficacia de las tioureas como catalizadores en transformaciones de este tipo en un brillante

[26] Pandey, G.; Banerjee, P; Grade, S. R. *Chem. Rev.* **2006**, *106*, 4484.
[27] Ibrahem, I.; Rios, R.; Vesely, R.; Córdova, A. *Tetrahedron Lett*. **2007**, *48*, 6252.
[28] Xue, M.-X.; Zhang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691.

trabajo de Takemoto y col.[29] en el que desarrollaron un protocolo de cicloadición (3+2) formal (los autores constatan que trascurre en un mecanismo por pasos adición de Michael/aza-Henry intramolecular) entre aldehídos aromáticos, α-aminomalonato de dietilo y nitroalquenos. Al mismo tiempo, Chen y col.[30] trabajaban en un proyecto similar en el que estudiaron la cicloadición 1,3-dipolar asimétrica tricomponente utilizando monotioureas y catalizadores bifuncionales tiourea-amina terciaria. Este grupo apostaba, al contrario que el citado anteriormente, por un mecanismo concertado. La reacción funciona de manera excelente con aldehídos y nitroalquenos aromáticos, obteniendo pobres diastereoselectividades con nitroalquenos alifáticos (Esquema 2.10).

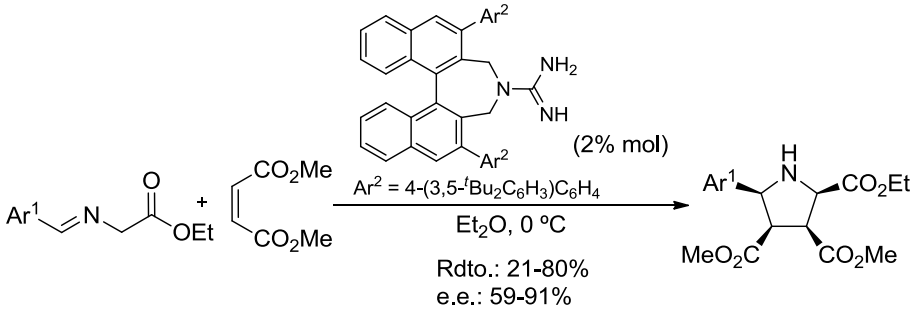
[29] Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett.* **2008**, 6910.
[30] Liu, Y.-K.; Liu, H.; Du, W.; Yue, L.; Chen, Y.-C. *Chem. Eur. J.* **2008**, *14*, 9873.



Esquema 2. 10

Por otra parte, Terada y Nakano[31] han desarrollado un procedimiento de cicloadición (3+2) entre maleato de dimetilo e iluros de azometino derivados de bases de Schiff, promovida por guanidinas quirales que rinde los productos deseados con elevada *endo* diastereoselectividad (>97%); es destacable la baja carga de catalizador (2% mol) necesaria para que la reacción transcurra (Esquema 2.11).

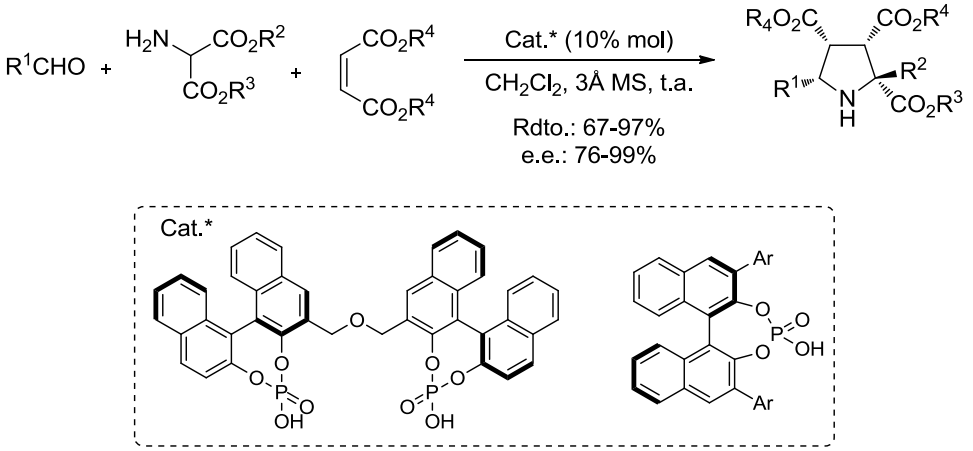
[31] Nakano, M.; Terada, M. *Synlett* **2009**, 1670



Esquema 2. 11

Los ácidos de Brønsted quirales también han mostrado buenos resultados en cicloadiciones con iluros de azometino. Así, Gong y col.[32] demostraron que ácidos fosfóricos derivados de BINOL son capaces de romover la formación de 1,3-dipolos de tipo iluro de azometino por condensación entre aldehídos, α-aminoésteres, así como de catalizar la siguiente cicloadición (3+2) con diversos dipolarófilos, conduciendo a pirrolidinas altamente sustituidas *endo* selectivamente con elevados rendimientos y excelentes enantioselectividades (Esquema 2.12). Posteriormente los mismos autores pusieron a punto una versión intramolecular accediendo a moléculas pirrolidínicas policíclicas de gran potencial sintético.[33] Otros trabajos destacables de este grupo de investigación en el ámbito de la cicloadición 1,3-dipolar con iluros de azometino implican el empleo de dipolarófilos de tipo 2,3-alenoatos,[34] quinona[35] y metilenindolinona.[36]

[32] Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z.; *J. Am. Chem. Soc.* **2008**, *130*, 5662.
[33] Li, N.; Song, J.; Tu, X.-F.; Chen, X.-H.; Gong, L.-Z. *Org. Biomol. Chem.* **2010**, *8*, 2016.
[34] Yu, J.; He, L.; Cheng, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2009**, *11*, 4946.
[35] Wang, C.; Chen, X.-H.; Zhou, S.-M.; Gong, L.-Z. *Chem. Commun.* **2010**, *46*, 1275.
[36] Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819.

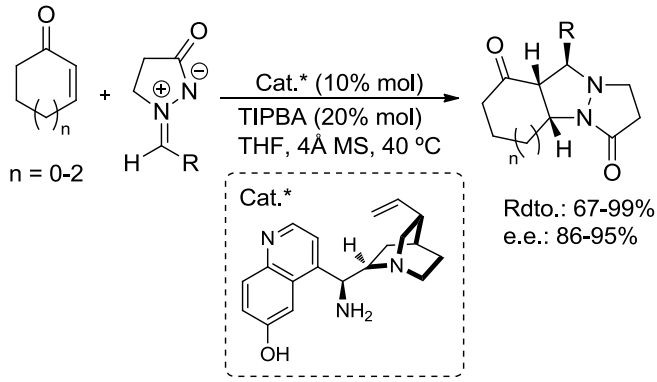


Esquema 2. 12

- Cicloadiciones (3+2) organocatalíticas asimétricas con otros 1,3-dipolos

Además de nitronas e iluros de azometino se han empleado otros dipolos en reacciones de cicloadición 1,3-dipolar organocatalíticas enantioselectivas. Por ejemplo iminas de azometino han resultado ser buenos dipolos en reacciones de cicloadición 1,3-dipolar catalizadas por aminas primarias.[37] Es destacable el primer trabajo de cicloadición (3+2) entre enonas cíclicas e iminas de azometino promovidas por un catalizador derivado de cincona realizado por Chen y col.[37b] Los puentes de hidrógeno formados por el 1,3-dipolo y el catalizador conducen a un excelente enantiocontrol en la transformación (Esquema 2.13).

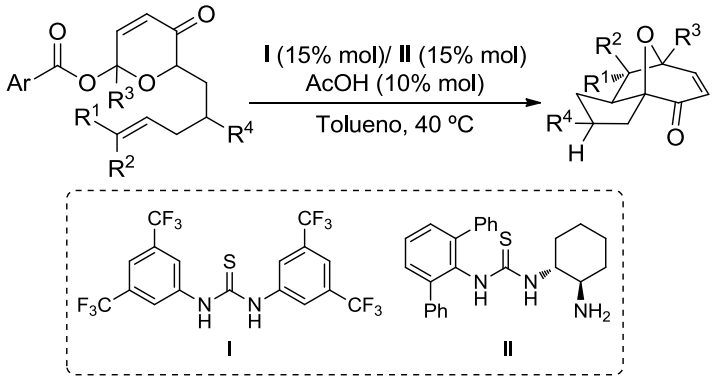
[37] (a) Suga, H.; Arikawa, T.; Itoh, K.; Okumura, Y.; Kakehi, A.; Shiro, M. *Heterocycles* **2010**, *81*, 1669. (b) Chen, W.; Du, W.; Duan, Y. Z.; Wu, Y.; Yang, S. Y.; Chen, Y. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7667. (c) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818.



Esquema 2. 13

Asimismo resulta interesante un trabajo de Jacobsen y col.[38] en el que lleva a cabo una reacción 1,3-dipolar intramolecular promovida por una combinación de tioureas basada en la formación de intermedios oxidopirílicos, generados *in situ* a partir de ariloxipiranonas por una secuencia de desprotonación/eliminación. Los datos experimentales obtenidos parecen apuntar a un tipo de catálisis cooperativa en la que es necesaria la participación de dos catalizadores, una tiourea aquiral, capaz de promover la formación del anión y la eliminación del grupo aroiloxilo que actúa como grupo saliente y una aminotiourea quiral que activa el carbonilo de la piranona por formación de una enamina además de proporcionar el requerido estereocontrol. Esta metodología permite obtener estructuras tricíclicas con elevado rendimiento y enantioselectividad (Esquema 2.14).

[38] Burn, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2011**, *133*, 14578.



Esquema 2. 14

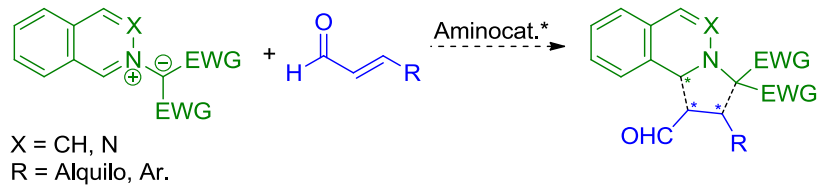
En vista de los trabajos examinados hemos constatado la amplia variedad de organocatalizadores que pueden promover este tipo de transformaciones. Así, por ejemplo, al utilizar nitronas como 1,3-dipolos, los mejores resultados se han obtenido empleando aminas secundarias, quedando abierto el camino para la mejora de los resultados obtenidos con derivados de tioureas y fosforamidas. En cuanto al empleo de iluros de azometino como 1,3-dipolos se ha conseguido acceder a productos de gran interés sintético como son los anillos pirrolidínicos, mediante procesos sencillos y obteniéndose los aductos deseados con rendimientos de moderados a excelentes y con elevado estereocontrol. Aún así es un área en la que queda mucho por explorar, por lo que hoy en día se sigue trabajando en el diseño de nuevos catalizadores y metodologías.

2. Objetivos y plan de trabajo

Como se ha puesto de manifiesto en la introducción de este capítulo, la mayor parte de los métodos descritos en cicloadiciones (3+2) organocatalíticas asimétricas que emplean como 1,3-dipolos iluros de azometino se limitan al uso de dipolos preparados *in situ*, generalmente desde los correspondientes α-iminoésteres, dada su inestabilidad debido fundamentalmente al carácter hidrolizable de la función azometínica. De hecho, hasta la fecha de inicio del presente trabajo de investigación no existía ningún ejemplo en el que se utilizaran iluros de azometino estables en cicloadiciones (3+2) organocatalíticas enantioselectivas. Así, en línea con las investigaciones iniciadas en nuestro grupo en reacciones organocatalíticas en las que se puso a punto con éxito la primera reacción de cicloadición (3+2) asimétrica mediante aceleración vía ión iminio, ya comentada en el apartado de antecedentes (página 33), nos propusimos poner a punto un procedimiento de cicloadición (3+2) asimétrica con iluros de azometino estables bajo condiciones de aminocatálisis. Así planteamos como primer **objetivo** del presente trabajo de investigación **el estudio de la reacción (3+2) organocatalítica enantioselectiva entre iluros heterocíclicos de azinio estables y aldehídos α,β-insaturados mediada por aminocatalizadores quirales**.

La elección del dipolo más adecuado a nuestros fines se fundamentó en los precedentes bibliográficos existentes en versiones no asimétricas de la cicloadición 1,3-dipolar con iluros estables, generalmente iluros heterocíclicos de

iminio derivados de piridina, isoquinolina o ftalazina con sustituyentes electronatractores en el carbono metilénico que estabilicen el anión.[39] Como dipolarófilo se emplearán aldehídos α,β-insaturados, aplicando el concepto de activación vía ión iminio. En este sentido, como organocatalizadores se ensayarán aminas secundarias, típicamente empleadas en reacciones organocatalíticas mediante este tipo de activación. Cabe destacar que el proceso de cicloadición que transcurre con la formación del ciclo pirrolidínico daría lugar a interesantes estructuras heterocíclicas tales como pirroloisoquinolinas y pirroloftalazinas (Esquema 2.15).



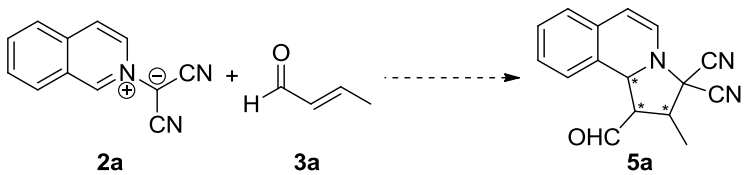
Esquema 2. 15

[39] (a) Alizadeh, A.; Zohreh, N. *Helv. Chim. Acta* **2008**, *91*, 844. (b) Yavari, I.; Mokhtarporyani-Sanandaj, A.; Moradi, L. *Tetrahedron Lett.* **2007**, *48*, 6709. (c) Butler, R. N.; Coyne, A. G.; Moloney, E. M. *Tetrahedron Lett*. **2007**, *48*, 3501. (d) Butler, R. N.; Coyne, A. G.; Cunningham, W. J.; Moloney, E. M.; Burke L. A. *Helv. Chim. Acta* **2005**, *88*, 1611. (e) Butler, R. N.; Coyne, A. G.; McArdle, P.; Cunningham, D.; M.; Burke L. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1391. (f) Butler, R. N.; Coyne, A. G.; Burke, L. A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1781. (g) Butler, R. N.; Farrel, D. M. C. S.; *J. Chem. Research (*S*)* **1998**, 214. (h) Butler, R. N.; Farrel, D. M.; Pyne, C. S. *J. Chem. Research (*S*)* **1996**, 418.

Así, el **plan de trabajo** a seguir para el desarrollo de este primer objetivo de la investigación fue el siguiente:

1. Preparación de los productos de partida y estudio de la viabilidad de la reacción:

Se comenzará con la elección de los productos de partida idóneos para la cicloadición 1,3-dipolar organocatalítica a estudiar. Para ello se proyectará una reacción modelo entre el iluro de azometino **2a** (no disponible comercialmente por lo que se tendrá que proceder a su preparación) y crotonaldehído **3a**, un aldehído α,β-insaturado estable, de bajo coste y comercialmente accesible, analizando la viabilidad de la reacción (Esquema 2.16).



Esquema 2. 16

2. Optimización de condiciones:

Sobre la reacción modelo planteada en el Esquema 2.16, se estudiarán las distintas condiciones experimentales requeridas para que la transformación tenga lugar y con los mejores valores de rendimiento, diastereo- y enantioselectividad. Asimismo se evaluarán diferentes organocatalizadores, definiendo los requisitos que han de cumplir para obtener los mejores resultados. También se estudiarán variables metodológicas como disolvente, temperatura etc. para cumplir los objetivos marcados en cuanto a la efectividad de la reacción.

3. Generalización de la metodología:

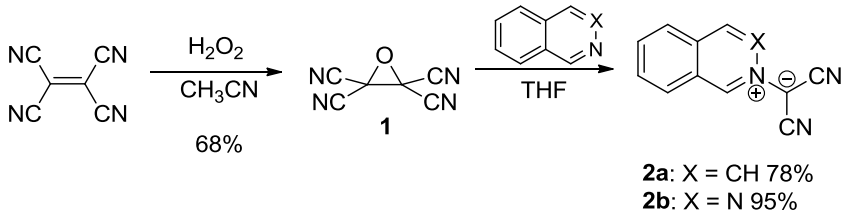
Una vez establecidas las condiciones óptimas, se evaluará el alcance de la metodología puesta a punto, variando para ello tanto el 1,3-dipolo como los aldehídos α,β-insaturados utilizados como dipolarófilos. Primeramente se analizará el alcance de la reacción en relación al dipolarófilo llevando a cabo la reacción con aldehídos α,β-insaturados con sustituyentes tanto alifáticos como aromáticos de diferentes tamaños, longitudes y requerimientos electrónicos. Finalmente analizaremos la influencia del iluro de azometino, con otro tipo de dipolos estabilizados como lo son los iluros de ftalazinio.

3. Results and discussion

Once the most relevant precedents related to organocatalytic enantioselective (3+2) cycloadditions have been presented and after establishing the objectives of our research and the associated work plan, the most relevant results obtained in this project will be discussed.

3.1. Preparation of starting materials

We proceeded with the preparation of the required stable azomethine ylides **2a**, **b** by the synthesis of isoquinolinium 2-dicyanomethylide **2a** which has been carried out according to a previously reported procedure.[40] This involves the use of tetracyanoethylene as starting material which is firstly oxidized to the corresponding epoxide and subsequently reacts with isoquinoline furnishing the desired ylide **2a** after ring opening/fragmentation in 53% overall yield. Following the same procedure we also synthesized phthalazinium 2-dicyanomethylide **2b**, with an overall yield of 65% (Scheme 2.17).

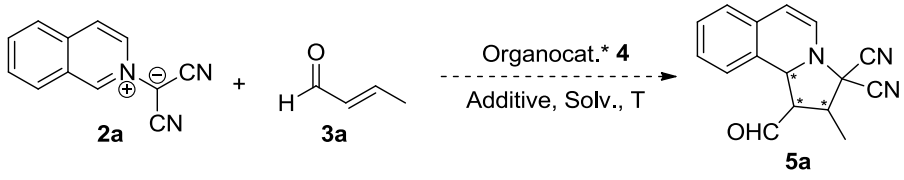


Esquema 2. 17

[40] Linn, W. J. *Organic Syntheses*, **1969**, *49*, 103.

3.2. Viability of the reaction

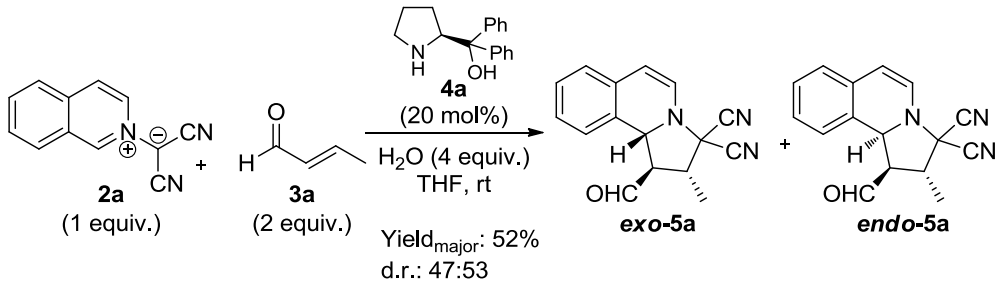
After synthesizing the required stable azomethine ylide we proceed to optimize the reaction parameters using the proposed model reaction which involved the reaction between **2a** and crotonaldehyde **3a** (Scheme 2.18).



Scheme 2. 18

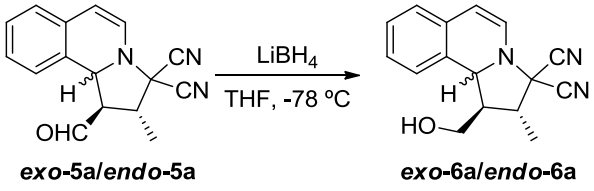
We initially carried out the transformation under the conditions optimized in our research group for the cycloaddition reaction using azomethine ylides and α,β-unsaturated aldehydes previously mentioned.[41] Employing α,α-diphenylprolinol as catalyst and H_2O as additive, using THF as solvent and running the reaction at room temperature, after four days, the formation of the desired product **5a** was observed as a mixture of diastereoisomers (Scheme 2.19). The diastereoisomers could be separated by flash column chromatography ($Yield_{major}$ = 52%) which allowed the complete characterization.

[41] Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. Highlighted in *Synfacts* **2007**, 813.



Scheme 2. 19

As the resulting products **5a** of the 1,3-dipolar cycloaddition reaction was found to be rather unstable we decided to reduce the formyl group under standard conditions ($NaBH_4$, MeOH, 0ºC) in order to obtain the corresponding primary alcohol, but the reaction furnished a complex mixture of products in which we were only able to detect the desired alcohol with a very poor yield (<20%). Longer reaction times or the use of more equivalents of the reducing agent resulted in an uncontrolled over-reduction of both formyl and the nitrile groups. Those products could not be isolated due to their high unstability. We therefore decided to test a stronger reducing agent which could allow us to operate at lower temperatures and hence, could possibly favor a cleaner and more selective reduction process. In this sense the reaction with $LiBH_4$ could be carried out in THF at -78ºC, obtaining the desired primary alcohols (Scheme 2.20).



Scheme 2. 20

At this point we tried to find out if the catalyst was exerting the supposed enantiocontrol; for that purpose we prepared the racemate of the mixture of *exo*- and *endo*-**6a** using a racemic mixture of the catalyst **4a** in the cycloaddition reaction and then applying the mentioned reducing protocol; the diastereoisomers and enantiomers obtained could be separated by chiral HPLC on a chiral stationary phase (Chiralcel OD column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). Simultaneously the same reducing conditions were applied to the pure major diastereoisomer *exo*-**5a** which was carried out with 72% yield, furnishing the enantiopure primary alcohol *exo*-**6a**. In Figure 2.3 it can be observed the chromatogram that belongs to the racemate (left), where the diastereoisomers and their corresponding enantiomers are separated; next to it the chromatogram of the enantiomerically enriched major diastereoisomer is placed. As the enantiomeric excess achieved was 82% we concluded that the transformation was being stereocontrolled, which encouraged us to go on studying the reaction.

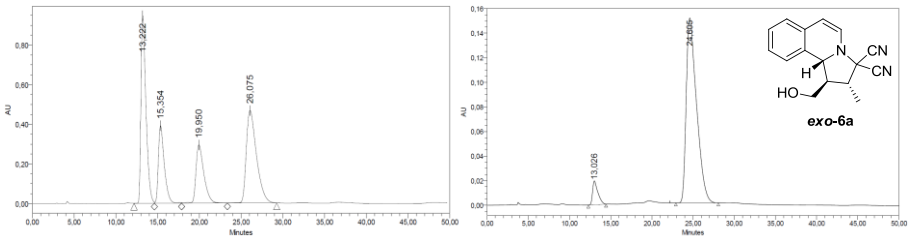
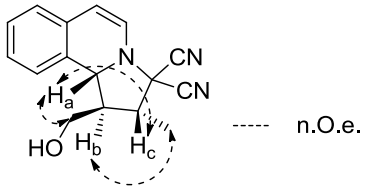


Figure 2. 3

We isolated the major diastereoisomer *exo*-**6a** and studied the n.O.e showed by the molecule. As it can be seen in Figure 2.4, there is n.O.e between H_a and H_c implying that both protons are positioned in relative *cis* configuration. The effect between H_b and the methyl group, showed that CH_3 and C**H**$_2$OH are placed in *anti* configuration, in correspondence with of *trans* α,β-unsaturated aldehyde used. We

concluded that the *exo* diastereoisomer was being mainly formed in the 1,3-dipolar cycloaddition reaction. The absolute configuration of the synthesized cycloadduct could not be fixed until further investigations were carried out.



6a

Figure 2. 4

Considering that previous work performed in our researching group involving (3+2) cycloadditions had shown *endo* selectivity,[41] it was interesting to find out that the major diastereoisomer formed was the *exo*.

Once the viability of the reaction was proved, we started with the identification of the most appropriate catalyst for the transformation in terms of achieving the highest possible yield and stereocontrol, also paying attention to the possible formation of two diastereoisomers.

3.3. Optimization of the reaction

The screening began with the evaluation of a series of organocatalysts typically used in cycloaddition reactions. Taking into account the need of activating the dipolarophile *via* iminium ion, different organocatalyst containing diverse functionalities were carefully chosen for the test (Figure 2.5). Firstly some proline derivatives with different substituents at the pyrrolidine ring (catalysts **4a-d**) were tested and also some of the catalysts developed in MacMillan's laboratories for the Diels-Alder reaction[42] which is isoelectronic with our projected 1,3-dipolar cycloaddition and, in fact, have been successfully used in 1,3-dipolar cycloadditions with nitrones[12] (catalysts **4e-h**).

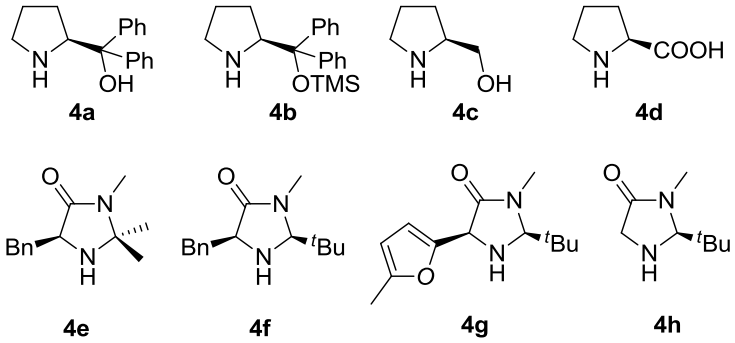


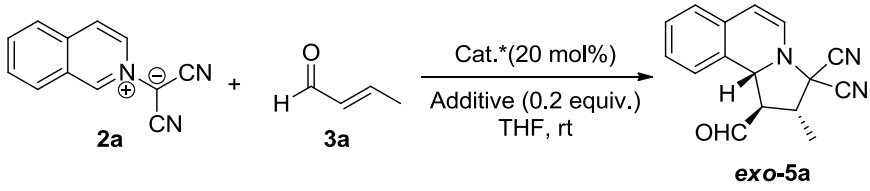
Figure 2. 5

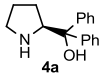
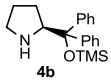
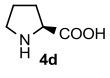
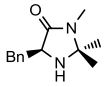
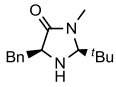
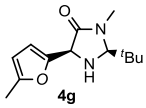
[42] (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.

For these model reactions we decided to operate under the same conditions as used before, that is, in THF and at room temperature. In all cases, except for prolinol **4c** and L-proline **4d** (entries 3 and 4, Table 2.1) we decided to incorporate a Brønsted acid cocatalyst, which are known to contribute positively in other cases of reactions under iminium ion activation due to its ability to favor the formation of the iminium ion[12,43] The nature of those acids had to be carefully selected for each of the chiral secondary amine catalyst **4** exposed. The obtained results in this catalyst survey are shown in Table 2.1.

[43] (a) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 611. (b) Groselj, U.; Seebach, D.; Badine, D. M.; Schweizer, W. B.; Beck, A. K.; Krossing, I.; Klose, P.; Hayashi, Y.; Uchimaru, T. *Helv. Chim. Acta* **2009**, *92*, 1225.

Table 2. 1: Influence of the catalysts and additives in the cycloaddition reaction.[a]



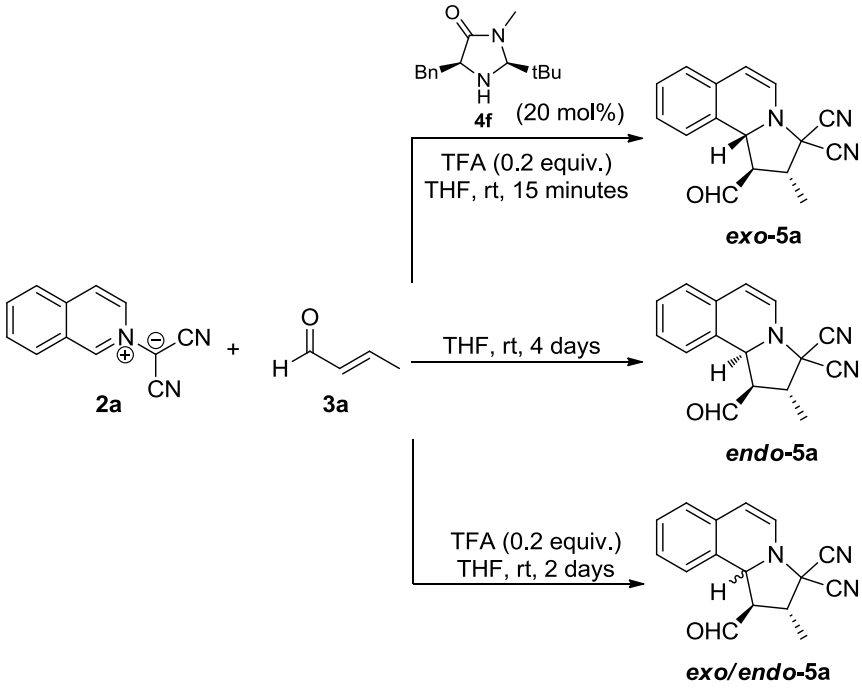
Entry	Catalyst	Additive	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[d]
1	 4a	TFA	96:4	61	44
2	 4b	$PhCO_2H$	80:20	83	20
3	 4c	-	83:17	13	28
4	 4d	-	59:41	71	12
5	 4e	HCl	94:6	47	0
6	 4f	TFA	88:12	87	88
7	 4g	TFA	55:45	32	46
8	 4h	TFA	>95:<5	33	44

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3a** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the *exo* diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group of *exo* diastereoisomer.

We initially tested the catalyst **4a** which had been used to prove the viability of the transformation (Scheme 2.19), but in the presence of TFA as cocatalyst (entry 1) achieving excellent diastereoselectivity although not so satisfactory yield and enantiomeric excess. When the substituent in α position of the catalyst was bulkier (entry 2) the yield improved, and a good diastereomeric ratio was observed, but the enantiomeric excess dropped down. Employing prolinol (**4c**), a good diastereoselectivity was achieved although the yield and enantiocontrol was very poor (entry 3) and when proline (**4d**) was used the product **5a** was obtained with good yield, although without significant diastereo- or enantiocontrol (entry 4). Then, we decided to test four different imidazolidinone derivatives developed by MacMillan's group. In our first attempt we tried catalyst first generation MacMillan catalyst **4e**, in combination with HCl, obtaining the desired compound with moderate yield and excellent diastereomeric ratio but no enantiocontrol was exerted (entry 5). The use of catalyst **4f**, with a bulkier substitution at the C2 of the imidazolidinone ring, provided promising result, achieving very good yield and good diastereoselectivity as well as very good value of enantiomeric excess (entry 6). Afterwards we tested the influence of the group in position 5 of the catalyst, running the reaction with catalyst **4g** cocatalyzed by TFA and achieving a poor yield and low diastereo- and enantiocontrol (entry 7). Finally we also surveyed the **4h**-TFA couple, observing low yield and enantioselectivity, but excellent diastereoselectivity (entry 8).

We also run some extra tests to know if any background reactions were taking place. Interestingly, when **2a** and crotonaldehyde **3a** were stirred in THF for 4 days in the absence of aminocatalyst or TFA, cycloadduct **5a** was formed in 40% yield as a single *endo* diastereoisomer. Moreover, we also observed that the addition of 20 mol% TFA in the absence of aminocatalyst accelerated the reaction,

leading to the formation of **5a** in good yield after two days, although as a mixture of diastereoisomers (Scheme 2.21). These two experiments indicate the tendency of the system to undergo reaction without the participation of the catalyst which could lead to low diastereomeric ratios. It also confirms an active role of the **4f**-TFA catalytic system to be responsible for the acceleration of the reaction.



Scheme 2. 21

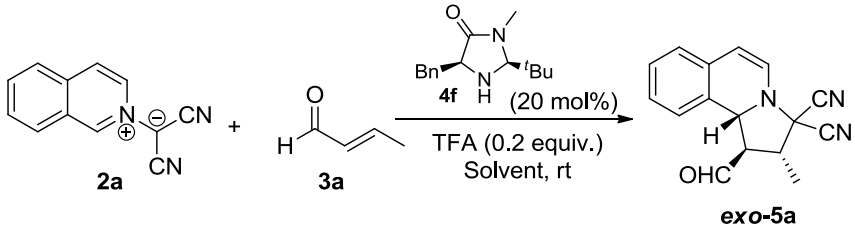
In conclusion, the best results achieved to that point are the ones depicted in entry 6, that is, using 20 mol% catalyst **4f** together with 20 mol% TFA in THF at room temperature. It should be stressed that, under these conditions, a remarkably fast reaction occurs, observing that the starting material was consumed in about 10 minutes, in contrast with other experiments involving the use of proline

derivatives **4a-d** as catalysts, in which 3-4 days where required to complete the reaction.

We wanted to know whether an excess of crotonaldehyde **3a** was necessary for achieving the cycloaddition product in a high yield, so we run the experiment repeating the conditions shown in entry 6 using equimolecular quantities of the starting materials. We found out that even though the diastereoselectivity improved slightly the yield and enantiomeric excess resulted significantly affected (55% yield and 77% e.e.). This led us to adopt the use of 1:2 ratio of **2a**:**3a** as the best conditions for the transformation.

Once imidazolidinone **4f** had been identified as the best catalyst for the projected 1,3-dipolar cycloaddition using ylide **2a** as 1,3-dipole, we continued our work with the identification of the most suitable solvent for the reaction. For that purpose we chose a battery of solvents with different polarity.

Table 2. 2: Influence of the solvent in the cycloaddition reaction.[a]



Entry	Solvent	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[d]
1	THF	88:12	87	88
2	Toluene	95:5	50	56
3	$CHCl_3$	>95:<5	57	38
4	Et_2O	87:13	74	86
5	Dioxane	82:18	56	74
6	CH_3CN	93:7	23	0
7	DMF	>95:<5	54	18
8	CH_3NO_2	94:6	18	0
9	EtOH	>95:<5	80	46
10	Ethylene glycol	87:13	66	68
11	MeOH	>95:<5	52	22
12	MeOH:H_2O (1:1)	84:16	<10	n.d.

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3a** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the *exo* diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group *exo* diastereoisomer.

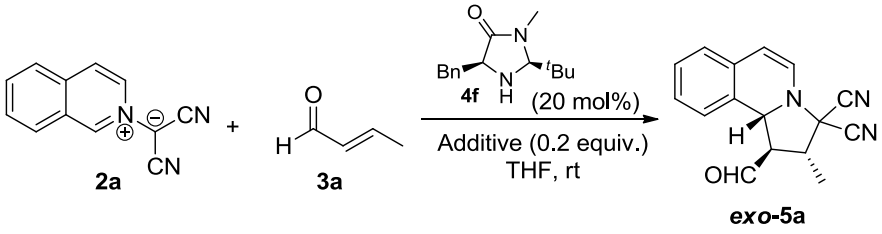
As it can be appreciated in Table 2.2, non polar solvents showed good results regarding the diastereoselectivity, but no improvement was noticed in terms of yield or enantioselectivity (entries 2 and 3) in comparison with the results

previously achieved in THF (entry 1). Ether-type solvents resulted to be the most efficient in terms of yield and enantioselection (entries 1, 4 and 5). On the other hand more polar solvents showed poor or no enantioselectivity at all although the diastereocontrol seems to be tough (entries 6-8). Protic solvents were also surveyed and, for example, the use of ethanol provided very good yield and a high diastereomeric ratio, although a very poor enantioselectivity was observed (entry 9), while ethylene glycol showed good values of yield and diastereoselectivity but poor enantioselectivity (entry 10) and methanol furnished *exo*-**5a** in moderate yield, excellent diastereoselectivity but very poor enantioselectivity (entry 11). Finally we also tested this transformation using a mixture of methanol:water but the reaction did not progress (entry 12).

The results obtained under the conditions depicted in entries 2, 3, 7-9 and 11 shown an interesting behavior in the reaction, observing that the diastereoselection levels are extremely high while the enantioselectivity remains rather low (0-56%). That can be attributed to the existence of the previously commented background reaction in which the organocatalyst is not taking part, which is favored in the protic medium.

After those experiments, it was concluded that the best conditions for the reaction were the ones exposed in entry 1, so the screening of the reaction went on using THF as solvent. The next step was to evaluate the influence of different Brønsted acid cocatalysts as additives which, as we have previously pointed out, are known to accelerate this type of reactions by favoring the formation of the intermediate iminium ion (Table 2.3).

Table 2. 3: Influence of Brønsted acids in the cycloaddition reaction.[a]



Entry	Additive	p*K*a[b]	*exo:endo*[c]	Yield (%)[d]	e.e. (%)[e]
1	TFA	-0.25	88:12	87	88
2	-	-	48:52	15	72
3	2,4-Dinitrobenzoic acid	1.43	>95:<5	47	88
4	HCl	-8	>95:<5	43	52
5	$HClO_4$	-10	67:33	40	32
6	TfOH	-14	89:11	36	10

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3a** were used. [b] p*K*a values measured in water.[44] [c] Determined by ^{1}H-RMN analysis of crude reaction mixture. [d] Referred to the *exo* diastereoisomer after flash column chromatography purification. [e] Calculated by HPLC after reduction of the formyl of *exo* diastereoisomer.

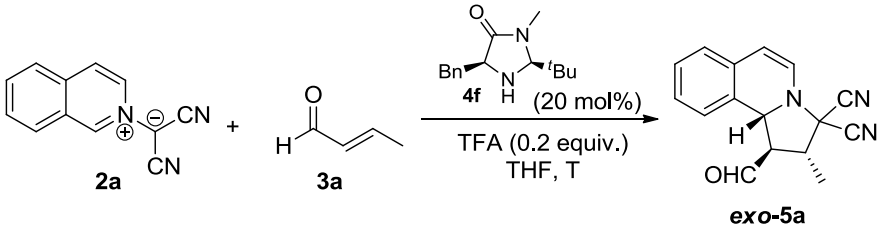
As it can be observed in Table 2.3 the absence of additive resulted in lower efficiency of the reaction, obtaining the desired product **5a** with low yield and poor diastereo- and enantioselection (entry 2) in comparison with the values achieved using TFA (entry 1). The weakest acid tested (2,4-dinitrobenzoic acid, p*K*a = 1.43[44]) furnished **5a** in moderate yield but excellent diastereoselectivity and very good enantiocontrol (entry 3). Then, we tested hydrochloric acid, obtaining

[44] Perrin, D. D.; Serjeant, E. P.; Dempsey, B. *pKa Predictions for Organic Acid and Bases.* Champman and Hall: London, **1981**.

moderate yield, high diastereoselectivity, but a poor enantioselectivity (entry 4). When stronger acids were tested, such as perchloric acid and *p*-toluenesulfonic acid (p*K*a = -10, -14 respectively), a drastic decrease in the enantioselectivity was observed (entries 5 and 6). With those results in our hands we decided that the most efficient catalytic system was the **4f**-TFA combination (entry 1), and therefore we went on with the screening of the reaction under those conditions.

Finally we proceeded to evaluate the influence of the temperature, in particular focusing on an expected improvement of diastereo- and enantioselectivity when working at lower temperatures (Table 2.4).

Table 2. 4: Influence of the temperature on the cycloaddition reaction.[a]

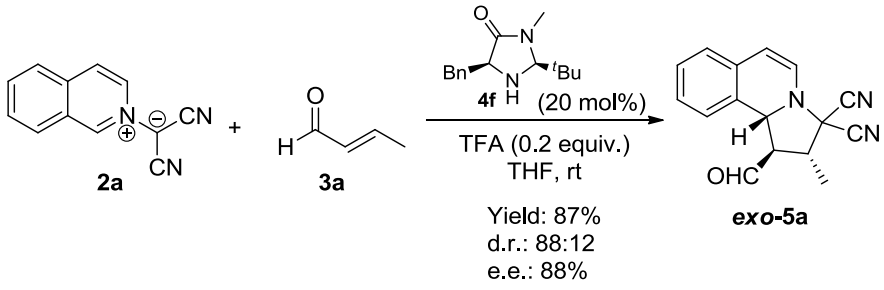


Entry	Temperature (°C)	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[d]
1	rt	88:12	87	88
2	4	82:18	57	87
3	-30	94:6	53	88
4	40	91:9	45	82

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3a** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the *exo* diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group of *exo* diastereoisomer.

As it can be seen in Table 2.4, no significant changes were appreciated in the enantiomeric excess when running the cycloaddition at lower temperatures while the yield became increasingly poorer as the temperature of the reaction decreased (entries 2 and 3). Regarding the diastereomeric ratio it has to be pointed out that when the reaction was carried out at -30 ºC an improved diastereoselection could be observed (entry 3). We also evaluated the use of a slightly higher temperature which led to a vague improvement on the diastereoselectivity while the yield became significantly affected.

After evaluating all the results obtained with those experiments, we concluded that the optimal conditions for the cycloaddition reaction between ylide **2a** and crotonaldehyde **3a** involved the use of the catalytic pair **4f**-TFA, using THF as solvent and running the reaction at room temperature (Scheme 2.22).

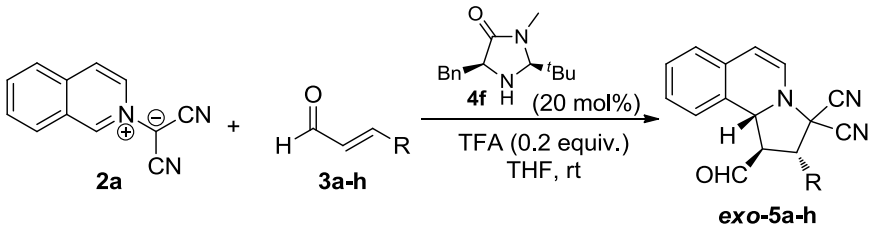


Scheme 2. 22

3.4. Scope of the methodology

Once the best protocol for the reaction had been set up (see Scheme 2.21), we proceeded to evaluate the scope of the reaction regarding the use of other dipolarophiles in this transformation. We studied the behavior of the reaction with different α,β-unsaturated aldehydes with and without substitution in β-position and showing different steric and electronic features in order to evaluate their influence in the cycloaddition process (Table 2.5).

Table 2. 5: Scope of the cycloaddition reaction: different α,β-unsaturated aldehydes.[a]



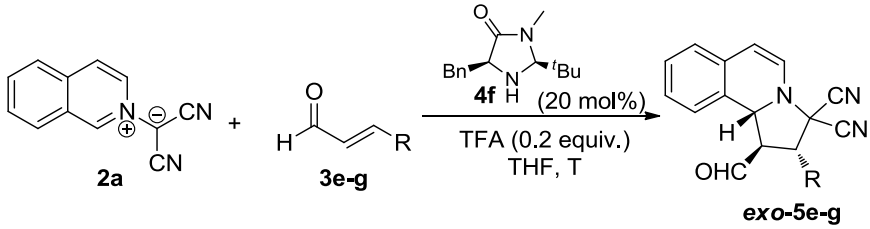
Entry	R	Product	*exo:endo*[b]	Yield[c] (%)	e.e. (%)[c]
1	Me	**5a**	88:12	87	88
2	^{n}Pr	**5b**	65:35	51	84
3	*n*-C_8H_{17}	**5c**	63:37	45	84
4	^{i}Pr	**5d**	20:80	54[e]	0
5	Ph	**5e**	91:9	72	78
6	*p*-OMePh	**5f**	>95:<5	53	70
7	*p*-NO_2Ph	**5g**	>95:<5	47	56
8	H	**5h**	46:45	88[e]	0

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3a-h** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the major diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group of major diastereoisomer. [e] Referred to the mixture of both diastereoisomers.

As it can be noticed in Table 2.5, the reaction worked in a satisfactory way in almost all the cases evaluated. The reaction tolerates well the use of different β-alkyl substituted α,β-unsaturated aldehydes, although the yield became importantly affected by the length and size of the substituent (entries 1-4). Regarding the enantioselectivity it has to be pointed out that the catalyst **4f** is exerting the expected enantiocontrol when the β-substitution of the enal is a linear alkyl chain obtaining very good enantioselectivities (entries 1-3), but a racemic product was isolated when the substituent in β position of the α,β-unsaturated aldehyde was bulkier (entry 4) or when acrolein was employed as dipolarophile (entry 8). It is remarkable that the diastereoselectivity suffered an inversion when a bulky substituent is used, as the *endo* product is mainly formed (entry 4), which can once again be explained in terms of the background reaction which takes place without the participation of the catalyst. The diastereomeric ratio remains acceptable for α,β-unsaturated aldehydes containing linear substituents (entries 2 and 3), good for the case of crotonaldehyde and 4-methyl-2-pentenal (entries 1 and 4) and almost 50:50 for acrolein **3h** (entry 8). β-aryl substituted dipolarophiles, containing both electron withdrawing and electron donating substituents reacted under the optimized reaction conditions, forming the cycloadducts **5e-g** in moderate yield and excellent diastereomeric ratio but with rather poor enantiocontrol (entries 5-7).

In order to improve those results for the α,β-unsaturated aldehydes with aromatic substitution in β-position, we tried running the reaction at lower temperatures. These results are shown in Table 2.6.

Table 2. 6: Influence of the temperature on the cycloaddition reaction for β-aryl substituted enals.



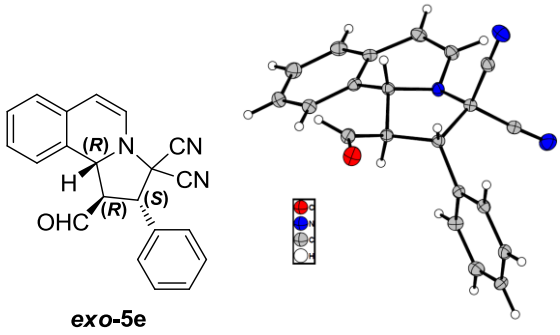
Entry	R	Product	T (ºC)	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[c]
1	Ph	**5e**	rt	91:9	72	78
2	Ph	**5e**	+4	>95:<5	70	88
3	Ph	**5e**	-30	>95:<5	70	94
4	*p*-OMePh	**5f**	rt	>95:<5	53	70
5	*p*-OMePh	**5f**	+4	>95:<5	63	84
6	*p*-OMePh	**5f**	-30	>95:<5	<10	n.d.
7	*p*-NO_2Ph	**5g**	rt	>95:<5	47	56
8	*p*-NO_2Ph	**5g**	+4	>95:<5	73	84
9	*p*-NO_2Ph	**5g**	-30	>95:<5	<10	n.d.

[a] One equivalent of ylide **2a** and two equivalents of α,β-unsaturated aldehyde **3e-g** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the *exo* diastereoisomer after flash column chromatography purification and calculated by HPLC after reduction of the formyl group.

Analyzing the data, it can be said that, in general, lower temperatures resulted in an improvement of diastereo- and enantioselectivity. In the case of phenyl substitued cycloadduct **5e**, the best values were achieved when the reaction was carried out at -30 ºC (entry 3), while hardly no product was obtained at that temperature for **5f** (entry 6) and **5g** (entry 9), probably because the reaction was

too slow and the cycloaddition products being formed decomposed during the process. Best results for those cases were observed when working at 4 ºC, achieving the desired products **5g** (entry 5) and **5h** (entry 8) with very good yields, excellent diastereomeric ratios and high levels of enantioselectivity.

Remarkably, cycloadduct **5e** could be crystallized in dichloromethane obtaining crystals suitable for X-ray analysis. This allowed us to establish the absolute configuration of the pyrroloisoquinoline **5e** that resulted to be 1*R*,2*S*,10b*R* (Figure 2.6). The assumption that the cycloaddition reaction courses with the same mechanism for all α,β-unsaturated aldehydes **3a-h** tested, led us to extend this absolute configuration to the rest of the cycloadducts **5a-h** prepared.

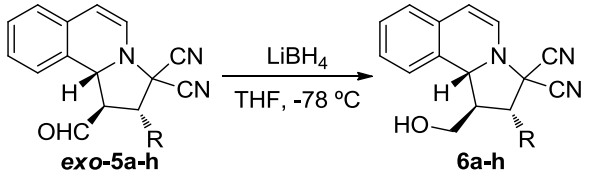


***exo*-5e**

Figure 2. 6

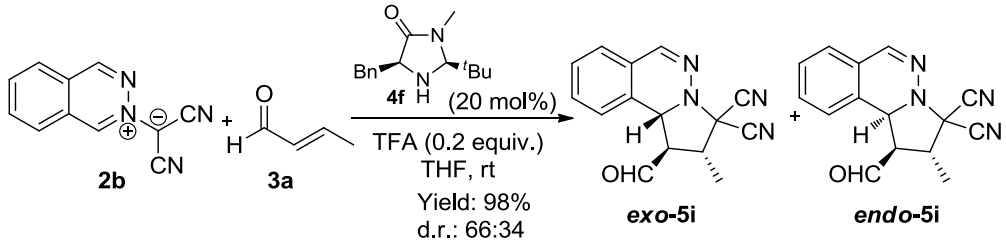
As mentioned before, the synthesized aldehydes **5a-h** were very unstable, and therefore we decided to carry out the reduction of the formyl group under the methodology tested for the model reaction, which consisted in performing the transformation at -78 ºC using $LiBH_4$ as the reducing agents. The reduction proceeded in a clean way furnishing the correspondent primary alcohols **6a-h** with acceptable to good yields (Table 2.7). These compounds were found to be stable enough to allow a full characterization.

Table 2. 7: Reduction of the aldehydes **5a-h** into corresponding alcohols **6a-h**.



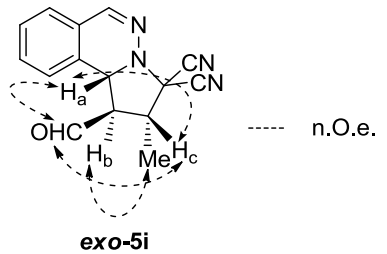
Entry	R	Product	Yield (%)	e.e. (%)
1	Me	**6a**	72	88
2	^{n}Pr	**6b**	57	84
3	*n*-C_8H_{17}	**6c**	34	84
4	Ph	**6e**	80	94
5	*p*-OMePh	**6f**	50	84
6	*p*-NO_2Ph	**6g**	46	84

After analyzing the influence of the dipolarophile in this cycloaddition reaction we proceeded to study the applicability of the optimized methodology in regard to other 1,3-dipoles. In this case, ylide **2b** was tested under the optimized conditions in the 1,3-dipolar cycloaddition with crotonaldehyde showing a promising result obtaining the corresponding cycloaddition products as 66:34 mixture of *exo* and *endo* diastereoisomers in a 98% combined yield (Scheme 2.23).



Scheme 2. 23

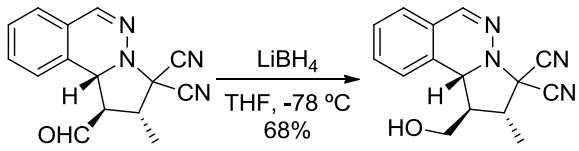
The two diastereoisomers could be separated and each one could be characterized and its relative configuration could be established. n.O.e. experiments carried out on the major diastereoisomer, showed the presence of a strong n.O.e. between H_a and H_c, which confirmed their *cis* relative configuration. Moreover the protons of the methyl group and H_b showed an additional n.O.e., meaning they were also *cis* positioned. As a conclusion of this experiment, the relative configuration of the major diastereoisomer resulting from the cycloaddition of ylide **2b** and crotonaldehyde **3b** has been established as *exo* (Figure 2.7).



***exo*-5i**

Figure 2. 7

The pyrrolophthalazine **5i** was also found to be unstable and therefore we decided to carried out the reduction of the formyl group under the same conditions previously used ($LiBH_4$, THF, -78 ºC). The reduction progressed in a satisfactory way leading to the desired primary alcohol **6i** with good yield (Scheme 2.24).



***exo*-5i** ***exo*-6i**

Scheme 2. 24

At this point and in order to determine the enantiomeric excess in which the cycloaddition product *exo*-**5i** had been obtained, we proceeded to synthesize the corresponding racemic mixture using D/L-proline **4d** as catalyst in the 1,3-cycloaddition. In this case, and to our surprise, the reaction provided three different diastereoisomers (identified by ^{1}H-NMR analysis) which could not be separated by flash column chromatography. As the mixture had also showed to be rather unstable, undergoing steady decomposition, it was subjected to reduction under the conditions used before and the corresponding mixture of three diastereoisomers, each of them in a racemic form, was next analyzed by HPLC under the conditions that allowed the separation of all stereoisomers (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). In Figure 2.8 the chromatogram corresponding to the racemic mixture of the three possible diastereoisomers formed and their enantiomers (left) is presented. We next proceeded to evaluate the enantiomeric excess of *exo*-**6i** obtained in the **4f**-catalyzed (3+2) cycloaddition/reduction sequence observing that it had been formed with an excellent enantiocontrol (<99% for the major diastereoisomer). In Figure 2.8 (right) the chromatogram of the enantioenriched major diastereoisomer is shown.

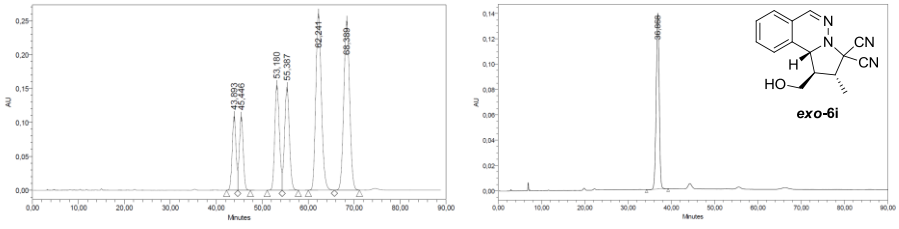
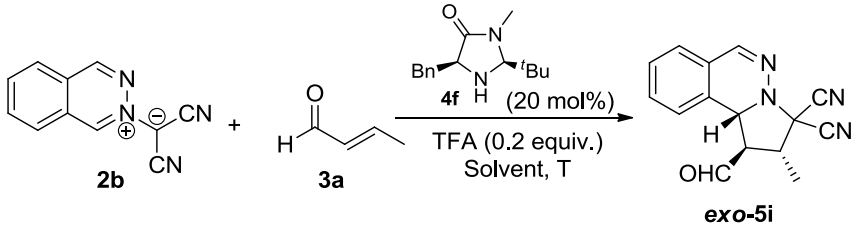


Figure 2. 8

Once the use of catalyst **4f** in combination with TFA had been established to be the most appropriate for the cycloaddition reaction using ylide **2b**, we decided

to refine the methodology in order to improve the efficiency of the reaction. We projected a model reaction between phthalazinium ylide **2b** and crotonaldehyde **3a** for testing methodological factors, such as solvent effect and the role played by the temperature of the reaction, which could provide better results.

Table 2. 8: Influence of the solvent and temperature on the cycloaddition reaction with **2b** ylide as dipole and crotonaldehyde as dipolarophile.[a]



Entry	Solvent	T (ºC)	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[d]
1	THF	rt	66:34	98	>99
2	THF	-30	34:66	>99	56
3	THF	-78	31:69	n.d.	72
4	THF	40	66:34	>99	>99
5	Toluene	rt	86:14	91	>99
6	$CHCl_3$	rt	86:14	89	>99

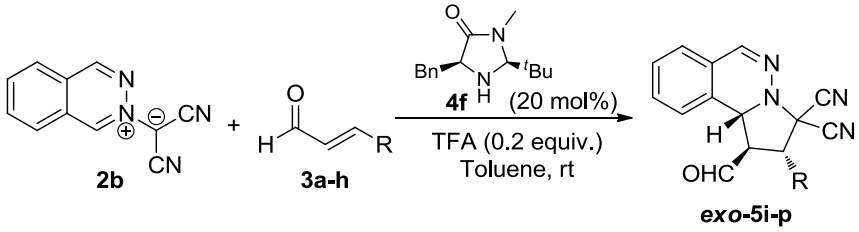
[a] One equivalent of ylide **2b** and two equivalents of α,β-unsaturated aldehyde **3a** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the major diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group of major diastereoisomer.

As we can observe in Table 2.8, even though the reaction proceeded well in the conditions employed initially, the diastereomeric ratio was poor (entry 1), so we tested the reaction at different temperatures in order to improve this parameter. Interestingly, working at lower temperatures resulted in the formation of *endo* as

major diastereoisomer and an important drop in the enantioselectivity was observed (entries 2 and 3), that once again might be related to the possible background reaction which takes place without the participation of the catalyst. On the other hand, when the reaction was performed at higher temperature, the obtained results were comparable to those observed at room temperature (entry 4 *vs* 1). We also evaluated the use of other solvents and, in fact, the diastereoselectivity improved when using toluene or $CHCl_3$, also obtaining excellent yield and enantiomeric excess (entries 5 and 6).

Considering those results, we concluded that the conditions shown in entry 5 were the optimal for the reaction and therefore, we proceeded to study teh scope of the reaction with respect to the use of other differently substituted a,b-unsaturated aldehydes as dipolarophiles (Table 2.9).

Table 2. 9: Scope of the cycloaddition reaction with **2b** ylide as dipole and different α,β-unsaturated aldehydes.[a]



Entry	R	Product	*exo:endo*[b]	Yield (%)[c]	e.e. (%)[d]
1	Me	**5i**	86:14	71	>99
2	^{n}Pr	**5j**	83:17	72	70
3	*n*-C_8H_{17}	**5k**	77:23	64	95
4	^{i}Pr	**5l**	77:23	51	84
5	Ph	**5m**	63:37	61	97
6	*p*-OMePh	**5n**	71:29	63	60
7	*p*-NO_2Ph	**5o**	67:33	60	>99
8	H	**5p**	57:43	54	84

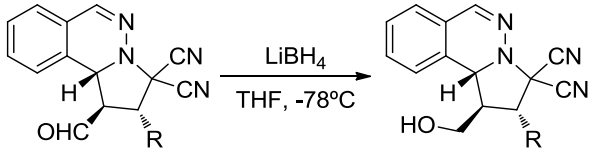
[a] One equivalent of ylide **2b** and two equivalents of α,β-unsaturated aldehydes **3a-h** were used. [b] Determined by ^{1}H-RMN analysis of crude reaction mixture. [c] Referred to the *exo* diastereoisomer after flash column chromatography purification. [d] Calculated by HPLC after reduction of the formyl group of *exo* diastereoisomer.

As it can be seen in Table 2.9, the reaction behaved similar to the one observed when dipole **2a** was used (see Table 2.5) although, in general, better enantioselectivities were achieved. β-Alkyl substituted enals obtaining linear aliphatic chains, furnished the corresponding cycloadducts in moderate to good yield, good *exo*/*endo* ratio and high enantioselectivity (entries 1-3). Moreover, it is interesting to point out that the reaction using 4-methyl-2-pentenal was also

successful, obtaining the expected cycloadduct *exo*-**5l** in an acceptable 51% yield and with good diastereo- and enantioselectivity (entry 4) in contrast with the same reaction using dipole **2a** for which a racemic mixture had been observed. This result also applies to the case in which acrolein was employed (entry 8) even though in this case, a nearly 1:1 mixture of *exo*:*endo* diastereoisomers was obtained. Finally, β-aryl substituted α,β-unsaturated aldehydes were also found to be active in this transformation, although the enantioselectivity of the reaction was highly dependent on the electronic nature of the aryl substituent, showing better results with an electron rich ring (entry 6) rather than with Ph (entry 5) or electron deficient rings (entry 7).

As it has been previously mentioned, those cycloadducts were unstable, so they needed to be transformed into the corresponding primary alcohols. The reduction of the pyrrolophthalazines **5i-p** under the typical conditions, proceeded in general in a successful way, isolating the alcohols **6i-p** in moderate to good yields (Table 2.10).

Table 2. 10: Reduction of the aldehydes **5i-p** into the corresponding alcohols **6i-p**.



***exo*-5i-p** **6i-p**

Entry	R	Product	Yield (%)	e.e. (%)
1	Me	**6i**	68	>99
2	^{n}Pr	**6j**	60	70
3	*n*-C_8H_{17}	**6k**	57	95
4	^{i}Pr	**6l**	62	84
5	Ph	**6m**	70	97
6	*p*-OMePh	**6n**	72	60
7	*p*-NO_2Ph	**6o**	70	>99
8	H	**6p**	34	84

3.5. Mechanistic aspects

Analyzing the products obtained and their stereochemistry, we tried to elucidate the mechanism of the reaction. Two different mechanistic can be proposed for the transformation in study (Scheme 2.25). The reaction might proceed over a concerted mechanism or through a stepwise process which would involve an initial Michael addition under iminium activation followed by intramolecular Mannich reaction under enamine catalysis.

In this context, previous studies focused on the mechanism of (3+2) cycloadditions using *N*-unsubstituted azomethine ylides closely related to those employed in this work have demonstrated that the stepwise or concerted nature of the reaction depends strongly on the structure and the nature of the substituents of the two reagents involved in the reaction.[9] In fact, literature precedents related to the (3+2) cycloaddition of azomethine ylides generated from diethyl arylideneaminomalonates with nitroalkenes indicate that this reaction proceeded in a stepwise manner,[45] detecting in this case the formation of the intermediates formed after the initial Michael addition step, which could be isolated and fully characterized. On the other hand, computational studies in our group related to the (3+2) cycloaddition between the same type of 1,3-dipoles and α,β-unsaturated aldehydes under iminium catalysis have led us to the conclusion that this aminocatalytic reaction, which is closely related to the one presented in this manuscript, also proceeds in a stepwise manner, combining iminium and enamine catalysis in a Michael/Mannich cascade reaction.[46]

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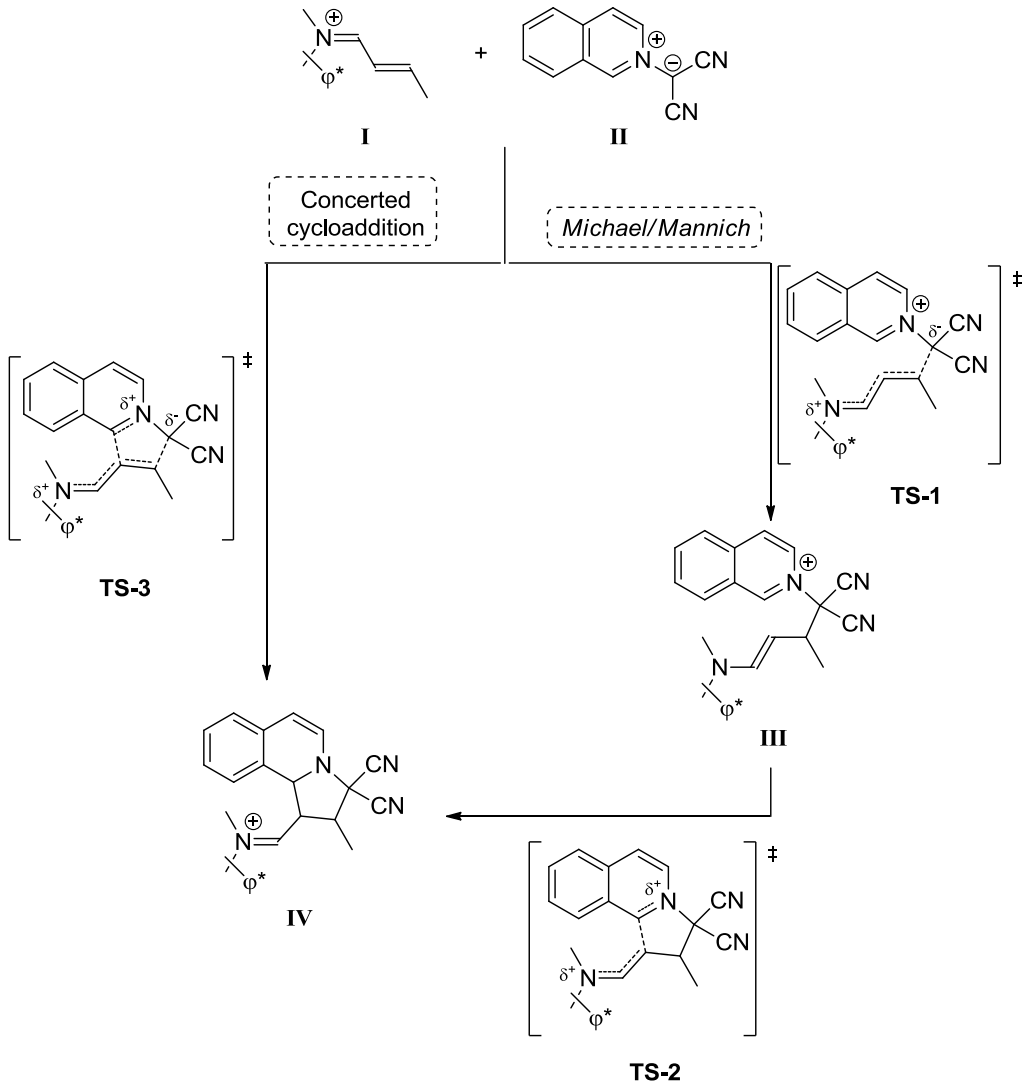
[45] Xie, J.; Yoshida, K.; Takasu, K.; Takemoto, Y. *Tetrahedron Lett*. **2008**, 6910.

[46] Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cózar, A.; Cossío, F. *Chem. Eur. J.* **2012**, *18*, 7179.



Scheme 2. 25

In our case, we have tried unsuccessfully to identify/isolate the possible intermediate on the hypothetical cascade-type mechanism. However, the lack of isolated product is not a concluding proof to exclude a stepwise mechanism. The

impossibility to observe the formation of this Michael addition intermediate can be also attributed to the fact that the subsequent intramolecular Mannich reaction takes place very fast, leading to the formation of the final cycloadducts instantaneously after the initial Michael reaction has happened. For this reason, we decided to carry out a computational study directed to shed light on the exact nature of the mechanism of this reaction.

According to these two possible reaction mechanisms outlined in Scheme 2.25 and also in line with what it has been proposed previously, the 1,3-dipole was identified as the reactive species participating in the cycloaddition reaction, interacting with the α,β-unsaturated aldehyde, being later activated by the catalyst as the corresponding iminium ion, we started by performing a conformational analysis of these two reagents and, as it can be observed in Figure 2.9[47], calculations indicated that the dipole (**II**) would remain in a planar arrangement and with respect to the preferred arrangement of iminium ion **I-a** generated by condensation of aldehyde and amine catalyst this intermediate would be formed preferentially as the more stable *E*-isomer, adopting a preferred *s-trans* conformation in which repulsion between the bulky *tert*-butyl substituent and the alkenyl side chain are minimized.[¡Error! Marcador no definido.] In order to simplificate geometries for all species, we have assumed a simplified iminium ion **I-b** for the subsequent calculations where imidazolidinone substituents have been eliminated.

[47] Main geometrical features of iminium ion **I** and dipoles **II-a** and **II-b** obtained at B3LYP/6-31G* level of theory.

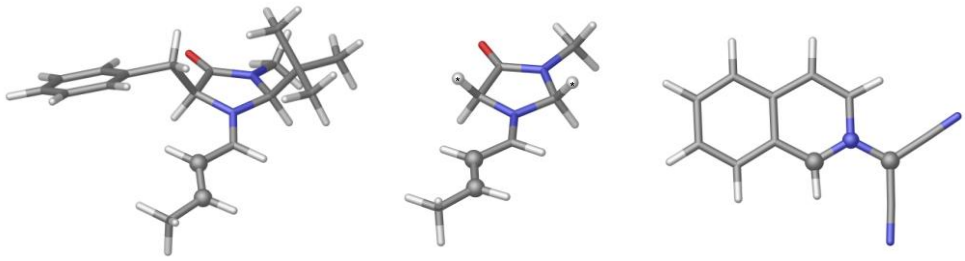


Figure 2. 9

We next proceed to study the (3+2) cycloaddition reaction between ylide **II** with the iminium ion **I-b** to provide the corresponding cycloadducts **IV** (Figure 2.10) through the stepwise Michael/Mannich process.[48] In all cases we considered that the approach of the nucleophile to the Michael acceptor should occur from its less hindered face, which is also consistent with the absolute configuration of the stereogenic center generated at this position at the final cycloadducts obtained (**5**). In this context, we initially considered a possible orientation for the approach of **II** to **I-b** in which the isoquinolinium ion would remain close to the enamine moiety which would also favour the subsequent intramolecular Mannich reaction in the following step. Assuming this conformational predisposition during the approach of these reagents, we calculated the transition states **TS-1-*exo*** and **TS-1-*endo*** resulting from the approach of the isoquinolinium ion **II** through its *Re* or *Si* faces[49] respectively named *exo* and *endo* approaches which would lead to the formation of Michael addition intermediates ***exo*-III** (ΔG^{react} = 4.72 kcal mol^{-1}) and ***endo*-III** (ΔG^{react} = 4.53 kcal mol^{-1}) respectively. The activation barrier associated

[48] Optimized transition states **TS-1-*exo***, **TS-1'-*exo*** and **TS-1-*endo*** for the Michael addition between azomethine ylide **II** and iminium ion **I** and ΔG^{react} for optimized structures ***exo*-III** and ***endo*-III**.

[49] The faces are referred to the C=N bond of the isoquinolinium ylide.

to the formation of ***endo*-III** (**TS-1-*endo***) is 0.29 kcal mol^{-1} higher than the one associated to the formation of ***exo*-III** (**TS-1-*exo***), which is also indicative of the fact that the formation of ***exo*-III** is favoured under kinetic control conditions. We have also evaluated an alternative possible approach of **II** to **I-b** (**TS-1'-*exo***) in which the orientation of the substituent in isoquinolinium ylide is rotated respect to the previously presented **TS-1-*exo*** (dihedral angles for C=C---C-N are $\varphi = 63.4^{\circ}$ and $\varphi = 178.4^{\circ}$ respectively). In this case again, the transition state calculated would also lead to the formation of ***exo*-III** enamine but which would place the isoquinolinium ion far away from the enamine reactive center for the subsequent Mannich reaction. However, the computed energy for this transition state resulted slightly higher than that obtained for **TS-1-*exo***, although lower than the computed energy for **TS-1-*endo***. This confirmed that the preferential approach of the two reagents, the azomethine ylide **II** and the iminium ion **I-b** had to occur in a geometrical arrangement which closely resembles that of the concerted mechanism, although the calculated C1-C10b distance (3.36 Å) in the most stable transition state **TS-1-*exo*** indicates that no appreciable bonding interaction occurs between these two atoms.

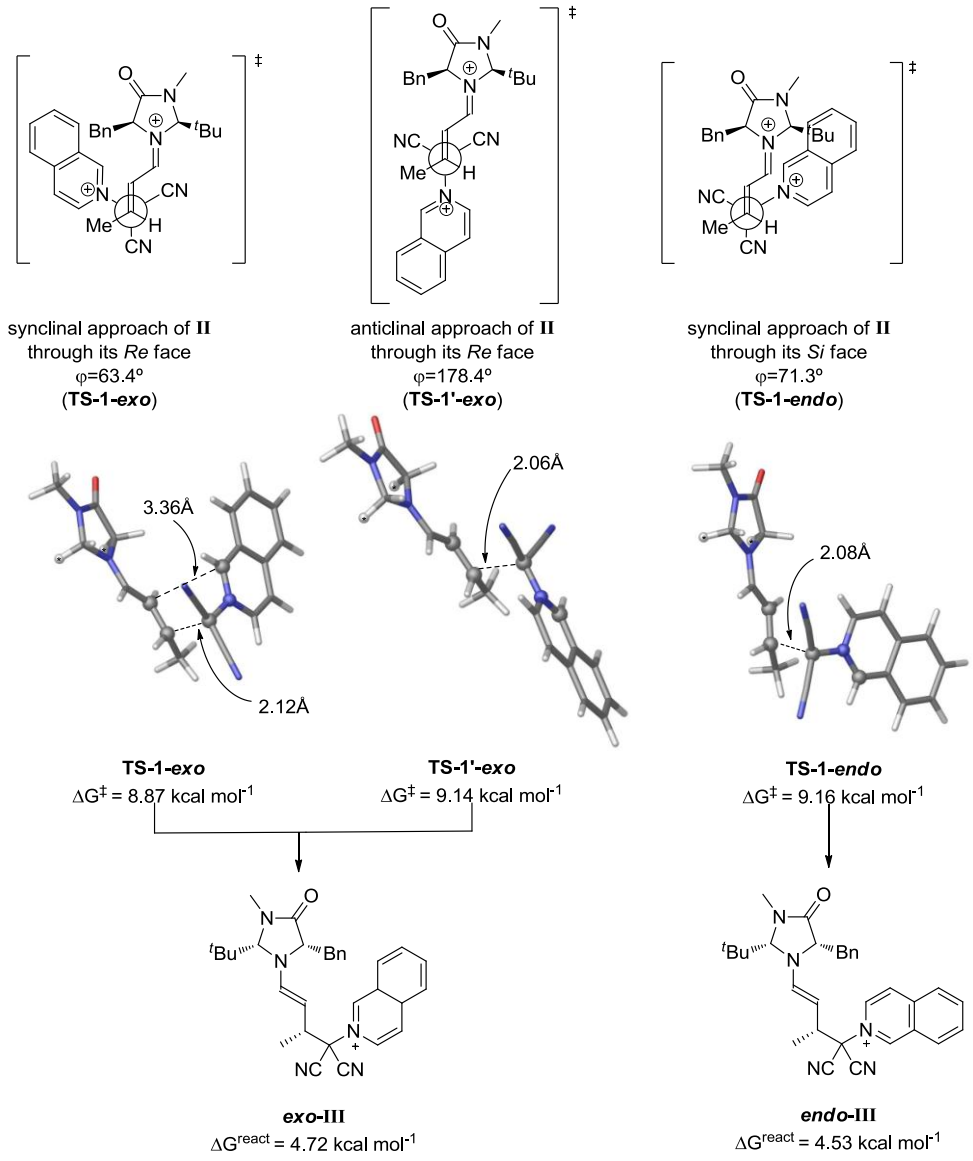


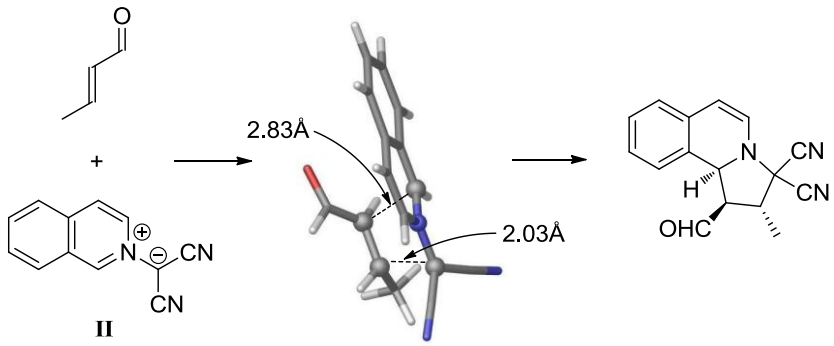
Figure 2. 10

The energy profile of the reaction proceeding through the stepwise Michael/Mannich mechanism has been previously described in our group showing

that this Michael addition step resulted to be the rate-limiting step of the process and therefore it is at this point in which the kinetic control of this transformation takes place.[46] This situation is also operating in this case, with an overall activation barrier of the rate determining step of 8.87 kcal mol^{-1}. Once this Michael addition takes place, the subsequent intramolecular Mannich reaction occurs very fast, leading to the formation of the final cycloadducts after releasing the catalyst. This might also explain the difficulties encountered during our attempts to isolate or detect the formation of this Michael addition intermediate. At this point it is also important to note that although in the first transition state **TS-1a-*exo*** and **TS-1a-*endo*** only the stereocenter C2 (of the same absolute configuartion in both cases) is generated, the coulombic stabilizing interactions in this intermediate maintain the geometry unaltered when it undergoes the subsequent intramolecular Mannich addition. Therefore, it is this initial Michael addition step which sets all the stereochemical information that will define the absolute configuration of all the stereocenters formed at the final cycloadducts. Finally, we also tried to evaluate the energy profile associated to the concerted pathway but all our attempts to find a transition state were unsuccessful.

For comparative purposes, we have evaluated the direct reaction between crotonaldehyde and isoquinolinium ion **II** in order to assess the influence of the catalyst in the mechanistic profile of the reaction and also to evaluate the ability of the catalyst to activate the α,β-unsaturated aldehyde through the cycloaddition process. In this case, and on the contrary to what happened in all our previous attempts, we were able to locate a transition state for the concerted pathway

leading to the formation of the *endo* cycloadduct (**TS-4** in figure 2.11).[50] At this point, it is important to note that, in this case, the calculated energy for the activation barrier associated to this transition state **TS-4**, participating in this uncatalyzed process, was found to be higher than the calculated energy for the corresponding **4f**-catalyzed reaction proceeding *via* iminium ion **I-b** (**TS-2-*exo***) (compare Figure 2.10 *vs* Figure 2.11). This is an indication of the ability of the catalyst to activate the α,β-unsaturated aldehyde towards the cycloaddition process *via* the reversible formation of an iminium ion intermediate but it also shows that the participation of these iminium ion intermediates leads to a change in the mechanistic pathway of the reaction from being pericyclic in the uncatalyzed version to stepwise in the amine-catalyzed procedure.



TS-4

$\Delta G^{\ddagger}$ = 32.10 kcal mol^{-1}

Figure 2. 11

[50] Optimized transition state **TS-4a** structure for the reaction of crotonaldehyde with azomethine ylide **II-a**. Note that the mayor isomer in the uncatalyzed reaction is the *exo* adduct. The ΔG^{react} here is refered to azomethine ylide **II-a** and crotonaldehyde not to iminium cation as in Figure 2.10.

In order to understand the reasons for this mechanistic change from concerted to stepwise cycloaddition due to the use of imidazolidinone **4f** as catalyst, we carried out a comparative study between crotonaldehyde and azomethine ylide **II** both in presence and in absence of catalyst (Figure 2.12). We considered again imidazolidinone as a simpler analog of catalyst **4f**. For the stepwise mechanism, the first step would involve nucleophilic attack of C3 to C2 and, in a second step, the enamine intermediate generated in the Michael reaction would have to react with the iminium ion moiety of the dipole forming the C1-C10b bond . In the case of concerted (3+2) cycloaddition, there is a $[\pi 4_s + \pi 2_s]$ process and an interaction between both C2-C3 and C1-C10b pairs is required, involving the corresponding molecular orbitals. These molecular orbitals in turn must have the appropriate symmetries to ensure a cyclic electronic delocalization associated with an aromatic transition structure.

Therefore we performed a relaxed scan of the possible reaction paths of both reactions (Figure 2.12). For the reaction of crotonaldehyde and azomethine ylide **II** in absence of catalyst only **TS-4** was found as saddle point connecting reactants and products through a concerted mechanism (Figure 2.12a). In the case of the imidazolidinone catalyzed reaction, the potential energy surface was found to be qualitatively different, since in this case the reaction does not follow the concerted mechanism obtained for the uncatalyzed reaction (Figure 2.12b). Instead, a stepwise mechanism was found to occur with **TS-1** connecting the reactants with a zwiterionic intermediate which in turn leads to the final products through a second transition state **TS-2**.

After those mechanistic theoretical studies, we can conclude that the reaction takes place stepwise, in a procedure that involves a Michael and a subsequent intramolecular Mannich reaction.

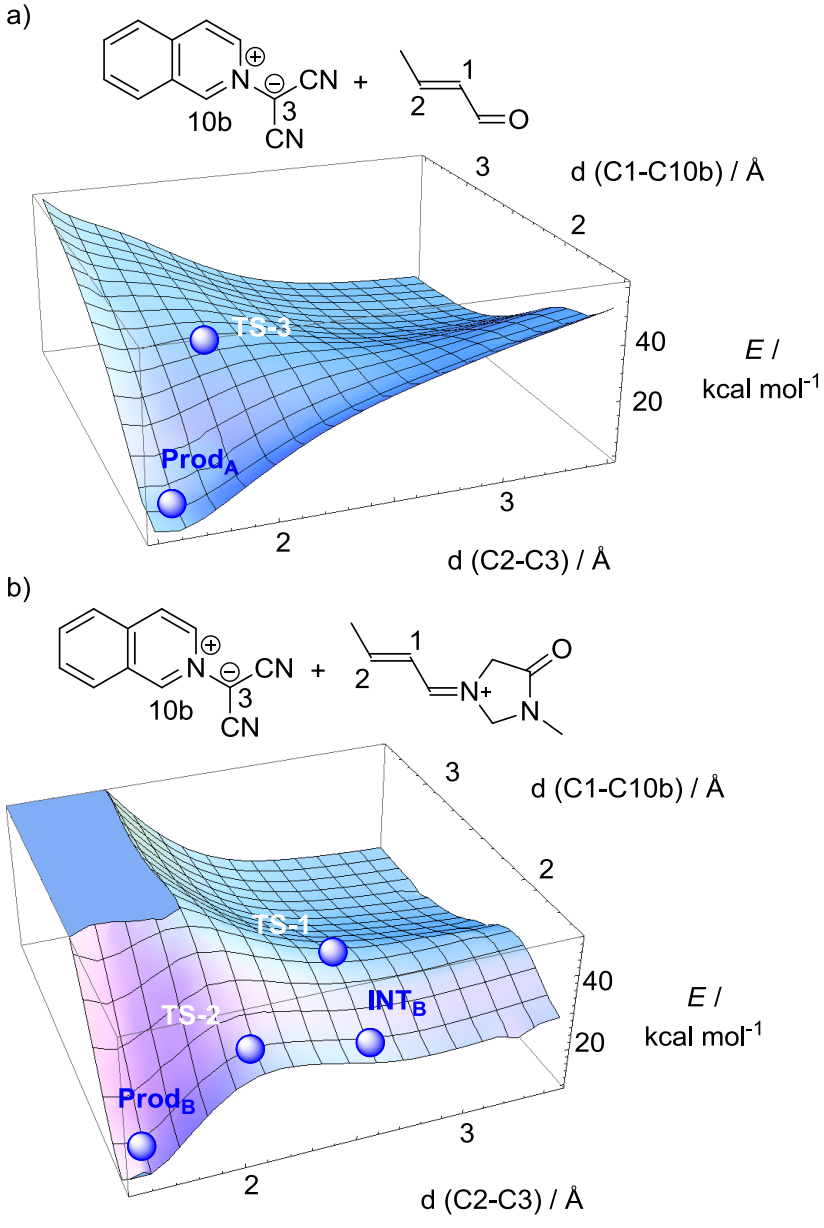

a)
10b
CN
CN
3
1
2
O
+
d (C1-C10b) / Å
3
2
TS-3
Prod$_A$
40
20
E /
kcal mol^{-1}
2
3
d (C2-C3) / Å
b)
10b
CN
CN
3
1
2
O
N+
N
+
d (C1-C10b) / Å
3
2
TS-1
INT$_B$
TS-2
Prod$_B$
40
20
E /
kcal mol^{-1}
2
3
d (C2-C3) / Å

Figure 2. 12

4. Conclusions

Along this chapter it has been proved that organocatalysis is an adequate and useful tool for carrying out enantioselective (3+2) cycloaddition reactions between stable azomethine ylides and α,β-unsaturated aldehydes catalyzed by secondary chiral amines, finding that (2S,5S)-(-)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone is the best catalyst to carry out the transformation with high yield and enantioselectivity. Moreover the use of an acid cocatalyst such as TFA is necessary to accelerate the reaction.

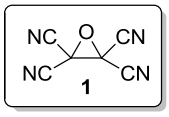
The scope of the reaction has been studied, evaluating different azomethine ylides and dipolarophiles. In almost every case tested the efficiency of the reaction has been high, obtaining a series of optically active pyrroloisoquinolines and pyrrolophthalazines with a varied substitution pattern in high values of diastereo- and enantioselectivity.

Finally, a mechanistic study of the cycloaddition reaction has been carried out, based on experimental data and DFT calculations, which make us postulate that the reaction takes place stepwise, involving a Michael/Mannich cascade reaction. After the aminocatalyst forms an iminium ion with the corresponding α,β-unsaturated aldehyde, it undergoes a Michael addition with the 1,3-dipole, leading to the formation of the enamine intermediate which next performes a diastereoselective intramolecular Mannich reaction.

5. Experimental

5.1. Preparation of starting materials

- Synthesis of tetracyanoethylene oxyde (**1**)



Tetracyanoethylene (10.00 g, 77.57 mmol) was dissolved in acetonitrile (60 mL) previously cooled at 4 ºC. Then, hydrogen peroxide (8.2 mL, 30%) was added dropwise to the solution, keeping the temperature of the reaction mixture between 10 y 12 ºC. Once all the hydrogen peroxyde has been completely added, the mixture was stirred for 3 minutes and afterwards it was slowly dropped to a mixture of water (200 mL) and ice (100 mg), stirring it vigorously. Then the formed solid was filtered and washed with water (3 × 25 mL). Finally it was recrystallized in dichloromethane affording the title compound **1** (7.59 g, 52.74 mmol) as a white solid.

Yield: 68%.

M.p.: 180-181 ºC (M.p. Lit.: 177-178 ºC).[40]

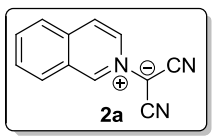
All other spectroscopic data matched with those given in the litereature.[40]

- Synthesis of ylides **2a**, **b**

General procedure

The corresponding nitrogen heterocycle (2.0 mmol) was added into a solution of tetracyanoethylene oxide (TCNEO) (1.0 mmol) in THF at 0 ºC. The reaction was stirred at 4 ºC during the necessary time and the formed solid was purified by the indicated method.

Isoquinolinium-2-dicyanomethanide (2a)



Following the general procedure **2a** (6.26 g, 32.4 mmol) was synthesized by adding isoquinoline (2.77 g, 21.4 mmol) to a solution of TCNEO **1** (6.00 g, 41.6 mmol) in THF (50 mL) at 0 ºC. The reaction was stirred at 4 ºC during 20 hours. Then, the solvent was evaporated and the formed solid was recrystallized in EtOH, affording **2a** as a yellow solid compound (3.21 g, 16.7 mmol).

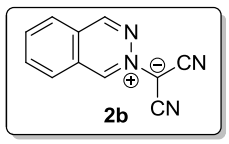
Yield: 78%.

M.p.: 253-255 ºC (M.p. Lit.: 258-259 ºC).[51]

All other spectroscopic data matched with those given in the litereature.[51]

[51] Matsumoto, K.; Ohta, R.; Uchida, T.; Nishioka, H.; Yoshida, M.; Kakehi, A. *J. Heterocyclic Chem*. **1997**, *34*, 203.

Phthalazinium-2-dicyanomethanide (2b)



Following the general procedure **2b** (0.89 g, 4.16 mmol) was synthesized by adding phthalazine (1.89 g, 14.58 mmol) to a solution of TCNEO **1** (0.70 g, 4.86 mmol) in THF (50 mL) at 0 ºC. The reaction was stirred at this temperature during 2 hours. Then, the formed solid was filtrated and washed with cold THF (3 × 25 mL), affording the yellow compound **2b** (4.4 g, 23.0 mmol).

Yield: 95%.

M.p.: 255-256 ºC (M.p. Lit.: 264-265 ºC). [52]

All other spectroscopic data matched with those given in the litereature.[52]

5.2. 1,3-Dipolar cycloaddition. Synthesis of pyrroloisoquinolines and pyrrolophthalazines 5a-p

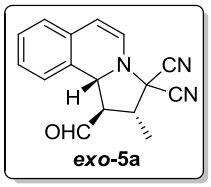
General procedure

(2*S*,5*S*)-(-)-5-Benzyl-2-*tert*-butyl-3-methyl-4-imidazolidinone **4f** (0.10 mmol) and trifluoroacetic acid (TFA) (0.10 mmol) were dissolved in THF (1 mL) and the excess of additive was evaporated under vacuum. After that, the α,β-unsaturated aldehyde (**3a-h**) was added (1.04 mmol), dissolved in the appropriate solvent (2 mL) and stirred for 30 minutes at the indicated temperature before the ylide **2a** (0.52 mmol) was added. The reaction was stirred at that temperature until full conversion was observed by t.l.c. Afterwards the solvent was evaporated under vacuum and directly charged onto silica gel and subjected to flash column

[52] Butler, R. N.; Farrell, D. M.; Pyne, C. S. *J. Chem. Research (S)* **1996**, 418.

chromatography obtaining the desired pyrroloisoquinoline **5a-p**. Racemic samples were prepared using a racemic mixture of the catalyst **4f**.

(1*R*,2*R*,10b*R*)-1-Formyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-5a)



***exo*-5a**

Following the general procedure, working at room temperature, starting from crotonaldehyde **3a** (86 μL, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 10 minutes, the title compound **5a** (0.12 g, 0.45 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 87%.

d.r.: 88:12 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (500 MHz, $CDCl_3$, 25 ºC): 1.53 (d, 3H, *J* = 6.4 Hz, CH_3), 3.05-3.50 (m, 2H, C**H**CHO + C**H**CH_3), 5.13 (d, *J* = 7.7 Hz, CCHN), 6.04 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.35 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 6.99-7.01 (m, 1H, C_{arom}-H), 7.10-7.12 (m, 1H, C_{arom}-H), 7.20-7.33 (m, 2H, C_{arom}-H), 9.90 (d, 1H, *J* = 2.2 Hz, CHO).

^{13}C-NMR (125.7 MHz, $CDCl_3$, 25 ºC): 14.4 (CH_3), 45.4 (**C**HCH_3), 59.3 (C**C**HN), 60.4 (**C**CN), 61.4 (**C**HCHO), 111.7 (CN), 111.8 (**C**H=CHN), 112.7 (CN), 123.6, 125.2 (C_{arom}-H), 126.6 (CH=**C**HN), 128.2, 128.6 (C_{arom}-H), 128.9, 130.8 (**C**$_{arom}$-C), 197.1 (CHO).

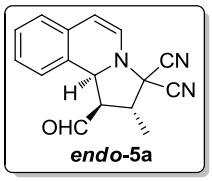
MS (EI) [m/z (%)]: 129 (45), 130 (81), 193 (60), 194 (100), 237 (56), 263 (4, M^+).

HRMS: Calculated for $[C_{16}H_{13}N_3O]^+$: 263.1059. Found: 263.1052.

IR (Film, cm^{-1}): 1725 (C=O).

$[\alpha]_D^{20}$: +400.3 (c = 0.8, CH_2Cl_2).

(1*R*,2*R*,10b*S*)-1-Formyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*endo*-5a)



***endo*-5a**

Yield: 11%.

^{1}H-NMR (500 MHz, $CDCl_3$, 25 ºC): 1.56 (d, 3H, *J* = 7.2 Hz, CH_3), 3.02-3.07 (m, 1H, C**H**CHO), 3.18-3.27 (m, 1H, C**H**CH_3), 5.14 (d, *J* = 6.6 Hz, 1H, CCHN), 5.84 (d, 1H, *J* = 7.7 Hz, C**H**=CHN), 6.43 (d, 1H, *J* = 7.7 Hz, CH=C**H**N), 7.03 (d, 1H, *J* = 7.5 Hz, C_{arom}-H), 7.10 (d, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.17-7.24 (m, 1H, C_{arom}-H), 7.26 (d, 1H, *J* = 7.5 Hz, C_{arom}-H), 9.75 (d, 1H, *J* = 3.6 Hz, CHO).

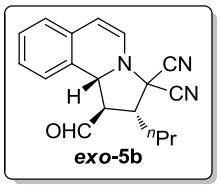
^{13}C-NMR (125.7 MHz, $CDCl_3$, 25 ºC): 16.2 (CH_3), 44.8 (**C**HCH_3), 57.6 (C**C**HN), 59.3 (**C**CN), 60.9 (**C**HCHO), 109.1 (**C**H=CHN), 111.0, 112.6 (CN), 125.4, 125.9 (C_{arom}-H), 126.2 (**C**$_{arom}$-C), 127.6 (CH=**C**HN), 127.9, 128.9, (C_{arom}-H), 131.6 (**C**$_{arom}$-C), 198.2 (CHO).

MS (EI) [m/z (%)]: 129 (45), 130 (81), 193 (60), 194 (100), 237 (56), 263 (4, M^+).

HRMS: Calculated for $[C_{16}H_{13}N_3O]^+$: 263.1059. Found: 263.1052.

IR (Film, cm^{-1}): 1725 (C=O).

(1*R*,2*R*,10b*R*)-1-Formyl-2-propyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-5b)



***exo*-5b**

Following the general procedure, working at room temperature, starting from (*E*)-2-hexenal **2b** (120 μL, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 2 hours, the title compound **5b** (77 mg, 0.26 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 51%.

d.r.: 65:35 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.03 (t, 3H, *J* = 7.2 Hz, CH_3), 1.43-1.70 (m, 2H, $CH_3CH_2C\mathbf{H}_2$), 1.67-2.02 (m, 2H, $CH_3C\mathbf{H}_2CH_2$), 3.09-3.51 (m, 2H, C**H**CHO + C**H**CH_2), 5.07 (d, 1H, *J* = 8.3 Hz, CCHN), 6.04 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.37 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 6.90 (d, 1H, *J* = 6.6 Hz, C_{arom}-H), 7.05 (d, 1H, *J* = 6.3 Hz, C_{arom}-H), 7.12-7.36 (m, 2H, C_{arom}-H), 9.93 (d, 1H, *J* = 2.7 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.9 (CH_3), 20.8 (CH_2), 33.0 (CH_2), 50.1 (C**H**CH_2), 59.1 (**C**CN), 59.5 (C**C**HN), 60.6 (**C**HCHO), 111.6 (**C**H=CHN), 111.7, 113.2 (CN), 123.6, 125.1, 126.6, 128.1, 128.6 (C_{arom}-H), 128.9, 130.9 (**C**$_{arom}$-C), 197.5 (CHO).

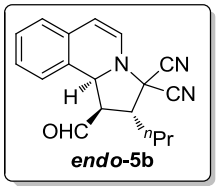
MS (EI) [m/z (%)]: 265 (100), 194 (43), 193 (44), 130 (66), 129 (26).

HRMS: Calculated for $[C_{18}H_{18}N_3O\ (M+H)]^+$: 291.1450. Found: 291.1443.

IR (Film, cm^{-1}): 1724 (C=O).

$[\alpha]_D^{20}$: +326.5 (c = 1.1, CH_2Cl_2).

(1*R*,2*R*,10b*S*)-1-Formyl-2-propyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (*endo*-5b)



***endo*-5b**

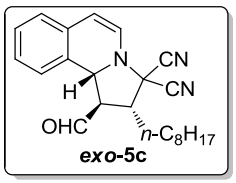
Yield: 21%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.04 (t, 3H, *J* = 7.3 Hz, CH_3), 1.47-1.64 (m, 2H, $CH_3CH_2C\mathbf{H}_2$), 1.71-2.04 (m, 2H, $CH_3C\mathbf{H}_2CH_2$), 2.94-3.13 (m, 2H, C**H**CHO + C**H**CH_2), 5.07 (d, 1H, *J* = 6.3 Hz, CCHN), 5.87 (d, 1H, *J* = 7.7 Hz, C**H**=CHN), 6.45 (d, 1H, *J* = 7.7 Hz, CH=C**H**N), 6.99 (d, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.08 (d, 1H, *J* = 7.5 Hz, C_{arom}-H), 7.14-7.29 (m, 2H, C_{arom}-H), 9.72 (d, 1H, *J* = 3.9 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.7 (CH_3), 20.9 (CH_2), 33.5 (CH_2), 49.8 (C**H**CH_2), 56.1 (**C**CN), 58.5 (C**C**HN), 60.9 (**C**HCHO), 109.6 (**C**H=CHN), 110.9, 112.8 (CN), 125.4, 125.9 (C_{arom}-H), 126.4 (**C**$_{arom}$-C), 127.6, 128.0, 128.9 (C_{arom}-H), 131.5 (**C**$_{arom}$-C), 198.5 (CHO).

$[\alpha]_D^{20}$: +22.8 (c = 0.6, CH_2Cl_2).

(1*R*,2*R*,10b*R*)-1-Formyl-2-octyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-5c)



***exo*-5c**

Following the general procedure, working at room temperature, starting from (*E*)-2-undecenal **3c** (206 μL, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 1 hour, the title compound **5c** (85 mg, 0.23 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 45%.

d.r.: 63:37 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.88 (t, 3H, *J* = 6.8 Hz, CH_3), 1.16-1.44 (m, 10H, $(CH_2)_5$), 1.45-1.58 (m, 2H, C**H**$_2$CH$_3$), 1.67-2.05 (m, 2H, C**H**$_2$(CH$_2$)$_6$CH$_3$), 3.49-3.14 (m, 2H, C**H**CHO + C**H**CH$_2$), 5.08 (d, 1H, *J* = 8.3 Hz, CCHN), 6.04 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.37 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 6.90 (d, 1H, *J* = 6.7 Hz, C_{arom}-H), 7.06 (d, 1H, *J* = 6.4 Hz, C_{arom}-H), 7.12-7.33 (m, 2H, C_{arom}-H), 9.94 (d, 1H, *J* = 2.7 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 14.1 (CH_3), 22.6, 27.5, 29.1, 29.4, 30.9, 31.7 (CH_2), 50.4 (C**H**CH$_2$), 59.1 (C**C**HN), 59.5 (**C**CN), 60.1 (**C**HCHO), 111.6 (**C**H=CHN), 111.7, 113.2 (CN), 123.5, 125.1, 126.6, 128.1, 128.6 (C_{arom}-H), 128.9, 130.9 (**C**$_{arom}$-C), 197.5 (CHO).

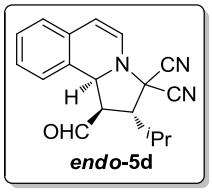
MS (EI) [m/z (%)]: 335 (16), 222 (16), 195 (15), 194 (100), 193 (52), 169 (19), 130 (11).

HRMS: Calculated for $[C_{23}H_{28}N_3O\ (M+H)]^+$: 363.2232. Found: 363.2242.

IR (Film, cm^{-1}): 1650 (C=O).

$[\alpha]_D^{20}$: +252.2 (c = 1.0, CH_2Cl_2).

(1*R*,2*R*,10b*S*)-1-Formyl-2-isopropyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (*endo*-5d)



Following the general procedure, working at room temperature, starting from (*E*)-4-methylpent-2-enal **3d** (121 μL, 1.04 mmol) and ylide **2a** (0.10g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 6 days, the title compound **5d** (82 mg, 0.28 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 54%.

d.r.: 80:20 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.10 (d, 3H, *J* = 6.6 Hz, CH_3), 1.32 (d, 3H, *J* = 6.4 Hz, CH_3), 2.06-2.27 (m, 1H, C**H**$(CH_3)_2$), 2.65 (dd, 1H, *J* = 11.2, 4.6 Hz, C**H**CH$(CH_3)_2$), 3.12-3.22 (m, 1H, C**H**CHO), 5.00 (d, 1H, *J* = 7.1 Hz, CCHN), 5.89 (d, 1H, *J* = 7.8 Hz, C**H**=CHN), 6.47 (d, 1H, *J* = 7.8 Hz, CH=C**H**N), 6.99 (d, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.08 (d, 1H, *J* = 7.5 Hz, C_{arom}-H), 7.13-7.30 (m, 2H, C_{arom}-H), 9.68 (d, 1H, *J* = 4.5 Hz, CHO).

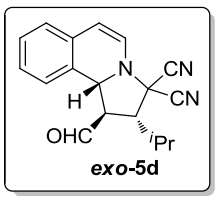
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 21.2, 21.6 (CH_3), 30.9 (**C**H$(CH_3)_2$), 54.9 (**C**HCH$(CH_3)_2$), 57.2 (C**C**HN), 57.9 (**C**CN), 61.1 (**C**HCHO), 109.9 (**C**H=CHN), 111.1, 113.0 (CN), 125.5, 125.9 (C_{arom}-H), 126.6 (**C**$_{arom}$-C), 127.6, 128.0, 128.9 (C_{arom}-H), 131.5(**C**$_{arom}$-C), 198.4 (CHO).

MS (EI) [m/z (%)]: 193 (40), 194 (22), 265 (100), 266 (18), 291 (20), 292 (16, M^+).

HRMS: Calculated for $[C_{18}H_{18}N_3O\ (M+H)]^+$: 292.1450. Found: 292.1459.

IR (Film, cm^{-1}): 1725 (C=O).

(1*R*,2*R*,10b*R*)-1-Formyl-2-isopropyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (*exo*-5d)

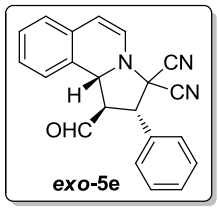


Yield: 10%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.05 (d, 3H, *J* = 6.7 Hz, CH_3), 1.26 (d, 3H, *J* = 6.6 Hz, CH_3), 2.10-2.39 (m, 1H, C**H**$(CH_3)_2$), 3.09-3.24 (m, 1H, C**H**CH$(CH_3)_2$), 3.51 (ddd, 1H, *J* = 9.6, 8.2, 3.1 Hz, C**H**CHO), 4.96 (d, 1H, *J* = 8.2 Hz, CCHN), 6.08 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.39 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 6.94-7.13 (m, 2H, C_{arom}-H), 7.17-7.32 (m, 2H, C_{arom}-H), 9.96 (d, 1H, *J* = 3.1 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 21.0, 21.9 (CH_3), 31.1 (**C**H$(CH_3)_2$), 57.1 (**C**HCH$(CH_3)_2$), 58.2 (C**C**HN), 60.1 (**C**CN), 58.7 (**C**HCHO), 111.9 (CN), 112.2 (**C**H=CHN), 113.5 (CN), 123.5, 125.2, 126.7, 128.1, 128.6 (C_{arom}-H), 128.8, 131.1 (**C**$_{arom}$-C), 197.7 (CHO).

(1*R*,2*S*,10b*R*)-1-Formyl-2-phenyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2H)-dicarbonitrile (*exo*-5e)



Following the general procedure, working at -30 ºC, starting from (*E*)-cinnamaldehyde **3e** (131 μL, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 5 days, the title compound **5e** (0.12 g, 0.36 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 70%.

d.r.: >95:<5 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (500 MHz, $CDCl_3$, 25 ºC): 4.05-4.18 (m, 1H, C**H**CHO), 4.40 (d, 1H, *J* = 10.8 Hz, CHPh), 5.24 (d, 1H, *J* = 8.5 Hz, CCHN), 6.08 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.39 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 7.00 (d, 1H, *J* = 6.8 Hz, C_{arom}-H), 7.12 (d, 1H, *J* = 7.1 Hz, C_{arom}-H), 7.20-7.33 (m, 2H, C_{arom}-H), 7.39-7.60 (m, 5H, C_{arom}-H), 9.90 (d, 1H, *J* = 1.6 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 55.4 (CHPh), 59.1 (C**C**HN), 59.2 (**C**HCHO), 61.4 (**C**CN), 111.7 (CN), 111.9 (**C**H=CHN), 112.7 (CN), 123.9, 125.4 (C_{arom}-H), 126.8 (CH=**C**HN), 128.3, 128.7, 128.8 (C_{arom}-H), 129.1(C_{arom}-C), 129.7, 130.4 (C_{arom}-H), 131.1, 131.2 (C_{arom}-C), 196.8 (CHO).

MS (EI) [m/z (%)]: 326 (2), 133 (100), 132 (31), 131 (33), 130 (52), 129 (33).

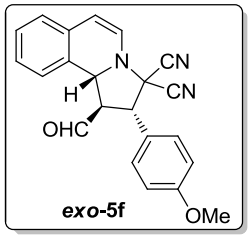
HRMS: Calculated for $[C_{21}H_{16}N_3O\ (M+H)]^+$: 326.1293. Found: 326.1299.

IR (KBr, cm^{-1}): 1725 (C=O).

$[\alpha]_D^{20}$: +402.2 (c = 1. 0, CH_2Cl_2).

M.p.: 115-120 ºC (recrystallized in CH_2Cl_2).

(1*R*,2*S*,10b*R*)-1-Formyl-2-(4-methoxyphenyl)-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-5f)



Following the general procedure, working at 4 ºC, starting from (*E*)-4-methoxycinnamaldehyde **3f** (0.180 g, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 7 days, the title compound **5f** (0.12 g, 0.32 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 63%.

d.r.: >95:<5 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

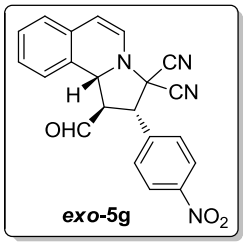
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 3.83 (s, 3H, CH_3), 4.07 (ddd, 1H, *J* = 10.9, 8.5, 2.1 Hz, C**H**CHO), 4.35 (d, 1H, *J* = 11.1 Hz, CHAr), 5.24 (d, 1H, *J* = 8.4 Hz, CCHN), 6.06 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.37 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 6.97-6.99 (m, 3H, C_{arom}-H), 7.09-7.10 (m, 1H, C_{arom}-H), 7.24-7.29 (m, 2H, C_{arom}-H), 7.46 (d, 2H, *J* = 7.8 Hz, C_{arom}-H), 9.87 (d, 1H, *J* = 2.1 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 55.0 (CHAr), 55.4 (CH_3), 58.9 (C**C**HN), 59.3 (**C**HCHO), 61.6 (**C**CN), 111.7 (**C**H=CHN), 111.8, 112.7 (CN), 115.0 (C_{arom}-H), 122.5 (**C**$_{arom}$-C), 123.8, 125.3, 126.7, 128.2 (C_{arom}-H), 128.7 (C_{arom}-H), 129.0 (**C**$_{arom}$-C), 130.0 (C_{arom}-H), 131.0 (C_{arom}-C), 161.0 (**C**OCH_3), 196.9 (CHO).

IR (Film, cm^{-1}): 1725 (C=O).

$[\alpha]_D^{20}$: +481.2 (c = 1.1, CH_2Cl_2).

(1*R*,2*S*,10b*R*)-1-Formyl-2-(4-nitrophenyl)-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2H)-dicarbonitrile (*exo*-5g)



Following the general procedure, working at 4 ºC, starting from (*E*)-4-nitrocinnamaldehyde **3g** (0.160 g, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 7 days, the title compound **5g** (0.14 g, 0.37 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 73%.

d.r.: >95:<5 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

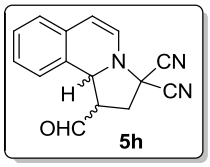
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 4.06-4.13 (m, 1H, C**H**CHO), 4.57 (d, 1H, *J* = 9.7 Hz, CHAr), 5.16 (d, 1H, *J* = 8.5 Hz, CCHN), 6.13 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.40 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 7.06 (d, 1H, *J* = 6.0 Hz, C_{arom}-H), 7.14 (d, 1H, *J* = 6.2 Hz, C_{arom}-H), 7.30-7.32 (m, 2H, C_{arom}-H), 7.70 (d, 2H, *J* = 8.5 Hz, C_{arom}-H), 8.28 (d, 2H, *J* = 8.5 Hz, C_{arom}-H), 9.95 (s, 1H, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 54.1 (CHAr), 59.3 (**C**HCHO), 59.4 (C**C**HN), 60.5 (**C**CN), 111.2, 112.1 (CN), 112.5 (**C**H=CHN), 123.6, 124.6, 125.6, 126.6, 128.5 (C_{arom}-H), 128.7 (C_{arom}-C), 129.1, 129.9 (C_{arom}-H), 130.9, 139.2 (C_{arom}-C), 148.8 (CNO_2), 195.8 (CHO).

IR (Film, cm^{-1}): 1726 (C=O).

$[\alpha]_D^{20}$: +245.5 (c = 1.0, CH_2Cl_2).

1-Formyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (5h)



5h

Following the general procedure, working at room temperature, starting from acroleine **3h** (68 μL, 1.04 mmol) and ylide **2a** (0.10 g, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using THF (2 mL) as solvent and after 30 minutes, the title compound **5h** (0.11 g, 0.45 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 88% (mixture of diastereoisomers).

d.r.: 46:54 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer) 2.86 (dd, 1H, *J* = 14.3, 7.7 Hz, C**H**$_A$H$_B$), 2.98* (dd, 1H, *J* = 13.6, 9.4 Hz, C**H**$_A$H$_B$), 3.11* (dd, 1H, *J* = 13.6, 8.3 Hz, CH$_A$**H**$_B$), 3.26 (dd, 1H, *J* = 14.3, 1.1 Hz, CH$_A$**H**$_B$), 3.50-3.64 (m, 1H, C**H**CHO), 3.74* (td, 1H, *J* = 9.9, 1.6 Hz, C**H**CHO), 4.89* (d, 1H, *J* = 8.6 Hz, CCHN), 5.15 (d, 1H, *J* = 5.1 Hz, CCHN), 5.80 (d, 1H, *J* = 7.8 Hz, C**H**=CHN), 6.04* (d, 1H, *J* = 7.5 Hz, C**H**=CHN), 6.42* (d, 1H, *J* = 7.5 Hz, CH=C**H**CN), 6.46 (d, 1H, *J* = 7.4 Hz, CH=C**H**CN), 6.96-7.04 (m, 1H, C_{arom}-H), 7.05-7.18 (m, 1H, C_{arom}-H), 7.18-7.34 (m, 2H, C_{arom}-H), 9.92 (d, 1H, *J* = 1.8 Hz, CHO), 9.97* (d, 1H, *J* = 1.6 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer) 38.2* (CH_2), 38.4 (CH_2), 49.4 (**C**HCHO), 51.5 (**C**CN), 53.1* (**C**CN), 53.2* (**C**HCHO), 59.7* (**C**CHN), 62.2 (**C**CHN), 108.8 (**C**H=CHN), 111.6* (**C**H=CHN), 112.7*,

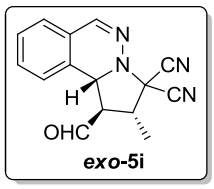
113.0, 113.9 (CN), 123.6*, 125.2*, 125.3, 126.0, 127.2*, 127.6, 127.7, 128.1*, 128.7*, 129.0 (C_{arom}-H), 131.1*, 131.7 (**C**$_{arom}$-C).

MS (EI) [*m/z* (%)]: 129 (22), 130 (58), 193 (37), 194 (41), 223 (100).

HRMS: Calculated for $[C_{15}H_{12}N_3O]^+$: 250.0980. Found: 250.0983.

IR (Film, cm^{-1}): 1724 (C=O).

(1*R*,2*R*,10b*R*)-1-Formyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5i)



***exo*-5i**

Following the general procedure, working at room temperature, starting from crotonaldehyde **3a** (86 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 10 minutes, the title compound **5i** (97 mg, 0.37 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 71%.

d.r.: 86:14 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.58 (d, 3H, *J* = 7.1 Hz, CH_3), 3.11 (ddd, 1H, *J* = 9.2, 7.0, 2.0 Hz, **CH**CHO), 3.23-3.46 (m, 1H, C**H**CH_3), 4.55 (d, 1H, *J* = 9.2 Hz, CHC**H**N), 7.10 (d, 1H, *J* = 7.2 Hz, C_{arom}-H), 7.30-7.61 (m, 3H, C_{arom}-H), 7.79 (s, 1H, CHN), 9.95 (d, 1H, *J* = 2.0 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 19.1 (CH_3), 42.6 (**C**HCH_3), 56.6 (CH**C**HN), 58.6 (**C**HCHO), 60.6 (**C**CN), 111.6, 113.0 (CN), 123.6 (C_{arom}-H), 125.0 (**C**$_{arom}$-C), 126.4, 129.2, 132.4 (C_{arom}-H), 132.5 (**C**$_{arom}$-C), 146.5 (C_{arom}-H), 196.6 (CHO).

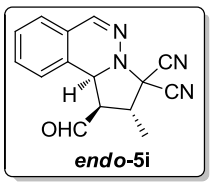
MS (EI) [m/z (%)]: 265 (12), 239 (15), 238 (100), 195 (43), 194 (24).

HRMS: Calculated for $[C_{15}H_{13}N_4O\ (M+H)]^+$: 265.1089. Found: 265.1094.

IR (Film, cm^{-1}): 1725 (C=O).

$[\alpha]_D^{20}$: -57.1 (c = 0.8, CH_2Cl_2).

(1*R*,2*R*,10b*S*)-1-Formyl-2-methyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*endo*-5i)



***endo*-5i**

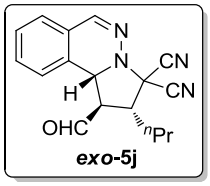
Yield: 10%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.56 (d, 3H, *J* = 7.2 Hz, CH_3), 2.95-3.04 (m, 1H, **C**$\mathbf{H}$CHO), 3.00 (dt, 1H, *J* = 7.5, 4.3 Hz, C**H**CH_3), 4.83 (d, 1H, *J* = 7.3 Hz, CHC**H**N), 7.10 (d, 1H, *J* = 7.1 Hz, C_{arom}-H), 7.29-7.54 (m, 3H, C_{arom}-H), 7.69 (s, 1H, CHN), 9.66 (d, 1H, *J* = 4.0 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 15.9 (CH_3), 42.7 (**C**HCH_3), 55.2 (CH**C**HN), 57.6 (**C**HCHO), 62.1 (**C**CN), 110.7, 112.9 (CN), 124.9 (**C**$_{arom}$-C), 125.3, 127.4, 129.4 (C_{arom}-H), 129.6 (**C**$_{arom}$-C), 132.3, 146.1 (C_{arom}-H), 197.6 (CHO).

$[\alpha]_D^{20}$: +5.2 (c = 0.8, CH_2Cl_2).

(1*R*,2*R*,10b*R*)-1-Formyl-2-propyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5j)



***exo*-5j**

Following the general procedure, working at room temperature, starting from (*E*)-2-hexenal **3b** (120 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 16 hours, the title compound **5j** (0.11 g, 0.37 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 72%.

d.r.: 83:17 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.02 (t, 3H, J = 7.3 Hz, CH_3), 1.41-1.64 (m, 2H, C**H**$_2$CH$_3$), 1.64-1.84 (m, 1H, CHC**H**$_A$H$_B$), 1.19-1.22 (m, 1H, CHCH$_A$**H**$_B$), 3.10-3.33 (m, 2H, C**H**CHO + C**H**CH$_2$), 4.55 (d, 1H, J = 8.8 Hz, CHC**H**N), 7.12 (d, 1H, J = 7.2 Hz, C$_{arom}$-H), 7.27-7.59 (m, 3H, C$_{arom}$-H), 7.80 (s, 1H, CHN), 9.93 (d, 1H, J = 2.1 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.6 (CH_3), 20.1, 35.3 (CH_2), 47.5 (**C**HCH$_2$), 56.7 (CH**C**HN), 56.9 (**C**HCHO), 60.2 (**C**CN), 111.6, 113.2 (CN), 123.6 (C$_{arom}$-H), 125.1 (**C**$_{arom}$-C), 126.4, 129.2, 132.3 (C$_{arom}$-H), 132.5 (**C**$_{arom}$-C), 146.4 (C$_{arom}$-H), 197.1 (CHO).

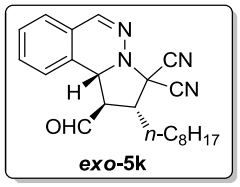
MS (EI) [m/z (%)]: 293 (11), 267 (12), 266 (100), 195 (22), 194 (41), 131 (14).

HRMS: Calculated for $[C_{17}H_{17}N_4O\ (M+H)]^+$: 293.1402. Found: 293.1491.

IR (Film, cm^{-1}): 1725 (C=O).

$[\alpha]_D^{20}$: +277.0 (c = 0.9, CH_2Cl_2).

(1*R*,2*R*,10b*R*)-1-Formyl-2-octyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5k)



***exo*-5k**

Following the general procedure, working at room temperature, starting from (*E*)-2-undecenal **3c** (206 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 1 hour, the title compound **5k** (0.12 g, 0.33 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 64%.

d.r.: 77:23 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.88 (t, 3H, J = 6.7 Hz, CH_3), 1.11-1.55 (m, 12H, $(CH_2)_6$), 1.66-1.83 (m, 1H, CHC**H**$_A$H$_B$), 1.98-2.14 (m, 1H, CHCH$_A$**H**$_B$), 3.11-3.24 (m, 2H, C**H**CHO+C**H**CH_2), 4.54 (d, 1H, J = 8.7 Hz, CHC**H**N), 7.12 (d, 1H, J = 7.5 Hz, C_{arom}-H), 7.29-7.58 (m, 3H, C_{arom}-H), 7.78 (s, 1H, CHN), 9.93 (d, 1H, J = 1.8 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 14.1 (CH_3), 22.6, 26.8, 29.1, 29.1, 29.2, 31.7, 33.3 (CH_2), 47.7 (**C**HCH_2), 56.7 (CH**C**HN), 57.0 (**C**HCHO), 60.2 (**C**CN), 111.6, 113.2 (CN), 123.6 (C_{arom}-H), 125.1 (**C**$_{arom}$-C), 126.4, 129.2, 132.4 (C_{arom}-H), 132.6 (**C**$_{arom}$-C), 146.4 (C_{arom}-H), 197.1 (CHO).

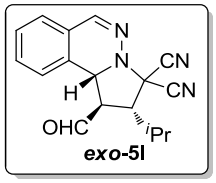
MS (EI) [m/z (%)]: 336 (63), 194 (37), 131 (100), 130 (49), 117 (43), 95 (59), 83 (28).

HRMS: Calculated for $[C_{22}H_{27}N_4O\ (M+H)]^+$: 363.2185. Found: 363.2191.

IR (Film, cm^{-1}): 1727 (C=O).

$[\alpha]_D^{20}$: -11.7 (c = 1.0, CH_2Cl_2).

(1*R*,2*R*,10b*R*)-1-Formyl-2-isopropyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*exo*-5l)



Following the general procedure, working at room temperature, starting from (*E*)-2,4-dimethylpentenal **3d** (118 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 1 hour, the title compound **5l** (76 mg, 0.26 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 51%.

d.r.: 77:23 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.00 (d, 3H, *J* = 8.7 Hz, CH_3), 1.17 (d, 3H, *J* = 8.7 Hz, CH_3), 2.35-2.45 (m, 1H, C**H**$(CH_3)_2$), 3.19 (dd, 1H, *J* = 7.0, 5.8 Hz, C**H**CH$(CH_3)_2$), 3.32 (ddd, 1H, *J* = 9.4, 7.1, 2.4 Hz, C**H**CHO), 4.51 (d, 1H, *J* = 9.4 Hz, CHC**H**N), 7.17 (d, 1H, *J* = 7.3 Hz, C_{arom}-H), 7.29-7.58 (m, 3H, C_{arom}-H), 7.79 (s, 1H, CHN), 9.93 (d, 1H, *J* = 2.4 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 18.4, 21.4 (CH_3), 30.4 (**C**H$(CH_3)_2$), 52.1 (**C**HCHO), 53.8 (**C**HCH$(CH_3)_2$), 56.8 (CH**C**HN), 59.7 (**C**CN), 111.9, 113.2 (CN), 123.9 (C_{arom}-H), 125.3 (**C**$_{arom}$-C), 126.4, 129.2, 132.3 (C_{arom}-H), 132.5 (**C**$_{arom}$-C), 146.5 (C_{arom}-H), 197.3 (CHO).

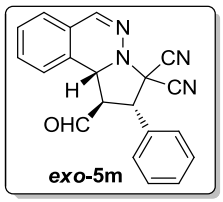
MS (EI) [m/z (%)]: 194 (16), 195 (10), 266 (100).

HRMS: Calculated for $[C_{17}H_{17}N_4O\ (M+H)]^+$: 293.1402. Found: 293.1411.

IR (Film, cm^{-1}): 1727 (C=O).

$[\alpha]_D^{20}$: -45.5 (c = 0.6, CH_2Cl_2).

(1*R*,2*S*,10b*R*)-1-Formyl-2-phenyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5m)



Following the general procedure, working at room temperature, starting from (*E*)-cinnamaldehyde **3d** (131 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 1 day, the title compound **5m** (0.13 g, 0.31 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 61%.

d.r.: 63:37 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 3.70-3.91 (m, 1H, C**H**CHO), 4.41 (d, 1H, *J* = 6.7 Hz, CHPh), 4.63 (d, 1H, *J* = 9.3 Hz, CHC**H**N), 7.19 (d, 1H, *J* = 7.4 Hz, C_{arom}-H), 7.32 (d, 1H, *J* = 2.8 Hz, C_{arom}-H), 7.36-7.62 (m, 7H, C_{arom}-H), 7.86 (s, 1H, CHN), 9.96 (s, 1H, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 53.3 (CHPh), 56.8 (**C**HCHO), 58.7 (CH**C**HN), 61.9 (**C**CN), 111.3, 112.8 (CN), 123.7 (C_{arom}-H), 125.3 (**C**$_{arom}$-C), 126.6, 128.6, 129.4, 129.5, 129.9 (**C**$_{arom}$-H), 132.5 (C_{arom}-C), 132.6 (**C**$_{arom}$-H), 135.9 (**C**$_{arom}$-C), 147.1 (C_{arom}-H), 196.1 (CHO).

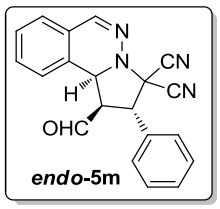
MS (EI) [m/z (%)]: 327 (15), 301 (22), 300 (100), 196 (14), 195 (65), 194 (38), 133 (39), 131 (22).

HRMS: Calculated for $[C_{20}H_{15}N_4O\ (M+H)]^+$: 327.1246. Found: 327.1244.

IR (Film, cm^{-1})**:** 1727 (C=O).

$[\alpha]_D^{20}$: + 402.2 (c = 1.0, CH_2Cl_2).

(1*R*,2*S*,10b*S*)-1-Formyl-2-phenyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*endo*-5m)

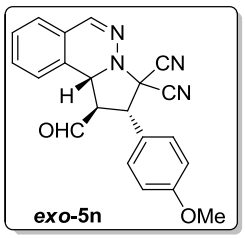


Yield: 20%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 3.70-3.85 (m, 1H, C**H**CHO), 4.37 (d, 1H, *J* = 5.5 Hz, CHPh), 5.19 (d, 1H, *J* = 7.8 Hz, CHC**H**N), 7.22-7.55 (m, 9H, C_{arom}-H), 7.71 (s, 1H, CHN), 9.96 (s, 1H, *J* = 3,2 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 53.3 (CHPh), 54.9 (**C**HCHO), 59.1 (CH**C**HN), 64.5 (**C**CN), 110.9, 112.6 (CN), 124.6 (**C**$_{arom}$-C), 125.8, 127.5, 128.9 (C_{arom}-H), 129.3 (**C**$_{arom}$-C), 129.5, 129.7, 129.9 (**C**$_{arom}$-H), 132.2 (**C**$_{arom}$-C), 132.4, 145.8 (C_{arom}-H), 197.1 (CHO).

(1*R*,2*S*,10b*S*)-1-Formyl-2-(4-methoxyphenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5n)



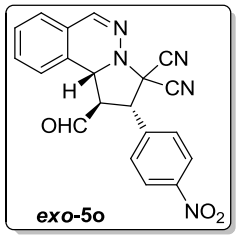
Following the general procedure, working at room temperature, starting from (*E*)-4-methoxycinnamaldehyde **3f** (0.180 g, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 1 day, the title compound **5n** (0.12 g, 0.32 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2). The compound had to be directly reduced to the corresponding primary alcohol due to stability issues.

Yield: 63%.

d.r.: 71:29 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

(The compound is highly unstable so no spectroscopic data could be obtained. See compound **6n**).

(1*R*,2*S*,10b*R*)-1-Formyl-2-(4-nitrophenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-5o)



Following the general procedure, working at room temperature, starting from (*E*)-*p*-nitrocinnamaldehyde **3g** (0.160 g, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 16 hours, the title compound **5o** (0.11 g, 0.31 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 60%.

d.r.: 67:33 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

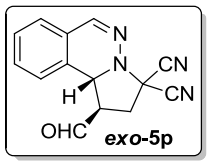
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 3.76 (dd, 1H, *J* = 9.2, 5.9 Hz, C**H**CHO), 3.69-3.81 (m, 2H, CHAr + CHC**H**N), 7.23 (d, 1H, *J* = 7.2 Hz, C_{arom}-H), 7.32-7.66 (m, 5H, C_{arom}-H), 7.90 (s, 1H, CHN), 8.21 (d, 2H, *J* = 8.6 Hz, C_{arom}-H), 9.99 (s, 1H, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 51.8 (CHAr), 56.9 (**C**HCHO), 58.6 (CH**C**HN), 61.3 (**C**CN), 111.0, 112.1 (CN), 123.5, 124.6 (C_{arom}-H), 125.2 (**C**$_{arom}$-C), 126.9, 129.7, 129.9 (C_{arom}-H), 132.4 (**C**$_{arom}$-C), 132.8 (C_{arom}-H), 143.3 (**C**$_{arom}$-C), 147.9 (C_{arom}-H), 148.5 (**C**$_{arom}$-C), 195.1 (CHO).

IR (Film, cm^{-1}): 1651 (C=O).

$[\alpha]_D^{20}$: +24.4 (c = 1.0, CH_2Cl_2).

(1*R*,10b*R*)-1-Formyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*exo*-5p)



Following the general procedure, working at room temperature, starting from acroleine **3h** (67 μL, 1.04 mmol) and ylide **2b** (99 mg, 0.52 mmol) in the presence of catalyst **4f** (25 mg, 0.10 mmol) and TFA (7.9 μL, 0.10 mmol), using toluene (2 mL) as solvent and after 45 minutes, the title compound **5p** (69 mg, 0.27 mmol) was isolated by flash column chromatography (hexanes:EtOAc 6:4).

Yield: 54%.

d.r.: 57:43 (Determined by ^{1}H-NMR analysis of crude reaction mixture).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 2,96-3.08 (m, 1H, C**H**$_A$H$_B$), 3.20 (dd, 1H, *J* = 14.2, 5.7 Hz, CH$_A$**H**$_B$), 3.50-3.70 (m, 1H, C**H**CHO), 4.45 (d, 1H, *J* = 9.4 Hz, CHC**H**N), 7.12-7.61 (m, 4H, C_{arom}-H), 7.81 (s, 1H, CH=N), 9.93 (d, 1H, *J* = 1.5 Hz, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 35.5 (CH_2), 49.4 (CHO), 54.6 (**C**CN), 56.5 (CH**C**HN), 112.5, 112.9 (CN), 123.6 (C_{arom}-H), 125.0 (**C**$_{arom}$-C), 126.5, 129.3, 132.4 (C_{arom}-H), 132.7, 146.8 (C_{arom}-H), 196.4 (CHO).

MS (EI) [m/z (%)]: 194 (19), 195 (11), 224 (100), 225 (17), 251 (10).

HRMS: Calculated for $[C_{14}H_{11}N_4O\ (M+H)]^+$: 251.0933. Found: 251.0945.

IR (Film, cm^{-1}): 1724 (C=O).

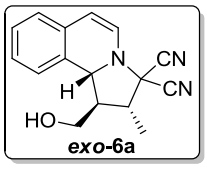
$[\alpha]_D^{20}$: -100.23 (c = 1.0, CH_2Cl_2).

5.3. Reduction of aldehydes 5a-p into the primary alcohols 6a-p

General procedure

The aldehyde **5a-p** (0.38 mmol) was dissolved in dry THF (15 mL) at -78 ºC and $LiBH_4$ (0.38 mmol) was added. The mixture was stirred until full conversion was observed by t.l.c. and afterwards the reaction was quenched with aqueous NH_4Cl (sat., 5 ml) and CH_2Cl_2 (20 mL) was added. The reaction was stirred for 30 minutes and then the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography to obtain alcohols **6a-p**. Racemic samples were prepared reducing the racemic mixtures of the aldehydes **5a-p**.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6a)



***exo*-6a**

Following the general procedure, aldehyde **5a** (99 mg, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 15 minutes the title compound **6a** (72 mg, 0.27 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 72%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.47 (d, 3H, *J* = 6.9 Hz, CH_3), 1.80 (bs, 1H, OH), 2.52-2.70 (m, 1H, C**H**CH_2), 2.97-3.12 (m, 1H, C**H**CH_3), 3.96-4.15 (m, 2H, CH_2), 4.68 (d, 1H, *J* = 8.0 Hz, CCHN), 6.05 (d, 1H, *J* = 7.3 Hz, C**H**=CHN), 6.37 (d, 1H, *J* = 7.3 Hz, CH=C**H**N), 7.00-7.09 (m, 1H, C_{arom}-H), 7.08-7.16 (m, 1H, C_{arom}-H), 7.18-7.26 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 15.0 (CH_3), 46.3 (**C**HCH_3), 51.3 (**C**HCH_2), 59.8 (C**C**HN), 60.2 (**C**CN), 62.0 (CH_2), 112.0 (**C**H=CHN), 112.4, 113.4 (CN), 123.1, 124.8, 127.4, 127.8 (C_{arom}-H), 128.0 (CH=**C**HN), 130.0, 131.3 (**C**$_{arom}$-C).

MS (EI) [m/z (%)]: 239 (100), 238 (26), 207 (12), 193 (28), 182 (14).

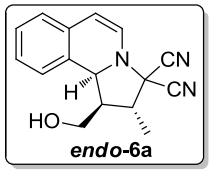
HRMS: Calculated for $[C_{16}H_{16}N_3O\ (M+H)]^+$: 266.1293. Found: 266.1304.

IR (Film, cm^{-1}): 3425 (OH).

$[\alpha]_D^{20}$: +425.8 (c = 0.9, CH_2Cl_2).

e.e.: 88%, calculated by HPLC (Chiralcel OD column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 26.07 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 13.22 min.

(1*R*,2*R*,10b*S*)-1-Hydroxymethyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*endo*-6a)

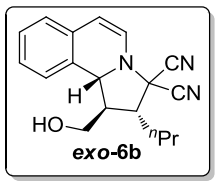


Yield: 30%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.51 (d, 3H, *J* = 7.3 Hz, CH_3), 1.59 (bs, 1H, OH), 2.43-2.57 (m, 1H, C**H**CH_2), 3.06-3.28 (m, 1H, C**H**CH_3), 3.60-3.79 (m, 1H, C**H**$_A$H$_B$), 3.81-3.98 (m, 1H, CH$_A$**H**$_B$), 5.14 (d, 1H, *J* = 5.7 Hz, CCHN), 5.64 (d, 1H, *J* = 7.6 Hz, C**H**=CHN), 6.37 (d, 1H, *J* = 7.6 Hz, CH=C**H**N), 6.99 (d_{ap}, 2H, *J* = 7.3 Hz, C_{arom}-H), 7.05-7.24 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 17.4 (CH_3), 45.9 (**C**HCH_3), 49.7 (**C**HCH_2), 59.3 (**C**CN), 60.4 (C**C**HN), 61.3 (CH_2), 106.2 (**C**H=CHN), 112.0, 113.8 (CN), 125.5, 125.6, 126.8 (C_{arom}-H), 127.5 (**C**$_{arom}$-C), 128.2, 128.4 (C_{arom}-H), 131.7 (**C**$_{arom}$-C).

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-propyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6b)



Following the general procedure, aldehyde **5b** (0.110 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 15 minutes the title compound **6b** (63 mg, 0.21 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 57%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.03 (t, 3H, *J* = 7.2 Hz, CH_3), 1.45-1.71 (m, 2H, C**H**$_2$CH$_3$), 1.72-1.95 (m, 3H, CHC**H**$_2$CH$_2$ + OH), 2.55-2.80 (m, 1H,

C**H**CH_2CH_2), 2.98 (dd, 1H, *J* = 15.6, 7.7 Hz, C**H**CH_2OH), 3.87-4.21 (m, 2H, C**H**$_2$OH), 4.64 (d, 1H, *J* = 7.8 Hz, CCHN), 6.06 (d, 1H, *J* = 7.3 Hz, C**H**=CHN), 6.41 (d, 1H, *J* = 7.3 Hz, CH=C**H**N), 7.02-7.09 (m, 1H, C_{arom}-H), 7.09-7.17 (m, 1H, C_{arom}-H), 7.18-7.25 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 14.1 (CH_3), 20.7 (**C**H_2CH_3), 33.5 (CH**C**H_2CH_2), 50.1 (**C**HCH_2CH_2), 50.6 (**C**HCH_2OH), 59.0 (**C**CN), 60.1 (C**C**HN), 62.3 (CH_2OH), 112.0 (**C**H=CHN), 112.4, 113.8 (CN), 123.2, 124.8, 127.5, 127.8, 128.0 (C_{arom}-H), 130.2, 131.5 (**C**$_{arom}$-C).

MS (EI) [m/z (%)]: 294 (54), 293 (39), 267 (100), 249 (68), 130 (72), 129 (38).

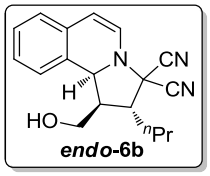
HRMS: Calculated for $[C_{18}H_{20}N_3O\ (M+H)]^+$: 294.1606. Found: 294.1608.

IR (Film, cm^{-1}): 3548 (OH).

$[\alpha]_D^{20}$: +260.1 (c = 1.1, CH_2Cl_2).

e.e.: 84%, calculated by HPLC (Chiralpak AS-H column, *n*-hexane:^{i}PrOH in gradient; 1.00 mL/min, linear curve: min 0, 100:0; min 20, 95:5; min 30, 90:10). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 43.07 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 29.46 min.

(1*R*,2*R*,10b*S*)-1-Hydroxymethyl-2-propyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (*endo*-6b)



Yield: 55%.

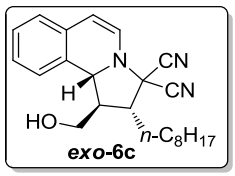
^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.06 (t, 3H, *J* = 7.2 Hz, CH_3), 1.66-1.42 (m, 3H, C**H**$_2$CH$_3$ + OH), 1.66-1.42 (m, 2H, CHC**H**$_2$CH$_2$), 2.40-2.57 (m, 1H, C**H**CH$_2$CH$_2$), 2.94-3.10 (m, 1H, C**H**CH$_2$OH), 3.59-3.77 (m, 1H, C**H**$_A$H$_B$OH), 3.77-3.98 (m, 1H, CH$_A$**H**$_B$OH), 5.01 (d, 1H, *J* = 6.0 Hz, CCHN), 5.67 (d, 1H, *J* = 7.7 Hz, C**H**=CHN), 6.39 (d, 1H, *J* = 7.7 Hz, CH=C**H**N), 7.01 (d, 2H, *J* = 7.4 Hz, C_{arom}-H), 7.06-7.22 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.8 (CH_3), 21.2 (**C**H$_2$CH$_3$), 34.4 (CH**C**H$_2$CH$_2$), 47.5 (**C**HCH$_2$CH$_2$), 51.2 (**C**HCH$_2$OH), 58.5 (**C**CN), 60.6 (C**C**HN), 61.7 (CH_2OH), 106.7 (**C**H=CHN), 111.9, 113.9 (CN), 125.5, 125.6, 126.8 (C_{arom}-H), 127.7 (**C**$_{arom}$-C), 128.3, 128.4 (C_{arom}-H), 131.8 (**C**$_{arom}$-C).

$[\alpha]_D^{20}$: +470.8 (c = 0.7, CH_2Cl_2).

e.e.: 5%, calculated by HPLC (Chiralpak AS-H column, *n*-hexane:^{i}PrOH in gradient; 1.00 mL/min, linear curve: min 0, 100:0; min 20, 95:5; min 30, 90:10). t_R for the major enantiomer (1*R*,2*R*,10b*S*): 34.28 min; t_R for the minor enantiomer (1*S*,2*S*,10b*R*): 41.36 min.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-octyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6c)



Following the general procedure, aldehyde **5c** (0.137 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 45 minutes the title compound **6c** (47 mg, 0.13 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 34%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.89 (t, 3H, *J* = 6.3 Hz, CH_3), 1.18-1.46 (m, 10H, $(CH_2)_5$), 1.48-1.71 (m, 2H, CHC**H**$_2$CH$_2$), 1.69-1.95 (m, 3H, C**H**$_2$CH$_3$ + OH), 2.56-2.74 (m, 1H, C**H**CH$_2$CH$_2$), 2.96 (m, 1H, C**H**CH$_2$OH), 3.88-4.15 (m, 2H, CH$_2$OH), 4.64 (d, 1H, *J* = 7.7 Hz, CCHN), 6.06 (d, 1H, *J* = 7.3 Hz, C**H**=CHN), 6.41 (d, 1H, *J* = 7.3 Hz, CH=C**H**N), 7.01-7.09 (m, 1H, C_{arom}-H), 7.10-7.17 (m, 1H, C_{arom}-H), 7.17-7.25 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 14.1 (CH_3), 22.6, 27.4, 29.1, 29.2, 29.6, 31.4, 31.8 $(CH_2)_7$), 50.1 (**C**HCH$_2$CH$_2$), 50.8, (**C**HCH$_2$OH), 59.1 (**C**CN), 60.1 (C**C**HN), 62.4 (CH$_2$OH), 112.0 (**C**H=CHN), 112.3, 113.8 (CN), 123.1, 124.7, 127.5, 127.7, 127.9 (C_{arom}-H), 130.2, 131.5 (**C**$_{arom}$-C).

MS (EI) [m/z (%)]: 364 (36), 363 (30), 338 (26), 337 (100), 336 (50), 305 (35), 280 (28), 193 (40).

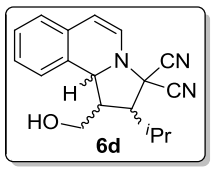
HRMS: Calculated for $[C_{23}H_{30}N_3O\ (M+H)]^+$: 364.2389. Found: 364.2384.

IR (Film, cm^{-1}): 3441 (OH).

$[\alpha]_D^{20}$: +260.1 (c = 1.1, CH_2Cl_2).

e.e.: 84%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 14.42 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 13.69 min.

1-Hidroxymethyl-2-isopropyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (6d)



6d

Following the general procedure, aldehyde **5d** (0.110 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 15 minutes the title compound **6d** (66 mg, 0.23 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 60%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.17 (d, 3H, *J* = 6.6 Hz, CH_3), 1.28 (d, 3H, *J* = 6.4 Hz, CH_3), 1.50-1.61 (m, 1H, C**H**CH(CH_3)$_2$), 1.98-2.20 (m, 1H, C**H**(CH_3)$_2$), 2.54-2.77 (m, 2H, C**H**CH_2O**H**), 3.78 (t_{ap}, 2H, *J* = 5.3 Hz, CH_2), 4.92 (d, 1H, *J* = 6.1 Hz, CCHN), 5.70 (d, 1H, *J* = 7.7 Hz, C**H**=CHN), 6.40 (d, 1H, *J* = 7.7 Hz, CH=C**H**N), 6.97-7.09 (m, 2H, C_{arom}-H), 7.10-7.24 (m, 2H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 21.4. 22.1 (CH_3), 30.7 (**C**H(CH_3)$_2$), 44.9 (**C**HCH(CH_3)$_2$), 58.1 (**C**CN), 58.7 (**C**HCH_2), 61.1 (C**C**HN), 62.27 (CH_2), 107.2 (**C**H=CHN), 112.1, 113.8 (CN), 125.7, 125.7 (C_{arom}-H), 126.9 (**C**$_{arom}$-C), 127.9, 128.3, 128.5 (C_{arom}-H), 131.7 (**C**$_{arom}$-C).

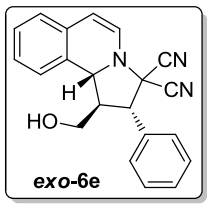
MS (EI) [m/z (%)]: 294 (55), 293 (63), 267 (100), 250 (41), 249 (35), 235 (29), 193 (64).

HRMS: Calculated for $[C_{18}H_{20}N_3O\ (M+H)]^+$: 294.1606. Found: 294.1618.

IR (Film, cm^{-1}): 3547 (OH).

e.e.: 0%, calculated by HPLC (Chiralpak IA column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the first enantiomer: 23.18 min; t_R for the second enantiomer: 26.86 min.

(1*R*,2*S*,10b*R*)-1-Hydroxymethyl-2-phenyl-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6e)



Following the general procedure, aldehyde **5e** (0.123 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6e** (99 mg, 0.30 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 80%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.94 (bs, 1H, OH), 3.25-3.45 (m, 1H, C**H**CH_2), 3.80-3.95 (m, 1H, C**H**$_A$H$_B$), 4.00-4.12 (m, 1H, CH$_A$**H**$_B$), 4.15 (d, 1H, *J* = 9.9 Hz, CHPh), 4.85 (d, 1H, *J* = 7.9 Hz, CCHN), 6.08 (d, 1H, *J* = 7.3 Hz, C**H**=CHN), 6.41 (d, 1H, *J* = 7.3 Hz, CH=C**H**N), 7.05-7.16 (m, 1H, C_{arom}-H), 7.20-7.35 (m, 3H, C_{arom}-H), 7.38-7.55 (m, 5H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 49.7 (CHPh), 56.4 (**C**HCH_2), 59.5 (C**C**HN), 61.0 (**C**CN), 61.4 (CH_2), 112.0 (**C**H=CHN), 112.3, 113.3 (CN), 123.3, 125.0, 127.5, 127.9, 128.2, 128.9, 129.3, 129.7 (C_{arom}-H), 130.2, 131.6, 133.2 (**C**$_{arom}$-C).

MS (EI) [m/z (%)]: 301 (51), 269 (100), 268 (83), 244 (52), 243 (75), 130 (40).

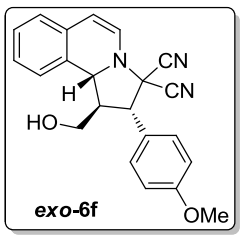
HRMS: Calculated for $[C_{21}H_{18}N_3O\ (M+H)]^+$: 328.1450. Found: 328.1472.

IR (Film, cm^{-1}): 3417 (OH).

$[\alpha]_D^{20}$: +60.4 (c = 1.1, CH_2Cl_2).

e.e.: 94%, calculated by HPLC (Chiralcel OD column, *n*-hexane:^{i}PrOH 85:15, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 20.56 min; t_R for the minor enantiomer (1*S*,2*S*,10b*R*): 12.41 min.

(1*R*,2*S*,10b*R*)-1-Hydroxymethyl-2-(4-methoxyphenyl)-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6f)



Following the general procedure, aldehyde **5f** (0.135 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6f** (68 mg, 0.19 mmol) was isolated by flash column chromatography (hexanes:EtOAc 6:4).

Yield: 50%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.87 (bs, 1H, OH), 3.21-3.43 (m, 1H, C**H**CH_2), 3.82 (s, 3H, OCH_3), 3.83-3.94 (m, 1H, C**H**$_A$H$_B$), 4.01-4.19 (m, 2H, CH$_A$**H**$_B$ + CHAr), 4.86 (d, 1H, *J* = 8.0 Hz, CCHN), 6.07 (d, 1H, *J* = 7.3 Hz, C**H**=CHN), 6.40 (d, 1H, *J* = 7.3 Hz, CH=C**H**N), 6.95 (d, 2H, *J* = 8.7 Hz, C_{arom}-H), 7.02-7.15 (m, 1H, C_{arom}-H), 7.20-7.30 (m, 3H, C_{arom}-H), 7.41 (d, 2H, *J* = 8.7 Hz, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 49.8 (CHAr), 55.4 (**C**HCH_2), 55.9 (OCH_3), 59.4 (C**C**HN), 61.1 (**C**CN), 61.5 (CH_2), 111.8 (**C**H=CHN), 112.4, 113.3 (CN), 114.7, 123.3 (C_{arom}-H), 124.7 (**C**$_{arom}$-C), 124.9, 127.5, 127.8, 128.1, 130.1 (C_{arom}-H), 131.6 (**C**$_{arom}$-C), 160.5 (**C**OCH_3).

MS (EI) [m/z (%)]: 331 (40), 299 (100), 298 (70), 274 (60), 273 (73).

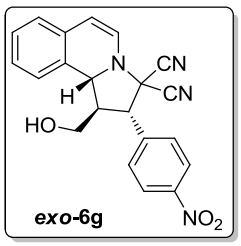
HRMS: Calculated for $[C_{22}H_{20}N_3O_2$ (M+H)$]^+$: 358.1556. Found: 358.1567.

IR (Film, cm^{-1}): 3536 (OH).

$[\alpha]_D^{20}$: -116.8 (c = 0.9, CH_2Cl_2).

e.e.: 88%, calculated by HPLC (Chiralcel OD column, *n*-hexane:^{i}PrOH 80:20, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 23.77 min; t_R for the minor enantiomer (1*S*,2*R*,10b*S*): 11.59 min.

(1*R*,2*S*,10b*R*)-1-Hydroxymethyl-2-(4-nitrophenyl)-1,10b-dihydropyrrolo[2,1-*a*]isoquinoline-3,3(2*H*)-dicarbonitrile (*exo*-6g)



Following the general procedure, aldehyde **5g** (0.141 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **5g** (65 mg, 0.17 mmol) was isolated by flash column chromatography (hexanes:EtOAc 6:4).

Yield: 46%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 2.16 (bs, 1H, OH), 3.21-3.41 (m,1H, C**H**CH_2), 3.94 (dd, 1H, *J* = 11.0, 4.2 Hz, C**H**$_A$H$_B$), 4.10 (dd, 1H, *J* = 11.0, 4.7 Hz

$CH_A\mathbf{H}_B$), 4.29 (d, 1H, *J* = 8.7 Hz, CHAr), 4.80 (d, 1H, *J* = 8.0 Hz, CCHN), 6.12 (d, 1H, *J* = 7.4 Hz, C**H**=CHN), 6.42 (d, 1H, *J* = 7.4 Hz, CH=C**H**N), 7.05-7.33 (m, 4H, C_{arom}-H), 7.65 (d, 2H, *J* = 8.7 Hz, C_{arom}-H), 8.25 (d, 2H, *J* = 8.7 Hz, C_{arom}-H).

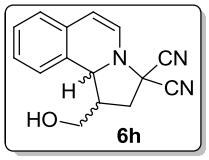
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 50.4 (CHAr), 56.0 (**C**HCH_2), 59.7 (C**C**HN), 60.2 (CCN), 61.6 (CH_2), 111.8 (CN), 112.5 (**C**H=CHN), 112.7 (CN), 123.1, 124.4, 125.2, 127.4, 128.1, 128.5 (C_{arom}-H), 129.9 (**C**$_{arom}$-C), 130.0 (C_{arom}-H), 131.4, 141.5 (**C**$_{arom}$-C), 148.5 (CNO_2).

IR (Film, cm^{-1}): 3552 (OH).

$[\alpha]_D^{20}$: +58.9 (c = 1.0, CH_2Cl_2).

e.e.: 84%, calculated by HPLC (Chiralcel OD column, *n*-hexane:^{i}PrOH 80:20, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 21.38 min; t_R for the minor enantiomer (1*S*,2*R*,10b*S*): 15.04 min.

1-Hydroxymethyl-1,10b-dihydropyrrolo[2,1-a]isoquinoline-3,3(2H)-dicarbonitrile (6h)



6h

Following the general procedure, aldehyde **5h** (94 mg, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6h** (57 mg, 0.22 mmol) was isolated by flash column chromatography (hexanes:EtOAc 7:3).

Yield: 60%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer) 2.03 (d, 1H, *J* = 10.8 Hz, OH), 2.77 (dd, 1H, *J* = 13.4, 7.6 Hz, CC$\mathbf{H}_A$H$_B$), 2.90 (dd, 1H, *J* =

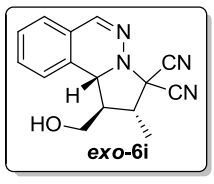
13.3, 9.1 Hz, CCH_AH_B), 3.01-3.25 (m, 1H, C**H**CH_2OH), 3.83-3.97 (m, 1H, C**H**$_A$H$_B$OH), 3.95-4.11 (m, 1H, CH_AH_BOH), 4.48 (d, 1H, *J* = 7.9 Hz, CCHN), 5.12* (d, 1H, *J* = 4.6 Hz, CCHN), 5.64* (d, 1H, *J* = 7.7 Hz, C**H**=CHN), 6.02 (d, 1H, *J* = 7.4 Hz, C**H**=CHCN), 6.37* (d, 1H, *J* = 7.7 Hz, CH=C**H**N), 6.44 (d, 1H, *J* = 7.4 Hz, CH=C**H**CN), 6.94-7.33 (m, 4H, C_{arom}-H).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer) 40.3* (C**C**H_2), 41.0 (C**C**H_2), 41.5* (**C**HCH_2OH), 43.4 (**C**HCH_2OH), 53.0 (**C**CN), 60.5* (C**C**HN), 60.6 (C**C**HN), 62.2* (CH_2OH), 63.4 (CH_2OH), 106.3* (**C**H=CHN), 111.3 (**C**H=CHN), 113.5, 113.7 (CN), 123.3, 124.8, 125.5*, 125.5*, 126.9*, 127.7, 127.8*, 127.9, 128.17, 128.4* (C_{arom}-H), 130.1, 131.6 (C_{arom}-C).

IR (Film, cm^{-1}): 3342 (OH).

e.e.: 0%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the first enantiomer of the major diastereoisomer: 11.45 min; t_R for the second enantiomer of the major diastereoisomer: 12.27 min; t_R for the first enantiomer of the minor diastereoisomer: 17.46 min; t_R for the second enantiomer of the minor diastereoisomer: 19.27 min.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-methyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6i)



***exo*-6i**

Following the general procedure, aldehyde **5i** (0.100 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6i** (69 mg, 0.25 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 68%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.49 (d, 3H, *J* = 7.2 Hz, CH_3), 1.95 (bs, 1H, OH), 2.40-2.53 (m, 1H, C**H**$_A$CH_BOH), 2.77-2.95 (m, 1H, CH_AC**H**$_B$OH), 3.99 (d_{ap}, 2H, *J* = 5.8 Hz, C**H**CH_2 + C**H**CH_3), 4.15 (d, 1H, *J* = 8.8 Hz, CHC**H**N), 7.27-7.54 (m, 4H, C_{arom}-H), 7.77 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 19.8 (CH_3), 44.2 (**C**HCH_3), 48.8 (**C**HCH_2), 58.4 (CH**C**HN), 60.7 (**C**CN), 63.0 (CH_2OH), 112.3, 113.6 (CN), 123.4 (C_{arom}-H), 125.4 (**C**$_{arom}$-C), 126.0, 128.5, 132.0 (C_{arom}-H), 134.3 (**C**$_{arom}$-C), 146.6 (CH=N).

MS (EI) [m/z (%)]: 267 (13), 241 (17), 240 (100), 222 (14), 208 (13), 194 (13), 183 (12).

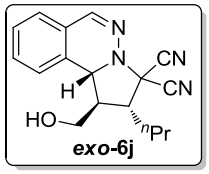
HRMS: Calculated for $[C_{15}H_{15}N_4O\ (M+H)]^+$: 267.1246. Found: 267.1259.

IR (Film, cm^{-1}): 3521 (OH).

$[\alpha]_D^{20}$: -29.6 (c = 1.1, CH_2Cl_2).

e.e.: >99%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 43.89 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 45.44 min.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-propyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6j)



***exo*-6j**

Following the general procedure, aldehyde **5j** (0.111 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 40 minutes the title compound **6j** (67 mg, 0.23 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 60%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.99 (t, 3H, J = 7.2 Hz, CH_3), 1.38-1.76 (m, 3H, $CH_2C\mathbf{H}_2CH_3$ + $C\mathbf{H}_AH_BCH_2CH_3$), 1.80-2.03 (m, 1H, $CH_A\mathbf{H}_BCH_2CH_3$), 2.13 (s, 1H, OH), 1.78-2.13 (m, 1H, $C\mathbf{H}_AH_BOH$), 2.48-2.61 (m, 1H, $CH_A\mathbf{H}_BOH$), 3.76-4.03 (m, 2H, $C\mathbf{H}CH_2OH$ + $C\mathbf{H}CH_2CH_2$), 4.14 (d, 1H, J = 8.5 Hz, CHC**H**N), 7.26-7.54 (m, 4H, C_{arom}-H), 7.74 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.8 (CH_3), 19.9 ($CH_2\mathbf{C}H_2CH_3$), 35.7 ($\mathbf{C}H_2CH_2CH_3$), 46.4 ($\mathbf{C}HCH_2CH_2$), 48.5 ($\mathbf{C}HCH_2OH$), 58.6 (CH**C**HN), 60.5 (**C**CN), 63.2 (CH_2OH), 112.4, 113.7 (CN), 123.6 (C_{arom}-H), 125.4 (C_{arom}-C), 125.9, 128.5, 132.0 (C_{arom}-H), 134.5 ($\mathbf{C}_{arom}$-C), 146.6 (CH=N).

MS (EI) [m/z (%)]: 295 (8), 269 (8), 268 (100), 267 (7), 211 (7), 194 (42).

HRMS: Calculated for $[C_{17}H_{19}N_4O\ (M+H)]^+$: 295.1559. Found: 295.1555.

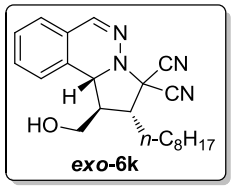
IR (Film, cm^{-1}): 3537 (OH).

$[\alpha]_D^{20}$: +11.2 (c = 1.1, CH_2Cl_2).

e.e.: 70%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH in gradient; flow 1.00 mL/min, linear curve: min 0, 100:0; min 20, 95:5; min 30,

90:10). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 44.38 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 50.61 min.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-octyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6k)



***exo*-6k**

Following the general procedure, aldehyde **5k** (99 mg, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6k** (78 mg, 0.22 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 57%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.88 (t, *J* = 6.5 Hz, 3H, CH_3), 1.15-1.40 (m, 10H, $(CH_2)_5$), 1.53-1.77 (m, 2H, CH_2), 1.83-2.20 (m, 2H, CH_2), 2.50-2.62 (m, 1H, C**H**CH_2CH_2), 2.62-2.74 (m, 1H, C**H**CH_2OH), 3.79-4.05 (m, 2H, C**H**$_2$OH), 4.15 (d, 1H, *J* = 8.3 Hz, CHC**H**N), 7.27-7.55 (m, 4H, C_{arom}-H), 7.76 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 14.1 (CH_3), 22.6, 26.7, 29.2, 29.3, 29.4, 31.7, 33.7 (CH_2), 46.4 (**C**HCH_2CH_2), 48.8 (**C**HCH_2OH), 58.7 (CH**C**HN), 60.6 (**C**CN), 63.4 (**C**H_2OH), 112.3, 113.6 (CN), 123.6 (C_{arom}-H), 125.5 (**C**$_{arom}$-C), 125.9, 128.5, 131.9 (C_{arom}-H), 134.6 (**C**$_{arom}$-C), 146.5 (CH=N).

MS (EI) [m/z (%)]: 365 (9), 339 (18), 338 (100), 337 (13), 336 (9), 194 (48).

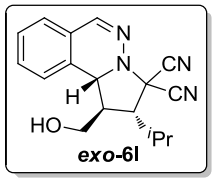
HRMS: Calculated for $[C_{22}H_{29}N_4O$ (M+H)$]^+$: 365.2341. Found: 365.2341.

IR (Film, cm^{-1}): 3546 (OH).

$[\alpha]_D^{20}$: +6.8 (c = 0.7, CH_2Cl_2).

e.e.: 95%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 8.86 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 9.83 min.

(1*R*,2*R*,10b*R*)-1-Hydroxymethyl-2-isopropyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*exo*-6l)



exo-6l

Following the general procedure, aldehyde **5l** (0.111 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6l** (69 mg, 0.23 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 62%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.91 (d, 3H, *J* = 6.7 Hz, CH_3), 1.09 (d, 3H, *J* = 6.9 Hz, CH_3), 1.87-1.98 (t, 1H, *J* = 4.1 Hz, OH), 2.30-2.49 (m, 1H, C**H**CHCH$_3$), 2.60-2.66 (m, 1H, C**H**(CH$_3$)$_2$), 2.69-2.79 (m, 1H, C**H**CH$_2$), 3.78-4.00 (m, 2H, C**H**$_2$OH), 4.12 (d, 1H, *J* = 7.9 Hz, CHC**H**N), 7.28-7.56 (m, 4H, C_{arom}-H), 7.78 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 17.4 (CH_3), 21.0 (CH_3), 30.1 (**C**H(CH$_3$)$_2$), 39.7 (**C**HCH$_2$), 53.7 (**C**HCHCH$_3$), 59.6 (**C**HCH$_2$), 60.2 (**C**CN), 64.8 (**C**H$_2$OH), 112.4, 113.4 (CN), 123.6 (**C**$_{arom}$-H), 125.7 (**C**$_{arom}$-C), 125.8, 128.4, 131.9 (C_{arom}-H), 134.5 (**C**$_{arom}$-C), 146.8 (CH=N).

MS (EI) [m/z (%)]: 295 (8), 269 (8), 268 (100), 267 (7), 250 (6), 211 (13), 194 (38).

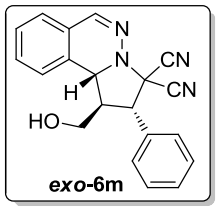
HRMS: Calculated for $[C_{17}H_{19}N_4O\ (M+H)]^+$: 295.1559. Found: 295.1567.

IR (Film, cm^{-1}): 3534 (OH).

$[\alpha]_D^{20}$: -47.8 (c = 0.6, CH_2Cl_2).

e.e.: 84%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*R*,10b*R*): 15.82 min; t_R for the minor enantiomer (1*S*,2*S*,10b*S*): 17.46 min.

(*1R*,2*S*,10b*R*)-1-Hydroxymethyl-2-phenyl-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6m)



Following the general procedure, aldehyde **5e** (0.124 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6m** (87 mg, 0.27 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 70%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 2.23 (s, 1H, OH), 3.00-3.15 (m, 1H, C**H**CH_2), 3.94 (d, 1H, *J* = 5.6 Hz, CHPh), 3.96-4.08 (m, 2H, CH_2), 4.32 (d, 1H, *J* = 8.7 Hz, CHC**H**N), 7.29-7.58 (m, 9H, C_{arom}-H), 7.80 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 49.7 (CHPh), 55.5 (**C**HCH_2), 58.4 (CH**C**HN), 61.9 (**C**CN), 62.5 (CH_2), 112.0, 113.4 (CN), 123.6 (C_{arom}-H), 125.6 (**C**$_{arom}$-C), 126.1, 128.7, 128.8, 129.2, 129.2, 132.2 (C_{arom}-H), 134.1, 137.9 (**C**$_{arom}$-C), 147.1 (CH=N).

MS (EI) [m/z (%)]: 303 (22), 302 (100), 301 (29), 284 (34), 271 (28), 270 (47), 269 (16), 245 (36), 244 (29), 194 (22).

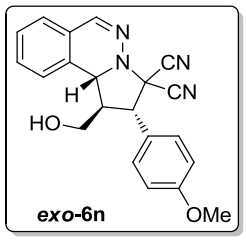
HRMS: Calculated for $[C_{20}H_{17}N_4O\ (M+H)]^+$: 329.1402. Found: 329.1391.

IR (Film, cm^{-1}): 3433 (OH).

$[\alpha]_D^{20}$: +147.5 (c = 0.9, CH_2Cl_2).

e.e.: 97%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 41.42 min; t_R for the minor enantiomer (1*S*,2*R*,10b*S*): 48.05 min.

(1*R*,2*S*,10b*R*)-1-Hydroxymethyl-2-(4-methoxyphenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6n)



Following the general procedure, aldehyde **5n** (0.138 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6n** (98 mg, 0.27 mmol) was isolated by flash column chromatography (hexanes:EtOAc 6:4).

Yield: 72%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.60 (bs, 1H, OH), 2.97-3.23 (m, 1H, C**H**CH_2), 3.68-3.90 (m, 2H, CH_2), 3.82 (s, 3H, CH_3), 4.05 (d, 1H, *J* = 5.9 Hz, CHC**H**N), 5.00 (d, 1H, *J* = 7.6 Hz, CHAr), 6.96 (d, 2H, *J* = 8.5 Hz, C_{arom}-H), 7.28-7.54 (m, 6H, C_{arom}-H), 7.61 (s, 1H, CH=N).

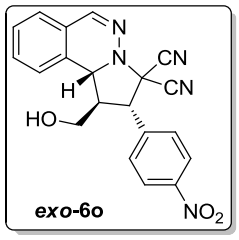
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 46.3 (CHAr), 55.4 (**C**HCH_2), 55.8 (CH_3), 58.8 (CH**C**HN), 61.5 (CH_2), 64.6 (**C**CN), 111.5, 113.3 (CN), 114.7 (C_{arom}-H), 125.0 (C_{arom}-C), 125.7, 125.9, 127.1, 129.1 (C_{arom}-H), 130.1, 131.1 (C_{arom}-C), 131.8 (C_{arom}-H), 144.7 (CH=N), 160.3 (**C**OCH_3).

IR (Film, cm^{-1}): 3425 (OH).

$[\alpha]_D^{20}$: -12.3 (c = 0.9, CH_2Cl_2).

e.e.: 60%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min, linear curve: min 0, 100:0; min 15, 80:20). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 49.79 min; t_R for the minor enantiomer (1*S*,2*R*,10b*S*): 44.99 min.

(1*R*,2*S*,10b*R*)-1-Hydroxymethyl-2-(4-nitrophenyl)-1,10b-dihydropyrrolo[2,1-*a*]phthalazine-3,3(2*H*)-dicarbonitrile (*exo*-6o)



Following the general procedure, aldehyde **5o** (0.140 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6o** (99 mg, 0.27 mmol) was isolated by flash column chromatography (hexanes:EtOAc 6:4).

Yield: 70%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 2.27 (bs, 1H, OH). 2.95-3.11 (m, 1H, C**H**CH_2), 3.97-4.07 (m, 2H, CH_2), 4.11 (d, 1H, *J* = 4.8 Hz, CHAr), 4.33 (d, 1H, *J* = 8.6 Hz, CHC**H**N), 7.26-7.52 (m, 4H, C_{arom}-H), 7.56 (d, 2H, *J* = 8.6 Hz, C_{arom}-H), 7.86 (s, 1H, CH=N), 8.19 (d, 2H, *J* = 8.6 Hz, C_{arom}-H).

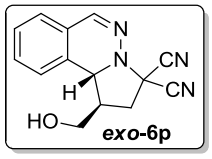
^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 50.1 (CHAr), 54.8 (**C**HCH$_2$), 58.1 (CH**C**HN), 61.3 (**C**CN), 62.5 (CH_2), 111.7, 112.8 (CN), 123.2, 124.3 (C_{arom}-H), 125.5 (**C**$_{arom}$-C), 126.4, 129.0, 129.9, 132.5 (C_{arom}-H), 133.7, 145.3 (**C**$_{arom}$-C), 147.7 (CH=N), 148.1 (**C**$_{arom}$-C).

IR (Film, cm^{-1}): 3540 (OH).

$[\alpha]_D^{20}$: +23.4 (c = 1.0, CH_2Cl_2).

e.e.: >99%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (1*R*,2*S*,10b*R*): 29.60 min; t_R for the minor enantiomer (1*S*,2*R*,10b*S*): 25.05 min.

(1*R*,10b*R*)-1-Hydroxymethyl-1,10b-dihydropyrrolo[2,1-a]phthalazine-3,3(2H)-dicarbonitrile (*exo*-6p)



***exo*-6p**

Following the general procedure, aldehyde **5p** (94 g, 0.38 mmol) was dissolved in dry THF (15 mL) and $LiBH_4$ (6 mg, 0.38 mmol) was added. After stirring the mixture for 30 minutes the title compound **6p** (32 mg, 0.13 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 34%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 2.00-2.14 (m, 1H, OH), 2.61-2.73 (m, 1H, CC**H**$_A$H$_B$), 2.76-3.08 (m, 3H, CCH$_A$**H**$_B$ + C**H**CH$_2$), 3.84-3.98 (m, 2H, C**H**$_2$OH), 4.12 (d, 1H, *J* = 8.0 Hz, CHC**H**N), 7.20-7.75 (m, 4H, C_{arom}-H), 7.76 (s, 1H, CH=N).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 38.2 (C**C**H_2), 39.5 (**C**HCH_2OH), 54.7 (**C**CN), 58.6 (CH**C**HN), 63.3 (CH_2OH), 113.4, 113.7 (CN), 123.5 (C_{arom}-H), 125.3 (**C**$_{arom}$-C), 126.0, 128.6, 132.1 (C_{arom}-H), 134.2 (**C**$_{arom}$-C), 146.7 (CH=N).

IR (Film, cm^{-1}): 3552 (OH).

$[\alpha]_D^{20}$: +58.9 (c = 1.0, CH_2Cl_2).

e.e.: 84%, calculated by HPLC (Chiralpak AD-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the major enantiomer (1*R*,10b*R*): 49.07 min; t_R for the minor enantiomer (1*S*,10b*S*): 52.14 min.

3

3

Enantioselective organocatalytic Michael/Henry cascade reaction

1. Introduction

Over the years chemists have been fascinated by the ability of Nature to generate complex molecules by several parallel reactions in a single cell. Current developments in the field of total synthesis indicate that chemists have adapted the fundamental principles of biosynthesis, such as cascade reactions,[1] protecting-group-free synthesis,[2] redox economic,[3] atom economic,[4] step economic[5] and biomimetic synthesis.[6]

The classification of those consecutive or simultaneous processes, usually named *domino*, *cascade*, *consecutive*, *tandem* and *sequential reactions* is not trivial. The subtle differences between the concepts, sometimes misrepresented in the chemical literature, can be messy if some parameters are not established.

The cascade or domino term is used if the reaction takes place without the need of adding extra reactants or changing the reaction conditions; that is, every compound that is needed for the reaction is in the reaction vessel from the beginning of the reaction. In consecutive reactions, the intermediate formed in the first reaction possess the necessary functionality for the second reaction to take place, but a lack of energy to overcome the activation barrier. This energy has to be provided externally, for example, by heating the mixture. On the other hand, reactions are classified as tandem when the functionality needed for the second

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[1] (a) Davies, H. M. L.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 2981. (b) Nicolau, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, 38, 2993. (c) Nicolau, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134.

[2] Young, I. S.; Baran, P. S. *Nature. Chem.* **2009**, *1*, 193.

[3] Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem. Int. Ed.* **2009**, *48*, 2854.

[4] Trost, B. M. *Science* **1991**, *254*, 1471.

[5] Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40.

[6] Kim, J.; Movassaghi, M. *Chem. Soc. Rev.* **2009**, *38*, 3035.

reaction is created in the first step, but the incorporation of additional reactants that will be integrated in the products, to the mixture is also necessary. Finally sequential reactions are defined as the transformations that involve two or more independent reactions taking place in a specific order and it also requires the addition of new reagents.

One of the biggest advantages of cascade or domino reactions over classical synthesis is that, at least, two reactions are carried out in a single operation under the same reaction conditions. This avoids time-consuming laboratory operations and product manipulation. Besides, they are often accompanied by high levels of stereoselectivity when the reaction proceeds currently with the generation of new stereocenters. A major topic of current research is the exploration of new catalyzed cascade reactions by employing a single catalyst able to promote each single step and also capable of inducing stereocontrol in order to obtain a single stereoisomer out of the possible ones.

The combination of multiple asymmetric transformations in a cascade sequence allows the creation of multiple stereocenters in a single-step process.[7] Moreover, an increase of the enantiomeric excess of the final product can be observed in comparison with the individual transformations. The Horeau principle[8] provides a mathematical tool to quantify the enantiomeric enrichment achieved along consecutive cycles. Simple calculations reveal that sequences in cascade can lead to the formation of the major diastereoisomer with high levels of enantiocontrol, even if the catalytic cycles operating result to be moderately selective.

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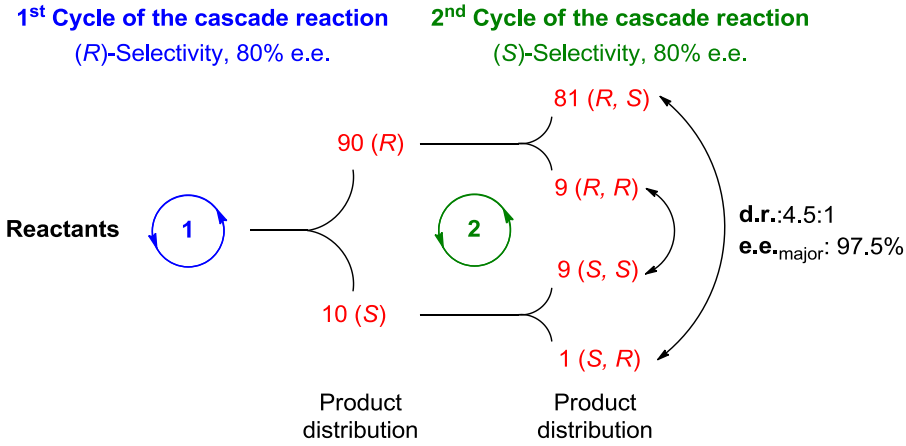
7 Vera, S.; Melchiorre, P. *An. Quim*. **2010**, *106*, 277.
8 Vigneron, J. P.; Dhaenens, M.; Horeau, A. *Tetrahedron* **1973**, *29*, 1055.

A good example is provided in Scheme 3.1 in which two reactions provide products in 80% enantiomeric excess are combined in a cascade process leading to the formation of one major diastereoisomer with enantiomeric excess higher than 95%.



Scheme 3. 1

This already mentioned ability to generate complex molecules together with the possibility to form multiple stereocenters in a very easy way has encouraged researchers to develop a variety of methodologies involving cascade processes.[1] In addition, the introduction of a convenient stereodirecting element, such as an organocatalyst, leads to optically active molecules. As we have commented in previous chapters, the use of organocatalysis as the vehicle to stereocontrol has shown up as a very efficient and convenient methodology to carry out numerous transformations due to the high tolerance of a wide range of functionalities. In this sense, and considering all the benefits of cascade type reactions in combination with the advantages of using organocatalysis, it is not surprising that

organocascades have gained a lot of attention recently.[9] Organocatalysts are particularly useful when used in cascade reactions because they allow distinct modes activation, which can be often combined.[10]

1.1. Organocatalytic cascade reactions initiated by Michael reactions

The nucleophilic 1,4-addition of stabilized carbon nucleophiles to electron poor olefins can be considered as one of the most powerful tools for the stereocontrolled C-C and C-heteroatom bond formation. In addition, one of the most attractive features of the Michael-type reactions is the fact that a nucleophilic intermediate is generated after the conjugate addition step, which is able to react with an electrophilic reagent present in the reaction medium either in an inter- or intramolecular fashion, in a typical domino or cascade process.

In this context, the use of organic molecules as catalysts in domino processes initiated by conjugate addition reactions, shows up as a very useful and competitive tool for the generation of molecular complexity from readily available and cheap starting materials and also displaying an exceptional performance with regard to stereochemical control.[11] In this way, many cascade processes in which

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[9] For some leading reviews about organocascades see: (a) Pellisier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. (b) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314. (c) Albrecht, L.; Jiang, H.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8492. (d) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (e) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (f) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (g) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, *1*, 1.

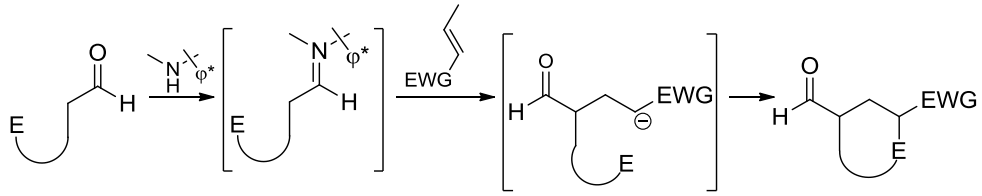
[10] (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570. (b) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.

[11] (a) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. (Ed.) *Organocatalytic Enantioselective Conjugate Addition Reactions*. RSC Publishing: Cambrigde, **2010**. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed*. **2007**, *46*, 1570. (d) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693.

catalysts operating by enamine, iminium, H-bonding, phase transfer catalysis, or other types of mechanisms can be found in the literature for the stereoselective preparation of complex molecules.[12]

In general, the enamine activation strategy has been employed in several efficient processes for the synthesis of complex molecules, especially focused in the stereoselective preparation of highly functionalized carbocyclic compounds. The most commonly found situation is that the amine catalyst is involved in the activation of an enolizable aldehyde *via* enamine formation (activation of the Michael donor), which undergoes the first Michael-type reaction delivering an iminium intermediate from which, in most cases, the catalyst is released by hydrolysis, leading to the formation of a multifunctional acyclic intermediate compound. The cascade process therefore continues by some kind of intramolecular reaction between the remaining carbonyl group and another functionality appropriately introduced in the starting materials, without the participation of the catalyst and therefore under substrate control (Scheme 3.2).

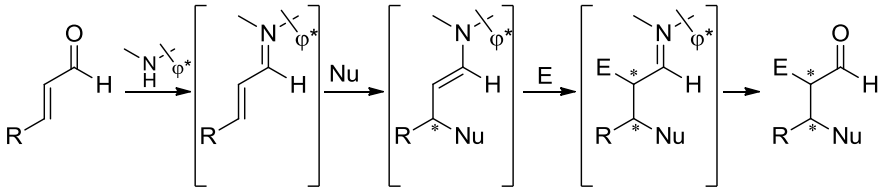
[12] For some recent examples see: (a) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 808. (b) Yu, C.; Zhang, Y.; Song, A.; Ji, Y.; Wang, W. *Chem. Eur. J.* **2011**, *17*, 770. (c) Fang, X.; Jiang, K.; Xing, C.; Hao, L.; Chi, Y. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 1910. (d) Tan, B.; Candeias, N. R.; Barbas III, C. F. *Nat. Chem.* **2011**, *3*, 473. (e) Noole, A.; Borissova, M.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2011**, *76*, 1538. (f) Gao, Y.; Ren, Q.; Siau, W.-Y.; Wang, J. *Chem. Commun.* **2011**, *47*, 5819. (g) Hu, Z.-P.; Lou, C.-L.; Wang, J.-J.; Chen, C.-X.; Yan, M. *J. Org. Chem.* **2011**, *76*, 3797. (h) Li, X.-M.; Wang, B.; Zhang, J.-M.; Yan, M. *Org. Lett.* **2011**, *13*, 374.(i) Hong, B.-C.; Kotame, P.; Liao, J.-H. *Org. Biomol. Chem.* **2011**, *9*, 382. (j) Ramachary, D. B.; Prasad, M. S.; Madhavachary, R. *Org. Biomol. Chem.* **2011**, *9*, 2715. (k) Wang, Y.; Zhu, S.; Ma, D. *Org. Lett.* **2011**, *13*, 1602. (l) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem. Eur. J.* **2011**, *17*, 2842. (m) Alza, E.; Sayalero, S.; Cambeiro, X. C.; Martin-Rapun, R.; Miranda, P. O.; Pericàs, M. A. *Synlett* **2011**, 464. (n) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835.



Scheme 3. 2

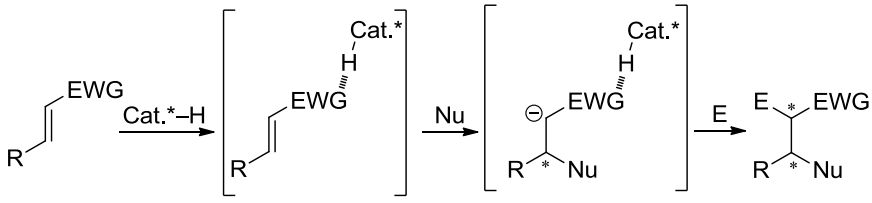
The combination of iminium and enamine activation in a single operation of an organocatalyzed cascade reaction (Scheme 3.3) constitutes a milestone in the area of the aminocatalysis which has reached a high level of sophistication in many reported examples. The most relevant feature of this combination of activation mechanisms relies on the fact that the catalyst is attached to the substrate during all the process, being able to exert a very effective stereochemical control of the whole transformation. Further attempts in the field of cascade reactions have been able to explore various ways of combining iminium and enamine catalysis by using a wide variety of functionalized reagents which can be engaged in different types of reactions with these nucleophilic and/or electrophilic intermediates. This concept is limited not only to the simple combination of two reactions, but also to triple-cascade extensions and, very recently impressive quadruple-cascades have also been reported.[13] The number of reactions for each activation mode and the exponential increase of combinations for multiple processes pave the way to various reaction combinations and new and rapid entries for the synthesis of complex and valuable synthetic building blocks.

[13] (a) Enders, D.; Krüll, R.; Bettray, W. *Synthesis* **2010**, *4*, 567. (b) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem. Eur. J.* **2009**, *15*, 6815. (c) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704.



Scheme 3. 3

The activation of the Michael acceptor by the formation of an H-bonded network with the catalyst has also been applied to many cascade processes, after incorporating a suitably electrophile to the reaction medium able to interact with the intermediate formed after the conjugate addition step. In this context, although this intermediate has the potential to remain linked to the catalyst and therefore allowing the participation of the later in the stereocontrol of the subsequent step, the weaker nature of the substrate-catalyst interaction –which on the other hand resulted to be the key feature for allowing turnover of the catalyst in the standard Michael-type reactions not proceeding in a cascade fashion– makes the second step to be generally controlled by the substrate, with no influence of the catalyst (Scheme 3.4).



Scheme 3. 4

Finally, several interesting cascade processes have also been developed under phase-transfer catalysis which are initiated by a conjugate addition reaction,

although the number of reports is remarkably more limited compared to other organocatalytic cascades proceeding *via* other different mechanisms of activation.

Due to the direct relation with this project the procedures found in the literature associated to domino reactions initiated by a Michael reaction activated by chiral organocatalysts will be reviewed, with the main focus on Michael/Henry cascade reactions.

1.2. Organocatalytic Michael/Henry cascade reactions

The Henry reaction has been associated to the Michael addition in domino type transformations, since it is an useful tool to form C-C bonds and also allows the preparation of a wide range of structurally different compounds due to the ability of the nitro group to be transformed into other nitrogen and oxygen containing functionalities.[14]

In this context many researchers have carried out their investigations in this field. The first enantioselective Michael-Henry organocascade reaction that we are aware of, was published in 2007 by Hayashi[15] who developed a cascade process to obtain nitrocyclohexane carbaldehydes from pentanedial and nitroalkenes promoted by diphenylprolinol silyl ether, which proceeded with high *syn* selectivity and excellent enantiomeric excess, controlling the formation of four stereogenic centers in a single operation (Scheme 3.5).

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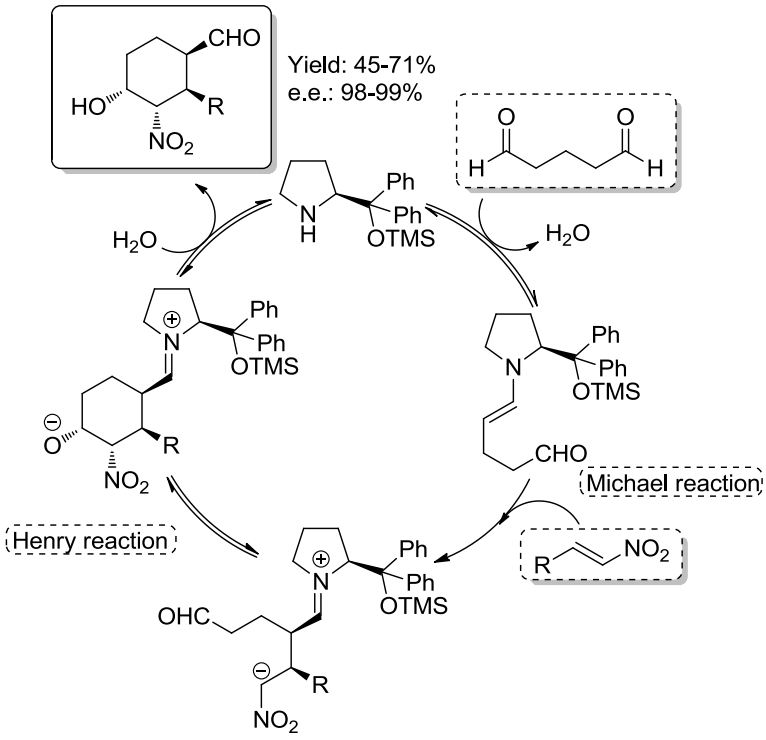
[14] Ono, N. *The Nitro Group in Organic Synthesis*. Wiley-VCH, **2001**.
[15] Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed*. **2007**, *46*, 4922.



Scheme 3. 5

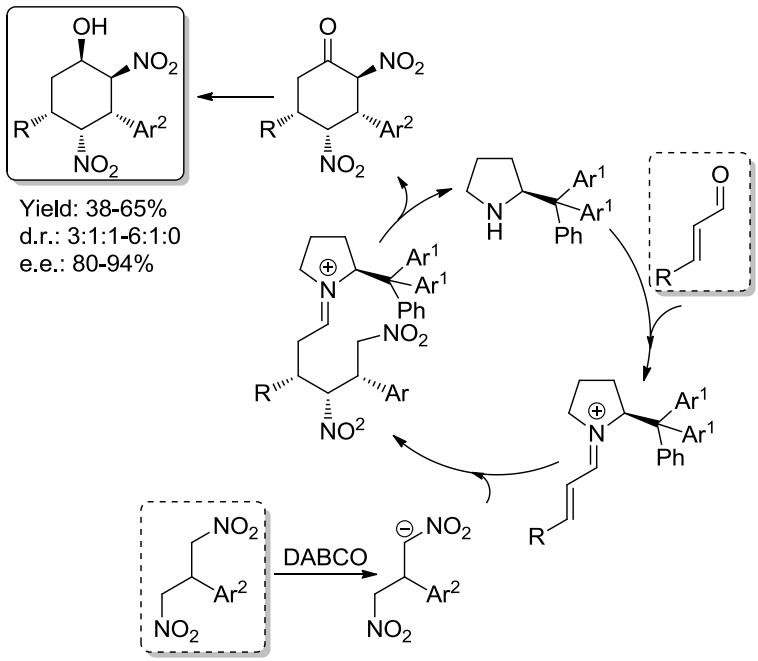
The author hypothesized that an enamine would be formed from the condensation of 1,5-pentanedial with the catalyst, which would be activated to react with a nitroalkene thought a Michael reaction to generate a zwitterionic nitronate/iminium ion. This intermediate is supposed to react intramolecularly with the remaining formyl group to provide the cyclohexane adduct that after hydrolysis would furnish the desired final product. Later on, the same group developed an efficient asymmetric four component synthesis to obtain highly

substituted piperidines, in which the key step was a diphenyprolinol silyl ether-mediated Michael addition followed by a domino aza-Henry reaction.[16]

Soon after this work had been published, Jørgensen *et al*.[17] developed the Michael addition of dinitroalkanes to α,β-unsaturated aldehydes followed by an intramolecular Henry reaction using a similar diarylprolinol silyl ether as catalyst, which led to the formation of highly substituted cyclohexanes with control over five contiguous stereocenters. The reaction proceeds with moderate to good yields and with high diastereo- and enantioselectivity. This asymmetric organocatalytic domino nitro-Michael/Henry reaction can be explained by the initial iminium activation of the α,β-unsaturated aldehyde through the condensation with the catalyst followed by the attack of the 1,3-dinucleophile. After hydrolysis of the resulting iminium ion, the nitroaldehyde intermediate undergoes a subsequent intramolecular Henry reaction under substrate control which generates the final product (Scheme 3.6).

[16] Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett*. **2010**, *20*, 4588.

[17] Reyes, E.; Jiang, A.; Milleli, A.; Elsner, P.; Hazell, R. T.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 9202.

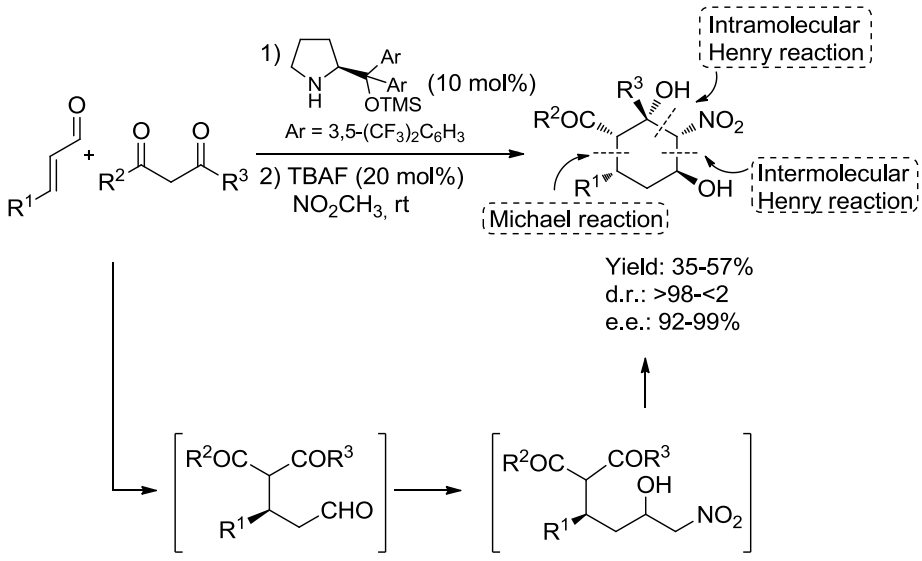


Scheme 3. 6

The performance of this type of *O*-silyl-protected diarylprolinol catalysts to promote Michael initiated cascades can also be observed in one example of Michael/Henry/Henry process developed by García-Ruano *et al*.[18] leading to densely substituted cyclohexanes from α,β-unsaturated aldehydes, nitromethane and β-dicarbonyl compounds, promoted by iminium activation using diarylprolinol silyl ether and assisted by catalytic TBAF (Scheme 3.7). The proposed mechanism for the reaction establishes that it should begin with the Michael addition of the nucleophile to the activated α,β-unsaturated aldehyde *via* iminium ion formation. The resulting adduct reacts with the nitronate anion as

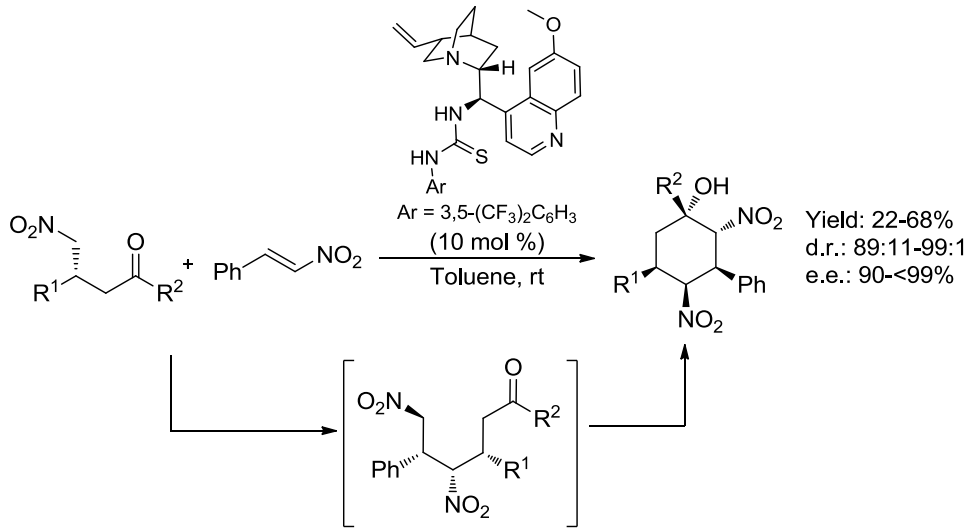
[18] García-Ruano, J. L.; Marcos, V.; Suanzes, J. A.; Marzo, L.; Alemán, J. *Chem. Eur. J.* **2009**, *15*, 6576.

nitromethane, generated by the fluoride anion, that would act later as a Brønsted base, according to an intermolecular Henry reaction to give a nitroalcohol intermediate. Next, this undergoes a final intramolecular Henry reaction, also catalyzed by the fluoride anion present in the reaction. The first step is controlled by the configuration of catalyst and the stereocontrol of the four centers created in the last two steps is proposed to be achieved by means of the stereoinduction exerted by the stereogenic center created in the first step. Nevertheless the complete stereoselectivity observed in these reactions must be a consequence of the reversibility of the two Henry reactions, which results in the formation of the thermodynamically favored product.



Scheme 3. 7

H-bonding catalysis has also become a very powerful and versatile approach for a variety of Michael-initiated cascade reactions. An illustrative example of the mentioned activation mode is the work developed by Soós *et al.*[19] in which a Michael-Henry cascade has been carried out, promoted by a thiourea-type catalyst (Scheme 3.8). The cascade consists of the 1,4-addition of differently substituted chiral nitroketones to a nitroolefin sterically controlled by the thiourea catalyst, followed by an intramolecular Henry reaction that led to the formation of densely substituted cyclohexanes with high diastereo- and enantioselectivity.

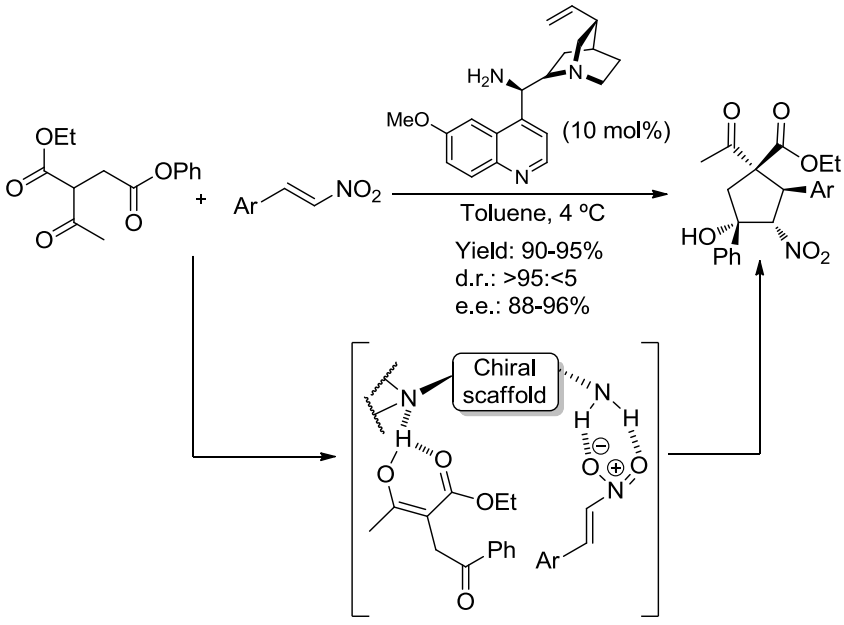


Scheme 3. 8

Other types of H-bonding catalysis have been also designed in order to activate simultaneously the nucleophile and the Michael acceptor in related cascade processes. For instance, in 2008 Zhong *et al.*[20] employed a cinchona-

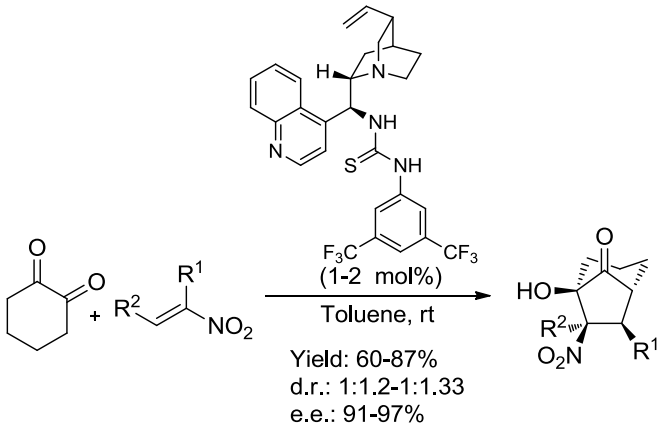
[19] Varga, S.; Jakab, G.; Drahos, L.; Holczbauer, T.; Czugler, M.; Soós, T. *Org. Lett.* **2011**, *20*, 5416.
[20] Tan, B.; Chua, P. J.; Zeng, X.; Lu, M.; Zhong, G. *Org. Lett.* **2008**, *10*, 3489.

derived organocatalyst to assist a tandem Michael/Henry reaction involving a nitroolefin and a series of carbon nucleophiles, leading to the formation of cyclopentanes containing four stereocenters, with excellent yields and a complete diastereo- and enantiocontrol (Scheme 3.9). A dual activation model was proposed for the initial Michael reaction step where the two substrates involved in the reaction are activated simultaneously by the catalyst. The nitroolefin interacts firstly with the primary amine moiety of the catalyst *via* multiple H-bonding, thus enhancing the electrophilic character of the reacting carbon center and the enol form on the nucleophile is assumed to interact with the tertiary amine group. Once the initial Michael reaction had occurred, a subsequent Henry reaction resulted in the formation of the final product.



Scheme 3. 9

Following the mentioned dual activation protocol, Rueping and coworkers[21] reported a domino Michael/Henry reaction induced by a chiral bifunctional cinchona thiourea which provided a range of chiral bicyclo[3.2.1]octan-8-ones containing four stereocenters, two of them being neighboring quaternary stereocenters, in good yields and excellent enantioselectivity. According to the dual activation model, previously mentioned, the two substrates are activated at the same time by the catalyst in the initial Michael reaction of the α-diketone to the nitroalkene and the final Henry reaction is also proposed to occur under catalyst control in which the thiourea moiety remains bonded to the diketone structure during the cyclization process (Scheme 3.10).



Scheme 3. 10

A similar kind of highly congested bicycles were obtained by Zhong *et al.*[22] through a reaction between nitroalkenes and 1,3-dicarbonyl compounds, also using a chiral thiourea catalyst. Theoretical calculations have shown that the chirality is

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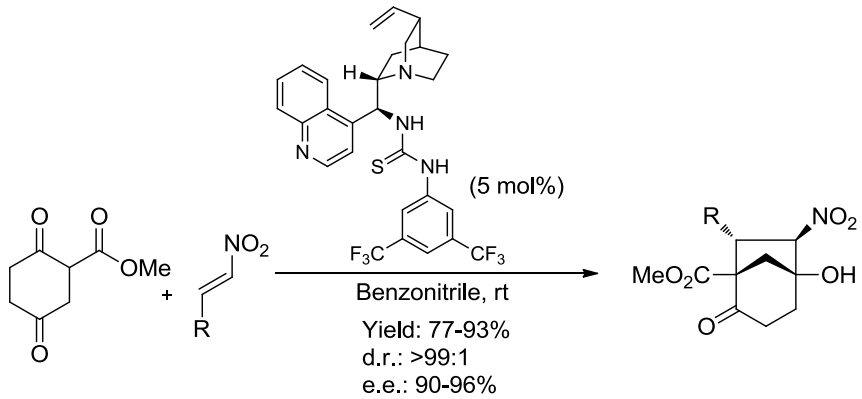
[21] (a) Rueping, M.; Kuenkel, A.; Fröhlich, R. *Chem. Eur. J.* **2010**, *16*, 4173. See also: (b) Ding, D.; Zhao, C.-G.; Guo, Q.; Arman, H. *Tetrahedron* **2010**, *66*, 4423.

[22] Tan, B.; Lu, Y.; Zeng, X.; Chua, P. J.; Zhong, G. *Org. Lett.* **2010**, *12*, 2682.

transferred from the catalyst to the products using a novel type of activation mode in which the thiourea group and an acidic proton in the aryl ring of the catalyst activated the 1,3-dicarbonyl substrate and at the same time, a tertiary amine activated the nitro group, promoting the domino reaction smoothly with excellent stereoselectivity (Scheme 3.11). It has to be pointed out that a rather low catalyst load is required for this highly enantioselective transformation.

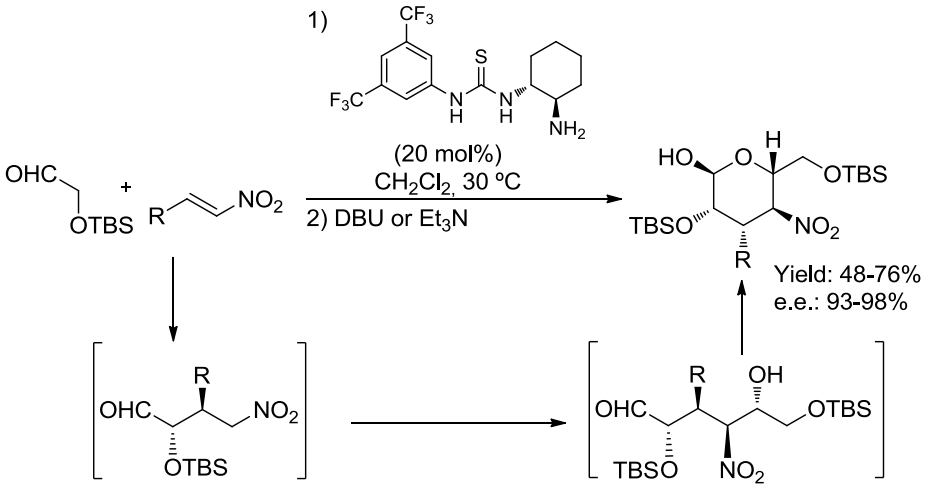


Scheme 3. 11

Inspired by previous works, Barbas III *et al*. have also employed a thiourea type catalyst in an excellent work directed to the synthesis of carbohydrate derivatives from simple non chiral precursors through organocatalytic asymmetric Michael/Henry reaction sequences. In this process (*tert*-butyldimethylsilyloxy)acetaldehyde was successfully used as the initial Michael donor in a highly selective *anti*-diastereoselective-Michael reaction.[23] Then the resulting product was used as a nucleophile in a consecutive Henry reaction with a second equivalent of the same aldehyde and the formed intermediate underwent a final hemiacetalization, allowing the construction of a wide range of pyranone

[23] Uehara, H.; Imashiro, R.; Hernández-Torres, G.; Barbas III, C. F. *PNAS*, **2010**, *107*, 20673.

derivatives in a highly stereoselective manner (Scheme 3.12). Later, encouraged by the results obtained, they reported an interesting synthesis of iminosugar derivatives using organocatalytic Michael/aza-Henry cascade sequence promoted by a chiral thiourea.[24]



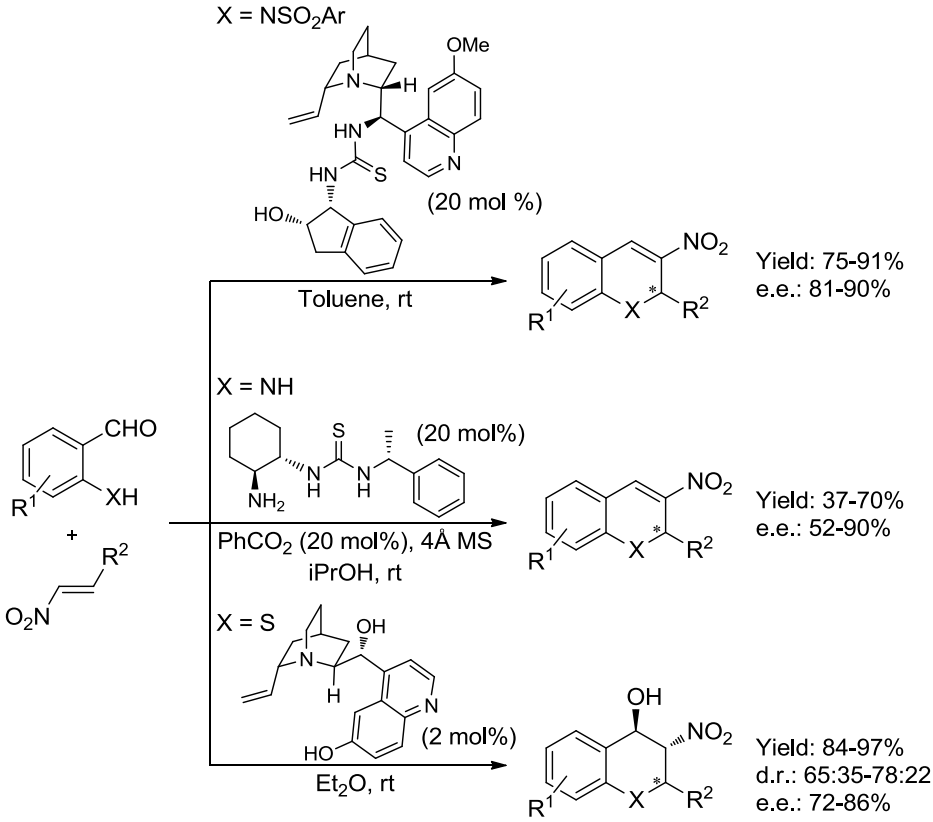
Scheme 3. 12

Some interesting hetero-Michael/Henry type reactions must be mentioned as well. Some of the most representative examples are depicted the Scheme 3.13, which includes the reaction between a functionalized benzaldehyde containing the heteronucleophile at *ortho* position. These consist in an initial hetero-Michael reaction with a nitroalkene which is followed by intramolecular Henry reaction.[25] In these cases the activation of the Michael acceptor has been faced by H-bonding

[24] Imashiro, R.; Uehara, H.; Barbas III, C. F. *Org. Lett.* **2010**, *22*, 5250.

[25] (a) Liu, X.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 4063. (b) Wang, Y.-F.; Zhang, W.; Luo, S.-P.; Li, B.-L.; Xia, A.-B.; Zhong, A.-G.; Xu, D.-Q. *Chem. Asian. J.* **2009**, 4, 1834. (c) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, R. T. *Adv. Synth. Catal.* **2008**, *350*, 537.

catalysis typically using chiral thioureas as promotors. A series of bicycles have been achieved by applying this cascade reaction methodology, obtaining regio-, diastereo- and enantioselectively controlled transformations.

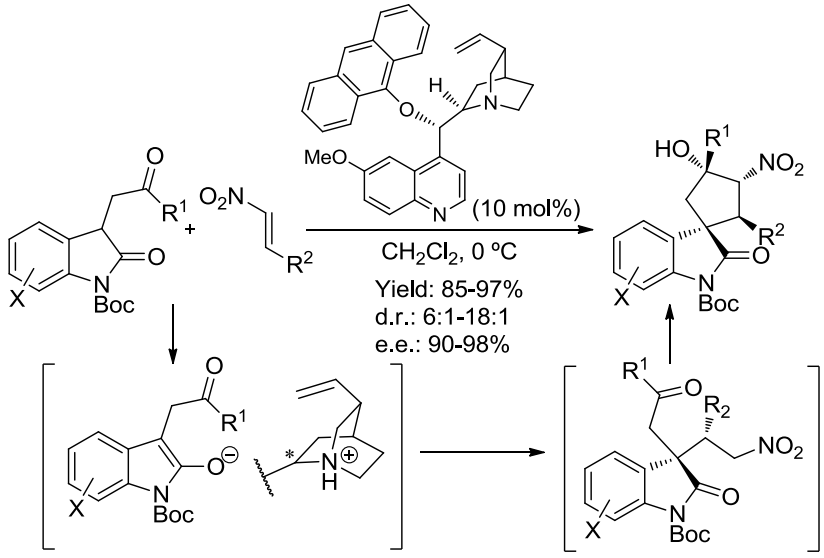


Scheme 3. 13

Finally, the methodology based on the use of chiral Brønsted bases to catalyze Michael/Henry reaction must be commented. The Michael addition step is promoted by the catalyst through activation of the pronucleophile, exerting its deprotonation. This leads to the formation of an anionic species which should

remain tightly bounded to the corresponding chiral cation, therefore allowing the later to control the stereochemical outcome of the reaction.

In this context, Barbas III has reported a novel organocatalytic strategy for the synthesis of polysubstituted spirocyclopentaneoxindoles with four stereocenters, including an all-carbon spyro quaternary center, in good yields and excellent enantioselectivity, employing simple nitrostyrenes and 3-susbtituted oxindoles as starting materials (Scheme 3.14). [26] Taking advantage of the high acidity of the C-3 proton of the oxindoles, the cascade reaction has been started by a catalyst-induced deprotonation, leading to the formation of the substrate-catalyst ionic pair, responsible for the stereocontrol of the initial Michael reaction and leading to the depicted tricycles after a second intramolecular Henry reaction.



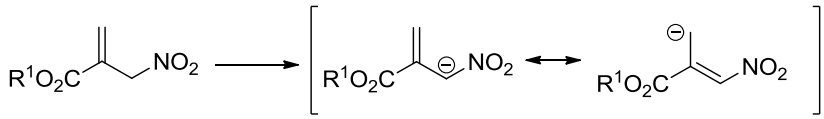
Scheme 3. 14

[26] Albertshofer, K.; Tan, B.; Barbas III, C. F. *Org. Lett.* **2012**, *14*, 1834.

In conclusion, the application of the Michael/Henry cascade reaction to the synthesis of optically active complex products is unquestionable and the examples analyzed, show its remarkable applicability making it a highly efficient tool for obtaining functionalized products with total diastereo- and enantiocontrol employing different types of catalyst. Both enamine an iminium activation together with the H-bonding catalysis strategy enable to carry out Michael/Henry cascade reactions with high efficiency. These methodologies allow the preparation of densely functionalized five or six membered carbocycles and heterocycles with an exceptional level of control of the stereocenters formed in most cases.

2. Objectives and work plan

In this context and taking into account the experience acquired in our research group in the field of conjugate additions, and encouraged by the success of the Michael addition reactions developed by us employing α,β-unsaturated aldehydes as Michael acceptors under iminium catalysis, we decided to survey the utility of 2-nitromethylacrylates (Scheme 3.15) as suitable functionalized compounds to be used in Michael/Henry cascade reactions under iminium activation.



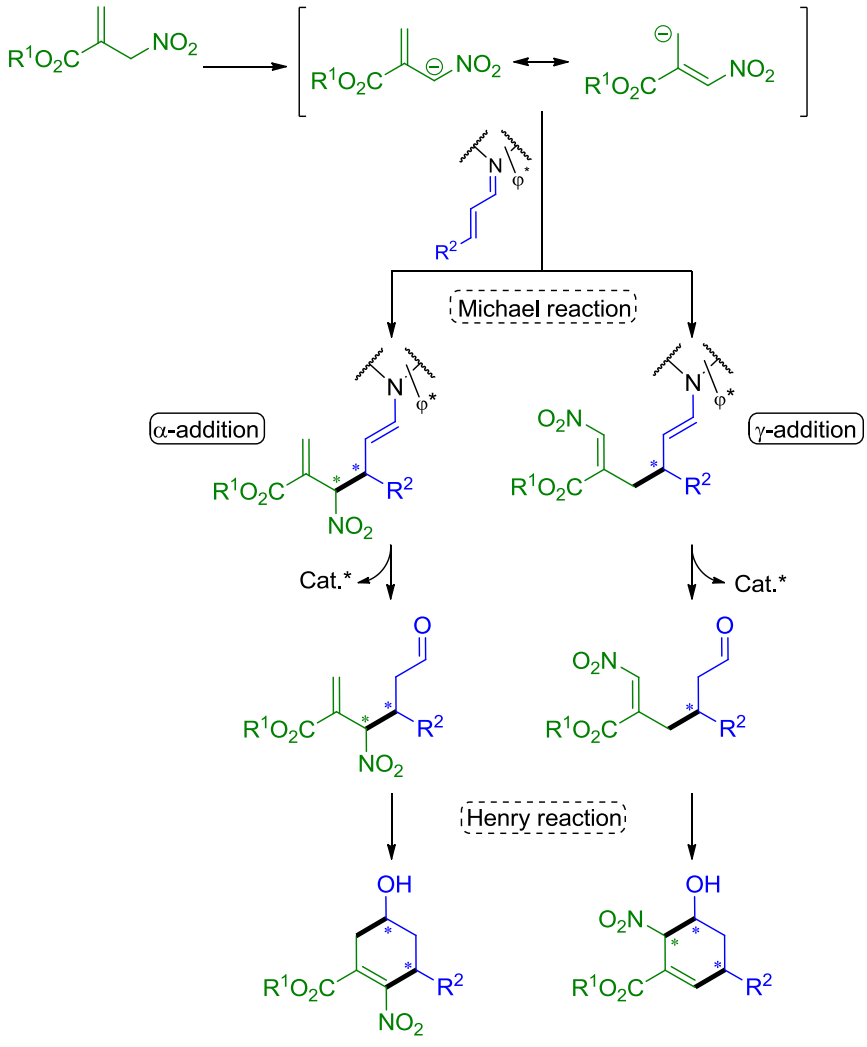
Scheme 3. 15

This type of compounds are expected to be active as carbon pronucleophiles in an initial Michael reaction because of the presence of two acidic protons in α position to the nitro group, according to a recent study that has pointed out that there must exist a p*K*a barrier for nucleophile activation in conjugate additions of carbon nucleophiles proceeding *via* iminium activation, which should lie between the p*K*a values of 16 and 17.[27] Moreover, the deprotonation of this 2-nitromethylacrylate would lead to the generation of a resonance-stabilized allylic anion, with potential to react either at C-α or at C-γ position.

Assuming that the selected pronucleophile can undergo a conjugate addition to the iminium ion resulting from the condensation of the Michael acceptor –an α,β-unsaturated aldehyde– and the aminocatalyst, the release of the catalyst after the

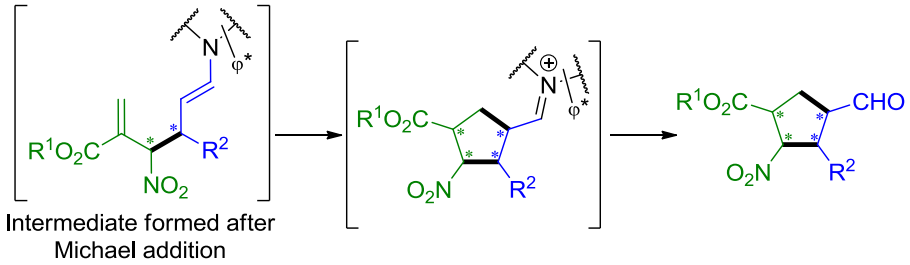
[27] Alonso, D. A.; Kitagaki, S.; Utsumi, N.; Barbas III, C. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 4588.

initial Michael reaction would form a nitroaldehyde intermediate which is expected to undergo intramolecular Henry reaction (Scheme 3.16).



Scheme 3. 16

Nevertheless, we have to be aware of the fact that if the catalyst is not released from the resulting Michael addition product, another intramolecular conjugate addition can take place between the enamine and the remaining α,β-unsaturated ester moiety, leading to the formation of cyclopentanes as shown in Scheme 3.17.



Scheme 3. 17

Taking into account all these possibilities and the different products that can be formed under the proposed aminocatalytic conditions, the most important issue to control during the investigation is the selective formation of a single product, avoiding simultaneous mechanisms participating in the reaction pathway. Considering the rules for ring closure postulated by Baldwin,[28] the formation of the cyclohexenes depicted in Scheme 3.16 as a result of Michael/Henry domino reaction, classified as 6-*endo*-trig, would be favored in comparison with the competitive formation of the cyclopentane achieved from an hypothetical Michael/Michael cascade reaction which would be unfavorable, considering the cycle formed 5-*exo*-trig.

Another crucial feature to be evaluated is the possibility to carry out this reaction in a stereocontrolled way. If the desired Michael/Henry cascade reaction takes place, the aminocatalyst has to direct the nucleophilic attack by the less

[28] Baldwin, J. E. *J. Chem. Soc., Chem. Commun*. **1976**, 734.

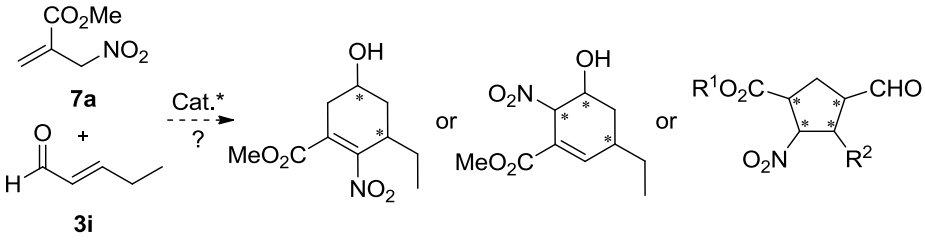
hindered face of the iminium ion, exerting stereocontrol during the conjugate addition step. On the other hand, the stereocenters generated during the Henry reaction should be controlled by the existing chiral centers at the nitroaldehyde intermediate.

With those ideas in mind we established the objective of the present work as **the study of the behavior of 2-nitromethylacrylates as functionalized Michael donors in cascade reactions with α,β-unsaturated aldehydes under iminium activation, with focus on developing an enantioselective procedure for the preparation of functionalized cyclohexenes through a plausible Michael/Henry cascade process.**

Based on those objectives, we designed the following working plan to allow a study of the mentioned transformation.

1. Viability of the reaction:

We will start studying the capacity of the acrylate **7a** to react with enals under iminium activation by using aldehyde **3i** as model substrate. This initial task would allow us to check whether the bifunctional compound behaves as expected or if other byproducts are obtained (Scheme 3.18).



Scheme 3. 18

2. Optimization of the reaction:

The influence of typical experimental factors such as catalyst, additive, solvent or temperature will be evaluated, paying attention to the yield and regioselectivity of the transformation as well as estereocontrol of the reaction with respect to the possible formation of diastereo- and enantiomers.

3. Scope of the methodology:

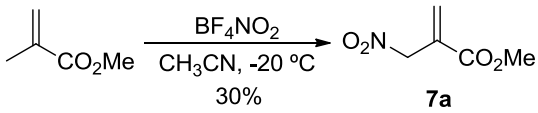
After optimizing the methodological parameters the chemical character of the substrates involved in the reaction will be tested; for that purpose other alkyl 2-nitromethylacrylates as Michael donors and some α,β-unsaturated aldehydes with different patterns of substitution as Michael acceptors will be used in the reaction.

3. Results and discussion

After a brief retrospective vision of organocatalytic Michael/Henry cascades has been made and once the objectives and work plan has been established, the most relevant results obtained from our investigation will be presented.

3.1. Preparation of starting materials

In line with the work plan, we started with the synthesis of the starting materials. A revision of the literature led us to follow the methodology published by Murphy and coworkers[29] to synthesize the Michael donor **7a**. Nitration of methy methacrylate with BF_4NO_2 in acetonitrile at -20 ºC resulted in the formation of **7a** with 30% yield (Scheme 3.19).



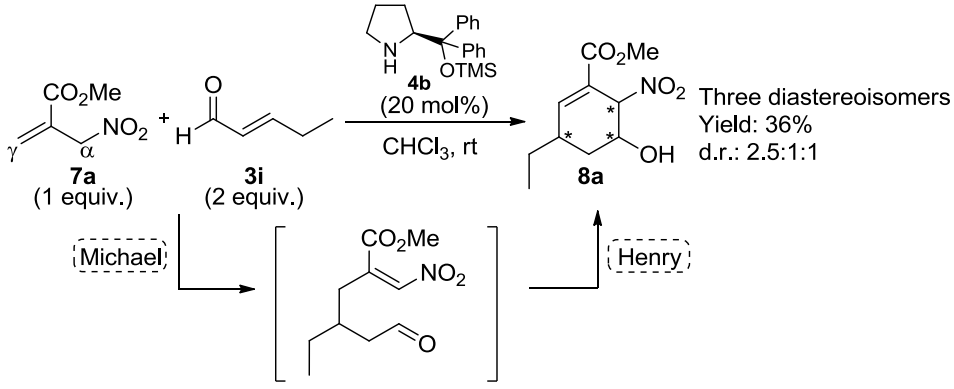
Scheme 3. 19

3.2. Viability of the reaction

With compound **7a** in our hands, we surveyed its behavior with *trans*-pentenal **3i** as model system in the presence of a chiral secondary amine catalyst. In a first attempt, we carried out the reaction using diphenylprolinoltrimethyl silyl ether **4b** as catalyst, in chloroform and at room temperature. When the compound **7a** was completely consumed (the reaction was followed by t.l.c. analysis), the ^{1}H-NMR

[29] Hewlins, S. A.; Murphy, J. A.; Lin, J.; Hibbs, D. E. Hursthouse, M. B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1559.

of the crude reaction mixture revealed that the cyclohexene **8a** had been formed without observing other possible byproducts previously predicted (Scheme 3.16 and 3.17). We concluded that the 2-nitromethylacrylate **7a** was behaving as a 1,3-nucleophile, leading to the polysubstituted cyclohexene after performing the projected cascade reaction through initial selective γ-addition to the intermediate iminium ion derived from pentenal, followed by catalyst releasing and intramolecular Henry reaction. The compound **8a** was isolated by flash column chromatography in 36% yield as a mixture of three diastereoisomers (Scheme 3.20).



Scheme 3. 20

To evaluate if the chosen catalyst was exerting the desired stereocontrol, the determination of the enantiomeric excess had to be carried out by HPLC analysis. For that reason, the racemate of the cyclohexene **8a** was prepared using a racemic mixture of **4b** as catalyst under the reaction conditions depicted in Scheme 3.20. The mixture containing the three formed diastereoisomers, all of them as racemic compounds, was isolated and as it can be seen in the chromatograms exposed in Figure 3.1 (left) all stereoisomers could be separated by HPLC on a chiral

stationary phase (Chiralpak AS-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). The major diastereoisomer of the enantioenriched mixture **8a** could be isolated by flash column chromatography and the enantiomeric excess measured from the first trial was 75%, which indicated that the catalyst was indeed very effective in assisting the enantioselective formation of the chiral product **8a** (Figure 3.1, right).

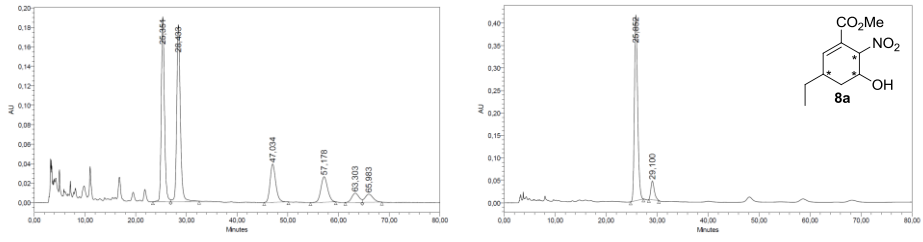


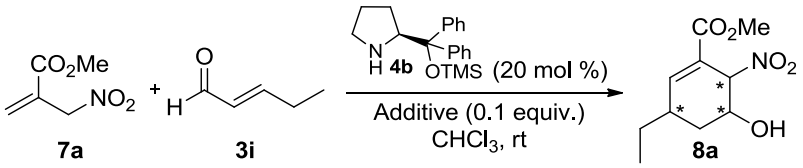
Figure 3. 1

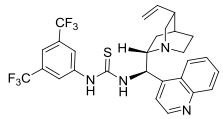
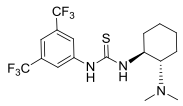
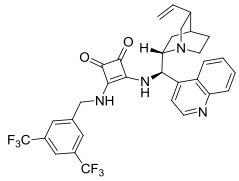
3.3. Optimization of the reaction

These results made us explore the possibilities that this reaction could offer. The first parameter to study was the organocatalyst employed and therefore, we tested some different chiral secondary amines in the model reaction. Taking into account the high enantioselectivity achieved with prolinol derivative **4b**, we decided to use other diphenylprolinol derivative with a bulkier *O*-protecting group and also diarylprolinol derivatives containing bulkier aryl substituents were evaluated as catalysts, but the reaction did not progress in any case and the starting materials were recovered in all cases. Imidazolidinone derivatives designed by MacMillan were also tested, but again no evolution of the reaction was observed.

As the other catalysts tested did not show any activity, we decided to combine the catalyst **4b** with several additives (Table 3.1).

Table 3. 1: Influence of the additive in the cascade reaction.[a]



Entry	Additive	d.r.[b]	Yield (%)[c]	e.e. (%)[d]
1	-	2.5:1:1	36	75
2	PhCOOH	-	-	-
3	DABCO	-	-	-
4	DBU	2.5:1:1	34	86
5	1,1,3,3-Tetramethyl-guanidine	2.5:1:1	53	88
6	Et_3N	2:1.4:1	76	86
7	DMAP	2.4:1.2:1	43	90
8		5:2:1	40	88
9		3.3:1.7:1	29	79
10		3.3:1.3:1	64	82
11	Ph_3P	3.3:1:1.6	52	86
12	Bu_3P	2.5:1.7:1	33	90
13	$^tBu_3P$	2.5:1:1.5	74	88

[a] One equivalent of **7a** and two equivalents of aldehyde **3i** were used. [b] Determined by ^{1}H-RMN analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

We started evaluating the influence of an acid additive which is known to facilitate the formation of the iminium ion and, consequently, contribute to a higher efficiency of the reaction. We firstly repeated the reaction under the conditions depicted on the Scheme 3.20 adding benzoic acid (entry 2) but the formation of the desired product **8a** could not be appreciated.

Then we decided to switch to the use of additives of a different chemical feature. Some examples in the literature,[30] made us think that Brønsted bases could be beneficial for the reaction, assuming that a base could help in the nucleophile formation by promoting the deprotonation of the substrate **7a**, and later on it could also assist the intramolecular Henry reaction. We began testing DABCO (entry 3), but disappointingly the formation of the cycloadduct **8a** was not observed, and a mixture of unidentified products was formed instead. Fortunately when other bases were used such as DBU, 1,1,3,3-tetramethylguanidine, triethylamine and DMAP (entries 4-7) cyclohexene **8a** was selectively obtained. The highest value regarding the yield was achieved with triethylamine but it showed poor diastereoselectivity (entry 6) and the best enantiocontrol was obtained when employing DMAP although the yield was not good enough (entry 7). DBU (entry 4) and 1,1,3,3-tetramethylguanidine (entry 5) presented quite different yields, getting better results with the guanidine derivative, although similar diastereo- and enantioselectivities were achieved in both cases and always comparable to the ones obtained without adding any additive (entry 1).

We also decided to try bifunctional Brønsted bases containing acidic H-donor sites as additives (entries 8-10) in order to evaluate their potential positive

[30] Zhang, B.; Cai, L.; Song, H.; Wang, Z.; He, Z. *Adv. Synth. Catal.* **2010**, *352*, 97.

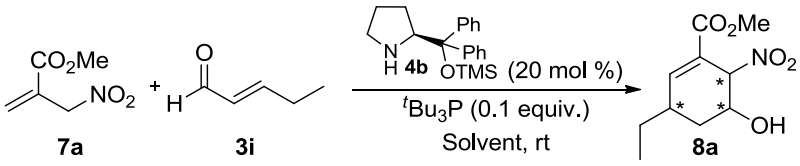
contribution to the reaction, but without giving better results than the ones obtained with triethylamine (entry 6).

Finally we decided to evaluate the use of phosphines as cocatalyst (entries 11-13) and in this sense, PPh_3 furnished the best diastereomeric ratio although the yield was low (entry 11). With Bu_3P (entry 12) poor yield was achieved, but excellent enantiomeric excess. Lastly, the use of a bulkier phosphine like $^tBu_3P$ gave a good yield and an acceptable value of diastereomeric excess and good enantioselectivity (entry 13).

Taking into account the obtained results, we observed that similar results were obtained when employing triethylamine (entry 6) and tri-*tert*-butylphosphine (entry 10) so we decided to continue with the optimization of the reaction conditions using $^tBu_3P$ as the additive due to the fact that the enantiomeric excess obtained was slightly higher. It has to be pointed out that, in all cases the formation of other regioisomers was not detected by NMR analysis of the crude reaction mixture.

The optimization of the model reaction went on with the election of the most suitable solvent for the Michael/Henry transformation (Table 3.2). A battery of tests were run to evaluate the influence of different solvents and it can be said that, in a general view, the diastereo- and enantioselection of the cascade reaction was not influenced by the change of solvents, except in the case of DMSO (entry 8) where the enantiomeric excess resulted quite affected, reaching a value of 68%. The tests run revealed that chloroform (entry 3) was the most suitable solvent for the reaction in terms of overall yield.

Table 3. 2: Influence of the solvent in the cascade reaction.[a]

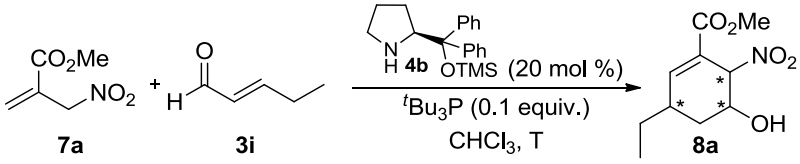


Entry	Solvent	d.r.[b]	Yield (%)[c]	e.e. (%)[d]
1	Hexane	2.5:1:1.5	58	86
2	Toluene	2:1.8:1	36	88
3	$CHCl_3$	2.5:1:1.5	74	88
4	THF	10:0.7:1	40	87
5	AcOEt	10:7:1	28	88
6	MeOH	1.7:1.3:1	57	83
7	DMF	2.5:1:1	40	87
8	DMSO	5:2:2	33	68

[a] One equivalent of **7a** and two equivalents of aldehyde **3i** were used. [b] Determined by ^{1}H-RMN analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

Once the appropriate solvent and cocatalyst had been identified, we went on with some other methodological parameters which could affect the efficiency of the reaction. In this sense, we firstly tried to improve the diastereo- and enantiomeric ratio by lowering the temperature (Table 3.3), but none of the experiments tests were successful.

Table 3. 3: Influence of the temperature in the cascade reaction.[a]

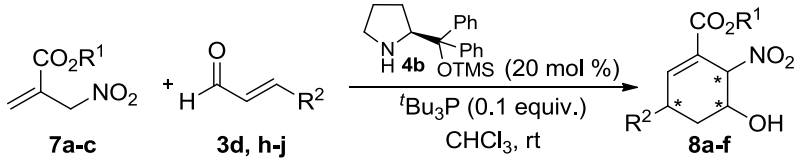


Entry	T (ºC)	d.r.[b]	Yield (%)[c]	e.e. (%)[d]
1	rt	2.5:1:1.5	74	88
2	4	5:2:1	32	82
3	-30	2.5:1.5:1	30	86

[a] One equivalent of **7a** and two equivalents of aldehyde **3i** were used. [b] Determined by ^{1}H-RMN analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

At that point of the investigation we thought about the possibility of improving the diastereomeric ratio by changing the carboxylate substituent present in the acrylate **7**. For this reason, we synthesized compounds **7b** and **7c** and proceeded to evaluate the reaction under the optimized conditions. We also decided to evaluate the use of other enals in order to observe the influence of the β-substitution of the Michael acceptor in the diastereoselection of the reaction (Table 3.4).

Table 3. 4: Influence of the substitution of the starting materials in the cascade reaction.[a]



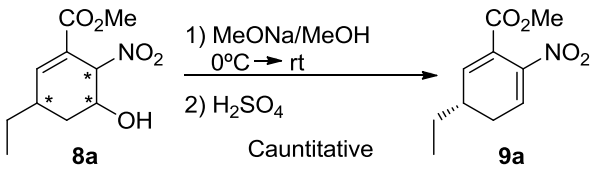
Entry	R^1	Acrylate	R^2	Enal	Product	d.r.[b]	Yield (%)	e.e. (%)[b]
1	Me	**7a**	Et	**3i**	**8a**	2.5:1:1.5	74	88
2	^{i}Bu	**7b**	Et	**3i**	**8b**	5:1:2.5	40	76
3	^{t}Bu	**7c**	Et	**3i**	**8c**	2.5:1:1.2	<10	n.d.
4	Me	**7a**	^{n}Bu	**3j**	**8d**	2.5:1:2.1	36	n.d.
5	Me	**7a**	n-C_8H_{17}	**3d**	**8e**	2:1	<10	n.d.
6	Me	**7a**	H	**3h**	**8f**	>20:<1	<10	n.d.

[a] One equivalent of **7a-c** and two equivalents of aldehyde **3d, h-j** were used. [b] Determined by ^{1}H-RMN analysis for the mixture of diastereoisomers after flash column chromatography purification. [c] Referred to the mixture of diastereoisomers after flash column chromatography purification. [d] Calculated by HPLC for the major diastereoisomer.

The reactions performed are summarized in Table 3.4 and reveal that diastereoselection is independent from the substitution of the acrylate or α,β-unsaturated aldehyde used. It should be stated that the size of the substituent present either in the acrylate or the enal traduces in a decrease of the yield, although the diastereoselectivity achieved is comparable to the one obtained in the model reaction (entry 1).

With those results in our hands, we understood that the poor diastereoselection of the reaction was a big handicap. The difficulty to control the three stereogenic centers formed in the transformation, might lay in the second step of the cascade reaction. Taking into account that the C-3 stereocenter that comes from the

Michael addition of the nucleophile to the iminium ion is expected to be efficiently controlled by the catalyst, it seems sensible to think that the lack of stereogenic control derives from the intramolecular Henry reaction in which the stereocenters C-5 and C-6 are created, after the release of the organocatalyst. Aware of this diastereoselection problem, we thought about possible transformations that could lead to a convenient process in which all diastereoisomers would converge into a single product. The dehydration of the cyclohexene **8a**, obtaining a cyclohexadiene **9a** seemed a promising way to eliminate two sterocenters and to simplify the structure of the compound, maintaining the stereocenter created at the initial Michael reaction step. Therefore a dehydration reaction was carried out, employing sodium methoxyde in methanol observing that the reaction took place in a quantitative way (Scheme 3.21).



8a **9a**

Scheme 3. 21

The racemate of the dehydrated product **9a** was prepared by dehydration of a racemic mixture of **8a** and the enantiomers could be separated by chiral HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min), which allowed us to confirm that the enantiomeric excess was maintained from the major diastereoisomer of compound **8a** to the dehydrated cycloadduct **9a**. The chromatogram of the racemic mixture can be seen on Figure 3.2 (left) and the chromatogram corresponding to the enantiomerically pure **9a** is placed on the right.

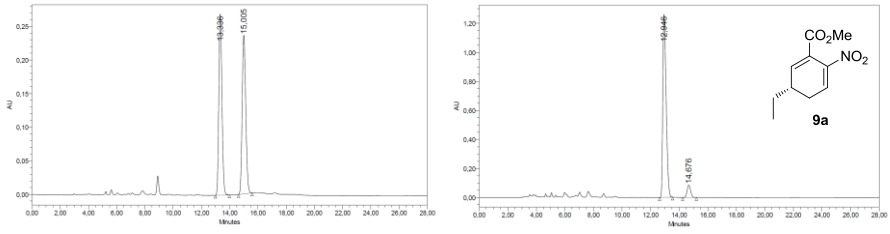
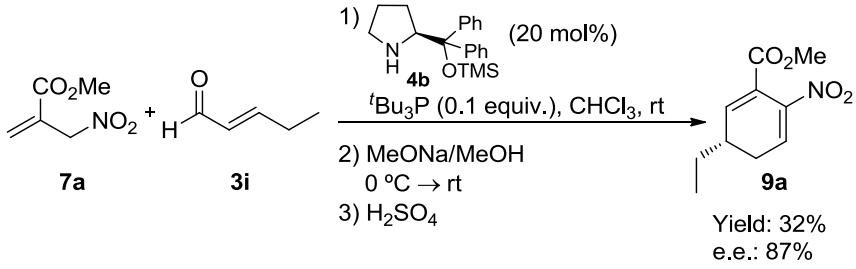


Figure 3. 2

In line with this change on the synthesis target from highly functionalized cyclohexenes **8** to cyclohexadienes **9**, we decided to perform the Michael /Henry cascade process together with a dehydration reaction in a sequential fashion. After carrying out the cascade reaction and once the transformation was completed, the solvent was evaporated, the crude was redissolved in methanol and it was added dropwise to a solution of cooled NaOMe/MeOH and finally quenched with a methanolic H_2SO_4 solution. The reaction progressed in the desired way, obtaining the cyclohexadiene **9a** in an efficient manner (Scheme 3.22).



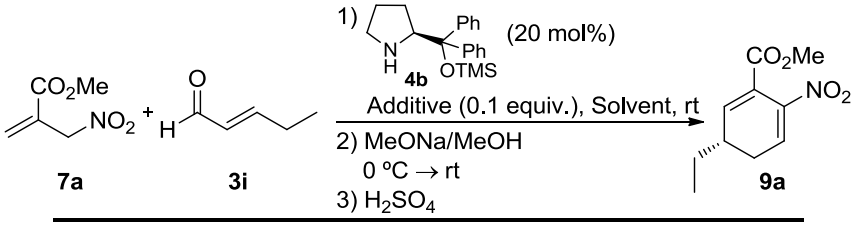
Scheme 3. 22

Whit this new objective in mind, we decided to reevaluate some of the experimental parameters in order to optimize this sequential reaction. In a first attempt we carried out the transformation with the same catalyst **4b** and we

changed some parameters such as additive and solvent in the initial Michael-Henry process under iminium activation (Table 3.5).

Working in chloroform as solvent we evaluated several additives (entries 1-3) In this sense, the use of triethylamine (entry 2) led to the formation of **9a** but in lower yield than achieved before employing $^{t}Bu_3P$ (entry 1), although similar enantioselection was obtained. Benzoic acid was tried in combination with the $^{t}Bu_3P$ (entry 3) in order to improve the efficiency of the reaction by assisting the formation of the intermediate iminium ion, but the yield was rather poor and the enantioselectivity did not improve.

Table 3. 5: Influence of the additive and solvent in the in the cascade-dehydration sequential reaction.[a]

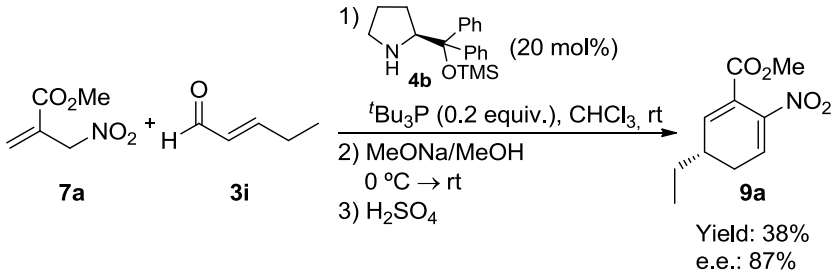


Entry	Additive	Solvent	Yield (%)	e.e. (%)[b]
1	$^{t}Bu_3P$	$CHCl_3$	32	87
2	Et_3N	$CHCl_3$	<20	88
3	$^{t}Bu_3P/PhCO_2H$[c]	$CHCl_3$	20	89
4	$^{t}Bu_3P$	$^{i}PrOH$	28	66
5	$^{t}Bu_3P$	Toluene	22	90
6[d]	$^{t}Bu_3P$	$CHCl_3$	38	87

[a] One equivalent of **7a** and two equivalents of aldehyde **3i** were used. [b] Calculated by HPLC after flash column chromatography purification. [c] 0.1 equivalent of each additive was added. [d] 0.2 equivalents of additive were used.

Setting $^{t}Bu_3P$ as the best additive, we changed the solvent but the use of a more polar solvent, like *iso*-propanol, resulted in an important decrease of the enantioselectivity (entry 4) and a non polar one, like toluene, afforded **9a** in low yield although with an excellent enantiocontrol was achieved (entry 5). Finally we also carried out the reaction using a 20% mol of cocatalyst in chloroform (entry 6), observing a slight improvement in the yield of the reaction while obtaining the same enantioselectivity.

After all these experiments we decided that the best reaction conditions for the reaction resulted to be the ones shown in the Scheme 3.23.

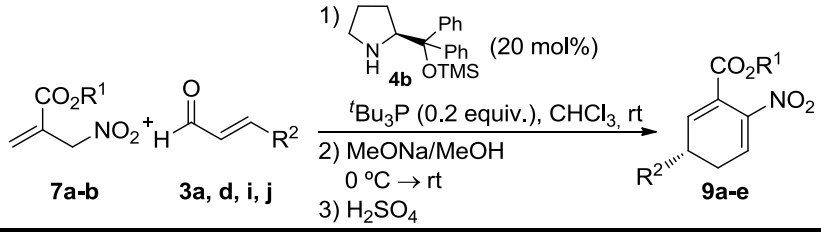


Scheme 3. 23

3.4. Scope of the methodology

With those results in our hands we decided to evaluate the importance of the substitution of the enals used as Michael acceptors and the substitution of the acrylate **7**, in order to see the influence of this substitution, in the sequential Michael/Henry/dehydration reaction.

Table 3. 6: Influence of the substitution of the starting materials in the sequential reaction.[a]



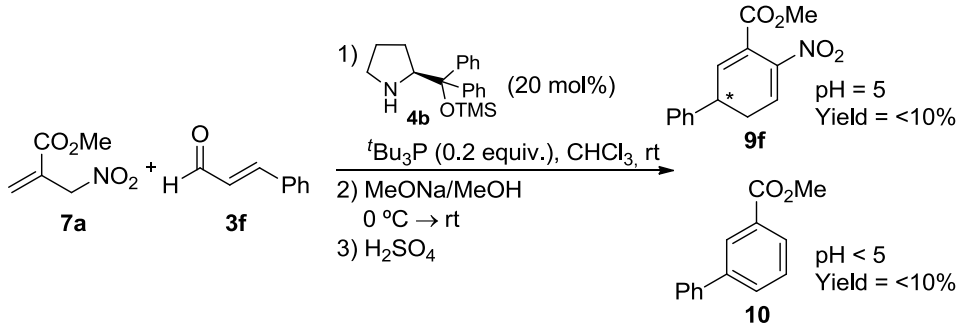
Entry	R^1	Acrylate	R^2	Enal	Product	Yield (%)	e.e. (%)[b]
1	Me	**7a**	Et	**3i**	**9a**	38	87
2	Me	**7a**	Me	**3a**	**9b**	32	85
3	Me	**7a**	^{n}Bu	**3j**	**9c**	33	92
4	Me	**7a**	^{i}Pr	**3d**	**9d**	17	93
5	^{i}Bu	**7b**	Et	**3i**	**9e**	12	88

[a] One equivalent of **7a-b** and two equivalents of aldehyde **3a, d, i, j** were used. [b] Calculated by HPLC after flash column chromatography purification.

As it can be seen in Table 3.6, overall yields obtained were around 30-40% in all cases in which linear aliphatic substituents were present at the β-position of the enal regardless the length of the chain. On the other hand, the enantiomeric excesses increased when longer chains were introduced (entries 1-3). In contrast, when a bulkier element, such as an ^{i}Pr group, was placed at the β position of the α,β-unsaturated aldehyde (entry 4) the yield decreased drastically although the enantioselection was very high. Similarly when the bulkier acrylate **7b** was employed a poor yield was achieved although very good enantiomeric excess.

The behavior of aromatic α,β-unsaturated aldehydes deserves special attention. The reaction between 2-nitromethylacrylate **7a** and cinnamaldehyde **3f** under the optimized reaction conditions, led to the formation of the expected product in very low yield together with a complex mixture of products. However,

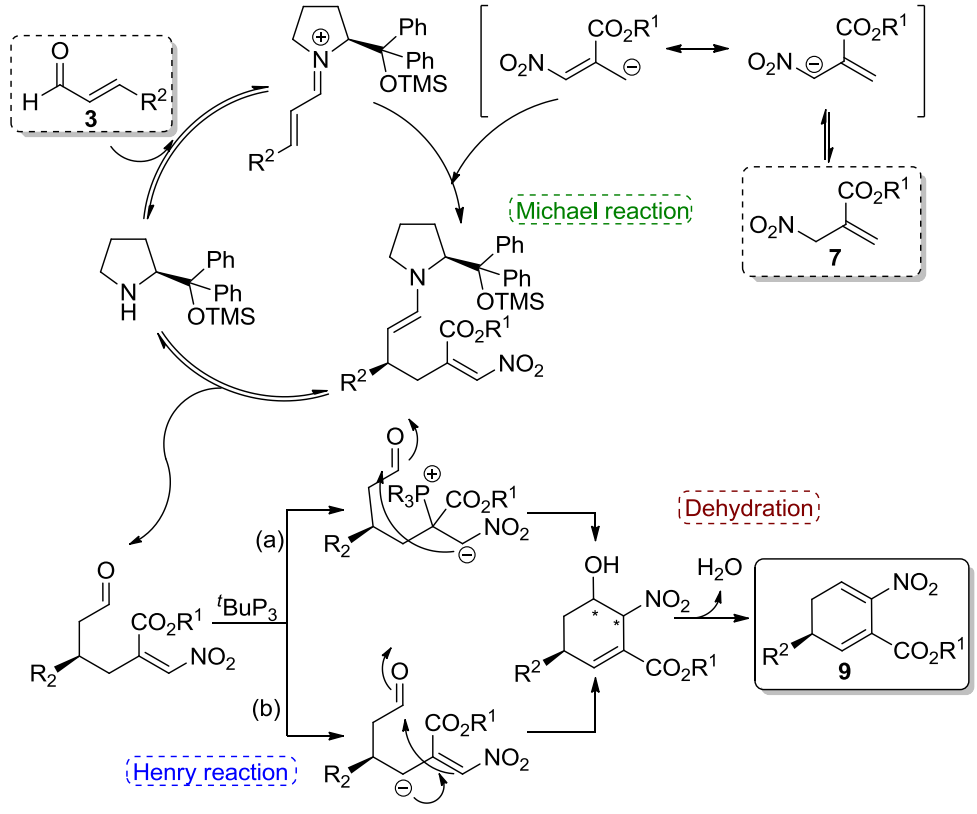
if the pH of the mixture obtained after the final quench of the dehydration reaction was lower that pH = 5, the reaction furnished a complete aromatized product **10**, where the dehydration process occurred together with elimination of HNO_2, probably due to the high stability of the resulting compound (Scheme 3.24). In order to avoid this problem, we also tried enals with other substituents at the aromatic rings (R = *o*-OMePh, *o*-NO_2Ph, *p*-OMePh, *p*-NO_2Ph) as Michael acceptors, but we were not able to obtain the desired cycloaddition chiral products.



Scheme 3. 24

3.5. Mechanistic aspects

In base of the achieved products, we have proposed a plausible mechanism for the cascade reaction (Scheme 3.25) in which, in a first step, the catalyst reacts with the α,β-unsaturated aldehyde forming an iminium ion which is susceptible of suffering a Michael addition of the nucleophile formed by deprotonation of the 2-nitromethyacrylate. After the reaction of the conjugate nitronate anion through its γ-carbon, with the iminium ion intermediate by the less hindered face (*Re* face), avoiding the steric hindrance, a new bond is stereoselectively created, leading to the formation of a new stereogenic center (C-3 of the final cyclohexene). At that point, according to our hypothesis, the intermediate is hydrolyzed and the catalyst is recovered for the next catalytic cycle. Then two possible pathways can happen for the Henry reaction: a) the phosphine undergoes an addition to the resulting product, promoting the Henry reaction through a Baylis-Hillman reaction type sequence or b) the phosphine acts as a base and after the deprotonation of the nitroalkane moiety and Henry reaction takes place leading to the formation of the desired cyclohexene. As we have been unable to establish the absolute configuration of the products **9** either by X-ray analysis or by chemical correlation, we have tentatively assumed an (*S*) configuration for this C-3 stereocenter according to this mechanistic proposal.


3
Ph
Ph
OTMS
R2
CO2R1
O2N
7
Michael reaction
NO2
(a)
(b)
tBuP3
R3P
Dehydration
OH
H2O
9
Henry reaction

Scheme 3. 25

4. Conclusions

To sum up we have developed a methodology that involves an organocatalytic Michael/Henry cascade reaction under iminium activation between enals and 2-nitromethylacrylates **7a-c**. The selected Michael donor, 2-nitromethylacrylate, has proved to be a suitable starting material for the reaction, acting as an appropriate nucleophile and has reacted with α,β-unsaturated aldehydes stereocontrolled by α,α-diphenylprolinol *O*-silylated catalyst, but showing poor diastereoselectivity.

In order to avoid this problem, we have designed a methodology involving Michael/Henry cascade reaction followed by a sequential dehydration leading to the enantiopure cyclohexadienes **9a-e** in a moderate yield but good enantioselectivity.

In a plausible mechanism Michael addition of the deprotonated 2-nitromethylacrylate to the iminium ion resulting from the fusion between the aminocatalyst and the α,β-unsaturated aldehyde would take place. After the catalyst is released, an intermolecular Henry cyclization occurs, achieving the cyclohexenes which would undergo a sequential dehydration step to provide the corresponding cyclohexadienes.

The project is still being studied in order to improve the results summarized in this work.

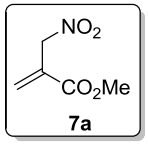
5. Experimental

5.1. Preparation of acrylates 7a-c

General procedure

The acrylates **7a-c** were synthesized adding nitronium tetrafluoroborate (7.53 mmol) to dry acetonitrile at -20 ºC. Then the corresponding methacrylate was added (15.06 mmol) and the mixture was stirred for 2 hours at that temperature. The reaction was quenched with water (100 mL) and it was stirred during 15 minutes at room temperature. Afterwards the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography to obtain the compounds **7a-c**.

Methyl 2-(nitromethyl)acrylate (7a)



Following the general procedure, methyl methacrylate (1.61 mL, 15.06 mmol) was added to a solution of nitronium tetrafluoroborate (1.00 g, 7.53 mmol) in acetonitrile. The compound **7a** (0.32 g, 2.26 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

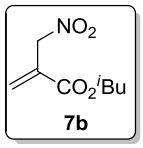
Yield: 30%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 5.17 (s, 3H, CH_3), 6.01 (s, 2H, CH_2NO_2), 6.63 (s, 1H, CH_2=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 52.6 (CH_3), 75.2 (CH_2NO_2), 130.5 (CH_2=**C**), 133.9 (**C**H_2=C), 164.8 (CO).

IR (Neat, cm^{-1}): 1719 (C=O), 1555 (NO_2).

Isobutyl 2-(nitromethyl)acrylate (7b)



Following the general procedure, isobutyl methacrylate (2.42 mL, 15.06 mmol) was added to a solution of nitronium tetrafluoroborate (1.00 g, 7.53 mmol) in acetonitrile. The compound **7b** (0.28 g, 1.51 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

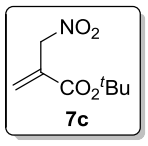
Yield: 20%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.93 (d, 6H, J = 6.7 Hz, $(CH_3)_2$), 1.84-2.04 (m, 1H, CH), 3.98 (d, 2H J = 6.5 Hz, C**H**$_2$CH), 5.16 (s, 1H, (CH_2NO_2), 5.99 (s, 1H, C**H**$_A$H$_B$=C), 6.62 (s, 1H, CH$_A$**H**$_B$=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 18.9 $(CH_3)_2$), 27.7 (CH), 71.7 (**C**H_2CH), 75.3 (CH_2NO_2), 130.8 (CH_2=**C**), 133.7 (**C**H_2=C), 164.3 (CO).

IR (Neat, cm^{-1}): 1719 (C=O), 1558 (NO_2).

***tert*-Butyl 2-(nitromethyl)acrylate (7c)**



Following the general procedure, *tert*-butyl methacrylate (2.45 mL, 15.06 mmol) was added to a solution of nitronium tetrafluoroborate (1.00 g, 7.53 mmol) in acetonitrile. The compound **7c** (0.183 g, 0.97 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 13%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 6.53 (s, 1H, $(CH_3)_3$), 1.49 (s, 4H, CH_2), 5.12 (s, 1H, C**H**$_A$H$_B$=C), 5.89 (s, 1H, CH$_A$**H**$_B$=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 27.8 ($(CH_3)_3$), 75.6 (CH_2), 82.5 (**C**$(CH_3)_3$), 132.2 (CH_2=**C**), 132.6 (**C**H_2=C), 163.4 (CO).

EM (EI) [m/z (%)]: 112 (11), 126 (13), 143 (35), 172 (24), 218 (71), 247 (19), 265 (100).

HRMS: Calculated for [$C_8H_{13}NO_4$]: 187.0845. Found: 187.0665.

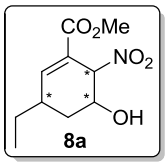
IR (Neat, cm^{-1}): 1712 (C=O), 1558 (NO_2).

5.2. Michael/Henry cascade reaction. Synthesis of cyclohexenes 8a-e

General procedure

The α,β-unsaturated aldehyde **3d, h, i, j** was added to a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **4b** (0.05 mmol), tri-*tert*-butylphosphine (0.05 mmol) and the corresponding acrylate **7a-c** (0.25 mmol) in chloroform (2 mL). The reaction was stirred at room temperature until full conversion was observed by t.l.c. Afterwards the reaction mixture was diluted in diethyl ether (10 mL) and washed with $NaHCO_3$ (1 × 8 mL), brine (2 × 8 mL) and H_2O (2 × 8 mL). The organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography to obtain the cyclohexenes **8a-e**. Racemic samples were prepared using a racemic mixture of the catalyst **4d**.

Methyl 3-ethyl-5-hydroxy-6-nitrocyclohex-1-enecarboxylate (8a)



Following the general procedure, the compound **8a** was prepared adding (*E*)-2-pentenal **3i** (49 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8a** (39 mg, 0.17 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 74%.

d.r.: 2.5:1.2:1.5 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): (*indicates the diastereoisomer of intermediate proportion, #indicates minor diastereoisomer, ▲indicates signals corresponding to the mixture of three diastereoisomers) 0.96-1.06▲ (m, 3H, $CH_2C\mathbf{H}_3$), 2.36-1.71▲ (m, 3H, $C\mathbf{H}_2CH_3$ + $C\mathbf{H}_AH_BCHOH$), 1.88-2.22▲ (m, 1H, $CH_A\mathbf{H}_BCHOH$), 2.34-2.72▲ (m, 2H, $C\mathbf{H}CH_2CH_3$ + OH), 3.75* (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3, signal corresponding to the major and minor diastereoisomers), 4.09-4.25* (m, 1H, C**H**OH), 4.39-4.51# (m, 1H, C**H**OH), 4.53-4.62 (m, 1H, C**H**OH), 5.20-5.36 (m, 1H, $CHNO_2$, signal corresponding to the major and minor diastereoisomers), 5.45-5.54* (m, 1H, $CHNO_2$), 7.18* (s, 1H, CH=C), 7.30# (d, 1H, J = 3.1 Hz, CH=C), 7.39 (d, 1H, J = 2.6 Hz, CH=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): (*indicates the diastereoisomer of intermediate proportion, #indicates minor diastereoisomer) 11.1*, 11.3, 11.7# ($CH_2\mathbf{C}H_3$), 26.7, 27.3*, 27.6# ($\mathbf{C}H_2CH_3$), 30.3, 31.1* ($\mathbf{C}H_2CHOH$), 33.5, 34.8* ($\mathbf{C}HCH_2CH_3$), 34.9# ($\mathbf{C}H_2CHOH$), 37.1# ($\mathbf{C}HCH_2CH_3$), 52.3, 52.3*, 52.4# (OCH_3),

65.5*, 67.7, 71.6[#] (CHOH), 84.1*, 84.6, 89.6[#] ($CHNO_2$), 121.9, 122.9*, 123.9[#] (CH=**C**), 149.8[#], 150.5*, 151.1 (**C**H=C), 164.9[#], 165.4*, 165.5 (C=O).

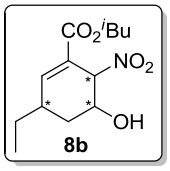
EM (EI) [m/z (%)]: 151 (86), 152 (6), 165 (100), 166 (10), 180 (12), 182 (6), 183 (14).

HRMS: Calculated for $[C_{10}H_{16}NO_5\ (M+H)]^+$: 230.1028. Found: 230.1021.

IR (Neat, cm^{-1}): 3461 (OH), 1713 (C=O), 1551 (NO_2).

e.e.: 88%, calculated by HPLC for the major diastereoisomer (Chiralpak AS-H column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the major enantiomer: 25.35 min; t_R for the minor enantiomer: 28.43 min.

Isobutyl 3-ethyl-5-hydroxy-6-nitrocyclohex-1-enecarboxylate (8b)



Following the general procedure, the compound **8b** was prepared adding (*E*)-2-pentenal **3i** (49 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7b** (46 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8b** (27 mg, 0.10 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 40%.

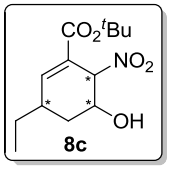
d.r.: 5:1:2.5 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer, ▲indicates signals corresponding to the mixture of two diastereoisomers) 0.93 (d, 6H, *J* = 6.7 Hz, $(CH_3)_2$), 0.89-0.96* (m, 6H, $(CH_3)_2$), 0.99-1.08▲ (m, 3H, CH_2CH_3,), 1.45-1.76 (m, 2H, C**H**$_2$OH + m, 1H, C**H**$(CH_3)_2$, signal corresponding to the minor diastereoisomer), 1.82-2.08 (m, 1H, $CHCH_2CH_3$), 2.07-2.23* (m, 2H, C**H**$_2CH_3$), 2.35-2.48 (m, 1H, C**H**CH_2CH_3), 2.49-2.64 (m, 1H, C**H**CH_2CH_3), 3.83-4.08▲ (m, 2H, C**H**$_2CH(CH_3)_2$), 4.08-4.25▲ (m, 1H, C**H**OH), 5.30* (d, 1H, *J* = 6.4 Hz, $CHNO_2$), 5.56 (d, 1H, *J* = 5.3 Hz, $CHNO_2$), 7.19* (bs, 1H, $CH=CCO_2{}^{i}Bu$), 7.34 (bs, 1H, $CH=CCO_2{}^{i}Bu$).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 11.1 (CH_2C**H**$_3$), 19.0 ($CH(C$**H**$_3)_2$), 27.25 (C**H**$_2CH_3$), 27.7 (C**H**$(CH_3)_2$), 30.0(C**H**$_2$CHOH), 38.1 (C**H**CH_2CH_3), 67.9 ($CHNO_2$), 71.5 (C**H**$_2CH(CH_3)_2$), 83.7 (**C**$CO_2{}^{i}Bu$), 123.4 (**C**$H=CCO_2{}^{i}Bu$), 151.8, 164.5 (C=O).

e.e.: 76%, calculated by HPLC for the major diastereoisomer (Chiralpak AS-H column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer: 8.16 min; t_R for the minor enantiomer: 9.42 min.

***tert*-Butyl 3-ethyl-5-hydroxy-6-nitrocyclohex-1-enecarboxylate (8c)**

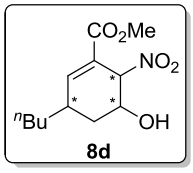


Following the general procedure, the compound **8c** was prepared adding (*E*)-2-pentenal **3i** (49 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7c** (46 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8c** was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: <15%.

d.r.: 2.5:1:1.2 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

Methyl 3-butyl-5-hydroxy-6-nitrocyclohex-1-enecarboxylate (8d)



8d

Following the general procedure, the compound **8d** was prepared adding (*E*)-2-heptenal **3j** (67 μL, 0.50 mmol) to solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8d** (23 mg, 0.09 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: 36%.

d.r.: 2.5:1.2:1 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): ($^{\#}$indicates the diastereoisomer of intermediate proportion, * indicates minor diastereoisomer,$^{\blacktriangle}$ indicates signals corresponding to the mixture of three diastereoisomers) 0.72-1.00$^{\blacktriangle}$ (m, 3H, $CH_2C\mathbf{H}_3$), 1.06-1.68$^{\blacktriangle}$ (m, 6H, $(CH_2)_3$), 1.85-2.26$^{\blacktriangle}$ (m, 1H, $C\mathbf{H}_AH_BCHOH$), 2.39-2.75 (m, 2H, $C\mathbf{H}CH_2CH_2$ + $CH_A\mathbf{H}_BCHOH^{\blacktriangle}$), 3.75$^{\#}$ (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3, signal corresponding to the major and minor diastereoisomers), 4.12-4.24* (m, 1H, C**H**OH), 4.33-4.50$^{\#}$ (m, 1H, C**H**OH), 4.50-4.63 (m, 1H, C**H**OH), 5.22-5.37 (m, 1H, $CHNO_2$, signal corresponding to the major and minor

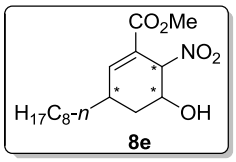
diastereoisomers), 5.51* (d, 1H, *J* = 4.8 Hz, $CHNO_2$), 7.17* (s, 1H, CH=C), 7.29[#] (d, 1H, *J* = 3.3 Hz, CH=C), 7.39 (d, 1H, *J* = 2.8 Hz, CH=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): (*indicates the diastereoisomer of intermediate proportion, [#]indicates minor diastereoisomer) 13.9*, 13.9 (CH_2**C**H_3), 22.5[#], 22.6*, 22.6 (**C**H_2CH_3), 28.6[#], 28.9*, 29.7 (**C**H_2CH_2), 30.7, 31.4* (CH_2CH_2), 32.0, 33.4* (C**H**CH_2CH_2), 33.53, 34.0*, 34.4[#] (**C**H_2CHOH), 35.3[#] (C**H**CH_2CH_2), 35.5[#] (**C**H_2CH_2), 52.2, 52.3* (OCH_3), 65.5*, 67.8, 71.6[#] (CHOH), 84.1*, 84.7, 89.5[#] ($CHNO_2$), 121.7, 122.7*, 123.8[#] (CH=**C**), 150.1[#], 150.8*, 151.3 (**C**H=C), 164.9[#], 165.4*, 165.5 (C=O).

EM (EI) [m/z (%)]: 137 (8), 179 (53), 193 (100), 208 (16), 211 (15).

IR (Neat, cm^{-1}): 3476 (OH), 1715 (C=O), 1553 (NO_2).

Methyl 5-hydroxy-6-nitro-3-octylcyclohex-1-enecarboxylate (8e)



8e

Following the general procedure, the compound **8e** was prepared adding (*E*)-2-undecenal **3d** (101 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8e** (23 mg, 0.09 mmol) was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: <10%.

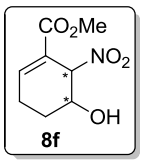
d.r.: 2:1 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer, ▲ indicates signals corresponding to the mixture of two diastereoisomers) 0.76-0.98▲ (m, 3H, $CH_2C\mathbf{H}_3$), 1.06-1.74▲ (m, 15H, $(CH_2)_7$ + OH), 1.88-2.09▲ (m, 1H, $C\mathbf{H}_AH_BCHOH$), 2.31-2.34▲ (m, 1H, $CH_A\mathbf{H}_BCHOH$), 2.48-2.64 (m, 1H, $C\mathbf{H}CH_2CH_2$), 3.77▲ (s, 3H, OCH_3), 4.37* (m, 1H, C**H**OH), 4.52-4.61 (m, 1H, C**H**OH), 5.04-4.18* (m, 1H, $CHNO_2$), 5.32 (d, 1H, *J* = 2.3 Hz, $CHNO_2$), 7.28-7.31* (m, 1H, CH=C), 7.39 (d, 1H, *J* = 3.1 Hz, CH=C).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): (*indicates minor diastereoisomer) 14.1 ($CH_2\mathbf{C}H_3$), 22.6 ($\mathbf{C}H_2CH_3$), 23.4* ($CH_2\mathbf{C}H_3$), 26.4*, 29.2, 29.4, 29.6, 29.7*, 29.9*, 29.9*, 30.8 ($\mathbf{C}H_2CH_2$), 32.0, 32.2*, ($\mathbf{C}HCH_2CH_2$), 32.2, 33.4*, 33.8, 34.3*, 36.6*, ($\mathbf{C}H_2CH_2$), 52.2, 52.3* (OCH_3), 65.6*, 67.8 (CHOH), 84.0*, 84.7 ($CHNO_2$), 121.8, 122.7* (**C**H=C), 150.7*, 151.2 (**C**H=C), 165.3*, 165.4 (C=O).

IR (Neat, cm^{-1}): 3453 (OH), 1716 (C=O), 1554 (NO_2).

Methyl 5-hydroxy-6-nitrocyclohex-1-enecarboxylate (8f)



8f

Following the general procedure, the compound **8f** was prepared adding acroleine **3h** (33 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the title compound **8f** was isolated by flash column chromatography (hexanes:EtOAc 8:2).

Yield: <10%.

d.r.: >20:<1 (Determined by ^{1}H-NMR analysis of the product after flash column chromatography purification).

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.62 (s, 1H, OH), 1.77-1.98 (m, 2H, C**H**$_2$CHOH), 2.37-2.53 (2H, m, C**H**$_2$CH$_2$CHOH), 3.76 (s, 3H, OCH_3), 4.37-4.51 (m, 1H, C**H**OH), 5.33 (d, 1H, $CHNO_2$), 7.43 (t, 1H, J = 4.0 Hz, CH=CCO_2CH_3).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 22.4 (**C**H_2CHOH), 25.8 (**C**H_2CH_2CHOH), 52.3 (OCH_3), 69.0 (CHOH), 86.1 ($CHNO_2$), 123.4 (**C**CO_2CH_3), 146.5 (**C**HCCO_2CH_3), 165.1 (C=O).

IR (Neat, cm^{-1}): 3468 (OH), 1713 (C=O), 1552 (NO_2).

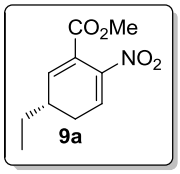
5.3. Sequential Michael/Henry/dehydration reaction. Synthesis of nitrocyclohexadienes 9a-e

General procedure

The α,β-unsaturated aldehyde **3a, d, i, j** was added to a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol trimethylsilyl ether **4b** (0.05 mmol), tri-*tert*-butylphosphine (0.05 mmol) and the acrylate **7a** (0.25 mmol) in chloroform (2 mL). The reaction was stirred at room temperature until full conversion was observed by t.l.c. The solvent was evaporated under vacuum and after dissolving the reaction crude in dry MeOH (2 mL) it was added *via canula* to a solution of metallic sodium (2 mmol) in MeOH (4 mL) at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred it for 1 hour. Then a solution of H_2SO_4:MeOH (1:5) was added until pH ≈ 5 was achieved and the solvent was evaporated under vacuum. H_2O (20 mL) and CH_2Cl_2 (20 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were dried on anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The crude was charged onto silica gel and subjected to flash column chromatography

to obtain the cyclohexadienes **9a-e**. Racemic samples were prepared using a racemic mixture of the catalyst **4d**.

(*S*)-Methyl 3-ethyl-6-nitrocyclohexa-1,5-dienecarboxylate (9a)



Following the general procedure, the compound **9a** was prepared adding (*E*)-2-pentenal **3i** (49 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the crude was added dropwise to a solution of NaOMe (0.11.00 g, 2.00 mmol) in MeOH (4 mL) at 0 ºC. After stirring it for 1 hour at room temperature a solution of H_2SO_4:MeOH (1:5) was carefully added until pH ≈ 5 was achieved. The title compound **9a** (16 mg, 0.07 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 38%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.99 (t, 3H, *J* = 7.4 Hz, $CH_2C\mathbf{H}_3$), 1.38-1.71 (m, 2H, $C\mathbf{H}_2CH_3$), 2.19-2.38 (m, 1H, $C\mathbf{H}_AH_B$), 2.39-2.63 (m, 2H, $CH_A\mathbf{H}_B$ + $C\mathbf{H}CH_2CH_3$), 3.75 (s, 3H, OCH_3), 6.84 (d, 1H, *J* = 3.3 Hz, $C\mathbf{H}$=CCO_2CH_3), 7.01 (t, 1H, *J* = 4.9 Hz, CH=CNO_2).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 11.4 ($CH_2\mathbf{C}H_3$), 25.8 ($\mathbf{C}H_2CH_3$), 28.0 ($CH\mathbf{C}H_2CH_3$), 35.2 ($\mathbf{C}HCH_2CH_3$), 52.3 (OCH_3), 125.3 ($\mathbf{C}CO_2CH_3$), 131.2 ($\mathbf{C}H$=CNO_2), 144.6 ($\mathbf{C}H$=CCO_2CH_3), 147.5 (CNO_2), 164.7 ($\mathbf{C}O_2CH_3$).

EM (EI) [m/z (%)]: 148 (3), 150 (3), 165 (4), 180 (100), 181 (9), 182 (3).

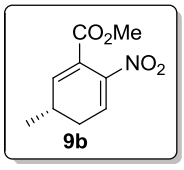
HRMS: Calculated for [$C_{10}H_{14}NO_4$]: 212.0923. Found: 212.0925.

IR (Neat, cm^{-1}): 3490 (OH), 1724 (CO), 1555 (NO_2).

$[\alpha]_D^{20}$: + 34.2 (c = 0.6, CH_2Cl_2).

e.e.: 87%, calculated by HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (*S*) : 13.33 min; t_R for the minor enantiomer (*R*) : 15.00 min.

(*S*)-Methyl 3-methyl-6-nitrocyclohexa-1,5-dienecarboxylate (9b)



Following the general procedure, the compound **9a** was prepared adding crotonaldehyde **3a** (42 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the crude was added drop wise to a solution of NaOMe (0.11.00 g, 2.00 mmol) in MeOH (4 mL) at 0 ºC. After stirring it for 1 hour at room temperature a solution of H_2SO_4:MeOH (1:5) was carefully added until pH ≈ 5 was achieved. The title compound **9b** (16 mg, 0.08 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 32%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 1.17 (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$), 2.11-2.34 (m, 1H, C**H**$_A$H$_B$), 2.42-2.60 (m, 1H, CH$_A$**H**$_B$), 2.60-2.81 (m, 1H, C**H**CH$_3$), 3.75 (s, 3H, OCH_3), 6.79 (d, 1H, *J* = 3.7 Hz, C**H**=CCO_2CH_3), 7.00 (t, 1H, CH=CNO_2).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 18.3 (CH**C**H$_3$), 28.6 (**C**HCH$_3$), 30.3 (CH_2), 52.3 (OCH_3), 125.0 (**C**CO_2CH_3), 131.1 (**C**H=CNO_2), 145.9 (**C**H=CCO_2CH_3), 147.3 (CNO_2), 164.7 (**C**O_2CH_3).

EM (EI) [m/z (%)]: 166 (100), 134 (3), 167 (9), 226 (4).

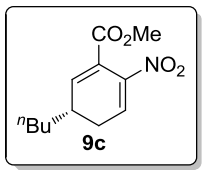
HRMS: Calculated for [$C_9H_{12}NO_4$]: 198.0770. Found: 198.0766.

IR (Neat, cm^{-1}): 1725 (C=O), 1523 (NO_2).

$[\alpha]_D^{20}$: - 47.6 (c = 0.7, CH_2Cl_2).

e.e.: 85%, calculated by HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH 90:10, 1.00 mL/min). t_R for the major enantiomer (*S*) : 13.81 min; t_R for the minor enantiomer (*R*): 15.17 min.

(*S*)-Methyl 3-butyl-6-nitrocyclohexa-1,5-dienecarboxylate (9c)



Following the general procedure, the compound **9a** was prepared adding (*E*)-2-heptenal **3j** (67 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the crude was added drop wise to a solution of NaOMe (0.11.00 g, 2.00 mmol) in MeOH (4 mL) at 0 ºC. After stirring it for 1 hour at room temperature a solution of H_2SO_4:MeOH (1:5) was carefully added until pH ≈ 5 was achieved. The title compound **9c** (15 mg, 0.06 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 33%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.76-0.97 (m, 3H, $CH_2C\mathbf{H}_3$), 1.1-1.79 (m, 6H, CH_2 × 3), 2.13-2.42 (m, 1H, C**H**$(CH_2)_3$), 2.44-2.63 (m, 2H, C**H**$_2$CH=$CHNO_2$), 3.76 (s, 3H, OCH_3), 6.85 (d, 1H, *J* = 3.5 Hz, C**H**=CCO_2CH_3), 7.01 (t, 1H, $CHNO_2$).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 13.9 ($CH_2\mathbf{C}H_3$), 22.6, 28.4, 29.0 (CH_2), 32.5 ($\mathbf{C}H_2CH{=}CHNO_2$), 33.6 ($\mathbf{C}H(CH_2)_3$), 52.3 (OCH_3), 125.2 ($\mathbf{C}CO_2CH_3$), 131.2 ($\mathbf{C}H{=}CNO_2$), 145.0 ($\mathbf{C}H{=}CCO_2CH_3$), 147.5 ($CHNO_2$), 164.7 ($\mathbf{C}OOCH_3$).

EM (EI) [m/z (%)]: 193 (8), 208 (100), 209 (14), 210 (5), 268 (10).

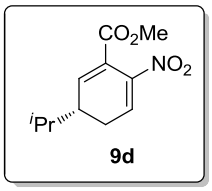
HRMS: Calculated for [$C_{12}H_{18}NO_4$]: 240.1236. Found: 240.1245.

IR (Neat, cm^{-1}): 1727 (CO), 1526 (NO_2).

$[\alpha]_D^{20}$: + 80.6 (c = 0.5, CH_2Cl_2).

e.e.: 92%, calculated by HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH 95:5, 1.00 mL/min). t_R for the major enantiomer (*S*): 15.12 min; t_R for the minor enantiomer (*R*): 16.44 min.

(*S*)-Methyl 3-isopropyl-6-nitrocyclohexa-1,5-dienecarboxylate (9d)



9d

Following the general procedure, the compound **9d** was prepared adding (*E*)-4-methyl-2-pentenal **3d** (59 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7a** (37 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the crude was added drop wise to a solution of NaOMe (0.11.00 g, 2.00 mmol) in MeOH (4 mL) at 0 ºC. After stirring it for 1 hour at room temperature a solution of H_2SO_4:MeOH (1:5) was carefully added until pH ≈ 5 was achieved. The title compound **9d** (7 mg, 0.03 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 17%.

^{1}H-NMR (300 MHz, $CDCl_3$, 25 ºC): 0.97 (d, 6H, *J* = 6.8 H, $(CH_3)_2$), 1.77-1.91 (m, 1H, C**H**$(CH_3)_2$), 2.26-2.54 (m, 3H, CH_2 + C**H**$CH(CH_3)_2$), 3.76 (s, 3H, OCH_3), 6.87 (d, 1H, *J* = 2.5 Hz, C**H**=CCO_2CH_3), 7.03 (t, 1H, *J* = 3.7 Hz, CH=CNO_2).

^{13}C-NMR (75 MHz, $CDCl_3$, 25 ºC): 19.8 (CH**C**H_3), 19.9 (CH**C**H_3), 25.5 (CH_2), 30.4 (**C**$H(CH_3)_2$), 40.19 (**C**$HCH(CH_3)_2$), 52.3 (OCH_3), 125.8 (**C**CO_2CH_3), 131.7 (**C**H=CNO_2), 143.7(**C**H=CCO_2CH_3), 147.5 (CNO_2), 164.7(**C**O_2CH_3).

EM (EI) [m/z (%)]: 162 (4), 194 (100), 195 (12), 254 (4).

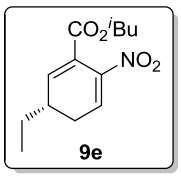
HRMS: Calculated for [$C_{11}H_{16}NO_4$]: 226.1079. Found: 226.1082.

IR (Neat, cm^{-1}): 1725 (CO), 1525 (NO_2).

$[\alpha]_D^{20}$: - 8.0 (c = 0,8, CH_2Cl_2).

e.e.: 93%, calculated by HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH 98:2, 1.00 mL/min). t_R for the major enantiomer (*S*): 27.68 min; t_R for the minor enantiomer (*R*): 30.21 min.

(*R*)-Isobutyl 3-ethyl-6-nitrocyclohexa-1,5-dienecarboxylate (9e)



Following the general procedure, the compound **9e** was prepared adding (*E*)-2-pentenal **3i** (49 μL, 0.50 mmol) to a solution of catalyst **4b** (16 mg, 0.05 mmol), tri-*tert*-butylphosphine (10 mg, 0.05 mmol) and the acrylate **7b** (46 mg, 0.25 mmol) in chloroform (2 mL). After stirring the mixture for 3 days the crude was added drop wise to a solution of NaOMe (0.11.00 g, 2.00 mmol) in MeOH (4 mL) at 0 ºC. After stirring it for 1 hour at room temperature a solution of H_2SO_4:MeOH (1:5)

was carefully added until pH ≈ 5 was achieved. The title compound **9e** (6 mg, 0.02 mmol) was isolated by flash column chromatography (hexanes:EtOAc 9:1).

Yield: 12%.

EM (EI) [m/z (%)]: 99 (42), 123 (10), 151 (18), 159 (20), 183 (40), 201 (24), 257 (100), 258 (12).

HRMS: Calculated for [$C_{13}H_{20}NO_4$]: 245.1392. Found: 245.1402.

IR (Neat, cm^{-1}): 1726 (CO), 1529 (NO_2).

$[\alpha]_D^{20}$: - 57.6 (c = 0.3, CH_2Cl_2).

e.e.: 88%, calculated by HPLC (Chiralpak OZ-3 column, *n*-hexane:^{i}PrOH in gradient; 1.00 mL/min, linear curve: min 0, 100:0; min 35, 95:5; min 45, 85:15). t_R for the minor enantiomer (*R*): 22.59 min; t_R for the major enantiomer (*S*): 23.64 min.

4

4

Conclusions

Along this work it has been proved that organocatalysis is an excellent and efficient tool to activate α,β-unsaturated aldehydes in diverse transformations that take place under ion iminium ion activation. In particular some concrete conclusion can be drawn:

- Secondary amines are able to catalyze enantioselective (3+2) cycloaddition between stable azomethine ylides and α,β-unsaturated aldehydes. In particular imidazolidinone derivatives have shown to exert a great enantiocontrol *via* the reversible formation of an iminium ion as a result of the union of the catalyst and the enal.

- A catalytic amount of (2*S*,5*S*)-(-)-2-*tert*-butyl-3-methyl-5-benzyl-4-imidazolidinone works well for differently substituted α,β-unsaturated aldehydes and isoquinolinium and phthalazinium derivative ylides, obtaining good results with both aromatic and aliphatic enals.

- The experimental results have been supported by computational data, postulating that the 1,3-dipolar reaction follows a stepwise pathway, in which the first step is a Michael addition of the dipole to the dipolarophile previously activated *via* iminium ion and the resulting enamine intermediate undergoes an intramolecular diastereoselective Mannich cyclization.

- Secondary amines have also been employed as catalysts in a Michael/Henry cascade reaction between 2-nitromethylacrylates and α,β-unsaturated aldehydes, *via* iminium ion activation. The selected Michael donor, 2-nitromethylacrylate has proved to be a suitable starting material for the reaction, acting as an appropriate nucleophile. The protons present in the acrylate are acidic enough to suffer the deprotonation, necessary for the nucleophilic attack.

Moreover, it has been observed that the reaction takes place by the γ position of the 2-nitromethylacrylate and exerting stereochemical control by *O*-trimethylsilyl α,α-diphenylprolinol catalyst, giving access to the formation of tetrasubtitued 6-nitrocyclohexenes, with acceptable yields, but poor diastereoselectivity.

- The proposed mechanism starts with the Michael addition of the deprotonated 2-nitromethylacrylate to the iminium ion resulting from the condensation between the aminocatalyst and the α,β-unsaturated aldehyde. After the releasing of the catalyst an intramolecular Henry reaction takes place, stereochemically controlled by the asymmetric centre created in the previous step. Regarding the results, the high enantiomeric excess support the idea that the prolinol derivative is exerting the desired enantiocontrol, but that the intermediate resulting from the conjugate addition is not able to control the diastereoselectivity of the subsequent Henry reaction.

- Due to the reaction pathway, our proposal to bypass the diastereoselection problem was the optimization a methodology that involved a Michael/Henry cascade reaction followed by a sequential dehydration leading to the enantiopure cyclohexadienes.

- After the screening of the reaction, the best conditions have been set and the methodology has been extended to different acrylates and α,β-unsaturated aldehydes synthesizing highly functionalized trisubtituted cyclohexadienes with very good enantioselectivity.

Anexo

Anexo

- **Técnicas experimentales**
- **Espectros de RMN**
- **Cromatogramas de HPLC**

- **Técnicas experimentales**

RMN: Los espectros de resonancia magnética nuclear de protón y carbono (RMN-^{1}H y RMN-^{13}C) monodimensionales y/o bidimensionales se realizaron a 25 °C en un espectrómetro Bruker AC-300 (300 MHz para ^{1}H y 75.5 MHz para ^{13}C) o en un espectrómetro Bruker AC-500 (500 MHz para ^{1}H y 125.7 MHz para ^{13}C) utilizando cloroformo deuterado como disolvente y patrón interno: $CDCl_3$, δ = 7.26 (^{1}H) y 77.0 ppm (^{13}C). Los desplazamientos químicos están dados en δ (ppm) y las constantes de acoplamiento (*J*) en hercios (Hz). Los espectros de RMN-^{13}C se realizaron con desacoplamiento total de protón, empleando experimentos DEPT para la asignación de los distintos tipos de carbono. Asimismo, se realizaron espectros, COSY y HSQC para la asignación de las señales en los casos en los que se consideró necesario, así como espectros NOESY en los casos en los que se buscaba la determinación de la configuración relativa.

EM: Los espectros de masas se registraron utilizando condiciones de impacto electrónico (IE) o ionización química (IQ). Los análisis GC-MS se realizaron con un cromatógrafo Agilent 7890A acoplado a un espectrómetro de masas Agilent 5975 usando una columna TRB-1 (100% metil polisiloxano, 30 m × 0.25 mm × 0.25 μm). Los espectros de masas de alta resolución (EMAR) fueron realizados por los Servicios Generales de Espectroscopía de Masas de la Universidad del País Vasco con un cromatógrafo de gases (Agilent 6890N) acoplado a un espectrómetro de masas con un analizador de tiempo de vuelo (TOF) (modelo GTC de micromass) en condiciones de impacto electrónico (IE) a 70 eV o ionización química (IQ) a 230eV (metano como gas reactivo, modo positivo). Los datos obtenidos están expresados en unidades de masa (*m/z*) y los valores entre paréntesis corresponden a las intensidades relativas respecto del pico base (100%).

IR: Los espectros de infrarrojo se realizaron en un espectrómetro Perkin Elmer 1600 Series FTIR, Perkin Elmer Spectrum BX FTIR y JASCO FTIR-4100 aparatus, en el intervalo de 4000 a 400 cm^{-1} con una resolución de 4 cm^{-1}, por deposición de una disolución saturada en CH_2Cl_2 del analito seguido de evaporación del disolvente (film) para los aceites o directamnete ne ATR. En cada caso únicamente se citan las bandas de absorción más características dadas en unidades de cm^{-1}.

Polarimetría: Los valores de rotación óptica se midieron en un polarímetro Perkin-Elmer 241 y Jasco P-2000 a 20 ^oC con una lámpara de sodio a 589 nm, en una celda de 1 dm y con la muestra en el disolvente y a la concentración que se indica en cada caso.

P.f.: Los puntos de fusión se midieron en un aparato Büchi Melting Point 540 en tubos capilares abiertos y se encuentran sin corregir.

HPLC: La cromatografía líquida de alta resolución en fase quiral se llevó a cabo empleando un cromatógrafo Waters 600A con detector de fotodiodos (Waters 996) y un cromatógrafo Waters 2695 con detector de fotodiodos (Waters 2998), utilizando columnas Chiralcel OD y OZ-3 y Chiralpak AD-H, AS-H e IA de 0.46 cm × 25 cm, en las condiciones indicadas en cada caso.

Rayos X: Los rayos X fueron realizados por el Servicio General de Rayos X (Unidad de Moléculas y Materiales) de la Universidad del País Vasco con un difractómetro STOE IPDS 2T equipado con un detector de tipo *image plate*, a una temperatura de 100 K usando un Cryostream 600 de Oxford Cryosystems alimentado con nitrógeno líquido para la determinación de la configuración relativa y un difractómetro Oxford Diffraction Xcalibur 2, equipado con detector de tipo CCD modelo Sapphire 2, a una temperatura de 100 K, usando un

Cryostream 700 de Oxford Cryosystems alimentado con nitrógeno líquido para la determinación de la configuración absoluta.

Varios: Las reacciones se monitorizaron por cromatografía en capa fina con cromatofolios de silicagel Merck 60 F_{254}, utilizando como revelador luz UV (λ= 254 nm y 360 nm) o reactivos como ácido fosfomolíbdico y/o *p*-anisaldehído.[1] Para las separaciones cromatográficas en columna se utilizó silicagel Merck 60.[2]

En aquellos casos en los que se trabajó bajo atmósfera inerte, el argón utilizado se secó previamente haciéndolo pasar a través de una precolumna de P_2O_5 y una columna de KOH y $CaCl_2$, los disolventes empleados se purificaron y secaron previamente a su utilización siguiendo los procedimientos descritos en la bibliografía.[3] Además, todo el material de vidrio necesario fue secado, antes de ser utilizado, en un horno a 140 °C durante 12 horas, y enfriado en atmósfera deshumificada. Las transferencias de disolventes o disoluciones se hicieron mediante jeringa o vía cánula.

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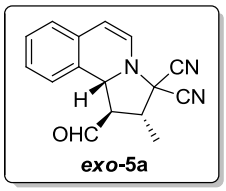
[1] Stahl, E. *Thin Layer Chromatography*, Springer-Verlag, Berlín, 1969.

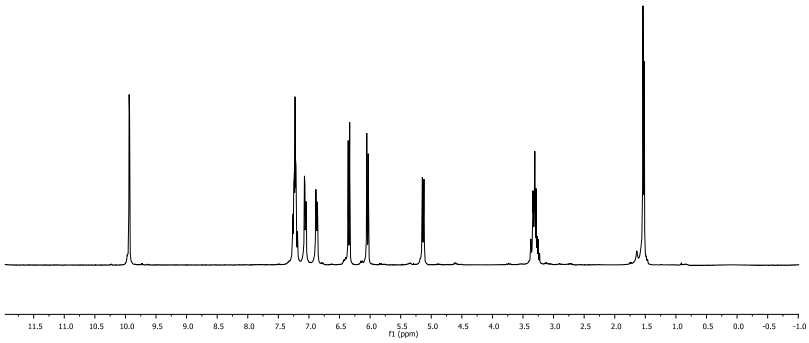
[2] Still, W. C.; Kann, H.; Mitra, A. J. *J. Org. Chem*. **1978**, *43*, 2923.

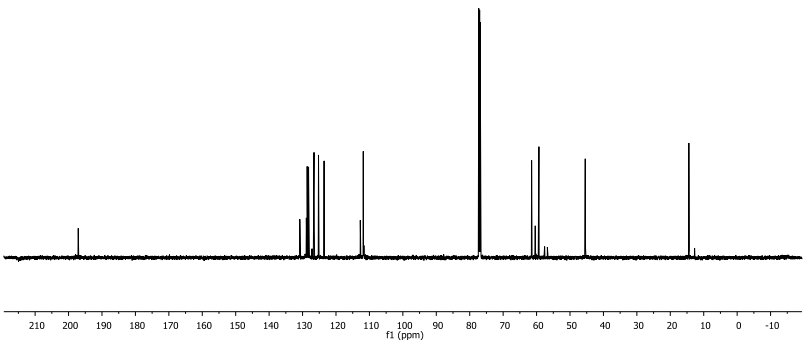
[3] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 1997.

- **Espectros de RMN**

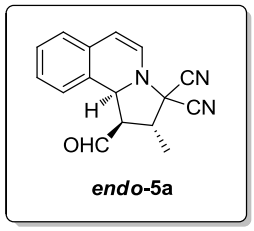
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5a**.



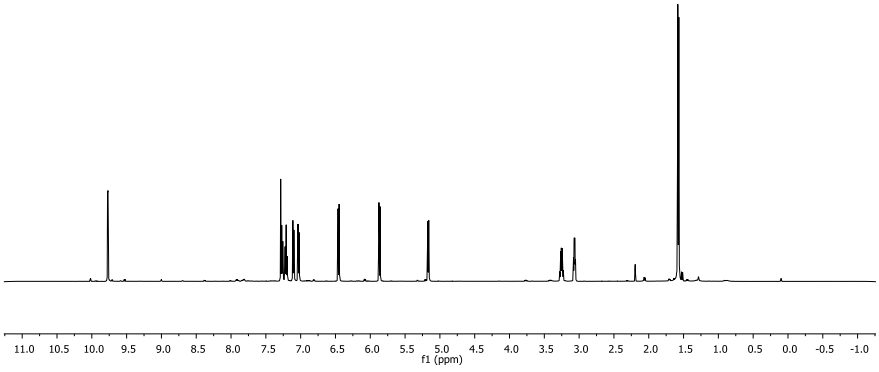


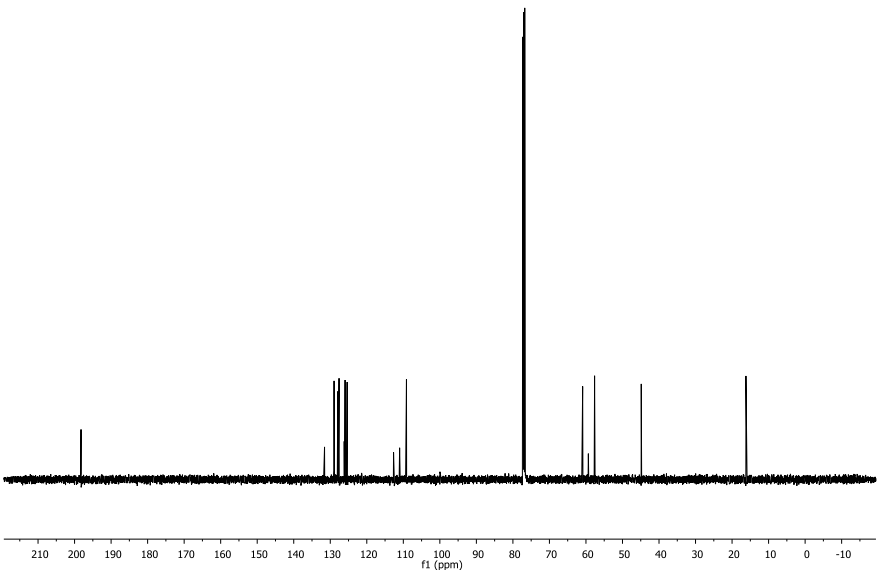


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***endo*-5a**.

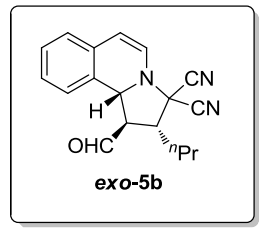


***endo*-5a**

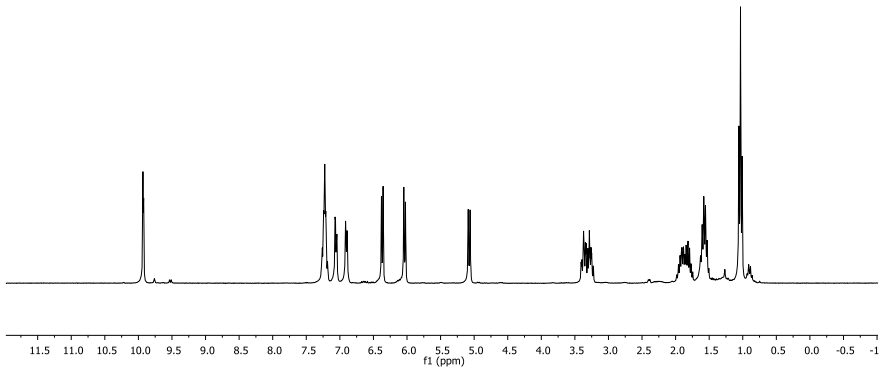


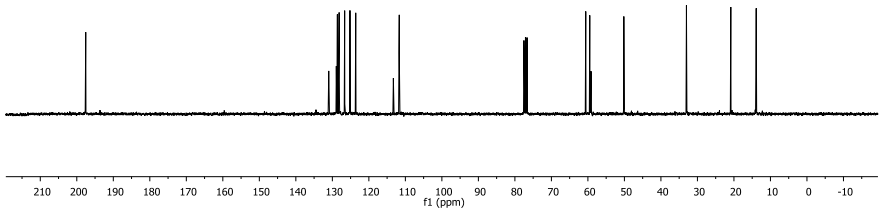


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5b**.



***exo*-5b**





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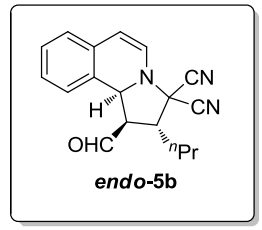
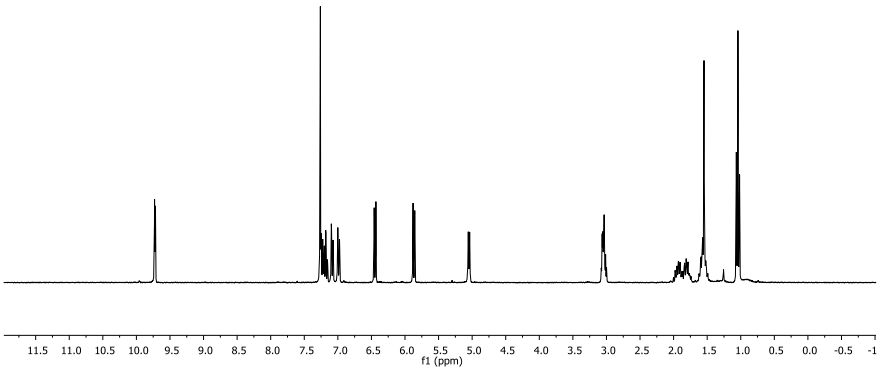
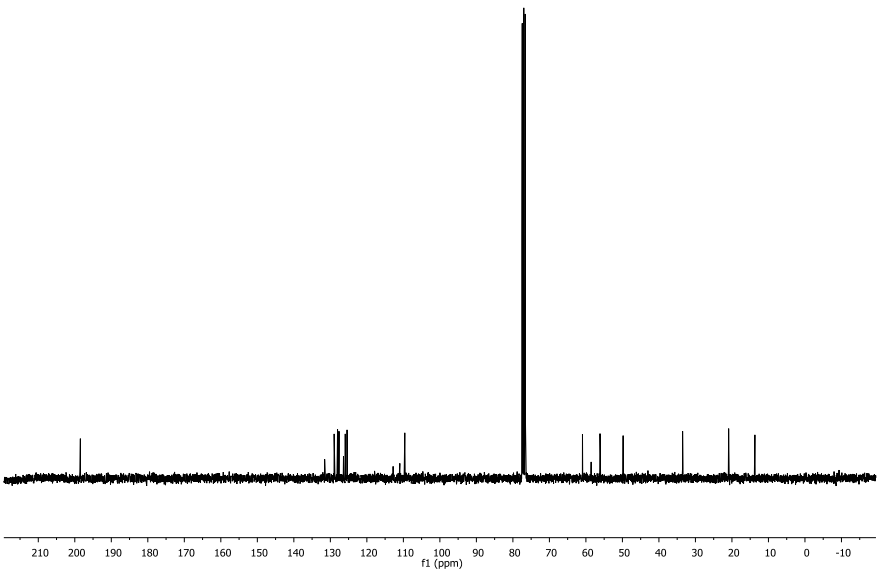


***endo*-5b**





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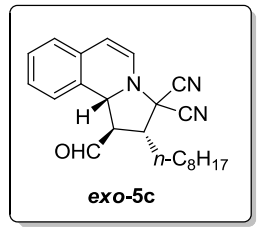
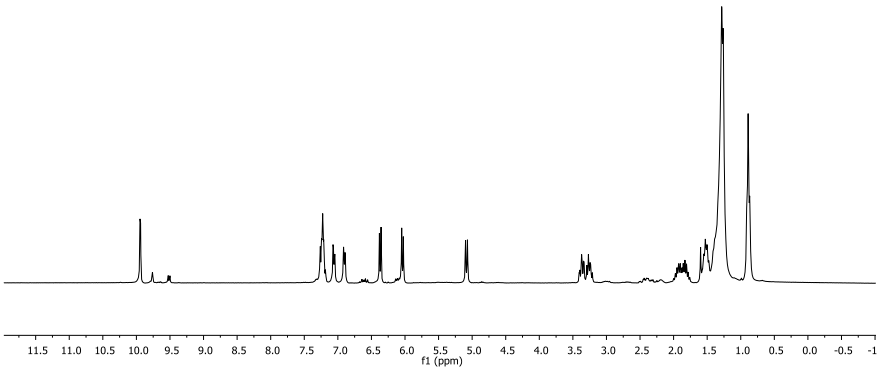
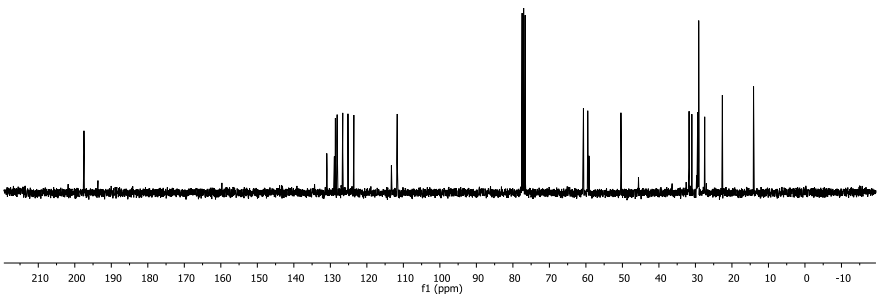


***exo*-5c**





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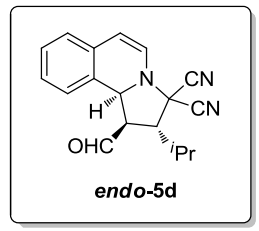
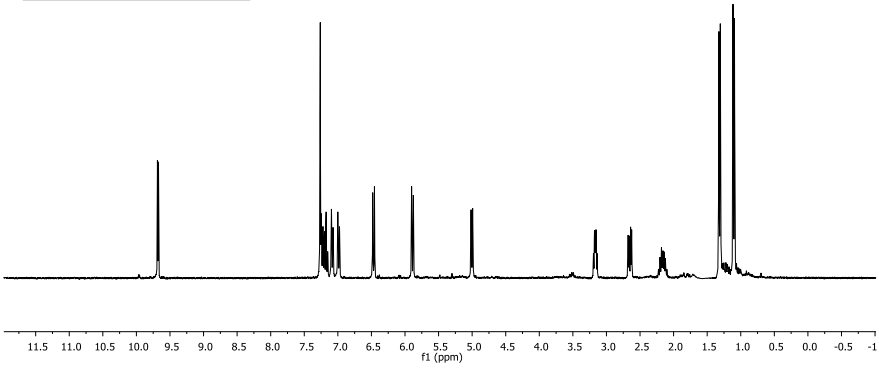
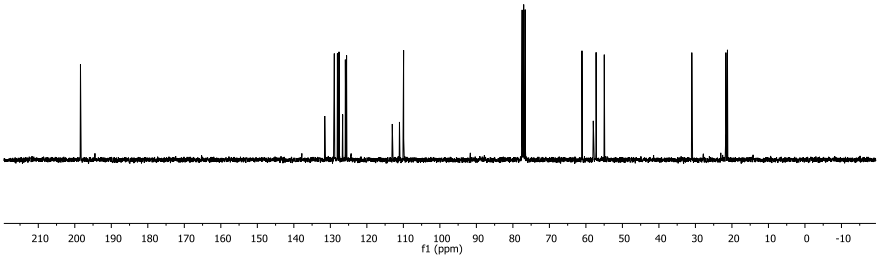


***endo*-5d**





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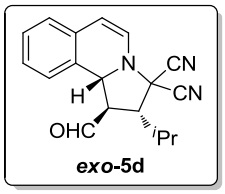
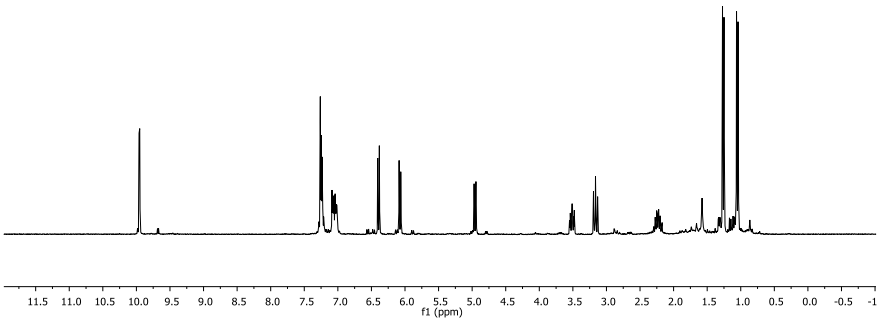
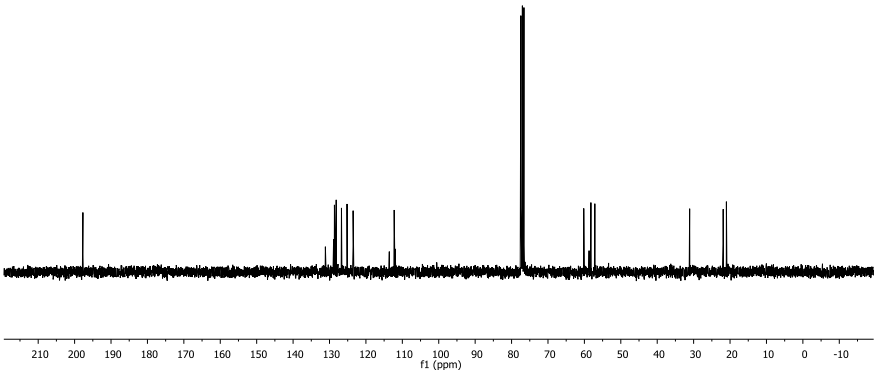


***exo*-5d**





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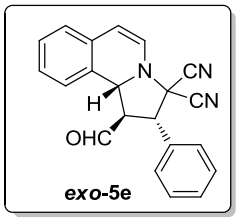
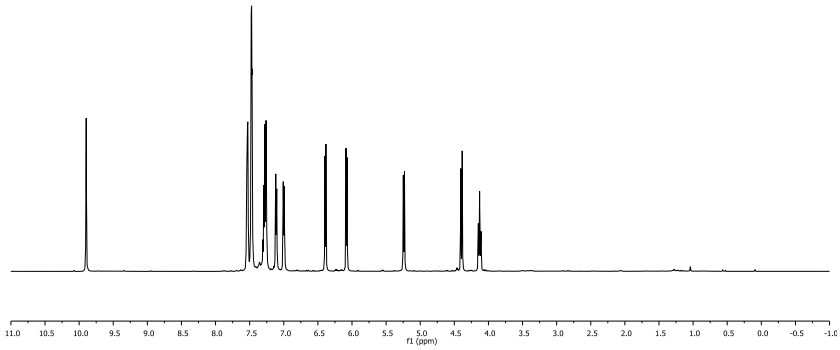
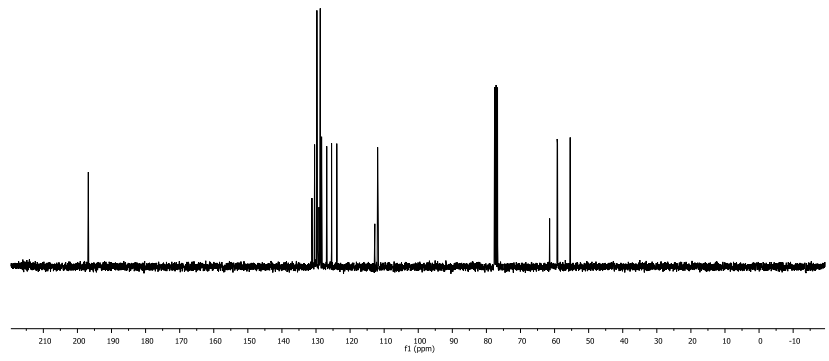
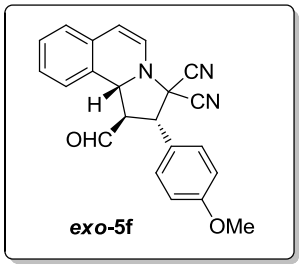


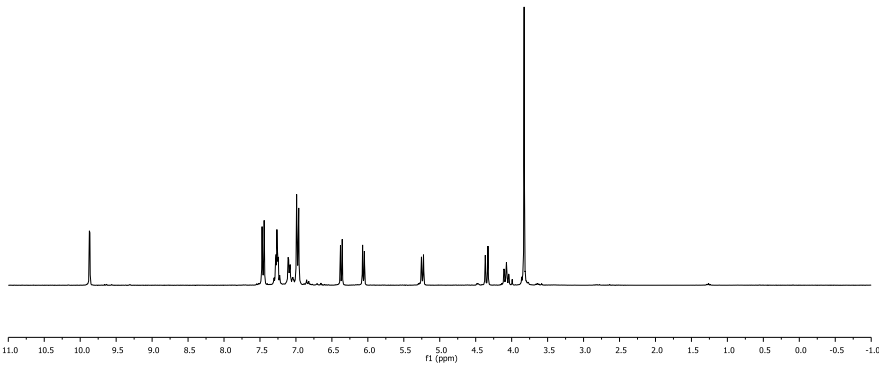


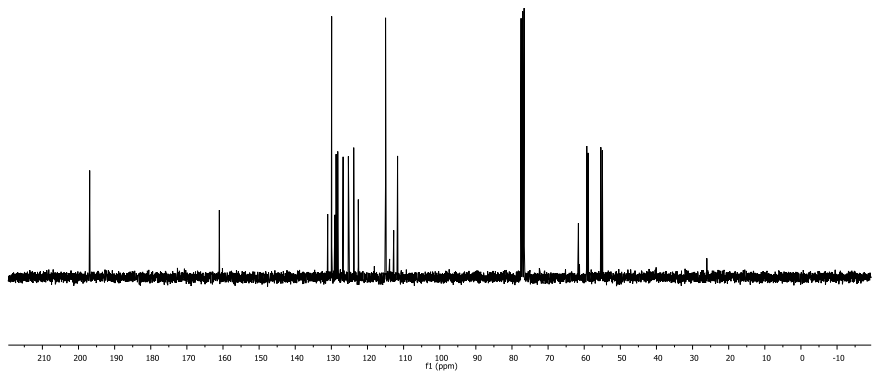


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5f**.



***exo*-5f**





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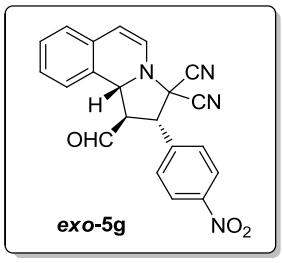
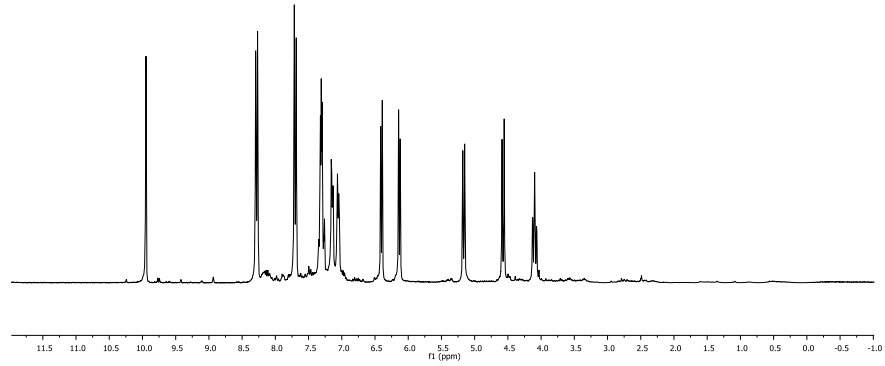
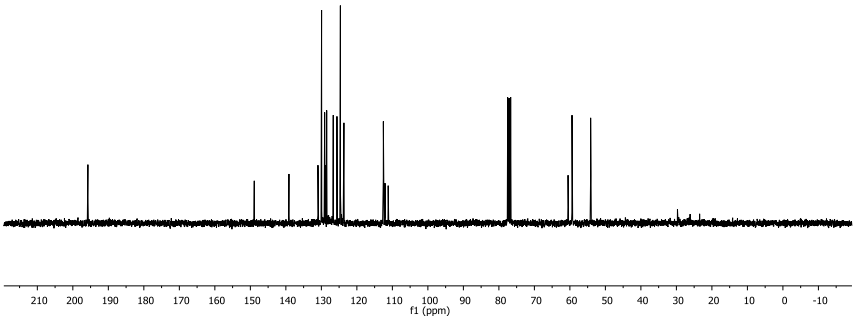
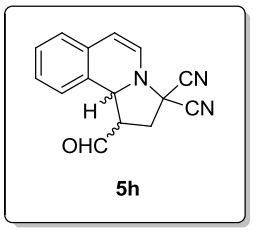


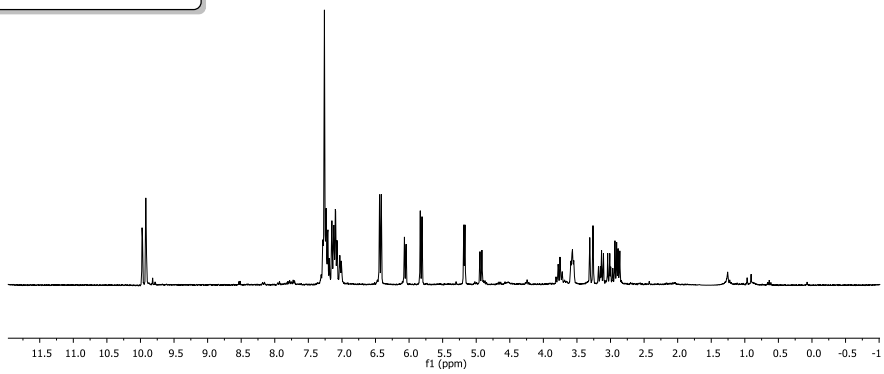


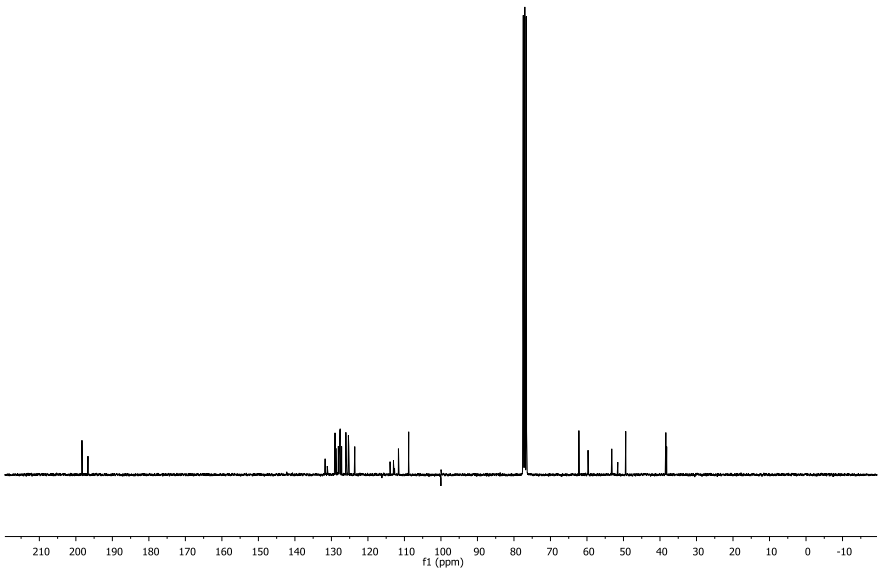


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **5h**.

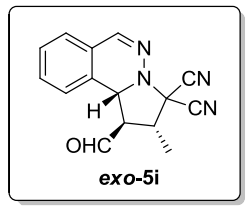


5h

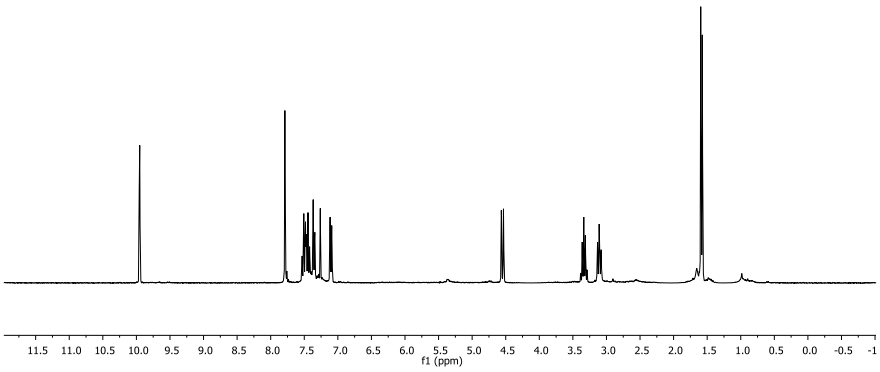


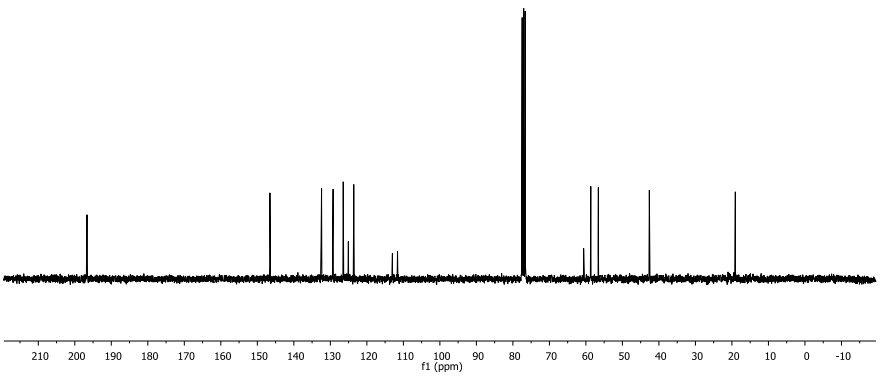


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5i**.

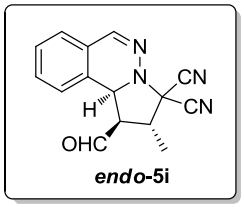


***exo*-5i**

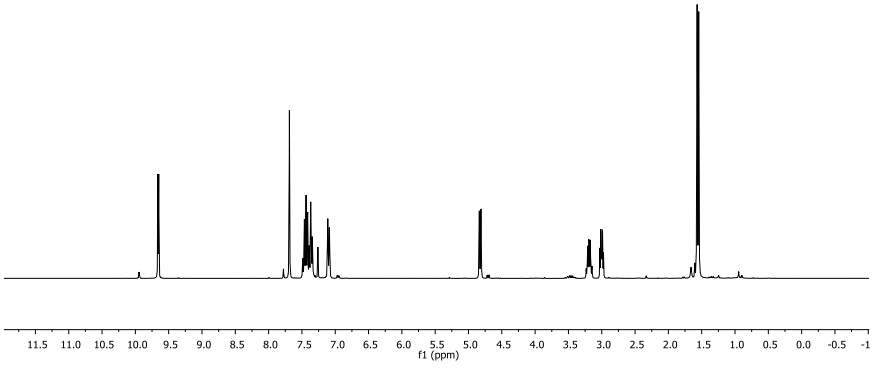


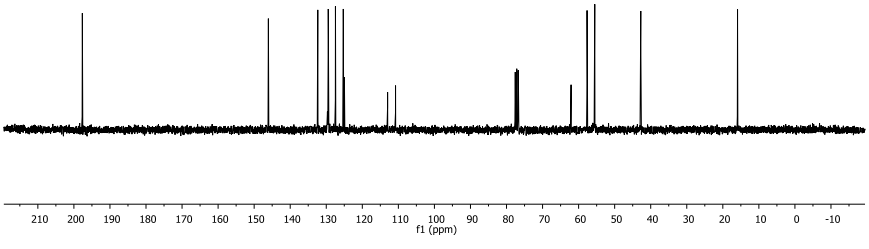


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***endo*-5i**.

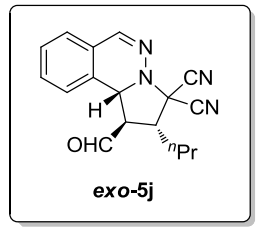


***endo*-5i**

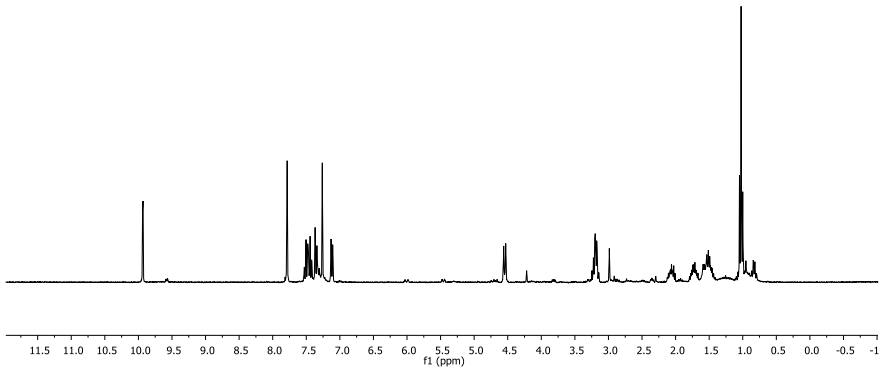


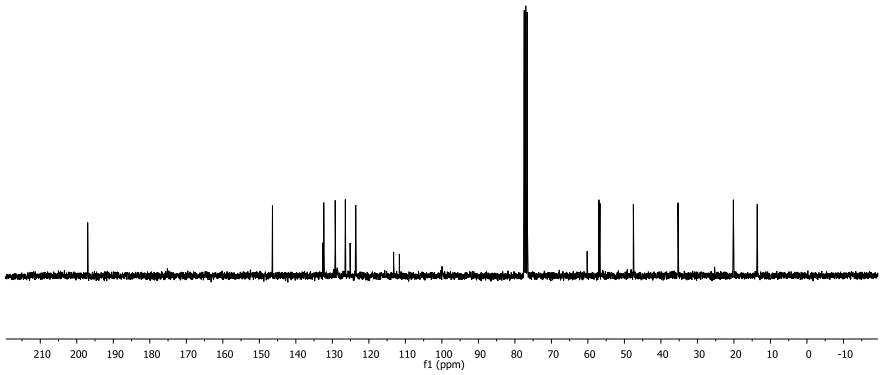


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5j**.

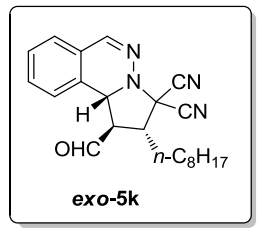


***exo*-5j**

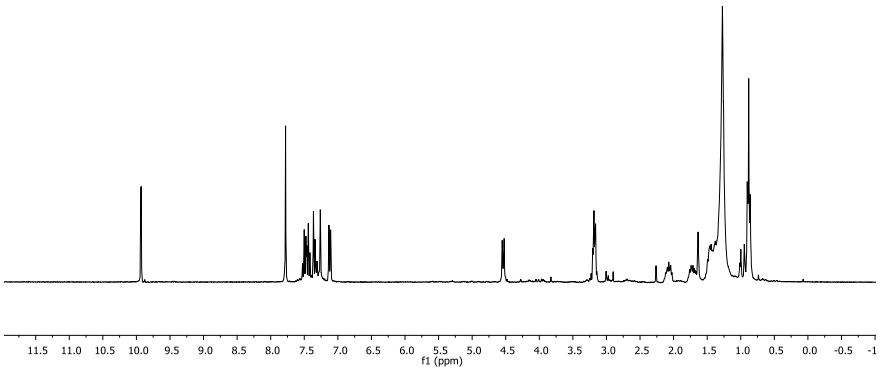


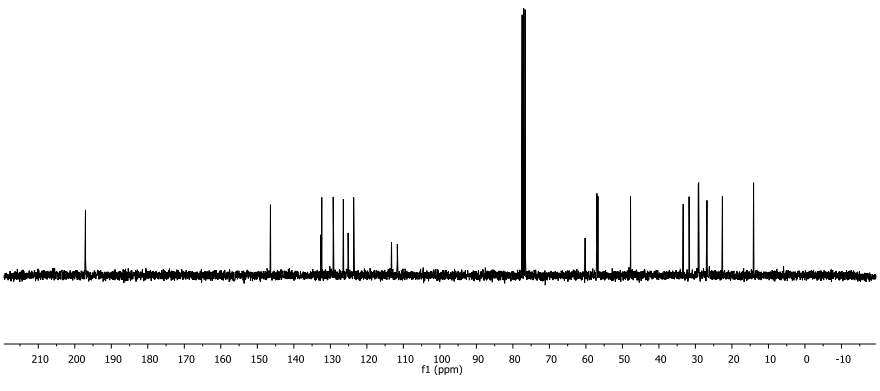


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5k**.

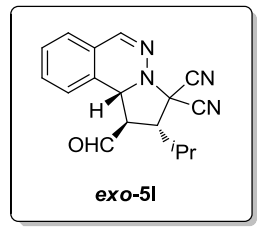


***exo*-5k**

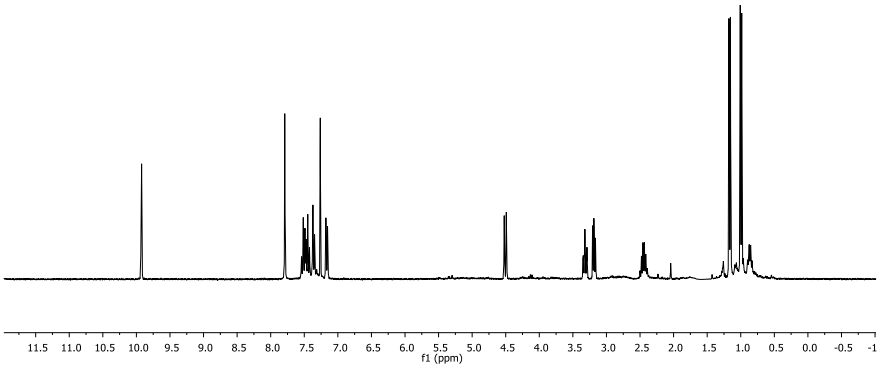


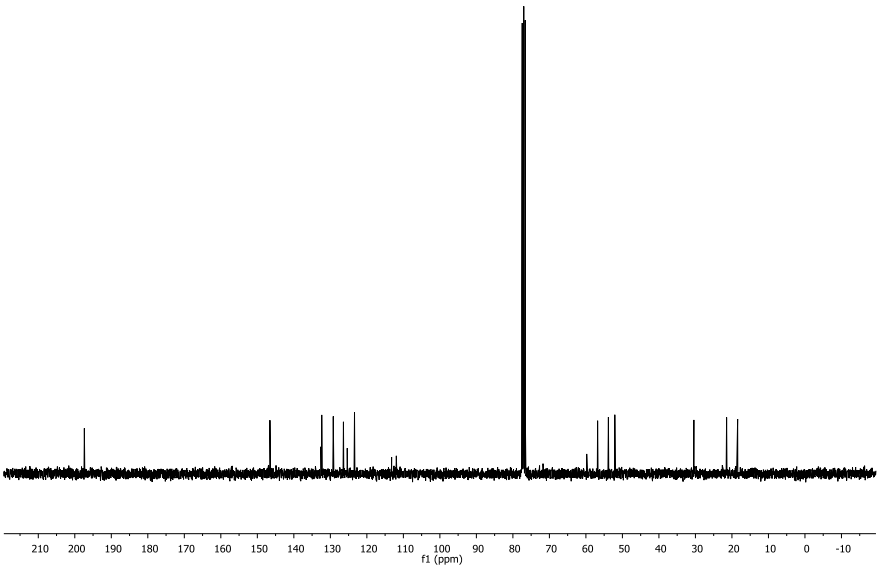


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5l**.

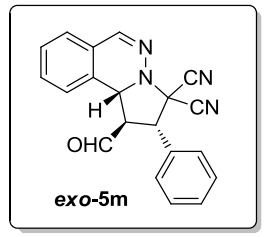


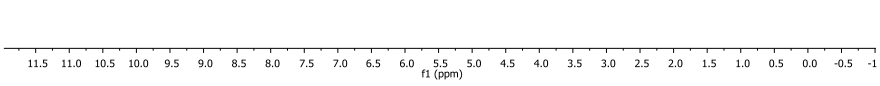
***exo*-5l**



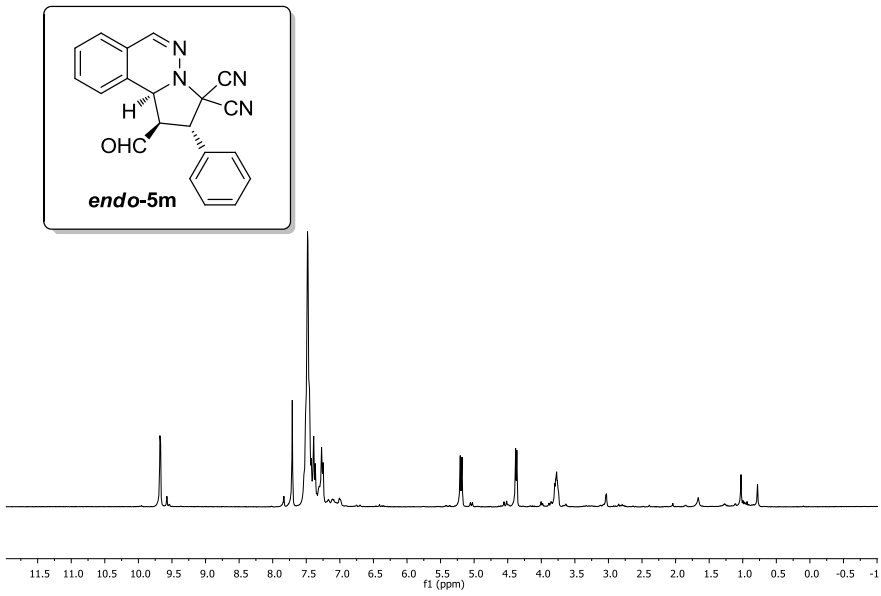


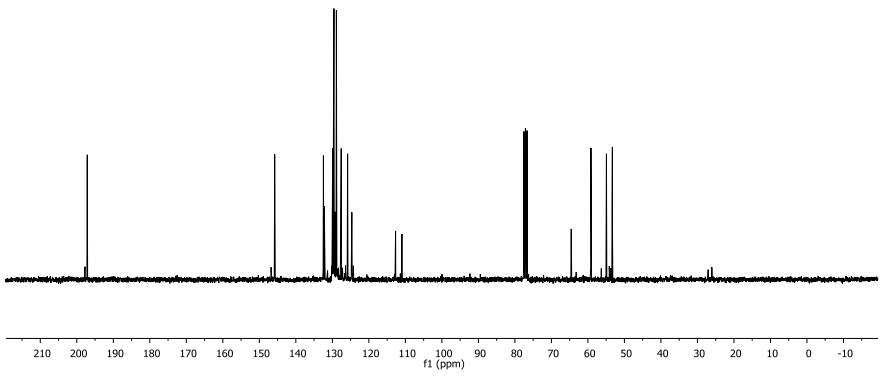
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5m**.



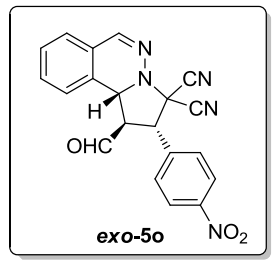


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***endo*-5m**.

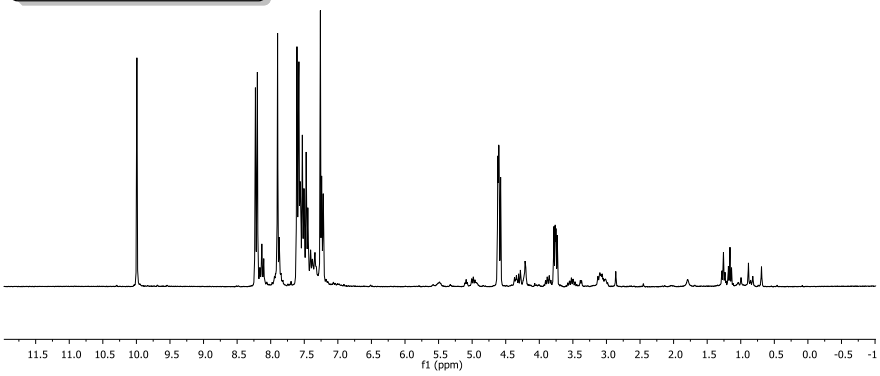


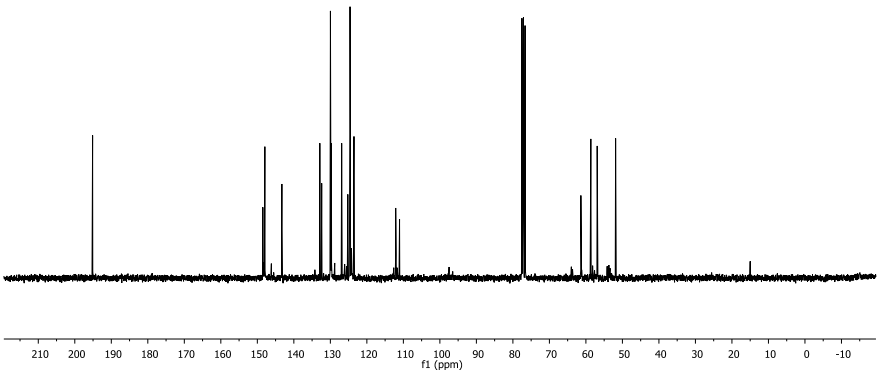


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-5o**.

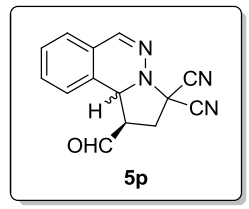


***exo*-5o**

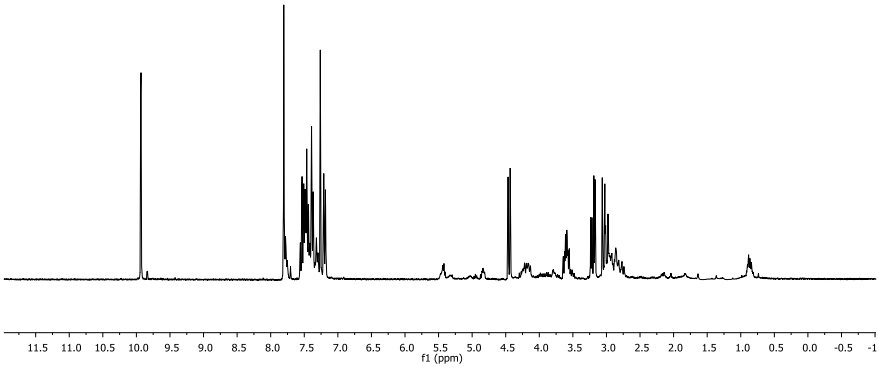


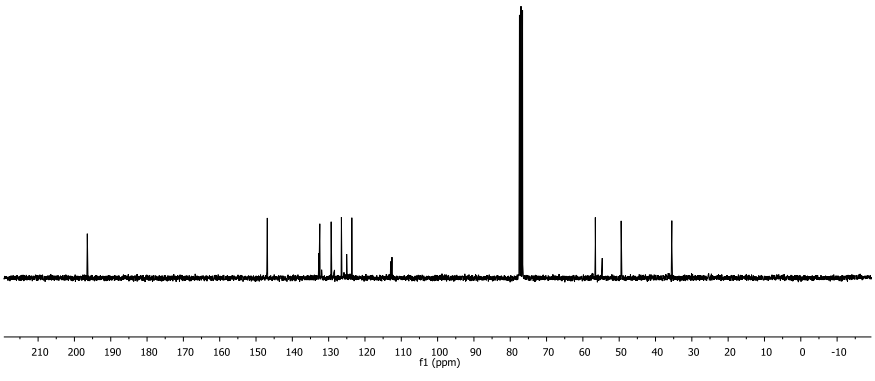


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **5p**.

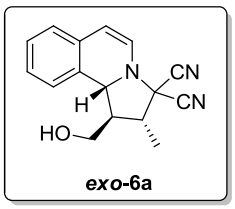


5p

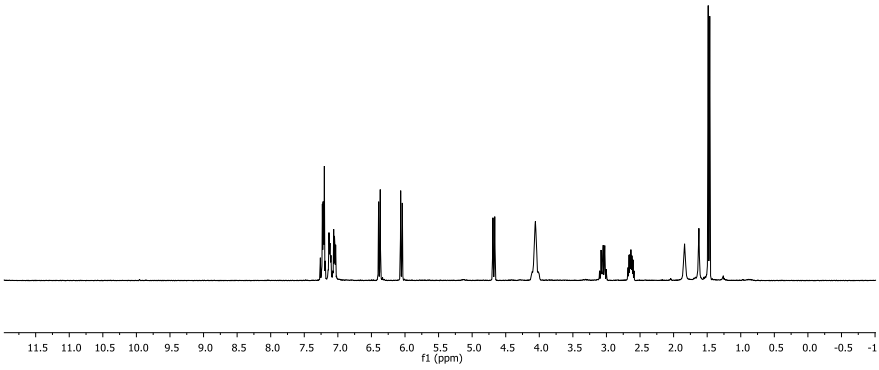


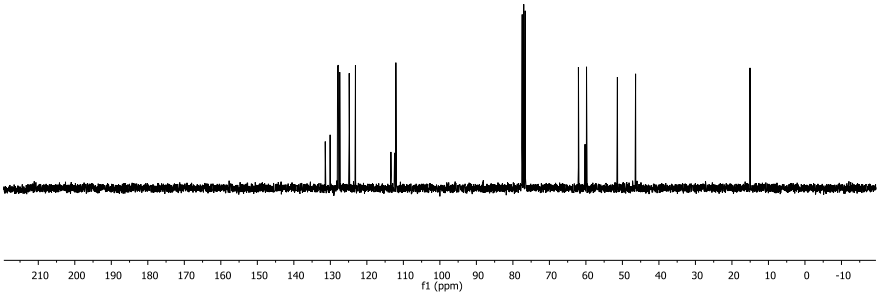


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6a**.

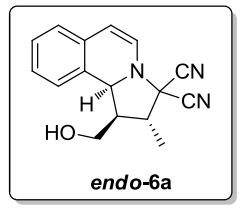


***exo*-6a**

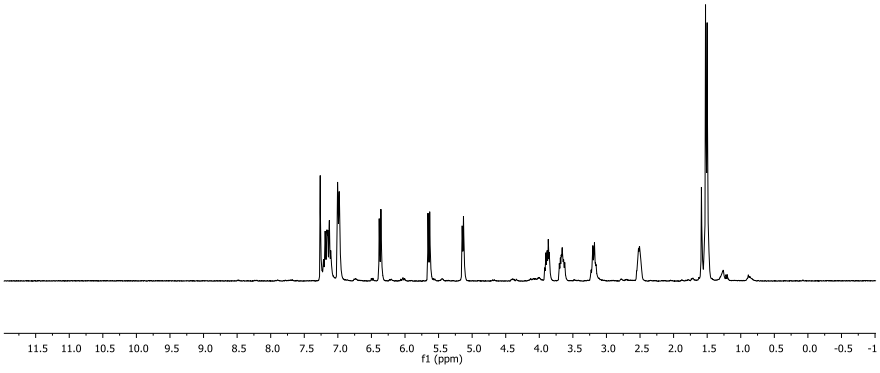


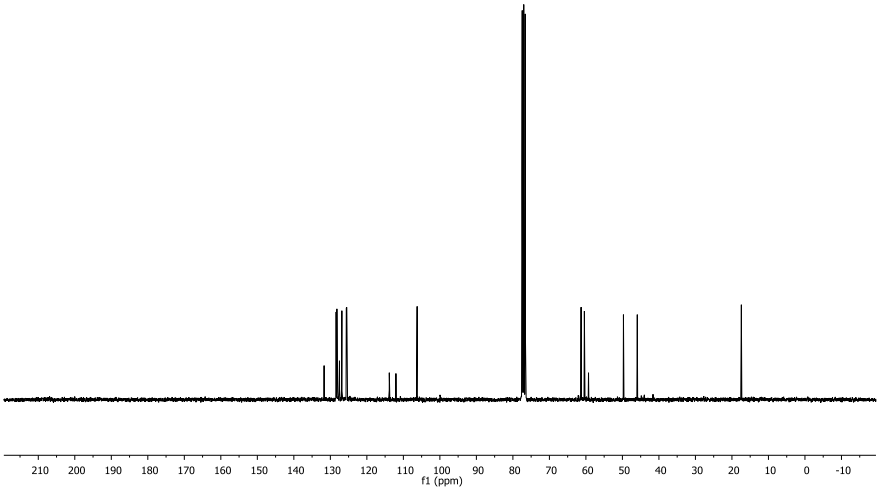


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***endo*-6a**.

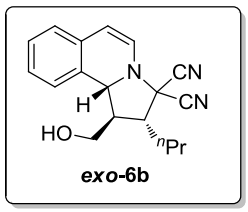


***endo*-6a**

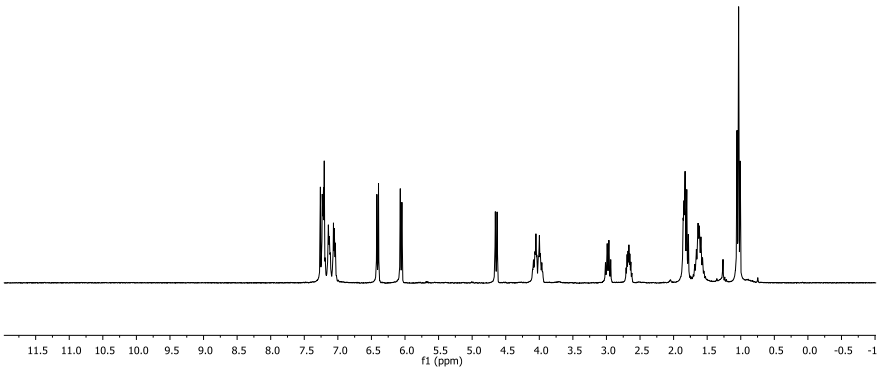


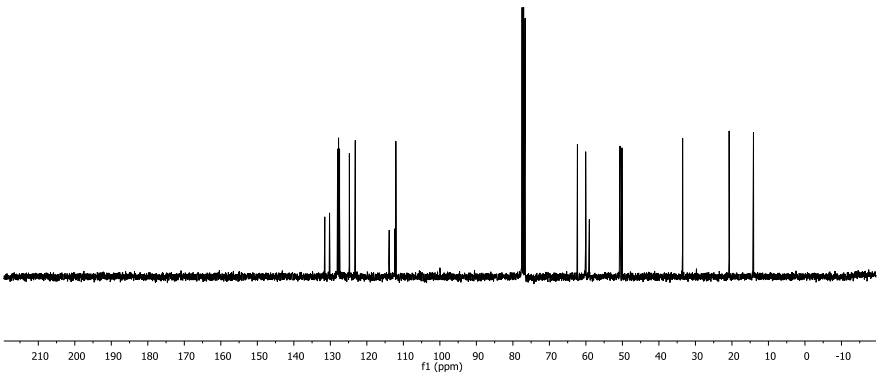


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6b**.

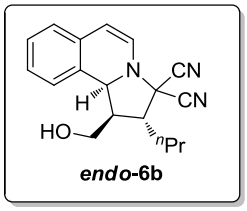


***exo*-6b**

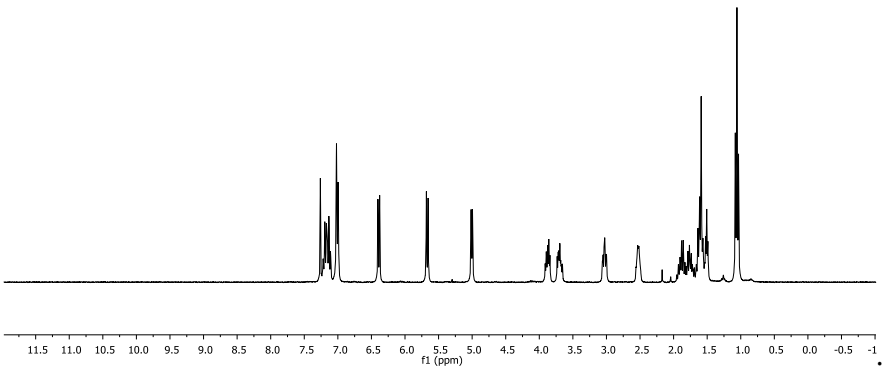


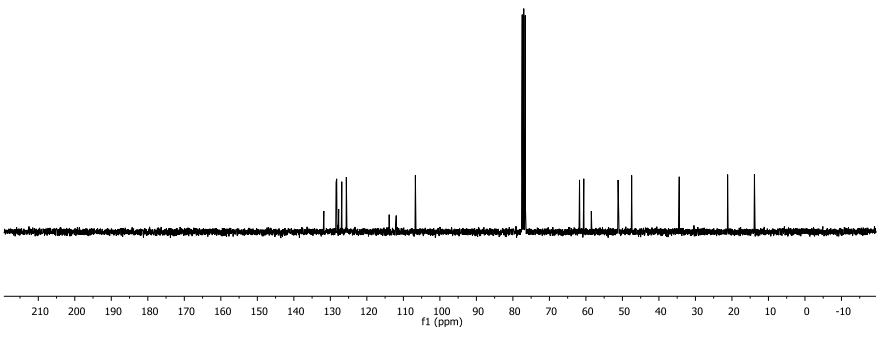


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***endo*-6b**.

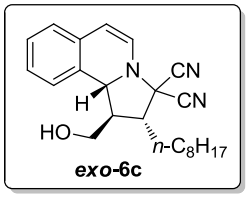


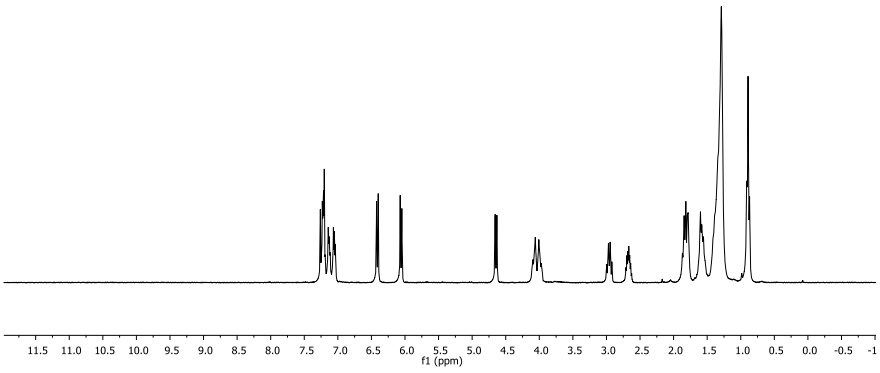
***endo*-6b**

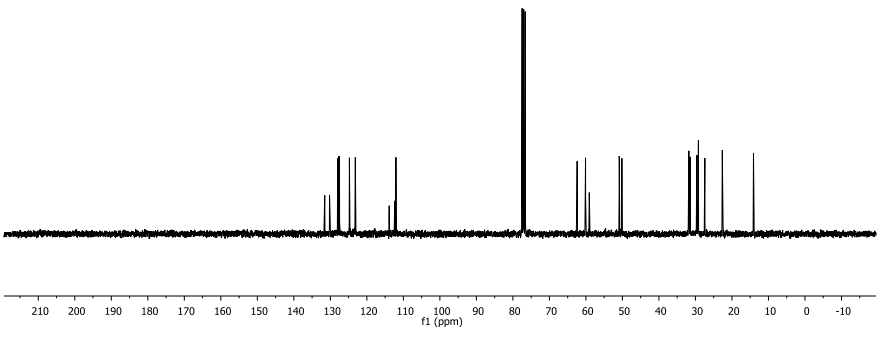




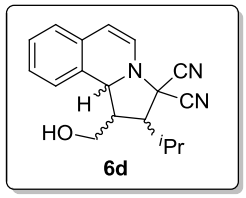
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6c**.

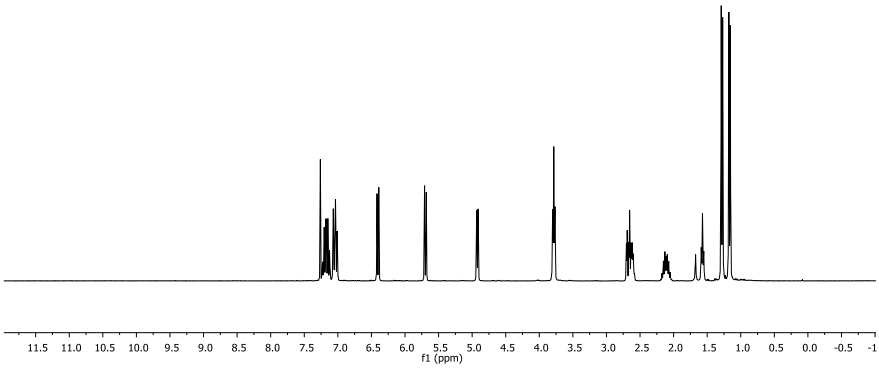


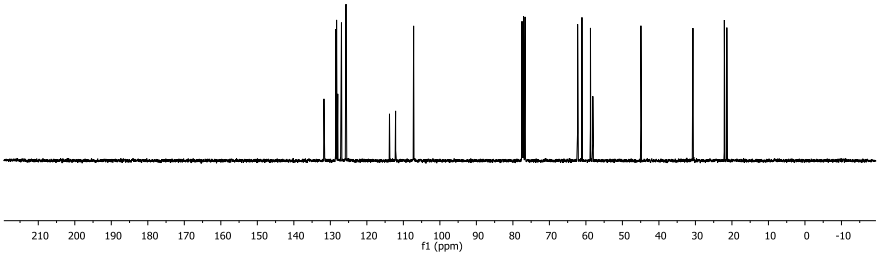




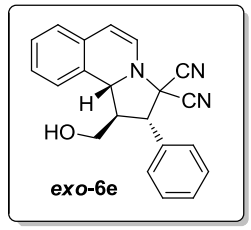
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **6d**.

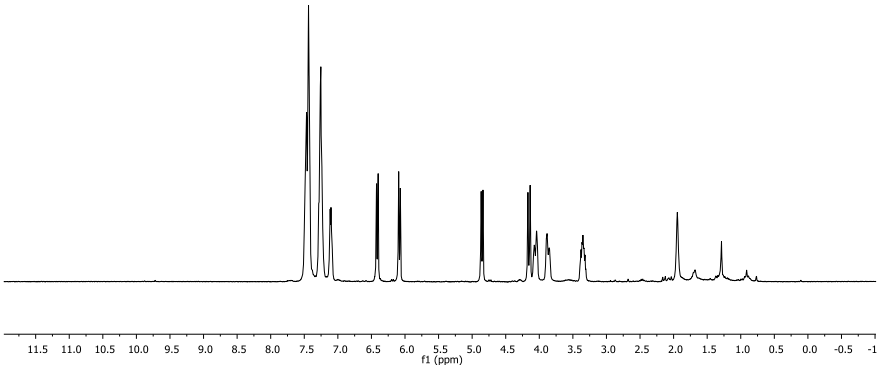


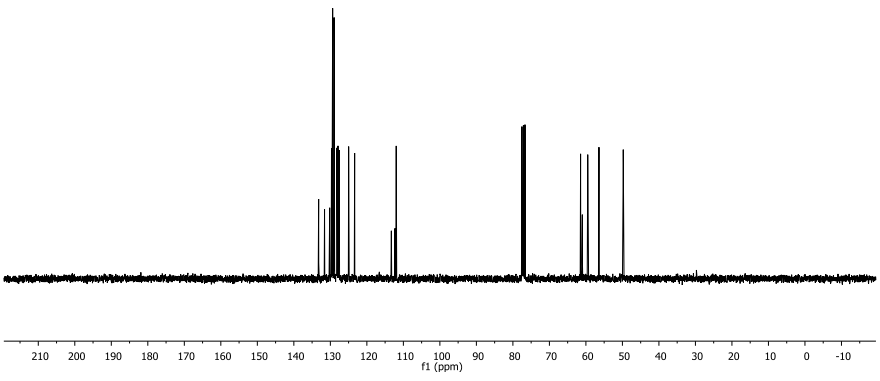




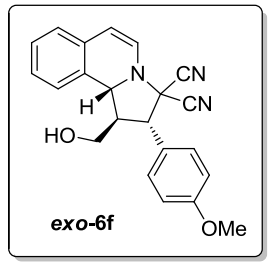
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6e**.

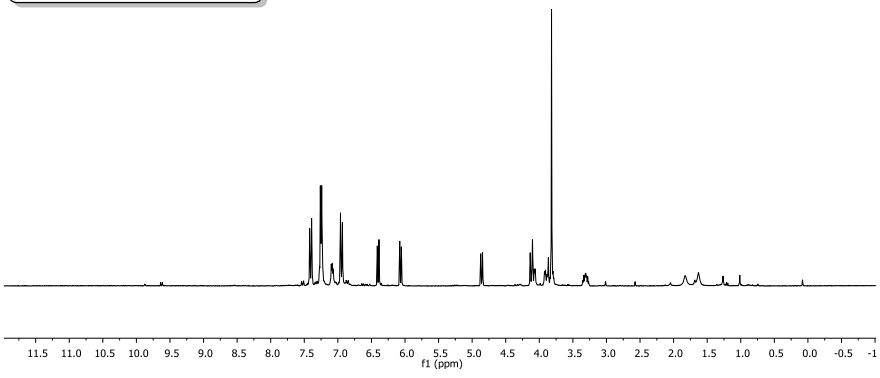


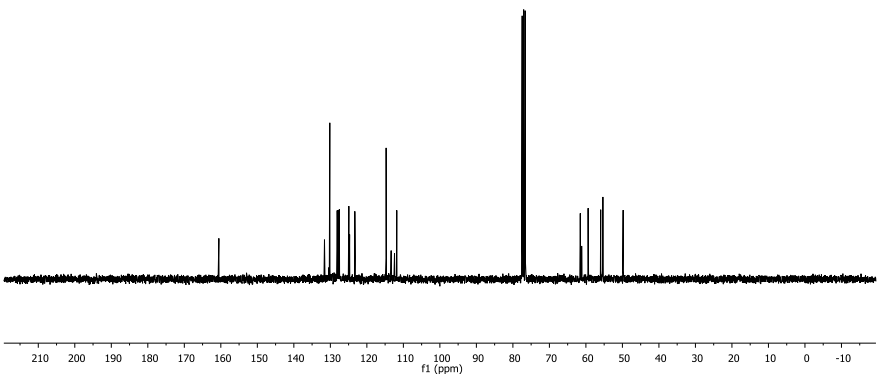




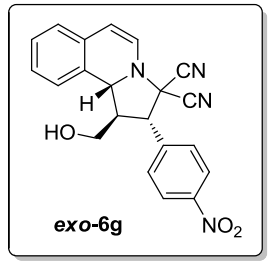
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6f**.

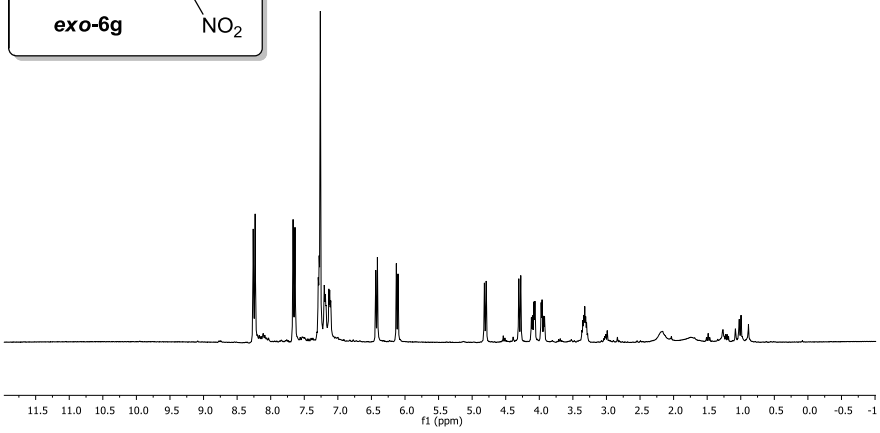


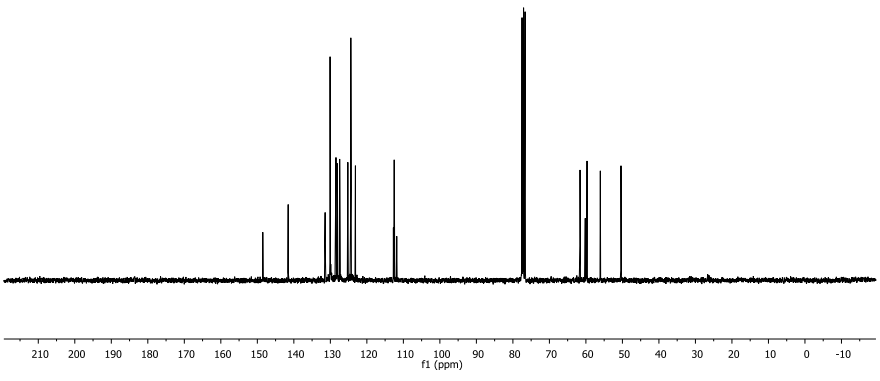




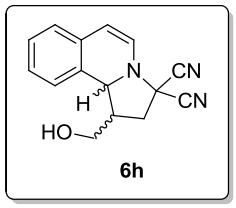
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6g**.



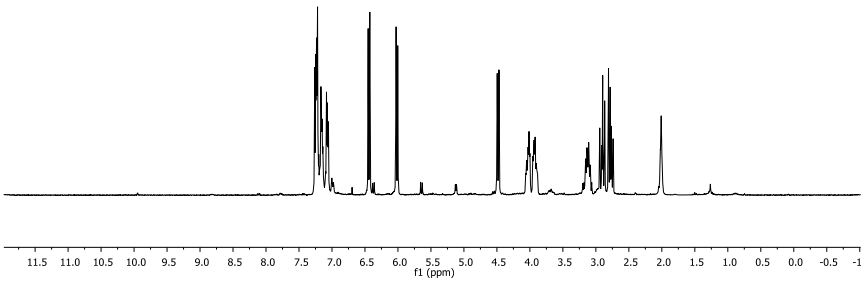


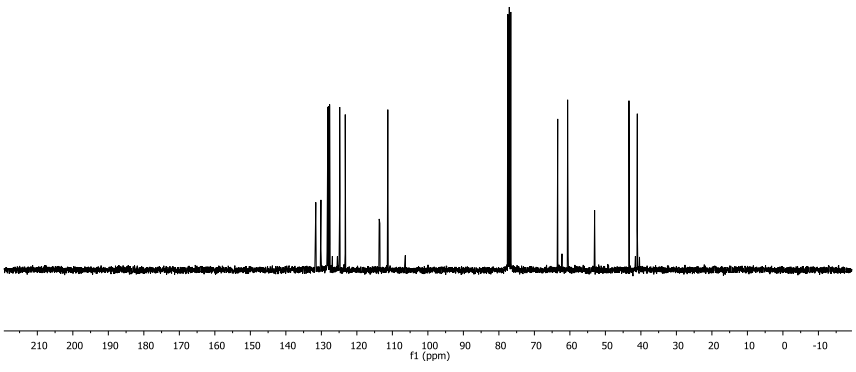


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **6h**.

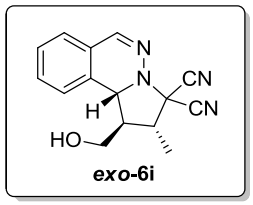


6h

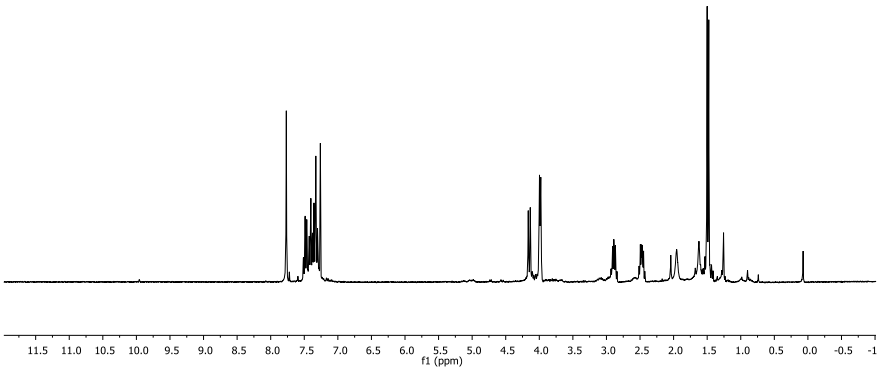


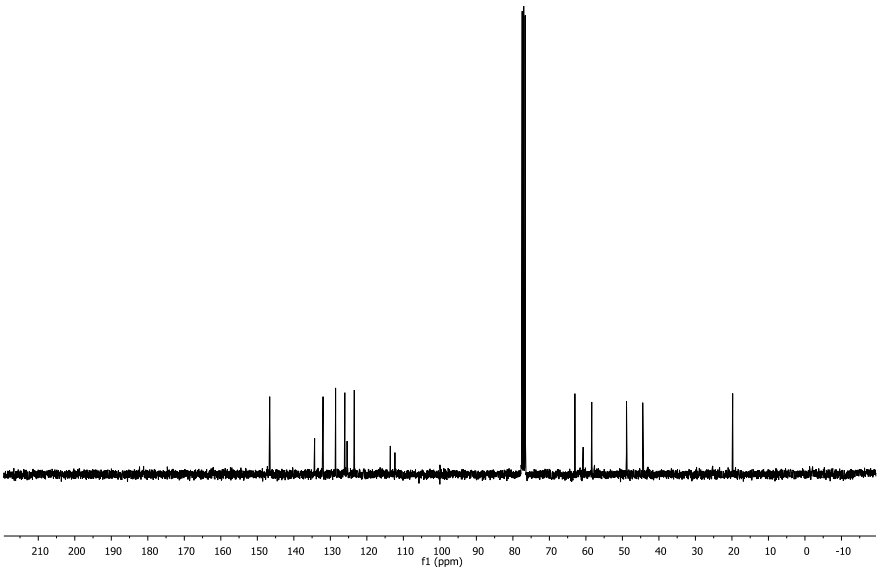


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6i**.

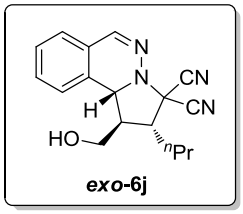


***exo*-6i**

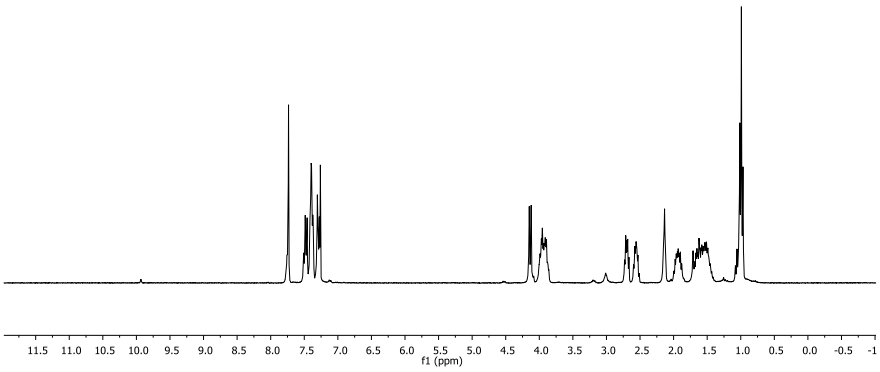


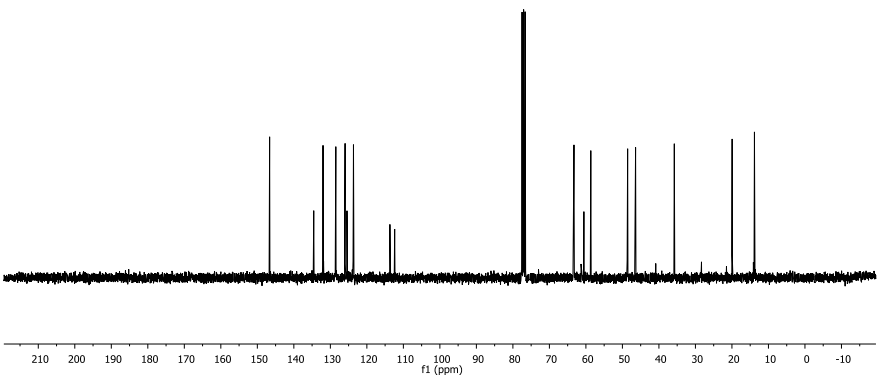


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6j**.

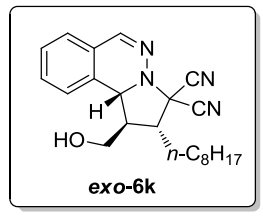


***exo*-6j**

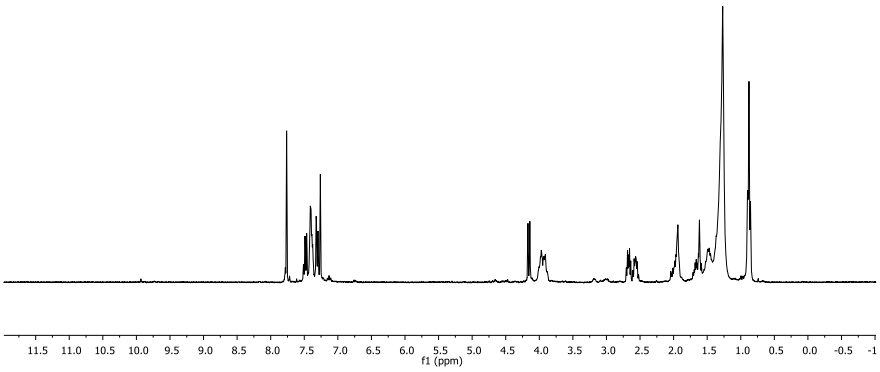


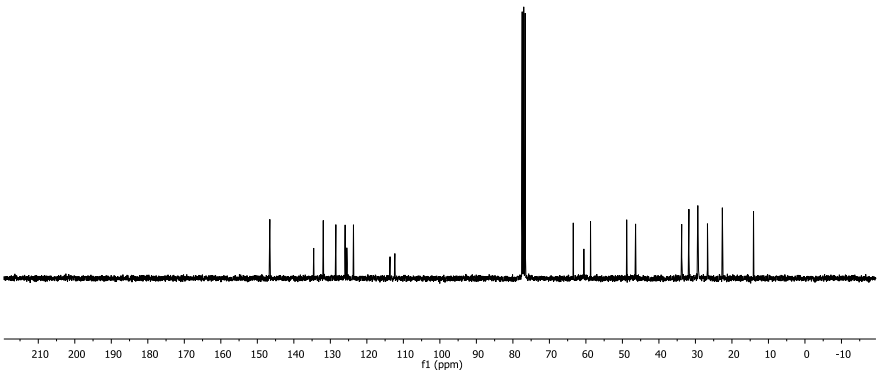


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6k**.

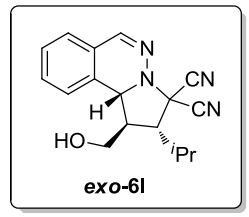


***exo*-6k**

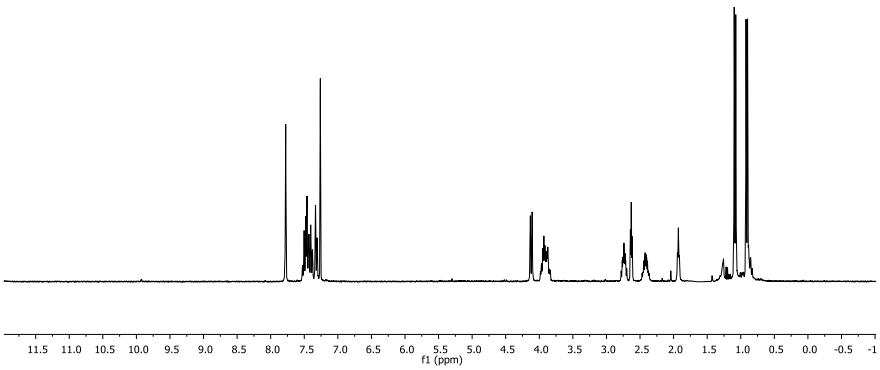


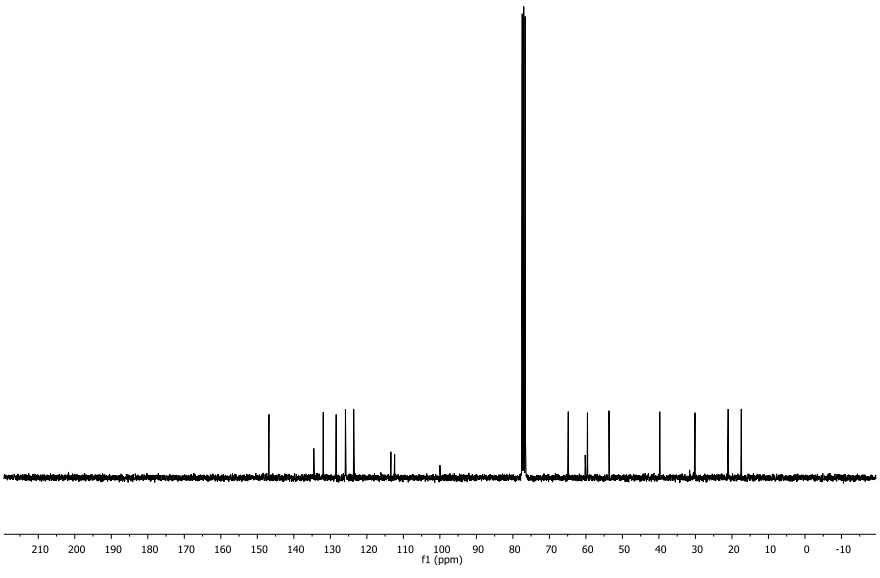


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6l**.

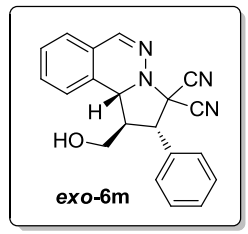


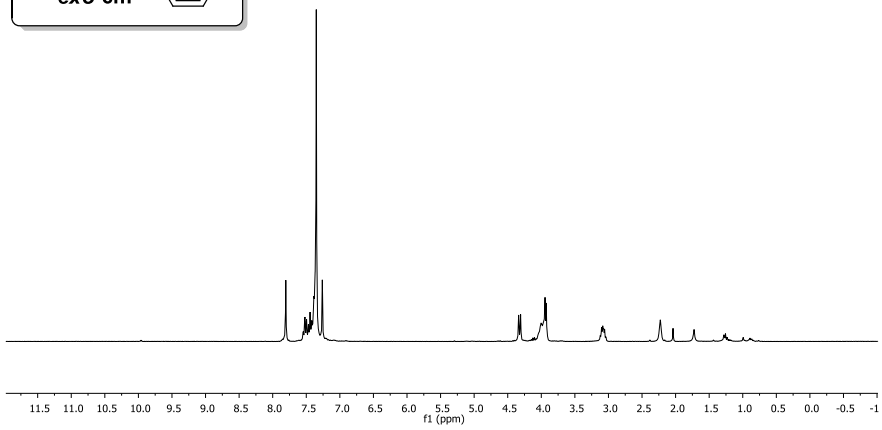
***exo*-6l**

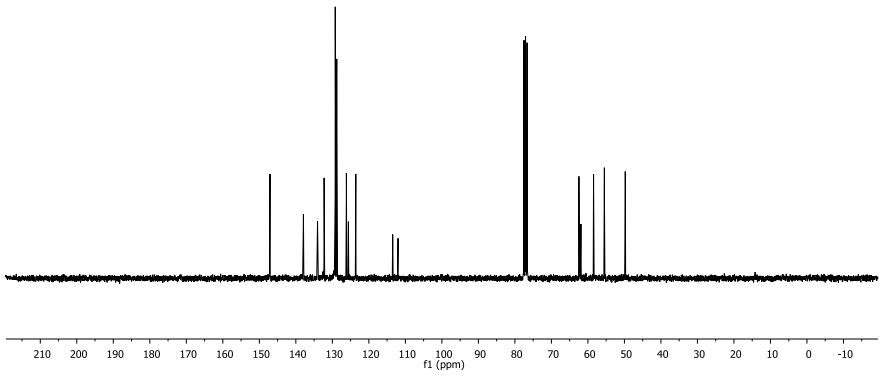




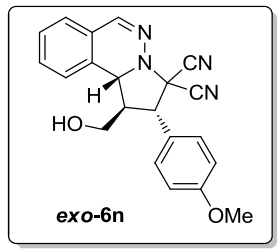
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6m**.



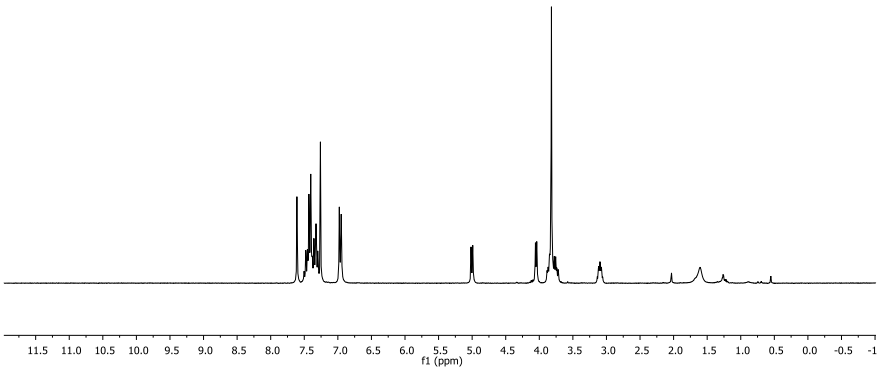


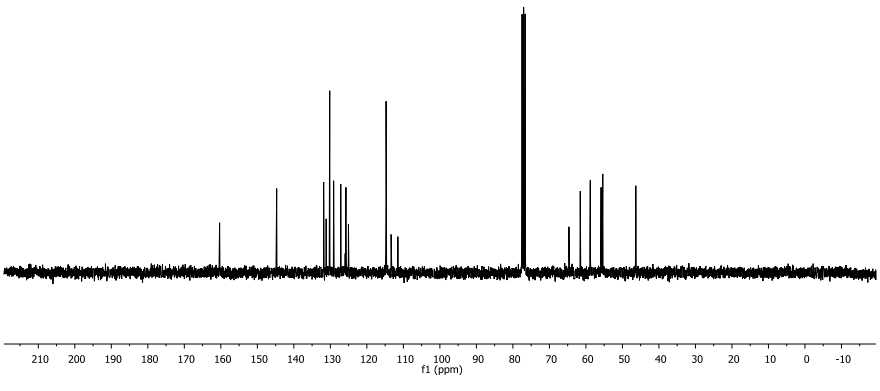


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6n**.

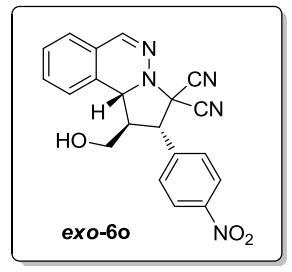


***exo*-6n**

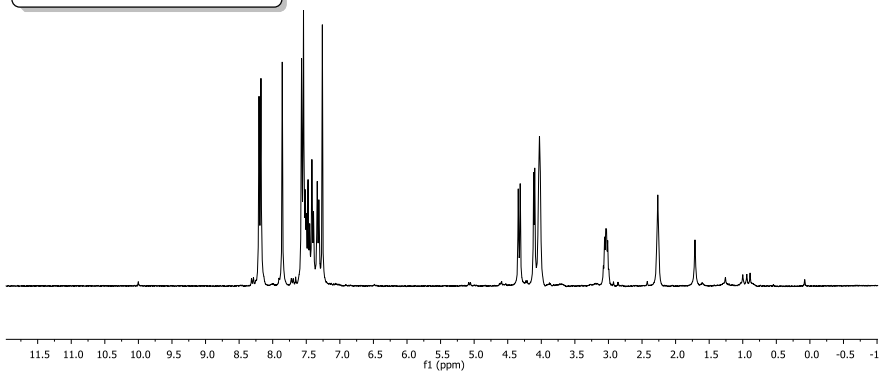


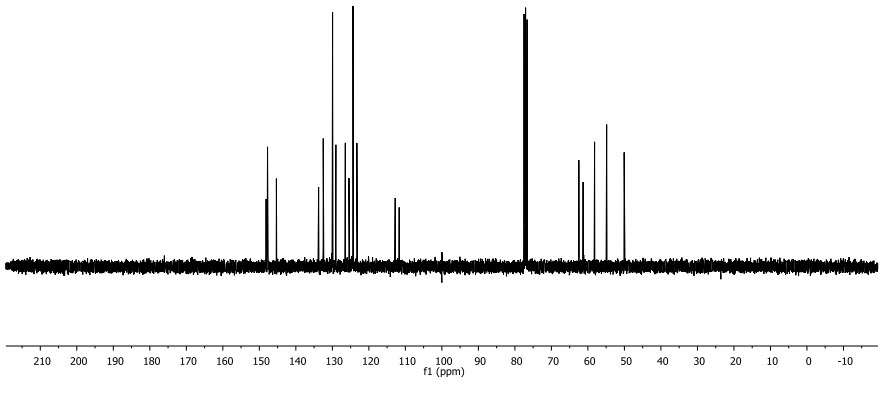


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6o**.

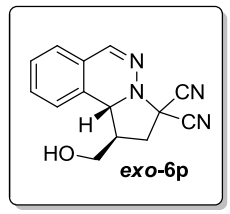


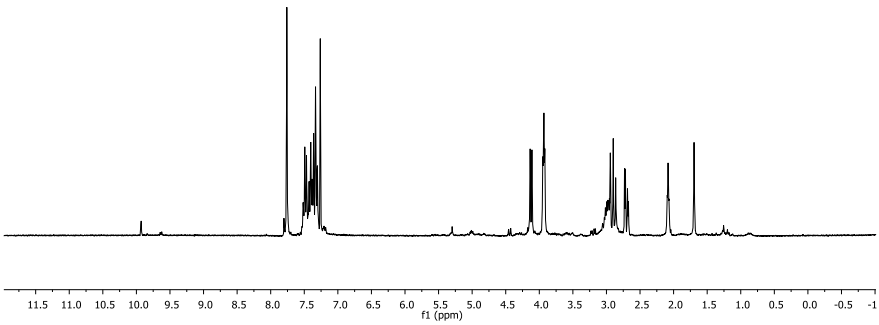
***exo*-6o**

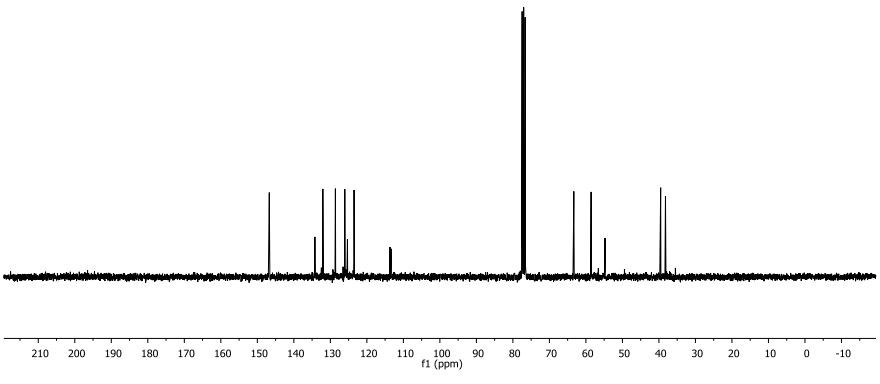




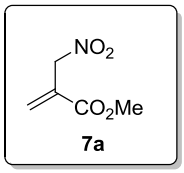
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto ***exo*-6p**.



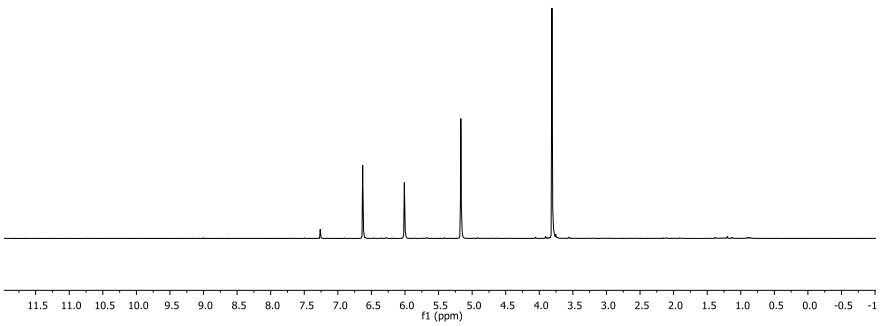


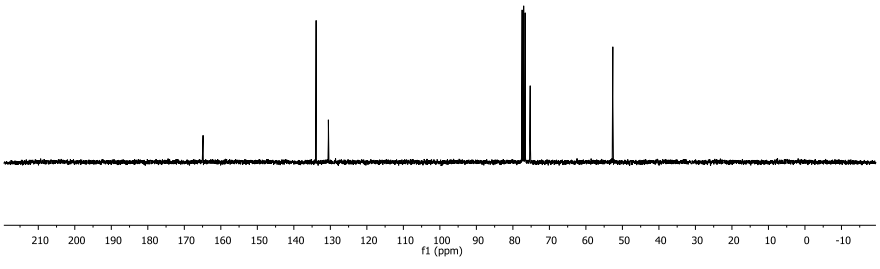


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **7a**.

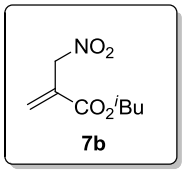


7a

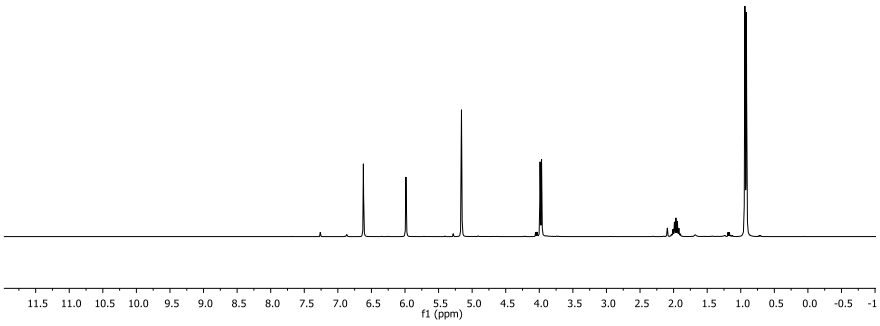


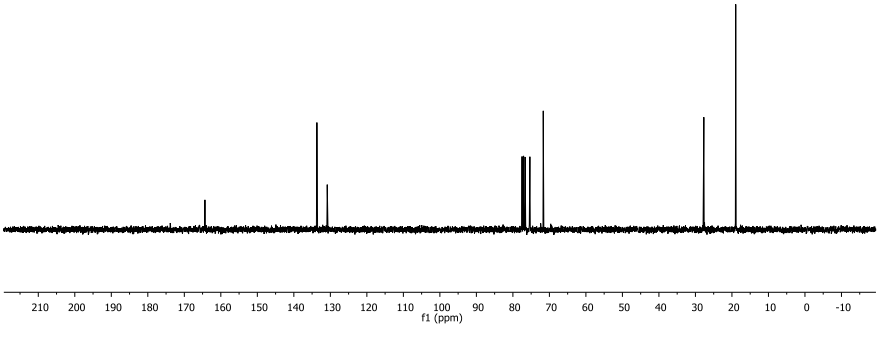


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **7b**.

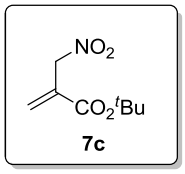


7b

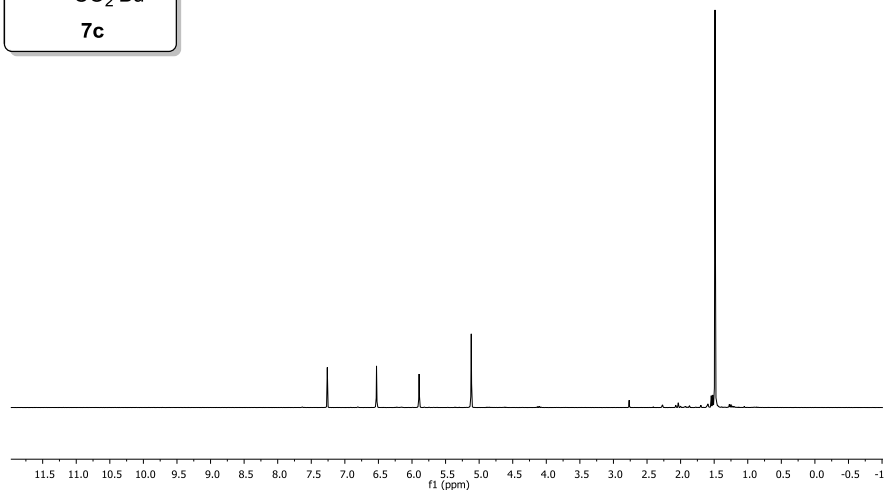


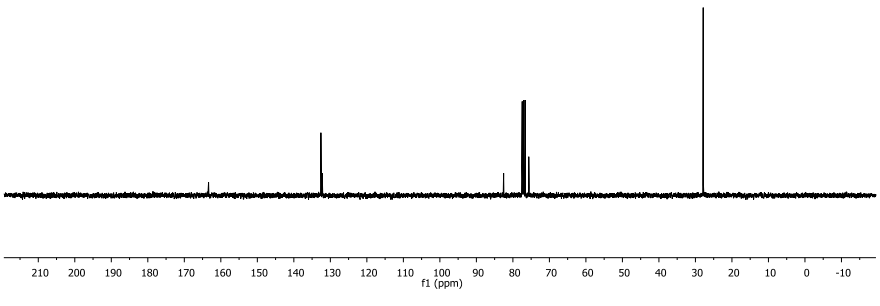


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **7c**.

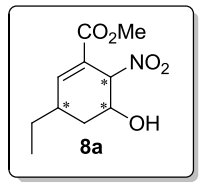


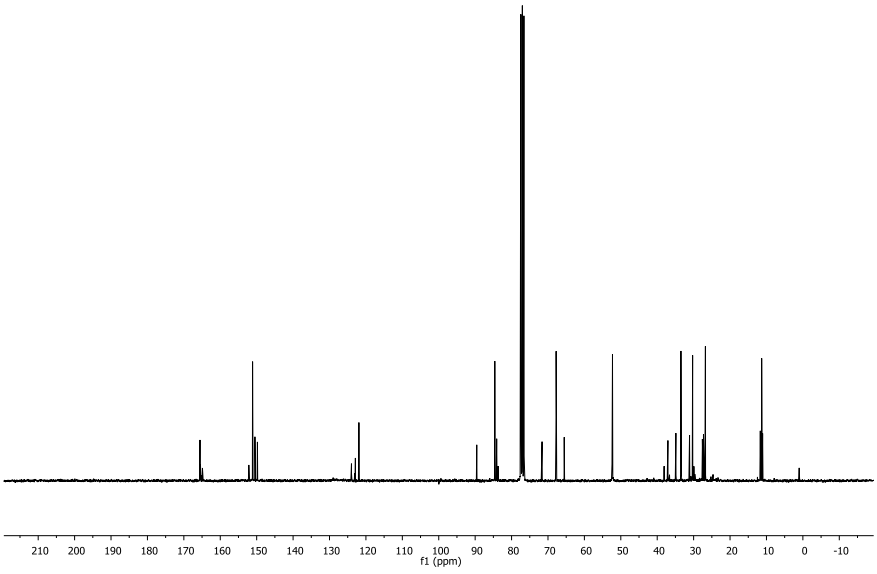
7c



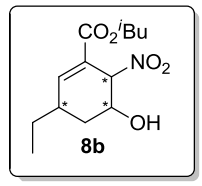


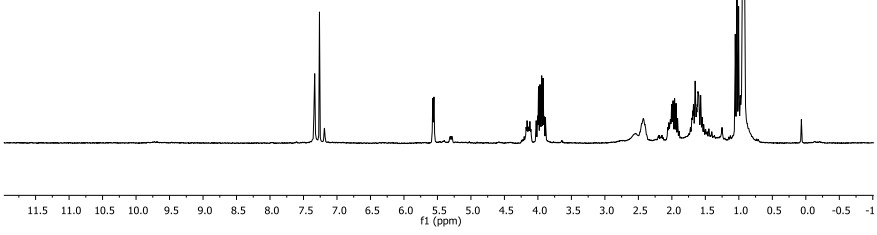
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **8a**.

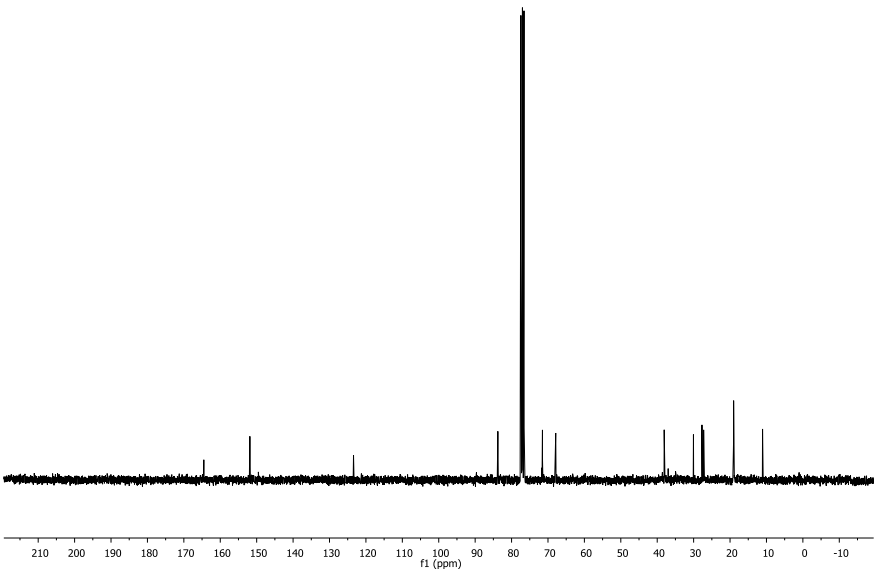




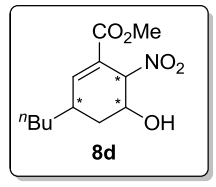
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **8b**.

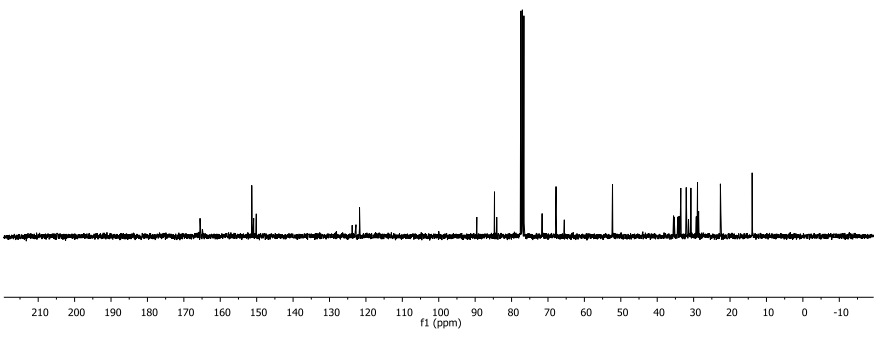




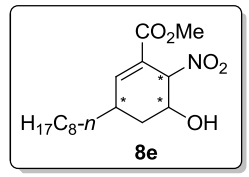


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **8d**.

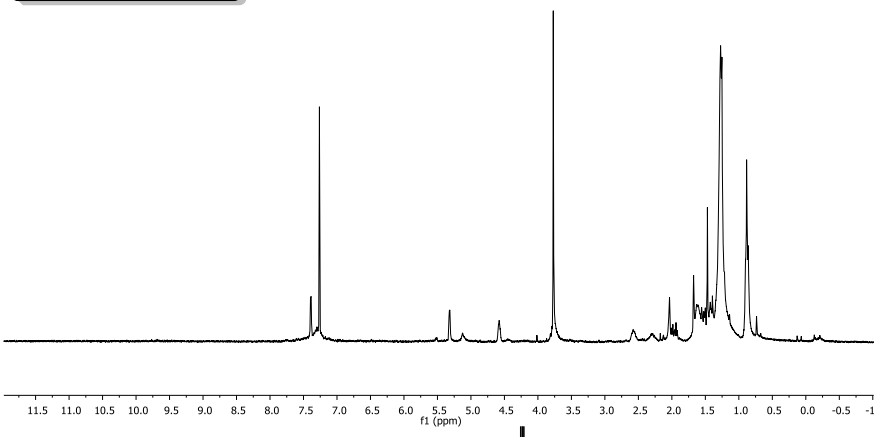


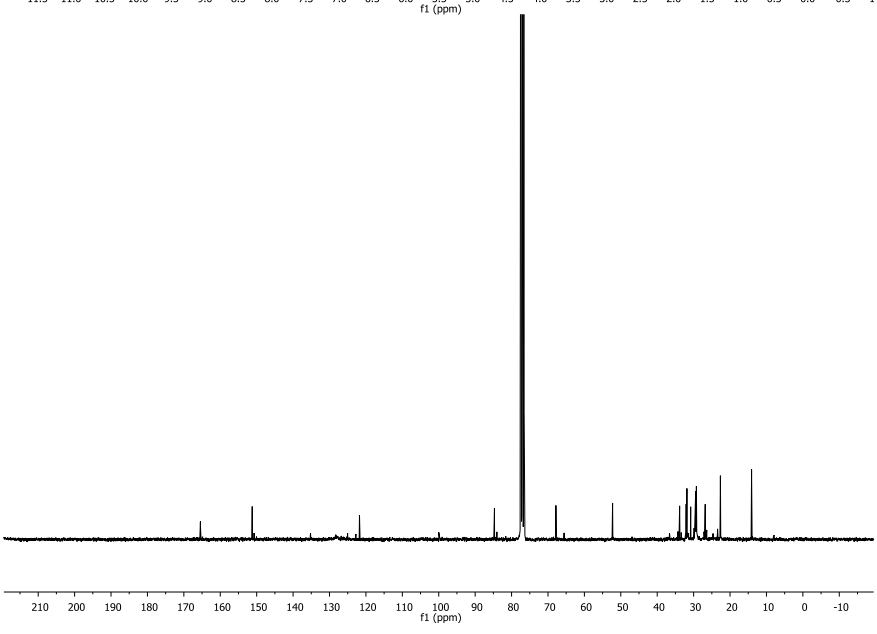


Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **8e**.

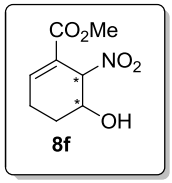


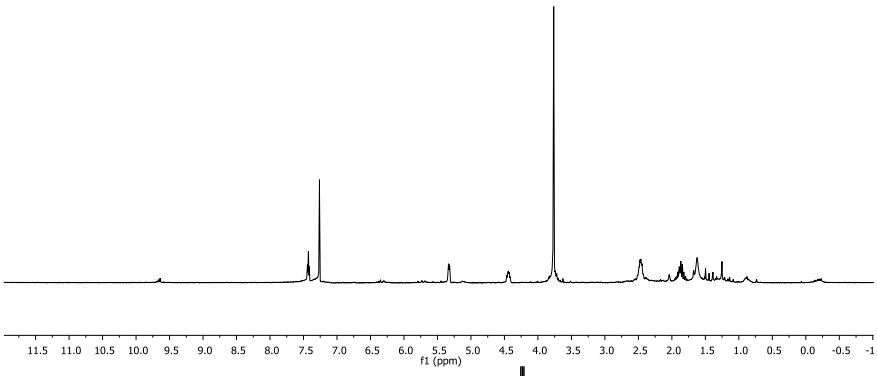
8e

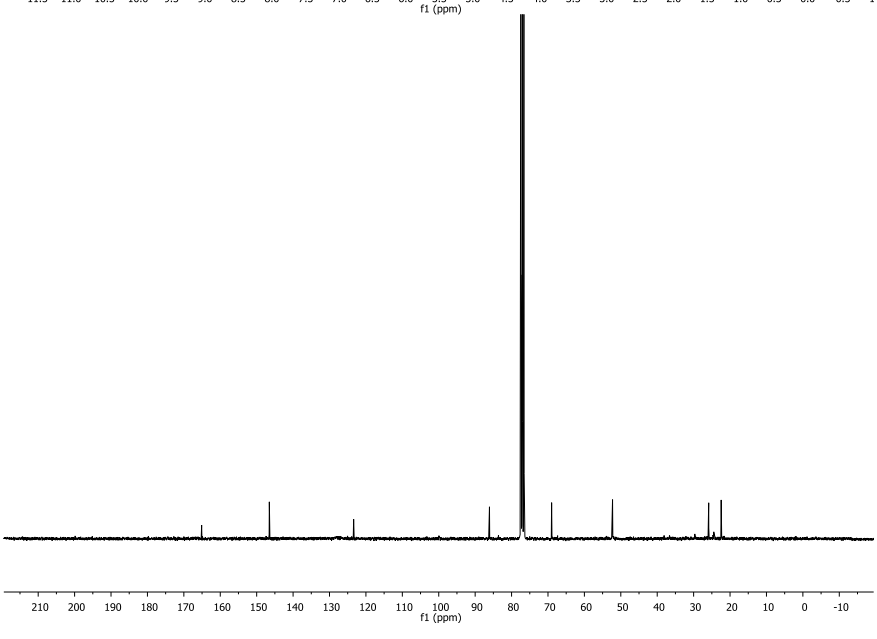




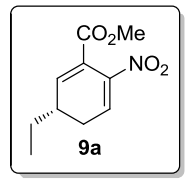
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **8f**.

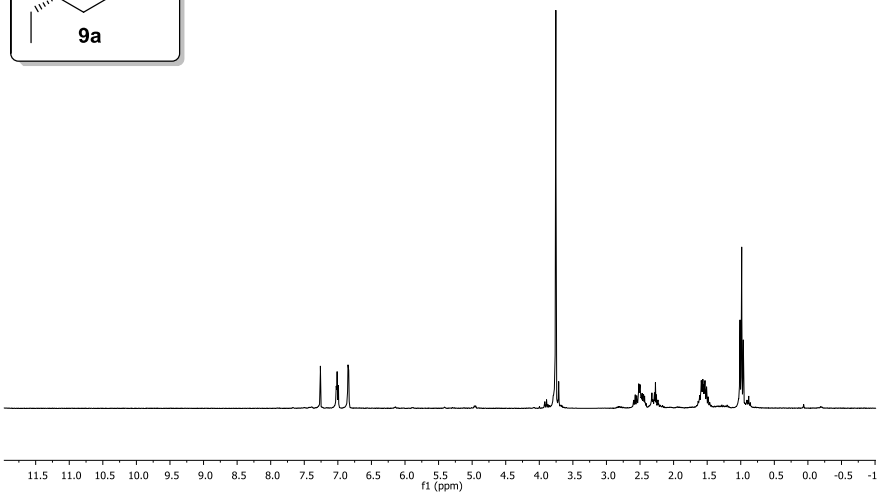


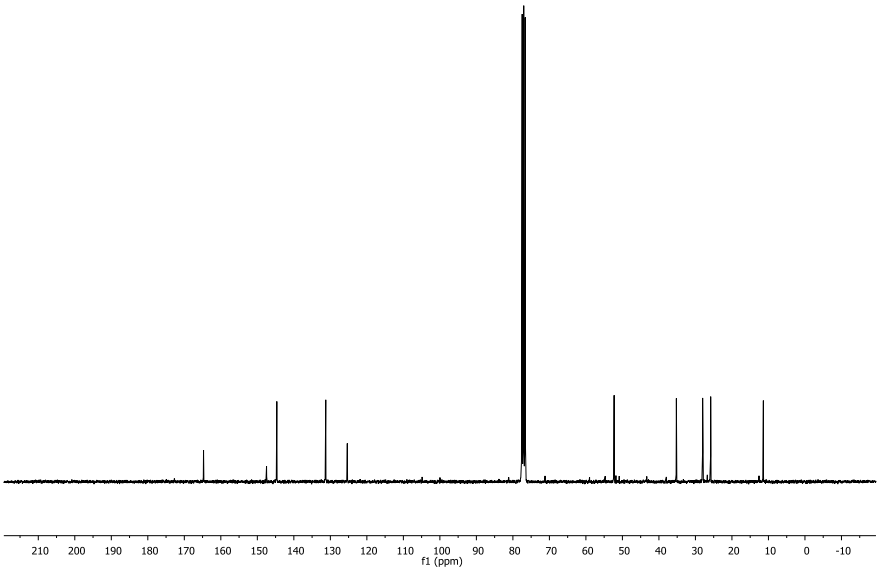




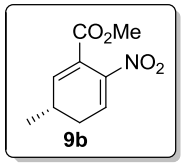
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **9a**.

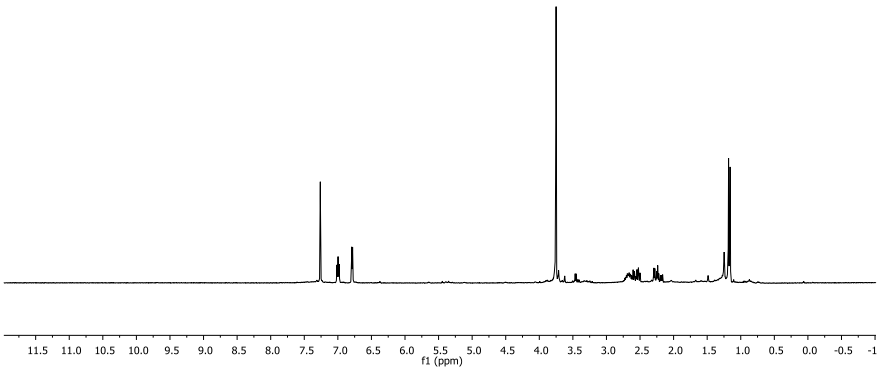


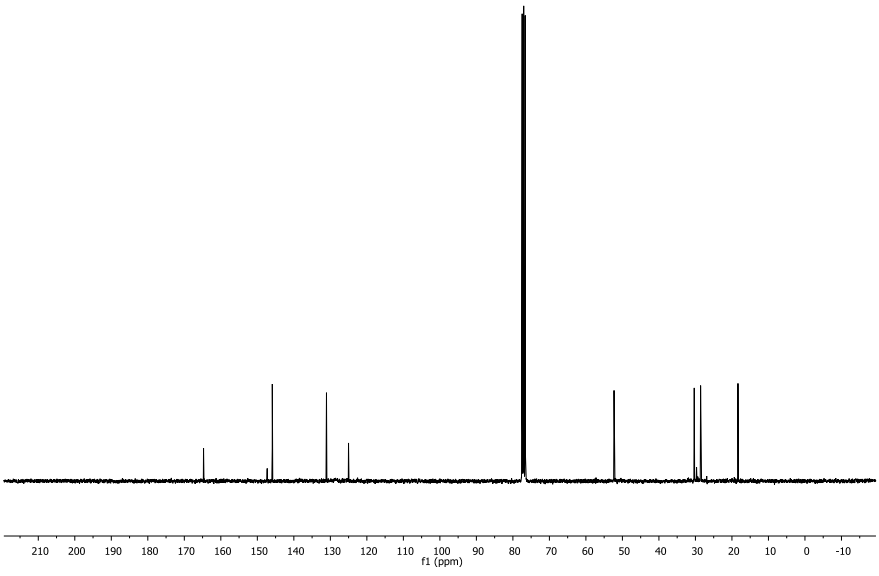




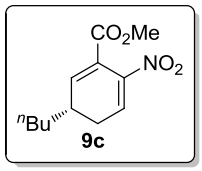
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **9b**.

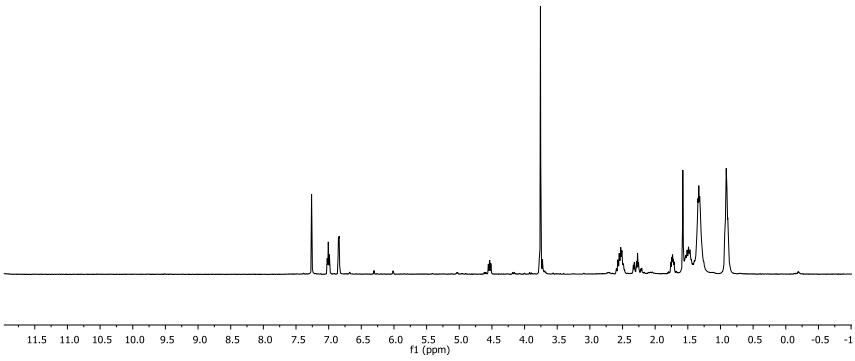


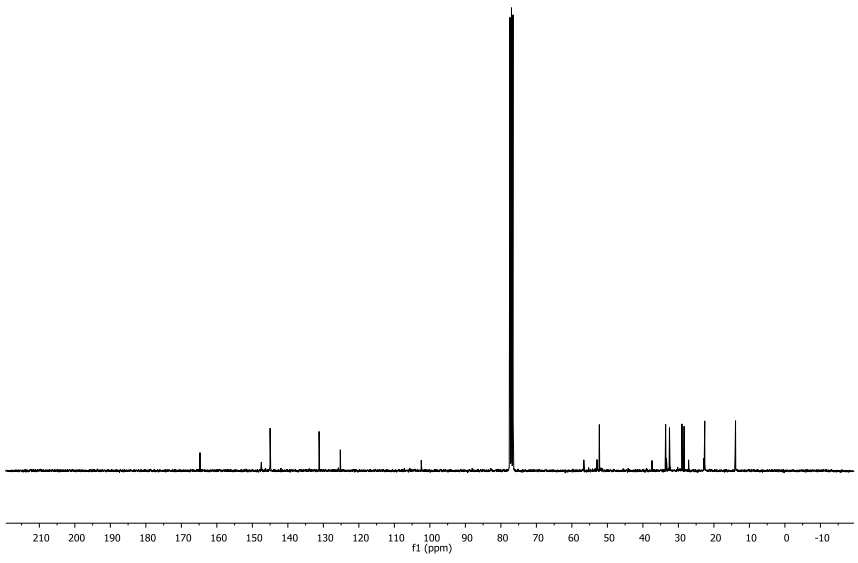




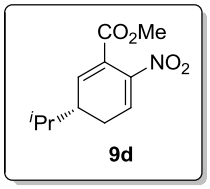
Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **9c**.

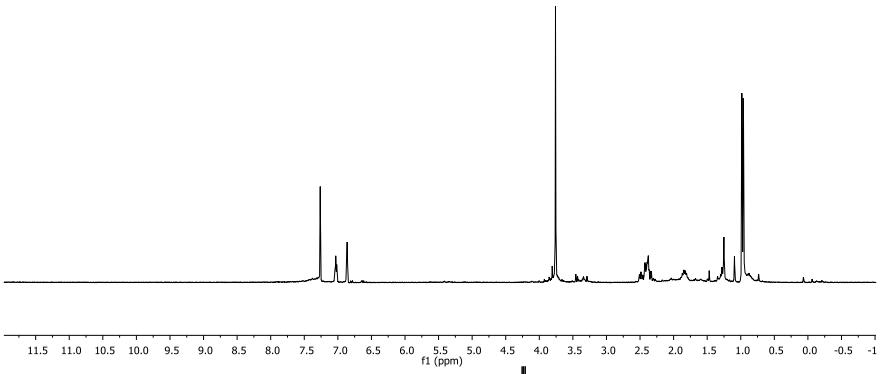


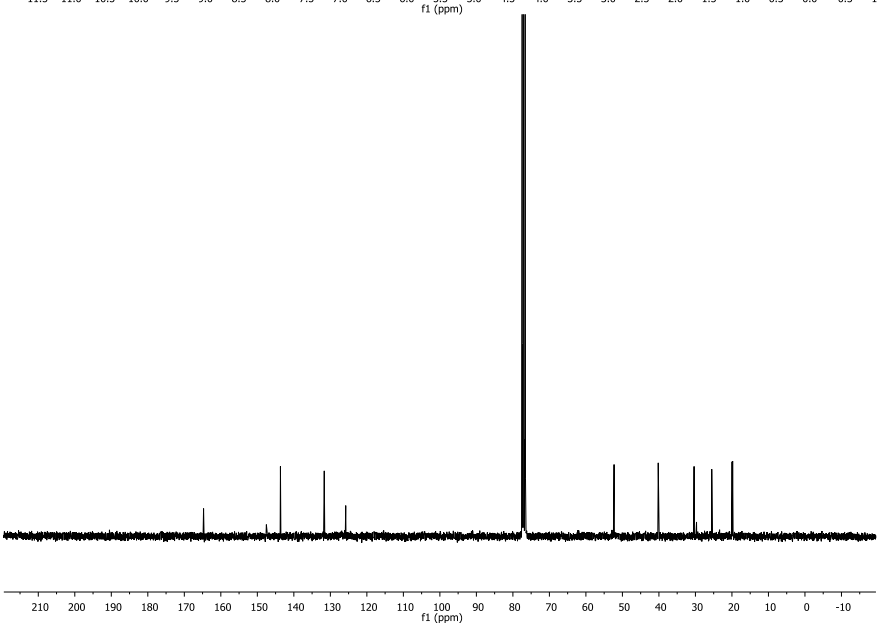




Espectros de ^{1}H-NMR y ^{13}C-NMR del compuesto **9d**.

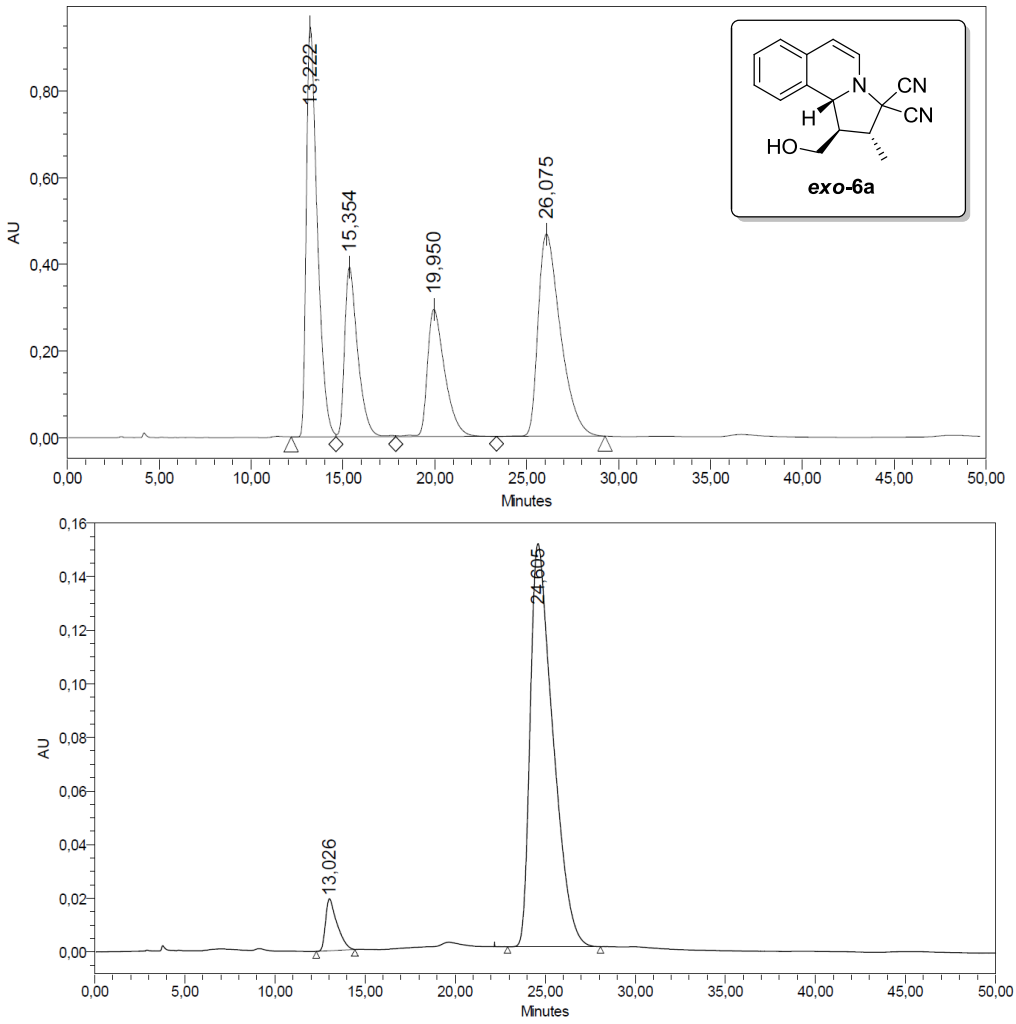




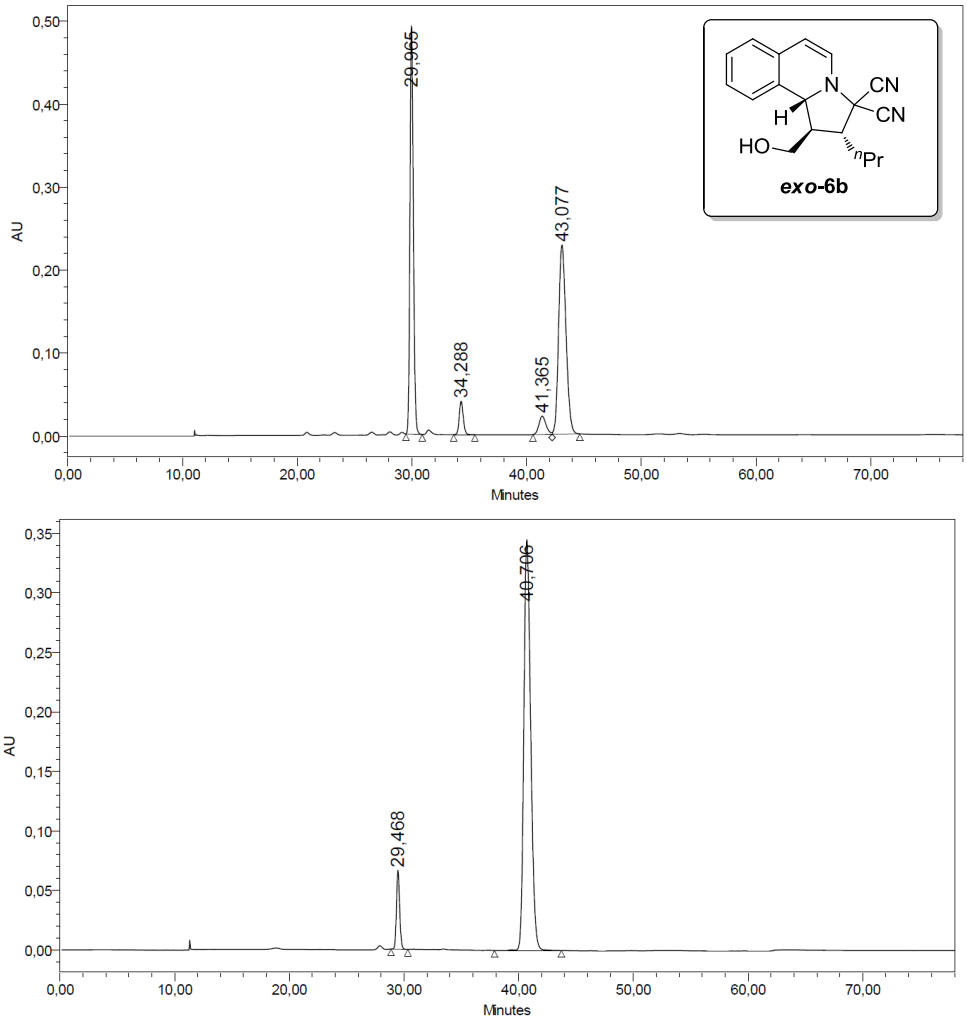


- **Cromatogramas de HPLC**

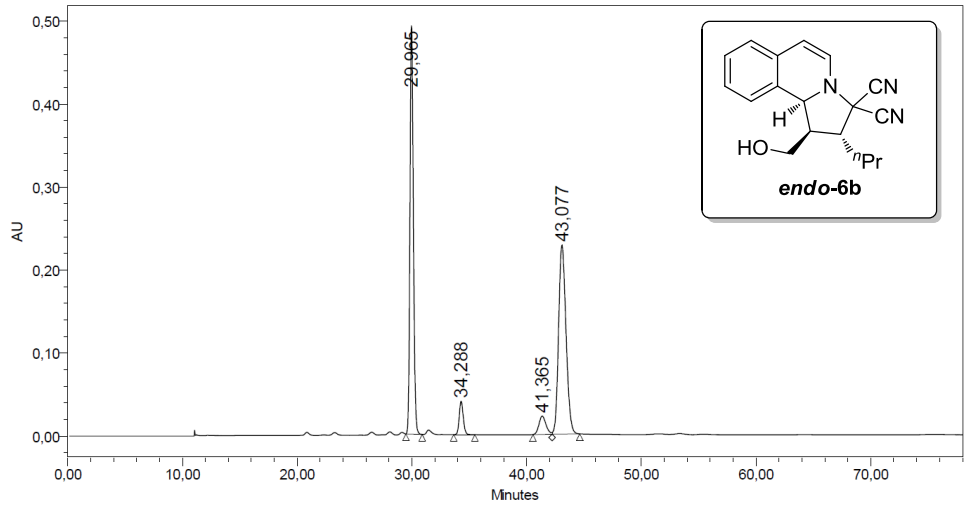
Cromatograma del compuesto ***exo*-6a**.

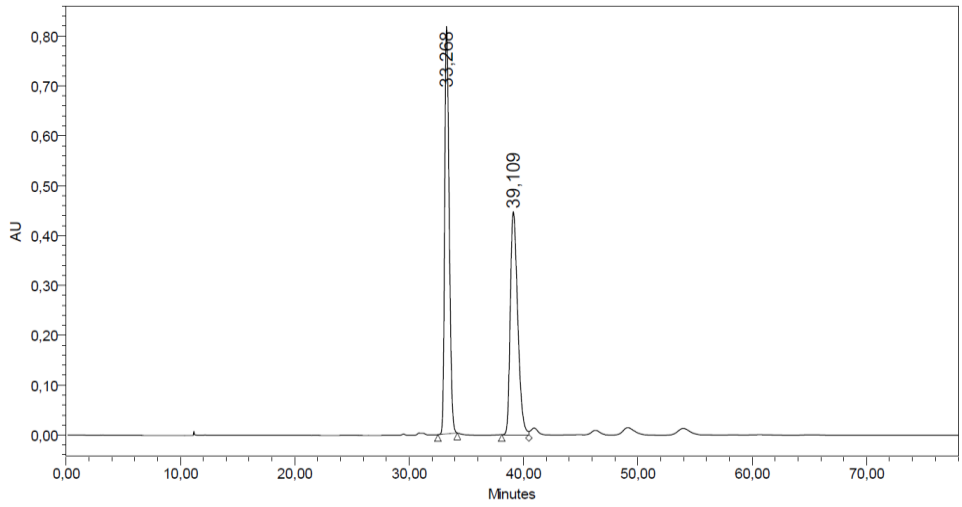


Cromatograma del compuesto ***exo*-6b**.

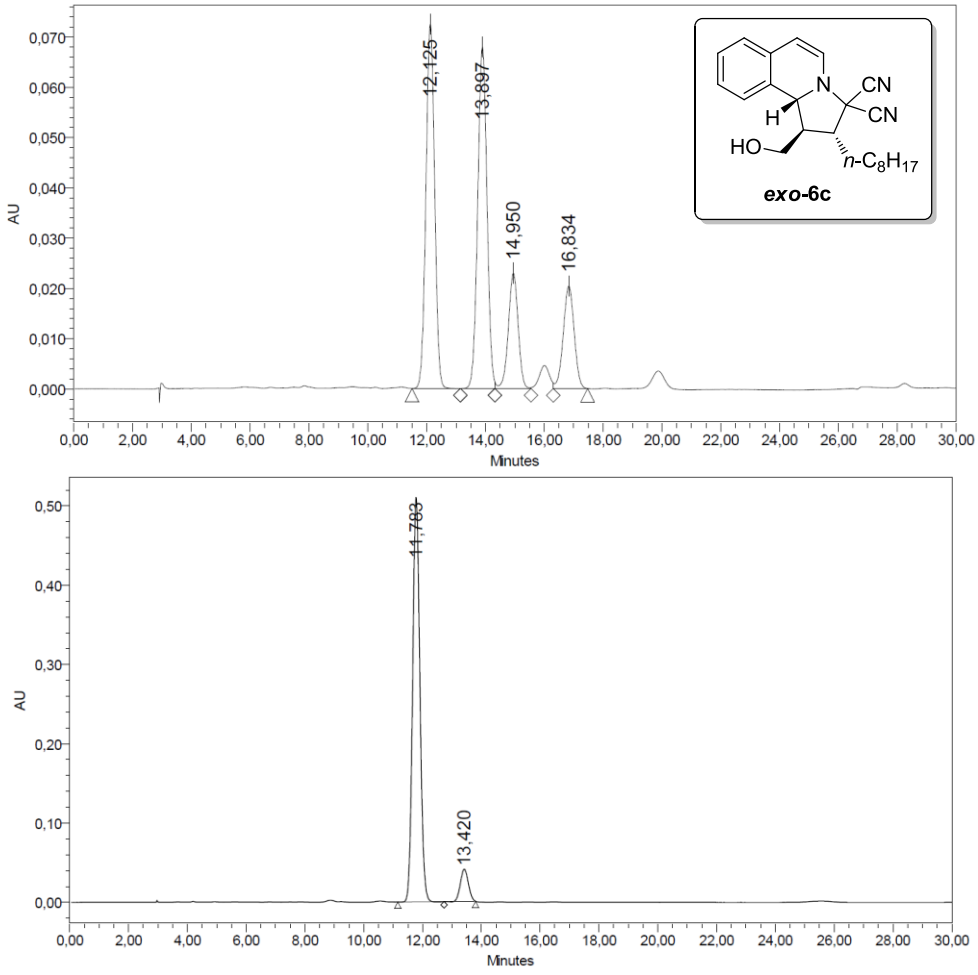


Cromatograma del compuesto ***endo*-6b**.

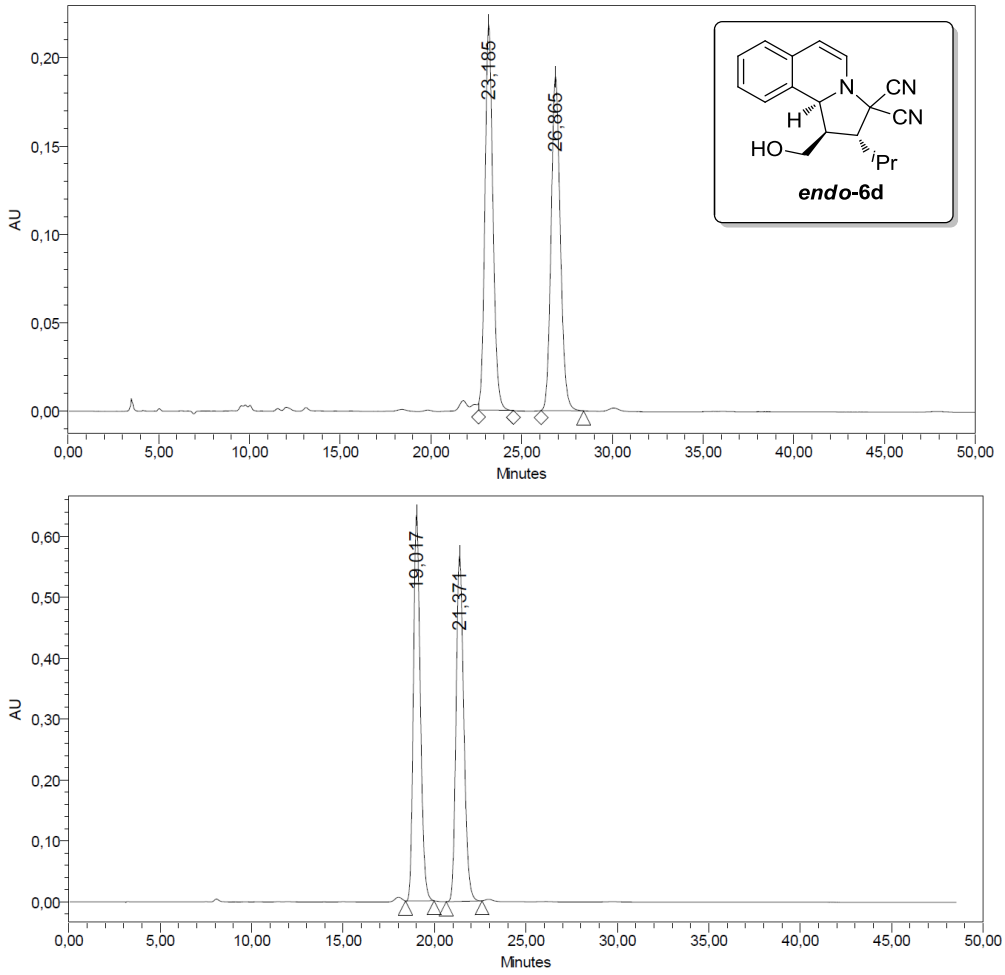




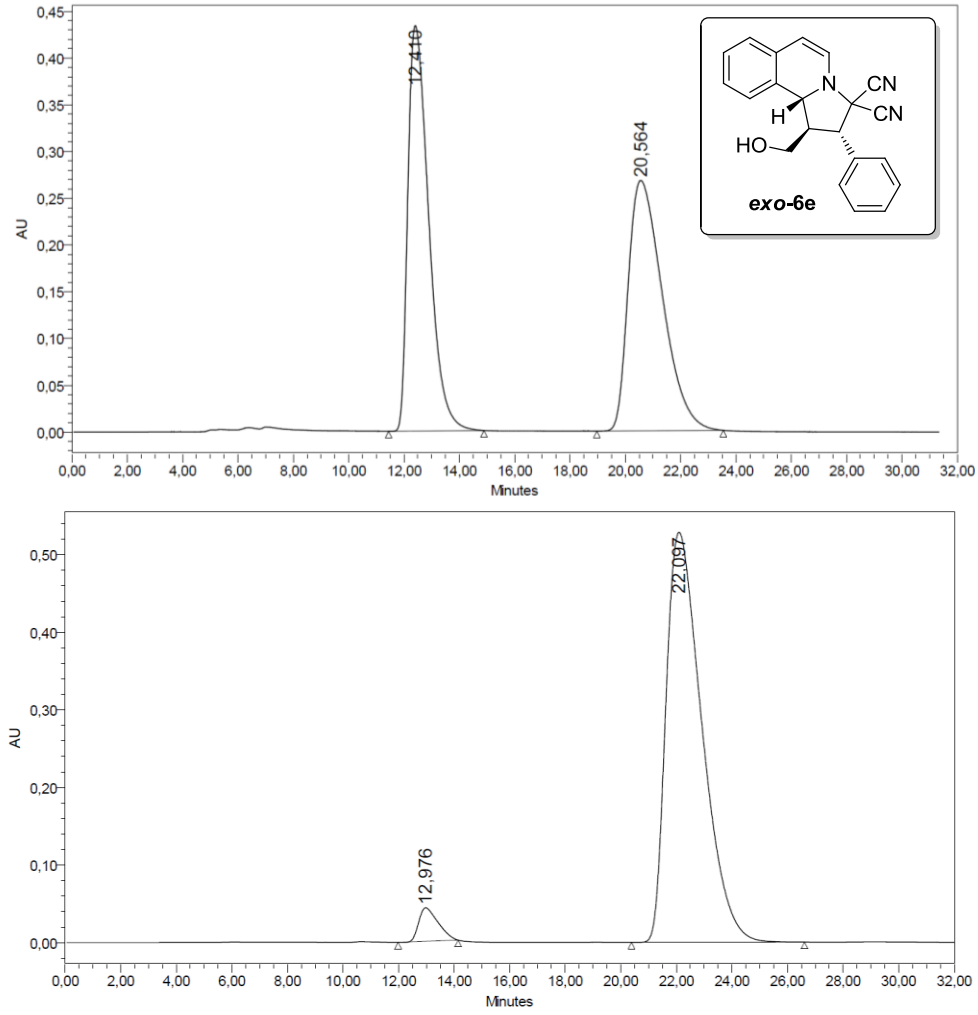
Cromatograma del compuesto ***exo*-6c**.



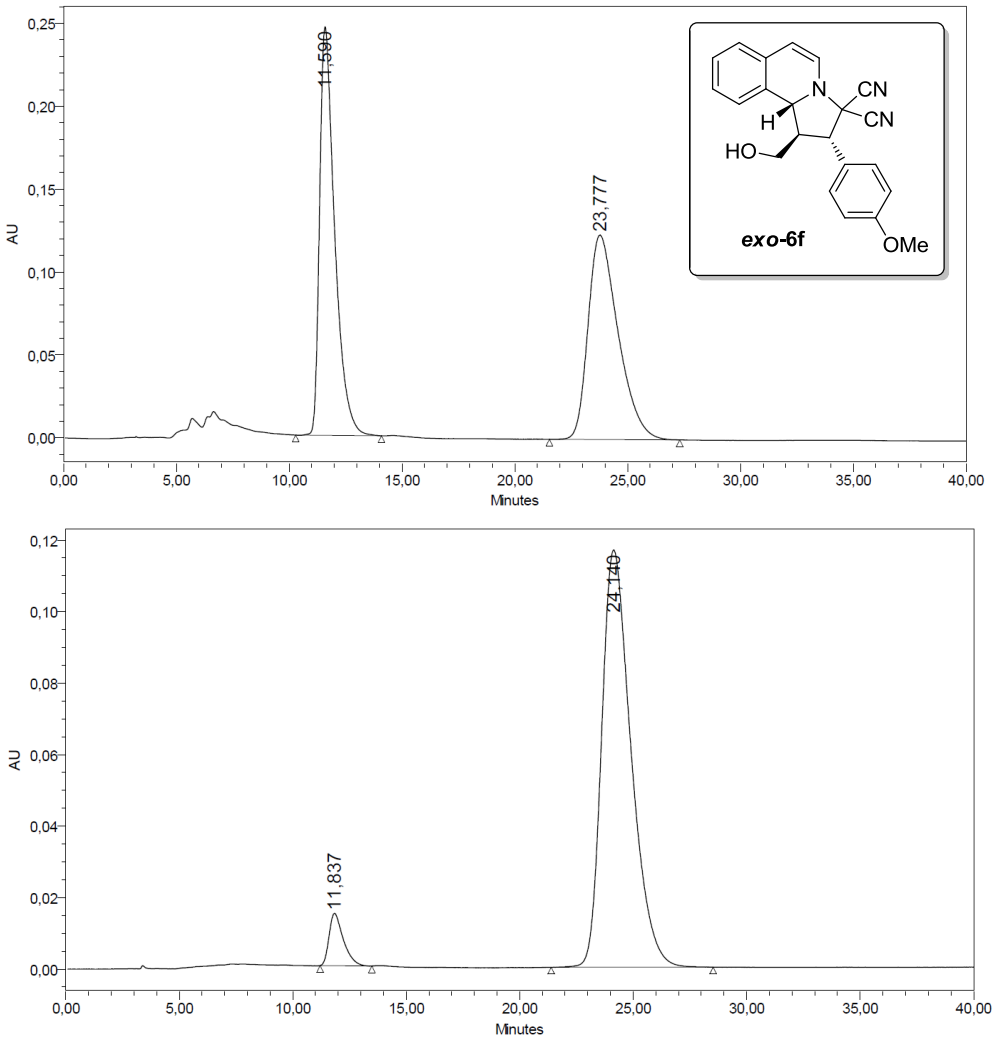
Cromatograma del compuesto ***endo*-6d**.



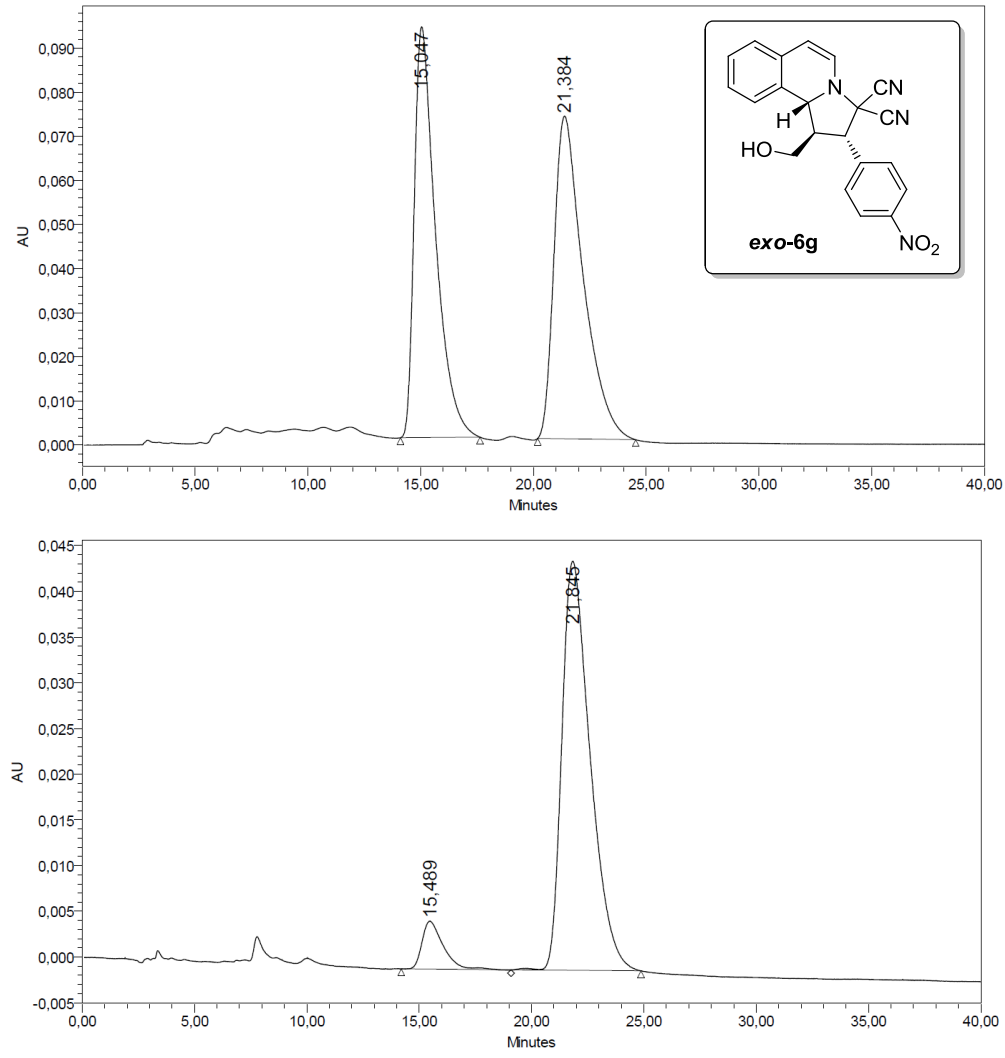
Cromatograma del compuesto ***exo*-6e**.



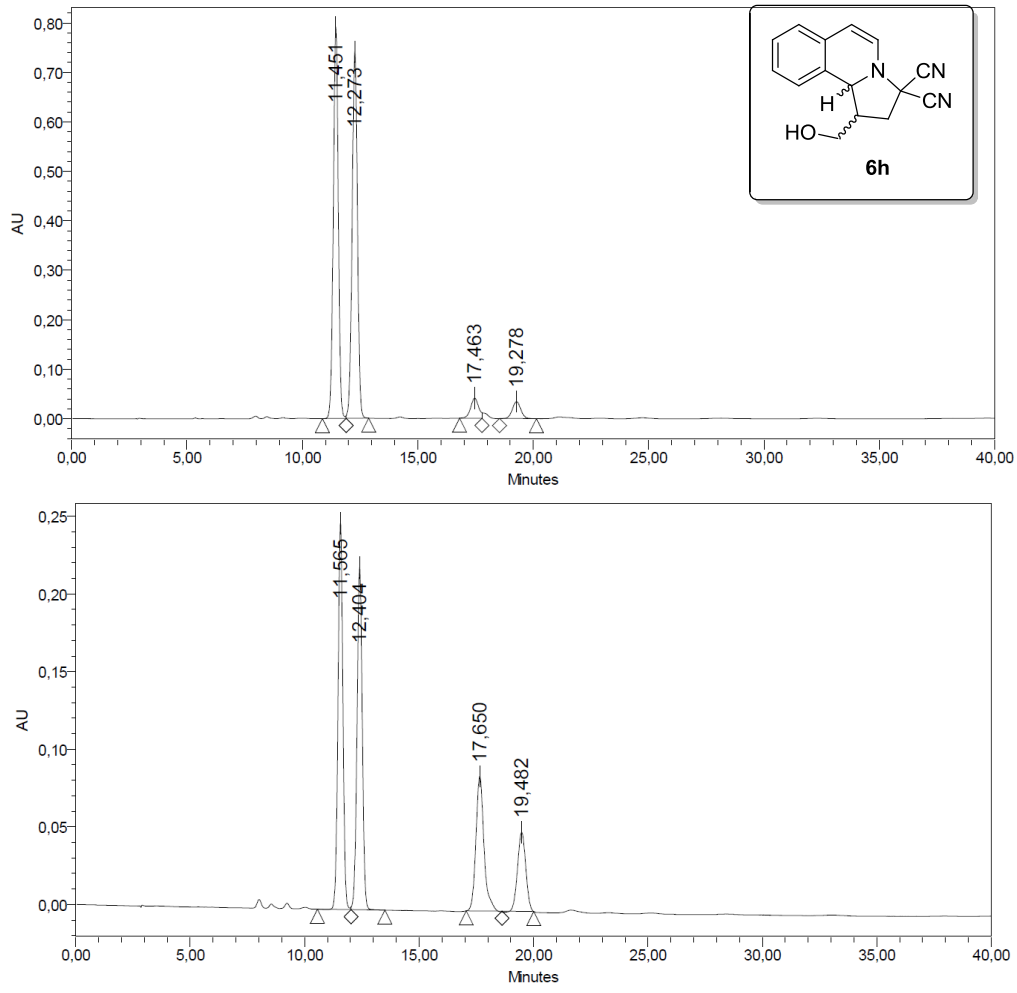
Cromatograma del compuesto ***exo*-6f**.



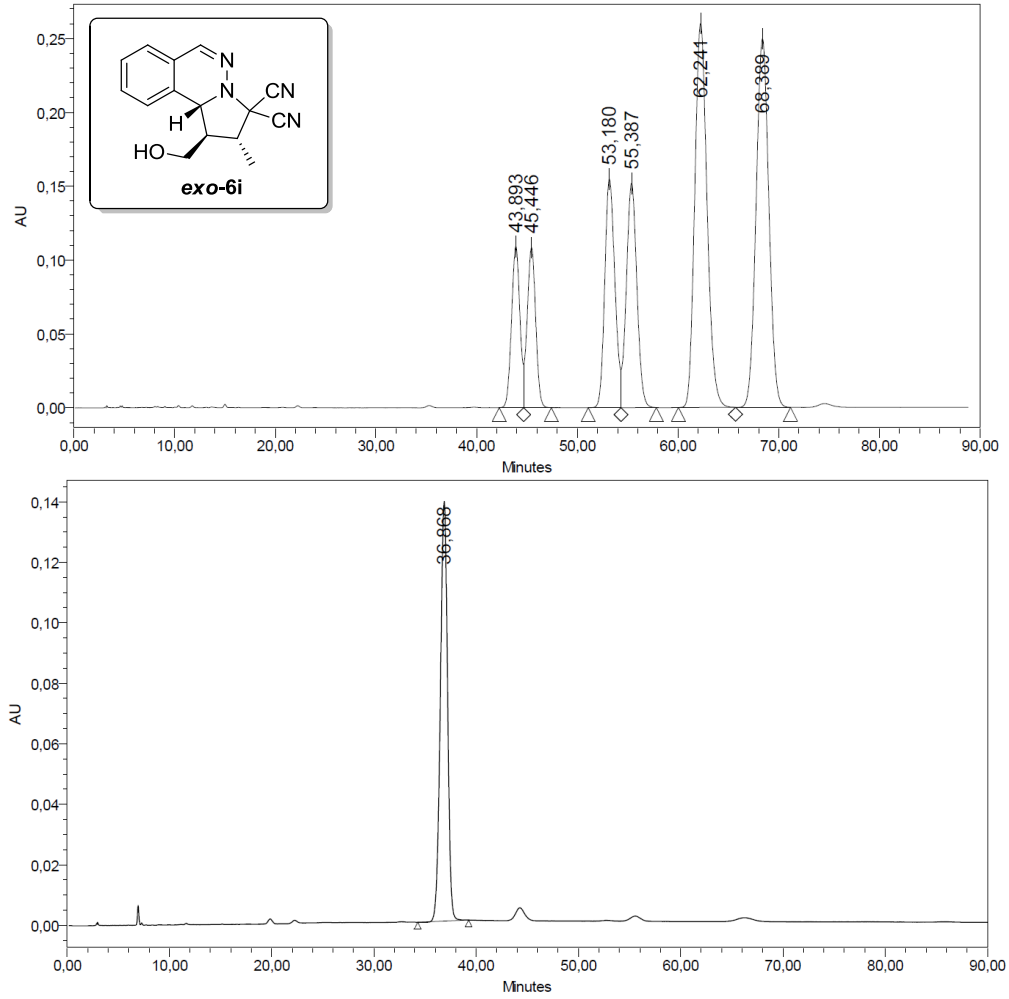
Cromatograma del compuesto ***exo*-6g**.



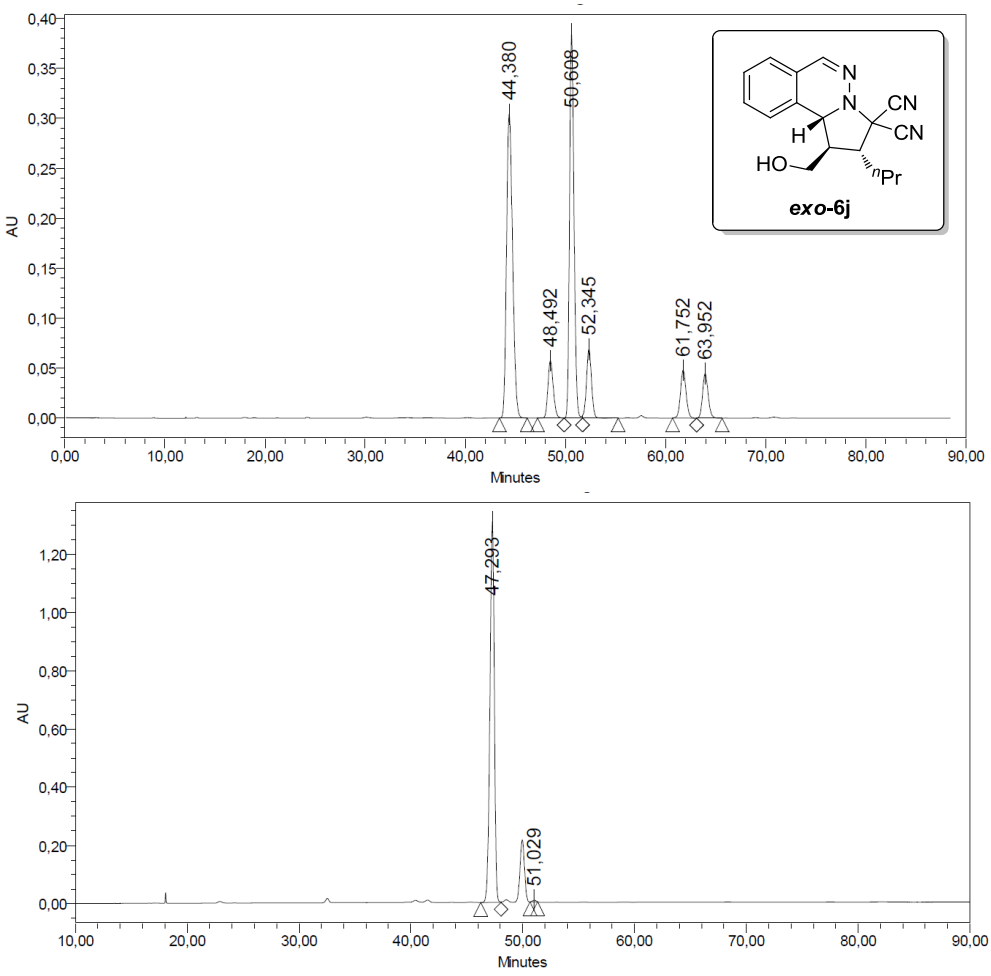
Cromatograma del compuesto **6h**.



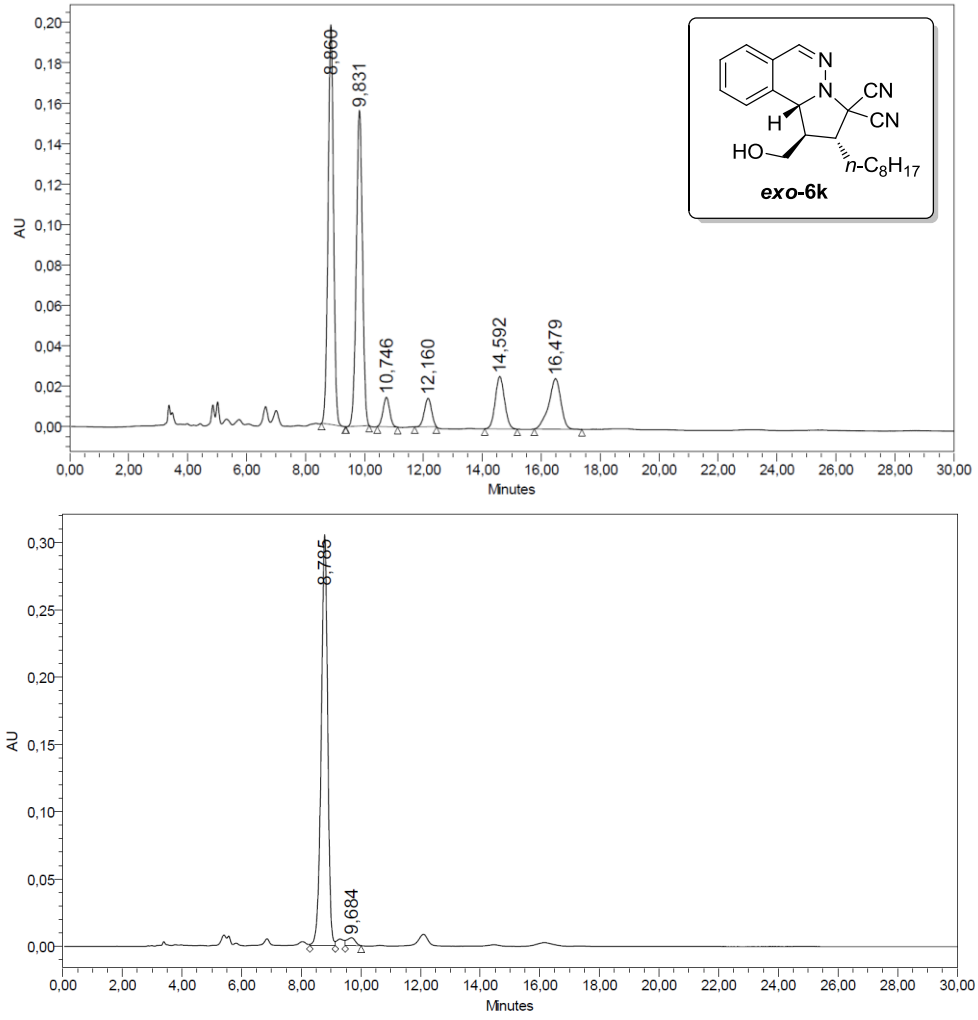
Cromatograma del compuesto ***exo*-6l**.



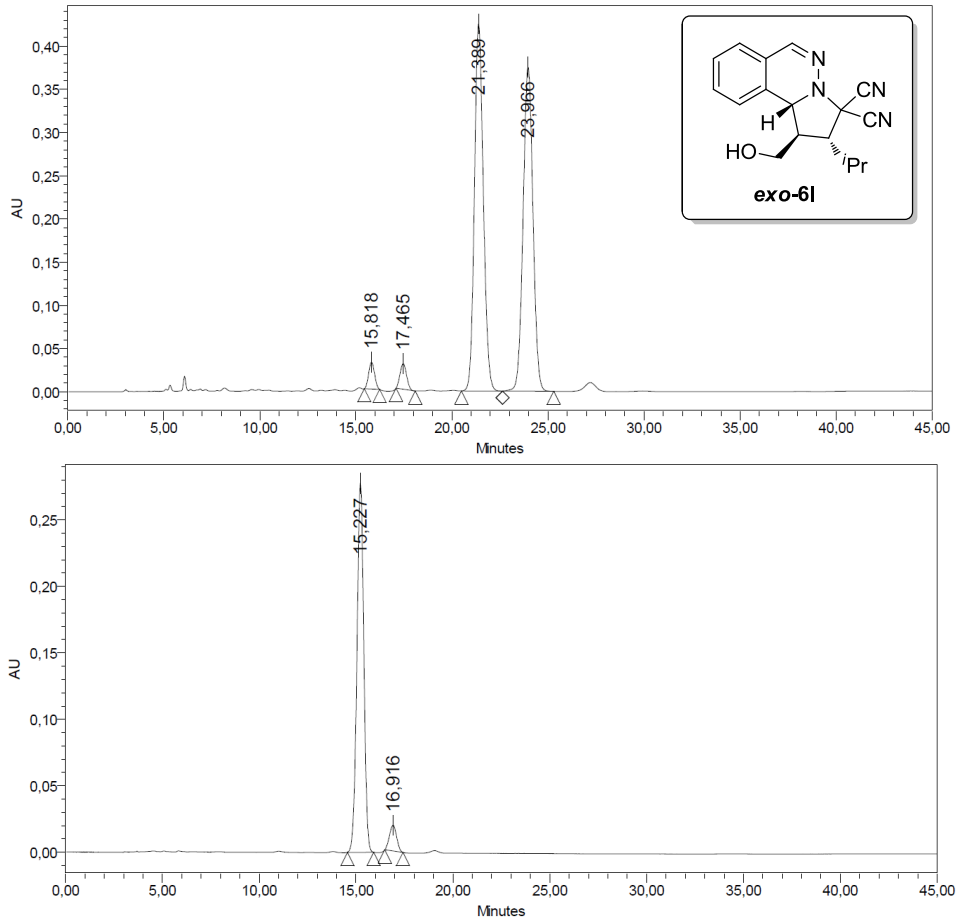
Cromatograma del compuesto ***exo*-6a**.



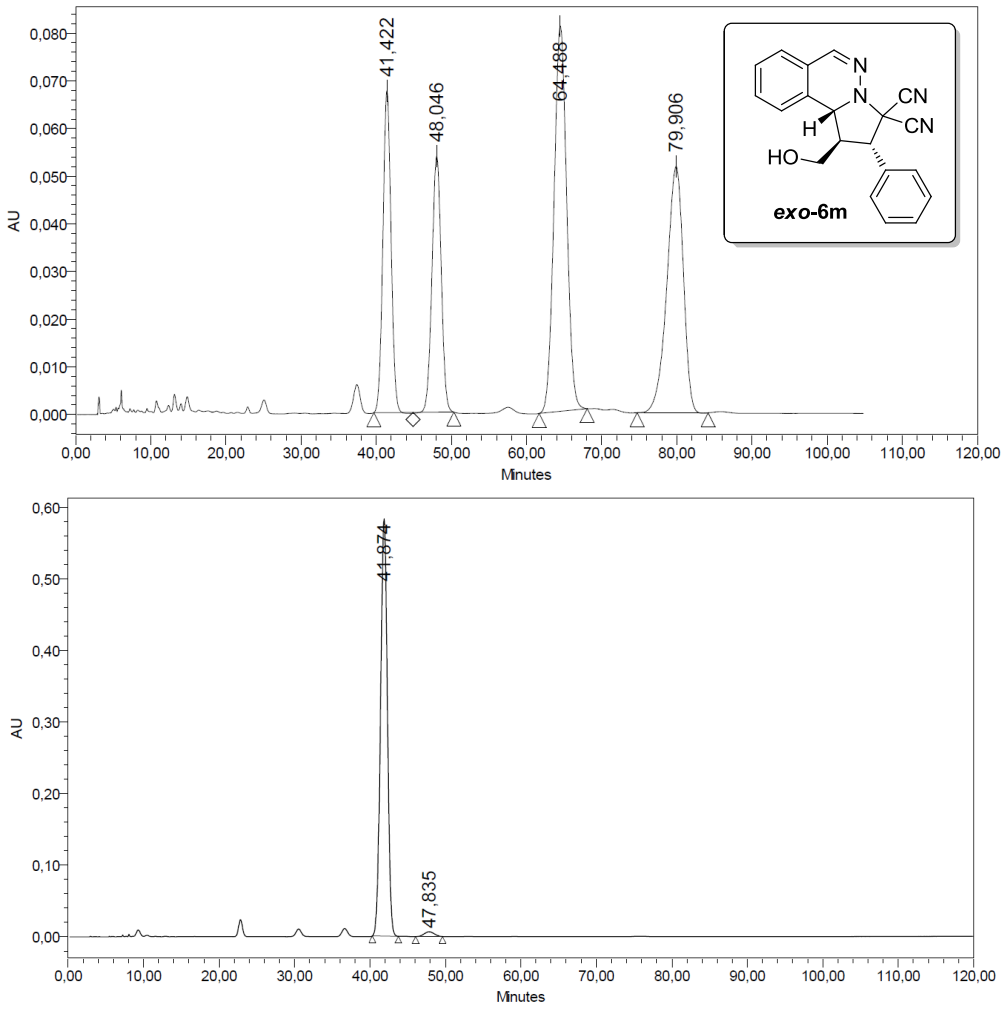
Cromatograma del compuesto ***exo*-6k**.



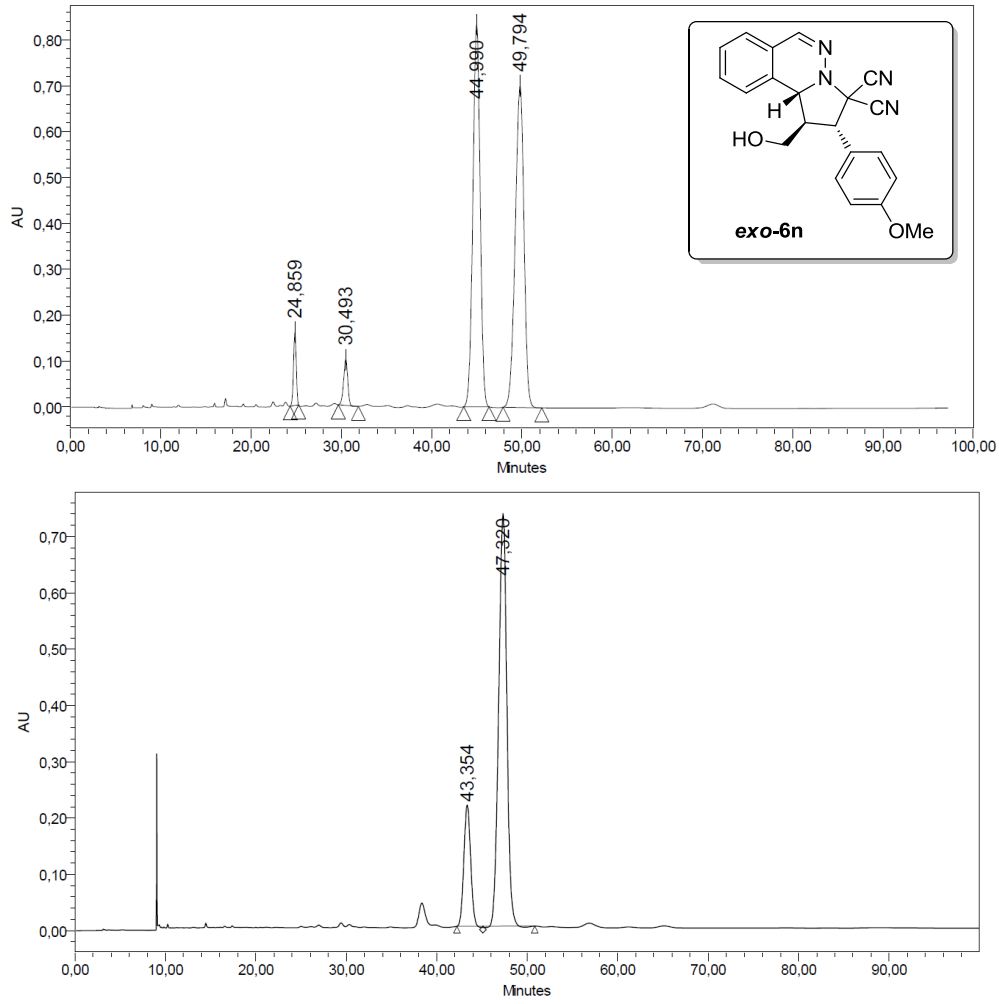
Cromatograma del compuesto ***exo*-6l**.



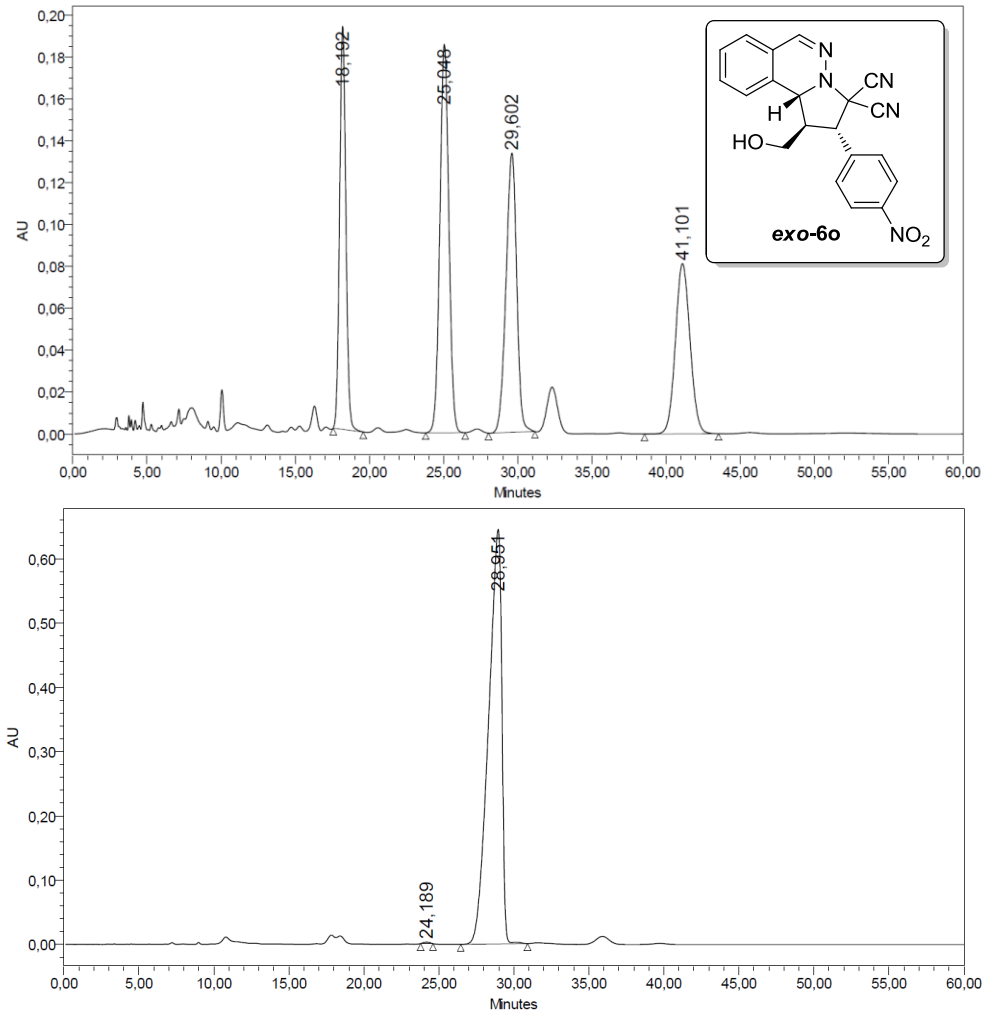
Cromatograma del compuesto ***exo*-6m**.



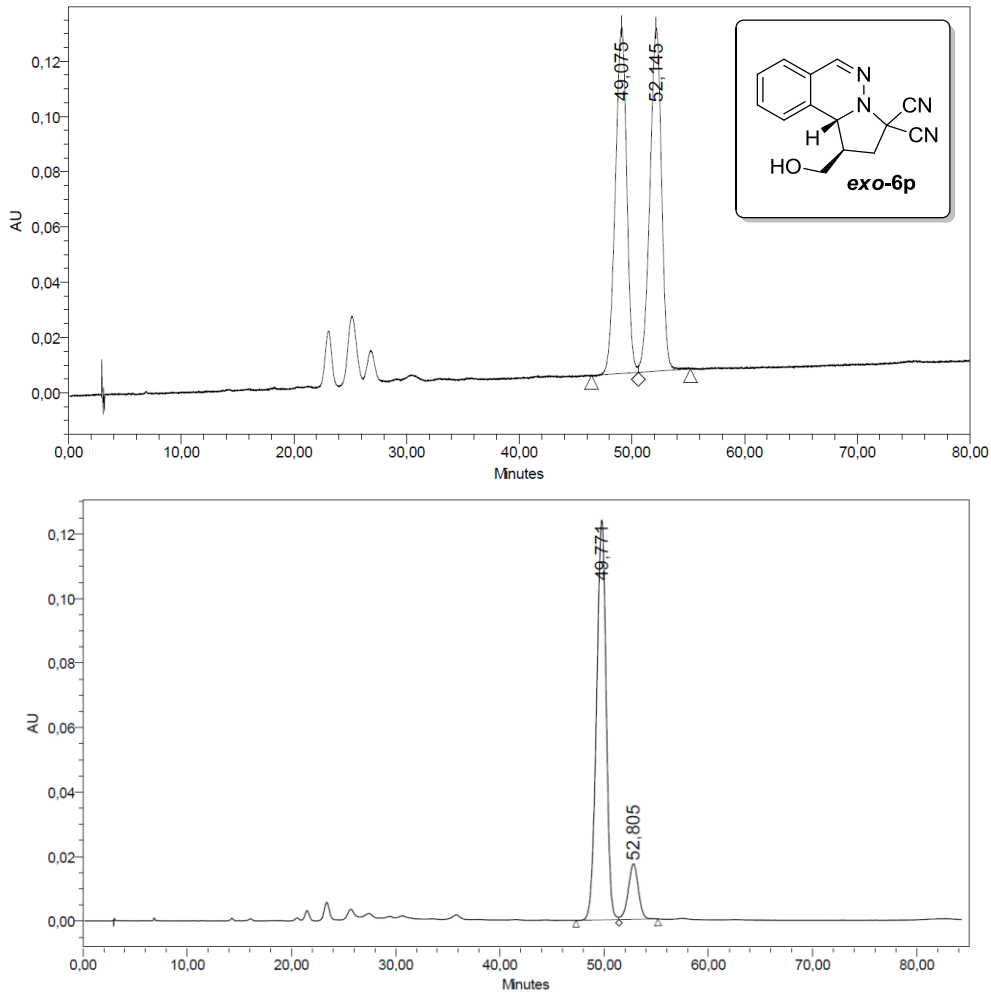
Cromatograma del compuesto ***exo*-6n**.



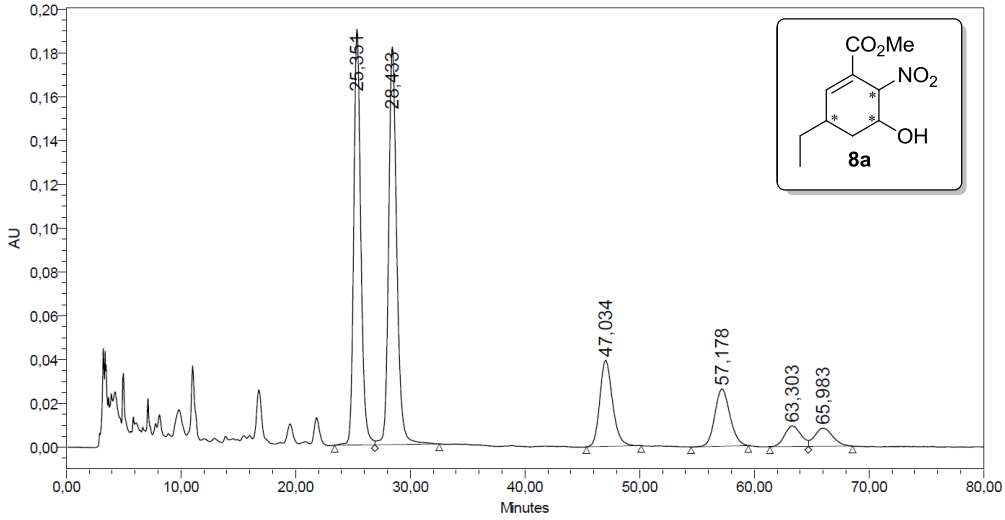
Cromatograma del compuesto ***exo*-6o**.

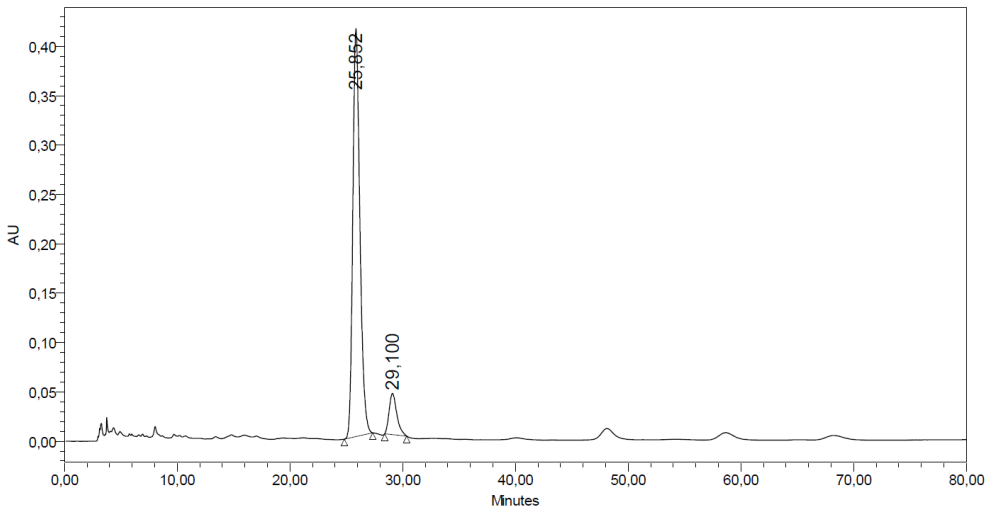


Cromatograma del compuesto ***exo*-6p**.

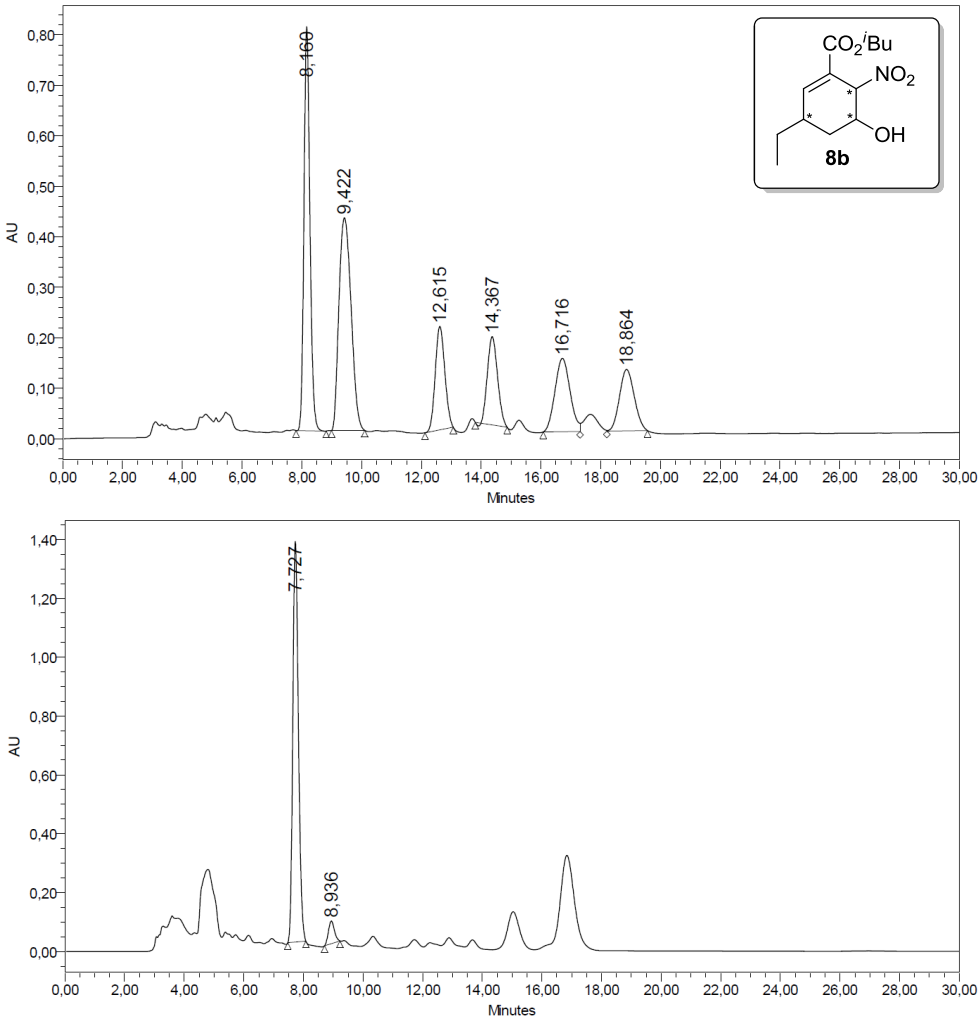


Cromatograma del compuesto **8a**.

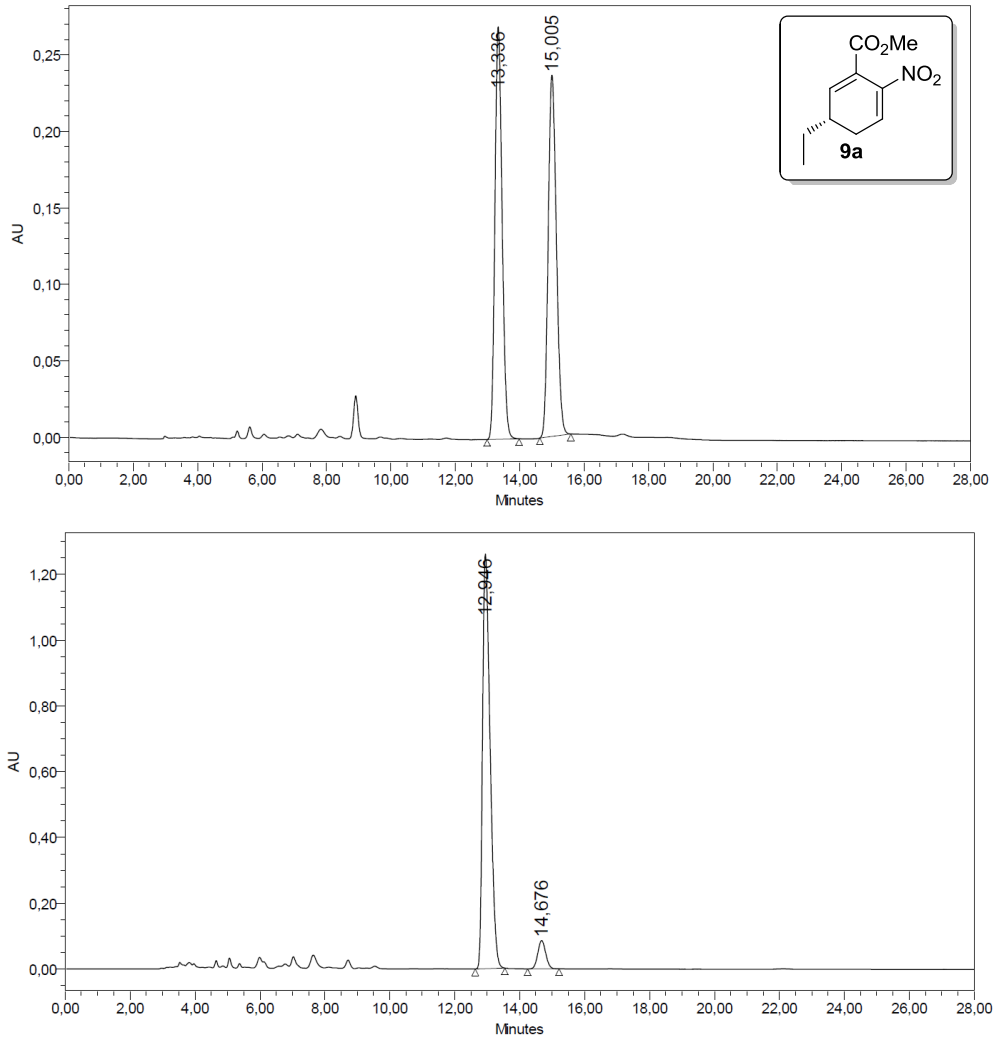




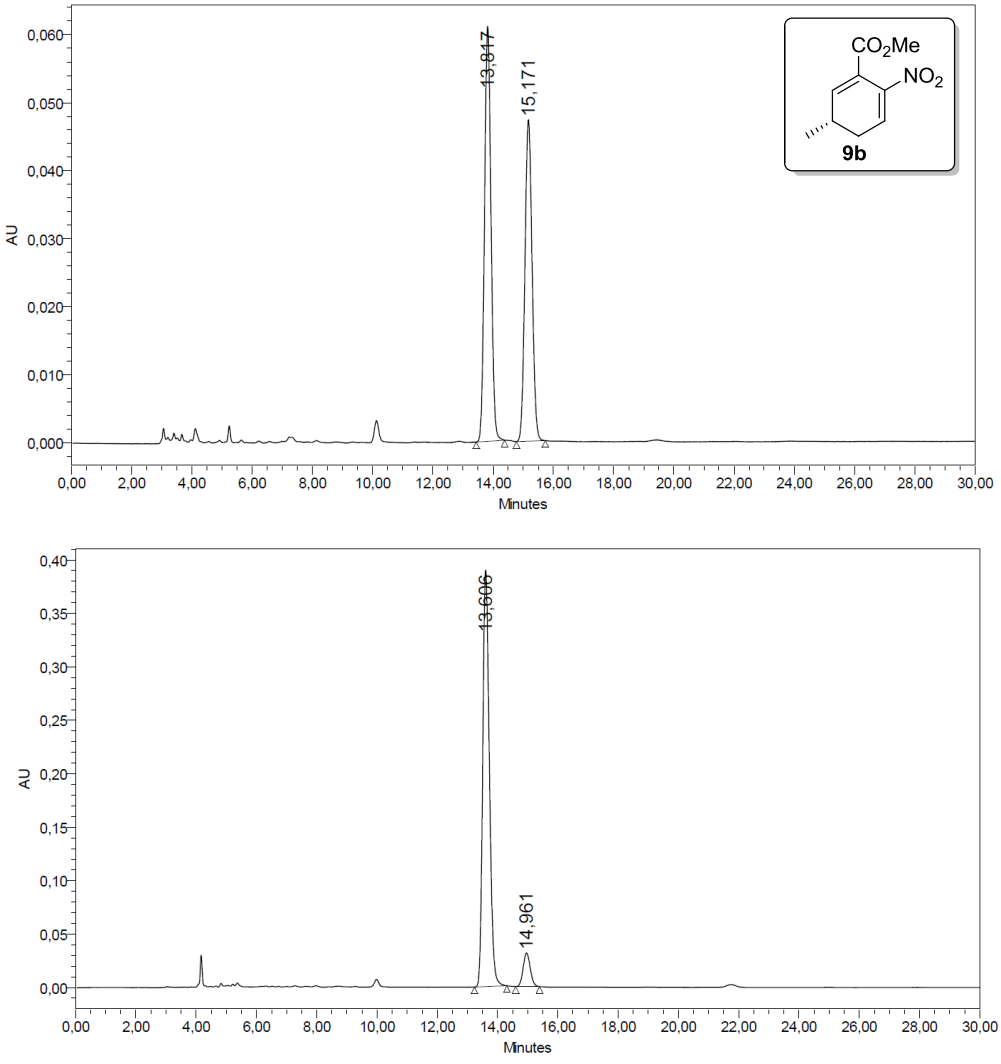
Cromatograma del compuesto **8b**.



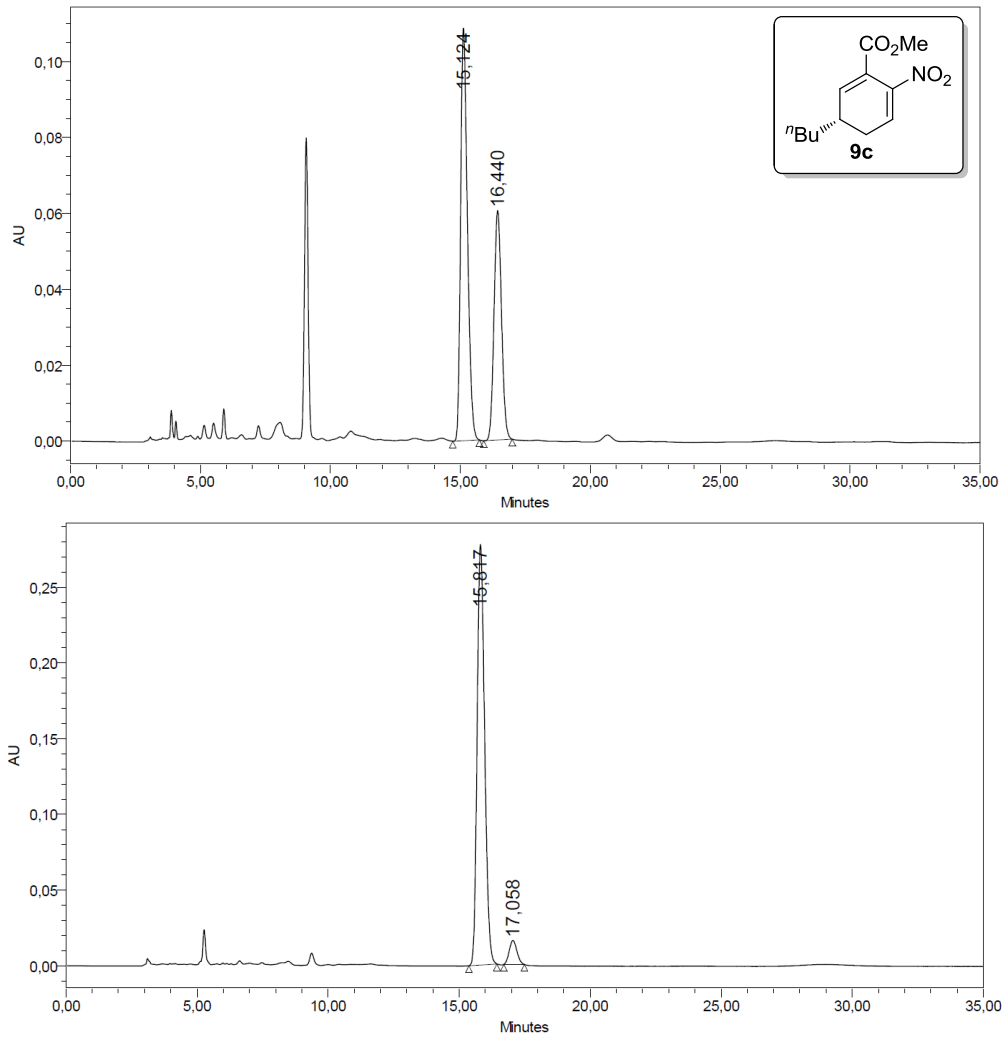
Cromatograma del compuesto **9a**.



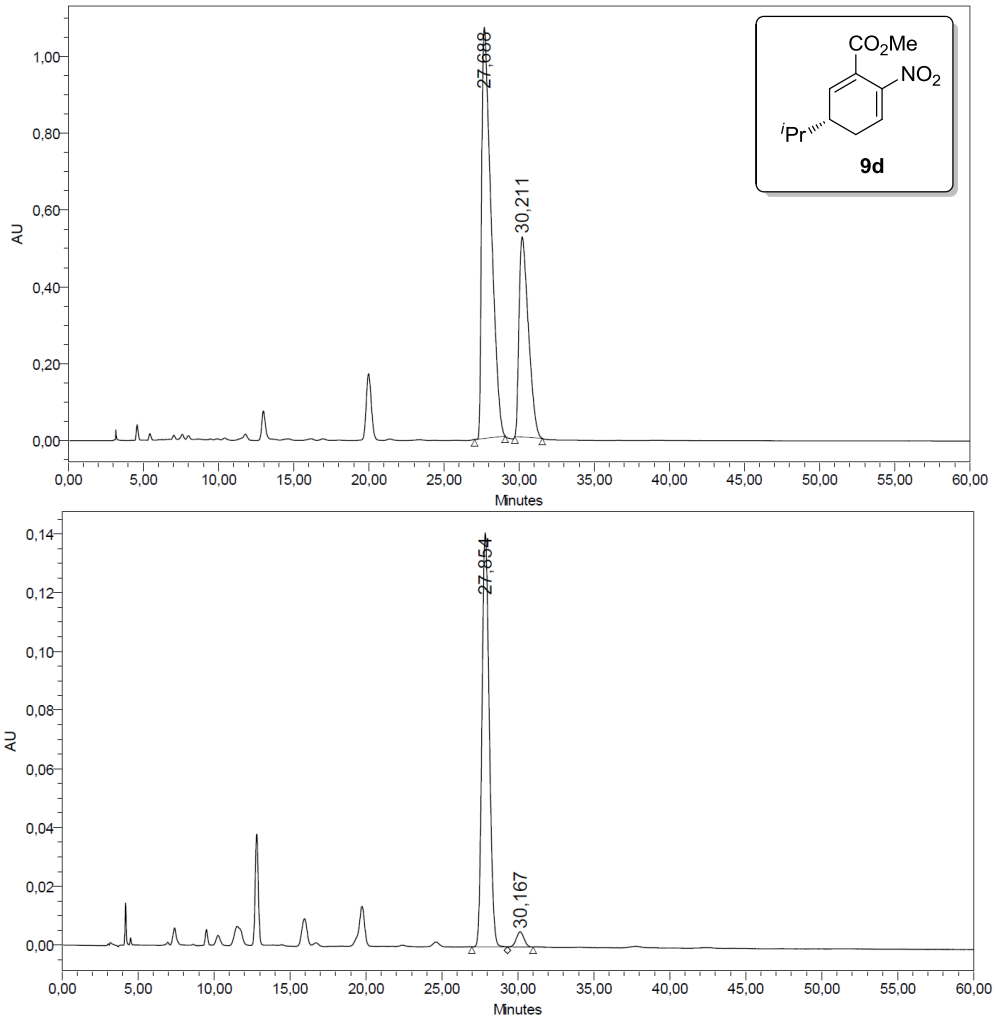
Cromatograma del compuesto **9b**.



Cromatograma del compuesto **9c**.



Cromatograma del compuesto **9d**.



Cromatograma del compuesto **9e**.