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# Covalent organocatalysis for the development of new methodologies in asymmetric synthesis

MEMORIA PRESENTADA POR

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*A mi familia y amigos*

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*I must also mention Professor F. Dean Toste. I would like to thank him for the opportunity he gave to me to work in his group, as well as for all the time he dedicated to me during my stay in Berkeley; always trying to make it the most enriching experience possible.*

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**Abstract**

In the work compiled in this thesis, different methodologies have been developed based on the organocatalytic activation of substrates through covalent intermediates in order to obtain enantioenriched interesting products. In particular, chiral *N*-Heterocyclic carbenes and secondary amines has been used as catalysis.

In this sense, first we evaluated α'- and β- substituted ynones as activated electrophilic partners in benzoin reactions with aldehydes. On the one hand, their ability as electrophilic counterpart in the enantioselective aldehyde-ketone cross-benzoin reaction has been established, using a variety of aldehydes as acyl anion equivalent precursors. In addition, this transformation has been postulated as an interesting alternative for the synthesis of enantioenriched propargylic alcohols, and the value of the obtained adducts as building block has been demonstrated in a series of transformations.

Secondly, the synthetic potential of donor-acceptor cyclopropanes has been studied under organocatalytic activation. On the one hand, formylcyclopropanes have been activated towards the ring-opening and subsequent formal (4+2) cycloaddition employing *N*-Heterocyclic carbene catalysis in highly enantioselective processes. Additionally, the potential of cyclopropaneacetaldehydes in ring-opening/Michael initiated cascade reactions has been demonstrated under iminium catalysis. This methodology has given

straightforward access to different complex heterocyclic structures, such as quinolines and pyrroloquinolines in highly enantioselective reaction sequences.

Finally, and as part of a short stay carried out in the laboratories of Prof. F. D. Toste in the University of California, Berkeley, I collaborated in a project directed towards the enantioselective aminofluorination of β-fluorostyrenes. This objective was approached employing high oxidation state palladium catalysis and using employing *N*-fluorobenzenesulfonimide as electrophilic fluorine source.

**Resumen**

En el trabajo de investigación recogido en la presente memoria, se han desarrollado nuevas metodologías en la activación organocatalítica de sustratos a través de intermedios covalentes para la obtención de productos enantioenriquecidos de interés. En particular, se han empleado tanto carbenos *N*-heterociclicos quirales como aminas secundarias quirales como catalizadores.

En este sentido, en primer lugar diferentes inonas α'- y β- sustituidas fueron testadas como reactivos electrófilos en la condensación benzoínica con aldehídos. Por un lado, se ha demostrado que estos compuestos son capaces de actuar como electrófilos en la condensación benzoínica cruzada enantioselectiva entre aldehídos y cetonas frente a diversos aldehídos empleados como precursores de equivalentes anión acilo. Además, esta transformación se presenta como una alternativa a la síntesis de alcoholes propargílicos enantioenriquecidos, al tiempo que mediante una serie de transformaciones de los aductos obtenidos, se ha demostrado el valor de estos como "building blocks"

En segundo lugar, se ha estudiado el potencial sintético de los cyclopropanos dadores-aceptores mediante el empleo de la organocátalisis como método de activación. Por un lado, se han empleado carbenos N-heterocíclicos en la activación de formilciclopropanos para su apertura y posterior participación en cicloadiciones formales (4+2) dentro de procesos altamente enantioselectivos. Por otro lado, el potencial de los ciclopropanoacetaldehídos para dar lugar a reacciones en cascada iniciadas por una secuencia de apertura de anillo seguida de una adición tipo Michael ha sido demostratada mediante el empleo de

catálisis *via* iones iminio. Esta metodología ha sido aplicada a la obtención de estructuras heterocíclicas complejas, como quinolinas y pirroloquinolinas, de manera directa y por medio de sequencias de reaction altamente enantioselectivas.

Por último y en el contexto de una estancia de corta duración en el grupo de investigación dirigido por el Prof. F. Dean Toste en la Universidad de California, Berkeley, se realizaron estudios sobre la aminofluorinación enantioselectiva de β-fluoroestirenos. Con este fin, se empleo una fuente de paladio como catalizador para que en presencia de N-fluorobencenosulfonamida como agente oxidante y fuente de fluor, tenga lugar la reacción a través de un mecanismo en el que participen especies catalíticas con estados de oxidación altos.

**Laburpena**

Doktorego tesi honetan, metodologia berriak garatu dira organokatalitikoki aktibatuta dauden substrato moldakorrak erabiliz. Horretarako, amina sekundarioen katalisian eta karbeno N-heterozikliko katalisian oinarrituta erreakzio enantioselektiboak garatu dira produktu interesgarriak sintetizatzeko.

Lehenik eta behin, α',β-ordezkaturiko inonak substrato egokiak direla egiaztatu da, zetona eta aldehido bitarteko "*cross-benzoin*" erreakzioa burutzeko, karbeno N-heterozikliko erabiliz katalitzaile gisa. Honela, hainbat ynona eta aldehido desberdinen arteko erreakzioak alkohol propargilikoak modu enantioselektiboan eta etekin altuarekin sintetizatzea ahalbidetzen du. Lortutako aduktuekin transformazio ugari egin dira, produktu hauen balio sintetikoa agerian utziz.

Bestalde, zikloadizio eta kaskada prozesuetarako erreaktibo multifuntzional gisa, formilziklopropanoak eta ziklopropanoazetaldehidoak erabili dira organokatilikoki eragindako eraztun irekieraz baliatuz. Alde batetik, karbeno N-heterozikliko erabili dira oxadienoekin batera [4+2] zikloadizioak burutzeko. Horrela, ketoester ugari erabilita piranona ezberdinak sintetizatu dira etekin altuekin. Bestalde, ziklopropanoazetaldehidoen balioa aza-Michael/aldol bidezko kaskada erreakzioetan frogatu da, hasierako emaile bezala aminobenzaldehidoak erabiliz eta iminio eta enamina bidezko aktibazioak konbinatuz. Gainera, pirrolokinolina eratorri sintetikoak modu estereokontrolatuan prestatu dira, *one-pot* bidezko aza-Michael/aldol/lakatmizazioa prozesuaren bitartez.

Azkenik, F. D. Tosteren taldean (University of California, Berkeley) buruturiko egonaldi laburrean, fluoroestirenoen aminofluorinazioan lan egiteko aukera izan nuen. Honelako transformazioa lortzeko paladio (IV) espeziek partu hartu behar dute eta horretarako N-fluorobenzenosulfonamida erabili izan da oxidatzaile eta fluor-iturri gisa.

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**The references and the numbering of figures, schemes and tables have been restarted at the beginning of each chapter**.

# 1

# 1

# Introduction

## 1.- ASYMMETRIC ORGANOCATALYSIS

The increased interest in asymmetric synthesis has led to the development of new strategies to satisfy the high demand of chiral compounds. In a field that has been dominated by enzymatic transformations[1] and metal catalysis,[2] asymmetric organocatalysis has emerged as a complementary methodology, as it has been stated by the large number of publications in the last two decades.[3] This method consists on the capability of small organic molecules that do not contain any metal

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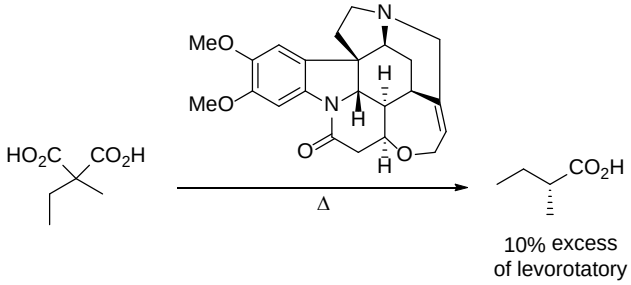
1 Enzymatic catalysis: a) *Enzyme Catalysis in Organic Chemistry*, 3rd ed. (Eds.: Drauz, K.; Waldmann, H.), Wiley-VCH, Weinheim, **2012**; b) Muhammad, M.; Noriho, K.; Masahiro, G. *Org. Biomol. Chem*. **2010**, *8*, 2887; c) Junhua, T.; Zhao, L.; Ran, N. *Org. Process Res. Dev*. **2007**, *11*, 259.

2 Metal catalysis: a) *Metal Catalyzed Reactions in Water* (Eds.: Dixneuf, P. H.; Cadierno, V.), Wiley-VCH, Weinheim, **2013**; b) *Homogeneus Catalysis with Metal Complexes* (Ed.: Temkin, O. N.), Wiley, **2012**; c) *Transition Metals for Organic Synthesis*, 2nd ed. (Eds.: Beller, M.; Bolm, C.), Wiley-VCH, Weinheim, **2004**; d) *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: Ojima, I.), Wiley-VCH, New York, **2000**.

3 General reviews on organocatalysis: a) Marson, C. M. *Chem. Rev*. **2012**, *41*, 7712; b) Jacobsen, E. N.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci*. USA **2010**, *107*, 20618; c) Marqués-Lopez, E.; Herrera, R. P.; Christmann, M. *Nat. Prod. Rep*. **2010**, *27*, 1138; d) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev*. **2009**, *38*, 2178; e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304; f) Special issue on organocatalysis: *Chem. Rev*. **2007**, *107*, 5413; g) Yang, J. W.; List, B. *Science* **2006**, 1584. See also: h) *Stereoselective Organocatalysis. Bond Formation and Activation Modes* (Ed.: Rios Torres, R.), Wiley, **2013**; i) *Asymmetric Organocatalysis in Natural Product Syntheses*. (Ed.: Waser, M.), Springer, Wien, **2012**; j) *Organocatalytic Enantioselective Conjugate Addition Reactions: A Powerful Tool for the Stereocontrolled Synthesis of Complex Molecules* (Eds.: Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.), RSC Publishing, Cambridge, **2010**.

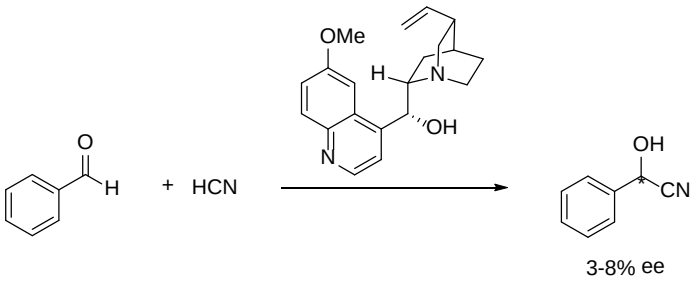
atom in their active site to act as highly selective and efficient catalyst in a variety of organic transformations.

The first organocatalytic enantioselective reaction dates back to 1904,[4] when Marckwald obtained a slight excess of the levorotatory form of α-methylbutyric acid in the enantioselective decarboxylation of 2-ethyl-2-methylmalonic acid upon heating the starting material in the presence of *brucine* (Scheme 1.1).




**Scheme 1. 1**

On the other hand, the first organocatalytic enantioselective C-C bond formation reaction has been attributed to Bredig and Fiske for their work on the synthesis of mandelonitrile in 1913. Although the addition of HCN to benzaldehyde in the presence of quinine or quinidine rendered the corresponding cyanohydrins with poor enantiocontrol (up to 8% ee) (Scheme 1.2),[5] this example is considered as an important precedent in the field.

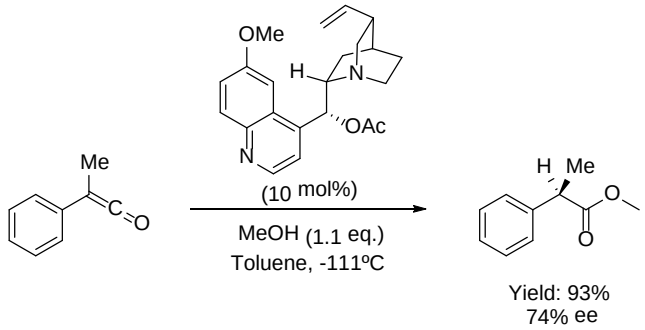



**Scheme 1. 2**

[4] a) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 349; b) Marckwald, W. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 1368.

[5] Bredig, G.; Fiske, P. S. *Biochem. Z.* **1913**, *46*, 7.

Later on, in 1949, Wolfgang Langebeck referred to those reactions promoted by organic molecules with the term "organic catalyst" for the first time.[6] In 1960 Pracejus published the addition of methanol to methylphenylketene in the presence of *O*-acetylquinine, which can be considered as the first organocatalytic transformation that proceeded with a significant levels of enantioselectivity (Scheme 1.3).[7]




**Scheme 1. 3**

In 1971 two industry research groups at Hoffmann-La Roche[8] and Schering-Plough[9] reported independently an L-proline catalyzed intramolecular aldol reaction, which gave access to chiral bicyclic intermediates employed in the synthesis of steroids and terpenes (Scheme 1.4). The reaction, nowadays known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction, is considered as an important landmark for the development of organocatalysis, since a reversibly formed nucleophilic enamine was tagged as a key intermediate in the catalytic cycle. This finding set the basis for what is nowadays known as aminocatalysis.

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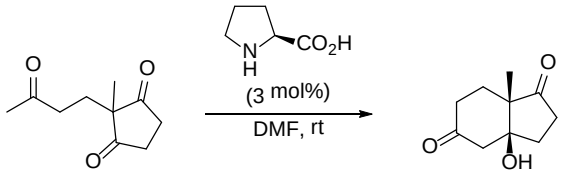
6 *Die Organiche Katalysatoren und ihre Beziehungen zu den Fermenten* (Ed.: Langebeck, W.), Springer-Verlag, Berlin, **1949**.

7 Pracejus, H. *Justus Liebigs Ann. Chem*. **1960**, *634*, 9.

8 a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem*. **1974**, *39*, 1615; b) Hajos, Z. G.; Parrish, D. R. *German Patent* DE 2102623, **1971**.

9 a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem. Int. Ed.* **1971**, *10*, 496; b) Eder, U.; Sauer, G.; Wiechert, R. *German Patent* DE 2014757, **1971**.




**Scheme 1. 4**

In the period from the 1980s to the late 1990s significant progresses were made in this field. For instance, chiral Brønsted acids were employed for the asymmetric hydrocyanation of aldehydes and imines described by Inoue[10] and Jacobsen[11]. Another example is the use of quaternary ammonium salts based on cinchona alkaloids for the enantioselective alkylation of enolates, under phase-transfer-catalysis conditions.[12]

Nevertheless, organocatalysis remained as a very limited research topic until 2000, when the first enantioselective intermolecular aldol reaction employing L-proline as catalyst was published by List, Lerner and Barbas III in an attempt to mimic the behaviour of the enzymes (Scheme 1.5).[13] Interestingly, this work was the culmination of a research that started with the use of aldolase antibodies as catalysts for aldol reactions.[14] Mechanistic studies on the aldolase catalyzed reaction gave proof of the participation of enamine intermediates in the reaction. Based on this fact, it was found out that a simple aminoacid (L-proline) was able to catalyze the aldol reaction between acetone and different aldehydes to obtain excellent yields and enantioselectivities.

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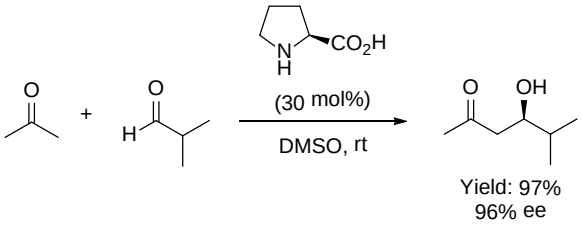
10 Oku, J.; Inoue, S. *J. Chem. Soc. Chem. Commun*. **1981**, 229.

11 a) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 10012; b) Sigman, M. N.; Pederson, R. L.; Wang, Y. F.; Wong, C. H. *J. Am. Chem. Soc*. **1998**, *120*, 4901.

12 a) Conn, R. S. E.; Lovell, A. V.; Karady, S.; Weinstock, L. M. *J. Org. Chem*. **1986**, *51*, 4710; b) Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*., **1984**, *106*, 446.

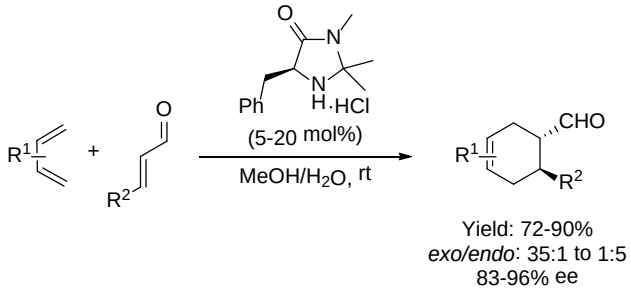
13 List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395.

14 Notz, W.; Tanaka, F.; Barbas III, C. F. *Acc. Chem. Res*. **2004**, *37*, 580.




**Scheme 1. 5**

On the other hand, that same year, MacMillan published the first enantioselective organocatalytic Diels-Alder reaction catalyzed by a chiral imidazolidinone salt. The secondary amine was able to reversibly condense with enals leading to a new activation concept named after the reactive intermediate generated, iminium catalysis (Scheme 1.6).[15] The generated iminium ion has a LUMO lower in energy in comparison with the starting α,β-unsaturated aldehyde, which results in a diene more reactive towards the Diels-Alder reaction, or in a more general way, a β-carbon more susceptible to nucleophilic attack.




**Scheme 1. 6**

These pioneering works on enamine and iminium catalysis have served as a precedent for the application of this concept leading to a high number of publications.[16] In addition, other organocatytic activation manifolds (for instance, hydrogen-bonding catalysis, PTC, NHC catalysis) has also contributed to expand the

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[15] Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243.

[16] For some recent reviews exclusively focused on asymmetric aminocatalysis, see: a) Li, J. L.; Liu, T. Y.; Chen, Y. C. *Acc. Chem. Res*. **2012**, *45*, 1491; b) Arceo, E.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 5290; c) Giacalone, F.; Gruttadauria, M.; Agrigento, P.; Noto, R. *Chem. Soc. Rev*. **2012**, *41*, 2406; d) Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084; e) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632.

range of organic reactions that are amenable to be catalyzed using a small chiral organic molecule. Nowadays organocatalysis is considered as a powerful tool in the area of asymmetric synthesis, together with already mentioned metal and enzymatic catalysis, for its application in basic and applied research.[17] The exponential development of this methodology relies on its numerous advantages when compared with other types of catalysis. In this regard, organocatalysts can be employed under milder and less rigorous conditions,[3f,18] as in general they are stable and insensitive to oxygen and moisture. Those are also the reasons why those catalysts are usually cheap and readily available. Moreover, the absence of metals in the reaction media makes this methodology environmentally friendly and of particular interest for certain porpoises, such as the synthesis of pharmaceutical drugs. All in all, it can be affirmed that this methodology falls under the banner of green chemistry. In addition, it should be mention that compared to highly specific enzymatic catalysts, organocatalysts are more stable and generic.

Despite of the abovementioned advantages, this synthetic strategy has several drawbacks that should be considered as well. Especially when compared to metal catalysis, organocatalyzed transformations typically require longer reaction times and higher catalyst loadings. On the other hand, its application in industry is rather limited, being the insufficient efficiency at large scale one of the main problems. Recently, this area has brought more interest with studies regarding the scale-up of the reactions and the recovery of the catalyst.[19]

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17 a) Howell, G. P. *Org. Process. Res. Dev*. **2012**, *16*, 1258; b) Busacca, C. A.; Frandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825.

18 Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discov. Today*, **2007**, *12*, 8.

19 a) Shaikh, I. R. *J. Catal.* **2014**, 402860; b) Li, S.; Wu, C.; Long, X.; Fu, X.; Chen, G.; Liu, Z. *Catal. Sci. Tech*. **2012**, *2*, 1068.

## 2.- ORGANOCATALYTIC ACTIVATION MECHANISMS

One of the reasons for the success of this methodology arises from the variety of generic modes of activation, asymmetric induction and reactivity exhibited by organocatalysts within the catalytic cycle. The value of those generic models is based on their simplicity and applicability for the design of new enantioselective transformations. Based on the interactions between the catalyst and the substrate, the most common generic activation modes have been classified on two groups. Processes which involve the formation of catalyst-substrate covalent adducts, will be included into the covalent catalysis, whilst those in which the catalyst activates the substrate *via* weaker interactions, such as ion pairs or hydrogen bonds, may be considered as a non-covalent catalysis. Some representative organic catalyst employed under different activation modes are shown in Figure 1.1 and divided attending to the already established classification.

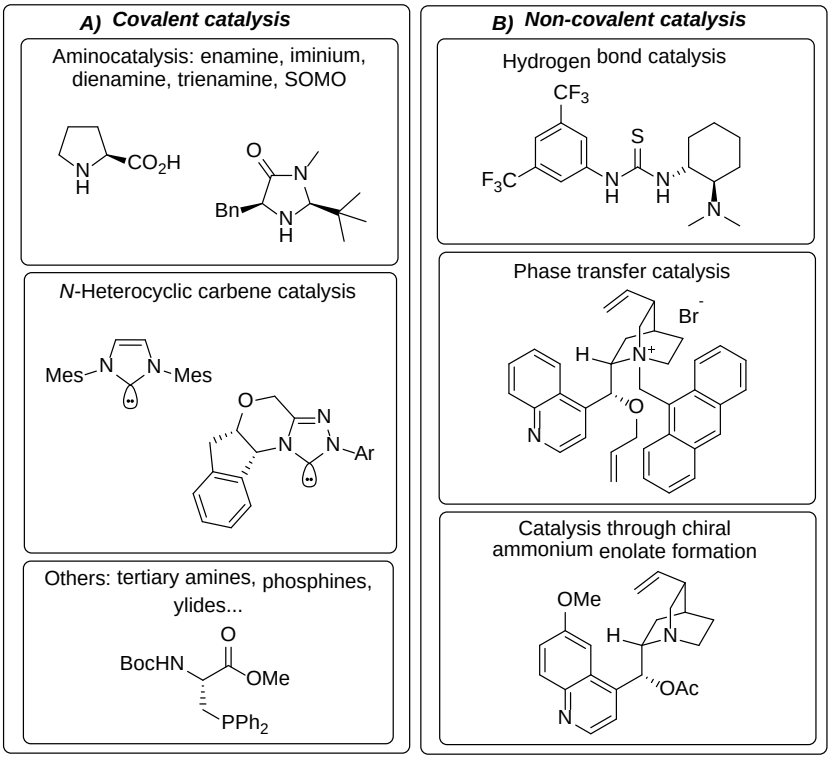


**Figure 1. 1**

The majority of reports on the field of organocatalysis refer to covalent catalysis. This activation relies on the capability of the catalyst to reversibly form a covalent bond with the substrate, assuring the generation of the activated catalyst-substrate adduct and enabling the catalyst turnover through the cleavage of that bond. An efficient transfer of the chiral information from the catalyst to the substrate can be achieved as a result of the strong interaction that binds them. However, this strong interaction may negatively affect the catalyst turnover step, requiring typically high catalyst loadings and longer reaction times.

**Aminocatalysis** and ***N*-heterocyclic carbene** catalysis are the most studied fields in the covalent catalysis. The first one, which consists on the use of chiral primary or secondary amines as catalyst, has been widely employed in a number of transformations through the reversible formation of enamine/iminium type intermediates.[16] The second is based on the use of *N*-heterocyclic carbenes (NHCs) in the generation of a nucleophilic intermediate (Breslow intermediate) upon condensation of the catalyst with an aldehyde. This species may attack an electrophile in an overall process that implies an inversion of the classical reactivity of aldehydes.[20] Those activation modes, due to their importance in the present work, will be later discussed in more detail. Other activation modes including the use of phosphines and tertiary amines acting as Lewis bases belong to this group. This manifold consists on the activation of multiple C-C bonds by conjugate addition of those nucleophilic catalyst to form **ylides** as reactive intermediates.

[20] For selected reviews on the use of NHCs as organocatalyst, see: a) Wang, M. H.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2016**, *55*, 14912; b) Walden, D. M.; Ogba, O. M.; Johnston, R. C.; Cheong, P. H. *Acc. Chem. Res.* **2016**, *49*, 1279; c) Flanigan, D. M.; Romanov-Michaidilis, F.; White, N. A.; Rovis, T. *Chem. Rev.* **2015**, *115*, 9307; d) Ryan, S. J.; Candish, L.; Lupton, D. W. *Chem. Soc. Rev.* **2013**, *42*, 4906;. e) Chen, X.-Y.; Ye, S. *Org. Biomol. Chem.* **2013**, *11*, 7991; f) Bugaut, X.; Glorius, F. *Chem. Soc. Rev.* **2012**, *41*, 3511; g) Biju, A. K.; Kuhl, N.; Glorius, F. *Acc. Chem. Res.* **2011**, *44*, 1182; h) Marion, N.; Díez-González, S.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; i) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606.

On the other hand, non-covalent catalysis comprehends all the organocatalytic transformation based on weaker interactions. Thus, the catalyst turnover is not affected to the same extent as in covalent catalysis, resulting in lower catalyst loadings and shorter reaction times. Despite the advantages of this approach regarding the thoroughly criticized aspects of organocatalysis, the weak catalyst-substrate interaction, which implies a higher conformational freedom, may pose a problem with respect to stereocontrol.

**Hydrogen bonding catalysis**[21] stands as one of the most relevant activation modes under non-covalent catalysis. Molecules bearing different hydrogen-bond donor motifs, such as ureas and thioureas,[22] squaramides,[23] and phosphoric acids,[24] are able to through the formation of this kind of interactions with several functional groups in the substrate catalyze a manifold of reactions. These interactions release electronic density from the substrate and simultaneously define the spacial disposition of the catalyst and substrate for the formation of new bonds, allowing for a high stereochemical control.[25] **Phase transfer catalysis** (PTC)[26] is another important activation method based on non-covalent catalysis. This particular mode consists on a two or three phase system, in which the formed catalyst-substrate ion pair migrates from one phase to the other in a reversible manner. Another relevant

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21 For recent reviews on hydrogen-bonding catalysis, see: a) Siau, W. Y.; Wang, J. *Catal. Sci. Technol*. **2011**, *1*, 1298; b) *Hydrogen Bonding in Organic Synthesis* (Ed.: Pihko, P. M.), Wiley-VCH, Weinheim, **2009**; c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*. **2007**, *107*, 5713; d) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed*. **2006**, *45*, 1520.

22 For specific review on ureas and thioureas as catalysts, see: Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev*. **2009**, *38*, 1187.

23 For specific review on squaramides as catalysts, see: Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J*. **2011**, *17*, 6890.

24 For specific review on phosphoric acids as catalysts, see: a) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev*. **2011**, *40*, 4539; b) Terada, M. *Curr. Org. Chem*. **2011**, *15*, 2227.

25 Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adan, E.; Melchiorre, P. *Org. Lett.* **2013**, *15*, 220.

26 For specific review on chiral phase-transfer catalysis, see: a) Kaneko, S.; Kumatabara, Y.; Shirakawa, S. *Org. Biomol. Chem.* **2016**, *14*, 5367; b) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312; c) Jew. S.; Park, H. *Chem. Commun*. **2009**, 7090; d) Ooi, T.; Maruoka, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 4222.

type of ion-pairing catalysis is based on the use of tertiary amines as Brønsted bases for the activation of nucleophiles by the formation of a chiral ammonium salt.[27]

[27] For a selected review on chiral Brønsted base catalysis, see: Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632.

## 3.- AMINOCATALYSIS

As stated before, aminocatalysis is a dominating activation mode in the field of asymmetric organocatalysis. Chiral primary and secondary amines are employed as catalyst based on their ability to reversibly condense with carbonyl compounds leading to active species. In this sense, the catalyst-substrate covalent interaction may lead to two different azomethine species; enamine and iminium ion. Thus, depending on which of those species promotes the catalyzed reaction, aminocatalysis may be classified into two main activation modes: enamine[28] and iminium[29] catalysis. Some variants of this activation have also been described, including the corresponding vinylogous versions; dienamine, trienamine and vinylogous iminium catalysis,[30] as well as SOMO catalysis.[31] The $\alpha, \beta, \gamma$ and $\delta$ functionalization of carbonyl compounds have been achieved in an efficient manner making use of this methodology.

### 3.1. Enamine catalysis

The term enamine catalysis refers to a catalytic transformation in which the reactive species is an enamine intermediate, generated through the condensation of

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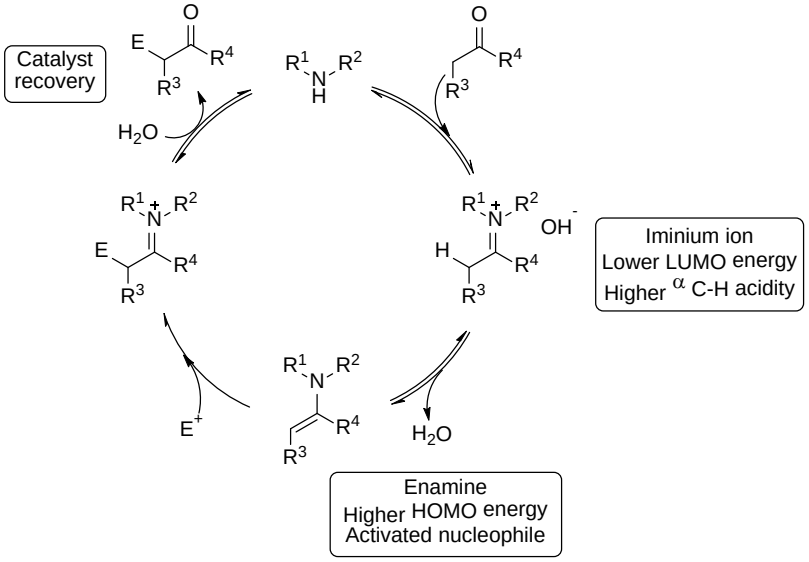
[28] For some general reviews on enamine catalysis, see: a) Desmarchelier, A.; Coeffard, V.; Moreau, X.; Greck, C. *Tetrahedron* **2014**, *70*, 2491; b) Kano, T; Maruoka, K. *Chem. Sci.* **2013**, *4*, 907; c) Rios, R.; Moyano, A. *Catalytic Asymmetric Conjugate Reactions* (Ed.: Córdova, A.), Wiley-VCH, Weinheim, **2010**; d) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465; e) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123; f) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

[29] For some reviews in iminium catalysis, see: a) Vicario, J. L.; Reyes, E.; Badía, D.; Carrillo, L. *Catalytic Asymmetric Conjugate Reactions* p. 219-294 (Ed.: Córdova, A.), Wiley-VCH, Weinheim, **2010**; b) Erkkilae, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416; c) Lelais, G.; MacMillan, D. W. C. *Aldrichim. Acta* **2006**, *39*, 79.

[30] Some recent reviews on vinylogous aminocatalysis: a) Jiang, H. J.; Albrech, L.; Jørgensen, K. A. *Chem. Sci*. **2013***, 4,* 2287; b) Juberg, I. D.; Chatterjee, I.; Tannert, R.; Melchiorre, P. *Chem. Commun*. **2013**, *49*, 4869; c) Li, J. L.; Liu, T. Y.; Chen. Y. C. *Acc. Chem. Res*. **2012**, *45*, 1491.

[31] For a review in SOMO catalysis, see: a) MacMillan, D. W. C.; Rendlen, S*. Asymmetric Synthesis II*. p. 87-94 (Eds.: Christmann, M.; Brase, S.), Wiley-VCH, Weinheim, **2012**. For some examples, see: b) Comito, R. J.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2013**, *135*, 9358; c) Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci*. **2011**, *2*, 1470; d) Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494; e) Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

a primary or secondary amine with an enolizable ketone or aldehyde. The activation of the substrate is based on that the generated catalyst-substrate iminium type adduct has a LUMO lower in energy, compared to the starting carbonyl compound, and therefore a more acidic proton at α–position. This will result in the formation of an enamine with a HOMO higher in energy, which results in an active species of enhanced nucleophilicity compared to the corresponding aldehyde or ketone. After the reaction with an electrophile a hydrolysis step is required to release the catalyst for another run of the catalytic cycle and generate the α–functionalized product (Scheme 1.7).

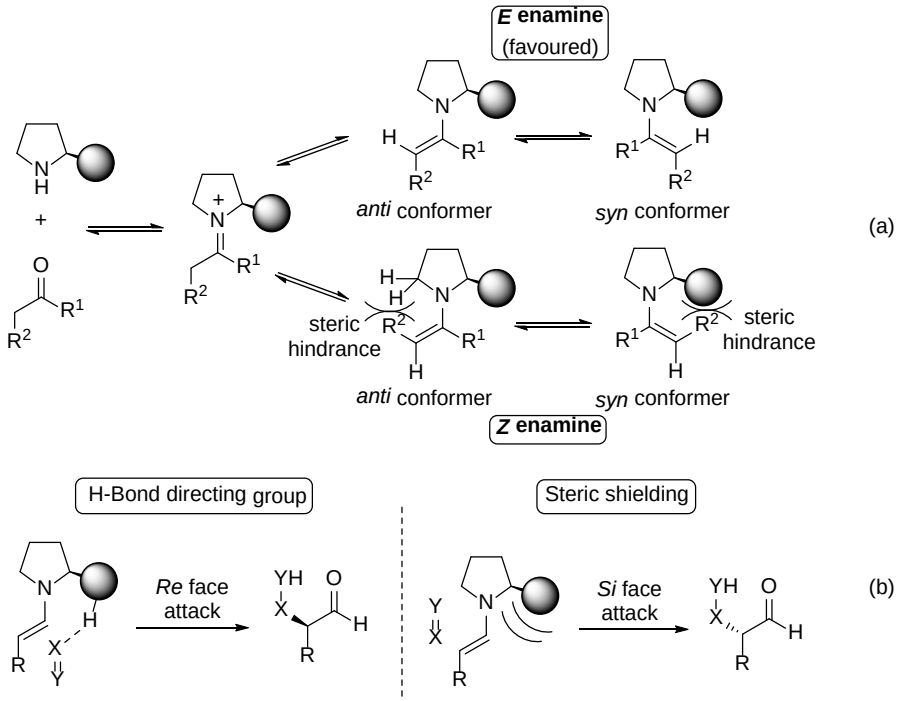



**Scheme 1. 7**

Regarding the stereochemistry of the aminocatalyzed reaction, intensive work has been done in the study of the structure of the enamine intermediates. [32] Thus, in a enantiocontrolled transformation, both the conformational structure of the enamine and the approach of the incoming electrophile should be controlled. First, the system should be restricted by introducing steric hindrance through a wise design of the catalyst in order to guarantee that among all possible enamine intermediates only one is formed (Scheme 1.8a). On the other hand, the chiral

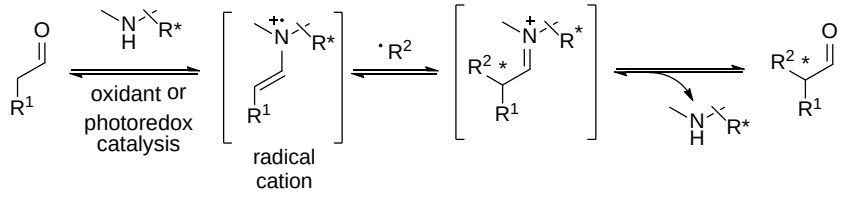
[32] Dinér, P.; Kjaersgaard, A.; Lie, M. A.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 122.

element within the catalyst structure is responsible for the differentiation of the two faces of the enamine nucleophile. In this sense, two strategies have been developed to control the trajectory of the electrophile, H-bond directing stereoinduction and steric shielding (Scheme 1.8b).




**Scheme 1. 8**

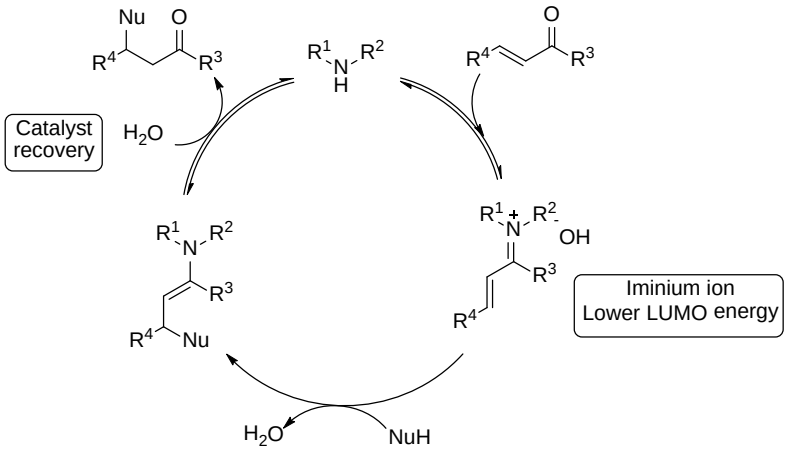
As a variant of the enamine activation, MacMillan introduced in 2007 the concept of SOMO catalysis. This manifold is based on the fact that enamine intermediates are prone to be oxidized and to form a radical-cation with an individually occupied orbital (SOMO). A SOMO-phile is able to trap this radical species to form a new radical intermediate, which upon further oxidation will return to the closed shell configuration (Scheme 1.9). This approach enables the functionalization at α position of the aldehyde or ketone compound in the presence of weak nucleophiles.




**Scheme 1. 9**

### 3.2. Iminium catalysis

This activation mode is based on the reversible condensation of the amine catalyst with a α,β-unsaturated carbonyl compound to form an iminium ion that would participate in the reaction as an electrophilic intermediate. The increased reactivity of this intermediate is explained by the LUMO energy lowering effect that, as it happened in the case of enamine activation, takes place upon condensation of the catalyst to form the iminium species. In this case α,β-unsaturated aldehydes or ketones are employed as substrates leading to an intermediate of increased electrophilic character at the β-position. Upon nucleophilic attack, an enamine type intermediate is generated, which at the final step is hydrolysed to render the β–functionalized product and the catalyst is released (Scheme 1.10).




**Scheme 1. 10**

So as to reach high levels of stereocontrol, the catalyst has to differentiate between the two diastereotopic faces of the Michael acceptor. On the one hand,

this selectivity can be achieved based on steric hindrance if a large substituent is introduced in the catalyst scaffold to shield one of the faces. Alternatively, the presence of a stereodirecting element on the catalyst may control the trajectory of the nucleophile through a secondary interaction of the catalyst (Figure 1.2).

Additionally, the geometry of the iminium ion (*Z* or *E*) has to be controlled if a highly stereoselective process is desired. In this regard, when the addition of the nucleophile is controlled by an stereodirecting group, this interaction would also define the configuration of the Michael acceptor. When the face selectivity is control by steric hindrance, the geometry of the iminium ion will be given by the stability of the possible isomers based on the interaction with the bulky substituent located within the catalyst or by the kinetic preference for one of the isomers to undergo reaction faster with the nucleophile. Thus, a substituent bulky enough would be able to provide a good π-facial discrimination as well as determine the geometry of the intermediate.

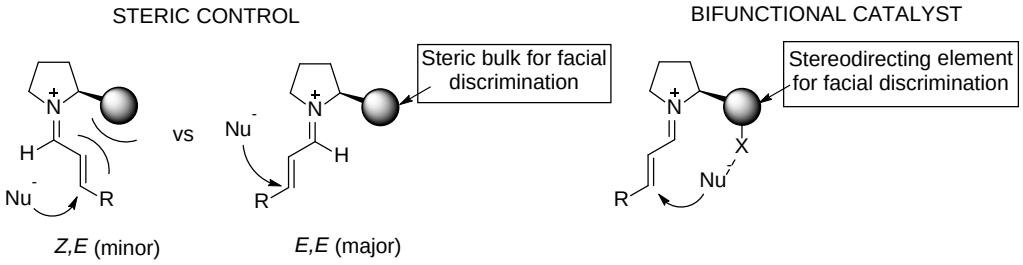
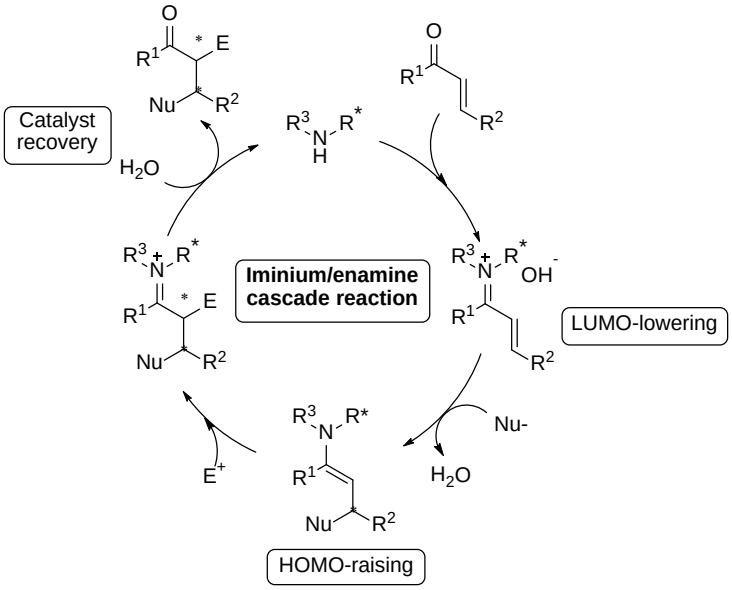



**Figure 1. 2**

As it has been stated in the previous pages, aminocatalysts can promote diverse reactivity patterns through the formation of species of different nature, such as electrophilic iminium ions or nucleophilic enamines. Moreover, those species are common intermediates of the different catalytic cycles (Scheme 1. 7 and Scheme 1. 10). The ability shown by the reaction itself to move from one intermediate to the other enables the combination of both catalytic cycles to promote a *cascade*

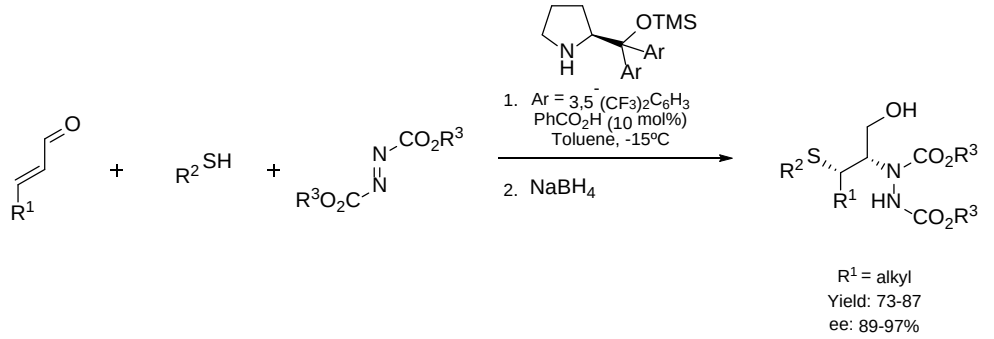
sequence (Scheme 1.11).[33] Thus, the enamine intermediate, generated after the nucleophilic addition to the β-position of the iminium intermediate, can be subsequently trapped by an electrophile leading to an α,β-difunctionalized compound. As in other cases, a final hydrolysis step renders the product and releases the catalyst to restart the catalytic cycle.




**Scheme 1. 11**

Importantly the reversibility of the reaction steps should be considered as it may lead to epimerization of the generated stereocentres. Indeed, hetero-Michael reactions, in which the addition step is reversible, are usually performed at low temperatures to avoid the epimerization (Scheme 1.12).

[33] For some reviews on organocatalytic cascade reactions, see: a) Vetica, F.; de Figueriedo, R. M.;Orsini, M.; Tofani, D.; Gasperi, T. *Synthesis* **2015**, *47*, 2139; b) Volla, C. M. R.; Atodiresei, L.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390; c) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442; d) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237; e) Enders, D.; Grondal, C.; Hütl, M. R. M. *Angew Chem. Int. Ed.* **2007**, *46*, 1570. For specific reviews on aminocatalysis cascade reactions, see: f) Song, A.; Wang, W. *Catalytic Cascade Reactions* (Eds.: Xu, P.-F.; Wang, W.), John Wiley & Sons, p. 1-52, New Jersey, **2014**; g) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.




**Scheme 1. 12**

### 3.3 Dienamine, trienamine and vinilogous iminium ion activation

Another variation of the methodology arose from the combination of the vinilogy concept with the two aminocatalytic activation manifolds. The effect of the catalyst is extended through the conjugated π-system leading to the activation of remote position.[34] Thus, the use of γ-enolizable α,β-unsaturated aldehydes or ketones based on the LUMO-lowering and HOMO-raising effects renders nucleophilic dienamine type intermediates. This concept has also been extended to the formation of trienamine[35] and tetraenamine[36] intermediates as well as the development of vinylogous iminium ions (Scheme 1.13). [37]

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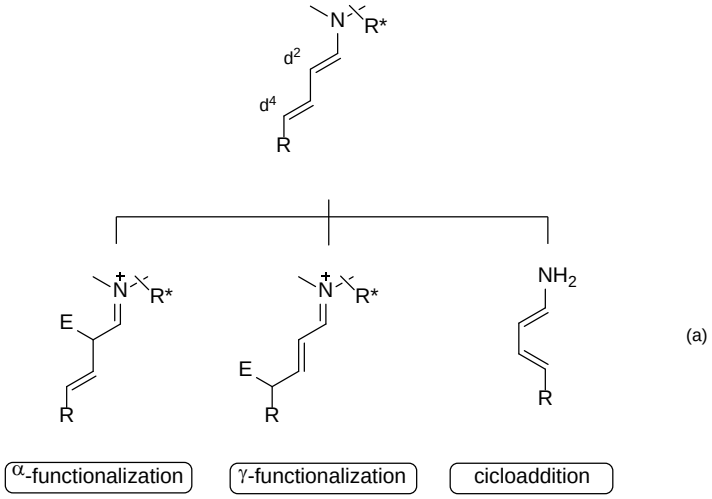
[34] Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem*. **2012**, 865.

[35] Pionering work on trienamine catalysis: Jia, Z. J.; Jiang, J.; Li, J. L.; Gschwend, N.; Li, Q. Z.; Yin, X.; Grouleff, J.; Chen, Y. C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *133*, 5053. A review on trienamine catalysis: Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem*. **2013**, *11*, 709.

[36] Tetraenamine catalysis: Stiller, J.; Poulsen, P. H.; Cruz, D. C.; Dourado, J.; Davis, R. L.; Jørgensen, K. A. *Chem. Sci*. **2014**, *5*, 2052.

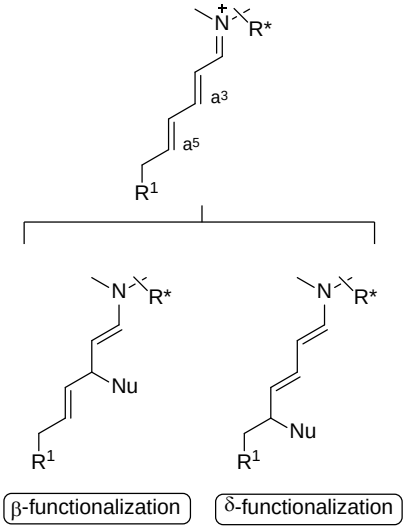
[37] Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem. Int. Ed*. **2012**, *51*, 6439.

**Di- Tri-enamine reactivity**




(a)

**Vinylogous iminium reactivity**

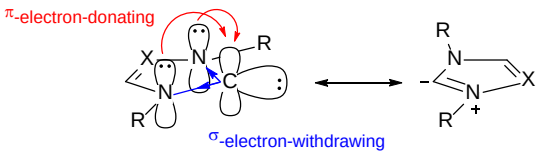



(b)

**Scheme 1. 13**

## 4.- *N*-HETEROCYCLIC CARBENE CATALYSIS

Carbenes, defined as neutral compounds bearing a bivalent carbon atom with a six electron valence shell, are in general, unstable species due to their incomplete electron octet. In contrast, molecules with at least one nitrogen adjacent to the open shell atom, referred to as N-heterocyclic carbenes (NHC),[38] are particularly stable and included in the subcategory of persistent carbenes.[39] NHCs are spin-paired systems in the ground state, showing a lone electron pair in a formal $sp^2$ orbital (HOMO) and an empty p-orbital (LUMO). The increased stability of this species, as well as the relative stabilization of the singlet state compared to the triplet one is mainly attributed to the ability of contiguous nitrogen atoms to donate electron density to the unoccupied p-orbital (LUMO) and concurrently to remove electron density from the carbene carbon through a σ-bond. The synergy of those mesomeric and inductive interactions results in a lowering of the HOMO energy whilst increasing the electron density at the empty LUMO. The singlet state is also favoured by the cyclic structure that forces the carbene to a more $sp^2$ like hybridation (Scheme 1.14).[40,41]




**Scheme 1. 14**

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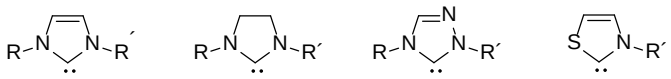
38 *N*-Heterocyclic carbene: a) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485; b) Cazin, C. S. J. *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*; Springer : London, **2011**; c) Díez-Gónzalez, S. *From Laboratory Curiosities to Efficient Synthetic Tools*; RSC Publishing: Cambridge, **2011**.

39 a) Bourissou, D.; Guerret, O.; Gabbaï,F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; b) de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862.

40 a) Dixon, D. A.; Arduengo, A. J. III. *J. Phys. Chem.* **1991**, *95*, 4180; b) Arduengo, A. J. III. *Acc. Chem. Res.* **1999**, *32*, 913.

41 Runyon, J. W.; Steinhof, O.; Dias, H. V. R.; Calabrese, J. C.; Marshall, W. J.; Arduengo, A. J. *Aust. J. Chem.* **2011**, *64*, 1165.

In addition to the stabilization through electronic effects, vicinal atoms are usually substituted with bulky groups to hinder the tendency to undergo dimerization towards the formation of alkenes (the Wanzlick equilibrium)[42]. In this regard, both the steric and electronic properties of those species are closely related to the substitution patterns, ring size and the contribution of the heteroatoms to stabilization.[43] Although a variety of NHCs have been design by modifying all these aspects, the scaffolds shown in Scheme 1.15 comprise the wide majority of them.




**Scheme 1. 15**

N-Heterocyclic carbenes have gathered an increasing relevance in the field of organocatalysis,[20] leading the subcategory of covalent catalysis in conjunction with aminocatalysis. However, the applicability of these compounds extends beyond their role in this field. As it has been stated, NHCs are nucleophilic species bearing a lone pair of electrons, thus can feature as sigma-donor ligands.[44] Moreover, NHCs are considered as sterically demanding ligands due to its sp2 hybridation, where the nitrogen atoms are oriented towards the metal centre. The ease to modify the structure and properties of NHCs has allowed for their application in a variety of reactions through the formation of unalike metal complexes.

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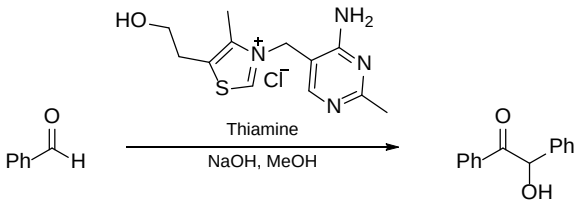
42 a) Wanzlick, H.-W. *Angew. Chem. Int. Ed.* **1962**, *1*, 75; b) Wanzlick, H.-W.; Kleiner, H.-J. *Angew. Chem. Int. Ed.* **1964**, *3*, 65.

43 Hermann, W. A.; Köcher, C. *Angew. Chem. Int. Edn. Engl.* **1997**, *36*, 2162.

44 For the use of NHCs as ligand, see: a) Ritleng, V.; Henrion, M.; Chetcuti, M. J. *ACS Catal.* **2016**, *6*, 890; b) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. *ACS Catal.* **2016**, *6*, 5972; c) Visbal, R.; Concepcion Gimeno, M. *Chem. Soc. Rev.* **2014**, *43*, 355; d) Schaper, L.-A.; Hock, S. J.; Hermann, W. A.; Kühn, F. E. *Angew. Chem. Int. Ed.* **2013**, *52*, 270; e) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612; f) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122; g) Nolan, S. P. *N-Heterocyclic Carbenes in Synthesis*; Wiley-VCH; Weinheim, **2006.**

Back to their capability as organocatalysts, the first example employing this activation mode dates back to 1943, when Ukai reported the benzoin condensation of benzaldehyde in the presence of a thiazolium salt (Scheme 1.16).[45]




**Scheme 1. 16**

Later on, Breslow[46] helped in the understanding of this transformation with a mechanistic proposal (Scheme 1.17) based on the generation of a nucleophilic intermediate, nowadays known as the Breslow intermediate, as the active species for the generation of the new C-C bond. First the actual catalyst is generated upon deprotonation of the thiazolium salt. Then the generated nucleophilic carbene catalyst undergoes 1,2-addition over the aldehyde. As a result, the acidity of the formerly aldehydic proton is dramatically increased, allowing a 1,2-proton shift process from the *ipso* position to the alkoxide moiety. Thus, an enaminol intermediate is generated as the result of the condensation of the carbene with an aldehyde. This covalent catalyst-substrate adduct is activated towards the reaction with an electrophile, in a transformation that involves a polarity reversal of the carbonyl group (umpollung).[47] Subsequent proton transfer leads to the formation of the product, concurrently to the elimination of the thiazolium moiety as a good leaving group so that it can restart the catalytic cycle. This mechanism will be further discussed in the context of the asymmetric benzoin condensation in the next chapter.

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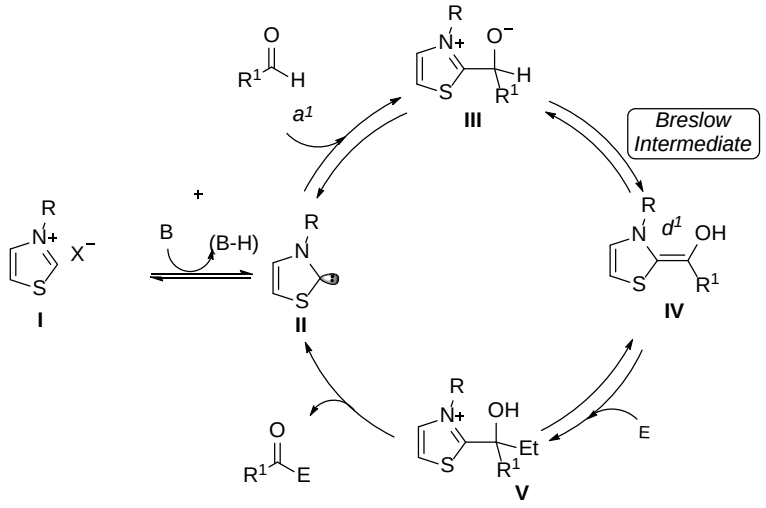
45 Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296.
46 Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.
47 Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.




**Scheme 1. 17**

This mechanistic proposal was crucial for the development of the reaction as well as to envision the possibility of an asymmetric version. Thus, in a enantiocontrolled transformation, both the conformational aspects of the enaminol intermediate and the trajectory of the approaching electrophile must be controlled. The geometry of the Breslow intermediate will be defined by the steric and electronic interactions between the substrate and the catalyst (Figure 1.3). First, the interactions between the lone electron pairs of the hydroxyl group and the nitrogen atoms may provide destabilising effect, that implies that, configurations in which the hydroxyl group is located at the same side of the molecule as other areas of high electron density will be disfavoured. However, this electronic interaction might be of little effect compared to introducing bulky substituents at the nitrogen atoms, being this steric effect particularly important for the substitution at the N1 position of imidazolium type carbenes. This is explained by the fact that N1 will preferentially adopt a sp2 hybridisation and N3 would turn to sp3 hybridisation.[48] Thus, the conformational freedom of the system should be restricted by introducing steric hindrance through a wise design of the catalyst. It should also be considered that the formation of the enaminol intermediates is reversible and despite the preferential

[48] Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, 5563.

formation of one diastereomer the reactivity of the different isomeric intermediates will determine which one participates in the catalytic cycle. On the other hand, the chiral element within the catalyst structure is responsible for the differentiation of the two diastereotopic faces of the enaminol intermediate. Hindering the approach of the electrophile by steric bias is the generally employed strategy for this purpose.

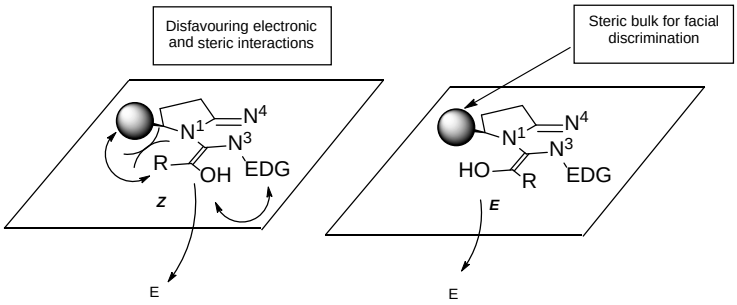


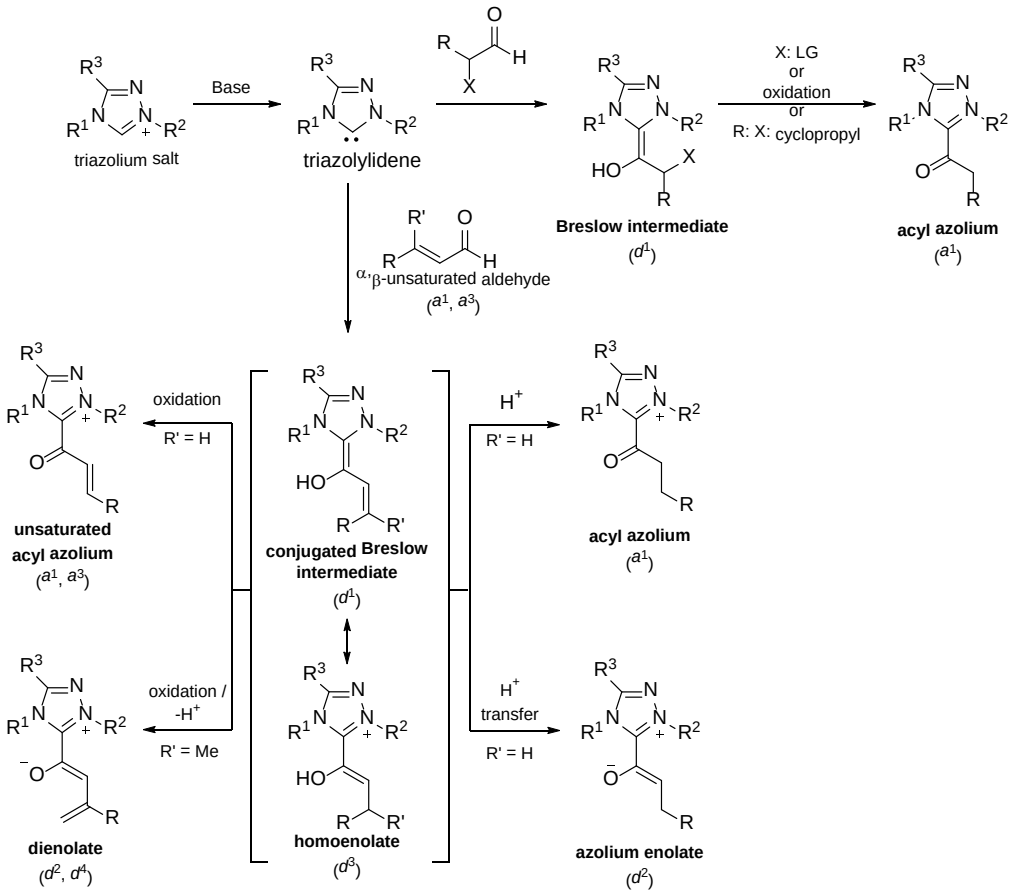

**Figure 1. 3**

Besides the *acyl anion* chemistry ($d^1$)[49,50] that can be directly promoted through the Breslow intermediate, this activation mode may lead to different intermediates depending on the nature of the substrate (Scheme 1.18). Thus, the use of α,β-unsaturated aldehydes renders a Breslow intermediate with extended conjugation, that may react with electrophiles at the β-position, showing *homoenolate* reactivity ($d^1$ type synthon). This intermediate can be protonated to form an *acyl azolium* intermediate ($a^1$ type synthon) or lead to an *azolium enolate* type intermediate ($d^2$ type synthon) through a proton transfer step. Alternatively, aldehydes with a leaving group at the α-position, or aliphatic aldehydes under oxidative conditions can be also employed as *acyl azolium/azolium enolate* precursors. Finally, subjecting the homologated Breslow intermediate to oxidation

[49] For reviews on NHC catalyzed benzoin reactions, see: a) Ref. 21i b) Menon, R. S.; Biju, A. T.; Nair, V *Beilstein J. Org. Chem.* **2016**, *12*, 444.

[50] a) Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639. For a review on Stetter reaction, see: b) De Alaniz, J. R.; Rovis, T. *Synlett* **2009**, *8*, 1189.

conditions gives access to the corresponding unsaturated *acyl azolium* and *dienolate* intermediates. The *ipso*, α,β and even γ functionalization of carbonyl compounds could be achieved employing this methodology. This implies a very rich reactivity profile and a wide world of possible organic transformations that can be promoted by NHCs through this variety of reactive intermediates.




**Scheme 1. 18**

In fact, NHC-promoted reactions have experienced a renaissance since these reactions that extend beyond the long-studied generation of acyl anion equivalents,

were discovered in 2004.[51] In the last decade, the activation modes presented on Scheme 1.18 together with the new discrete reactive species involved in those transformations have been studied in depth.

[51] a) Sohn, S.; Rosen, E. L.; Bode, J. *J. Am. Chem. Soc.* **2004**, *126*, 14370; b) Burstein, C.; Glorius, F. *Angew. Chem. Int. Ed.* **2004**, *116*, 6331.

## 5.- PRECEDENTS OF THE GROUP

Historically, our research group is primarily aimed toward the development of new methodologies in the field of asymmetric synthesis and their application to the synthesis of chiral building blocks, drugs and natural products. Initially, the chiral auxiliary strategy was employed for this task, leading to satisfactory results in the use of β-aminoalcohol (*S*,*S*)-(+)-pseudoephedrine in a variety of transformations, such as enolate chemistry[52] and several conjugate additions.[53]

More recently, we moved to the field of asymmetric catalysis focusing on the organocatalytic approach. In this regard, the first work in the area consisted in an aminocatalyzed Michael reaction between enolizable aldehydes and β-nitroacroleine dimethyl acetal, employing prolinol derivatives for the generation of the key enamine intermediate (Scheme 1.19).[54] A protocol for the preparation of highly functionalized pyrrolidines by further transformation of the obtained Michael adducts was designed.[55]

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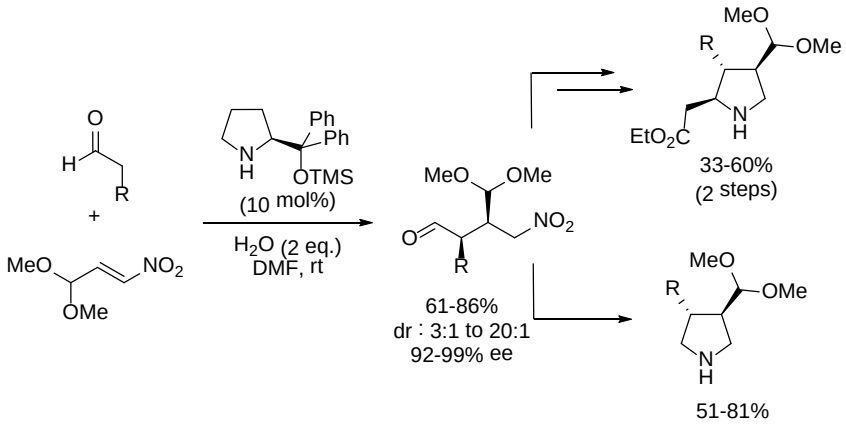
[52] Most recent aldol reaction: a) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem*. **2011**, *76*, 460. Most recent Mannich reaction: b) Iza, A.; Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2006**, 4065. Most recent electrophilic amination reaction: c) Vicario, J. L.; Badía, D.; Carrillo, L. *Tetrahedron: Asymmetry* **2002**, *13*, 745. Aziridine ring opening reaction: d) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem*. **2001**, *66*, 5801. Tandem reaction: e) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Iza, A.; Uria, U. *Org. Lett*. **2006**, *8*, 2535.

[53] Conjugate addition reactions: a) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem*. **2009**, *74*, 4404; b) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem*. **2006**, *71*, 7763. Aza-Michael reactions: c) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L.; Ruiz, N. *J. Org. Chem.* **2005**, *70*, 8790; d) Etxebarria, J.; Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2004**, *69*, 2588.

[54] Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett*. **2006**, *8*, 6135.

[55] Ruiz, N.; Reyes, E.; Vicario, J.; Badía, D.; Carrillo, L.; Uria, U. *Chem. Eur*. **2008**, *14*, 9357.




**Scheme 1. 19**

Iminium catalysis has been also studied leading to a variety of transformations on α,β-unsaturated aldehydes and ketones (Scheme 1.20). Initially, we centered our efforts on aza-Michael type reactions employing tetrazoles as nucleophiles.[56] Furthermore, *N*-nitromethylphthalimide and hydrazones were successfully employed as hydroxymetanimidoyl anion and glyoxyl anion equivalents respectively, in an umpolung enantioselective conjugate addition to enals.[57, 58] On the other hand, this activation mode has been applied to the use of bis-nucleophiles, such as aminoketones,[59] hydrazides[60] and dialkyl aminomalonate.[61] After an initial (aza)-Michael addition over the activated conjugated acceptor, those substrates bearing a nucleophilic nitrogen atom, are able to undergo an intramolecular hemiaminalization step to yield the corresponding cyclic adducts.

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56 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.

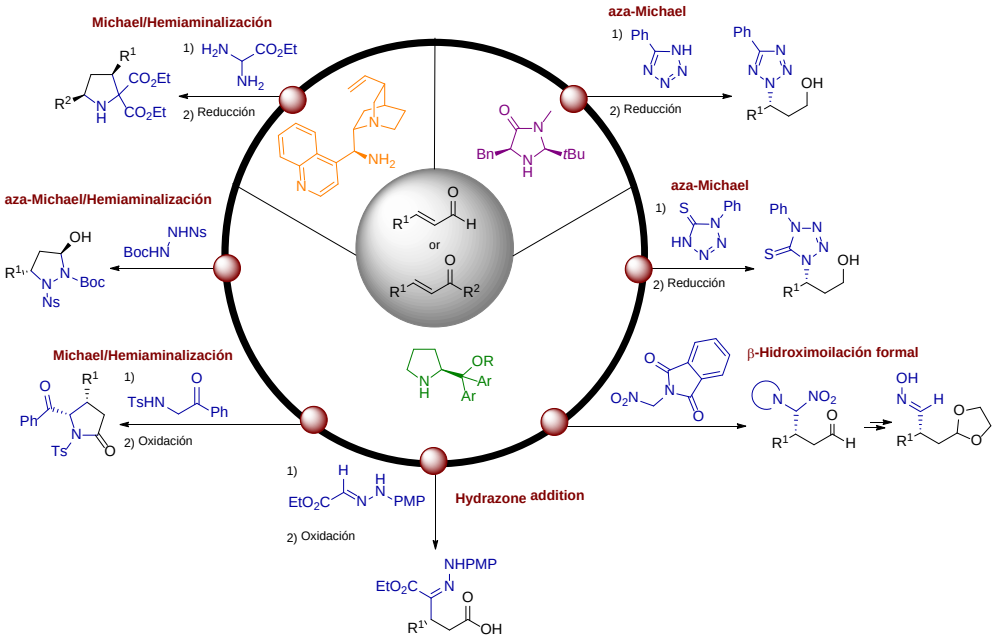
57 Alonso, B.; Reyes, E.; Carrillo, L.; Vicario, J. L.; Badía, D. *Chem. Eur. J.* **2011**, *17*, 6048.

58 Fernández, M.; Uria, U.; Vicario, J. L.; Reyes, E; Carrillo, L. *J. Am. Chem. Soc*. **2012**, *134*, 11872.

59 Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Adv. Synth. Catal*. **2013**, *355*, 653.

60 Fernandez, M.; Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Adv. Synth. Catal.* **2012**, *354*, 371.

61 Riaño, I.; Díaz, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2016**, *52*, 2330.




**Scheme 1. 20**

The LUMO lowering effect observed on iminium activated conjugated systems makes them suitable for cycloaddition reactions. This approach was applied by our group for the development of the first [3+2] cycloaddition employing azomethine ylides as 1,3-dipoles (Scheme 1.21).[62] This transformation has shown good tolerance to modifications in the substrates, which has been exhibited in variants of the initial reaction[63] and the application of the methodology to the synthesis of diverse heterocyclic structures.[64] Computational studies, carried out in collaboration with Prof. Fernando Cossio, proved that the reaction actually proceeded through a stepwise mechanism.[65] The proposed Michael/Mannich cascade sequence is

62 a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Cat*. **2011**, *353*, 3307; b) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed*. **2007**, *46*, 5168.

63 a) Reboredo, S.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. *Adv. Synth. Cat*. **2011**, *353*, 3307; b) Fernandez, N.; Carrilo, L.; Vicario, J. L.; Badia, D.; Reyes, E.*Chem.Commun.* **2011**, *47*, 12313; c) Reboredo, S.; Vicario, J. L.; Carrillo, L.; Reyes, E.; Uria, U. *Synthesis* **2013**, 2669.

64 a) Iza, A.; Carrillo, L.; Vicario, J. L.; Badia, D.; Reyes, E.; Martinez, J. I. *Org. Biomol. Chem.* **2010**, *8*, 2238; b) Iza, A.; Ugarriza, I.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Tetrahedron* **2013**, *69*, 8878.

65 Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; de Cozar, A.; Cossio, F. P. *Chem. Eur. J.* **2012**, *18*, 7179.

initiated by a conjugated addition of the 1,3-dipole to the α,β-unsaturated iminium ion, which renders the corresponding enamine that undergoes intramolecular cyclization with the azomethine. The combination of the iminium/enamine activation has been employed to promote a variety of cascade sequences such as oxa-Michael/aldol/hemiacetalization,[66] oxa-Michael/Michael,[67] Michael/aldol/dehydration,[68] Michael/Michael,[69] Michael/α-alkylation.[70] More recently, we have developed a (3+2) cycloaddition with nitrones through a cooperative hydrogen-bonding catalysis/Iminium activation.[71]

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66 Reyes, E.; Talavera, G.; Vicario, J. L.; Badia, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 5701.

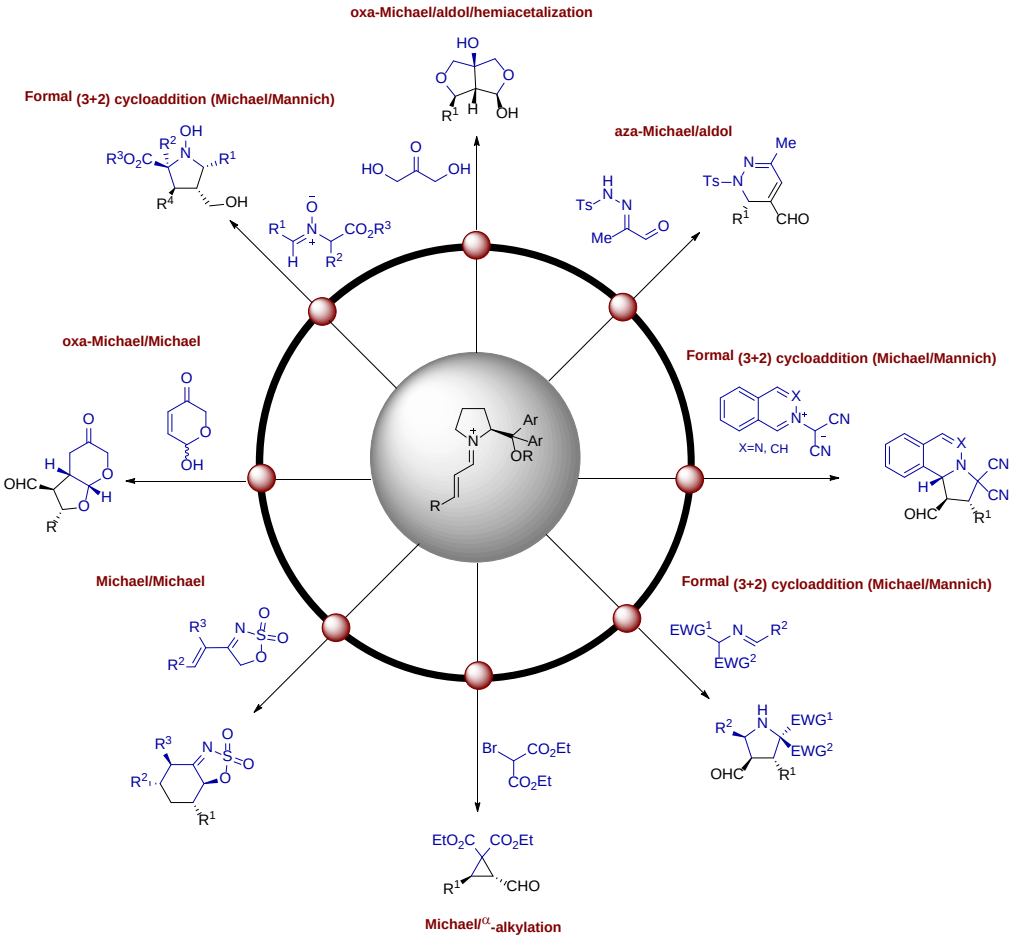
67 Orue, A.; Uria, U.; Roca-López, D.; Delso, I.; Reyes, E.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Sci.* **2017**, *in press*. DOI: 10.1039/c7sc00009j

68 Fernandez, M.; Vicario, J. L.; Reyes, E.; Carrillo, L; Badía, D. *Chem. Commun*. **2012**, *48*, 2092.

69 Riaño, I.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Org. Chem. Front.* **2015**, *2*, 206.

70 a) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; Pesquera, A. *Synthesis* **2010**, *4*, 701; b) Martinez, J. I.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *ChemCatChem* **2013**, *5*, 2240.

71 Prieto, L.; Yuste, V.; Uria, U.; Delso, I.; Reyes, E.; Tejero, T.; Carrillo, L.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2017**, *23*, 2764.



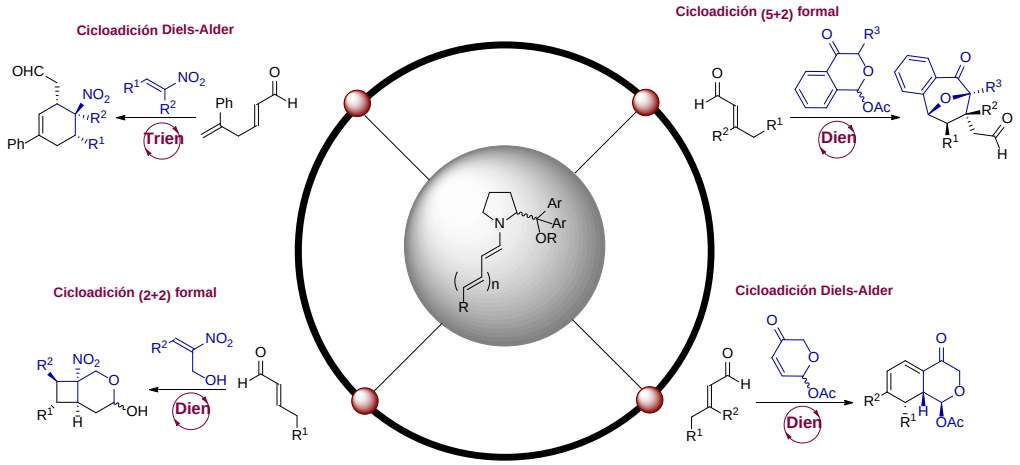

**Scheme 1. 21**

On the other hand, we have successfully developed formal (2+2)[72] and (5+2)[73] cycloadditions by applying the concept of vinilogy to aminocatalysis, which enables the functionalization of carbonyl compounds at more remote positions (Scheme 1.22). Thus, nitroalkenes and oxidopyrilium ylides proved to be suitable for the reaction with extended conjugated π-systems under dienamine catalysis.

[72] Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed***. 2012**, *51*, 4104.

[73] a) Orue, A.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J.L. *Angew. Chem. Int.* **2015**, *54*, 3043; b) Roca-López, D.; Uria, U.; Reyes, E.; Carrillo, L.; Jørgensen, K. A.; Vicario, J. L.; Merino, P. *Chem. Eur. J.***2016**, *18*, 884.

Morevover, this approach was extended to the use of unsaturated enals as dienes y Diels-Alder type reaction employing dienamine and trienamine catalysis.[74,75]




**Scheme 1. 22**

In the context of non-covalent activation modes, hydrogen-bond catalysis has been employed in the development of a diastereodivergent strategy for the enantioselective synthesis of densely functionalized cyclohexanes through a Michael/Henry cascade between alkyl nitroacetates and enals and nitroalkenes employing a bifunctional tertiary amine/squaramide catalyst (Scheme 1.23).[76]

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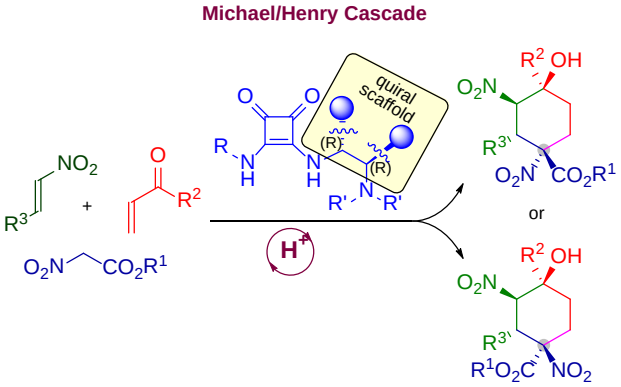
74 Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740.

75 Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.

76 a) Martinez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627; b) Martinez, J. I.; Uria, U.; Muñiz, M.; Reyes, E.; Vicario, J. L. *Beils. J. Org. Chem.* **2015**, *11*, 2577.

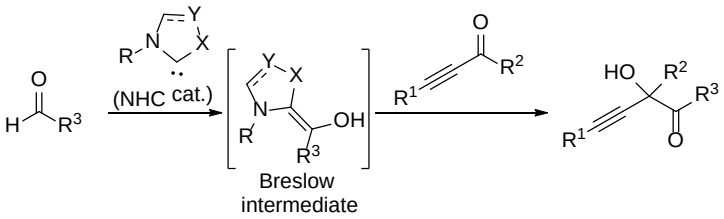



**Scheme 1. 23**

## 6.- GENERAL OBJECTIVES OF THE PRESENT WORK

The work comprised in this thesis has been developed in line with the current research activity of the group. Thereby, it is oriented to the study of new asymmetric methodologies within the field of organocatalysis. In this sense, we wish to find solutions to challenging reactions for which nowadays there is no general approach, as it is the case of the cross-benzoin condensation under NHC catalysis. On the other hand, we also wish to explore the potencial of D-A cyclopropane precursors as unconventional substrates undergoing organocatalyzed activation. This research work will be presented in three different parts.

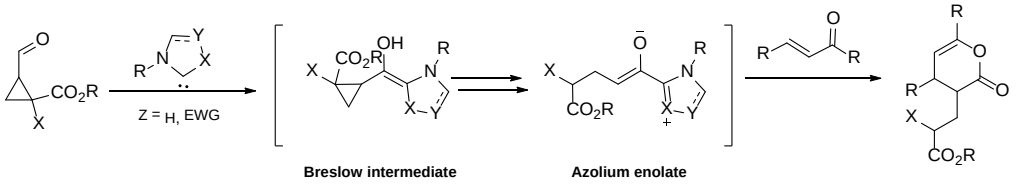
In the first part, based on the limited number of reports on the enantioselective intermolecular aldehyde-ketone cross-benzoin reaction and the lack of examples employing functionalized carbonyl compounds, the ability of ynones to perform as the electrophilic counterpart in the *N*-heterocyclic carbene catalyzed benzoin reaction will be studied (Scheme 1. 24). Additionally, the reaction will give access to enantioenriched tertiary propargylic alcohols, considered as important chiral building blocks.




**Scheme 1. 24**

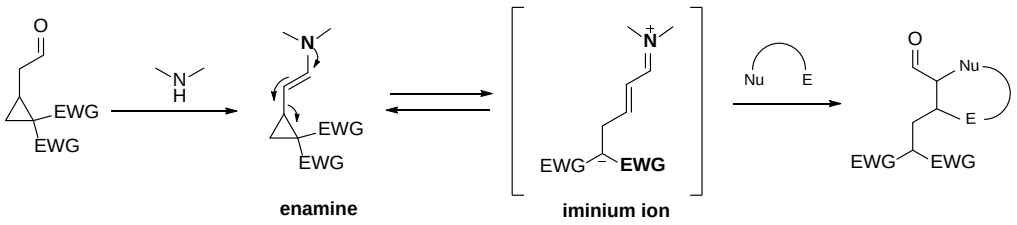
On the second part, the catalytic generation of D-A cyclopropanes from suitably substituted and functionalized cyclopropanes will surveyed under two organocatalytic activation manifolds that involve covalent interactions, namely, NHC catalysis and iminium activation. Once the catalytically generated D-A cyclopropane is generated, a ring-opening event is expected to occur to form an active

intermediate that will be reacted with additional reagents towards the development of cycloaddition chemistry. In particular, formyl cyclopropanes, that have been described as potential acyl azolium/azolium enolate precursos under *N*-heterocyclic carbene catalysis, will be employed to explore this kind of reactivity in cycloaddition reactions employing electron-poor dienes (Scheme 1. 25).




**Scheme 1. 25**

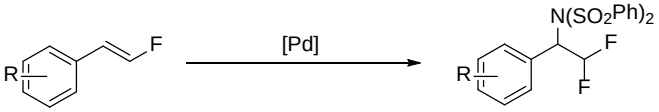
On the other hand, the capability of cycloprpaneacetaldehydes to undergo ring-opening in the presence of chiral secondary amines will be surveyed. The ring opening process may take place through the activation of the cyclopropane as an enamine intermediate, that upon the C-C bond cleavage would render an iminium species suitable for Michael/Aldol cascade reactions (Scheme 1. 26).




**Scheme 1. 26**

Finally a short chapter including the work performed in the context of a short stay at the University of California, Berkeley under the supervision of Prof. F. Dean Toste is included. Considering that the participation of high oxidation palladium species (Pd IV) has been crucial in the C-F bond formation chemistry, the possibility to access α-amino geminal difluoro derivatives from fluorstyrenes will be surveyed

employing *N*-fluorobenzenesulfonimide as both strong oxidant and fluorine source. (Scheme 1.27).




**Scheme 1. 27**

# 2

# 2

# NHC catalyzed Enantioselective Cross-Benzoin Reaction with Ynones

## 1.- INTRODUCTION

The benzoin reaction (condensation), named after the product that is generated at the end of the process, consists on the formation of benzoin through the assembly of two molecules of benzaldehyde. This reaction that can be promoted by cyanide or *N*-heterocyclic carbene (NHC), can also be described, in a more general way, as the coupling of an aldehyde with a carbonyl compound in the synthesis of α-hydroxyketones. The generated product is particularly interesting as the new carbon-carbon bond formed would imply an anomalous disconnection from the retrosynthetic[1] point of view. In addition to this, a perfect atom-economy, the generation of a new stereogenic centre as well as the use of reaction partners ubiquitous in organic chemistry, have promoted intensive investigations on this topic.[2]

Discovered in 1832 by Friedrch Wöhler (1800-1882) and Justus von Liebig (1803-1873)[3] the benzoin condensation is among the earliest known carbon-carbon

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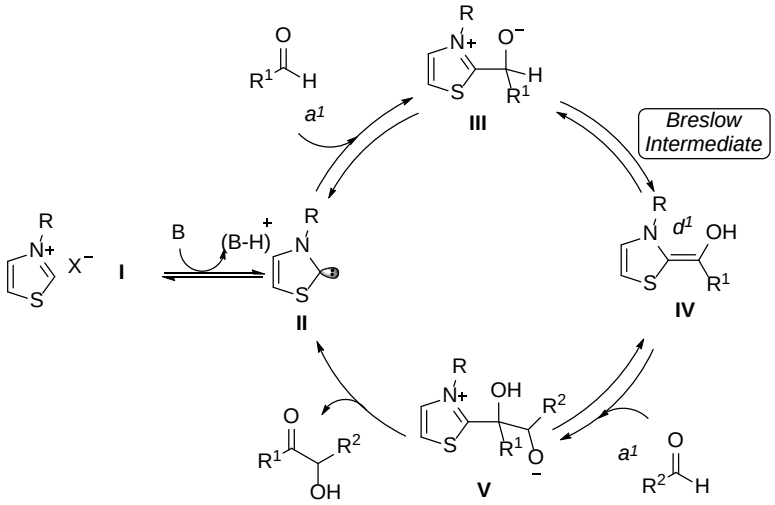
1 Corey, E. J.; Cheng, X-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1995.

2 For reviews on benzoin condensation or acyloin chemistry see: a) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534; b) Johnson, J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1326; c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606; d) Menon, R. S.; Biju, A. T.; Nair, V *Beilstein J. Org. Chem.* **2016**, *12*, 444. e) Suzuki, K.; Takikawa, H. *Carbene-Catalyzed Benzoin Reactions;* Eds.: List, B.; Georg Thieme Verlag KG: Stuttgart, **2012**, p. 591-618.

3 Wöhler, F.; Liebig, J. *Ann. Pharm.* **1832**, *3*, 249.

bond-forming reactions, that has recently found the corresponding catalytic enantioselective version under NHC catalysis. Despite this, the first example using thiazolium salts as promoters of a benzoin reaction was reported by Ukai in 1943.[4] From the very beginning, Lapworth considered a polarity reversal of the aldehyde for the transformation under cyanide anion catalysis.[5] In the 1950s, Mizuhara demonstrated that the thiazolium unit of thiamine (vitamine B1) was responsible for its catalytic activity;[6] whilst based on the work of Lapworth, R. Breslow[7] proposed in 1958 a mechanistic model for the NHC-catalyzed benzoin condensation which involved the participation of a carbene generated after deprotonation of the thiazolium salt (Scheme 2.1).




**Scheme 2. 1**

In this mechanism, the thiazolium salt (I) is deprotonated to form *in situ* the catalytically active species (II). It is assumed that this thiazolin-2-ylidene undergoes nucleophilic attack over the aldehyde to generate adduct (IV) after a

[4] Ukai, T.; Tanaka, R.; Dokawa, T. *J. Pharm. Soc. Jpn.* **1943**, *63*, 296 (*Chem. Abstr.* **1951**, *45*, 5148).
[5] Lapworth, A. *J. Chem. Soc.* **1903**, *83*, 995.
[6] Mizuhara, S.; Handler, P. *J. Am. Chem. Soc.* **1954**, *76*, 571.
[7] Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

deprotonation/reprotonation sequence.[8] Being this key step of the mechanism and involving a polarity reversal (*umpolung*) of the aldehyde.[9] The enaminol intermediate (IV) is an acyl anion equivalent, known as the "Breslow intermediate", that reacts with an electrophile such as another molecule of aldehyde. An internal proton transfer step and subsequent release of the catalyst affords the final product and the active carbene ready to participate in a new cycle. The stereochemistry of the reaction is defined in the formation of intermediate (V), proving that the NHC backbone incorporates a stereodirecting element that differentiates both prostereogenic faces.[8a,10]

Those significant discoveries, in conjunction with the work of Bertrand[11] and Arduengo'[12] to isolate stable NHCs, paved the way for further developments in the area of carbene catalysis. Since then, a number of NHCs have been synthesized and applied in benzoin type and many other reactions.[13]

The first enantioselective benzoin reaction date back to 1966, when Sheehan obtained (*S*)-benzoin with poor enantiocontrol using a chiral thiazolium salt as catalyst (Scheme 2.2).[14] Years later, by using a modified thiazolium salt, (*S*)-benzoin

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8 a) Hawkes, K. J.; Yates, B. F. *Eur. J. Org. Chem.* **2008**, *55*, 63; b) He, Y.; Xue, Y. *J. Phys. Chem.* **2011**, *115*, 1408.

9 Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

10 Dudding, T.; Houk, K. N. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5770.

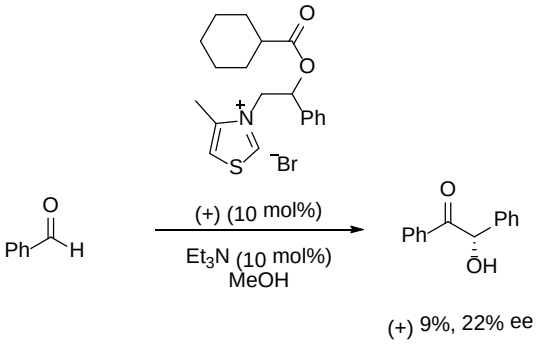
11 Igau, A.; Baceiredo, A.; Trinquier,G.; Betrand, G. *Angew. Chem. Int. Ed.* **1989**, *28*, 621.

12 Arduengo III, A. J.; Dias, H. V. R.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530.

13 a) Arduengo III, A. J.; Kraftczyk, R. *Chem. Unserer Zeit* **1998**, *32*, 6; b) Hermann, W. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290; c) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev*. **2004**, *33*, 619; d) Nair, V.; Santhamma, B.; Vellalath, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130; e) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978; f) Tekavec, T. N.; Louie, J. *Top. Organomet. Chem.* **2007**, *21*, 195; g) Crabtree, R. H. *Coord. Chem. Rev.* **2007**, *251*, 5; h) Herrmann, W. A.; Koecher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162; i) Arduengo III, A. J. *Acc. Chem. Res.* **1999**, *32*, 913; j) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; k) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, 14, 951; l) Korotkikh, N. I.; Shvaika, O. P.; Rayenko, G. F.; Kiselyov, A. V.; Knishevitsky, A. V.; Cowley, A. H.; Jones, J. N.; Macdonald, C. L. B. *Arkivoc* **2005**, *8*, 10; m) Hahn, F. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 1348; n) Bertrand, G. *Carbene Chemistry*; Marcel Dekker: New York, **2002**.

14 Sheehan, J.; Hunneman, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 3666.

was isolated in a 52% ee,[15] yet in a very low yield.[16] These examples open the opportunity for further design of new catalysts.




**Scheme 2. 2**

It was not until the 1990s, when after a series of failed attempts to increase the enantiocontrol of the reaction by using different thiazolium salts,[17,18,19] Enders, who have excelled in the field of the synthesis and application of triazolium salts,[20] reported the ability of those to promote the benzoin condensation leading to a significant improvement in the yield and the enantioselectivity for the synthesis of benzoin (66% yield, 75% ee) (Scheme 2. 3), whereas the asymmetric inductions achieved with electron deficient aldehydes were lower.[21]

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15 Sheehan, J.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196.

16 Further studies improved the yield up to 48%: Dvorak, C.; Rawal, V. H. *Tetrahedron Lett.* **1998**, *39*, 2925.

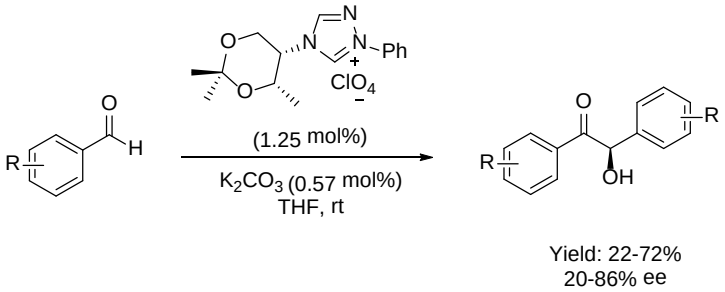
17 Takagi, W.; Tamura, Y.; Yano, Y. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478.

18 Zhao, C.; Chen, S.; Wu, P.; Wen, Z. *Huaxue Xuebao* **1988**, *46*, 784.

19 Martí, J.; Castells, J.; López Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521.

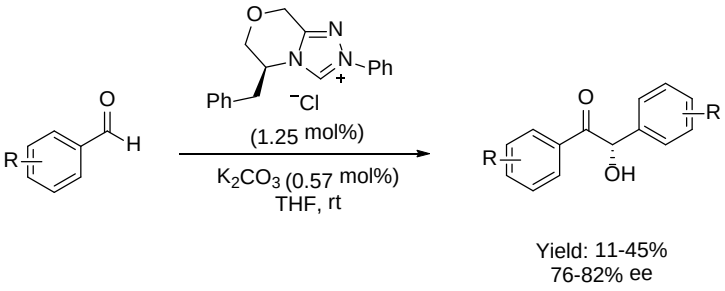
20 a) Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J.-P.; Ebel, K.; Brode, S. *Angew. Chem. Int. Ed.* **1995**, *34*, 1021; b) Enders, D.; Breuer, K.; Runsik, J.; Teles, J. H. *Liebigs Ann. Naturforsch.* **1996**, 2019; c) Raabe, G.; Runsik, J.; Enders, Z. *Z. Naturfrosch.* **1996**, *51a*, 95; d) Enders, D.; Breuer, K.; Teles, J. H.; Ebel, K. *J Prakt. Chem.* **1997**, *339*, 397; e) Enders, D.; Breuer, K.; Raabe, G.; Simonet, J.; Ghanimi, A.; Stegmann, H. B.; Teles, J. H. *Tetrahedron Lett.* **1997**, *38*, 2833; f) Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrer, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61; g) Teles, J. H.; Breuer, K.; Enders, D.; Gielen, H. *Synth. Commun.* **1999**, *29*, 1; h) Enders, D.; Breuer, K.; Kallfass, U.; Balensiefer, T. *Synthesis* **2003**, 1292

21 Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217.




**Scheme 2. 3**

In contrast to previously developed catalyst, which bear a chiral group attached solely to the nitrogen atom and thus allow the free rotation of this stereodirecting element, Leeper synthesized a variety of conformationally-restricted chiral bicylic catalysts in which the chiral group is part of a further ring.[22] In 1998, a novel chiral bicyclic triazolium salt that produced benzoin with good enantiocontrol (45% yield, 80% ee) served as proof of the applicability of this concept (Scheme 2. 4).[23]



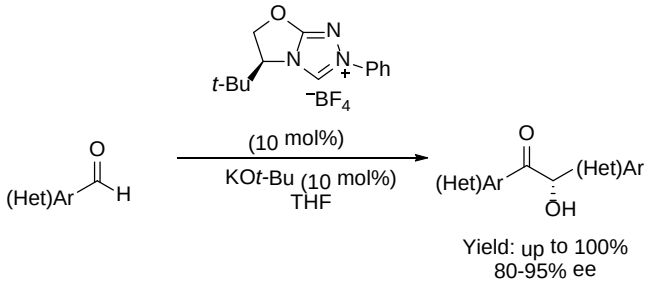

**Scheme 2. 4**

Based on this protocol, another chiral byclic triazolium catalyst was developed by Enders in 2002, which enable the production of (*S*)-benzoin in a very good enantioselectivity (90% ee, 83% yield) as well as the successful extension of the

[22] a) Knight, R. L.; Leeper, F. *Tetrahedron Lett.* **1997**, *38*, 3611; b) Gerhards, A. U.; Leeper, F. *Tetrahedron Lett.* **1997**, *38*, 3615.

[23] Knight, R. L.; Leeper, F. *J. Chem. Soc, Perkin Trans. 1* **1998**, 1891.

methodology to synthesis a variety of hydroxyketones as almost enantiopure compounds (Scheme 2. 5).[24]




**Scheme 2. 5**

Although, other forms of chirality, such as axial chirality, have been explored in the design of new catalysts,[25] central chirality based triazolium-derived NHCs remain as the best in both terms of yield and enantiocontrol, see (Scheme 2. 6).[26] In an attempt to reach high levels of enantiocontrol several modifications have been introduced in the chiral scaffold of the triazolium catalyst so as to efficiently block one of the faces of the Breslow intermediate due to steric hindrance. Alternatively, hydrogen bond donating substituents have been incorporated, in catalyst such as those reported by Connon,[26b] Zeitler[27] and Waser,[26c] to improve the enantiocontrol based on this new interaction. The bis-triazolium catalyst of You (95% ee, 95% yield)[28] and the bifunctional triazolium catalyst of Zeitler and Connon (>99% ee, 90% yield)[27] featured in the most efficient synthesis of benzoin reported so far.

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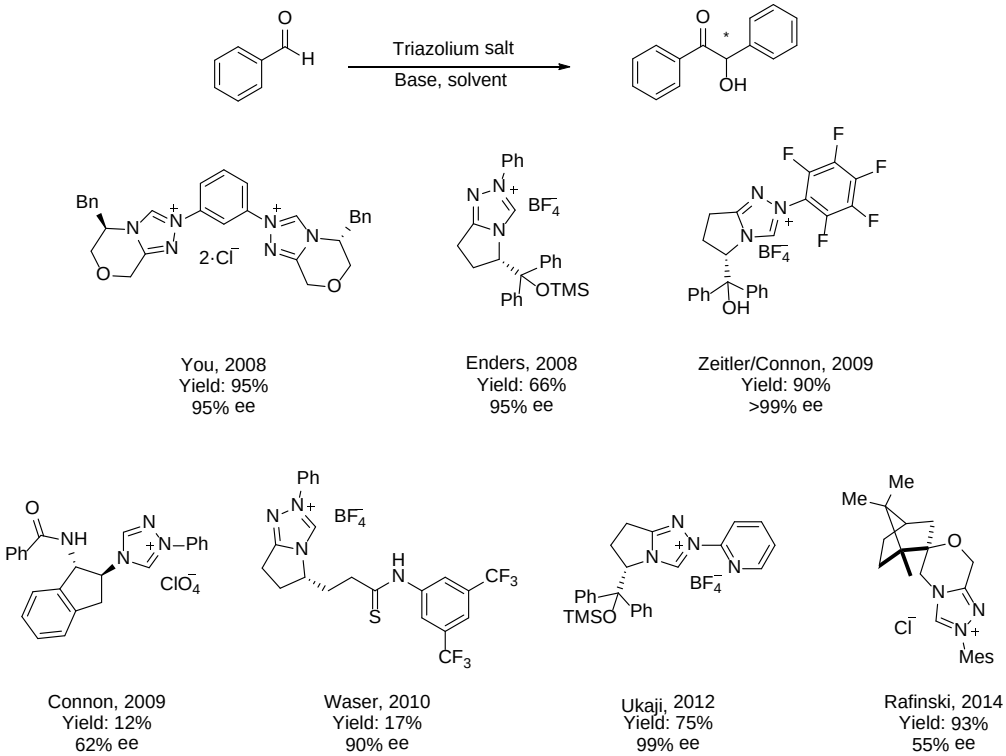
[24] Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.

[25] a) Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* **2004**, 2025; b) Orlandi, S.; Caporale, M.; Benagli, M.; Annunziata, R. *Tetrahedron: Asymmetry* **2003**, *14*, 3827; c) Tachibana, Y.; Kihara, N.; Takaka, T.; *J. Am. Chem. Soc.* **2004**, *126*, 3438.

[26] a) Enders, D.; Han, J. *Tetrahedron: Asymmetry* **2008**, *19*, 1367; b) O'Toole, S. E.; Connon, S. J. *Org. Biomol.Chem.* **2009**, *7*, 3584; c) Brand, J. P.; Osuna Siles, J. I.; Waser, J. *Synlett* **2010**, 881; d) Soeta, T.; Tabatake,Y.; Inomata, K.; Ukaji, Y. *Tetrahedron* **2012**, *68*, 894; e) Rafinski, Z.; Kozakiewicz, A.; Rafinska, K. *Tetrahedron* **2014**, *70*, 5739; f) Rafinski, Z. *Tetrahedron* **2016**, *72*, 1860.

[27] Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214.

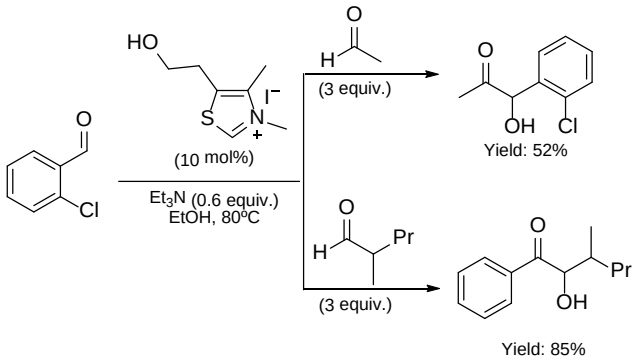
[28] Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645.




**Scheme 2. 6**

An obvious extension of the benzoin reaction is the cross-benzoin reaction, which consists on the coupling of two different aldehydes. This transformation presents important challenges as now four possible products of similar thermodynamic stability, namely the two possible homo-benzoin adducts and the corresponding cross-benzoin adducts, can be obtain. Indeed, the main problem can be attributed to reactivity of the aldehydes, since if one of them is preferred for the formation of the Breslow intermediate due to a greater electrophilicity or for being more accessible, that aldehyde should be also preferred for the carbon-carbon bond formation as well. Although different strategies have been employed to approach the chemoselectivity problem, the enantioselective cross-benzoin reaction of aldehydes remains as a challenge.

Initial studies in this context focused on substrate-driven selectivity, based on using two aldehydes with different reactivity in terms of steric or electronic properties,[29] and in some cases making use of a considerable excess of one of the coupling reagents, the latter resulting in the formation of self-condensation product of the aldehyde in higher ratio. An illustrative example of this approach is the early work reported by Stetter, in which the chemoselectivity of the reaction vary strongly depending on the nature of the substrates, thus, aromatic aldehydes can perform as nucleophilic or electrophilic counterpart in the present of different aliphatic aldehydes (Scheme 2. 7).[29a]

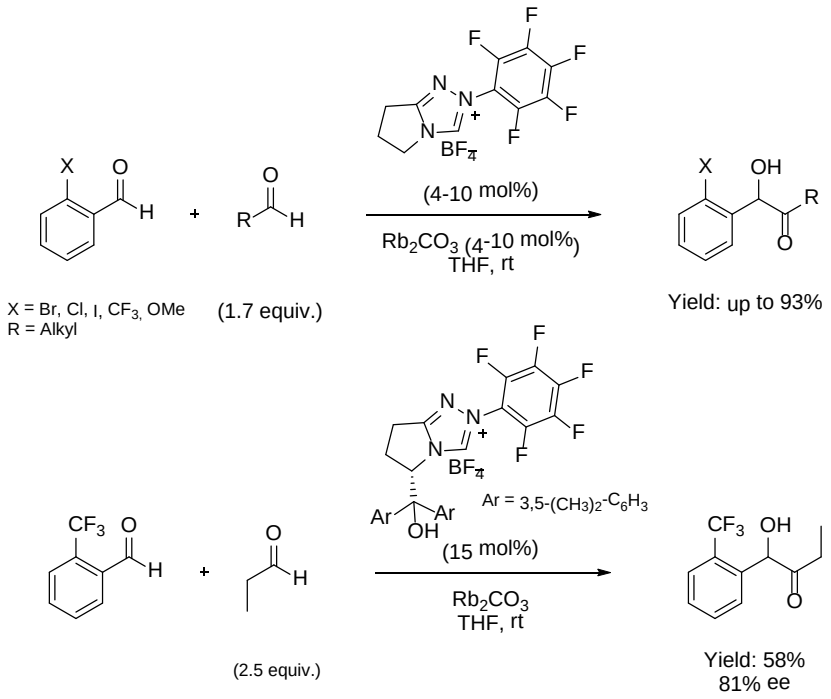



**Scheme 2. 7**

The idea of considering a synergistic combination of the steric effect of the substrate and the catalyst control was first developed by Zeitler and Connon, who in 2011 envisioned that a removable directing group could be introduced in the substrate to regulate the chemoselectivity of the reaction based on its ability to tune the electronic and steric properties of the aldehyde and how this effect could be enhanced by interaction with the a bulky catalyst. Thus, it was demonstrated that the highly chemoselective cross-benzoin reaction between *o*-substituted benzaldehyde derivatives and aliphatic aldehydes could be promoted by a triazolium

[29] a) Stetter, H.; Dämbkes, G. *Synthesis* **1977**, 403; b) Stetter, H.; Dämbkes, G. *Synthesis* **1980**, 309; c) Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem*. **2001**, 2623. For examples employing formaldehyde as electrophilic counterpart, see: d) Matsumoto, T.; Ohishi, M.; Inoue, S. *J. Org. Chem*. **1985**, *50*, 603; e)Kuhl, N.; Glorius, F. *Chem. Commun.* **2011**, *47*, 573

precatalyst.[30] Noteworthy, it was proved that the directing group could be removed in a palladium catalyzed debromination when *o*-bromo benzaldehydes were employed. Moreover, preliminary studies regarding the asymmetric version were carried out employing a chiral triazolium salt for the cross-coupling of 2-trifluoromethyl benzaldehyde and propanal (81% ee) (Scheme 2. 8).

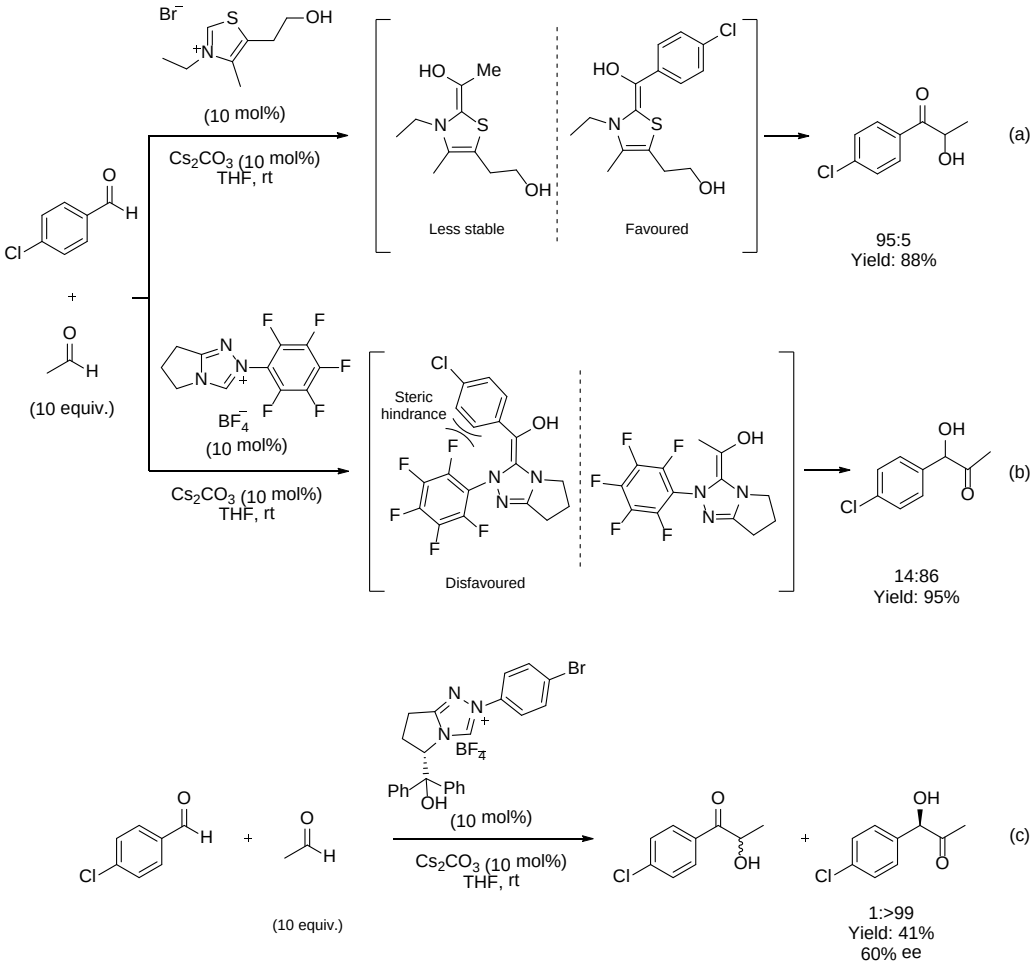



**Scheme 2. 8**

Almost simultaneously, Yang reported a catalyst controlled regiodivergent cross-benzoin reaction between *p*-chlorobenzaldehyde and ethanal, in which the regioselectivity is determined by the stability of the possible aldehyde-catalyst enaminol adducts (Scheme 2. 9).[31] In this work, the thiazolium based catalyst was found to preferentially attack the aromatic aldehyde since it leads to the more resonance-stabilized Breslow intermediate and subsequently undergo nucleophilic

[30] O'Toole, S.; Rose, C. A.; Gundala, S.; Zeitler, K., Connon, S. J. *J. Org. Chem.* **2011**, *76*, 347.
[31] Jin, M. Y.; Kim, S. M.; Han, H.; Ryu, D. H.; Yang, J. W. *Org. Lett.* **2011**, *13*, 880.

attack on the acetaldehyde, whilst negative aldehyde-catalyst steric interactions, when employing the triazolium catalyst, disfavor the formation of the adduct between the latter and aromatic aldehydes, which perform solely as electrophilic counterpart to render the other possible regioisomer. Noteworthy, no product of the homo-benzoin condensation of the *p*-chlorobenzaldehyde is observed as a consequence of the large excess of acetaldehyde employed, yet no reference to the self-condensation of ethanal is included.




**Scheme 2. 9**

The development of the regioselective cross-benzoin reaction has been centered on the application of thiazolium and triazolium catalyst to particular systems utilizing substrate control,[32,] until that very recently Gravel reported a highly chemoselective coupling of a variety of benzaldehyde derivatives and aliphatic aldehydes and attributed this selectivity to the size of the fused ring in the triazolium salt, being this the first general approach which relied exclusively in catalyst control Thus, a catalyst bearing a six-membered fused ring showed higher selectivity towards the alkyl-aryl cross-benzoin product than the catalysts with a five- and seven-membered fused ring, the latter leading to higher amounts of the self-condensation product. Moreover, a morpholine derived chiral catalyst was employed in preliminary experiments of the enantioselective that coursed with moderate enantioselectivity (40% ee) (Scheme 2. 10).[33]

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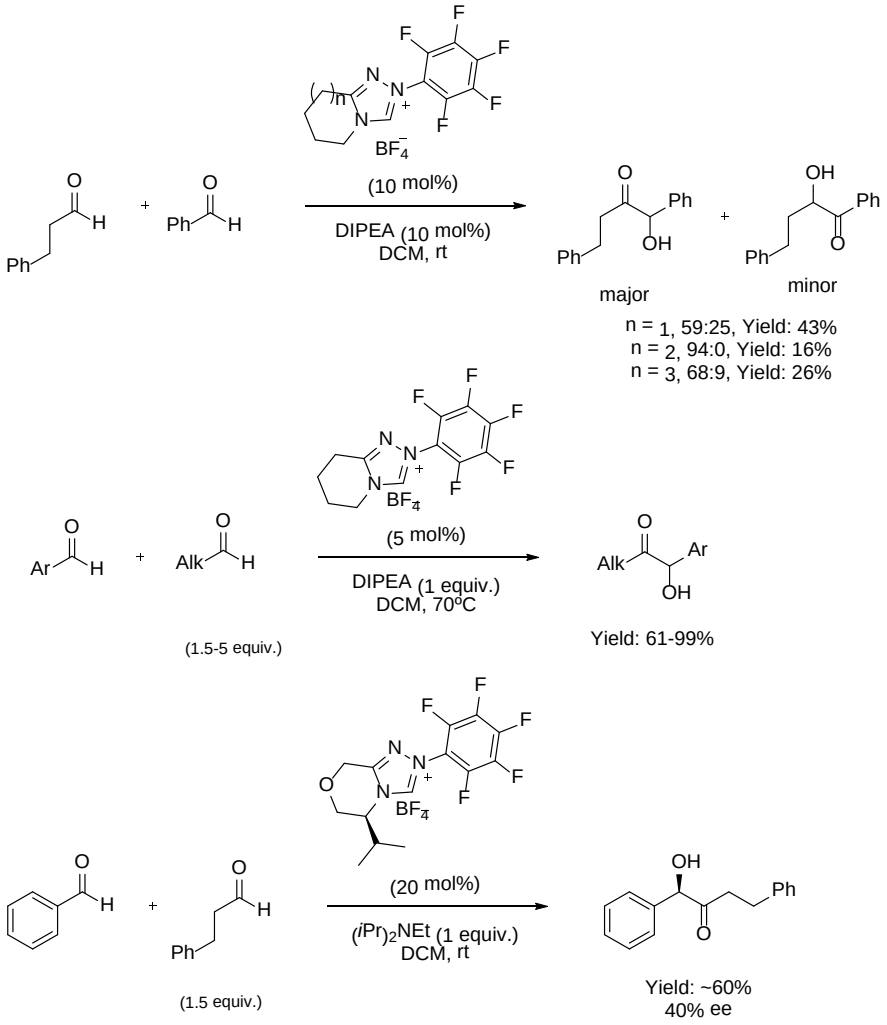
[32] a) Rose, C. A.; Gundala, S.; Connon, S.; Zeitler, K. *Synthesis* **2011**, 190; b) Piel, I.; Pawelczyk, M. D.; Hirano, K.; Fröhlich, R.; Glorius, F. *Eur. J. Org. Chem.* **2011**, 5475; c) Jin, M. Y.; Kim, S. M.; Mao, H.; Ryu, D. H.; Song, C. E.; Yang, J. W. *Org. Biomol. Chem.* **2014**, *12*, 1547; d) Haghshenas, P.; Gravel, M. *Org. Lett.* **2016**, *18*, 4518; e) Haghshenas, P.; Quail, J. W.; Gravel, M. *J. Org. Chem.* **2016**, *81*, 12075

[33] Langdon, S. M.; Wilde, M. M.; Thai, K.; Gravel, M. *J. Am. Chem. Soc.* **2014**, *136*, 7539



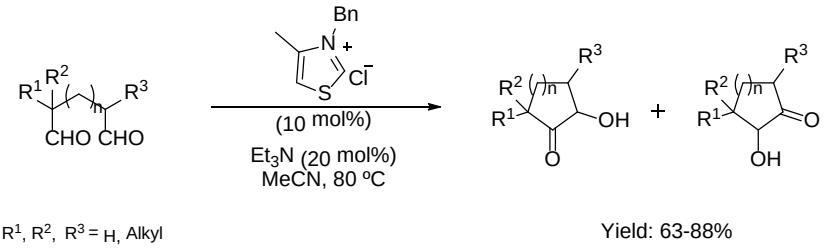

**Scheme 2. 10**

Mechanistic studies regarding the chemoselectivity of this reaction,[34] showed that the chemoselectivity in the piperidinone-based triazolium catalyst is kinetically derived and that the C-C bond formation is the rate limiting step for three potential pathways: the homo-alkyl and both cross-benzoin reactions. Moreover, the importance of the fused ring was evaluated and although the pyrrolidinone-based

[34] a) Langdon, S. M.; Legault, C. Y.; Gravel, M. *J. Org. Chem.* **2015**, *80*, 3597; b) Liu, T.; Han, S.-M-; Han, L.-L.; Wang, L.; Cui, X.-Y.; Du, C.-Y.; Bi, S. *Org. Biomol. Chem.* **2015**, *13*, 3654.

precatalyst was found to display a similar energy profile, experimentally a less chemoselective reaction was observed. However, under thermodynamic control both pyrrolidine and piperidine-based precatalys are able to achieve a chemoselective cross-benzoin reaction towards the formation of the alkyl-aryl cross-benzoin product. An evaluation of the transition states for pyrolidinone-, piperidinone- and caprolactam-derived catalysts suggested that steric interactions with the catalyst backbone are responsible for the chemoselectivity, leading to non selective transformations when the interactions are too little or to slow reactions and concomitant side reactions and degradation when the interactions are too strong.

Whilst, the asymmetric aldehyde-aldehyde[35] coupling remains limited to those particular examples there are also intramolecular versions of the cross-benzoin reaction between unsymmetrical dialdehydes. This reaction still stands as a problematic issue because of the lack of chemoselectivity control and only non-asymmetric version has been reported to date. In 1976, Cookson[36] reported the benzoin cyclization of aliphatic dialdehydes tethered by aliphatic carbon chains of different length employing a thiazolium based catalyst (Scheme 2. 11). The corresponding carbocycles were obtained as a mixture of regioisomers that are equilibrated under the reaction conditions.




**Scheme 2. 11**

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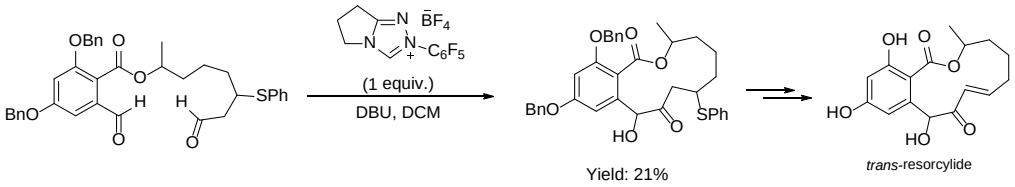
[35] Asymmetric cross-benzoin condensation between acylsilanes (donor) and aldehydes (acceptor) with chiral phosphates: Linghu, X.; Potnick,J. R.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 3070.

[36] Cookson, R.; Lane, R. M. *J. Chem. Soc., Chem. Commun.* **1976**, 804.

Another intramolecular version involving coupling of one aromatic aldehyde with an aliphatic one was applied by Miller[37] to the synthesis of macrocyclic *trans*-resorcylide. Although the adduct was obtained in low yield, even in the presence of equimolar amount of precatalyst, the benzoin reaction proceeded with high chemoselectivity (Scheme 12).



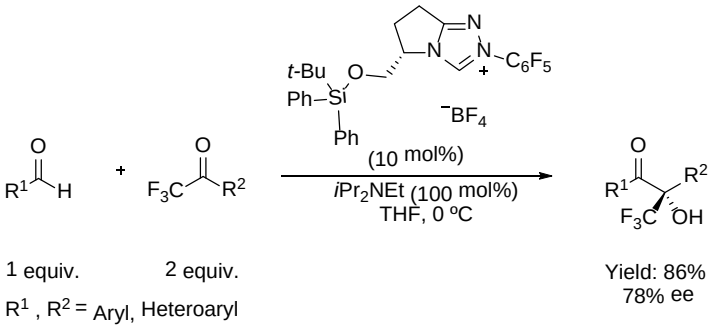

**Scheme 2. 12**

A soon alternative to carry out cross-benzoin reactions relies on the use of a ketone as a potential electrophilic counterpart. Compared to the coupling between two aldehydes this reduces the chemoselectivity issues, since only one possible acyloin anion equivalent can be generated. However the high tendency of aldehydes to undergo self-condensation is a significant problem in this variant of the reaction. An additional problem of the reaction consists on the lower reactivity of ketones towards the addition of the acyloin/benzoin equivalent compared to aldehydes.

In 2009, Enders published the first NHC catalyzed intermolecular aldehyde-ketone cross-benzoin reaction.[38] Although the methodology was limited to the coupling of (hetero)aryl aldehydes with aryl trifluoromethyl ketones, this report proved the synthetic potential of the benzoin reaction to synthesize tertiary alcohols. Later, it was found that in the presence of a chiral triazolium salt, moderate to good enantioselectivities could be achieved when heteroaryl aldehydes were

[37] Mennen, S. M.; Miller, S. J. *J. Org. Chem.* **2007**, *72*, 5260.
[38] Enders, D.; Henseler, A. *Adv. Synth, Catal.* **2009**, *351*, 1749.

employed (39-85% ee) (Scheme 2. 13).[39] An excess of the trifluoromethyl ketone was employed to accelerate the reaction. $^1$H-NMR experiments revealed that the reversible homobenzoin reaction of the aldehyde takes place prior to the formation of the cross-benzoin product which is irreversibly formed under kinetic control.




**Scheme 2. 13**

Following the precedent settled by Enders in the use of activated carbonyl compounds,[38,39] the efficient cross-coupling of a variety of aldehydes with α-ketoesters to produce acyloin products was reported.[40] Those products are particularly interesting as by a simple decarboxylation process analogous aldehyde-aldehyde coupling adduct can be obtained. Therefore, α-ketoesters can be employed as aldehyde surrogates. Despite of the novelty of the work and the wide scope regarding both the nature of the aldehyde and the ketoester counterpart, only a particular example of the enantioselective version was reported. A good level of asymmetric induction (up to 76% ee) was achieved when sterically hindered non-enolizable aryl ketoester was coupled with acetaldehyde (Scheme 2. 14a). This first example was followed by a high yielding enantioselective coupling of a series of aliphatic aldehydes and aryl α-ketoesters published by Gravel (Scheme 2. 14b).[41]

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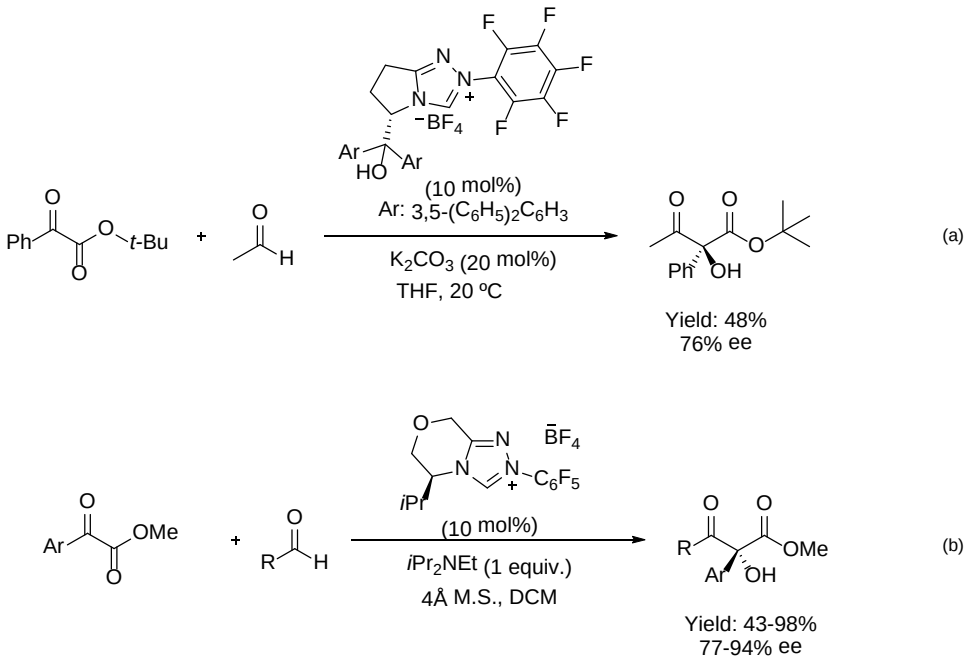
39 Enders, D.; Grossmann, A.; Fronert, J.; Raabe, G. *Chem. Commun.* **2010**, *46*, 6282.

40 Rose, C. A.; Gundala, S.; Fagan, C.-L., Franz, J. F.; Connon, S. J.; Zeitler, K. *Chem. Sci.* **2012**, *3*, 735.

41 Thai, K.; Langdon, S. M.; Bilodeau, F.; Gravel, M. *Org. Lett.* **2013**, *15*, 2214.

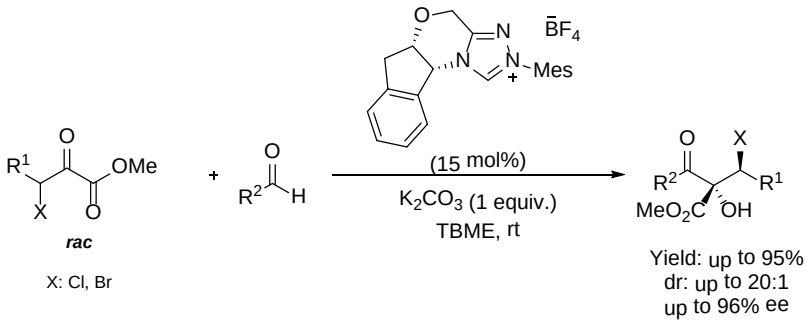
Although, high enantioselectivity values were reported, the scope was not extended further than the use of non-enolizable ketoesters and aliphatic aldehydes.




**Scheme 2. 14**

In the same context, Johnson[42] proposed the dynamic kinetic resolution of β-halo-α-ketoesters through an asymmetric cross-benzoin reaction (Scheme 2. 15). The use of enolizable ketoester bearing an acidic proton enables the racemization of the substrate to render a stereoconvergent benzoin reaction. Thus, a series of chloro- and bromo-ketoesters were successfully coupled with different aldehydes to yield fully substituted β-halo-α-glycolic acid derivatives in high diastereoselectivity and enantioselectivity using an amino-indanol derived chiral triazolium salt as catalyst.

[42] Goodman, C. G.; Johnson, J. S. *J. Am. Chem. Soc.* **2014**, *136,* 14698.




**Scheme 2. 15**

In contrast to the limitations for the intermolecular aldehyde-ketone benzoin reaction, a significant progress has been made regarding the intramolecular variant. It took almost forty years since the report of Cookson[36] on the cyclization glutaraldehyde shown in Scheme 2. 11, until Suzuki applied the aldehyde-ketone cross-benzoin intramolecular condensation to the synthesis of preantraquinones (Scheme 2. 16a) ponía 2.13a.[43] Despite possible homobenzoin or intramolecular aldol reactions, further studies revealed that the reaction was general for different medium-sized cyclic α–hydroxy ketones.[44] In 2006, an enantioselective version of the reaction was realized using an amino-indanol derived catalyst, generating highly enantioenriched tertiary alcohols, however observing lower enantioselectivities in the formation of five-membered rings compared to the six-membered counterparts. Moreover, the reactions conditions were successfully extended for the selective cyclization of a aliphatic, and therefore enolizable, ketoaldehyde,[45] although the corresponding homo-acyloin product was also formed (Scheme 2. 16b)[45]

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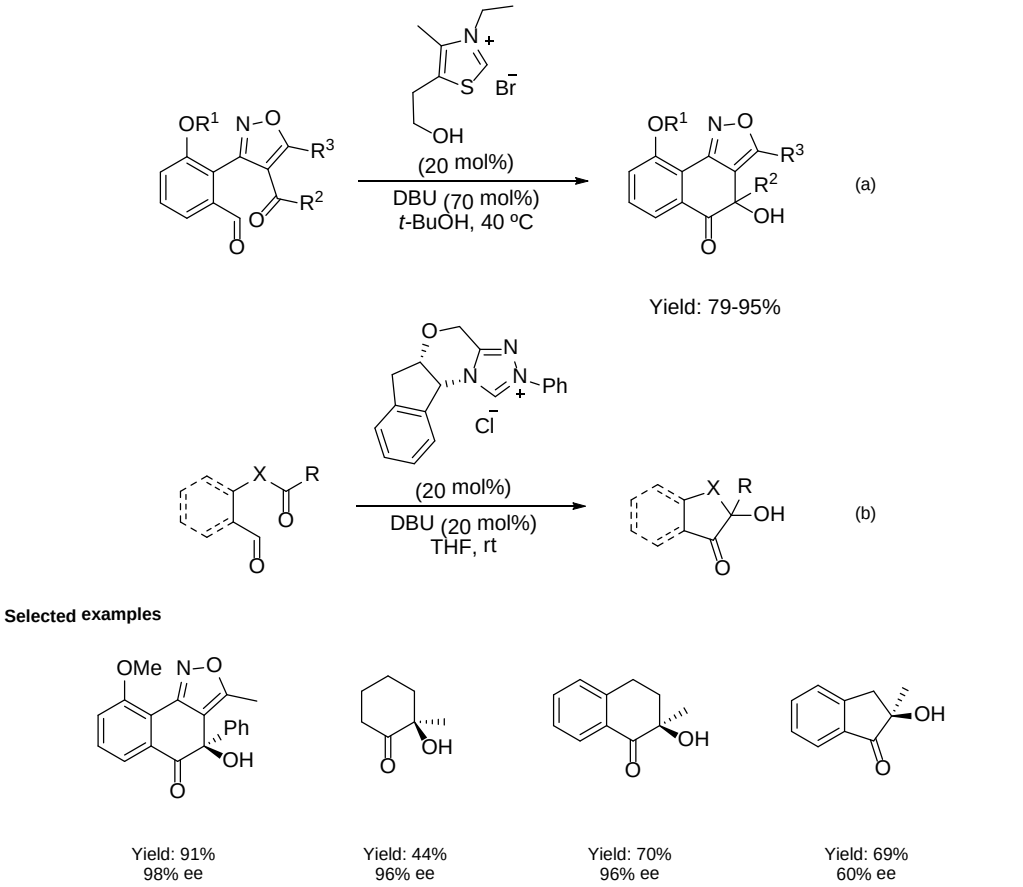
43 Hachisu, Y.; Bode, J. W.; Suzuki, K. *J. Am. Chem. Soc.* **2003**, *125*, 8432.

44 a) Hachisu, Y.; Bode, J. W.; Suzuki, K. *Adv. Synth. Catal.* **2004**, *346*, 1097; b) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111.

45 Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 3492.



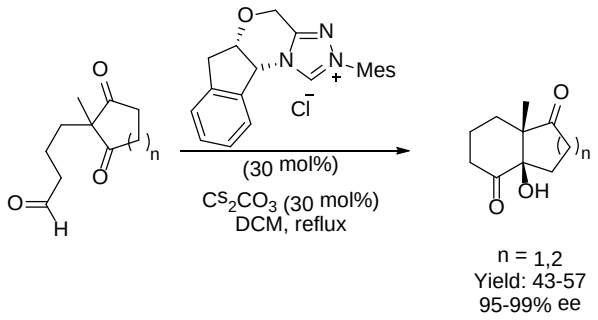

**Scheme 2. 16**

The intramolecular aldehyde-ketone cross-benzoin reaction has been extended to the use of other catalyst and applied to a variety of substrates.[46] Additionally, Ema[47] reported an elegant process for the desymmetrization of 1,3-diketones with a lateral chain at the 2-position, which contains a terminal formyl

[46] a) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1463; b) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431; c) Li, Y.; Feng, Z.; You, S.-L. *Chem. Commun.* **2008**, 2263; d) Rafinski, Z.; Kozakiewicz, A. *J. Org. Chem.* **2015**, *80*, 7468; e) Wen, G.; Su, Y.; Zhang, Lin, Q.; Zhu, Y.; Zhang, Q.; Fang, X. *Org. Lett.* **2016**, *18*, 3980; f) Ema, T.; Nanjo, Y.; Shiratori, S.; Terao, Y.; Kimura, R. *Org. Lett.* **2016**, *18*, 5764.

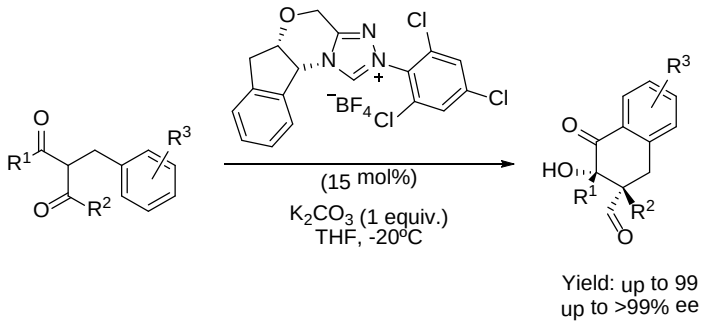
[47] Ema, T.; Oue, Y.; Akihara, K.; Miyazaki, Y.; Sakai, T. *Org. Lett.* **2009**, *11*, 4866

moiety, as suitable substrates to undergo intramolecular cross-benzoin reaction.[48] Even if the scope was limited it was proven that contiguous quaternary estereocenters could be generated with high selectivities (Scheme 2. 17).




**Scheme 2. 17**

Later on, Fang reported the dynamic kinetic resolution (DKR) of β-ketoester and 1,3-diketones employing this methodology. Those highly acidic dicarbonylic compounds can lead to a unique enantiomer upon benzoin condensation in the presence of a chiral triazolium catalyst (Scheme 2. 18). [49]



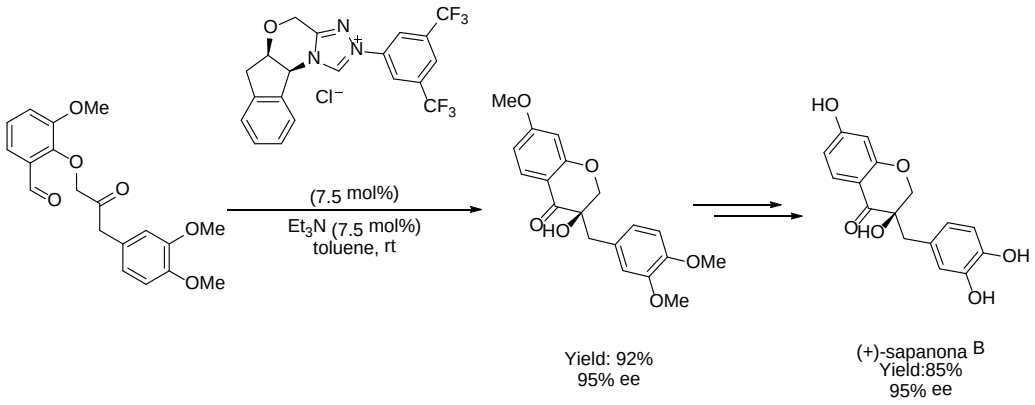

**Scheme 2. 18**

Intramolecular version of the aldehyde-ketone cross-benzoin cyclization has also been employed as key step in the synthesis of complex of several natural

[48] a) Ema, T.; Akihara, K.; Obayashi, R.; Sakai, T. *Adv. Synth. Catal.* **2012**, *354*, 3283; b) Li, Y.; Yang, S.; Wen, G.; Lin, Q.; Zhang, G.; Qiu, L.; Zhang, X.; Du, G.; Fang, X. *J. Org. Chem.* **2016**, *81*, 2763.

[49] Zhang, G.; Yang, S.; Zhang, X.; Lin, Q.; Das, D. K.; Liu, J.; Fang, X. *J. Am. Chem. Soc.* **2016**, *178*, 7932.

products.[50] Suzuki was the pioneer applying this methodology, thus the synthesis of (+)-sapanone B was accomplished with execellent enantioselectivity (Scheme 2. 19).[51] The same group achieved the first asymmetric total synthesis of seragakinone A in a seven step sequence in which the key cross-benzoin reaction occurred with excellent enantiocontrol and that also included a second cross-benzoin condensation in the synthetic route (Scheme 2. 20).[52]

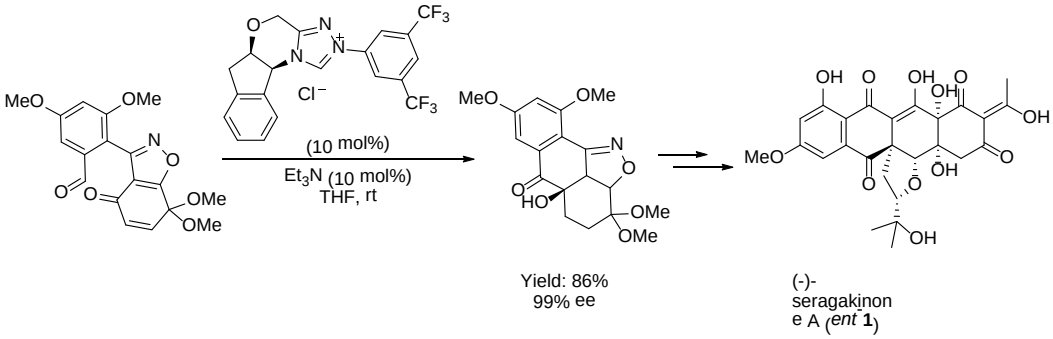



**Scheme 2. 19**

[50] a) Lathrop, S. P.; Rovis, T. *J. Am. Chem. Soc.* **2011**, *131*, 13628; b) Ozboya, K. E.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1835; c) Enders, D.; Grossmann, A.; Huang, H.; Raabe, G. *Eur. J. Org. Chem.* **2011**, 4298; d) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310; e) Ma, C.; Gu, J.; Teng, B.; Zhou, Q.-Q.; Li, R.; Chen, Y.-C. *Org. Lett.* **2013**, *15*, 6206.

[51] Takikawa, H.; Suzuki, K. *Org. Lett.* **2007**, *9*, 14.

[52] Takada, A.; Hashimoto, Y.; Takikawa, H.; Hikita,Y.; Suzuki, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 2297.

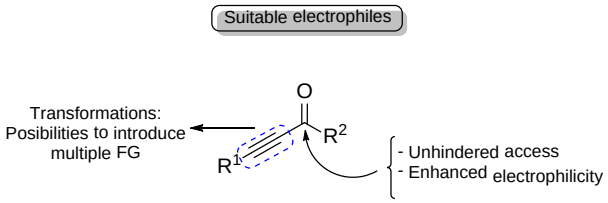



**Scheme 2. 20**

From this literature survey, it can be concluded that NHC catalysis is an excellent approach to carry out *umpollung* reactivity on demanding transformations. In the last decades the knowledge gathered on the enantioselective benzoin condensation has been exponential, thus, a wide variety of aldehydes and electrophiles have been successfully employed. However, the number of reported examples for the intermolecular aldehyde-ketone coupling is limited and the use of non-activated ketones remains elusive. For this reason, research in this topic directed to broaden the scope of the reaction stands as an interesting area of study.

## 2.- SPECIFIC OBJECTIVES AND WORK PLAN

From the literature summary presented in the introduction it can be appreciated that the enantioselective intermolecular aldehyde-ketone coupling is an area of great interest. Remarkably, this methodology has been exclusively developed in recent years and the number of examples is rather low and limited to the use of a highly electrophilic ketones as substrates. In this sense, alkynones stand as an interesting alternative possessing a carbonyl group with significant electrophilicity and highly exposed towards the attack of the Breslow intermediate due to the intrinsic planarity of the molecule. Furthermore, the use of these functionalized carbonyl compounds is expected to increase the interest of this methodology due to the possibility of further transformations available to be carried out on the alkyne functionality that can be directed to diverse oriented synthesis.

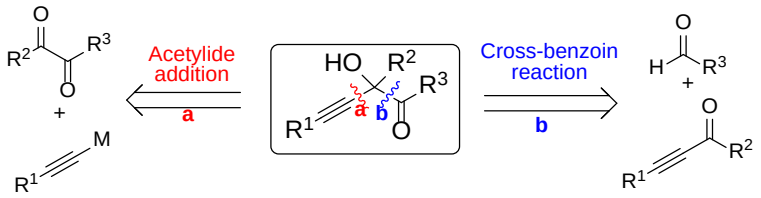



**Scheme 2. 21**

The enantioselective cross-benzoin reaction of alkynones would provide an easy access to enantioenriched tertiary propargylic alcohols bearing a carbonyl moiety at the tetrasubstitued stereocentre. Although considered as important chiral building blocks,[53] the asymmetric synthesis of this particular group of α-

[53] For some selected examples see: a) Kusakabe, T.; Kawai, Y.; Kato, K. *Org. Lett.* **2013**, *15*, 5102; b) Lu, S.; Poh, S. B.; Siau, W.-Y.; Zhao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1731; c) Adachi, S.; Watanabe, K.; Iwata, Y.; Kameda, S.; Miyaoka, Y.; Onozuka, M.; Mitsui, R.; Saikawa, Y.; Nakata, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2087; d) Ghosh, S.; Kinthada, L. K.; Bhunia, S.; Bisai, A. *Chem. Commun.* **2012**, *48*, 10132; e) Ghosh, A. K.; Kass, J. *Org. Lett.* **2012**, *14*, 510; f) Nicolau, K. C.; Sanchini, S.; Sarlah, D.; Lu, G.; Wu, T. R.; Nomura, D. K.; Cravatt, B. F.; Cubitt, B.; de La Torre, J. C.; Hessel, A. J.; Burton, D. R. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6715; g) Aikawa, K.; Hioki, Y.; Mikami, K. *Org. Lett.* **2010**, *12*, 5716; h) Urgaonkar, S.; Cortese, J. F.; Barker, R. H.; Cromwell, M.; Serra, A. E.; Wirth, D. F.; Clardy, J.; Mazitschek, R. *Org. Lett.* **2010**, *12*, 3998; i) Yoshida, S.; Fukui, K.; Kikuchi, S.; Yamada, T. *J. Am.*

hydroxyketones is limited to metal mediated asymmetric alkynylation of ketoeshters[54] and trifluoromethylpyruvates (Scheme 2. 22a).[55]



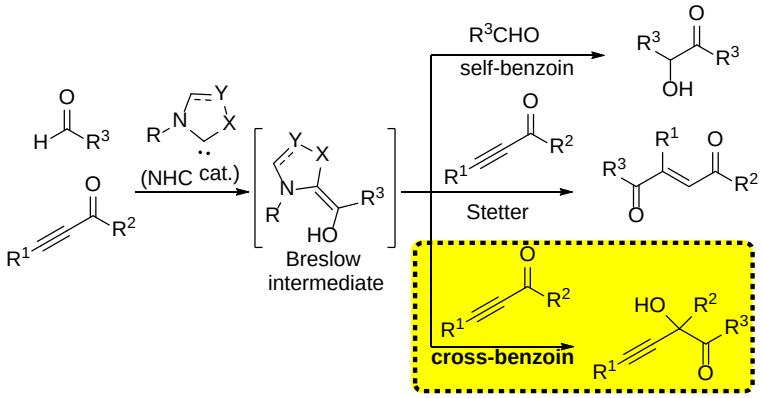

**Scheme 2. 22**

Considering these limitations, we decided to direct our efforts to the **development of a cross-benzoin condensation of aldehydes and a variety of α'- and β- substituted ynones employing chiral triazolium salts as organocatalysts** (Scheme 2. 22b). In order to carry out the proposed transformations, different challenges have to be faced: on the one hand, the chemoselectivity issue intrinsic to the cross-benzoin reaction, as a result of the tendency of aldehydes to yield the homo-benzoin adduct has to be overcome. On the other hand, the regioselectivity of the reaction has to be controlled as the bidentate electrophilic ynones can render either the 1,2-desired product or the competitive 1,4-addition of the acyl anion equivalent, also known as the Stetter reaction (Scheme 2. 23).

*Chem. Soc.* **2010**, *132*, 4072; j) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.; k)* Knueppel, D.; Martin, S. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 2569; l) Ogawa, K.; Koyama, Y.; Ohashi, I.; Sato, I.; Hirama, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1110; m) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282.

54 Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

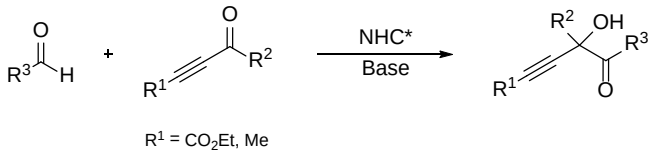
55 a) Ohshima, T.; Kawabata, T.; Takeuchi, Y.; Kakinuma, T.; Iwasaki, T.; Yonezawa, T.; Murakami, H.; Nishiyama, H.; Mashima, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 6296; b) Wang, T.; Niu, J.-L.; Liu, S.-L.; Huang, J.-J.; Gong, J.-F.; Song, M.-P. *Adv. Synth. Catal.* **2013**, *355*, 927.




**Scheme 2. 23**

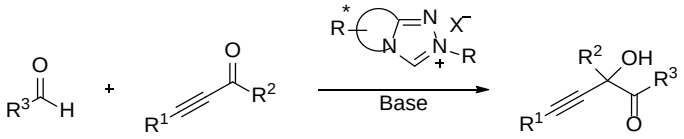
In order to achieve the stated objective, the following work plan was designed:

1. *Proof of concept*: First of all, the viability of the reaction employing ynones as electrophiles will be studied with a model system employing activated ynones ($R^1 = CO_2R$). In case the desired products are successfully obtained, the use of non-activated ynones ($R^1$ = Me) to confirm if these ynones are reactive enough.



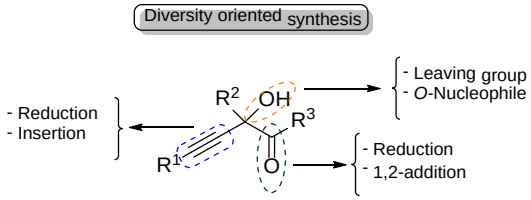

**Scheme 2. 24**

2. *Optimization of the reaction*: Once the viability of the reaction has been proved, different reaction parameters will have to be optimized for the best possible performance. We will start surveying chiral triazolium salts will be performed to identify the best catalyst in terms of regio- chemo- and stereocontrol. Afterwards, other experimental variables will be studied, such as the solvent, the temperature or the use of additives, in an attempt to obtain the optimal experimental conditions.




**Scheme 2. 25**

3. *Scope of the reaction*: With the best conditions in hand, the scope and limitations of the methodology will be studied. In this sense, different alkyl and aryl aldehydes as well as a variety of α'- alkyl and trifluoromethyl ynones will be tested. Additionally, the substitution at the β- position of the electrophile will be modified.
4. *Transformations of the cycloadducts*: Since the obtained adducts are interesting polyfunctional molecules, bearing alkyne, ketone and alcohol moieties, we will proceed to explore their reactivity performing different transformations to demonstrate their applicability as intermediates in complex molecule synthesis (Scheme 2. 26).



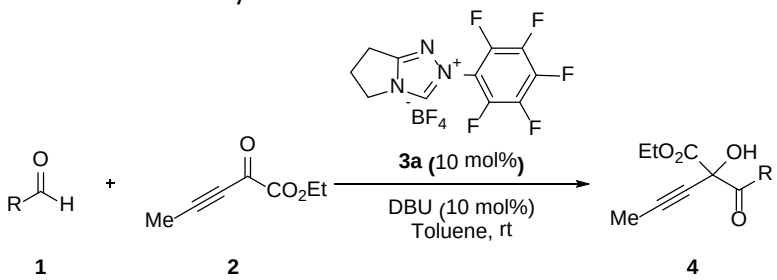

**Scheme 2. 26**

# 3.- RESULTS AND DISCUSSION

## 3.1. PROOF OF CONCEPT

Inspired by the successful use of α-ketoesters as electrophiles in the cross-benzoin condensation with NHC catalysts,[40,41,42] an activated ynone bearing the ketoester moiety was chosen for some preliminary studies. Regarding the nucleophilic counterpart and considering the different performance of aldehydes depending on the reaction conditions, benzaldehyde as well as both linear and branched aliphatic aldehydes were tested as representative substrates. Thus, the reaction between ethyl 2-oxopent-3-ynoate (**2**) with a variety of aldehydes (**1**) catalyzed by 6,7-dihydro-2-pentafluorophenyl-5*H*-pyrrolo[2,1-*c*]-1,2,4-triazolium tetrafluoroborate (**3a**) in the presence of DBU for the generation of the carbene catalyst was evaluated. Complete regioselectivity was observed towards the formation of 1,2-addition products (**4**) although in moderate yield, not observing in any case the product corresponding to the Stetter reaction (Table 2. 1, Entries 1-4). In addition, no product arising from the self-benzoin condensation was observed when employing cyclopropane carbonxaldehyde, leading to an increase of the yield (Entry 4).

**Table 2. 1:** Preliminary studies




**1** **2** **4**

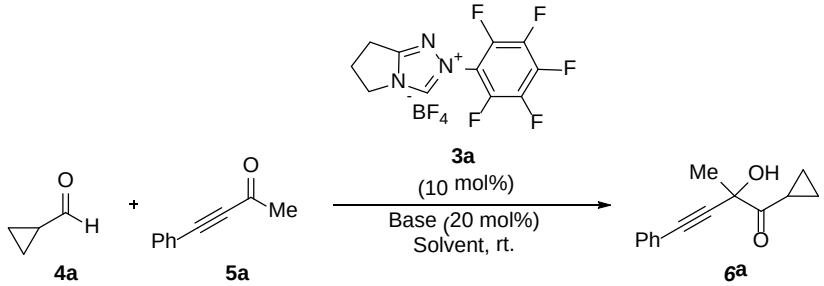
| Entry | R | Yield (%)[a] |
|---|---|---|
| 1 | Ph (**1a**) | 31 |
| 2 | Pr (**1b**) | 28 |
| 3 | -$CH_2CH_2$Ph (**1c**) | 30 |
| 4 | Cyclopropyl (**1d**) | 53 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

The good performance of ynone (**2**), especially when cyclopropane carboxaldehyde was employed as nucleophilic counterpart (Entry 4), prompted us to explore the use of more challenging non-activated ynones. As the model reaction, we chose the condensation of cyclopropane carboxaldehyde and 4-phenyl-3-butyn-2-one (**5a**). An aryl substituent at the terminal position leads to a less volatile substrate and therefore more convenient for the study of the reaction. Preliminary results summarized in (Table 2. 2) showed that, in the conditions previously employed, the triazolium salt-based precatalyst **3a** provided the cross-benzoin condensation adduct in moderate yield in the presence of DBU and using toluene as solvent (Entry 1). Employing a more polar solvent as tetrahydrofuran resulted in a decrease of the yield (Entry 2), whilst running the reaction in chlorinated solvents led to moderate yield similar to the result obtained in toluene (Entry 3-4). Since, dichloromethane proved to be slightly better (Entry 4), it was employed to test the influence of the base. The use of another organic base, as *N*,*N*-diisopropylethylamine did not result in any change (Entry 5), whereas strong inorganic bases led to a slight decrease in the yield (entry 6-7). The reaction coursed slightly better when

employing potassium carbonate, however it can be affirmed that no significant differences were observed among the tested bases. The volatile character of the product prompted us to exchange toluene for benzene, which indeed led to an improvement of the yield (Entry 9). It is worth noting that no product from the possible competitive Stetter or homo-benzoin side reaction was detected.

**Table 2. 2:** Solvent and base effect



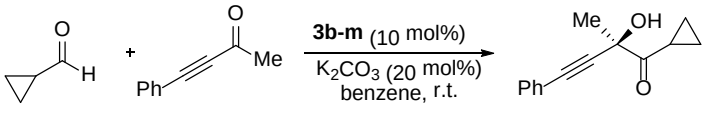

| Entry | Base | Solvent | Yield (%)[a] |
|---|---|---|---|
| 1 | DBU | Toluene | 53 |
| 2 | DBU | THF | 45 |
| 3 | DBU | $CHCl_3$ | 50 |
| 4 | DBU | $CH_2Cl_2$ | 62 |
| 5 | DIPEA | $CH_2Cl_2$ | 62 |
| 6 | KO*t*-Bu | $CH_2Cl_2$ | 42 |
| 7 | KHMDS | $CH_2Cl_2$ | 47 |
| 8 | $K_2CO_3$ | $CH_2Cl_2$ | 54 |
| 9 | $K_2CO_3$ | Benzene | 60 |

[a] Yield of pure product isolated after flash chromatography.

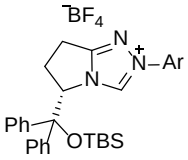
## 3.2. OPTIMIZATION OF THE REACTION CONDITIONS

Once that a triazolium salt was identified as suitable precatalysts for this transformation, a variety of chiral triazolium salts were tested to carry out the asymmetric version of reaction. In accordance to the results obtained previously, potassium carbonate was chosen as base for experimental convenience and benzene employed as solvent to reduce losses of product due to the already mentioned volatile character of the product (Table 2. 3).

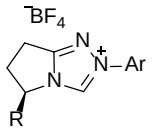
**Table 2. 3:** Evaluation of a series of catalyst.



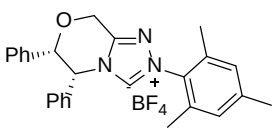

**1d** **5a** **6a**



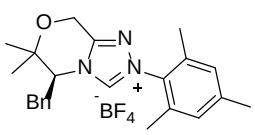

**3b:** Ar: $C_6H_5$
**3c:** Ar: $C_6F_5$



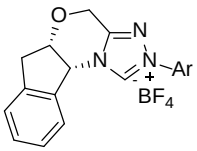

**3d:** R: Bn; Ar: $C_6H_5$
**3e:** R: Bn; Ar: $C_6F_5$
**3f:** R: *i*Pr; Ar: $C_6F_5$




**3g**




**3h**




**3i:** Ar: $C_6F_5$; X: $BF_4$
**3j:** Ar: 2,4,6-$(Cl)_3C_6H_2$; X: $BF_4$
**3k:** Ar: 3,5-$(CF_3)_2C_6H_3$; X: $BF_4$
**3l:** Ar: naphtyl; X: $BF_4$
**3m:** Ar: naphtyl; X: $BF_4$

| Entry | Catalyst | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|
| 1 | **3b** | <10 | n.d.[c] |
| 2 | **3c** | 11 | 33 |
| 3 | **3d** | <10 | -14 |
| 4 | **3e** | 12 | -6 |
| 5 | **3f** | 23 | -40 |
| 6 | **3g** | 12 | 42 |
| 7 | **3h** | <10 | n.d.[c] |
| 8 | **3i** | 30 | 4 |
| 9 | **3j** | 36 | 43 |
| 10 | **3k** | <10 | n.d.[c] |
| 11 | **3l** | 10 | 80 |
| 12 | **3m** | 39 | 80 |

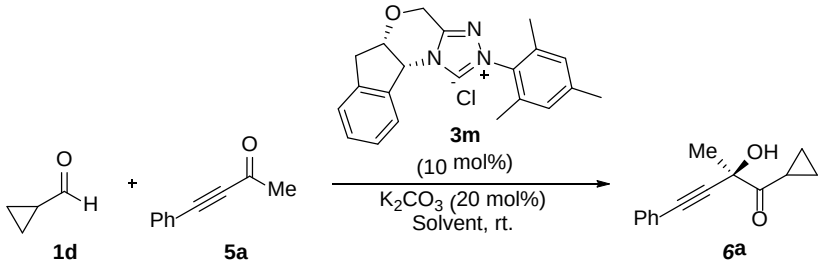
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product. [c] Not determined.

An obvious attempt to develop the asymmetric version of the reaction was to test some chiral triazolium based precatalysts (**3b-3f**) containing a fused

dihydropyrrol ring analogous to the successfully employed catalyst **3a**. A dramatic drop of the yield was observed when introducing a bulky substituent in the α-position to the *N3* of the triazolium ring (Entries 1-2), yet the product could be obtained with a promising enantiocontrol (**3c**, Entry 2). Exchanging the substitution at the dihydropyrrol ring did not led to significant improvement on the yield (Entries 3-4 *vs* Entry 2). However, modifying the aryl substituent at the triazol ring resulted in a slight improvement of the yield and enantiocontrol (Entry 5). The exchange of the dihydropyrrol ring for a morpholine did not improve the results (Entries 6-7). However, the use of aminoindanol based precatalyst, which did not lead to such a congestionated reactive centre compared to previous catalysts allowed to obtain the product with better yield (Entry 8). Exchanging the arene substituent resulted in a significant improvement in the enantiocontrol (Entry 9) and thus highlighted the influence of the substituent in *N1*-position. Bulky groups lead to a decrease of the yield (Entries 10-11) whilst regarding the enantiocontrol the negative effect of electron-poor arenes at this position was confirmed (**3i**, **3j**, **3k, 3l**). Thus, precatalyst **3m** bearing a mesityl moiety lead us to obtain the product in a moderate yield but importantly with good levels of enantiocontrol (Entry 12).

In view of these results, it was decided to employ catalyst **3m** for the study of other experimental parameters. We started evaluating the influence of running the reaction in solvents of different nature (Table 2. 4).

**Table 2. 4:** Solvent effect




| Entry | Solvent | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|
| 1 | THF | 31 | 70 |
| 2 | $CHCl_3$ | 28 | 60 |
| 3 | $CH_2Cl_2$ | 37 | 64 |
| 4 | Benzene | 39 | 80 |
| 5 | Toluene | 39 | 82 |
| 6 | Chlorobenzene | 30 | 74 |
| 7 | Trifluorotoluene | 23 | 72 |
| 8 | Pyridine | 30 | 74 |
| 9 | *o*-xylene | 23 | 72 |

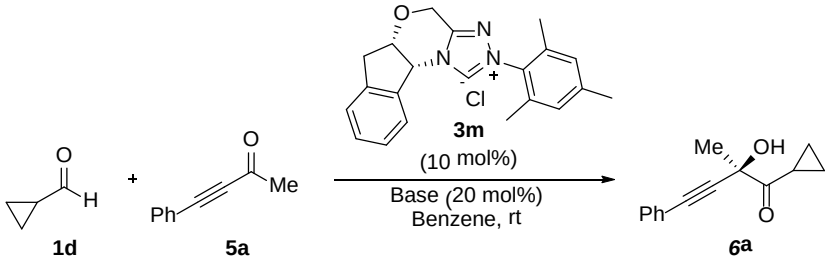
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

From the experiments carried out it can be highlighted that the enantiocontrol is slightly affected by the nature of the solvents. While the reaction could be carried out in THF and chlorinated solvents without compromising the yield (Entries 1-3), none of the tested solvents proved to be better that benzene and toluene regarding the enantiocontrol of the reaction (Entries 4-5). A decrease in both yield and enantioselectivity was observed when other aromatic solvents were employed (Entries 6-9).

At this stage, it was decided to study the influence of the base employed to generate the carbene, on the performance of the reaction. Representative bases used in other benzoin-type reactions, such as DBU, $K_2CO_3$ or KO*t*Bu, were tested. Among all bases shown in this table no significant difference was observed, which was in concordance with the preliminary results obtained when employing non-chiral catalyst **3a**, which indicates that the base is only acting in the triazolium salt

deprotonation**.** Those experiments indicated that in terms of practical utility potassium carbonate was more appropriate for the generation of the catalytically active species, in general observing cleaner reactions than those carried out using other bases.

**Table 2. 5:** Influence of the base



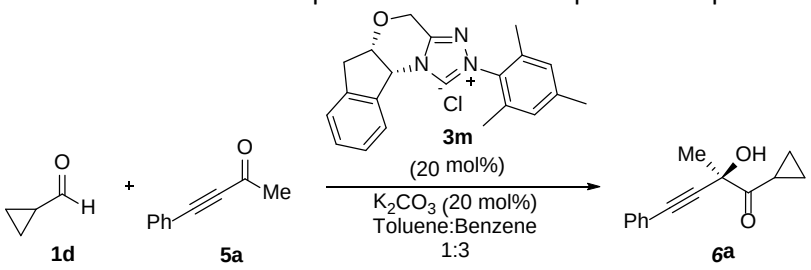

| Entry | Base | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|
| 1 | $K_2CO_3$ | 39 | 80 |
| 2 | KO*t*Bu | 34 | 82 |
| 3 | KHMDS | 33 | 80 |
| 4 | DBU | 34 | 72 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

Since no significant improvement was observed after this first stage of the screening and in view of the moderate yield obtained, the catalyst loading was increased up to 20 mol% (Table 2. 6, Entry 1). In addition, the use of a small excess of ynone accelerated the reaction, which allowed us to perform the reaction at lower temperatures without this affecting the yield. Thus, decreasing the temperature to 0°C together with employing 2 equivalents of ynone, allowed to obtain the product in good yield and an increase on the enantioselectivity was observed (Entry 2). As a result of lowering the temperature below 5°C, the use of a toluene/benzene solvent mixture to prevent freezing was required. Decreasing the temperature even more, resulted in an increase of the enantiocontrol (Entries 3-4), which resulted in obtaining the product in good yield and excellent enantiomeric excess values when

the reaction was carried out at -15ºC (Entry 4). No further improvement was observed when the reaction was set up at 20°C (Entry 5).

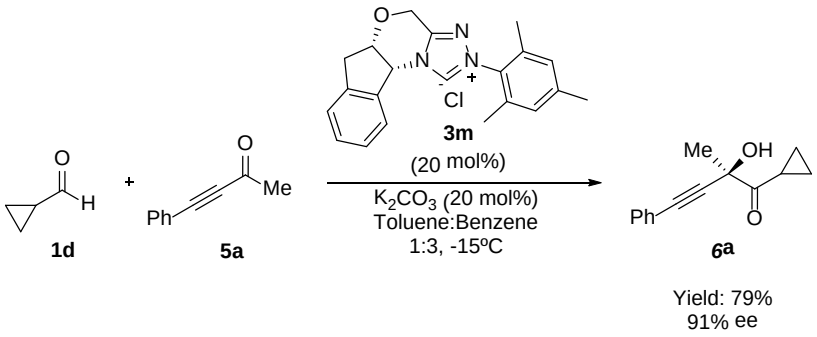
**Table 2. 6:** Influence of the temperature and other experimental parameters




| Entry | 5a (equiv.) | T (ºC)[a] | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | 1 | rt | 75 | 80 |
| 2 | 2 | 0 | 83 | 87 |
| 3 | 2 | -10 | 82 | 89 |
| 4 | 2 | -15 | 79 | 91 |
| 5 | 2 | -20 | 74 | 90 |

[a] Benzene was used as solvent. [b] Yield of pure product isolated after flash chromatography.
[c] Determined by HPLC analysis of the pure product.

The study of all those parameters led us to establish a robust protocol for the cross-benzoin reaction of aldehydes and ynones as it is shown in Scheme 2. 27. The absolute configuration of the adduct will be confirmed later by X-ray analysis.




**Scheme 2. 27**

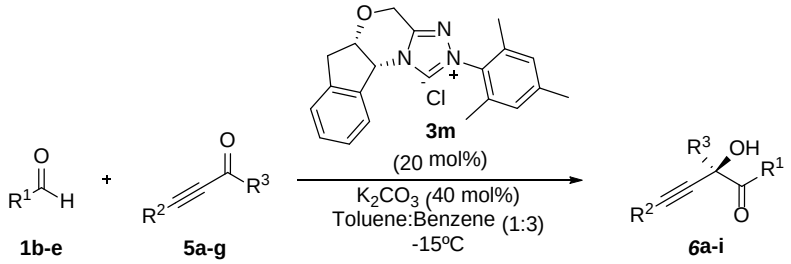
### 3.3. SCOPE OF THE REACTION

With the best conditions in hand, we proceeded to explore other aldehydes and alkynones with different substitution patterns so as to determine the scope of the reaction

First a variety of ynones with different substituents at the β-position were surveyed. As it is shown in Table 2. 7 although the reaction performed with excellent levels of enantiocontrol for a variety of γ-(hetero)aryl-ynones regardless the nature of the substituent (Entries 1-5) the yield of the reaction was compromised. In this regard, introducing electron-donating substituents at the terminal position of the alkyne, including electron-rich arenes and heteroarenes, allowed to obtain the propargylic alcohols in moderate yield (Entries 2-3 and Entry 5). On the other hand, the yield was especially affected when an electron-withdrawing group containing arene was introduced (Entry 4). Noteworthy, the product was satisfactorily obtained when a silyl-protected alkynone was employed, which may led to interesting transformations in that position (Entry 6). However, introducing a group different from an aromatic ring significantly affected the stereoselectivity.

Additionally, we proved that more challenging substrates, such as ynone **5g** with a bulkier substituent at the carbonyl group, could be selectively led to the formation of the corresponding adduct **6g** in moderate yield and with good enantiocontrol (Entry 7). Linear aliphatic aldehydes showed a higher tendency to undergo self-condensation which resulted in a dramatic drop in the yield of cross-benzoin product (Entries 8-9).

**Table 2. 7:** Scope of the reaction using α',γ-substitued alkynones




| Entry | $R^1$ | $R^2$ | $R^3$ | Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | cyclopropyl | Ph | Me | **6a** | 79 | 91 |
| 2 | cyclopropyl | *p*-$MeC_6H_4$ | Me | **6b** | 55 | 94 |
| 3 | cyclopropyl | *p*-$MeOC_6H_4$ | Me | **6c** | 53 | 93 |
| 4 | cyclopropyl | *p*-$BrC_6H_4$ | Me | **6d** | 30 | 92 |
| 5 | cyclopropyl | 3-thiophenyl | Me | **6e** | 59 | 93 |
| 6 | cyclopropyl | TIPS | Me | **6f** | 46 | 78 |
| 7 | cyclopropyl | Ph | Et | **6g** | 40 | 83 |
| 8 | Pr | Ph | Me | **6h** | 30 | 82 |
| 9 | Et | Ph | Me | **6i** | 25 | 75 |

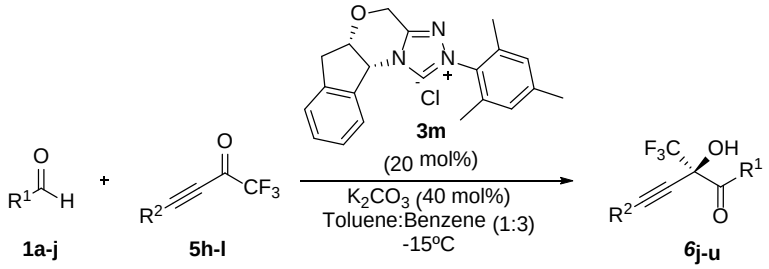
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

In view of these results, we explored the possibility of extending the methodology to more reactive trifluoromethyl alkynones, and therefore to reverse the tendency of the acyl anion equivalent to undergo self-condensation (Table 2. 8). In general the reaction of the trifluoromethyl alkynones with aromatic aldehydes performed better in terms of yield and selectivity. First, we surveyed the use of different aromatic aldehydes and observed that in all the cases, the propargyl alcohols were obtained with excellent enantioselectivities. Thus, aldehydes bearing an electron-withdrawing group gave better results than benzaldehyde (Entries 1-5), leading to the formation of the products in good yields. Electron-rich heteroaromatic aldehydes successfully employed in cross-benzoin condensation reactions,[38,39,56] render excellent yields (Entries 6-8). In addition, this cross-benzoin reaction showed good tolerance to introduce substituents at the acetylenic position; indeed both

[56] Enders, D.; Henseler, A.; Lowins, S. *Synthesis*, **2009**, 4125.

compounds incorporating aryl and alkyl groups at this position could be obtained in good to excellent yields (Entries 3, 7 and 9-12). It should be mentioned that no product derived from the Stetter or homobenzoin reactions was observed in the stated conditions.

**Table 2. 8:** Scope of the reaction using trifluoromethyl ynones

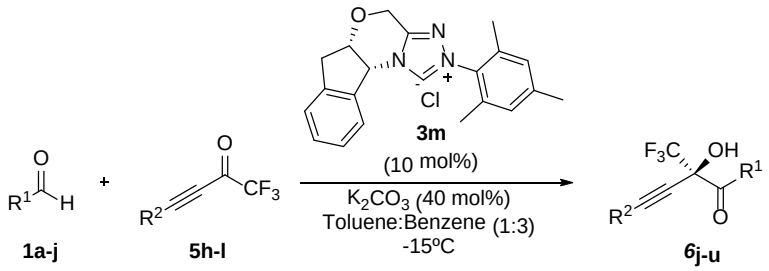



| Entry | $R^1$ | $R^2$ | Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | Ph | Ph | **6j** | 59 | 99 |
| 2 | *p*-F-$C_6H_4$ | Ph | **6k** | 71 | >99 |
| 3 | *p*-F-$C_6H_4$ | *p*-Me$C_6H_4$ | **6l** | 93 | 98 |
| 4 | *p*-Br-$C_6H_4$ | Ph | **6m** | 74 | 99 |
| 5 | *p*-$CF_3$-$C_6H_4$ | Ph | **6n** | 69 | 99 |
| 6 | furyl | Ph | **6o** | 86 | 87 |
| 7 | furyl | *p*-Me$C_6H_4$ | **6p** | 96 | 84 |
| 8 | thiophenyl | Ph | **6q** | 99 | 97 |
| 9 | thiophenyl | *p*-Me$C_6H_4$ | **6r** | 99 | 95 |
| 10 | thiophenyl | TIPS | **6s** | 83 | 89 |
| 11 | thiophenyl | Pr | **6t** | 51 | 98 |
| 12 | thiophenyl | Cy | **6u** | 72 | 98 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

As a last remark, the reaction of a series of representative substrates (**6l, 6o, 6p, 6q** and **6r**) was carried out using a catalyst loading of 10 mol% in order to demonstrate that the reaction performed with similar levels of enantiocontrol under these conditions and even if a decrease in the yield was observed in some cases, the products were obtained in good to excellent yields (Table 2. 9).

**Table 2. 9:**




| Entry | $R^1$ | $R^2$ | Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | *p*-F-$C_6H_4$ | *p*-Me$C_6H_4$ | **6l** | 67 | 99 |
| 2 | furyl | Ph | **6o** | 89 | 86 |
| 3 | furyl | *p*-Me$C_6H_4$ | **6p** | 93 | 88 |
| 4 | thiophenyl | Ph | **6q** | 72 | 96 |
| 5 | thiophenyl | *p*-Me$C_6H_4$ | **6r** | 89 | 97 |

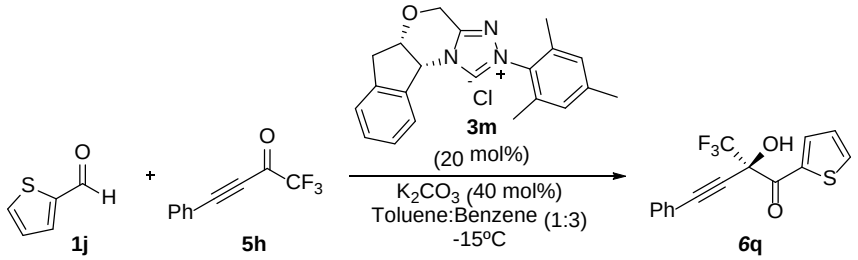
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

In view of these results and that lowering the catalyst loading resulted in a decrease of the yield, we designed an experiment to prove the living nature of the carbene catalyst and to highlight the efficiency of the methodology. The experiment consisted on a successive feeding of the system with additional aldehyde (**1j**) and alkynone (**5h**) upon full conversion of the initial aldehyde was observed. The experiment is based on that a lower catalyst/substrate ratio (<0.2) results in lower efficiency (Table 2. 8, Entry 8 vs Table 2. 9, Entry 4) and therefore this ratio should be maintained. Experimentally, a first run of the reaction was carried out in the conditions defined as optimal in the screening. The reaction was monitored by TLC and GC-MS until complete consumption of the aldehyde was achieved (Table 2. 10, Entry 1, 48h). At this point, once that 1 equivalent (0.3 mmol) of the aldehyde have reacted, an additional equivalent of both reagents is added for a second run, to the system already containing a mixture of the catalyst, the cross-benzoin adduct and the remaining ynone (Entry 2). The reaction was again monitored until completion and this cycle was repeated several times.

As shown in Table 2. 10, up to three consecutive batch cycles of the process were accomplished without significantly affecting the overall yield while maintaining

an excellent enantiocontrol. At the end, we checked that up to 0.9 mmol of starting material could be converted employing the same amount of catalyst. Therefore, two possibilities are available for carrying out the reaction, either use of higher catalyst loading in favour of shorter reaction times or work with a low catalyst loading at longer reaction time.

**Table 2. 10:** Successive feeding of the system

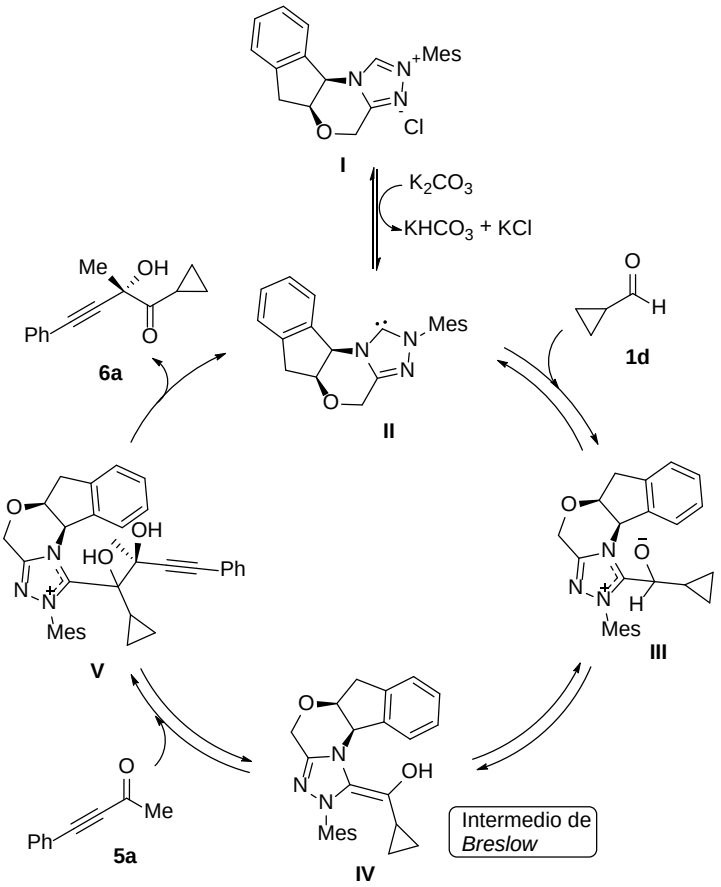



| Number of batch cycles | Time | [mmol] of 1j | Overall cat. loading | Yield[a] of 6q | ee[b] |
|---|---|---|---|---|---|
| 1 | 48h | 0.3 | 20 mol% | 99% | 97% |
| 2 | 96h | 0.6 | 10 mol% | 87% | 97% |
| 3 | 144h | 0.9 | 6.7 mol% | 67% | 97% |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

### 3.4. MECHANISTIC PROPOSAL

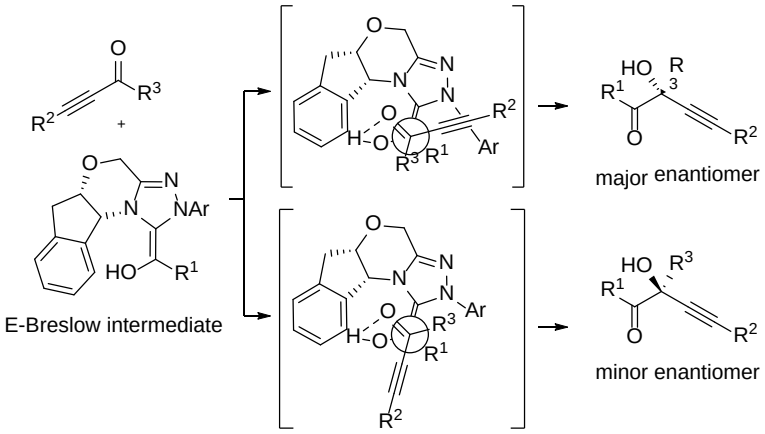
Based on the obtained stereochemical outcome of the products and in agreement with the studies of Ronald Breslow in 1958, our mechanism proposal for the aldehyde-ynone cross-benzoin condensation is showed is presented in Scheme 2. 28.




**Scheme 2. 28**

First, the catalytically active carbene species (**II**) might be generated after a potassium carbonate mediated deprotonation of the chiral triazolium salt (**I**). The reversible condensation of the aldehyde (**1d**) with the carbene (**II**) would form the initial adduct (**III**), which through a (1,2) proton shift would lead to the formation of the *Breslow intermediate* (**IV**). The addition of this nucleophilic enaminol type intermediate to the electrophilic ynone (**5a**) would form the stereocenter of the reaction, which will be controlled by the catalyst in the generation of the C-C bond. A last elimination step would yield the product (**6a**) of the benzoin reaction and release the catalyst.

In order to explain the stereochemistry of the reaction, we propose the model in Scheme 2. 29. The high electron density on the $sp^3$ *N* added to the bulky chiral scaffold of the catalyst disfavour the *Z* isomer of the enaminol.8[a] Therefore, considering that the *E* isomer is participating in the hypothetical catalytic cycle, the *Re* face would be shielded by the aminoindanol moiety, then the reaction with the ynone would take place through the *Si* face. Under the stated premise and based on that the C-C formation event takes place through a five-membered transition state,[10] the two possible transition states are depicted.



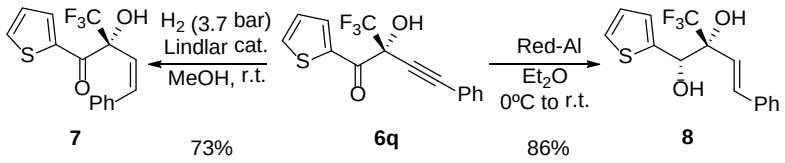

**Scheme 2. 29**

In the first case, while there is an H-bonding between the hydroxyl group and the ketone moiety, the $R^2$ substituent of the ynone is oriented away from the carbene catalyst to minimize steric interactions. In addition, the alkyne moiety, placed towards the carbene, may lead to some π-iminium interactions favouring this transition state, as it was reported by Houk *et al.*[10] On the other hand, the approaching of the ynone through its *Re* face would lead to the formation of the minor enantiomer due to steric repulsion between the catalyst and the $R^2$ substituent.

### 3.5. TRANSFORMATIONS OF THE ADDUCTS

The newly developed cross-benzoin reaction afforded propargyl alcohols with multiple functionalities, such as an alkyne, a ketone and a hydroxyl group. With the aim of demonstrating their potential as chiral building blocks, compound **6q** was elected as representative model to be subjected to different modifications

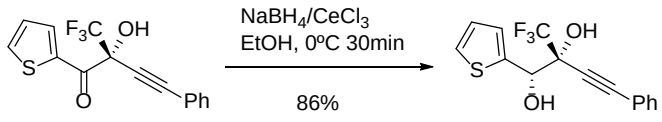
First, the transformation of the alkyne moiety was approached (Scheme 2. 30). In this sense, the *cis*-alkene (**7**) was selectively afforded by semi-hydrogenation with Lindlar catalyst. Noteworthy, the use of methanol as solvent was required to reach full conversion. Alternatively, the use of Red-Al as reducing agent was employed to access the corresponding *trans* diastereomer **8**, but in this case, in addition to the selective hydrogenation of the triple bond the concomitant diastereoselective reduction of the ketone moiety was observed.




**7** 73% **6q** 86% **8**

**Scheme 2. 30**

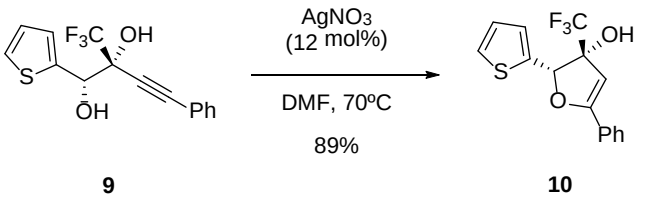
On the other hand, Luche reduction of the ketone moiety was carried out to obtain the corresponding acetylenic diol as a single diastereomer (**9**) (Scheme 2. 31). The reaction proceeded smoothly in ethanol at 0ºC in the presence of $NaBH_4$ and $CeCl_3$, the former being able to activate sodium borohydride towards the selective 1,2-reduction of the ynone.



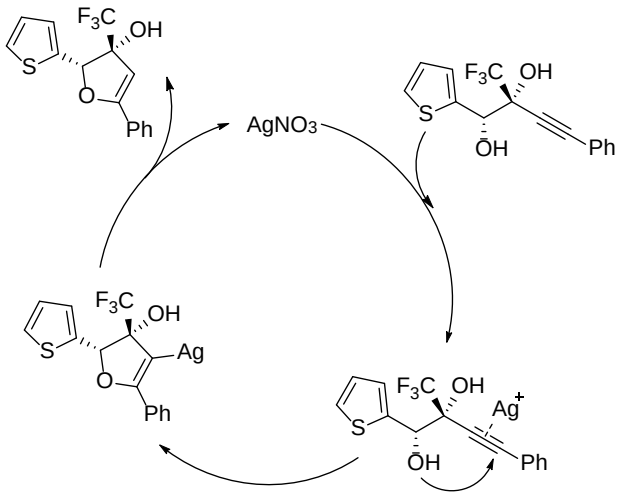

**6q** **9**

**Scheme 2. 31**

This diol **9** was further reacted in the presence of silver nitrate, undergoing a cycloisomerization process that rendered the dihydrofuran **10** in a 89% yield. The silver catalyst is expected to coordinate the alkyne moiety, activating the triple bond towards an intramolecular nucleophilic attack in a *5-endo-dig* type cyclization. Then the catalyst is released and the final dihydrofuran product is formed (Scheme 2. 32).

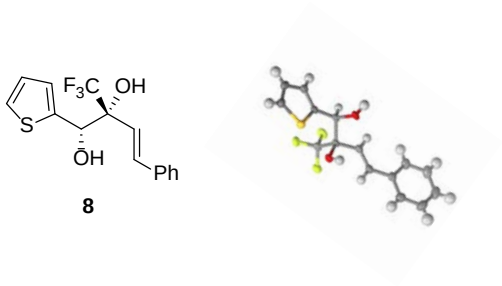



**9** **10**




**Scheme 2. 32**

Diol **8** could be crystallized, thus the absolute configuration of all the stereogenic centers could be determined at this point by X-ray analysis. Based on mechanistic analogy, this absolute configuration was extended to its precursor **6q** and to all the other propargylic alcohols (6a-u) (Scheme 2. 33).




**8**

**Scheme 2. 33**

As a last remark, in consideration of our participation in the "Lilly Open Innovation Drug Discovery (OIDD)" program implemented by Lilly, the pharmaceutical company, the therapeutic potential of the synthesized propargylic alcohols was evaluated. Different adducts presented activity towards the stimulation of GLP-1 (Glucagon-like Peptide 1). Among them, compound **6j** showed promising results (EC50 = 2.35µM) and further *in vivo* studies are ongoing.

GLP- 1 is a potent antihyperglycemic hormone, inducing the release of insulin in response to rising glucose, while suppressing glucagon secretion. Such glucose-dependent action is particularly interesting for the GLP-1, since it no longer stimulates the release of insulin when the levels of glucose in the plasma are in the fasting rate. The GLP-1 secretion is measured in a Lily patented test named ELISA (enzyme-linked immunosorbent assay), specially designed to detect the GLP-1 secreted in the gastrointestinal tissue of mice and humans.

## 4.- CONCLUSIONS

1. It has been probed that alkynones are a competent partner in the cross-benzoin reaction, thus, the limited scope for the aldehyde-ketone has been widen, being this the first example employing non activated ketones in the NHC catalyzed intermolecular cross-benzoin reaction. Under NHC catalysis the reaction proceeds with complete chemoselectivity avoiding the formation of self-benzoin and Stetter side products.
2. A new organocatalytic route for the enantioselective synthesis of tertiary propargylic alcohol has been described, through the NHC catalyzed cross-benzoin reaction employing ynones as electrophiles.
3. The scope of the methodology has been demonstrated as a variety of substituents in the α'- and γ-positions of the alkynones, in addition to the use of different alkyl- and aryl- aldehydes is well tolerated.
4. The value of the synthetized carbinols as building block has been proved through a series of transformation.
5. Noteworthy, some of the synthesized propargylic alcohols present interesting levels of activity towards the stimulation of GLP-1 secretion. In particular in vivo experiments are ongoing employing adduct **6j.**

# 3

# 3

# Organocatalytic generation of donor-acceptor cyclopropanes in cycloaddition reactions

## 1.- INTRODUCTION

Cyclopropanes occupy a privileged position in organic chemistry[1,2] due to their intrinsic characteristics; such as conformational rigidity, ring strain energy and π-character.[3] Despite their strain, cyclopropanes are rather kinetically inert molecules that can only react under particular conditions.[4] However through the strategic placement of substituents on the ring, the strain on the cycle can be increased leading to a more easily cleavage of the C-C bond and therefore interesting reactivity profiles. Thus, these three-membered rings have the ability to act as γ-carbonyl cation equivalents/homologous Michael acceptors when substituted by a carbonyl group or related functionality (Scheme 3. 1(a)) or homologous enolate equivalents when bearing a OR, NR or SR substituent (Scheme 3. 1(b)). More interestingly, a synergistic effect can be observed in cyclopropanes with both an electron-

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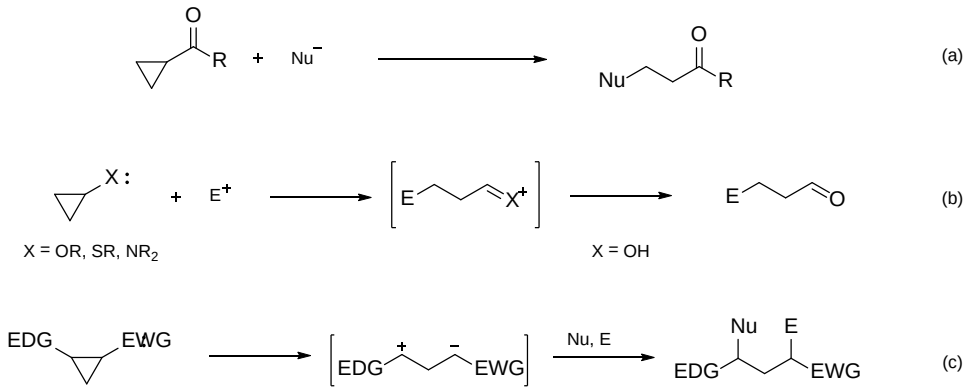
1 a) Reissig, H. U. *In The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, **1987**, 375-443; b) *Carbocyclic Three- and Four- Membered Ring Compounds,* In *Houben-Weyl Methods of Organic Chemistry*, Vol. E17a-d; de Meijere, A., Ed.: Thieme: Stuttgart, **1997**.

2 For cyclopropanes in medicinal chemistry and natural products: a) Donaldson, W. A. *Tetrahedron* **2000**, *56*, 8589; b) Faust, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2251; c) Chen, D. Y.-K.; Pouwer, R. H.; Richard, J.-A. *Chem. Soc. Rev.* **2012**, *41*, 4631.

3 De Meijere, A. *Angew. Chem. Int. Ed.* **1979**, *18*, 809.

4 a) Schlag, E. W.; Rabinovitch, B. S. *J. Am. Chem. Soc.* **1960**, *82*, 5996; b) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229; c) Gajewski, J. J.; Olson, L. P.; Willcott, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 299; d) Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 10545; e) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

withdrawing and electron-donating group in vicinal position, since a push-pull effect results in a particularly weak C-C bond to an extent that those molecules can be depicted as source of 1,3 zwiterionic reactive species (Scheme 3. 1(c)). Therefore, those reagents are referred as Donor-Acceptor (D-A) cyclopropanes and much of their chemistry derives from their use as versatile building blocks through ring-opening processes.[5,6] Their intrinsic bifunctional nature made them suitable for reactions involving the formation of multiple bonds, for instance as source of dipolar reagents in cycloaddition reactions.




**Scheme 3. 1**

Despite pioneering work of Danishefsky and Corey,[5] among others, "activated cyclopropanes", in particular donor-acceptor cyclopropanes, has exploded in popularity in the last few years.[6] Moreover, new activation modes have been

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[5] For a review on early work on acceptor-substituted cyclopropanes, see: a) Danishefsky, S. *Acc. Chem. Res*. **1979**, *12*, 66. For early work on donor-substituted cyclopropanes, see: b) Saluan, J. R. Y. *Top. Curr. Chem.* **1988**, *144*, 1; c) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem*. **1990**, *155*, 1; d) Kulinkovich, O. G.; *Chem. Rev.* **2003**, *103*, 1071. For early work on donor-acceptor cyclopropanes, see: e) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. f) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

[6] For selected review on recent advances in ring opening of activated cyclopropanes, see: a) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353; b) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504; c) Wang, L.; Tang, Y. *Isr. J. Chem.* **2016**, *56*, 463; d) Ganesh, V.; Chandrasekaran, S. *Synthesis* **2016**, 4347.

explored for promoting ring-opening of the D-A cyclopropane,[7,8] resulting in an extension of the range of transformation in which these reactive intermediates can be employed.

In this sense, Lewis acid catalysis has been the most prolific approach to the activation of cyclopropanes as stated by the number of publications on this field. The catalyst, typically a metal based Lewis acid, interacts with the electron-withdrawing group(s) present in the molecule, increasing the polarization of the C-C bond which serves to promote the ring-opening event and to form virtual 1,3-dipoles that subsequently react with an external reagent. Whilst a variety of donor groups have been reported, the geminal ester groups are virtually the only acceptors described to date. The widespread use of Lewis acids in this field has defined D-A cyclopropanes as suitable source of three carbon dipoles for their reaction with a variety of dipolarophiles in a variety of [3+n] cycloaddition reactions that will be surveyed in the following pages. Furthermore, D-A cyclopropanes have also served as precursors of a variety of intermediates that also including their use as two and four carbon synthons in other related cycloadditions.

### 1.1. [3+2] Cycloaddition

Since the first reports on [3+2] cycloadditions between D-A cyclopropanes and carbonyl compounds,[9] that were almost limited to the use of alkoxy groups as donors on the cyclopropane scaffold, several recent advances have been made

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7 For H-bonding activation manifold on ring-opening event, see:a) Dickmeiss, G.; De Sio, V.; Udmark, J.; Poulsen, T. B.; Marcos, V.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6650. b) So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444; c) Hardman, A. M.; So, S. S.; Mattson, A. E. *Org. Biomol. Chem.* **2013**, *11*, 5793.

8 For iminium catalysis promoted ring-opening, see: a) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886; b) Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8391; c) Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 18756.

9 a) Reissig, H. U. *Tetrahedron Lett.* **1981**, *22*, 2981; b) Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasegawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126; c) Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 5226; d) Shimada, S.; Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Tetrahedron* **1993**, *49*, 1589.

towards the extension of the methodology.[10,11,12,13] In 2009, Johnson[14] reported a dynamic kinetic asymmetric transformation (DyKAT) as an alternative to the use of enantiopure cyclopropanes[10] for obtaining enantioenriched tetrahydrofurans (Scheme 3. 2). Based on the interconversion of cyclopropane enantiomers that takes places by action of the (4-Cl-*t*Bu-pybox)$Mg^{II}$ catalyst when electron donor substituted cyclopropanes are employed, the racemic mixture can be resolved. The chiral catalyst leads to the cycloaddition reaction of the aldehyde with one of the two enantiomers of the cyclopropane to render the final thetrahydrofurane adduct with high enantiomeric excess. Previous reports of Johnson and co-workers[10] proposed a tight ion-pair intermediate for this transformation. Later on, the methodology was applied successfully to the use of imines to form the corresponding pyrrolidines.[15] Other electrophiles, such as nitriles[16] or electron-poor pyridines and quinolines,[17] have featured in [3+2] cycloaddition, however in most of the cases only limited studies have been carried out.[18]

---

[10] a) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014; b) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057; c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

[11] a) Benfatti, F.; de Nanteuil, F.; Waser, J. *Org. Lett.* **2012**, *14*, 386; b) Haubenreisser, S.; Hensenne, P.; Schröfder, S.; Niggermann, M. *Org. Lett.* **2013**, *15*, 2262.

[12] Tropone as carbonyl counterpart lead to formal [8+3] cycloadditions: Rivero, A. R.; Fernández, I.; Sierra, M. Á. *Org. Lett.* **2013**, *15*, 4928.

[13] Cyclopropyl acetal: Sabbatani, J.; Maulide, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 6780.

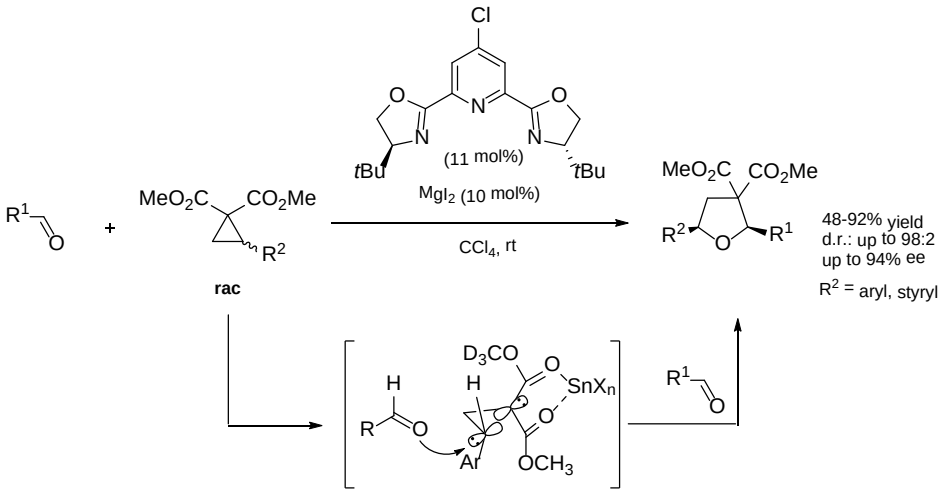
[14] Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.

[15] Enantioselective [3+2] cycloaddition with imines: a) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. Early work with imines: b) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3186; c) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196.

[16] a) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099;. b) Sathishkannan, G.; Srinivasan, K. *Org. Lett.* **2011**, *13*, 6002.

[17] Morra, N. A.; Morales, C. L.; Bajitos, B.; Wang, X.; Jang, H.; Wang, J.; Yu, M.; Pagenkopf, B. L. *Adv. Synth. Catal.* **2006**, *348*, 2385.

[18] Carbon disulfide: a) Bruckner, C.; Reissig, H. U. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 588. Isocyanates and isothiocyanates: b) Graziano, M. L.; Iesce, M. R. *J. Chem. Res., Synop.* **1987**, 362; c) Graziano, M. L.; Cimminiello, G. *J. Chem. Res., Synop.* **1989**, 42; d) Goldberg, A. F. G.; O'Connor, N. R.; Craig, R. A.; Stoltz, B. M. *Org. Lett.* **2012**, *14*, 5314. Diazenes: e) Graziano, M. L.; Iesce, M. R.; Cermola, F. *J. Chem. Res., Synop.* **1996**, 82; f) Korotkov, V. S.; Larionav, O. V.; Hoftneister, A.; Magul, J.; De Meijere, A. *J. Org. Chem.* **2007**, *72*, 7504. Nitrosyl chloride: g) Cermola, F.; Di Gioia, L.; Graziano, M. L.; Iesce, M. R. *J. Chem. Res., Synop.* **2005**, 677. Isonitriles: Korotkov, V. S.; Larionov, O. V.; De Meijere, A. *Synthesis* **2006**, 3542. In situ generated hydrazones h) Lebold, T. P.; Ker, M. A.




**Scheme 3. 2**

Alternatively transition metals have been employed as catalysts involved in the activation of the cyclopropanes bearing alkyne and alkene moieties through the formation of organometallic species. Thus, in 2008 Johnson[19] reported the use of a. Pd(0) based catalyst for the activation of a cyclopropane through the formation of a stabilized palladium-allyl intermediate (Scheme 3. 3). This species undergoes nucleophilic attack over the aldehyde and subsequent final cyclization to yield the corresponding tetrahydrofuran. Based on this work, Trost[19b,c] developed a vinylogous asymmetric version of the reaction employing a phosphine based chiral ligand (Scheme 3. 3). A series of Michael acceptors were employed as dipolarophiles leading to a family of spirocyclic compounds. Those examples served as precedent for new studies employing different metal catalysts, such as ruthenium and nickel.[20]

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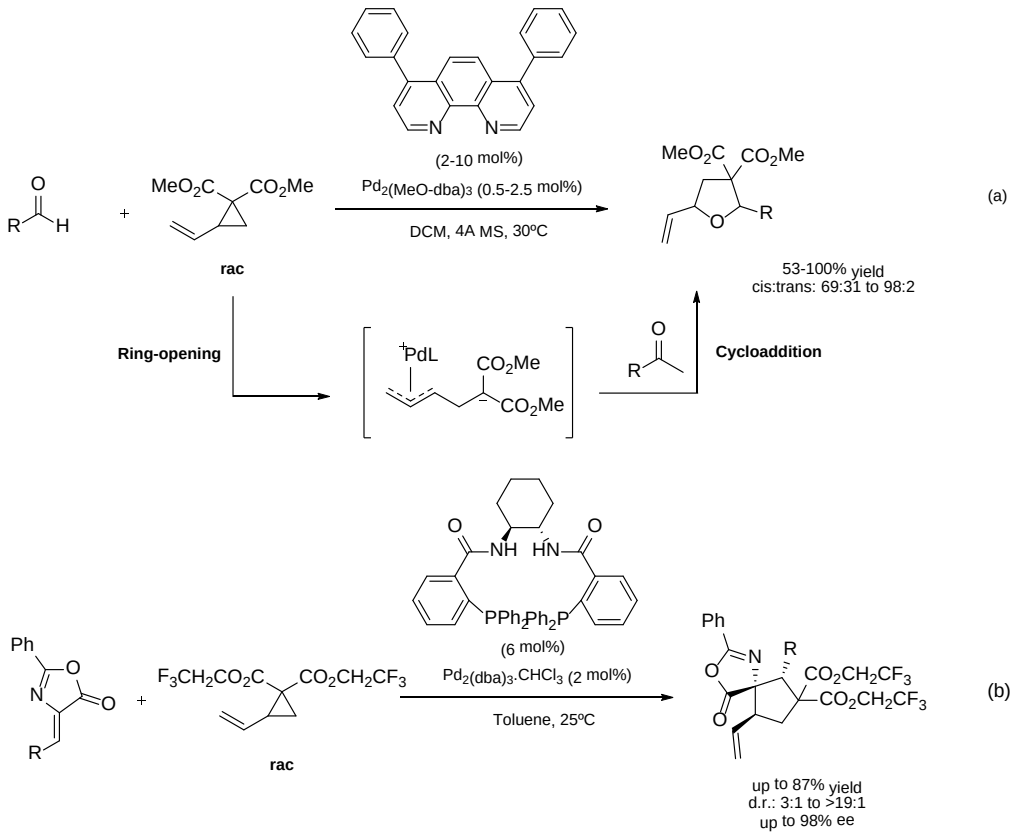
*Org. Lett.* **2009**, *11*, 4354. Nitrosoarenes: Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5964. Acetylenes: Yadav, V. K.; Sriramurthy, V. *Angew. Chem. Int. Ed.* **2004**, *43*, 2669.

19 a) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541; b) Trost, B. M.; Morris, P. J. *Angew. Chem. Int. Ed.* **2011**, *50*, 6167; c) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823.

20 Palladium activation of vinyl cyclopropanes: a) Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474; b) Mei, L.-y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2012**, *31*, 7591; c) Wei, F.; Ren, C.-L.; Wang, D.; Liu, L. *Chem. Eur. J.* **2015**, *21*, 2335; d) Xie, M.-S.; Wang, Y.; Li, J.-P.; Du, C.; Zhang, Y.-Y.;



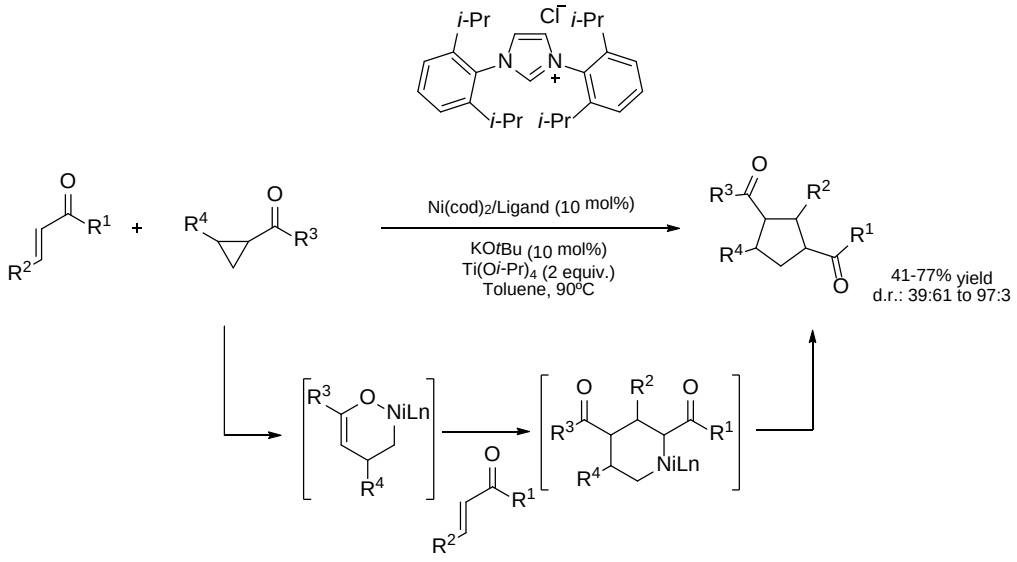

**Scheme 3. 3**

In a conceptually different approach, the cycloaddition of enals with acylcyclopropanes has been described based on the oxidative insertion of Ni(0) across the C-C bond to generate nickelacycles enolates.[21] THis intermediate has the ability to subsequently react with the enal in an insertion/reductive elimination sequence that enables the access to densely substituted cyclopentanes in a single

Hao, E.-J.; Zhang, Y.-M.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2015**, *51*, 12451; e) Ma, C.; Huang, Y.; Zhao, Y. *ACS Catal.* **2016**, *6*, 6408. Ruthenium activation of alkynyl cyclopropanes: f) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2012** *52*, 1758. Nickel activation of vinyl cyclopropanes: g) Tombe, R.; Iwamoto, T.; Kurahashi, T.; Matsubara, S. *Synlett* **2014**, 2281.

21 a) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128*, 5348; b) Liu, L.; Montgomery, J. *Org. Lett.* **2007**, *9*, 3885.

step (Scheme 3. 4). This methodology is particularly interesting as it allowed the use of simple non-activated cyclopropyl ketones in the reaction.

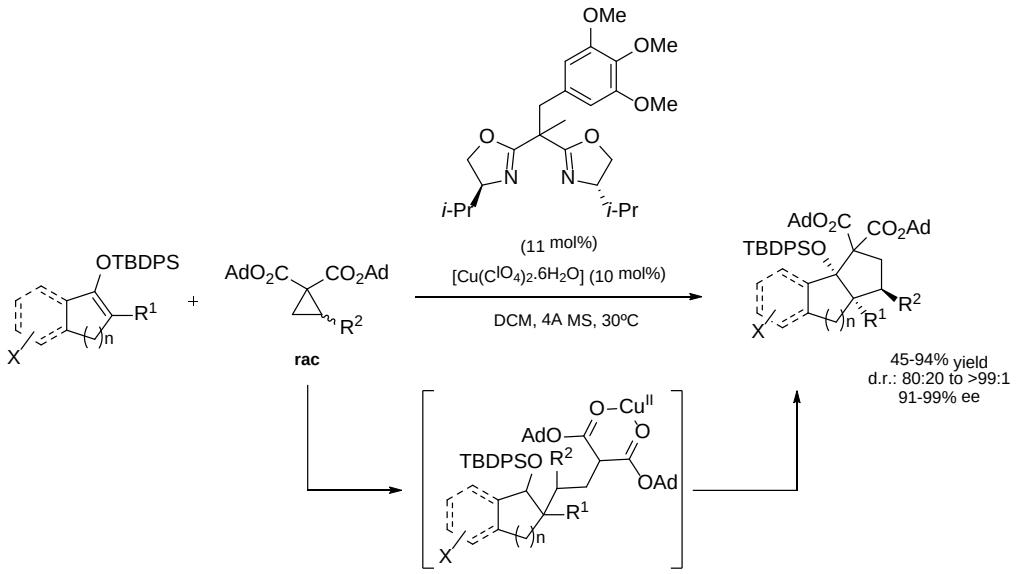



**Scheme 3. 4**

The use of electron-rich olefins to initiate the ring-opening event enables the access to carbocyclic products. In particular, a good example is the report by Tang[22] showing the enantioselective cycloaddition of silyl enol ethers with aryl substituted D-A cyclopropanes under Lewis Acid catalysis (Scheme 3. 5). The initial nucleophilic ring opening step is followed by intramolecular cyclization, defined as the rate-limiting step. After some early work and examples that highlighted the need of bulky acceptor groups in the ester substituents of the cyclopaprane as well as in the silyl

[22] Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4004.

group,[23] DFT studies led to conclude that a stepwise process would explain this formal cycloadittion.[24]




**Scheme 3. 5**

The copper catalyzed formation of highly enantioenriched carbobicycles was extended to the synthesis of tricylic systems by employing enol silyl ethers with a fused benzene ring. Further investigations have lead to enantioselective cycloadditions with indoles[25] and the use of other electron-rich arenes[26] and particular electron-rich alkenes.[27]

---

[23] a) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771; b) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasegawa, M. *Chem. Lett.* **1990**, 1093. Enantiospecific cycloadditions: c) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684; d) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12075. More recent work of Waser e) Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 8484.

[24] Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang, Y. *Chem. Eur. J.* **2012**, *18*, 2196.

[25] a) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851; b) de Nanteuil, F.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 6239.

[26] Furans: a) Chagarovskiy, A. O.; Budynina, E. M.; Ivvanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385. 2-Naphthols: b) Kaicharla, T.; Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 10061.

[27] Enamine: a) Verma, K.; Banerjee, P. *Adv. Synth. Catal.* **2016**, *358*, 2053. Vinyl azides: Dey, R.; Banerjee, P. *Org. Lett.* **2017**, *19*, 304. Enoldiazoacetates: Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568.

### 1.2. [3+3] Cycloaddition

As stated previously the use of cyclopropanes in cycloaddition reactions has been extended to the synthesis of other ring systems by exchanging the previously used 1,2 dipolarophiles for 1,3 and 1,4 homologues. Notwithstandingly, formal [3+3] cycloaddition reactions of D-A cyclopropanes with 1,3 dipoles as nitrones and azomethine imines has only very recently been developed. In this regard, great effort was made by Kerr[28] and co-workers to get an insight into the performance of nitrones in the reaction and the possible mechanistic pathway.[29] Following to these initial studies, in 2005, Sibi[30] reported the first enantioselective method for the preparation of tetrahydro-1,2-oxazines, although with problems with the diastereoselectivity, employing a chiral $Ni^{II}$ complex through a mechanism involving an extensive or total ring opening to a zwitterionic species trapped by the nitrone ($S_N1$).

Almost simultaneously, Tang[31] reported a versatile chiral trisoxazoline/$Ni^{II}$ catalytic system employed in both enantioselective synthesis of 1,2-isoxazines and the kinetic resolution of racemic mixtures of cyclopropanes. Thus, the asymmetric [3+3] cycloaddition with nitrones could be carried out resulting in the synthesis of highly enantioenriched 3,6-substitued-(3*R*,6*R*)-tetrahydro-1,2-oxazine-4,4-dicarboxylates with good levels of diastereoslectivity (Scheme 3. 6a). Alternatively, racemic mixtures of cyclopropanes bearing a phenyl or electron-poor arenes as substituents could be resolved to obtain chiral cyclopropanes with high enantiomeric excess and later on access the oxazines of inverse configuration (Scheme 3. 6b).

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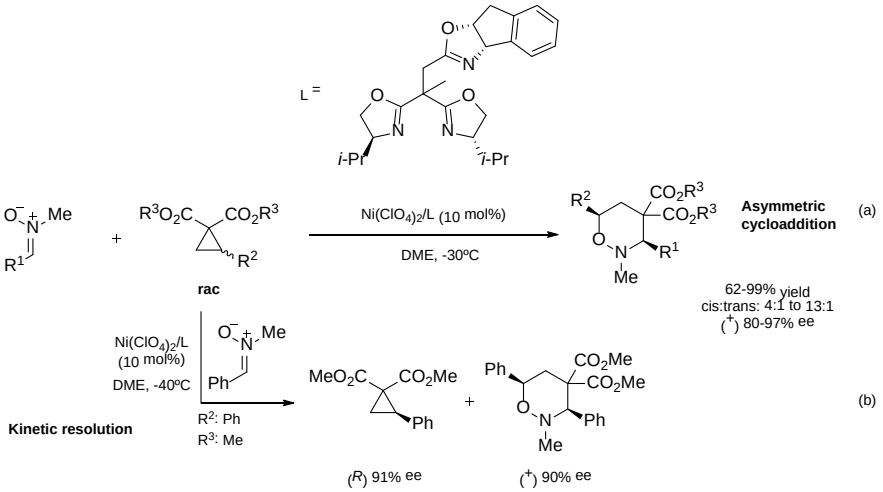
[28] a) Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023; b) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139; c) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554.

[29] a) Wanapun, D.; Van Gorp, K. A.; Mosey, N. J.; Kerr, M. A.; Woo, T. K. *Can. J. Chem.* **2005**, *83*, 1752; b) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 10251.

[30] Sibi, M. P.; Ma, Z. H.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764.

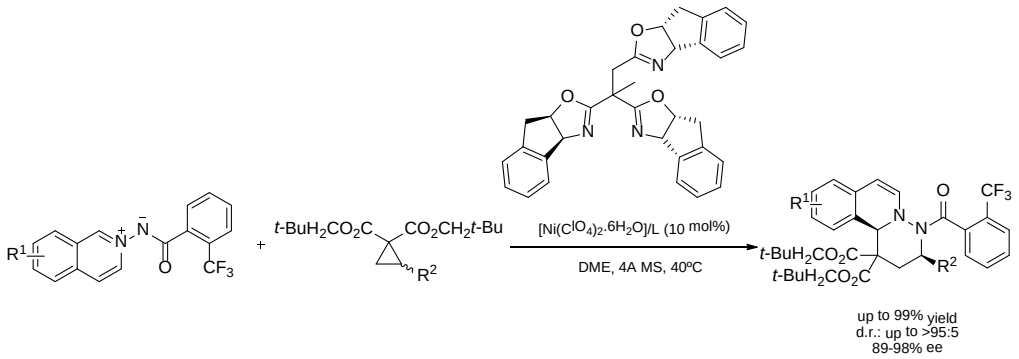
[31] Kang, Y. B.; Sun, X. L.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, *46,* 3918.




**Scheme 3. 6**

This chemistry has also been extended to the use of azomethine imines as 1,3-dipoles reacting with the D-A cyclopropane.[32] The first report of enantioselective cycloaddition involving D-A cyclopropanes and those ylides was reported by Tang[32b] employing a chiral indanyl trioxazoline ligand in combination with $Ni(ClO_4)_2$. Tricyclic dihydro(iso)quinoline derivates bearing a hydropyridazine ring were obtained in high yields and with excellent diastereo- and enantioselectivities (Scheme 3. 7). The size of the aliphatic chains in the ester moieties of the cyclopropane, the role of the sidearm of the ligand[32b] and the presence of a trifluoromethyl group in the azomethine imine proved to be crucial for the high enantioselectivity values obtained. In this sense, a π-π interaction between the indane group at the sidearm and the aromatic group of the cyclopropane was proposed.

[32] a) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.Charette, A. B. *Org. Lett.* **2008**, *10*, 689; b) Zhou, Y. Y.; Li, J.; Ling, L.; Liao, S. H.; Sun, X. L.;Li, Y. X.; Wang, L. J.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1452.




**Scheme 3. 7**

### 1.3. [3+3] Annulation

In a different context, cyclopropanes may feature in processes that have a ring-opening event clearly distinguished from the later cyclization step. Those transformations may occur in a domino sequence[33] or in other cases a change of the reaction conditions is required.[34] Thus, Kerr *et al* have had significant relevance in this kind of [3+3] annulations, such as the synthesis of highly substituted piperidines employing propargyl amines (Scheme 3. 8).[33a] An inicial nucleophilic attack over the sufficiently electrophilic cyclopropane due to the activation of the esters by the zinc catalyst forces the ring-opening. This linear intermediate undergoes a Conia-ene reaction to form the annulation product. Noteworthy, enantioenriched piperidines could be successfully accessed by employing chiral cyclopropanes.

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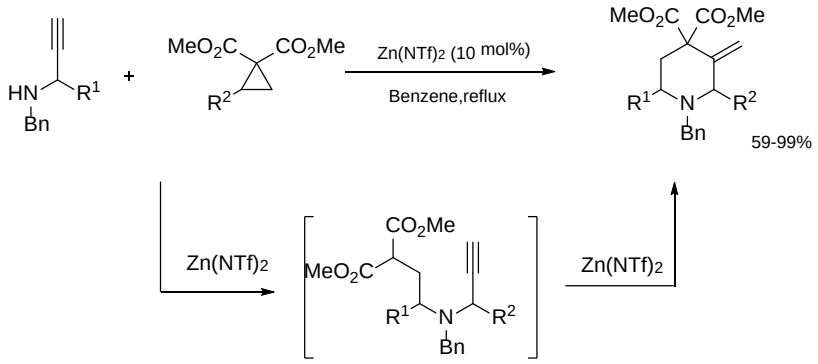
[33] Selected examples of nucleophilic ring-opening promoted intermolecular cascades. a) Lebold, T. P.; Leduc, A. B.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3770; b) Ghorai, M. K.; Talukdar, R.; Tiwari, D. P. *Chem. Commun.* **2013**, *49*, 8205; c) Taludkar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954; d) Sin, S.; Kim, S.-G. *Adv. Synth. Catal.* **2016**, *358*, 2701.

[34] a) Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081; b) Leduc, A. B.; Lebold, T. P.; Kerr, M. A. *J. Org. Chem.* **2009**, *74*, 8414; c) Liu, Q.-J.; Yan, W.-G.; Wang, L.; Zhang, X. P.; Tang, Y. *Org. Lett.* **2015**, *17*, 4014.




**Scheme 3. 8**

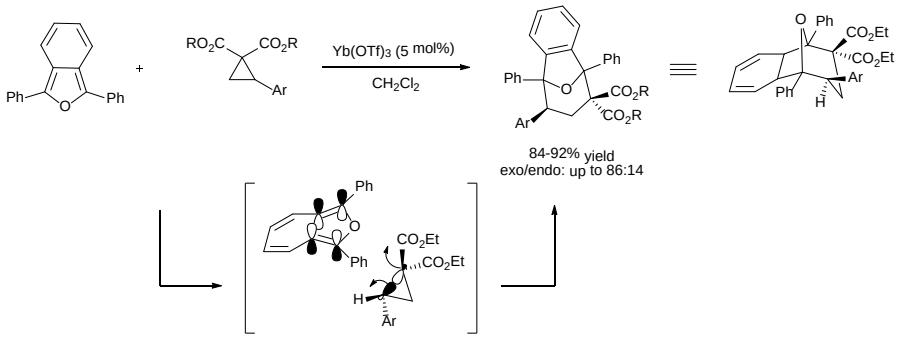
### 1.4. [3+4] Cycloaddition

Formal [3+4] cycloadditions of cyclopropanes that entail the reaction of the zwitterionic intermediate generated after the ring opening event with a suitable diene as the four carbon counterpart remain almost limited to the pioneering work of Budynina.[35] Dienes, such as 1,2-diphenylisobenzofurans, with a high reactivity as well as considerable steric hindrance are required for this transformation .[36] The predominant formation of the less stable *exo* isomer supports the theory of a concerted mechanism, in which the stereochemistry is given by orbital control in a diastereospecific transformation (Scheme 3. 9).[35a]

---

[35] a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 1107; b) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Org. Chem.* **2008**, *53*, 5329; c) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur.J.* **2016**, *22*, 521.

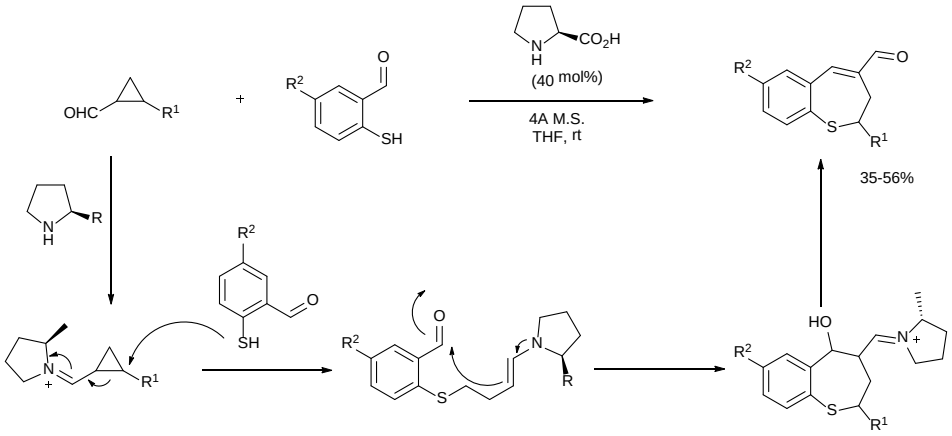
[36] Asymmetric [4+3] annulations *via* [3+2] cycloaddition/ring-opening/cyclization sequence: Xu, H., Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006.




**Scheme 3. 9**

In 2009, Wang *et al* published an example of [3+4] annulation employing cyclopropanes (Scheme 3. 10).[37] Although as in the abovementioned examples the reaction sequence is initiated by a nucleophilic ring opening event, in contrast to them a secondary amine was employed to activate a formylcyclopropane through the formation of an iminium ion species, which plays the role of the acceptor group.8 Under this covalent catalyst *o*-thiosalicylaldehydes were employed in an homoconjugated addition/aldol sequence to render benzo[*b*]thiephines in moderate yields. The $S_N2$ type attack of the mercapto moiety rules the stereochemistry of the reaction, which is given by the configuration of the starting cyclopropane (92% ee), leading to a highly enantioespecific transformation (up to 88% ee). The generated linear enamine type intermediate further reacts with the aldehyde moiety of the salicylaldehyde to render the corresponding seven-membered ring.

[37] Li, L.; Li, Z.; Wang, Q. *Synlett* **2009**, *11*, 1830.




**Scheme 3. 10**

### 1.5. [2+3] Cycloaddition

The activation of formylcyclopropnaes has been studied under the strategy of *N*-heterocyclic carbene catalysis. In this sense, the acyl azolium equivalent generated upon NHC mediated[38] ring-opening has been employed as a two carbon synthon in formal [2+3] and [2+4] cycloadditions. Thus, Wang[39] reported the formal [2+3] cycloaddition of formylcyclopropane 1,1-diesters and *1H*-indole-2-carbaldehyde in the presence of a benzimidazolium catalyst (Scheme 3. 11). Upon condensation of the catalyst and the formylcyclopropane, a D-A cyclopropane is formed, activated with a donor group (the enaminol moiety) and two electron-withdrawing esters. The strained three-membered ring undergoes spontaneous ring-opening and azolium enolate type intermediate is generated. Authors postulated that a redox amination that releases the catalyst is followed by Knoevenagel type reaction between the enolate of the new amide and the aldehyde. This methodology gives straightforward access to pyrroloindole skeleton, yet with limited scope and only in moderate yields.

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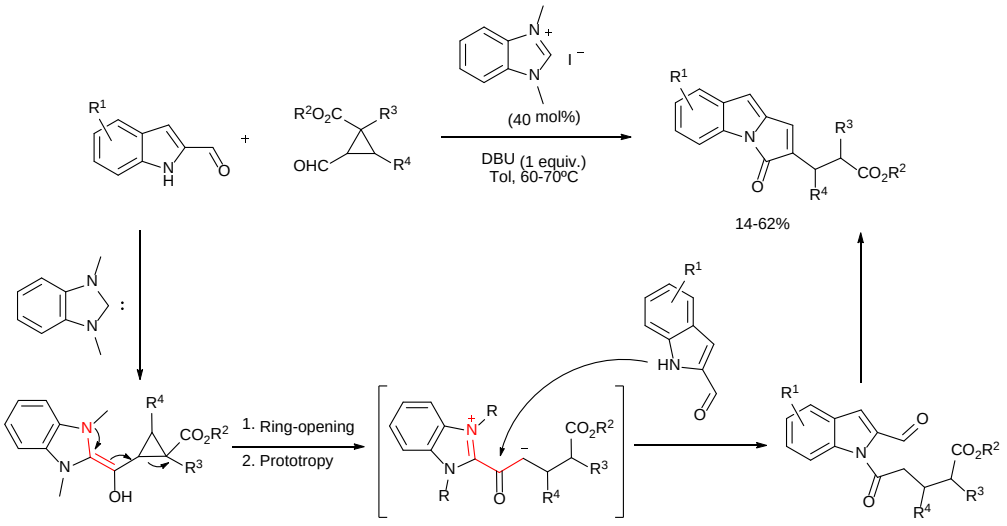
[38] a) Sohn, S. S.; Bode, J. W. *Angew. Chem. Int. Ed.* **2006**, *45*, 6021; b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798; c) Vesely, J.; Zhao, G.-L.; Bartoszewicz, A.; Cordova, A. *Tetrahedron Lett.* **2008**, *49*, 4209.

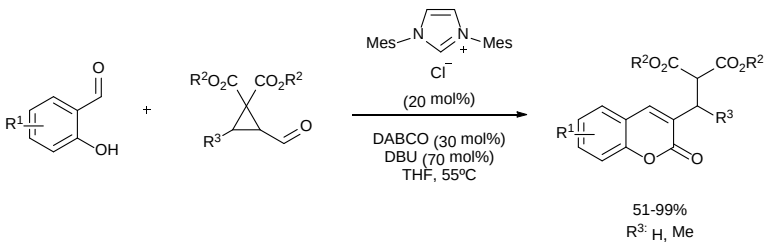
[39] Li, L.; Du, D.; Ren, J.; Wang, Z. *J. Org. Chem.* **2011**, 614.




**Scheme 3. 11**

## 1.6. [2+4] Cycloaddition

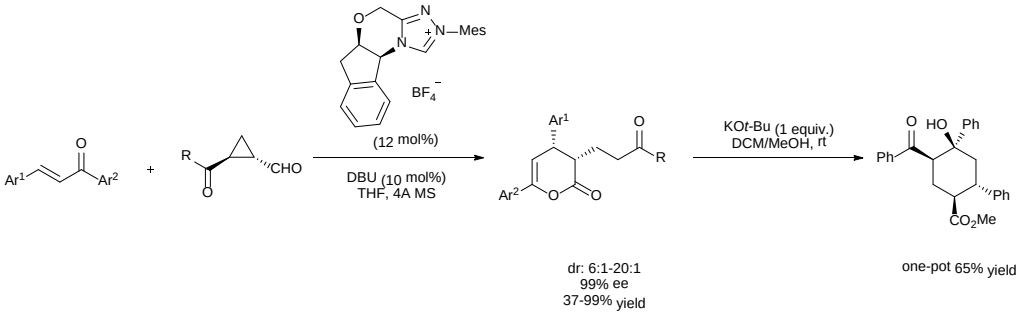
Wang group excelled in the synthesis of heteroaromatic scaffolds from FCP,[40,41] thus previously a domino sequence for the synthesis of coumarins was reported based on a similar mechanistic pathway. In this example the hydroxyl group of salicylaldehyde is responsible for the release of the catalyst and the formal [2+4] cycloaddition is achieved through a redox lactonization process that includes a Knoevenagel type reaction for the final cyclization (Scheme 3. 12).[40]




**Scheme 3. 12**

[40] Du, D.; Wang, Z. *Eur. J. Org. Chem.* **2008**, 4949.
[41] Du, D.; Li, L.; Wang, Z. *J. Org. Chem.* **2009**, *74*, 4379.

Inspired by previous work on azolium enolate chemistry to develop Diels-Alder type cycloadditions,[42] Chi *et al*[43] published the first enantioselective formal [2+4] cycloaddition employing cyclopropanes. The stereochemistry of this inverse electron-demand Hetero-Diels-Alder reaction of chalcones and formylcyclopropanes is defined by the aminoindanol derived chiral catalyst that remains attached to the substrate blocking one of the faces of the enol in the formation of the new two bonds. It is worth noting, the convenient use of FCP as precursors enabled the use of less reactive α'-β-substitued chalcones as oxodienes, in contrast to the use of enals that may lead to dimerization side reactions.[42a] Nevertheless, multisubstitued formylcyclopropanes were not well tolerated and no example of alkyl substituted unsaturated ketones was reported. In addition, a base promoted transesterification/aldol reaction was performed leading to the formation of formal [3+3] cycloaddition product (Scheme 3. 13).



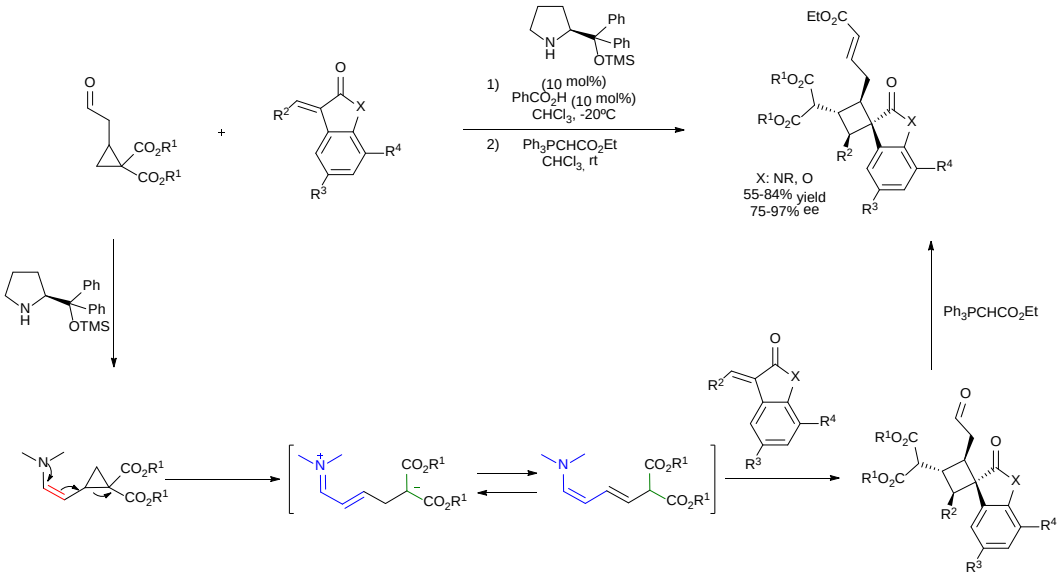

**Scheme 3. 13**

[42] a) He, M.; Struble, J. R.; Bode, J.W. *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088; c) Fang, X.; Chen, X.; Chi, R. Y. *Org. Lett.* **2011**, *13*, 4708; d) Yang, L.; Wang, F.; Chua, P. J.; Lv, Y.; Zhong, L.-J.; Zhong, G. *Org. Lett.* **2012**, *14*, 2894.

[43] Lv, H.; Mo, J.; Fang, X.; Chi, Y. R. *Org. Lett.* **2011**, *13*, 5366.

### 1.7. [2+2] Cycloaddition

Very recently, Jørgensen and co-workers[44] carried out a formal enantioselective [2+2] cycloaddition with a variety of 3-olefinic oxindoles (Scheme 3. 14). The aminocatalyzed ring-opening of cyclopropaneacetaldehydes is based on the formation of a D-A cyclopropane bearing an enamine moiety that activates the cyclopropane in synergy with the acceptor groups. Thus, a new class of cyclopropanes stands as suitable substrate for the development of complex reaction sequences based on opening D-A cyclopropanes. Noteworthy, interesting spirocyclobutaneoxindoles could be obtained in a highly enantioselective process mediated by a chiral pyrrolidine derivative.

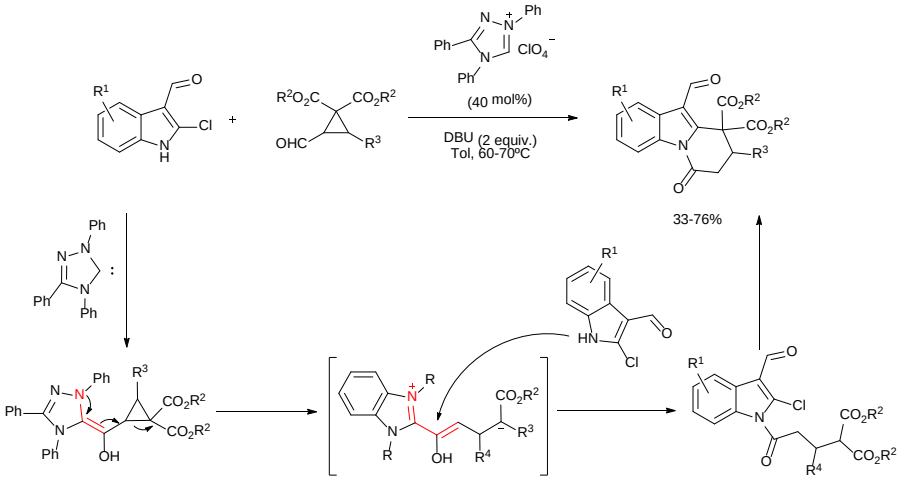



**Scheme 3. 14**

[44] Halskov, K.S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685.

### 1.8. [4+2] Cycloaddition

The use of cyclopropanes as 1,4 dipoles was explored by Wang[41] in a formal [4+2] cycloaddition. In the presense of 2-chloro-1*H*-indole-3-carboaldehyde FCP 1,1-diesters upon addition of the amine moiety to form the linear amide, react through the malonate moiety on the pendant alkylic displacing the halogen atom at the 2 position, to form a six-membered ring that contains the whole cyclopropane structure. Thus, the synthesis of hydropyrido[1,2-*a*]indoles through a domino ring-opening/redox amination/cyclization sequence was achieved in moderate yields (Scheme 3. 15).




**Scheme 3. 15**

The performance of the most common intermediates generated in the ring-opening of D-A cyclopropanes[45] has been reviewed probing their value as versatile precursors in cycloaddition reactions. The variety of strategies to activate cyclopropanes has been highlighted. In this sense, organocatalysis, especially NHC

[45] Upon ring-opening the generated 1,3 dipoles can lead to transposition and elimination reaction and thus render even membered dipoles or alkenes respectively. For 1,2 and 1,4 dipoles, see: a) Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 3187. For alkene precursors: b) Zhu, M.; Liu, J.; Yu, J.; Chen, L.; Zhang, C.; Wang, L. *Org. Lett.* **2014**, *16*, 1856; c) Borisov, D. B.; Novikov, R. A.; Tomilov, Y. V. *Angew. Chem. Int. Ed.* **2016**, *55*, 12233.

catalysis, is emerging as an alternative to the long-studied Lewis acid promoted ring-opening reaction, by leading to interesting active species such azolium enolates or enamine type intermediates. Covalent catalysis, due to its capability to render highly enantioselective processes stands as an appealing strategy considering the rather limited number of examples in this field, mainly limited to [3+2] cycloadditions.

## 2.- SPECIFIC OBJECTIVES AND WORK PLAN

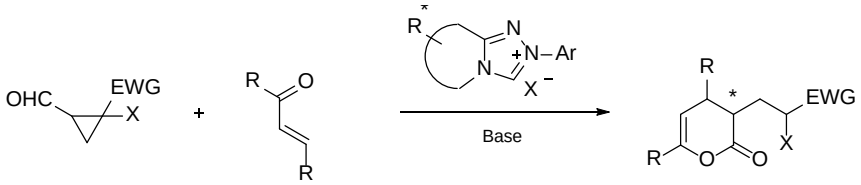
From the presented literature review, it can be appreciated that Lewis Acids have been widely used for initiating a cyclopropane ring-opening event followed by a subsequent reaction. In contrast to the this well established chemistry the use of organocatalysis is underdeveloped. Approaching the activation of cyclopropanes to promote ring-opening processes from different strategies would lead to expand the range of transformations those molecules can take part in. On the other hand, when seeking for enantioenriched products, employing chiral cyclopropanes has been a recurring strategy whilst the development of asymmetric transformations is rather limited to [3+2] cycloadditions. In this sense, a covalent interaction between the catalyst and the substrate may result in a more efficient transfer of the chiral information.

Considering the potencial of organocatalysis, we decided to focus on the generation of D-A cyclopropanes following this approach for the development of new enantioselective complex cycloadditions. With this aim in mind, we set two more specific objectives employing NHC and secondary amine catalysis respectively.

### 2.1. Specific objectives: NHC promoted formation of D-A cyclopropanes

*N*-heterocyclic carbene mediated activation of formylcyclopropanes remains as the most popular approach in the field of the organocatalysis, since it converged with the emergence of new reactive intermediates in this type of catalysis, azolium enolates. Since the early work of Bode[38a] probing that formylcyclopropanes may serve as acyl azolium precursors under NHC catalysis, the performance of those in different reactions including formal cycloadditions have been studied.[39,40,41,43]

Nevertheless, despite the benefits of this methodology (atom economy, stability),[46] NHC promoted cycloadditions is a relatively unexplored field. Thus we decided to focus on the **development of the [2+4] cycloaddition reaction between polysubstitued formylcyclopropanes and oxadienes, under NHC catalysis employing chiral triazolium salts as organocatalysts (**Scheme 3. 16**).**

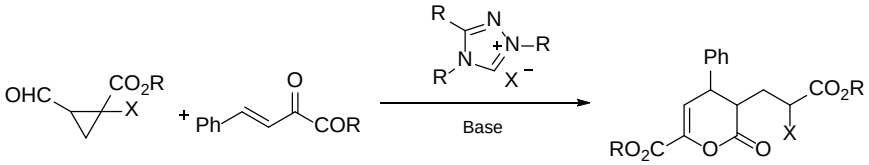



**Scheme 3. 16**

The main aim will be to develop a methodology of wide scope, especially regarding the potential use of polysubstitued cyclopropanes and the substituents at the terminal position of the diene, till now nearly limited to arenes and esters in the reported Diels-Alder cycloadditions. In order to achieve the stated objective, the following work plan was designed:

1. *Proof of concept*: First of all, the viability of the reaction will be studied employing activated formylcyclopropanes. Initially formylcyclopropane mono and di-esters will be evaluated towards the ring-opening event, in order to test their performance in the cycloaddition reaction with different oxadienes, among which β-γ unsaturated α-ketoesters will be firstly studied (Scheme 3. 17).

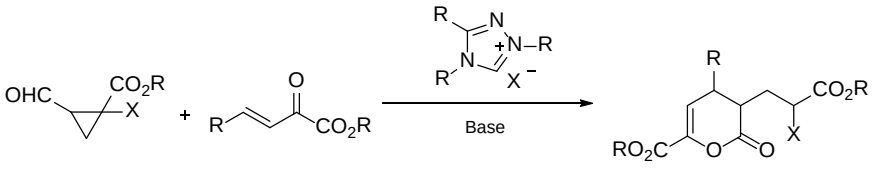
[46] In comparision with other precursors there is no need for a leaving group and formylcyclopropanes are relatively more stable than enals, ketenes or α-chloroaldehydes




**Scheme 3. 17**

2. *Optimization of the reaction*: The reaction between diethyl-2-formylcyclopropane-1,1-dicarboxylate **11a** and methyl (*E*)-2-oxo-4-phenylbut-3-enoate **12a** will be chosen as model reaction for the study of a variety of chiral triazolium salts. Once that the catalyst which provides the best results in terms of yield and enantioselectivity has been identified, other parameters will be studied to obtain the optimal experimental conditions for the selected system.

3. *Scope of the reaction*: With the best conditions in hand, the extension of the methodology will be studied. In this sense, the substitution at the γ-position of the ketoesters will be modified and different cyclopropanes will be tested.

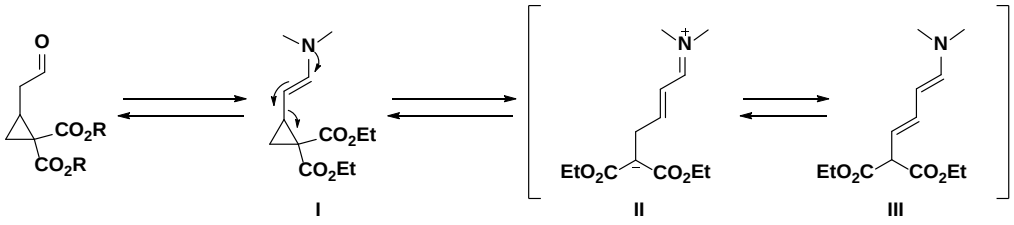



**Scheme 3. 18**

**2.2. Specific objective: aminocatalytic activation of cyclopropylacetaldehydes.**

The lack of examples on aminocatalyzed cyclopropane ring-opening processes is in great contrast with the number of reports proficiently employing this activation mode in cycloaddition reactions. Interestingly, those catalysts may lead to the formation of different intermediates, as iminium ion and enamine, that can be combined in complex reaction sequences, such as Michael initiated cascade reactions.

In this context, we envisioned that a Michael-acceptor intermediate generated upon an aminocatalysis promoted cyclopropane ring-opening would serve as platform for *domino* sequences. With this aim in mind, it was decided to focus on the **development of an aminocatalyzed ring-opening initiated cascade reaction using cyclopropaneacetaldehydes (**Scheme 3. 19**).**



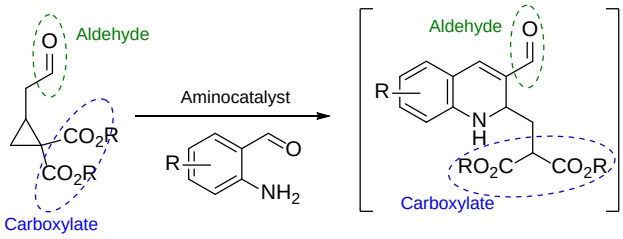

**Scheme 3. 19**

We envisioned the possibility of using aminobenzaldehydes, successfully employed in iminium promoted aza-Michael reactions.[47] In such a complex

[47] a) Sundén, H.; Rios, R.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827. b) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. c) Yoshitomi, Y.; Arai, H.; Makino, K.; Hamada, Y. *Tetrahedron* **2008**, *64*, 11568. d) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, *24*, 4119. e) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem. Eur. J.* **2010**, *16,* 440. f) Bae, J.-Y.; Lee, H.-J.; Youn, S.-H.; Kwon, S.-H.; Cho, C.-W. *Org. Lett.* **2010**, *12*, 4352. g) Fernández, M.; Vicario, J. L.; Reyes, E.; Carrillo, L.; Badía, D. *Chem. Commun.* **2012**, *48*, 2092. h) Zhang, X.; Song, X.; Li, H.; Zhang, S.; Chen, X.; Yu, X.; Wang, W. *Angew. Chem. Int. Ed.* **2012**, *51*, 7282. i) Qian, H.; Zhao, W.; Sung, H. H.-Y.; Williams, I. D.; Sun, J. *Chem. Commun.* **2013**, *49*, 4361. j) Lee, H.-J.; Cho, C.-W. *J. Org. Chem.* **2013**, *78*, 3306. k) Lee, H.-J.; Cho, C.-W. *Eur. J. Org. Chem.* **2014**, 387. l) Joie, C.; Deckers, K.; Enders, D. *Synthesis* **2014**, *46*, 799.

sequence several selectivity problems have to be faced, including the possible competitive pathways through enamine type intermediates (III) as well as stereoselectivity issues. Furthermore, the possible condensation of the catalyst with the aldehyde moiety of the aminobenzaldehyde should be taken into account as well. The selectivity problems inherent to the aza-Michael reaction that arises from the possibility of the aminobenzaldehyde to condense with the cyclopropaneacetalhyde and render a non-enantiocontrolled processes are an additional challenge.

Donor-Acceptor cyclopropanes have been depicted as polyfunctional intermediate precursors, however, some of those functionalities may be considered as innocent elements along the processes the cyclopropane takes part in after the ring-opening event. In this sense, we direct our efforts to make good use of these innocent functionalities in further transformations (Scheme 3. 20). Tuning the reaction conditions to selectively afford a single product, in addition to control functionalization at remote positions are the main challenges regarding this objective.

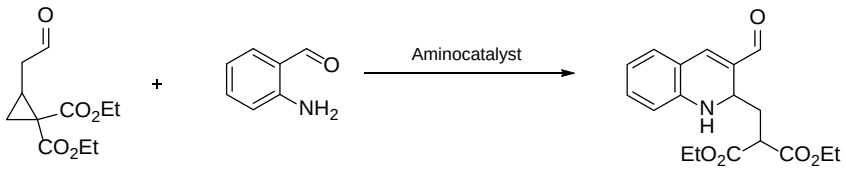



**Scheme 3. 20**

In order to achieve the stated objective, the following work plan was designed:

1. *Proof of concept:* The ability of the cyclopropaneacetaldehyde to undergo ring-opening under aminocatalysis will be studied towards the reaction with 2-aminobenzaldehyde.

2. *Optimization of the reaction*: Once the right reactivity has been observed the performance of different chiral amines in order to identify the best catalyst in terms of yields, regio- and stereoselectivity. Right after, a series of experimental parameters will be optimized for the defined reaction system.




**Scheme 3. 21**

3. *Scope of the reaction*: Once that the optimal conditions have been defined, the extension of the methodology to other cyclopropaneacetaldehydes and aminobenzaldehydes will be studied.

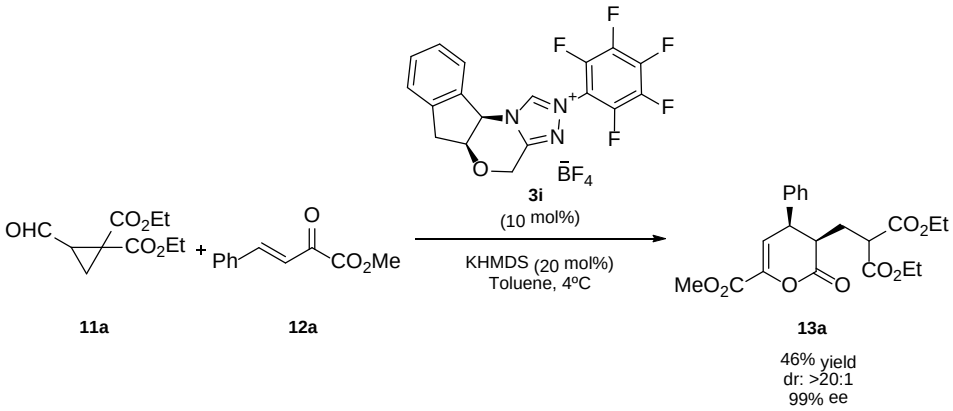
4. *Chemical manipulations*: The reactivity of other functional groups present in the molecule so as to incorporate them into the final product through possible multiple bond forming reaction sequences, such as triple cascade or subsequent reactions will be explored. Additional aldol and lactamization reactions that can render complex tricyclic scaffolds will be evaluated. The extension of the new methodologies to other substrates will also be studied.

# 3.- RESULTS AND DISCUSSION

## *3.1 FORMAL [2+4] CYCLOADDITION OF β-γ-UNSATURATED α-KETOESTERS THROUGH NHC-MEDIATED CYCLOPROPANE RING OPENING.*

### 3.1.1. PROOF OF CONCEPT

In initial trials it was decided to evaluate the performance of formylcyclopropane with one or two ester substituents as potential electron-withdrawing groups towards the projected cycloaddition reaction, with β,γ-unsaturated α-ketoesters in the presence of a series of triazolium based carbene catalysts. To our delight the desired dihydropyranone **13a** was obtained, yet in a very low yield and no other major products could be indetified besides complex mixtures of byproducts attributed to cyclopropane and product decomposition. Apparently, the formed product was unstable under reaction conditions, and further studies, probed that by decreasing the temperature, decomposition of the product could be avoided leading to the obtention of **13a** in moderate yields and as a single diastereomer (Scheme 3. 22). The reaction proceeds *via* a formal [2+4] cycloaddition of the acyl enolate, generated upon ring opening of the cyclopropane **11a**, with unsaturated α-ketoester **12a**. Based on the literature[42,43] reports for this type of inverse electron demand hetero-Diels-Alder cycloaddition the formation (*R,R*)-configured pyranone is postulated.




**Scheme 3. 22**

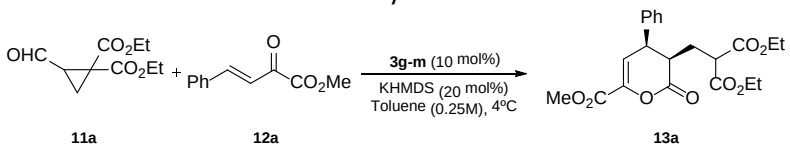
### 3.1.2. OPTIMIZATION OF THE REACTION

As stated in the work plan and once that the viability of the reaction has been proved, a variety of standard experimental parameters were studied employing the diethyl 2-formylcyclopropane-1,1-dicarboxylate and methyl (E)-2-oxo-4-phenylbut-3-enoate as substrates in the model reaction.

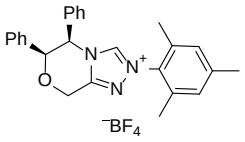
Initially, a variety of chiral triazolium salts were synthetized and tested to find out the catalyst that performs better. Although chiral triazolium based precatalysts bearing a morpholine fused ring (**3g-3h**) performed well in terms of enantiocontrol, the product was obtained in low yield. By extending the number of fused ring to tetracyclic aminoindanol based catalysts (**3i, 3j, 3m, 3n**) the enantiopure dihydropyranone could be obtained in moderate yield. Modifications at the aryl substituent of the triazol ring showed that only when a very electron poor arene was introduced as slight decrease in the yield was observed (**3i** vs **3j, 3n**). On the other hand, no significant change was observed when modifying the counteranion of the

triazolium salt (**3m, 3n**) under these conditions. In view of these results, triazolium salt **3n** was chosen as the best catalyst for further optimization studies.

**Table 3. 1:** Evaluation of a series of catalysts.

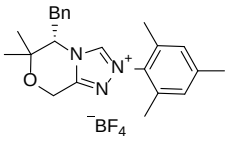



**11a** **12a** **13a**



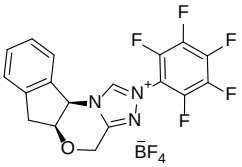

**3g**

Yield: 21%
dr: >20:1
97% ee



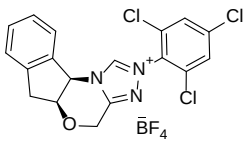

**3h**

Yield: 41%
dr: >20:1
-92% ee



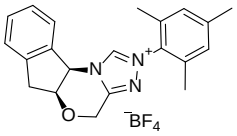

**3i**

Yield: 46%
dr: >20:1
99% ee



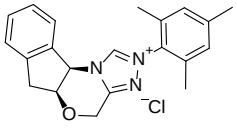

**3j**

Yield: 59%
dr: >20:1
99% ee




**3n**

Yield: 55%
dr: >20:1
99% ee



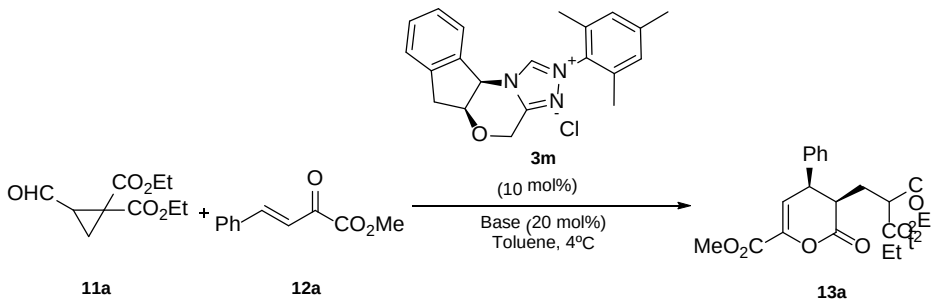

**3m**

Yield: 54%
dr: >20:!
99% ee

Next, the importance of the employed base to generate the carbene in the performance of the reaction was evaluated (Table 3. 2). Representative bases in acyl azolium/azolium enolate chemistry,[39,40,41,42a] such as KHMDS, $K_2CO_3$ or DIPEA, were tested, observing little effect on the reaction. As complete consumption of the aldehyde was observed whilst only moderate conversion of the ketoester was observed that led to moderate yields of the adduct **13a**. Higher amounts of base (up to 1 equiv.) as well as stronger bases (LDA) were tested in an attempt to ensure the presence of the azolium enolate species in the media by preventing its protonation that would quench the reactivity towards the diene, not observing in any case better

yields. In view of these results, an easy to handle salt as potassium carbonate was chosen as base for convenience.

**Table 3. 2:** Influence of the base

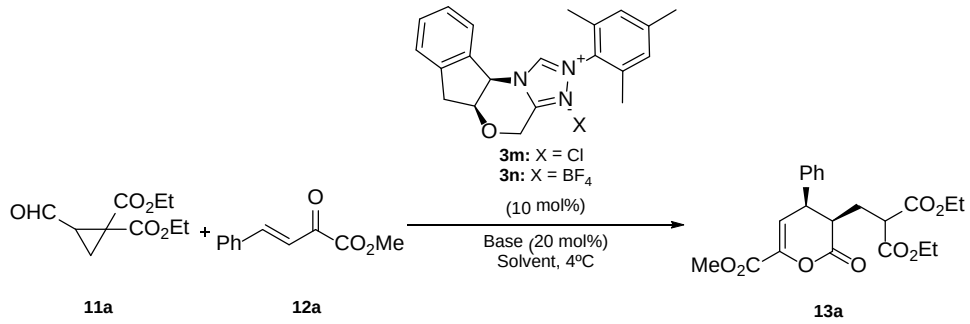



| Entry | Base | dr[a] | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | KHMDS | >20:1 | 55 | 99 |
| 2 | $K_2CO_3$ | >20:1 | 54 | 99 |
| 3 | DIPEA | >20:1 | 52 | 99 |

[a] Determined by $^1$H-NMR analysis of the crude reaction mixture. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product.

At this stage solvents of different nature were tested without this parameter affecting significantly the enantioselectivity (Table 3. 3, Entries 1-4). When carrying out the reaction in dichloromethane a slight improve in the yield was observed (Entry 2), whilst the use of more polar solvents resulted in lower yields (Entries 3-4). Thus, dichloromethane was employed in further screening of reaction parameters, with selected results summarized in Table 3. 3. Due to changes in the performance of the base depending on the reaction solvent, a reevaluation of this parameter was carried out (Entries 5-6). In addition, the effect of the counterion of the catalyst and the base seemed to be not orthogonal parameters, due to electrostatic interactions, that can be more significant in the case of inorganic bases. The combination of using DIPEA and a less coordinating counteranion, in addition to increasing the formylcyclopropane/ketoester ratio resulted in the obtention of the [2+4] cycoaddition adduct in good yield and excellent enantiocontrol (Entries 6-7).

**Table 3. 3:** Selected optimization studies




| Entry | Catalyst | Solvent | Base | dr [a] | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **3m** | Toluene | $K_2CO_3$ | >20:1 | 54 | 99 |
| 2 | **3m** | $CH_2Cl_2$ | $K_2CO_3$ | >20:1 | 58 | 97 |
| 3 | **3m** | $CHCl_3$ | $K_2CO_3$ | >20:1 | 30 | 99 |
| 4 | **3m** | THF | $K_2CO_3$ | >20:1 | 26 | 99 |
| 5 | **3n** | $CH_2Cl_2$ | $K_2CO_3$ | >20:1 | 62 | 97 |
| 6 | **3n** | $CH_2Cl_2$ | DIPEA | >20:1 | 65 | 97 |
| 7[d] | **3n** | $CH_2Cl_2$ | DIPEA | >20:1 | 73 | 97 |

[a] Determined by $^1$H-NMR analysis of the crude reaction mixture. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product. [d] 1.5 equivalents of formylcyclopropane were employed.

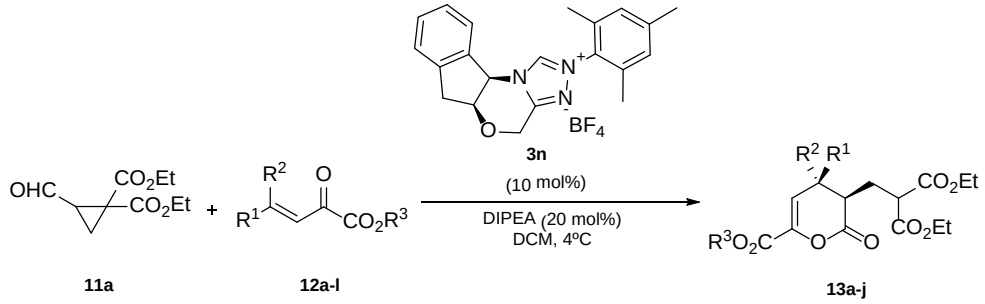
The study of all those parameters led us to establish a robust protocol for the formal [2+4] cycloaddition of formylcyclopropanes and β,γ-unsaturated α-ketoesters. Following the stated work plan, the extension of the methodology will be studied for the obtention of a variety of chiral dihydropyranones.

### 3.1.3. SCOPE OF THE REACTION

Once the optimal conditions were defined, a variety of β,γ-unsaturated α-ketoesters were tested to evaluate the scope and limitations of the reaction (Table 3. 4). First, the influence of the ester substituent of the electrophile was studied using both ethyl and methyl esters **12a** and **12b** (Entries 1-2), and it was observed that the reaction performed excellently in both cases. Regarding the substituents, a variety of ketoesters with γ-aryl groups were tested, observing that electron-donor

substituents at the *para*-position of the arene led to final product in good yields and with excellent enantioselectivity (Entries 3,4). Moreover, it was observed that the reaction could be carried out using a lower catalyst loading (Entry 5, 5 mol%) only requiring for slightly longer reaction time. Different substitutions patterns at the aryl substituent were well tolerated (Entries 6-8). However, introducing a bulky 2-ortho substitued aryl group (Entry 7) in the reactive γ-position resulted in significantly less reactive ketoester, which was not completely consumed even in the presence of an excess of formylcyclopropane. It should be highlighted as well, that high yields and enantiocontrol could be achieved even when a strong donor substituent was introduced (Entry 8). The reaction proceeded satisfactorily when *p*-fluorophenyl was introduced in the alkene as an example of electron-poor substituted unsaturated α-ketoesters (Entry 9).

**Table 3. 4:** Scope of γ-aryl substitued β,γ-unsaturated α-ketoesters




| Entry | $R^1$ | $R^3$ | $R^3$ | Product | dr[a] | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | H | Me | **13a** | >20:1 | 73 | 97 |
| 2 | Ph | H | Et | **13b** | >20:1 | 77 | >99 |
| 3 | *p*-$MeOC_6H_4$ | H | Me | **13c** | >20:1 | 81 | >99 |
| 4 | *p*-$MeC_6H_4$ | H | Me | **13d** | >20:1 | 85 | 99 |
| 5[d] | *p*-$MeC_6H_4$ | H | Me | **13d** | >20:1 | 82 | 99 |
| 6 | *m*-$MeC_6H_4$ | H | Me | **13e** | >20:1 | 82 | 99 |
| 7 | *o*-$MeC_6H_4$ | H | Me | **13f** | >20:1 | 66 | >99 |
| 8 | 3,4-$OCH_2OC_6H_3$ | H | Me | **13g** | >20:1 | 78 | >99 |
| 9 | *p*-$FC_6H_4$ | H | Me | **13h** | >20:1 | 72 | >99 |
| 10 | 2-furyl | H | Me | **13i** | 2:1 | 46 | >99 |
| 11 | 2-thienyl | H | Me | **13j** | 2:1 | 68 | >99 |
| 12 | Ph | Me | Me | | | n.r.[e] | |

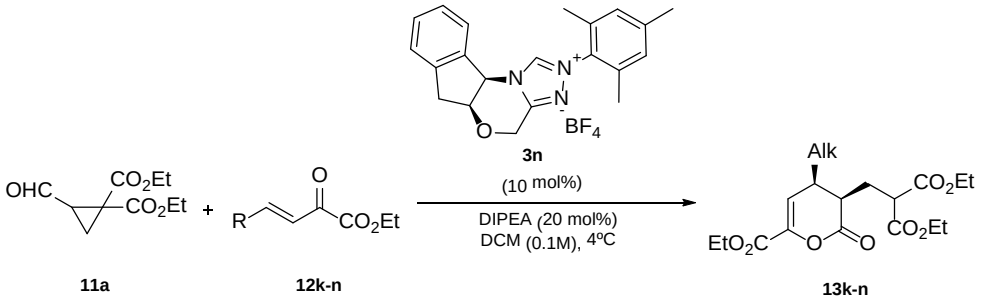
| | | | | |
|---|---|---|---|---|
| 13 | Me | Ph | Me | n.r.[e] |

[a] Determined by $^1$H-NMR analysis of the crude reaction mixture. [b] Yield of pure product isolated after flash chromatography. [c] Determined by HPLC analysis of the pure product. [d] The reaction was carried out in the presence of 5 mol% of **3n**. [e] No reaction.

Substrates with heteroaryl substituents led to the formation of the corresponding adducts in good yield and high enantiocontrol, yet as 2:1 mixture of diastereomers (Entries 10-11). Further experiments showed that the corresponding adducts were unstable leading to epimerization and dehydrogenation reaction with the concomitant loss of the chiral information. As a limitation of the system, it was observed that γ,γ-aryl, alkyl substituted ketoesters which would render a quaternary estereocenter did not react under the described conditions (Entries 12-13).

Next, the use of those more challenging γ-alkyl-substitued β,γ-unsaturated-α-ketoesters was also surveyed, as it is shown in Table 3. 5. The reaction performed efficiently in both terms of yield and diastereo- and enantioselectivity, for substrates bearing either linear or branched alkyl substituents (Entries 1-2) as well as when functionalized alkyl chains were introduced (Entries 3-4). By correlation of the NMR data it can be concluded that the same diastereoisomer is obtained when using either γ-alkyl or γ-aryl ketoesters.

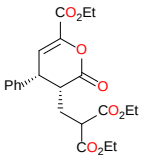
**Table 3. 5:** Scope of γ-alkyl substituted β,γ-unsaturated α-ketoesters



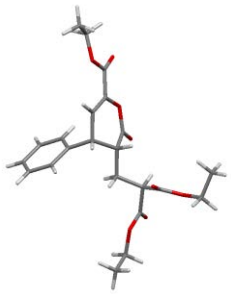

| Entry | R | Product | dr[a] | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | Me | **13k** | >20:1 | 83 | >99 |
| 2 | *i*Pr | **13l** | >20:1 | 85 | >99 |
| 3 | $CH_2OBn$ | **13m** | >20:1 | 58 | >99 |
| 4 | $CH_2CH_2Ph$ | **13n** | >20:1 | 72 | 97 |

[a]Determined by $^1$H-NMR analysis of the crude reaction mixture. [b]Yield of pure product isolated after flash chromatography. [c]Determined by HPLC analysis of the pure product.

One of the products, 3,4-dihydro-2*H*-pyran-2-one **13b** could be crystallized, thus the absolute configuration of all the stereogenic centers could be determined by X-ray analysis (Scheme 3. 23). The absolute stereostructure could be extended to all other dihydro-2*H*-pyran-2-one (**13a-o**) assuming the same reaction mechanism.



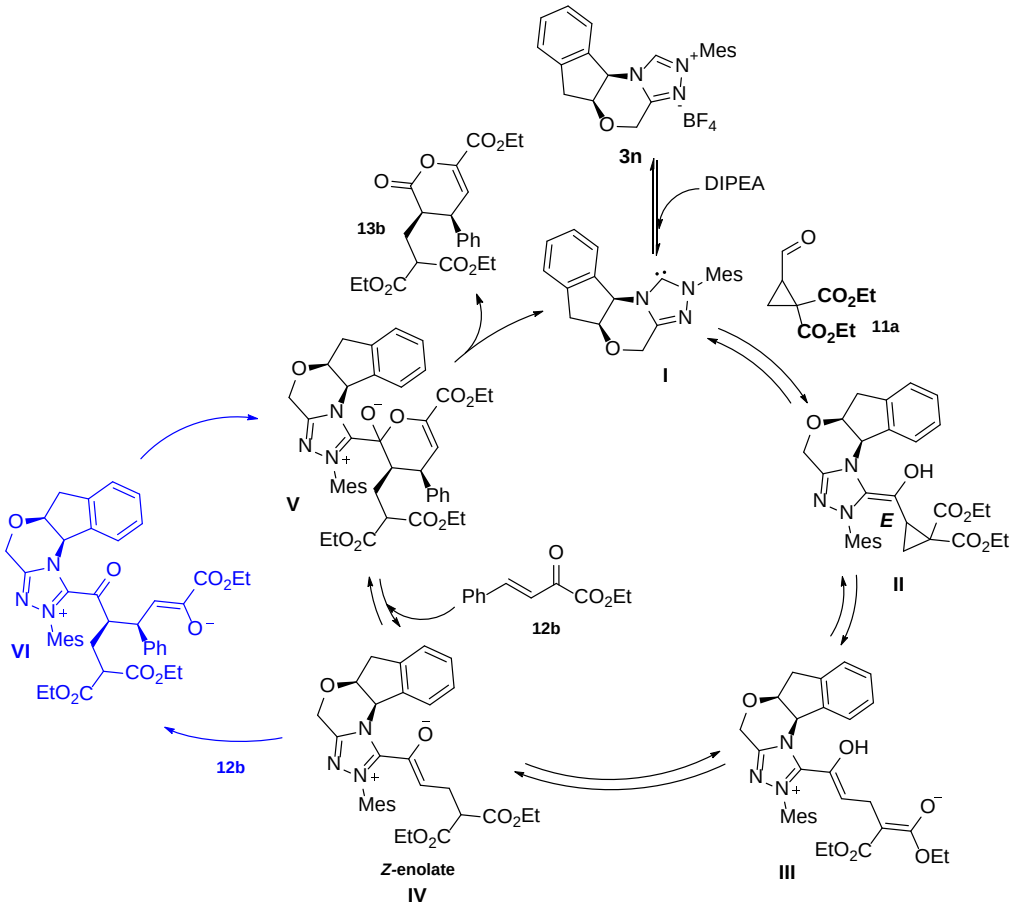

**(*R*,*R*)-13b**



**Scheme 3. 23**

### 3.1.4. MECHANISTIC PROPOSAL

Considering that the obtained stereochemical outcome was in agreement with the examples of hetero Diels-Alder in the literature, the possible reaction pathways are depicted in Scheme 3. 24.

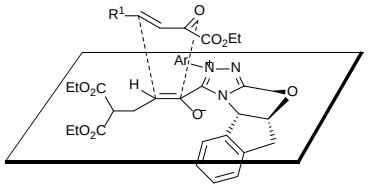



**Scheme 3. 24**

First, the catalytic species (**I**) is generated after a Hünig's base mediated deprotonation of the chiral triazolium salt (**3n**). The reversible condensation of the aldehyde (**11a**) with the carbene (**I**) would lead to the formation of enaminol (**II**), known as *Breslow intermediate*. This intermediate might lead to a ring-opening process to generate the achiral acyl azolium equivalent (**III**), which through the

subsequent proton transfer step would form the enolate (**IV**). At this point two alternative reaction pathways (a) and (b) serve as explanation for the formal [2+4] cycloaddition product. On the one hand, a reverse-electron demand Diels-Alder reaction with ketoester (**12b**) would take place to render pyran (**V**) from intermediate **IV**. Alternatively, a less likely[42] sequential Michael addition/C-O bond formation pathway through intermediate (**VI**) is shown. In a common final step, the dihydropyranone (**13b**) is formed and the catalyst is released.

The stereochemistry of the reaction may be explained considering the high preference for the *endo* transition state in a Diels-Alder reaction. The *s-cis* isomer (**IV**) were the alkyl chain of the aldehyde is set away from the aminoindanol moiety is favoured. Considering that the *Z*-configurated enolate would react, the *Re* face of the azolium enolate would be shielded by the catalyst. Thus, the formation of the C-C bond would take place through the *Si* face of the β,γ-unsaturated-α-ketoesters in an *endo* fashion (Scheme 3. 25).

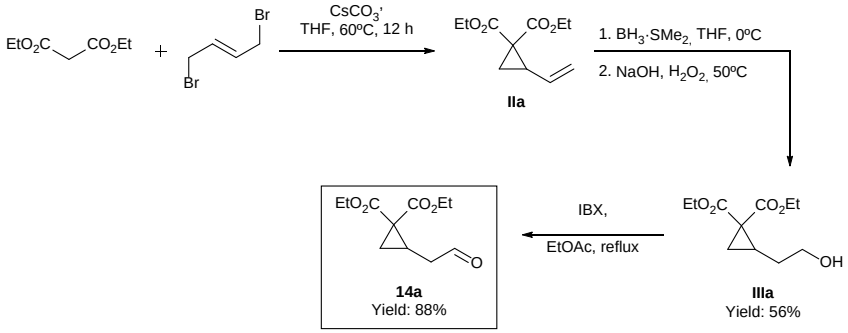


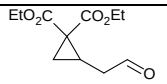
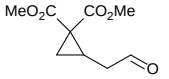

**Scheme 3. 25**

## 3.2. AMINOCATALYTIC ACTIVATION OF CYCLOPROPANES TOWARDS DOMINO SYNTHESIS OF QUINOLINE DERIVATIVES

Prior to conduct the preliminary studies directed towards the possibility of using cyclopropaneacetaldehydes as starting material undergoing ring opening under enamine activation, the starting material had to be prepared. This was carried out through a 3 step synthetic route. In a first step vinylcyclopropanes (**IIa-d**) were obtained following literature procedures in a $S_N2$ and $S_N2'$ sequence. Next, an hydroboration/oxidation of those alkenes employing borane dimethylsulfide complex lead us to obtain the corresponding primary alcohols (I**IIa-d**) in moderate yields while the cyclopropane ring remained inaltered.[48] Finally, 2-iodoxobenzoic acid proved to be a suitable oxidizing agent for the preparation of the final aldehydes (Table 3. 6).[49].

**Table 3. 6:** Synthesis of cyclopropaneacetaldehydes

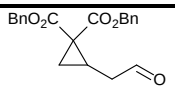
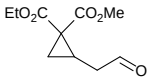



| Entry | $R^1$ | Product | Yield II (%)[a] | Yield 14 (%)[a] |
|---|---|---|---|---|
| 1 |  | **14a** | 56 | 88 |
| 2 |  | **14b** | 33 | 92 |



[48] A modified of the following procedure has been used: Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196.

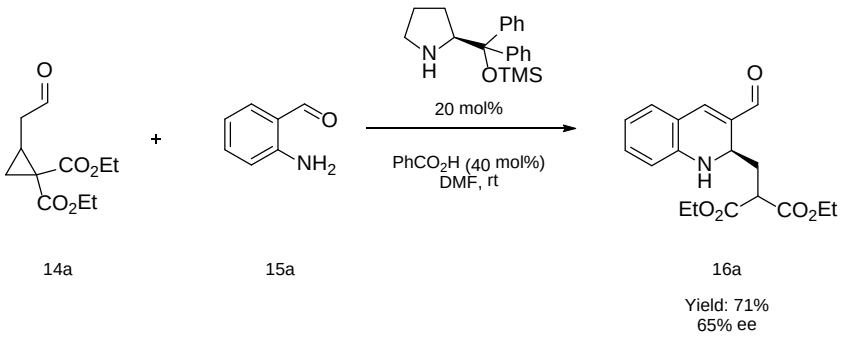
[49] Ocejo, M.; Vicario, J. L.; Carrillo, L.; Badia, D.; Reyes, E. *Synlett.* **2005**, 2110.

| | | | | |
|---|---|---|---|---|
| 2 |  | **14c** | 57 | 80 |
| 3 |  | **14d** | 18 | 70 |

[a] Yield of pure product isolated after flash chromatography.

### 3.2.1. PROOF OF CONCEPT

With key cyclopropylacetaldehyde **14** in hand, we moved next to evaluate the projected cascade ring-opening/aza-michael/aldol between these derivatives and o-amonibenzaldehyde under aminocatalytic activation. Based on literature precedents on other cases of aza-Michael/aldol reactions,[47a] we decided to carry out the reaction in dimethylformamide (DMF) as solvent in the presence of the archetypical *O*-TMS diphenylprolinol catalyst (**17a**) and substoichiometric amounts of benzoic acid under these conditions, the selective formation of dihydroquinoline (**16a**) was observed with promising results (71% yield, 65% ee) (Scheme 3. 26). Noteworthy, no evidence other side products that may arise from 1,2-additon over the cyclopropaneacetaldehyde were observed.

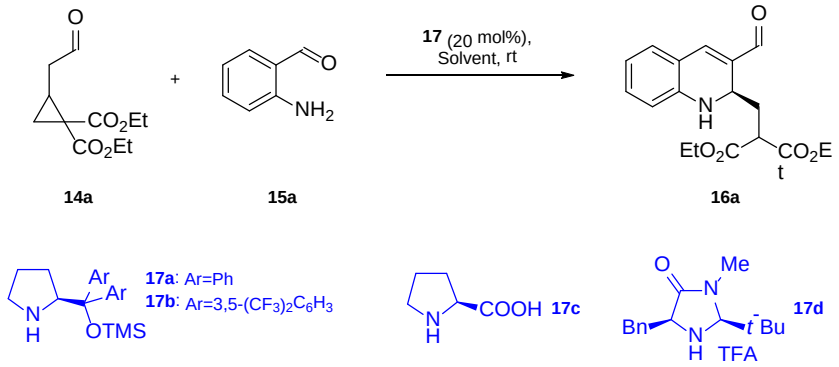



**Scheme 3. 26**

### 3.2.2. OPTIMIZATION OF THE REACTION CONDITIONS

Once that the feasibility of the reaction was demonstrated we proceeded to identify the best catalyst and reaction conditions to carry out this reaction (Table 3. 7).

**Table 3. 7:** Evaluation of a series of catalyst and the influence of the solvent.




| Entry | Catalyst | Solvent | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **17a** | EtOH | 60 | 76 |
| 2 | **17a** | THF | 54 | 89 |
| 3 | **17a** | $CHCl_3$ | 72 | 89 |
| 4 | **17a** | $CH_2Cl_2$ | 66 | 91 |
| 5 | **17a** | $(CH_2)_2Cl_2$ | 57 | 88 |
| 6 | **17a** | Toluene | 40 | 88 |
| 7 | **17b** | $CHCl_3$ | 10 | n.d.[c] |
| 8 | **17c** | $CHCl_3$ | <5 | |
| 9 | **17d** | $CHCl_3$ | <5 | |

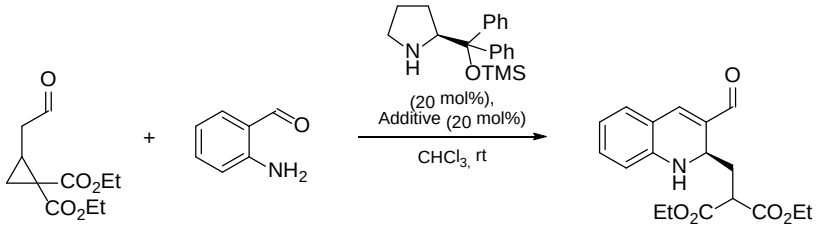
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product. [c] Not determined.

Considering the high polarity of the solvent employed in preliminary experiments the influence of this parameter was studied first. Indeed using catalyst **17a**, the reaction proceeded with high levels of enantiocontrol but when a protic polar solvent as ethanol was employed (Entries 1-6). On the other hand, chlorinated solvents proved to be the best regarding the yield (Entries 3-5). L-proline **17c** as well

as imidazolidinone **17d** performed poorly compared to (*S*)-diphenylprolinol trimethylsilyl ether when using chloroform, whilst the prolinol derivative **17b** only render the product in low yield.

Further screening of standard reaction parameters resulted in an improvement of the yield when acid additives where employed (Entries 1-2). This is in good accordance with the reported capability of mild acids such as carboxylics acids to favour the condensation of the aldehyde with the catalyst, increasing the amount of active species present in the reaction. Moreover, the influence of the acid additive in this kind of transformation has already been considered,[47a] as it can push the equilibrium of the catalyst towards the iminium ion formation and/or favour an irreversible dehydratation step of the reaction sequence. The good performance of benzoic acid prompted us to evaluate other aromatic carboxylic acids. In contrast, the presence of a base inhibits the reaction (Entries 7-9), which was confirmed when a suppression of the reactivity was observed after replacing acetic acid by its conjugated base (Entries 1 and 9).

**Table 3. 8:** Effect of acidic and basic additives




**14a** **15a** **16a**

| Entry | Additive | pKa | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | AcOH | 4.76 | 80 | 82 |
| 2 | $PhCO_2H$ | 4.19 | 88 | 93 |
| 3 | *p*-$NO_2C_6H_4CO_2H$ | 3.41 | 99 | 90 |
| 4 | *o*-$IC_6H_4CO_2H$ | 2.85 | 99 | 89 |

| | | | | |
|---|---|---|---|---|
| 5 | *o*-$BrC_6H_4CO_2H$ | 2.84 | 84 | 88 |
| 6 | *o*-$NO_2C_6H_4CO_2H$ | 2.16 | >99 | 83 |
| 7 | DBU | | <5 | n.d.[c] |
| 8 | DABCO | | 8 | 85 |
| 9 | AcOLi | | 10 | 90 |

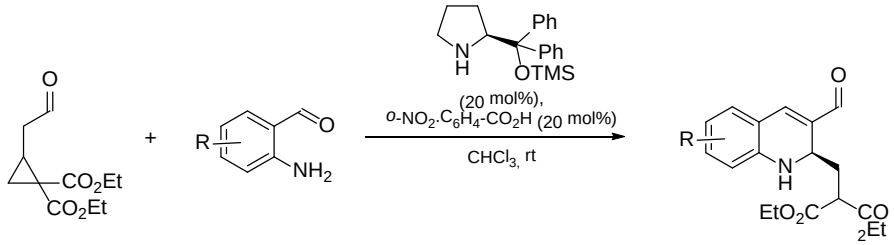
[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product. [c] Not determined.

Thus, employing *p*-nitrobenzoic acid and chloroform as solvent in the presence of **17a** resulted in a high yielding and highly enantioselective protocol for the synthesis of **16a** (Entry 3), which was selected to evaluate the scope of the reaction.

### 3.2.3. SCOPE OF THE REACTION

With the optimal conditions in hand, we first decided to evaluate several aminobenzaldehydes with a variety of substitution patterns (Table 3. 9). Thus, aminobenzaldehydes with either electro-withdrawing or electron-donating substituents at 4- and 5-positions were well tolerated (Entries 1-9). High yields and enantiocontrol were achieved in all the cases yet slightly lower enantiopurities were observed with electron-donating groups (Entries 5, 6 and 9). Importantly, even the more sterically hindered 3- and 6- substituted aminobenzaldehydes rendered the product in good yield (Entries 10-12). Significantly lower enantioselectivity values were observed when a substituent was introduced in a vicinal position to the carbonyl moiety (Entry 12), as well as for the 4,5-dimethoxy aminobenzaldehyde (Entry 13). Benzoquinoline **16o** could be obtained with the same level of efficiency and enantioselectivity when 3-amino-2-naphtaldehyde was employed as starting material (Entry 14).

**Table 3. 9:** Scope of aminobenzaldehydes



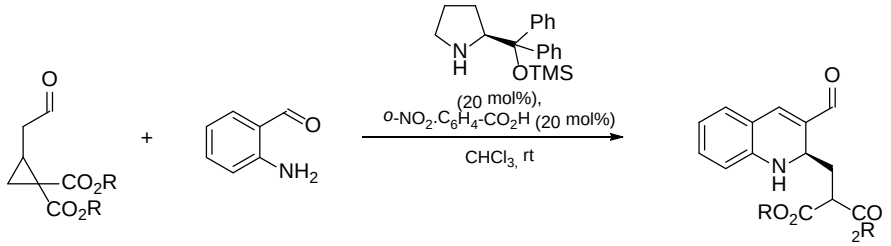

**14a** **15b-o** **16b-o**

| Entry | R | Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | 4-F | **16b** | 86 | 95 |
| 2 | 4-Cl | **16c** | 97 | 96 |
| 3 | 4-Br | **16d** | 87 | 89 |
| 4 | 4-$CF_3$ | **16e** | 90 | 96 |
| 5 | 4-Me | **16f** | 91 | 85 |
| 6 | 4-MeO | **16g** | 81 | 80 |
| 7 | 5-Cl | **16h** | 93 | 95 |
| 8 | 5-Br | **16i** | 89 | 94 |
| 9 | 5-Me | **16j** | 80 | 81 |
| 10 | 3-Me | **16k** | 64 | 97 |
| 11 | 3-MeO | **16l** | 64 | 79 |
| 12 | 6-Cl | **16m** | 53 | 69 |
| 13 | 4,5-$(MeO)_2$ | **16n** | 71 | 64 |
| 14 | Benzo[*d*] | **16o** | 93 | 85 |

[a]Yield of pure product isolated after flash chromatography. [b]Determined by HPLC analysis of the pure product. [c]Not determined.

On the other hand, different electron-withdrawing substituents at the cyclopropane ring were surveyed. As shown in Table 3. 10, the reaction proceeded with good yield and excellent levels of enantioselectivity regardless the nature of the alkoxide moiety of the ester substituents at the ring (Entries 1-3).

**Table 3. 10:** Scope of cyclopropaneacetaldehydes

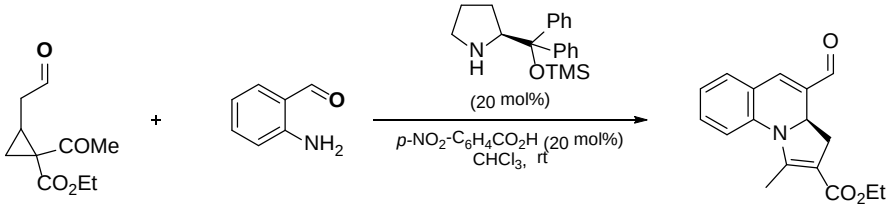



**14a-c** **15a** **16a-q**

| Entry | R | Product | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | Et | **16a** | 99 | 90 |
| 2 | Me | **16p** | 86 | 91 |
| 3 | Bn | **16q** | 69 | 88 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product. [c] Not determined.

It was also decided to survey the possibility of employing asymmetrically substituted cyclopropaneacetaldehydes. In this sense, it was decided to evaluate the performance of aldehyde **1d** bearing an alkoxycarbonyl group and an acyl moiety. The ketone moiety proved to be reactive enough to undergo an hemiaminal formation/dehydratation sequence. Thus, after the formation of the quinoline an intramolecular attack of the nitrogen led to the formation of the enantiopure pyrroloquinoline **18** in moderate yield but excellent ee (Scheme 3. 27).

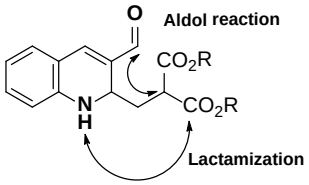



**14d** **15a** **18**
60% yield
>99% ee

**Scheme 3. 27**

### 3.2.4. CHEMICAL MANIPULATION OF THE ADDUCTS

The aza-Michael/aldol cascade adducts **16** present different functionalities within the structure that upon further intramolecular transformations would lead to more complex structures. With the aim of incorporating the whole cyclopropane structure and its functionalities into the final product, we envisioned that an aldol reaction between the pendant malonate and the aldehyde or a lactamization reaction with the ester group would be plausible transformations. However, none of the abovementioned reactions took place under the conditions defined as optimal for the *domino* aza-Michael/aldol reaction even in the presence of the screened acid additives (Table 3. 8) or at higher temperatures. Therefore, to evaluate the viability of these reactions it was decided to carry out an extensive screening of conditions employing dihydroquinoline **16a** as model substrate (Scheme 3. 28).

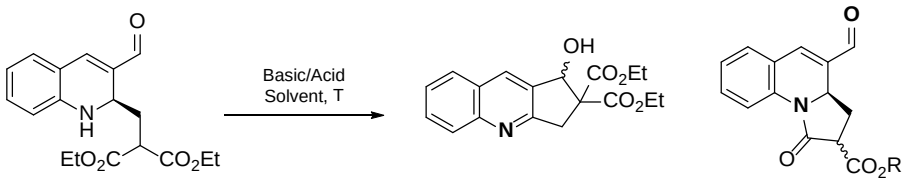



**Scheme 3. 28**

Initial trials employing DBU as a base to promote the cyclization step resulted in the formation of both the aldol **19a** and lactamization **20a** products, yet in low yields (Table 3. 12, Entry 1). The intramolecular reaction between the aldehyde moiety and the pendant alkyl malonate formed cyclopentaquinoline (**19a**), which was isolated as a racemic mixture since an aromatization of the quinoline ring took place concomitant to the aldol cyclization leading to a loss of the chiral information. Thus, in order to selectively access the aldol product different additives were evaluated. When carrying out the reaction in the presence of Brønsted acid the aldol product could be obtained in moderate yield, however, significant amounts of the

lactam **20a** were observed (Entry 2). Moving from acetic acid to Lewis acids resulted in a completely chemoselective transformation towards the cyclocyclopentaquinoline formation (Entries 3-5), which proceed with excellent yield when cerium (III) chloride was employed (Entry 4).

**Table 3. 11:** Selected optimization studies

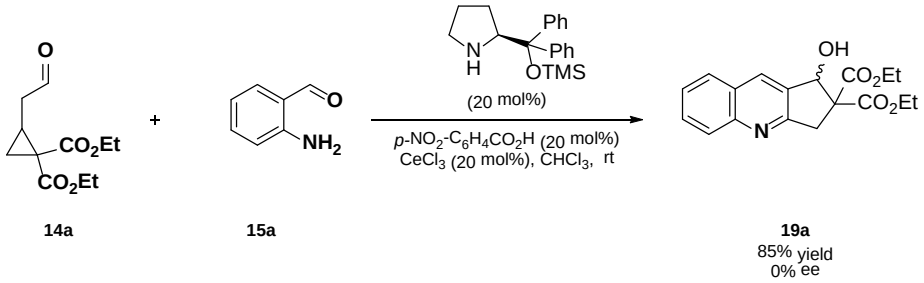



**16a** **19a** **20a**

| Entry | Reagent (equiv.) | Yield (%)[a] | |
|---|---|---|---|
| | | **19a** | **20a** |
| 1 | DBU (0.2) | 12 | 26 |
| 2 | AcOH (2) | 54 | 34 |
| 3 | $MgI_2$ (1) | 43 | - |
| 4 | $CeCl_3$ (1) | 94 | - |
| 5 | $FeCl_3$ (1) | 24 | - |

[a]Yield of pure product isolated after flash chromatography.

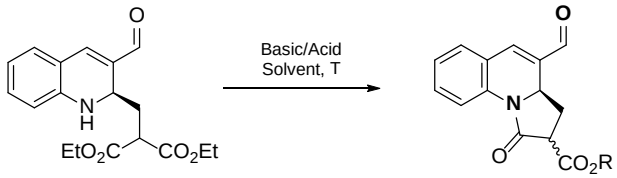
Noteworthy, the complete ring-opening/aza-Michael/aldol/aldol sequence could be performed in a single step from the starting cyclopropane acetalhyde and aminobenzaldehyde, however, also in that case the aromatization step was taking place prior to the aldol cyclization step leading to **19a** as racemic material (Scheme 3. 29). Further experiments proved that when the oxidation step could not take place, for instance in the absence of atmospheric oxygen or for *N*-substituted quinolines, only starting material was isolated.




**Scheme 3. 29**

On the other hand, selected results of the extensive screening of the standard reaction parameters performed for the attempts directed to carry out the selective lactamization are summarized in Table 3. 13. As it is shown in this table, the formation of pyrroloquinoline **19a** could be promoted by using a variety of organic and inorganic bases (Entries 1-6) yet only in low to moderate yields. Similar results were obtained when camphorsulfonic acid (CSA) was employed, although in this case degasification of the solvent was required to avoid the formation of aromatic side product **19a** (Entry 7). Considering that the reaction proceeded with better yields at higher temperatures and that the replacement of the solvent could be problematic when trying to combine the lactamization step with the *cascade* reaction in a *one-pot* sequence, a neat process was considered. Thus, the reaction proceeded with good yield in refluxing acetic acid (Entry 8).

**Table 3. 12:** Selected optimization studies



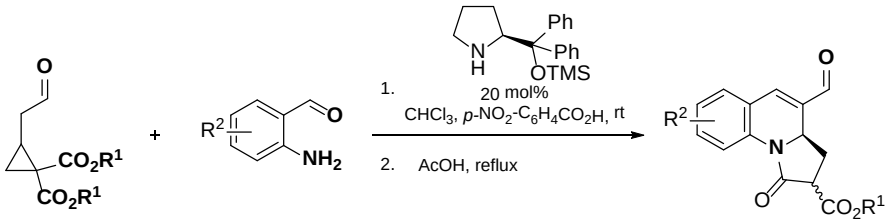

| Entry | Reagent (equiv.) | Solvent | T(ºC) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | DBU (2) | Toluene | reflux | 46 |

| | | | | |
|---|---|---|---|---|
| 2 | TBD (1) | $CHCl_3$ | r.t. | 37 |
| 3 | NaOH (1) | $CHCl_3$ | r.t. | 47 |
| 4 | KO*t*Bu (1) | $CHCl_3$ | r.t. | 33 |
| 5 | NaH (1) | $CHCl_3$ | r.t. | 50 |
| 6 | LiHMDS (1.1) | THF | 60 | 67 |
| 7 | CSA (1) | Toluene[b] | reflux | 62 |
| 8 | AcOH (175) | . | reflux | 80 |

[a]Yield of pure product isolated after flash chromatography. [b]Degased toluene.

In view of this results, a protocol for the sequential synthesis of pyrrolo[*1,2-a*]quinolines from cyclopropaneacetaldehydes was evaluated. Thus, the lactamization conditions could be applied to the efficient and highly enantioselective *one-pot* synthesis of **19a** from **14a** and **15a** (Table 3. 14, Entry 1). Importantly this protocol enables the straightforward enantioselective synthesis of complex quinoline based structures. Moreover, this protocol could be extended to a variety of aminobenzaldehydes and different cyclopropanes (Table 3. 13)

**Table 3. 13:** *One-pot* synthesis of pyrroloquinolines




**14a-c** **15a-o** **20a-o**

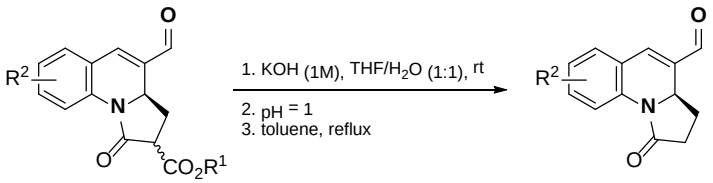
| Entry | $R^1$ | $R^2$ | 20 | Yield (%)[a] | ee (%)[b,c] |
|---|---|---|---|---|---|
| 1 | Et | H | **20a** | 81 | 91/87 |
| 2 | Me | H | **20b** | 81 | 91/89 |
| 3 | Bn | H | **20c** | 60 | 90/89 |
| 4 | Et | 4-F | **20d** | 77 | 95/95 |
| 5 | Et | 4-Cl | **20e** | 83 | 97/97 |
| 6 | Et | 4-Br | **20f** | 86 | 96/96 |
| 7 | Et | 4-$CF_3$ | **20g** | 74 | 94/96 |
| 8 | Et | 4-Me | **20h** | 69 | 85/87 |
| 9 | Et | 4-MeO | **20i** | 48 | 75/78 |
| 10 | Et | 5-Cl | **20j** | 75 | 94/91 |
| 11 | Et | 5-Br | **20k** | 79 | 96/94 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | Et | 5-Me | **20l** | 81 | 84/87 |
| 13 | Et | 6-Cl | **20m** | 53 | 69/70 |
| 14 | Et | 4,5-$(MeO)_2$ | **20n** | 38 | 63/63 |
| 15 | Et | Benzo[*d*] | **20o** | 69 | 84/85 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product. [c] The ee of each diastereoisomer is given.

Compared to the aza-Michael/aldol reaction that led to adducts **16,** the one-pot cyclopropane ring-opening aza-Michae/aldol lactamization process reaction performed equally well. This comparable behavior of the reaction prompted us to consider that the *in situ* acid-promoted lactamization proceeds almost quantitatively. In this sense, aminobenzaldehydes with either electro-withdrawing or electron-donating substituents at 4- and 5-positions were well tolerated leading to moderate to good yields (Entries 4-12). Even more sterically hindered 6-substitued aminobenzaldehyde and electron rich 4,5-dimethoxy aminobenzaldehyde render the product in moderate yield (Entries 13-14). Nevertheless, 8-substitued quinolines (**16m**, **16n**) did not afford the lactamization product due to the proximity of the substituents to the reactive amine. More importantly, despite the acidic thermal conditions employed in the transformation, the stereochemical integrity was no compromised. The configurational lability of the new stereocentre generated resulted in mixture of diastereoisomers. In this regard, a one-pot hydrolysis/decarboxylation process was developed so as to obtain pyrroloquinolines **21** that ease the characterization of the final products (Table 3. 15).

**Table 3. 14:** One-pot hydrolisis/decarboxylation of adduct **17**.

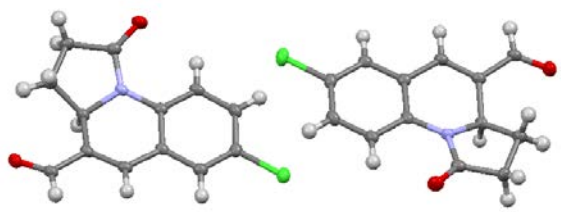


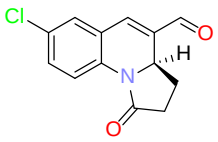

**20a-o** **21a-m**

| Entry | $R^1$ | $R^2$ | 21 | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|
| 1 | Et | H | **21a** | 87 | 89 |
| 2 | Me | H | **21a** | 63 | 87 |
| 3 | Bn | H | **21a** | 45 | 90 |
| 4 | Et | 8-F | **21b** | 53 | 93 |
| 5 | Et | 8-Cl | **21c** | 72 | 94 |
| 6 | Et | 8-Br | **21d** | 69 | 95 |
| 7 | Et | 8-$CF_3$ | **21e** | 35 | 97 |
| 8 | Et | 8-Me | **21f** | 74 | 84 |
| 9 | Et | 8-MeO | **21g** | 75 | 73 |
| 10 | Et | 7-Cl | **21h** | 66 | 94 |
| 11 | Et | 7-Br | **21i** | 56 | 94 |
| 12 | Et | 7-Me | **21j** | 64 | 83 |
| 13 | Et | 6-Cl | **21k** | 44 | 68 |
| 14 | Et | 7,8-$(MeO)_2$ | **21l** | 53 | 65 |
| 15 | Et | Benzo[*g*] | **21m** | 63 | 87 |

[a] Yield of pure product isolated after flash chromatography. [b] Determined by HPLC analysis of the pure product.

The decarboxylated adducts were obtained in moderate yields and no evidence of racemization was observed. At this stage, the absolute configuration of the product **21h** could be determined by X-ray analysis (Scheme 3. 30). Based on mechanistic analogy, this absolute configuration could be extended to all other dihydroquinoline (**16a-q**) and pyrroloquinoline adducts (**20a-o**, **21a-m**).



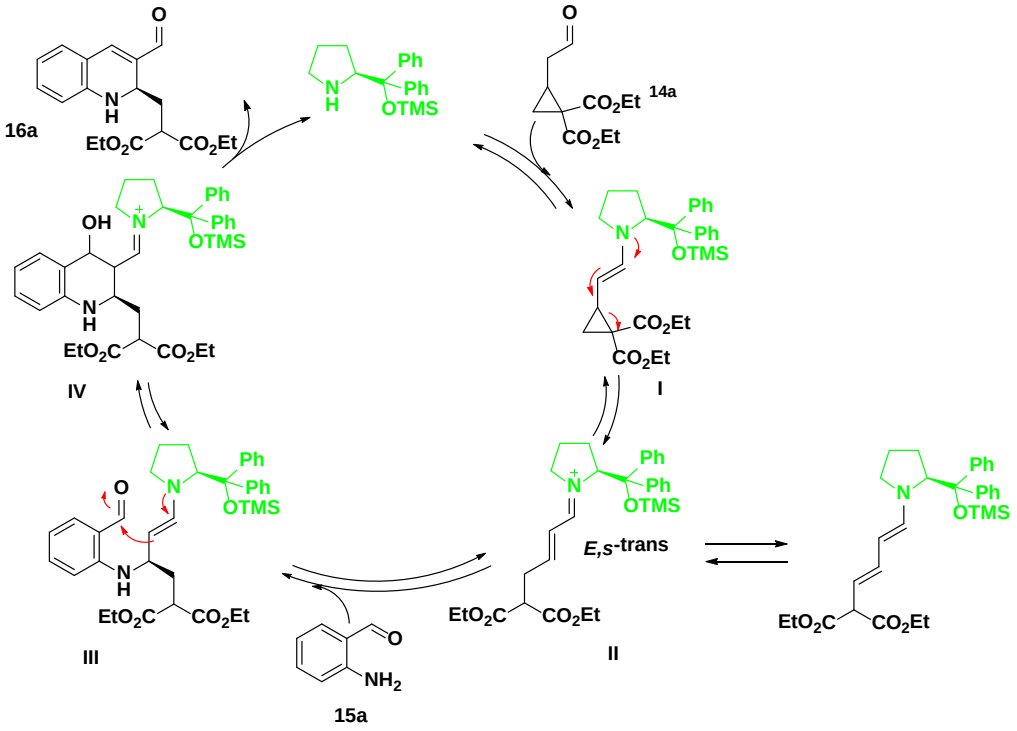



(*R*)-21h

**Scheme 3. 30**

### 3.2.5. MECHANISTIC PROPOSAL

Considering that the obtained stereochemical outcome was in agreement with the examples in the literature,[47a] the proposal for the reaction mechanism is presented in Scheme 3. 31.




**Scheme 3. 31**

First, the chiral amine (**17a**) would condense with the cyclopropaneacetaldehyde (**14a**) to generate the activated corresponding Donor-Acceptor cyclopropane (**I**). The *cascade* sequence starts with an enamine promoted ring-opening step that leads to the formation of iminium ion (**II**). Then an aza-Michael type addition from the less hindered face of the iminium species renders the enamine intermediate (**III**), which upon subsequent aldol cyclization forms the tetrahydroquinoline scaffold. Finally the catalyst is released and the dehydration of **IV** yields the final dihydroquinoline **16a**. It should be mention, that the role of the acid additive is not clear, as it can take part in different steps. While it is known that the condensation of the catalyst with the aldehyde moiety is favoured in an acidic media, the additive can also increase the rate of iminium species by pushing the

equilibrium of the catalyst. In addition, the Brønsted acid may favour the final dehydration step avoiding possible retro-aldo/retro-aza-Michael reactions.

The stereochemistry of the reaction may be explained considering that the more stable *E*,*s*-trans iminium species is participating in the hypothetical catalytic cycle. Thus, the aminobenzaldehyde approaches the *Si* face of the iminium ion to form the new C-N bond that defines the stereochemistry of the final quinoline, whilst the *Re* face remains blocked by effect of the catalyst.

## 4.- CONCLUSIONS

From the results obtained during the research presented in this chapter the following conclusions can be drawn:

A new enantioselective formal [4+2] cycloaddition between multisubstitued formylcyclopropane 1,1-diesters and a variety of (hetero)aryl and alkyl γ-substitued β,γ-unsaturated-α-ketoesters has been described. It has been probed that formyl cyclopropanes bearing two electron-withdrawing alkoxycarbonyl substituents can lead to acyl azolium equivalents upon a NHC mediated ring-opening process that undergo a hetero-Diels-Alder cycloaddition to render a variety of 3,4-dihydro-2*H*-pyran-2-one adducts in good yield and excellent enantiocontrol.

The value of formylcyclopropanes as azolium enolate precursors has been highlighted and the use of multisubstitued formylcyclopropane in enantioselective cycloadditions has been implemented.

A cyclopropane ring-opening/aza-Michael/aldol/dehydration *cascade* reaction for the formation of highly enantioenriched dihydroquinolines has been developed. Thus, the capability of aminocatalysis promoted cyclopropane ring-openings as suitable platform for *domino* sequences has been proved. In particular, it has been shown that the intermediate formed can also show iminium-type reactivity.

Moreover, different strategies have been applied to make full use of all the functionalities present in the cyclopropane. A *one-pot* synthesis of enantioenriched pyrroloquinolines has been achieved in a process that combines the aza-Michael/aldol *domino* reaction with an acid-promoted lactamization step. Alternatively, the pyrroloquinoline scaffold could be accessed in a triple cascade sequence straight from ethyl 1-acetyl-2-(2-oxoethyl)cyclopropane-1-carboxylate (**14d**) and aminobenzaldehyde (**15a**). Additionally, the synthesis of

cyclopentaquinole **19a** through an aminocatalysis/Lewis-Acid promoted aza-Michael/aldol/aldol sequence has been reported.

The reported transformations have been successfully extended to the use of a variety of aminobenzaldehydes and cyclopropaneacetaldehydes.

# 4

# 4

# Enantioselective aminofluorination of β-fluorostyrenes

## 1.- INTRODUCTION

Incorporation of fluorine atom(s) or fluorinated moieties into organic molecules causes significant changes in their physical, chemical and biological properties.[1] The high electronegativity and small size of fluorine might be responsible for improvements in solubility, bioavailability and metabolic stability, thus proving the importance of fluorinated compounds in pharmaceuticals.[2] Despite the utility of organofluorine compounds, relatively few methods exist for the generation of carbon-fluorine bonds[3] in organic building blocks in comparison with the number of transformations for the generation of other carbon-halogen bonds. In this sense, difunctionalization of alkenes, which has received increased attention in

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1 a) Gouverneur, V.; Seppelt, K. *Chem. Rev.* **2015**, *115*, 563; b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH; Weinheim, **2008**; c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactiviy and Applications*; Wiley-VCH; Weinheim, **2004**; d) *Organofluorine Compounds: Chemistry and Applications* (Eds.: Hiyama, T.), Springer, New York , **2000.**

2 a) Fluorine in Bioorganic Chemistry Chemistry (Eds.: Welch, J. T.; Eswarakrishman, S.), Wiley, New York, **1991**; b) *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: Banks, R. E.; Smart, B. E.; Tatlow, J. C.) Plenum Press, New York, **1994**; c) Muller, K.; Faeh, C.; Diederich, F. *Science* **2007***, 317*, 1881.

3 a) Baudoux, J.; Cahard, D. *Org. React.* **2007**, *69*, 347; b) Kirk, K. L. *Org. Process. Res. Dev.* **2008**, *12*, 305; c) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803; d) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470; e) Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950.

recent years,[4] stands as an appealing transformation for the simultaneous introduction of fluorine together with other functionalities in organic compounds.[5]

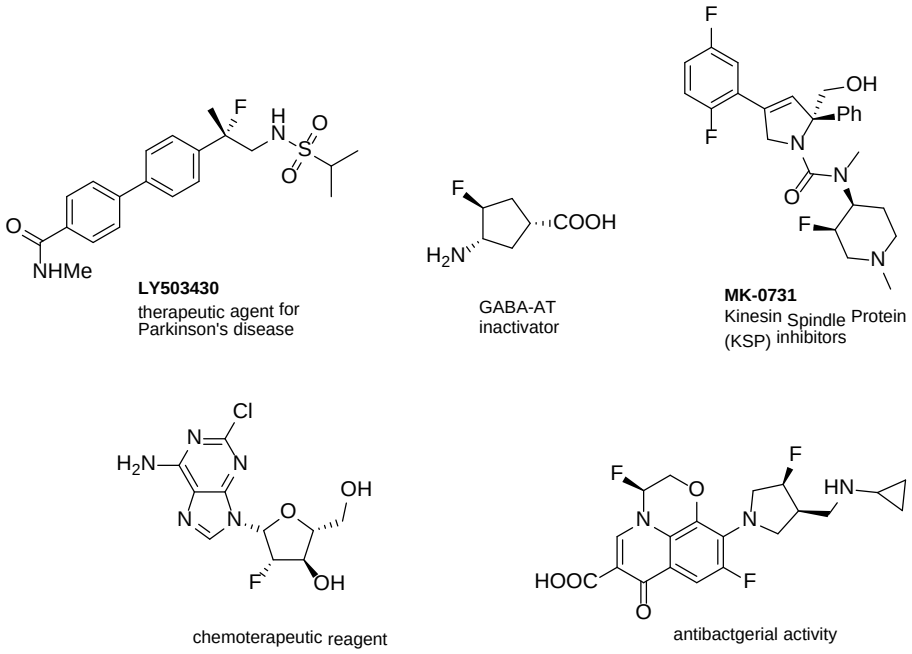
In this regard, alkene aminofluorination processes are of particular interest since they give access to β-fluoroamines, which are considered as class of key moieties in bioactive compounds (Scheme 4. 1).[6] It has been proven that the biological properties of the amine are strongly affected by the presence of a vicinal fluorine atom.[7]

[4] a) Jacques, B.; Muñiz, K. *in Catalyzed Carbon Heteroatom Bond Formation* (Ed.: Yuding, A. K.), Wiley-VCH Verlag GmbH & Co., KGaA, **2010**, p. 119-131; b) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083.

[5] For recent reviews on Pd-catalyzed oxidative difunctionalization of alkenes, see: a) Yin, G.; Mu, X.; Liu, G. *Acc. Chem. Res.* **2016**, *49*, 2413; b) Chemler, S. R.; Bovino, M. T. *ACS Catal.* **2013**, *3*, 1076. Fluoroesterification: c) Peng, H.-H.; Yuan, Z.-L.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. S. Chem. Sci. **2013**, *4*, 3172. Flurorosulfonylation: d) Yuan, Z.-L.; Wang, H.-Y.; Mu, X.; Chen, P.-H.; Guo, Y.-L.; Liu, G.S. *J. Am. Chem. Soc.* **2015**, *137*, 2468. Fluoroarylation: e) Talbot, E. P. A.; Fernandes, T. A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101; f) He, Y.; Yang, Z.; Thornbury, R. T.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 12207; g) Miró, J.; del Pozo, C.; Toste, F. D.; Fustero, S. *Angew. Chem. Int. Ed.* **2016**, *55*, 9045. Silver catalyzed Phosphosofluorination: h) Zhang, C.-W.; Li, Z.-D.; Zhu, L.; Yu, L.-M.; Wang, Z.-T.; Li, C.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 14082.

[6] McCarthy, J. R. *Fluorine in Drug Design: A Tutorial Review*; 17th Winter Fluorine Conference; St. Pete Beach, FL, **2005.**

[7] a) Donetti, A.; Cereda, E.; Ezhaya, A.; Micheetti,R. *J. Med. Chem.* **1989**, *32*, 957; b) van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O´Connor, D.; Pike, A.; Rowley, M.; Russel, M. G. N.; Sohal, B.; Stanton, J. A.; S. Thomas, Verrier, H.; Watt, A. P.; Castro, J. L. *J. Med. Chem.* **1999**, *42*, 2087; c) Böhm, H.-J.; Banner, D.; Bendels, S.; Bendels, M.; Kansy, M.; Kuhn, B.; Müller, K.; ObstSander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.




**Scheme 4. 1**

Since traditional methodologies to access β-fluoroamines from alkenes imply several multi-step transformations, direct aminofluorination of alkenes has focused the attention of several studies in recent years.[8] However, the highly desirable and more challenging use of non-activated alkenes stands as an interesting topic, and in this way, it has been demonstrated that the introduction of the required functionalization has been made possible by operating through different mechanisms depending on the nature of the fluorine source (electrophilic, nucleophilic, radical and metal-mediated reactions).[9]

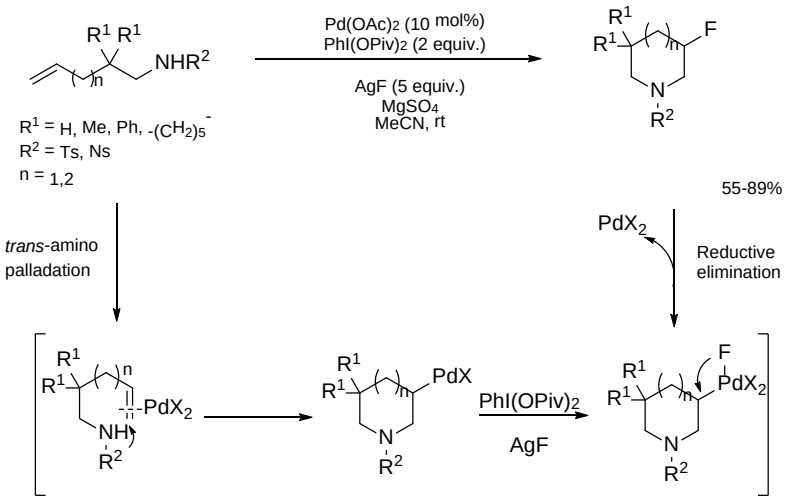
In this regard, transition-metal catalysis is a valuable approach to the synthesis of organofluorine compounds, especially when seeking for milder reaction conditions in the C-F bond formation. In comparison with the classic electrophilic

[8] a) Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A. M.; McCarthy, T. D. *Synlett* **2004**, 791; b) Appayee, C.; Brenner-Moyer, S. E. *Org. Lett.* **2010**, *12*, 3356.

[9] a) Kong, W.; Merino, E.; Nevado, C. *Chimia* **2014**, *68*, 430; b) Chen, P.; Liu, G. *Eur. J. Org. Chem.* **2015**, 4295.

fluorination, a selective process can be achieved by choosing a correct metal-ligand combination, and although a variety of catalysts have been employed in fluorination chemistry, only a few of them have proved their efficiency in the functionalization of multiple carbon-carbon bonds.[10]

In this context, Liu and co-workers reported the first selective aminofluorination of alkenes promoted by a transition metal.[11] This reaction consists on a intramolecular example in which as in other functionalization of alkenes[4,5] an initial nucleopalladation leads to a new $sp^3$ C-$Pd^{II}$ bond after a six-endo or seven-endo cyclization. Then the oxidating system $PhI(OPiv)_2$/AgF further oxidizes the metal centre to form a Pd (IV) species. This high–valent complex undergoes reductive elimination to render the $sp^3$ C-F bond Scheme 4. 2.

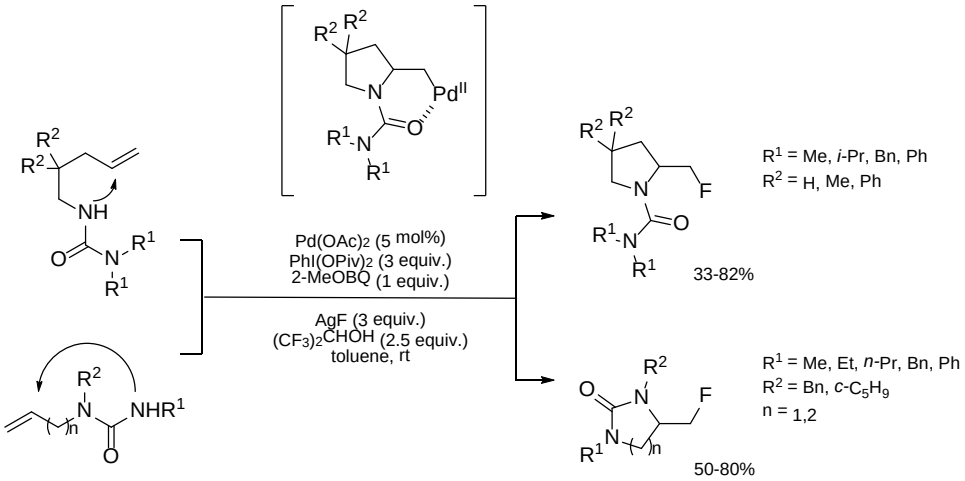



**Scheme 4. 2**

Later, it was proven that by introducing a chelating group in the nitrogen atom the regioselectivity of the transaminopalladation could be switched from 6-*endo* to 5-*exo* cyclization (Scheme 4. 3).[12] The chelating group coordinates the palladium

[10] For reviews on fluorinations of alkenes, see: Liu, G. *Org. Biomol. Chem.* **2012**, *10*, 6243.
[11] Wu, T.; Cheng, J.; Chen, P.; Liu, G. *J. Am. Chem. Soc.* **2009**, *131*, 16354.
[12] Wu, T.; Cheng, J.; Chen, P.; Liu, G. *Chem. Commun.* **2013**, *49*, 8707.

centre promoting the kinetically favoured and irreversible *5-exo* aminopalladation. This way it was proved that the methodology allowed the formation of different heterocycles with the concomitant fluorination of the primary carbon just by modifying the substrate. Recently, this methodology was extended to the synthesis of fluorinated cyclic sulfamide derivates[13] and to the total synthesis of 6-(*R*)-Fluoroswainsonine and 5-(*R*)-Fluorofebrifugine.[14]




**Scheme 4. 3**

Another 5-exo cyclization/fluorination sequence was reported by Li in 2013 for the synthesis of fluorinated lactams.[15a] *N*-arylpent-4-enamides were successfully employed in a radical-involving transformation[16,17] under silver catalysis (Scheme 4. 4). Selectfluor oxidizes the silver (I) complex to silver (III), which gets an electron from the enamide to form a Ag(II)-F complex and an arene radical cation. This is

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13 Cheng, J.; Chen, P.; Liu, G. *Chin. J. Catal.* **2015**, *36*, 40.

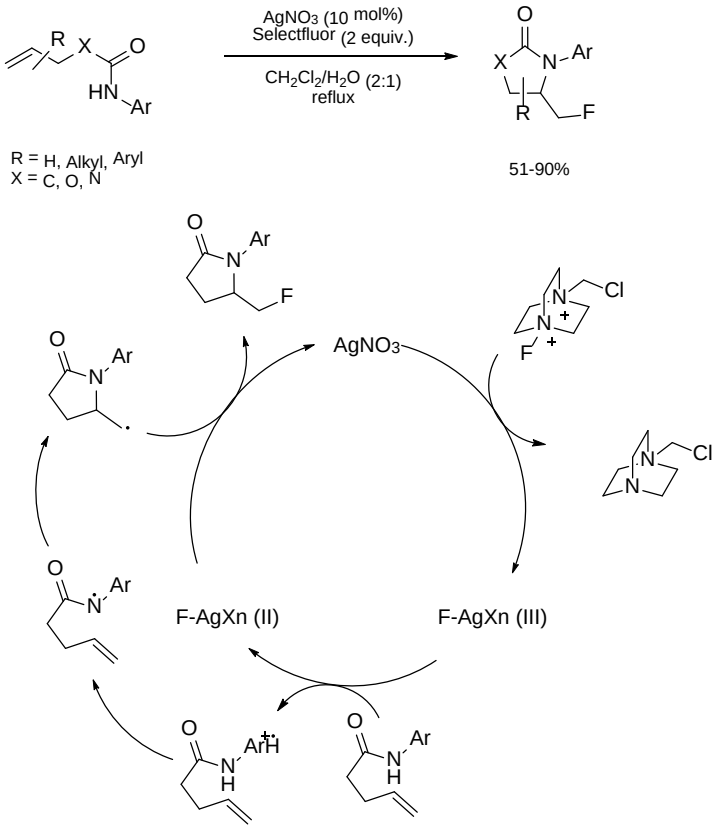
14 Wu, L.; Chen, P.; Liu, G. *Org. Lett.* **2016**, *18*, 960.

15 a) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 4640; b) Zhang, X. *J. Phys. Org. Chem.* **2016**, 1.

16 Cooper catalyzed radical mediated aminofluorination of styrenes Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 11079.

17 For copper catalysis in radical aminofluorination, see: a) Saavedra-Olavarría, J.; Arteaga, G. C.; López, J. J.; Pérez, E. G. For iron catalysis in radical aminofluorination, see: b) Lu, D.-F.; Liu, G.-S.; Zhu, C.-L.; Yuan, B.; Xu, H. *Org. Lett.* **2014**, *16*, 2912; c) Lu, D.-F.; Zhu, C.-L.; Sears, J. D.; Xu, H. *J. Am. Chem. Soc.* **2016**, *138*, 11360.

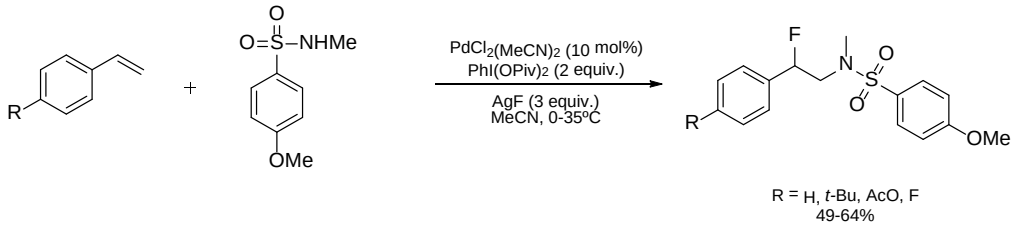
deprotonated to render an amidyl radical that gives intramolecular *5-exo* addition to onto the alkene. The generated carbon-centered radical undergoes a fluorination step with Ag(II)-F to form the final lactam and recover the catalyst.[15b]




**Scheme 4. 4**

In 2012, Liu *et al* reported the intermolecular aminofluorination of styrenes under similar conditions employing sulfonamides. An anti-Markovnikov aminopalladation, which was stabilized by a π–benzylic intermediate, led to the α-fluorination of styrenes in moderate yields (Scheme 4. 5).[18] The regioselectivity is given by the starting material that favours the fluorination of the internal position of the alkene.

[18] Zhu, H.; Liu, G. *Acta Chim. Sinica* **2012**, *70*, 2404.

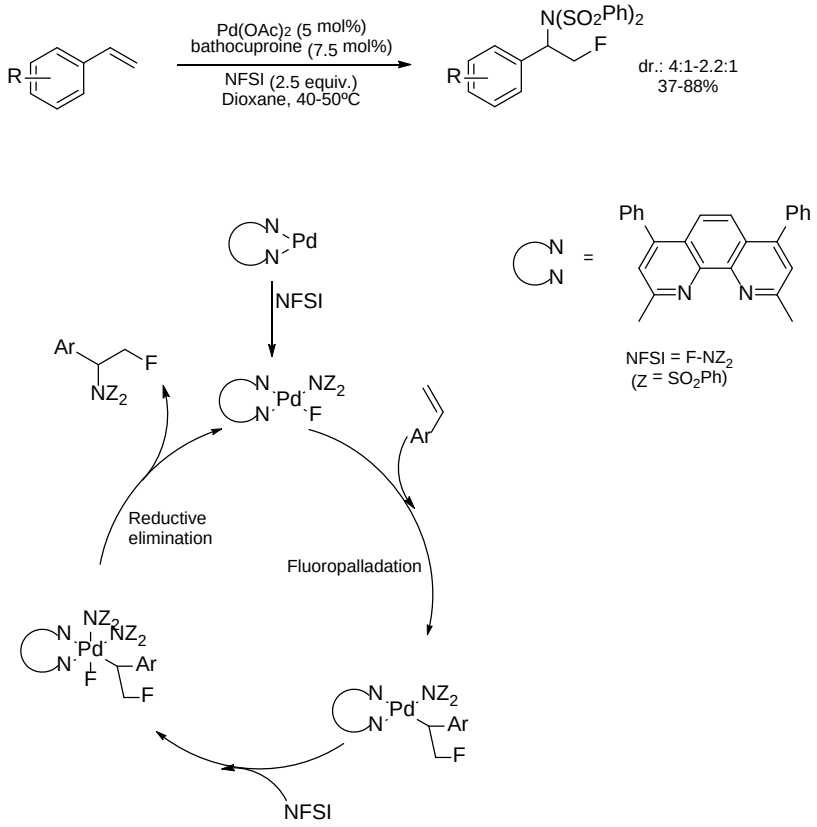



**Scheme 4. 5**

On the other hand, a completely new pathway for the aminofluorination reaction was postulated by Liu and co-workers,[19] which involves fluoropalladation of styrenes for the C-F bond formation (Scheme 4. 6). Remarkably, this was the first report on nucleophilic attack of fluorine on a Pd-coordinated alkene, a particularly challenging possibility due to its low nucleophilicity. *N*-fluorobenzenesulfonimide (NFSI), which was employed as the fluorine and amine source, was responsible for the oxidation of palladium (0)-bathocuproine (BC) complex to form the catalytically active (BC)$Pd^{II}$F complex. In contrast with other examples in which the nucleophilic attack of the amine moiety promoted the palladium insertion, in this case is the fluorine atom coming from the metal complex the one able to react with the alkene moiety. A $Pd^{II}/Pd^{IV}$ mechanism initiated by the fluoropalladation of (BC)$Pd^{II}$F complex was proposed. NFSI would further oxidize the resulting species to a $Pd^{IV}$ intermediate that undergoes reductive elimination to form the C-N bond.[20]

[19] Qiu, S.; Xu, T.; Zhou, J.; Guo, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 2856.

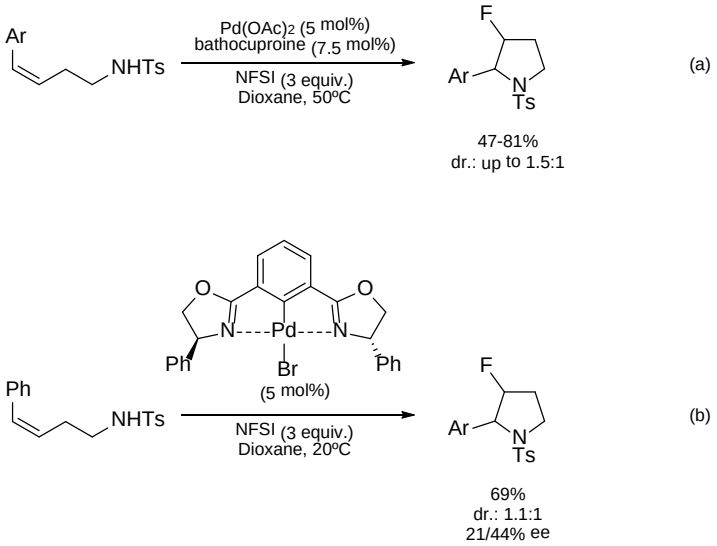
[20] For related examples of this model on fluorooxylation processes, see: a) Peng, H.; Yuan, Z.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *Chem. Sci.* **2013**, *4*, 3172; b) Yuan, Z.; Peng, H.; Liu, G. *Chin. J. Chem.* **2013**, *31*, 908.




**Scheme 4. 6**

By applying this strategy, Liu and co-workers developed an intramolecular *endo*-selective version of the reaction with amine-tethered styrenes to afford a series of fluorinated pyrrolidines.[21] The reaction followed the same mechanism and lead to obtain the *5-endo* product (Scheme 4. 7a), although the reaction proceeded with low levels of diastereoselectivity. When a chiral pincer-Pd catalyst was employed in the asymmetric version a promising enantioselectivity (up to 44% ee) was obtained for the *cis* diastereomer. However the reaction did not proceed diastereoselectively, thus the *trans* diastereomer was obtained as the major product in a 21% ee (Scheme 4. 7b).

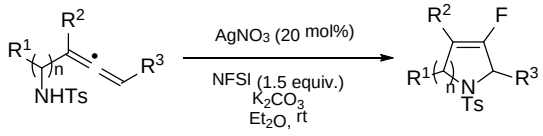
[21] Xu, T.; Qiu, S.; Liu, G. *Chin. J. Chem.* **2011**, *29*, 2785.




**Scheme 4. 7**

Significant advances have been made in the use of other unsaturated coumpounds such as allenes and alkynes. In this context, other metals than palladium, for instance silver and gold are of great importance in those aminofluorinations. Thus, in 2011 Liu *et al* published an intramolecular aminofluorination of allenes employing silver nitrate as catalyst. The synthesis of 4-fluoro-2,5-dyhydropyrroles can be explained based on a $Ag^{I}/Ag^{II}$ mechanistic proposal. Analogously to the methodology applied in Pd-catalyzed reactions, a nucleophilic amination of allene results in the new C-Ag bond formation, which upon oxidation of the metal centre is cleaved to form the fluorination product (Scheme 4. 8).[22]

[22] Xu, T.; Mu, X.; Peng, H., Liu, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 8176.

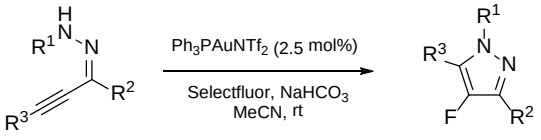



28-92%

$R^1$ = H, Alkyl, *Ar*
$R^2$ = Alkyl, $CO_2R$, Ar, $SO_2Ph$
$R^3$ = H, Alkyl, Aryl
*n* = *1,2*

**Scheme 4. 8**

Different authors have proved that intramolecular aminofluorination of alkynes can be performed under similar reaction conditions. In this sense, silver (I)[23] and gold (I)[24] catalysts, which are particularly effective in the electrophilic activation of alkynes, featured efficiently in the synthesis of fluorinated cyclic compounds. For instance, a gold(I)-catalyzed intramolecular aminofluorination of alkynes was reported by Xu, Liu and co-workers in 2011. The reaction proceeds under analogous Au(I)/Au(III) mechanism, yet the high tendency of C-Au bond to undergo protonolysis results in the formation of hydroaminated products. Those products can be converted to the fluorinated pyrazoles in the presence of selectfluor (Scheme 4. 9).




43-90%
d.r.: up to 7.2:1

$R^1$ , $R^2$, $R^3$ = H, Alkyl, Aryl

**Scheme 4. 9**

[23] a) Xu, T.; Liu, G. *Org. Lett.* **2012**, *14*, 5416; b) Liu, Q.; Wu, Y.; Chen, P.; Liu, G. *Org. Lett.* **2013**, *15*, 6210.

[24] a) Qian, J.; Liu, Y.; Zhu, J.; Jiang, B.; Xu, Z. *Org. Lett.* **2011**, *13*, 4220; b) Li, S.; Li, Z.; Yuan, Y.; Li,Y.; Zhang, L.; Wu, Y. *Chem. Eur. J.* **2013**, *19*, 1496; c) Arcadi, A.; Pietropaolo, E.; Alvino, A.; Michelet, V. *Org. Lett.* **2013**, *15*, 2766; d) Arcadi, A.; Pietropaolo, E.; Alvino, A.; Michelet, V. *Beilstein J. Org. Chem.* **2014**, *10*, 449.

Noteworthy, recent experimental and mechanistic studies[25] on the silver catalyzed reaction support a reaction pathway which involves mesoionic carbene silver complexes as the generated intermediate after the amination step.

In summary, the reviewed literature shows the value of aminofluorination as an efficient strategy for fluorination of C-C multiple bonds, yet there is still a lack of enantioselective examples, being the preliminary results of Liu with a 44% ee one of those.[21] The F. D. Toste research group, aware of the importance of the synthesis of organofluorine compounds, have centered his activity in the formation of new C-F bonds and reported several examples in fluorination of alkenes employing high oxidation state palladium. In this regard, the use of both activated alkenes and non-activated ones has been studied. In the latter case, employing directing groups has been an successful approach for selectively obtain vicinal functionalization in fluoroarylation reactions. However, the 1,1-fluoroarylation proved to be possible employing similar conditions when aliphatic alkenes were employed (Scheme 4. 10).[26,5e,f,g] However, much of this effort has been directed to the synthesis of monofluorinated compounds, whilst the synthesis of geminal-difluorinated compounds[27] remains as a challenging task to be studied.

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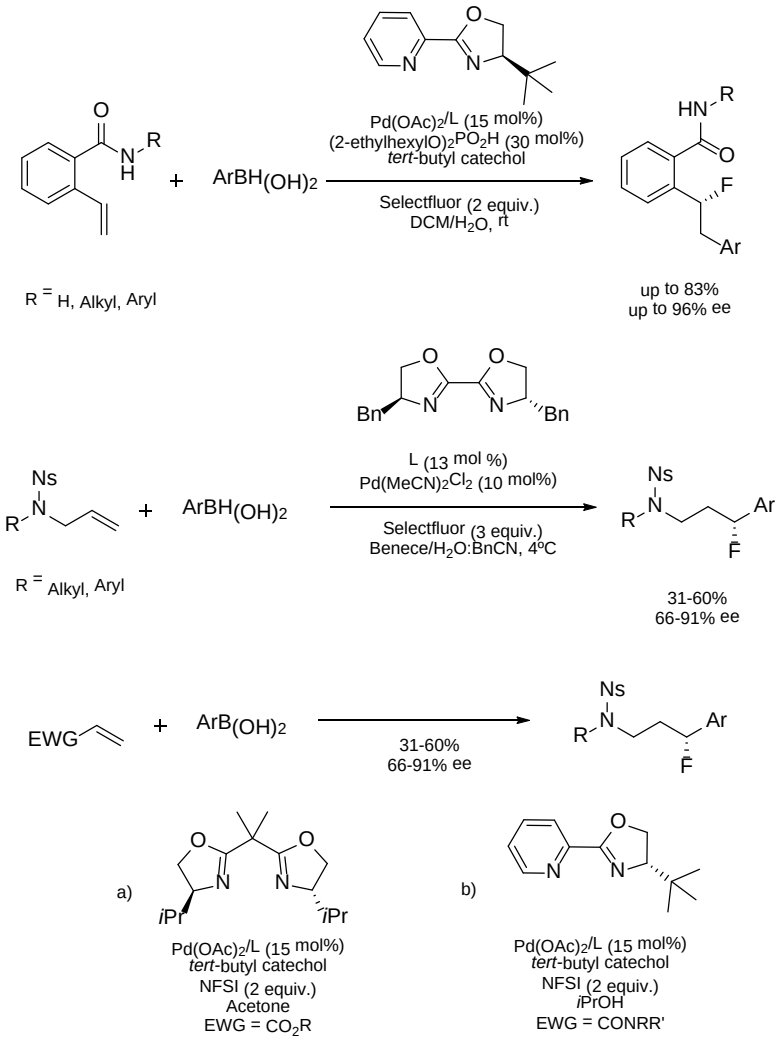
[25] a) Liu, Q.; Yuan, Z.; Wang, H.-y.; Li, Y.; Wu, Y.; Xu, T.; Leng, X.; Chen, P.; Guo, Y.-l.; Lin, Z.; Liu, G. *ACS Catal.* **2015**, *5*, 6732; b) Xu, T.; Wu, Y.; Yuan, Z.; Guan, H.; Liu, G. *Organometallics* **2016**, *35*, 1347.

[26] For recent examples, see: a) Thornbury, R. T.; Toste, F. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 11629; b) Hiramatsu, K.; Honjo, T.; Rauniyar, V.; Toste, F. D. *ACS Catal.* **2016**, *6*, 161.

[27] Difluorination of alkenes: a) Kitamura, T.; Muta, K.; Oyamada, J. *J. Org. Chem.* **2015**, *80*, 10431; b) Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science* **2016**, *353*, 51; c) Arimitsu, S.; Nakasone, M. *J. Org. Chem.* **2016**, *81*, 6707; d) Zhou, B.; Yan, T.; Xue, X.-S.; Cheng, J.-P. *Org. Lett.* **2016**, *18*, 6128.


Pd(OAc)2/L (15 mol%)
(2-ethylhexylO)2PO2H (30 mol%)
tert-butyl catechol
Selectfluor (2 equiv.)
DCM/H2O, rt
R = H, Alkyl, Aryl
up to 83%
up to 96% ee
L (13 mol %)
Pd(MeCN)2Cl2 (10 mol%)
Selectfluor (3 equiv.)
Benece/H2O:BnCN, 4ºC
R = Alkyl, Aryl
31-60%
66-91% ee
31-60%
66-91% ee
a)
Pd(OAc)2/L (15 mol%)
tert-butyl catechol
NFSI (2 equiv.)
Acetone
EWG = CO2R
b)
Pd(OAc)2/L (15 mol%)
tert-butyl catechol
NFSI (2 equiv.)
iPrOH
EWG = CONRR'

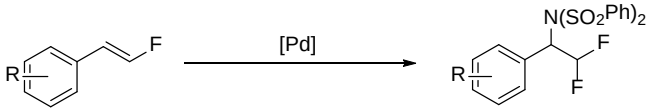
**Scheme 4. 10**

## 2.- SPECIFIC OBJECTIVES AND WORK PLAN

From the presented literature review, it can be appreciated that the metal-mediated aminofluorination of alkenes is an interesting approach for the direct access to 1,2-aminofluorinated compounds. Additionally, it has been mentioned the wide experience of the Toste research group in the field of fluorination. In this context, I joined the University of California for a three month short stay, from September to December of 2015.

In this regard, the difluoromethyl group is also able to modify the biological properties of the compounds, and event show enhanced activity when compared to monofluoro- or trifluoromethyl moieties.[28] In addition, it can work as chemically inert surrogate of alcohol, thiols and other polar functional groups.[29]

Considering the great interest of this family of compounds, we decided to direct our efforts to the **enantioselective synthesis of 1-amine-2,2-difluoroethyl arenes through a palladium catalyzed aminofluorination of monofluorostyrenes** (Scheme 4. 11).




**Scheme 4. 11**

The possible formation of difluoroalkenes through a β-hydride elimination step that may compete with the oxidation of Pd(II) to the relatively unstable Pd(IV) species, is one of the main challenges for this transformation, as well as developing a robust protocol and reaching high levels on enantiocontrol will be the main challenges to be faced. In order to do this, first a screening of the reaction conditions for the non-asymmetric version will be performed so as to have an insight of the performance of different substrates and catalytic systems.

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[28] Rueeger, H.; Lueoend, R.; Rogel, O.; Rondeau, J.-M.; Möbitz, H.; Machauer, R.; Jacobson, L.; Staufenbiel, M.; Desrayaud, S.; Neumann, U. *J. Med. Chem.* **2012**, *55*, 3364.

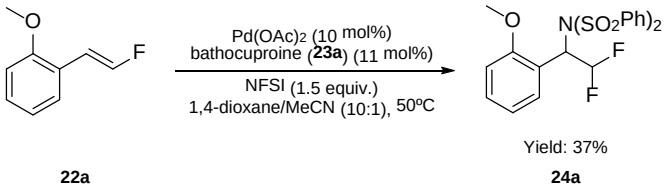
[29] Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.

# 3.- RESULTS AND DISCUSSION

## 3.1. OPTIMIZATION OF THE REACTION

Once that the objectives have been stated, the most relevant results from this part of the research will be presented and discussed in this section. (*E*)-1-(2-fluorovinyl)-2-methoxybenzene[30] was chosen as a model substrate for the palladium catalyzed aminofluorination reaction.

Based on literature precedents for the initial test experiments,[19] it was observed that carrying out the reaction in a mixture of 1,4-dioxane and acetonitrile[5f] as solvent and in the presence of bathocuproine (BC) and $Pd(OAc)_2$ as palladium source resulted in the formation of the desired difluorocompound (**23a**) in moderate yield (Scheme 4. 12).



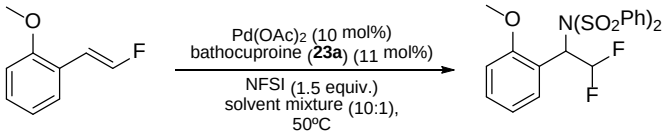

**Scheme 4. 12**

After having demonstrated the feasibility of the reaction, a screening of standard experimental parameters was performed. Several preliminary experiments were performed modifying the palladium source only observing similar results when $Pd(TFA)_2$ was employed, yet a cleaner reaction was observed when employing $Pd(OAc)_2$.

[30] a) Zhao, Y.; Huang, W.; Zhu, L.; Hu, J. *Org. Lett.* **2010**, *12*, 1444; b) Wu, J.; Xiao, J.; Dai, W.; Cao,S. *RSC. Adv.* **2015**, *5*, 34498.

This palladium source was chosen for further studies on the solvent effect (Table 4. 1). Previous work performed in the group had indentified the 1,4-dioxane/MeCN solvent system as the only one that led to obtain the product in reasonable yields. Based on these results, selected experiments regarding the performance of each component of this mixture were performed. Thus, different ethers were tested to evaluate the influence of the 1,4-dioxane (Entries 1-4). It was observed that more polar ethers such as THF and dimethoxyethane (DME) resulted in no product formation, whilst a decrease in the yield was observed when performing the reaction in methyl *tert*-butyl ether. Based on precedent studies, in which no improvement was observed when other nitriles were observed it was decided to evaluate a more polar solvent like dimethylformamide (Entry 5). As no reaction was observed, it cannot be discarded that the effect of using acetonitrile is not entirely related to its role as co-solvent.

**Table 4. 1:** Effect of solvent




**22a** **24a**

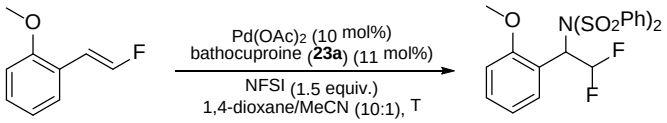
| Entry | Solvent | Co-solvent | Yield (%)[a] |
|---|---|---|---|
| 1 | 1,4-dioxane | MeCN | 37 |
| 2 | THF | MeCN | - |
| 3 | DME | MeCN | <5 |
| 4 | MTBE | MeCN | 20 |
| 5 | 1,4-dioxane | DMF | <5 |

[a]Yield of pure product isolated after flash chromatography.

From the previous results, it was decided to employ the 1,4-dioxane/MeCN solvent mixture to evaluate the influence of the temperature on the performance of the reaction (Table 4. 2). In this table, it can be seen that the yield of the reaction was not significantly affected by the temperature, and only slightly better results

were obtained when carrying the reaction at room temperature or 40ºC (Entries 1-2). However, when the temperature of the system was set below 40ºC a drop on the reaction rate was observed, whilst running the reaction at 50ºC or 70ºC (Entries 3-4) only resulted in slightly lower reaction times yet in more complex mixture of products. Thus, carrying out the reaction at 40ºC was defined as the optimal conditions.

**Table 4. 2:** Effect of the temperature




**22a** **24a**

| Entry | T (ºC) | t (h) | Yield (%)[a] |
|---|---|---|---|
| 1 | r.t. | 42 | 41 |
| 2 | 40 | 14 | 43 |
| 3 | 50 | 12 | 36 |
| 4 | 70 | 11 | 35 |

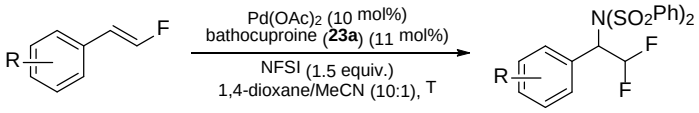
[a]Yield of pure product isolated after flash chromatography.

At this stage we considered that we had to explore the use of different substrates[30,31] in order to develop the asymmetric version of the reaction and to guarantee the best performing or most suitable one in terms of reactivity. For this reason, other styrenes bearing different substituents were surveyed (Table 4. 3). First prospective studies on the achiral version showed that the reaction performed with good yield when an electron-donating group was installed at the *para*- position of the phenyl ring (Entry 2), thus leading to a less bulky alkene and an significant increase of the yield compared to the ortho-methoxy substitued fluorostyrene. Nevertheless, when fluoroalkenes bearing a more electron-rich arene were

[31] a) Hu, M.; He, Z.; Gao, B.; Li, L.; Ni, C.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 17302; b) Hu, M.; Ni, C.; Li, L. Han, Y.; Hu, J. *J. Am. Chem. Soc.* **2015**, *137*, 14496; c) Thomoson, C. S.; Martinez, H.; Dolbier Jr., W. R. *J. Fluorine Chem.* **2013**, *150*, 53.

employed an increased reactivity was observed which unfortunately resulted in the formation of complex mixtures of products (Entries 4-5). Only when the reaction was carried out at room temperature the product could be obtained in low yield (Entry 6). Although fluorostyrenes with different substitutions patterns could be employed, introducing electron-withdrawing substituents affected negatively to the yield (Entries 7-9). The reaction of α,α-disubstitued fluoroalkenes did not lead to the formation of the product (Entry 10). It is worth noting, that (*E*)-1-(tert-butyl)-4-(2-fluorovinyl)benzene performed equally well when the reaction was performed at room temperature (Entry 3), this is particularly interesting in connection to an enantioselective transformation.

**Table 4. 3:** Evaluation of fluorostyrenes




**22a-h** **24a.g**

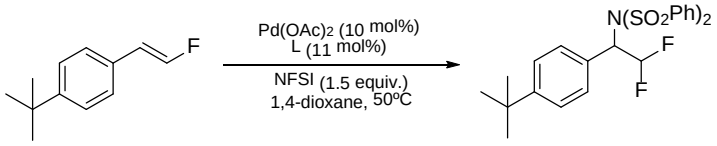
| Entry | $R^1$ | $R^2$ | Product | T (°C) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | *o*-MeO | H | **24a** | 40 | 43 |
| 2 | *p*-*t*Bu | H | **24b** | 40 | 75 |
| 3 | *p*-*t*Bu | H | **24b** | rt | 75 |
| 4 | 3,4-$OCH_2O$- | H | **24c** | 40 | -[b] |
| 5 | 3,4-MeO | H | **24d** | 40 | -[b] |
| 6 | 3,4-MeO | H | **24d** | rt | <10 |
| 7 | *o*-Br | H | **24e** | 40 | 21 |
| 8 | *p*-Br | H | **24f** | 40 | 29 |
| 9 | *m*-Cl | H | **24g** | 40 | 20 |
| 10 | Ph | Ph | - | 40 | . |

[a]Yield of pure product isolated after flash chromatography. [b]Complex mixture of compounds

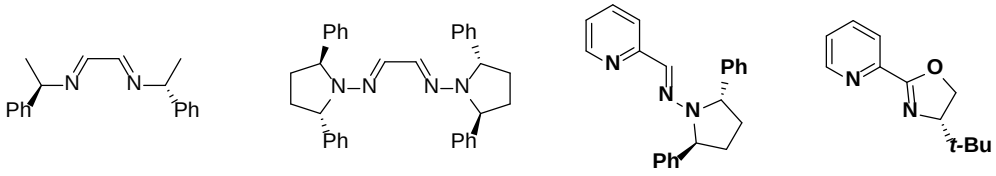
In view of these results, *para*-*t*-Bu substituted fluorostyrene was considered suitable for studying the asymmetric version of the reaction. Thus, monofluoroalkene **24b** was chosen for a screening of the catalytic systems in order to find out which type of ligands may be suitable for the developing an

enantioselective transformation. Thus a series of ligands were synthetized and tested in the reaction with (*E*)-1-(tert-butyl)-4-(2-fluorovinyl)benzene (Table 4. 4). Based on the good performance of the bathocuproine, different *N*-based ligands were tested (**23b-e**). However, when another relatively rigid and bulky N-based ligand, such as diimine **23b** was employed no product formation was observed. Hydrazone based ligands **23c** and **23d** were not suitable for this transformation and we decided to focus our study in oxazoline based ligands previously employed in the group for the fluorination of alkenes.[5e,f,g] After unfruitful results employing some commercial oxazolines, the use of a pyridine ring flanked by an oxazoline, pyrOX (**23e**) led us to obtain small amounts of the aminofluorination product. Alternatively, NHC type ligands, for instance triazolium salt **23f**, were tested with unsatisfactory results, same as when phosphoramidite **23g** and (*R*)-BINAP **23h** were employed.

**Table 4. 4:** Evaluation of ligands of different nature




**22b** **24b**

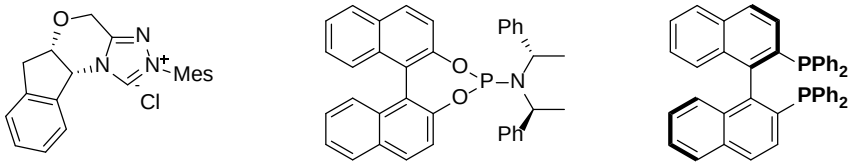



**23b** Yield: -

**23c** Yield: -

**23d** Yield: -

**23e** Yield: <5%




**23f** Yield: -

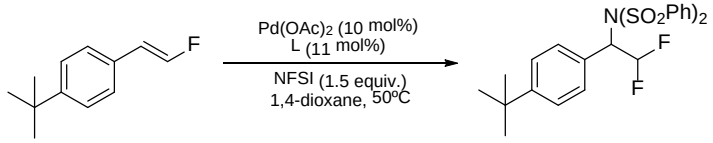
**23g** Yield: -

**23h** Yield: -

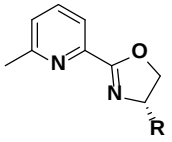
Since, oxazoline based ligands proved to be the only ones to promote the reaction, and by. analogy to the bathocuproine scaffold, oxazoline based ligands bearing methylpyridine and quinoline substituents were studied (**23i-n**) (Table 4. 5). Oxazoline **23i** with a methylpyridine substituent and *i*-Pr as a bulky substituent to induce a enantioselective process, led to the aminofluorination product in good yield and an interesting 20% ee. Modiying the oxazoline ring by introducing substituentes with arene moieties (**23j-k**) resulted in a slight decrease in the yield and the enantiocontrol. Exchanging the methylpyridine ring for a quinoline resulted in a better enantiocontrol albeit a decrease in the yield was observed (**23i** vs **23l**). More bulky *t*-Bu substituted ligand **23m** led to a dramatic drop of both the yield and the enantiomeric excess. The later might be explained by a non-efficient coordination of

the ligand due to sterics, resulting in a poor enantiocontrol. On the other hand, a phenyl substituent also gave a poor enantiocontrol even if the yield was slightly better in comparision with other quinoline oxazolines (**23n**).

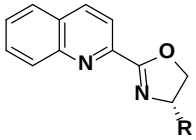
**Table 4. 5:** Evaluation of *N*-based chiral ligands




**22b** **24b**




**23i,** R = *i*-Pr, Yield: 60%, 20% ee
**23j,** R = Bn, Yield: 49%, 10% ee
**23k,** R = 1-naphtyl, Yield: 37%, 6% ee

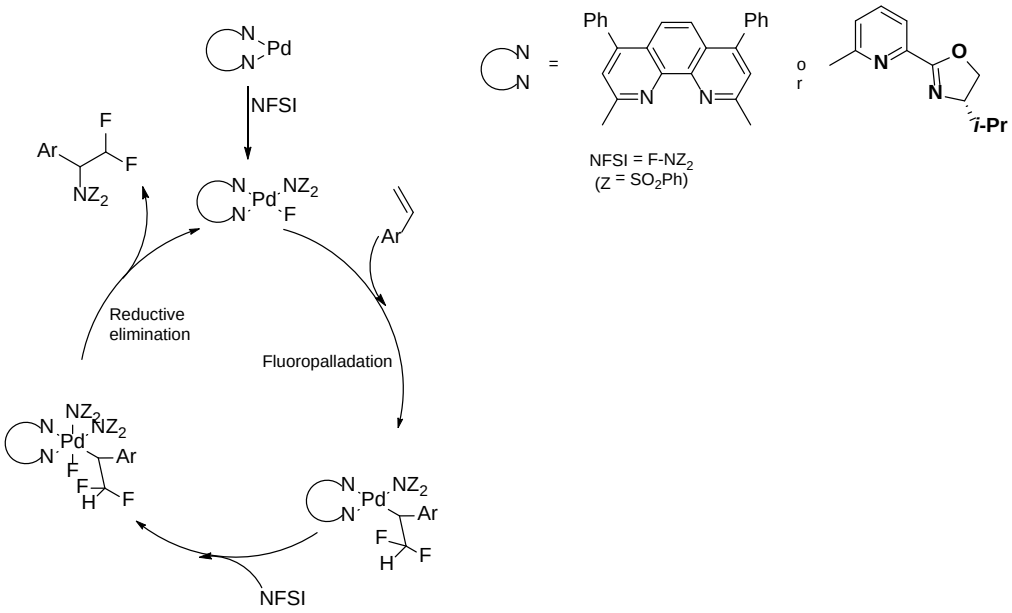



**23l,** R = *i*-Pr, Yield: 12%, 32% ee
**23m** R = *t*-Bu, Yield: <5%, 9% ee
**23n,** R = Ph, Yield: 31%, 10% ee

Therefore methylpyridine and quinoline substituted oxazolines **23m** and **23p** led to promising results in the aminofluorination of fluorostyrenes, that encourage continuing with the study of the asymmetric version.

### 3.2. MECHANISTIC PROPOSAL

Based on the mechanism proposal of Liu[19] a possible reaction pathway is depicted in Scheme 4. 13. First, the $L_nPd(0)$ species **I** is oxidized by NFSI to form the $Pd^{II}$ active species **II**. This undergoes an insertion reaction over the monofluoroalkene to render intermediate **III**. The stereochemistry of the reaction is defined at this fluoropalladation step, in which the new C-F and C-Pd bonds are formed. Then, in the strong oxidant media a $Pd^{IV}$ species (**IV**) can be formed in a oxidative addition step. This high valent complex leads to a reductive elimination to form the C-N and generate the aminofluorinated product.


NFSI
Reductive elimination
Fluoropalladation
NFSI
NFSI = F-NZ2
(Z = SO2Ph)
or
i-Pr

**Scheme 4. 13**

## 4.- CONCLUSIONS

From the work presented in this chapter, the following conclusions can be outlined:

1. A new method for the synthesis of geminal difluorinated compounds bearing a vicinal amino moiety has been studied starting from a variety of monofluorostyrenes.
2. Promising results regarding the palladium catalyzed enantioselective aminofluorination of alkenes have been achieved. In this regard, methylpyridine oxazolines and quinoline oxazolines are presented as interesting scaffold as chiral ligands for this transformation.

It should be mentionted that this work was developed in collaboration with Richard T. Thornbury, who currently continues with the study of the reaction in Toste's group.

# 5

# 5

# Final conclusions

## CONCLUSIONS

Throughout the present work it has been demonstrated that covalent catalysis, in particular, *N*-Heterocyclic carbine catalysis and aminocatalysis, is a versatile tool for the discovery of new methodologies and the enantioselective synthesis of building blocks as well as complex polycyclic compounds in a simple way. From all the obtained results, we could conclude the following:

**a) Ynones as electrophilic counterparts in aldehyde-ketone cross-benzoin reactions.** It has been probed that alkynones are a competent partner in the cross-benzoin reaction, thus, the limited scope for the aldehyde-ketone has been widen. Employing an aminoindanol based triazolium salt as precatalyst the reaction proceeds with complete chemoselectivity avoiding the formation of self-benzoin and Stetter side products. For the first time non-activated ketones have been successfully employed in the intramolecular cross-benzoin reaction of aldehydes and ketones. Moreover, a new organocatalytic route for the enantioselective synthesis of tertiary propargylic alcohols has been described, and the value of the obtained adducts as building block has been proved through a series of transformation.

**b) Formylcyclopropanes in *N*-Heterocyclic carbene promoted ring-opening/formal (4+2) cycloaddition.** A new enantioselective formal [4+2] cycloaddition between multisubstitued formylcyclopropane 1,1-diesters and a variety of (hetero)aryl and alkyl γ-substitued β,γ-unsaturated-α-ketoesters has been described. It has been probed that formyl cyclopropanes bearing two electron-withdrawing alkoxycarbonyl substituents can lead to azolium enolate equivalents upon a NHC mediated ring-opening process that undergo a hetero-Diels-Alder cycloaddition to render a variety of 3,4-dihydro-2*H*-pyran-2-one adducts in good yield and excellent enantiocontrol.

**c) Cyclopropaneacetaldehydes in aminocatalyzed ring-opening/aza-Michael/aldol cascade sequences.** A variety of new cyclopropane acetaldehydes have been synthesized and their value as donor-acceptor cyclopropane precursors has been demonstrated. Moreover, the synthetic power of those molecules has been explored in aza-Michael/aldol *domino* reactions towards the synthesis of highly enantioenriched quinolines and pyrroloquinolines. Moreover, the whole scaffold of the cycloprane and all the functionalities in there has been included into the final structure of the studied reactions in both *one-pot* and cascade reactions.

**d)** Finally, in a different field, the **asymmetric aminofluorination of β-fluorostyrenes** has been studied in the research group of Prof. F. D. Toste in University of California, Berkeley. A new method for the synthesis of geminal difluorinated compounds bearing a vicinal amino moiety has been reported starting from a variety of monofluorostyrenes. Promising results regarding the palladium catalyzed enantioselective aminofluorination of alkenes have been achieved. In this regard, methylpyridine oxazolines and quinoline oxazolines are presented as interesting scaffold as chiral ligands for this transformation.

# 6

# 6

# Experimental

## 1.- GENERAL METHODS AND MATERIALS

Monodimensional and/or bidimensional nuclear magnetic resonance proton carbon and fluorine spectra ($^{1}$H NMR, $^{13}$C NMR, $^{19}$F NMR) were acquired at 25ºC on a Bruker AC-300 spectrometer (300 MHz for $^{1}$H, 75.5 MHz for $^{13}$C and 283 MHz for $^{19}$F) or a Bruker AC-500 spectrometer (500 MHz for $^{1}$H and 125.7 MHz for $^{13}$C). Chemical shifts (δ) are reported in ppm relative to residual solvent signals[1] ($CHCl_3$, 7.26 ppm for $^{1}$H NMR, $CDCl_3$, 77.0 ppm for $^{13}$C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in $^{1}$H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal, app, apparent. $^{13}$C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distortionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY and HSQC experiments were acquired to confirm precise molecular configuration and to assist in convoluting complex multiplet signals.[2] Infrared spectra (IR) were measured in a Jasco FT/IR 4100 (ATR), in the interval between

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1 H. E. Gottlieb, V. Kotlyar, A. Nudelman *J. Org. Chem.* **1997**, *62*, 7512.

2 Kinss, M.; Sanders, J. K. M. *J. Mag. Res.* **1984**, *56*, 518.

4000 and 400 $cm^{-1}$ with a 4 $cm^{-1}$ resolution. Only characteristic bands are given in each case. Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975 mass spectrometer under electronic impact (EI) conditions (70eV). The obtained data is presented in mass units (m/z) and the values found in brackets belong to the relative intensities comparing to the base peak (100%). High-resolution mass spectra (HRMS) were recorded on an Acquity GC coupled to a TOF mass spectrometer (GCT Micromass) using chemical ionization (CI) or an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI+ or ESI-) at the SGIker Unit of the University of the Basque Country (UPV/EHU). Melting points (M.p.) were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC performed in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel Chiralpak ADH, ASH, AZ-3 and Chiralcel OZ-3, OD-3, OD, OJH columns (0.46 cm x 25 cm) were used; specific conditions are indicated for each case. Optical rotations ($[\alpha]_D^{rt}$) were measured at 20ºC on a Jasco P-2000 polarimeter with a sodium lamp at 589 nm and a path length of 1 dm. Solvent and concentration are specified in each case. X-ray data collections were performed in an *Agilent Supernova* diffractometer equipped with an *Atlas* CCD area detector, and a CuKα micro-focus source with multilayer optics ($\lambda$ = 1.54184 Å, 250 µm FWHM beam size). The sample was kept at 120 K with a *Oxford Cryosystems Cryostream 700* cooler. The quality of the crystals was checked under a polarizing miscroscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone N inert oil and transferred to the diffractometer.

Analytical grade solvents and commercially available reagents were used without further purification. Anhydrous solvents were purified and dried with activated molecular sieves prior to use. For reactions carried out under inert

conditions, the argon was previously dried through a column of $P_2O_5$ and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140ºC, and allowed to cool under a dehumidified atmosphere.[3] Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kieselgel 60 F254). These were visualized by ultraviolet irradiation, phosphomolybdic acid, potasium permanganate or *p*-anisaldehyde dips.[4] For flash chromatography Merck 60, 230-400 mesh or Silicycle 40-63, 230-400 mesh silica gel was used.[5] For the removal of solvents under reduced pressure Büchi R-210 rotary evaporators were used.

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[3] G. W. Kramer, A. B. Levy, M. M. Midland *Organic Synthesis via Boranes*, John Wiley & Sons, New York, **1975**.

[4] E. Stahl, *Thin Layer Chromatography*, Springer-Verlag, Berlin, **1969**.

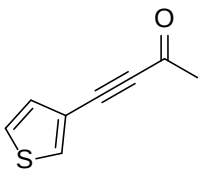
[5] W. C. Still, H. Kahn, A. J. Mitra *J. Org. Chem*. **1978**, *43*, 2923.

## 2.- NHC CATALYZED ENANTIOSELECTIVE CROSS-BENZOIN REACTION WITH YNONES

### 2.1. Synthesis of 1'-alkyl 3-butyn-2-ones (5a-g)

*General Procedure:* Activated $MnO_2$ (8.6 equiv.) was added in small portions over 12 min to a stirred solution of the appropriate propargylic alcohol[6] (1 equiv.) in $CHCl_3$ (0.17M) at r.t.. Once the addition was finished the reaction was stirred over night at r.t. and then filtered through a short pad of Celite®. EtOAc was employed to wash the ynone down and after removing the solvent *in vacuo*. The crude was then purified by flash column chromatography to afford pure ynones (**5**).

Compounds **5a-g** were prepared according to the general procedure and spectroscopic data were identical to those previously reported.[7]




**4-(thiophen-3-yl)-3-butyn-2-one (5e).** Following the general procedure, **5e** (957 mg, 5.70 mmol) was isolated by FC (*n*-hexane/EtOAc 8:2) in 83% yield as a yellow oil starting from 4-(thiophen-3-yl)-3-butyn-2-ol[8] (1.05 g, 6.90 mmol) and $MnO_2$ (5.15 g, 59.3 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm): 7.58 (dd, *J* = 2.9, 1.1 Hz, 1H, S-$C_{arom.}$-H-C≡C), 7.18 (dd, *J* = 5.0, 3.0 Hz, 1H, S- $C_{arom.}$-*H* $C_{arom.}$-H), 7.03 (dd, *J* = 5.0, 1.1 Hz, 1H, CH- $C_{arom.}$-*H*-C≡C), 2.25 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 184.5 (C=O), 133.9 ($C_{arom.}$-H), 130.2 ($C_{arom.}$-H), 126.2 ($C_{arom.}$-H), 119.2 ($C_{arom.}$), 88.5 (*C*≡C), 85.7 (C≡*C*), 73.0 (C-OH), 32.6 ($CH_3$). IR (ATR): 3106, 2187, 1666 cm$^{-1}$. MS (EI) m/z (%): 150 ($M^+$, 60), 135 (100), 63 (22) cm$^{-1}$. HRMS: Calculated for $[C_8H_7OS]^+$: 151.0218 ($M^+$); found: 151.0203.

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6 a) Collins, B. S. L.; Suero, M. G.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 5799; b) Schurbert, T.; Hummel, W.; Kula, M-R.; Müller, M. *Eur. J. Org. Chem.* **2001**, 4181

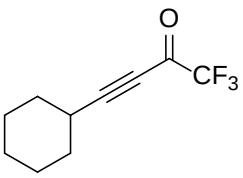
7 a) Marshall, J. A.; Eidam, P.; Eidam, H. S. *J. Org. Chem.* **2006**, *71*, 4840; b) Lee, K. Y.; Lee, M. Y.; GowriSankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5043; c) Shatskiy, A.; Kivijärvi, T.; Lundberg, H.; Tinnis, F.; Adolfsson, H. *ChemCatChem* **2015**, *7*, 3818.

8 Panteleev, J.; Huang, R. Y.; Lui, E. K. J.; Lautens, M. *Org. Lett.* **2011**, *13*, 5314.

## 2.2. Synthesis of 1,1,1-trifluoromethyl-3-butyn-2-ones (5h-l)

*General procedure*:[9] An *n*-hexane solution of *n*-BuLi (16.5 mmol) was added to a solution of the alkyne derivatives (15 mmol) in 22 mL of dry THF at -78 °C. The solution was stirred for 30 min at -78 °C, and ethyl trifluoroacetate (16.5 mmol, 2.34 g) as a solution in THF (30 mL) and boron trifluoride etherate (2.09 mL) were added successively. The reaction mixture was stirred an additional 90 min at -78 °C, saturated $NH_4Cl$ aq. (8 mL) was then added, and the slurry was allowed to warm to room temperature. The THF was removed *in vacuo*, and the residue was diluted with ether (75 mL), washed with water and brine (25 mL, 2 times), and dried over anhydrous $MgSO_4$ and then evaporated. The residue was purified by distillation under reduced pressure.

Compounds **5h-k** were prepared according to the general procedure and spectroscopic data were identical to those previously reported.[9,10]




**4-cyclohexyl-1,1,1-trifluorobut-3-yn-2-one (5l).** Following the general procedure, **5l** (505 mg, 2.47 mmol) was isolated after distillation under reduced pressure in 55% yield as a colourless oil starting from cyclohexylacetylene (0.500 g, 4.53 mmol), ethyl trifluoroacetate (716 mg, 4.98 mmol) and boron trifluoride etherate (0.64 mL, 4.98 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm): 2.70 (tt, *J* = 8.5, 3.9 Hz, 1H, C≡C-CH), 1.95-1.82 (m, 2H, C*H*$_a$H$_b$-CH-C*H*$_a$H$_b$), 1.80-1.67 (m, 2H, CH$_a$*H*$_b$-CH-CH$_a$*H*$_b$), 1.67-1.31 (m, 6H, CH$_a$H$_b$-C*H*$_2$-C*H*$_2$-C*H*$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 167.3 (q, *J* = 41.8 Hz, C=O), 114.7 (q, *J* = 288.4 Hz, $CF_3$), 108.6 (*C*≡C), 76.1 (C≡*C*), 31.0 (*C*H$_2$-CH-*C*H$_2$), 29.5 (CH), 25.4 (*C*H$_2$-CH$_2$-CH-CH$_2$-*C*H$_2$), 24.4 (CH-CH$_2$-CH$_2$-*C*H$_2$). IR (ATR): 3100,

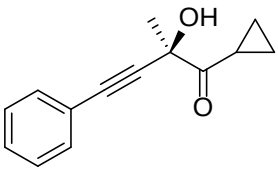
[9] Linderman R. J.; Lonikar, M. S. *J. Org. Chem.* **1988**, *53*, 6013.

[10] a) Aristov, S.A.; Vasil'ev, A. V.; Fukin, G. K.; Rudenko, A.P.; *Russ. J. Org. Chem.*, **2007**, *43*, 691; b) Maraval, V.; Leroyer, L.; Harano, A.;Barthes, C.; Saquet, Al.; Duhayon, C.; Shinmyozu, T.; Chauvin, R. *Chem. Eur. J.,* **2011**, *17*, 5086.

1645 $cm^{-1}$. MS (EI) m/z (%): 204 ($M^+$, 40), 107 (25), 83 (100) $cm^{-1}$. HRMS: Calculated for $[C_8H_7OS]^+$: 205.0845 ($M^+$); found: 205.0840.

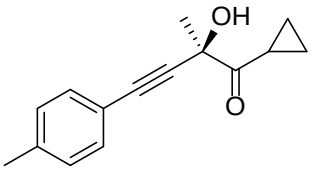
## 2.3. Synthesis of propargylic alcohols 6a-u

*General procedure*: An ordinary vial was charged with pre-catalyst **3m** (0.06 mmol, 20 mol%) and $K_2CO_3$ (0.12 mmol, 40 mol%), equipped with a magnetic stirring bar and put under an argon atmosphere. A mixture of benzene/toluene (3:1, 1 mL) was added and the mixture was stirred for 10 min at room temperature. The vial was the placed at -15 ºC and stirred for further 10 min prior to the addition of the aldehyde **1** (0.30 mmol) and ynone **5** (0.60 mmol). The stirring was maintained at this temperature until the reaction was complete. Solvents were evaporated and the crude was charged onto silica gel and subjected to FC. Racemic standards for HPLC separation conditions were prepared using pre-catalyst **3a** (0.06 mmol, 10 mol%) and running the reaction at room temperature.

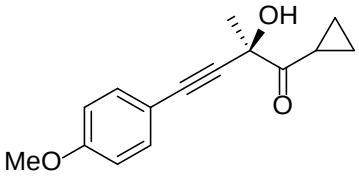



**(*R*)-1-cyclopropyl-2-hydroxy-2-methyl-4-phenylbut-3-yn-1-one (6a).** Following the general procedure **6a** (51 mg, 0.24 mmol) was isolated after 16h by FC (*n*-hexane/$Et_2O$ 8:2) in 79% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5a** (92 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.50–7.39 (m, 2H, $C_{arom.}$-H), 7.36–7.27 (m, 3H, $C_{arom.}$-H), 4.29 (s, 1H, OH), 2.61–2.34 (m, 1H, CO-CH), 1.78 (s, 3H, $CH_3$), 1.35–1.24 (m, 1H, ($CH_aH_b$), 1.18–1.08 (m, 3H, ($CH_aH_b$-$CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.4 (C=O), 131.8 ($C_{arom.}$-H), 128.7 ($C_{arom.}$-H), 128.3 ($C_{arom.}$-H), 122.1 ($C_{arom.}$), 88.2 (*C*≡C), 85.5 (C≡*C*), 73.0 (C-OH), 27.6 ($CH_3$), 16.0 (CH), 13.2 ($CH_2$), 12.4 ($CH_2$). IR: 3450, 1699 $cm^{-1}$. MS (EI) m/z (%): 213 ($M^+$ - H, 7), 171 (14), 145 (100), 129 (25), 115 (9), 102 (11), 69 (26), 43 (64). HRMS: Calculated for $[C_{14}H_{15}O_2]^+$: 215.1072 [$(M+H)^+$];

found: 215.1090. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 11.48 min, $\tau_{minor}$ = 10.31 min (91% ee). $[\alpha]_D^{rt}$: -182.5 (*c* = 0.9, $CH_2Cl_2$).

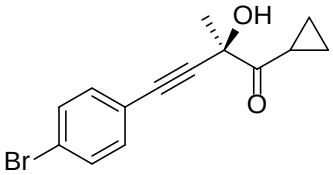



**(*R*)-1-cyclopropyl-2-hydroxy-2-methyl-4-(p-tolyl)but-3-yn-1-one (6b).** Following the general procedure **6b** (38 mg, 0.16 mmol) was isolated after 72h by FC (*n*-hexane/$Et_2O$ gradient from 9:1 to 8:2) in 55% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5b** (95 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.34 (d, *J* = 8.1 Hz, 2H, $C_{arom.}$-H), 7.12 (d, *J* = 7.9 Hz, 2H, $C_{arom.}$-H), 4,28 (s, 1H, OH), 2.53-2.40 (m, 1H, CH), 2.35 (s, 3H, $C_{arom.}$-$CH_3$), 1.78 (s, 3H, HO-C-$CH_3$), 1.33-1.23 (m, 1H, C$H_a$H$_b$), 1.17-1.08 (m, 3H, CH$_a$$H_b$-C$H_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.6 (C=O), 138.9 (Me-$C_{arom.}$), 131.7 ($C_{arom.}$-H), 129.1 ($C_{arom.}$-H), 119.1 ($C_{arom.}$), 87.6 (*C*≡C), 85.8 (C≡*C*), 73.0 (C-OH), 27.7 (OH-C-*C*H$_3$), 21.5 ($C_{arom.}$-*C*H$_3$), 16.0 (CO-*C*H), 13.2 ($CH_2$), 12.4 ($CH_2$). IR (ATR): 3451, 1702 cm$^{-1}$. MS (EI) m/z (%): 228 ($M^+$, 3), 213 (7), 185 (15), 159 (100), 143 (24), 115 (32), 91 (6), 69 (20), 43 (72). HRMS: Calculated for $[C_{15}H_{17}O_2]^+$: 229.1229 [$(M+H)^+$]; found: 229.1238. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 9.64 min, $\tau_{minor}$ = 9.02 min (94% ee). $[\alpha]_D^{rt}$: -168.0 (*c* = 1.0, $CH_2Cl_2$).



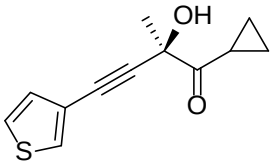

**(*R*)-1-cyclopropyl-2-hydroxy-4-(4-methoxyphenyl)-2-methylbut-3-yn-1-one (6c).** Following the general procedure **6c** (39 mg, 0.16 mmol) was isolated after 72h by FC (*n*-hexane/$Et_2O$ gradient from 9:1 to 8:2) in 53% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5c** (104 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol)

and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.38 (d, *J* = 8.9 Hz, 2H, $C_{arom.}$-H), 6.84 (d, *J* = 8.9 Hz, 2H, $C_{arom.}$-H), 4.27 (s, 1H, OH), 3.81 (s, 3H, O-$CH_3$), 2.60-2.30 (m, 1H, CO-CH), 1.77 (s, 3H, C-$CH_3$), 1.34-1.23 (m, 1H, CO-CH(C$H_a$H$_b$)), 1.19-1.06 (m, 3H, CH$_a$$H_b$-C$H_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.6 (C=O), 159.9 (MeO-$C_{arom.}$), 133.3 ($C_{arom.}$-H), 114.2 ($C_{arom.}$), 114.0 ($C_{arom.}$-H), 86.9 (*C*≡C), 85.6 (C≡*C*), 73.0 (C-OH), 55.3 ($C_{arom.}$-*C*H$_3$), 27.7 (OH-C-*C*H$_3$), 16.0 (CO-*C*H), 13.2 ($CH_2$), 12.4 ($CH_2$). IR (ATR): 3451, 1702 cm$^{-1}$. MS (EI) m/z (%): 244 ($M^+$, 4), 201 (5), 175 (100), 159 (9), 133 (8), 43 (29). HRMS: Calculated for $[C_{15}H_{17}O_3]^+$: 245.1178 [$(M+H)^+$]; found: 245.1189. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 18.96 min, $\tau_{minor}$ = 13.11 min (93% ee). $[\alpha]_D^{rt}$: -124.3 (*c* = 0.9, $CH_2Cl_2$).

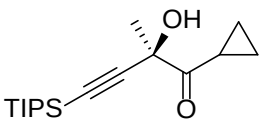



**(*R*)-1-cyclopropyl-2-hydroxy-4-(4-bromophenyl)-2-methylbut-3-yn-1-one (6d).** Following the general procedure **6d** (36 mg, 0.12 mmol) was isolated after 88h by FC (*n*-hexane/$Et_2O$ gradient from 9:1 to 8:2) in 41% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5d** (134 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.45 (d, *J* = 8.5 Hz, 2H, $C_{arom.}$-H), 7.30 (d, *J* = 8.5 Hz, 2H, $C_{arom.}$-H), 4.30 (s, 1H, OH), 2.52-2.34 (m, 1H, CH), 1.77 (s, 3H, $CH_3$), 1.34-1.24 (m, 1H, C$H_a$H$_b$), 1.18-1.06 (m, 3H, CH$_a$$H_b$-C$H_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.2 (C=O), 133.2 ($C_{arom.}$-H), 131.6 ($C_{arom.}$-H), 123.1 ($C_{arom.}$), 121.1 ($C_{arom.}$), 89.4 (*C*≡C), 84.5 (C≡*C*), 73.0 (C-OH), 27.6 (OH-C-$CH_3$), 16.0 (CO-*C*H), 13.3 ($CH_2$), 12.5 ($CH_2$). IR (ATR): 3468, 2166, 1695 cm$^{-1}$. MS (EI) m/z (%): 294 and 292 ($M^+$, 1 and 1), 251 (5), 223 (100), 209 (9), 69 (40), 43 (52). HRMS: Calculated for $[C_{14}H_{14}O_2]^+$: 293.0177 [$(M+H)^+$]; found: 293.0168. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow

rate 1.0 mL/min; $\tau_{major}$ = 9.39 min, $\tau_{minor}$ = 8.77 min (91% ee). $[\alpha]_D^{rt}$: -152.5 (*c* = 1.0, $CH_2Cl_2$).

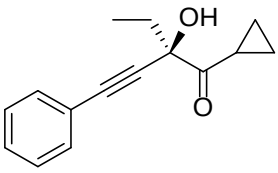



**(*R*)-1-cyclopropyl-2-hydroxy-2-methyl-4-(thiophen-3-yl)but-3-yn-1-one (6e).** Following the general procedure **6e** (39 mg, 0.18 mmol) was isolated after 48h by FC (*n*-hexane/$Et_2O$ gradient from 9:1 to 8:2) in 59% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5e** (90 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.47 (dd, *J* = 3.0, 1.1 Hz, 1H, S-$C_{arom.}$-*H*-$C_{arom.}$), 7.26 (dd, *J* = 4.9, 3.1 Hz, 1H, S-$C_{arom.}$-*H*-$C_{arom.}$-H), 7.11 (dd, *J* = 5.0, 1.1 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*.) 4.28 (s, 1H, OH), 2.50-2.38 (m, 1H, CH), 1.77 (s, 3H, $CH_3$), 1.34-1.23 (m, 1H, $CH_aH_b$), 1.19-1.06 (m, 3H, $CH_aH_b$-$CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.4 (C=O), 129.9 (S-$C_{arom.}$-H), 129.6 (S-$C_{arom.}$-H), 125.4 (S-$C_{arom.}$-H-$C_{arom.}$), 121.2 ($C_{arom.}$), 87.9 (*C*≡C), 80.8 (C≡*C*), 73.0 (C-OH), 27.7 (OH-C-$CH_3$), 16.0 (CO-*C*H), 13.3 ($CH_2$), 12.5 ($CH_2$). IR (ATR): 3443, 1702 $cm^{-1}$. MS (EI) m/z (%): 220 ($M^+$, 4), 192 (6), 177 (9), 151 (100), 135 (21), 109 (10), 69 (28), 43 (59). HRMS: Calculated for $[C_{12}H_{13}O_2S]^+$: 221.0636 $[(M+H)^+]$; found: 221.0645. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 16.49 min, $\tau_{minor}$ = 14.82 min (93% ee). $[\alpha]_D^{rt}$: -166.6 (*c* = 1.0, $CH_2Cl_2$).

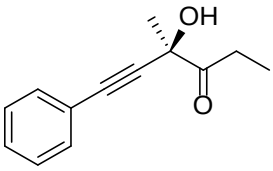



**(*R*)-1-cyclopropyl-2-hydroxy-2-methyl-4-(triisopropylsilyl)but-3-yn-1-one (6f).** Following the general procedure **6f** (41 mg, 0.14 mmol) was isolated by FC (*n*-hexane/$Et_2O$ gradient from 19:1 to 9:1) in 46% yield starting from aldehyde **1d** (23 µL, 0.30 mmol) and ynone **5f** (135 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1,

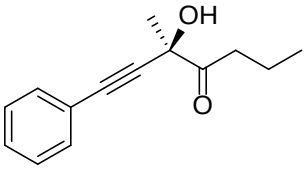
1 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 4.13 (bs, 1H), 2.51 – 2.22 (m, 1H, CO-CH), 1.70 (s, 3H, C-$CH_3$), 1.29 – 0.90 (m, 25H, $CH_2CH_2$ + (C*H*($CH_3$)$_2$)$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.4 (C=O), 106.6 (*C*≡C), 87.1 (C≡*C*), 73.0 (C-OH), 27.7 (OH-C-$CH_3$), 18.5 (Si-CH), 16.0 (CO-*C*H), 13.0 ($CH_2$), 12.7 ($CH_2$), 11.1 (Si-CH-(*C*$H_3$)$_2$). IR: 3454, 1706 cm$^{-1}$. MS (EI) m/z (%): 279 ($M^+$, $M^+$- $CH_3$, 10), 251 (100), 225 (46), 209 (7), 181 (7), 157 (35), 127 (40), 91 (25), 87 (20), 75 (65), 61 (30). HRMS: Calculated for [$C_{17}H_{31}O_2Si$]$^+$: 295.2100 [(M+H)$^+$]; found: 295.2093. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99.5:0.05)]; flow rate 0.5 mL/min; $\tau_{major}$ = 12.64 min, $\tau_{minor}$ = 16.44 min (78% ee). $[\alpha]_D^{rt}$: -109.8 (*c* = 1.0, $CH_2Cl_2$).




**(*R*)-1-cyclopropyl-2-ethyl-2-hydroxy-4-phenylbut-3-yn-1-one (6g).** Following the general procedure **6g** (18 mg, 0.08 mmol) was isolated after 72h by FC (*n*-hexane/$Et_2O$ 8:2) in 40% yield starting from aldehyde **1d** (15 µL, 0.20 mmol) and ynone **5g** (63 mg, 0.40 mmol) in the presence of **3m** (15 mg, 0.04 mmol) and $K_2CO_3$ (11 mg, 0.08 mmol) and using benzene/toluene mixture (3:1, 0.7 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.52–7.40 (m, 2H, $C_{arom.}$-H), 7.37–7.27 (m, 3H, $C_{arom.}$-H), 4.22 (s, 1H, OH), 2.47 (tt, *J* = 7.4, 5.4, 1H, CO-CH), 2.21 (dq, *J* = 14.9, 7.5 Hz, 1H, $CH_3$-C$H_a$H$_b$), 1.99 (dq, *J* = 14.3, 7.3 Hz, 1H, $CH_3$-C$H_a$*H$_b$*), 1.34–1.24 (m, 1H, HC-C*H$_a$*H$_b$), 1.18–1.09 (m, 3H, C$H_a$*H$_b$*-C$H_2$), 1.04 (t, *J* = 7.4 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.4 (C=O), 131.8 ($C_{arom.}$-H), 128.7 ($C_{arom.}$-H), 128.3 ($C_{arom.}$-H), 122.3 ($C_{arom.}$-H), 87.7 (*C*≡C), 86.1 (C≡*C*), 76.6 (C-OH), 33.5 (*C*$H_2$-$CH_3$), 16.3 (CH), 13.1 (HC-*C*$H_2$), 12.4 (HC-*C*$H_2$), 7.9 ($CH_3$). IR (ATR): 3447, 1702 cm$^{-1}$. MS (EI) m/z (%): 228 ($M^+$, 1), 227 ($M^+$-H, 3), 199 (5), 171 (7), 159 (100), 129 (26), 115 (17), 102 (9), 91 (12), 77 (9), 69 (20), 57 (27). HRMS: Calculated for [$C_{15}H_{17}O_2$]$^+$: 229.1225 [(M+H)$^+$]; found: 229.1229. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{major}$ = 11.42 min, $\tau_{minor}$ = 12.21 min (83% ee). $[\alpha]_D^{rt}$: -140.0 (*c* = 0.5, $CH_2Cl_2$).

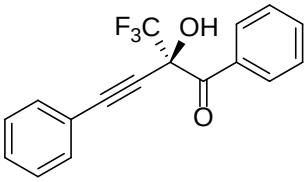


**(*R*)-4-hydroxy-4-methyl-6-phenylhex-5-yn-3-one (6h).** Following the general procedure **6h** (18 mg, 0.09 mmol) was isolated after 16h by FC (*n*-hexane/$Et_2O$ gradient from 9:1 to 8:2) in 30% yield starting from aldehyde **1b** (23 µL, 0.30 mmol) and ynone **5a** (92 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.43 (dd, *J* = 6.9, 2.0 Hz, 2H, $C_{arom.}$-H), 7.36-7-28 (m, 3H, $C_{arom.}$-H), 4.23 (s, 1H, OH), 3.03 (dq, *J* = 17.3, 7.3 Hz, 1H, C*Ha*Hb), 2.72 (dq, *J* = 17.4, 7.0 Hz, 1H, CHa*Hb*), 1.71 (s, 3H, HO-C-$CH_3$), 1.21 (t, *J* = 7.3 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm): 208.9 (C=O), 131.8 ($C_{arom.}$-H), 128.8 ($C_{arom.}$-H), 128.3 ($C_{arom.}$-H), 122.0 ($C_{arom.}$), 88.3 (*C*≡C), 85.3 (C≡*C*), 72.7 (C-OH), 29.1 (CO-$CH_2CH_3$), 27.3 (HO-C-$CH_3$), 8.3 (CO-$CH_2CH_3$). IR (ATR): 3451, 2230, 1720 $cm^{-1}$. MS (EI) m/z (%): 201 ($M^+$-H, 3), 173 (6), 159 (27), 145 (100), 129 (25), 115 (11), 102 (19), 91 (14), 77 (14), 57 (15), 43 (83), 29 (11). HRMS: Calculated for $[C_{13}H_{15}O_2]^+$: 203.1072 $[(M+H)^+]$; found: 203.1087. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 12.39 min, $\tau_{minor}$ = 10.13 min (82% ee). $[\alpha]_D^{rt}$: -164.4 (*c* = 0.7, $CH_2Cl_2$).



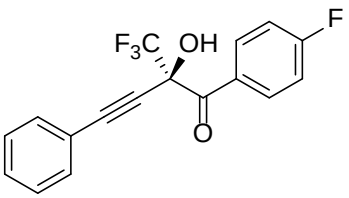
**(*R*)-3-hydroxy-3-methyl-1-phenylhept-1-yn-4-one (6i).** Following the general procedure **6i** (16 mg, 0.07 mmol) was isolated after 16h by FC (*n*-hexane/$Et_2O$ gradient from 19:1 to 8:2) in 25% yield starting from aldehyde **1e** (40 µL, 0.30 mmol) and ynone **5a** (92 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.43 (dt, *J* = 6.4, 2.7 Hz, 2H, $C_{arom.}$-H), 7.35–7.29 (m, 3H, $C_{arom.}$-H), 4.24 (s, 1H, OH), 2.96 (dt, *J* = 17.3, 7.3Hz, 1H,

CO-C*Ha*Hb), 2.66 (dt, *J* = 17.4, 7.0 Hz, 1H, CO- CHa*Hb*), 1.80–1.72 (m, 2H, CO-$CH_2CH_2CH_3$), 1.70 (s, 3H, HO-C-$CH_3$), 0.98 (t, *J* = 7.4 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 208.1 (C=O), 131.8 ($C_{arom.}$-H), 128.8 ($C_{arom.}$-H), 128.3 ($C_{arom.}$-H), 122.0 ($C_{arom.}$), 88.2 (*C*≡C), 85.4 (C≡*C*), 72.8 (C-OH), 37.5 (CO-*C*$H_2CH_2CH_3$), 27.1 (HO-C-*C*$H_3$), 17.6 (CO-$CH_2$*C*$H_2CH_3$), 13.6 (CO-$CH_2CH_2$*C*$H_3$). IR (ATR): 3447, 2205, 1720 $cm^{-1}$. MS (EI) m/z (%): 215 ($M^+$-H, 2), 173 (16), 145 (100), 129 (16), 115 (7), 102 (11), 77 (9), 43 (59). HRMS: Calculated for $[C_{14}H_{17}O_2]^+$: 217.1229 [$(M+H)^+$]; found: 217.1241. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 11.56 min, $\tau_{minor}$ = 9.33 min (75% ee). $[\alpha]_D^{rt}$: -97.4 (*c* = 0.9, $CH_2Cl_2$).

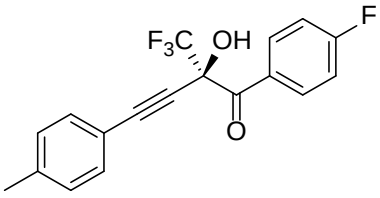



**(*R*)-2-hydroxy-1,4-diphenyl-2-(trifluoromethyl)but-3-yn-1-one (6j).** Following the general procedure with **6j** (54 mg, 0.18 mmol) was isolated after 16h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 59% yield starting from aldehyde **1a** (32 µL, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.9 Hz, 2H, CO-$C_{arom.}$-$C_{arom.}$-H), 7.69 (t, *J* = 7.4 Hz, 1H, CO-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-*H*), 7.57-7.46 (m, 4H), 7.45-7.30 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 5.36 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (C=O), 135.2 ($C_{arom.}$-H), 132.0 ($C_{arom.}$-H), 131.8 ($C_{arom.}$), 131.5 (q, *J* = 0.8 Hz, $C_{arom.}$-H), 129.9 ($C_{arom.}$-H), 128.6 ($C_{arom.}$-H), 128.5 ($C_{arom.}$-H), 122.0 (q, *J* = 286.6 Hz, $CF_3$), 120.6 ($C_{arom.}$), 90.2 (*C*≡C), 81.6 (C≡*C*), 74.4 (q, *J* = 33.2 Hz, $CF_3$-*C*). IR (ATR): 3401, 1687, 1264, 1221, 1185, 1114 $cm^{-1}$. MS (EI) m/z (%): 304 ($M^+$, 2), 288 (2), 129 (32), 105 (100), 77 (38), 51 (9). HRMS: Calculated for $[C_{17}H_{12}O_2F_3]^+$: 305.0789 [$(M+H)^+$]; found: 305.0775. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow

rate 1.0 mL/min; $\tau_{major}$ = 9.78 min, $\tau_{minor}$ = 11.20 min (99% ee). $[\alpha]_D^{rt}$: +55.8 (*c* = 0.8, $CH_2Cl_2$).

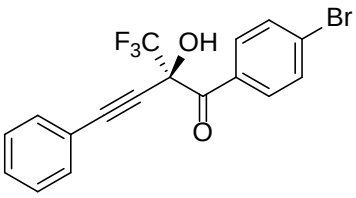



**(*R*)-1-(4-fluorophenyl)-2-hydroxy-4-phenyl-2-(trifluoromethyl)but-3-yn-1-one (6k).** Following the general procedure **6k** (69 mg, 0.21 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 71% yield starting from aldehyde **1f** (32 µL, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 8.9, 5.4 Hz, 2H, CO-$C_{arom.}$-$C_{arom.}$-H), 7.54-7.46 (m, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.44-7.30 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 7.24-7.14 (m, 2H, F-$C_{arom.}$-$C_{arom.}$-H), 5.32 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.3 (C=O), 166.9 (d, *J* = 259.7 Hz, F-$C_{arom.}$), 134.5 (d, *J* = 9.9 Hz, CO-$C_{arom.}$-*C*$_{arom.}$-H), 131.9 (C≡C-$C_{arom.}$-*C*$_{arom.}$-H), 129.9 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.6 (C≡C-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.1 (d, *J* = 2.9 Hz, CO-$C_{arom.}$), 120.4 (C≡C-*C*$_{arom.}$), 121.9 (q, *J* = 286.7 Hz, HO-C-*C*$F_3$), 115.9 (d, *J* = 22.1 Hz, F-$C_{arom.}$-*C*$_{arom.}$-H), 90.5 (*C*≡C), 81.4 (C≡*C*), 74.4 (q, *J* = 33.2 Hz, *C*-$CF_3$). IR (ATR): 3404, 1688, 1598, 1221, 1189, 1160, 1114 $cm^{-1}$. MS (EI) m/z (%): 322 ($M^+$, 5), 306 (2), 123 (100), 95 (26), 75 (8), 51 (2). HRMS: Calculated for $[C_{17}H_{11}O_2F_4]^+$: 323.0695 [$(M+H)^+$]; found: 323.0688. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 9.18 min, $\tau_{minor}$ = 10.53 min (>99% ee). $[\alpha]_D^{rt}$: +40.4 (*c* = 1.0, $CH_2Cl_2$).



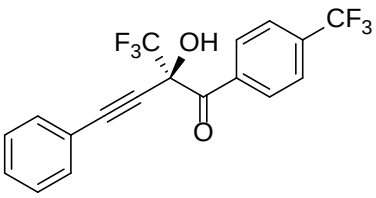

**(*R*)-1-(4-fluorophenyl)-2-hydroxy-4-p-tolyl-2-(trifluoromethyl)but-3-yn-1-one (6l).** Following

the general procedure **6l** (94 mg, 0.28 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 93% yield starting from aldehyde **1f** (32 µL, 0.30 mmol) and ynone **5i** (127 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 8.8, 5.4 Hz, 2H, CO-$C_{arom.}$-$C_{arom.}$-H), 7.39 (d, *J* = 8.1 Hz, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.24-7.12 (m, 4H, $C_{arom.}$-H), 5.34 (s, 1H, OH), 2.37 (s, 3H, Me). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 188.4 (C=O), 166.9 (d, *J* = 259.6 Hz, F-$C_{arom.}$), 140.4 (Me-$C_{arom.}$), 134.5 (d, *J* = 9.1 Hz, CO-$C_{arom.}$-*C*$_{arom.}$-H), 131.9 (C≡C-$C_{arom.}$-*C*$_{arom.}$-H), 129.3 (C≡C-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.1 (d, *J* = 2.9 Hz, CO-*C*$_{arom.}$), 121.9 (q, *J* = 286.7 Hz, HO-C-*C*$F_3$), 117.3 (C≡C-*C*$_{arom.}$), 115.9 (d, *J* = 22.0 Hz, F-$C_{arom.}$-*C*$_{arom.}$-H), 90.8 (*C*≡C), 80.8 (C≡*C*), 74.4 (q, *J* = 33.1 Hz, *C*-$CF_3$). IR (ATR): 3408, 1687, 1598, 1508, 1221, 1189, 1164, 1117 cm$^{-1}$. MS (EI) m/z (%): 336 ($M^+$, 6), 143 (21), 123 (100), 95 (24), 75 (5). HRMS: Calculated for $[C_{18}H_{13}O_2F_4]^+$: 337.0852 [$(M+H)^+$]; found: 337.0835. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99.5:0.5)]; flow rate 0.5 mL/min; $\tau_{major}$ = 32.26 min, $\tau_{minor}$ = 35.47 min (98% ee). $[\alpha]_D^{rt}$: +25.0 (*c* = 1.0, $CH_2Cl_2$).

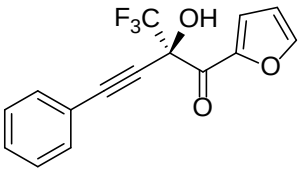



**(*R*)-1-(4-bromophenyl)-2-hydroxy-4-phenyl-2-(trifluoromethyl)but-3-yn-1-one (6m).** Following the general procedure **6m** (85 mg, 0.22 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 74% yield starting from aldehyde **1g** (56 mg, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (6:4, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.6 Hz, 2H, CO-$C_{arom.}$-$C_{arom.}$-H), 7.72-7.64 (m, 2H, Br-$C_{arom.}$-$C_{arom.}$-H), 7.49 (dd, *J* = 8.0, 1.6 Hz, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.46-7.31 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*) 5.25 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.1 (C=O), 132.7 ($C_{arom.}$-H), 132.0 ($C_{arom.}$), 132.0 ($C_{arom.}$), 131.1 (CO-*C*$_{arom.}$), 130.4

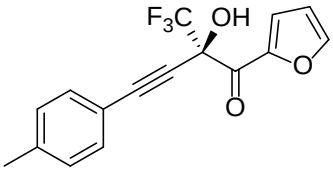
(C≡C-$C_{arom.}$), 130.0 ($C_{arom.}$-H), 121.8 (q, *J* = 286.7 Hz, $CF_3$), 120.0 ($C_{arom.}$), 90.6 (*C*≡C), 81.2 (C≡*C*), 74.4 (q, *J* = 33.2 Hz, *C*-$CF_3$). IR (ATR): 3412, 1687, 1580, 1260, 1221, 1181, 1117 $cm^{-1}$. MS (EI) m/z (%): 384 ($M^+$, 2), 382 ($M^+$, 2), 368 (7), 183 (100), 157 (27), 155 (25), 129 (35), 105 (8), 75 (14), 51 (5). HRMS: Calculated for $[C_{17}H_{11}O_2F_3Br]^+$: 382.9895 [$(M+H)^+$]; found: 382.9879. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 10.45 min, $\tau_{minor}$ = 12.88 min (99% ee). $[\alpha]_D^{rt}$: 55.8 (*c* = 1.0, $CH_2Cl_2$).




**(*R*)-2-hydroxy-4-phenyl-2-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)but-3-yn-1-one (6n).** Following the general procedure **6n** (77 mg, 0.21 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 69% yield starting from aldehyde **1h** (41 µL, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 8.4 Hz, 2H, $CF_3$-$C_{arom.}$-$C_{arom.}$-H), 7.79 (d, *J* = 8.4 Hz, 2H, CO-$C_{arom.}$-$C_{arom.}$-H), 7.53-7.48 (m, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.47-7.32 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 5.16 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.5 (C=O), 136.0 (q, *J* = 33.2 Hz, $CF_3$-$C_{arom.}$), 134.8 (CO-$C_{arom.}$), 131.9 (C≡C-$C_{arom.}$-$C_{arom.}$-H), 131.6 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 130.2 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 128.6 (CO-$C_{arom.}$-$C_{arom.}$-H), 125.6 (q, *J* = 3.7 Hz, $CF_3$-$C_{arom.}$-$C_{arom.}$-H), 123.2 (q, *J* = 273.0 Hz, $CF_3$-$C_{arom.}$), 121.8 (q, *J* = 286.7 Hz, HO-C-$CF_3$), 91.0 (*C*≡C), 80.8 (C≡*C*), 74.8 (q, *J* = 33.3 Hz, *C*-$CF_3$). IR (ATR): 3418, 1699, 1325, 1221, 1171, 1117, 1066 $cm^{-1}$. MS (EI) m/z (%): 372 ($M^+$, 1), 275 (1), 173 (100), 145 (39), 129 (33), 95 (4), 75 (8), 51 (3). HRMS: Calculated for $[C_{18}H_{11}O_2F_6]^+$: 373.0663 [$(M+H)^+$]; found: 373.0664. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 11.05 min, $\tau_{minor}$ = 14.02 min (99% ee). $[\alpha]_D^{rt}$: 16.9 (*c* = 1.0, $CH_2Cl_2$).

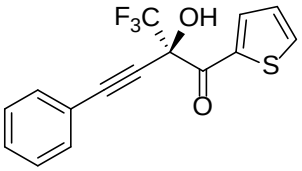


**(*R*)-1-(furan-2-yl)-2-hydroxy-4-phenyl-2-(trifluoromethyl)but-3-yn-1-one (6o).** Following the general procedure with **6o** (76 mg, 0.26 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 8:2) in 86% yield starting from aldehyde **1i** (25 µL, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.8 Hz, 1H, O-$C_{arom.}$-$C_{arom.}$-H), 7.82 (dd, *J* = 1.6, 0.6 Hz, 1H, O-$C_{arom.}$-H), 7.51-7.46 (m, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.44-7.30 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 6.67 (dd, *J* = 3.8, 1.7 Hz, 1H, O-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.36 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 177.1 (C=O), 150.0 (O-$C_{arom.}$-H), 147.6 (O-$C_{arom.}$), 140.3 (Me-*C*$_{arom.}$), 132.0 (C≡C-$C_{arom.}$-*C*$_{arom.}$-H), 129.9 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.5 (C≡C-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 126.0 (q, *J* = 1.7 Hz, O-$C_{arom.}$-*C*$_{arom.}$-H), 121.8 (q, *J* = 286.8 Hz, $CF_3$), 120.5 (C≡C-*C*$_{arom.}$), 113.2 (O-$C_{arom.}$-H-$C_{arom.}$-H), 89.2 (*C*≡C), 81.5 (C≡*C*), 73.8 (q, *J* = 33.5 Hz, C-$CF_3$). IR (ATR): 3397, 1674, 1462, 1235, 1193, 1128 cm$^{-1}$. MS (EI) m/z (%): 294 ($M^+$, 2), 278 (2), 266 (12), 129 (30), 95 (100), 75 (4), 51 (3). HRMS: Calculated for $[C_{15}H_{10}O_3F_3]^+$: 295.0576 [$(M+H)^+$]; found: 295.0582. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 13.86 min, $\tau_{minor}$ = 15.68 min (87% ee). $[\alpha]_D^{rt}$: +6.1 (*c* = 1.0, $CH_2Cl_2$).



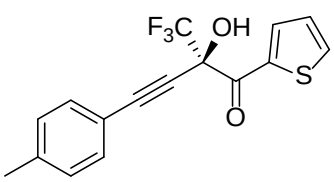
**(*R*)-1-(furan-2-yl)-2-hydroxy-4-*p*-tolyl-2-(trifluoromethyl)but-2-yn-1-one (6p).** Following the general procedure **6p** (89 mg, 0.29 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in 96% yield starting from aldehyde **1i** (25 µL, 0.30 mmol) and ynone **5i** (127 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12

mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 3.7 Hz, 1H, O-$C_{arom.}$-$C_{arom.}$-H), 7.81 (dd, *J* = 1.6, 0.6 Hz, 1H, O-$C_{arom.}$-H), 7.38 (d, *J* = 7.9 Hz, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.16 (d, *J* = 8.3 Hz, 2H, Me-$C_{arom.}$-$C_{arom.}$-H), 6.66 (dd, *J* = 3.8, 1.7 Hz, 1H, O-$C_{arom.}$-H-$C_{arom.}$-H), 5.24 (s, 1H, OH), 2.37 (s, 3H, Me). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 177.2 (C=O), 149.9 (O-$C_{arom.}$-H), 147.6 (O-$C_{arom.}$), 140.3 (Me-*C*$_{arom.}$), 131.9 (C≡C-$C_{arom.}$-*C*$_{arom.}$-H), 129.3 (Me-$C_{arom.}$-*C*$_{arom.}$-H), 125.9 (q, *J* = 1.9 Hz, O-$C_{arom.}$-*C*$_{arom.}$-H), 121.8 (q, *J* = 286.8 Hz, $CF_3$), 117.4 (C≡C-*C*$_{arom.}$), 113.2 (O-$C_{arom.}$-H-$C_{arom.}$-H), 89.4 (*C*≡C), 80.9 (C≡*C*), 73.8 (q, *J* = 33.5 Hz, C-$CF_3$) 21.6 ($CH_3$). IR (ATR): 3401, 1670, 1458, 1235, 1189, 1124, 1031 cm$^{-1}$. MS (EI) m/z (%): 308 ($M^+$, 5), 293 (9), 280 (20), 213 (16), 197 (13), 143 (76), 115 (13), 95 (100). HRMS: Calculated for $[C_{16}H_{12}O_3F_3]^+$: 309.1739 [$(M+H)^+$]; found: 309.0729. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 12.31 min, $\tau_{minor}$ = 11.47 min (84% ee). $[\alpha]_D^{rt}$: +28.0 (*c* = 1.0, $CH_2Cl_2$).

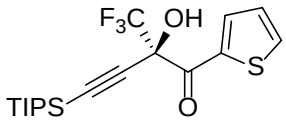



**(*R*)-2-hydroxy-4-phenyl-1-(thiophen-2-yl)-2-(trifluoromethyl)but-3-yn-1-one (6q).** Following the general procedure **6q** (92 mg, 0.30 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 8:2) in 99% yield starting from aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5h** (119 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.44 (d, *J* = 3.0, 1.0 Hz, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.89 (dd, *J* = 4.9, 1.0 Hz, 1H, S-$C_{arom.}$-H), 7.55-7.48 (m, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.45-7.32 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 7.25 (m, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.26 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 182.3 (C=O), 138.3 (q, *J* = 2.2 Hz, S-$C_{arom.}$-*C*$_{arom.}$-H ), 138.2 (S-$C_{arom.}$-H), 137.0 (S-*C*$_{arom.}$-CO), 132.0 (C≡C-$C_{arom.}$-*C*$_{arom.}$-H), 129.9 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.9 (S-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.5 (C≡C-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 121.9 (q, *J* = 286.9 Hz, $CF_3$), 120.5 (C≡C-*C*$_{arom.}$), 89.7 (*C*≡C), 81.8 (C≡*C*), 74.3 (q, *J* = 33.4 Hz, *C*-$CF_3$). IR (ATR):

3404, 1656, 1412, 1354, 1228, 1189, 1120 $cm^{-1}$. MS (EI) m/z (%): 310 ($M^+$, 2), 294 (1), 129 (24), 111 (100), 83 (6), 75 (4), 51 (2). HRMS: Calculated for $[C_{15}H_{10}O_2F_3S]^+$: 311.0354 $[(M+H)^+]$; found: 311.0360. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 13.04 min, $\tau_{minor}$ = 14.85 min (97% ee). $[\alpha]_D^{rt}$: +46.1 (*c* = 1.0, $CH_2Cl_2$).

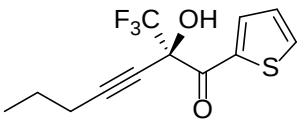



**(*R*)-2-hydroxy-1-(thiophen-2-yl)-4-p-tolyl-2-(trifluoromethyl)but-3-yn-1-one (6r).** Following the general procedure **6r** (98 mg, 0.30 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 19:1 to 9:1) in >99% yield starting from aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5i** (127 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 3.8 Hz, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.87 (dd, *J* = 4.9, 0.7 Hz, 1H, S-$C_{arom.}$-H), 7.40 (d, *J* = 8.1 Hz, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H), 7.22 (m, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 7.16 (d, *J* = 8.0 Hz, 2H, Me-$C_{arom.}$-$C_{arom.}$-H ), 5.27 (s, 1H, OH), 2.37 (s, 3H, Me). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 182.4 (C=O), 140.4 (CO-$C_{arom.}$), 138.3 (q, *J* = 2.0 Hz, S-$C_{arom.}$-$C_{arom.}$-H), 138.2 (S-$C_{arom.}$-H), 137.1 (Me-$C_{arom.}$), 131.9 (C≡C-$C_{arom.}$-$C_{arom.}$-H), 129.3 (Me-$C_{arom.}$-$C_{arom.}$-H), 128.8 (S-$C_{arom.}$-H-$C_{arom.}$-H), 121.9 (q, *J* = 287.0 Hz, $CF_3$), 117.4 (C≡C-$C_{arom.}$), 90.0 (*C*≡C), 81.2 (C≡*C*), 74.4 (q, *J* = 33.3 Hz, *C*-$CF_3$) 21.6 ($CH_3$). IR (ATR): 3386, 1656, 1508, 1412, 1354, 1228, 1185, 1117 $cm^{-1}$. MS (EI) m/z (%): 324 ($M^+$, 34), 308 (15), 212 (9), 197 (33), 143 (54), 111 (100), 91 (13), 65 (7), 51 (2). HRMS: Calculated for $[C_{16}H_{12}O_2F_3S]^+$: 325.0510 $[(M+H)^+]$; found: 325.0501. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99.5:0.5)]; flow rate 0.5 mL/min; $\tau_{major}$ = 53.72 min, $\tau_{minor}$ = 50.70 min (95% ee). $[\alpha]_D^{rt}$: +34.3 (*c* = 1.0, $CH_2Cl_2$).



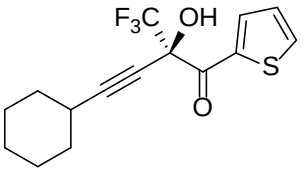

**(*R*)-2-hydroxy-1-(thiophen-2-yl)-4-p-tolyl-2-(trifluoromethyl)but-3-yn-1-one (6s).** Following the

general procedure **6s** (97 mg, 0.25 mmol) was isolated after 48h by FC (*n*-hexane/EtOAc gradient from 49:1 to 9:1) in 83% yield starting from aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5j** (127 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.54-8.38 (m, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.87 (dd, *J* = 4.9, 1.0 Hz, 1H, S-$C_{arom.}$-H), 7.19 (dd, *J* = 4.9, 4.1 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.12 (s, 1H, OH), 1.14-1.00 (m, 21H, (C*H*($CH_3$)$_2$)$_3$)). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 182.2 (C=O), 138.6 (q, *J* = 2.4 Hz, S-$C_{arom.}$-*C*$_{arom.}$-H), 138.2 (S-$C_{arom.}$H), 137.0 (S-*C*$_{arom.}$-CO), 128.5 (S-$C_{arom.}$-H-*C*$_{arom.}$-H), 121.8 (q, *J* = 286.8 Hz, $CF_3$), 99.2 (C≡*C*), 93.9 (*C*≡C), 74.1 (q, *J* = 33.2 Hz, *C*-$CF_3$), 18.4 ($CH_3$), 11.0 (CH). IR (ATR): 3404, 2945, 2869, 1656, 1466, 1412, 1246, 1196, 1135, 1056 cm$^{-1}$. MS (EI) m/z (%): 347 ($M^+$, 21), 185 (3), 157 (2), 129 (2), 77 (6), 111 (100). HRMS: Calculated for $[C_{18}H_{26}O_2F_3SSi]^+$: 391.1375 [$(M+H)^+$]; found: 391.1362. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99.5:0.5)]; flow rate 0.5 mL/min; $\tau_{major}$ = 12.7 min, $\tau_{minor}$ = 13.9 min (89% ee). $[\alpha]_D^{rt}$: +41.1 (*c* = 1.0, $CH_2Cl_2$).




**(*R*)-2-hydroxy-1-(thiophen-2-yl)-2-(trifluoromethyl)hept-3-yn-1-one (6t).** Following the general procedure **6t** (42 mg, 0.15 mmol) was isolated after 24h by FC (*n*-hexane/EtOAc gradient from 49:1 to 9:1) in 51% yield starting from aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5k** (98 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 8.42-8.30 (m, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.86 (dd, *J* = 5.0, 1.1 Hz, 1H, S-$C_{arom.}$-H), 7.21 (dd, *J* = 4.9, 4.0 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.10 (s, 1H, OH), 2.30 (t, *J* = 7.0 Hz, 2H, C≡C-$CH_2$), 1.85-1.37 (m, 2H, C*H*$_2$-$CH_3$), 0.99 (t, *J* = 7.4 Hz, 2H, $CH_3$) $^{13}$C NMR (75 MHz, $CDCl_3$) δ 182.8 (C=O), 138.3 (q, *J* = 2.1 Hz, S-$C_{arom.}$-*C*$_{arom.}$-H), 137.9 (S-$C_{arom.}$-H), 137.1 (S-$C_{arom.}$), 128.6 (S-$C_{arom.}$-H-*C*$_{arom.}$-H), 121.9 (q, *J* = 286.6 Hz, $CF_3$), 91.6 (Pr-*C*≡C), 73.9 (q, *J* = 33.2

Hz, *C*-$CF_3$), 73.7 (C≡*C*-COH), 21.2 (*C*$H_2$-$CH_3$), 20.7 (C≡C-*C*$H_2$), 13.4 (*C*$H_3$). IR (ATR): 3401, 2970, 1656, 1408, 1354, 1250, 1193, 1164, 1060 $cm^{-1}$. MS (EI) m/z (%): 276 ($M^+$, 1), 258 (1), 248 (3), 233 (1), 207 (1), 165 (1), 111 (100), 95 (2), 83 (6), 69 (2), 57 (1). HRMS: Calculated for $[C_{12}H_{12}O_2F_3S]^+$: 277.0510 [$(M+H)^+$]; found: 277.0497. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 6.86 min, $\tau_{minor}$ = 7.60 min (98% ee). $[\alpha]_D^{rt}$: +76.9 (*c* = 1.0, $CH_2Cl_2$).

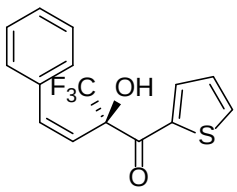



**(*R*)-4-cyclohexyl-2-hydroxy-1-(thiophen-2-yl)-2-(trifluoromethyl)but-3-yn-1-one (6u).** Following the general procedure **6u** (68 mg, 0.22 mmol) was isolated after 24h by FC (*n*-hexane/EtOAc gradient from 49:1 to 9:1) in 72% yield starting from aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5l** (126 mg, 0.60 mmol) in the presence of **3m** (22 mg, 0.06 mmol) and $K_2CO_3$ (17 mg, 0.12 mmol) and using benzene/toluene mixture (3:1, 1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 8.43-8.29 (m, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.86 (dd, *J* = 5.0, 1.1 Hz, 1H, S-$C_{arom.}$-H), 7.21 (dd, *J* = 5.0, 4.0 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.10 (s, 1H), 2.51 (tt, *J* = 9.1, 3.8 Hz, 1H, C≡C-CH), 1.89-1.76 (m, 2H, C*H*$_a$H$_b$-CH-C*H*$_a$H$_b$), 1.74-1.63 (m, 2H, CH$_a$*H*$_b$-CH-CH$_a$*H*$_b$), 1.58-1.23 (m, 6H, CH$_a$H$_b$-C*H*$_2$-C*H*$_2$-C*H*$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 182.9 (C=O), 138.3 (q, *J* = 2.5 Hz, S-$C_{arom.}$-*C*$_{arom.}$-H), 137.8 (S-$C_{arom.}$-H), 137.2 (S-$C_{arom.}$), 128.5 (S-$C_{arom.}$-H-*C*$_{arom.}$-H), 121.9 (q, *J* = 286.6 Hz, $CF_3$), 95.2 (Pr-*C*≡C), 73.9 (q, *J* = 33.0 Hz, *C*-$CF_3$), 73.6 (C≡*C*-COH), 31.6 (*C*$H_2$-CH-*C*$H_2$), 29.0 (CH), 25.6 (*C*$H_2$-$CH_2$-CH-$CH_2$-*C*$H_2$), 24.6 (CH-$CH_2$-$CH_2$-*C*$H_2$). IR (ATR): 3401, 2934, 1652, 1408, 1354, 1246, 1193, 1164, 1064 $cm^{-1}$. MS (EI) m/z (%): 316 ($M^+$, 1), 288 (2), 234 (3), 111 (100), 83 (12), 67 (2), 53 (3). HRMS: Calculated for $[C_{15}H_{16}O_2F_3S]^+$: 317.0823 [$(M+H)^+$]; found: 317.0828. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; $\tau_{major}$ = 8.30 min, $\tau_{minor}$ = 9.08 min (98% ee). $[\alpha]_D^{rt}$: +100.0 (*c* = 1.0, $CH_2Cl_2$).

## 2.4. General procedure for the reaction under conditions shown in Table 2.10 (three consecutive batch cycles)

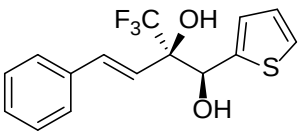
An ordinary vial was charged with pre-catalyst **3m** (0.06 mmol, 20 mol%) and $K_2CO_3$ (0.12 mmol, 40 mol%), equipped with a magnetic stirring bar and under an argon atmosphere. A mixture of benzene/toluene (3:1, 1 mL) was added and the mixture was stirred for 10 min at room temperature. The vial was then placed at -15 $^oC$ and stirred for further 10 min prior to the addition of the aldehyde **1j** (29 µL, 0.30 mmol) and ynone **5h** (59 mg, 0.60 mmol). The stirring was maintained at this temperature for 48h. Then additional 29 µL, 0.30 mmol of aldehyde **1j**, immediately followed by 59 mg, 0.3 mmol of ynone **5h** were added to the crude reaction mixture and the reaction was stirred for further 48h. Afterwards, additional 29 µL, 0.30 mmol of aldehyde **1j** immediately followed by 59 mg, 0.3 mmol of ynone **5h** were added to the crude reaction mixture and the reaction was stirred for further 96h. Solvents were evaporated and the crude was directly subjected to FC isolating **6q** (187 mg, 0.60 mmol) in 67% yield.

## 2.5. Reduction of propargylic alcohol adducts (7-9)



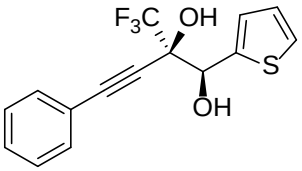

**(*R*,*Z*)-2-hydroxy-4-phenyl-1-(thiophen-2-yl)-2-(trifluoromethyl)but-3-en-1-one (7).** To a solution of the propargylic alcohol **6q** (45.8 mg, 0.15 mmol) in MeOH (1.5 mL) Lindlar catalyst (17 mg, 0.008 mmol). The argon atmosphere was replaced with hydrogen and the reaction mixture was stirred at room temperature under hydrogen (5.0 bar) for 62h. The suspension was then filtered through a celite pad, the filtrate was concentrated *in vacuo*. The crude was then purified by flash column chromatography (*n*-hexane/EtOAc gradient from 49:1 to 9:1) to afford the pure *cis*-alkene **5** (40 mg, 0.13 mmol) in 85% yield. $^1H$ NMR (300

MHz, $CDCl_3$) (δ, ppm) 7.98-7.85 (m, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.68 (dd, *J* = 5.0, 1.0 Hz, 1H, S-$C_{arom.}$-H), 7.22-7.13 (m, 3H, $C_{arom.}$-H), 7.11-7.03 (m, 3H, S-$C_{arom.}$-H-$C_{arom.}$-*H* + $C_{arom.}$-H), 6.99 (d, *J* = 12.2 Hz, 1H, HC=C*H*-$C_{arom.}$), 6.43 (d, *J* = 12.2 Hz, 1H, *H*C=CH-$C_{arom.}$), 5.07 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 186.3 (C=O), 139.3 (S-$C_{arom.}$-H), 138.4 (S-*C*$_{arom.}$-CO), 137.0 (HC=*C*H-$C_{arom.}$), 136,6 (q, *J* = 3.0 Hz, S-$C_{arom.}$-*C*$_{arom.}$-H), 135.0 (HC=CH-*C*$_{arom.}$), 128.7 ($C_{arom.}$-H), 128.2 (C=C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 128.1 (S-$C_{arom.}$-H-$C_{arom.}$-*H*), 127.9 ($C_{arom.}$-H), 124.3 (q, *J* = 1.4 Hz, H*C*=CH-$C_{arom.}$), 123.5 (q, *J* = 287.1 Hz, $CF_3$), 79.3 (q, *J* = 28.5 Hz, *C*-$CF_3$). IR (ATR): 3412, 1645, 1408, 1275, 1243, 1174, 1166, 1064 cm$^{-1}$. MS (EI) m/z (%): 324 ($M^+$-$H_2O$, 11), 197 (13), 183 (5), 152 (4), 131 (16), 111 (100), 103 (16), 83 (9), 77 (18), 63 (4), 51 (8). HRMS: Calculated for $[C_{15}H_{12}O_2F_3S]^+$: 313.0510 [$(M+H)^+$]; found: 313.0499. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 0.8 mL/min; $\tau_{major}$ = 14.99 min, $\tau_{minor}$ = 13.79 min (95% ee). $[\alpha]_D^{rt}$: +108.9 (*c* = 1.0, $CH_2Cl_2$).




**(1*S*,2*R*,*E*)-4-phenyl-1-(thiophen-2-yl)-2-(trifluoromethyl)but-3-ene-1,2-diol (8).** A 3.07 M solution of Red-Al (140 µL, 0.44 mmol) in toluene was diluted in anhydrous $Et_2O$ (0.83 mL) under an argon atmosphere and cooled down to 0ºC. A solution of propargylic alcohol **6q** (63 mg, 0.2 mmol) in $Et_2O$ (0.43 mL) was introduced dropwise. After stirring for further 30 min at 0ºC the temperature was gradually raised to room temperature and the reaction stirred for an additional 3h. Afterwards the reaction was quenched with 2 mL of aq. saturated $NH_4Cl$ solution. The phases were separated and the aqueous layer was extracted with EtOAc (3 x 4 mL) and then with $CH_2Cl_2$ (3 x 4 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude was then purified by flash column chromatography (*n*-hexane/EtOAc gradient from 9:1 to 8:2) to afford the pure diol **6** (54mg, 0.17 mmol) in 86% yield. $^1$H NMR (300 MHz, $CDCl_3$) δ 7.48-7.41 (m, 2H, $C_{arom.}$-H), 7.40-7-27 (m, 4H, S-$C_{arom.}$-*H* + $C_{arom.}$-H), 7.16-7.12 (m, 1H, S-$C_{arom.}$-

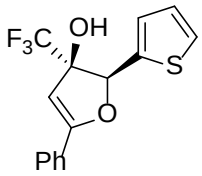
$C_{arom.}$-*H*), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.85 (d, *J* = 16.1 Hz, 1H, HC=C*H*-$C_{arom.}$), 6.57 (d, *J* = 16.1 Hz, 1H, *H*C=CH-$C_{arom.}$), 5.40 (d, *J* = 3.6 Hz, 1H, *H*C-OH), 2.54 (d, *J* = 3.8 Hz, 1H, HC-O*H*), 2.51 (s, 1H, $CF_3$-C-OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 140.3 (S-*C*$_{arom.}$), 135,6 (HC=CH-*C*$_{arom.}$), 135,4 (HC=*C*H-$C_{arom.}$), 128.7 ($C_{arom.}$-H), 128.6 (C=C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 127.3 (S-$C_{arom.}$-*C*$_{arom.}$-H), 127.0 ($C_{arom.}$-H), 126.8 (S-$C_{arom.}$-H), 126.6 (S-$C_{arom.}$-H-*C*$_{arom.}$-H), 123.6 (q, *J* = 286.3 Hz, $CF_3$), 121.5 (H*C*=CH-$C_{arom.}$), 77.6 (q, *J* = 26.9 Hz, *C*-$CF_3$), 72.7 (CH). IR (ATR): 3501.1, 3479.0, 3120.3, 1386.6, 1282.4, 1195.6, 1178.3, 1160.0, 1138.8, 1026.9 cm$^{-1}$. MS (EI) m/z (%): 296 ($M^+$-$H_2O$, 1) 199 (34), 165 (27), 131 (39), 113 (100), 103 (40), 77 (39), 51 (23). HRMS: Calculated for $[C_{15}H_{14}OF_3S]^+$: 297.0561 [$(M+H)^+$]; found: 297.0561. M.p. (*n*-hexane/$Et_2O$): 113-115 ºC. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 12.29 min, $\tau_{minor}$ = 32.02 min (97% ee). $[\alpha]_D^{rt}$: -234.04 (*c* = 1.0, $CH_2Cl_2$).




**(1*S*,2*R*)-4-phenyl-1-(thiophen-2-yl)-2-(trifluoromethyl)but-3-yne-1,2-diol (9).** To a solution of **6q** (62 mg, 0.2 mmol) in EtOH (0.7 mL) $NaBH_4$ (12 mg, 0.4 mmol) and $CeCl_3$ (74 mg, 0.3 mmol) were added at 0ºC. The reaction was stirred at 0ºC for 30 min. Then 2 mL of water were added and the reaction mixture was extracted with EtOAc (3 x 4 mL) and then with $CH_2Cl_2$ (3 x 4 mL). The combined organic fractions were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude was then purified by flash column chromatography (*n*-hexane/EtOAc 8:2) to afford the pure diol **7** (54 mg, 0.17 mmol) in 86% yield. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.56-7.48 (m, 2H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-*H* + S-$C_{arom.}$-H), 7.42-7-31 (m, 4H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 7.46-7-31 (m, 3H, C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*), 7.29-7.22 (m, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.05 (dd, *J* = 5.1, 3.6 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.36 (d, *J* = 5.9 Hz, 1H, *H*C-OH), 2.92 (s, 1H, $CF_3$-C-OH), 2.68 (d, *J* =6.0 Hz, 1H, HC-O*H*). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 140.3 (S-*C*$_{arom.}$), 132.2

($C_{arom.}$-H), 129.7 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 128.4 (C≡C-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 127.5 (S-$C_{arom.}$-$C_{arom.}$-H), 126.7 (S-$C_{arom.}$-H), 126.5 (S-$C_{arom.}$-H-$C_{arom.}$-H), 123.6 (q, *J* = 286.3 Hz, $CF_3$), 120.7 (C≡C-$C_{arom.}$), 89.8 (*C*≡C), 81.3 (C≡*C*), 74.3 (q, *J* = 29.6 Hz, *C*-$CF_3$), 72.2 (CH). IR (ATR): 3501, 3433, 1235, 1203, 1185, 1164, 1103, 10356 $cm^{-1}$. MS (EI) m/z (%): 312 ($M^+$, 1), 294 (100), 275 (5), 215 (11), 197 (36), 139 (10), 105 (67), 77 (35), 51 (12). HRMS: Calculated for $[C_{15}H_{12}O_2F_3S]^+$: 313.0510 $[(M+H)^+]$; found: 313.0512. M.p. (*n*-hexane/EtOAc): 131-133 ºC. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{major}$ = 15.80 min, $\tau_{minor}$ = 22.44 min (98% ee). $[\alpha]_D^{rt}$: -104.4 (*c* = 1.0, $CH_2Cl_2$).

## 2.6. Silver catalyzed cycloisomerization of propargylic alcohol 9. Synthesis of dihydrofuran 10.



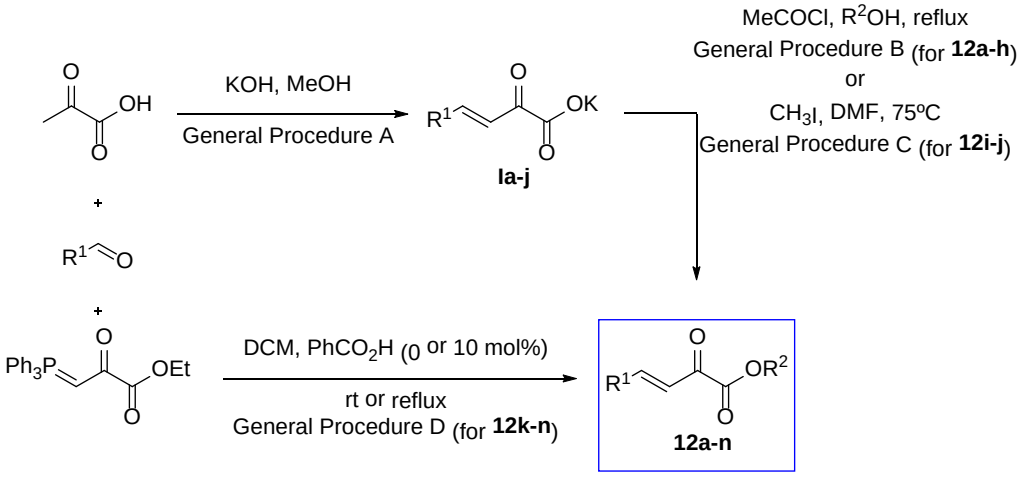

**(2*S*,3*R*)-5-phenyl-2-(thiophen-2-yl)-3-(trifluoromethyl)-2,3-dihydrofuran-3-ol (10).** To a solution of the propargylic alcohol **9** (72 mg, 0.23 mmol) in DMF (0.23 mL) $AgNO_3$ (5 mg, 0.028 mmol) was added. The reaction mixture was then heated at 70ºC for 16h, before being cooled and diluted with water (1 mL). The resulting mixture was then extracted with EtOAc (3 x 5 mL). The combined organic fractions were dried and the solvent was removed *in vacuo*. The crude was then purified by flash column chromatography (*n*-hexane/EtOAc 8:2) to afford the pure dihydrofuran **10** (64 mg, 0.20 mmol) in 89% yield. $^1$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.62-7.27 (m, 2H, $C_{arom.}$-H), 7.49-7-36 (m, 4H, S-$C_{arom.}$-H + $C_{arom.}$-H), 7.21 (dd, *J* = 3.5, 1.0 Hz, 1H, S-$C_{arom.}$-$C_{arom.}$-*H*), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.10 (s, 1H, C=CH), 5.57 (s, 1H, OCH), 2.21 (s, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 162.4 (C=*C*O), 135.2 (S-

$C_{arom}$.), 130.4 ($C_{arom}$.-H), 128.7 ($C_{arom}$.), 128.6 ($C_{arom}$.-H), 127.4 ($C_{heterarom}$.-H), 127.2 ($C_{heterarom}$.-H), 127.1 ($C_{heterarom}$.-H), 126.2 ($C_{arom}$.-H), 124.7 (q, *J* = 287.1 Hz, $CF_3$), 93.5 (q, *J* = 1.6 Hz, C=*C*H), 84.4 (q, *J* = 30.1 Hz, *C*-$CF_3$), 82.3 (q, *J* = 1.8 Hz, HC-O). IR (ATR): 3727, 1646, 1450, 1167, 1092, 1051 $cm^{-1}$. MS (EI) m/z (%): 324 ($M^+$, 3), 294 (100), 265 (4), 215 (23), 197 (25), 189 (10), 147 (10), 131 (8), 105 (92), 77 (27), 63 (2), 51 (6). HRMS: Calculated for $[C_{15}H_{12}O_2F_3S]^+$: 313.0510 $[(M+H)^+]$; found: 313.0510. The ee was determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{major}$ = 10.11 min, $\tau_{minor}$ = 25.66 min (97% ee). $[\alpha]_D^{rt}$: -78.4 (*c* = 1.0, $CH_2Cl_2$).

## 3.- ORGANOCATALYTIC GENERATION OF DONOR ACCEPTOR CYCLOPROPANES IN CYCLOADDITION REACTIONS

### 3.1. Formal [2+4] cycloaddition of β-γ-unsaturated α-ketoesters through NHC-mediated cyclopropane ring opening

#### 3.1.1. Synthesis of γ-aryl-β,γ-unsaturated-α-keto esters 12a-n




**12a**: $R^1$ = Ph; $R^2$ = Me
**12b**: $R^1$ = Ph; $R^2$ = Et
**12c**: $R^1$ = *p*-$MeOC_6H_4$; $R^2$ = Me
**12d**: $R^1$ = *p*-$MeC_6H_4$; $R^2$ = Me
**12e**: $R^1$ = *m*-$MeC_6H_4$; $R^2$ = Me
**12f**: $R^1$ = *o*-$MeC_6H_4$; $R^2$ = Me
**12g**: $R^1$ = 3,4-$(OCH_2O)C_6H_3$; $R^2$ = Me
**12h**: $R^1$ = *p*-$FC_6H_4$; $R^2$ = Me
**12i**: $R^1$ = 2-furyl; $R^2$ = Me
**12j**: $R^1$ = 2-thienyl; $R^2$ = Me
**12k**: $R^1$ = Me; $R^2$ = Et
**12l**: $R^1$ = *i*Pr; $R^2$ = Et
**12m**: $R^1$ = $BnOCH_2$; $R^2$ = Et
**12n**: $R^1$ = $PhCH_2CH_2$; $R^2$ = Et

*General Procedure A*

The preparation of potassium salts **Ia-j** was accomplished using a modified procedure to the one outlined by Smith *et al.*[11] A solution of potassium hydroxide (1.85 equiv) in MeOH (3.7 M), was added dropewise over a solution of solution of

[11] Belmessieri, D.; Morrill, C.; Simal, L. C.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2011**, *133*, 2714.

pyruvic acid (1 equiv) in MeOH (2 M) at 0ºC while stirring vigorously. Then a solution of (hetero)arylaldehyde (1.1 equiv) in MeOH (1 M) was added dropewise. The reaction was stirred at 0ºC for 15 min followed by rt overnight. The precipitate was collected by filtration, washed twice with cold MeOH, once with ether and dried under vacuum to furnish potassium salt which was used as an intermediate, without further purification.

*General Procedure B*

The preparation of γ-aryl-β,γ-unsaturated-α-keto esters **12a-h** was accomplished using a modified procedure to the one outlined by Smith *et al.*[11] Acetyl chloride (11.5 equiv) was added to the desired alcohol at 0°C to generate hydrochloric acid. Potassium salt (1 equiv) was added and the mixture stirred at 0°C for 30 min then warmed to rt for 2h before heating at reflux overnight. Concentration *in vacuo* gave a solid which was dissolved in water and extracted twice with DCM. The combined organics were washed with sat. aq. $NaHCO_3$, water and brine before being dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude was then purified by flash column chromatography to afford pure γ-aryl-β,γ-unsaturated-α-keto esters (**12a-h**).[11,12]

*General Procedure C*

The preparation of potassium salts **12i-j** was accomplished using a modified procedure to the one outlined by Smith *et al.*[11] To a solution of the corresponding potassium salt (1equiv) in DMF (0.4 M) iodomethane (1.5 equiv) was added. The reaction was stirred at 75ºC for 4 h and then cooled to rt. The reaction mixture was poured into water and extracted 3 times with $CH_2Cl_2$. The combined extracts were washed with water and brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*.

[12] (a) Y-Z. Hua, M-M. Liu, P-J. Huang, X. Song, M-C. Wang, J-B. Chang, *Chem. Eur. J.* 2015, *21*, 11994. (b) E. Li, Y. Huang, *Chem. Eur. J.* **2014**, *20*, 3520.

The crude was then purified by flash column chromatography to afford pure γ-aryl-β,γ-unsaturated-α-keto esters (**12i and 12j**).[11,12]

*General Procedure D*

The Preparation of γ-alkyl-β,γ-unsaturated-α-keto esters **12k-n** was accomplished using the procedure outlined by Jørgensen *et al.*[13] A solution of the "Wittig reagent" oxo-(triphenyl-λ$^5$-phosphanylidene)propionic acid ethyl ester (1 equiv) and aldehyde (1.5 equiv) in DCM (1 M) was stirred at rt (reflux and 10 mol % of benzoic acid may be needed depending on the aldehyde) until complete consumption of the ylide. The solvent is then removed *in vacuo* and the crude purified by flash column chromatography to afford pure γ-alkyl-β,γ-unsaturated-α-keto esters (**12k,**[13] **12l,**[14] **12m,**[13] **and 12n**[15])

### 3.1.2. Synthesis of lactones 13a-o

*General Procedure:* An ordinary vial was charged with pre-catalyst **3n** (0.02 mmol, 10 mol%), equipped with a magnetic stirring bar and placed under an argon atmosphere. Dichloromethane (1 mL) and *N*,*N*-diisopropylethylamine (7 µL, 20 mol%) were added at once and the mixture was stirred for 10 min at room temperature. The mixture was next cooled down to 5 $^{o}$C and stirred for further 10 min prior to the addition of aldehyde **11** (0.30 mmol as a solution in 1 mL of dichloromethane) and ketoester **12** (0.20 mmol). The stirring was maintained at this temperature until the reaction was completed (TLC analysis). Solvents were evaporated and the crude was charged onto silica gel and subjected to flash column chromatography purification. Racemic standards for HPLC separation conditions were prepared using 2-(pentafluorophenyl)-6,7-dihydro-5*H*-pyrrolo[2,1-*c*][1,2,4]triazol-2-ium tetrafluoroborate (0.02 mmol, 10 mol%) as pre-catalyst.

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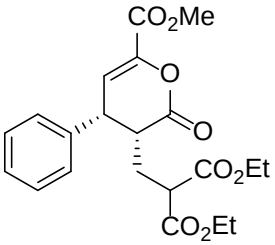
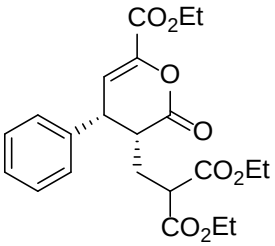
13 K. B. Jensen, J. Thorhauge, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2001**, *40*, 160.
14 C. Allais, F. Liéby-Muller, J. Rodriguez, T. Constantieux, *Eur. J. Org. Chem.* **2013**, 4131.
15 H. Sugimura, K. Yoshida, *Bull. Chem. Soc. Jpn.* **1992**, *62*, 3209.

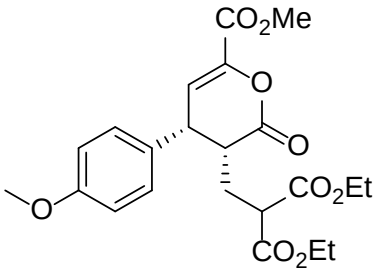


**Diethyl 2-(((3*R*,4*R*)-6-(methoxycarbonyl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13a).** Following the general procedure **13a** (59 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 73% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12a** (38 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.38–7.15 (m, 3H, $C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*-$C_{arom.}$-H), 7.05 (dd, *J* = 7.3, 2.2 Hz, 2H, $C_{arom.}$-H-$C_{arom.}$-$C_{arom.}$-H), 6.66 (d, *J* = 6.6 Hz, 1H, $CH^5$), 4.23–3.99 (m, 4H, 2 x $CO_2CH_2$), 3.80* (s, 3H, $CO_2CH_3$), 3.84-3-75* (m, 1H, $CH^4$), 3.66 (dd, *J* = 9.3, 5.6 Hz, 1H, HC-$CO_2$Et), 3.02 (ddd, *J* = 8.6, 7.1, 4.5 Hz, 1H, $CH^3$), 2.05-1.72 (m, 2H, $CH_3$), 1.28-1.12 (m, 6H, 2x $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.0 ($CO_2$Et), 168.8 ($CO_2$Et), 168.2 ($C^2$), 160.7 ($CO_2$Me), 142.0 ($C^6$), 135.2 ($C_{arom.}$), 129.3 ($C_{arom.}$-H), 128.4 ($C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 128.0 ($C_{arom.}$-H), 118.3 ($C^5$), 61.6 ($CO_2CH_2$), 52.6 ($CO_2CH_3$), 49.5 (HC-$CO_2$Et), 42.4 ($C^4$), 40.7 ($C^3$), 26.5 ($C^3$-$CH_2$), 14.0 ($CH_3$). IR (ATR): 1766, 1724, 1656, 1443, 1325, 1243, 1106 $cm^{-1}$. MS (EI) m/z (%): 404 ($M^+$, 1), 376 (6), 359 (12), 344 (11), 313 (11), 231 (56), 214 (18), 186 (100), 157 (17), 141 (27), 131 (79), 115 (33), 77 (17), 55 (18). HRMS (ESI+): Calculated for $[C_{21}H_{25}O_8]^+$: 405.1549 $[(M+H)^+]$; found: 405.1555. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 18.18 min, $\tau_{minor}$ = 33.91 min (97% ee). $[\alpha]_D^{rt}$: -24.7 (*c* = 1.0, $CH_2Cl_2$). M.p.: 94-96ºC.



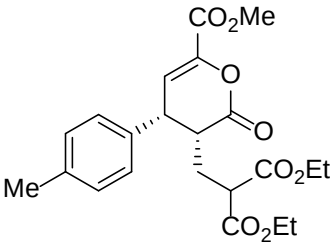
**Diethyl 2-(((3*R*,4*R*)-6-(ethoxycarbonyl)-2-oxo-4-phenyl-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13b).** Following the general procedure **13b** (64 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 77% yield starting from aldehyde **11a** (64

mg, 0.30 mmol) and ketoester **12b** (41 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) δ $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) 7.36–7.23 (m, 3H, $C_{arom.}$-H-$C_{arom.}$-*H*-$C_{arom.}$-*H*-$C_{arom.}$-H), 7.14-7-04 (m, 2H, $C_{arom.}$-H-$C_{arom.}$-$C_{arom.}$-H), 6.69 (d, *J* = 6.7 Hz, 1H, $CH^5$), 4.30 (q, *J* = 7.1 Hz, 2H, $C^6$-$CO_2CH_2$), 4.24–4.05 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 3.80 (appt, J = 6.9 Hz, 1H, $CH^4$), 3.69 (dd, *J* = 9.4, 5.6 Hz, 1H, $CHCO_2Et$), 3.03 (ddd, *J* = 8.7, 7.2, 4.5 Hz, 1H, $CH^3$), 2.04-1.79 (m, 2H, $C^3$-$CH_2$), 1.32 (t, J = 7.1 Hz, 3H, $C^6$-$CO_2CH_2CH_3$), 1.27-1.18 (m, 6H, $CH(CO_2CH_2CH_3)_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2Et$), 168.8 ($CO_2Et$), 168.3 ($C^2$), 160.3 ($C^6$-*C*O), 142.2 ($C^6$), 135.3 ($C_{arom.}$), 129.3 ($C_{arom.}$-H), 128.4 ($C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 128.1 ($C_{arom.}$-H), 118.0 ($C^5$), 62.0 ($C^6$-$CO_2CH_2$), 61.7 ($CO_2CH_2$), 49.5 ($CHCO_2$), 42.5 ($C^4$), 40.8 ($C^3$), 26.6 ($C^3$-$CH_2$), 14.1 (C=C-$CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$). IR (ATR): 1774, 1727, 1659, 1368, 1253, 1099 $cm^{-1}$. MS (EI) m/z (%): 418 ($M^+$, 1), 389 (7), 373 (8), 343 (7), 327 (7), 299 (10), 258 (10), 245 (26), 214 (16), 186 (96), 171 (14), 157 (17), 141 (25), 131 (100), 115 (48), 103 (39), 77 (19), 55 (19). HRMS (ESI+): Calculated for $[C_{22}H_{27}O_8]^+$: 419.1706 [$(M+H)^+$]; found: 419.1710. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 12.85 min, $\tau_{minor}$ = 21.68 min (>99% ee). $[\alpha]_D^{rt}$: -182.0 (*c* = 1.0, $CH_2Cl_2$).



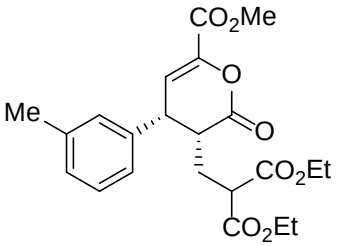

**Diethyl 2-(((3*R*,4*R*)-6-(methoxycarbonyl)-4-(4-methoxyphenyl)-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13c).** Following the general procedure **13c** (70 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 81% yield starting from aldehyde **11a** (43 mg, 0.20 mmol) and ketoester **12c** (44 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using

dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ $^{1}$H NMR (300 MHz, $CDCl_3$) (δ, ppm) (* denotes partially overlapped signals) 7.00 (d, *J* = 8.7 Hz, 2H, MeO-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.83 (dd, *J* = 8.7 Hz, 2H, MeO-$C_{arom.}$-$C_{arom.}$-H), 6.69 (d, *J* = 6.7 Hz, 1H, $CH^5$), 4.25–4.08 (m, 4H, $CO_2CH_2$), 3.85 (s, 3H, $CO_2CH_3$), 3.78* (s, 3H, MeO), 3.76* (appt, *J* = 7.0 Hz, 1H, $CH^4$), 3.70 (dd, *J* = 9.5, 5.6 Hz, 1H, C*H*$CO_2$Et), 3.00 (ddd, *J* = 8.8, 7.2, 4.4 Hz, 1H, $CH^3$), 2.05-1.81 (m, 2H, $C^3$-$CH_2$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.23* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.9 ($CO_2$Et), 168.3 ($C^2$), 160.9 ($C^6$-*C*O), 159.6 (MeO-$C_{arom.}$), 141.8 ($C^6$), 129.2 (MeO-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 126.9 (HC-$C_{arom.}$), 118.6 ($C^5$), 114.7 (MeO-$C_{arom.}$-$C_{arom.}$-H), 61.7 ($CO_2CH_2$), 55.3 (MeO), 52.7 ($CO_2CH_3$), 49.5 ($CHCO_2$), 41.8 ($C^4$), 41.0 ($C^3$), 26.6 ($C^3$-$CH_2$), 14.0 ($CH_2CH_3$). IR (ATR): 1766, 1727, 1512, 1437, 1322, 1254, 1099 cm$^{-1}$. MS (EI) m/z (%): 434 ($M^+$, 1), 273 (4), 261 (14), 221 (3), 187 (4), 161 (100), 133 (9), 115 (5), 77 (3), 55 (4). HRMS (ESI+): Calculated for $[C_{22}H_{27}O_9]^+$: 435.1655 [$(M+H)^+$]; found: 435.1648. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 26.19 min, $\tau_{minor}$ = 43.43 min (>99% ee). $[\alpha]_D^{rt}$: -228.4 (*c* = 1.0, $CH_2Cl_2$).



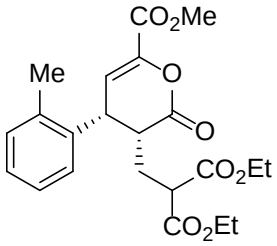

**Diethyl 2-(((3*R*,4*R*)-6-(methoxycarbonyl)-2-oxo-4-(p-tolyl)-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13d).** Following the general procedure **13d** (71 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 85% yield starting from aldehyde **11a** (43 mg, 0.20 mmol) and ketoester **12d** (41 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.11 (d, *J* = 7.8 Hz, 2H, Me-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.96 (dd, *J* = 8.1 Hz, 2H, Me-$C_{arom.}$-$C_{arom.}$-H), 6.69 (d, *J* = 6.7 Hz, 1H,

CH[5]), 4.28–4.02 (m, 4H, $CO_2CH_2$), 3.85 (s, 3H, $CO_2CH_3$), 3.77 (appt, *J* = 7.0 Hz, 1H, CH[4]), 3.70 (dd, *J* = 9.4, 5.6 Hz, 1H, HC-$CO_2$Et), 3.01 (ddd, *J* = 8.8, 7.2, 4.4 Hz, 1H, CH[3]), 2.30 (s, 3H, $H_3C$-$C_{arom.}$), 2.11-1.72 (m, 2H, C[3]-$CH_2$), 1.24* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.23* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.9 ($CO_2$Et), 168.2 (C[2]), 160.8 (C[6]-*C*O), 141.9 (C[6]), 138.3 (HC-$C_{arom.}$), 132.0 (Me-$C_{arom.}$), 130.0 (Me-$C_{arom.}$-$C_{arom.}$-H), 127.9 (Me-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 118.5 (C[5]), 61.6 ($CO_2CH_2$), 52.7 ($CO_2CH_3$), 49.5 (*C*H$CO_2$), 42.2 (C[4]), 40.8 (C[3]), 26.5 (C[3]-*C*$H_2$), 21.0 ($H_3C$-$C_{arom.}$), 14.0 ($CH_2CH_3$). IR (ATR): 1766, 1727, 1437, 1325, 1260, 1099 cm$^{-1}$. MS (EI) m/z (%): 418 (M$^+$, 1), 358 (5), 257 (6), 245 (27), 214 (6), 186 (48), 145 (100), 115 (35), 91 (11), 55 (9). HRMS (ESI+): Calculated for $[C_{22}H_{27}O_8]^+$: 419.1706 [(M+H)$^+$]; found: 419.1704. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 14.22 min, $\tau_{minor}$ = 25.90 min (99% ee). $[\alpha]_D^{rt}$: -209.8 (*c* = 1.0, $CH_2Cl_2$).



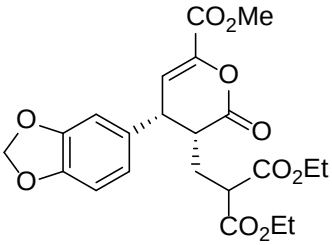

**Diethyl 2-(((3*R*,4*R*)-6-(methoxycarbonyl)-2-oxo-4-(m-tolyl)-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13e).** Following the general procedure **13e** (69 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 82% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12e** (41 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.20 (t, *J* = 7.3 Hz, 1H, Me-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*), 7.09 (d, *J* = 7.6 Hz, 1H, Me-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.93-6.83 (m, 2H, $C_{arom.}$-*H*-Me-$C_{arom.}$-$C_{arom.}$-*H*-$C_{arom.}$-H-$C_{arom.}$-H), 6.69 (d, *J* = 6.6 Hz, 1H, CH[5]), 4.27–4.07 (m, 4H, $CO_2CH_2$), 3.86 (s, 3H, $CO_2CH_3$), 3.77 (appt, *J* = 7.0 Hz, CH[4]), 3.71 (dd, *J* = 9.4, 5.5 Hz, 1H, HC-$CO_2$Et), 3.09 (ddd, *J* = 8.8, 7.2, 4.3 Hz, 1H, CH[3]), 2.31 (s, 3H, $H_3C$-$C_{arom.}$), 2.08-1.80 (ddd, m, 2H, C[3]-$CH_2$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.23* (t, *J*

= 7.1 Hz, 3H, $CH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2Et$), 168.9 ($CO_2Et$), 168.2 ($C^2$), 160.9 ($C^6$-*C*O), 141.9 ($C^6$), 139.2 (Me-$C_{arom.}$), 135.1 (HC-$C_{arom.}$), 129.2 ($C_{arom.}$-H), 129.2 ($C_{arom.}$-H), 128.5 ($C_{arom.}$-H), 125.2 ($C_{arom.}$-H), 118.4 ($C^5$), 61.7 ($CO_2CH_2$), 52.7 ($CO_2CH_3$), 49.6 (H*C*-$CO_2Et$), 42.5 ($C^4$), 40.7 ($C^3$), 26.5 ($C^3$-$CH_2$), 21.4 ($H_3C$-$C_{arom.}$), 14.0 ($CH_2CH_3$). IR (ATR): 1770, 1727, 1437, 1368, 1322, 1268, 1089 $cm^{-1}$. MS (EI) m/z (%): 418 ($M^+$, 2), 373 (7), 358 (7), 327 (14), 258 (11), 245 (42), 214 (14), 199 (12), 186 (99), 171 (17), 145 (100), 129 (24), 115 (49), 91 (17), 55 (16). HRMS (ESI+): Calculated for $[C_{22}H_{27}O_8]^+$: 419.1706 $[(M+H)^+]$; found: 419.1711. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 12.49 min, $\tau_{minor}$ = 23.79 min (99% ee). $[\alpha]_D^{rt}$: -205.8 (*c* = 1.0, $CH_2Cl_2$).



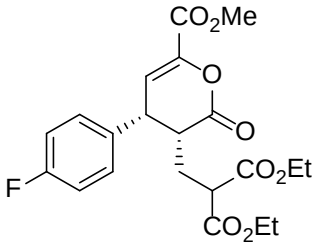

**Diethyl 2-(((3*R*,4*R*)-6-(methoxycarbonyl)-2-oxo-4-(2-tolyl)-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13f).** Following the general procedure **13f** (55 mg, 0.13 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 66% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12f** (41 mg, 0.20 mmol) in the presence of **3c** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.22-7.10 (m, 3H, $C_{arom.}$-H), 7.00-6.92 (m, 1H, $C_{arom.}$-H), 6.65 (d, *J* = 6.3 Hz, 1H, $CH^5$), 4.29–4.07 (m, 5H, 2 x $CO_2CH_2$, $CH^4$), 3.84 (s, 3H, $CO_2CH_3$), 3.66 (dd, *J* = 9.8, 5.0 Hz, 1H, HC-$CO_2Et$), 3.09 (ddd, *J* = 9.4, 7.6, 3.7 Hz, 1H, $CH^3$), 2.42 (s, 3H, $H_3C$-$C_{arom.}$), 2.09 (ddd, *J* = 14.4, 9.5, 5.0 Hz, 1H, $C^3$-$CH_aH_b$), 1.85 (ddd, *J* = 14.0, 9.8, 3.7 Hz, 1H, $C^3$-$CH_aH_b$), 1.24* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.23* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2Et$), 168.9 ($CO_2Et$), 168.6 ($C^2$), 160.8 ($C^6$-*C*O), 141.6 ($C^6$), 135.9 ($C_{arom.}$), 134.3 ($C_{arom.}$), 131.2 ($C_{arom.}$-H), 128.1 ($C_{arom.}$-H), 127.3 ($C_{arom.}$-H), 126.8 ($C_{arom.}$-H), 118.1 ($C^5$), 61.7 ($CO_2CH_2$), 52.7 ($CO_2CH_3$), 49.7 (H*C*-$CO_2Et$),

40.2 ($C^3$), 37.6 ($C^4$), 26.2 ($C^3$-*C*$H_2$), 19.9 ($H_3C$-$C_{arom.}$), 14.0 ($CH_2$*C*$H_3$). IR (ATR): 1767, 1731, 1440, 1368, 1322, 1260, 1095 $cm^{-1}$. MS (EI) m/z (%): 418 ($M^+$, 3), 373 (9), 327 (10), 245 (37), 214 (13), 186 (91), 171 (18), 145 (100), 128 (29), 115 (63), 91 (20), 77 (4), 55 (16). HRMS (ESI+): Calculated for $[C_{22}H_{27}O_8]^+$: 419.1706 [$(M+H)^+$]; found: 419.1707. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 13.58 min, $\tau_{minor}$ = 21.68 min (>99% ee). $[\alpha]_D^{rt}$: -113.5 (*c* = 1.0, $CH_2Cl_2$).



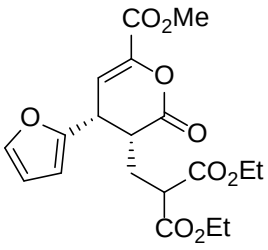

**Diethyl 2-(((3*R*,4*R*)-4-(benzo[d][1,3]dioxol-5-yl)-6-(methoxycarbonyl)-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13g).** Following the general procedure **13g** (71 mg, 0.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 1:1) after 36 h in 79% yield starting from aldehyde **11a** (43 mg, 0.20 mmol) and ketoester **12g** (47 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 6.71 (d, *J* = 7.8 Hz, 1H, $OCH_2O$-$C_{arom.}$-$C_{arom.}$-*H*-$C_{arom.}$-H), 6.65 (d, *J* = 6.7 Hz, 1H, $CH^5$), 6.59-6.50 (m, 2H, $C_{arom.}$-*H*-$C_{arom.}$-$OCH_2O$-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-*H*), 5.93 (s, 2H, $OCH_2O$), 4.26–4.06 (m, 4H, $CO_2CH_2$), 3.84 (s, 3H, $CO_2CH_3$), 3.77-3.63 (m, 2H, $CH^4$, C*H*$CO_2$Et), 2.97 (ddd, *J* = 8.9, 7.2, 4.3 Hz, 1H, $CH^3$), 2.07-1.80 (m, 2H, $C^3$-$CH_2$), 1.23* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.22* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.9 ($CO_2$Et), 168.1 ($C^2$), 160.8 ($C^6$-*C*O), 148.4 ($C_{arom.}$-H-$C_{arom.}$-$OCH_2O$-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 147.7 ($OCH_2O$-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 141.9 ($C^6$), 128.6 (HC-$C_{arom.}$), 121.6 ($OCH_2O$-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 118.3 ($C^5$), 108.8 ($C_{arom.}$-H-$C_{arom.}$-$OCH_2O$-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H), 108.0 ($OCH_2O$-$C_{arom.}$-$C_{arom.}$-H), 101.4 ($OCH_2O$), 61.7 ($CO_2CH_2$), 52.7 ($CO_2CH_3$), 49.5 (H*C*-$CO_2$Et), 42.2 ($C^4$), 40.9 ($C^3$), 26.5 ($C^3$-*C*$H_2$), 14.0 ($CH_2CH_3$). IR (ATR): 1774, 1731, 1656, 1487, 1324, 1246, 1095 $cm^{-1}$. MS (EI) m/z (%): 448 ($M^+$, 24), 403

(19), 357 (26), 329 (32), 301 (90), 288 (100), 269 (24), 256 (16), 241 (55), 229 (42), 213 (54), 207 (33), 199 (55), 185 (28), 175 (54), 156 (17), 143 (20), 127 (21), 115 (34), 99 (13), 77 (13), 55 (20). HRMS (ESI+): Calculated for $[C_{22}H_{25}O_{10}]^+$: 449.1448 $[(M+H)^+]$; found: 449.1460. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 37.48 min, $\tau_{minor}$ = 60.59 min (>99% ee). $[\alpha]_D^{rt}$: -204.4 (*c* = 1.0, $CH_2Cl_2$).



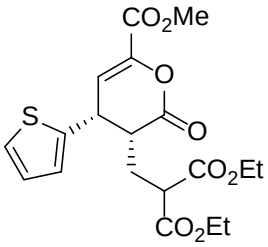

**Diethyl 2-(((3*R*,4*R*)-4-(4-fluorophenyl)-6-(methoxycarbonyl)-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13h).** Following the general procedure **13h** (61 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 72% yield starting from aldehyde **11a** (43 mg, 0.20 mmol) and ketoester **12h** (42 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.12–6.95 (m, 4H, $C_{arom.}$-H), 6.69 (dd, *J* = 6.6 Hz, 1H, $CH^5$), 4.27–4.06 (m, 4H, $CO_2CH_2$), 3.87* (s, 3H, $CH_3$), 3.89-3-78* (m, 1H, $CH^4$), 3.70 (dd, *J* = 9.3, 5.6 Hz, 1H, C*H*$CO_2$Et), 3.03 (ddd, *J* = 8.8, 7.2, 4.5 Hz, 1H, $CH^3$), 2.02-1.76 (m, 2H, $C^3$-$CH_2$), 1.25* (t, *J* = 7.0 Hz, 3H, $CH_2CH_3$), 1.23* (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.8 ($CO_2$Et), 168.0 ($C^2$), 162.6 (d, *J* = 248.0 Hz, F- $C_{arom.}$), 160.7 ($C^6$-*C*O), 142.1 ($C^6$), 130.9 (d, *J* = 3.3 Hz, HC-$C_{arom.}$), 129.7 (d, *J* = 8.2 Hz, F-$C_{arom.}$-$C_{arom.}$-$C_{arom.}$-H), 118.0 ($C^5$), 116.3 (d, *J* = 21.7 Hz, F-$C_{arom.}$-$C_{arom.}$-H), 61.7 ($CO_2CH_2$), 52.8 ($CO_2CH_3$), 49.5 (H*C*-$CO_2$Et), 41.8 ($C^4$), 40.8 ($C^3$), 26.6 ($C^3$-$CH_2$), 14.0 ($CH_3$). $^{19}$F NMR (283 MHz, $CDCl_3$) (δ, ppm) -113.1.IR (ATR): 1770, 1727, 1508, 1437, 1322, 1228, 1160, 1095 cm$^{-1}$. MS (EI) m/z (%): 422 ($M^+$ , 1), 377 (10), 362 (9), 331 (6), 317 (6), 270 (10), 261 (12), 249 (56), 214 (13), 203 (17), 186 (87), 175 (16), 161 (19), 149 (100), 133 (42), 127 (17), 121 (31), 115 (27), 101 (31), 85 (10), 55 (23). HRMS (ESI+): Calculated for $[C_{21}H_{24}FO_8]^+$: 423.1455 $[(M+H)^+]$; found:

423.1458. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 17.60 min, $\tau_{minor}$ = 28.89 min (>99% ee). $[\alpha]_D^{rt}$: -113.9 (*c* = 1.0, $CH_2Cl_2$).



**Diethyl 2-((4-(furan-2-yl)-6-(methoxycarbonyl)-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13i).** Following the general procedure **13i** (36 mg, 0.09 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) after 36 h in 46% yield (dr: 1:1.5) starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **5i** (36 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. Mayor diastereoisomer 3*R*,4*R*: $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.33 (dd, *J* = 1.9, 0.8 Hz, 1H, O-$C_{arom.}$-H), 6.58 (d, *J* = 6.7 Hz, 1H, $CH^5$), 6.29 (dd, *J* = 3.3, 1.9 Hz, 1H, O-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.19 (dd, *J* = 3.3, 0.8 Hz, 1H, O-$C_{arom.}$-$C_{arom.}$-*H*), 4.27–4.11 (m, 4H, 2 × $CO_2CH_2$), 3.93 (appt, *J* = 6.8 Hz, 1H, $CH^4$), 3.85 (s, 3H, $CH_3$), 3.73 (dd, *J* = 9.1, 6.0 Hz, 1H, HC-$CO_2$Et), 2.96 (ddd, *J* = 8.5, 6.9, 4.9 Hz, 1H, $CH^3$), 2.18 (ddd, *J* = 14.6, 8.6, 6.1 Hz, 1H, $C^3$-C*H*$_a$H$_b$), 1.93 (ddd, *J* = 14.3, 9.1, 4.9 Hz, 1H, $C^3$-CH$_a$*H*$_b$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.0 ($CO_2$Et), 168.8 ($CO_2$Et), 167.7 ($C^2$), 160.7 ($C^6$-*C*O), 148.4 (O-$C_{arom.}$), 143.3 (O-$C_{arom.}$-H), 142.7 ($C^6$), 114.9 ($C^5$), 110.5 (O-$C_{arom.}$-H-$C_{arom.}$-H), 108.8 (O-$C_{arom.}$-$C_{arom.}$-H), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 52.7 ($CO_2CH_3$), 49.5 (H*C*-$CO_2$Et), 39.5 ($C^3$), 35.6 ($C^4$), 26.4 ($C^3$-$CH_2$), 14.0 ($CH_3$). IR (ATR): 1741, 1731, 1368, 1264, 1203, 1156 cm$^{-1}$. MS (EI) m/z (%): 394 ($M^+$, 5), 349 (26), 320 (29), 302 (100), 288 (17), 275 (46), 247 (53), 215 (91), 187 (47), 175 (44), 159 (43), 131 (46), 91 (42), 77 (34), 55 (30). HRMS (ESI+): Calculated for $[C_{19}H_{23}O_9]^+$: 395.1342 [$(M+H)^+$]; found: 395.1348. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 24.75 min, $\tau_{minor}$ = 42.25 min (>99% ee). $[\alpha]_D^{rt}$: -201.2 (*c* = 1.0, $CH_2Cl_2$). Minor diastereoisomer 3*R*,4*S*: $^1$H

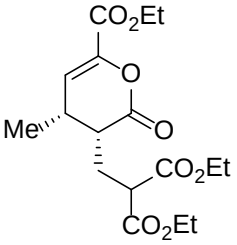
NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.8 Hz, 1H, O-$C_{arom.}$-H), 6.85 (d, *J* = 3.5 Hz, 1H, O-$C_{arom.}$-$C_{arom.}$-H), 6.45 (dd, *J* = 3.5, 1.8 Hz, 1H, O-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.41 (d, *J* = 5.3 Hz, 1H, $CH^5$), 5.52 (dd, *J* = 5.4, 1.5 Hz, 1H, $CH^4$), 4.39–4.29 (m, 2H, $CO_2CH_2$), 4.17 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2$), 3.97 (dd, *J* = 11.9, 3.4 Hz, 1H, HC-$CO_2$Et), 3.82 (s, 3H, $CH_3$), 3.63 (ddd, *J* = 12.1, 3.9, 1.6 Hz, 1H, $CH^3$), 2.55 (ddd, *J* = 14.1, 11.8, 3.9 Hz, 1H, $C^3$-C*H*$_a$H$_b$), 2.22 (ddd, *J* = 14.0, 12.1, 3.4 Hz, 1H, $C^3$-CH$_a$*H*$_b$), 1.33 (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.25 (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.2 ($CO_2$Et), 168.9 ($CO_2$Et), 168.5 ($C^2$), 168.2 ($C^6$-*C*O), 149.4 (O-$C_{arom.}$), 143.4 (O-$C_{arom.}$-H), 129.9 ($C_6$), 111.9 ($C^5$), 111.9 (O-$C_{arom.}$-H-*C*$_{arom.}$-H), 109.2 (O-$C_{arom.}$-*C*$_{arom.}$-H), 76.4 ($C^4$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 53.1 ($CO_2CH_3$), 49.2 (H*C*-$CO_2$Et), 38.7 ($C^3$), 32.0 ($C^3$-*C*H$_2$), 14.1 ($CH_3$), 14.0 ($CH_3$). IR (ATR): 1741, 1727, 1440, 1372, 1268, 1257, 1156 $cm^{-1}$. MS (EI) m/z (%): 394 ($M^+$ - H, 6), 349 (24), 302 (100), 275 (46), 247 (59), 215 (99), 186 (46), 175 (49), 159 (45), 131 (42), 91 (42), 55 (30). HRMS (ESI+): Calculated for $[C_{19}H_{23}O_9]^+$: 395.1342 $[(M+H)^+]$; found: 395.1346. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 28.99 min, $\tau_{minor}$ = 50.56 min (93% ee). $[\alpha]_D^{rt}$: -3.4 (*c* = 0.5, $CH_2Cl_2$). M.p.: 92-94ºC.



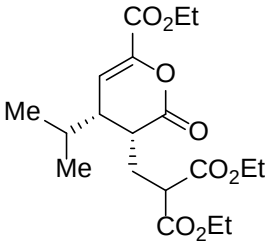

**Diethyl 2-((6-(methoxycarbonyl)-2-oxo-4-(thiophen-2-yl)-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13j).** Following the general procedure **13j** (56 mg, 0.14 mmol) was isolated by FC (*n*-hexane/$Et_2O$ gradient from 7:3 to 1:1) after 36 h in 68% yield (dr: 1.5:1) starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12j** (40 mg, 0.20 mmol) in the presence of **3c** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. Mayor diastereoisomer 3*R*,4*R*: $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.23 (dd, *J* = 5.1, 1.2 Hz, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 6.96 (dd, *J* = 5.2, 3.5 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-H), 6.86 (dd, *J* = 3.6, 1.2 Hz, 1H, S-$C_{arom.}$-H), 6.74 (d, *J* = 6.7 Hz, 1H, $CH^5$), 4.29–4.06 (m, 4H, 2 × $CO_2CH_2$, $CH^4$),

3.86 (s, 3H, $CH_3$), 3.72 (dd, *J* = 9.4, 5.6 Hz, 1H, HC-$CO_2$Et), 3.02 (ddd, *J* = 8.8, 6.8, 4.4 Hz, 1H, $CH^3$), 2.15 (ddd, *J* = 14.4, 8.9, 5.6 Hz, 1H, $C^3$-C$H_aH_b$), 1.99 (ddd, *J* = 14.2, 9.4, 4.4 Hz, 1H, $C^3$-C$H_aH_b$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$), 1.24* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.0 ($CO_2$Et), 168.8 ($CO_2$Et), 167.7 ($C^2$), 160.7 ($C^6$-*C*O), 141.9 (S-$C_{arom.}$), 137.0 ($C^6$), 127.6 (S-$C_{arom.}$-H-$C_{arom.}$-H), 126.5 (S-$C_{arom.}$-$C_{arom.}$-H), 125.8 (S-$C_{arom.}$-H), 117.8 ($C^5$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 52.8 ($CO_2CH_3$), 49.5 (H*C*-$CO_2$Et), 41.4 ($C^3$), 37.2 ($C^4$), 26.6 ($C^3$-$CH_2$), 14.0 ($CH_3$). IR (ATR): 1770, 1720, 1662, 1437, 1368, 1314, 1282, 1239, 1210, 1174, 1109 $cm^{-1}$. MS (EI) m/z (%): 410 ($M^+$, 2), 382 (6), 350 (4), 319 (10), 258 (9), 249 (11), 237 (29), 186 (29), 163 (8), 137 (100), 109 (19), 55 (10). HRMS (ESI+): Calculated for $[C_{19}H_{23}O_8S]^+$: 411.1114 $[(M+H)^+]$; found: 411.1117. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 21.56 min, $\tau_{minor}$ = 41.55 min (>99% ee). $[\alpha]_D^{rt}$: -219.9 (*c* = 0.3, $CH_2Cl_2$). M.p.: 95-97ºC. Minor diastereoisomer 3*R*,4*S*: $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.44 (dd, *J* = 3.7, 1.1 Hz, 1H, S-$C_{arom.}$-H), 7.28 (dd, *J* = 5.2, 1.1 Hz, 1H, S-$C_{arom.}$-$C_{arom.}$-H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 1H, S-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.28 (d, *J* = 5.4 Hz, 1H, $CH^5$), 5.49 (dd, *J* = 5.4, 1.5 Hz, 1H, $CH^4$), 4.40–4.22 (m, 2H, $CO_2CH_2$), 4.16 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2$), 3.94 (dd, *J* = 11.8, 3.5 Hz, 1H, HC-$CO_2$Et), 3.84* (s, 3H, $CH_3$), 3.82* (ddd, *J* = 11.8, 4.1, 1.5 Hz, 1H, $CH^3$), 2.59 (ddd, *J* = 14.0, 11.8, 4.1 Hz, 1H, $C^3$-C$H_aH_b$), 2.20 (ddd, *J* = 14.1, 12.1, 3.5 Hz, 1H, $C^3$-C$H_aH_b$), 1.33* (t, *J* = 7.2 Hz, 3H, $CH_2CH_3$), 1.25* (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.9 ($CO_2$Et), 168.6 ($C^2$), 168.1 ($C^6$-*C*O), 139.2 (S-$C_{arom.}$), 134.3 ($C^6$), 128.2 (S-$C_{arom.}$-H-$C_{arom.}$-H), 126.2 (S-$C_{arom.}$-$C_{arom.}$-H), 125.7 (S-$C_{arom.}$-H), 113.2 ($C^5$), 76.1 ($C^4$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 53.2 ($CO_2CH_3$), 49.2 (H*C*-$CO_2$Et), 40.4 ($C^3$), 31.8 ($C^3$-$CH_2$), 14.1 ($CH_3$), 14.0 ($CH_3$). IR (ATR): 1752, 1727, 1441, 1372, 1311, 1264, 1225, 1164, 1135, 1099 $cm^{-1}$. MS (EI) m/z (%): 410 ($M^+$, 5), 392 (8), 365 (35), 319 (96), 291 (61), 263 (89), 231 (100), 203 (90), 191 (60), 175 (57), 147 (66), 115 (30), 91 (25), 55 (27). HRMS (ESI+): Calculated for $[C_{19}H_{23}O_8S]^+$: 411.1114 $[(M+H)^+]$; found: 411.1124. The ee was determined by HPLC using a

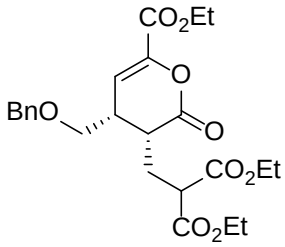
*Chiralcel OD3* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 20.46 min, $\tau_{minor}$ = 32.81 min (61% ee). $[\alpha]_D^{rt}$: -13.8 (*c* = 0.5, $CH_2Cl_2$). M.p.: 86-88ºC



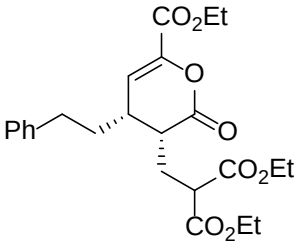

**Diethyl 2-(((3*R*,4*R*)-6-(ethoxycarbonyl)-4-methyl-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13k).** Following the general procedure **13k** (59 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) after 24 h in 83% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12k** (28 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 6.58 (d, *J* = 6.2 Hz, 1H, $CH^5$), 4.28 (q, *J* = 7.2 Hz, 2H, $C^6$-$CO_2CH_2$), 4.24–4.11 (m, 4H, HC-$CO_2CH_2$), 3.67 (dd, *J* = 9.5, 5.4 Hz, 1H, HC-$CO_2$Et), 2.82-2.60 (m, 1H, $CH^3$, $CH^4$), 2.40 (ddd, *J* = 14.2, 8.8, 5.4 Hz, 1H, $C^3$-$CH_aH_b$), 2.01 (ddd, *J* = 14.0, 9.5, 3.9 Hz, 1H, $C^3$-$CH_aH_b$), 1.32* (t, J = 7.1 Hz, 3H, $C^6$-$CO_2CH_2CH_3$), 1.26* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$), 1.25* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$), 1.02 (d, J = 6.8 Hz, 3H, $C^4$-$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.1 ($CO_2$Et), 168.8 ($CO_2$Et), 168.8 ($C^2$), 160.3 ($C^6$-CO), 141.7 ($C^6$), 120.5 ($C^5$), 61.9 ($C^6$-$CO_2CH_2$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 49.7 (HC-$CO_2$Et), 40.5 ($C^3$), 30.5 ($C^4$), 26.1 ($C^3$-$CH_2$), 14.1 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 13.5 ($C^4$-$CH_3$).IR (ATR): 1765, 1727, 1372, 1304, 1254, 1092 $cm^{-1}$. MS (EI) m/z (%): 341 ($M^+$ - H, 1), 327 (20), 311 (), 281 (29), 246 (10), 237 (34), 209 (20), 186 (100), 161 (34), 140 (33), 115 (23), 95 (38), 81 (16), 69 (86), 55 (38). HRMS (ESI+): Calculated for $[C_{17}H_{25}O_8]^+$: 357.1549 [$(M+H)^+$]; found: 357.1559. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 14.47 min, $\tau_{minor}$ = 20.99 min (>99% ee). $[\alpha]_D^{rt}$: -53.4 (*c* = 1.0, $CH_2Cl_2$).




**Diethyl 2-(((3*R*,4*R*)-6-(ethoxycarbonyl)-4-isopropyl-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13l).** Following the general procedure **13l** (65 mg, 0.17 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) after 24 h in 85% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12l** (34 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 6.48 (d, *J* = 6.1 Hz, 1H, $CH^5$), 4.30 (q, *J* = 7.2 Hz, 2H, $C_6$-$CO_2CH_2$), 4.26–4.09 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 3.71 (dd, *J* = 9.9, 5.2 Hz, 1H, HC-$CO_2$Et), 2.72 (ddd, *J* = 9.4, 7.2, 4.0 Hz, 1H, $CH^3$), 2.62 (ddd, *J* = 7.2, 6.2, 4.6 Hz, 1H, $CH^4$), 2.37 (ddd, *J* = 14.6, 9.5, 5.2 Hz, 1H, $C_3$-$CH_aH_b$), 2.16-1.94 (m, 2H, $C_3$-$CH_aH_b$, $C_4$-CH), 1.34 (t, J = 7.1 Hz, 3H, $C_6$-$CO_2CH_2CH_3$), 1.26* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$), 1.25* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$), 0.98 (d, J = 6.9 Hz, 3H, HC-$CH_3$), 0.78 (d, J = 6.7 Hz, 3H, HC-$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.7 ($CO_2$Et), 169.1 ($CO_2$Et), 168.8 ($C^2$), 160.2 ($C^6$-CO), 142.9 ($C^6$), 116.0 ($C^5$), 61.9 ($C^6$-$CO_2CH_2$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 49.8 (HC-$CO_2$Et), 41.7 ($C^3$), 38.8 ($C^4$), 27.6 ($C^4$-CH), 25.7 ($C^3$-$CH_2$), 21.1 ($CH_3$CH), 14.1 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$). IR (ATR): 1770, 1727, 1659, 1368, 1307, 1250, 1124, 1095 $cm^{-1}$. MS (EI) m/z (%): 355 ($M^+$ - Me, 16), 339 (11), 309 (18), 295 (48), 265 (21), 249 (100), 221 (21), 211 (52), 186 (66), 161 (16), 141 (24), 125 (36), 115 (25), 95 (53), 81 (14), 55 (36). HRMS (ESI+): Calculated for $[C_{19}H_{29}O_8]^+$: 385.1862 $[(M+H)^+]$; found: 385.1871. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 9.10 min, $\tau_{minor}$ = 13.10 min (>99% ee). $[\alpha]_D^{rt}$: -90.9 (*c* = 1.0, $CH_2Cl_2$).

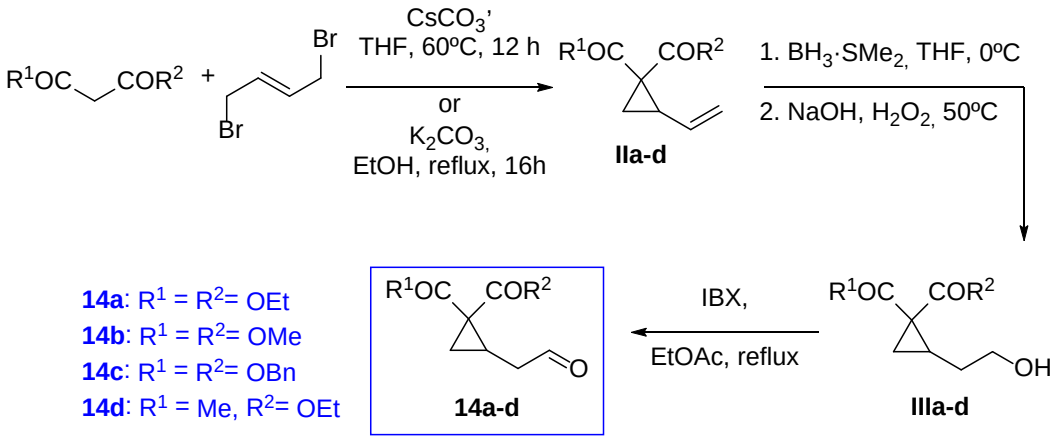



**Diethyl 2-(((3*R*,4*R*)-6-(ethoxycarbonyl)-4-isopropyl-2-oxo-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13m).** Following the general procedure **13m** (54 mg, 0.12 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) after 24 h in 58% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **12m** (50 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.36-7.19 (m, 5H, $C_{arom.}$-H), 6.45 (d, *J* = 6.1 Hz, 1H, $CH^5$), 4.53-4.57 (m, 2H, Ph$CH_2$), 4.29 (q, *J* = 7.1 Hz, 2H, $C^6$-$CO_2CH_2$), 4.26–4.04 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 3.77 (dd, *J* = 9.7, 5.4 Hz, 1H, HC-$CO_2$Et), 3.55 (dd, *J* = 9.7, 3.2 Hz, 1H, $CH_aH_b$-O), 3.43 (dd, *J* = 9.7, 2.2 Hz, 1H, $C^4$-$CH_aH_b$), 2.81-2.65 (m, 2H, $CH^3$, $CH^4$), 2.40 (ddd, *J* = 13.8, 8.5, 5.3 Hz, 1H, $C^3$-$CH_aH_b$), 2.03 (ddd, *J* = 13.3, 9.7, 3.4 Hz, 1H, $C^3$-$CH_aH_b$), 1.33 (t, J = 7.1 Hz, 3H, C=C-$CO_2CH_2CH_3$), 1.26* (t, J = 7.2 Hz, 3H, HC-$CO_2CH_2CH_3$), 1.24* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.2 ($CO_2$Et), 168.9 ($CO_2$Et), 168.7 ($C^2$), 160.4 ($C^6$-*C*O), 143.5 ($C^6$), 137.3 ($C_{arom.}$), 128.4 ($C_{arom.}$-H), 127.7 ($C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 127.6 ($C_{arom.}$-H), 115.7 ($C^5$), 73.4 (Ph-$CH_2$-O), 66.8 ($C^4$-*C*$H_2$), 61.8 ($C^6$-$CO_2CH_2$), 61.6 ($CO_2CH_2$), 49.8 (H*C*-$CO_2$Et), 37.5 ($C^3$), 37.0 ($C^4$), 25.9 ($C^3$-*C*$H_2$), 14.1 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$). IR (ATR): 1770, 1727, 1451, 1372, 1257, 1095 $cm^{-1}$. MS (EI) m/z (%): 371 ($M^+$ - $C_2H_{11}$, 2), 353 (2), 325 (5), 295 (6), 279 (100), 249 (25), 181 (4), 125 (3), 91 (100), 65 (3). HRMS (ESI+): Calculated for $[C_{24}H_{31}O_9]^+$: 447.2019 $[(M+H)^+]$; found: 447.2018. The ee was determined by HPLC using a *Chiralpak ASH* column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 19.40 min, $\tau_{minor}$ = 29.08 min (>99% ee). $[\alpha]_D^{rt}$: -35.0 (*c* = 1.0, $CH_2Cl_2$).




**Diethyl 2-(((3*R*,4*R*)-6-(ethoxycarbonyl)-2-oxo-4-phenethyl-3,4-dihydro-2*H*-pyran-3-yl)methyl)malonate (13n).** Following the general procedure **13n** (64 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) after 24 h in 72% yield starting from aldehyde **11a** (64 mg, 0.30 mmol) and ketoester **5n** (46 mg, 0.20 mmol) in the presence of **3n** (8 mg, 0.02 mmol) and *N*,*N*-diisopropylethylamine (7 µL, 0.04 mmol) and using dichloromethane (2 mL) as solvent. $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially overlapped signals) δ 7.33-7.23 (m, 2H, $C_{arom.}$-H), 7.23-7.11 (m, 3H, $C_{arom.}$-H), 6.63 (d, *J* = 6.3 Hz, 1H, $CH^5$), 4.30 (q, *J* = 7.3 Hz, 2H, $C^6$-$CO_2CH_2$), 4.25–4.08 (m, 4H, $CH(CO_2CH_2CH_3)_2$), 3.61 (dd, *J* = 9.7, 5.1 Hz, 1H, HC-$CO_2$Et), 2.82-2.67 (m, 2H, Ph$CH_aH_b$, $CH^3$), 2.67-2.49 (m, 2H, $CH^4$, Ph$CH_aH_b$), 2.37 (ddd, *J* = 14.6, 9.6, 5.2 Hz, 1H, $C^3$-$CH_aH_b$), 2.03 (ddd, *J* = 14.1, 9.7, 4.1 Hz, 1H, $C^3$-$CH_aH_b$), 1.96-1.81 ($C^4$-$CH_aH_b$), 1.65-1.46 (m, 1H, $C^4$-$CH_aH_b$), 1.34 (t, J = 7.1 Hz, 3H, $C^6$-$CO_2CH_2CH_3$), 1.25* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$), 1.25* (t, J = 7.1 Hz, 3H, HC-$CO_2CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (δ, ppm) 169.0 ($CO_2$Et), 168.9 ($CO_2$Et), 168.8 ($C^2$), 160.2 ($C^6$-*C*O), 142.0 ($C^6$), 140.6 ($C_{arom.}$), 128.6 ($C_{arom.}$-H), 128.2 ($C_{arom.}$-H), 126.4 ($C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H), 119.2 ($C^5$), 62.0 ($C^6$-$CO_2CH_2$), 61.7 ($CO_2CH_2$), 61.7 ($CO_2CH_2$), 49.7 (H*C*-$CO_2$Et), 39.9 ($C^3$), 34.9 ($C^4$), 32.8 (Ph$CH_2$), 30.8 ($C^4$-$CH_2$), 26.0 ($C^3$-$CH_2$), 14.1 ($CO_2CH_2CH_3$), 14.0 ($CO_2CH_2CH_3$). IR (ATR): 1770, 1727, 1372, 1308, 1268, 1095 $cm^{-1}$. MS (EI) m/z (%): 446 ($M^+$, 1), 417 (11), 371 (14), 325 (10), 295 (9), 273 (29), 249 (15), 186 (34), 159 (12), 129 (14), 115 (13), 105 (18), 91 (100), 77 (7), 65 (8), 55 (17). HRMS (ESI+): Calculated for $[C_{24}H_{31}O_8]^+$: 447.2019 $[(M+H)^+]$; found: 447.2018. The ee was determined by HPLC using a *Chiralcel OD3* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; $\tau_{major}$ = 17.28 min, $\tau_{minor}$ = 20.52 min (97% ee). $[\alpha]_D^{rt}$: -73.3 (*c* = 1.0, $CH_2Cl_2$).

## 3.2. Aminocatalytic activation of cyclopropanes towards domino synthesis of quinoline derivatives



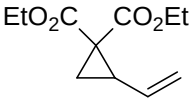

### 3.2.1. Synthesis of vynilcyclopropanes IIa-d

*General procedure (A):*[16] To a solution of the corresponding malonate (10 mmol, 1 eq) and *(E)*-1,4-dibromobut-2-ene (10 mmol, 1 eq) in dry THF (50 mL) was added cesium carbonate (25 mmol, 2.5 eq). The reaction mixture was then heated to 60ºC over night. After cooling down to r.t., the reaction was filtered over celite washed with $Et_2O$. The organic phase was washed with satured aq. $NaHCO_3$ (20 mL), followed by water (20 mL) and brine (20 mL). After filtration over anh. $Na_2SO_4$, the solvent was removed under reduced pressure. Pure products were isolated after flash column chromatography purification.

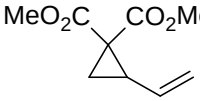
*General procedure (B):*[17] To a solution of the corresponding malonate (5 mmol, 1 eq) and *(E)*-1,4-dibromobut-2-ene (5.5 mmol, 1.1 eq) in dry EtOH (15 mL) was added potassium carbonate (10 mmol, 2 eq). The reaction mixture was then heated to reflux temperature and stirred for 16 h. After cooling down to r.t., the reaction was

[16] Plietker, B.; Holzwarth, M. S.; Dieskau, A. P. *J. Am. Chem. Soc.* **2012**, *134*, 5048.
[17] Bowman, R. K.; Johnson, J.S. *Org. Lett.* **2006**, *8*, 573.

filtered through celite and the organic layer was washed with satured aq. $NH_4Cl$ (20 mL) and extracted with EtOAc (3x15 mL). The combined organics layers were dried over anhydrous $Na_2SO_4$, the solvent was removed under reduced pressure. The product was isolated after flash column chromatography purification as a mixture of diastereoisomers.

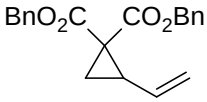


**Diethyl 2-vinylcyclopropane-1,1-dicarboxylate (IIa).** Following the *general procedure (A)* **IIa** (3.498 g, 16.48 mmol) was isolated by FC (hexanes/$Et_2O$ gradient from 9:1 to 8:2) after 48 h in 82% yield as a colorless oil starting from diethyl malonate (3.0 mL, 20 mmol), *(E)*-1,4-dibromobut-2-ene (4.28 g, 20 mmol) and cesium carbonate (16.30 g, 50 mmol) in THF (100 mL). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 5.51–5.35 (m, 1H, C$H_a$=CH$_b$H$_c$ ), 5.28 (dd, *J* = 17.0, 1.7 Hz, 1H, CH$_a$=CH$_b$$H_c$), 5.12 (dd, *J* = 10.0, 1.5 Hz, 1H, CH$_a$=C$H_b$H$_c$), 4.34–4.01 (m, 4H, C$H_2$CH$_3$), 2.56 (q, *J* = 8.2 Hz, 1H, C*H*CH=CH$_2$), 1.71-1.62 (m, 1H, C$H_a$H$_b$C), 1.54 (dd, *J* = 9.0, 4.9 Hz, 1H, CH$_a$$H_b$C), 1.26* (t, *J* = 7.1, 3H, CH$_3$), 1.25* (t, *J* = 7.1, 3H, CH$_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.3, 166.1 (C=O), 132.8 (*C*H=CH$_2$), 117.2 (CH=*C*H$_2$), 60.5, 60.3 (CH$_2$), 35.1 (*C*-CO), 29.8 (*C*HCH=CH$_2$), 19.1 (C-*C*H$_2$), 13.3, 13.2 (CH$_3$). IR (ATR): 2984, 1724, 1637, 1268, 1196 cm$^{-1}$. MS (EI) m/z (%): 212 (M$^+$, 19), 166 (73), 138 (45), 121 (100), 110 (41), 94 (55), 79 (48), 66 (92), 55 (20).

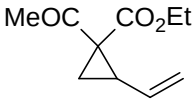


**Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (IIb).** Following the *general procedure* **IIb** (1.583 g, 8.59 mmol) was isolated by FC (hexanes/$Et_2O$ gradient from 9:1 to 8:2) after 48 h in 86% yield as a colorless oil starting from dimethyl malonate (1.1 mL, 10 mmol), *(E)*-1,4-dibromobut-2-ene (2.14 g, 10 mmol) and cesium carbonate (8.15 g, 25 mmol) in THF (50 mL). $^1$H NMR (300 MHz, $CDCl_3$) δ 5.51–5.36 (m, 1H, C$H_a$=CH$_b$H$_c$), 5.29 (dd, *J* = 17.0, 1.6 Hz, 1H, CH$_a$=CH$_b$$H_c$), 5.14 (dd, *J* = 9.9, 1.7 Hz, 1H, CH$_a$=C$H_b$H$_c$), 3.74 (s, 6H, CH$_3$), 2.58 (q, *J* = 8.2 Hz, 1H, C*H*CH=CH$_2$), 1.72 (dd, *J* = 7.5, 5.0 Hz, 1H, C$H_a$H$_b$C), 1.64–1.52 (m, 1H,

$CH_aH_bC$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.1, 167.8 (C=O), 133.0 ($CH=CH_2$), 118.7 ($CH=CH_2$), 52.8, 52.6 ($CH_3$), 35.8 (*C*CO), 31.5 ($CHCH=CH_2$), 20.6 ($CCH_2$). IR (ATR): 2955, 1720, 1634, 1267, 1207 $cm^{-1}$. MS (70 eV) *m/z* (%): 184 ($M^+$, 15), 169 (7), 152 (94), 124 (100), 121 (77), 113 (13), 93 (67), 79 (65), 71 (65), 65 (77), 59 (97), 53 (33).




**Dibenzyl 2-vinylcyclopropane-1,1-dicarboxylate (IIc).** Following the *general procedure* **IIc** (3.037 g, 9.04 mmol) was isolated by FC (hexanes/$Et_2O$ gradient from 9:1 to 8:2) after 48 h in 90% yield as a colorless oil starting from dibenzyl malonate (2.5 mL, 10 mmol), *(E)*-1,4-dibromobut-2-ene (2.14 g, 10 mmol) and cesium carbonate (8.15 g, 25 mmol) in THF (50 mL). $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.35 (s, 10H, $CH_{arom}$), 5.61–5.43 (m, 1H, $CH_a=CH_bH_c$), 5.36 (s, 1H, $CH_a=CH_bH_c$), 5.29 (dd, *J* = 9.62, 3.0 Hz, 1H, $CH_a=CH_bH_c$), 5.26–5.11 (m, 4H, $OCH_2$), 2.75 (q, *J* = 8.3 Hz, 1H, $CHCH=CH_2$), 1.84 (dd, *J* = 7.5, 4.9 Hz, 1H, $CH_aH_bC$), 1.66 (dd, *J* = 9.0, 4.8 Hz, 1H, $CH_aH_bC$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 168.8, 166.7 (C=O), 135.3, 135.2 ($C_{arom}$), 132.7 ($CH=CH_2$), 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 ($CH_{arom}$), 118.4 ($CH=CH_2$), 66.9, 66.8 ($CH_2$), 35.6 (*C*CO), 31.2 ($CHCH=CH_2$), 20.3 ($CCH_2$). IR (ATR): 3031, 1720, 1501, 1268, 1188 $cm^{-1}$. MS (70 eV) *m/z* (%): 107 ($M^+$-$C_{14}H_3O_3^{\cdot}$, 2), 91 (100), 77 (6), 65 (11), 51 (3).

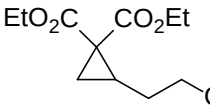



**Ethyl 1-acetyl-2-vinylcyclopropane-1-carboxylate (IId):** Following the *general procedure* (B) **IId** (710mg, 3.9 mmol) was isolated by FC (hexanes/$Et_2O$ gradient from 19:1 to 9:1) after 16h in 78% yield as a colorless oil starting from ethyl acetoacetate (886 µL, 5 mmol), *(E)*-1,4-dibromobut-2-ene (1.17 g, 5.5 mmol) and potassium carbonate (1.38 g, 10 mmol) in EtOH (15 mL). $^1H$ NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer) δ 5.62-5.42 (m, 0.6H, $C_{alkene}$-H), 5.37-5.22 (m, 1.4H, $C_{alkene}$-H), 5.20-5.08 (m, 0.9H, $C_{alkene}$-H), 4.33–4.13 (m, 2H, $OCH_2$), 2.71-2.54 (m, 1H, CH), 2.40 (s, 1.8H, $COCH_3$), 2.32* (s, 1.0H, $COCH_3$), 1.84 (dd, *J* = 7.5, 4.6 Hz, 0.4H, CH-$CH_2$), 1.76* (dd, *J* = 7.7, 4.3 Hz, 0.6H, CH-$CH_2$), 1.65-1.49 (m, 1H, CH-$CH_2$), 1.37-1.21

(m, 3H, $OCH_2CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 201.5 (*C*OMe), 200.5*(*C*OMe), 170.1* ($CO_2Et$), 168.5 ($CO_2Et$), 133.0 (H*C*=$CH_2$), 132.7* (H*C*=$CH_2$), 118.7* (HC=*C*$H_2$), 118.6 (H*C*=$CH_2$), 61.3*($OCH_2$), 61.2 ($OCH_2$), 43.0 (*C*-$CO_2Et$), 42.5* (*C*-$CO_2Et$), 34.0 ($COCH_3$), 33.3*($COCH_3$), 30.3*(CH-*C*$H_2$), 29.3 (CH-C*H*$_2$), 22.8 (CH), 19.9* (CH), 14.1 ($OCH_2CH_3$), 14.0*($OCH_2CH_3$). IR (ATR): 2984, 1724, 1699, 1639, 1260, 1181 $cm^{-1}$. MS (70 eV) *m/z* (%): 182 ($M^+$, 3), 167 (2), 139 (61), 121 (100), 109 (21), 94 (54), 66 (72), 55 (12).

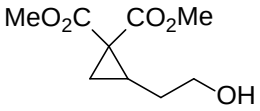
### 3.2.2. Synthesis of hydroxyethylcyclopropane carboxylates IIIa-d

*General procedure:* A borane dimethylsulfide complex (2M in THF) (1.2 eq) was added to a solution of the corresponding vinylcyclopropane (**IIa-d**) (1 eq) in dry THF (0,53M) at 0ºC. The reaction mixture was stirred at 0ºC for 3h. Then NaOH 3M (1.2 eq) was added dropwise, followed by $H_2O_2$ (1.2 eq). The mixture was then heated to 50ºC over night. The reaction was quenched with $H_2O$ (5 mL) and extracted with EtOAc (3 x 15 mL). The organic extracts were washed with brine (20 mL). After filtration over anh. $Na_2SO_4$, the solvent was removed under reduced pressure. Pure products (**IIIa-d**) were isolated after flash column chromatography purification.

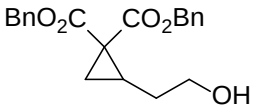



**Diethyl 2-(2-hydroxyethyl)cyclopropane-1,1-dicarboxylate (IIIa).** Following the *general procedure* **IIIa** (660 mg, 2.87 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 16 h in 56% yield as a colorless oil starting from **IIa** (1.093 g, 5.15 mmol), borane dimethylsulfide complex (3.09 mL, 6.18 mmol), NaOH (2.06 mL, 6.18 mmol), and $H_2O_2$ (2.06mL 6.18 mmol) in THF (9.71 mL) $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.09–3.81 (m, 4H, $CH_2$), 3.43 (t, *J* = 6.4 Hz, 2H, $CH_2OH$), 1.81–1.66 (m, 1H, C$H_a$$H_b$C), 1.54-1.38 (m, 1H, $CH_aH_bC$), 1.31–1.09 (m, 3H, C*H*C$H_2$$CH_2$), 1.09-0.97 (m, 6H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 170.1, 167.9 (C=O), 61.1, 61.0 ($OCH_2$), 60.9 ($CH_2OH$), 33.4 (*C*CO), 31.4 (*C*$H_2$$CH_2OH$), 24.7 (*C*H$CH_2$$CH_2$), 20.1 (C*C*$H_2$), 13.7, 13.6 ($CH_3$). IR (ATR): 2922, 1720, 1285, 1203, 1041,

1024 $cm^{-1}$. MS (70 eV) *m/z* (%): 185 ($M^+$-$C_2H_5O^·$, 19), 160 (43), 139 (53), 125 (24), 108 (100), 97 (15), 81 (23), 67(23), 53 (45).

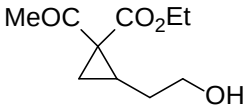



**Dimethyl 2-(2-hydroxyethyl)cyclopropane-1,1-dicarboxylate (IIIb).** Following the *general procedure* **IIIb** (172 mg, 0.85 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 16 h in 33% yield as a colorless oil starting from **IIb** (471 mg, 2.55 mmol), borane dimethylsulfide complex (1.53 mL, 3.06 mmol), NaOH (1.02 mL, 3.06 mmol), and $H_2O_2$ (1.02 mL 3.06 mmol) in THF (4.81 mL). $^1$H NMR (300 MHz, $CDCl_3$) δ 3.69–3.51 (m, 8H, C*H*$_3$, C*H*$_2$OH), 2.89-2.77 (bs, 1H, OH), 1.96–1.76 (m, 1H, C*H*$_a$H$_b$C), 1.65–1.49 (m, 1H, CH$_a$*H*$_b$C), 1.46–1.20 (m, 3H, C*H*C*H*$_2$CH$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.7, 168.7 (C=O), 61.3 ($CH_2OH$), 52.5, 52.4 ($CH_3$), 33.4 (*C*CO), 31.6 (*C*H$_2$CH$_2$OH), 25.5 (*C*HCH$_2$CH$_2$), 20.7 (C*C*H$_2$). IR (ATR): 3441, 1719, 1282, 1214 $cm^{-1}$. MS (70 eV) *m/z* (%): 171 ($M^+$-$CH_3O^·$, 7), 152 (8), 139 (50), 132 (53), 124 (11), 97 (8), 80 (30), 67(20), 53 (52). HRMS: Calculated for $[C_9H_{15}O_5]^+$: 203.0919 [$(M+H)^+$]; found: 203.0927.




**Dibenzyl 2-(2-hydroxyethyl)cyclopropane-1,1-dicarboxylate (IIIc).** Following the *general procedure* **IIIc** (1.47 g, 4.16 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 1:1) after 16 h in 57% yield as a colorless oil starting from **IIc** (2.45 g, 7.28 mmol), borane dimethylsulfide complex (4.37 mL, 8.74 mmol), NaOH (2.91 mL, 8.74 mmol), and $H_2O_2$ 2.91 mL 8.74 mmol) in THF (13.74 mL) $^1$H NMR (300 MHz, $CDCl_3$) δ 7.43–7.19 (m, 10H, $CH_{arom}$), 5.23–5.06 (m, 4H, $OCH_2$), 3.70–3.50 (m, 2H, $CH_2OH$), 2.08-1.96 (m, 1H, C*H*$_a$H$_b$C), 1.70–1.52 (m, 1H, CH$_a$*H*$_b$C), 1.51-1.37 (m, 3H, C*H*C*H*$_2$CH$_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.1, 168.2 (C=O), 135.6, 135.5 ($C_{arom}$), 128.6, 128.6, 128.6, 128.6, 128.5, 128.4, 128.2, 128.0 ($CH_{arom}$), 67.6, 67.3 ($OCH_2$), 61.9 ($CH_2OH$), 33.91 (*C*CO), 31.7 (*C*H$_2$CH$_2$OH), 25.8 (*C*HCH$_2$CH), 21.0 (C*C*H$_2$). IR (ATR): 3487, 1720, 1285, 1192, 1070, 1038 $cm^{-1}$. MS (70 eV) *m/z* (%): 247

($M^+$-$C_7H_7O^\cdot$, 1), 140 (43), 112 (82), 91 (100), 77 (18), 65 (26), 51 (13). HRMS: Calculated for $[C_{14}H_{15}O_4]^+$: 247.0970 [(M+H)-BnOH$^+$]; found: 247.0985.




**Ethyl 1-acetyl-2-(2-hydroxyethyl)cyclopropane-1-carboxylate (IIId).** Following the *general procedure* **IIId** (275 mg, 1.38 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 1:1) after 1 h in 18% yield as a colorless oil starting from **IId** (1.01g, 6.0 mmol), borane dimethylsulfide complex (3.60 mL, 7.20 mmol), NaOH (2.4 mL, 7.20 mmol), and $H_2O_2$ (2.4 mL 7.20 mmol) in THF (11.3 mL). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 4.23–4.07 (m, 2H, $COCH_2$), 3.56 (t, *J* = 6.5 Hz, 2H, $CH_2OH$), 2.97-2.81 (bs, 1H, OH), 2.30* (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$), 2.00–1.83 (m, 1H, $CH_aH_bC$), 1.71-1.39 (m, 2H, $CH_aH_bC$), 1.41–1.27 (m, 2H, $CHCH_2CH_2$), 1.21 (t, *J* = 7.1 Hz, 3H, $CH_2CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 203.1, 202.3*, 171.1*, 169.7, 61.7*, 61.5, 61.4, 61.3*, 41.2, 40.2*, 31.3, 30.7*, 30.2*, 29.1, 28.6*, 28.0, 23.1, 20.4*, 14.1, 14.0*. IR (ATR): 3422, 2926, 1720, 1695, 1311, 1189 cm$^{-1}$. MS (70 eV) *m/z* (%): 185 ($M^+$-$OH^\cdot$, 2), 169 (12), 154 (41), 139 (56), 135 (17), 130 (100), 124 (80), 109 (51), 102 (21), 97 (54), 81 (82), 67 (54), 55 (59), 53 (56). HRMS: Calculated for $[C_{10}H_{17}O_4]^+$: 201.1127 [$(M+H)^+$]; found: 201.1132.

### 3.2.3. Synthesis of cyclopropaneacetaldehydes 14a-d

*General procedure:* IBX (2.5 eq) was added to a solution of the corresponding alcohol (**IIIa-d**) (1 eq) in EtOAc (0.1M). The reaction mixture was stirred at reflux for 3h. Afterwards, the reaction was filtered through a celite pad. The solvent was removed under reduced pressure and pure products were isolated after flash column chromatography purification.

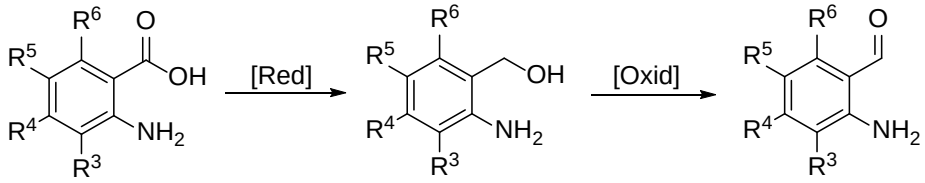
**Diethyl 2-(2-oxoethyl)cyclopropane-1,1-dicarboxylate (14a).** Following the *general procedure* **14a** (1.13 g, 4.93 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) after 3 h in 88% yield as a yellow oil starting from **IIIa** (1.30 g, 5.62 mmol) and IBX (3.94 g, 14.05 mmol) in EtOAc (56.2 mL). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 4.42 – 3.86 (m, 4H, $OCH_2$), 2.64-2.41 (m, 2H, C$H_2$CHO), 2.26–2.11 (m, 1H,C$H$C$H_2$CHO), 1.54 (dd, *J* = 9.0, 4.8 Hz, 1H, C$H_a$H$_b$C), 1.38 (dd, *J* = 7.2, 5.1 Hz, 1H, CH$_a$$H_b$C), 1.32-1.18 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.2 (CHO), 168.9, 167.2 (C=O), 60.8, 60.8 ($OCH_2$), 41.9 ($CH_2$CHO), 32.4 (*C*CO), 20.2 ($CH_2$C$H_2$C$H_2$), 19.2 (*C*HC$H_2$CHO), 13.3, 13.2 ($CH_3$). IR (ATR): 2984, 1724, 1275, 1207 cm$^{-1}$. MS (70 eV) *m/z* (%): 183 ($M^+$-$C_2H_5O^\cdot$, 15), 160 (41), 136 (47), 108 (100), 81 (46), 53 (26). HRMS: Calculated for $[C_{11}H_{17}O_5]^+$: 229.1076 [$(M+H)^+$]; found: 229.1091.

**Dimethyl 2-(2-oxoethyl)cyclopropane-1,1-dicarboxylate (3b).** Following the *general procedure* **14b** (56 mg, 0.28 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) after 3 h in 92% yield as a yellow oil starting from **IIIb** (59 mg, 0.30 mmol), and IBX (202 mg, 0.72 mmol) in EtOAc (3 mL). $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 9.75 (s, 1H, CHO), 3.74* (s, 3H, $CH_3$), 3.73* (s, 3H, $CH_3$), 2.66–2.38 (m, 2H, C$H_2$CHO), 2.20 (dq, *J* = 14.8, 7.4 Hz, 1H, C$H$C$H_2$CHO), 1.57 (dd, *J* = 9.1, 4.9 Hz, 1H, C$H_a$H$_b$C), 1.41 (dd, *J* = 7.5, 5.0 Hz, 1H, CH$_a$$H_b$C). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.6 (CHO), 170.0, 168.5 (C=O), 52.9, 52.8 ($OCH_3$), 42.8 ($CH_2$CHO), 32.9 (*C*CO), 21.4 (*C*HC$H_2$CHO), 20.5 ($CH_2$C$H_2$C$H_2$). IR (ATR): 2923, 1716, 1282, 1218 cm$^{-1}$. MS (70 eV) *m/z* (%): 169 ($M^+$-$CH_3O^\cdot$, 29), 157 (10), 140 (35), 108 (100), 97 (7), 81 (29), 69 (12), 59 (31), 53 (31). HRMS: Calculated for $[C_9H_{12}O_5]^+$: 200.0685 [$(M+H)^+$-H]; found: 200.0624.

**Dibenzyl 2-(2-oxoethyl)cyclopropane-1,1-dicarboxylate (14c).** Following the *general procedure* **14c** (1.17 g, 3.33 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 3 h in 80% yield as a yellow oil starting from **IIIc** (1.47 g, 4.16 mmol), and IBX (2.91 g, 10.40 mmol) in EtOAc (41.6 mL). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H, CHO), 7.42–7.07 (m, 10H, $CH_{arom}$), 5.23-5.09 (m, 4H, $OCH_2$), 2.60–2.34 (m, 2H, C$H_2$CHO), 2.25 (dq, *J* = 14.8, 7.4 Hz, 1H, C$H$C$H_2$CHO), 1.60 (dd, *J* = 9.1, 4.9 Hz, 1H, C$H_a$H$_b$C), 1.45 (dd, *J* = 7.6, 5.0 Hz, 1H, CH$_a$$H_b$C). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.3 (CHO), 169.2, 167.7 (C=O), 135.3, 135.2 ($C_{arom}$), 128.4, 128.3, 128.3, 128.2, 128.1, 128.9 ($CH_{arom}$), 67.4, 67.2 ($OCH_2$), 42.4 (*C*H$_2$CHO), 33.0 (*C*CO), 21.5 (*C*HCH$_2$CHO), 20.5 (*C*H$_2$CHCH$_2$). IR (ATR): 2955, 1720, 1274, 1199 cm$^{-1}$. MS (70 eV) *m/z* (%): 246 ($M^+$-$C_7H_6O^{\cdot}$, 1), 140 (37), 112 (78), 91 (100), 79 (22), 65 (24), 53 (11). HRMS: Calculated for $[C_{11}H_{17}O_5]^+$: 229.1076 [$(M+H)^+$]; found: 229.1091.

Ethyl 1-acetyl-2-(2-oxoethyl)cyclopropane-1-carboxylate **(14d).** Following the *general procedure* **14d** (157 mg, 0.79 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 3 h in 70% yield as a yellow oil starting from **IIId** (227 mg, 1.13 mmol), and IBX (794 mg, 2.84 mmol) in EtOAc (11.3 mL). $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer), (** denotes the ring-opened isomer) δ 9.76 (s, 1H, CHO), 9.71* (s, 1H, CHO), 9.49** (dd, *J* = 7.7 Hz, 1H, CHO), 6.78** (dt, 15.6, 6.8 Hz, 1H, CHO-C*H*), 6.13** (dd, *J* = 15.7, 7.7 Hz, 1H, CHO-CH=C*H*), 4.31-4.11 (m, 2H, $OCH_2$), 3.64** (t, *J* = 7.2 Hz, 1H, CO-CH), 2.86** (td, *J* = 7.0, 1.4 Hz, 2H, HC-C$H_2$), 2.67 (dd, *J* = 7.2, 0.9 Hz, 2H, CHO-C$H_2$), 2.43 (s, 3H, $COCH_3$), 2.41* (s, 3H, $COCH_3$), 2.29** (s, 3H, $COCH_3$), 2.10 (dd, *J* = 9.0, 7.4 Hz, 1H, CH), 1.60 (dd, *J* = 9.1, 4.4 Hz, 1H, C$H_a$H$_b$), 1.41 (dd, *J* = 7.7, 4.4 Hz, 1H, CH$_a$$H_b$, 1.34-1.23 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer), (** denotes the ring-opened isomer) δ 202.1* (*C*OMe), 202.0 (*C*OMe), 201.0** (*C*OMe), 199.7 (CHO), 199.3* (CHO), 193.3** (CHO), 170.4* ($CO_2$Et), 169.3 ($CO_2$Et), 168.4**

($CO_2Et$), 153.3** (C=C), 134.4** (C=C), 61.8** ($OCH_2$), 61.6 ($OCH_2$), 61.4* ($OCH_2$), 57.7** (CO-H*C*-CO), 42.4 ($CH_2CHO$), 41.6* ($CH_2CHO$), 40.0 (CCO), 39.5* (CCO), 30.5** ($COCH_3$), 30.4** (C=C-*C*$H_2$), 29.2 (*C*$HCH_2CHO$), 29.1** (*C*$HCH_2CHO$), 24.3* ($COCH_3$), 23.4 ($COCH_3$), 22.0 (*C*$H_2CHCH_2$), 20.4* (*C*$H_2CHCH_2$), 14.0* ($CH_2CH_3$), 14.0 ($CH_2CH_3$), 14.0** ($CH_2CH_3$). IR (ATR): 2920, 1724, 1699, 1264, 1196 $cm^{-1}$. MS (70 eV) *m/z* (%): 198 ($M^+$, 8), 170 (9), 154 (97), 125 (100), 69 (109), 99 (27), 81 (84), 68 (55), 55 (51), 53 (55). HRMS: Calculated for $[C_{10}H_{15}O_4]^+$: 199.0970 $[(M+H)^+]$; found: 199.0974.

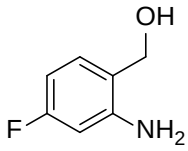



**3.2.4. Synthesis of aminobenzyl alcohols Iva-o**

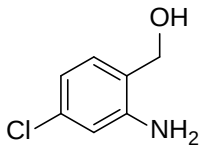
*General procedure (A):* To a solution of the corresponding anthranilic acid derivative (1 eq) in THF (1.75M) was added dropwise 1.08M borane dimethyl sulfide complex in THF (3 eq) at 0ºC under argon atmosphere for 10 min. After 24 h with stirring at 30ºC, the reaction mixture was cooled to 0ºC, added aqueous THF (THF/$H_2O$ 1:1.4) and $K_2CO_3$ (1 eq) in portions. The reaction was extracted with $Et_2O$ (3 x 15 mL). The combined organic extracts were washed with brine (20 mL), dried over anh. $Na_2SO_4$ and evaporated in vacuo. Pure products were isolated after flash column chromatography purification.

*General procedure (B):* To a suspension of LAH (9 mmol, 3 eq) in dry THF (0.33M) cooled at -10ºC, the corresponding 2-aminobenzoic acid (3.3 mmol, 1eq) was added portion-wise under argon atmosphere. The reaction mixture was warmed slowly to ambient temperature and stirred at r.t. for 4 h. The reaction was quenched slowly with sat. $NH_4Cl$ (3 mL) at -10ºC and then warmed to ambient temperature.

Afterwards it was diluted with EtOAc and filtered over celite. The filtrate was successively washed with water and brine solution and dried over anh. $Na_2SO_4$. The solvent was removed under reduced pressure and pure products were isolated after flash column chromatography purification.

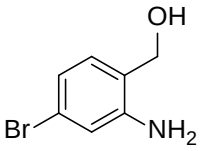



**(2-Amino-4-fluorophenyl)methanol (IVb).** Following the *general procedure (B)* **IVb** (382 mg, 2.71 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 2.5 h in 84% yield as a white solid starting from LAH (368 mg, 9.7 mmol) in THF (9.8 mL) and 2-amino-4-fluorobenzoic acid (500 mg, 3.22 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 7.04-6.94 (m, 1H, $C_{arom}HC_{arom}CH_2$), 6.49 – 6.23 (m, 2H, $C_{arom}HC_{arom}FC_{arom}H$), 4.63 (s, 2H, $CH_2$), 4.56-3.96 (bs, 2H, $NH_2$), 2.01-1.22 (bs, 1H, OH). $^{13}$C NMR (75 MHz, $CDCl_3$) δ163.8 (d, *J*=244.2 Hz, $C_{arom}F$), 147.9 (d, *J*=11.1 Hz, $C_{arom}NH_2$), 130.5 (d, *J*=10.3 Hz, $C_{arom}HC_{arom}HC_{arom}F$), 120.5 (d, *J*=2.9 Hz, $C_{arom}CH_2$), 104.3 (d, *J*=21.5 Hz, $C_{arom}HC_{arom}HC_{arom}F$), 102.6 (d, *J*=24.6 Hz, $C_{arom}HC_{arom}NH_2$), 63.8 ($CH_2OH$). IR (ATR): 3389, 3156, 1612, 1598, 1511, 1160, 991 $cm^{-1}$. MS (70 eV) *m/z* (%): 140 ($M^+$-H, 6), 139 (93), 122 (5), 111 (100), 94 (20), 83 (67), 57 (20). M.p.: 45-47°C.

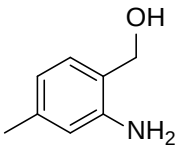



**(2-Amino-4-chlorophenyl)methanol (IVc).** Following the *general procedure (A1)* **IVc** (297 mg, 1.88 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 6:4) after 24 h in 32% yield as a white solid starting from 2-amino-5-chlorobenzoic acid (1g, 5.83 mmol) in THF (3.3 mL) and a solution of borane-tetrahidrofuran complex (8.7 mL) in THF (7.4 mL). $^1$H NMR (300 MHz, MeOD) δ 7.02 (d, *J* = 8.0 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 6.72 (d, *J* = 2.0 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Cl$), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 4.52 (s, 2H, $CH_2$). $^{13}$C NMR (75 MHz, MeOD) δ 147.6 ($C_{arom}NH_2$), 133.6 ($C_{arom}CH_2$), 129.5

($C_{arom}HC_{arom}CH_2$), 123.8 ($C_{arom}Cl$), 116.7 ($C_{arom}HC_{arom}HC_{arom}Cl$), 114.8 ($C_{arom}HC_{arom}NH_2$), 61.5 ($CH_2OH$). IR (ATR): 3383, 3285, 1605, 1583, 1494, 1074, 999 $cm^{-1}$. MS (70 eV) *m/z* (%): 159 ($M^+$, 29), 157 ($M^+$, 100), 139 (98), 138 (100), 127 (51), 112 (24), 93 (36), 83 (65), 63 (34), 51 (22). M.p.: 138-140ºC.

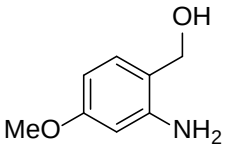



**(2-Amino-4-bromophenyl)methanol (IVd).** Following the *general procedure (B)* **IVd** (406 mg, 2.01 mmol) was isolated by FC (hexanes/EtOAc 3:7) after 2.5 h in 87% yield as a white solid starting from LAH (262 mg, 6.9 mmol) in THF (7.0 mL) and 2-amino-4-bromobenzoic acid (500 mg, 2.30 mmol). $^1$H NMR (300 MHz, MeOD) δ 6.97 (d, *J* = 8.0 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 6.88 (d, *J* = 1.9 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 6.74 (dd, *J* = 8.0, 1.9 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Br$), 4.51 (s, 2H, $CH_2$). $^{13}$C NMR (75 MHz, MeOD) δ 147.9 ($C_{arom}NH_2$), 129.7 ($C_{arom}HC_{arom}CH_2$), 124.2 ($C_{arom}CH_2$), 121.6 ($C_{arom}Br$), 119.7 ($C_{arom}HC_{arom}HC_{arom}Br$), 117.7 ($C_{arom}HC_{arom}NH_2$), 61.6 ($CH_2OH$). IR (ATR): 3361, 3297, 3149, 1602, 1573, 1487, 1060, 991 $cm^{-1}$. MS (70 eV) *m/z* (%): 203 ($M^+$, 31), 201 (100), 183 (66), 173 (85), 127 (10), 92 (87), 75 (28), 65 (82), 52 (43). M.p.: 140-142ºC.

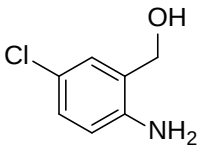



**(2-Amino-4-methylphenyl)methanol (IVf).** Following the *general procedure (A)* **IVf** (273 mg, 1.99 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) after 24 h in 60% yield as a white solid starting from 2-amino-4-methylbenzoic acid (500 mg, 3.30 mmol) in THF (4.2 mL) and a solution of borane-tetrahidrofuran complex (4.9 mL) in THF (4.2 mL). $^1$H NMR (300 MHz, MeOD) δ 6.95 (d, *J* = 7.5 Hz, 1H,$C_{arom}HC_{arom}CH_2$), 6.59 (s, 1H, $C_{arom}HC_{arom}NH_2$), 6.50 (d, *J* = 7.4 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}CH_3$), 4.54 (s, 2H, $CH_2$), 2.22 (s, 3H, $CH_3$). $^{13}$C NMR (70 MHz, MeOD) δ 147.1 ($C_{arom}NH_2$), 139.6 ($C_{arom}CH_3$), 130.0 ($C_{arom}HC_{arom}CH_2$), 124.3 ($C_{arom}CH_2$), 120.0 ($C_{arom}HC_{arom}HC_{arom}CH_3$), 118.0 ($C_{arom}HC_{arom}NH_2$), 63.4 ($CH_2OH$), 21.3($CH_3$). IR (ATR): 3379, 3095, 1622, 1587, 1515,

1002 $cm^{-1}$. MS (70 eV) *m/z* (%): 137 ($M^+$, 74), 118 (100), 106 (27), 91 (51), 77 (21), 65 (14), 51 (8). M.p.: 138-140ºC.

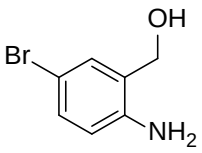



**(2-Amino-4-methoxyphenyl)methanol (IVg).** Following the *general procedure (2)* **4j** (338 mg, 2.20 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 2.5 h in 74% yield as a white solid starting from LAH (340 mg, 8.97 mmol) in THF (9.0 mL) and 2-amino-6-chlorobenzoic acid (500 mg, 2.99 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 6.93 (d, *J* = 8.1 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 6.24 (m,2H, $C_{arom}HC_{arom}C_{arom}H$), 4.54 (s, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ160.8 ($C_{arom}OCH_3$), 147.4 ($C_{arom}NH_2$), 130.4 ($C_{arom}HC_{arom}CH_2$), 118.1 ($C_{arom}CH_2$), 103.3 ($C_{arom}HC_{arom}HC_{arom}OCH_3$), 101.8 ($C_{arom}HC_{arom}NH_2$), 63.7 ($CH_2OH$), 55.2 ($CH_3$). IR (ATR): 3397, 3206, 1622, 1583, 1512, 1196, 1089, 984 $cm^{-1}$. MS (70 eV) *m/z* (%): 153 ($M^+$, 19), 137 (63), 122 (34), 105 (57), 92 (25), 83 (100), 65 (27), 51 (25). M.p.: 78-80ºC.

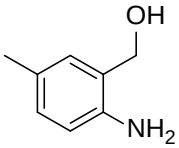



**(2-Amino-5-chlorophenyl)methanol (IVh).** Following the *general procedure (A)* **IVh** (800 mg, 5.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to EtOAc) after 24 h in 87% yield as a white solid starting from 2-amino-5-chlorobenzoic acid (1g, 5.83 mmol) in THF (3.3 mL) and a solution of borane-tetrahidrofuran complex (8.7 mL) in THF (7.4 mL). $^1$H NMR(300 MHz, $CDCl_3$) δ 7.07 (m, 2H, $C_{arom}HC_{arom}ClC_{arom}H$), 6.62 (d, *J* = 8.3 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 4.61 (s, 2H, $CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.6 ($C_{arom}NH_2$), 129.0 ($C_{arom}HC_{arom}HC_{arom}Cl$), 128.8 ($C_{arom}HC_{arom}CH_2$), 126.1 ($C_{arom}CH_2$), 122.6 ($C_{arom}Cl$), 117.1 ($C_{arom}HC_{arom}NH_2$), 63.8 ($CH_2OH$). IR (ATR): 3383, 3116, 1493, 1099, 1006 $cm^{-1}$. MS (70 eV) *m/z* (%): 159 ($M^+$, 20), 157 ($M^+$, 74), 138 (100), 127 (47), 112 (37), 93 (34), 77 (38), 65 (25), 51 (17). M.p.: 106-108ºC.

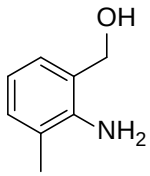
**(2-Amino-5-bromophenyl)methanol (IVi).** Following the *general procedure (B)* **IVi**



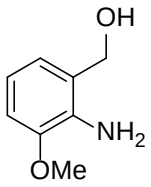

(383 mg, 1.90 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 2.5 h in 77% yield as a white solid starting from LAH (282 mg, 7.42 mmol) in THF (7.5 mL) and 2-amino-5-bromobenzoic acid (500 mg, 2.47mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, *J* = 2.3 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 7.13 (dd, *J* = 8.5, 2.4 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Br$), 6.64 (d, *J* = 8.5 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 4.51 (s, 2H, $CH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 145.1 ($C_{arom}NH_2$), 130.6 ($C_{arom}HC_{arom}CH_2$), 130.4 ($C_{arom}HC_{arom}HC_{arom}Br$), 127.6 ($C_{arom}CH_2$), 117.1 ($C_{arom}HC_{arom}NH_2$), 108.6 ($C_{arom}Br$), 61.3 ($CH_2OH$). IR (ATR): 3354, 3268, 1598, 1472, 1002 $cm^{-1}$. MS (70 eV) *m/z* (%): 203 ($M^+$, 55), 201 ($M^+$, 96), 185 (100), 171 (81), 156 (25), 147 (12), 117 (10), 92 (69), 85 (27), 77 (80), 65 (76), 52 (43). M.p.: 105-109°C.




**(2-Amino-5-methylphenyl)methanol (IVj).** Following the *general procedure (B)* **IVj** (197 mg, 1.45 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 2.5 h in 73% yield as a white solid starting from LAH (226 mg, 5.95mmol) in THF (6.0 mL) and 2-amino-5-methylbenzoic acid (300 mg, 1.98 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.0 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}CH_3$), 6.89 (s, 1H, $C_{arom}HC_{arom}CH_2$), 6.62 (d, *J* = 7.9 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 4.63 (s, 2H, $CH_2$), 3.27 (bs, 2H, $NH_2$), 2.24 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 143.5 ($C_{arom}NH_2$), 130.0 ($C_{arom}HC_{arom}CH_2$), 129.9 ($C_{arom}CH_2$), 127.6 ($C_{arom}CH_3$), 125.2 ($C_{arom}HC_{arom}HC_{arom}CH_3$), 116.4 ($C_{arom}HC_{arom}NH_2$), 64.5 ($CH_2OH$), 20.5 ($CH_3$). IR (ATR): 3389, 3120, 1637, 1508, 1020 $cm^{-1}$. MS (70 eV) *m/z* (%): 137 ($M^+$, 66), 118 (100), 106 (65), 91 (52), 77 (29), 65 (15), 51 (13). M.p.: 122-124°C.

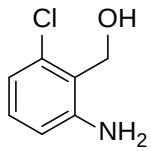



**(2-Amino-3-methylphenyl)methanol (IVk).** Following the *general procedure (B)* **IVk** (355 mg, 2.59 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 1:1) after 4 h in 78% yield as a white solid starting from LAH (376 mg, 9.9 mmol) in THF (10.0 mL) and 2-amino-3-methylbenzoic acid (500 mg, 3.30 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.5 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 6.92 (d, *J* = 7.5 Hz, 1H, $C_{arom}HC_{arom}CH_3$), 6.66 (t, *J* = 7.5 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}H$), 4.61 (s, 2H, $CH_2$), 4.17-2.97 (bs, 2H, $NH_2$), 2.18 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 144.0 ($C_{arom}NH_2$), 130.5 ($C_{arom}HC_{arom}CH_3$), 127.2 ($C_{arom}HC_{arom}CH_2$), 124.6 ($C_{arom}CH_2$), 122.9 ($C_{arom}CH_3$), 117.9 ($C_{arom}HC_{arom}HC_{arom}H$), 64.0 ($CH_2OH$), 17.3 ($CH_3$). IR (ATR): 3404, 3322, 3278, 1634, 1469, 1020 $cm^{-1}$. MS (70 eV) *m/z* (%): 137 ($M^+$, 77), 119 (100), 106 (31), 91 (61), 77 (23), 65 (14), 51 (10). M.p.: 62-66$^{o}$C.

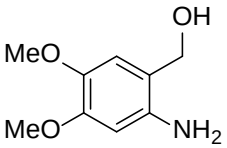



**(2-Amino-3-methoxyphenyl)methanol (IVl).** Following the *general procedure (A)* **IVl** (335 mg, 2.19 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 24 h in 73% yield as a brown oil from 2-amino-3-methoxybenzoic acid (500 mg, 2.99 mmol) in THF (1.8 mL) and a solution of borane-tetrahidrofuran complex (4.5 mL) in THF (3.8 mL). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.79 (dd, *J* = 7.5, 1.8 Hz, 1H, $C_{arom}HC_{arom}CH_2$), 6.73 (dd, *J* = 7.5, 1.8 Hz, 1H, $C_{arom}HC_{arom}OCH_3$), 6.71–6.64 (m, 1H, $C_{arom}HC_{arom}HC_{arom}H$), 4.67 (s, 2H, $CH_2$), 3.86 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 147.3 ($C_{arom}OCH_3$), 134.9 ($C_{arom}CH_2$), 125.3 ($C_{arom}NH_2$), 121.0 ($C_{arom}HC_{arom}CH_2$), 117.4 ($C_{arom}HC_{arom}HC_{arom}CH_2$), 109.9 ($C_{arom}HC_{arom}OCH_3$), 62.8 ($CH_2OH$), 55.47 ($CH_3$). IR (ATR): 3364, 1612, 1482, 1239, 1000 $cm^{-1}$. MS (70 eV) *m/z* (%): 153 ($M^+$, 100), 134 (22), 120 (16), 106 (72), 92 (77), 80 (12), 65 (40), 52 (12).

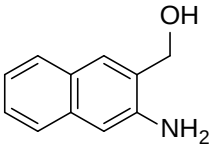
**(2-Amino-6-chlorophenyl)metanol (IVm).** Following the *general procedure (B )* **IVm**




(400 mg, 2.54 mmol) was isolated by FC (hexanes/EtOAc gradient from 7:3 to 3:7) after 1.5 h in 88% yield as a white solid starting from LAH (332mg, 8.7mmol) in THF (3.3 mL) and 2-amino-6-chlorobenzoic acid (500 mg, 2.90 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.02 (t, *J* = 8.0 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Cl$), 6.76 (d, *J* = 8.0 Hz, 1H, $C_{arom}HC_{arom}Cl$), 6.60 (d, *J* = 7.8 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 4.90 (s, 2H, $CH_2$), 1.80-1.39 (bs, 2H, $NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ148.0 ($C_{arom}NH_2$), 134.1 ($C_{arom}Cl$), 129.6($C_{arom}HC_{arom}HC_{arom}Cl$), 122.1 ($C_{arom}CH_2$), 119.2 ($C_{arom}HC_{arom}Cl$), 114.7 ($C_{arom}HC_{arom}NH_2$), 59.5 ($CH_2OH$). IR (ATR): 3386, 3285, 1601, 1577, 1451, 1006, 991 $cm^{-1}$. MS (70 eV) *m/z* (%): 159 ($M^+$, 24), 157 ($M^+$, 76), 138 (100), 127 (18), 112 (39), 104 (18), 93 (24), 85 (6), 77 (37), 65 (28), 51 (17). M.p.: 82-84$^{o}$C.




**(2-Amino-4,5-dimethoxyphenyl)methanol (IVn).** Following the *general procedure (B)* **IVn** (169 mg, 0.92 mmol) was isolated by FC (hexanes/EtOAc gradient from 3:7 to 2:8) after 4 h in 28% yield as a brown oil starting from LAH (376 mg, 9.90 mmol) in THF (10.0 ml) and 2-amino-4,5-dimethoxybenzoic acid (631 mg, 3.30 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 6.58 (s, 1H, $C_{arom}HC_{arom}CH_2$), 6.23 (s, 1H, $C_{arom}HC_{arom}NH_2$), 4.49 (s, 2H, $CH_2$), 3.77 (s, 3H, $CH_3$), 3.74 (s, 3H, $CH_3$), 3.56–3.31 (bs, 2H, $NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ149.8 ($NH_2C_{arom}C_{arom}HC_{arom}H$), 141.4 ($C_{arom}C_{arom}HC_{arom}CH_2$), 139.9 ($C_{arom}NH_2$), 116.8 ($C_{arom}CH_2$), 114.1 ($C_{arom}HC_{arom}CH_2$), 101.4 ($C_{arom}HC_{arom}NH_2$), 63.5 ($CH_2OH$), 56.8 ($CH_3$), 55.9 ($CH_3$). IR (ATR): 3368, 1616, 1511, 1454, 1203 , 1124, 998 $cm^{-1}$. MS (70 eV) *m/z* (%): 183 ($M^+$, 2), 181 (100), 166 (91), 138 (48), 110 (19), 94 (34), 83 (83), 65 (16), 52 (22).

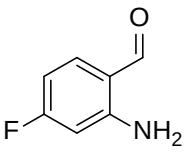



**(2-aminonaphthalen-3-yl)methanol (IVo).** Following the *general procedure (B)* **IVo** (270 mg, 1.56 mmol) was isolated by

FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 2.5 h in 59% yield as a yellow-brown solid starting from LAH (304 mg, 8.00 mmol) in THF (8.0 mL) and 3-aminonaphthalene-2-carboxylic acid (500 mg, 2.67 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 1H, $C_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 7.63 (s, 1H, $C_{arom}HC_{arom}CH_2$), 7.57 (d, *J* = 8.3 Hz, 1H, $C_{arom}HC_{arom}C_{arom}HC_{arom}CH_2$), 7.31 (t, *J* = 7.2 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}C_{arom}H_2$), 7.18 (t, *J* = 7.4 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 7.09 (s, 1H, $C_{arom}HC_{arom}NH_2$), 4.76 (s, 2H, $CH_2$). **$^{13}$C** NMR (75 MHz, $CDCl_3$) δ 145.6 ($C_{arom}NH_2$), 136.2 ($C_{arom}C_{arom}HC_{arom}NH_2$), 130.1 ($C_{arom}C_{arom}HC_{arom}CH_2$), 129.3 ($C_{arom}CH_2$), 128.6 ($C_{arom}HC_{arom}C_{arom}HC_{arom}CH_2$), 128.5 ($C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 127 ($C_{arom}HC_{arom}CH_2$), 126.4 ($C_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 123.3 ($C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}CH_2$), 110.9 ($C_{arom}HC_{arom}NH_2$),63.9 ($CH_2OH$). IR (ATR): 3407, 3386, 3285, 1637, 1508, 1466, 1012 $cm^{-1}$. MS (70 eV) *m/z* (%): 173 ($M^+$, 55), 155 ($M^+$, 83), 143 (27), 128 (100), 115 (29), 102 (5), 89 (6), 85 (6), 77 (10), 64 (9), 51 (6). M.p.: 179-182$^{o}$C.

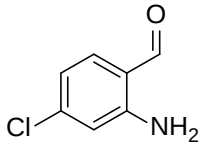
### 3.2.5. Synthesis of aminobenzaldehydes (15b-o)

*General procedure:* $MnO_2$ (4 eq) was added in five portions to a solution of the corresponding 2-aminobenzyl alcohol (**Ivb-o**) (1 eq) in dry DCM under argon atmosphere. The reaction mixture was stirred at room temperature for 24h. Afterwards, the reaction mixture was filtered over celite, washed with EtOAc. The solvent was removed under reduced pressure and pure products were isolated after flash column chromatography purification.

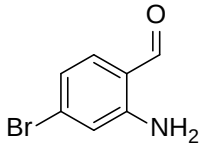



**2-Amino-4-fluorobenzaldehyde (15b)**. Following the *general procedure* **15b** (252 mg, 1.81 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 16 h in 85% yield as a orange solid starting from (2-Amino-4-fluorophenyl)methanol (300 mg, 2.13 mmol)

in $CH_2Cl_2$ (7.6 mL) and $MnO_2$ (727 mg, 14.70 mmol). $^1$H NMR (300 MHz, $CDCl_3$)(* denotes partially solaped signals) δ 9.80 (s, 1H, CHO), 7.47 (dd, *J* = 8.6, 6.4 Hz, 1H, $C_{arom}$*H*$C_{arom}$CHO), 6.45 (td, *J* = 8.4, 2.3 Hz, 1H, $C_{arom}HC_{arom}$*H*$C_{arom}$F), 6.39-6.09* (bs, 2H, $NH_2$), 6.31* (dd, *J* = 10.9, 2.2 Hz, 1H, $C_{arom}$*H*$C_{arom}NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.7 (CHO), 167.3 (d, *J* = 254.2 Hz, $C_{arom}$F), 152.3 (d, *J* = 13.5 Hz, $C_{arom}NH_2$), 138.7 (d, *J* = 12.6 Hz, *C*$_{arom}$HC$_{arom}$CHO), 116.1 (s, *C*$_{arom}$CHO), 104.8 (d, *J* = 23.6 Hz, $C_{arom}HC_{arom}HC_{arom}$F), 101.7 (d, *J* = 24.8 Hz, *C*$_{arom}$HC$_{arom}NH_2$). IR (ATR): 3476, 3350, 1656, 1623, 1558, 1497, 984 cm$^{-1}$. MS (70 eV) *m/z* (%): 139 ($M^+$, 94), 122 (4), 111 (100), 94 (19), 83 (47), 75 (4), 63 (14), 57 (19), 52 (8). M.p.: 99-103ºC.

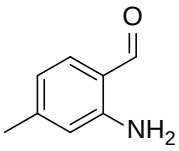



**2-Amino-4-chlorobenzaldehyde (15c)**. Following the *general procedure* **15c** (202 mg, 1.30 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 84% yield as a yellow solid starting from (2-Amino-4-chlorophenyl)methanol (243 mg, 1.54 mmol) in $CH_2Cl_2$ (3.3 mL) and $MnO_2$ (527 mg, 6.10 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.34 (d, *J* = 8.3 Hz, 1H, $C_{arom}HC_{arom}$CO), 6.75 – 6.48 (m, 2H, $C_{arom}HC_{arom}ClC_{arom}$H), 6.48-5.98 (bs, 2H, $NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.0 (CHO), 150.6 ($C_{arom}NH_2$), 141.5 ($C_{arom}$Cl), 137.0 (*C*$_{arom}$HC$_{arom}$CHO), 117.3 (*C*$_{arom}$CHO), 116.9 ($C_{arom}$H*C*$_{arom}HC_{arom}$Cl), 115.5 ($C_{arom}HC_{arom}NH_2$). IR (ATR): 3433, 3329, 1666, 1612, 1587, 1541, 1089 cm$^{-1}$. MS (70 eV) *m/z* (%): 157 ($M^+$, 23), 155 ($M^+$, 70), 138 (2), 127 (100), 110 (9), 99 (16), 92 (23), 75 (9), 63 (19), 52 (9). M.p.: 80-82ºC.

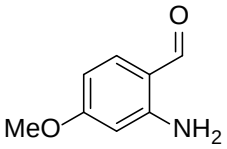



**2-Amino-4-bromobenzaldehyde (15d)**. Following the *general procedure* **5d** (287 mg, 1.44 mmol) was isolated by FC (hexanes/EtOAc 9:1) after 24 h in 93% yield as a yellow solid starting from (2-Amino-4-bromophenyl)methanol (309 mg, 1.53 mmol) in $CH_2Cl_2$ (7.6 mL) and $MnO_2$ (930 mg, 10.70 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H, CHO),

7.33 (d, *J* = 8.2 Hz, 1H, $C_{arom}HC_{arom}CHO$), 6.89 (d, *J* = 1.7 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 6.87-6.83 (m, 1H, $C_{arom}HC_{arom}Br$), 6.31-6.04 (bs, 2H, $NH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.3 (CHO), 150.5 ($C_{arom}NH_2$), 137.0 ($C_{arom}HC_{arom}CHO$), 130.5 ($C_{arom}Br$), 119.7 ($C_{arom}HC_{arom}HC_{arom}Br$), 119.0 ($C_{arom}HC_{arom}NH_2$), 117.6 ($C_{arom}CHO$). IR (ATR): 3249, 3322, 1659, 1605, 1533, 1476, 905 $cm^{-1}$. MS (70 eV) *m/z* (%): 201 ($M^+$, 72), 199 ($M^+$, 74), 173 (97), 171 (100), 156 (8), 154 (8), 145 (9), 143 (9), 92 (89), 75 (16), 65 (55), 52 (24). M.p.: 84-85ºC.

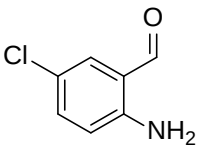



**2-Amino-4-methylbenzaldehyde (15f)**. Following the *general procedure* **15f** (218 mg, 1.61 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 87% yield as a golden solid starting from (2-Amino-4-methylphenyl)methanol (255 mg, 1.86mmol) in $CH_2Cl_2$ (12 mL) and $MnO_2$ (641 mg, 7.37 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.30 (d, *J* = 7.9 Hz, 1H, $C_{arom}HC_{arom}CHO$), 6.52 (d, *J* = 7.9 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}CH_3$),6.41 (s, 1H, $C_{arom}C_{arom}HC_{arom}$),6.31-5.96 (bs, 2H, $NH_2$), 2.24 (s, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.2 (CHO), 150.1 ($C_{arom}NH_2$), 146.3 ($C_{arom}CH_3$), 135.6 ($C_{arom}HC_{arom}CHO$), 117.8 ($C_{arom}HC_{arom}CH_3$), 116.9 ($C_{arom}CHO$), 116.0 ($C_{arom}HC_{arom}NH_2$), 21.8 ($CH_3$). IR (ATR): 3389, 1724, 1659, 1634, 1573, 1257 $cm^{-1}$. MS (70 eV) *m/z* (%): 135 ($M^+$, 74), 106 (100), 89 (13), 77 (22), 63 (6),51 (7). M.p.: 73-74ºC.

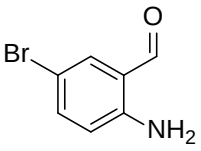



**2-Amino-4-methoxybenzaldehyde (15g)**. Following the *general procedure* **15g** (217 mg, 1.44 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 68% yield as a yellow solid starting from (2-Amino-4-methoxyphenyl)methanol (326 mg, 2.12 mmol) in $CH_2Cl_2$ (5.6 mL) and $MnO_2$ (725 mg, 8.42 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H, CHO), 7.27 (d, *J* = 8.7 Hz, 1H, $C_{arom}HC_{arom}CHO$), 6.46-6.27 (bs, 2H, $NH_2$), 6.23 (dd, *J* = 8.7, 2.3 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}OCH_3$), 6.02 (d, *J* = 2.2 Hz, 1H,

$C_{arom}HC_{arom}NH_2$), 3.70 (s, 3H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 191.8 (CHO), 165.1 ($C_{arom}OCH_3$), 152.4 ($C_{arom}NH_2$), 137.6 ($C_{arom}HC_{arom}CHO$), 113.6 ($C_{arom}CHO$), 105.0 ($C_{arom}HC_{arom}HC_{arom}OCH_3$), 98.2 ($C_{arom}HC_{arom}NH_2$), 55.1 ($CH_3$). IR (ATR): 3423, 3316, 1645, 1615, 1542, 1465, 1205 $cm^{-1}$. MS (70 eV) *m/z* (%): 151 ($M^+$, 100), 123 (35), 106 (18), 94 (40), 80 (17), 63 15), 52 (13). M.p.: 70-72°C.

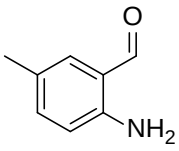



**2-Amino-5-chlorobenzaldehyde (15h)**. Following the *general procedure* **15h** (573 mg, 3.68 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 9:1 to 8:2) after 24 h in 79% yield as a yellow solid starting from (2-Amino-5-chlorophenyl)methanol (736 mg, 4.67 mmol) in $CH_2Cl_2$ (12.0 mL) and $MnO_2$ (853 mg, 9.81 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H, CHO), 7.40 (d, *J* = 2.5 Hz, 1H, $C_{arom}HC_{arom}CHO$), 7.21 (dd, *J* = 8.8, 2.5 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Cl$), 6.59 (d, *J* = 8.8 Hz, 1H, $C_{arom}HNH_2$), 6.38-5.87 (bs, 2H, $NH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ192.9 (CHO), 148.4 ($C_{arom}NH_2$), 135.2 ($C_{arom}HC_{arom}HC_{arom}Cl$), 134.3 ($C_{arom}HC_{arom}CHO$), 120.7($C_{arom}CHO$), 119.2 ($C_{arom}Cl$), 117.7 ($C_{arom}HC_{arom}NH_2$). IR (ATR): 3440, 3339, 1685,1583, 1545, 1469,1149 $cm^{-1}$. MS (70 eV) *m/z* (%): 157 ($M^+$, 19), 155 ($M^+$, 60), 127 (100), 110 (9), 92 (21), 75 (9), 63 (18), 52 (7). M.p.: 69-73°C.

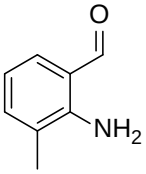



**2-Amino-5-bromobenzaldehyde (15i)**. Following the *general procedure 1***5i** (326 mg, 1.62 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 85% yield as a yellow solid starting from (2-Amino-5-bromophenyl)methanol (383 mg, 1.90 mmol) in $CH_2Cl_2$ (5 mL) and $MnO_2$ (649 mg, 7.51 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H, CHO), 7.55 (d, *J* = 2.4 Hz, 1H, $C_{arom}HC_{arom}CHO$), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}Br$), 6.55 (d, *J* = 8.8 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 6.38-5.90 (bs, 2H, $NH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 192.8 (CHO), 148.8 ($C_{arom}NH_2$), 137.9 ($C_{arom}HC_{arom}HC_{arom}Br$), 137.4 ($C_{arom}HC_{arom}CHO$), 119.9 ($C_{arom}CHO$), 118.0 ($C_{arom}C_{arom}NH_2$), 107.1 ($C_{arom}Br$). IR (ATR): 3429, 3325, 1648, 1612, 1545, 1466, 819

$cm^{-1}$. MS (70 eV) *m/z* (%): 201 ($M^+$, 61), 199 ($M^+$, 62), 173 (96), 171 (17), 156 (8), 154 (8), 145 (9), 143 (9), 92 (63), 75 (15), 65 (55), 52 (17). M.p.: 75-77ºC.



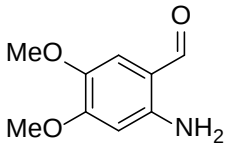
**2-Amino-5-methylbenzaldehyde (15j)**. Following the *general procedure* **15j** (143 mg, 1.06 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 66% yield as a yellow solid starting from (2-Amino-5-methylphenyl)methanol (221 mg, 1.61 mmol) in $CH_2Cl_2$ (8.0 mL) and $MnO_2$ (980 mg, 11.27 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H, CHO), 7.26 (s, 1H, $C_{arom}HC_{arom}$CHO), 7.14 (dd, *J* = 8.3, 1.8 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}CH_3$), 6.58 (d, *J* = 8.4 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 6.16-5.73 (bs, 2H, $NH_2$), 2.27 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ194.1 (CHO), 147.9 ($NH_2$), 136.5 ($C_{arom}C_{arom}HC_{arom}CH_3$), 135.2 ($C_{arom}HC_{arom}$CHO), 125.5 ($C_{arom}$CHO), 118.8 ($C_{arom}CH_3$), 116.2 ($C_{arom}HCNH_2$), 20.1 ($CH_3$). IR (ATR): 3468, 3347, 1656, 1576, 1555, 1483,1225 $cm^{-1}$. MS (70 eV) *m/z* (%): 135 ($M^+$, 82), 106 (100), 89 (16), 77 (26), 63 (6), 51 (9). M.p.: 47-49ºC.



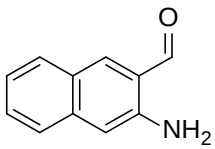
**2-Amino-3-methylbenzaldehyde (15k)**. Following the *general procedure* **15k** (282 mg, 2.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 24 h in 83% yield as a yellow oil starting from (2-Amino-3-methylphenyl)methanol (347 mg, 2.53 mmol) in $CH_2Cl_2$ (6.6 mL) and $MnO_2$ (866 g, 14.70 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H, CHO), 7.29 (d, *J* = 7.4 Hz, 1H, $C_{arom}HC_{arom}$CHO), 7.15 (d, *J* = 7.1 Hz, 1H, $C_{arom}HC_{arom}CH_3$), 6.64 (t, *J* = 7.5 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}$H), 6.40-6.07 (bs, 2H, $NH_2$), 2.09 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ194.0 (CHO), 148.3 ($C_{arom}NH_2$), 135.6 ($C_{arom}HC_{arom}CH_3$), 133.6 ($C_{arom}HC_{arom}$CHO), 122.5 ($C_{arom}$CHO), 118.0 ($C_{arom}CH_3$), 115.7 ($C_{arom}HC_{arom}HC_{arom}$H), 16.3 ($CH_3$). IR (ATR): 3479, 3347, 1656, 1612, 1558, 1218 $cm^{-1}$. MS (70 eV) *m/z* (%): 135 ($M^+$, 87), 106 (100), 89 (21), 77 (29), 68 (4), 63 (7), 51 (10).

**2-Amino-3-methoxybenzaldehyde (15l)**. Following the *general procedure* **15l** (290 mg, 1.92 mmol) was isolated by FC (hexanes/EtOAc 9:1) after 24 h in 90% yield as a yellow oil starting from (2-Amino-3-methoxyphenyl)methanol (325 mg, 2.12 mmol) in $CH_2Cl_2$ (7.4 mL) and $MnO_2$ (737 mg, 8.5 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.85 (s, 1H,CHO), 7.07 (dd, *J* = 7.9, 1.2 Hz, 1H, $C_{arom}HC_{arom}CHO$), 6.82 (d, *J* = 7.7 Hz, 1H, $C_{arom}HC_{arom}OCH_3$), 6.63 (t, 1H, $C_{arom}HC_{arom}HC_{arom}H$), 6.55-6.19 (bs, 2H, $NH_2$), 3.81 (s, 1H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.7 (CHO), 146.4 ($C_{arom}OCH_3$), 140.8 ($C_{arom}NH_2$), 126.3 ($C_{arom}HC_{arom}CHO$), 118.0 ($C_{arom}CHO$), 114.9 ($C_{arom}HC_{arom}OCH_3$), 113.5 ($C_{arom}HC_{arom}HC_{arom}H$), 55.5 ($CH_3$). IR (ATR): 3483, 3353, 1659, 1616, 1548, 1476, 1210 $cm^{-1}$. MS (70 eV) *m/z* (%): 151 ($M^+$, 100), 136 (38), 123 (62), 108 (72), 90 (18), 80 (20), 63 (8), 52 (16).

**2-Amino-6-chlorobenzaldehyde (15m)**.Following the *general procedure* **15m** (294 mg, 1.89 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 24 h in 90% yield as a yellow solid starting from (2-Amino-6-chlorophenyl)methanol (333 mg, 2.10 mmol) in $CH_2Cl_2$ (10.4 mL) and $MnO_2$ (1.278 g, 14.70 mmol). $^1$H NMR (300 MHz, $CDCl_3$)(* denotes partially solaped signals) δ 10.48 (s, 1H, CHO), 7.18 (t, *J* = 8.1 Hz, 1H, $C_{arom}HC_{arom}HC_{arom}H$), 6.67 (d, *J* = 7.7 Hz, 1H, $C_{arom}HC_{arom}Cl$), 6.54* (d, *J* = 8.5 Hz, 1H, $C_{arom}HC_{arom}NH_2$), 6.59 – 6.34* (bs, 2H, $NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 192.7 (CHO), 152.1 ($C_{arom}NH_2$), 139.5 ($C_{arom}Cl$), 135.5 ($C_{arom}HC_{arom}HC_{arom}H$), 117.6 ($C_{arom}HC_{arom}Cl$), 115.6 ($C_{arom}HC_{arom}NH_2$), 114.3 ($C_{arom}CHO$). IR (ATR): 3418, 3314, 1645, 1580, 1537, 1458, 1035 $cm^{-1}$. MS (70 eV) *m/z* (%): 157 ($M^+$, 22), 155 ($M^+$, 68), 127 (100), 110 (11), 100 (13), 90 (26), 75 (10), 65 (23), 52 (7). M.p.: 92-95°C.



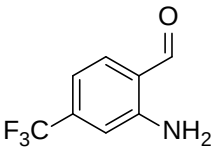
**2-amino-4,5-dimethoxybenzaldehyde (15n)**. Following the *general procedure* **15n** (25 mg, 0.14 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 7:3 to 1:1) after 24 h in 23% yield as a brown oil starting from (2-Amino-4,5-dimethoxyphenyl)methanol (110 mg, 0.60 mmol) in $CH_2Cl_2$ (1.6 mL) and $MnO_2$ (206 mg, 2.38 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 9.68 (s, 1H, CHO), 6.87 (s, 1H, $C_{arom}HC_{arom}CHO$), 6.11* (s, 1H, $C_{arom}HC_{arom}NH_2$), 6.15-6.04 (bs, 2H, $NH_2$), 3.87 (s, 3H, $CH_3$), 3.83 (s, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ191.5 (CHO), 156.2 ($C_{arom}C_{arom}HC_{arom}NH_2$), 147.4 ($C_{arom}NH_2$), 141.0 ($C_{arom}CHC_{arom}CHO$), 116.1 ($C_{arom}HC_{arom}CHO$), 111.4 ($C_{arom}CHO$), 98.5 ($C_{arom}HC_{arom}NH_2$), 56.6 ($CH_3$), 56.1 ($CH_3$). IR (ATR): 3454, 3343, 3339, 1649, 1551, 1505, 1465, 1239, 1143 cm$^{-1}$. MS (70 eV) *m/z* (%): 181 ($M^+$, 100), 166 (80), 138 (43), 123 (10), 110 (13), 94 (23), 78 (9), 65 (8), 52 (10).



**3-aminonaphthalene-2-carbaldehyde (15o)**. Following the *general procedure* **15o** (130 mg, 0.76 mmol) was isolated by FC (hexanes/EtOAc gradient from 19:1 to 9:1) after 24 h in 49% yield as a orange solid starting from (2-aminonaphthalen-3-yl)methanol (270 mg, 1.56 mmol) in $CH_2Cl_2$ (5.5 mL) and $MnO_2$ (542 mg, 6.24 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 10.10 (s, 1H, CHO), 8.07 (s, 1H, $C_{arom}HC_{arom}CHO$), 7.77 (d, *J* = 8.3 Hz, 1H, $C_{arom}HC_{arom}C_{arom}HC_{arom}CHO$), 7.54 (t, *J* = 9.4 Hz, 1H, $C_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 7.47 (m, 1H, $C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 7.25 (m, 1H, $C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}CHO$), 6.92 (s, 1H, $C_{arom}HC_{arom}NH_2$), 6.00-5.99 (bs, 2H, $NH_2$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 194.7 (CHO), 145.3 ($C_{arom}NH_2$), 139.8 ($C_{arom}HC_{arom}CHO$), 137.9 ($C_{arom}C_{arom}HC_{arom}NH_2$), 129.9 ($C_{arom}HC_{arom}C_{arom}HC_{arom}CHO$), 129.4 ($C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 126.2 ($C_{arom}C_{arom}HC_{arom}CHO$), 125.6 ($C_{arom}HC_{arom}C_{arom}HC_{arom}NH_2$), 122.9 ($C_{arom}HC_{arom}HC_{arom}C_{arom}HC_{arom}CHO$), 122.4 ($C_{arom}CHO$), 109.6 ($C_{arom}C_{arom}NH_2$). IR (ATR): 3472, 3357, 1685, 1630, 1580, 1497 cm$^{-1}$.

MS (70 eV) *m/z* (%): 171 ($M^+$, 86), 143 (100), 126 (57), 115 (65), 89 (10), 72 (9), 63 (10). M.p.: 164-167$^oC$.

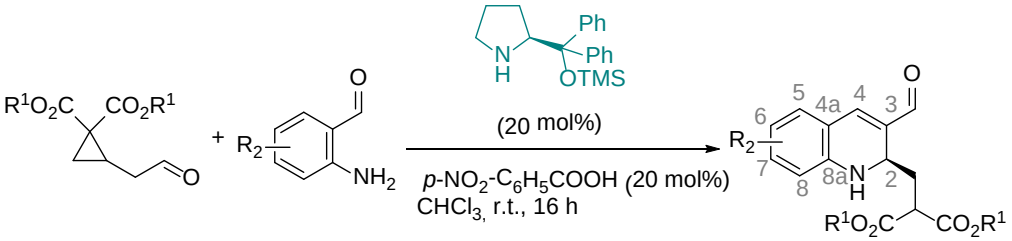
*Synthesis of 2-Amino-4-trifluoromethylbenzaldehyde (***15e***):*



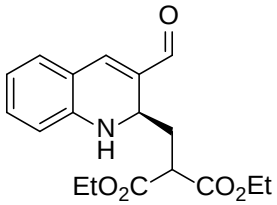

**2-Amino-4-trifluoromethylbenzaldehyde (15e)**. To a solution of EtOH/$H_2O$ (3:1) (25 mL), (2-amino-4-trifluoromethyl)phenyl)methanol (500 mg, 2.28 mmol) was added with electrolytic iron powder (1.273 g, 22.8 mmol) and conc. HCl (3 drops). The resultant mixture was heated at 70ºC for 60 min. The reaction mass was allowed to cool to rt and then diluted with ethyl acetate and filtered over celite bed. The filtrate was concentrated under vacuum and the resultant residue was diluted with ethyl acetate and washed successively with water and then brine solution. The organic layer was dried over anh. $Na_2SO_4$ and evaporated ander reduced pressure. The final product **15e** (300 mg, 1.59 mmol) was isolated in 70% as a yellow solid. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.92 (s, 1H, CHO), 7.59 (d, *J* = 8.0 Hz, 1H,$C_{arom}HC_{arom}$CHO), 6.94 (d, *J* = 9.1 Hz, 1H, $C_{arom}HC_{arom}HCC_{arom}F_3$), 6.90 (s, 1H, $C_{arom}HC_{arom}NH_2$), 6.55-6.10 (s, 2H, $NH_2$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 193.8 (CHO), 149.66 ($C_{arom}NH_2$), 136.5 ($C_{arom}$CHO), 136.3 (q, *J* = 32 Hz, $C_{arom}CF_3$), 123.5 (q, *J* = 273.1 Hz, $CF_3$), 120.3 ($C_{arom}HC_{arom}$CHO), 113.2 (q, *J* = 4.1 Hz, $C_{arom}HC_{arom}HC_{arom}CF_3$), 112.6 (q, *J* = 3.5 Hz, $C_{arom}HC_{arom}NH_2$). IR (ATR): 3447, 3343, 1666, 1558, 1501, 1447, 1124, 783 $cm^{-1}$. MS (70 eV) *m/z* (%): 189 ($M^+$, 65), 161 (100), 142 (25), 114 (35), 95 (4), 83 (6), 75 (8), 63 (11), 52 (6). M.p.: 42-44$^oC$.

### 3.2.6. Organocatalytic aza-Michael/Aldol Cascade reaction (16a-q and 18)

*General procedure:* To a solution of catalyst **17** (0.02 mmol, 20 mol%), *p*-nitrobenzoic acid (0.02 mmol, 20 mol%) and aldehyde **14** in $CHCl_3$ (1 mL) at room temperature, aminobenzaldehyde **15** was added**.** The stirring was maintained at this temperature until the reaction was complete by TLC. Solvent was evaporated and the crude was directly subjected to FC.

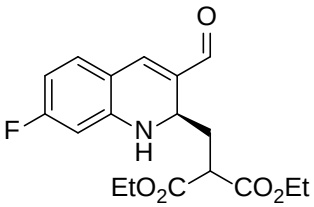



**16a-p**



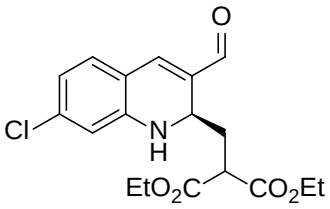

**Diethyl 2-(((*R*)-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16a)**. Following the general procedure **16a** (33 mg, 0.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 99% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO), 7.19 (s, 1H, $CH^4$), 7.17–7.02 (m, 2H, $CH^5CH^6CH^7$), 6.62 (td, *J* = 7.5, 1.1 Hz, 1H, $CH^6$), 6.46 (d, *J* = 8.1 Hz, 1H, $CH^8$), 4.76-4.71 (ddd, *J* = 7.1, 4.6, 2.0, 1H, $CH^2$), 4.65-4.49 (bs, 1H, NH), 4.25-4.01 (m, 4H, $OCH_2$), 3.48 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.22 (ddd, *J* = 14.1, 7.4, 6.7 Hz, 1H, $CH_aH_b$), 2.06 (ddd, *J* = 14.3, 7.8, 4.5 Hz, 1H, $CH_aH_b$), 1.32-1.15 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.4 (CHO), 169.5, 169.4 (C=O), 145.4 ($C^{8a}$), 144.6 ($C^4H$), 133.3 ($C^7H$), 132.7 ($C^3$), 130.2 ($C^5H$), 117.9 ($C^6H$), 117.8 ($C^{4a}$), 114.0 ($C^8H$), 61.8, 61.7 ($OCH_2$), 48.5 ($CHCO_2Et$),

47.9 ($C^2H$), 35.2 ($CH_2CCO_2Et$), 14.0 , 14.0 ($CH_3$). IR (ATR): 3382, 2980, 1724, 1659, 1627, 1605, 1570, 1164, 1143 $cm^{-1}$. MS (70 eV) *m/z* (%): 331 ($M^+$, 5), 171 (5), 158 (100), 143 (7), 130 (8). HRMS: Calculated for $[C_{18}H_{22}NO_5]^+$: 332.1498 [$(M+H)^+$]; found: 332.1499. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 41.46 min, $\tau_{minor}$ = 51.77 min (90% ee). $[\alpha]_D^{20}$: +41.3 (*c* = 1.0, $CH_2Cl_2$).



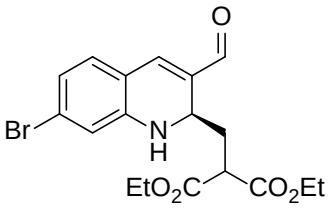

**Diethyl 2-(((*R*)-7-fluoro-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16b)**. Following the general procedure **16b** (30 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 86% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15b** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H, CHO), 7.16 (s, 1H, $CH^4$), 7.05 (dd, *J* = 8.4, 6.3 Hz, 1H, $CH^5$), 6.34 (td, *J* = 8.6, 2.4 Hz, 1H, $CH^6$), 6.17 (dd, *J* = 10.5, 2.2 Hz, 1H, $CH^8$), 4.77–4.68 (m, 1H, $CH^2$), 4.29–4.00 (m, 4H, $OCH_2$), 3.48 (dd, *J* = 7.6, 6.7 Hz, 1H, OCCHCO), 2.21 (dt, *J* = 13.6, 6.8 Hz, 1H, $CH_aH_b$), 2.08 (ddd, *J* = 14.3, 7.7, 4.3 Hz, 1H, $CH_aH_b$), 1.33–1.15 (m, 1H, $CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 190.22 (CHO), 169.5, 169.4 (C=O), 166.38 (d, *J* = 251.0 Hz, $C^7F$), 147.19 (d, *J* = 12.5 Hz, $C^{8a}$), 143.7 ($C^4H$), 132.21 (d, *J* = 11.2 Hz, $C^5H$), 131.90 (d, *J* = 2.2 Hz, $C^3$), 114.3 (d, *J* = 1.8 Hz, $C^{4a}$), 105.7 (d, *J* = 23.1 Hz, $C^6H$), 100.4 (d, *J* = 25.6 Hz, $C^8H$). 61.9, 61.8 ($OCH_2$), 48.5 ($CHCO_2Et$), 47.9 ($C^2H$), 35.3 ($CH_2CHCO_2Et$), 14.1, 14.1 ($CH_3$). $^{19}F$ NMR (283 MHz, $CDCl_3$) δ -105.6 ($C^7F$). IR (ATR): 3378, 2980, 1720, 1666, 1630, 1580, 1511, 1260, 1163, 1149 $cm^{-1}$. MS (70 eV) *m/z* (%): 349 ($M^+$, 4), 274 (5), 256 (5), 228 (9), 200 (7), 176 (100), 161 (8), 146 (10). HRMS: Calculated for $[C_{18}H_{21}NO_5F]^+$: 350.1404 [$(M+H)^+$]; found: 350.1417. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow

rate 1.0 mL/min; $\tau_{major}$ = 28.17 min, $\tau_{minor}$ = 35.63 min (95% ee). $[\alpha]_D^{20}$: +56.3 (*c* = 1.0, $CH_2Cl_2$).

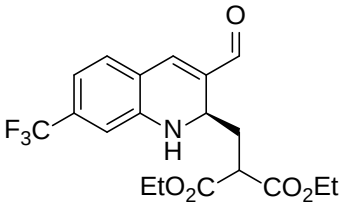



**Diethyl 2-(((*R*)-7-chloro-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16c)**. Following the general procedure **16c** (35 mg, 0.10 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 97% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15c** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO), 7.16 (s, 1H, $CH^4$), 7.00 (d, *J* = 8.1 Hz, 1H, $CH^5$), 6.59 (dd, *J* = 8.1, 1.9 Hz, 1H, $CH^6$), 6.48 (d, *J* = 1,9 Hz, 1H, $CH^8$), 4.72 (ddd, *J* = 7.1, 4.5, 2.6, 1H, $CH^2$), 4.68-4.59 (bs, 1H, NH), 4.26-4.00 (m, 4H, $OCH_2$), 3.47 (dd, *J* = 7.7, 6.5 Hz, 1H, OCCHCO), 2.20 (dt, *J* = 13.9, 6.8 Hz, 1H, $CH_aH_b$), 2.08 (ddd, *J* = 14.2, 7.8, 4.4 Hz, 1H, $CH_aH_b$), 1.27-1.17 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.0 (CHO), 169.3, 169.2 (C=O), 146.0 ($C^{8a}$), 143.2 ($C^4$H), 138.8 ($C^7$Cl), 132.6 ($C^3$), 131.0 ($C^5$H), 118.1 ($C^6$H), 116.2 ($C^{4a}$), 113.4 ($C^8$H), 61.8, 61.7 ($OCH_2$), 48.3 ($CHCO_2Et$), 47.8 ($C^2$H), 35.2 ($CH_2CHCO_2Et$), 13.9, 13.9 ($CH_3$). IR (ATR): 3379, 2926, 1724, 1662, 1631, 1598, 1483, 1145, 1041 $cm^{-1}$. MS (70 eV) *m/z* (%): 367 ($M^+$, 2), 365 ($M^+$, 5), 290 (10), 281 (26) 244 (13), 215 (10), 207 (67), 194 (35), 192 (100), 177 (10), 164 (8), 128 (11), 83 (28), 73(10). HRMS: Calculated for $[C_{18}H_{21}NO_5Cl]^+$: 366.1108 $[(M+H)^+]$; found: 366.1103. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 47.94 min, $\tau_{minor}$ = 74.95 min (96% ee). $[\alpha]_D^{20}$: -6.9 (*c* = 1.0, $CH_2Cl_2$).

**Diethyl 2-(((*R*)-7-bromo-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16d)**.



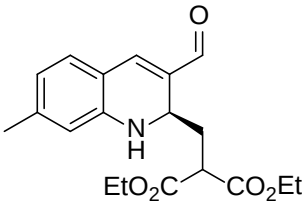
Following the general procedure **16d** (36 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 87% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15d** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.47 (s, 1H, CHO), 7.15 (s, 1H, $CH^4$), 6.92 (d, *J* = 8.1 Hz, 1H, $CH^5$), 6.74 (dd, *J* = 8.1, 1.8 Hz, 1H, $CH^6$), 6.64 (d, *J* = 1,8 Hz, 1H, $CH^8$), 4.72 (ddd, *J* = 7.2, 4.4, 2.7, 1H, $CH^2$), 4.63 (d, *J* = 2.7 Hz, 1H, NH), 4.25-4.00 (m, 4H, $OCH_2$), 3.47 (dd, *J* = 7.8, 6.5 Hz, 1H, OCCHCO), 2.20 (dt, *J* = 13.9, 6.8 Hz, 1H, C$H_a$H$_b$), 2.07 (ddd, *J* = 14.3, 7.8, 4.5 Hz, 1H, $CH_aH_b$), 1.28-1.16 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 169.3, 169.2 (C=O), 146.0 ($C^{8a}$), 143.2 ($C^4$H), 132.8 ($C^3$), 131.1 ($C^5$H), 127.3 ($C^7$Br), 121.0 ($C^6$H), 116.6 ($C^{4a}$), 116.5 ($C^8$H), 61.8 ($OCH_2$), 61.7 (O-$CH_2$), 48.4 (*C*H$CO_2$E), 47.8 ($C^2$H t), 35.2 (*C*$H_2$CH$CO_2$Et), 14.0, 14.0 ($CH_3$). IR (ATR): 3379, 2976, 1716, 1662, 1623, 1595, 1455, 1143, 1038 cm$^{-1}$. MS (70 eV) *m/z* (%): 411 ($M^+$, 3), 409 ($M^+$, 4), 336 (5), 318 (7), 290 (10), 238 (91), 236 (100), 157 (19), 129 (14). HRMS: Calculated for $[C_{18}H_{21}NO_5Br]^+$: 410.0603 $[(M+H)^+]$; found: 410.0619. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 27.09 min, $\tau_{minor}$ = 44.74 min (95% ee). $[\alpha]_D^{20}$: -24.2 (*c* = 1.0, $CH_2Cl_2$).



**Diethyl 2-(((*R*)-3-formyl-7-(trifluoromethyl)-1,2-dihydroquinolin-2-yl)methyl)malonate (16e)**.

Following the general procedure **16e** (34 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 90% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15e** (19 mg, 0.10 mmol) in the

presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H, CHO), 7.20 (s, 1H, $CH^4$), 7.17 (d, *J* = 8.0 Hz, 1H, $CH^5$), 6.85 (d, *J* = 7.9, 0.8 Hz, 1H, $CH^6$), 6.70 (s, 1H, $CH^8$), 4.83–4.68 (m, 2H, N*HCH*$^2$), 4.30–3.96 (m, 4H, $OCH_2$), 3.48 (dd, *J* = 7.6, 6.6 Hz, 1H, OCCHCO), 2.23 (dt, *J* = 13.7, 6.8 Hz, 1H, C$H_a$H$_b$), 2.15–2.00 (m, 1H, $CH_aH_b$), 1.29–1.11 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.4 (CHO), 169.5, 169.4 (C=O), 145.3 ($C^{8a}$), 142.8 ($C^4$H), 134.4 ($C^3$), 134.3 (q, *J* = 32 Hz, *C*$^7$$CF_3$), 130.5 ($C^5$H), 123.7 (q, *J* = 272.7 Hz, $CF_3$), 120.2 ($C^{4a}$), 114.0 (q, *J* = 3.8 Hz, $C^6$H), 110.6 (q, *J* = 4.0 Hz, $C^8$H), 61.9, 61.8 ($OCH_2$), 48.4 (*C*H$CO_2$Et), 48.0 ($C^2$H), 35.3 (*C*$H_2$CH$CO_2$Et), 14.0, 13.8 ($CH_3$). $^{19}$F NMR (283 MHz, $CDCl_3$) δ -63.7 ($C^7CF_3$). IR (ATR): 3379, 2984, 1724, 1670, 1641, 1519, 1483, 1243, 1149, 1120 cm$^{-1}$. MS (70 eV) *m/z* (%): 399 ($M^+$, 3), 278 (4), 239 (6), 226 (100), 211 (12), 197 (7), 55 (4). HRMS: Calculated for $[C_{19}H_{21}NO_5F_3]^+$: 400.1372 [$(M+H)^+$]; found: 400.1388. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 14.95 min, $\tau_{minor}$ = 17.42 min (96% ee). $[\alpha]_D^{20}$: -22.8 (*c* = 1.0, $CH_2Cl_2$).

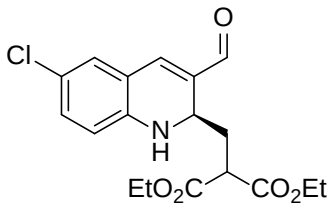



**Diethyl 2-(((*R*)-3-formyl-1,2-dihydro-7-methylquinolin-2-yl)methyl)malonate (16f)**. Following the general procedure **16f** (32 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 91% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15f** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 9.44 (s, 1H, CHO), 7.16 (s, 1H, $CH^4$), 6.96 (d, *J* = 7.7 Hz, 1H, $CH^5$), 6.45 (d, *J* = 7.7 Hz, 1H, $CH^6$), 6.29 (s, 1H, $CH^8$), 4.69 (t, *J* = 4.8 Hz, 1H, $CH^2$), 4.57-4.41 (bs, 1H, NH), 4.34–3.89 (m, 4H, $OCH_2$), 3.47 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.31–2.13* (m, 1H, C$H_a$H$_b$), 2.21* (s, 1H, $CH_3$C$H^7$) 2.04 (ddd, *J* = 20.6, 12.6, 8.7 Hz, 1H, $CH_aH_b$), 1.38–1.04 (m, 6H, $CH_3$). $^{13}$C NMR (75

MHz, $CDCl_3$) δ 190.2 (CHO), 169.5, 169.4 (C=O), 145.4 ($C^{8a}$), 144.6 ($C^4H$), 144.3 ($CH_3C^7$), 131.8 ($C^3$), 130.2 ($C^5H$), 119.3 ($C^6H$), 115.6 ($C^{4a}$), 114.3 ($C^8H$), 61.7, 61.7 ($OCH_2$), 48.5 ($CHCO_2Et$), 47.8 ($C^2H$), 35.1 ($CH_2CHCO_2Et$), 21.9 ($CH_3C^7$), 14.0, 14.0 ($CH_3$). IR (ATR): 3383, 2984, 1724, 1662, 1623, 1558, 1476, 1167, 1145 $cm^{-1}$. MS (70 eV) *m/z* (%): 345 ($M^+$, 3), 270 (4), 253 (5), 224 (7), 208 (3), 196 (5), 180 (8), 172 (100), 142 (9), 115 (6). HRMS: Calculated for $[C_{19}H_{24}NO_5]^+$: 346.1654 $[(M+H)^+]$; found: 36.1656. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 44.99 min, $\tau_{minor}$ = 77.90 min (85% ee). $[\alpha]_D^{20}$: +43.7 (*c* = 1.0, $CH_2Cl_2$).

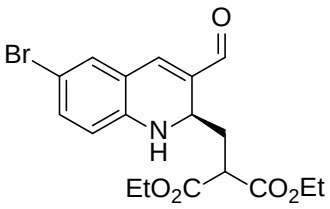
**Diethyl 2-(((*R*)-3-formyl-1,2-dihydro-7-methoxyquinolin-2-yl)methyl)malonate (16g)**. Following the general procedure **16g** (29 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 81% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15g** (15 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1H, CHO), 7.15 (s, 1H, $CH^4$), 7.00 (d, *J* = 8.5 Hz, 1H, $CH^5$), 6.22 (dd, *J* = 8.5, 2.3 Hz, 1H, $CH^6$), 5.97 (d, *J* = 2.2 Hz, 1H, $CH^8$), 4.70 (ddd, *J* = 7.0, 4.5, 2.4 Hz, 1H, $CH^2$), 4.63-4.55 (bs, 1H, NH), 4.24–3.99 (m, 4H, $OCH_2$), 3.76 (s, 3H, $OCH_3$), 3.49 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.21 (dt, *J* = 13.9, 6.9 Hz, 1H, $CH_aH_b$), 2.08 (ddd, *J* = 14.1, 7.8, 4.6 Hz, 1H, $CH_aH_b$), 1.46–0.78 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 169.6, 169.4 (C=O), 164.3 ($C^7OCH_3$), 147.2 ($C^{8a}$), 144.6 ($C^4H$), 131.9 ($C^5H$), 130.1 ($C^3$), 111.7 ($C^{4a}$), 105.6 ($C^6H$), 97.8 ($C^8H$), 61.7, 61.7 ($OCH_2$), 55.3 ($OCH_3$), 48.4 ($CHCO_2Et$), 47.9 ($C^2H$), 35.3 ($CH_2CHCO_2Et$), 14.0, 14.0 ($CH_3$). *IR* (ATR): 3382, 2984, 1724, 1656, 1616, 1565, 1512, 1272, 1174, 1143, 1031 $cm^{-1}$. MS (70 eV) *m/z* (%): 361 ($M^+$, 2), 269 (6), 242 (4), 207 (5), 188 (100), 173 (6), 145 (9), 127 (4). HRMS: Calculated for $[C_{19}H_{24}NO_6]^+$: 362.1604

[(M+H)$^+$]; found: 362.1603. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 83.53 min, $\tau_{minor}$ = 254.01 min (80% ee). $[\alpha]_D^{20}$: +53.4 (*c* = 1.0, $CH_2Cl_2$).

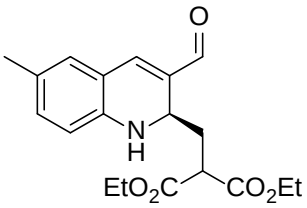



**Diethyl 2-(((*R*)-6-chloro-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16h)**. Following the general procedure **16h** (34 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 93% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15h** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H, CHO), 7.12 (s, $CH^4$), 7.10–7.01 (m, 2H, $CH^5CH^6CH^7$), 6.48-6-37 (m, 1H, $CH^8$), 4.71 (ddd, *J* = 7.3, 4.4, 2.7, 1H, $CH^2$), 4.62-4.54 (bs, 1H, NH), 4.25-4.01 (m, 4H, $OCH_2$), 3.46 (dd, *J* = 7.6, 6.7 Hz, 1H, OCCHCO), 2.20 (dt, *J* = 14.2, 7.1 Hz, 1H, $CH_aH_b$), 2.04 (ddd, *J* = 14.2, 7.7, 4.5 Hz, 1H, $CH_aH_b$), 1.28-1.17 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 169.2, 169.2 (C=O), 143.6 ($C^{8a}$), 142.7 ($C^4H$), 133.4 ($C^3$), 132.6 ($C^5H$), 128.9 ($C^7H$), 122.2 ($C^6Cl$), 118.7 ($C^{4a}$), 115.1 ($C^8H$), 61.7, 61.6 ($OCH_2$), 48.3 ($CHCO_2Et$), 47.8 ($C^2H$), 34.9 ($CH_2CHCO_2Et$), 13.9, 13.9 ($CH_3$). IR (ATR): 3376, 2980, 1724, 1662, 1631, 1566, 1480, 1156, 1031 cm$^{-1}$. MS (70 eV) *m/z* (%): 367 (M$^+$, 2), 365 (M$^+$, 5), 274 (5), 246 (6), 205 (6), 194 (32), 192 (100), 177 (7), 164 (7), 128 (8). HRMS: Calculated for $[C_{18}H_{21}NO_5Cl]^+$: 366.1108 [(M+H)$^+$]; found: 366.1101. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; $\tau_{major}$ = 97.04 min, $\tau_{minor}$ = 158.28 min (95% ee). $[\alpha]_D^{20}$: -34.5 (*c* = 1.0, $CH_2Cl_2$).

**Diethyl 2-(((*R*)-6-bromo-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16i)**.

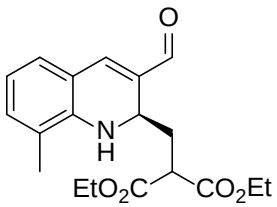


Following the general procedure **16i** (37 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 89% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15i** (20 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H, CHO), 7.22-7.15 (m, 2H, C*H*$^4$C$^{4a}$CH$^5$C$^6$C*H*$^7$), 7.11 (s, 1H, CH$^5$), 6.37 (d, *J* = 8.1 Hz, 1H, CH$^8$), 4.71 (ddd, *J* = 7.2, 4.4, 2.2 Hz, 1H, CH$^2$), 4.67-4.55 (bs, 1H, NH), 4.25-3.99 (m, 4H, $OCH_2$), 3.46 (dd, *J* = 7.7, 6.6 Hz, 1H, OCCHCO), 2.20 (ddd, J = 14.2, 7.5, 6.7 Hz, 1H, C$H_a$H$_b$), 2.04 (ddd, J = 14.3, 7.7, 4.4 Hz, 1H, CH$_a$$H_b$), 1.29-1.16 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 169.3, 169.2 (C=O), 144.0 (C$^{8a}$), 142.6 (C$^4$H), 135.4 (C$^7$H), 133.4 (C$^3$), 131.9 (C$^5$H), 119.3 (C$^{4a}$), 115.5 (C$^8$H), 109.0 (C$^6$Br), 61.8, 61.7 ($OCH_2$), 48.4 (*C*H$CO_2$Et), 47.8 (C$^2$H), 35.0 (*C*$H_2$C$CO_2$Et), 14.0, 13.9 ($CH_3$). IR (ATR): 3375, 2984, 1727, 1666, 1631, 1562, 1476, 1156, 1131, 1038 cm$^{-1}$. MS (70 eV) *m/z* (%): 411 (M$^+$, 4), 409 (M$^+$, 5), 336 (5), 318 (8), 288 (9), 238 (90), 236 (100), 157 (20), 129 (17). HRMS: Calculated for [$C_{18}H_{21}NO_5Br$]$^+$: 410.0603 [(M+H)$^+$]; found: 410.0619. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 28.45 min, $\tau_{minor}$ = 36.27 min (94% ee). $[\alpha]_D^{20}$: +27.9 (*c* = 1.0, $CH_2Cl_2$).



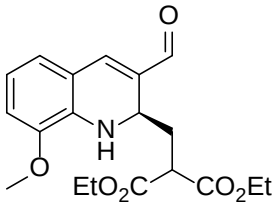
**Diethyl 2-(((*R*)-3-formyl-1,2-dihydro-6-methylquinolin-2-yl)methyl)malonate (16j)**. Following the general procedure **16j** (28 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 80% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15j** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02

mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 9.48 (s, 1H, CHO), 7.16 (s, 1H, $CH^4$), 6.95 (dd, *J* = 8.2, 1.6 Hz, 1H, $CH^7$), 6.90 (s, 1H, $CH^5$), 6.41 (d, *J* = 8.2 Hz, 1H, $CH^8$), 4.74–4.62 (m, 1H, NCH), 4.45-4.33 (bs, 1H, NH), 4.27–4.00 (m, 4H, $OCH_2$), 3.47 (dd, *J* = 7.5, 7.0 Hz, 1H, OCCHCO), 2.27–2.12* (m, 1H, $CH_aH_b$), 2.20* (s, 1H, $CH_3C^6$), 2.03 (ddd, *J* = 14.2, 7.7, 4.5 Hz, 1H, $CH_aH_b$), 1.31–1.08 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.4 (CHO), 169.5, 169.4 (C=O), 144.6 ($C^4$H), 143.1 ($C^{8a}$), 134.3 ($C^7$H), 133.0 ($C^3$), 130.2 ($C^5$H), 127.2 ($C^6CH_3$), 118.1 ($C^{4a}$), 114.1 ($C^8$H), 61.8, 61.7 ($OCH_2$), 48.6 ($CHCO_2Et$), 47.9 ($C^2$H), 34.9 ($CH_2CHCO_2Et$), 20.32 ($C^6CH_3$), 14.1, 14.1 ($CH_3$). IR (ATR): 3389, 2923, 1724, 1659, 1634, 1572, 1497, 1156, 1128 $cm^{-1}$. MS (70 eV) *m/z* (%): 345 ($M^+$, 4), 270 (6), 253 (8), 224 (10), 208 (5), 196 (7), 180 (13), 172 (100), 142 (11), 115 (7). HRMS: Calculated for $[C_{19}H_{24}NO_5]^+$: 346.1654 $[(M+H)^+]$; found: 36.1654. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 63.33 min, $\tau_{minor}$ = 44.83 min (81% ee). $[\alpha]_D^{20}$: -6.88 (*c* = 1.0, $CH_2Cl_2$).



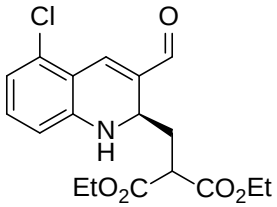

**Diethyl 2-(((*R*)-3-formyl-8-methyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16k).** Following the general procedure **16k** (22 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 64% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15k** (15 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) (* denotes partially solaped signals) δ 9.50 (s, 1H, CHO), 7.22 (s, 1H, $CH^4$), 7.06–6.65 (m, 2H, $CH^5CH^6CH^7$), 6.57 (t, *J* = 7.5 Hz, 1H, $CH^6$), 4.81 (ddd, *J* = 7.3, 4.7, 2.8, 1H, $CH^2$), 4.45-4.37 (bs, 1H, NH), 4.23-3.97 (m, 4H, $OCH_2$), 3.48 (dd, *J* = 8.3, 6.4 Hz, 1H, OCCHCO), 2.19 (dt, *J* = 13.7, 6.6 Hz, 1H, $CH_aH_b$), 2.15-2-03* (m, 1H, $CH_aH_b$), 2.10* (s, 3H, $CH_3CH^8$), 1.26-1.28 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ

190.2 (CHO), 169.4, 169.1 (C=O), 145.0 ($C^4H$), 143.4 ($C^{8a}$), 134.2 ($C^7H$), 132.0 ($C^3$), 128.2 ($C^5H$), 121.2 ($CH_3\mathit{C}^8$), 117.2 ($C^6H$), 117.1 ($C^{4a}$), 61.6, 61.6 ($OCH_2$), 48.2 ($\mathit{C}HCO_2Et$), 47.8 ($C^2H$), 35.4 ($\mathit{C}H_2CCO_2Et$), 16.5 ($\mathit{C}H_3C^8$), 14.1, 14.0. ($CH_3$). IR (ATR): 3383, 2923, 1724, 1662, 1627, 1580, 1466, 1145 $cm^{-1}$. MS (70 eV) *m/z* (%): 345 ($M^+$, 4), 254 (4), 185 (4), 172 (100), 157 (5), 143 (5), 115 (5). HRMS: Calculated for $[C_{19}H_{24}NO_5]^+$: 346.1654 [$(M+H)^+$]; found: 36.1655. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 41.48 min, $\tau_{minor}$ = 136.52 min (97% ee). $[\alpha]_D^{20}$: +24.0 (*c* = 1.0, $CH_2Cl_2$).

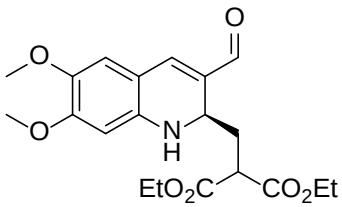



**Diethyl 2-(((*R*)-3-formyl-8-methoxy-1,2-dihydroquinolin-2-yl)methyl)malonate (16l)**. Following the general procedure **16l** (23 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 64% yield as a red solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15l** (15 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H, CHO), 7.21 (s, 1H, $CH^4$), 6.80–6.69 (m, 2H, $C\mathit{H}^5CH^6C\mathit{H}^7$), 6.58 (t, *J* = 7.8 Hz, 1H, $CH^6$), 4.94-4.86 (bs, 1H, NH), 4.79 (ddd, *J* = 7.3, 4.7, 2.6, 1H, $CH^2$), 4.26-4.01 (m, 4H, $OCH_2$), 3.83 (s, 3H, $OCH_3$), 3.48 (dd, *J* = 8.1, 6.8 Hz, 1H, OCCHCO), 2.21 (dt, *J* = 14.2, 7.3 Hz, 1H, $C\mathit{H}_aH_b$), 2.04 (ddd, *J* = 14.1, 8.1, 4.7 Hz, 1H, $CH_a\mathit{H}_b$), 1.26-1.21 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.5 (CHO), 169.3, 169.2 (C=O), 146.1 ($\mathit{C}^8OCH_3$), 144.6 ($C^4H$), 135.8 ($C^{8a}$), 132.5 ($C^3$), 122.0 ($C^5H$), 117.4 ($C^{4a}$), 116.7 ($C^6H$), 112.8 ($\mathit{C}^7H$), 61.7, 61.6 ($OCH_2$), 55.7 ($OCH_3$), 48.2 ($\mathit{C}HCO_2Et$), 47.4 ($C^2H$), 35.3 ($\mathit{C}H_2CHCO_2Et$), 14.1 ($CH_3$). IR (ATR): 3411, 2923, 1724, 1652, 1620, 1565, 1512, 1250, 1174, 1143, 1041 $cm^{-1}$. MS (70 eV) *m/z* (%): 361 ($M^+$, 3), 316 (3), 201 (4), 188 (100), 173 (25), 145 (5), 127 (3). HRMS: Calculated for $[C_{19}H_{24}NO_6]^+$: 362.1604 [$(M+H)^+$]; found: 362.1600. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH

(90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 46.07 min, $\tau_{minor}$ = 194.45 min (79% ee). $[\alpha]_D^{20}$: -26.0 (*c* = 1.0, $CH_2Cl_2$). M.p.: 87-89ºC.



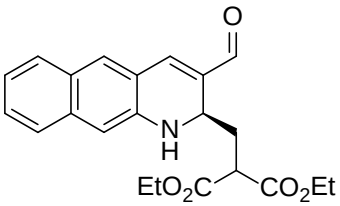

**Diethyl 2-(((*R*)-5-chloro-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16m)**. Following the general procedure **16m** (19 mg, 0.05 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 53% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15m** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 7.60 (s, 1H, $CH^4$), 7.02 (t, *J* = 8.0 Hz, 1H, $CH^7$), 6.67 (dd, *J* = 7.9, 0.9 Hz, 1H, $CH^6$), 6.39 (d, *J* = 8.2 Hz, 1H, $CH^8$), 4.78–4.63 (m, 2H, N*HCH*$^2$), 4.27–3.95 (m, 4H, $OCH_2$), 3.47 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.31–2.12 (m, 1H, C$H_a$H$_b$), 2.04 (ddd, *J* = 14.3, 7.5, 4.3 Hz, 1H, $CH_aH_b$), 1.32 – 1.15 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.5 (CHO), 169.4, 169.4 (C=O), 146.6 ($C^{8a}$), 140.1 ($C^4$H), 134.8 ($C^3$), 133.4 ($C^5$HCl), 133.3 ($C^7$H), 118.5 ($C^6$H), 115.9 ($C^{4a}$), 112.8 ($C^8$H), 61.9, 61.9 ($OCH_2$), 48.6 ($CHCO_2Et$), 47.5 ($C^2$H), 35.1 ($CH_2CHCO_2Et$), 14.1, 14.1 ($CH_3$). IR (ATR): 3386, 2977, 1724, 1662, 1626, 1497, 1138, 1045 $cm^{-1}$. MS (70 eV) *m/z* (%): 367 ($M^+$, 1), 365 ($M^+$, 4), 290 (6), 273 (6), 244 (9), 216 (7), 192 (100), 164 (10), 128 (9), 99 (6), 55(4). HRMS: Calculated for $[C_{18}H_{21}NO_5Cl]^+$: 366.1108 $[(M+H)^+]$; found: 366.1124. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 21.8 min, $\tau_{minor}$ = 29.91 min (69% ee). $[\alpha]_D^{20}$: +18.3 (*c* = 1.0, $CH_2Cl_2$).




**Diethyl 2-(((*R*)-3-formyl-6,7-dimethoxy-1,2-dihydroquinolin-2-yl)methyl)malonate (16n)**. Following the general procedure **16n** (28 mg, 0.07

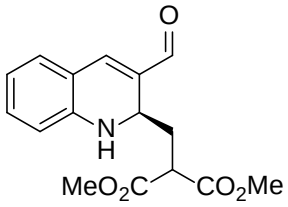
mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 71% yield as an orange oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15n** (18 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H, CHO), 7.11 (s, 1H, $CH^4$), 6.58 (s, 1H, $CH^5$), 6.03 (s, 1H, $CH^8$), 4.67 (ddd, *J* = 7.2, 4.7, 1.8, 1H, $CH^2$), 4.52-4.44 (bs, 1H, NH), 4.31-3.95 (m, 4H, $OCH_2$), 3.83 (s, 3H, $C^6OCH_3$), 3.78 (s, 3H, $C^7OCH_3$), 3.47 (dd, *J* = 7.6, 6.8 Hz, 1H, OCCHCO), 2.25-2.12 (m, 1H, $CH_aH_b$), 2.01 (ddd, *J* = 14.1, 7.7, 4.7, 1H, $CH_aH_b$), 1.26-1.16 (m, 6H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.5 (CHO), 169.4, 169.4 (C=O), 154.4 ($C^7OCH_3$), 144.2 ($C^4H$), 142.2 ($C^3$), 141.4 ($C^{8a}$), 129.7 ($C^6OCH_3$), 112.3 ($C^5H$), 109.9 ($C^{4a}$), 97.4 ($C^8H$), 61.6, 61.5 ($OCH_2$), 56.5, 55.9 ($OCH_3$), 48.4 ($CHCO_2Et$), 47.6 ($C^2H$), 34.6 ($CH_2CHCO_2Et$), 14.0, 14.0 ($CH_3$). IR (ATR): 3372, 2934, 1727, 1656, 1627, 1570, 1505, 1242, 1139, 1027 $cm^{-1}$. MS (70 eV) *m/z* (%): 299 ($M^+$- 2 x $C_2H_5OH$, 100), 272 (22), 254 (20), 226 (53), 212 (13), 183 (16), 141 (12). HRMS: Calculated for $[C_{20}H_{26}NO_7]^+$: 392.1709 $[(M+H)^+]$; found: 392.1702. The ee was determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 39.89 min, $\tau_{minor}$ = 64.27 min (64% ee). $[\alpha]_D^{20}$: +32.2 (*c* = 1.0, $CH_2Cl_2$).

**Diethyl 2-(((*R*)-3-formyl-1,2 dihydrobenzo[g]quinolin-2-yl)methyl)malonate (16o)**.



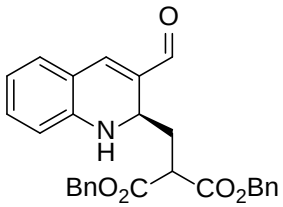

Following the general procedure **16o** (35 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 93% yield as a red solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15o** (17 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol) and using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H, CHO), partially overlapped signals 7.63;7.60 (d, *J* = 8.5 Hz, 1H, $CH^6$); (s, 1H, $CH^5$), 7.46 (d, *J* = 8.0 Hz, 1H, $CH^9$), 7.38; 7.33 partially overlapped signals (s, 1H, $CH^4$); (m, 1H, $CH^7$), 7.16 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, $CH^8$),

6.73 (s, 1H, $CH^{10}$), 4.72 (t, *J* = 5.7, 1H, $CH^{2}$), 4.56 (bs, 1H, NH), 4.26-3.93 (m, 4H, $OCH_2$), 3.49 (dd, *J* = 7.8, 6.5 Hz, 1H, OC-CH-CO), 2.29-2.13 (m, 2H, $CH^{2}$-C*H*$_2$), 1.21 (t, *J* = 7.1 Hz, 3H, $CH_3$), 1.09 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.4 (CHO), 169.3, 169.2 (*C*$O_2$Et), 143.9 ($C^{4}$H), 141.8 ($C^{4a}$), 137.1 ($C^{5a}$), 136.7 ($C^{3}$), 130.5 ($C^{5}$H), 128.6 ($C^{6}$H), 128.2 ($C^{7}$H), 127.7 ($C^{9a}$), 125.4 ($C^{9}$H), 122.8 ($C^{8}$H), 120.7 ($C^{10a}$), 107.2 ($C^{10}$H), 61.7, 61.6 ($OCH_2$), 48.5 ($CHCO_2Et$), 48.1 ($C^{2}$H) 35.4 ($C^{2}HCH_2$), 13.9 ($CH_3$), 13.8 ($CH_3$). IR (ATR): 3347, 2984, 1745, 1713, 1662, 1634, 1156, 1135 cm$^{-1}$. MS (70 eV) *m/z* (%): 208 ($M^+$- $C_8H_{13}O_4$, 82), 178 (43), 151 (38), 126 (6), 103 (12), 83 (10), 77 (8), 55(6). HRMS: Calculated for $[C_{20}H_{18}NO_4]^{\bullet}$: 336.1236 $[(M+-C_2H_5O)^{\bullet}]$; found: 336.0874. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 49.45 min, $\tau_{minor}$ = 70.19 min (85% ee). $[\alpha]_D^{20}$: -326.6 (*c* = 1.0, $CH_2Cl_2$). M.p.: 113-115ºC.

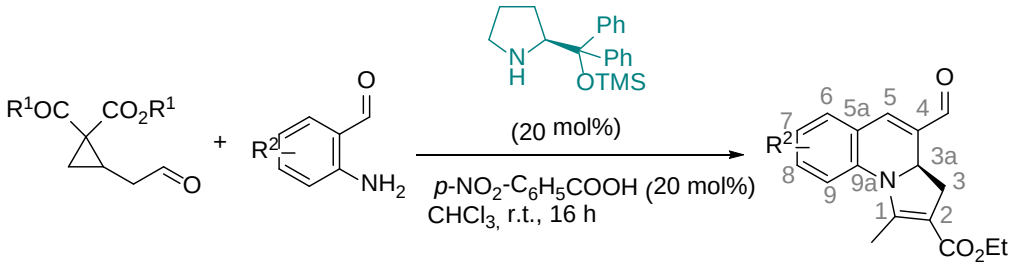



**Dimethyl 2-(((*R*)-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16p)**. Following the general procedure **16p** (26 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 86% yield as an orange oil starting from aldehyde **14b** (19 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H, CHO), 7.21 (s, 1H, $CH^{4}$), 7.17–7.03 (m, 2H, C*H*$^{5}$C*H*$^{6}$C*H*$^{7}$), 6.65 (t, *J* = 7.4 Hz, 1H, $CH^{6}$), 6.48 (d, *J* = 8.1 Hz, 1H, $CH^{8}$), 4.73 (ddd, *J* = 7.2, 4.6, 2.7 Hz, 1H, $CH^{2}$), 4.53-4.38 (bs, 1H, NH), 3.73 (s, 3H, $CH_3$), 3.66 (s, 3H, $CH_3$), 3.52 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.24 (dt, *J* = 14.1, 7.0 Hz, 1H, C*H*$_a$H$_b$), 2.09 (ddd, *J* = 14.2, 7.6, 4.7 Hz, 1H, CH$_a$*H*$_b$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.5 (CHO), 169.9, 169.8 (C=O), 145.3 ($C^{8a}$), 144.7 ($C^{4}$H), 133.4 ($C^{7}$H), 132.6 ($C^{3}$), 130.3 ($C^{5}$H), 118.1 ($C^{6}$H), 117.9 ($C^{4a}$H), 114.1 ($C^{8}$H), 52.8 ($OCH_3$), 48.1 (*C*H$CO_2$Me), 47.9 ($C^{2}$H), 35.4 (*C*H$_2$C$CO_2$Me). IR (ATR): 3382, 2955, 1727, 1662, 1627, 1566, 1158, 1146 cm$^{-1}$. MS (70 eV) *m/z* (%): 303

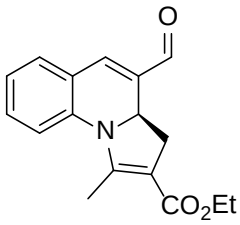
($M^+$, 4), 241 (4), 225 (5), 210 (7), 181 (5), 166 (7), 158 (100), 130 (10), 102 (5), 77 (6), 59 (6). HRMS: Calculated for $[C_{16}H_{18}NO_5]^+$: 304.1185 [$(M+H)^+$]; found: 304.1179. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 57.52 min, $\tau_{minor}$ = 83.68 min (91% ee). $[\alpha]_D^{20}$: +26.3 (*c* = 1.0, $CH_2Cl_2$).




**Dibenzyl 2-(((*R*)-3-formyl-1,2-dihydroquinolin-2-yl)methyl)malonate (16q)**. Following the general procedure **16q** (31 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 69% yield as an orange oil starting from aldehyde **14c** (35 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H, CHO ), 7.38–7.19 (m, 10H, $C_{arom}H$), 7.15 (s, 1H, $CH^4$), 7.14–7.04 (m, 2H, $CH^5CH^6CH^7$), 6.63 (td, *J* = 7.6, 0.9 Hz, 1H, $CH^6$), 6.41 (d, *J* = 8.1 Hz, 1H, $CH^8$), 5.18–4.95 (m, 4H, $CH_2Ph$), 4.76 (ddd, *J* = 7.2, 4.5, 2.7 Hz, 1H, $CH^2$), 4.49-4.38 (bs, 1H, NH), 3.62 (t, *J* = 7.2 Hz, 1H, OCCHCO), 2.29 (dt, *J* = 14.1, 7.0 Hz, 1H, $CH_aH_b$), 2.13 (ddd, *J* = 14.2, 7.5, 4.6 Hz, 1H, $CH_aH_b$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.4 (CHO), 169.2, 169.1 (C=O), 145.2 ($C^{8a}$), 144.6 ($C^4H$), 135.3, 135.2 ($OCH_2Ph$), 133.4 ($C^7H$), 132.6 ($C^3$), 130.3 ($C^5H$), 128.7, 128.5, 128.4, 128.4 ($C_{arom}H$) 118.0 ($C^6H$), 117.7 ($C^{4a}H$), 113.9 ($C^8H$), 67.4, 67.4 ($OCH_2Ph$), 48.5 ($CHCO_2Bn$), 48.0 ($C^2H$), 35.3 ($CH_2CHCO_2Bn$). IR (ATR): 3386, 3024, 1730, 1662, 1627, 1164, 1143 $cm^{-1}$. MS (70 eV) *m/z* (%): 107 ($M^+$-$C_{21}H_{18}NO_4^{\cdot}$, 58), 91 (30), 82 (46), 79 (100), 63 (10), 51 (31). HRMS: Calculated for $[C_{28}H_{26}NO_5]^+$: 456.1811 [$(M+H)^+$]; found: 456.1829. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 80.41 min, $\tau_{minor}$ = 201.79 min (88% ee). $[\alpha]_D^{20}$: +31.2 (*c* = 1.0, $CH_2Cl_2$).



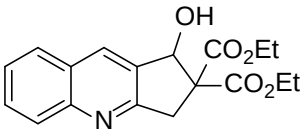

**18**




**Ethyl (R)-4-formyl-1-methyl-3,3a-dihydropyrrolo[1,2-a]quinoline-2-carboxylate (18).** Following the general procedure **18** (17 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 7:3) after 16 h in 60% yield as an orange oil starting from aldehyde **14d** (20 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H, CHO), 7.38-7.27 (m, 2H, C*H*$^6$CH$^7$C*H*$^8$), 7.25-7.17 (m, 2H, CH$^5$ + CH$^9$), 7.04 (t, *J* = 7.4 Hz, 1H, CH$^7$), 4.88-4.72 (m, 1H, CH$^{3a}$), 4.30-4-00 (m, 2H, $OCH_2$), 3.42 (dd, *J* = 16.1, 12.1 Hz, 1H, CH$^3_a$), 3.12-2.89 (m, 1H, C*H*$^3_b$), 2.51 (s, 3H, $CCH_3$), 1.28 (t, *J* = 7.2 Hz, 3H, $CH_2$-$CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.8 (CHO), 167.0 (C=O), 155.2 (N-C=C), 142.8 (C$^5$), 139.3 (C$^4$), 139.0 (C$^{9a}$), 131.5 (C$^6$), 130.0 (C$^8$), 125.5 (C$^{5a}$), 122.8 (C$^7$), 119.9 (C$^9$), 103.0 (C=C-*C*O), 59.2 ($OCH_2$), 57.8 (C$^{3a}$), 33.9 (*C*$^3$), 14.6 ($CH_3$),14.4 ($CH_3$). IR (ATR): 2926, 1670, 1598, 1483, 1387, 1225, 1149 cm$^{-1}$. MS (70 eV) *m/z* (%): 283 (M$^+$, 2), 281 (66), 252 (100), 178 (34), 152 (13), 128 (7), 89 (10), 77 (7). HRMS: Calculated for $[C_{17}H_{18}NO_3]^+$: 284.1287 [(M+H)$^+$]; found: 284.1298. The ee was determined by HPLC using a Chiralpak IC column [*n*-hexane/*i*-PrOH (40:60)]; flow rate 1.0 mL/min; $\tau_{major}$ = 62.06 min, $\tau_{minor}$ = 49.28 min (>99% ee). $[\alpha]_D^{20}$: +1548.1 (*c* = 1.0, $CH_2Cl_2$).

### 3.2.7. Synthesis of cyclopentaquinoline (19)

**Diethyl 1-hydroxy-1,3-dihydro-2H-cyclopenta[b]quinoline-2,2-dicarboxylate (19a)**.

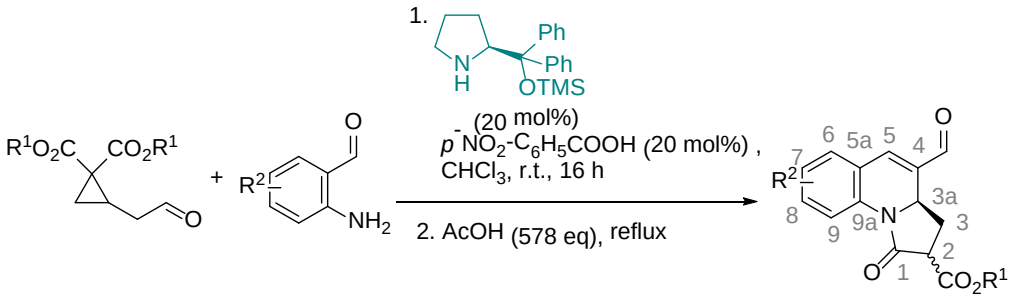


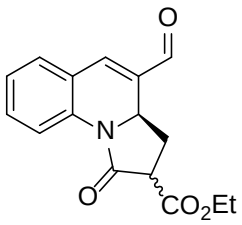

To a solution of catalyst **19a** (7 mg, 0.02 mmol, 20 mol%), *p*-nitrobenzoic acid (3 mg, 0.02 mmol, 20 mol%), cerium(III) chloride (5mg, 0.02 mmol, 20 mol%) and aldehyde **14a** (23mg, 0.10 mmol) in $CHCl_3$ (1 mL) at room temperature, aminobenzaldehyde **15a** (12 mg, 0.10 mmol) was added**.** The stirring was maintained at this temperature until the reaction was complete by TLC. Solvent was evaporated and the crude was directly subjected to FC (hexanes/EtOAc gradient from 8:2 to 7:3) to afford the pure cyclopentaquinoline **19a** (28 mg, 0.08 mmol) in 85% yield. $^{1}$H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H, $CH^{9}$), 8.03 (d, *J* = 8.1 Hz, 1H, $CH^{5}$), 7.81 (dd, *J* = 8.1, 1.4 Hz, 1H, $CH^{8}$), 7.68 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H, $CH^{6}$), 7.50 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H, $CH^{7}$), 5.77 (d, *J* = 6.6 Hz, 1H, $CH^{1}$), 4.36-4.13 (m, 4H, $COCH_2$), 3.93 (bs, 1H, OH), 3.88 (d, *J* = 17.4 Hz, 1H, $CH_aH_b^{3}$), 3.65 (d, *J* = 17.5 Hz, 1H, $CH_aH_b^{3}$), 1.29 (t, *J* = 7.1 Hz, 3H, $CH_3$), 1.23 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 170.0 (CO), 169.9 (CO), 161.3 ($C^{3a}$), 148.8 ($C^{4a}$), 133.8 ($C^{9a}$), 131.8 ($C^{9}$), 129.6 ($C^{6}$), 128.8 ($C^{5}$), 128.2 ($C^{8}$), 127.6 ($C^{8a}$), 126.2 ($C^{7}$), 77.6 ($C^{1}$), 64.4 ($C^{2}$), 62.2 ($COCH_2$), 62.1 ($COCH_2$), 39.8 ($C^{3}$), 14.0 ($CH_3$), 14.0 ($CH_3$). IR (ATR): 3118, 1650, 1607 $cm^{-1}$. HRMS: Calculated for $[C_{16}H_{16}NO_4]^+$: 330.1342 $[(M+H)^+]$; found: 330.1346.

### 3.2.8. Synthesis of lactams (20a-o)

*General procedure:* To a solution of catalyst **17a** (0.02 mmol, 20 mol%), *p*-nitrobenzoic acid (0.02 mmol, 20 mol%) and aldehyde **14** in $CHCl_3$ (1 mL) at room temperature, aminobenzaldehyde **15** was added**.** The reaction mixture was stirred for 16 h. Then acetic acid (578 eq, 57.80 mmol) was added and the reaction was

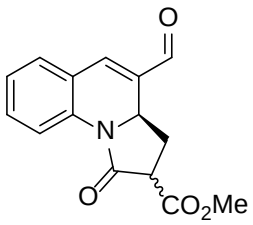
heated to reflux until it was complete by TLC (time given in each case). Solvent was removed and the crude was directly subjected to FC.



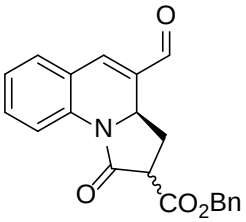
**(*R*)-Ethyl 4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20a)**. Following the general procedure **20a** (23 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 3h in 81% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.58 (s, 1H, CHO), 9.56* (s, 1H, CHO), 8.24 (d, *J* = 8.2 Hz, 1H, $CH^6$), 7.49–7.39 (m, 1H, $CH^7$), 7.35-7.30 (m, 1H, $CH^9$), 7.27–7.14 (m, 2H, $CH^5CH^8$), 5.19* (ddd, *J* = 9.9, 6.3, 1.8 Hz, 1H, $CH^{3a}$), 4.89 (ddd, *J* = 10.4, 6.0, 1.6 Hz, 1H, $CH^{3a}$), 4.35–4.17 (m, 2H, $OCH_2$), 3.64 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.55-3.48* (m, 1H, $CH^2$), 3.26-3.17 (m, 1H, $CH^3$), 2.61-2.49 (m, 1H, $CH^{3'}$), 2.37* (m, 1H, $CH^{3'}$), 1.37-1.28 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.0*, 190.0 (CHO), 170.0, 169.7* ($C^1$=O), 169.5*, 168.9 ($CO_2Et$), 143.3*, 143.2 ($C^5H$), 137.6*, 137.2 ($C^4$), 136.0*, 136.0 ($C^{9a}$), 132.5 ($C^8H$), 129.7*, 129.7 ($C^6H$), 125.4*, 125.3 ($C^7H$), 124.0*, 123.9 ($C^{5a}$), 120.9*, 120.4 ($C^9H$), 61.9*, 61.8 ($OCH_2$), 54.8*, 54.5

($C^2H$), 49.1*, 49.0 ($C^{3a}H$), 30.7*, 30.7 ($C^3H_2$), 14.2*,14.1 ($CH_3$). IR (ATR): 2987, 1720, 1695, 1662, 1631, 1570, 1364, 1170 $cm^{-1}$. MS (70 eV) *m/z* (%): 285 ($M^+$, 98), 256 (17), 238 (46), 212 (100), 184 (29), 166 (10), 156 (85), 142 (23), 128 (79), 115 (13), 101 (32), 77 (19), 55 (76). HRMS: Calculated for $[C_{16}H_{16}NO_4]^+$: 286.1079 $[(M+H)^+]$; found: 286.1094. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 66.02 min, $\tau_{minor,7}$ = 88.94 min (91% ee); $\tau_{major,7*}$ = 176.14 min, $\tau_{minor,7*}$ = 53.07 min (87% ee). M.p.: 145-147ºC.



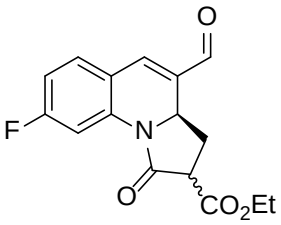

**(*R*)-Methyl 4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20b)**. Following the general procedure **20b** (22 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 1 h 45 min 81% yield as a yellow solid starting from aldehyde **14b** (19 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1H$ NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.58 (s, 1H, CHO), 9.57* (s, 1H, CHO), 8.25 (d, *J* = 8.3 Hz, 1H, $CH^6$), 7.48-7.42 (m, 1H, $CH^7$), 7.35-7.30 (m, 1H, $CH^9$), 7.28–7.13 (m, 2H, $CH^5CH^8$), 5.19* (ddd, *J* = 9.8, 6.3, 1.7 Hz, 1H, $CH^{3a}$), 4.90 (ddd, *J* = 10.3, 6.0, 1.4 Hz, 1H, $CH^{3a}$), 3.81 (d, *J* = 1.2 Hz, 3H, $CH_3$), 3.68 (dd, *J* = 12.1, 7.9 Hz, 1H, $CH^2$), 3.53-3.50* (m, 1H, $CH^2$), 3.31–3.14 (m, 1H, $CH^3$), 2.62-2.50 (m, 1H, $CH^{3'}$), 2.43-2.32* (m, 1H, $CH^{3'}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.0 (CHO), 169.9, 169.8* ($C^1$=O), 169.5*, 168.3 ($CO_2Et$), 143.3*, 143.2 ($C^5H$), 137.6*, 137.2 ($C^4$), 136.0 ($C^{9a}$), 132.7 ($C^8H$), 129.7*, 129.7 ($C^6$), 125.4*, 125.3 ($C^7H$), 124.1*, 123.8 ($C^{5a}$), 120.9*, 120.5 ($C^9H$), 55.8*, 54.6 ($C^2H$), 52.9*, 52.8 ($CH_3$). 49.0*, 48.8 ($C^{3a}H$), 30.6 ($C^3H_2$). IR (ATR): 2951, 1741, 1702, 1670, 1630, 1368, 1170 $cm^{-1}$. MS (70 eV) *m/z* (%): 271 ($M^+$, 91), 238 (27), 212 (82), 184 (44), 156 (100), 142 (32),128 (95), 115 (17), 101 (40), 77 (28), 55 (60). HRMS: Calculated for $[C_{15}H_{14}NO_4]^+$: 272.0923 $[(M+H)^+]$; found:

272.0933. The ee of both diastereoisomers were determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 154.18 min, $\tau_{minor,7}$ = 165.33 min (91% ee); $\tau_{major,7*}$ = 92.62 min, $\tau_{minor,7*}$ = 111.27 min (89% ee). M.p.: 157-159$^{o}$C



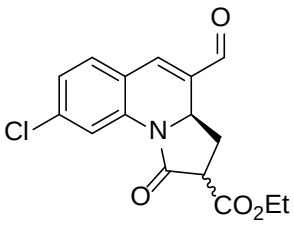

**(*R*)-Benzyl 4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20c)**. Following the general procedure **20c** (21 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 2 h 15min in 60% yield as a brown oil starting from aldehyde **14c** (35 mg, 0.10 mmol) and aminobenzaldehyde **15a** (12 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^{1}$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.56 (s, 1H, CHO), 9.55* (s, 1H, CHO), 8.26-8.22 (m, 1H, $CH^{6}$), 7.51–7.11 (m, 9H, $C_{arom.}$-H), 5.31–5.19 (m, 2H, $CH_2$), 5.19–5.11 (m, 1H, $CH^{3a}$), 4.94–4.83* (m, 1H, $CH^{3a}$), 3.71 (dd, *J* = 12.1, 8.0 Hz, 1H, $CH^{2}$), 3.59* (d, *J* = 9.4 Hz, 1H, $CH^{2}$), 3.31–3.11 (m, 2H, $CH^{3}$), 2.63-2.51 (m, 1H, $CH^{3'}$), 2.38 (m, 1H, $CH^{3'}$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.1 (CHO), 169.9, 169.6* ($C^{1}$=O), 169.4*, 168.9 ($CO_2Et$), 143.4* ($C^{5}H$), 143.3 ($C^{5}H$), 137.7* ($C^{4}$), 137.3 ($C^{4}$), 136.1 ($C^{9a}$), 135.5, 135.4* ($CH_2C_{arom}$), 132.8, 132.7* ($C^{8}H$), 129.8, 129.7* ($C^{6}H$), 128.8*, 128.7, 128.6*, 128.5, 128.4, 128.2* ($C_{arom}H$), 125.5*, 125.4 ($CH^{7}$), 124.2*, 124.0 ($C^{5a}$), 121.1*, 120.6 ($CH^{9}$), 67.7 ($OCH_2$), 67.6* ($OCH_2$), 55.9* ($C^{2}H$), 54.7 ($C^{2}H$), 49.3* ($C^{3a}H$), 49.1 ($C^{3a}H$), 30.8 ($C^{3}H_2$). IR (ATR): 2955, 1734, 1701, 1670, 1626, 1572, 1364, 1163 cm$^{-1}$. MS (70 eV) *m/z* (%): 107 ($M^{+}$-$C_{14}H_{10}NO_3^{\cdot}$, 54), 91 (28), 83 (78), 79 (100), 51 (29). HRMS: Calculated for $[C_{21}H_{18}NO_4]^{+}$: 348.1236 $[(M+H)^{+}]$; found: 348.1255. The ee of both diastereoisomers were determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major,7}$ =

109.42 min, $\tau_{minor,7}$ = 145.78 min (90% ee), $\tau_{major,7^*}$ = 295.66 min, $\tau_{minor,7^*}$ = 85.64 min (89% ee).



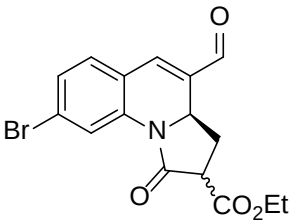

**(*R*)-Ethyl 8-fluoro-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20d)**. Following the general procedure **20d** (23 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 9 h in 77% yield as a yellow oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15b** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.57 (s, 1H, CHO), 9.55* (s, 1H, CHO), 8.09 (dd, *J* = 10.7, 2.3 Hz, 1H, $CH^9$), 7.33-7.28 (m, 1H, $CH^6$), 7.22 (d, *J* = 1.4 Hz, 1H, $CH^9$), 7.19* (d, *J* = 1.5 Hz, 1H, $CH^9$), 6.93–6.82 (m, 1H, $CH^7$), 5.18* (ddd, *J* = 10.2, 6.2, 1.8 Hz, 1H, $CH^{3a}$), 4.88 (ddd, *J* = 10.3, 5.8, 1.5 Hz, 1H, $CH^{3a}$), 4.35–4.18 (m, 2H, $OCH_2$), 3.64 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.59-3.51* (m, 1H, $CH^2$), 3.32–3.16 (m, 1H, $CH^3$), 2.60-2.48 (m, 1H, $CH^{3'}$), 2.37* (dt, *J* = 13.6, 9.9 Hz, 1H, $CH^{3'}$), 1.35-1.30 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.9*, 189.9 (CHO), 170.3, 170.0* ($C^1$=O), 169.3*, 168.8 ($CO_2$Et), 165.1 (d, *J* = 253.2 Hz, $C^8$F), 142.5* (d, *J* = 1.4 Hz), 142.4 (d, *J* = 1.4 Hz) ($C^5$H), 137.9* (d, *J* = 12.1 Hz), 137.8* (d, *J* = 12.2 Hz) ($C^{9a}$), 136.4* (d, *J* = 2.6 Hz), 136.0 (d, *J* = 2.5 Hz) ($C^4$), 131.4 (d, *J* = 10.1 Hz), 131.4* (d, *J* = 10.2 Hz) ($C^6$H), 120.4* (d, *J* = 3.2 Hz), 120.2 (d, *J* = 3.2 Hz) ($C^{5a}$), 112.6* (d, *J* = 22.7 Hz), 112.6* (d, *J* = 22.7 Hz) ($C^7$H), 109.0* (d, *J* = 28 Hz), 108.6* (d, *J* = 28.1 Hz) ($C^9$H), 62.2*, 62.1 ($OCH_2$), 55.8*, 54.6 ($C^{3a}$H), 49.2*, 49.1 ($C^2$H), 30.9*, 30.8* ($C^3H_2$), 14.2 ($CH_3$). $^{19}$F NMR (283 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ -103.1, -103.2* ($C^8$F). IR (ATR): 2984, 1735, 1706, 1670, 1634, 1605, 1577, 1372, 1189, 1164 $cm^{-1}$. MS (70 eV) *m/z* (%): 303 ($M^+$, 58), 256 (40), 230 (86), 207 (94), 176 (100), 146 (80), 119 (23), 83 (66), 55 (59). HRMS: Calculated for

$[C_{16}H_{15}NO_4F]^+$: 304.0985 [$(M+H)^+$]; found: 304.0994. The ee was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 105.46 min, $\tau_{minor,7}$ = 89.41 min (95% ee), $\tau_{major,7^*}$ = 63.41 min, $\tau_{minor,7^*}$ = 68.31 min (95% ee).




**(*R*)-Ethyl 8-chloro-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20e)**. Following the general procedure **20e** (26 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 1:1) after 8 h 30min in 83% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15c** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.57 (s, 1H, CHO), 9.55* (s, 1H, CHO), 8.32 (d, *J* = 2.0 Hz, 1H, $CH^9$), 7.28-7.12 (m, 3H, $CH^5CH^6CH^7$), 7.21-7.19 (m, 1H, $CH^7$), 7.17-7.13 (m, 1H, $CH^6$), 5.16* (ddd, *J* = 9.9, 6.1, 1.7 Hz, 1H, $CH^{3a}$), 4.87 (ddd, *J* = 9.9, 6.1, 1.7 Hz, 1H, $CH^{3a}$), 4.37–4.15 (m, 2H, $OCH_2$), 3.64 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.54-3.51* (m, 1H, $CH^2$), 3.30–3.16 (m, 1H, $CH^3$), 2.59-2.47 (m, 1H, $CH^{3'}$), 2.41-2.31* (m, 1H, $CH^{3'}$), 1.37–1.29 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.9 (CHO), 170.2, 169.9* ($C^1$=O), 169.3*, 168.7 ($CO_2Et$), 142.2*, 142.1 ($C^5H$), 138.7 ($C^8Cl$), 137.4*, 137.0 ($C^4$), 136.9*, 136.8 ($C^{9a}$), 130.5, 130.4* ($C^6H$), 125.7*, 125.6 ($C^7H$), 122.5*, 122.3 ($C^{5a}$), 121.3*, 120.9 ($C^9H$), 62.2*, 62.1 ($OCH_2$), 55.9*, 54.6 ($C^{3a}H$), 49.2*, 49.0 ($C^2H$), 30.9*, 30.8 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2987, 1724, 1702, 1666, 1627, 1590, 1361, 1163, 1118 $cm^{-1}$. MS (70 eV) *m/z* (%): 321 ($M^+$, 2), 319 ($M^+$, 13), 281 (28), 273 (16), 246 (34), 218 (41), 207 (100), 192 (93), 163 (33), 135 (11), 128 (31), 96 (22), 85 (67), 55 (44). HRMS: Calculated for $[C_{16}H_{15}NO_4Cl]^+$: 320.0690 [$(M+H)^+$]; found: 320.0700 The ee of both diastereoisomers were determined by HPLC using a Chiralpak ASH column [*n*-

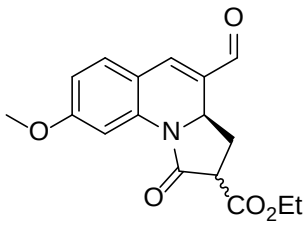
hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 60.19 min, $\tau_{minor,7}$ = 38.98 min (97% ee); $\tau_{major,7*}$ = 109.55 min, $\tau_{minor,7*}$ = 45.93 min (97% ee). M.p.: 152-154ºC.




**(*R*)-Ethyl 8-bromo-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20f)**. Following the general procedure **20f** (31 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 8 h in 86% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15d** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.57 (s, 1H, CHO), 9.55* (s, 1H, CHO), 8.49-8.46 (m, 1H, $CH^9$), 7.33-7.29 (m, 1H, $CH^6$), 7.20–7.15 (m, 2H, $CH^5$ + $CH^7$), 5.15* (ddd, *J* = 10.1, 6.2, 1.8 Hz, 1H, $CH^{3a}$), 4.86 (ddd, *J* = 10.6, 5.9, 1.8 Hz, 1H, $CH^{3a}$), 4.34–4.14 (m, 2H, $OCH_2$), 3.63 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.52* (d, *J* = 9.4 Hz, 1H, $CH^2$), 3.27–3.16 (m, 1H, $CH^3$), 2.60–2.45 (m, 1H, $CH^{3'}$), 2.36* (dt, *J* = 13.6, 9.8 Hz, 1H, $CH^{3'}$), 1.37–1.27 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.9 (CHO), 170.2, 169.8* ($C^1$=O), 169.3*, 168.7 ($CO_2Et$), 142.3*, 142.2 ($C^5H$), 137.6*, 137.2 ($C^4$), 136.9*, 136.8 ($C^{9a}$), 130.6, 130.6* ($C^6H$), 128.7*, 128.6 ($C^7H$), 127.0 ($C^{5a}$), 124.1*, 123.7 ($C^9H$), 122.9*, 122.7 ($C^8Br$), 62.2*, 62.1 ($OCH_2$), 55.9*, 54.7 ($C^{3a}H$), 49.2*, 49.0 ($C^2H$), 30.9*, 30.8 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2977, 1735, 1706, 1674, 1631, 1587, 1558, 1364, 1164, 1038 $cm^{-1}$. MS (70 eV) *m/z* (%): 290 ($M^+$-$C_3H_5O_2$, 32), 262 (60), 236 (100), 207 (18), 154 (21), 127 (34), 101 (19), 77 (20), 56 (16). HRMS: Calculated for $[C_{16}H_{15}NO_4Br]^+$: 364.0184 $[(M+H)^+]$; found: 364.0201 The ee was determined by HPLC using a Chiralcel OJH column [*n*-hexane/*i*-PrOH (30:70)]; flow rate 0.8 mL/min; $\tau_{major,7}$ = 17.85 min, $\tau_{minor,7}$ = 11.53 min (96% ee), $\tau_{major,7*}$ = 9.58 min, $\tau_{minor,7*}$ = 20.45 min (96% ee). M.p.: 167-169ºC.

**(*R*)-ethyl 8-(trifluoromethyl)-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20g)**. Following the general procedure **20g** (26 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 10 h in 74% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15e** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.61 (s, 1H, CHO), 9.59* (s, 1H, CHO), 8.58* (s, 1H, $CH^9$), 8.54 (s, 1H, $CH^9$), 7.47–7.35 (m, 2H, $CH^6CH^7$), 7.30-7.20 (m, 1H, $CH^5$), 5.19* (ddd, *J* = 10.2, 6.3, 2.0 Hz, 1H, $CH^{3a}$), 4.90 (ddd, *J* = 10.6, 6.0, 2.0 Hz, 1H, $CH^{3a}$), 4.36–4.17 (m, 2H, $OCH_2$), 3.66 (dd, *J* = 12.2, 7.9 Hz, 1H, $CH^2$), 3.53* (dd, *J* = 9.4, 1.0 Hz, 1H, $CH^2$), 3.31-3.16 (m, 1H, $CH^3$), 2.64-2.45 (m, 1H, $CH^{3'}$), 2.37* (dt, *J* = 13.5, 9.8 Hz, 1H, $CH^3$), 1.42-1.24 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.8 (CHO), 170.2, 169.8* ($C^1$=O), 169.1*, 168.5 ($CO_2Et$), 141.3*, 141.2 ($C^5H$), 139.2*, 138.8 ($C^4$), 136.3*, 136.2 ($C^{9a}$), 133.7 (q, *J* = 32.9 Hz, $C^8CF_3$), 129.8, 129.8* ($C^6H$), 126.8* (q, *J* = 0.9 Hz, $C^{5a}$), 126.5 (q, *J* = 0.8 Hz, $C^{9a}$), 123.3 (q, *J* = 272.9, $CF_3$), 121.8 (q, *J* = 4.1 Hz, $C^7H$), 117.8* (q, *J* = 3.9 Hz, $C^9H$), 117.8 (q, *J* = 4.2 Hz, $C^9H$), 62.2*, 62.0 ($OCH_2$), 55.7*, 54.5 ($C^{3a}H$), 49.0*, 48.8 ($C^2H$), 30.8*, 30.7 ($C^3H_2$), 14.1 ($CH_3$). $^{19}$F NMR (283, $CDCl_3$) (* denotes minor diastereoisomer signals) δ -63.1, -63.27 ($C^8F_3$). IR (ATR): 2984, 1724, 1670, 1641, 1343, 1243, 1149, 1120 $cm^{-1}$. MS (70 eV) *m/z* (%): 353 ($M^+$, 54), 306 (34), 280 (65), 252 (63), 226 (100), 210 (18), 196 (67), 169 (28), 55 (70). HRMS: Calculated for $[C_{17}H_{17}NO_3F_3]^+$: 354.0953 [$(M+H)^+$]; found: 354.0948. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 19.80 min, $\tau_{minor,7}$ = 17.17 min (91% ee); $\tau_{major,7*}$ = 25.04 min, $\tau_{minor,7*}$ = 66.12 min (96% ee). M.p.: 148-150ºC.

**(*R*)-Ethyl 8-methyl-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylateDiethyl (20h)**. Following the general procedure **20h** (21 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 3 h in 69% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15f** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) ($^+$ denotes partially solaped signals) δ 9.55 (s, 1H, CHO), 9.53* (s, 1H, CHO), 8.12-8.08 (m, 1H, $CH^9$), 7.21 (dd, *J* = 7.3, 1.7 Hz, 2H, $CH^5CH^6$), 6.99 (d, *J* = 7.4 Hz, 1H, $CH^7$), 5.15* (ddd, *J* = 10.0, 6.4, 1.7 Hz, 1H, $CH^{3a}$), 4.86 (ddd, *J* = 10.4, 6.0, 1.6 Hz, 1H, $CH^{3a}$), 4.35–4.13 (m, 2H, $OCH_2$), 3.63 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.54–3.49* (m, 1H $CH^2$), 3.28-3.13 (m, 1H, $CH^3$), 2.62-2.43 (m, 1H, $CH^{3'}$), 2.44–2.32*$^+$ (m, 1H, $CH^{3'}$) 2.40*$^+$ (s, 3H, $C^8CH_3$), 2.38$^+$ (s, 3H, $C^8CH_3$), 1.37–1.27 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.3 (CHO), 170.2*, 169.8 ($C^1$=O), 169.6*, 169.0 ($CO_2Et$), 144.0 ($C^8CH_3$), 143.6*, 143.5 ($C^5H$), 136.7*, 136.3 ($C^4$), 136.1*, 136.1 ($C^{9a}$), 129.7, 129.6* ($C^6H$), 126.3*, 126.2 ($C^7H$), 121.7*, 121.6 ($C^{5a}$), 121.4*, 121.2 ($C^9H$), 62.0*, 61.9 ($OCH_2$), 56.0*, 54.7 ($C^{3a}H$), 49.3*, 49.2 ($C^2H$), 30.8*, 30.7 ($C^3H_2$), 22.3 ($C^8CH_3$), 14.3 ($CH_3$). IR (ATR): 2977, 1731, 1695, 1666, 1602, 1566, 1372, 1168 cm$^{-1}$. MS (70 eV) *m/z* (%): 299 ($M^+$, 81), 252 (35), 226 (100), 198 (23), 170 (68), 142 (46), 115 (38), 55 (54). HRMS: Calculated for $[C_{17}H_{18}NO_4]^+$: 300.1236 $[(M+H)^+]$; found: 300.1247. The ee of both diastereoisomers were determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 89.23 min, $\tau_{minor,7}$ = 63.68 min (85% ee); $\tau_{major,7*}$ = 104.86 min, $\tau_{minor,7*}$ = 156.54 min (87% ee). M.p.: 154-156ºC.



**(*R*)-Ethyl 8-methoxy-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylateDiethyl (20i)**. Following the general procedure **20i** (15 mg, 0.05 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 5 h in 48% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15g** (15 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) ($^+$ denotes partially overlapped signals) δ 9.51 (s, 1H, CHO), 9.49* (s, 1H, CHO), 7.93 (d, *J* = 2.4 Hz, 1H, $CH^9$), 7.91* (d, *J* = 2.4 Hz, 1H, $CH^9$), 7.23$^+$ (d, *J* = 8.5 Hz, 1H, $CH^6$), 7.23$^{+*}$ (d, *J* = 8.5 Hz, 1H, $CH^6$), 7.19 (d, *J* = 1.8 Hz, 1H, $CH^5$), 7.17* (d, *J* = 1.9 Hz, 1H, $CH^5$), 6.71 (dd, *J* = 8.5, 2.4 Hz, 1H, $CH^7$), 6.71* (dd, *J* = 8.5, 2.4 Hz, 1H, $CH^9$), 5.16* (ddd, *J* = 10.0, 6.3, 1.7 Hz, 1H, $CH^{3a}$), 4.86 (ddd, *J* = 10.6, 5.9, 1.5 Hz, 1H, $CH^{3a}$), 4.35–4.16 (m, 2H, $OCH_2$), 3.86* (s, 3H, $OCH_3$), 3.84 (s, 3H, $OCH_3$), 3.63 (dd, *J* = 12.3, 7.9 Hz, 1H, $CH^2$), 3.54-3.50* (m, 1H, $CH^2$), 3.29–3.17 (m, 1H, $CH^3$), 2.59-2.47 (m, 1H, $CH^{3'}$), 2.37* (dt, *J* = 13.6, 9.9 Hz, 1H, $CH^{3'}$), 1.32 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.8 (CHO), 170.3*, 170.0 ($C^1$=O), 169.6*, 168.9 ($CO_2$Et), 163.4 ($C^8OCH_3$), 143.6*, 143.5 ($C^5$H), 137.9*, 137.8 ($C^4$), 134.5*, 134.1 ($C^{9a}$), 131.2*, 131.1 ($C^6$H), 117.1*, 116.9 ($C^{5a}$),112.1, 112.1* ($C^7$H), 106.2*, 105.6 ($C^9$H), 62.0*, 62.0 ($OCH_2$), 56.0*, 55.8 ($C^{3a}$H), 55.8, 54.8* ($OCH_3$), 49.3*, 49.2 ($C^2$H), 30.7 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2988, 1735, 1701, 1666, 1598, 1562, 1368, 1214, 1160, 1031 cm$^{-1}$. MS (70 eV) *m/z* (%): 315 ($M^+$, 73), 268 (22), 242 (100), 214 (30), 186 (57), 158 (22), 116 (18), 55 (42). HRMS: Calculated for $[C_{17}H_{18}NO_5]^+$: 316.1185 [$(M+H)^+$]; found: 316.1196. The ee of both diastereoisomers were determined by HPLC using a Chiralcel OD column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 0.8 mL/min; $\tau_{major,7}$ = 58.05 min, $\tau_{minor,7}$ = 45.40 min (72% ee); $\tau_{major,7^*}$ = 31.42 min, $\tau_{minor,7^*}$ = 52.74 min (78% ee). M.p.: 145-146$^o$C.

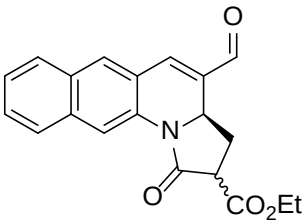
**(*R*)-Ethyl 7-chloro-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20j)**. Following the general procedure **20j** (24 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 9:1 to 1:1) after 5 h in 75% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15h** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.59 (s, 1H, CHO), 9.57* (s, 1H, CHO), 8.21 (d, *J* = 8.8 Hz, 1H, $CH^9$), 7.42-7.25 (m, 1H, $CH^8$), 7.30 (d, *J* = 2.0 Hz, 1H, $CH^6$), 7.17 (d, *J* = 1.9 Hz, 1H, $CH^5$), 7.15* (d, *J* = 2.0 Hz, 1H, $CH^5$), 5.17* (ddd, *J* = 9.9, 6.4, 1.9 Hz, 1H, $CH^{3a}$), 4.87 (ddd, *J* = 10.5, 6.0, 1.8 Hz, 1H, $CH^{3a}$), 4.34–4.14 (m, 2H, $OCH_2$), 3.63 (dd, *J* = 12.1, 8.0 Hz, 1H, $CH^2$), 3.51* (d, *J* = 9.3 Hz, 1H, $CH^2$), 3.27–3.15 (m, 1H, $CH^3$), 2.60–2.46 (m, 1H, $CH^{3'}$), 2.36* (dt, *J* = 13.6, 9.8 Hz, 1H, $CH^{3'}$), 1.38–1.26 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.5 (CHO), 170.1, 169.8* ($C^1$=O), 169.4*, 168.8 ($CO_2Et$), 141.8*, 141.7 ($C^5H$), 138.6*, 138.3 ($C^4$), 134.5*, 134.5 ($C^{9a}$), 132.2 ($C^8H$), 130.6*, 130.5 ($C^7Cl$), 129.1, 129.1* ($C^6H$), 125.6*, 125.4 ($C^{5a}$), 122.3*, 121.9 ($C^9H$), 62.2*, 62.0 ($OCH_2$), 55.9*, 54.6 ($C^{3a}H$), 49.1*, 48.9 ($C^2H$), 30.9*, 30.7 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2984, 1734, 1670, 1634, 1558, 1480, 1364, 1167, 1084 $cm^{-1}$. MS (70 eV) *m/z* (%): 321 ($M^+$, 18), 319 ($M^+$, 61), 290 (15), 272 (33), 246 (85), 218 (60), 192 (100), 176 (21), 162 (60), 127 (34), 99 (22), 83 (20), 55 (75). HRMS: Calculated for $[C_{16}H_{15}NO_4Cl]^+$: 320.0690 $[(M+H)^+]$; found: 320.695. The ee of both diastereoisomers were determined by HPLC using a Chiralcel OD-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 0.8 mL/min; $\tau_{major,7}$ = 56.56 min, $\tau_{minor,7}$ = 80.75 min (94% ee); $\tau_{major,7*}$ = 40.77 min, $\tau_{minor,7*}$ = 107.34 min (91% ee). M.p.: 135-138ºC.

**(*R*)-Ethyl 7-bromo-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20k)**. Following the general procedure **20k** (29 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 2 h in 79% yield as a yellow oil starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15i** (20 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.58 (s, 1H, CHO), 9.56* (s, 1H, CHO), 8.14 (d, *J* = 8.7 Hz, 1H, $CH^9$), 7.50-7.54 (m, 1H, $CH^8$), 7.44 (d, *J* = 1.9 Hz, 1H, $C^6H$), 7.15-7.13 (m, 1H, $CH^9$), 5.17* (ddd, *J* = 10.0, 6.3, 1.9 Hz, 1H, $CH^{3a}$), 4.87* (ddd, *J* = 10.5, 6.0, 1.8 Hz, 1H, $CH^{3a}$), 4.34–4.13 (m, 2H, $OCH_2$), 3.62 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.51* (d, *J* = 8.6 Hz, 1H, $CH^2$), 3.29–3.13 (m, 1H, $CH^3$), 2.59-2.47 (m, 1H $CH^{3'}$), 2.35* (dt, *J* = 13.5, 9.8 Hz, 1H, $CH^{3'}$), 1.35–1.26 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.8*, 189.9 (CHO), 170.1, 169.8* ($C^1$=O), 169.3*, 168.8 ($CO_2Et$), 141.7*, 141.6 ($C^5H$), 138.6*, 138.2 ($C^4$), 135.1, 135.1* ($C^8H$), 135.0*, 135.0 ($C^{9a}$), 132.1, 132.0* ($C^6H$), 126.0*, 125.7 ($C^{5a}$), 122.6*, 122.1 ($C^9H$), 118.1*, 118.0 ($C^7Br$), 62.2*, 62.1 ($OCH_2$), 55.9*, 54.6 ($C^{3a}H$), 49.1*, 49.0 ($C^2H$), 30.9*, 30.8 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2984, 1735, 1706, 1674, 1631, 1558, 1364, 1171, 1020 cm$^{-1}$. MS (70 eV) *m/z* (%): 363 ($M^+$, 1), 293 (55), 291 (69), 264 (47), 262 (61), 238 (54), 236 (100), 209 (16), 207 (67), 154 (28), 127 (41), 83 (47). HRMS: Calculated for $[C_{16}H_{15}NO_4Br]^+$: 364.0184 [$(M+H)^+$]; found: 364.0196. The ee was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; $\tau_{major,7}$ = 226.34 min, $\tau_{minor,7}$ = 248.18 min (96% ee), $\tau_{major,7*}$ = 119.15 min, $\tau_{minor,7*}$ = 167.90 min (94% ee).

**(*R*)-Ethyl 7-methyl-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylateDiethyl (20l)**. Following the general procedure **20l** (24 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 3 h in 81% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15j** (14 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) ($^+$ denotes partially solaped signals) δ 9.56* (s, 1H, CHO), 9.54 (s, 1H, CHO), 8.13 (d, *J* = 8.3 Hz, 1H, $CH^9$), 7.24 (dd, *J* = 8.3, 2.6 Hz, 1H, $CH^8$), 7.20 (d, *J* = 1.9 Hz, 1H, $CH^6$) 7.18* (d, *J* = 1.9 Hz, 1H, $CH^6$), 7.12 (d, *J* = 2.0 Hz, 1H, $CH^5$), 5.15* (ddd, *J* = 9.9, 6.4, 1.8 Hz, 1H, $CH^{3a}$), 4.85 (ddd, *J* = 10.4, 6.0, 1.6 Hz, 1H, $CH^{3a}$), 4.36–4.14 (m, 2H, $OCH_2$), 3.62 (dd, *J* = 12.1, 8.0 Hz, 1H, $CH^2$), 3.51-3.48* (m, 1H, $CH^2$), 3.25–3.13 (m, 1H, $CH^3$), 2.61-2.45 (m, 1H, $CH^{3'}$), 2.41-2.30*$^+$ (m, 1H, $CH^{3'}$), 2.33$^+$ (s, 3H, $C^7CH_3$), 1.36–1.26 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.1 (CHO), 169.9, 169.7* ($C^1$=O), 169.6*, 168.2 ($CO_2Et$), 143.6*, 143.5 ($C^5H$), 137.7*, 137.3 ($C^4$), 135.2*, 135.1 ($C^{9a}$), 133.7 ($C^7CH_3$), 133.3 ($C^8H$), 130.2, 130.1* ($C^6H$), 124.1*, 123.9 ($C^{5a}$), 120.9*, 120.4 ($C^9H$), 62.0*, 61.9 ($OCH_2$), 55.9*, 54.7 ($C^{3a}H$), 49.3*, 49.1 ($C^2H$), 30.8*, 30.7 ($C^3H_2$), 20.9 ($C^7CH_3$), 14.3 ($CH_3$). IR (ATR): 2970, 1739, 1699, 1670, 1570, 1494, 1368, 1171 $cm^{-1}$. MS (70 eV) *m/z* (%): 299 ($M^+$, 81), 252 (31), 226 (100), 198 (22), 170 (65), 142 (47), 115 (38), 83 (22), 55 (51). HRMS: Calculated for $[C_{17}H_{18}NO_4]^+$: 300.1236 [$(M+H)^+$]; found: 300.1252. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 79.44 min, $\tau_{minor,7}$ = 65.60 min (84% ee); $\tau_{major,7*}$ = 72.12 min, $\tau_{minor,7*}$ = 168.28 min (87% ee). M.p.: 162-164ºC.

**(*R*)-Ethyl 6-chloro-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20m)**. Following the general procedure **20m** (17 mg, 0.05 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 10 h in 53% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15m** (16 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and p-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.65 (s, 1H, CHO), 9.63* (s, 1H, CHO), 8.22-8.14 (m, 1H, $CH^6$), 7.71 (d, J = 2.0 Hz, 1H, $CH^5$), 7.68* (d, J = 2.1 Hz, 1H, $CH^5$), 7.41–7.32 (m, 1H, $CH^8$), 7.22 (d, J = 8.1 Hz, 1H, $CH^7$), 5.15* (ddd, J = 9.8, 6.4, 1.9 Hz, 1H, $CH^{3a}$), 4.86 (ddd, J = 10.3, 6.1, 1.8 Hz, 1H, $CH^{3a}$), 4.35–4.13 (m, 2H, $OCH_2$), 3.65 (dd, J = 12.1, 8.1 Hz, 1H, $CH^2$), 3.53* (d, J = 9.4 Hz, 1H, $CH^2$), 3.28–3.16 (m, 1H, $CH^3$), 2.64–2.48 (m, 1H, $CH^{3'}$), 2.39* (dt, J = 13.7, 9.8 Hz, 1H, $CH^{3'}$), 1.37–1.27 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.2*, 190.1 (CHO), 170.2, 169.9* ($C^1$=O), 169.4*, 168.7 ($CO_2Et$), 139.1*, 138.9 ($C^5H$), 138.5*, 138.2 ($C^4$), 137.4*, 137.4 ($C^{9a}$), 134.2, 134.1* ($C^6Cl$), 132.9 ($C^8H$), 126.2*, 126.1 ($C^7H$), 122.4*, 122.2 ($C^{5a}$), 119.7*, 119.2 ($C^9H$), 62.2*, 62.1 ($OCH_2$), 55.6*, 54.3 ($C^{3a}H$), 49.3*, 49.1 ($C^2H$), 30.7*, 30.5 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2923, 1735, 1706, 1674, 1450, 1358, 1167, 1057 cm$^{-1}$. MS (70 eV) m/z (%): 319 ($M^+$, 6), 290 (11), 281 (37), 246 (24), 209 (13), 207 (100), 164 (23), 133 (14), 83 (71), 50 (16). HRMS: Calculated for $[C_{16}H_{15}NO_4Cl]^+$: 320.0690 [$(M+H)^+$]; found: 320.0699. The ee was determined by HPLC using a Chiralpak AZ-3 column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 0.8 mL/min; $\tau_{major,7}$ = 88.46 min, $\tau_{minor,7}$ = 103.02 min (69% ee), $\tau_{major,7*}$ = 56.25 min, $\tau_{minor,7*}$ = 61.64 min (70% ee). M.p.: 118-120$^o$C.

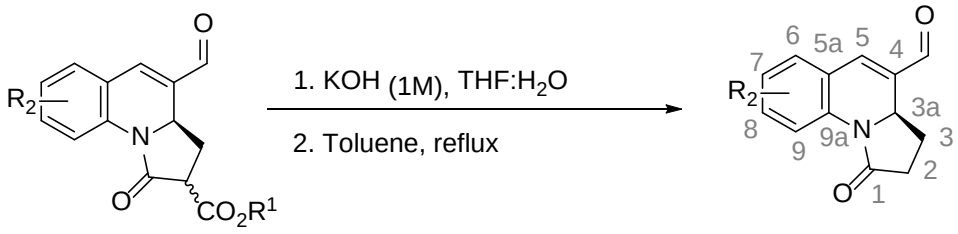
**(*R*)-ethyl 4-formyl-1,2,3,3a-tetrahydro-7,8-dimethoxy-1-oxopyrrolo[1,2-a]quinoline-2-carboxylate (20n)**. Following the general procedure **20n** (13 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 140 min in 38% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15n** (18 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H, CHO), 9.50* (s, 1H, CHO), 7.98 (s, 1H, $CH^9$), 7.96* (s, 1H, $CH^9$), 7.17 (d, *J* = 1.9 Hz, 1H, $CH^5$), 7.14* (d, *J* = 1.9 Hz, 1H, $CH^5$), 6.81-6.75 (s, 1H, $CH^6$), 5.15* (ddd, *J* = 9.5, 6.4, 1.6 Hz, 1H, $CH^{3a}$), 4.85 (ddd, *J* = 9.5, 6.4, 1.6 Hz, 1H, $CH^{3a}$), 4.32–4.21 (m, 2H, $OCH_2$), 3.95* (s, 3H, $OCH_3$), 3.93 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 3.62 (dd, *J* = 12.3, 8.1 Hz, 1H, $CH^2$), 3.51* (d, *J* = 9.4 Hz, 1H, $CH^2$), 3.28–3.14 (m, 1H, $CH^3$), 2.61-2.49 (m, 1H, $CH^{3'}$), 2.39* (dt, *J* = 13.5, 9.8 Hz, 1H, $CH^{3'}$), 1.32 (t, *J* = 7.1 Hz, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 189.7 (CHO), 170.2, 169.8* ($C^1$=O), 169.0 ($CO_2$Et), 152.5 ($C^8OCH_3$), 146.4 ($C^7OCH_3$), 143.6*, 143.5 ($C^5$H), 135.1*, 134.7 ($C^4$), 131.4*, 131.3 ($C^{9a}$), 116.7*, 116.5 ($C^{5a}$), 111.5 ($C^6$H), 104.7*, 104.3 ($C^9$H), 62.1*, 62.0 ($OCH_2$), 56.5* ($OCH_3$), 56.4 ($OCH_3$), 56.3 ($OCH_3$), 56.1* ($OCH_3$), 54.9 ($C^{3a}$H), 49.3*, 49.2 ($C^2$H), 30.6 ($C^3H_2$), 14.3 ($CH_3$). IR (ATR): 2923, 1734, 1695, 1666, 1565, 1508, 1466, 1339, 1257,1214, 1160 $cm^{-1}$. MS (70 eV) *m/z* (%): 345 ($M^+$, 1), 342 (100), 299 (49), 270 (61), 254 (65), 226 (49), 207 (58), 183 (22), 91 (28), 60 (34). HRMS: Calculated for $[C_{18}H_{20}NO_{66}]^+$: 346.1291 $[(M+H)^+]$; found: 346.1296. The ee of both diastereoisomers were determined by HPLC using a Chiralpak ADH column [*n*-hexane/*i*-PrOH (60:40)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 7.41 min, $\tau_{minor,7}$ = 11.73 min (63% ee); $\tau_{major,7*}$ = 9.96 min, $\tau_{minor,7*}$ = 12.85 min (63% ee). M.p.: 126-128ºC.



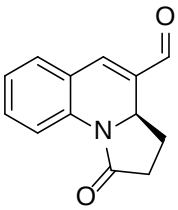
**(*R*)-Ethyl 8-methoxy-4-formyl-1,2,3,3a-tetrahydro-1-oxopyrrolo[1,2-a]quinoline-2-carboxylateDiethyl (20o)**. Following the general procedure **20o** (23 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc gradient from 8:2 to 1:1) after 5 h min in 69% yield as a yellow solid starting from aldehyde **14a** (23 mg, 0.10 mmol) and aminobenzaldehyde **15o** (17 mg, 0.10 mmol) in the presence of **17a** (7 mg, 0.02 mmol) and *p*-$NO_2$-$C_6H_4$-$CO_2H$ (3 mg, 0.02 mmol), using $CHCl_3$ (1 mL) as solvent, and HOAc (3.3 mL, 57.80 mmol). $^1$H NMR (300 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 9.61 (s, 1H, CHO), 9.61* (s, 1H, CHO), 8.65 (s, 1H, $CH^{11}$), 7.85-7-75 (m, 3H, $CH^6CH^7$, $CH^{10}$), 7.56-7.36 (m, 3H, $CH^5$, $CH^8CH^9$), 5.22* (ddd, *J* = 10.3, 6.3, 2.0 Hz, 1H, $CH^{3a}$), 4.91 (ddd, *J* = 10.6, 6.0, 1.9 Hz, 1H, $CH^{3a}$), 4.39–4.17 (m, 2H, $OCH_2$), 3.70 (dd, *J* = 12.2, 8.0 Hz, 1H, $CH^2$), 3.57* (dd, *J* = 9.5, 1.0 Hz, 1H, $CH^2$), 3.24 (dd, *J* = 13.9, 8.1, 6.1 Hz, 1H, $CH^3$), 2.61-2.44 (m, 1H, $CH^{3'}$), 2.33* (dt, *J* = 13.5, 9.8 Hz, 1H, $CH^3$), 1.41-1.27 (m, 3H, $CH_3$). $^{13}$C NMR (75 MHz, $CDCl_3$) (* denotes minor diastereoisomer signals) δ 190.1 (CHO), 169.8, 169.5* ($C^1$=O), 169.5*, 168.9 ($CO_2Et$), 143.3*, 143.2 ($C^5H$), 138.6*, 138.1 ($C^4$), 135.3 ($C^{11a}$), 131.8 ($C^{10a}$), 130.6*, 130.6 ($C^{6a}$) 130.5*, 130.5 ($C^7H$), 128.5, 128.5* ($C^9H$) 128.4 ($C^6H$), 128.3*, 128.2 ($C^8H$), 126.4 ($C^{10}H$), 123.7*, 123.5 ($C^{5a}$), 62.0*, 61.9 ($OCH_2$), 55.9*, 54.6 ($C^{3a}H$), 49.2*, 49.1 ($C^2H$), 30.5*, 30.4 ($C^3H_2$), 14.2 ($CH_3$). IR (ATR): 2818, 1734, 1685, 1662, 1469, 1368, 1168 $cm^{-1}$. MS (70 eV) *m/z* (%): 263 ($M^+$-$CO_2Et$, 89), 234 (100), 208 (82), 178 (43), 151 (38), 103 (12), 83 (10), 77 (8), 55 (6). HRMS: Calculated for $[C_{20}H_{18}NO_4]^+$: 336.1236 [$(M+H)^+$]; found: 336.1245. The ee of both diastereoisomers were determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major,7}$ = 42.26 min, $\tau_{minor,7}$ = 51.95 min (84% ee); $\tau_{major,7*}$ = 74.05 min, $\tau_{minor,7*}$ = 32.04 min (85% ee). M.p.: 182-184ºC.

### 3.2.9. Synthesis of decarboxylated products (21a-m)

*General procedure:* To a solution of lactam **20** (0.1 mmol) in THF:$H_2O$ (1:0.8, 0.9 mL) at room temperature, a solution of KOH (1M, 1 eq, 0.1 mL) was added**.** The reaction mixture was stirred for 8 h. Then the solution was acidified to pH 1 by adding HCl (1M) and extracted with EtOAc (3x3 mL). The organics were collected and dried over $Na_2SO_4$, the drying agent was filtered and the solvent removed *in vacuo*. The crude was dissolved in toluene (1 mL) and heated at reflux temperature for 14 h. Solvent was removed and the crude was directly subjected to FC.

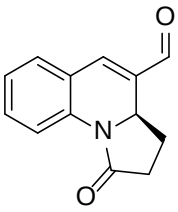



**19a-m**



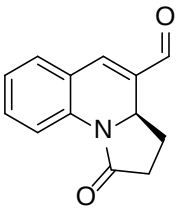
**(R)-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21a)**. Following the general procedure **21a** (19 mg, 0.09 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 87% yield as a yellow solid starting from lactam **20a** (29 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H, CHO), 8.26 (d, *J* = 8.2 Hz, 1H, $CH^6$), 7.39 (td, *J* = 7.8, 1.6 Hz, 1H, $CH^7$), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H, $CH^9$), 7.17 (d, J = 1.9 Hz, 1H, $CH^5$), 7.11 (td, *J* =7.5, 1.1 Hz, 1H, $CH^8$), 4.88 (ddd, *J* = 10.6, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.11-2.93 (m, 1H, $CH^{2'}$). 2.66-2.37 (m, 2H, $CH^{2''}CH^{3'}$), 2.12-1.94 (m, 1H, $CH^{3''}$) $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 174.8 ($C^1$=O), 143.3 ($C^5$H), 137.9 ($C^4$), 136.5 ($C^{9a}$), 132.5 ($C^8$H), 129.6 ($C^6$H), 124.7 ($C^7$H), 123.7 ($C^{5a}$), 120.4 ($C^9$H), 56.5 ($C^{3a}$H), 31.8 ($C^2$H), 26.9 ($C^3H_2$). IR (ATR):

1695, 1670, 1634, 1487, 1362, 1171, 1156 $cm^{-1}$. MS (70 eV) *m/z* (%): 213 ($M^+$, 100), 184 (82), 158 (86), 128 (55), 101 (20), 77 (13), 63 (6), 51 (7). HRMS: Calculated for $[C_{13}H_{12}NO_2]^+$: 214.0868 [$(M+H)^+$]; found: 214.0883. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 52.66 min, $\tau_{minor}$ = 46.16 min (89% ee). $[\alpha]_D^{20}$: +227.3 (*c* = 1.0, $CH_2Cl_2$). M.p.: 122-124ºC.

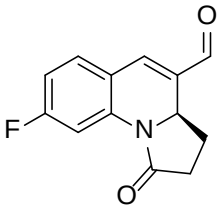


**(R)-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21a)**. Following the general procedure **21a** (13 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 63% yield as a yellow solid starting from lactam **20b** (27 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H, CHO), 8.26 (d, *J* = 8.2 Hz, 1H, $CH^6$), 7.39 (td, *J* = 7.8, 1.6 Hz, 1H, $CH^7$), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H, $CH^9$), 7.17 (d, J = 1.9 Hz, 1H, $CH^5$), 7.11 (td, *J* =7.5, 1.1 Hz, 1H, $CH^8$), 4.88 (ddd, *J* = 10.6, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.11-2.93 (m, 1H, $CH^{2'}$). 2.66-2.37 (m, 2H, $CH^{2''}CH^{3'}$) 2.12-1.94 (m, 1H, $CH^{3''}$) $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 174.8 ($C^1$=O), 143.3 ($C^5$H), 137.9 ($C^4$), 136.5 ($C^{9a}$), 132.5 ($C^8$H), 129.6 ($C^6$H), 124.7 ($C^7$H), 123.7 ($C^{5a}$), 120.4 ($C^9$H), 56.5 ($C^{3a}$H), 31.8 ($C^2$H), 26.9 ($C^3H_2$). IR (ATR): 1695, 1670, 1634, 1487, 1362, 1171, 1156 $cm^{-1}$. MS (70 eV) *m/z* (%): 213 ($M^+$, 100), 184 (82), 158 (86), 128 (55), 101 (20), 77 (13), 63 (6), 51 (7). HRMS: Calculated for $[C_{13}H_{12}NO_2]^+$: 214.0868 [$(M+H)^+$]; found: 214.0883. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 52.66 min, $\tau_{minor}$ = 46.16 min (87% ee). $[\alpha]_D^{20}$: +335.3 (*c* = 1.0, $CH_2Cl_2$). M.p.: 122-124ºC.

**(R)-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21a)**.



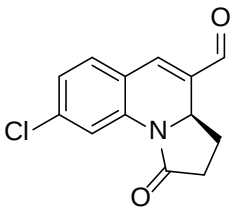
Following the general procedure **21a** (10 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 45% yield as a yellow solid starting from lactam **20c** (35 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H, CHO), 8.26 (d, *J* = 8.2 Hz, 1H, $CH^6$), 7.39 (td, *J* = 7.8, 1.6 Hz, 1H, $CH^7$), 7.27 (dd, *J* = 7.6, 1.6 Hz, 1H, $CH^9$), 7.17 (d, J = 1.9 Hz, 1H, $CH^5$), 7.11 (td, *J* =7.5, 1.1 Hz, 1H, $CH^8$), 4.88 (ddd, *J* = 10.6, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.11-2.93 (m, 1H, $CH^{2'}$). 2.66-2.37 (m, 2H, $CH^{2''}CH^{3'}$), 2.12-1.94 (m, 1H, $CH^{3''}$) $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 174.8 ($C^1$=O), 143.3 ($C^5$H), 137.9 ($C^4$), 136.5 ($C^{9a}$), 132.5 ($C^8$H), 129.6 ($C^6$H), 124.7 ($C^7$H), 123.7 ($C^{5a}$), 120.4 ($C^9$H), 56.5 ($C^{3a}$H), 31.8 ($C^2$H), 26.9 ($C^3H_2$). IR (ATR): 1695, 1670, 1634, 1487, 1362, 1171, 1156 $cm^{-1}$. MS (70 eV) *m/z* (%): 213 ($M^+$, 100), 184 (82), 158 (86), 128 (55), 101 (20), 77 (13), 63 (6), 51 (7). HRMS: Calculated for $[C_{13}H_{12}NO_2]^+$: 214.0868 [$(M+H)^+$]; found: 214.0883. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 52.66 min, $\tau_{minor}$ = 46.16 min (90% ee). $[\alpha]_D^{20}$: +154.0 (*c* = 0.8, $CH_2Cl_2$). M.p.: 122-124ºC.



**8-fluoro-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21b)**. Following the general procedure **21b** (12 mg, 0.05 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 53% yield as a yellow solid starting from lactam **20d** (30 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.12 (dd, *J* = 10.9, 2.6 Hz, 1H, $CH^9$), 7.28 (dd, *J* = 8.5, 6.1Hz, 1H, $CH^6$), 7.18 (d, *J* = 2.0 Hz, 1H, $CH^5$), 6.84 (td, *J* = 8.2, 2.6 Hz, 1H, $CH^7$), 4.91 (ddd, *J* = 10.7, 6.1, 2.0 Hz, 1H, $CH^{3a}$), 3.10-2.88 (m, 1H, $CH^{2'}$), 2.73-2.41 (m, 2H, $CH^{2''}CH^{3'}$), 2.27-1.89 (m, 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 175.0 ($C^1$=O), 165.0 (d, *J* = 252.6 Hz, $C^8$), 142.4 ($C^5$H), 138.2 (d, *J* = 12.4 Hz, $C^{9a}$), 136.5 (d, *J* =

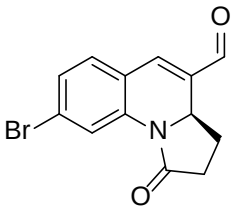
2.7 Hz, $C^4$), 131.1 (d, *J* = 10.4 Hz, $C^6H$), 119.9 (d, *J* = 2.9 Hz, $C^{5a}$) 111.9 (d, *J* = 22.9 Hz, $C^7$), 108.3 (d, *J* = 28.0 Hz, $C^9$), 56.4 ($C^{3a}H$), 31.8 ($C^2H$), 26.9 ($C^3H_2$). $^{19}F$ NMR (283, $CDCl_3$) δ -103.5. I R (ATR): 1702, 1670, 1627, 1605, 1577, 1357, 1181, 1168 $cm^{-1}$. MS (70 eV) *m/z* (%): 231 ($M^+$, 88), 202 (71), 176 (100), 146 (59), 119 (15), 99 (13), 75 (8), 56 (14). HRMS: Calculated for $[C_{13}H_{11}NO_2F]^+$: 232.0774 [$(M+H)^+$]; found: 232.0791. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 48.77 min, $\tau_{minor}$ = 44.65 min (93% ee). $[\alpha]_D^{20}$: +335.8 (*c* = 0.5, $CH_2Cl_2$). M.p.: 141-143ºC.

**(*R*)-8-chloro-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde**



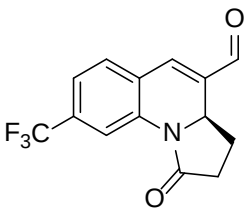

**(21c)**. Following the general procedure **21c** (18 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 72% yield as a yellow solid starting from lactam **20e** (32 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.36 (d, *J* = 2.0 Hz, 1H, $CH^9$), 7.22 (d, *J* = 8.2 Hz, 1H, $CH^6$), 7.16 (d, *J* = 1.9 Hz, 1H, $CH^5$), 7.11 (dd, *J* = 8.2, 2.0 Hz, 1H, $CH^7$), 4.90 (ddd, *J* = 10.6, 6.1, 1.9 Hz, $CH^{3a}$), 3.15-2.88 (m, 1H, $CH^{2'}$), 2.80-2.36 (m, 2H, $CH^{2''}CH^{3'}$), 2.22-1.93 (m, 1H, $CH^{3''}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 174.8 ($C^1$=O), 142.1 ($C^5H$), 138.4 ($C^8Br$), 137.6 ($C^4$), 137.3 ($C^{9a}$), 130.2 ($C^6H$), 124.9 ($C^7H$), 122.0 ($C^{5a}$), 120.6 ($C^9H$), 56.5 ($C^{3a}H$), 31.7 ($C^2H$), 27.0 ($C^3H_2$). IR (ATR): 2826, 1691, 1674, 1630, 1595, 1358, 1168 $cm^{-1}$. MS (70 eV) *m/z* (%): 249 ($M^+$, 32), 247 (94), 220 (26), 218 (78), 192 (100), 162 (30), 128 (13), 99 (8), 75 (6), 56 (5). HRMS: Calculated for $[C_{13}H_{11}NO_2Cl]^+$: 248.0478 [$(M+H)^+$]; found: 248.0482. The ee of both diastereoisomers were determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (85:15)]; flow rate 1.0 mL/min; $\tau_{major}$ = 51.40 min, $\tau_{minor}$ = 84.59 min (94% ee). $[\alpha]_D^{20}$: +331.6 (*c* = 1.0, $CH_2Cl_2$). M.p.: 168-170ºC.

**(*R*)-8-bromo-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde**



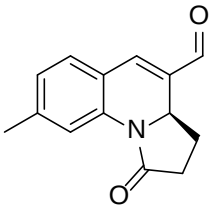
**(21d)**. Following the general procedure **21d** (20 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 69% yield as a yellow solid starting from lactam **20f** (36 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.54 (s, 1H, CHO), 8.50 (d, J = 1.6 Hz, $CH^9$), 7.26 (dd, J = 8.1, 1.9 Hz, 1H, $CH^6$), 7.15 (s, 1H, $CH^5$), 7.16-7.11 (m, 1H, $CH^7$), 4.88 (ddd, J = 10.6, 6.1, 1.9 Hz, 1H, $CH^{3a}$), 3.11-2.80 (m, 1H, $CH^{2'}$), 2.77-2.34 (m, 2H, $CH^{2''}CH^{3'}$), 2.06 (m 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 174.8 ($C^1$=O), 142.2 ($C^5$H), 137.7 ($C^4$H), 137.2 ($C^{9a}$), 130.4 ($C^6$H), 127.9 ($C^7$H), 126.8 ($C^{5a}$), 123.4 ($C^9$H), 122.4 ($C^8$Br), 56.5 ($C^{3a}$H), 31.7 ($C^2$H), 26.9 ($C^3H_2$). IR (ATR): 1699, 1674, 1627, 1476, 1358, 1318, 1168 $cm^{-1}$. MS (70 eV) m/z (%):293 ($M^+$, 64), 291 ($M^+$, 63), 264 (58), 262 (57), 236 (100), 234 (40), 208 (19), 206 (17), 154 (15), 127 (25), 75 (10). HRMS: Calculated for $[C_{13}H_{11}NO_2Br]^+$: 291.9973 $[(M+H)^+]$; found: 291.9976. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; $\tau_{major}$ = 28.17 min, $\tau_{minor}$ = 47.20 min (95% ee). $[\alpha]_D^{20}$: +243.4 (*c* = 1.0, $CH_2Cl_2$). M.p.: 165-167ºC.

**(*R*)-1-oxo-8-(trifluoromethyl)-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-**



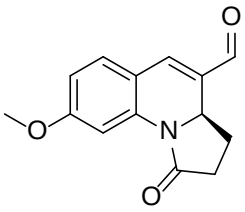
**carbaldehyde (21e)**. Following the general procedure **21e** (10 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 35% yield as a yellow solid starting from lactam **20g** (32 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1H, CHO), 8.61 (s, 1H, $CH^9$), 7.44-7.32 (m, 2H, $CH^6CH^7$), 7.23 (d, *J* = 2.1 Hz, 1H, $CH^5$), 4.96 (ddd, 10.7, 6.0, 2.0 Hz, 1H, $CH^{3a}$), 3.17-2.82 (m, 1H, $CH^{2'}$), 2.77-2.39 (m, 2H, $CH^{2''}CH^{3'}$), 2.24-1.89 (m 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.8 (CHO), 175.0 ($C^1$=O), 141.4 ($C^5$H), 139.5 ($C^4$), 136.8 ($C^{9a}$), 133.8 (q, *J* = 32.4 Hz, $C^8$), 129.6 ($C^6$H),

126.4 ($C^{5a}$), 123.4 (q, *J* = 272.9, $CF_3$), 121.3 (q, *J* = 3.9 Hz, $C^7H$), 117.4 (q, *J* = 4.1 Hz, $C^9H$), 56.5 ($C^{3a}H$), 31.7 ($C^2H$), 27.1 ($C^3H_2$). $^{19}F$ NMR (283, $CDCl_3$) δ -63.2. IR (ATR): 2993, 1710, 1677, 1437, 1329, 1264, 1168, 1120 $cm^{-1}$. MS (70 eV) *m/z* (%): 281 ($M^+$, 81), 252 (74), 226 (100), 196 (37), 169 (14), 154 (4), 75 (4). HRMS: Calculated for $[C_{14}H_{11}NO_2F_3]^+$: 282.0742 $[(M+H)^+]$; found: 282.0739. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; $\tau_{major}$ = 16.72 min, $\tau_{minor}$ = 33.88 min (97% ee). $[\alpha]_D^{20}$: -317.4 (*c* = 0.5, $CH_2Cl_2$).

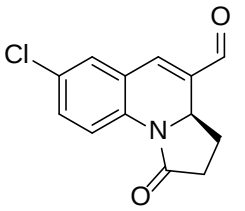


**(R)-8-methyl-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21f)**. Following the general procedure **21f** (17 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 74% yield as a yellow solid starting from lactam **20h** (30 mg, 0.10 mmol) in the presence of KOH (1M, 100 μL) using THF:$H_2O$ (0.9 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H, CHO), 8.13 (d, *J* = 1.5 Hz, 1H, $CH^9$), 7.22-7.16 (m, 2H, $CH^6CH^5$), 6.95 (dd, *J* = 7.8, 0.8 Hz, 1H, $CH^7$), 4.89 (ddd, *J* = 10.5, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.10-2.84 (m, 1H, $CH^{2'}$), 2.67-2.42 (m, 2H, $CH^{2''}CH^{3'}$), 2.39 (s, 3H, $CH_3$), 2.18-1.99 (m, 1H, $CH^{3''}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 190.0 (CHO), 174.9 ($C^1$=O), 143.7 ($C^8$Me), 143.6 ($C^5H$), 136.9 ($C^4$), 136.5 ($C^{9a}$), 129.5 ($C^6H$), 125.6 ($C^7H$), 121.2 ($C^{5a}$), 121.0 ($C^9H$), 56.7 ($C^{3a}H$), 31.9 ($C^2H$), 26.8 ($C^3H_2$), 22.2 ($CH_3$). IR (ATR): 1699, 1670, 1630, 1404, 1364 $cm^{-1}$. MS (70 eV) *m/z* (%): 227 ($M^+$, 100), 198 (87), 172 (76), 142 (47), 115 (38), 89 (13), 63 (11). HRMS: Calculated for $[C_{14}H_{14}NO_2]^+$: 228.1025 $[(M+H)^+]$; found: 228.1021. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 28.67 min, $\tau_{minor}$ = 36.93 min (84% ee). $[\alpha]_D^{20}$: +286.6 (*c* = 1.0, $CH_2Cl_2$). M.p.: 145-147ºC.

**(*R*)-8-methoxy-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde**



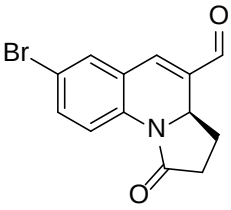
**(21g)**. Following the general procedure **21g** (18 mg, 0.08 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 75% yield as a yellow solid starting from lactam **20i** (31 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.49 (s, 1H, CHO), 7.97 (d, *J* = 2.6 Hz, 1H, $CH^9$), 7.21 (d, *J* = 8.5 Hz, 1H, $CH^6$), 7.15 (d, *J* = 1.9 Hz, 1H, $CH^5$), 6.67 (dd, *J* = 8.5, 2.5 Hz, 1H, $CH^7$), 4.89 (ddd, *J* = 10.6, 6.1, 1.9 Hz, 1H, $CH^{3a}$), 3.86 (s, 3H, $OCH_3$), 3.15-2.75 (m, 1H, $CH^{2'}$), 2.72-2.36 (m, 2H, $CH^{2''}CH^{3'}$), 2.22-1.83 (m, 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 175.1 ($C^1$=O'), 163.3 ($C^8$OMe), 143.6 ($C^5$H), 138.3 ($C^4$), 134.8 ($C^{9a}$), 131.0 ($C^8$H), 116.8 ($C^{5a}$), 111.2 ($C^7$H), 105.6 ($C^9$H), 56.7 ($C^{3a}$H), 55,7 ($OCH_3$), 32.0 ($C^2H_2$), 26.8 ($C^3H_2$). IR (ATR): 2920, 1687, 1659, 1602, 1562, 14.08, 1364, 1318, 1285, 1203, 1164 $cm^{-1}$. MS (70 eV) *m/z* (%): 243 ($M^+$, 100), 214 (72), 186 (52), 158 (23), 143 (18), 116 (15), 89 (11), 63 (8). HRMS: Calculated for $[C_{14}H_{14}NO_3]^+$: 244.0974 $[(M+H)^+]$; found: 244.0975. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (50:50)]; flow rate 1.0 mL/min; $\tau_{major}$ = 25.30 min, $\tau_{minor}$ = 12.47 min (73% ee). $[\alpha]_D^{20}$: +154.1 (*c* = 1.0, $CH_2Cl_2$). M.p.: 143-145ºC.



**(*R*)-7-chloro-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21h)**. Following the general procedure **21h** (16 mg, 0.07 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 66% yield as a yellow solid starting from lactam **20j** (32 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.23 (d, *J* = 8.8 Hz, 1H, $CH^9$), 7.34 (dd, 8.8, 2.4 Hz, 1H, $CH^8$), 7.25 (d, 2.4 Hz, 1H, $CH^6$), 7.11 (d, *J* = 2.0 Hz, 1H, $CH^5$), 4.89 (ddd, *J* = 10.6, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.06-2.83 (m, 1H, $CH^{2'}$), 2.75-2.33 (m, 2H, $CH^{2''}CH^{3'}$), 2.20-1.89 (m, 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 189.9 (CHO), 174.8 ($C^1$=O), 141.7 ($C^5$H), 138.8 ($C^4$), 134.9 ($C^{9a}$), 131.9 ($C^8$H), 129.7

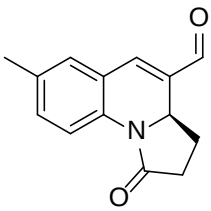
($C^7Cl$), 128.8 ($C^6H$), 125.1 ($C^{5a}$), 121.7 ($C^9H$), 56.5 ($C^{3a}H$), 31.7 ($C^2H$), 26.9 ($C^3H_2$). IR (ATR): 1677, 1472, 1362, 1164 $cm^{-1}$. MS (70 eV) *m/z* (%): 249 ($M^+$, 29), 247 (88), 220 (25), 218 (73), 192 (100), 162 (31), 128 (14), 99 (11), 75 (9), 56 (9). HRMS: Calculated for $[C_{13}H_{11}NO_2Cl]^+$: 248.0478 $[(M+H)^+]$; found: 248.0475. The ee of both diastereoisomers were determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 42.70 min, $\tau_{minor}$ = 36.99 min (94% ee). $[\alpha]_D^{20}$: +307.4 (*c* = 1.0, $CH_2Cl_2$). M.p.: 194-196ºC.

**(R)-7-bromo-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde**

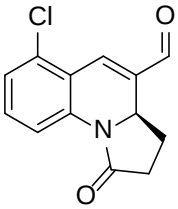



**(21i)**. Following the general procedure **21i** (16 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 56% yield as a yellow solid starting from lactam **20k** (36 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H, CHO), 8.20 (d, *J* = 8.8 Hz, 1H, $CH^9$), 7.51 (dd, *J* = 8.8, 2.3 Hz, 1H, $CH^8$), 7.42 (d, *J* = 2.3 Hz, 1H, $CH^6$), 7.12 (d, *J* = 2.0 Hz, 1H, $CH^5$), 4.92 (ddd, *J* = 10.5, 6.2, 2.0 Hz, 1H, $CH^{3a}$), 3.09-2-85 (m, 1H, $CH^{2'}$), 2.77-2.37 (m, 2H, $CH^{2''}CH^{3'}$), 2.08 (m, 1H, $CH^{3''}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 189.8 (CHO), 174.8 ($C^1$=O), 141.6 ($C^5H$), 138.8 ($C^4$), 135.4 ($C^{9a}$), 134.9 ($C^8H$), 131.8 ($C^6H$), 125.5 ($C^{5a}$), 122.0 ($C^9H$), 117.3 ($C^7Br$), 56.5 ($C^{3a}H$), 31.7 ($C^2H$), 27.0 ($C^3H_2$). IR (ATR): 1697, 1674, 1358, 1168 $cm^{-1}$. MS (70 eV) *m/z* (%): 293 ($M^+$, 73), 291 ($M^+$, 73), 264 (62), 262 (63), 236 (100), 234 (40), 208 (21), 206 (18), 154 (17), 127 (25), 75 (11). HRMS: Calculated for $[C_{13}H_{11}NO_2Br]^+$: 291.9973 $[(M+H)^+]$; found: 291.9969. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; $\tau_{major}$ = 73.79 min, $\tau_{minor}$ = 68.70 min (94% ee). $[\alpha]_D^{20}$: +307.8 (*c* = 0.5, $CH_2Cl_2$). M.p.: 183-185ºC.

**(R)-7-methyl-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde**

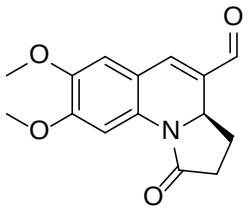


**(21j)**. Following the general procedure **21j** (14 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 64% yield as a yellow solid starting from lactam **20l** (30 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 8.17 (d, *J* = 8.3 Hz, 1H, $CH^9$), 7.26-7.20 (m, 1H, $CH^8$), 7.16 (d, *J* = 1.9 Hz, 1H, $CH^6$), 7.11 (d, *J* = 2.1 Hz, 1H, $CH^5$), 4.90 (ddd, 10.4, 6.2, 1.9 Hz, 1H, $CH^{3a}$), 3.13-2.82 (m, 1H, $CH^{2'}$), 2.68-2.42 (m, 2H, $CH^{2''}CH^{3'}$), 2.34 (s, 3H, $CH_3$), 2.18-1.89 (m 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 174.7 ($C^1$=O), 143.6 ($C^5$H), 137.9 ($C^4$), 134.4 ($C^7$Me), 134.2 ($C^{9a}$), 133.2 ($C^8$H), 129.9 ($C^6$H), 123.6 ($C^{5a}$), 120.3 ($C^9$H), 56.6 ($C^{3a}$H), 31.8 ($C^2$H), 26.9 ($C^3H_2$), 20.7 ($CH_3$). IR (ATR): 2920, 1738, 1695, 1668, 1573, 1487, 1364, 1322, 1279, 1171 $cm^{-1}$. MS (70 eV) *m/z* (%): 227 ($M^+$, 100), 198 (83), 172 (85), 142 (43), 115 (34), 89 (11), 63 (9). HRMS: Calculated for $[C_{14}H_{14}NO_2]^+$: 228.1025 [$(M+H)^+$]; found: 228.1021. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 45.33 min, $\tau_{minor}$ = 35.48 min (83% ee). $[\alpha]_D^{20}$: +307.3 (*c* = 0.5, $CH_2Cl_2$). M.p.: 157-159ºC.



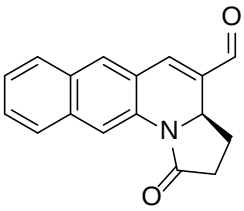
**(*R*)-6-chloro-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21k)**. Following the general procedure **21k** (11 mg, 0.04 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 44% yield as a yellow solid starting from lactam **20m** (32 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H, CHO), 8.41-8.02 (m, 1H, $CH^9$), 7.67 (d, *J* = 1.7 Hz, 1H, $CH^5$), 7.35 (t, *J* = 8.2 Hz, 1H, $CH^8$), 7.18 (dd, 8.1, 1.1 Hz, 1H, $CH^7$), 4.90 (ddd, *J* = 10.4, 6.3, 2.0 Hz, 1H, $CH^{3a}$), 3.09-2.89 (m, 1H, $CH^{2'}$), 2.72-2.44 (m, 2H, $CH^{2''}CH^{3'}$), 2.21-2.01 (m, 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.1 (CHO), 174.9 ($C^1$=O), 138.9 ($C^5$H), 138.7 ($C^4$), 137.8 ($C^{9a}$), 133.8 ($C^6$Cl), 132.7 ($C^8$H), 125.4 ($C^7$H), 121.9 ($C^{5a}$), 119.1 ($C^9$H), 56.2

($C^{3a}H$), 31.8 ($C^{2}H$), 26.7 ($C^{3}H_2$). IR (ATR): 2923, 1701, 1670, 1623, 1583, 1555, 1451, 1350, 1196, 1170, 1145 $cm^{-1}$. MS (70 eV) *m/z* (%): 249 ($M^+$, 25), 247 (72), 220 (24), 218 (74), 192 (100), 162 (36), 128 (19), 99 (15), 75 (15), 56 (15). HRMS: Calculated for $[C_{13}H_{11}NO_2Cl]^+$: 248.0478 $[(M+H)^+]$; found: 248.0475. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 35.70 min, $\tau_{minor}$ = 26.29 min (68% ee). $[\alpha]_D^{20}$: +242.7 (*c* = 0.5, $CH_2Cl_2$). M.p.: 149-151ºC.



**(R)-7,8-dimethoxy-1-oxo-1,2,3,3a-tetrahydropyrrolo[1,2-a]quinoline-4-carbaldehyde (21l)**. Following the general procedure **21l** (17 mg, 0.05 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 53% yield as a yellow solid starting from lactam **20n** (34 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H, CHO), 8.04 (s, 1H, $CH^9$), 7.13 (d, *J* = 1.8 Hz, 1H, $CH^5$), 6.77 (s, 1H, $CH^6$), 4.90 (ddd, *J* = 10.5, 6.1, 1.8 Hz, 1H, $CH^{3a}$), 3.96 (s, 3H, $OCH_3$), 3.89 (s, 3H, $OCH_3$), 2.98 (dt, *J* = 12.9, 7.0, 1H, $CH^{2'}$), 2.69-2.41 (m, 2H, $CH^{2''}CH^{3'}$), 2.23-1.99 (m, 1H, $CH^{3''}$). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 189.7 (CHO), 174.8 ($C^1$=O), 152.4 ($C^8$OMe), 145.9 ($C^7$OMe), 143.6 ($C^5H$), 135.3 ($C^4$), 131.9 ($C^{9a}$), 116.2 ($C^{5a}$), 111.4 ($C^6H$), 104.2 ($C^9H$), 56.8 ($C^{3a}H$), 56.3 ($OCH_3$), 56.2 ($OCH_3$), 31.9 ($C^2H_2$), 26.6 ($C^3H_2$). IR (ATR): 2923, 1666, 1566, 1516, 1454, 1383, 1164 $cm^{-1}$. MS (70 eV) *m/z* (%): 273 ($M^+$, 100), 244 (53), 228 (10), 218 (32), 207 (66), 174 (14), 117 (10), 103 (10), 89 (9), 77 (9). HRMS: Calculated for $[C_{15}H_{16}NO_4]^+$: 274.1079 $[(M+H)^+]$; found: 274.1078. The ee was determined by HPLC using a Chiralcel OZ-3 column [*n*-hexane/*i*-PrOH (70:30)]; flow rate 1.0 mL/min; $\tau_{major}$ = 52.43 min, $\tau_{minor}$ = 76.65 min (65% ee). $[\alpha]_D^{20}$: +180.6 (*c* = 0.5, $CH_2Cl_2$). M.p.: 200-202ºC

**(R)-1-oxo-1,2,3,3a-tetrahydrobenzo[g]pyrrolo[1,2-a]quinoline-4-carbaldehyde**

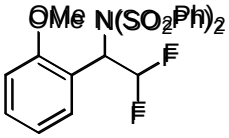


**(21m)**. Following the general procedure **21m** (17 mg, 0.06 mmol) was isolated by FC (hexanes/EtOAc 7:3) in 63% yield as a yellow solid starting from lactam **20o** (34 mg, 0.10 mmol) in the presence of KOH (1M, 100 µL) using THF:$H_2O$ (0.9 mL) as solvent. $^1$H NMR (300 MHz, $CDCl_3$) δ 9.63 (s, 1H, CHO), 8.70 (s, 1H, $CH^{11}$), 7.87-7.75 (m, 3H, $CH^6$, $CH^7$, $CH^{10}$), 7.52 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H, $CH^9$), 7.44 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H, $CH^8$), 7.39 (d, *J* = 1.9 Hz, 1H, $CH^5$), 4.98 (ddd, *J* = 10.8, 6.1, 2.0 Hz, 1H, $CH^{3a}$), 3.11-2.94 (m, 1H, $CH^{2'}$), 2.76-2.48 (m, 2H, $CH^{2''}CH^{3'}$), 2.22-1.89 (m, 1H, $CH^{3''}$). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.2 (CHO), 174.6 ($C^1$=O), 143.3 ($C^5$H), 139.0 ($C^4$), 135.5 ($C^{11a}$), 132.4 ($C^{10a}$), 130.4 ($C^{6a}$), 130.4 ($C^7$H), 128.3 ($C^9$H), 128.3 ($C^6$H), 128.2 ($C^8$H), 126.1 ($C^{10}$H), 123.7 ($C^{5a}$), 118.2 ($C^{11}$H), 56.7 ($C^{3a}$H), 32.0 ($C^2H_2$), 26.7 ($C^3H_2$) IR (ATR): 2923, 1708, 1670, 1627, 1468, 1372, 1228 $cm^{-1}$. MS (70 eV) *m/z* (%): 263 ($M^+$, 87), 234 (100), 208 (75), 178 (34), 151 (35), 103 (9), 75 (6). HRMS: Calculated for $[C_{17}H_{14}NO_2]^+$: 264.1025 [$(M+H)^+$]; found: 264.1025. The ee was determined by HPLC using a Chiralpak ASH column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major}$ = 55.93 min, $\tau_{minor}$ = 45.32 min (87% ee). $[\alpha]_D^{20}$: +25.0 (*c* = 0.5, $CH_2Cl_2$). M.p.: 185-187$^o$C

## 4.- ENANTIOSELECTIVE AMINOFLUORINATION OF β-FLUOROSTYRENES

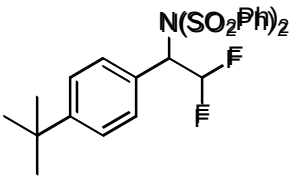
### 2.1. Aminofluorination of fluoroalkenes (24a-g)

*General procedure:* An ordinary vial was charged with pre-catalyst $Pd(OAc)_2$ (0.02 mmol, 10 mol%), the corresponding ligand (**23**) (0.02 mmol, 11 mol%), alkene **22** (0.2 mmol) and N-fluorobenzenesulfonimide (0.3 mmol) and equipped with a magnetic stirring bar. A mixture of 1,4-dioxane:MeCN 1:0.1 (1.1 mL) was added and the mixture was stirred at 40ºC for 12h. Then water was added and the mixture was extracted with $CH_2Cl_2$ (3 x 5 mL) and the collected organic fractions were dried over $Na_2SO_4$, filtered and the solvents were removed under reduced pressure. The crude was charged onto silica gel and subjected to FC




***N*-(2,2-difluoro-1-(2-methoxyphenyl)ethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (24a).** Following the general procedure **24a** (40 mg, 0.09 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 43% yield starting from styrene **22a** (30 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23a** (7 mg, 0.02 mmol) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent. $^1$H NMR (400 MHz, $CD_2Cl_2$) (δ, ppm) (* denotes partially solaped signals) 8.08–7.18 (m, 11H, $N(SO_2Ph)_2$ + $C_{arom.}$-H), 7.11 (dd, *J* = 7.9, 1.5 Hz, 1H, $C_{arom.}$-H), 6.90* (d, *J* = 7.7 Hz, 1H, $C_{arom.}$-H), 6.76* (td, *J* = 57.2, 7.8 Hz, 1H, $F_2CH$), 6.22 (d, *J* = 8.1 Hz, 1H, $C_{arom.}$-H), 6.14 (appdt, *J* = 10.5, 7.7 Hz, 1H, *H*C-$N(SO_2Ph)_2$), 3.37 (s, 3H, $OCH_3$). $^{13}$C NMR (150 MHz, $CD_2Cl_2$) (δ, ppm) 158.1 (MeO-$C_{arom.}$), 140.2 ($C_{arom.}$-$SO_2$), 133.2 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 130.9 (MeO-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 129.5 (d, *J* = 2.4 Hz, MeO-$C_{arom.}$-$C_{arom.}$-*C*$_{arom.}$-H), 128.7 (*C*$_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 128.1 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-$SO_2$), 119.9 (MeO-$C_{arom.}$-$C_{arom.}$-*C*$_{arom.}$-H-*C*$_{arom.}$-H), 117.6 (d, *J* = 8.1 Hz, MeO-$C_{arom.}$-*C*$_{arom.}$), 114.9 (appt, *J* = 242.9 Hz, $F_2CH$), 110.1 (MeO-$C_{arom.}$-*C*$_{arom.}$-H), 58.2 (dd, *J* = 34.2,

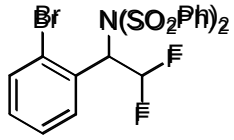
24.3 Hz, H*C*-N($SO_2Ph)_2$), 54.4 (MeO). $^{19}$F NMR (376.5 MHz, $CD_2Cl_2$) (δ, ppm) -118.3 (dddd, *J* = 289.6, 55.9, 7.6, 3.3 Hz, HC$F_a$$F_b$), -125.8 (ddd, *J* = 289.8, 57.4, 10.6 Hz, HC$F_a$$F_b$).



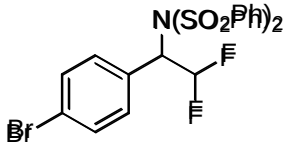

***N*-(2,2-difluoro-1-(2-methoxyphenyl)ethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (24b).** Following the general procedure **24b** (74 mg, 0.15 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 75% yield starting from styrene **22b** (36 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23a** (7 mg, 0.02 mmol) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent. $^1$H NMR (400 MHz, $CDCl_3$) (δ, ppm) (* denotes partially solaped signals) 8.36–7.17 (m, 14H, $N(SO_2Ph)_2$ + $C_{arom.}$-H), 6.78 (td, *J* = 57.0, 7.4 Hz, 1H, $F_2CH$), 5.82-5.60 (m, 1H, *H*C-$N(SO_2Ph)_2$), 1.35 (s, 9H, *t*-Bu). $^{13}$C NMR (150 MHz, $CDCl_3$) (δ, ppm) 152.2 (*t*-Bu-$C_{arom.}$), 139.6 ($C_{arom.}$-$SO_2$), 133.6 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 130.9 (MeO-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 129.0 ($C_{arom.}$-H), 128.7 ($SO_2Ph$), 128.6 (*C*$_{arom.}$-HC-$N(SO_2Ph)_2$), 128.4 ($SO_2Ph$), 125.5 ($C_{arom.}$-H), 114.0 (appt, *J* = 241.9 Hz, $F_2CH$), 63.6 (dd, *J* = 35.4, 23.9 Hz, H*C*-$N(SO_2Ph)_2$), 36.4 (*C*$(CH_3)_3$), 31.3 ($CH_3$). $^{19}$F NMR (376.5 MHz, $CDCl_3$) (δ, ppm) -118.3 (dddd, *J* = 289.6, 55.9, 7.6, 3.3 Hz, HC$F_a$$F_b$), -125.8 (ddd, *J* = 289.8, 57.4, 10.6 Hz, HC$F_a$$F_b$).

**Asymmetric syntheis of *N*-(2,2-difluoro-1-(2-methoxyphenyl)ethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (24b).** Following a modified procedure **24b** (59 mg, 0.12 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 60% yield starting from styrene **22b** (36 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23i** (8 mg, 0.04 mmol, 20 mol%) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent and running the reaction at room temperature..

***N*-(1-(2-bromophenyl)-2,2-difluoroethyl)-*N*-(phenylsulfonyl)benzenesulfonamide**

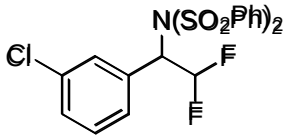


**(24e).** Following the general procedure **24e** (22 mg, 0.04 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 21% yield starting from styrene **22e** (40 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23a** (7 mg, 0.02 mmol) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent. $^1$H NMR (400 MHz, $CD_2Cl_2$) (δ, ppm) (* denotes partially solaped signals) 7.92–7.79 (m, 3H, $N(SO_2Ph)_2$), 7.64–7.52 (m, 3H, $N(SO_2Ph)_2$), 7.44-7.38* (m, 4H, $N(SO_2Ph)_2$ + $C_{arom.}$-Cl-$C_{arom.}$-H) 7.35* (td, *J* = 7.6, 1.6 Hz, 1H, $C_{arom.}$-Br- $C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-*H*), 7.14 (dd, *J* = 8.1, 1.5 Hz, 1H, $C_{arom.}$-Br-$C_{arom.}$-$C_{arom.}$-H), 7.11-7.06 (m, 1H, $C_{arom.}$-Br-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.80 (td, *J* = 56.1, 7.4 Hz, 1H, $F_2CH$), 6.10 (appdt, *J* = 10.7, 7.3 Hz, 1H, *H*C-$N(SO_2Ph)_2$). $^{13}$C NMR (150 MHz, $CD_2Cl_2$) (δ, ppm) 139.6 ($C_{arom.}$-$SO_2$), 133.6 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 133.5 (Br-$C_{arom.}$-*C*$_{arom.}$-H), 132.1 (Br-$C_{arom.}$-*C*$_{arom.}$), 130.9 (Br-$C_{arom.}$-$C_{arom.}$-*C*$_{arom.}$-H), 128.7 (*C*$_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 128.3 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-$SO_2$ + Br-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 127.2 (Br-$C_{arom.}$-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 126.7 (Br-$C_{arom.}$), 114.6 (appt, *J* = 244.5 Hz, $F_2CH$), 62.7 (dd, *J* = 33.5, 25.4 Hz, H*C*-$N(SO_2Ph)_2$). $^{19}$F NMR (376.5 MHz, $CD_2Cl_2$) (δ, ppm) -118.8 (dd, *J* = 289.6, 55.5 Hz, HC$F_aF_b$), -124.0 (dd, *J* = 290.2, 56.8 Hz, HC$F_aF_b$).



***N*-(1-(4-bromophenyl)-2,2-difluoroethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (24f).** Following the general procedure **24f** (30 mg, 0.06 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 29% yield starting from styrene **22f** (40 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23a** (7 mg, 0.02 mmol) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent. $^1$H NMR (400 MHz, $CD_2Cl_2$) (δ, ppm)

(* denotes partially solaped signals) 7.94–7.57 (m, 5H, $SO_2Ph$), 7.53-7.42* (m, 5H, $SO_2Ph$), 7.42* (d, *J* = 8.6 Hz, 2H, $C_{arom.}$-H-$C_{arom.}$-Br-$C_{arom.}$-H), 7.30* (d, *J* = 8.7 Hz, 2H, $C_{arom.}$-H-$C_{arom.}$-$C_{arom.}$-H), 6.84 (td, *J* = 56.8, 7.3 Hz, 1H, $F_2CH$), 5.66 (appdt, *J* = 10.4, 7.8 Hz, 1H, *H*C-N$(SO_2Ph)_2$). $^{13}$C NMR (150 MHz, $CD_2Cl_2$) (δ, ppm) 139.3 ($C_{arom.}$-$SO_2$), 134.0 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 131.7 (Br-$C_{arom.}$-*C*$_{arom.}$-H-$C_{arom.}$-H), 130.8 (Br-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 130.5 (d, *J* = 7.8 Hz, *C*$_{arom.}$-HC-N$(SO_2Ph)_2$), 128.6 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-$SO_2$), 128.5 (*C*$_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 123.3 (Br-$C_{arom.}$), 114.1 (dd, *J* = 246.9, 241.5 Hz, $F_2CH$), 110.1 (MeO-$C_{arom.}$-*C*$_{arom.}$-H), 63.1 (dd, *J* = 35.9, 23.8 Hz, H*C*-N$(SO_2Ph)_2$). $^{19}$F NMR (376.5 MHz, $CD_2Cl_2$) (δ, ppm) -116.4 (ddd, *J* = 293.6, 57.1, 10.4 Hz, $HCF_aF_b$), -124.6 (ddd, *J* = 293.5, 56.4, 8.2 Hz, $HCF_aF_b$).




***N*-(1-(3-chlorophenyl)-2,2-difluoroethyl)-*N*-(phenylsulfonyl)benzenesulfonamide (24g).** Following the general procedure **24g** (19 mg, 0.04 mmol) was isolated by FC (*n*-hexane/EtOAc gradient from 8:2 to 7:3) in 20% yield starting from styrene **22g** (31 mg, 0.20 mmol) and N-fluorobenzenesulfonimide (95 mg, 0.30 mmol) in the presence of **23a** (7 mg, 0.02 mmol) and $Pd(OAc)_2$ (4 mg, 0.02 mmol) and using 1,4-dioxane:MeCN mixture (10:1, 1.1 mL) as solvent. $^1$H NMR (600 MHz, $CD_2Cl_2$) (δ, ppm) (* denotes partially solaped signals) 8.15–7.40 (m, 11H, $N(SO_2Ph)_2$ + $C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-Cl-$C_{arom.}$-*H*), 7.38* (s, 1H, $C_{arom.}$-$C_{arom.}$-*H*-$C_{arom.}$-Cl-$C_{arom.}$-H) 7.35* (dd, *J* = 7.9, 2.0 Hz, 1H, $C_{arom.}$-Cl-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-*H*), 6.85 (td, *J* = 56.8, 7.3 Hz, 1H, $F_2CH$), 5.68 (appdt, *J* = 10.9, 7.5 Hz, 1H, *H*C-N$(SO_2Ph)_2$). $^{13}$C NMR (150 MHz, $CD_2Cl_2$) (δ, ppm) 139.2 ($C_{arom.}$-$SO_2$), 134.6 ($C_{arom.}$-Cl), 134.1 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 133.2 (d, *J* = 7.8 Hz, Cl-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$), 130.0 (Cl-$C_{arom.}$-$C_{arom.}$-H-*C*$_{arom.}$-H), 129.3 (Cl-$C_{arom.}$-*C*$_{arom.}$-H-$C_{arom.}$-H), 129.2 (Cl-$C_{arom.}$-*C*$_{arom.}$-H-$C_{arom.}$), 128.6 (*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-$SO_2$), 128.5 (*C*$_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H-$C_{arom.}$-H-$C_{arom.}$-$SO_2$), 127.1 (Cl-$C_{arom.}$-$C_{arom.}$-H-$C_{arom.}$-H-*C*$_{arom.}$-H), 114.1 (dd, *J* = 247.3, 241.6 Hz, $F_2CH$), 63.1 (dd, *J* =

35.9, 23.6 Hz, H*C*-N($SO_2Ph)_2$). $^{19}$F NMR (376.5 MHz, $CD_2Cl_2$) (δ, ppm) -116.0 (ddd, *J* = 293.6, 57.1, 10.8 Hz, $HCF_a\mathit{F}_b$), -124.5 (ddd, *J* = 293.8, 56.3, 7.8 Hz, $HC\mathit{F}_aF_b$).

# Appendix

# Abbreviations, acronyms and symbols

| | |
|---|---|
| **Ac** | Acetyl |
| **acac** | Acetylacetonate |
| **$Ac_2O$** | Acetic anhydride |
| **AcOH** | Acetic acid |
| **Aminocat*** | Chiral aminocatalyst |
| **aq.** | Aqueous |
| **Ar** | Aryl |
| **AU** | Absorbance units |
| **ATR** | Atenuated total reflectance |
| **B** | Base |
| **BINAP** | 2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene |
| **Bn** | Benzyl |
| **Boc** | *tert*-Butoxycarbonyl |
| **bs** | Broad signal |
| ***n*-Bu** | *n*-Butyl |
| ***t*-Bu** | *tert*-Butyl |
| **Bz** | Benzoyl |
| **c** | Concentration (measured in g/100mL) |
| **ºC** | Degree Celsius |
| **$C_{arom}$** | Aromatic carbon |
| **Cat.** | Catalyst |
| **Cbz** | Benzoxycarbonyl |
| **CI** | Chemical ionization |
| **COSY** | Correlation spectroscopy |
| ***m*CPBA** | *meta*-Chloroperbenzoic acid |
| **CPME** | Cyclopentyl methyl ether |
| **δ** | Chemical shift |
| **d** | Doublet |

| | |
|---|---|
| **DABCO** | 1,4-diazabicyclo[2.2.2]octane |
| **DBU** | 1,5-diazabycyclo[5.4.0]undec-5-ene |
| **DCE** | 1,2-dichloroethane |
| **dd** | Double of doublets |
| **de** | Diastereomeric excess |
| **DEA** | Diethylamine |
| **DEAD** | Diethyl azodicarboxylate |
| **DEPT** | Distortionless Enhancement by Polarization Transfer |
| **DFT** | Density functional theory |
| **DIPEA** | *N*,*N*-Diisopropylethylamine |
| **DKR** | Dynamic kinetic resolution |
| **DMAP** | *N*,*N*-Dimethylaminopyridine |
| **DMF** | *N*,*N*-Dimethylformamide |
| **DMSO** | Dimethylsulfoxide |
| **dr** | Diastereomeric ratio |
| **E** | Electrophile or Energy |
| ***e.g.*** | *Exempli gratia* (for example) |
| **ee** | Enantiomeric excess |
| **EI** | Electron ionization |
| **eq.** | Equivalent |
| **Et** | Ethyl |
| ***et al.*** | *Et alii* (and others) |
| **EtCN** | Propionitrile |
| **EtOAc** | Ethyl acetate |
| **EtOH** | Ethanol |
| **EWG** | Electron-withdrawing group |
| **FC** | Flash column chromatography |
| **g** | Gram |
| **GC** | Gas chromatography |
| **h** | Hours |
| **HOMO** | Highest occupied molecular orbital |
| **HPLC** | High performance liquid chromatography |

| | |
|---|---|
| **HRMS** | High resolution mass spectrometry |
| **HSQC** | Heteronuclear single-quantum correlation spectroscopy |
| **HTBU** | 2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate |
| **Hz** | Hertz |
| ***i.e.*** | *Id est* (that is) |
| **IR** | Infrared |
| ***J*** | Coupling constant |
| **kcal** | kilocalorie |
| **LG** | Leaving group |
| **LUMO** | Lowest unoccupied molecular orbital |
| **m** | Multiplet or metres |
| ***m*** | *meta* |
| **M** | Molar concentration |
| **M.p.** | Melting point |
| **m/z** | Mass-to-charge ratio |
| $\mathbf{M^+}$ | Molecular ion |
| **Me** | Methyl |
| **MeCN** | Acetonitrile |
| **Mes** | Mesityl |
| **MeOH** | Methanol |
| **mg** | Milligrams |
| **min** | Minutes |
| **mL** | Millilitres |
| **μL** | Microlitres |
| **mm** | Millimetres |
| **mmol** | Millimole |
| **MS** | Mass spectrometry or Molecular sieves |
| **NCS** | *N*-chlrosuccinimide |
| **n.d.** | Not determined |
| **n.O.e.** | Nuclear Overhauser effect |
| **NHC** | *N*-Heterocyclic carbene |

| | |
|---|---|
| **NMR** | Nuclear magnetic resonance |
| **NOESY** | Nuclear Overhauser effect correlation spectroscopy |
| **Nu** | Nucleophile |
| ***o*** | *orto* |
| **OAc** | Acetate |
| ***p*** | *para* |
| **PCC** | Pyridinium chlorochromate |
| **Ph** | Phenyl |
| **ppm** | Parts per million |
| ***i*-Pr** | *iso*-Propyl |
| ***n*-Pr** | *n*-Propyl |
| ***i*-PrOH** | *iso*-Propanol |
| **PTC** | Phase-Transfer Catalysis |
| **q** | Quartet |
| **R** | Alkyl group |
| **rt** | Room temperature |
| ***rac*** | Racemic |
| **s** | Singlet |
| **sat.** | Aqueous saturated solution |
| **SOMO** | Single Occupied Molecular Orbital |
| **t** | Triplet or time |
| **T** | Temperature |
| **TBAF** | Tetrabutylammoniun fluoride |
| **TBD** | 1,5,7-Triazabicyclo[4.4.0]dec-5-ene |
| **TBDPS** | *tert*-Butyldiphenylsilyl |
| **TBS** | *tert*-Butyldimethylsilyl |
| **TCA** | Trichloroacetic acid |
| **TES** | Triethylsilyl |
| **Tf** | Trifluoromethanesulfonyl |
| **TFA** | Trifluoroacetic acid |
| **THF** | Tetrahydrofuran |
| **TIPS** | Triisopropyl silyl |

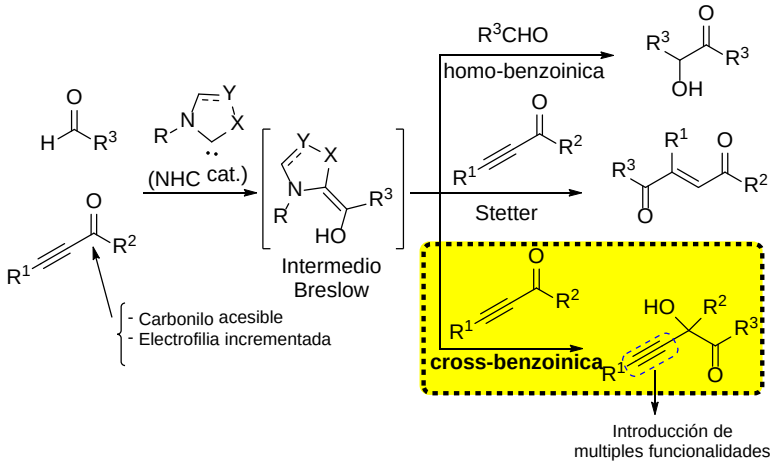
| | |
|---|---|
| **TLC** | Thin layer chromatography |
| **TMAF** | Tetramethylammonium fluoride |
| $\tau_{major}$ | Retention time of the major enantiomer |
| $\tau_{minor}$ | Retention time of the minor enantiomer |
| **TMS** | Trimethysilyl |
| **Ts** | Tosyl |
| **TS** | Transition state |
| ***p*TSA** | *p*-Toluenesulfonic acid |
| ***vs.*** | Versus |
| **X** | Halogen |
| $\lambda$ | Wavelength |

## Resumen extendido

En el trabajo de investigación recogido en la presente memoria, se han desarrollado nuevas metodologías en el ámbito de la activación de compuestos versátiles mediante catálisis covalente. Para ello se ha empleado dos modos de activación pertenecientes al ámbito de la organocatálisis, como son las aminas secundarias y los carbenos *N*-heterocíclicos quirales, en la obtención de compuestos altamente enantioenriquecidos mediante procesos de síntesis asimétrica. Cabe decir que el campo de la organocatálisis ha cobrado una gran importancia significativa en los últimos quince años, convirtiéndose en una de las herramientas sintéticas más importantes de la química orgánica, junto a la catálisis metálica y enzimática.

Dada la dilatada experiencia del grupo en el ámbito de la aminocatálisis, considerada una de las ramas más destacadas dentro de la organocatálisis, y a fin de abrir camino a nuevas líneas de investigación, se propuso el empleo de otros métodos de activación, como lo es el uso de carbenos *N*-heterocíclicos, así como la aplicación de este tipo de catálisis a sustratos aparentemente inertes, como lo son los ciclopropanos tensionados.

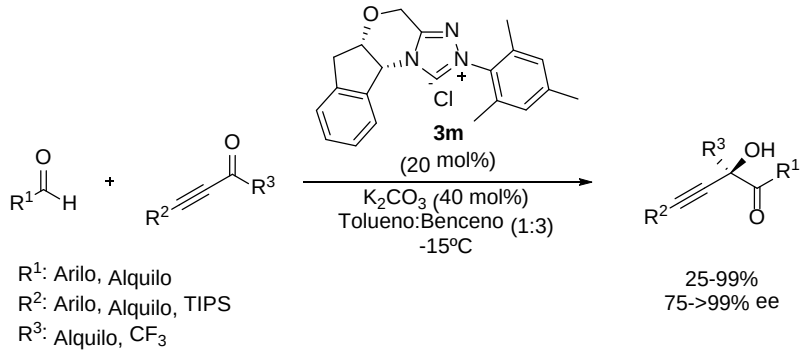
En este sentido, se demostró en primer lugar la capacidad de diferentes inonas α'- y β- sustituidas como electrófilos en el desarrollo de la reacción benzoínica cruzada enantioselectiva entre aldehídos y cetonas catalizada por sales de triazolio quirales. Estos compuestos presentan un grupo carbonilo accesible debido a la inherente planaridad de la molécula lo que les convierte en sustratos adecuados para esta transformación evitando reacciones de homo-condensación no deseadas. Además, la alta funcionalización del sustrato lo hace particularmente interesante de cara a su aplicación como "building blocks" (Esquema 1).




**Esquema 1**

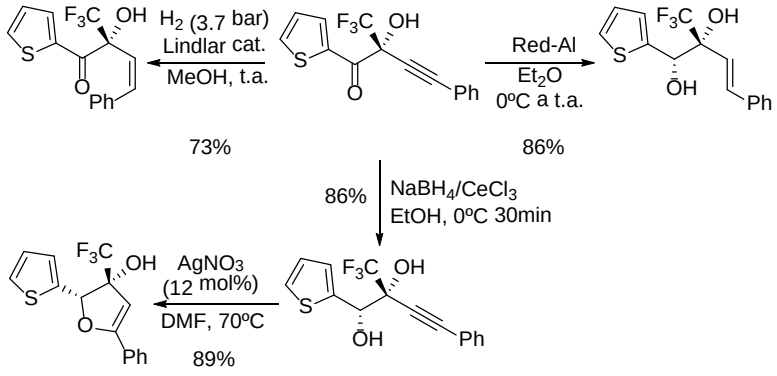
Una vez probada la viabilidad de la reacción y tras un extenso proceso de optimización para identificar las condiciones óptimas para la síntesis de alcoholes propargílicos enantioenriquecidos, se pudo extender la metodología al empleo de diferentes aldehídos y gran variedad de inonas tanto activadas como no activadas, siendo este el primer ejemplo en el que se emplean cetonas no

activadas como electrófilos en la reacción benzoínica cruzada intermolecular (Esquema 2).



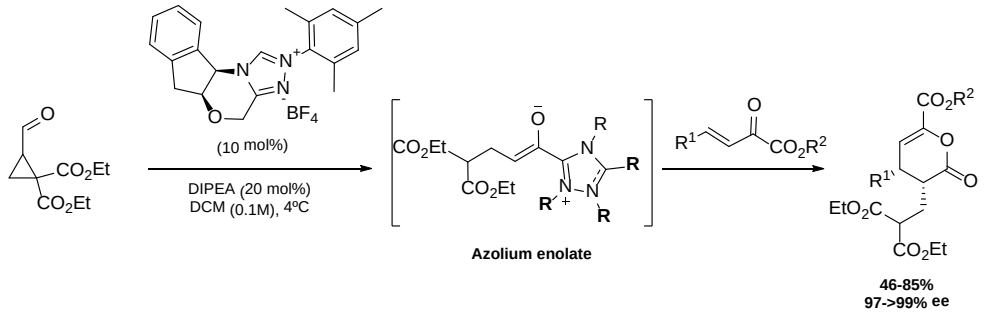

**Esquema 2**

Además, la utilidad sintética de los alcoholes propargílicos obtenidos fue demostrada a través de diversas transformaciones (Esquema 3).



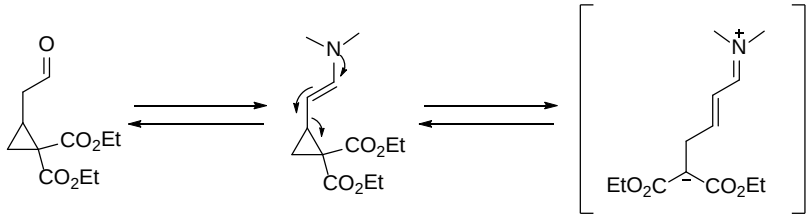

**Esquema 3**

En segundo lugar, se ha estudiado el potencial sintético de los ciclopropanos dadores-aceptores, moléculas relativamente inertes que pueden ser activadas para promover la apertura de ciclo y su participación en reacciones complejas como las cicloadiciones. Por un lado y en base a la capacidad de los carbenos *N*-heterocíclicos para activar formilciclopropanos, se propuso el uso de los mismos para su reacción con oxadienos en cicloadiciones formales [4+2], a través de intermedios de tipo enolato de azolio. De este modo, se ha desarrollado una metodología organocatalítica empleando formilciclopropanos 1,1-dicarboxilatos y α-cetoésteres β,γ-insaturados para la síntesis de piranonas quirales. Del mismo modo que en el ejemplo anterior un exhaustivo estudio de las variables experimentales nos sirvió para alcanzar las condiciones óptimas de reacción y extender la metodología al empleo de diferentes cetoésteres (Esquema 4).



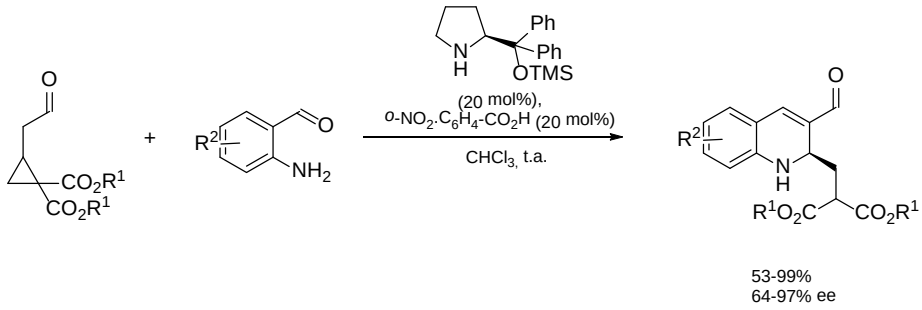

**Esquema 4**

Por otro lado, en vista de que un catalizador nucleófilo podía promover la apertura de ciclopropanos a través de la formación de intermedios enaminólicos, se propuso el empleo de aminocatalizadores para a través de la generación de intermedios tipo enamina análogos a los previamente citados promover la apertura del anillo y dar lugar a reacciones derivadas de la activación clásica con este tipo de catalizadores (Esquema 5).



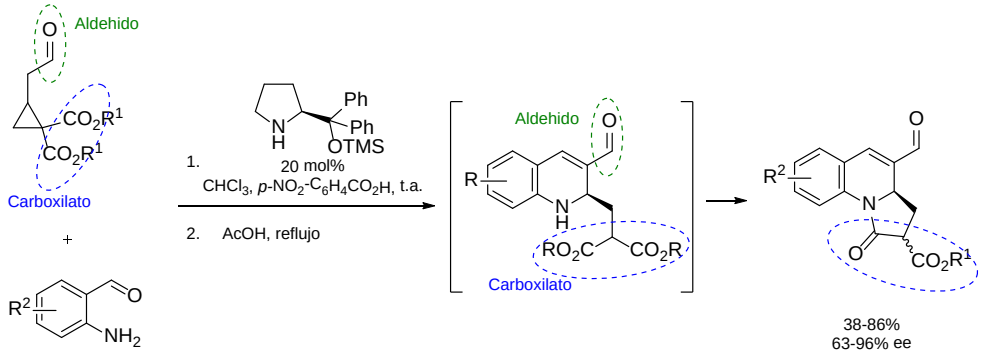

**Esquema 5**

Así, se demostró que los ciclopropanoacetaldehidos pueden dar aperturas de ciclo tras condensar con aminas secundarias quirales y posteriormente participar en reacciones en cascada de tipo aza-Michael/aldol cuando se hacen reaccionar con aminobenzaldehidos. Tras el correspondiente proceso de optimización, la metodología se extendió al uso de diferentes ciclopropanos y aminobenzaldehidos para la obtención de una amplia gama de quinolinas quirales (Esquema 6).



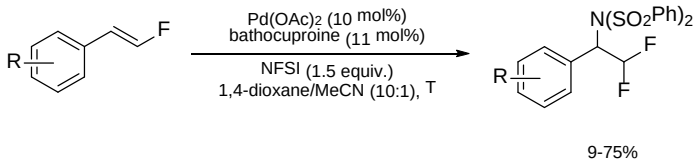

**Esquema 6**

Sin embargo y a fin de explotar todas las funcionalidades presentes en la molécula al tiempo que poder incorporar por completo la estructura del ciclopropano en el nuevo compuesto formado, se realizaron nuevos estudios y se consiguió desarrollar un proceso *one-pot* para la obtención de una gran variedad de pirroloquinolinas tras una lactamización promovida por ácido (Esquema 7).

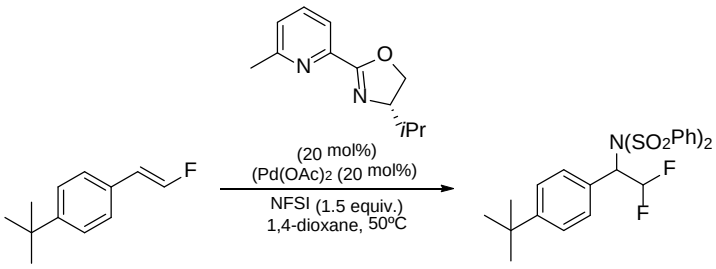



**Esquema 7**

Finalmente, se incluye el trabajo realizado durante una estancia de tres meses en el grupo del profesor F. D. Toste, en la Universidad de California, Berkeley. Se desarrolló un estudio sobre la aminofluorinación enantioselectiva de β-fluoroestirenos mediante el empleo de *N*-fluorobencenosulfonamida como agente oxidante y de fluoración en presencia de una fuente de paladio. Así, el agente oxidante es capaz de oxidar el paladio, para tras una etapa de fluoropaladación en la que se genera el enlace C-F, generar especies con estados de oxidación alto (Pd IV) que dan lugar a la formación de compuestos difluorados en posición geminal. Comprobada la viabilidad de la reacción la metodología se testó empleando varios estirenos (Esquema 8) y se comenzó la optimización de la versión enantioselectiva de la reacción (Esquema 9), punto en el cual se encuentra actualmente este proyecto.




**Esquema 8**




60%, 20% ee

**Esquema 9**

Parte del trabajo recogido en la presente memoria ha dado lugar a las siguientes publicaciones:

1. *"Enantioselective Synthesis of Tertiary Propargylic Alcohols under N-Heterocyclic Carbene Catalysis"*
Eduardo Sánchez Díez, Maitane Férnandez, Uxue Uria, Efraím Reyes, Luisa Carrillo, Jose L. Vicario.
*Chem. Eur. J.*, **2015**, *21*, 8384.

2. *"Organocatalytically Generated Donor-Acceptor Cyclopropanes in Domino Reactions. One Step Synthesis of Pyrrolo[1,2-a]quinolines"*
Eduardo Sánchez Díez, Diana L. Vesga, Efraím Reyes, Uxue Uria, Luisa Carrillo, Jose L. Vicario.
avier Izquierdo, Ane Orue, Karl A. Scheidt.
*Org. Lett*, **2016**, *18*, 1270.

3. *"Catalytic Generation of Donor-Acceptor Cyclopropanes under N-Heterocyclic Carbene Activation .and their Stereoselective Reaction with Alkylideneoxindoles"*
Liher Prieto, Eduardo Sánchez Díez, Uxue Uria, Efraím Reyes, Luisa Carrillo, Jose L. Vicario.
*Adv. Synth. Catal.* **2017**, *in press.* DOI: 10.1002/adsc.201700198.