UPV/EHU
FACULTAD DE CIENCIA Y TECNOLOGÍA
DEPARTAMENTO DE QUÍMICA ORGÁNICA II

Asymmetric Transformations of Donor-Acceptor Cyclopropanes under Brønsted Acid Catalysis

MEMORIA PRESENTADA POR

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Leioa, 2019

Quiero expresar mi agradecimiento a los Profesores Dr. Jose L. Vicario y Dra. Uxue Uria por la dirección y supervisión de este trabajo, así como la ayuda y confianza depositadas en mí. Igualmente agradezco a la Profesoras Dra. Marisa Carrillo y al Profesor Dr. Efraim Reyes y al resto del grupo de investigación su continuo apoyo durante este periodo.

También me gustaría agradecer a las personas que de una forma u otra han contribuido a que este trabajo se pudiera llevar a cabo.

Asimismo, agradezco a la Universidad del País Vasco UPV/EHU la concesión de una "Beca para Formación y Perfeccionamiento de Personal investigador" y por el proyecto EHUA 12/09. De la misma manera, agradezco al Gobierno Vasco por la subvención a grupos de investigación IT328-10 y IT908-16, y al MICINN (Proyecto CTQ2011-22790, CTQ2014-52107 y CTQ2017-83633-P) por la financiación otorgada. Finalmente, agradecer también el apoyo técnico y humano de los SGIker de la UPV/EHU.

Abstract

Cyclopropanes, and especially donor-acceptor cyclopropanes, are considered powerful building blocks for the construction of interesting more complex structures due to their thermodynamic tendency to undergo ring-opening driven by strain release. Brønsted acids are suitable catalysts for hydrogen-bonding activation of acyl-substituted donor-acceptor cyclopropanes, which increased the *push-pull* effect, inducing a high polarization of the C-C bond that is between both substituents and favoring its easier cleavage that leads to reactive 1,3-dipoles. The work complied in this manuscript is focused on intra- and intermolecular reactions of donor-acceptor cyclopropanes by Brønsted acid activation.

In this context, the Cloke-Wilson rearrangement of donor-acceptor cyclopropanes has been demonstrated for the synthesis of enantioenriched 2,3-dihydrofuran derivatives employing BINOL-derived chiral phosphoric acids as catalysts, providing a wide scope of differently substituted heterocycles with good yields and enantiomeric excesses starting from a variety of donor-acceptor cyclopropanes. Mechanistic studies together with experimental analysis revealed the formation of a transitory carbocationic intermediate, enabling the use of racemic substrates for a DYKAT process, confirming that the reaction did not proceeded through an enantioespecific process.

On the other hand, it has been found that acyl-substituted donor-acceptor cyclopropanes reacted with 3-substituted indole derivatives under Brønsted-acid catalysis for the successful construction of dihydropyridoindole derivatives, isolating a variety of differently substituted tricyclic compounds in high yields. In this case, it can be assumed that achiral diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate acted as bifunctional catalyst, activating both the cyclopropane and the indole moiety. The reaction occurred through a stepwise process, which involves the first C2 nucleophilic addition of the indole to the cyclopropane followed by intramolecular *N* nucleophilic addition. Finally, it was tried to carry out the asymmetric version of such transformation under BINOL-derived chiral phosphoric acid activation. Although it has been demonstrated that such catalysts are able to promote the reaction, further modifications in the reaction conditions have to be considered in order to achieve a regio- and enantioselective process.

Resumen

Los ciclopropanos, y especialmente los ciclopropanos dadores-aceptores, son considerados importantes productos de partida para la construcción de interesantes estructuras más complejas, debido a su tendencia termodinámica a sufrir apertura de anillo impulsada por la liberación de tensión. Los ácidos de Brønsted son catalizadores adecuados para la activación de ciclopropanos dadores-aceptores sustituidos por un grupo acilo, lo cual aumenta el efecto *push-pull* a través de la formación de enlace de hidrógeno, induciendo una alta polarización del enlace C-C que se encuentra entre ambos sustituyentes, favoreciendo su escisión, y dando lugar a la formación del reactivo 1,3-dipolo intermedio. El trabajo realizado en este manuscrito se centra en las reacciones intra- e intermoleculares de los ciclopropanos dadores-aceptores mediante su activación con ácidos de Brønsted.

En este contexto, se ha demostrado la síntesis de 2,3-dihidrofuranos enantioenriquecidos mediante el reagrupamiento de Cloke-Wilson de ciclopropanos dadores-aceptores empleando ácidos fosfóricos quirales derivados del BINOL como catalizadores, proporcionando una variedad de heterociclos con bueno rendimientos y excesos enantioméricos. Los estudios mecanísticos, junto con los análisis experimentales llevados a cabo revelaron la formación de un intermedio carbocatiónico transitorio, el cual permite el uso de sustratos racémicos para llevar a cabo una DYKAT, confirmando que la reacción no procede a través de un proceso enantioespecífico.

Por otro lado, se ha comprobado que los ciclopropanos sustituidos con un grupo acilo reaccionan con derivados de indol 3-sustituidos, empleando catálisis de ácidos de Brønsted para la construcción de dihidropiridoindoles, aislando una variedad de compuestos tricíclicos diferentemente sustituidos con altos rendimientos. En este caso, se puede suponer que el catalizador aquiral difenil((trifluorometil)sulfonil)fosforamidato actúa como catalizador bifuncional, activando tanto el ciclopropano como el indol. La reacción ocurre a través de un proceso por pasos, el cual se basa en una adición nucleofílica del C2 del indol al ciclopropano, seguido de una *N*-adición intramolecular. Por último, se intentó llevar a cabo la versión asimétrica de dicha transformación mediante activación de ácidos fosfóricos quirales derivados de BINOL. Aunque se ha comprobado que este tipo de catalizadores son capaces de promover la reacción, deben considerarse modificaciones adicionales en las condiciones de reacción con el objetivo de lograr un proceso totalmente regio- y enantioselectivo.

Laburpena

Ziklopropanoak, eta bereziki ziklopropano emaile-hartzaileak, egitura konplexu interesgarriak eraikitzeko substratu garrantzitsuak kontsidera daitezke, tentsio askapenaren bitartez ziklo irekiera jasatzeko joera termodinamikoa dela eta. Brønsted azidoak karbonilo talde batekin ordezkaturiko ziklopropano emaile-hartzaileak aktibatzeko katalizatzaile egokiak direla esan daiteke, hidrogeno-loturen bitartez *push-pull* efektua biziagotuz. Izan ere, honek, bi ordezkatzaileen arteko C-C loturaren polarizazioa areagotuko du bere apurketa faboratuz eta 1,3-dipolo erreaktiboa eratuz. Idatzi honetan azaltzen den lana zizklopropano emaile-hartzaileen erreakzio intra- eta intermolekularretan oinarritzen da, Brønsted azidoen bidezko aktibazioa erabiliz.

Era honetan, 2,3-dihidrofurano enantiopuruen sintesia burutu da ziklopropano emaile-hartzaileen Cloke-Wilson-en berrantolaketaren bitartez, BINOL azpiegitura duten azido fosforiko kiralak katalizatzaile bezala erabiliz, hainbat heteroziklo desberdin etekin eta gaindikin enantiomeriko altuekin isolatuz. Azterketa mekanistiko teorikoek, buruturiko analisi esperimentalekin batera, tartekari karbokationiko baten eraketa erakutsi zuten, substratu razemiko bat erabiliz DYKAT prozesu bat ahalbideratuz, erreakzioa prozesu enantioespezifiko bat ez dela baieztatuz.

Beste alde batetik, karbonilo talde batekin ordezkaturiko ziklopropano emaile-hartzaileek, hirugarren posizioan ordezkaturiko indol deribatuekin erreakziona dezaketela frogatu da. Erreakzio hau ere katalizatzaile bezala Brønsted azido bat erabiliz eraman da aurrera, ordezkatzaile desberdinak dituzten hainbat konposatu trizikliko etekin altuekin isolatuz. Kasu honetan, suposa daiteke difenil ((trifluorometil) sulfonil) fosforamidak katalizatzaile bifuntzional moduan joka dezakeela, era berean zizklopropanoa eta indola aktibatuz. Erreakzioa pausuzko prozesu baten bitartez gertatzen da, izan ere, indolaren C2-adizio nukleofilikoaren ondoren, bigarren *N*-adizio nukleofiliko intramolekular batek hartzen du parte konposatu ziklikoa eratuz. Azkenik, ziklopropano emaile-hartzaileen eta hirugarren posizioan ordezkaturiko indolen arteko ziklokonsentsazioaren bertsio asimetrikoa burutzen saiatu ginen BINOL azpiegitura duten azido fosforiko kiralen katalisipean. Katalizatzaile hauek erreakzioa sustatzeko gai direla frogatu zen arren, erreakzio baldintzak aldatzea kontutan hartu beharko litzateke, prozesu guztiz regio- eta enantioselektiboa burutzeko asmoz.

Index

Chapter 1 – INTRODUCTION

Chapter 2 - GENERAL OBJECTIVES

Chapter 3 - CATALYTIC ENANTIOSELECTIVE CLOKE-WILSON REARRANGEMENT

Chapter 4 - ACID-CATALYZED CYCLOCONDENSATION OF DONOR-ACCEPTOR CYCLOPROPANES WITH 3-SUBSTITUTED INDOLES

Chapter 5

Chapter 6 – EXPERIMENTAL SECTION

Appendix

Supplementary Information

Chapter 1

1

Reactivity of Cyclopropanes

1. REACTIVITY OF CYCLOPROPANES

As useful three-carbon scaffolds, cyclopropanes have attracted much attention in organic chemistry due to the importance of these substrates as powerful building blocks for the synthesis of natural products and pharmaceuticals,[1] as well as for their olefin-like reactivity.[2] Therefore, their unique structural and electronic properties give rise to a variety of very interesting transformations. It is well known that cyclopropanes are highly strained systems with a conventional ring strain energy of 27.5 kcal/mol,[3] which can be attributed to two main structural features: angular and torsional strain. Regarding the angular strain, the first point to notice about cyclopropanes is the non-ideal C-C-C bond angle of 60º, instead of the expected tetrahedral carbon angle of 109.5º (Figure 1. 1a). This implies that the electron clouds surrounding each atom are considerably closer than ideally, being energetically more disfavored than in a linear alkane. On the other hand, the CH_2 groups of cyclopropanes are locked in a disfavored eclipsed conformation, which leads to torsional strain (Figure 1. 1b).[4]

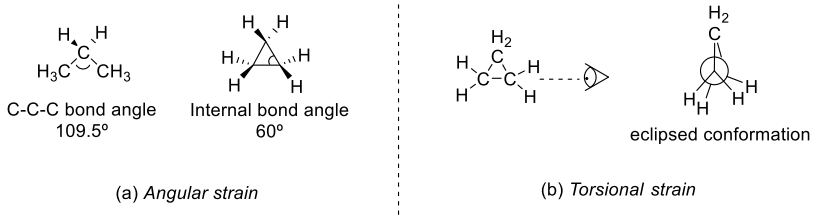


Figure 1. 1 Angular and torsional strain of cyclopropanes

There are two main models to explain bonding between carbons in cyclopropane. The Coulson-Moffitt Model describes the construction of the cyclopropane ring from three sp^3 hybridized carbons, which requires that two orbitals from each carbon center in the plane of the ring make an angle of about 106º with one another (Figure 1. 2a).[5]. As such, the sp^3 hybrids are pointed approximately 22º outward from the imaginary line connecting the two

[1] Carson, C. A.; Michael, A. K. *Chem. Soc. Rev.* **2009**, *38*, 3051.
[2] Peters, D. *Tetrahedron* **1963**, *19*, 1539.
[3] Wiberg, K. W.; Fenoglio, R. A. *J. Am. Chem. Soc.* **1968**, *90*, 3395.
[4] Brown, W. H.; Iverson, B. L.; Anslyn, E. V. *Organic Chemistry*, 8th ed; Cengage Learning: Boston, 2018.
[5] Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys.* **1947**, *15*, 151.

carbon centers, forming like this 'bent bonds', also known as 'banana bonds'. Otherwise, the Walsh Model considers that cyclopropane consists of three methylene sp^2 hybridized carbons, in which both σ-type and π-type methylene orbitals are involved in the formation of the C-C bonds. [6] In this sense, the Walsh model suggests that while the sp^2 orbitals are oriented towards the center of the cyclopropane ring to form one bonding and two antibonding molecular orbitals, the overlap of *p* orbitals in the plane of the ring results in the formation of two C-C bonding and one antibonding bent interactions (Figure 1. 2b). In both cases, angular strain could be attributed to poor overlap of orbitals, which also explained the cause of 'bent bonds'.

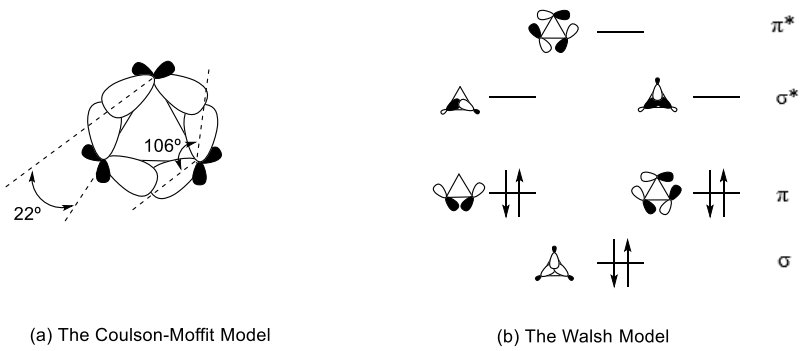
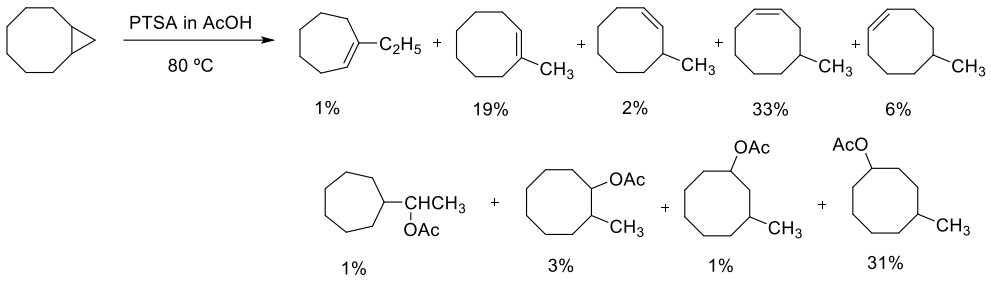


Figure 1. 2 Orbital models of cyclopropanes

Bonds subjected to strain are generally expected to be weaker and, consequently, longer. However, both the C-C and C-H bonds of a cyclopropane are found to be experimentally shorter than those in *n*-alkanes, even though the C-C bonds in cyclopropane are considered to be weaker than in an unstrained alkane, due to both angular and torsional strain explained before.[7] The cyclopropanes are rather kinetically inert despite the weaker nature of its C-C bonds, so they need to be activated to be involved in reactions. The methods for cyclopropane activation by external factors, such as heating or photochemical activation, have a limited synthetic potential since the drastic reaction conditions usually required, also promote the

[6] Walsh, A. D. *Nature* **1947**, *159*, 508.
[7] Karadakov, P. B.; Gerratt, J.; Cooper, D. L.; Raimondi, M. *J. Am. Chem. Soc.* **1994**, 116, *7714.*

formation of a variety of side-products. A good example is found in the pioneering work published by Wiberg and Mejiere about the acid-catalyzed ring-opening reaction of bicyclo[6,1,0]nonane. The substrate was treated with *para*-toluensulfonic acid in acetic acid at high temperature, observing the cleavage of different cyclopropane bonds and subsequent elimination after acetylation, achieving a mixture of products (Scheme 1. 1).[8]

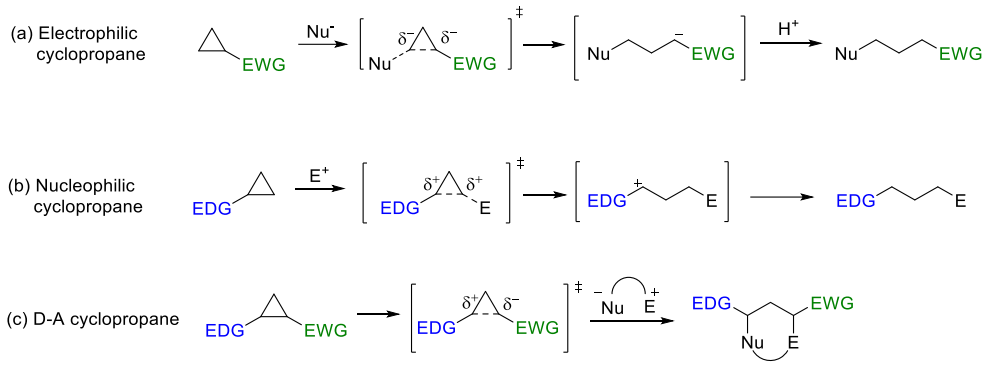


Scheme 1. 1 Acid-catalyzed ring-opening reaction of bicyclo[6,1,0]nonane using PTSA in AcOH

Conversely, an efficient way of activating a cyclopropane is to introduce substituents in the structure in order to increase the polarization of the C-C bonds within the cyclic scaffold, favoring the ring-opening under mild conditions. In this context, the cyclopropane can be activated placing acceptor substituents (electrophilic cyclopropanes), donor substituents (nucleophilic cyclopropanes) or both electron-donating and electron-withdrawing substituents in vicinal positions (donor-acceptor cyclopropanes), giving place to different reactivity patterns. Therefore, electron-withdrawing groups at the cyclopropane moiety will stabilize the negative charge formed after ring-opening reaction promoted by a nucleophile, showing the typical reactivity as homo-Michael acceptors (Scheme 1. 2a). On the other hand, when the cyclopropane is substituted with an electron-donating group, the ring-opening process initiated by the reaction with an electrophile occurs assisted by the stabilization exerted by the donor substituent, thus offering the typical homo-enolate reactivity (Scheme 1. 2b). Alternatively, 1,3-zwiteronic reactive species is generated when the ring-opening event occurs with a donor-acceptor cyclopropane, which possesses an electron-withdrawing and an electron-donating group at vicinal carbons of the ring (Scheme 1. 2c). In the latter

[8] Wiberg, K. B.; Meijere, A. *Tetrahedron Lett.* **1969**, 519.

one, a *push-pull* effect is generated due to the enlargement of the C-C bond between both substituents.



Scheme 1. 2 Reactivity of differently substituted cyclopropanes

1.1. Electrophilic cyclopropanes

Cyclopropanes bearing electron-withdrawing substituents typically react with nucleophiles, and therefore, they are generally considered as electrophilic cyclopropanes. As it is well known, these substrates usually bear two activating electron-withdrawing groups at geminal position in order to increase their reactivity toward nucleophilic additions, however, less reactive cyclopropyl ketones and aldehydes have also been employed in ring-opening reactions (Figure 1. 3).

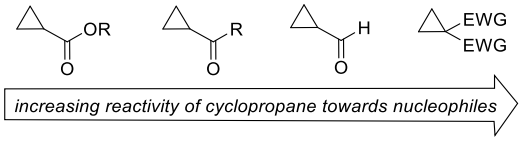
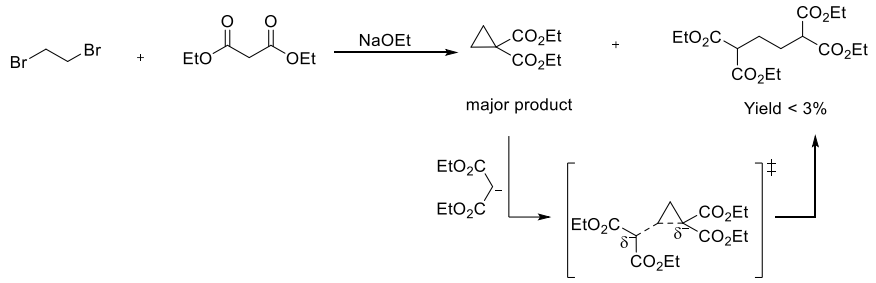


Figure 1. 3 Substituents generally employed in electrophilic cyclopropanes

In 1895, Bone and Perkin observed the generation of tetraethyl 1,1,4,4-butanetetracarboxylate in very low yield during the preparation of diethyl cyclopropane-1,1-dicarboxylate by condensation of 1,2-dibromoethane and diethyl malonate in the presence of sodium ethoxide (Scheme 1. 3).[9] They demonstrated that this byproduct came from the ring-opening reaction of the desired cyclopropane by the malonate anion nucleophile, showing like this the typical homo-Michael reactivity of the cyclopropane.



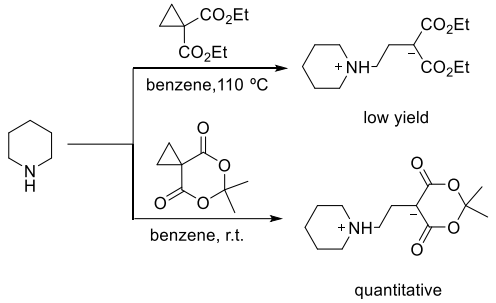
Scheme 1. 3 Proof of concept of nucleophilic ring-opening reaction of acceptor cyclopropanes

After this pioneering discovery, some efforts have been carried out on the study of the ring-opening reaction of differently substituted electrophilic cyclopropanes with a variety of nucleophiles, showing that these substrates need to be further activated in order to promote the nucleophilic addition.

In this sense, Danishefsky and co-workers demonstrated that slight changes in the substrate scaffold could enhance the reactivity of the cyclopropane. They suggested that the presence of spirocyclic carbons, such as in the case of Meldrum acid derived cyclopropanes, would increase the ring-strain of the electrophilic cyclopropane promoting an easier ring-opening reaction under milder conditions.[10] Moreover, taking into account the acidity of Meldrum acid ($pk_a \approx 5$), which is about 8 orders more acidic than the corresponding diethyl malonate, the homo-Michael reactivity of its cyclopropane would be favored, due to its best ability to stabilize negative charges. In this context, they demonstrated that, while the ring-opening event of Meldrum acid derived cyclopropane took place easily at room temperature

[9] Bone, W. A.; Perkin, W. H. *J. Chem. Soc.* **1895**, *67*, 108.
[10] (a) Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239. (b) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

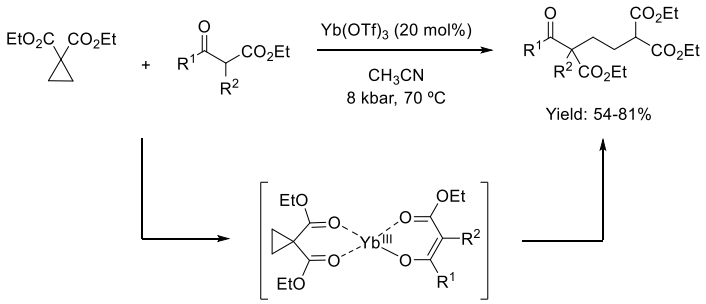
with a variety of nucleophiles such as piperidine or even pyridine, the corresponding diethyl cyclopropanedicarboxylate was unreactive under the same reaction conditions, being necessary 110 ºC and 20 hours to provide the desired zwitterionic product (Scheme 1. 4)..



Scheme 1. 4 Reactivity of diethyl cyclopropanedicarboxylate *vs* Meldrum acid derived cyclopropane

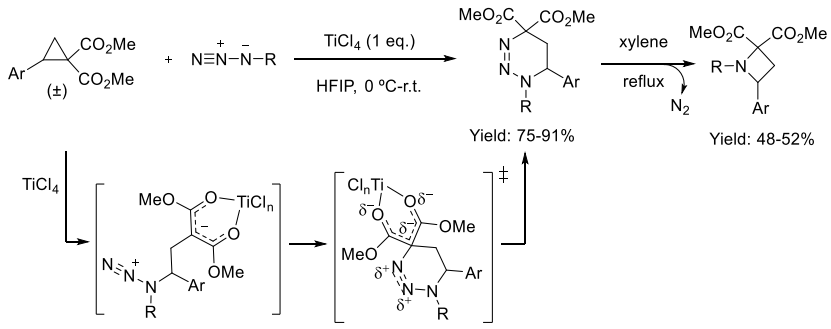
However, the employment of activated bicyclic cyclopropanes is not always possible, being necessary to use external promoters. In this sense, the most appropriate methodology is based on the use of Lewis acids to carry out the ring-opening reaction without the requirement of so high temperatures. As an example, ytterbium(III) triflate was found to be a suitable catalyst for the homo-conjugate addition reaction of β-ketoesters to diethyl 1,1-cyclopropanedicarboxylate.[11] In addition of enhancing the electrophilicity of the cyclopropane by coordination with the two ester groups, the Lewis acid also facilitated the reaction by promoting the approach of both reagents, the cyclopropane and the nucleophile, through chelation as it can be seen in Scheme 1. 5.

[11] Kotsuki, H.; Arimura, K.; Maruzawa, R.; Ohshima, R. *Synlett* **1999**, *5*, 650.



Scheme 1. 5 Nucleophilic ring-opening of diethyl 1,1-cyclopropanedicarboxylate catalyzed by Yb(III).

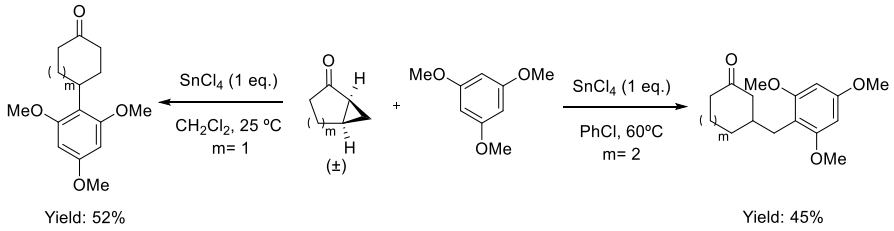
Moreover, in order to obtain more complex adducts, these substrates have been reacted with dipolarophiles in order to generate cyclic products. Thus, after a first nucleophilic addition, a cascade reaction could occur by a subsequent intramolecular electrophilic addition. In this line, a work published in 2014 by Luo, Xu and co-workers described the synthesis of highly functionalized tetrahydrotriazines through a $TiCl_4$ assisted formal [3+3] cycloaddition between similar dimethyl 1,1-cyclopropanedicarboxylates and azides (Scheme 1. 6).[12] Moreover, the authors demonstrated that the obtained products could be easily converted into biologically important highly substituted azetidines by simple thermolysis.



Scheme 1. 6 $TiCl_4$-promoted formal [3+3] cycloaddition of dimethyl 1,1-cyclopropanedicarboxylates with azides

[12] Zhang, H.-H.; Luo, Y.-C.; Wang, H.-P.; Chen, W.; Xu, P.-F. *Org. Lett.* **2014**, *16*, 4896.

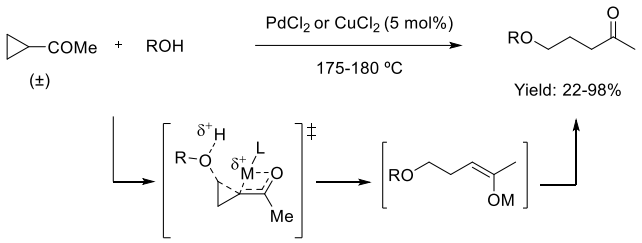
Additionally, the use of cyclopropanes fused to other cyclic molecules, which would increase the ring strain of the cyclopropane moiety, also facilitates the ring-opening reaction avoiding the use of harsh reaction conditions. In this way, Yeung and co-workers reported in 2013 a $SnCl_4$-mediated Friedel-Crafts reaction between bicyclo[n,1,0]alkanones and electron-rich aromatic systems (Scheme 1. 7).[13] It is noteworthy that the nucleophilic addition could occur in two different positions of the cyclopropane scaffold, achieving two different products due to the modification observed in the regioselectivity of the process when the size of the fused cycle changes.



Scheme 1. 7 $SnCl_4$-promoted ring-opening of cyclic acetylcyclopropanes

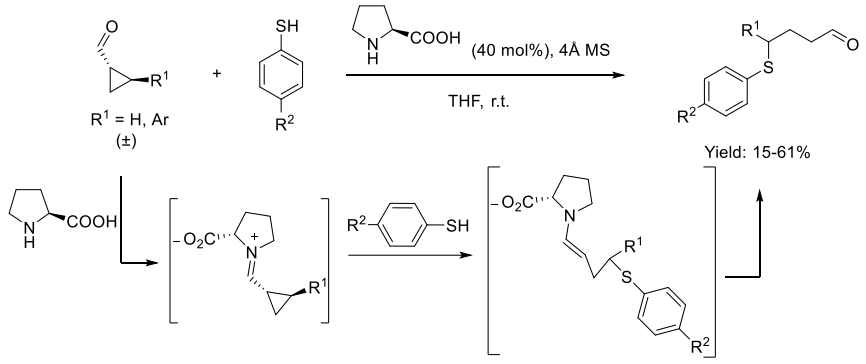
Another activation mode of electrophilic cyclopropanes is through the formation of organometallic intermediates after interaction with transition metal complexes. In this sense, Khusnutdinov and Tomilov developed in 2001 a methodology for the C-C bond cleavage of acetylcyclopropane under copper or palladium catalysis through π-metal activation in the presence of water or alcohols as nucleophiles at high temperatures (Scheme 1. 8).[14] The nucleophilic ring-opening reaction proceeded successfully under the action of a variety of alcohols providing the final dialkyl ethers with moderate to good yields in most of the cases.

[13] Jiang, X.; Lim, Z.; Yeung, Y.-Y. *Tetrahedron Lett.* **2013**, *54*, 1798.
[14] Dzhemilev, U. M. Khusnutdinov, R. I.; Atnabaeva, A. M.; Muslimov, Z. S.; Parfenova, R. I.; Tomilov, Y. V. *Russ. Chem. Bull. Int. Ed.* **2001**, *50*, 1242.



Scheme 1. 8 Ring-opening of acetylcyclopropane under the employment of copper and palladium salts

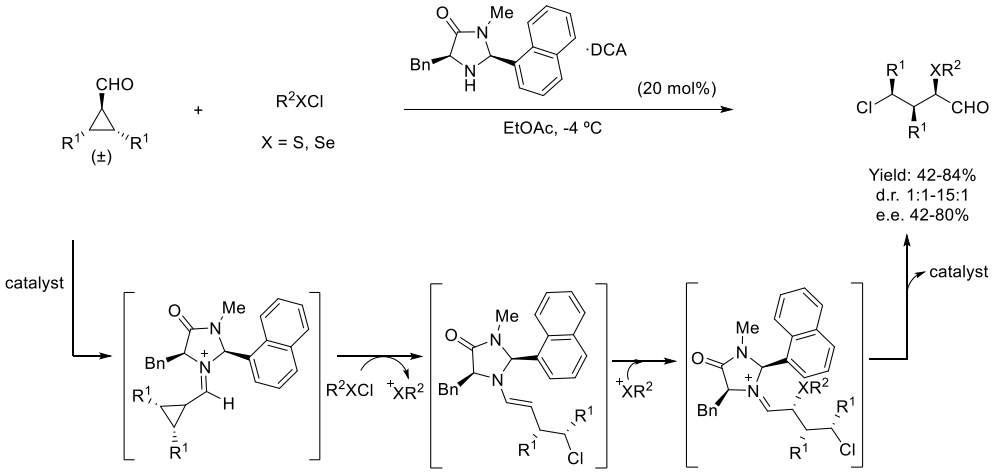
Organocatalytic activation can also be applied to conveniently functionalized cyclopropanes to trigger the ring-opening process. In particular, iminium catalysis can be used on the ring-opening of cyclopropanecarbaldehydes with thiols, in which the LUMO-lowering effect associated to the formation of the cyclopropyl iminium ion increases the reactivity of the substrate, promoting the nucleophilic attack (Scheme 1. 9).[15] In this context, Wang and co-workers reported the proline-catalyzed ring-opening of substituted cyclopropanecarbaldehydes by regioselective nucleophilic attack of benzenethiols at the most substituted carbon of the iminium ion intermediate, obtaining the desired products in moderate to good yields as racemic mixtures.



Scheme 1. 9 Aminocatalytic ring-opening of cyclopropanecarbaldehydes

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

More recently, Werz and co-workers showed that *meso*-cyclopropylcarbaldehydes react with highly polarized selenyl and sulfonyl chlorides providing enantioenriched 1,3-chlorochalcogenated products in high yields and enantiocontrol (Scheme 1. 10).[16] The reaction occurred through nucleophilic chloride-initiated ring-opening of the activated iminium ion, followed by subsequent reaction of the emerging enamine with the electrophilic $^{+}XR^{2}$ species released initially.

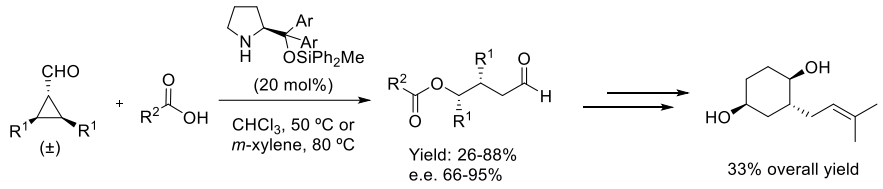


Scheme 1. 10 Asymmetric 1,3-chlorochalcogenation of cyclopropanecarboxylates *via* iminium ion activation.

Based on this reactivity, our research group has also described the ring-opening of cyclopropanecarbaldehydes with carboxylic acids, which are typically considered poor nucleophiles (Scheme 1. 11).[17] In this sense, the cyclopropane was activated by the formation of an iminium ion intermediate after reacting with the chiral secondary amine. Next, nucleophilic addition of a carboxylic acid promoted the ring-opening of the three-membered ring, thus providing γ-acyloxy substituted aldehydes in high yields and enantioselectivities. Chiral information of the catalyst provided stereodiscrimination of the two prochiral

[16] Wallbaum, J.; Garve, L. K. B.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 18756.
[17] Díaz, E; Reyes, E.; Uria, U.; Carrillo, L.; Tejero, T.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2018**, *24*, 8764. This work is based on the reactivity reported by Sparr and Gilmour in which the asymmetric 1,3-dichlorination of cyclopropanecarbaldehydes is described: Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8391.

electrophilic carbon atoms of the *meso* cyclopropane substrate. Moreover, the synthetic potential of this methodology was demonstrated with the total synthesis of Speciosin H.



Scheme 1. 11 Enantioselective ring-opening of cyclopropanecarbaldehydes with carboxylic acids under iminium ion catalysis

1.2. Nucleophilic cyclopropanes

Cyclopropanes containing electron-donating substituents can react with electrophiles, leading to C-C bond cleavage, and generating ring-opened intermediates in which the positive charge is stabilized by the donor group. In this sense, the electron donating character of the substituent leads to a better stabilization of the increasing positive charge that develops during the reaction, which favors the overall process (Figure 1. 4).

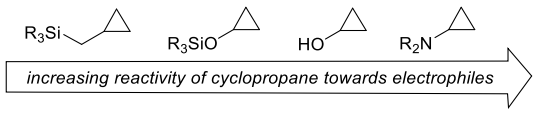
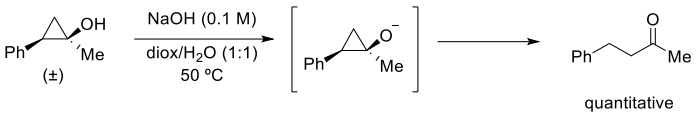


Figure 1. 4 Substituents generally employed in nucleophilic cyclopropanes

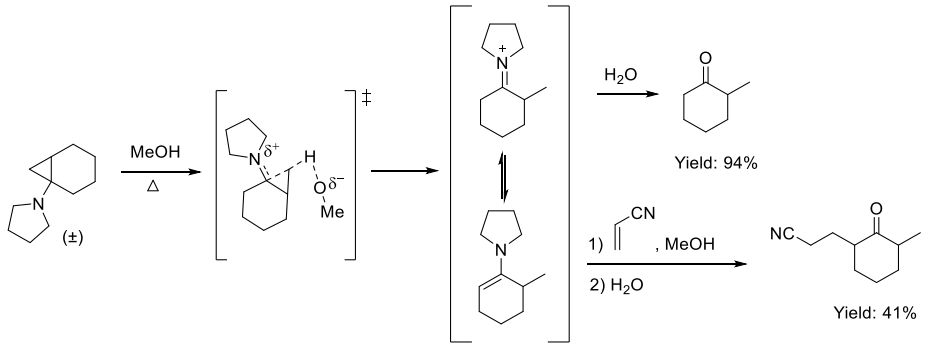
The first ring-opening reaction of nucleophilic cyclopropanes was carried out employing cyclopropanols as substrates, in which deprotonation of the hydroxyl group promoted the ring-opening process, giving rise to the open-chain carbonyl compound (Scheme 1. 12).[18]

[18] (a) DePuy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, *88*, 3347. (b) Kuehne, M. E.; King, J. C. *J. Org. Chem.* **1973**, *38*, 304.



Scheme 1. 12 Formation of carbonyl compounds by ring-opening of nucleophilic cyclopropanols

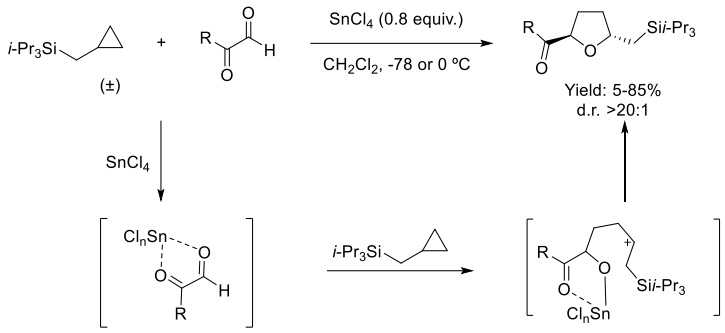
Thermal opening of aminocyclopropanes in a protic media is also a feasible transformation that leads to carbonyl derivatives after hydrolysis of the iminium species that is generated on the ring-opening process. Alternatively, if the reaction is carried out in the absence of water and an external electrophile is incorporated such as acrylonitrile, enamine formation can take place, reacting it with the electrophile *via* a Michael addition (Scheme 1. 13).[18]



Scheme 1. 13 Thermal ring-opening of aminocyclopropanes

Trialkylsilylmethylcyclopropanes are another class of interesting nucleophilic cyclopropanes, which despite their lower electron-donating ability, can also undergo ring-opening reaction due to the ability of the trialkylsilyl group to stabilize a positive charge in the β-position to the silicon atom. In 2015, the research group of Dobbs reported the synthesis of 2,5-disubstituted tetrahydrofurans by the ring-opening of such substrates through addition to glyoxals upon activation by a Lewis acid with further cyclization (Scheme 1. 14).[19]

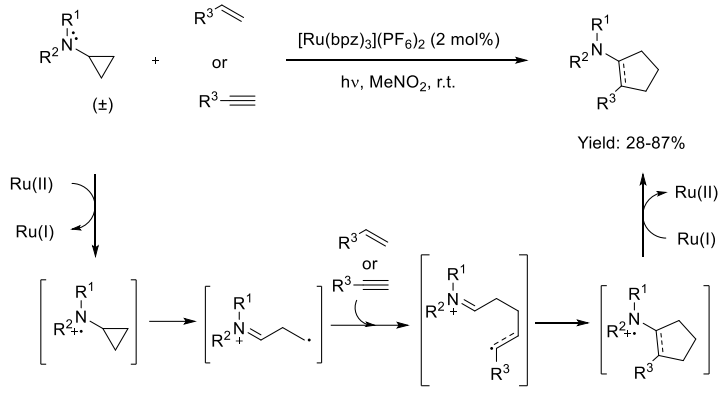
[19] Dunn, J.; Dobbs, A. P. *Tetrahedron* **2015**, *71*, 7386.



Scheme 1. 14 Synthesis of tetrahydrofurans by ring-opening of silylmethylcyclopropane under Lewis acid activation

In a completely different approach, single-electron oxidation is another possible mode of reactivity, in which the resulting radical rapidly undergoes ring-opening process. Based on this mechanism, it has been demonstrated that visible-light photocatalysis using a ruthenium catalyst is an effective method for the single electron oxidation of *N*-aryl aminocyclopropanes, promoting a formal [3+2] cycloaddition with activated alkenes and alkynes (Scheme 1. 15).[20] The transformation would begin by the formation of a heteroatom radical cation that, after forming a radical species as a consequence of C-C bond cleavage, reacted with different alkenes or alkynes undergoing the final ring-closure and leading to the formation of cyclopentane derivatives with moderate to good yields.

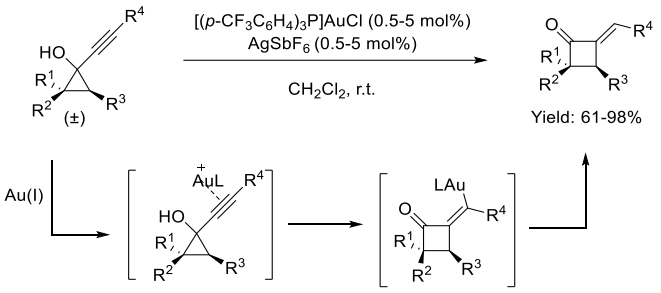
[20] (a) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 222. (b) Maity, S.; Zheng, N. *Synlett* **2012**, 1851. (c) Nguyen, T. H.; Maity, S.; Zheng, N. *Beilstein J. Org. Chem*. **2014**, *10*, 975. (d) Nguyen, T. H.; Morris, S. A.; Zheng, N. *Adv. Synth. Catal*. **2014**, *356*, 2831.



Scheme 1. 15 Single-electron oxidation for ring-opening of aminocyclopropanes

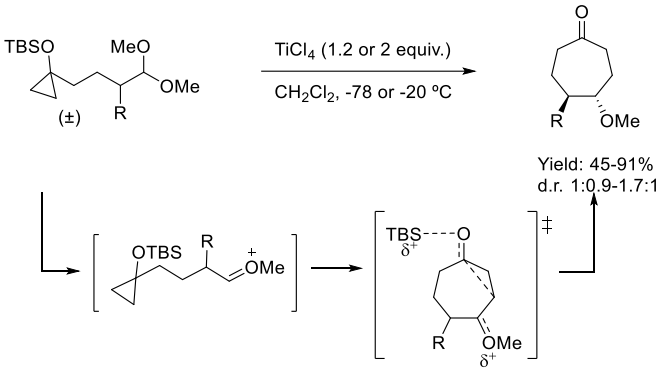
On the other hand, the use of cyclopropanols with a quaternary stereocenter as starting materials that, in addition to the electron-donating substituent also contain another reactive position such as an alkyne, could be a useful strategy for the construction of more complex cyclic structures through ring-expansion reactions. A good example of this reactivity is the rearrangement of propargylcyclopropanols under gold(I)-catalysis, generating substituted alkylidenecyclobutanones in good to excellent yields as single olefin isomers. Regarding the substituents in the ring, the reaction proceeded stereospecifically, maintaining the stereochemistry of the stereocenters in the substrate. Mechanistically, coordination of cationic gold(I) catalyst to the alkyne moiety induced a 1,2-alkyl shift followed by protodeauration (Scheme 1. 16).[21]

[21] Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708.



Scheme 1. 16 Rearrangement of cyclopropanol to cyclobutanone under gold(I) catalysis

Ring expansions to larger cyclic scaffolds are also possible, as it can be seen in the example shown in Scheme 1. 17. In this reaction, silyloxycyclopropanes containing an acetal moiety as the internal electrophilic site were found to be suitable starting materials for the construction of cycloheptanones.[22] In this work, stoichiometric amount of $TiCl_4$ generated an oxacarbenium ion by coordination with one of the methoxy groups of the acetal, promoting the intramolecular reaction of the three-membered ring with the oxocarbenium ion through the ring-opening of the silyloxycyclopropane, thus affording a seven-membered carbocycle in good yield as a mixture of diastereoisomers.

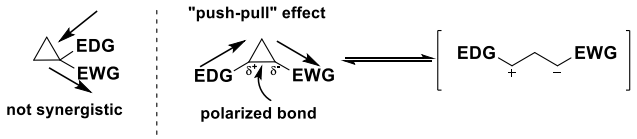


Scheme 1. 17 $TiCl_4$-promoted ring expansion of cyclopropyl silyl ethers

[22] Epstein, O. L.; Lee, S.; Cha, J. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 4988.

1.3. Donor-Acceptor cyclopropanes

An efficient alternative for the activation of cyclopropanes is the combination of donor and acceptor substituents at vicinal positions of the cyclopropane moiety. Cyclopropanes substituted by both electron-withdrawing and electron-donating groups are particularly suitable for synthetic applications, since electronic effects of these substituents guarantee the activation of the three-membered ring. Generally, there are two arrangements for donor and acceptor groups in the cyclopropane ring: geminal and vicinal positioning. In the case of geminally substituted donor-acceptor cyclopropanes, substituents do not act in a synergistic manner, and therefore, there is not a crucial polarization of the C-C bond. In contrast, vicinally positioned donor and acceptor groups act in a controllable *push-pull* manner, which induces a high polarization of the C-C bond between both substituents, leading to a rather weak C-C bond. Therefore, this bond can undergo an easy cleavage process that allows the donor-acceptor cyclopropanes to be represented as zwitterionic structural scaffolds, with the carbocation stabilized by an electron-donating group and the carbanion stabilized by an electron-withdrawing group (Scheme 1. 18).



Scheme 1. 18 Geminally substituted *vs* vicinally substituted donor-acceptor cyclopropanes

In 1980, Reissig and Hirsch[23] proposed the term "donor-acceptor substituted cyclopropanes" for these structures, and during that decade the first golden age for these compounds began at the hands of Wenkert and Reissig.[24] Although all the fundamental type of reactions employing these substrates were reported during that period, previously uninvestigated donor-acceptor cyclopropanes are nowadays being evaluated due to the

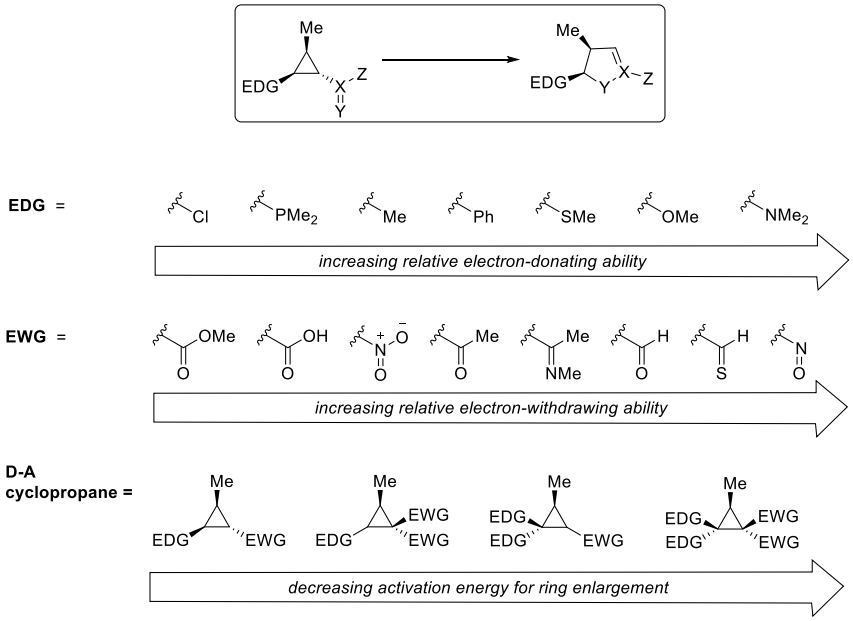
[23] Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 813.
[24] (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778. (b) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (c) Reissig, H.-U.; *Tetrahedron Lett.* **1981**, *22*, 2981. (d) Brückner, C.;Reissig, H.-U. *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 588. (e) Grimm, E. L.; Zschiesche, R.; Reissig, H.-U. *J. Org. Chem*. **1985**, *50*, 5543. (f) Brueckner, C.; Reissig, H.-U. *J. Org. Chem.* **1988**, *53*, 2440. (g) Reissig, H.-U. Holzinger, H.; Glomsda, G. *Tetrahedron Lett.* **1989**, *45*, 3139. (h) Hofmenn, B.; Reissig, H.-U. *Chem. Ber.* **1994**, *127*, 2327.

possibility of being used as key steps in total synthesis of some natural products. As a consequence, the chemistry of such activated cyclopropanes has been intensively studied, forming a wide research area nowadays.[25]

With the aim of quantifying the polarizing effect of various donor and acceptor substituents, Werz calculated the activation barriers and transition states of ring-enlargement reactions employing some differently substituted donor-acceptor cyclopropanes (Scheme 1. 19).[26] As expected, while increasing the electron-donating and electron-accepting character of the substituents, lower energy transition states were observed, favoring the ring-opening reaction by the higher polarization of the C-C bond. Moreover, it was also demonstrated that the donor group has more influence than the acceptor one lowering the energy of the transition state associated to the ring-opening process.

[25] (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (b) Mel`nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293. (c) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504. (d) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804. (e) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13*, 655. (f) Budynina, E. M.; Ivanov, K. L.; Sorokin, I. D.; Melnikov, M. Y. *Synthesis* **2017**, *49*, 3035.

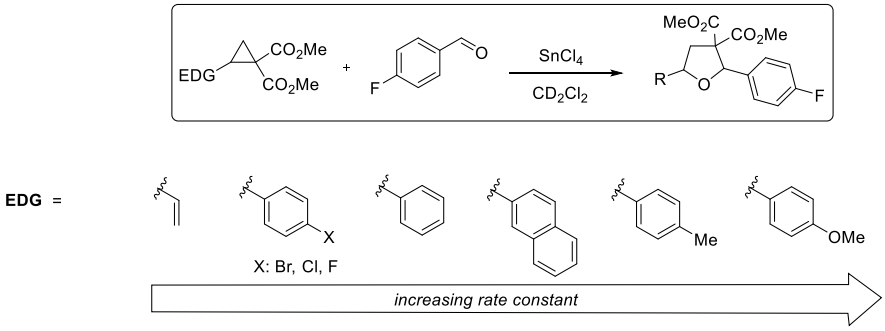
[26] Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848.



Scheme 1. 19 Theoretical study of ring-enlargement reaction of a variety of donor-acceptor cyclopropanes

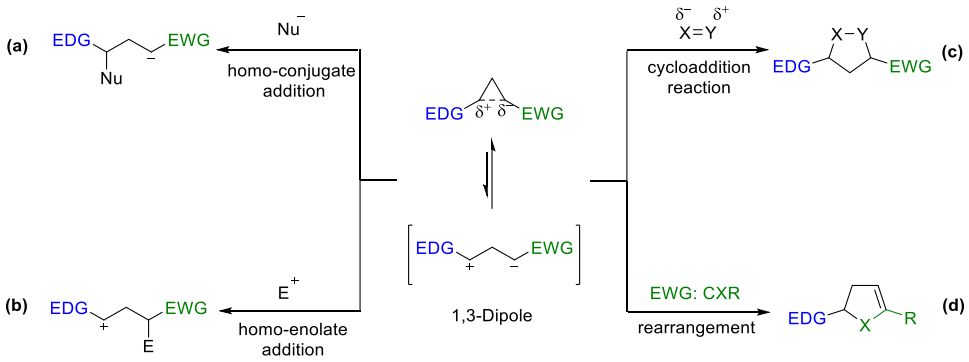
In the same line, a kinetic study of a variety of donor-acceptor cyclopropanes has been recently carried out by the same authors using the [3+2] reaction between diester substituted cyclopropanes and 4-fluorobenzaldehyde as model system to determine the corresponding rate constants (Scheme 1. 20).[27] As expected, increasing the electron density of the donor substituent accelerated the reaction, and remarkably, while the presence of *para*-methoxyphenyl substituent accelerated the reaction by a factor of around 50 compared to the phenyl substituted cyclopropane, when an electron-withdrawing *para*-nitrophenyl substituent was used as substituent the reaction was 666 times slower.

[27] Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2019**, *58*, 1955.



Scheme 1. 20 Kinetic studies of a variety of donor-acceptor cyclopropanes in the [3+2] cycloaddition

The polarization of the C-C bond induced by the *push-pull* effect gives place to different pathways for the ring-opening reaction. When heterolytic ring-opening occurs, donor-acceptor cyclopropanes can be used to form a 1,3-dipole intermediate that is reactive towards nucleophiles (Scheme 1. 21a), electrophiles (Scheme 1. 21b) and usually dipolarophiles (Scheme 1. 21c) in a variety of reactions. Furthermore, intramolecular rearrangement reactions can also occur (Scheme 1. 21d) with participation of atoms from electron-donating or electron-withdrawing substituents.



Scheme 1. 21 General reactivity of donor-acceptor cyclopropanes

In the following lines, relevant examples of this type of different reactivity profiles will be discussed in order to provide an overview on the reactivity of donor-acceptor cyclopropanes.

1.3.1. Reactions with nucleophiles: Homo-conjugate addition

The most basic transformation of donor-acceptor cyclopropanes consists on the reaction of a nucleophile leading to the formation of a final product that can be regarded as the homo-conjugate addition product, exactly as it happens with electrophilic cyclopropanes (see section 1.1). In this transformation, the 1,3-bifunctionalized open-chain system generated after the ring-opening event interacts with an heteroatom-containing nucleophile or electron-rich arene, while the negatively charged carbon is neutralized by a proton. In this context, this reaction has been developed with a variety of heteroatom-based nucleophiles, such as, amines,[28] alcohols,[29] thiols[30] and azides.[31] As a representative example, Mattson and co-workers reported the Brønsted acid-catalyzed nucleophilic ring-opening of donor-acceptor cyclopropanes with a variety of primary and secondary amines (Scheme 1. 22).[32] In this sense, activation of nitrocyclopropanecarboxylates by coordination of the boronate urea catalyst to the nitro group promoted the ring-opening reaction through an S_N2 reaction pathway, which is supported by the chirality transfer observed when starting with an

[28] (a) Blanchard, L. A.; Schneider, J. A. *J. Org. Chem.* **1986**, *51*, 1372. (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (c) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809. (e) Nickerson, D. M.; Angeles, V. V.; Auvil, T. J.; So, S. S.; Mattson, A. E.; *Chem. Commun.* **2013**, *49*, 4289. (f) Martin, M. C.; Patil, D. V.; France, S. *J. Org. Chem.* **2014**, *79*, 3030. For enantioselective examples: (g) Kang, Q.; Wang, L.; Zheng, Z.; Li, J.; Tang, Y. *Chin. J. Chen.* **2014**, *32*, 669. (h) Xia, Y.; Liu, X.; Zheng, H.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed*. **2015**, *54*, 227.

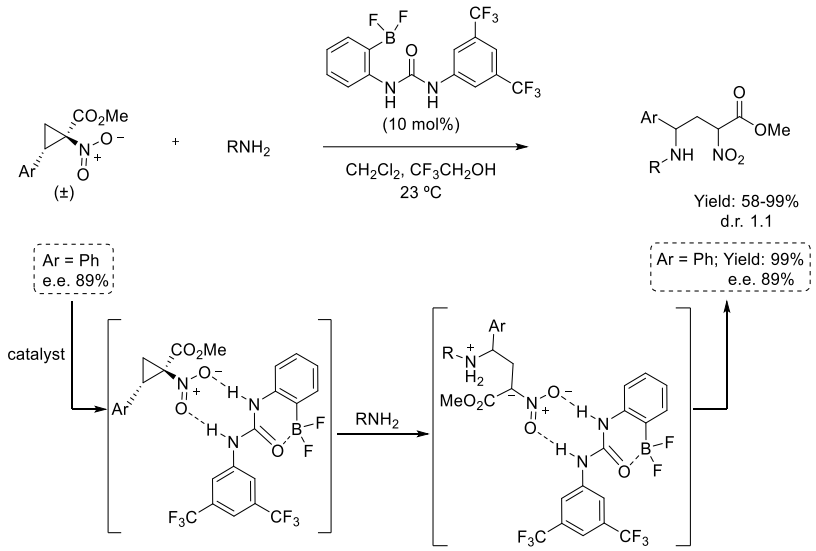
[29] (a) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838. (b) Zhu, X; Hong, G.; Hu, C.; Wu, S.; Wang, L. *Eur. J. Org. Chem.* **2017**, 1547. For enantioselective examples: (c) Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Li, J.-F.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14594. (d) Xia, Y.; Lin, L.; Chang, F.; Fu, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed*. **2015**, *54*, 13748.

[30] (a) Braun, C. M.; Shema, A. M.; Dulin, C. C.; Nolin, K. A. *Tetrahedron Lett.* **2013**, *54*, 5889. (b) Wang, H.-P.; Zhang, H.-H.; Hu, X.-Q.; Xu, P.-F.; Luo, Y.-C. Eur. *J. Org. Chem.* **2015**, *2015*, 3486.

[31] (a) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem*. **2012**, *77*, 6634. (b) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y. *Chem. Eur. J.* **2015**, *21*, 4975. (c) Boichenko, M. A.; Ivanova, O. A.; Andreev, I. A.; Chagarovskiy, A. O.; Levina, I. I.; Rybakov, V. B.; Skvortsov, D. A.; Trushkov, I. V. *Org. Chem. Front.* **2018**, *5*, 2829.

[32] So, S. S.; Auvil, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444.

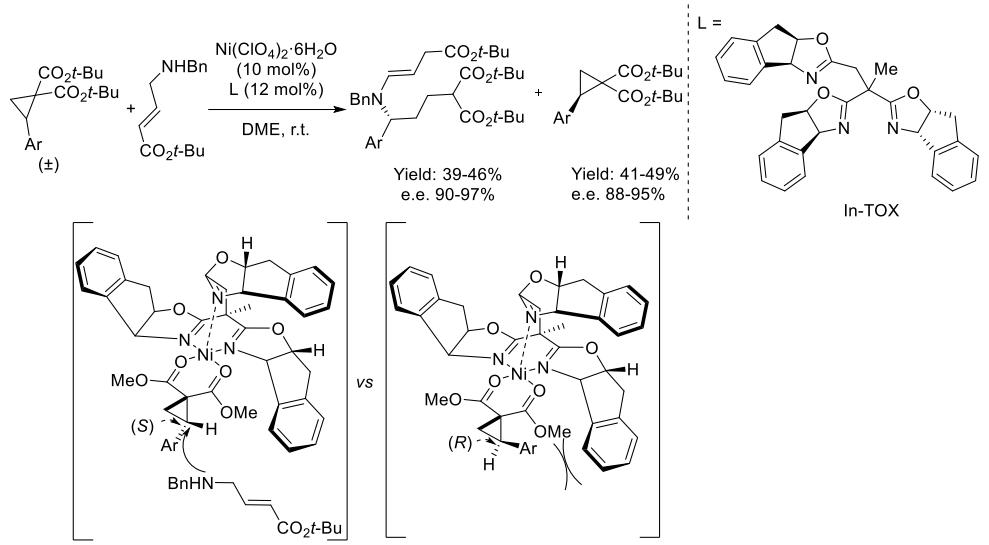
enantioenriched cyclopropane, leading to 1:1 diastereomeric mixtures of γ-substituted esters in good yields.



Scheme 1. 22 Nucleophilic amine ring-opening of nitrocyclopropane carboxylates

Lewis acid catalysis can also be used to trigger the ring-opening process of donor-acceptor cyclopropanes towards nucleophiles. For instance, Tang and co-workers reported the kinetic resolution of di(*tert*-butyl) 2-arylcyclopropane-1,1-dicarboxylates with a secondary amine, in the presence of the Ni(II) complex of an indene-derived trioxazoline (In-TOX) ligand, providing both δ-amino acid derivatives and cyclopropanes with high enantioselectivity (Scheme 1. 23). The side-arm of the catalyst complex proved to be crucial for the stereochemical control of the reaction. Therefore, the *S* enantiomer of the racemic cyclopropane was preferentially activated because of the steric repulsion presented in the *R* enantiomer between the aryl group and the indanyl moiety. Subsequent attack of the amine afforded *R* product, recovering the *R* enantiomer of the untouched cyclopropane.[33]

[33] Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc*. **2012**, *134*, 9066.

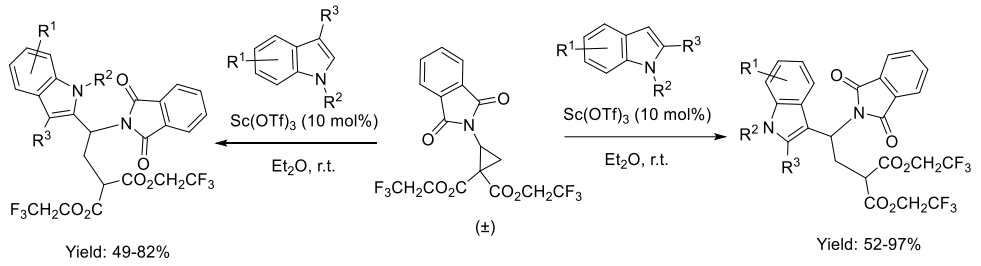


Scheme 1. 23 Kinetic resolution of di(*tert*-butyl) 2-arylcyclopropane-1,1-dicarboxylates by nucleophilic addition of amines

As mentioned before, electron-rich arenes have also been used as nucleophiles able to react with the zwitterionic intermediate generated after the ring-opening of the donor-acceptor cyclopropane. Among the different heteroarenes involved in these transformations, indoles have attracted a particular attention due to its presence in many bioactive molecules. It is noteworthy that this electron-rich heteroaromatic system shows enhanced reactivity through electrophilic substitution preferably at the nucleophilic C3 position. However, N1 and C2 are also potential reaction sites, mainly when 3-substituted indoles are employed. In this context, Waser and co-workers demonstrated the possibility of directing the reaction at both C2 and C3 positions of the indole using a Sc(III) complex as Lewis acid catalyst (Scheme 1. 24).[34] In this case, indole alkylation at C3 position was selectively observed when

[34] (a) Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15*, 3738. For other related examples using indole: (b) Harrington, P.; Kerr, M. A. *Tetrahedron Lett.* **1997**, *38*, 5949. (c) Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2011**, *13*, 4180. (d) Selvi. T.; Srinivasan, K. *Adv. Synth. Catal.* **2015**, *357*, 2111. (e) Karmakar, R.; Suneja, A.; Singh, V. K. *Org. Lett.* **2016**, *18*, 2636. (f) Lee, J.; Ko, K. M.; Kim, S.-G. *Eur. J. Org. Chem.* **2016**, 4166. (g) Yu, L.; Zhu, Z.-Q.; Sun, M.; Mei, G.-J.; Shi, F. *Synthesis* **2018**, *50*, A-G. (h) Irwin, L. C.; Renwick, C. R.; Kerr, M. A. *J. Org. Chem.* **2018**, *83*, 6235. For intramolecular examples: (i) De Simone, F.; Gertsch, J.; Waser, J *Angew. Chem. Int. Ed.* **2010**, *49*, 5767. (n) De Simone, F.; Waser, J. *Synlett* **2011**, 589.

2-substituted indoles were used as starting materials. Conversely, the authors favored regioselective C2-alkylation when using 3-substituted indoles. Remarkably, the *N*-alkylation did not occur in any case, not even using *N*-H unprotected indole scaffold. In addition to indole, other carbon nucleophiles usually involved the employment of nitromethane[35] or organoboron reagents[36] and more generally the use of other electron-rich arenes,[37] such as, anilines,[38] 2-naphtol,[39] furan[40] and derivatives.



Scheme 1. 24 Regioselective nucleophilic indole addition to aminocyclopropane-1,1-dicarboxylate under Sc(III) activation

Moreover, the combination of Lewis acid catalyst with a chiral ligand gives access to the formation of enantiomerically pure alkylated indoles. In this line, Johnson and co-workers developed an asymmetric Friedel-Crafts type alkylation of indoles at C3 position with 2-arylcyclopropane-1,1-dicarboxylates employing a chiral pybox·MgI_2 complex, providing the final products with very good yields and enantiocontrol in most of the cases (Scheme 1. 25).[41]

---

[35] Budynina, E. M.; Ivanov, K.L.; Chagarovskiy, A. O.: Rybakov, V. B.; Trushkov, I. V.; Melnikov, M. Y. *Chem. Eur. J.* **2016**, *22*, 3692.

[36] (a) Yin, J. X.; Hyland, C. J. T. *J. Org. Chem.* **2015**, *80*, 6529. (b) Nguyen, T. N.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2016**, *18*, 3786. (c) Ortega, V.; Csaky, A. G. *J. Org. Chem.* **2016**, *81*, 3917. (d) Nguyen, T. N.; Nguyen, T. S.; May, J. A. *Org. Lett.* **2016**, *18*, 3786. (f) González-Pelayo, S.; López, L. A. *Chem. Plus. Chem.* **2018**, *83*, 1008.

[37] (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. Eur. *J. Org. Chem.* **2008**, *2008*, 5329. (b) Jiang, X.; Lim, Z.; Yeung, Y.-Y. *Tetrahedron Lett.* **2013**, *54*, 1798. (c) Garve, L. K. B.; Werz, D. B. *Org. Lett.* **2015**, *17*, 596. (d) Talukdar, R.; Saha, A.; Tiwari, D. P.; Ghorai, M. K. *Tetrahedron* **2016**, *72*, 613. (e) Richmond, E.; Vukovi´c, V. D.; Moran, J. *Org. Lett.* **2018**, *20*, 574.

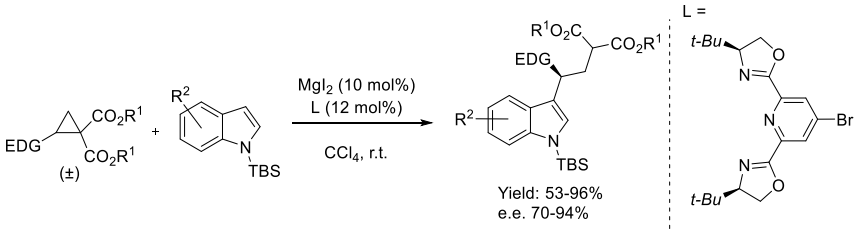
[38] (a) Kim, A.; Kim, S.-G. Eur. *J. Org. Chem.* **2015**, *2015*, 6419. (b) Sin, S.; Kim, S.-G. *Adv. Synth. Catal.* **2016**, *358*, 2701.

[39] Kaicharla, T.; Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. *Angew. Chem., Int. Ed.* **2016**, *55*, 10061.

[40] Chagarovskiy, A. O.; Budynina, E. M.; Ivanova, O. A.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Tetrahedron* **2009**, *65*, 5385.

[41] (a) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558. For other enantioselective examples: (b) Liu, Z-S.; Li, W.-K.; Kang, T.-R.; He, L.; Liu, Q.-Z. *Org Lett.* **2015**, *17*, 150. (c) Perrotta, D.; Wang, M.-M.;

The reaction proceeded *via* a dynamic kinetic asymmetric transformation (DYKAT), as an interconversion of the cyclopropane enantiomers was possible when the transition metal coordinated them and the (*S*)-enantiomer reacted much faster than the (*R*)-enantiomer. Therefore, nucleophilic attack to the Lewis acid activated (*S*)-cyclopropane occurred through a transient diastereomeric intermediate, *via* an S_N2 type mechanism.



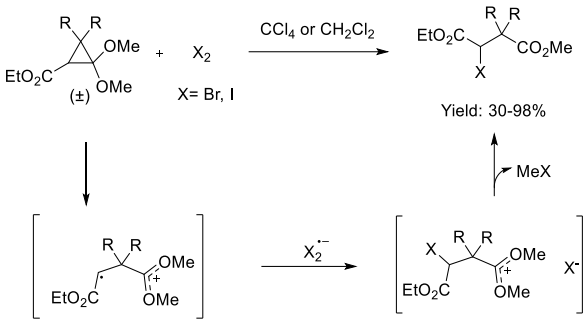
Scheme 1. 25 Enantioselective nucleophilic ring-opening of arylcyclopropane-1,1-dicarboxylates catalyzed by a chiral pybox·MgI_2 complex

1.3.2. Reactions with electrophiles: Homo-enolate reactivity

As mentioned, 1,3-substituted acyclic systems can also be favored by the ring-opening of donor-acceptor cyclopropanes with electrophiles, although it has not been so deeply studied. One of the few examples of this type of reactivity is the one reported by Piccialli, Graziano and co-workers, in which the bromination and iodination of donor-acceptor cyclopropanes is described. They demonstrated that ethyl 2,2-dimethoxycyclopropanecarboxylates easily react with Br_2 and I_2, leading the corresponding haloalkanes in high yields (Scheme 1. 26).[42] The authors proposed the transfer of an electron from the C1-C2 bond of the cyclopropane to the halogen generating the cation radical, which would further undergo halogenation.

Waser, J. *Angew. Chem. Int. Ed.* **2018**, *57*, 5120 (d) Trost, B. M.; Bai, W.-J.; Hohn, C.; Bai, Y.; Cregg, J. J. *J. Am. Chem. Soc.* **2018**, *140*, 6710.

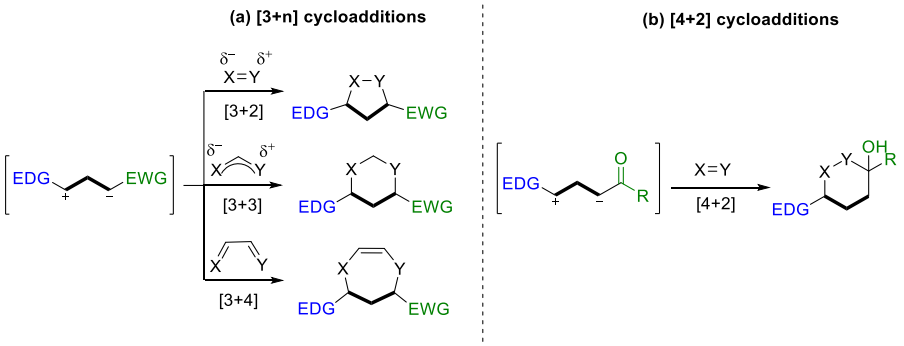
[42] Piccialli, V.; Graziano, L.; Iesce, M. R.; Cermola, F. *Tetrahedron Lett.* **2002**, *43*, 8067.



Scheme 1. 26 Bromination and iodination of donor-acceptor cyclopropanes

1.3.3. Formal cycloaddition reactions

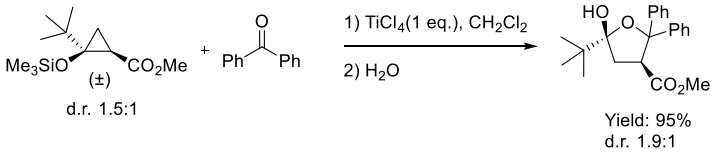
Usually, when donor-acceptor cyclopropanes are reacted with substrates containing the nucleophile and the electrophile at the same molecule, cycloaddition processes occur affording polycyclic structures (Scheme 1. 27). In earlier investigations, these donor-acceptor cyclopropanes have mainly shown reactivity as 1,3-dipoles for the construction of more stable five-, six, and seven-membered rings by their participation in [3+n] cycloaddition reactions (Scheme 1. 27a). On the other hand, they can also behave as 1,4-synthetic equivalents when one of the adjacent atoms of the electron-donating or electron-withdrawing groups participate in the reaction, allowing them to take part in formal [4+2] cycloadditions for the construction of six-membered rings (Scheme 1. 27b).



Scheme 1. 27 Formal cycloadditions of donor-acceptor cyclopropanes

[3+2] Cycloadditions

Formal [3+2] cycloadditions involving donor-acceptor cyclopropanes have been widely studied in the presence of a variety of dipolarophiles. The first examples of [3+2] cycloaddition processes employing donor-acceptor cyclopropanes involved the use of carbonyl compounds as dipolarophiles, as it is shown in the work reported by Reissig and co-workers, in which treatment of a methyl trimethylsiloxycyclopropanecarboxylate with benzophenone in the presence of $TiCl_4$ afforded the corresponding lactol in 95% yield as a mixture of diastereoisomers (Scheme 1. 28).[24c]



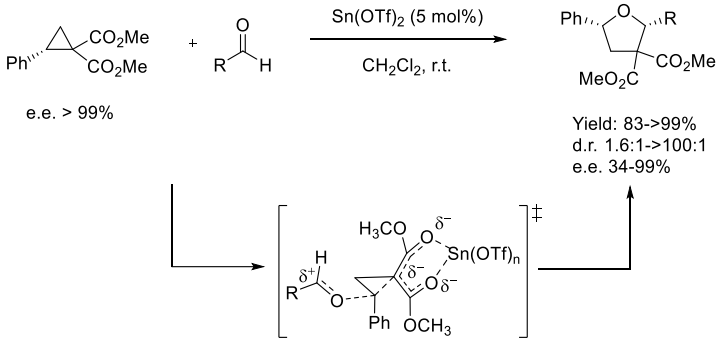
Scheme 1. 28 Lewis acid promoted [3+2] cycloaddition employing benzophenone as dipolarophile

After this pioneering example, several more recent approaches have been carried out towards the extension of this methodology using a variety of differently substituted cyclopropanes as 1,3-dipoles and carbonyl compounds as dipolarophiles.[43] This reaction has reached to high levels of developments, which included the possibility of absolute stereochemical control. Johnson and co-workers have developed an enantioespecific cycloaddition between phenyl substituted cyclopropanedicarboxylates and aldehydes, demonstrating the complete transfer of the chiral information from the cyclopropane to the final product during the process (Scheme 1. 29).[44] The authors suggested an S_N2 process, in

[43] (a) Shimada, S.; Hashimoto, Y.; Sudo, A.; Hasagawa, M.; Saigo, K. *J. Org. Chem.* **1992**, *57*, 7126. (b) Shimada, S.; Hashimoto, Y.; Saigo, K. *J. Org. Chem.* **1993**, *58*, 5226. (c) Shimada, S.; Hashimoto, Y.; Nagashima, T.; Hasegawa, M.; Saigo, K. *Tetrahedron* **1993**, *49*, 1589. Early work with imines: (d) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3186. (e) Pohlhaus, P. D.; Johnson, J. S. *J. Org. chem.* **2005**, *70*, 1057. (f) Siyang, X.; Li, Y.; Li, Z.; Liu, C.; Ren, J.; Wang, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 12605. (g) Benefatti, F.; de Nanteuil, F.; Waser, j. *Org. Lett.* **2012**, *14*, 386. (h) Haubenreisser, S.; Hensenne, P.; Schröfder, S.; Niggermann, M. *Org. Lett.* **2013**, *15*, 2262. (i) Yang, G.; Sun, Y.; Shen, Y.; Chai, Z.; Zhou, S.; Chu, J.; Chai, J. *J. Org. Chem.* **2013**, *78*, 5393. (j) Rivero, A. R.; Fernández, I.; Ramírez de Arellano, C.; Sierra, M. A. *J. Org. Chem.* **2015**, *80*, 1207. Employing cyclopropyl acetal: (k) Sabbatani, J.; Maulide, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 6780.

[44] (a) Pohlhaus, P. D.; Johnson, J. S. *J Am. Chem. Soc.* **2005**, *127*, 16014. Another stereospecific example: (b) Pohlhaus, P. D.; Sanders, S. D.; Parson, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

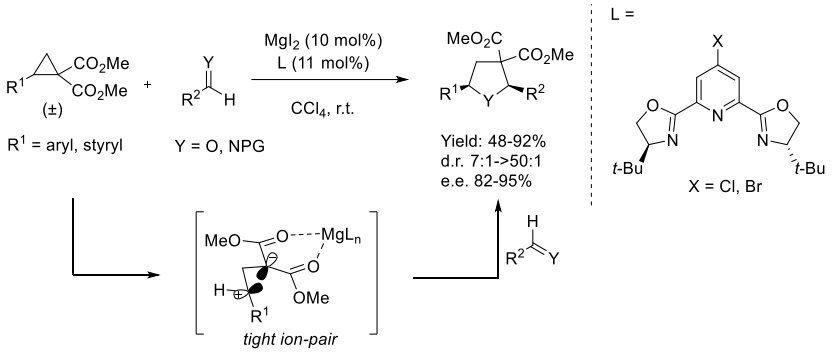
which the aldehyde acted as a nucleophile inverting the stereochemistry at the activated C2 carbon of the cyclopropane.



Scheme 1. 29 Enantioespecific [3+2] cycloaddition employing aldehydes

As an alternative to the use of enantiopure cyclopropanes, the same group described in 2009 the preparation of enantioenriched tetrahydrofuran derivatives in very good yields, through a dynamic kinetic asymmetric [3+2] cycloaddition between racemic donor-acceptor cyclopropanes and aldehydes, employing a chiral complex of Mg(II) as catalyst (Scheme 1. 30).[45] The chiral catalyst, as well as promoting the interconversion of cyclopropane enantiomers, favored the participation of one of the two enantiomers of the cyclopropane in the cycloaddition process through a diastereomeric transition state. The generated intermediate retained the pyramidal structure maintaining the disposition of the substituents, thanks to the formation of a tight ion-pair, giving place to the attack of the nucleophile from the opposite site through an S_N2-type mechanism, providing the final product with inversion of configuration in the carbon attached to the donor group. Employing the same methodology, the synthesis of enantioenriched pyrrolidines has also been carried out by the same authors, extending the previously employed enantioselective methodology to the use of aldimines as dipolarophiles.[46]

[45] Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122.
[46] (a) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688. For related examples: (b) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196. Iminooxindoles: (c) Akaev, A. A.; Bezzubov, S. I.; Desyatkin, V. G.; Vorobyeva, N. S.; Majouga, A. G.; Melnikov, M. Y.; Budynina, E. M. *J. Org. Chem.* **2019**, *84*, 3340.

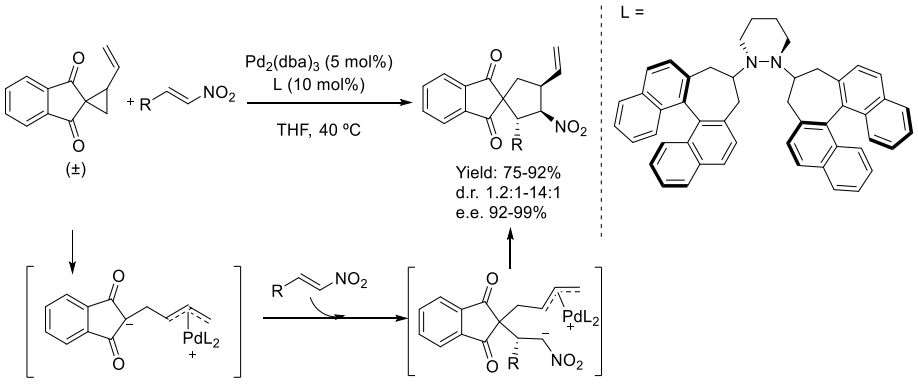


Scheme 1. 30 Enantioselective [3+2] cycloaddition between donor-acceptor cyclopropanes and aldehydes or aldimines

In addition, dipolarophiles of different nature such as nitriles,[47] isonitriles,[48] nitrosyl chloride,[49] diazenes,[50] isocyanates,[51] acetylenes,[52] nitrosoarenes,[53] nitrosocarbonyl compunds,[54] triazinanes,[55] thioesters,[56] *in situ* generated hydrazones[57] or electron poor quinolones and pyridines[58] have also been employed in a number of [3+2] cycloaddition reactions with donor-acceptor cyclopropanes under Lewis acid activation, however, in most of the cases limited studies have been carried out.

[47] (a) Yu, M.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8122. (b) Sathishkannan, G.; Srinivasan, K. *Org. Lett.* **2011**, *13*, 6002. (c) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2013**, *15*, 5099.
[48] Korotkov, V. S.; Larionov, O. V.; De Mejiere, A. *Synthesis* **2006**, 3542.
[49] Cermola, F.; Di Gioia, L.; Graziano, M. L.; Iesce, M. R. *J. Chem. Res.* **2005**, 677.
[50] Korotkov, V. S.; Larionav, O. V.; Hoftneister, A.; Magul, J.; De mejiere, A. *J. Org. Chem.* **2007**, *72*, 7504.
[51] Goldberg, A. F. G.; O'Connor, N. R.; Craig II, R. A.; Stoltz, B, M. *Org. Lett.* **2012**, *14*, 5314.
[52] (a) Ydav, V. K.; Sriramurthy, V.; *Angew. Chem. Int. Ed.* **2004**, *43*, 2669. (b) Mackay, W. D.; Fistikci, M.; Carris, R. M.; Johnson, J. S. *Org. Lett.* **2014**, *16*, 1626.
[53] Chakrabarty, S.; Chatterjee, I.; Wibbeling, B.; Daniliuc, C. G.; Studer, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5964.
[54] Varshnaya, R. K.; Banerjee, P. *Eur. J. Chem.* **2016**, 4059.
[55] Chu, Z.-y.; Liang, D.; Li, Z.-H.; Zheng, Y.-S.; Liu, J.-K. *Tetrahedron Lett.* **2018**, *59*, 715.
[56] Matsumoto, Y.; Nakatake, D.; Yazaki, R.; Ohshima, T. *Chem. Eur. J.* **2018**, *24*, 6062.
[57] Lebold, T. P.; Ker, M. A. *Org. Lett.* **2009**, *11*, 4354.
[58] 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.

Transition metal complexes, particularly ruthenium, nickel or palladium complexes, have also been employed as catalysts through the formation of organometallic compounds especially in [3+2] reactions involving donor-acceptor vinylcyclopropanes.[59] As a representative example, Liu and co-workers described a palladium(0) catalyzed enantioselective [3+2] cycloaddition of vinylcyclopropanes and nitroalkenes, carrying out the synthesis of spirocyclopentylindane-1,3-dione derivatives in good yields, with good diastereoselectivities and excellent enantioselectivities starting from indane-1,3-dione-derived vinylcyclopropanes (Scheme 1. 31). [60] The authors proposed the formation of a zwitterionic π-allylpalladium complex, which could react with the nitroalkene followed by ring-closure reaction.

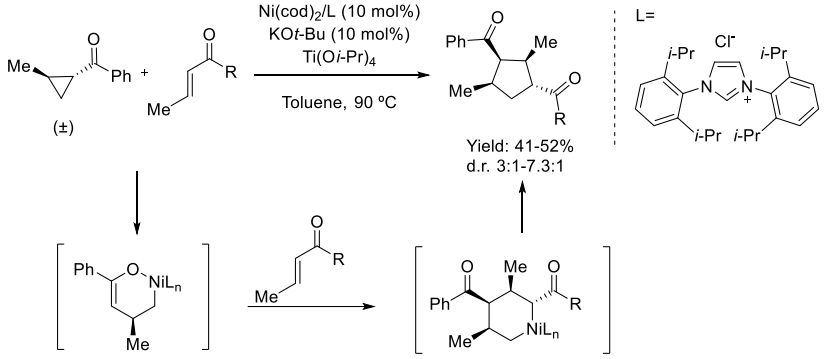


Scheme 1. 31 Palladium-catalyzed [3+2] cycloaddition of vinylcyclopropane with nitroalkenes

[59] Ruthenium activation of alkynylcyclopropanes: (a) Miyake, Y.; Endo, S.; Moriyama, T.; Sakata, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 1758. Nickel activation of vinylcyclopropanes (b) Tombe, R.; Iwamoto, T.; Kurahshi, T.; Matsubara, S. *Synlett*, **2014**, 2281. Palladium activation of vinylcyclopropanes: (c) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (d) Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474.

[60] (a) Wei, F.; Ren, C.-L.; Wang, D.; Liu, L. *Chem. Eur. J.* **2015**, *21*, 2335. For other enantioselective palladium activation of vinylcyclopropanes: (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. (d) Mei, L.-Y.; Wei, Y.; Xu, Q.; Shi, M. *Organometallics* **2012**, *31*, 7591. (e) (i) Xie, M.-S.; Wang, Y.; Li, J.-P.; Du, C.; Zhang, Y.-Y.; Hao, E.-J.; Zhang, Y.-M.; Qu, G.-R.; Guo, H.-M. *Chem. Commun.* **2015**, *51*, 12451. (f) Ma, C.; Huang, Y.; Zhao, Y. *ACS Catal.* **2016**, *6*, 6408.

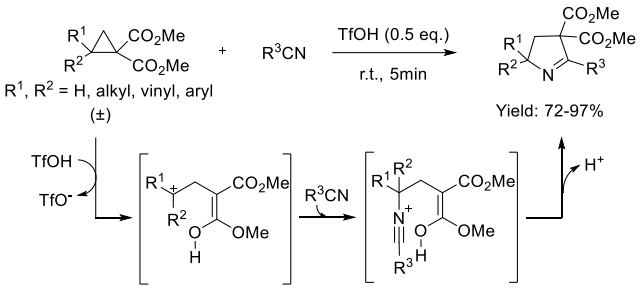
In a conceptually different approach, the [3+2] cycloaddition of simple cyclopropylketones to enones has been developed, promoted by the oxidative insertion of Ni(0) species, generating a nickelacycle-type enolate, which could then react with the enone in an insertion/reductive elimination process, affording successfully substituted cyclopentanes (Scheme 1. 32).[61]



Scheme 1. 32 Ni(0)-catalyzed [3+2] cycloaddition employing enones

Additionally, Brønsted acids can also be considered as suitable catalysts for the activation of cyclopropane-1,1-dicarboxylates. In this context, Wang and co-workers published in 2013 a Brønsted acid mediated formal [3+2] cycloaddition employing nitriles, yielding 1-pyrrolines in an efficient way (Scheme 1. 33).[62] Protonation of the alkoxycarbonyl moiety with triflic acid, promoted the ring-opening reaction that was followed by addition of the nitrile to the electrophilic site of the cyclopropane generating the nitrilium intermediate that would then undergo intramolecular addition forming 1-pyrrolines in high yields.

[61] (a) Liu, L.; Montgomery, J. *J. Am. Chem. Soc.* **2006**, *128,* 5348. (b) Montgomery, J. *Org. Lett.* **2007**, *9*, 3885.
[62] Cui, B.; Ren, J.; Wang, Z. *J. Org. Chem.* **2014**, *79*, 790.

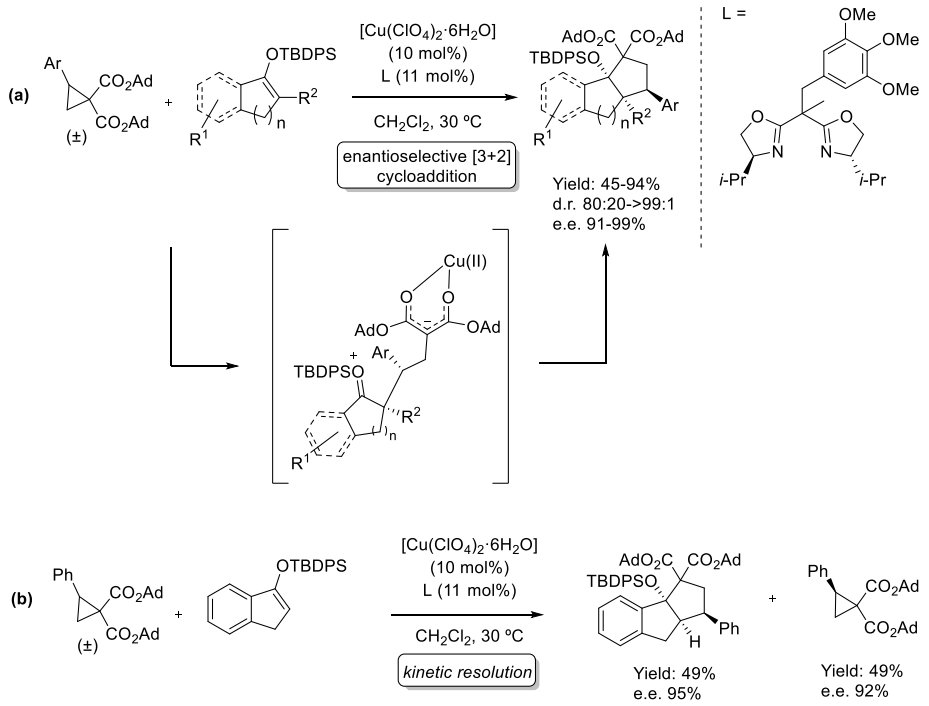


Scheme 1. 33 Brønsted acid catalyzed [3+2] cycloaddition with nitriles

Electron-rich olefins can also be used as dipolarophiles in this reaction, and in this context, the use of silyl enol ethers has been extensively investigated.[63] For the synthesis of enantioenriched substituted cyclopentane derivatives, by the use of chiral ligands starting from racemic donor-acceptor cyclopropanes. In particular, a good example is the work reported by Tang and co-workers, in which a highly enantioselective formal [3+2] cycloaddition of cyclic silyl enol ethers and aryl substituted cyclopropanecarboxylates was described employing a chiral Cu(II) complex as catalyst (Scheme 1. 34a).[64] As explained before, the nucleophilic addition of the alkene to the generated tight ion-pair intermediate underwent through an S_N2-type mechanism, followed by intramolecular cyclization. Conversely, for less reactive cyclopropanes, such as phenyl substituted cyclopropanecarboxylates, the present reaction could proceed through a kinetic resolution obtaining both, the enantioenriched product and the recovered enantiopure cyclopropane, with high yield and enantioselectivity (Scheme 1. 34b).

[63] (a) Saigo, K.; Shimada, S.; Shibasaki, T.; Hasagawa, M. *Chem. Lett.* **1990**, 1093. (b) Komatsu, M.; Suehiro, I.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1991**, 771. (c) Fang, J.; Ren, J.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 6659. (d) Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 8484. (e) Qu, J.-P.; Liang, Y.; Xu, H.; Sun, X.-L.; Yu, Z.-X.; Tang. Y. *Chem. Eur. J.* **2012**, *18*, 2196. (f) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568.

[64] (a) Xu, H.; Qu, J.-P.; Liao, S.; Xiong, H.; Tang, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4004. For other enantioselective examples: (b) Qu, J.-P.; Deng, C.; Zhou, J.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684. (c) de Nanteuil, F.; Waser, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12075. (d) De Nanteuil, F.; Serrano, E.; Perrotta, D.; Waser, J. *J. Am. Chem. Soc.* **2014**, *136*, 6239.

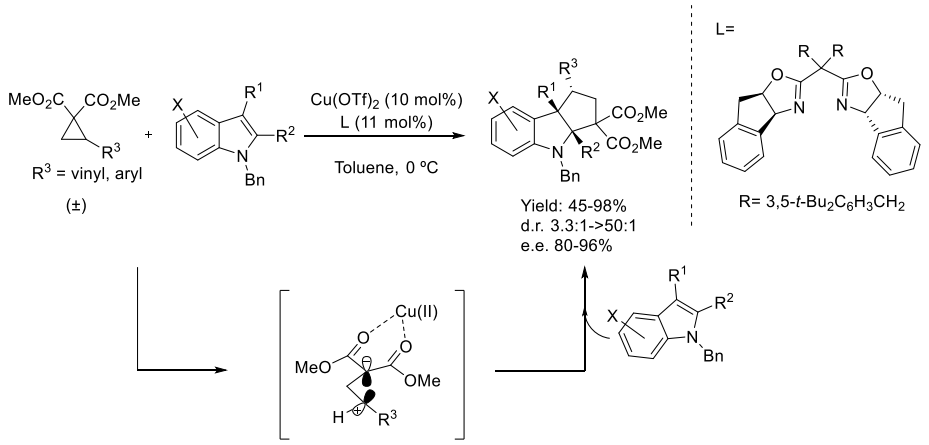


Scheme 1. 34 [3+2] cycloaddition employing silyl enol ethers: enantioselective version *vs* kinetic resolution

Indoles have also been used as dipolarophiles in [3+2] cycloadditions due to the electron-rich character of its enamine moiety. [65] The reaction implies dearomatization of the indole scaffold, generating complex structures with multiple contiguous stereocenters. For instance, a highly diastereo- and enantioselective formal [3+2] cycloaddition of indoles with donor-acceptor cyclopropanes catalyzed by BOX/Cu(II) complex has been reported by Tang and

[65] (a) Kerr, M. A.; Keddy, R. G. *Tetrahedron Lett.* **1999**, *40*, 5671. (b) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704. (c) Venkatesh, C.; Singh, P. P.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2006**, 5378. (d) Bajitos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631. (e) Tanaka, M.; Ubukata, M.; Matsuo, T.; Yasue, K.; Matsumoto, K.; Kajimoto, Y.; Ogo, T.; Inaba, T. *Org. Lett.* **2007**, *9*, 3331. Intramolecular [3+2] cycloaddition: (e) Zhu, J.; Liang, Y.; Wang, L.; Zheng, Z.-B.; Houk, K. N.; Tang, Y. *J. Am. Chem. Soc.* **2014**, *136*, 6900. Indolenine: (f) Li, J.; Xiao, J.-A.; Zhao, S.-J.; Xiang, H.-Y.; Yang, H. *Synthesis* **2017**, *49*.

co-workers.[66] The reaction provided a successful access to a variety of complex indoline products with good yields and stereocontrol in most of the cases (Scheme 1. 35). The close ion-pair intermediate formed through activation of cyclopropane with the catalyst led to a stereospecific nucleophilic addition of the indole with inversion of configuration. Moreover, the reaction proceed *via* a dynamic kinetic asymmetric transformation, as an interconversion of the cyclopropane enantiomers was possible when the transition metal coordinated to the three-membered ring.



Scheme 1. 35 BOX/Cu(II)-catalyzed enantioselective formal [3+2] cycloaddition of indoles

Additionally, other electron-rich olefins, such as vinyl azides,[67] 2-naphtols,[39] and furans[40] have also been employed in related [3+2] cycloaddition reactions with donor-acceptor cyclopropanes, enabling access to multiple cyclopentene scaffolds with different functionalities.

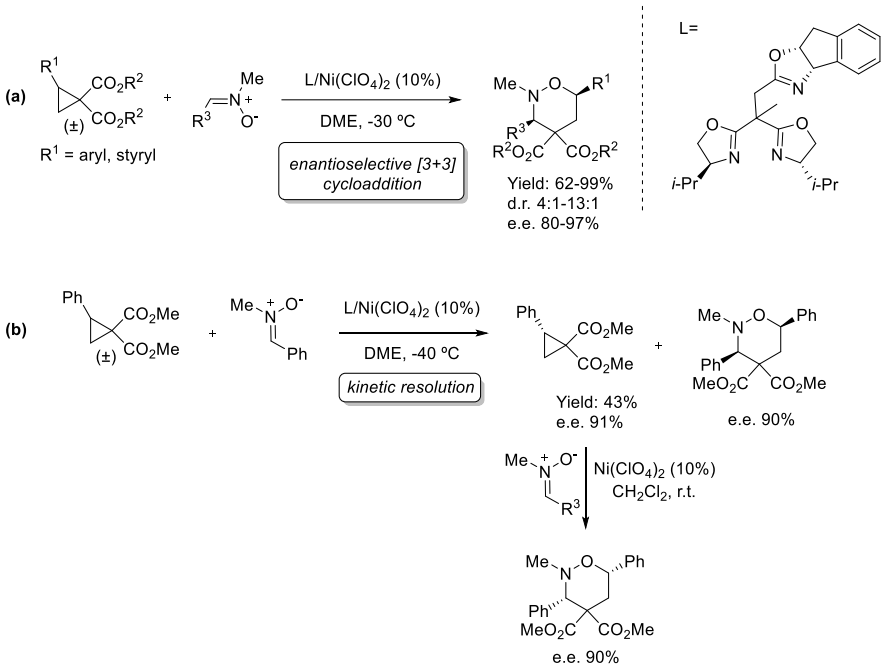
[66] (a) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851.
[67] Dey, R.; Banerjee, P. *Org. Lett.* **2017**, *19*, 304.

[3+3] Cycloadditions

[3+3] cycloaddition is an efficient approach for a rapid access to six-membered cyclic scaffolds, in which donor-acceptor cyclopropane plays the role of the 1,3-dipole. Most research has been focused on Lewis acid catalyzed reactions involving nitrones as the other 3-atom component.[68] A representative example of an asymmetric version of this type of reactivity was reported by Tang and co-workers, in which a highly diastereo- and enantioselective cycloaddition of cyclopropanes bearing electron-rich aryl substituents with nitrones was described, leading to 1,2-oxazines in high yields, employing a chiral trioxazoline/Ni(II) catalyst (Scheme 1. 36a).[69] Alternatively, racemic cyclopropanes bearing a phenyl as substituent in C2 could be resolved under similar conditions, recovering a highly enantioenriched cyclopropane that could then provide the desired oxazines of inverse configuration (Scheme 1. 36b).

[68] (a) Young, I. S.; Kerr, M. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023. (b) Ganton, M. D.; Kerr, M. A. *J. Org. Chem.* **2004**, *69*, 8554. (c) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139. (d) Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 3497. (e) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (f) Gorbacheva, E. O.; Tabolin, A. A.; Novikov, R. A.; Khomutova, Y. A.; Nelyubina, Y. V.; Tomilov, Y. V.; Ioffe, S. L. *Org. Lett.* **2013**, *15*, 350. (g) Braun, C. M.; Congdon, E. A.; Nolin, K. A. *J. Org. Chem.* **2015**, *80*, 1979. (h) Tabolin, A. A.; Novikov, R. A.; Khomutova, Y. A.; Zharov, A. A.; Stashina, G. A.; Nelyubina, Y. V.; Tomilov, Y. V.; Ioffe, S. L. *Tetrahedron Lett.* **2015**, *56*, 2102. For mechanistic studies: (i) Wanapun, D.; Van Gorp, K. A.; Mosey, N. J.; Kerr, M. A.; Woo, T. K. *Can. J. Chem.* **2005**, *83*, 1752. (j) Karadeolian, A.; Kerr, M. A.; *J. Org. Chem.* **2007**, *72*, 10251.

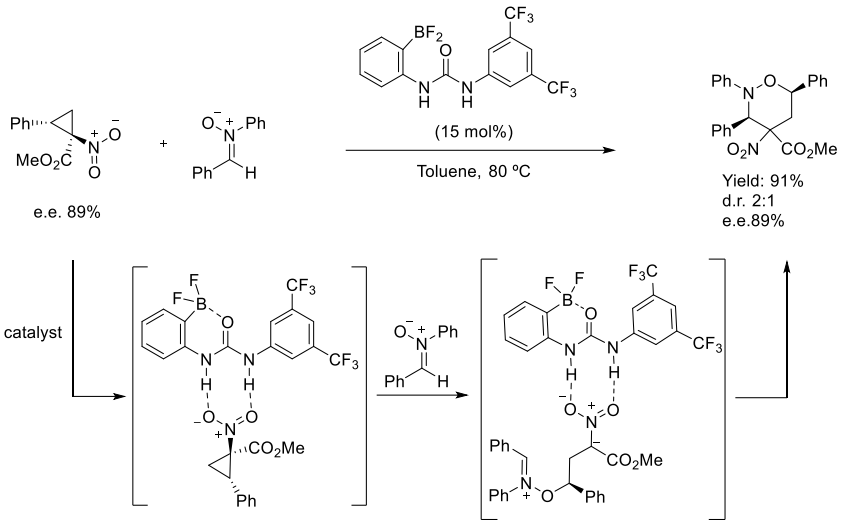
[69] (a) Kang, Y.-B.; Sun, X.-L.; Tang, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3918. For other works in asymmetric [3+3] cycloadditions with nitrones: (b) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 5764. (c) Xu, P.-W.; Liu, J.-K.; Shen, L.; Cao, Z.-Y.; Zhao, X.-L.; Yan, J.; Zhou, J. *Nature Commun.* **2017**, *8*, 1.



Scheme 1. 36 Lewis acid-catalyzed asymmetric [3+3] cycloaddition employing nitrones as dipolarophiles

Taking into account the capability of Brønsted acids for a suitable activation of donor-acceptor cyclopropanes, the chirality transfer from enantioenriched cyclopropane to the final cycloadduct has been demonstrated in a [3+3] cycloaddition with nitrones.[70] In this sense, Mattson and co-workers have demonstrated that the urea shown in Scheme 1. 37 could be a suitable catalyst for the activation of nitrocyclopropanecarboxylates towards their participation in enantioespecific cycloaddition reactions with nitrones, enabling the preparation of enantioenriched oxazine products. The authors suggested a stepwise reaction pathway, in which after the initial activation of the nitrocyclopropanecarboxylate with the urea catalyst as it has been previously discussed (see Scheme 1. 22), the nucleophilic nitrone underwent the addition with inversion of configuration followed by a cyclization process.

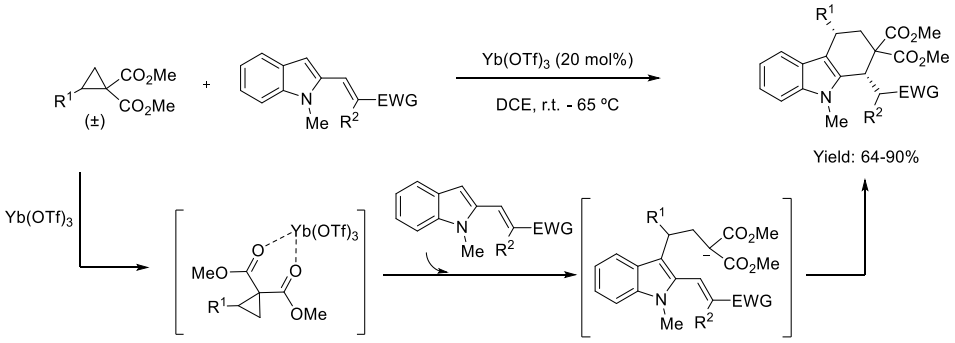
[70] Hardmen, A. M.; So, S. S.; Mattson, A. E. *Org. Biomol. Chem.* **2013**, *11*, 5793.



Scheme 1. 37 Urea-catalyzed enantioespecific [3+3] cycloaddition employing nitrones

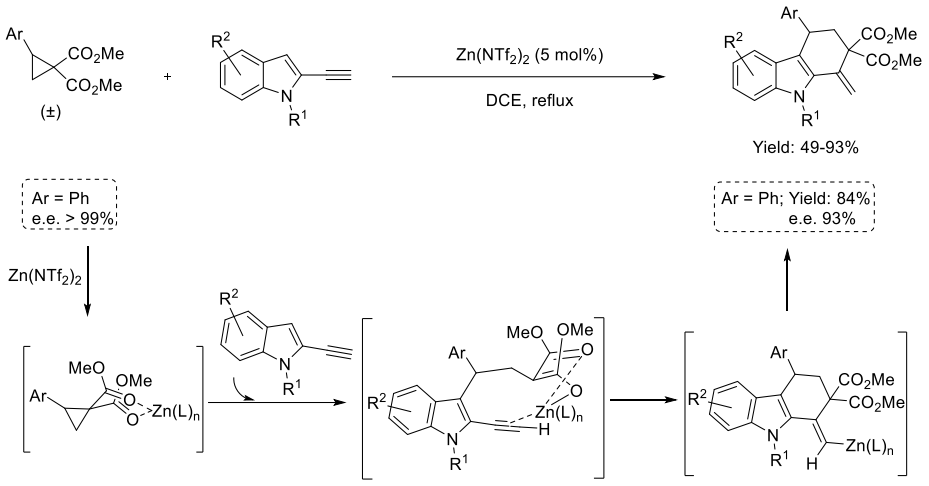
Apart from nitrones, vinyl and propargyl indoles have also been successfully employed as three carbon components in [3+3] cycloadditions with cyclopropanes to provide tetrahydrocarbazoles. In this sense, Ghorai and co-workers described the domino ring-opening/cyclization of donor-acceptor cyclopropanes with activated indole derivatives.[71] Regarding to the mechanism, the $Yb(OTf)_3$-activated the cyclopropane by coordination to the esters, which upon attack of the nucleophilic indole led to a C3 alkylated indole intermediate that would undergo an intramolecular Michael reaction to produce the tetrahydrocarbazole scaffolds (Scheme 1. 38). The products were isolated as single diastereoisomers, because of the existence of a disfavored conformation due to steric interactions of the Michael acceptor with both ester groups.

[71] Taludkar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954.



Scheme 1. 38 $Yb(OTf)_3$-catalyzed domino ring-opening/cyclization of vinylindoles

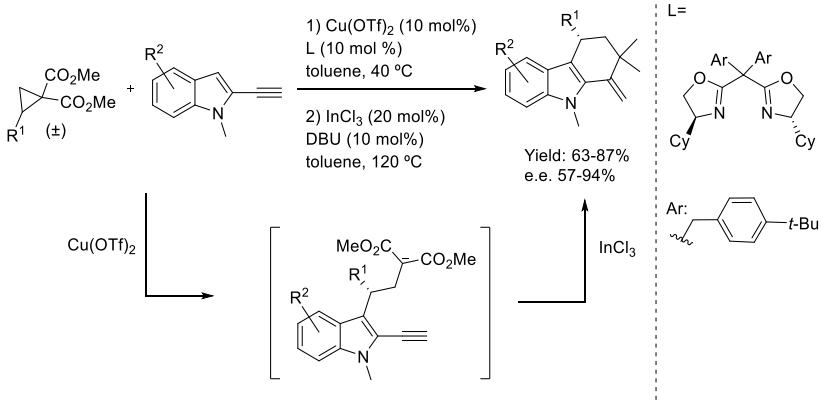
Kerr and co-workers developed a tandem formal [3+3] cycloaddition between dimethyl 1,1-cyclopropanecarboxylated and 2-alkynyl indoles to form tetrahydrocarbazoles under $Zn(NTf_2)_2$ catalysis by a two step sequence, involving nucleophilic ring-opening reaction of the cyclopropane and subsequent intramolecular Conia-ene reaction between the generated enol and the alkynyl moiety (Scheme 1. 39). The target products were successfully obtained with differently substituted indoles and cyclopropanes. Moreover, the reaction turned out to be enantioespecific, as the authors synthesized an enantioenriched tetrahydrocarbazole derivative by stereochemical transfer of optically active starting cyclopropane.



Scheme 1. 39 $Zn(NTf_2)_2$-catalyzed tandem ring-opening/cyclization with propargylindoles

Based on this methodology, the research group of Zhang and Tang developed the corresponding enantioselective version, starting from racemic donor-acceptor cyclopropanes and employing a chiral Cu(II) complex as chiral Lewis acid catalyst, isolating the products in high yields and good to excellent levels of enantiomeric excesses (Scheme 1. 40).[72] In this case, the transformation proceeded by a two-step one-pot process that involved a first Cu(II) complex-catalyzed enantioselective alkylation at the C3 position through cyclopropane ring-opening reaction, followed by the intramolecular Conia-ene reaction that required $InCl_3$ as Lewis acid catalyst.

[72] Liu, Q.-J.; Yan, W.-G.; Wang, L.; Zhang, X. P.; Tang, Y. *Org. Lett.* **2015**, *17*, 4014.



Scheme 1. 40 Lewis acid catalyzed enantioselective one-pot synthesis of tetrahydrocarbazole derivatives

Additionally, other substrates has also been employed in [3+3] cycloaddition reactions with donor-acceptor cyclopropanes, providing a variety of polisubstituted six-membered rings.[73]

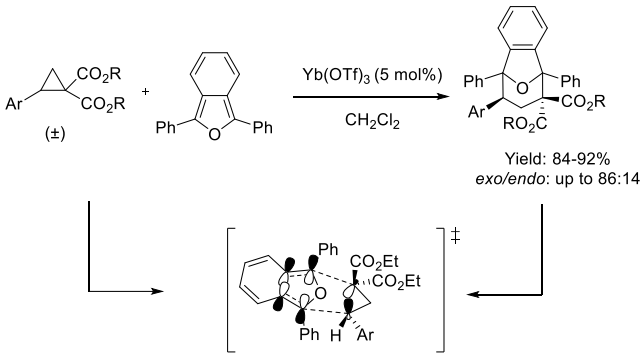
[3+4] Cycloadditions

Formal [3+4] cycloadditions for the construction of seven-membered rings using donor-acceptor cyclopropanes are more limited. The first report in the literature was published by Ivanova and co-workers, who investigated the reaction between 2-aryl cyclopropane-1,1-carboxylates and 1,3-diphenylisobenzofuran leading to highly substituted cycloheptenes under $Yb(OTf)_3$ catalysis (Scheme 1. 41).[74] The predominant formation of the less stable *exo*

[73] Azomthine imines: (a) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* 2008, 10, 689. Nitrile imines: (b) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18*, 564. Diaziridines: (c) Chagarosvkiy, A. O.; Vasin, V. S.; Kuzenetsov, V. V.; Ivanova, O. A.; Rybakov, V. B.; Shumsky, A. N.; Makhova, N. N.; Trushkov, I. V. *Angew. Chem. Int. Ed.* **2018**, *57*, 10338.

[74] (a) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Angew. Chem. Int. Ed.* **2008**, *47*, 1107. For other examples of [3+4] cycloadditions: (b) Ivanova, O. A.; Budynina, E. M.; Grishin, Y. K.; Trushkov, I. V.; Verteletskii, P. V. *Eur. J. Chem.* **2008**, *53*, 5329. (c) Ivanova, O. A.; Budynina, E. M.; Chagarovskiy, A. O.; Kaplun, A. E.; Trushkov, I. V.; Melnikov, M. Y. *Adv. Synth. Catal.* **2011**, *353*, 1125 (d) Chagarovskiy, A.O.; Ivanova, O. A.; Budynina, E. M.; kolychev, E. L.; M. S. Nechaev, I. V.; Mel´nikov, M. Y. *Russ. Chem. Bull. Int. Ed.* **2013**, *62*, 2407. (e) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 521. (f) Kim, S.; Kim, H.; Um, K.; Lee, P. H. *J. Org. Chem.* **2017**, *82*, 9808.

isomer could be explained by a concerted cycloaddition mechanism with orbital control of the stereochemical course of the reaction.

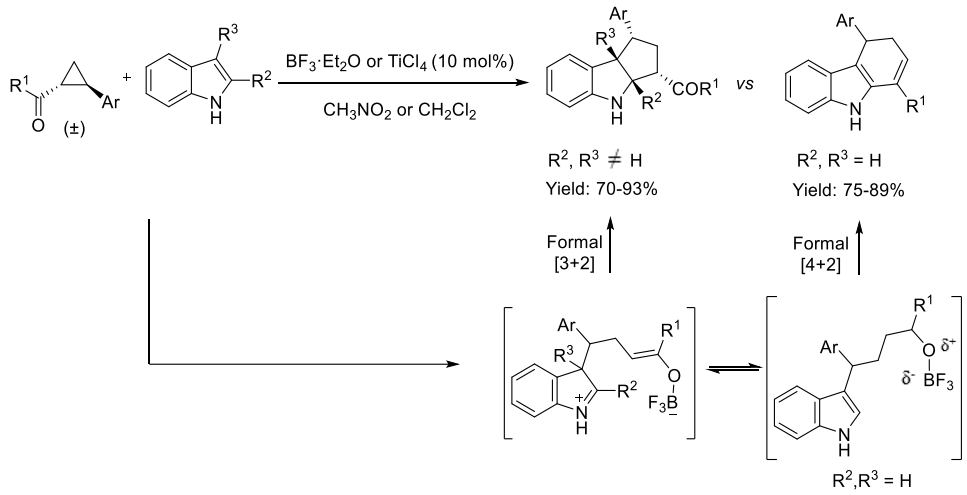


Scheme 1. 41 Lewis acid catalyzed [4+3] cycloaddition employing 1,3-diphenylisobenzofuran

[4+2] Cycloadditions

Moreover, donor-acceptor cyclopropanes can operate as four carbon component in formal [4+2] cycloadditions when one additional carbon atom from the electron-withdrawing substituent that activates the donor-acceptor cyclopropane also participates in the process. Few examples reported up to date involve the use of indoles as the other two carbon atom component. It is noteworthy to comment that competition between formal [3+2] and [4+2] cycloadditions could occur depending the reagents employed. A good example of this behavior is the work reported by Ila and co-workers, in which, in addition to [3+2] cycloaddition products, the authors also observed the formation of dihydrocarbazole derivatives coming from the formal [4+2] cycloaddition between the cyclopropane and the indole scaffold under Lewis acid catalysis (Scheme 1. 42).[65c] In order to explain the possible formation of both cycloaddition products, the authors proposed two probable mechanistic pathways: in both cases, the reaction would start through the formation of a stable zwitterionic intermediate by ring-opening reaction, which would generate the iminium intermediate after nucleophilic reaction with the C3 site of the indole. The subsequent intramolecular nucleophilic attack of the enol to the iminium intermediate would afford the [3+2] cyclopentannulated product. Conversely, when the indole did not possess any substitution at C2 and C3 (R^2, R^3 = H), the iminium ion could undergo a fast aromatization,

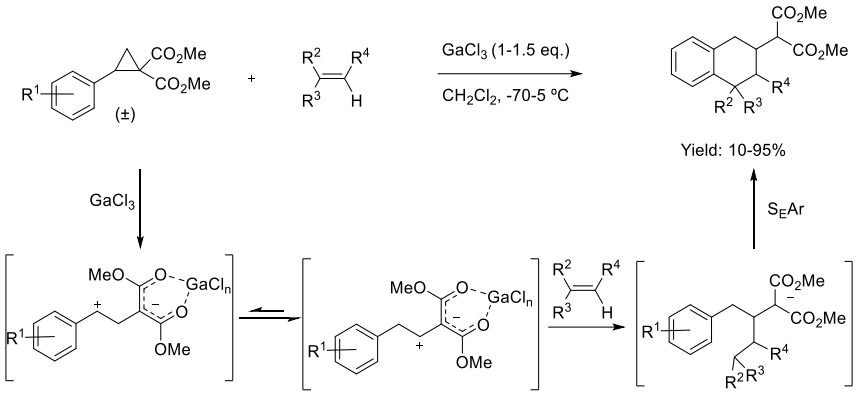
which followed by a second intramolecular nucleophilic attack of C2 of the indole to the ketone would afford the dihydrocarbazole derivative after a dehydration step.



Scheme 1. 42 Lewis acid-catalyzed [4+2] cycloaddition *vs* [3+2] cycloaddition with indole

Donor-acceptor cyclopropanes also undergo [4+2] annulation processes with other alkenes or alkynes as the two carbon component. In this sense, cycloaddition of aryl substituted donor-acceptor cyclopropanes with unsaturated compounds, such as alkenes or acetylenes have been reported by Tomilov and co-workers using Ga(III) salt as Lewis acid catalyst (Scheme 1. 43).[75] The reaction took place through the formation of the 1,2-dipolar gallium complex *via* [1,2]-H shift occurred in the 1,3-dipole generated by the ring-opening of the three-membered ring. The addition of the olefin to the carbocation and further intramolecular electrophilic aromatic substitution afforded the final tetralins in moderate to good yields.

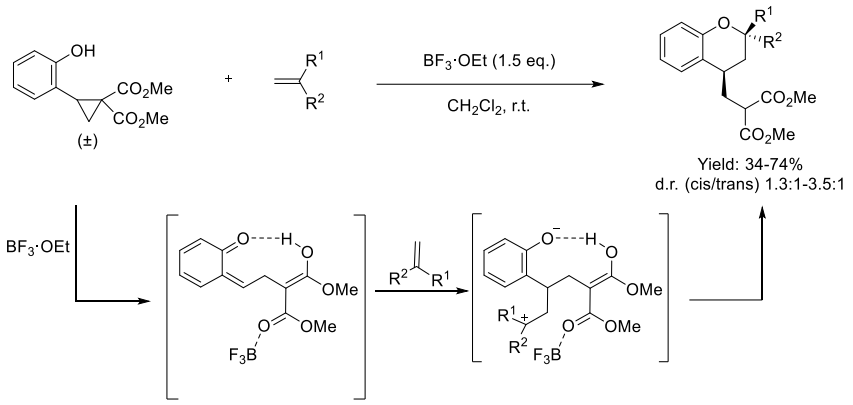
[75] Novikov, R. A.; Tarasova, A. V.; Korolev, V. A.; Shulishov, E. V.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2015**, *80*, 8225. (b) Novikov, R. A.; Tarasova, A. V.; Denisov, D. A.; Borisov, D. D.; Korolev, V. A.; Timofeev, V. P.; Tomilov, Y. V. *J. Org. Chem.* **2017**, *82*, 2724.



Scheme 1. 43 $GaCl_3$-mediated [4+2] annulation with alkenes

Alternatively, very recently Budynina and co-workers described a previously unreported donor-acceptor cyclopropane reactivity employing *ortho*-phenolcyclopropanes as starting material and, acting as synthetic equivalents of *ortho*-quinone methides once the ring-opening process take place (Scheme 1. 44).[76] In this sense, the Lewis acid promoted the ring-opening event, which after the addition of the alkene to the carbocation and subsequent cyclization through the nucleophilic phenol moiety afforded the final products in moderate to good yields.

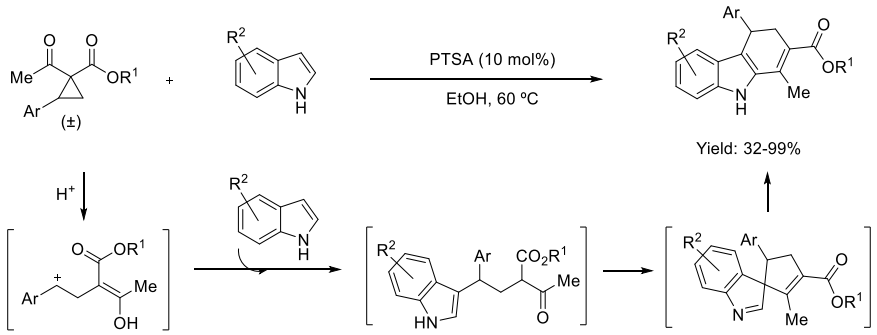
[76] Ivanov, K. L.; Bezzubov, S. I.; Melnikov, M. Y.; Budynina, E. M. *Org. Biomol. Chem.* **2018**, *16*, 3897.



Scheme 1. 44 Donor-acceptor cyclopropanes as *ortho*-quinone methide equivalents in formal [4+2] cycloadditions to alkenes

Other catalytic systems have been employed for promoting this type of transformation, demonstrating the possibility of carrying out the reaction also under transition metal[77] or Brønsted acid catalysis.[78] For instance, Gu and co-workers synthesized a wide scope of dihydrocarbazoles in good to excellent yields, using catalytic amounts of *para*-toluensulfonic acid as catalyst (Scheme 1. 45).[78] Regarding the mechanism, in a similar way to previous examples, the authors suggested cyclopropane ring-opening by PTSA activation leading to a carbocationic intermediate that suffered the nuclcophilic attack of the indole, followed by the second intramolecular nucleophilic addition to offer a spiro intermediate. Eventually, the formed spiro iminium intermediate would provide the corresponding dihydrocarbazole through an intramolecular migration process.

[77] Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814.
[78] Liu, C.; Zhou, L.; Huang, W.; Wang, M.; Gu, Y. *Tetrahedron* **2016**, *72*, 563.

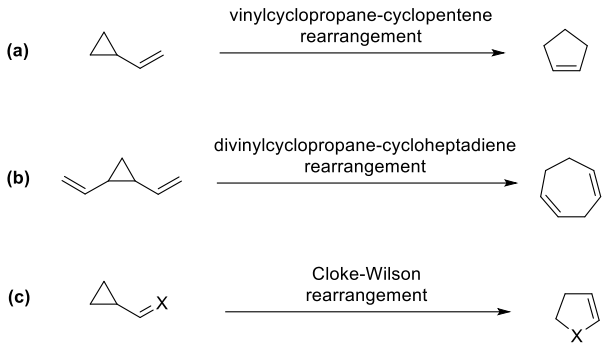


Scheme 1. 45 PTSA-catalyzed [4+2] annulation with indoles

1.3.4. Rearrangement reactions

Apart from cycloaddition chemistry, cyclopropanes also show an outstanding ability to undergo rearrangement processes giving more stable larger cyclic products by the release of the ring strain, usually associated to the formation of the less strained five-membered cycloadducts.[79] In this context, the most studied reorganization process has been the vinylcyclopropane-cyclopentene rearrangement (Scheme 1. 46a), and the corresponding vinylogous version (the divinylcyclopropane-cycloheptadiene rearrangement) which provides larger seven-membered rings (Scheme 1. 46b). Moreover, rearrangements of acylcyclopropanes or related azomethine derivatives, known as Cloke-Wilson rearrangement, have also been explored (Scheme 1. 46c).

[79] For selected reviews of vinylcyclopropanes: (a) sarel, S.; Jovell, J.; Sarel-Imber, M. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 5. (b) Willcot, M. R.; Cargill, R. L.; Sears, A. B. *Prog. Phys. Org. Chem.* **1972**, *9*, 25. (c) Willcott, M. R.; Cargle, V. H. *J. Am. Chem. Soc.* **1967**, *89*, 723. (d) Dolbier, W. R. *Acc. Chem. Res.* **1981**, *14*, 195. (e) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (f) Thakur, A.; Louie, J. *Molecular Rearrangements in Organic Synthesis*, Rojas, C. M., Ed.; Wiley & Sons: University of Utah, 2016; pp 323-362. (g) Vshyvenko, S.; Reed, J. W.; Piers, E. *comprehensive Organic Synthesis II*, Trost, B., Ed.; Elsveier: Canada, 2014; pp 999-1076.



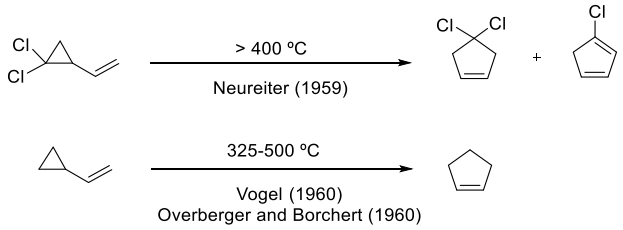
Scheme 1. 46 Possible rearrangement processes

In the following lines, a variety of examples of these reactivity patterns will be described in order to provide an overview on the chemistry of donor-acceptor cyclopropanes when undergoing rearrangement processes.

Vinylcyclopropane-cyclopentene rearrangement

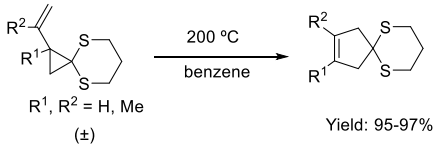
The first report of vinylcyclopropane-cyclopentene rearrangement was attributed to Neureiter in 1959 by the pyrolysis of 1,1-dichloro-2-vinylcyclopropane to yield a mixture of 4,4-dichlorocyclopentene and monochlorocyclopentadiene together with unidentified chlorinated hydrocarbons (Scheme 1. 47).[80] The all-carbon vinylcyclopropane-cyclopentene rearrangement was discovered independently by Vogel[81] and Overberger and Borchert[82] in 1960.

[80] Neureiter N. P. *J. Org. Chem.* **1959**, *24*, 2044.
[81] Vogel, E. *Angew.Chem.* **1960**, *72*, 4.
[82] Overberger, C. G.; Borchert, A. E. J. *Am.Chem.Soc*. **1960**, *82*, 1007.



Scheme 1. 47 Pioneering work on rearrangement of vinylcyclopropane to cyclopentene

Despite the early discovery, the harsh reaction conditions required for this transformation have limited its application to synthetic processes and several efforts have been made in order to find milder reaction conditions, such as placing additional activating groups in the three-membered ring or employing external activating agents. Therefore, since the discovery of the vinylcyclopropane-cyclopentene rearrangement, important developments have been made in the field employing thermal conditions, acid catalysis or transition metal-promoted activation. For instance, in 1972 Corey and co-workers synthesized an activated dithiospiro vinylcyclopropane, in which the ring-opening reaction would be presumably favored due to its higher ring strain (Scheme 1. 48).[83] However, 200 ºC were necessary to promote the rearrangement process, affording the cyclopentene derivatives with excellent yield.

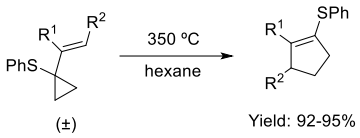


Scheme 1. 48 Thermal cyclopentene synthesis through activated vinylcyclopropane rearrangement

Other very specific vinylcyclopropane-cyclopentene rearrangements have been disclosed during the 70's and 80's. These include the work carried out by Trost and co-workers, in

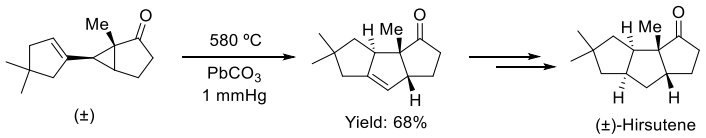
[83] (a) Corey, E. J.; Walinsky, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 8932.

which activated vinylcyclopropyl sulfides rearranged to the corresponding cyclopentene derivatives at very high temperatures (Scheme 1. 49).[84]



Scheme 1. 49 Thermal rearrangement of vinylcyclopropylsulfide

It should be highlighted that although the required harsh conditions, during these decades stereocontrolled vinylcyclopropane-cyclopentene rearrangement was especially employed as key step in a few total synthesis of natural products. As an example, Hudlicky and co-workers described the stereospecific vinylcyclopropane-cyclopentene rearrangement in the total synthesis of (±)-Hirsutene, which took place exposing the sample at 580 ºC in a lead carbonate conditioned tube at 0.1 mmHg, providing the desired cyclopentene in 68% yield as single diastereoisomer (Scheme 1. 50).[85]

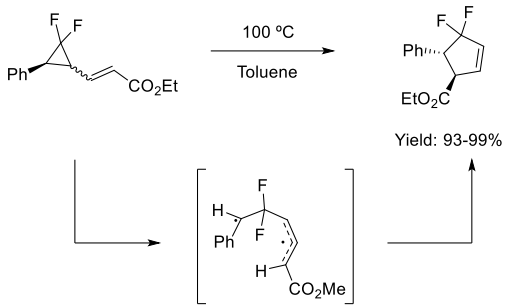


Scheme 1. 50 Stereocontrolled vinylcyclopropane-cyclopentene rearrangement as key step for the total synthesis of (±)-Hirsutene

More recently, other thermal vinylcyclopropane rearrangement reactions have been reported, such as the ring expansion of difluorinated donor-acceptor cyclopropanes carried out at 100 ºC studied by Percy and co-workers (Scheme 1. 51).[86] Although the reaction could

[84] Trost, B. M.; Keeley, D. E. *J. Am. Chem. Soc*. **1976**, *98*, 248.
[85] (a) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. For other stereocontrolled VCP-CP rearrangements in total synthesis: (b) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopoulos, P. *Tetrahedron* **1987**, *43*, 5685. (c) Hudlicky, T.; Heard, N. E.; Fleming A. *J. Org. Chem.* **1990**, *55*, 2570. (d) Hudlicky, T.; Heard, N.; Fleming, A. *Tetrahedron Lett.* **1991**, *32*, 1107.
[86] (a) Orr, D.; Percy, J. M.; Tuttle, T.; Kennedy, A. R.; Harrison, Z. A. *Chem. Eur. J.* **2014**, *20*, 14305. For other recent thermal VCP-CP rearrangements: (b) Aono, T.; Sasagawa, H.; Fuchibe, K.; Ichikawa, J *Org. Lett.* **2015**, *17*,

occur through a concerted pathway, the mechanism tends to involve the homolytic fission of the C-C bond of the cyclopropane ring to generate biradical species, which then recombines to form the cyclopentene ring. Moreover, it has been observed that the relative stereochemistry of the starting cyclopropane has not any influence in the stereochemistry of the final product, so isomerization from *cis* to *trans*-diastereoisomer before cyclization has been proposed to occur at the temperature of the reaction.



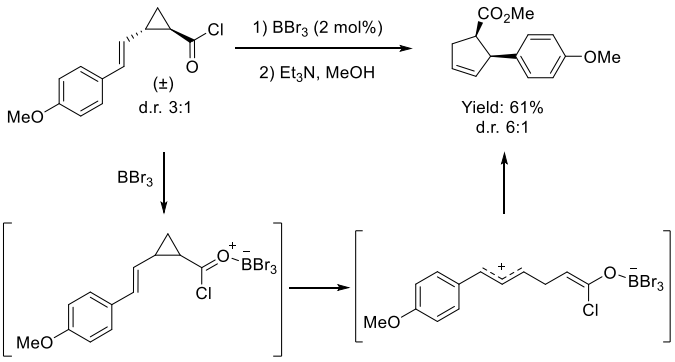
Scheme 1. 51 Thermal rearrangement of difluorinated vinylcyclopropane

A possibility to promote the vinylcyclopropane-cyclopentene rearrangement under milder reaction conditions involves the activation of the cyclopropane through coordination with a Lewis acid, which increases the polarization of the cyclopropane C-C bond that undergoes ring cleavage. In 1986, Suzukamo and co-workers reported the first Lewis acid catalyzed cyclopropane-cyclopentene rearrangement reaction, in which 2-styrylcyclopropanecarbonyl chlorides formed methyl-2-arylcyclopent-3-enecarboxilates in good yields after esterification.[87] The reaction worked efficiently with a variety of Lewis acids such as BBr_3 although it had a limited substrate scope, and only cyclopropanes having electron-rich aryl groups reorganized to the desired cyclopentenes (Scheme 1. 52). The proposed mechanism involved the initial activation of the acceptor substituent by

5736. (d) Yuan, Z.; Gai, K.; Wu, Y.; Lin, A.; Yao, H. *Chem. Commun.* **2017**, *53*, 3485. (e) Takayama, R.; Fuchibe, K.; Ichikawa, J. *Arkivoc* **2018**, 72.

[87] (a) Sakito, Y.; Suzukamo, G. *Chem. Lett.* **1986**, 621. For other Lewis acid catalyzed VCP-CP rearrangements: (b) Harvey, D. F.; Brown, M. F. *Tetrahedron Lett.* **1991**, *32*, 2871. (c) Thangamani, M; Srinivasan, K. *J. Org. Chem.* **2018**, *83*, 571. (d) Ivanova, O. A.; Chagarovskiy, A. O.; Shumsky, A. N.; Krasnorov, V. D.; Levina, I. I.; Trushkov, I. V. *J. Org. Chem.* **2018**, *83*, 543.

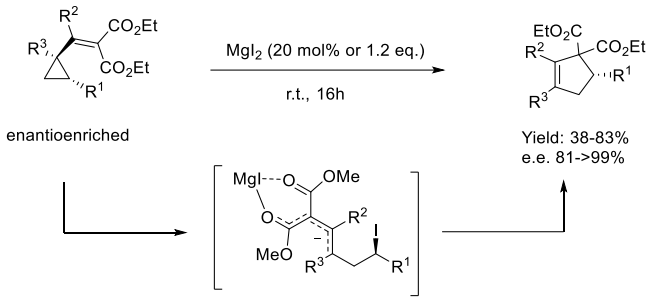
coordination to the Lewis acid leading to a zwitteronic intermediate, which eventually reclosed to form the cyclopentene ring.



Scheme 1. 52 Lewis acid catalyzed vinylcyclopropane-cyclopentene rearrangement

It has been demonstrated that the use of MgI_2 as Lewis acid to promote this type of rearrangements involves a different mechanistic pathway, in which the ring-opening reaction is initiated by the homoconjugate addition of the iodide to the vinylcyclopropane, due to its high nucleophilic character.[88] In this sense, Robiette and co-workers developed the enantioespecific MgI_2-catalyzed vinylcyclopropane-cyclopentene rearrangement, reaching cyclopentene derivatives with excellent enantiomeric excesses (Scheme 1. 53).[89] Experimental and computational studies supported that after the coordination of the metal to the electron withdrawing groups, the reaction was initiated through the ring-opening process promoted by the nucleophilic S_N2-type addition of the iodide, followed by an intramolecular S_N2 cyclization, giving place to a double-inversion mechanism with retention of configuration.

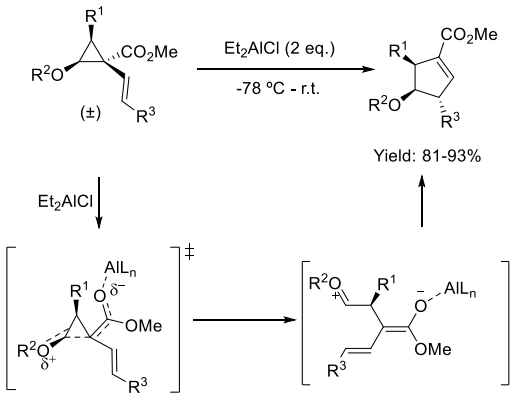
[88] Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496.
[89] Clergue, S.; Rousseau, O.; Delaunay, T.; Daquirez, G.; Tran, T.-V.; Aakchioui S. E.; Barozzino-Consiglio, G.; Robiette, R. *Chem. Eur. J.* **2018**, *24*, 11417.



Scheme 1. 53 MgI_2-mediated enantioespecific vinyl-cyclopropane rearrangement

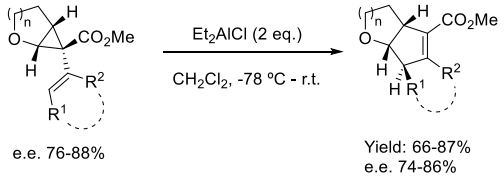
On the other hand, cyclopropanes with a donor group at the vicinal position of the geminally placed vinyl and carbonyl substituents also rearrange to give the corresponding cyclopentene. Davies and co-workers carried out a diastereoselective rearrangement of such substrates, yielding highly substituted cyclopentenes very efficiently using stoichiometric amount of Et_2AlCl to promote the reaction (Scheme 1. 54).[90] It is proposed that the initial activation of the acceptor group would favor the donor group-assisted ring-opening reaction into a zwitteronic enolate/oxonium ion intermediate, which cyclized to the final product.

[90] (a) Davies, H. M.; Hu, B. *J. Org. Chem.* **1992**, *57*, 3186. (b) Davies, H. M. L.; Hu, B. *J. Org. Chem.* **1992**, *57*, 4309.



Scheme 1. 54 Et_2AlCl-mediated vinylcyclopropane-cyclopentene rearrangement

Chirality transfer in such transformations has also been studied by the same authors.[91] They described the rearrangement of some enantioenriched bicyclic cyclopropanes to cyclopentenes with very little, if any, racemization employing stoichiometric amounts of Et_2AlCl (Scheme 1. 55). The stereochemical control could be explained assuming a mechanism in which the generated zwitterionic intermediates cyclized to the corresponding cyclopentenes before bond rotation. However, this mechanism is inconsistent with the partial racemization observed in some of the examples, so the authors suggested that the control of the stereochemistry came from the kinetically favored ring-closure, which turn out to be highly stereoselective in this system.



Scheme 1. 55 Et_2AlCl-promoted enantioespecific rearrangement

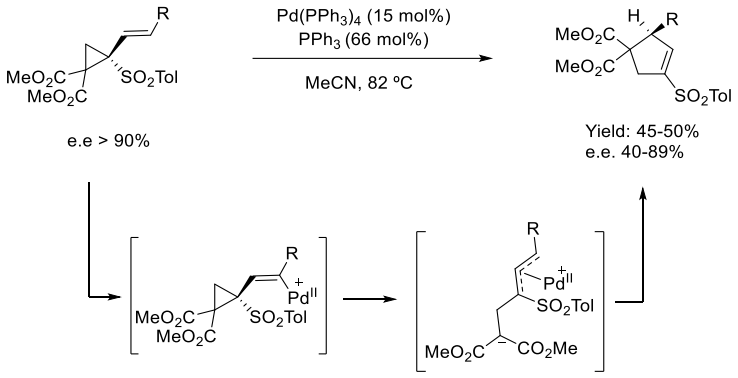
[91] (a) Davies, H. M. L.; Kong, N.; Churchill, M. R. *J. Org. Chem.* **1998**, *63*, 6586. For other stereoespecific VCP-CP rearrangements: (b) Wu, J.; Becerril, J.; Lian, Y.; Davies, H. M. L.; Porco, J. A.; Panek, J. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5938.

As it has been previously commented, another significant advance in vinylcyclopropane-cyclopentene rearrangement has been the discovery of transition metal catalysis in this field through the formation of organometallic intermediates. Although metal-mediated vinylcyclopropane rearrangements have been widely studied,[92] it has been established that only some selected metals are able to carry out the reaction in a catalytic manner.[93] The first example of enantioespecific vinylcyclopropane-cyclopentene rearrangement was reported by Hiroi and co-workers, in which a palladium-catalyzed reorganization of enantioenriched vinylcyclopropanes was developed for the preparation of optically active cyclopentenes.[94] Although nickel and platinum catalysts were also able to promote the reaction, these only provided the rearrangement product in low or moderate yield and with low stereoespecificity. On the contrary, treatment of enantioenriched vinylcyclopropane with $Pd(PPh_3)_4$ afforded the desired cyclopentene with high enantiomeric excess (Scheme 1. 56). It is suggested that the reaction occurs through the formation of the π-allyl metal complex by coordination with the metal from the back side of the dissecting C-C bond of the cyclopropane, followed by the nucleophilic substitution of the carbanion in an *anti* approach to the π-allyl complex intermediate.

[92] (a) Hudlicky, T.;Kutchan, T. M.; Naqvi, S.M. *Org. React.* **1985**, *33*, 247. (b) Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229. (c) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197. (e) Baldwin, J. E.; Leber, P. A. *Org. Biomol. Chem.* **2008**, *6*, 36. (f) Wang, S. C.; Tantillo, D. J. *J. Organomet. Chem.* **2006**, *691*, 4386.

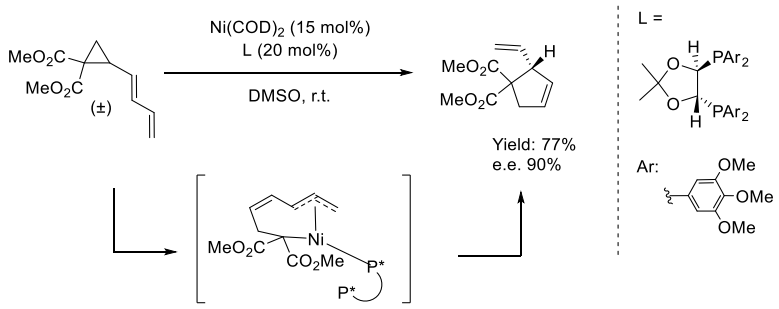
[93] Palladium catalysis: (a) Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871. (c) Hiroi, K.; Yoshida, Y.; Kaneko, Y. *Tetrahedron Lett.* **1999**, *40*, 3431. (d) Lingam, K. A. P.; Shanmugam, P. *Tetrahedron Lett.* **2013**, *54*, 4202. Rhodium catalysis: (e) Hayashi, M.; Ohmatsu, T.; Meng, Y.-P.; Saigo, K. *Angew. Chem. Int. Ed.* **1998**, *37*, 837.

[94] Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153.



Scheme 1. 56 Palladium-catalyzed synthesis of enantioenriched cyclopentenes

Alternatively, starting from racemic cyclopropanes, Hiroi and co-workers developed a highly enantioselective synthesis of a cyclopentene derivative by Ni(II)-catalyzed reaction using chiral phosphine ligands (Scheme 1. 57).[95] The cyclopropane ring would be dissected through the formation of π-allylnickel complex with subsequent intramolecular asymmetric carbon-carbon bond-forming from the same direction of the metal. In the cyclization process the nucleophilic addition occurred in a regioselective manner to the internal carbon, forming a pentacyclic adduct instead of a seven-membered ring.

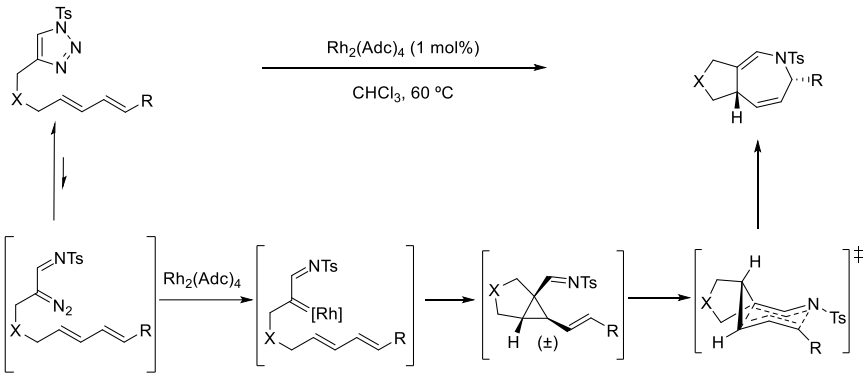


Scheme 1. 57 Nickel(II) catalyzed enantioselective rearrangement

[95] Hiroi, K.; Arinaga, Y.; Ogino, T. *Chem. Pharm. Bull.* **1994**, *42*, 470.

Divinylcyclopropane-cycloheptadiene rearrangement

Donor-acceptor divinylcyclopropanes sometimes rearrange to form larger seven-membered rings, which could be competing with the formation of the cyclopentene scaffold.[96] Regarding the construction of these larger ring systems, Sarpongand co-workers investigated the rearrangement of *in situ* generated 1-imino-2-vinylcyclopropanes for the synthesis of fused dihydroazepine derivatives catalyzed by a rhodium(II) complex (Scheme 1. 58).[97] The authors suggested that the reaction proceeded through a sequential intramolecular [2+1] cycloaddition of the azavinyl-substituted rhodium carbenoid species with the proximal alkenyl group forming the *cis*-iminovinylcyclopropane, followed by [3,3] sigmatropic aza-Cope rearrangement to yield the dihydroazepine product.

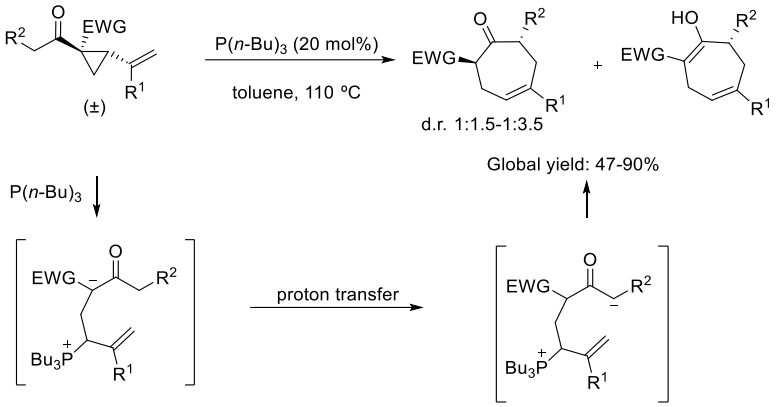


Scheme 1. 58 Rhodium (II)-catalyzed [3+3] sigmatropic rearrangement of 1-imino-2-vinylcyclopropanes

In the same line, Xu and co-workers very recently reported a phosphine-catalyzed vinylcyclopropylketone rearrangement to form cycloheptenone derivatives as a mixture with the corresponding enol tautomers in moderate to good yields (Scheme 1. 59).[98] The reaction tolerated different ketone, amide or ester moieties as electron withdrawing groups, as well as a variety of substituents at the vinyl chain. Mechanistically, the authors suggested that the reaction started with the homoconjugated addition of phosphine, followed by ring-opening

[96] Orr, D.; Percy, J. M.; Harrison, Z. A. *Chem. Sci.* **2016**, *7*, 6369.
[97] Schultz, E. E.; Lindsay, V. N. G.; Sarpong, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 9904.
[98] Wu, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. *Angew. Chem. Int. Ed.* **2018**, *57*, 6284.

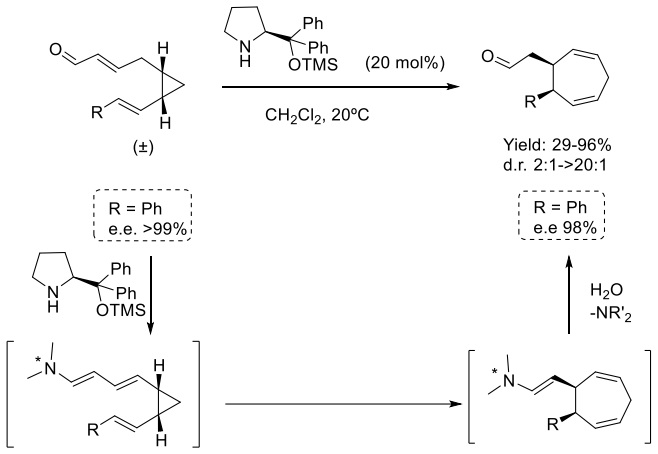
that delivered a zwitterionic intermediate that after a proton transfer, suffered an S_N2' ring closure.



Scheme 1. 59 Phosphine-catalyzed vinylcyclopropane-cycloheptenone rearrangement

Finally, Christmann and co-workers have also described the rearrangement of *in-situ* generated divinylcyclopropanes into cycloheptadienes, proceeding under dienamine activation.[99] Treatment of *cis*-4-(2-(2-phenyl)-vinylcyclopropyl)but-2-enals with a secondary amine generated the reactive dienamine intermediate that led to the formation of cycloheptadienes by spontaneous [3,3]-sigmatropic rearrangement. Hydrolysis of the enamine released the catalyst and the desired cycloheptadienals. The use of enantiopure secondary amines provided the final product with excellent yield and diastereoselectivity, but no enantiocontrol was observed. However, the rearrangement was shown to proceed with chirality transfer from the cyclopropane to the final desired cycloheptadiene when enantioenriched starting materials were employed (Scheme 1. 60).

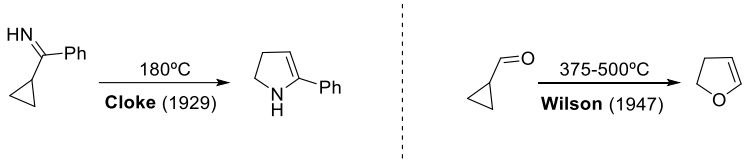
[99] Apel, C.; Hartmann, S. S.; Lentz, D.; Christmann, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 5075.



Scheme 1. 60 Enantioespecific Cope rearrangement of *in situ* generated divinylcyclopropanes into cycloheptadienes

Cloke-Wilson rearrangement

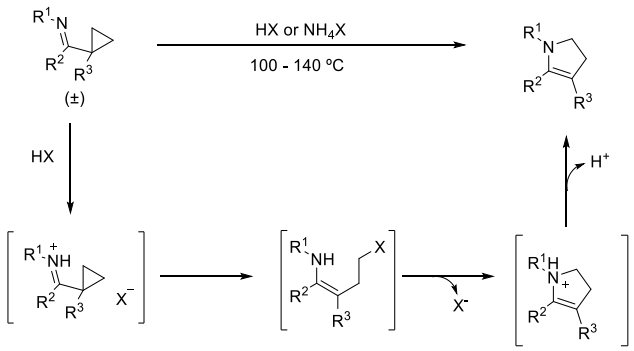
The so-called Cloke-Wilson rearrangement is a particular case of vinylcyclopropane-cyclopentene rearrangement, where carbonyl or imine substituted cyclopropanes reorganize, providing the corresponding dihydrofurans or pyrrolines under thermal conditions. The first work reported of this transformation was carried out by Cloke in 1929, in which the synthesis of 2-phenylpyrroline was described by heating the corresponding cyclopropylimine.[100] Some years later, the rearrangement of cyclopropyl carbaldehyde to 2,3-dihydrofuran was described by Wilson, heating above 375 ºC (Scheme 1. 61).[101]



Scheme 1. 61 Cloke and Wilson rearrangements

[100] Cloke, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1174.
[101] Wilson, C. L. *J. Am. Chem. Soc.* **1947**, *69*, 3002.

Since these pioneering discoveries, cyclopropylimines have been used for the synthesis of a variety of cyclic and polycyclic structures under acid treatment under thermal conditions. The transformation of cyclopropylimines into dihydropyrrole derivatives could be considered the simplest reaction of such rearrangement, which has been widely applied as the key step for the construction of more complex structures. For example, Stevens used this rearrangement for the synthesis of a variety of pyrrolidine containing natural products and suggested that an acid catalyst possessing a nucleophilic was required for the reorganization, (Scheme 1. 62).[102] In this sense, the author proposed halohydrogen acids and ammonium halides as appropriate catalysts to perform the rearrangement of cyclopropylimines. The mechanism involved the *N*-protonation followed by a homoconjugate addition of the corresponding anion, finishing with an intramolecular *N*-alkylation that afforded the corresponding dihydropyrrole derivatives. However, other catalysts, as aluminium trichloride[103] and phosphorous oxychloride,[104] have been also employed.

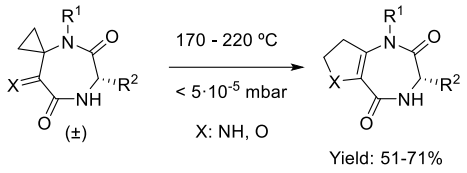


Scheme 1. 62 Cyclopropylimine rearrangement under thermal and acid conditions

On the other hand, Meijere and co-workers studied the construction of dihydropyrroles and dihydrofurans starting from the corresponding cyclopropylimines and

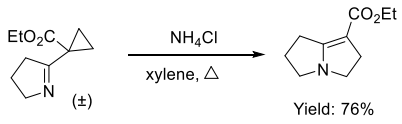
[102] (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. For other examples of Cloke-Wilson using ammonium halides: (b) Gräbe, K.; Zwafelink, B.; Doye, S. *Eur. J. Org. Chem.* **2009**, 5565. (c) Saha, S.; Reddy, V. R.; Patro, B. *Tetrahedron Lett.* **2011**, *52*, 4014. Cloke-Wilson rearrangement of azole hydrogenides: (d) Tomilov, Y. V.; Platonov, D. N. Frumkin, A. E.; Lipilin, D. L.; Salikov, R. F. *Tetrahedron Lett.* **2010**, *51*, 5120.
[103] Howell, A. R.; Martin, W. R.; Sloan, J. W.; Smith, W. T. *J. Heterocyclic Chem.* **1991**, *28*, 1147.
[104] Cai, J.; Li, F.; Deng, G.-J.; Ji, X.; Huang, H. *Green Chem.* **2016**, *18*, 3503.

cyclopropylketones, obtaining the desired dihydropyrroles and dihydrofurans by heating at high pressure (Scheme 1. 63).[105]



Scheme 1. 63 Cyclopropylimine and cyclopropylketone rearrangement under thermal conditions at high pressure

Based on this reactivity pattern, the employment of cyclic imines enable the construction of pyrrolizine and indolizine polycyclic derivatives, being the key step in these approaches the cyclopropylimine rearrangement. The first example of such transformation was reported by Pinnick and Chang, in which the ethyl tetrahydropyrrolizine carboxylate was obtained in 76% yield by refluxing the imine in xylene (Scheme 1. 64).[106]

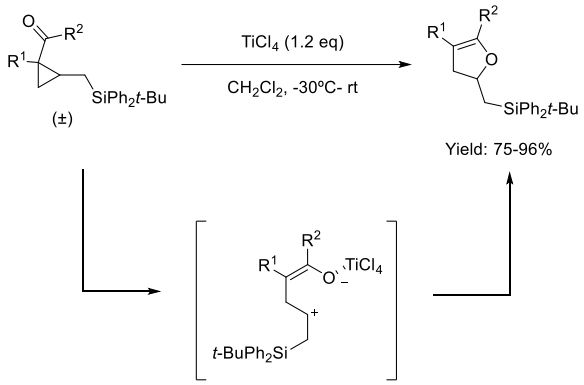


Scheme 1. 64 Synthesis of pyrrolizine derivative through cyclopropylimine rearrangement

The usually harsh reaction conditions required for this transformation have limited its applicability to synthetic routes, thus the finding of mild conditions has become a field of great interest in the last decades. In this sense, some efforts have been made in order to carry out this rearrangement process under different activation modes, employing the more reactive cyclopropylketones instead of the analogous cyclopropylimines. Most of the rearrangements of such substrates reported in the literature are carried out by Lewis acid activation of the

[105] Funke, C.; Es-Sayed, M.; Meijere, A. *Org. Lett.* **2000**, *2*, 4249.
[106] (a) Pinnick, H. W.; Chang, Y.-H. *Tetrahedron Lett.* **1979**, 837. For other exampples of synthesis of pyrrolizines and indolizines: (b) Wasserman, H. H.; Dion, R. P. *Tetrahedron Lett.* **1982**, *23*, 1413. (c) Wasserman, H. H.; Dion, R. P.; Fukuyama, J. M. *Tetrahedron* **1989**, *45*, 3203. (c) Heidt, P. C.; BergmeieePearson, W. H. *Tetrahedron Lett.* **1990**, *31*, 5441.

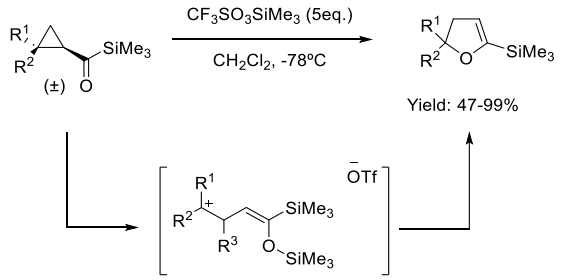
carbonyl group. In this line, Ydav and co-workers described the synthesis of substituted dihydrofurans through the ring-opening reaction of (*tert*-butyldiphenylsilyl) methylcyclopropylketones by treatment with $TiCl_4$ (Scheme 1. 65).[107] The generation of the final product was suggested to proceed through the cyclization of titanium enolate on the silicon-stabilized carbocation. In contrast with previous works,[108] the carbon-silicon bond is not cleaved in the cyclization process, and it is preserved in the final product allowing further synthetic manipulations.



Scheme 1. 65 Lewis acid promoted rearrangement of silylated D-A cyclopropanes

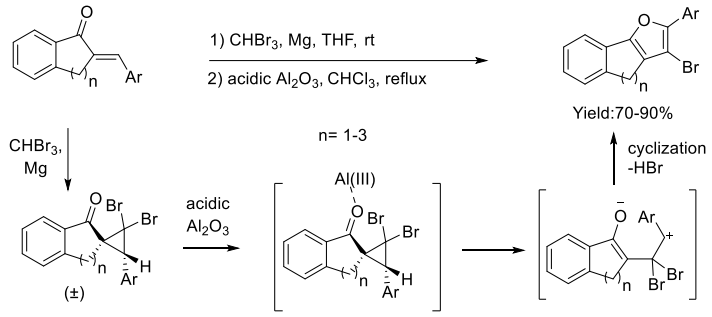
Similarly, the research group of Honda reported the TMSOTf promoted ring-enlargement of cyclopropyl silyl ketones as an efficient novel synthetic method for the construction of 5-silyl-2,3-dihydrofuran derivatives (Scheme 1. 66).[109] The trimethylsilyl moiety of TMSOTf activated the cyclopropane by coordination with the acyl moiety promoting the ring-opening reaction and leading to a carbocationic species that after cyclization afforded the desired silyl substituted dihydrofurans in good to excellent yields.

[107] Ydav, V. K.; Balamurugan, R. *Org. Lett.* **2001**, *3*, 2717.
[108] (a) Ochiai, M.; Sumi, K.; Fujita, E. *Tetrahedron Letters* **1982**, *23*, 5419. (b) Ochiai, M.; Sumi, K.; Fujita, E. *Chem. Pharm. Bull.* **1983**, *31*, 3931. (d) Hirao, T.; Misu, D.; Agawa, T. *Chem. Commun.* **1986**, 26.
[109] Honda, M.; Naitou, T.; Hoshino, H.; Takagi, S.; Segi, M.; Nakajima, T. *Tetrahedron Lett.* **2005**, *46*, 7345.



Scheme 1. 66 Lewis acid promoted rearrangement of cyclopropyl silyl ketones

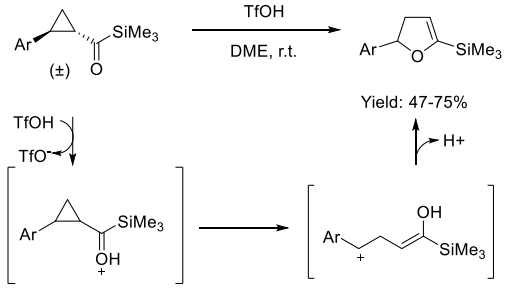
An alternative strategy to increase the ring-strain on the cyclopropane substrate in order to favor the ring-opening process is to incorporate a cyclic geminal substitution pattern on the molecule in the form of a spirocyclopropane scaffold. This approach was used by Namboothiri and co-workers on a two-step sequence for the transformation of alkylidencycloalkanones to 3-halofurans in good to excellent yields (Scheme 1. 67).[110] The process involved Mg-mediated diastereoselective dibromocyclopropanation of the starting material followed by regioselective ring expansion of the formed cyclopropyl ketone, *via* Lewis acid activation.



Scheme 1. 67 Acidic Al_2O_3 mediated rearrangement of spirocyclopropanes

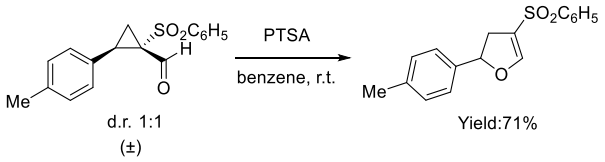
[110] Gopi, E.; Namboothiri. I. N. N. *J. Org. Chem.* **2013**, *78*, 910.

Donor-acceptor cyclopropanes can also be activated by the employment of Brønsted acids protonating the carbonyl moiety as it has been commented before, and this activation mode could be employed to promote the Cloke-Wilson rearrangement. In this context, Nakajima and co-workers described a trifolic acid promoted rearrangement of cyclopropylsilylketones, affording 2,3-dihydrofurans in moderate to good yields (Scheme 1. 68).[111]



Scheme 1. 68 Brønsted-acid catalyzed rearrangement of cyclopropylsilylketones

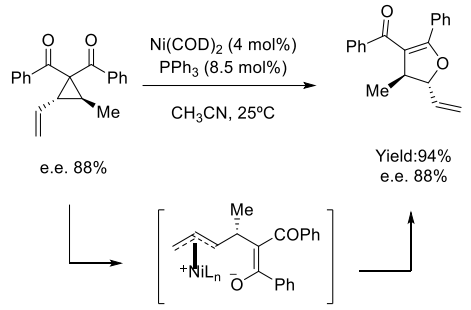
Another example of Brønsted acid activated Cloke-Wilson rearrangement was reported by Piras and co-workers, where tolyl-substituted phenylsulfonylcyclopropanecarbaldehyde underwent ring-enlargement employing *p*-toluensulfonic acid as catalyst (Scheme 1. 69).[112]



Scheme 1. 69 Brønsted-acid catalyzed rearrangement of phenylsulfonylcyclopropanecarbaldehyde

[111] Nakajima, T.; Segi, M.; Mituoka, T.; Fukute, Y.; Honda, M.; Naitou, K. *Tetrahedron Lett.* **1995**, *36*, 1667.
[112] (a) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F.; Spiga, M. *Org. Lett.* **2005**, *7*, 4565. For other Cloke-Wilson rearrangement by Brønsted acid catalysis: (c) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317. (d) Kashel, J.; Schneider, T. F.; Schirmer, P.; Maaβ, C.; Stalke, D.; Werz, D. B. *Eur. J. Org. Chem.* **2013**, 4539.

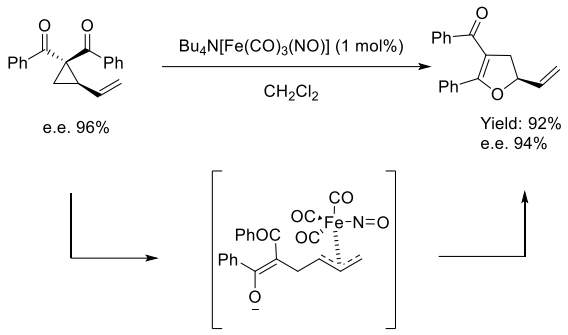
There are also examples of Cloke-Wilson rearrangements under organometallic catalysis through formation of π-allylmetal complexes. Based on this reactivity pattern, Johnson and co-workers described the construction of a single enantioenriched substituted dihydrofuran under Ni(0) catalysis (Scheme 1. 70). [113] The authors started from an enantiopure cyclopropane including an aditional substituent in the cyclopropane scaffold that can be used as stereochemical marker, observing complete chirality transfer to the final dihydrofuran. The observed stereochemical outcome was consistent with a previously proposed double-inversion mechanism.[114]



Scheme 1. 70 Ni(0)-mediated enantioespecific rearrangement of donor-acceptor cyclopropane

Iron based catalysts have also been found to be useful in Cloke-Wilson rearrangement. Therefore, Plietker and co-workers elucidated that diacyl substituted vinyl cyclopropanes resulted in an efficient rearrangement process providing the corresponding five-membered ring products under catalytic amounts of $Bu_4N[Fe(CO)_3(NO)]$.[115] The authors analyzed the stereoselectivity of the reaction observing a near-complete transfer of enantiopurity of the substrate to the new cycloadduct, in which the new C-O bond was formed with retention of configuration (Scheme 1. 71). This result, indicated that the reaction could proceed through a double S_N2-type mechanism. However, computational studies revealed that that S_N2`-type mechanism can not be rejected.

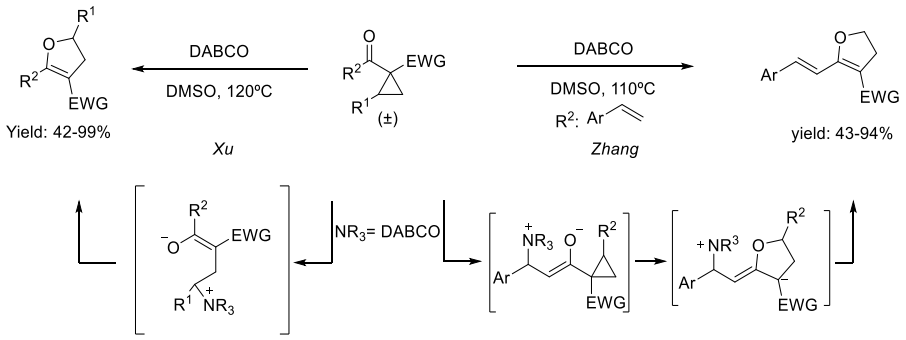
[113] Johnson, J. S.; Bowman, R. K. *Org. Lett.* **2006**, *8*, 573.
[114] Hayashi, T.; Yamane, M.; Ohno, A. *J. Org. Chem.* **1997**, *62*, 204.
[115] (a) Klein, J. E. M. N.; Knizia, G.; Miehlich, B.; Kästner, J.; Plietker, B. *Chem. Eur. J.* **2014**, *20*, 7254. (b) Lin, C.-H.; Pursley, D.; Klein, J. E. M. N.; Teske, J.; Allen, J. A.; Rami, F.; Kön, A.; Plietker, B. *Chem Sci.* **2015**, *6*, 7034.



Scheme 1. 71 Possible mechanistic pathway for the enantioespecific rearrangement

A final possibility for activating donor-acceptor cyclopropanes in Cloke-Wilson rearrangements involves the use of a nucleophilic catalyst to promote the ring-opening event through a nucleophilic addition to the cyclopropane moiety. In this context, there are some examples in the literature where activated cyclopropyl ketones reorganized to substituted 2,3-dihydrofurans using DABCO as organocatalyst. Zhang,[116] Xu[117] and co-workers described this reactivity pattern starting from similar substrates, affording highly functionalized dihydrofurans in good to excellent yields in both cases (Scheme 1. 72). Zhang proposed that, when an α,β-unsaturated ketone was used as electron-withdrawing group at the cyclopropane moiety, the intermolecular Michael addition of DABCO to the cyclopropane initiated the reaction, followed by the ring-opening promoted by the enolate and final cyclization process. Conversely, Xu suggested that a direct nucleophilic ring-opening of the three-membered ring took place in cyclopropanes bearing a simple ketone as electron-withdrawing substituent. Although initially the authors assumed a S_N2-type reaction for the DABCO addition, stereochemical analysis with an optically active substrate disfavored this pathway, since the reaction under the standard conditions provided the final product with complete loss of stereochemical integrity, leading to assume a S_N1-type mechanism.

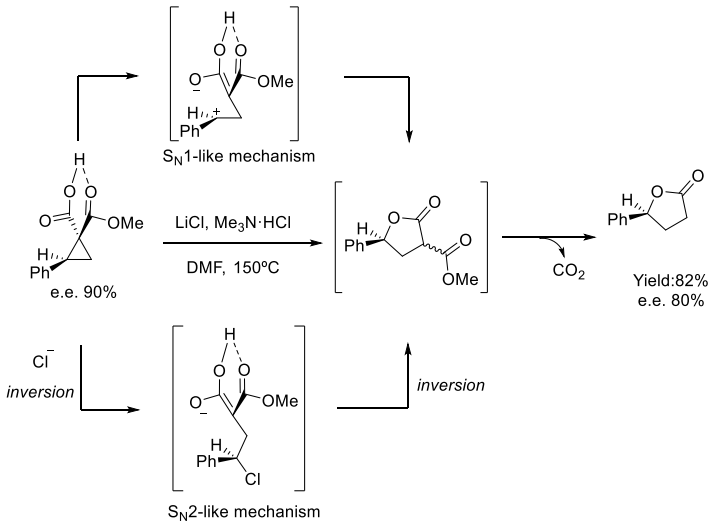
[116] Li, M.; Lin, S.; Dong, Z.; Zhang, X.; Liang, F.; Zhang, J. *Org. Lett.* **2013**, *15*, 3978.
[117] Zheng, J.; Tang, Y.; Wei, W.; Wu, Y.; Li, Y.; Zhang, J.; Zheng, Y.; Xu, S. *Org. Lett.* **2017**, *19*, 3043.



Scheme 1. 72 DABCO-catalyzed rearrangement of acylcyclopropanes

Finally, the use of catalysts with a nucleophilic counteranion to promote the ring-opening reaction has been also a suitable strategy employed for the Cloke-Wilson rearrangement. For instance, Kerr and co-workers focused their attention toward the synthesis of γ-butanolides starting from cyclopropane hemimalonates (Scheme 1. 73).[118] The authors assumed a one-pot two-step process that includes the initial butanolide formation followed by decarboxylation that underwent very successfully using lithium chloride and trimethyl ammonium chloride in DMF at 150 ºC under microwave irradiation. In order to shed light onto the mechanism, an enantioenriched cyclopropane was subjected to reaction conditions leading to the corresponding γ-lactone with only slight decrease of enantiomeric excess. This transformation showed that the reaction occurred with retention of the stereochemistry, so the authors proposed two possible mechanistic explanations. An S_N1-like opening of the cyclopropane ring may occur forming a tight ion-pair between the benzylic carbocation and the malonate ion, which promoted the retention of configuration during the reaction process. Alternatively, the nucleophilic attack of chloride with inversion of configuration followed by O-alkylation of the malonic anion with a second inversion would give rise to the same product.

[118] (a) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2013**, *15*, 4838. For another example: (b) Huang, P.; Zhang, N.; Zhang, R.; Dong, D. *Org. Lett.* **2012**, *14*, 370.



Scheme 1. 73 Enantioespecific rearrangement of cyclopropane hemimalonate

Chapter 2

2

General objectives

1. BACKGROUND

Our research group has focused the research activities on the development of new asymmetric transformations. Although initially the stereocontrol of the reactions was achieved by the use of chiral auxiliaries,[1] more recently the group focused its interest towards asymmetric organocatalysis. The most studied activation mode has been aminocatalysis,[2] however, different type of covalent organocatalysis, such as, *N*-heterocyclic carbene[3] and phosphine[4] catalysis has also been employed successfully in some asymmetric transformations. Additionally, non-covalent organocatalysis, more specifically hydrogen-bonding activation,[5] has also been explored to carry out enantioselective transformations.

In recent years, our research group has been interested in employing the released ring-strain energy associated to the ring-opening event to promote new transformations under organocatalytic activation. Our first report in this field made use of aminocatalysis as activation manifold in order to carry out a highly enantioselective cascade aza-Michael /aldol reaction between *ortho*-aminobenzaldehyde and cyclopropylacetaldehydes delivering pyrrolo[1,2-*a*]quinolones in good yields (Scheme 2. 1).[6] In this sense, cyclopropylacetaldehydes were used as useful substrates to undergo enamine formation that would deliver a catalytically formed donor-acceptor cyclopropane with ability to proceed through ring opening process that generated an α,β-unsaturated iminium ion intermediate.

---

[1] Selected examples: (a) Reyes, E.; Vicario, J. L.; Carrillo, L.; Badía, D.; Uria, U.; Iza, A. *J. Org. Chem.* **2006**, *71*, 7763. (b) Ocejo, M.; Carrillo, L.; Badía, D.; Vicario, J. L.; Fernández, N.; Reyes, E. *J. Org. Chem.* **2009**, *74*, 4404. (d) Ocejo, M.; Carrillo, L.; Vicario, J. L.; Badía, D.; Reyes, E. *J. Org. Chem.* **2011**, *76*, 460.

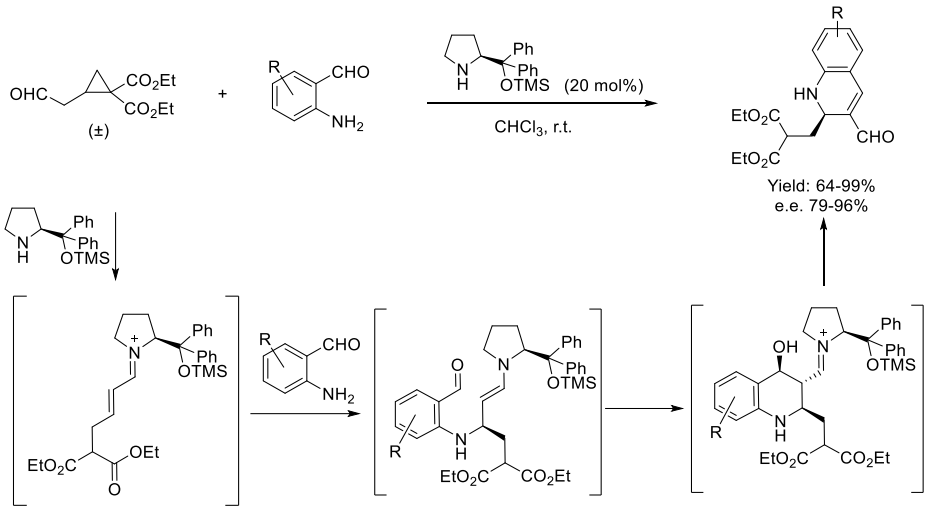
[2] Selected examples: (a) Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2006**, *8*, 6135. (b) Uria, U.; Vicario, J. L.; Badía, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509. (b) Vicario, J. L.; Reboredo, S.; Badía, D.; Carrillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168. (c) Uria, U.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336. (d) Talavera, G.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 4104. (e) Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem. Eur. J.* **2014**, *20*, 2145.

[3] Sánchez-Díez, E.; Fernández, M.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Eur. J.* **2015**, *21*, 8384.

[4] Mato, R.; Manzano, R.; Reyes, E.; Carrillo, L.; Uria, U.; Vicario, J. L. *J. Am. Chem. Soc.* **2019**, *141*, 9495.

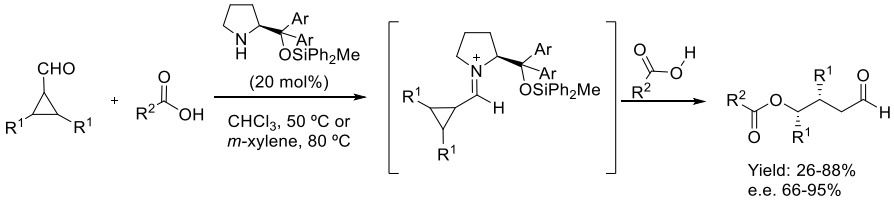
[5] (a) Martínez, J. I.; Villar, L.; Uria, U.; Carrillo, L.; Reyes, E.; Vicario, J. L. *Adv. Synth. Catal.* **2014**, *356*, 3627. See also: (b) Zabaleta, N.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Chem. Commun.* **2018**, *54*, 8905.

[6] Sánchez-Díez, E.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, *18*, 1270.



Scheme 2. 1 *In situ* generation of donor-acceptor cyclopropanes *via* aminocatalysis

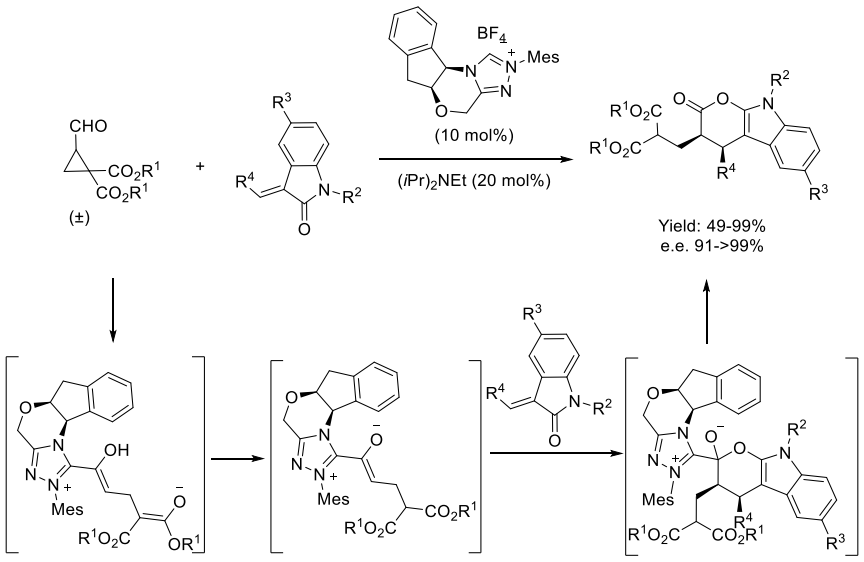
On the other hand, iminium ion activation of formylcyclopropanes, as it has been previously explained would increase the polarity of the C-C bond of the cyclopropane leading to an easier cleavage, and this event has also been explored in our group. In this way, a variety of γ-acyloxy-substituted aldehydes have been achieved in high yields and enantioselectivities through the desymmetrization of substituted *meso*-cyclopropanecarbaldehydes by nucleophilic ring-opening of the three-membered ring employing carboxylic acids as suitable pronucleophiles (Scheme 2. 2).[7]



Scheme 2. 2 Enantioselective desymmetrization of cyclopropanecarbaldehydes by the addition of carboxylic acids

[7] Díaz, E.; Reyes, E.; Uria, U.; Carrillo, L.; Tejero, T.; Merino, P.; Vicario, J. L. *Chem. Eur. J.* **2018**, *24*, 8764.

Alternatively, NHC catalysis has also been employed for the *in situ* generation of donor-acceptor cyclopropanes starting from formylcyclopropanes (Scheme 2. 3).[8] In this example, a formal [4+2] cycloaddition has been developed in the presence of a chiral *N*-heterocyclic carbene, achieving a wide scope of differently substituted tetrahydropyrano[2,3-*b*]indoles with excellent yields, diastereo- and enantioselectivities. The activation of formylcyclopropane by condensation of the aldehyde with the carbene promoted the ring-opening reaction giving place to an acyl azolium equivalent, which next underwent proton transfer to generate a acyl azolium enolate, which is a suitable electron-rich dienophile to undergo inverse electron-demand Diels-Alder reaction with a variety of heterodienes.

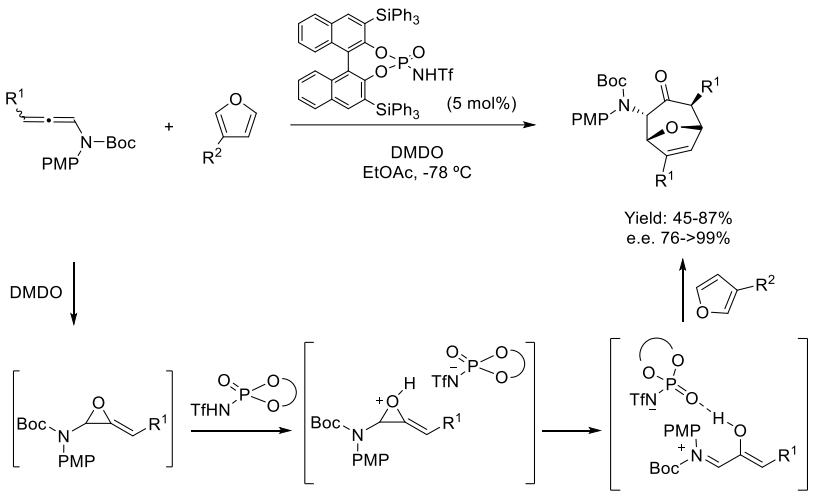


Scheme 2. 3 *In situ* generation of donor-acceptor cyclopropanes *via* NHC catalysis

Finally, it has to be highlighted that the ring-opening of epoxides has also been studied, evaluating the employment of alkylideneoxiranes as strained intermediates in organocatalytic reactions. In particular, these epoxides have been used as precursors of oxallyl cations in enantioselective [4+3] cycloadditions, using a BINOL-based chiral *N*-

[8] Prieto, L.; Sánchez-Díez, E.; Uria, U.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Adv. Synth. Catal.* **2017**, *359*, 1678.

trifluoromethanesulfonyl phosphoramide as catalyst (Scheme 2. 4).[9] Moreover, the reactive alkylideneoxiranes have been formed from the corresponding allenamides by *in situ* oxidation with DMDO.



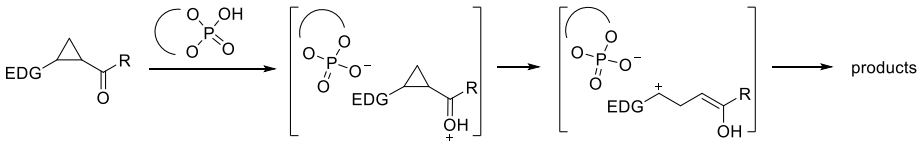
Scheme 2. 4 [4+2] cycloaddition between furans and oxallyl cations

All these examples show the state of the art of the activities of our research group dealing with the organocatalytic activation of strained small molecules, which is directly related with the objectives set for the research covered in this manuscript.

[9] Villar, L.; Uria, U.; Martínez, J. I.; Prieto, L.; Reyes, E.; Carrillo, L.; Vicario, J. L. *Angew. Chem. Int. Ed.* **2017**, *56*, 10535.

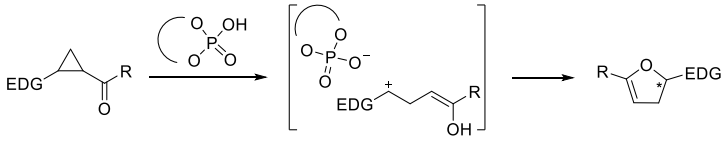
2. GENERAL OBJECTIVES

In the line with the recent research of the group and based on the aforementioned reactivity of small rings through release of the ring strain under organocatalytic activation, the work presented in this thesis has been focused on the study of new reactivity patterns of donor-acceptor cyclopropanes under activation by Brønsted-acid catalysis (Scheme 2. 5). As it has been previously summarized, activated cyclopropanes tend to react with different substrates through ring-opening reaction process. Especially, ring-opening of donor-acceptor cyclopropanes generate zwitterionic species that can further react with a variety of nucleophiles, electrophiles or dipolarophiles, as well as intramolecular reactions, generating larger ring systems. In this context, we turned our attention to the investigation of both intra- and intermolecular reactions of donor-acceptor cyclopropanes, employing chiral Brønsted acids as catalysts.



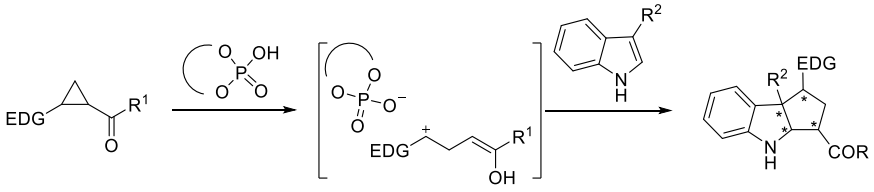
Scheme 2. 5 Brønsted-acid activation of donor-acceptor cyclopropanes

On one hand, we envisioned that Brønsted-acid catalysis could be a useful approach for carrying out Cloke-Wilson rearrangement reaction. Taking into account that there are no enantioselective examples of this reaction in the literature, being only a few enantioespecific examples for the generation of optically active hydrofuran derivatives, it was thought to carry out the asymmetric version of such reaction under BINOL-derived chiral Brønsted acid activation (Scheme 2. 6).



Scheme 2. 6 Enantioselective Cloke-Wilson rearrangement

Alternatively, the zwitterionic species formed through the ring-opening of donor-acceptor cyclopropanes has also the possibility to react with a variety of reactants of different nature. In this line, we decided to survey the plausibility of using the donor-acceptor cyclopropane as 1,3-dipole in [3+2] reactions using 3-substituted indoles as dipolarophiles. Once again, it was envisioned to employ chiral BINOL-derived Brønsted acids to promote enantiocontrol in the transformation (Scheme 2. 7).



Scheme 2. 7 Enantioselective cycloaddition between donor-acceptor cyclopropanes and 3-substituted indoles

Chapter 3

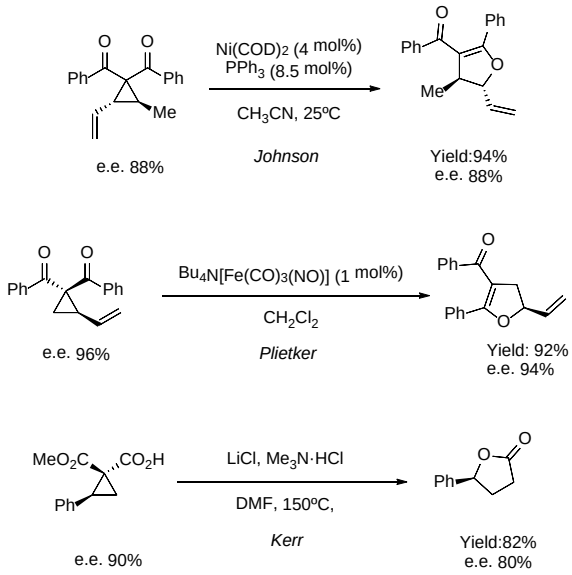
3

Catalytic Enantioselective Cloke-Wilson Rearrangement

1. INTRODUCTION

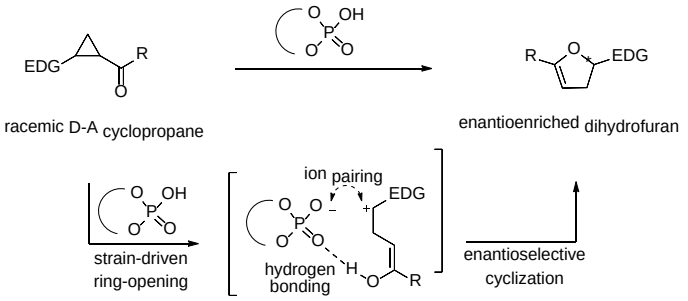
From the literature examples presented before, it can be concluded that donor-acceptor cyclopropanes are suitable starting materials for the construction of more complex molecules due to their thermodynamic tendency to undergo ring-opening driven by strain release. In recent years, the investigation of mild conditions for the reorganization of cyclopropyl ketones to dihydrofurans has been intensely studied in order to extend its synthetic application. The Cloke-Wilson rearrangement is a good example of the synthetic potential of donor-acceptor cyclopropanes for the easy generation of interesting heterocyclic scaffolds. As mentioned in Chapter 1 and 2, no catalytic enantioselective Cloke-Wilson rearrangements can be found in the literature. The only examples for the synthesis of enantioenriched dihydrofuran derivatives are based on enantioespecific reactions, in which enantiopure final products are obtained through chirality transfer from the starting enantiomerically enriched cyclopropanes (Scheme 3. 1).[1]

[1] (a) Johnson, J. S.; Bowman, R. K. *Org. Lett.* **2006**, *8*, 573. (b) Klein, J. E. M. N.; Knizia, G.; Miehlich, B.; Kästner, J.; Plietker, B. *Chem. Eur. J.* **2014**, *20*, 7254. (d) Grover, H. K.; Emmett, M. R.; Kerr, M. A. *Org. Lett.* **2013**, *15*, 4838.



Scheme 3. 1 Enantioespecific Cloke-Wilson rearrangements

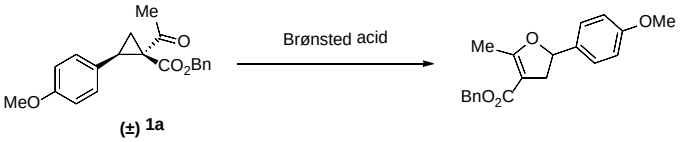
With these precedents in mind, we turned our attention to the construction of 2,3-dihydrofurans through Cloke-Wilson rearrangement starting from donor-acceptor cyclopropanes activated by a Brønsted acid. In this sense, the ring opening reaction would lead to a zwitteronic carbocation/enol intermediate that after ring-closure would generate the dihydrofuran scaffold. This hypothetical pathway would enable the use of racemic donor-acceptor cyclopropanes as starting materials with the potential to be converted into the final dihydrofurans in a stereocontrolled way employing a chiral Brønsted acid catalyst through a dynamic kinetic asymmetric transformation (DYKAT). In this sense, it was expected that both the hydrogen bonding between the phosphate anion and the enol moiety, and the ion-pair interactions between the phosphate and the carbocationic moiety could operate during the cyclization process, providing the necessary rigid conformation for the sought enantiocontrol (Scheme 3. 2).



Scheme 3. 2 First objective of this work

To accomplish the aforementioned objective, the subsequent work plan was followed:

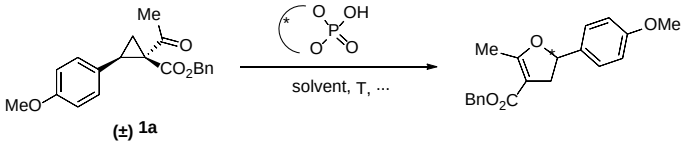
1. *Proof of concept:* In order to demonstrate the capacity of donor-acceptor cyclopropanes to experience the target Cloke-Wilson rearrangement process, we will evaluate a model substrate such as the one shown in Scheme 3. 3 in combination with a variety of Brønsted acids. This model substrate was selected according to the previous work reported by Werz[2] that indicated the high reactivity of *para*-methoxy phenyl substituted cyclopropane towards ring opening in comparison with other donor substituents. In addition, it was also decided to incorporate an additional electron-withdrawing substituent at geminal position to the acyl group in order to increase the polarization of the C-C bond, favoring the ring-opening of the three-membered ring.



Scheme 3. 3 Proof of concept

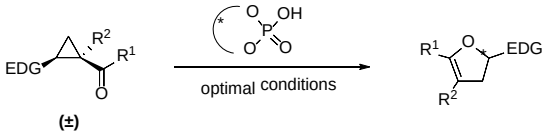
[2] (a) Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848. (b) Kreft, A.; Lücht, A.; Grunenberg, J.; Jones, P. G.; Werz, D. B. *Angew. Chem. Int. Ed.* **2019**, *58*, 1955.

2. *Optimization of the reaction conditions:* Using the aforementioned donor-acceptor cyclopropane as model compound, a variety of chiral BINOL-derived Brønsted acids will be tested with the aim of determining the catalyst that provides the best reaction outcome in terms of both yield and enantiocontrol. Moreover, other parameters such as the solvent and the temperature will also be optimized (Scheme 3. 4).



Scheme 3. 4 Optimization of the reaction conditions

3. *Scope of the reaction:* With the optimal reaction conditions in hand, the applicability of the methodology will be extended to the use of differently substituted cyclopropanes. In this context, cyclopropanes with different donor and acceptor substituents will be tested in the reaction (Scheme 3. 5).



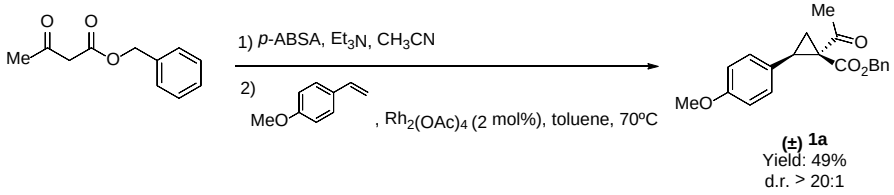
Scheme 3. 5 Scope of the reaction

2. RESULTS AND DISCUSSION

Once the objectives of the project have been determined and the work plan discussed and established, the most relevant results obtained in this research will be presented in the following paragraphs.

2.1. Proof of concept

As proposed in the initial objectives, we started our work by evaluating the capacity of cyclopropane **1a** to undergo Cloke-Wilson rearrangement under Brønsted acid catalysis. For this reason, we first faced the synthesis of this substrate, which was carried out using rhodium-catalyzed cyclopropanation approach. This methodology requires first the synthesis of the corresponding diazoacetate reagent, which had to be prepared by treatment of commercially available benzyl 3-oxobutanoate with *para*-acetamidobenzenesulfonyl azide (Scheme 3. 6). Once prepared, this was subjected to cyclopropanation without purification, using $Rh_2(OAc)_4$ as catalyst under standard conditions, obtaining cyclopropane **1a** as single diastereoisomer in 49% yield for the overall two-step process.



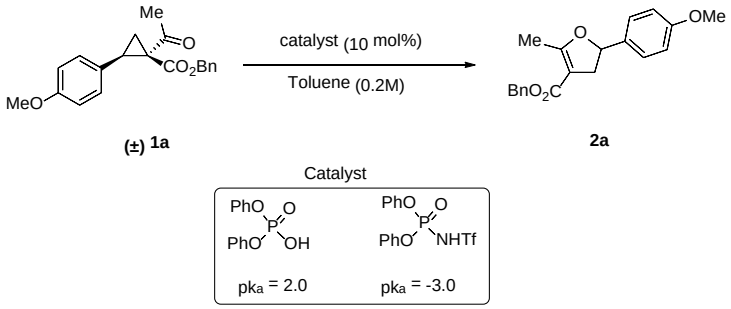
Scheme 3. 6 Synthesis of model cyclopropane **1a**

With the model substrate in hand, we proceeded to test the rearrangement reaction. We initially surveyed the use of diphenylphosphoric acid ($pk_a \approx 2.0$) or the more acidic diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate ($pk_a \approx -3.0$),[3] which are the standard non-chiral Brønsted acids used in previous studies in our group (Table 3. 1). Through these preliminary experiments, we observed that the compound **1a** was undergoing fast rearrangement (4h and 2h respectively) at room temperature in toluene, to yield dihydrofuran **2a** in an efficient way

[3] (a) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J. M.; Berkessel, A.; O'Donoghue, A. C. *Chem. Eur. J.* **2011**, *17*, 8524. (b) Desai, A.; Wulff, W. D. *Synthesis* **2010**, *21*, 3670.

(entries 1-2). Moreover, it was noticed that the reaction was also taking place in temperatures as low as -30 ºC, affording the final product in excellent yield after overnight reaction (entries 3-4). In order to determine if the Brønsted acid was necessary, the reaction was carried out in the absence of it, recovering the unreacted starting cyclopropane after two days; therefore, concluding that no background reaction was taking place (entry 5).

Table 3. 1 Cloke-Wilson rearrangement of **1a** employing achiral Brønsted acids.[a]



Entry	Catalyst	T (ºC)	t (h)	Yield 2a (%)[b]
1	**$(PhO)_2P(O)OH$**	r.t.	4	95
2	**$(PhO)_2P(O)NHTf$**	r.t.	2	93
3	**$(PhO)_2P(O)OH$**	-30	12	91
4	**$(PhO)_2P(O)NHTf$**	-30	12	94
5	**--**	r.t.	48	<5

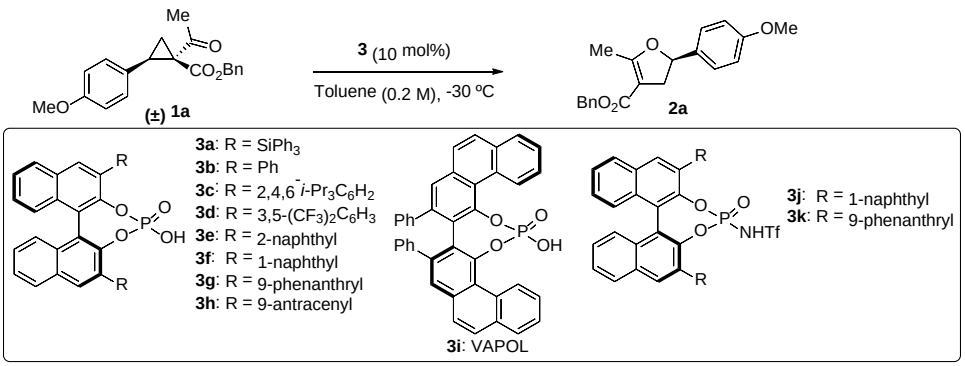
[a] Reactions performed in a 0.1 mmol scale of **1a**, using 10 mol% of catalyst in toluene (0.2M).
[b] Yield of isolated product after flash column chromatography purification.

With these initial experiments, it has been demonstrated the feasibility of carrying out the Cloke-Wilson rearrangement of donor-acceptor cyclopropanes under mild conditions, using catalytic amounts of diphenylphosphoric acid or diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate as Brønsted acid, which would be the ring opening promoter.

2.2. Optimization of the reaction conditions

Once the viability of the reaction was demonstrated, different chiral Brønsted acids were tested in the reaction under analogous reaction conditions. In this sense, we initially focused on the identification of the best catalyst in terms of both the yield and the enantioselectivity of the reaction. In view that the reaction proceeded successfully employing the achiral diphenylphosphoric acid, which is around 5 pk_a units less acidic than the corresponding achiral diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate, it was first decided to carry out the reaction using chiral phosphoric acids as catalysts, due to their easier preparation and the commercial availability of some of them (Table 3. 2).

Table 3. 2 Chiral BINOL-derived Brønsted acid catalysts evaluated on the model reaction.[a,b]



Entry	Catalyst	t (h)	Yield 2a (%)[c]	e.e. 2a (%)[d]
1	**3a**	48	<5	-
2	**3b**	48	7	10
3	**3c**	48	<5	-
4	**3d**	48	13	34
5	**3e**	48	45	50
6	**3f**	48	72	80
7	**3g**	48	82	82
8	**3h**	48	<5	-
9	**3i**	48	70	56
10	**3j**	12	90	0
11	**3k**	12	91	0
12[e]	**3k**	48	38	6

[a] Reactions performed in a 0.1 mmol scale of **1a**, using 10 mol% of catalyst **3** in toluene (0.2M) at -30 ºC. [b] The absolute stereocehemistry of the product was determined by X-ray analysis of an analogous derivatized product (For more details see page 22). [c] Yields of isolated products after flash column chromatography purification. [d] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section). [e] Reaction carried out at -78ºC.

To start with the catalyst screening, some BINOL-derived phosphoric acids were initially tested, such as the 3,3'-triphenylsilyl or the more simple phenyl-substituted BINOL-based ones (**3a** and **3b**). Although triphenylsilyl BINOL-substituted phosphoric acid **3a** was unable to perform the reaction recovering the unreacted starting material after 48h (entry 1), phenyl-substituted catalyst **3b** turned out to be active for such transformation (entry 2). As the formation of the adduct **2a** was observed in only low amount and with a low enantiocontrol using **3b**, it was decided to modify the electronic nature of the substituents of the catalyst, placing both electron-donating and electron-withdrawing groups at the 3,3'-aryl moiety, modifying like this the acidity of the catalyst.[4] In this sense, when the archetypical less acidic TRIP catalyst **3c** was employed, no reaction was observed, recovering the unreacted starting cyclopropane (entry 3), which, could be attributed to steric hindrance, associated to the bulky substituents placed on the BINOL moiety. Conversely, when 3,5-$(CF_3)_2C_6H_3$ aryl substituent was placed (catalyst **3d**), product **2a** was isolated in slightly higher yield and with better enantiomeric excess, which was interpreted in terms of the more acidic nature of the catalyst because of the electron-withdrawing character of these 3,3'-aryl substituents (entry 4).

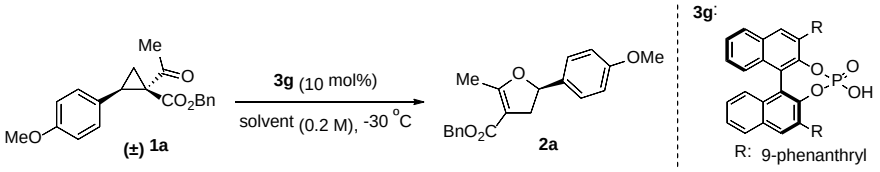
On the other hand, the size of the aromatic system was also evaluated. In this sense, when more extended π systems were placed at the BINOL moiety, such as naphthyl or phenanthryl groups (catalysts **3e-g**), a notable improvement of both the yield and the enantiomeric excess was observed (entries 5-7). While the use of 2-naphtyl substituted BINOL-based catalyst **3e** provided the target product **2a** in moderate 45% yield and with a promising 50% enantiocontrol (entry 5), the 1-naphtyl substituted one (**3f**) afforded dihydrofuran **2a** with a significant increase of both yield and enantioselectivity (entry 6). Interestingly, phenanthryl containing catalyst **3g** resulted to be the most promising one achieving the target compound with 82% yield and 82% enantiomeric excess (entry 7). Surprisingly, the reaction did not take place when anthracenyl-substituted catalyst **3h** was used (entry 8). Additionally, we also tested a different BINOL-related chiral scaffolds, such as VAPOL-derived catalyst **3i**, but this furnished the final product with lower yield and enantiocontrol (entry 9). Finally, 1-naphtyl and 9-phenanthryl substituted BINOL-derived *N*-triflyl phosphoramides (**3j-k**) were tested, which are known to be 6-7 pk_a units more acidic than their corresponding phosphoric acids.[5] As expected, in both cases the reaction resulted to be much faster compared to the

[4] Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.
[5] Rueping and Leito reported a full study on stablishing an acidity scale for the most widely used Brønsted acids: Kaupmees, K.; Tolstoluzhsky, N.; Raja, S; Rueping, M; Leito, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 11569.

reaction catalyzed by phosphoric acids, but although the yield of **2a** increased, these catalysts were not able to control the enantioselectivity of the process at -30 ºC (entries 10-11). In view of these results, it was also decided to lower the temperature employing the catalyst **3k**, hoping to improve the enantiomeric excess. However, when the reaction was carried out at -78 ºC, the results did not improve (entry 12).

Encouraged by the promising results obtained with catalyst **3g**, we next decided to evaluate solvents of different nature employing this catalyst, in order to achieve the product **2a** with the highest possible yield and enantioselectivity (Table 3. 3). Initially, non-polar solvents related to toluene were examined, such as benzene or xylene, observing that, although benzene gave similar results to those obtained with toluene (entry 2), the use of *o*- or *m*-xylene brought a considerable improvement of the enantiomeric excess (up to 92% e.e.), although together with a decrease of the yield (entries 1 *vs* entries 3-4). These results could be attributed to the uncompleted conversion of the process, probably due to the low solubility of the substrate in xylene at low temperatures. Remarkably, when more polar chlorinated solvents were used, such as CH_2Cl_2, $CHCl_3$ or 1,2-dichloroethane, the reaction occurred as an homogeneous mixture, observing a much faster reaction and isolating the desired adduct **2a** with very good yield, although with a slightly lower enantiocontrol (entries 5-7). Finally, no reactivity was observed when the reaction was performed using ethers as solvent (entries 8-9). Based on these results, binary mixtures of *m*-xylene with 1,2-dichloroethane were evaluated, with the objective of obtaining a perfect combination between the reaction rate and the enantioselectivity of the process. Different proportions of these solvent mixtures were tested compromising always the enantioselectivity of the reaction and increasing the yield of the process while the reaction proceeded faster (entries 10-11). Employing a 1:1 mixture of *m*-xylene/1,2-dichloroethane as solvent mixture dihydrofuran **2a** was isolated with an excellent yield and with a high 88% e.e. in 24 hours (entry 10). In order to further improve the enantioselectivity of the transformation other proportions of these solvents were examined, hence obtaining the optimal result with a 3:1 mixture of *m*-xylene and 1,2-dichloroethane, although in a longer reaction time (entry 11).

Table 3. 3 Evaluation of the effect of the solvent.[a]

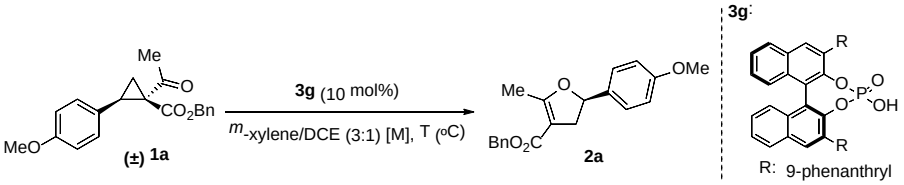


Entry	Solvent	t (h)	Yield 2a (%)[b]	e.e. 2a (%)[c]
1	Toluene	48	82	82
2	Benzene	48	71	80
3	*o*-xylene	48	65	88
4	*m*-xylene	48	63	92
5	CH_2Cl_2	12	80	87
6	$CHCl_3$	12	83	79
7	$Cl(CH_2)_2Cl$	12	85	82
8	THF	48	<5	-
9	Et_2O	48	<5	-
10	*m*-xylene/ $Cl(CH_2)_2Cl$ (1:1)	24	91	88
11	*m*-xylene/ $Cl(CH_2)_2Cl$ (3:1)	48	90	90

[a] Reactions performed in a 0.1 mmol scale of **1a**, using 10 mol% of catalyst **3g** in the indicated solvent (0.2M) at -30 ºC. [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

Finally, the influence of other parameters, such as the temperature and concentration were evaluated (Table 3. 4). Starting with the effect of the temperature, the reaction proceeded considerably faster when it was carried out at -20 ºC isolating dihydrofuran **2a** with excellent yield but compromising the enantioselectivity (entry 2). In contrast, when lowering the reaction temperature to -40 ºC the process becomes much slower, observing almost full conversion after 84 hours and thus, isolating the final product with lower yield despite the slight increase noticed in the e.e. value (entry 3). Next, the effect of the concentration in the reaction outcome was evaluated and, in this sense, although a faster reaction was observed at higher concentration, the results did not end up in any improvement in any of the cases (entries 4-5).

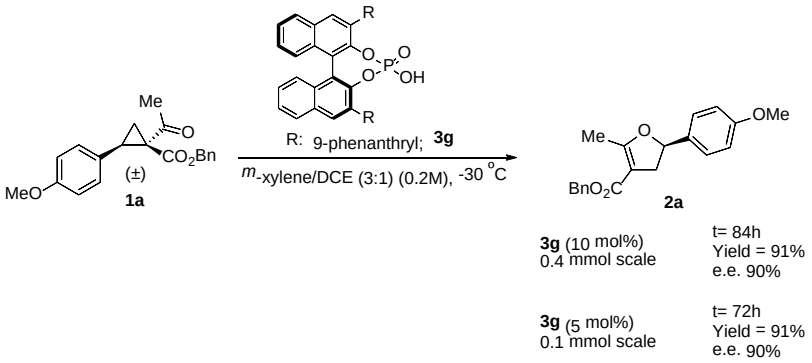
Table 3. 4 Influence of temperature and concentration in the reaction.[a]



Entry	T (ºC)	[M]	Additive	t (h)	Yield 2a (%)[b]	e.e. 2a (%)[c]
1	-30	0.2	-	48	90	90
2	-20	0.2	-	20	90	84
3	-40	0.2	-	84	84	92
4	-30	0.1	-	48	86	90
5	-30	0.4	-	15	85	90

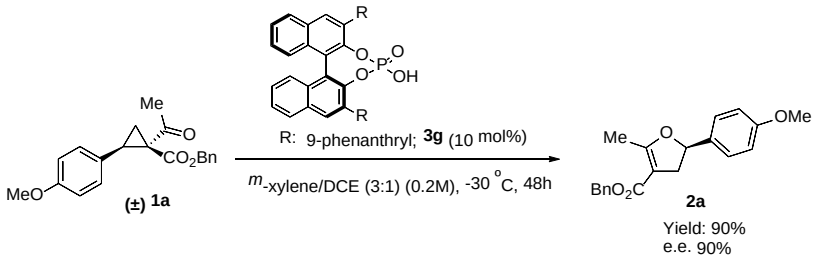
[a] Reactions performed in a 0.1 mmol scale of **1a**, using 10 mol% of catalyst **3g** in *m*-xylene/DCE (1:1) (0.2M) at the indicate T (ºC). [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

Finally, we also examined the performance of the reaction at a larger fourfold scale, observing that it performed equally well. Moreover, we also checked if the catalytic loading could be reduced, and remarkably, the final product was afforded with excellent yield and enantiocontrol when lowering the catalyst loading down to 5 mol%, only compromising the reaction time (Scheme 3. 7).



Scheme 3. 7 Modification of the reaction scale and catalyst loading

Once evaluated the most important reaction parameters, the optimal conditions for performing the reaction were established, implying the use of 10 mol% of phenanthryl substituted BINOL-based phosphoric acid **3g** in a 3:1 mixture of *m*-xylene and 1,2-dichloroethane (0.2 M) at -30 ºC and running the reaction for two days, obtaining the corresponding 2,3-dihydrofuran with 90% yield and 90% enantiomeric excess (Scheme 3. 8).

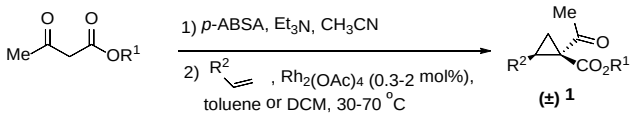


Scheme 3. 8 Optimal conditions for the Cloke-Wilson rearrangement

2.3. Scope of the reaction

Once having established an optimal experimental procedure for the organocatalytic enantioselective Cloke-Wilson rearrangement, we proceeded to extend the methodology to differently substituted cyclopropanes. The synthesis of these cyclopropanes was carried out through the same synthetic route employed for the preparation of cyclopropane **1a**, using rhodium-catalyzed cyclopropanation of styrenes with the corresponding diazocompounds, which had to be prepared starting from different β-ketoesters. First, 1-acetyl-1-alkoxycarbonylcyclopropanes with different donor substituents were synthesized, obtaining most of them in good to moderate yields and as single diastereoisomer (Table 3. 5).

Table 3. 5 Synthesis of donor-acceptor cyclopropanes with different electron-donating groups.



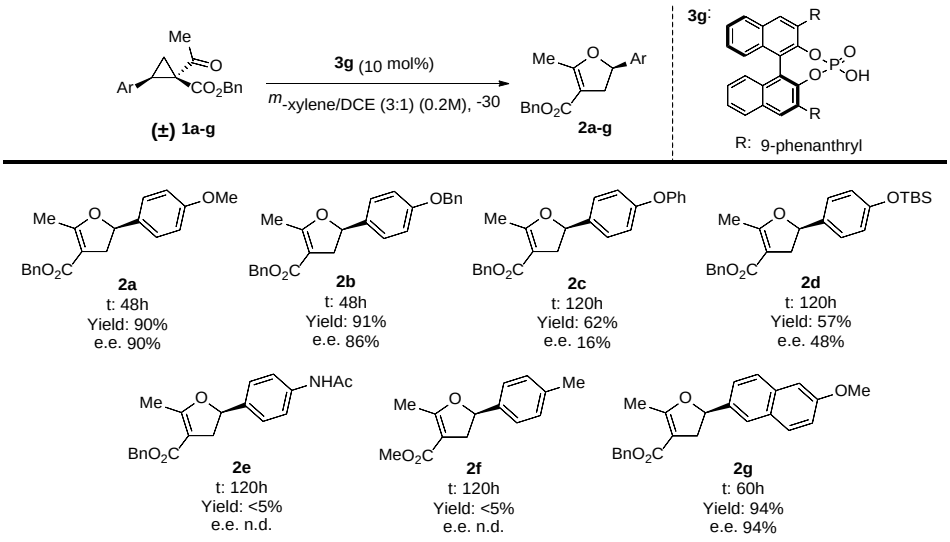
Entry	Cycloprop	R^1	R^2	Yield 1 (%)[a]	d.r. 1
1	**1b**	Bn	4-$BnOC_6H_4$	36	>20:1
2	**1c**	Bn	4-$PhOC_6H_4$	21	>20:1
3	**1d**	Bn	4-$TBSOC_6H_4$	30	>20:1
4	**1e**	Bn	4-$AcNHC_6H_4$	15	>20:1
5	**1f**	Me	4-Me-C_6H_4	84	3.5:1
6	**1g**	Bn	6-methoxynaphthalen-2-yl	67	>20:1
7	**1h**	Bn	2-$OMeC_6H_4$	78	5:1
8	**1i**	Bn	3-Me-4-$MeOC_6H_3$	46	>20:1
9	**1j**	Bn	2,3-dihydrobenzofuran-5-yl	25	3.5:1
10	**1k**	Bn	benzofuran-5-yl	15	>20:1
11	**1l**	Bn	3,4-$(OCH_2O)C_6H_3$	21	>20:1
12	**1m**	Bn	3-Cl-4-$MeOC_6H_3$	19	>20:1
13	**1n**	Bn	2-furyl	10	>20:1
14	**1o**	Bn	2-thienyl	32	>20:1
15	**1p**	Bn	*N*-Boc-indol-3-yl	29	>20:1

[a] Yields of isolated products after flash column chromatography purification for the overall two-step procedure.

In order to evaluate the effect of the nature of the donor group placed at the cyclopropane moiety, we turned to carry out the Cloke-Wilson rearrangement of these cyclopropanes under optimal conditions at -30 ºC (Table 3. 6). Firstly, we focused on replacing the methoxy group by other substituents at the 4-position of the phenyl moiety of the electron-donating substituent at the cyclopropane (Substrates **1b-1f**). Whereas the reaction proceeded

successfully replacing the methoxy group by a benzyloxy group (compound **2b**), when 4-phenoxy or 4-*tert*-buthyldimethylsilyloxy substituents were inserted, the yield and the stereoselectivity considerably decreased (Substrate **1a-b** *vs* **1c-d**). Furthermore, if an amide or a simple alkyl group was placed as 4-substituent of the aryl group, the reaction did not take place because of the less donor-character of such substituents (Substrates **1e-f**). Moreover, when a bigger π-system was placed as electron-donating group, such as 6-methoxynaphthyl derivative, product **2g** was provided with excellent 94% yield and 94% enantiomeric excess.

Table 3. 6 Study of the modification of the donor group: modification at 4-position.[a]

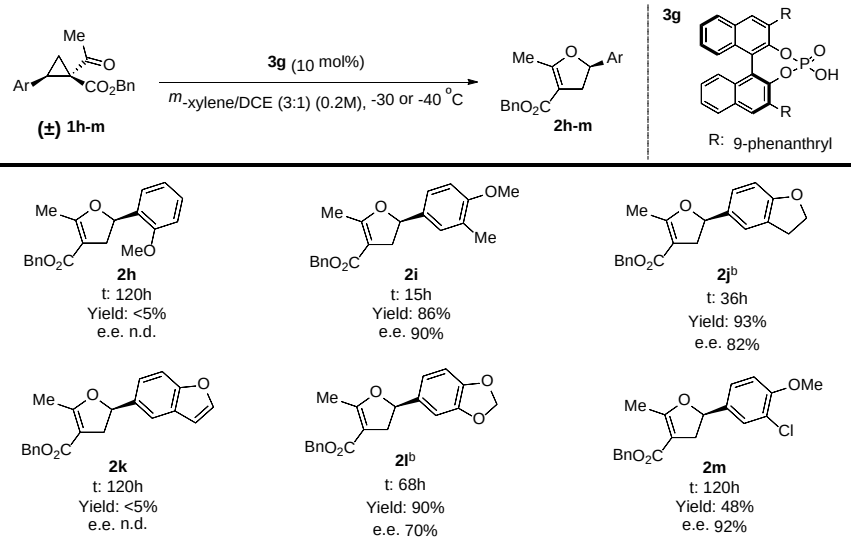


[a] Reactions performed in a 0.05 mmol scale of **1a-g**, using 10 mol% of catalyst **3g** in m-xylene/DCE (3:1) (0.2M) at -30 ºC; yields of isolated products after flash column chromatography purification; enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

Next, we turned our attention to analyze the effect of the substitution pattern at the phenyl group (Table 3. 7). In this sense, the reaction with the cyclopropane bearing a 2-methoxyphenyl group (Substrate **1h**) as donor unit was evaluated, but the reaction did not take place probably by cause of steric hindrance generated by the methoxy group in *ortho* position. Considering these unsuccessful results, it was decided to incorporate different substituents at the aryl moiety, but always maintaining an alkoxy group in the 4 position

(Substrates **1i-1m**). In this sense, when an additional alkyl group was introduced at the third position of the 4-methoxyphenyl (Substrates **1i-1j**), as expected, a much faster reaction was observed due to the more electron rich arene, affording the final products in high yields in both of the cases. The enantiomeric excess of product **2i** was excellent, albeit a slight decrease could be perceived in the enantiomeric excess of **2j**, being necessary to lower the temperature to -40 ºC. Conversely, the reaction did not work when placing benzofuran-5-yl group (Substrate **1k**), probably as a result of the lower accessibility of the electron-pair in the oxygen, as happened with the 4-phenoxy and 4-*tert*-buthylsililoxy groups. Moreover, using benzo-1,3-dioxole as donor substituent the dihydrofuran **2l** was reached with excellent yield although moderate enantioselectivity. Finally, as expected, when an electron-withdrawing group was placed at the third position of the *para*-methoxyphenyl group, decreasing the donating effect of the aryl substituent, the yield of the reaction remarkably decreased to 48% in a much longer reaction time as a consequence of a low conversion in the process; however, the enantiocontrol of the process for the obtention of **2m** remained being excellent.

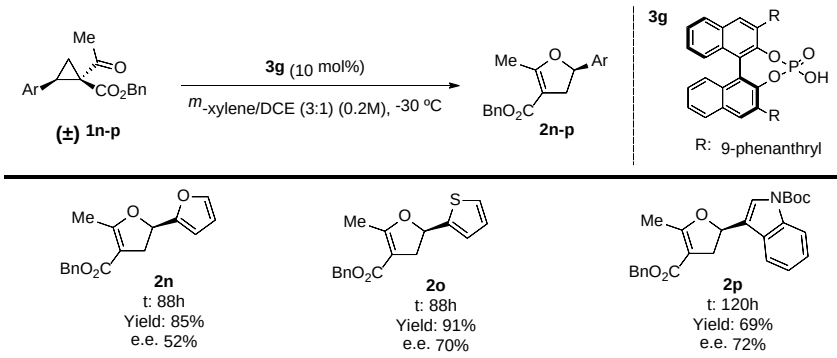
Table 3. 7 Study of the modification of the donor group: substitution pattern.[a]



[a] Reactions performed in a 0.05 mmol scale of **1h-m**, using 10 mol% of catalyst **3g** in m-xylene/DCE (3:1) (0.2M) at -30 or -40 ºC; yields of isolated products after flash column chromatography purification; enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section). [b] Reactions at -40 ºC.

Remarkably, cyclopropanes containing aromatic heterocycles as donor substituents were also able to provide the desired dihydrofuran (Table 3. 8). Whereas 2-furyl substituted cyclopropane afforded product **2n** with moderate enantiocontrol, when 2-thienyl and *N*-Boc-indol-3-yl heteroaromatic cycles were placed, final products **2o** and **2p** were obtained with good yield and better enantiomeric excess values in both cases. It is noteworthy that the lower yield of product **2p** is due to the hydrolisis of *N*-Boc-indole derivative under the reaction conditions and during the purification process.

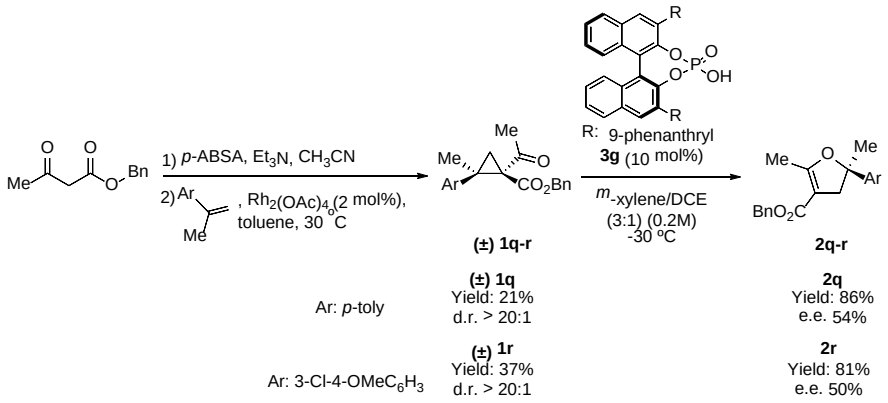
Table 3. 8 Study of the modification of the donor group: heterocyclic substitution.[a]



[a] Reactions performed in a 0.05 mmol scale of **1n-p**, using 10 mol% of catalyst **3g** in *m*-xylene/DCE (3:1) (0.2M) at -30 ºC; yields of isolated products after flash column chromatography purification; enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

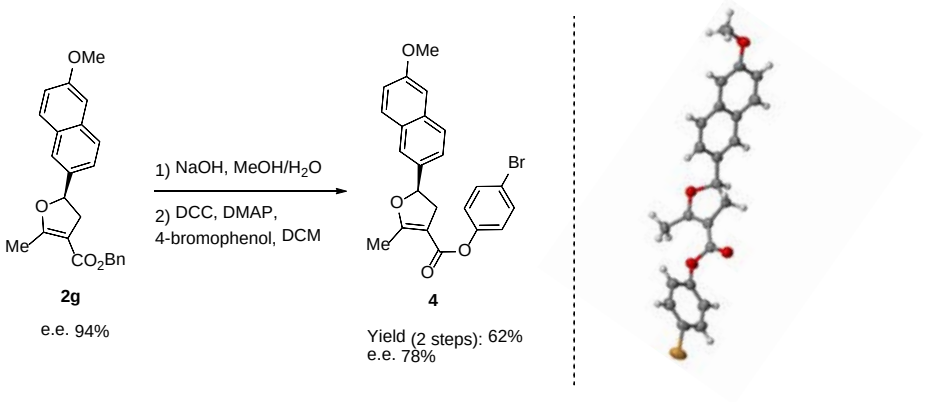
In addition, we turned our attention to the synthesis of the more challenging dihydrofuran derivatives containing a quaternary stereocenter. To reach that goal, we first prepared cyclopropanes **1q** and **1r** with an additional methyl group at the carbon where the electron-donating substituent is placed, using the previously explained $Rh_2(OAc)_4$-catalyzed methodology and obtaining the desired cyclopropanes with low yield but as single diastereoisomer. Interestingly, when both cyclopropanes were subjected to the optimal reaction conditions, products **2q-r** were furnished with high yields but with moderate enantioselectivities (Scheme 3. 9). In order to increase the selectivity of the process, the reaction was tested at a lower temperature employing the substrate **2r**. Unfortunately, no significant improvement of the enantioselectivity was observed in any case, being 56% the

highest enantiomeric excess value obtained when performing the reaction in toluene at -60 ºC, although with a slight decrease in the yield.



Scheme 3. 9 Synthesis of dihydrofurans with a quaternary stereocenter

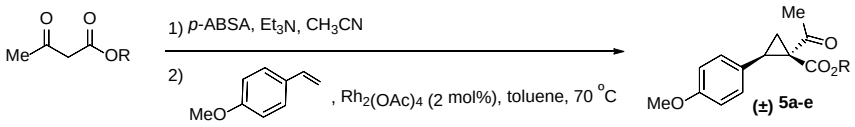
All the Cloke-Wilson rearrangement products were isolated as oils and could not be recrystallized, which precluded the possibility to determine their absolute configuration through X-ray analysis. For this reason we decided to carry out further transformations on dihydrofuran **2g** in order to obtain a crystalline product (Scheme 3. 10). Thus, the benzyl ester was transformed into a *para*-bromophenyl ester through a first hydrolysis step, followed by esterification that led to product **4**, which was found to be a white solid. After recrystallization, the absolute configuration was determined by single crystal X-ray analysis, and therefore the absolute configuration of the other adducts **2a-2r** was stablished assuming an identical mechanistic pathway for all reactions.



Scheme 3. 10 Transformation of product **2g** for the determination of the absolute configuration by X-ray structure of dihydrofuran **4**

Next, we focused our attention on investigating the effect of the alkoxy substituent at the electron withdrawing group. For this reason, cyclopropanes with diverse substituents in the ester moiety were synthesized. Following the same procedure explained before, cyclopropanes **5a-e** were obtained in moderate yields and, in most of the cases, as diastereomeric mixtures, being the *cis* isomer the major one (Table 3. 9).

Table 3. 9 Synthesis of cyclopropanes with two electron-withdrawing groups: modifying the alcoxy substituent.[a]

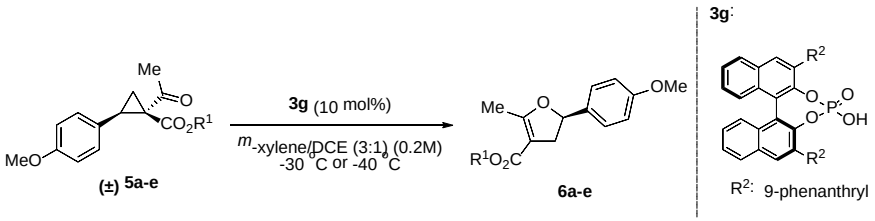


Entry	Cycloprop. 5	R	Yield 5 (%)[a]	d.r. 5
1	**5a**	Me	57	3:1
2	**5b**	Et	54	13:1
3	**5c**	*n*-Pr	52	16:1
4	**5d**	*i*-Pr	47	>20:1
5	**5e**	*t*-Bu	59	1.2:1

[a] Yields of isolated products after flash column chromatography purification for the overall two-step procedure.

We next evaluated the performance of these substrates **5a-e** in the catalytic enantioselective Cloke-Wilson rearrangement (Table 3. 10). As it can be observed in this Table, the reaction performed excellently in terms of yield and enantiocontrol when small methyl substituent was placed at the ester moiety (entries 1-2), obtaining slightly better e.e. at -40 ºC, but in a much longer reaction time. In order to evaluate the importance of the diastereomeric ratio of cyclopropanes in the reaction outcome, the transformation was carried out with a different diastereoisomeric mixture of substrate **5a**, yielding product **6a** with the same results in all the cases, hence concluding that the diastereomeric ratio of the starting material had no influence in the reaction pathway. Cyclopropane carboxylate esters with longer alkyl substituents in the alcoxy moiety, such as ethyl or *n*-propyl groups, also provided the desired dihydrofurans **6b-c** in high yields and enantioselectivities (entries 3-6). However, when a bulkier *iso*-propyl group was placed, it was necessary to carry out the reaction at -40 ºC in order to gain a high enantiocontrol during process, which required for a very long reaction time to achieve full conversion (entries 7-8). Furthermore, when the most sterically demanding *tert*-butyl ester was employed, the reaction did not take place (entry 9).

Table 3. 10 Study of the effect of the ester moiety in the reaction outcome.[a]

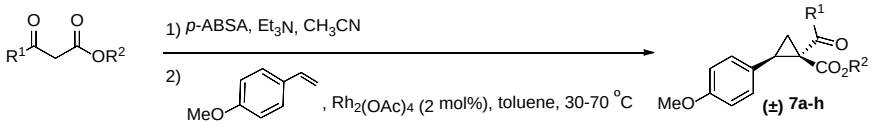


Entry	R^1	Prod. 6	T (ºC)	t (h)	Yield 6 (%)[b]	e.e. 6 (%)[c]
1	Me	**6a**	-30	48	93	87
2	Me	**6a**	-40	84	95	90
3	Et	**6b**	-30	48	91	84
4	Et	**6b**	-40	84	92	85
5	*n*-Pr	**6c**	-30	48	93	86
6	*n*-Pr	**6c**	-40	84	93	88
7	*i*-Pr	**6d**	-30	72	90	79
8	*i*-Pr	**6d**	-40	144	92	86
9	*t*-Bu	**6e**	-40	144	<5	-

[a] Reactions performed in a 0.05 mmol scale of **5a-e**, using 10 mol% of catalyst **3g** in *m*-xylene/DCE (3:1) (0.2M) at -30 or -40 ºC; most of the cyclopropanes are employed as mixture of diastereomers in different proportions (for more details see experimental section). [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

Our next objective was to study the influence of the substituent at the ketone moiety, and for this reason, following the same procedure explained before, cyclopropanes with different substituents in the ketone moiety were synthesized, obtaining **7a-h** in moderate to good yields as mixture of diastereoisomers (Table 3. 11).

Table 3. 11 Synthesis of cyclopropanes with two electron-withdrawing groups: varying the ketone substituent.[a]



Entry	Cycloprop. 7	R^1	R^2	Yield 7 (%)[b]	d.r. 7
1	**7a**	Et	Bn	44	5:1
2	**7b**	Et	Et	41	3.4:1
3	**7c**	*n*-Pr	Et	64	3:1
4	**7d**	*i*-Pr	Et	42	2.5:1
5	**7e**	*t*-Bu	Et	43	6:1
6	**7f**	Ph	Et	62	14:1
7	**7g**	4-ClC_6H_4	Et	58	>20:1
8	**7h**	4-$NO_2C_6H_4$	Et	71	6:1

[a] Yields of isolated products after flash column chromatography purification for the overall two-step procedure.

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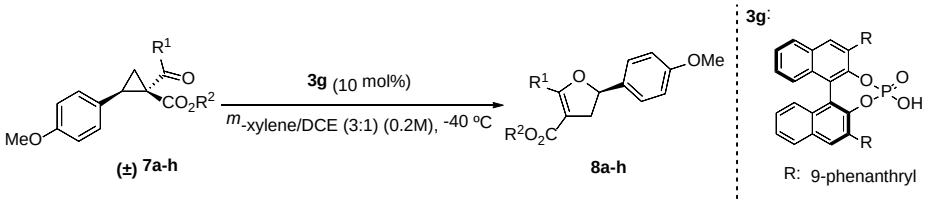
We next studied the influence of the modification of the substituents at the ketone subunit on the Cloke-Wilson rearrangement, performing in this case the reaction at -40ºC in order to obtain the highest possible e.e. value (Table 3. 12). When cyclopropyl ethyl ketone substrates **7a-b** were tested, dihydrofuran **8a** and **8b** were obtained with very good yield and enantiocontrol (entries 1-2). When propyl substituted ketone was placed, although the yield remained being excellent, enantiomeric excess slightly decreased (entry 3). Furthermore, when the bulkier *iso*-propyl substitutent was employed, both the yield and enantiocontrol were negatively affected (entry 4). Finally, no reactivity was observed when employing *tert*-butyl cyclopropyl ketone, very likely due to steric hindrance (entry 5). On the other hand, we also tested several aroyl-substituted cyclopropanes, observing that the simple benzoyl-substituted cyclopropane was inert to the ring-opening process (entry 6). Otherwise, when a more electron-withdrawing 4-chlorobenzoyl substituent was used, the reaction provided the product **8g** with moderate enantiocontrol but with rather low yield, because of the little electron-withdrawing character of the substituent (entry 7). Based on this result, 4-nitrobenzoyl derivative **7h** was examined under optimal reaction conditions in order to facilitate the ring opening reaction due to the higher polarization of the C-C bond of the

cyclopropane. As expected, dihydrofuran **8h** was obtained successfully with 91% yield and 84% enantiomeric excess (entry 8).

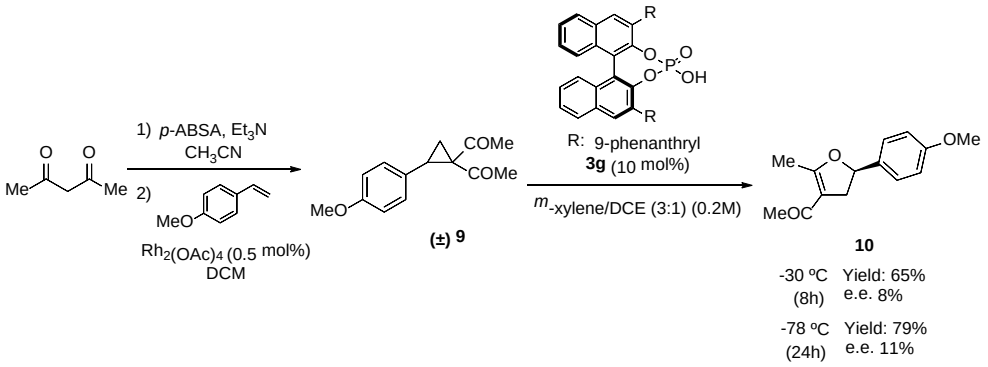
Table 3. 12 Study of the effect of the ketone moiety in the reaction outcome.[a]



Entry	R^1	R^2	Prod. 8	t (h)	Yield 8 (%)[b]	e.e. 8 (%)[c]
1	Et	Bn	**8a**	84	91	87
2	Et	Et	**8b**	84	91	88
3	*n*-Pr	Et	**8c**	84	90	76
4	*i*-Pr	Et	**8d**	144	51	66
5	*t*-Bu	Et	**8e**	144	<5	-
6	Ph	Et	**8f**	144	<5	-
7	4-ClC_6H_4	Et	**8g**	144	25	76
8	4-$NO_2C_6H_4$	Et	**8h**	15	91	84

[a] Reactions performed in a 0.05 mmol scale of **7a-h**, using 10 mol% of catalyst **3g** in *m*-xylene/DCE (3:1) (0.2M) at -40 ºC. [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

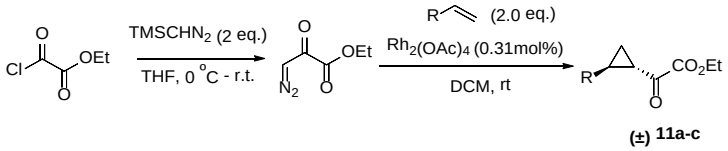
Finally, it was decided to study the possibility of using a more reactive 1,1-diacyl-substituted cyclopropane, which was prepared through the aforementioned procedure starting from commercially available acetylacetone. In this sense, when the reaction was carried out starting from cyclopropane **9** under the same reaction conditions, the desired 2,3-dihydrofuran **10** was successfully isolated in 65% yield in only 8h, although the product turned to be almost racemic (Scheme 3. 11). In view of the fast reaction observed this time, it was also possible to lower the temperature in order to try to increase the stereocontrol of the process. However, when the reaction was carried out a -78ºC for 24 hours, although the final product was afforded in a higher 79% yield, no significant improvement was observed in the enantiomeric excess.



Scheme 3. 11 Cloke-Wilson rearrangement of 1,1-diacyl substituted cyclopropane

In order to continue evaluating the scope of the reaction, the challenging possibility of using less reactive donor-acceptor cyclopropanes with a single electron-withdrawing substituent was investigated. In this sense, it was first decided to evaluate a cyclopropane with an α-ketoester as a single electron-withdrawing group. In a similar way as before, these cyclopropanes were also synthesized through rhodium-catalyzed cyclopropanation of styrenes with ethyl 3-diazo-2-oxopropanoate, which was prepared by treatment of ethyl 2-chloro-2-oxoacetate with (trimethylsilyl)diazomethane (Table 3. 13).

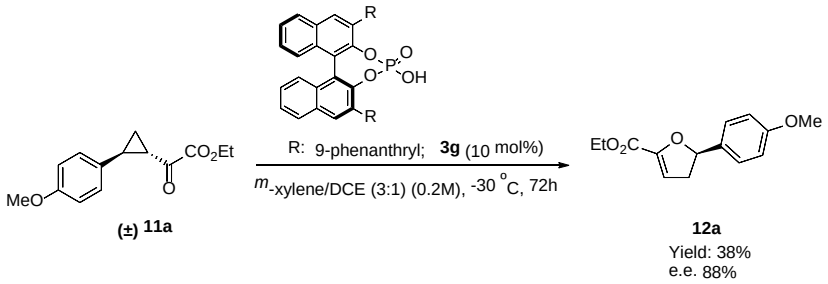
Table 3. 13 Synthesis of glyoxyl-substituted cyclopropanes.[a]



Entry	Cycloprop. 11	R	Yield 11 (%)[a]
1	**11a**	4-$MeOC_6H_4$	27
2	**11b**	2,3-dihydrobenzofuran-5-yl	33
3	**11c**	2-thienyl	14

[a] Yields of isolated products after flash column chromatography purification.

However, when cyclopropane **11a** was subjected to the optimal conditions for the catalytic enantioselective Cloke-Wilson rearrangement, the corresponding dihydrofuran **12a** was isolated with good enantioselectivity but in a moderate yield due to low conversion (Scheme 3. 12). For this reason, we decided to reevaluate the reaction conditions in order to accelerate the ring opening and reach the final product with the highest possible yield and enantioselectivity.



(±) 11a

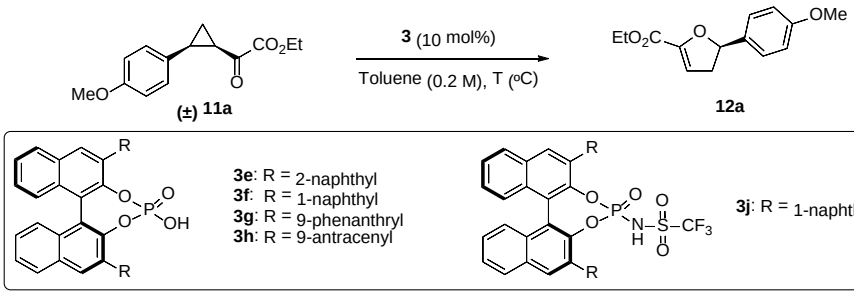
12a
Yield: 38%
e.e. 88%

Scheme 3. 12 Asymmetric Cloke-Wilson rearrangement of donor-acceptor cyclopropane **11a**

Based on the results obtained in our initial model reaction and taking into account that 3,3'-bis(aryl) substituted BINOL-based phosphoric acids turned to be the most successful ones, initially, some catalysts **3** bearing an aryl group at the BINOL moiety were tested in toluene at room temperature, observing that the reaction ended in 24 hours when working at this temperature (Table 3. 14). Catalyst **3e** with 1-naphthyl substituent at the 3,3'-position of the BINOL scaffold yielded the desired product successfully but in low enantiomeric excess (entry 1), while the 2-naphthyl containing derivative **3f** provided dihydrofuran **12a** with a promising 54% of enantiomeric excess (entry 2). Moreover, the reaction also proceeded well placing phenanthryl or anthracenyl groups at the BINOL moiety (**3g**-**3h**), but obtaining in both cases the dihydrofuran with both lower yield and enantioselectivity (entries 3-4). The more acidic 1-naphthyl BINOL-derived *N*-triflyl phosphoramide **3j** was also tested, which provided the desired product much faster (12h) and in high yield, although as a racemic mixture (entry 5). In order to check that the selected catalyst **3f** was able to control the selectivity of the process at lower temperatures, the reaction was carried out at -30ºC obtaining the target product with 90% of enantiomeric excess, despite with low yield afterα a considerably long reaction time (Entry 6). Considering this remarkable improvement in the

enantiocontrol of the process by lowering the temperature, and taking into account the rather faster transformation employing the more acidic *N*-triflyl phosphoramide derivative **3j**, the reaction was performed at lower temperatures under **3j** catalysis, observing a lower conversion as the temperature was decreasing and obtaining always the desired product with an almost no enantiocontrol (entries 7-8).

Table 3. 14 Chiral BINOL-derived Brønsted acid catalyst survey for cyclopropane **11a**.[a]



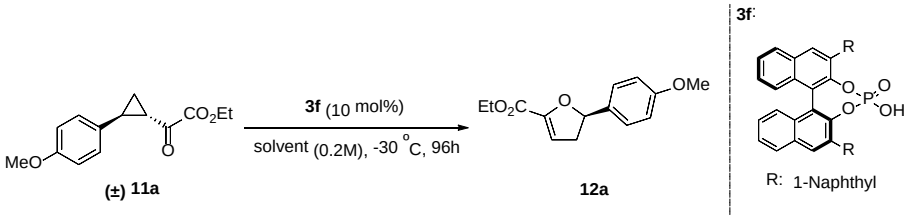
Entry	Catalyst	T (ºC)	t (h)	Yield 12a (%)[b]	e.e. 12a (%)[c]
1	**3e**	25	24	81	14
2	**3f**	25	24	79	54
3	**3g**	25	24	77	40
4	**3h**	25	24	63	40
5	**3j**	25	15	83	0
6	**3f**	-30	96	16	90
7	**3j**	-30	48	81	2
8	**3j**	-78	96	23	8

[a] Reactions performed in a 0.1 mmol scale of **11a**, using 10 mol% of catalyst in toluene (0.2M) at the indicated T (ºC). [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

At this point, in view that the catalyst **3f** had afforded the 2,3-dihydrofuran with good enantiocontrol when working at -30 ºC (see entry 6 of Table 3. 14), we turned our attention to the evaluation of different solvents at this temperature in order to improve the yield of the process maintaining the enantioselectivity (Table 3. 15). Firstly, when the non-polar *m*-xylene was used, a slight improvement in both the yield and the enantiocontrol of the process was observed, although the conversion of the cyclopropane **11a** to product **12a** remained being low, isolating only few amount of final product (entry 2). This might also be due to the low solubility of the substrate in non-polar solvents at low temperature, so it was decided to

test more polar chlorinated solvents, such as dichloromethane and 1,2-dichloroethane. As expected, while the use of CH_2Cl_2 afforded the desired product **12a** with excellent enantioselectivity, but with moderate conversion, the conversion of the reaction turned to be complete when using 1,2-dichloroethane, isolating the product with excellent yield but slightly compromising the enantiomeric excess (entries 3-4). After evaluation of these results, binary mixtures between these two solvents were tested (entries 5-6), obtaining the desired product with best results (entry 6).

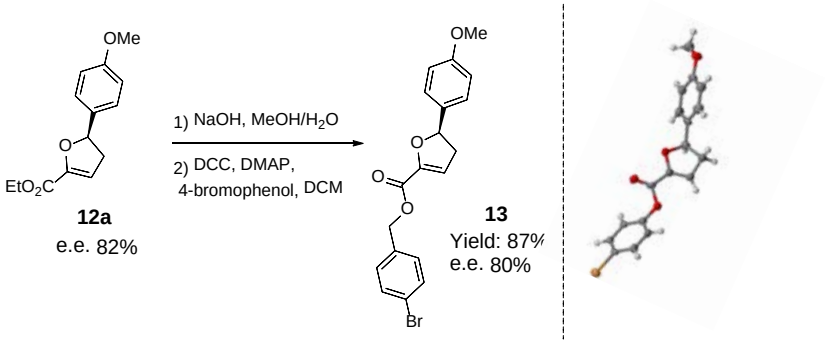
Table 3. 15 Evaluation of different solvents.[a]



Entry	Solvent	Yield 12a (%)[b]	e.e. 12a (%)[c]
1	Toluene	16	90
2	*m*-xylene	26	92
3	CH_2Cl_2	60	94
4	$Cl(CH_2)_2Cl$	90	76
5[d]	*m*-xylene/ $Cl(CH_2)_2Cl$	83	78
6[d]	CH_2Cl_2/ $Cl(CH_2)_2Cl$	75	82

[a] Reactions performed in a 0.1 mmol scale of **11a**, using 10 mol% of catalyst in indicated solvent (0.2M) at -30 °C. [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section). [d] 1:1 mixture of solvents.

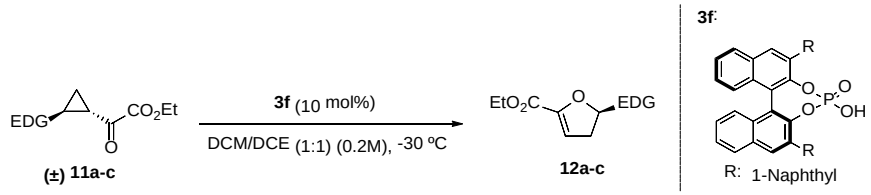
In this compound **12a**, as it happened with dihydrofuran **2g**, further transformations were necessary in order to obtain a crystalline sample to determine the absolute configuration (Scheme 3. 13). In the same way as before, the ethyl ester moiety was converted into a bromophenyl ester through hydrolysis followed by esterification. After recrystallization from product **13**, which was isolated as a white solid, the absolute configuration was determined by single crystal X-ray analysis, observing a (*R*) stereostructure.

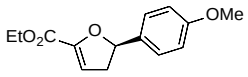


Scheme 3. 13 Transformation of product **12a** for the determination of the absolute configuration by X-ray structure of dihydrofuran **13**

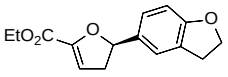
With the optimal conditions to carry out the Cloke-Wilson rearrangement in hands, the scope of the reaction was studied with respect to potential variations on the structure of this type of donor-acceptor cyclopropanes, regarding the electron-donating group. Substrate **11b**, which posses a dihydrobenzofuran scaffold as donor substituent turned to give a much faster reaction, providing the final product **12b** in only 15 hours with excellent 94% yield and 82% e.e. Moreover, lowering the reaction temperature to -60ºC could improve the result of the process, affording product **12b** with 92% yield and 88% e.e. in 24 hours. In addition, substrate **11c** with an heteroaromatic donor substituent was also found to perform excellently the Cloke-Wilson rearrangement, yielding 2,3-dihydrofuran **12c** with good yield and enantiocontrol (Table 3. 16).

Table 3. 16 Different donor groups in glyoxyl-substituted cyclopropanes.[a]

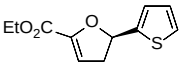




12a
t: 96h
Yield 75%
e.e. 82%



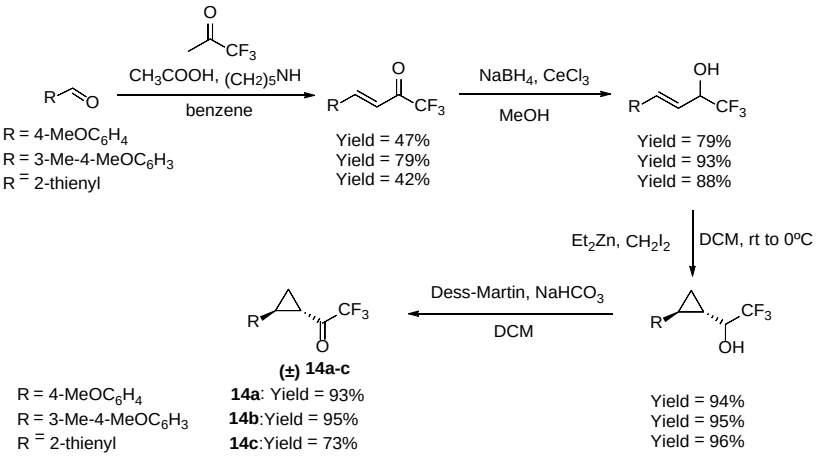
12b
t: 15h (-30 °C)
Yield: 94%
e.e. 82%
t: 24h (-60 °C)
Yield: 92%
e.e. 88%



12c
t: 96h
Yield: 92%
e.e. 82%

[a] Reactions performed in a 0.05 mmol scale of **11a-c**, using 10 mol% of catalyst **3f** in DCM/DCE (1:1) (0.2M); yields of isolated products after flash column chromatography purification; enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more details see experimental section).

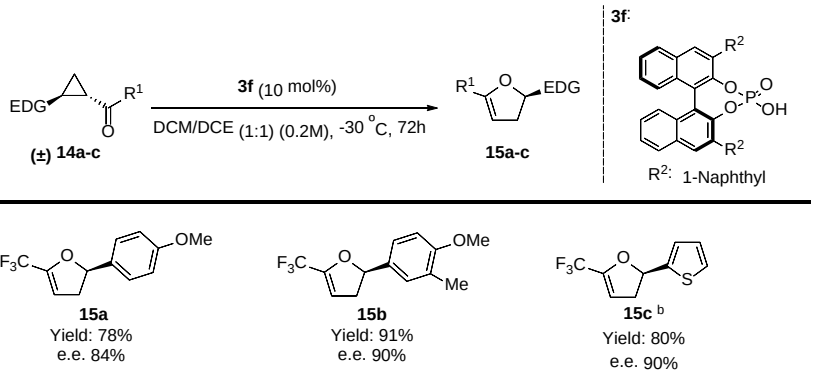
Finally, we turned to test the most challenging trifluoroacetyl-substituted cyclopropanes. The preparation of these substrates was carried out in a four-step synthesis, in which the key step was based on the zinc-catalyzed Simmons-Smith cyclopropanation of the corresponding allylic alcohol (Scheme 3. 14). The synthesis started with a Claisen-Smith condensation between 1,1,1-trifluoroacetone and the corresponding aldehyde to yield the α,β-unsaturated ketones. The Luche reduction afforded the required allylic alcohols in good yields, which after Simmons-Smith cyclopropanation provided the cyclopropyltrifluoroethanols in excellent yields. A final Dess-Martin oxidation furnished the desired trifluoroacetylcyclopropanes in high yields.



Scheme 3. 14 Synthesis of trifluoroacetylcyclopropanes

Once these substrates had been prepared, they were subjected to optimal conditions for catalytic enantioselective Cloke-Wilson rearrangement. As it can be seen in Table 3. 17, products **15a-c** were successfully isolated with high yield and enantiocontrol in the three cases.

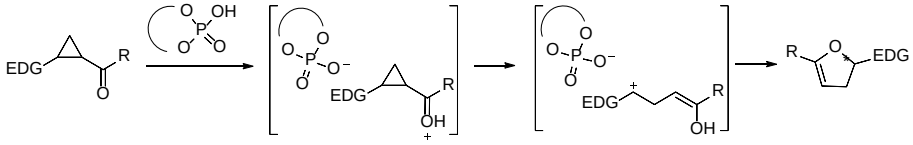
Table 3. 17 Different donor groups in trifluoroacetyl substituted cyclopropanes.[a]



[a] Reactions performed in a 0.05 mmol scale of **14a-c**, using 10 mol% of catalyst **3f** in DCM/DCE (1:1) (0.2M) at -30 ºC; yields of isolated products after flash column chromatography purification; enantiomeric excesess determined by HPLC analysis on a chiral stationary phase (for more details see experimental section). [b] Reaction carried out in DCE.

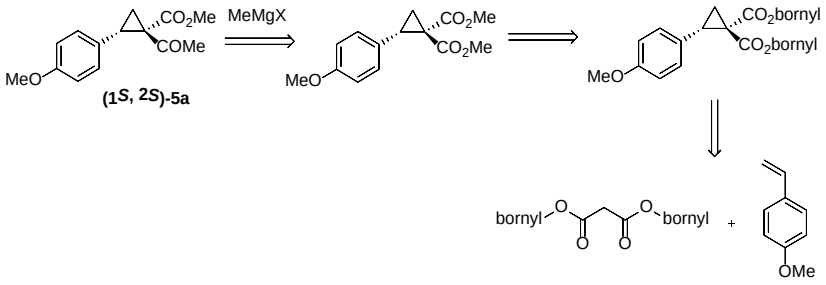
2.4. Mechanistic insights

Once studied the scope and limitations of the methodology, we tried to provide an overall understanding of the reaction from a mechanistic point of view. Our mechanistic proposal is based on the activation of the donor-acceptor cyclopropane by protonation of the carbonyl system with the Brønsted acid catalyst, which would increase the polarity of the C-C bond of the donor-acceptor cyclopropane favouring the ring-opening process. As it has been demonstrated, highly enantioenriched substituted 2,3-dihydrofurans have been obtained with good yields starting from racemic mixture of donor-acceptor cyclopropanes, which made us to suppose that such transformation should occur through a DYKAT process (Scheme 3. 15).



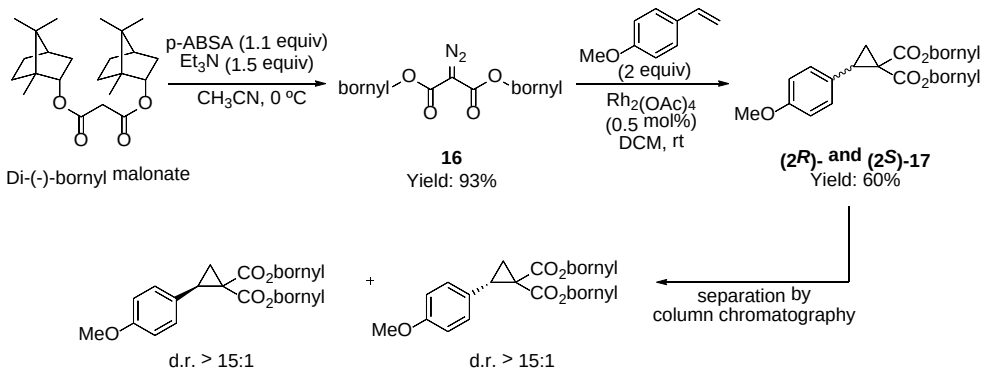
Scheme 3. 15 Mechanistic proposal for the Cloke-Wilson rearrangement involving DYKAT

In order to verify this proposal, we decided to test the performance of an enantioenriched cyclopropane such as **(1*S*,2*S*)-5a** in the Cloke-Wilson rearrangement, so our next goal was focused on synthesizing the enantioenrichedsubstrate. The synthesis was planed through the resolution of the 1,1-cyclopropyldiester using borneol as chiral auxiliary followed by the selective addition of MeMgX to one of the carboxylate moieties to obtain the desired enantiomerically enriched β-ketoester-substituted cyclopropane **5a** (Scheme 3. 16).



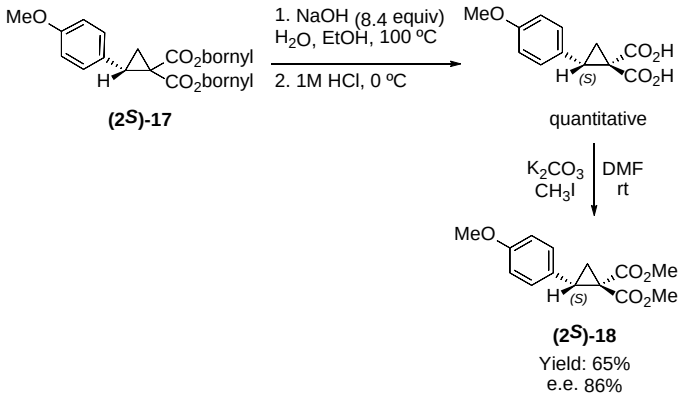
Scheme 3. 16 Proposed synthetic route for the preparation of **(1*S*,2*S*)-5a**

We started with the preparation of the corresponding diazocompound employing di-(-)-bornyl malonate as substrate *via* the addition of 4-acetamidobenzenesulfonyl azide, and after 12 hours the corresponding diazocompound **16** was isolated as a yellow solid in 93% yield. As usual, rhodium(II) acetate dimer was employed as catalyst for the cyclopropanation process with and 4-methoxystyrene, in which a mixture of diastereoisomers **(2*R*)-** and **(2*S*)-17** was formed (Scheme 3. 17). Both cyclopropane diastereomers have essentially the same R_f, but partial separation could be achieved through iterative purifications by column chromatography (PE/Et_2O 20:1), allowing the progressive enrichment of the diastereomixtures up to dr > 15:1 for both diastereomers separately.



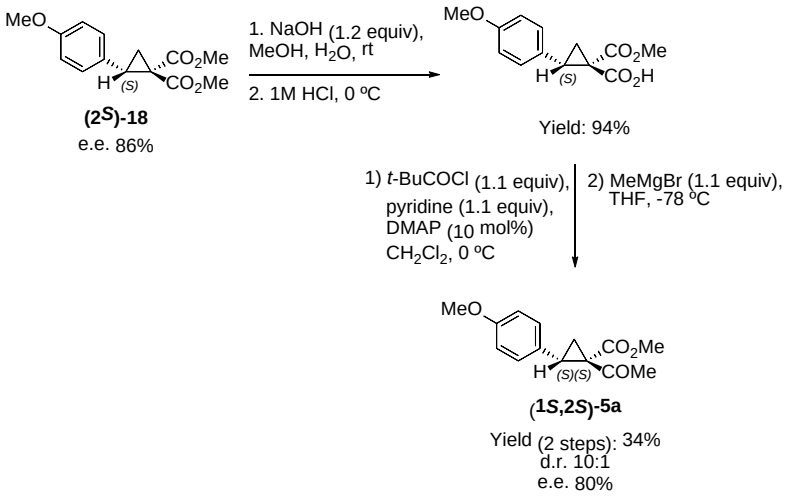
Scheme 3. 17 Preparation of cyclopropanes **(2*R*)-** and **(2*S*)-17**

Once the diastereoisomers of the cyclopropane **17** were separated, hydrolysis of both bornylesters of cyclopropane **(*2S*)-17** was accomplished under basic conditions and next esterification process was carried out with iodomethane after treating the diacid with K_2CO_3, isolating the pure dimethyl ester in 65% yield (Scheme 3. 18). At this point, the enantiopurity of the cyclopropane was measured by HPLC, observing that the enantioenriched cyclopropane **(2S)-18** had been satisfactorily synthesized with 86% of enantiomeric excess.



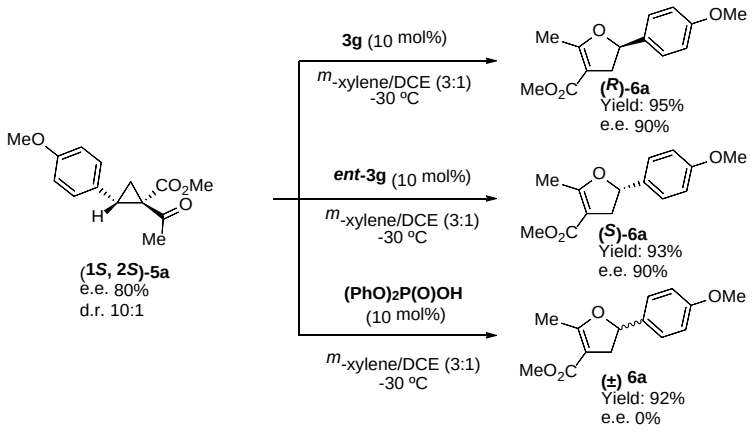
Scheme 3. 18 Preparation of **(2*S*)-18** through hydrolysis and esterification of **(2*S*)-17**

Finally, we focused our efforts on the selective addition of MeMgX to one of the carboxylate moieties (Scheme 3. 19). For this purpose, diastereoselective hydrolysis of the *trans* ester moiety took place using 1.2 equivalents of NaOH at room temperature for two hours, obtaining the desired monoester in 94% yield as a single diastereoisomer. The obtained monoester was next transformed into the corresponding mixed anhydride by treatment with pivaloyl chloride at 0 ºC, and after the subsequent addition of MeMgBr, the enantioenriched cyclopropane **(1*S*,2*S*)-5a** was isolated in 34% yield (two steps) with 10:1 d.r. and 80% enantiomeric excess.



Scheme 3. 19 Synthesis of **(1*S*,2*S*)-5a** by transformation of the *trans* ester into an acetyl group

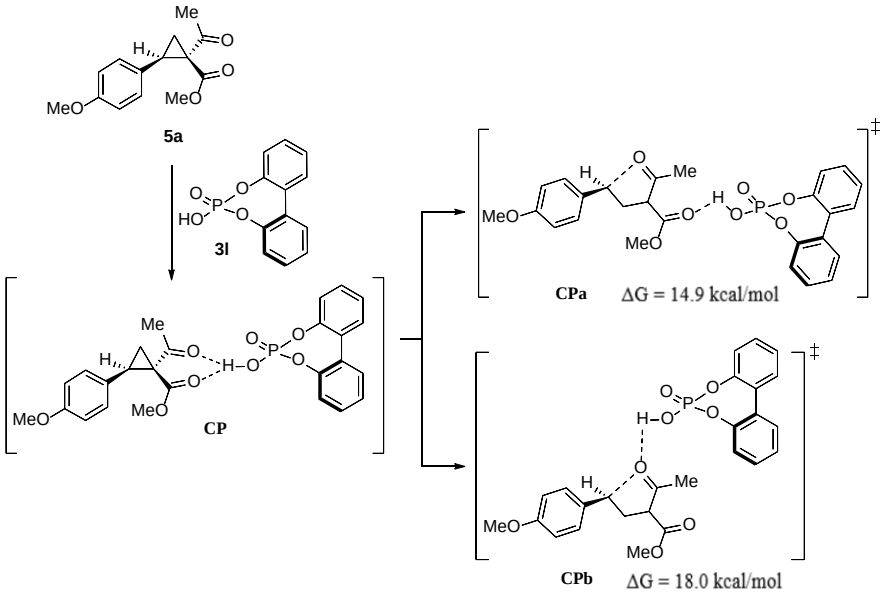
Once the desired enantioenriched cyclopropane was prepared, it was subjected to the Cloke-Wilson reaction employing catalyst **3g**. The reaction took place in a similar way as when the racemic starting cyclopropane **5a** was used, obtaining product (*R*)-**6a** with comparable yield and enantiomeric excess. Remarkably, when catalyst ***ent*-3g** was applied, adduct (*S*)-**6a** was isolated with the same yield and opposite configuration. Moreover, the reaction catalyzed by the achiral diphenylphosphoric acid provided dihydrofuran **6a** as a racemic mixture as it was expected (Scheme 3. 20).



Scheme 3. 20 Experiments employing enantioenriched cyclopropane **(1S, 2S)-5a** as starting material

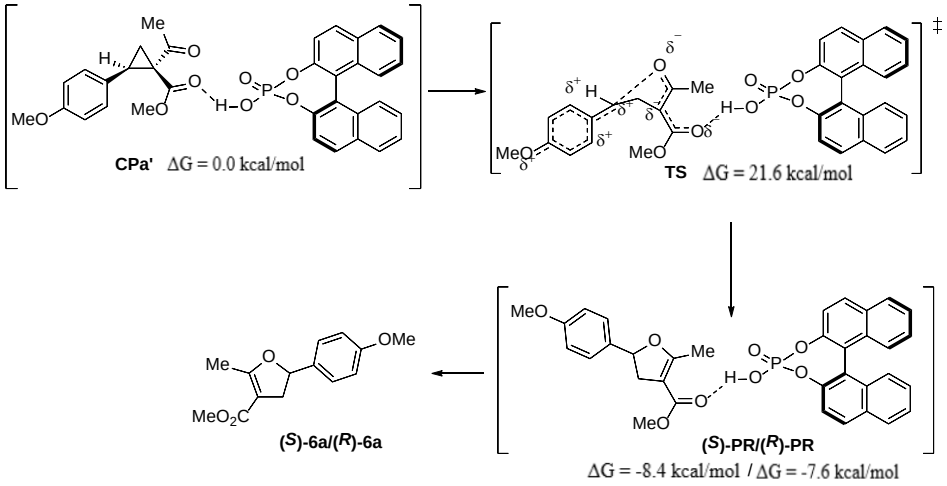
These results indicated that the studied reaction is not an enantioespecific process, as the chirality of the substrate is not transferred to the final product and it is the catalyst the one that controls the stereochemistry of the process. In addition, as it has been commented earlier, the diastereomeric ratio of the starting material has no influence in the outcome of the reaction. With these results in hand, it can be concluded that the reaction proceeded through the formation of a common achiral intermediate, giving place to a dynamic kinetic asymmetric transformation (DYKAT).

In addition, in order to gain further insights on the mechanistic pathway and with the aim of understanding the origin of the stereocontrol, DFT calculations were carried out in collaboration with the research group of Profesor Merino in the University of Zaragoza. For the initial evaluation of both, the mechanism and the species involved in the reaction, preliminary studies were performed employing cyclopropane **5a** as model substrate and the simplest biphenyl phosphoric acid **3l**. As proposed, the reaction is initiated through the coordination of the catalyst to cyclopropane **5a** giving place to the formation of complex CP (Scheme 3. 21). At this point, two possible scenarios should be considered in which the catalyst is coordinated either at the ester carbonyl group or the acyl moiety. Calculations showed a clear preference (3 kcal/mol) for the interaction of the acid catalyst with the ester carbonyl group.



Scheme 3. 21 Coordination of the acid catalyst to the cyclopropane

In order to continue with the elucidation of the reaction mechanism, the simplest BINOL-derived phosphoric acid was used as catalyst assuming coordination of the catalyst to the ester moiety **Cpa'** (Scheme 3. 22). At this point, any attempt to locate a carbocationic intermediate failed and only the transition state **TS** was located, that after cyclization and catalyst release would afford one of the two possible final products, **(*S*)-6a** or **(*R*)-6a**.



Scheme 3. 22 Mechanism for the Cloke-Wilson rearrangement of **5a**

Despite the concerted mechanism depicted above, the geometry of transition structure **TS** revealed the planarity of the cyclopropane carbon attacked by the ketone oxygen, which is compatible with the formation of a carbocation and enolization at β-ketoester moiety, although it has not been possible to locate such an intermediate. Because of this, it was decided to develop a deep study of the reaction employing computational different techniques. In particular, IRC analysis revealed that **TS** connects **5a** with the catalyst along a concerted but very asynchronous pathway. Indeed, the IRC showed a shoulder, suggesting the formation, of a hidden intermediate during the first step of the reaction, in which both initial cyclopropane carbons are planar, a situation often found when carbocations that are not specially stable are involved. As it has been previously demonstrated in the study of the mechanism of the thionation of alcohols with Lawesson's reagent,[6] always the complete formation of carbocations as stable intermediates is not necessary when reactions occur through carbocationic mechanistic pathway. However, the formation of such planar carbocation can be supported measuring the planarity of the four atoms involved.

[6] Chiacchio, M. A.; Legnani, L.; Caramella, P.; Tejero, T.; Merino, P. *Eur. J. Org. Chem.* **2017**, 1952.

A topological analysis of electron localization function (ELF) was carried out to verify the sequence of events during the reaction. The detailed analysis of the evolution of the electron population along the reaction coordinate revealed the existence of a gap between the cyclopropane ring-opening and dihydrofuran formation, which is compatible with the formation of a carbocationic species. The illustration of the ELF analysis (Figure 3. 1) shows that while the C9-C10 bond is broken at P72 of the IRC, the formation of C9-O13 bond starts at P147, indicating the early cyclopropane ring-opening and the late C-O bond formation, providing enough time for the virtual existence of a carbocation. When C9-C10 is broken population of C10-C15 increases indicating a partial double bond character, in the same way that O13 losses electron population with the formation of C9-O13 bond, which is in agreement with a nucleophilic attack.

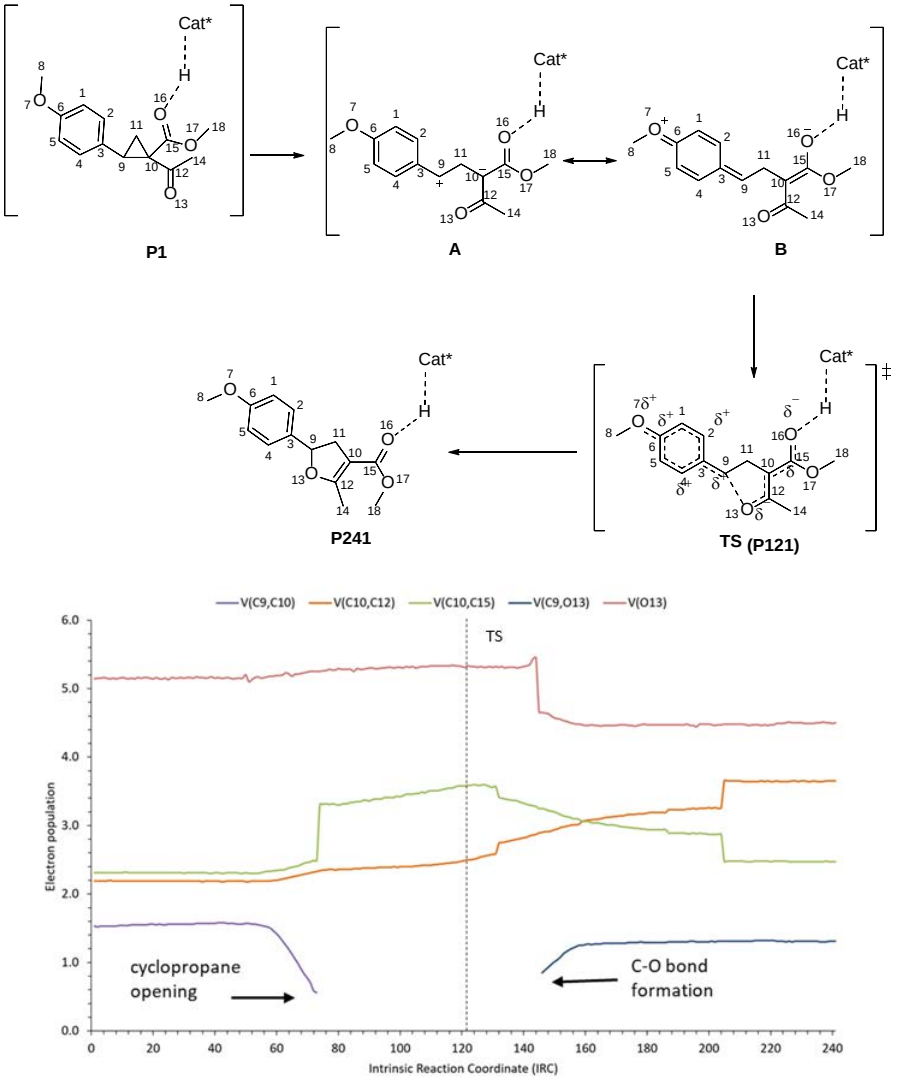


Figure 3. 1 Graphical representation of ELF analysis for the dihydrofuran formation

The formation of the carbocationic species could be supported by the evolution of electron population for the disynaptic basins corresponding to the *para*-methoxy phenyl substituent

(Figure 3. 2). In this sense, a slight increasing of electron population for C1-C2, C4-C5, C3-C9 and C6-O7 can be observed, a slight decreasing of electron population is perceived at the same time for C2-C3, C3-C4, C5-C6 and C1-C6. These observations are consistent with the resonant structure **B** for the proposed ring-opened carbocation/enol intermediate.

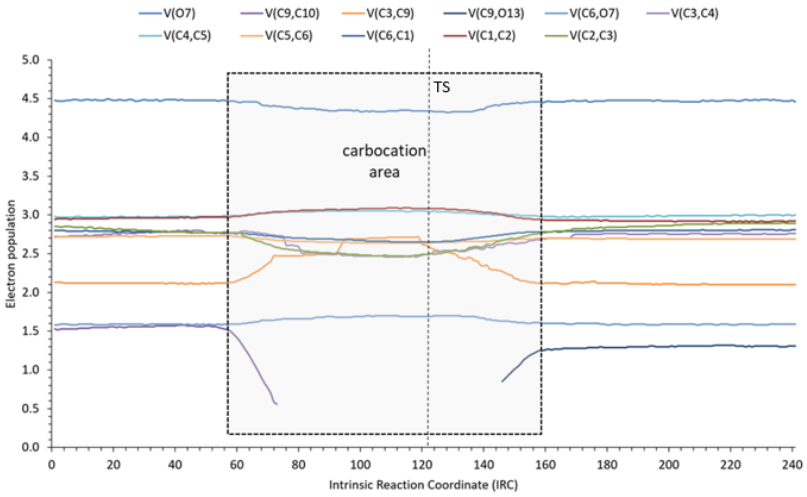


Figure 3. 2 Graphical representation of ELF analysis for the aromatic ring

To evaluate the stereochemistry of the reaction is necessary to consider the real catalyst **3g** and not the previous simplified models, since several orientations might not be possible caused by steric hindrance. Due to the presence of a chiral catalyst, two diastereotopic faces would be susceptible to be attacked with two different orientations depending on the angle attack, thus, four interconnected transition structures were found (Figure 3. 3). These four transition states can be directly achieved from the common hidden intermediate formed in the first stage of the reaction, so a dynamic kinetic asymmetric transformation of type II (DYKAT II) can be assumed, in which the stereodefining step would be the ring-closure step. The lowest-energy transition-state corresponded to **(*R*)-TS2**, that leads to the *R*-configured isomer of the final product, which is in concordance with experimental results. Moreover, favorable London interactions where observed in **(*R*)-TS2** between the phenanthryl moiety and the aromatic ring, justifying its higher stability, which are not present in the transition

state leading to the *S*-configured enantiomer. These London interactions are π-stacking interactions that become cation-π interactions during the carbocation phase, which explained why aromatic rings, such as phenanthryl groups at 3,3' position of the catalyst, provided the best results.

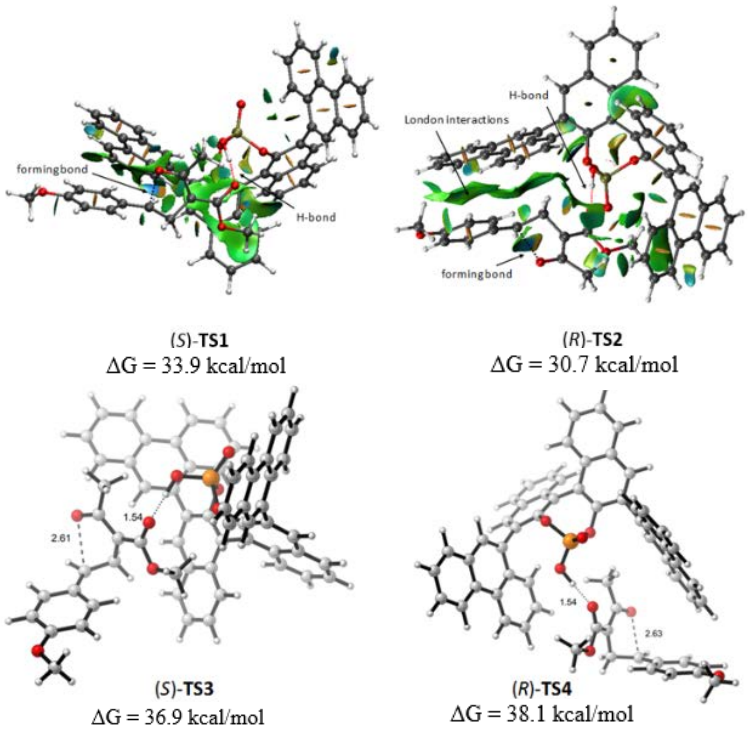


Figure 3. 3 Transition-state structures for the reaction

All these computational studies provided a useful explanation and further support the experimental evidences obtained during the study of the reaction with different substrates.

3. CONCLUSIONS

Considering the results presented through this chapter, the following conclusions can be outlined:

- Chiral Brønsted acid catalysis is an efficient methodology for the activation of acyl-substituted donor-acceptor cyclopropanes, obtaining highly enantioenriched 2,3-dihydrofurans through Cloke-Wilson rearrangement.

- Chiral 3,3'-(9-phenanthryl) substituted BINOL-derived phosphoric acid **3g** is the most appropriate catalyst to carry out the reaction employing racemic acyl-substituted cyclopropanes with two electron-withdrawing groups in germinal position, obtaining up to 95% yield and 94% enantiomeric excess. On the other hand, chiral 3,3'-(9-naphthyl) substituted BINOL-derived phosphoric acid **3f** was proved to be the most suitable catalyst for the construction of highly enantioenriched dihydrofurans when cyclopropanes contained a single acyl substituent as the electron-withdrawing group were employed as starting materials, providing the desired products with up to 94% yield and 90% enantiomeric excess.

- The method has demonstrated to have a wide scope regarding both the donor and the acceptor substituents of the cyclopropane.

- Experimental and computational mechanistic studies demonstrated a DYKAT process, suggesting that the reaction proceeded through the formation of a transitory carbocationic intermediate enabling the use of racemic substrates. The substrate would be activated through hydrogen-bonding between the catalyst and the carbonyl moiety of the donor-acceptor cyclopropane, which would favor the ring-opening process. Moreover, it has been demonstrated that π-stacking interactions between the catalyst and the aromatic ring of the cyclopropane enabled the formation of a single enantiomer.

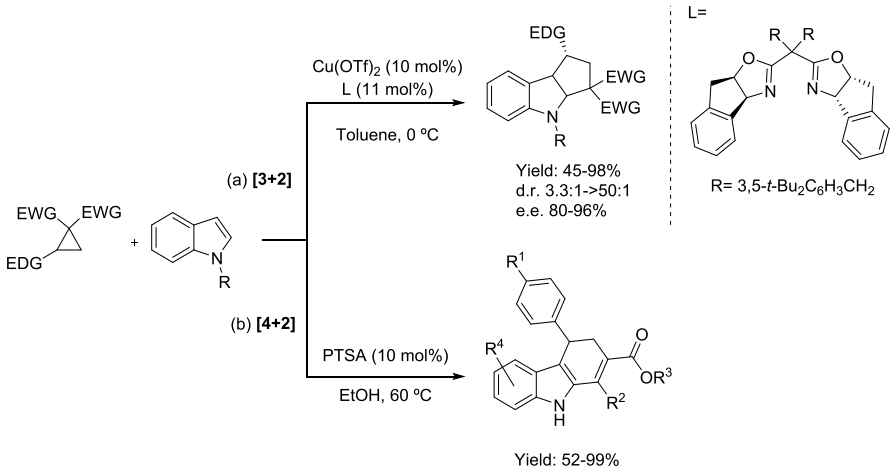
Chapter 4

4

Acid-catalyzed Cyclocondensation of Donor-Acceptor Cyclopropanes with 3-substituted Indoles

1. INTRODUCTION

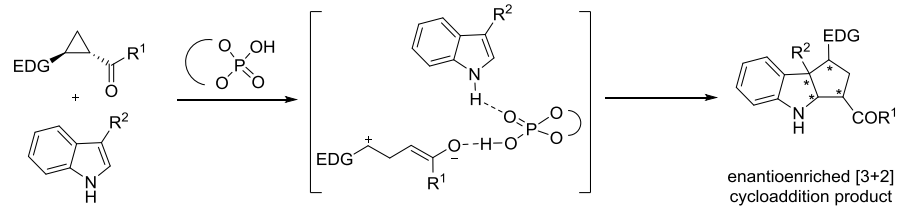
As it has been previously disclosed, the intrinsic bifunctional nature of donor-acceptor cyclopropanes made them suitable starting materials as source of dipolar reagents in a variety of cycloaddition reactions involving the formation of multiple bonds. In this sense, it has been demonstrated that the indole scaffold is a suitable reactant as electron-rich dipholarophile for [3+2] cycloaddition reactions with donor-acceptor cyclopropanes, typically under Lewis acid catalysis. It has to be mentioned, that taking into account the literature precedents, regioselectivity issues are commonly observed in reactions where indole derivatives take part due to the high nucleophilicity of its C3, C2 and N1 positions. Moreover, although donor-acceptor cyclopropanes usually act as 1,3-zwitterionic species, these could also behave as synthetic equivalents of 1,4-synthons, allowing them this way to take part in formal [3+2] or [4+2] cycloaddition processes with indoles (Scheme 4. 1).[1]



Scheme 4. 1 [3+2] *vs* [4+2] cycloaddition of donor-acceptor cyclopropanes with indoles

[1] (a) Xiong, H.; Xu, H.; Liao, S.; Xie, Z.; Tang, Y. *J. Am. Chem. Soc.* **2013**, *135*, 7851. (b) Liu, C.; Zhou, L.; Huang, W.; Wang, M.; Gu, Y. *Tetrahedron* **2016**, *72*, 563.

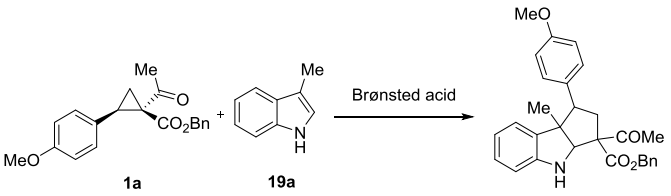
Taking these precedents into account, we focused our attention on performing a formal [3+2] cycloaddition between donor-acceptor cyclopropanes and 3-substituted indole derivatives in a regio-, diastereo- and enantioselective manner under Brønsted acid catalysis. In this sense, we envisioned that *in situ* generated dipoles would undergo cycloaddition process with C3 and C2 positions of indole derivatives affording tricyclic products. Moreover, the use of BINOL-derived chiral phosphoric acids would enable the formation of enantioenriched products, acting as bifunctional catalysts and activating the cyclopropane and the indole moiety at the same time (Scheme 4. 2).



Scheme 4. 2 Objective of this work

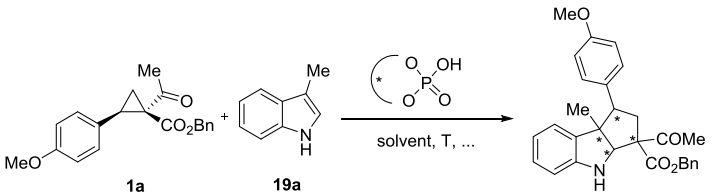
To accomplish this objective, the subsequent work plan was followed:

1. *Proof of concept:* In order to evaluate the feasibility of the proposed reaction, the reactivity of cyclopropane **1a** towards 3-methylindole under Brønsted acid catalysis will be evaluated with the aim to promote the formation of a [3+2] cycloaddition product. The reaction will provide a cycloadduct with four contiguous stereocenters, being quaternary one of them (Scheme 4. 3).



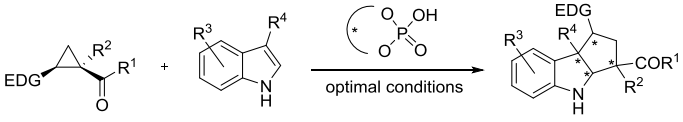
Scheme 4. 3 Proof of concept

2. *Optimization of the reaction conditions:* Employing the aforementioned model reaction system, the catalyst that provides the best reaction outcome will be determined by examining a diversity of chiral BINOL-derived Brønsted acids. Additionally, with the aim of isolating the desired product with the optimal yield and selectivity, other parameters, such as solvent and temperature, will also be tested (Scheme 4. 4).



Scheme 4. 4 Optimization of the reaction conditions

3. *Scope of the reaction:* With the optimal reaction conditions in hand, the scope of the reaction will be studied, using differently substituted cyclopropanes and indole derivatives. In this context, regarding the cyclopropane, different donor and acceptor substituents will be placed at the three-membered ring. On the other hand, substituents of different nature will be located at C3 as well as at different positions of the aromatic ring of the indole scaffold (Scheme 4. 5).



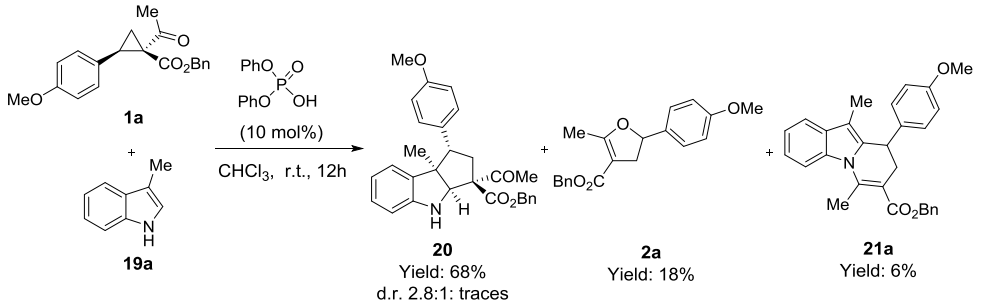
Scheme 4. 5 Scope of the reaction

2. RESULTS AND DISCUSSION

Once having clarified the objective and work plan of this work, we will continue with the discussion of the most relevant results obtained in this project.

2.1. Proof of concept

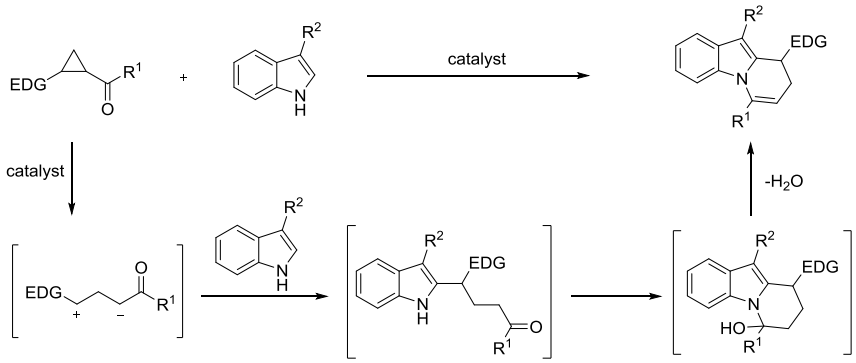
As it has been advanced in the initial objectives, it was decided to study the capability of donor-acceptor cyclopropanes to participate in a formal [3+2] cycloaddition reaction with 3-substituted indoles. In this sense, cyclopropane **1a**, which was already prepared and used as model substrate for the intramolecular Cloke-Wilson rearrangement, was reacted with commercially available 3-methylindole **19a** at room temperature in chloroform under catalytic amounts of diphenyl phosphoric acid. In this preliminary experiment, the starting material was consumed after an overnight reaction, observing the formation of a mixture of products. Despite the major product corresponded to the [3+2] cycloaddition product of the indole with the cyclopropane (**20** in 68% yield), formation of dihydrofuran derivative **2a** was also observed as a result of the competitive intramolecular Cloke-Wilson process. More interestingly, a new product was also isolated in 6% yield, which was identified as dihydropyridoindole **21a** (Scheme 4. 6).



Scheme 4. 6 Intermolecular reaction between 3-methylindole **19a** and cyclopropane **1a** employing achiral Brønsted acid

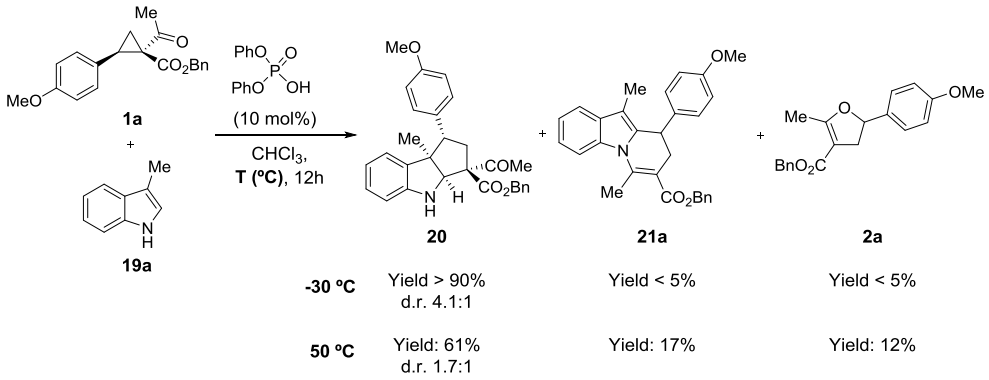
This dihydropyridoindole derivative was presumably formed through a first C2-alkylation of the indole, followed by the *N* nucleophilic addition to the ketone moiety and a subsequent dehydration process in a cyclocondensation between cyclopropane and the

indole, the latter involving the C2 and *N* positions in the reaction (Scheme 4. 7). It is noteworthy that there is no any precedent in the literature of the formation of dihydropyridoindoles through a double nucleophilic addition of indoles to donor-acceptor cyclopropanes through this regioselectivity pattern.



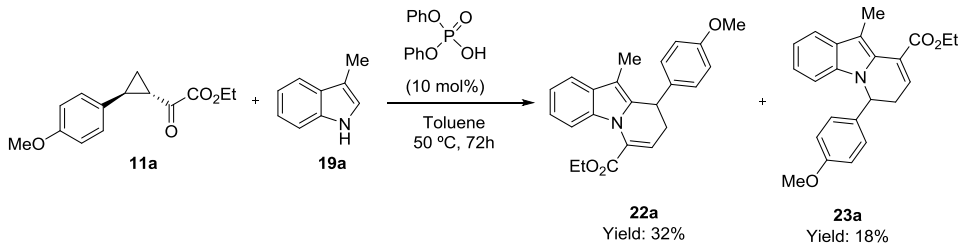
Scheme 4. 7 Unprecedented observed reactivity

Encouraged with this new reactivity pattern, we changed our objective to the study and optimization of such transformation. In order to obtain **21a** as major product, different temperatures were employed to carry out the reaction, observing that while [3+2] cycloaddition product was kinetically favored at -30 ºC, the yield of product **21a** slightly increased when working at higher temperatures (Scheme 4. 8).



Scheme 4. 8 Intermolecular reaction between 3-methylindole and cyclopropane **1a** at different temperatures

At this point, a glyoxyl-substituted cyclopropane, such as α-ketoester substituted cyclopropane **11a**, was also surveyed as starting material of the reaction, in combination with 3-methylindole. As higher temperatures seemed to be favorable for such transformations, the reaction between cyclopropane **11a** and indole **19a** was carried out in toluene at 50 ºC employing the same achiral phosphoric acid as catalyst (Scheme 4. 9). Fortunately, under this reaction conditions, the formation of [3+2] cycloaddition product was not observed and in addition, the desired compound **22a** was isolated in 32% yield, together with the regioisomer **23a**, which came from a first nucleophilic *N*-addition of the indole to the cyclopropane followed by aldol condensation at C2. Although dihydropyridoindole **22a** was isolated as major product, the yield remained being quite low.



Scheme 4. 9 Reaction between glyoxyl-substituted cyclopropane **11a** and 3-methylindole **19a**

Moreover, compound **22a** was a white solid, which after crystalization from dichloromethane/hexane gave a single crystal suitable for X-ray analysis, thus being able to confirm its structure and verify the cyclocondensation between donor-acceptor cyclopropane and C2 and *N* positions of the indole (Figure 4. 1).

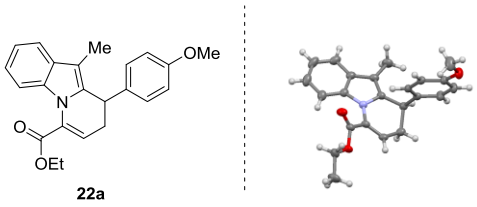
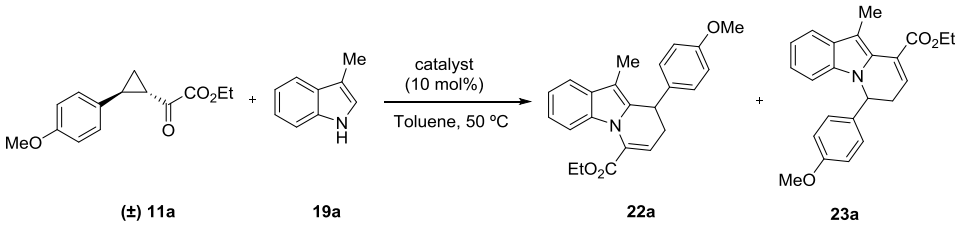


Figure 4. 1 X-ray structure of **22a**

2.2. Optimization of the reaction conditions

With these preliminar experiments in hand, we focused our attention on optimizing the reaction between **11a** and **19a** in order to obtain the target product **22a** with the highest possible yield and minimizing the formation of competitive regioisomer **23a**. For this reason, our first efforts were directed to the identification of the best catalyst in terms of both the yield of the product **22a** and the regioselectivity of the reaction. Therefore, in order to analyze the effect of the nature and acidity of the catalyst in the course of the reaction, some achiral Brønsted acids were firstly employed, involving organic and inorganic acids with different pk_a values (Table 4. 1).

Table 4. 1 Survey of Brønsted acid catalysts for the reaction of cyclopropane **11a** with 3-methylindole **19a**.[a]



(±) 11a 19a 22a 23a

Entry	Catalyst	pk_a (in H_2O)	t (h)	Yield (%)[b,c]	(22a/23a) (%)[c]
1	$(PhO)_2POOH$	1.9	72	50	1.8:1
2	CH_3COOH	4.7	72	<5	--
3	CSA	1.2	12	69	1:1
4	CF_3COOH	0.23	24	39	2.5:1
5	PTSA	-2.6	12	59	1.3:1
6	$(PhO)_2PONHTf$	-3.0	12	61	2.5:1
7	$NHTf_2$	~ -3.0	12	51	3.8:1
8	HCl (water, 37%)	-7.0	12	66	1.2:1

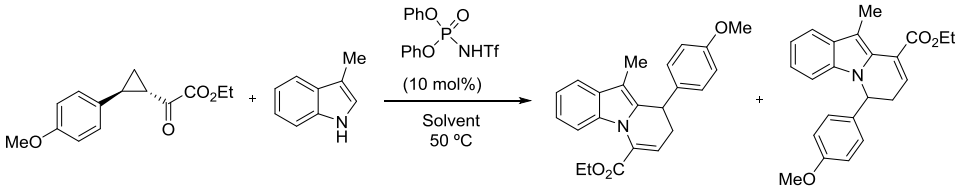
[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a** using 10 mol% of catalyst in toluene (0.2M) at 50 ºC. [b] Yield of isolated products after column chromatography purification. [c] Products **22a** and **23a** were independently isolated by flash column chromatography purification; for more information see experimental section. [d] Regioisomeric ratio measured in the crude of the reaction.

As it can be seen in this table, the less acidic acetic acid was unable to promote the reaction, recovering the unreacted starting materials after three days (entry 2). The more acidic camphorsulphonic acid promoted the reaction much faster, reacting to full conversion

after overnight, but providing 1:1 mixture of regioisomers **22a** and **23a** (entry 3). Conversely, although the regioselectivity improved when carrying out the reaction in the presence of trifluoroacetic acid, the products were isolated with lower yield (entry 4). Next, more acidic *para*-toluensulfonic acid and diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate were employed as Brønsted acid catalysts, which have similar pk_a values. In both cases, the reaction proceeded smoothly in only 12 hours, isolating the final products with a considerably higher overall yield (entries 5-6). It is noteworthy that triflimide, shown in entry 6, afforded the desired product **22a** with a better regioselectivity and in 43% isolated yield. In addition, the bistriflimide showed in entry 7 provided the final product more regioselectively, but a considerable decrease was observed in the yield of the reaction. Finally, aqueous concentrated hydrochloric acid provided the cyclocondensation products **22a** and **23a** with moderate 66% yield, although with a poor regioselectivity, isolating the desired cycloadduct **22a** after purification in 36% yield (entry 8).

With these results in hand, solvents of different nature were next evaluated employing $(PhO)_2P(O)NHTf$ as catalyst, with the aim of improving both the regioselectivity and the yield of the process (Table 4. 2). Initially, moving to a more polar solvent, such as tetrahydrofuran, the reaction did not take place after 72 hours (entry 2). On the other hand, the use of chlorinated solvents, such as chloroform and 1,2-dichloroethane, afforded the final products in similar global yields but with a quite lower regioselectivities, providing the target product **22a** with 41% and 39% yield respectively (entries 3-4). Finally, other aromatic non-polar solvents, such as benzene and *m*-xylene were analyzed, obtaining in both cases the reaction products with almost the same yield and regioselectivity as with toluene (entries 5-6 *vs* entry 1). With these results, it could be concluded that the reaction is not very sensitive to the solvent, although the regioselectivity was lower when using chlorinated solvents compared to toluene or related arenes.

Table 4. 2 The solvent effect in the reaction outcome.[a]

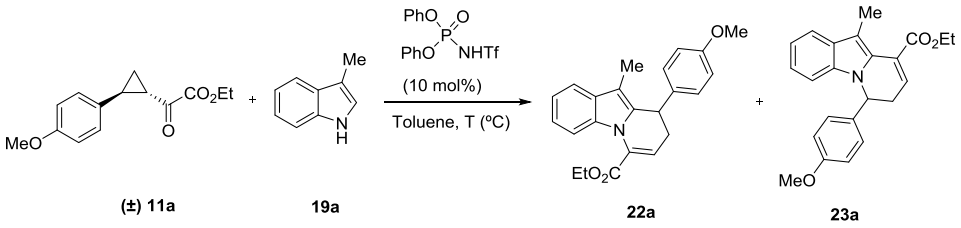


Entry	Solvent	t (h)	Yield (%)[b,c]	(22a/23a) (%)[d]
1	Toluene	12	61	2.5:1
2	THF	72	<5	n.d.
3	$CHCl_3$	12	63	2:1
4	$Cl(CH_2)_2Cl$	12	56	2.3:1
5	benzene	12	61	2.5:1
6	*m*-xylene	12	59	2.5:1

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a** using 10 mol% of $(PhO)_2P(O)NHTf$ in the corresponding solvent (0.2M) at 50 ºC. [b] Yield of isolated products after column chromatography purification. [c] Products **22a** and **23a** were independently isolated by flash column chromatography purification; for more information see experimental section. [d] Regioisomeric ratio measured in the crude reaction mixture.

In view of the importance of the temperature in the initial experiments, we next turned our attention to examine this parameter (Table 4. 3). Firstly, when the reaction was carried out at 25 ºC, no reactivity was observed between the cyclopropane and the indole scaffold (entry 2). On the other hand, increasing the reaction temperature to 70 ºC led to similar results but in much shorter reaction time (entry 3). Moreover, when the reaction was carried out at 100 ºC, the regioselectivity was significantly improved, implying a slight increase in the isolated yield of the target product **22a** (50% yield) in only two hours (entry 4).

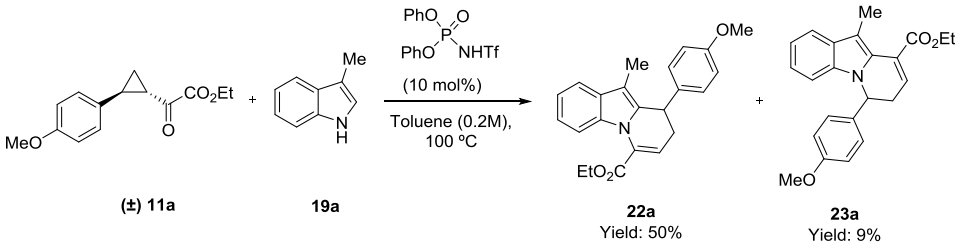
Table 4. 3 Influence of temperature on the reaction outcome.[a]



Entry	T (ºC)	t (h)	Yield (%)[b,c]	(22a/23a) (%)[d]
1	50	12	61	2.5:1
2	25	72	<5	n.d.
3	70	7	65	2.8:1
4	100	2	60	5:1

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2M) at different temperatures. [b] Yield of isolated products after column chromatography purification. [c] Products **22a** and **23a** were independently isolated by flash column chromatography purification; for more information see experimental section. [d] Regioisomeric ratio measured in the crude of the reaction.

After the examination of all these parameters, it was concluded that the best results were obtained when the reaction was performed using 10 mol% of diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate as catalyst in toluene at 100 ºC affording the desired dihydropyridoindole **22a** with 50% yield (Scheme 4. 10).



Scheme 4. 10 Best conditions for the cyclocondensation reaction of donor-acceptor cyclopropanes with 3-substituted indoles

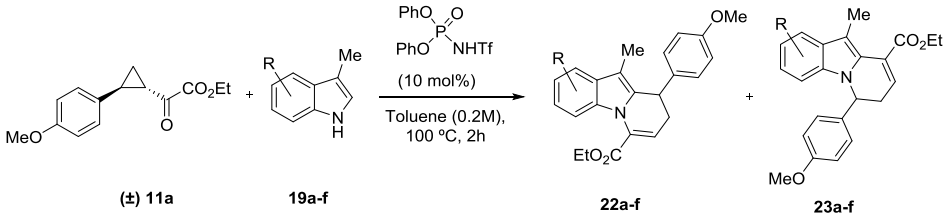
2.3. Scope of the reaction

Once the best reaction conditions for carrying out the cyclocondensation between donor-acceptor cyclopropanes and 3-substituted indoles had been established, we decided to extend the methodology to differently substituted indoles and cyclopropanes.

Initially, it was decided to study the substitution pattern and the electronic nature of the aromatic ring of the indole moiety, thus evaluating a variety of 3-methyl indoles with different substituents at the benzene ring towards reaction with cyclopropane **11a** (Table 4. 4). When a methoxy substituent was placed at the 5 position of the indole moiety, the regioselectivity of the process did not change, but the product **22b** was isolated in lower yield due to the decomposition of the products during the reaction (entry 2). Next, we turned to evaluate the effect of donor and acceptor groups at 6 position, presuming that the nucleophilicity of C2 would increase by placing a donor substituent at this position.[2] In this sense, substitution of position 6 by donor substituents improved the regioselectivity towards the desired product **22** (entries 3-4), suppressing the formation of product **23d** when a methoxy group was located at C6 (entry 4). Surprisingly, the substitution of C6 by a fluorine atom also favored the C-alkylation against *N*-alkylation, obtaining a more regioselective transformation and isolating the product **22e** with 60% yield (entry 5). Finally, it was decided to evaluate the introduction of a substituent at 7 position of the indole scaffold, hoping that steric hindrance for the first alkylation at *N*-position could favor the formation of regioisomer **22**. In this sense, when a methyl group was placed at that position, very low amount of byproduct **23f** was observed, obtaining the target product **22f** with 54% yield (entry 6).

[2] Wu, Q.; Ma, C.; Du, X.-H.; Chen, Y.; Huang, T.-Z.; Shi, X.-Q.; Tu, S.-J.; Cai, P.-J. *Tetrahedron: Asymmetry* **2016**, *27*, 307.

Table 4. 4 Influence of substitution at the benzene ring of the indole for the cyclocondensation.[a]

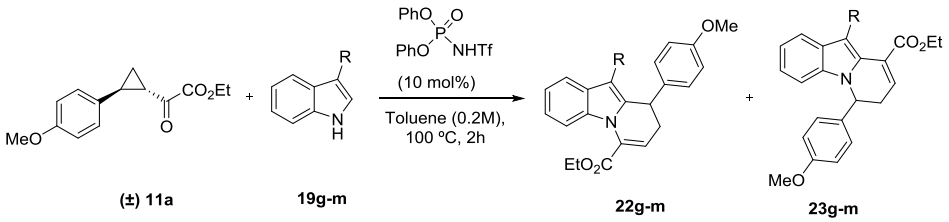


Entry	R	Prod. 22/23	Yield (%)[b,c]	(22/23) (%)[d]
1	H	**22a/23a**	60	5:1
2	5-OMe	**22b/23b**	50	5:1
3	6-Me	**22c/23c**	60	6.1:1
4	6-OMe	**22d/23d**	61	>20.1
5	6-F	**22e /23e**	65	10:1
6	7-Me	**22f/23f**	56	13:1

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a-f** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 °C. [b] Yields of isolated products after column chromatography purification. [c] Products **22a-f** and **23a-f** were independently isolated by flash column chromatography purification; for more information see experimental section. [d] Regioisomeric ratio measured in the crude of the reaction.

At this point, the insertion of substitution at C3 of the indole was studied, evaluating both the volume and the electronic nature of such substituent towards the addition to cyclopropane **11a** (Table 4. 5). In this sense, when the methyl group was replaced by another alkyl substituent, such as ethyl group, the reaction also proceeded well, although product **22g** was isolated with a slightly lower yield (entry 1). Similarly, the 3-benzyl indole also afforded product **22h** with a slightly lower regioselectivity in 47% yield (entry 2). Surprisingly, incorporating a phenyl group at C3 position of the indole improved the regioselectivity of the process, thus obtaining the target product **22i** in 62% yield (entry 3). In addition, indoles with *para*-methoxyphenyl and *para*-fluorophenyl groups at C3 position provided the desired products **22j** and **22k** in very good yields with high regioselectivity (entries 4-5). In contrast, the incorporation of an allyl group decreased the regioselectivity of the process obtaining **22l** in a lower 34% yield (entry 6). Finally, as it was expected, no reaction was observed substituting the C3 position of the indole by an electron-withdrawing substituent (entry 7).

Table 4. 5 Influence of the substituent at C3 position of the indole for the cyclocondensation.[a]



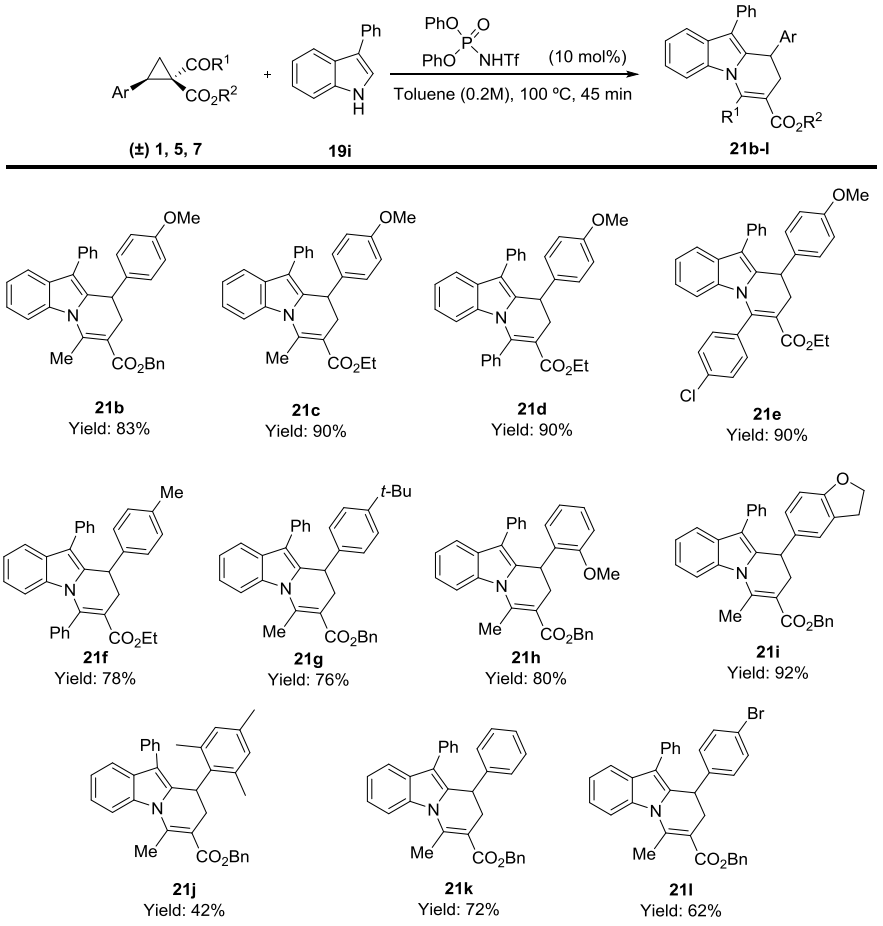
(±) 11a 19g-m 22g-m 23g-m

Entry	R	Prod. 22/23	Yield (%)[b,c]	(22/23) (%)[d]
1	Et	**22g/23g**	56	4.3:1
2	Bn	**22h/23h**	60	3.4:1
3	Ph	**22i/23i**	69	7.6:1
4	4-OMe-C_6H_4	**22j/23j**	85	11:1
5	4-F-C_6H_4	**22k/23k**	82	8:1
6	Allyl	**22l/23l**	57	1.5:1
7	CO_2Et	**22m/23m**	<5	n.d.

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19g-m** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 ºC. [b] Yields of isolated products after column chromatography purification. [c] Products **22g-m** and **23g-m** were independently isolated by flash column chromatography purification; for more information see experimental section. [d] Regioisomeric ratio measured in the crude of the reaction.

Once differently substituted indoles were tested in the reaction with glyoxyl-derived cyclopropane **11a**, we next focused on the study of introducing structural diversity in the cyclopropane moiety. We started evaluating cyclopropanes with two geminal electron-withdrawing substituents, such as compounds **1, 5** and **7** towards the reaction with 3-phenyl indole **19i** (Table 4. 6). In this sense, when previously employed cyclopropane **1a** was reacted with 3-phenylindole **19i**, dihydropyridoindole **21b** was isolated regioselectively with very good yield in a lower reaction time. In addition, when the benzyloxy substituent of the ester moiety was replaced by an ethoxy group, adduct **21c** was isolated in slightly higher 90% yield. Next, the nature of the substituent at the acyl moiety was evaluated, which in principle would have a significant influence, due to its participation as electrophile in the second nucleophilic addition. However, when phenyl or electron-deficient aryl substituents were placed at the ketone moiety, there was no effect on the reaction course, obtaining products **21d** and **21e** in 90% yield.

Table 4. 6 Scope of cyclocondensation employing cyclopropanes with two germinal electron-withdrawing groups: influence of the substitution pattern of the cyclopropane.[a]

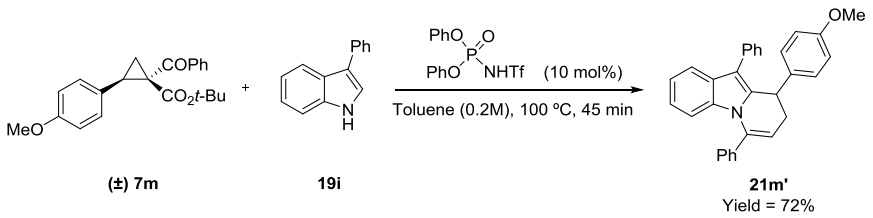


[a] Reactions performed in a 0.05 mmol scale of cyclopropanes **1, 5, 7** and **19i** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 ºC; yields of isolated products **21b-l** after column chromatography purification.

In order to continue studying the scope and limitations of the reaction regarding the cyclopropane scaffold, cyclopropanes with a variety of aryl substituents as the donor group were evaluated. In this way, firstly, the nature of the substituent at *para* position of the phenyl

group was examined. When the methoxy group was replaced by a methyl or *tert*-butyl group, the reaction underwent smoothly and in a regioselective manner, although providing products **21f-g** in a lower yields. Next, we examined the substitution pattern at the phenyl ring, and when a methoxy group was introduced in the *ortho* position instead of *para* position, the reaction afforded the desired product **21h** as single regioisomer with 80% yield. Moreover, as expected, when 2,3-dihydrobenzofuran-5-yl was placed as donor unit, in which the alkoxy group at 4-position of the phenyl group was maintained, the reactivity of cyclopropane increased because of the higher donating character of this substituent, thus isolating product **21i** in excellent 92% yield. Additionally, when the bulkier mesityl substituent was used as donor group, a dramatical negative effect was observed in the yield of **21j**, presumably because of steric hindrance generated by the two methyl groups placed at C-2 and C-6 positions of the phenyl ring. Interestingly, the more challenging phenyl substituted cyclopropane, which did not present any reactivity in the Cloke-Wilson reaction, also provided product **21k** in a regioselective manner with a slightly lower 72% yield. Finally, the cyclopropane bearing a *para*-bromophenyl substituent at that position also provided the desired dihydropyridoindole derivative **21l** in 62% yield.

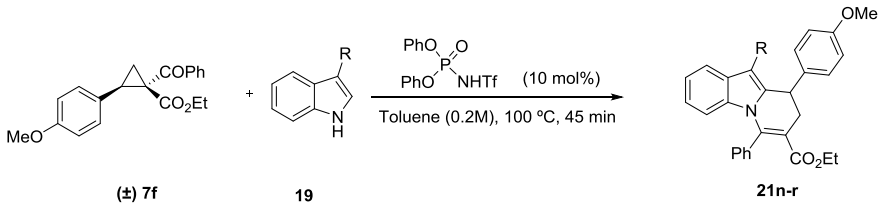
Interestingly, the formation of a different product was observed using *tert*-butylcyclopropyl calboxylate derivative as starting material in the reaction with 3-phenylindole. In this case, an additional decarboxylation process occurred after the formation of the dihydropyridoindole, affording **21m'** as single product in 72% yield (Scheme 4. 11).



Scheme 4. 11 Reaction of *tert*-butyl ester substituted doubly activated cyclopropane **7m** with 3-phenylindole **19i**

Next, a variety of indole derivatives were tested employing cyclopropane **7f** as model substrate, so as to investigate the scope of the reaction when cyclopropanes with two geminally positioned electron-withdrawing groups where employed (Table 4. 7). First, differently substituted C3 indoles were evaluated, observing that while 3-methyl or 3-ethyl substituted indoles afforded the desired products **21n** and **21o** satisfactorily and in a fully regioselective manner (entries 1-2). Similarly, the 3-benzylindole provided compound **21p** as single isomer and with very high yield (entry 3). Encouraged by these results, aryl substituted indoles were tested, observing that the reaction tolerated aryl substituents with different electronic nature, achieving successfully compounds **21q** and **21r** (entries 4-5), although *para*-fluorophenyl substituent slightly decreased the yield of dihydropyridoindole **21r** (entry 5).

Table 4. 7 Scope of cyclocondensation employing cyclopropanes with two germinal electron-withdrawing groups: influence of the C3 substituent at the indole.[a]



(±) 7f 19 21n-r

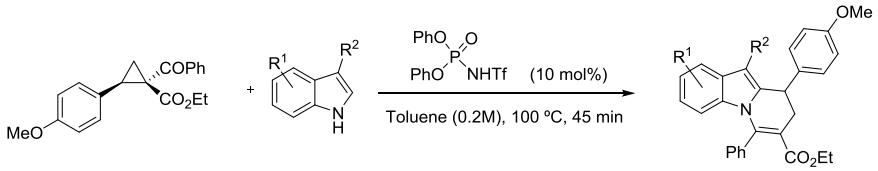
Entry	R	Prod. 21	Yield 21 (%)[b]
1	Me	**21n**	94
2	Et	**21o**	92
3	Bn	**21p**	81
4	4-OMe-C_6H_4	**21q**	86
5	4-F-C_6H_4	**21r**	82

[a] Reactions performed in a 0.05 mmol scale of **7f** and **19a, g, h, j, k** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 ºC. [b] Yields of isolated products **21n-r** after column chromatography purification.

On the other hand, the incorporation of substituents of different electronic nature and substitution pattern at the indole moiety was also evaluated with this type of cyclopropanes (Table 4. 8). As it happened with glyoxyl-substituted cyclopropanes, the introduction of a methoxy group at 5 position of the indole, led to a significant decreased in the yield of the reaction, isolating **21s** with 71% yield (entry 1). Conversely, different substituents at 6

position of the indole scaffold generally behaved similarly providing final products **21t-v** in high yields regardless the electronic nature of the substituent (entries 2-4). However, it has to be mentioned that in this case the incorporation of a methoxy substituent at that position slightly compromised the yield of the reaction (entry 3). Finally, 3,7-dimethylindole was used, observing that yield of the cyclocondensation product **21w** was dramatically decreased, probably due to the steric hindrance that difficulted the second *N* nucleophilic addition of the indole (entry 5).

Table 4. 8 Scope of cyclocondensation employing cyclopropanes with two germinal electron-withdrawing groups: influence of the substitution at the benzene ring of the indole.[a]



(±) 7f 19 21s-w

Entry	R^1	R^2	Prod. 21	Yield 21 (%)[b]
1	5-OMe	Ph	**21s**	71
2	6-Me	Me	**21t**	93
3	6-OMe	Ph	**21u**	79
4	6-F	Ph	**21v**	87
5	7-Me	Me	**21w**	54

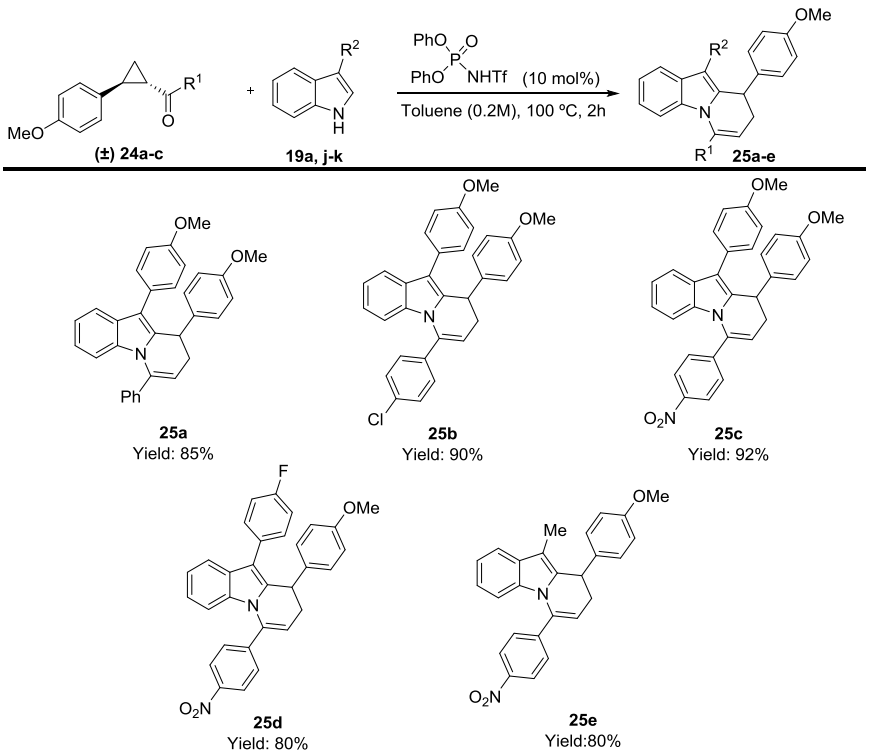
[a] Reactions performed in a 0.05 mmol scale of **7f** and **19c, f, n-p** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 ºC. [b] Yields of isolated products **21s-w** after column chromatography purification.

Finally, the most challenging aryl cyclopropylketones were surveyed, in which a simple acyl substituent exists as electron-withdrawing group (Table 4. 9). In this sense, the simplest cyclopropyl phenyl ketone **24a**, which was easily synthesized by Corey-Chaykovsky cyclopropanation of the corresponding chalcone,[3] was first evaluated towards the reaction with 3-(4-methoxyphenyl)indole **19j**. The reaction performed successfully, isolating dihydropyridoindole **25a** in 85% yield; however, the reaction was not completely regioselective, observing traces of the byproduct that came from the first nucleophilic attack of the nitrogen of the indole. Encouraged by this result, we next surveyed cyclopropylketones

[3] For more information about the synthesis of cyclopropane **24a** see experimental section.

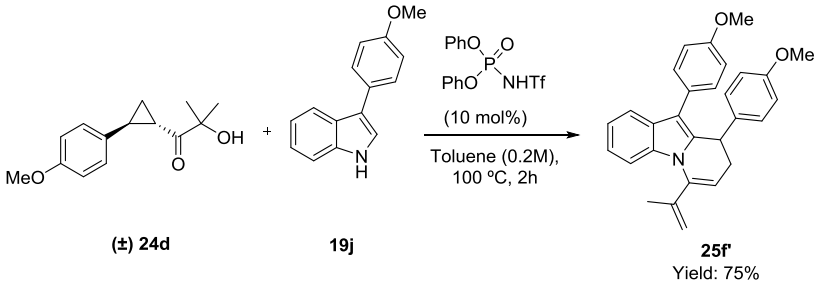
24b and **24c**, that incorporate different substituents at *para* position of the phenyl ring of the ketone moiety. As it could be observed, both of them showed an excellent reactivity, performing the reaction with complete regioselectivity and increasing slightly the yield as more electrophilic ketone was disposed at cyclopropane moiety (**25b-c)**, obtaining up to 92% yield with 4-nitrophenyl cyclopropyl ketone. Employing the latter cyclopropane as substrate model, different indole derivatives containing other aryl (**19k**) or alkyl (**19a**) substituents at C3 position were tried; in both cases the desired products **25d** and **25e** were achieved with very good yields. However, the reactions were not completely regioselective, observing traces of the product that resulted from a first nucleophilic attack of the nitrogen of the indole.

Table 4. 9 Study of the scope of the reaction between cyclopropyl ketones and 3-substituted indoles.[a]



[a] Reactions performed in a 0.05 mmol scale of **24a-c** and **19a, j-k** using 10 mol% of $(PhO)_2P(O)NHTf$ in toluene (0.2 M) at 100 °C; yields of isolated products **25a-e** after column chromatography purification.

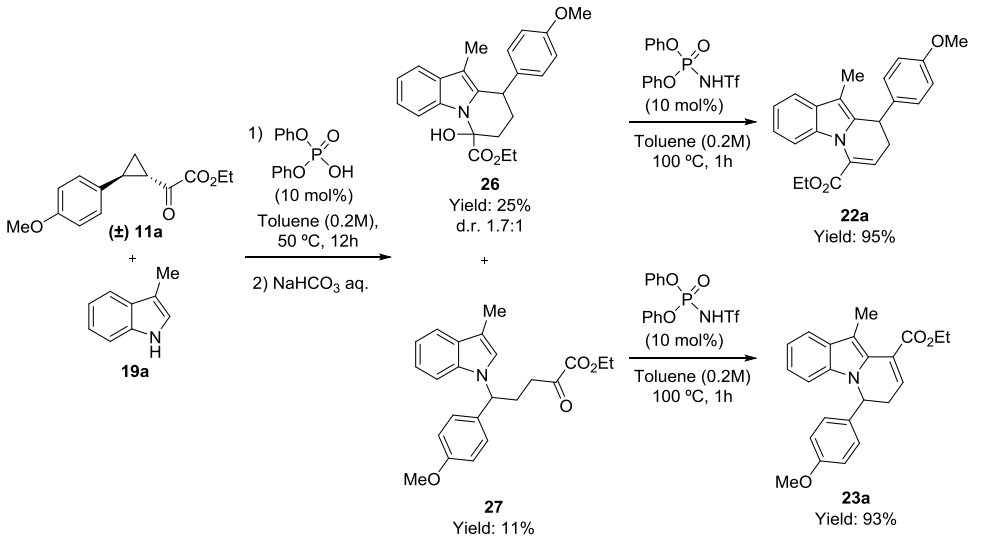
Finally, we also evaluated α-hydroxi cyclopropylketone **24d** as potential interesting substrate. To our delight, the reaction proceeded well, obtaining product **25f'** in 75% yield, which came from an additional dehydration step of the alcohol after the cyclocondensation process (Scheme 4. 12).



Scheme 4. 12 Reaction between cyclopropane **24d** and indole **19j**

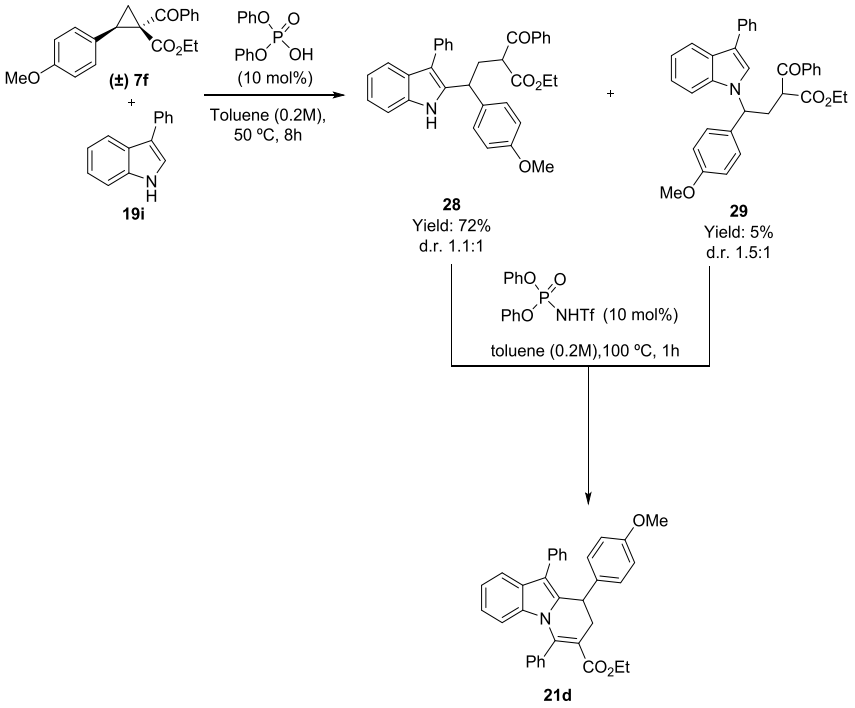
2.4. Study of the reaction mechanism

In order to elucidate the mechanistic pathway of this transformation, some attempts were carried out with the aim of isolating and elucidating the structure of some reaction intermediates. In fact, analysis of evolution of the crude reaction mixture showed the formation of multiple intermediates after consumption of starting materials, which were slowly converted into the final products. Taking this into account, we proceeded to run the reaction between glyoxyl-substituted cyclopropane **11a** and indole **19a** in the presence of the less acidic diphenyl phosphoric acid and at 50 ºC, in order to slow down the reaction and to be able to isolate and identify the intermediates generated (Scheme 4. 13). After 12 hours, the reaction was quenched by the addition of aqueous saturated sodium bicarbonate. Analysis of the reaction crude revealed a complex mixture of products, from which we were able to identify two new compounds, **26** and **27**, by purification by flash column chromatography. Hemiaminal **26** corresponded to an intermediate of dihydropyridoindole **22a** before dehydration, conversely, intermediate **27** was determined as the *N*-alkylation product, prior to cyclization. With the aim of demonstrating that these compounds were indeed reaction intermediates, intermediates **26** and **27** were submitted to the best reaction conditions of the cyclocondensation (10 mol% ((trifluoromethyl)sulfonyl) phosphoramidate in toluene (0.2 M) at 100 ºC), isolating after 1 hour of reaction dihydropyridoindole **22a** and **23a** respectively in excellent yield. It is noteworthy that although *N*-alkylation product **27** afforded **23a** as major product, traces of dihydropyridoindole **22a** were observed in the crude of the reaction, indicating that the addition to the indole nitrogen atom could be a reversible process.



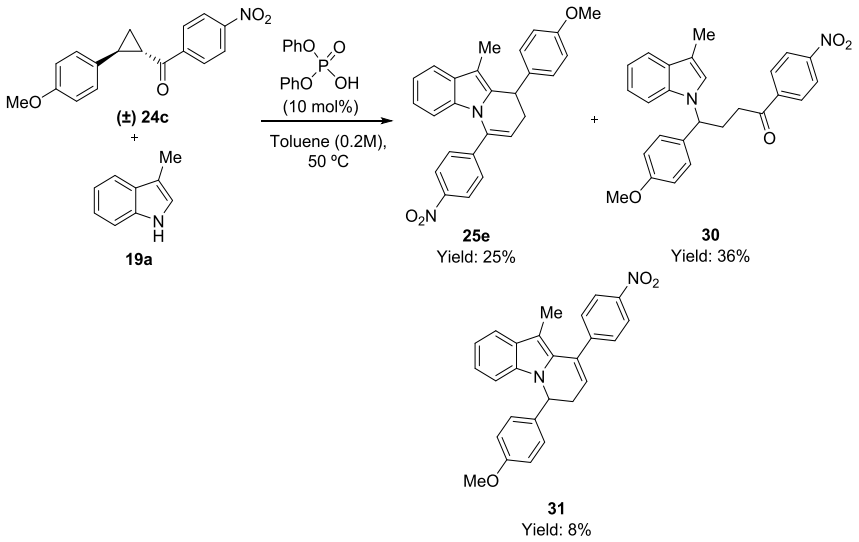
Scheme 4. 13 Intermediate isolation in the reaction between **11a** and **19a**

The same experiment was carried out using cyclopropane **7f** as substrate, which bears two electron-withdrawing groups (Scheme 4. 14). In this case, compounds **28** and **29** could be isolated and determined from the crude reaction mixture, which were identified as C2-alkylation and *N*-alkylation products respectively. In order to demonstrate that the isolated products were actually reaction intermediates, and that could be further transformed into final products, some experiments were carried out, exposing these compounds to the best reaction conditions. From these experiments we could conclude that C2-alkylated adduct **28** was readily converted into dihydropyridoindole **21d**, whereas *N*-alkylated product **29** also afforded quantitatively the corresponding dihydropyridoindole derivative **21d**, as ^{1}H-NMR analysis of the reaction crude revealed. Therefore, it could be confirmed that the addition to the indole nitrogen is a reversible process.



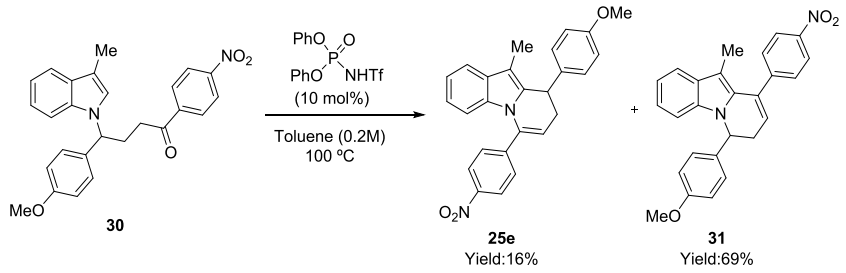
Scheme 4. 14 Intermediate isolation in the reaction between **7f** and **19i**

Finally, these experiments were repeated using the most challenging cyclopropyl 4-nitrophenyl ketone substituted cyclopropane **24c**, achieving after 12 hours the *N*-alkylated product **30** as major product, together with final tricyclic compounds **25e** and **31** (Scheme 4. 15).



Scheme 4. 15 Reaction of cyclopropyl 4-nitrophenyl ketone **24c** with 3-methylindole under milder conditions

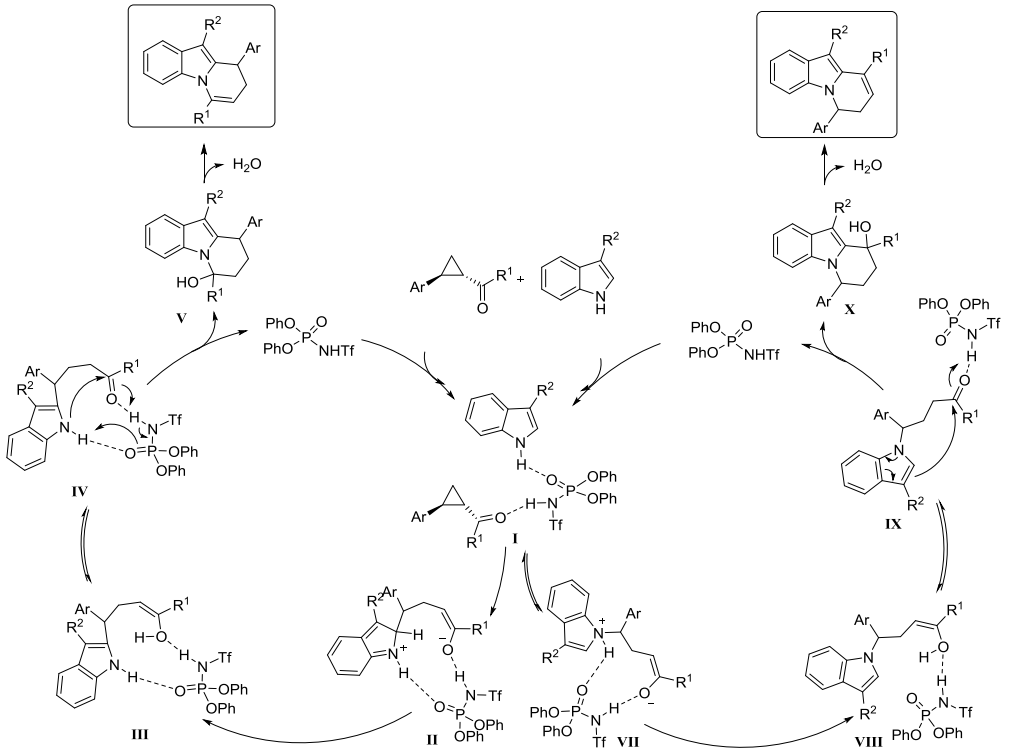
When *N*-alkylated product **30** was exposed to best reaction conditions, both dihydropyridoindole **25e** and cycloadduct **31** were obtained, as a result of the reversible reaction of the addition to the indole nitrogen (Scheme 4. 16).



Scheme 4. 16 Transformation of intermediate **30** to the mixture of **25e** and **31**

After isolating a variety of reaction intermediates, it could be concluded that the reaction occurs through a stepwise reaction mechanism: a first nucleophilic addition of C2 of the indole, followed by the *N* nucleophilic cyclization. Moreover, this reaction competes with the analogous *N*-nucleophilic addition followed by an intramolecular C2-nucleophilic addition. Although C2-alkylated intermediate only afforded the desired dihydropyridoindole derivative, the *N*-alkylated intermediates could be converted into both tricyclic final products depending on the cyclopropane used, indicating that the *N*-addition of cyclopropane to the indole is a reversible reaction.

Taking this into account, a general mechanistic pathway could be explained, as it is presented in Scheme 4. 17. As it is depicted in intermediate **I**, $(PhO)_2P(O)NHTf$ should act as bifunctional catalyst, activating both the cyclopropane by coordination to carbonyl groups, and the nucleophile through H-bonding with the NH of the indole. This would promote the nucleophilic ring-opening of the donor-acceptor cyclopropane leading to iminium ion intermediate **II**, that after H-migration afforded the enol **III** in equilibrium with the isolated C2-alkylated indole intermediate **IV**. Although in the literature is usually proposed that alkylation at C2 position of the indole occurs through a first C3-alkylation followed by [1,2]-alkyl shift, preliminary mechanistic studies through computational methods suggested that in this case a direct C2-alkylation is taking place. A next intramolecular nucleophilic *N*-addition of the indole to the carbonyl moiety in compound **IV** would afford the tricyclic isolated intermediate **V** and the regeneration of the catalyst. After a final dehydration process, the more stable conjugated dihydropyridoindole derivative is released. In contrast, the nucleophilic ring-opening reaction could also led to intermediate **VII**, formed by the nucleophilic *N* attack to cyclopropane, that would give place to previously isolated *N*-alkylated intermediate **VIII**, which after intramolecular nucleophilic C2-addition of the indole would afford the tricyclic intermediate **X** by release of the Brønsted acid. The final dehydration process would provide the regioisomeric dihydropyridoindole. As it has been previously demonstrated, the *N*-nucleophilic addition is a reversible process and as a consequence, at high temperatures the major formation of the desired diydropyridoindole has been observed, which is the thermodynamic product.

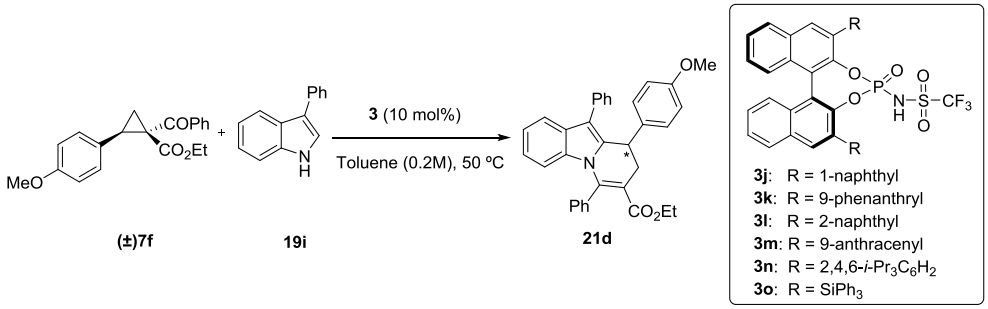


Scheme 4. 17 Proposed catalytic cycle for the cyclocondensation

2.5. Towards a catalytic enantioselective version of the reaction

In view that the reaction proceeded successfully with a wide range of substrates under non-chiral reaction conditions, and considering that both $(PhO)_2P(O)OH$ and $(PhO)_2P(O)NHTf$ were suitable catalysts, our next efforts were directed to the development of the enantioselective version of such transformation. Taking into account that the reaction has been performed employing diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate as catalyst, we focused our attention on the employment of chiral BINOL-derived *N*-triflylphosphoramides under similar reaction conditions, with the aim of achieving enantiomerically enriched cycloadducts. In this context, it was decided to employ cyclopropane **7f** as model substrate, reacting it with 3-phenylindole **19i**, in the presence of a variety of BINOL-derived *N*-triflyl phosphoramides **3j-o** in toluene (0.2M) at 50 ºC (Table 4. 10).

Table 4. 10 Chiral BINOL-derived *N*-triflyl phosphoramide survey for the enantioselective cyclocondensation.[a]



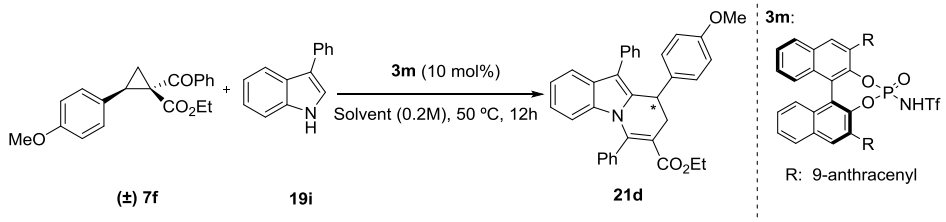
Entry	Catalyst	t (h)	Yield 21d (%)[b]	e.e. 21d (%)[c]
1	**3n**	12	84	2
2	**3j**	12	78	10
3	**3l**	12	75	6
4	**3k**	12	80	20
5	**3m**	12	85	26
6	**3o**	24	52	4

[a] Reactions performed in a 0.05 mmol scale of **7f** and **19i** using 10 mol% of catalyst **3j-o** in toluene (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

Initially, when the reaction was carried out with the archetypical TRIP-derived *N*-triflyl phosphoramide **3n**, product **21d** was isolated in very good yield, although the catalyst was not able to control the enantioselectivity of the process (entry 1). Similarly, 3,3'-bis(naphtyl)-substituted BINOL-based phosphoramides **3j** and **3l** were also able to perform the reaction in 75 and 78% yield respectively, although the product resulted to be almost racemic in both cases (entries 2-3). Moreover, when larger arenes were placed at the BINOL scaffold, such as phenanthryl or anthracenyl groups (catalysts **3k** and **3m**), in addition to obtaining compound **21d** with good yield, a slight improvement was observed in the enantiomeric excess, probably favored by the π-π stacking between the catalyst and the substrate, although remained below expectations (entries 4-5). Finally, triphenylsilyl BINOL-substituted phosphoramide **3o** afforded the desired product with a lower 52% yield in a longer reaction time and as almost racemic material (entry 5). However, it is noteworthy to comment that in this last case formation of C2-alkylation product **27** was also observed, decreasing the yield of the product of interest.

Based on these results, we next turned our attention to evaluate the solvent effect, testing solvents of different nature with catalyst **3m**, with the final aim of gaining a better enantiocontrol of such transformation (Table 4. 11). When the reaction was carried out in non-polar solvents, such as benzene chlorobenzene and trifluorotoluene or xylene derivatives, the transformation proceeded similarly, achieving product **21d** with good yield but poor enantiocontrol (entries 2-6). Additionally, the use of chlorinated solvents, such as $CHCl_3$ or CCl_4, did not improve the results previously obtained regardless their polarity. From these results, it could be concluded again that the nature of the solvent had no significant effect over the reaction outcome, isolating in all the cases the final product with 84-90% yield and 20-26% enantiomeric excess, obtaining in all cases full conversion after 12 hours.

Table 4. 11 Effect of the solvent on the cyclocondensation.[a]



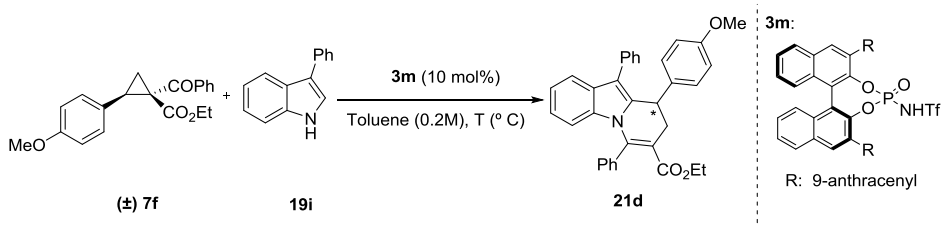
(±) 7f 19i 21d

Entry	Solvent	Yield 21d (%)[b]	e.e. 21d (%)[c]
1	Toluene	85	26
2	Benzene	89	25
3	*m*-xylene	90	22
4	*o*-xylene	87	22
5	chlorobenzene	90	20
6	trifluorotoluene	86	20
7	$CHCl_3$	85	20
8	CCl_4	84	24

[a] Reactions performed in a 0.05 mmol scale of **7f** and**1 19i** using 10 mol% of catalyst **3m** in the corresponding solvent (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

Finally, the influence of temperature in the reaction outcome was also explored, summarizing the results in Table 4. 12. As expected, the reaction became much slower when decreasing the temperature to 30 ºC, and surprisingly, poorer enantiocontrol was achieved (entry 2). It is noteworthy that in this case there was no full conversion to the final product observing the formation of some intermediates that did not converge into the final product. Conversely, the reaction was substantially accelerated at 70 or 100 ºC, although no improvement was perceived either in the yield or in the enantioselectivity of the process (entries 3-4).

Table 4. 12 Evaluation of different temperatures in the cyclocondensation.[a]



(±) 7f 19i 21d

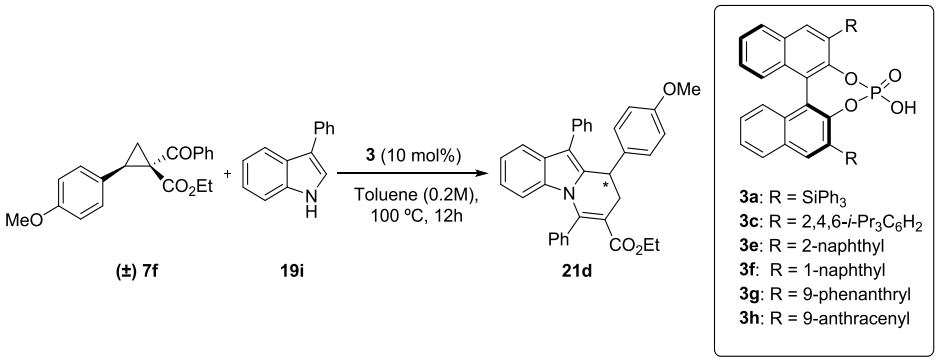
Entry	T (ºC)	t (h)	Yield 21d (%)[b]	e.e. 21d (%)[c]
1	50	12	85	26
2	30	48	67	15
3	70	4	86	24
4	100	3	86	21

[a] Reactions performed in a 0.05 mmol scale of **7f** and **19i** using 10 mol% of catalyst **3m** in toluene (0.2M). [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

As it was observed that at high temperatures there was not a considerable decrease in the enantiomeric excess of the product, and that therefore it seemed possible to gain high enantioselectivities, it was decided to test less acidic chiral catalysts, such as BINOL-derived phosphoric acids at 100 ºC (Table 4. 13). In this context, it was decided to use the catalysts analogous to those previously employed (see Table 4. 10). As expected, these catalysts turned to be less active promoting such transformation, obtaining in all cases poorer yields in longer periods of time (12h). When TRIP was employed as catalyst, a 12% of **21d** was isolated with poor 37% enantiomeric excess (entry 1). Interestingly, other 3,3'-bis(aryl) substituted BINOL-based phosphoric acids (**3e**-**3h**) enhanced the reactivity of the process, affording adduct **21d** with moderate to good yields (entries 2-5). Eventhough the use of 2-naphtyl BINOL-substituted phosphoric acid **3e** afforded the desired product in promising yield but as a racemic mixture (entry 3), when 1-naphtyl substituent was placed compound **21d** was obtained with gratifying 60% yield and a promising 40% enantiomeric excess (entry 2). Encouraged with this result, larger π-systems, such as phenanthryl and anthracenyl groups, were placed at the BINOL moiety (entries 4-5), unfortunately, both the yield and the enantiocontrol decreased, isolating an almost racemic compound **21d** in the case of anthracenyl substituted phosphoric acid (entry 5). In addition, triphenylsilyl substituent at the BINOL scaffold (**3a**) afforded the desired product with low yield and enantioselectivity

(entry 6), observing important amounts of intermediates. Thus, it could be concluded that higher enantioselectivities could be reached employing chiral phosphoric acids as catalyst at 100 ºC, achieving promising 37% and 40% enantiomeric excesses with the archetypical TRIP (**3c**) and with the 1-naphthyl BINOL-substituted phosphoric acid (**3a**) respectively.

Table 4. 13 Chiral BINOL-derived phosphoric acid survey for the cyclocondensation at 100 ºC.[a]



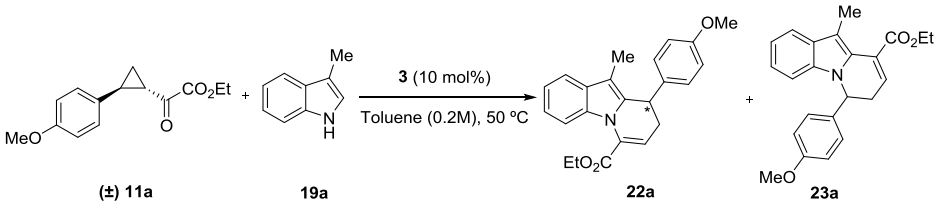
Entry	Catalyst	Yield 21d (%)[b]	e.e. 21d (%)[c]
1	**3c**	12	37
2	**3f**	60	40
3	**3e**	58	1
4	**3g**	44	16
5	**3h**	40	2
6	**3a**	13	23

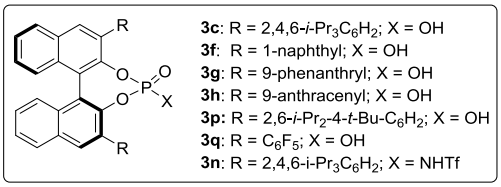
[a] Reactions performed in a 0.05 mmol scale of **7f** and **19i** using 10 mol% of catalyst in toluene (0.2M) at 100 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

Next, cyclopropane **11a** was decided to evaluate as potential substrate. To start with, some catalysts were evaluated in order to attain a regio- and enantioselective transformation (Table 4. 14). Initially, cyclopropane **11a** was reacted with the commercially available 3-methylindole **19a** under the archetypical TRIP phosphoric acid **3c**, which provided product **22a** with poor regioselectivity, obtaining also cycloadduct **23a** that came from the competitive *N*-alkylation instead of C2-alkylation of the indole in the first step. However, and to our delight, dihydropyridoindole **22a** was isolated with a promising 68% of enantiomeric excess (entry 1). With the purpose of favoring π-stacking interactions between

catalyst and both substrates, a variety of 3,3'-bis(aryl) substituted BINOL-based phosphoric acids with larger π-systems were tested in the reaction (entries 2-4). When a 1-naphtyl substituent was placed at the BINOL moiety, the yield of the reaction decreased, isolating a 26% of **22a** as almost racemic mixture (entry 2). Carrying out the reaction with larger phenanthryl or anthracenyl substituted BINOL-derived catalyst **3g** and **3h)**, the reaction performed similarly, obtaining product **22a** with poor yield and enantiomeric excess (entries 3-4). With these results in hand, could be concluded that the reaction is not favored through π-stacking of catalyst with the substrates. On the other hand, TRIP-related catalyst **3p** was tested in order to examine if bulkier substituents were able to improve the results obtained. However, the bulkier *tert*-butyl substituent at 4-position of the catalyst did not improve the results previously obtained with TRIP (entry 5). Finally, an electron-poor aryl group, such as perfluorophenyl substituent, was placed at the BINOL scaffold. This catalyst **3q** slightly increased the regioselectivity and yield of the target product, although dihydropyridoindole **22a** turned to be completely racemic (entry 6).

Table 4. 14 Chiral BINOL-derived phosphoric acid survey for reaction employing glyoxyl-substituted cyclopropane **11a**.[a]





Entry	Catalyst	Yield 22a (%)[b]	e.e. 22a(%)[c]	Yield 23a (%)[b]	e.e. 23a (%)[c]
1	**3c**	32	68	45	41
2	**3f**	26	5	34	19
3	**3g**	26	5	28	2
4	**3h**	19	20	20	0
5	**3p**	34	40	40	40
6	**3q**	42	0	23	16
7	**3n**	33	0	17	6

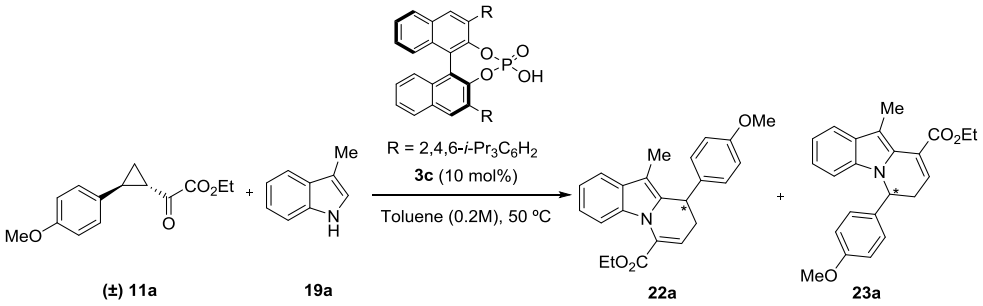
[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a** using 10 mol% of catalyst **3** in toluene (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

As the best enantiocontrol was obtained when performing the reaction with the bulky phosphoric acid TRIP (**3c**), the more acidic *N*-triflyl phosphoramide derivative containing the same substituent was next examined. In this sense, TRIP-derived *N*-triflyl phosphoramide **3n** afforded compound **22a** as major product and with similar regioselectivity and yield as when TRIP catalyst was used, however, the product **22a** turned to be completely racemic (entry 7).

Next, in order to reach the best possible regio- and enantiocontrol, solvent effect was evaluated selecting catalyst **3c** for performing such transformation (Table 4. 15). When the reaction was carried out in non-polar solvents, such as benzene or xylene derivatives,

although the regioselectivity of the process slightly improved, **22a** was isolated with lower enantiomeric excess (entries 2-3). On the other hand, when trifluorotoluene was used as solvent, the results were very similar to those obtained when toluene was employed (entry 4). Additionally, while the use of $CHCl_3$ afforded dihydropyridoindole **22a** with similar yield and a slightly higher enantiomeric excess (entry 5), the use of 1,2-dichloroethane did not improve the previous results, decreasing the enantiocontrol to 40% e.e. (entry 6).

Table 4. 15 Evaluation of different solvents in two-step reaction of cyclopropane **11a** with 3-phenylindole **19a**.[a]



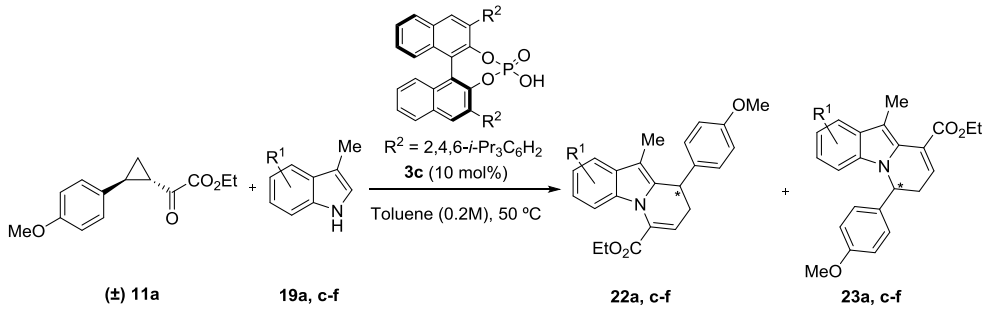
Entry	Solvent	Yield 22a (%)[b]	e.e. 22a (%)[c]	Yield 23a (%)[b]	e.e. 23a (%)[c]
1	Toluene	31	63	45	43
2	Benzene	32	54	43	39
3	*m*-xylene	38	52	43	44
4	CF_3-toluene	30	60	49	32
5	$CHCl_3$	31	65	48	38
6	$Cl(CH_2)_2Cl$	34	40	37	34

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a** using 10 mol% of catalyst **3c** in the corresponding solvent (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

With these reaction conditions in hands, we decided to evaluate the influence of the substitution pattern of the indole in the reaction outcome reacting the model cyclopropane **11a** with a variety of substituted indole derivatives **19a, c-f** (Table 4. 16). As observed before, donor substituents at 6 position of the indole moiety enhanced the nucleophilicity at C2 position of the indole, observing an improvement in the regioselectivity towards the desired products **22c-e**, although with a slight decrease in the enantiomeric excesses (entries 2-4).

However, it should be highlighted that the enantiomeric excess of the regioisomer **23** increased, especially for product **23d** (entry 3). Moreover, when 7-methyl substituted indole was employed, byproduct **23f** was formed in very few amount, obtaining the target product **21f** with 34% yield, probably due to steric hindrance promoted by the methyl group during the first *N*-alkylation process. However, the isolated product **22f** was completely racemic, whereas side-product **23f** was achieved with good 84% enantiomeric excess (entry 5).

Table 4. 16 The tolerance of different indoles in the asymmetric cyclocondensation: substitution pattern at the benzene ring of the indole moiety.[a]



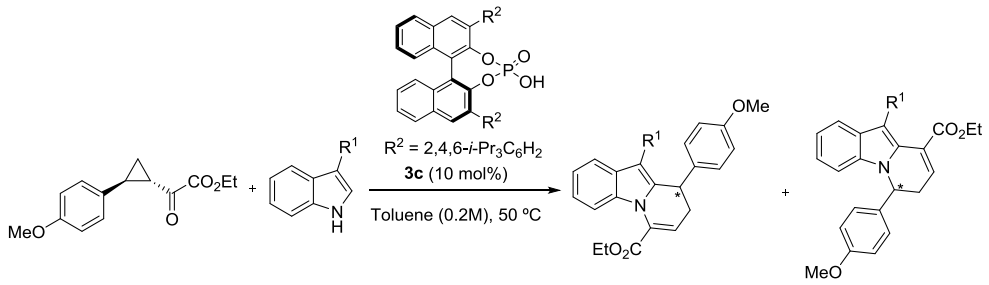
Entry	R^1	22/23	Yield 22 (%)[b]	e.e. 22 (%)[c]	Yield 23 (%)[b]	e.e. 23 (%)[c]
1	H	**22a/23a**	32	68	45	41
2	6-Me	**22c/23c**	43	58	20	47
3	6-OMe	**22d/23d**	40	56	16	72
4	6-F	**22e/23e**	42	42	18	54
5	7-Me	**22f/23f**	34	0	8	84

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19a, c-f** using 10 mol% of catalyst **3c** in toluene (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

Finally, substituents of different nature at C3 position of the indole were evaluated (Table 4. 17). When the methyl group was replaced by an ethyl group, product **22g** was isolated with similar yield but considerably lower enantiomeric excess (entry 1). In addition, the incorporation of a benzyl group at C3 position of the indole afforded product **22h** in 32% yield with almost 1:1 regioselectivity and low 16% enantiomeric excess (entry 2). Interestingly, placement of a phenyl substituent at that position exhibited a better

regioselectivity, isolating dihydropyridoindole **22i** in 39% yield with moderate 55% enantioselectivity (entry 3).

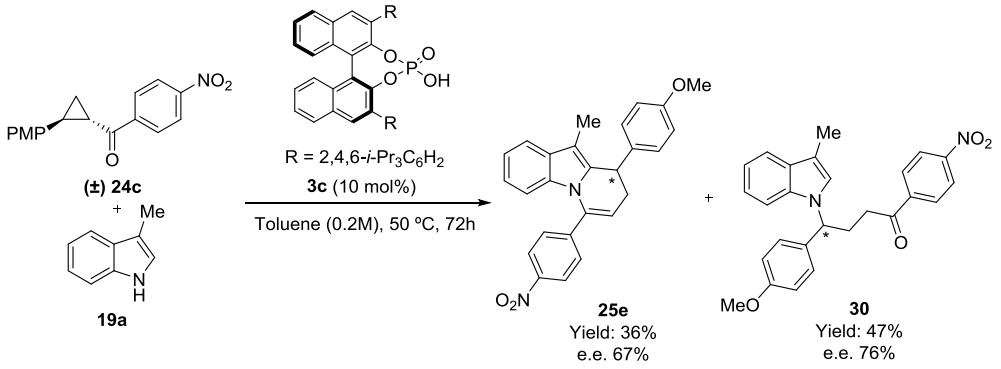
Table 4. 17 The tolerance of different indoles in the asymmetric cyclocondensation: substitution at C3 position of the indole moiety.[a]



Entry	R^1	22/23	Yield 22 (%)[b]	e.e. 22 (%)[c]	Yield 23 (%)[b]	e.e. 23 (%)[c]
1	Et	**22g/23g**	35	36	36	32
2	Bn	**22h/23h**	32	16	36	32
3	Ph	**22i/23i**	39	55	33	57

[a] Reactions performed in a 0.05 mmol scale of **11a** and **19g-i** using 10 mol% of catalyst **3c** in toluene (0.2M) at 50 ºC. [b] Yields of isolated products after flash column chromatography purification.[c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase (for more information see experimental section).

In a final attempt of improving the enantioinduction and regioselectivity of the process, cyclopropyl 4-nitrophenyl ketone **24c** was tested in the reaction employing 10% TRIP **3c** in toluene (0.2M) at 50 ºC (Scheme 4. 18). Unfortunately, the reaction did not perform regioselectively, obtaining the *N*-alkylation product **30** as major compound in addition to the dihydropyridoindole derivative **25e** after 72h. Interestingly, promising enantioselectivities of both products were achieved and although other catalysts even different reaction conditions have been tried, in none of the cases we could improve these results.



Scheme 4. 18 Reaction of cyclopropyl 4-nitrophenyl ketone **24c** and 3-methyl indole **19a**

In summary, chiral BINOL-derived phosphoric acids seemed to be promising catalysts to carry out the asymmetric version of this reaction, however, additional modifications in the reaction conditions have to be done in order to gain a regio- and enantioselective of process.

3. CONCLUSIONS

Considering the results presented through this chapter, the following conclusions can be outlined:

- Diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate turned to be a suitable catalyst to promote the cyclocondensation of donor-acceptor cyclopropanes with 3-substituted indole derivatives, affording successfully a variety of differently substituted dihydropyridoindoles.

- The methodology tolerates a wide scope of both donor-acceptor cyclopropanes and indole moieties. Differently substituted cyclopropanes containing two electron-withdrawing groups afforded the final dihydropyridoindole derivatives with good to excellent yields and as a single regioisomer. Moreover, cyclopropanes bearing a single acyl group as electron-withdrawing substituent also performed the reaction efficiently, although glyoxyl-substituted cyclopropanes showed regioselectivity issues. On the other hand, a number of different substituents at C3 position of the indole moiety, such as alkyl or aryl groups, or even different substituents at the benzene-ring of the indole, provided effectively the dihydropyridoindole derivatives, being possible to improve the regioselectivity of the process when glyoxyl-substituted cyclopropanes were employed.

- The asymmetric version of this transformation has been studied employing BINOL-derived chiral phosphoric acids as catalysts. However, enantiomeric excesses remained moderate, and regioselective issues make the reaction not to perform well in terms of chemical efficiency. Therefore, further modifications in the reaction conditions have to be considered in order to achieve a completely regio- and enantioselective process.

- The reaction proceeded through C2-alkylation followed by intramolecular condensation by activation of both the cyclopropane and the indole moiety. However, competitive *N*-nucleophilic addition and subsequent intramolecular nucleophilic C2 addition can also take place, which is a reversible process. As a

consequence, at high temperatures major formation of the desired diydropyridoindole was observed, which is the thermodynamic product.

Chapter 5

5

Final Conclusions

FINAL CONCLUSIONS

Throughout the present work it has been demonstrated that Brønsted acids are suitable catalysts for the activation of acyl substituted donor-acceptor cyclopropanes, promoting the ring opening-reaction that leads to reactive 1,3-dipoles. This zwitterionic intermediate species are able to undergo a rearrangement process or react with an external nucleophile, generating interesting more complex structures. Experimental results collected during the accomplishment of this work leads to the following conclusions:

Enantioselective Cloke-Wilson Rearrangement.

It has been shown that the enantioselective synthesis of 2,3-dihydrofuran derivatives could be successfully carried out through the Cloke-Wilson rearrangement of activated donor-acceptor cyclopropanes. The method has a wide scope regarding both the donor and the acceptor substituents of the cyclopropane, exhibiting excellent reactivity with two geminal or even one acceptor substituent at the cyclopropane moiety. Computational studies together with experimental analysis confirmed that the reaction proceeded through the formation of a carbocationic intermediate *via* a DYKAT process, making possible the use of racemic substrates.

Acid-Catalyzed Cyclocondensation of Donor-Acceptor Cyclopropanes with 3-substituted Indoles.

The ability of diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate to act as a bifunctional catalyst has been outlined in the cyclocondensation process of donor-acceptor cyclopropanes with 3-substituted indoles. This strategy has been applied for the effective construction of a wide range of dihydropyridoindole derivatives, as 3-substituted indoles has demonstrated their ability to act as bisnucleophiles through their C2 and *N* positions. Therefore, the reaction proceeds through a double nucleophilic addition of C2 and *N* positions of the indole to the cyclopropane moiety, using a phosphoric acid derivative as bifunctional catalyst. Moreover, it was tried to perform the asymmetric version of such transformation employing chiral BINOL-derived phosphoric acids. Although these catalysts seemed to perform suitably the reaction, further modifications in the reaction conditions are necessary in order to gain a completely stereoselective transformation.

Chapter 6

6

Experimental Section

1. GENERAL METHODS AND MATERIALS

NMR: Monodimensional and/or bidimensional nuclear magnetic resonance proton and carbon spectra (^{1}H NMR and ^{13}C NMR) were adquired at 25 ºC on a Bruker AC-300 spectrometer (300 MHZ for ^{1}H and 75.5 MHz for ^{13}C) and a Bruker AC-500 spectrometer (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) at the indicated temperature. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.16 ppm for ^{13}C NMR) and coupling constants (*J*) in hertz (Hz). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; app, m, multiplet; bs, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode using DEPT experiments (Distorsionless Enhancement by Polarization Transfer) for assigning different types of carbon environment. Selective n.O.e., NOESY, COSY, HSQC and HMBC experiments were acquired to confirm precise molecular conformation and to assist in deconvoluting complex multiplet signals.[1]

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100 (ATR) in the interval between 4000 and 400 cm^{-1} with a 4 cm^{-1} resolution. Only characteristic bands are given in each case.

MS: Mass spectra (MS) were recorded on an Agilent 7890A gas chromatograph coupled to an Agilent 5975C quadrupole mass spectrometer under electronic impact ionization (EI) 70 eV. 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%).

HRMS: High-resolution mass spectra on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionization (ESI^+ or ESI^-).

HPLC: The enantiomeric excess (e.e.) of the products was determined by High Performance Liquid Chromatography on a chiral stationary phase in a Waters 2695 chromatograph coupled to a Waters 2998 photodiode array detector. Daicel *Chiralpak IA*, and *IC* columns (0.46 × 25 cm) were used; specific conditions are indicated for each case.

M.p.: Melting points were measured in a Stuart SMP30 apparatus in open capillary tubes and are uncorrected.

Optical rotations $[\alpha]_D^{20}$: were measured at 20 ºC on a Jasco P-2000 polarimeter with sodium lamp at 589 nm and a path of length of 1 dm. Solvent and concentration are specified in each case.

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[1] Kinss, M.; Sanders, J. K. M. *J. Mag. Res.* **1984**, *56*, 518.

X-ray: Data collections were performed using an Agilent Supernova diffractometer equipped with an Atlas CCD area detector, and a CuKα micro-focus source with multilayer optics (λ = 1.54184Å, 250μm FWHM beam size). The sample was kept at 150 K with an Oxford Cryosystems Cryostream 700 cooler. The quality of the crystals was checked under a polarizing microscope, and a suitable crystal or fragment was mounted on a Mitegen Micromount™ using Paratone N inert oil and transferred to the diffractometer.

Miscellaneous: 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.[2] EtCN was distilled over CaH_2 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 $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 ºC, and allowed to cool under a dehumidified atmosphere. Reactions at reduced temperatures were carried out using a Termo Haake EK90 refrigerator. Reactions were monitored using analytical thin layer chromatography (TLC), in pre-coated silica-backed plates (Merck Kiesegel 60 F254). These were visualized by ultraviolet irradiation, *p*-anisaldehyde, phosphomolybdic acid or potassium permanganate dips.[3] For flash chromatography Silicycle 40-63, 230-400 mesh silica gel was used.[4] For the removal of the solvents under reduced pressure Büchi R-210 rotatory evaporators were used. For precision weighing Sartorius Analytical Balance Practum 224-1S was used (± 0.1 mg).

[2] (a) Amarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals 7th* ed.; Elsveier: Oxford, 2012. (b) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351.
[3] Stahl, E. *Thin Layer Chromatography*, Springer Verlag: Berlin, 1969.
[4] Still, W. C.; Kahn, H.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

2. SYNTHESIS OF STARTING MATERIALS

2.1 Synthesis of acetoacetates and vinylarenes

2.1.1 Synthesis of acetoacetates (SI-1a-n)

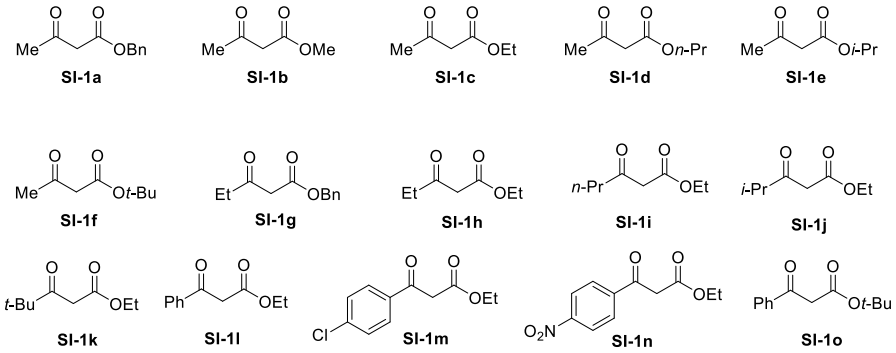


Figure 4. 1 Acetoacetates employed for the synthesis of donor-acceptor cyclopropanes

Acetoacetates **SI-1a-c**, **SI-1e-l** and **SI-1n-o** were obtained from commercial sources. Intermediates **SI-1d**[5] and **SI-1m**[6] were prepared following the procedures described in the literature.

[5] Maryam, I.; Asghar, D.; Reza, N. A.; Rerza, D. A.; Abbas, S. *Arch. Pharm. Res.* **2011**, *34*, 1417.
[6] Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617.

2.1.2 Synthesis of vinylarenes (SI-2a-ah)

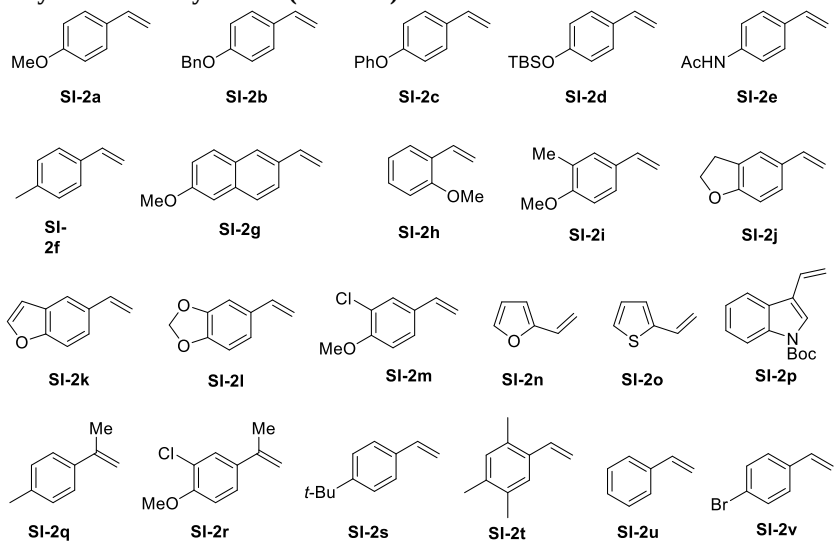
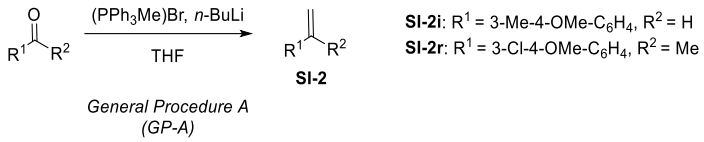


Figure 4. 2 Vinylarenes employed for the synthesis of donor-acceptor cyclopropanes

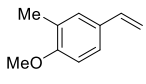
Vinylarenes **SI-2a**, **SI-2f**, **SI-2h**, **SI-2q** and **SI-2s-2v** were obtained from commercial sources. Vinylarenes **SI-2b**,[7] **SI-2c**,[8] **SI-2d**,[9] **SI-2e**,[10] **SI-2g**,[11] **SI-2j**,[12] **SI-2k**,[13] **SI-2l**,[14] **SI-2m**,[15] **SI-2n**,[9] **SI-2o**[16] and **SI-2p**[9] are reported compounds and were prepared following the procedures described in the literature. Vinylarenes **SI-2i** and **SI-2r** were prepared following the General Procedure A.

[7] Gieshoff, T. N.; Chakraborty, U.; Villa, M.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 3385.
[8] Wei, L.; Ren, W.; Li, J.; Shi, Y.; Chang, W.; Shi, Y. *Org. Lett.* **2017**, *19*, 1448.
[9] Garcia-Barrantes, P. M.; Lindsley, C. W. *Org. Lett.* **2016**, *18*, 3810.
[10] Li, R.; Chen, X.; Song, X.-R.; Ding, H.; Wang, P.; Xiao, Q.; Liang, Y.-M. *Adv. Synth. Catal.* **2017**, *359*, 3962.
[11] Butcher, T. W.; McClain, E. J.; Hamilton, T. G.; Perrone, T. M:; Kroner, K. M:; Donohoe, G. C.; Akhmedov, N. G.; Petersen, J. L.; Popp, B. V. *Org. Lett.* **2016**, *18*, 6428.
[12] Li, R.; Chen, X.; Song, X.-R.; Ding, H.; Wang, P.; Xiao, Q.; Liang, Y.-M. *Adv. Synth. Catal.* **2017**, *359*, 3962.
[13] Zhou, Y.; Bandar, J. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 8126.
[14] Audubert, C.; Gamboa Marin, O. J.; Lebel, H. *Angew. Chem. Int. Ed.* **2017**, *56*, 6294.
[15] Katritzky, A. R.; Wang, Z.; Wang, M.; Wilkerson, C. R.; Hall, C. D.; Akhmedov, N. G. *J. Org. Chem.* **2004**, *69*, 6617.
[16] Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693.

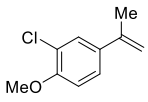


Scheme 4. 1 General Procedure A for the synthesis of vinylarenes from carbonyl compounds

General Procedure A (GP-A) for the synthesis of vinylarenes from carbonyl compounds. To a stirred solution of methyltriphenylphosphonium bromide (15.8 mmol, 1.2 eq) in THF (140 mL), cooled to -78 ºC, *n*-butyllithium (14.5 mmol, 2.2M in hexanes, 1.1 eq) was slowly added. The resulting suspension was allowed to warm to 0 ºC and stirred for an hour. A solution of the corresponding carbaldehyde or ketone (13.2 mmol, 1.0 eq) in THF (18 mL) was then added. The resulting solution was stirred at room temperature for an hour, then poured onto water and extracted with EtOAc (2×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was then purified by flash column chromatography.

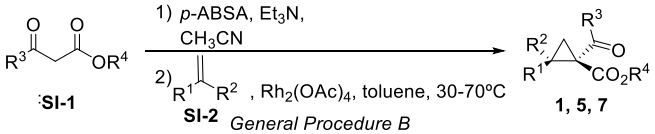


1-Methoxy-2-methyl-4-vinylbenzene (SI-2i). Following *GP-A*, **SI-2i** (1.6 g, 10.8 mmol, 82%) was isolated by FC (petroleum ether/EtOAc, 19:1) on silica gel as a colorless oil, starting from a solution of methyltriphenylphosphonium bromide (5.6 g, 15.8 mmol, 1.2 eq) in THF (140 mL), *n*-butyllithium (6.6 mL, 14.5 mmol, 2.2M in hexanes, 1.1 eq), and a solution of 4-methoxy-3-methylbenzaldehyde (2.0 g, 13.2 mmol, 1.0 eq) in THF (18 mL). R_f= 0.60 (petroleum ether). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.12 (m, 2H, C_{arom}-H), 6.81 (d, *J* = 8.3, Hz, 1H, C_{arom}-H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H, C**H**=CH_2), 5.66 (dd, *J* = 17.6, 1.1 Hz, 1H, CH=C**H$_a$**H$_b$), 5.34 (dd, *J* = 10.9, 1.0 Hz, 1H, CH=CH$_a$**H$_b$**), 3.87 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.7 (**C**$_{arom}$-OCH_3), 136.5 (**C**H=CH_2), 130.0 (**C**$_{arom}$-CH=CH_2), 128.4 (C_{arom}-H), 126.5 (C_{arom}-H), 125.0 (C_{arom}-H), 111.1 (CH=**C**H_2), 109.7 (C_{arom}-H), 55.1 (OCH_3), 16.2 (CH_3). **IR** (ATR): 2835 (C-H st), 1636 (C=C st) cm^{-1}. **MS** (EI) m/z (%): 148.1 (M^+, 100), 133.1 (57), 79.1 (19), 77.1 (22). **HRMS**: Calculated for $[C_{10}H_{13}O]^+$: 149.0966 $[M+H]^+$; found: 149.0970.



2-Chloro-1-methoxy-4-(prop-1-en-2-yl)benzene (SI-2r). Following *GP-A*, **SI-2r** (1.9 g, 10.5 mmol, 80%) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a white solid, starting from a solution of methyltriphenylphosphonium bromide (5.6 g, 15.8 mmol, 1.2 eq) in THF (140 mL), *n*-butyllithium (6.6 mL, 14.5 mmol, 2.2M in hexanes, 1.1 eq), and a solution of 1-(3-chloro-4-methoxyphenyl)ethan-1-one (2.4 g, 13.2 mmol, 1.0 eq) in THF (18 mL). R_f= 0.60 (petroleum ether). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.3 Hz, 1H, C_{arom}-H), 7.33 (dd, *J* = 8.6, 2.3 Hz, 1H, C_{arom}-H), 6.88 (d, *J* = 8.6 Hz, 1H, C_{arom}-H), 5.30 (br s, 1H, CH=C**H$_a$**H$_b$), 5.03 (quintet, *J* = 1.4 Hz, 1H, CH=CH$_a$**H$_b$**), 3.91 (s, 3H, OCH_3), 2.11 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.4 (**C**$_{arom}$-OCH_3), 141.6 (**C**=CH_2), 134.9 (C_{arom}), 127.6 (C_{arom}-H), 124.9 (C_{arom}-H), 122.3 (C_{arom}-Cl), 111.9 (CH=**C**H_2), 111.8 (C_{arom}-H), 56.3 (OCH_3), 21.9 (CH_3). **IR** (ATR): 1624 (C=C st), 1062 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 182.0 (M^+, 100), 169.0 (26), 167.0 (47), 103.1 (82), 77.0 (31), 63.1 (18). **M.p.**: 43-45 ºC (petroleum ether/EtOAc).

2.2 Synthesis of doubly activated cyclopropanes (1a-r, 5a-e, 7a-m)



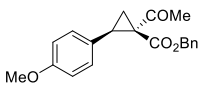
General Procedure B (GP-B)

1a: R^1 = 4-OMe-C_6H_4 R^2 = H, R^3 = Me, R^4 = Bn
1b: R^1 = 4-OBn-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
1c: R^1 = 4-OPh-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
1d: R^1 = 4-OTBS-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
1e: R^1 = 4-NHAc-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
1f: R^1 = 4-Me-C_6H_4, R^2 = H, R^3 = Me, R^4 = Me
1g: R^1 = 6-methoxynaphthalen-2-yl, R^2 = H, R^3 = Me, R^4 = Bn
1h: R^1 = 2-OMe-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
1i: R^1 = 3-Me-4-OMe-C_6H_3, R^2 = H, R^3 = Me, R^4 = Bn
1j: R^1 = 2,3-dihydrobenzofuran-5-yl, R^2 = H, R^3 = Me, R^4 = Bn
1k: R^1 = benzofuran-5-yl, R^2 = H, R^3 = Me, R^4 = Bn
1l: R^1 = 3,4-(OCH_2O)-C_6H_3, R^2 = H, R^3 = Me, R^4 = Bn
1m: R^1 = 3-Cl-4-OMe-C_6H_3, R^2 = H, R^3 = Me, R^4 = Bn
1n: R^1 = 2-furyl, R^2 = H, R^3 = Me, R^4 = Bn
1o: R^1 = 2-thienyl, R^2 = H, R^3 = Me, R^4 = Bn
1p: R^1 = *N*-Boc-indol-3-yl, R^2 = H, R^3 = Me, R^4 = Bn
1q: R^1 = 4-Me-C_6H_4, R^2 = Me, R^3 = Me, R^4 = Bn
1r: R^1 = 3-Cl-4-OMe-C_6H_3, R^2 = Me, R^3 = Me, R^4 = Bn

5a: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3= Me, R^4 = Me
5b: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Me, R^4 = Et
5c: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Me, R^4 = *n*-Pr
5d: R^1 =4-OMe-C_6H_4, R^2 = H, R^3 = Me, R^4 = *i*-Pr
5e: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Me, R^4 = *t*-Bu
7a: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Et, R^4 = Bn
7b: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Et, R^4 = Et
7c: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = *n*-Pr, R^4 = Et
7d: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = *i*-Pr, R^4 = Et
7e: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = *t*-Bu, R^4 = Et
7f: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Ph, R^4 = Et
7g: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = 4-Cl-C_6H_4, R^4 = Et
7h: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = 4-NO_2-C_6H_4, R^4 = Et
7i: R^1 = 4-Me-C_6H_4, R^2 = H, R^3 = Ph, R^4 = Et
7j: R^1 = 4-*t*-Bu-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn
7k: R^1 = 2,4,6-Me_3-C_6H_2, R^2 = H, R^3 = Me, R^4 = Bn
7l: R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Bn
7m: R^1 = 4-OMe-C_6H_4, R^2 = H, R^3 = Ph, R^4 = *t*-Bu
7n: R^1 = 4-Br-C_6H_4, R^2 = H, R^3 = Me, R^4 = Bn

Scheme 4. 2 General Procedure B for the synyhesis of doubly activated cyclopropanes

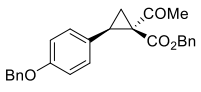
General Procedure B (GP-B) for the synthesis of donor-acceptor cyclopropanes 1a-ah. To a solution of the corresponding β-ketoester **SI-1** (1.0 eq) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (1.2 eq) in acetonitrile (0.13M), triethylamine (1.5 eq) was added dropwise at 0 ºC. The resulting mixture was stirred at room temperature for 8-12 hours, time during which the corresponding sulfonamide precipitated. Volatiles were evaporated, the residue was was suspended in CH_2Cl_2, silica gel was added and solvent was evaporated. The resulting solid mixture was loaded onto a pad of silica and eluted with petroleum ether/EtOAc (10:1) to provide the corresponding diazocompound. Benzyl 2-diazo-3-oxobutanoate[17] was synthesized in 10 g-scale[18] and used for the synthesis of cyclopropanes **1a-e**, **1g-r** and **7j-l**. The rest of diazocompounds were immediately used in the next step without further purification. Cyclopropanes **1a-r**, **5a-e**, **7a-m** were prepared following a modified procedure.[19] The catalyst $Rh_2(OAc)_4$ (0.3-2 mol%) was added to a solution of the corresponding crude diazocompound (1.0 eq) and vinylarene in dry toluene or dichloromethane (0.15-1 M) and the mixture was stirred between 30-70 ºC. After completion of the reaction, the mixture was quenched with H_2O. The aqueous phase was extracted with EtOAc (2×20 mL) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and purified by flash column chromatography after evaporation of volatiles for the obtention of pure cyclopropane.



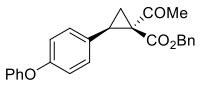
Benzyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (1a). Following *GP-B*, **1a** (556.0 mg, 2.5 mmol, 49%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as white solid starting from benzyl 2-diazo-3-oxobutanoate benzyl 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), 4-methoxystyrene (3.6 mL, 26.0 mmol, 5.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 3H, C_{arom}-H), 7.15-6.95 (m, 4H, C_{arom}-H), 6.75 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 4.88 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.75 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.78 (s, 3H, OCH_3), 3.24 (app t, *J*= 8.7 Hz, 1H, C**H**CH_2), 2.43 (s, 3H, CH_3C=O), 2.21 (dd, *J* = 8.2, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.74 (dd, *J* = 9.2, 4.5 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.2 (CH_3**C**=O), 168.3 (COO), 159.0 (**C**$_{arom}$-OCH_3), 135.1 (C_{arom}), 130.0 (2×C_{arom}-H), 128.51 (2×C_{arom}-H), 128.48 (2×C_{arom}-H), 128.3 (C_{arom}-H), 126.6 (C_{arom}), 113.7 (2×C_{arom}-H), 67.1 (OCH_2), 55.2

[17] Meyer, M. E.; Ferreira, E. M.; Stoltz, B. M. *Chem. Commun.* **2006**, 1316.
[18] From benzyl acetoacetate (10.0 g, 52.0 mmol, 1.0 eq) and *p*-ABSA (15.0 g, 62.4 mmol, 1.2 eq) in CH_3CN (370 mL), and Et_3N (10.9 mL, 78.0 mmol, 1.5 eq), to afford bezyl 2-diazo-3-oxobutanoate in >90% yield.
[19] Liu, C.; Zhou, L.; Huang, W.; Wang, M.; Man, G. *Tetrahedron* **2016**, *72*, 563.

(OCH_3), 44.8 (**C**CH_2), 35.5 (**C**H_3C=O), 29.8 (**C**HCH_2), 21.9 (CH**C**H_2). **IR** (ATR): 1728 (C=O st), 1689 (C=O st), 1183 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 324.1 (M^+, 7), 233.1 (19), 91.1 (100), 77.1 (18). **HRMS**: Calculated for $[C_{20}H_{21}O_4]^+$: 325.1440 [M+H]$^+$; found: 325.1452. **M.p.**: 81-84 ºC (petroleum ether/EtOAc).

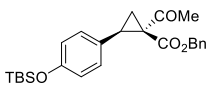


Benzyl 1-acetyl-2-(4-(benzyloxy)phenyl)cyclopropane-1-carboxylate (1b). Following *GP-B*, **1b** (1.02 g, mmol, 36%, dr > 20:1) was isolated by FC (petroleum ether/dichloromethane, 2:3) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.53 g, 7.0 mmol, 1.0 eq), 4-benzoxystyrene (1.90 g, 9.1 mmol, 1.3 eq), dichloromethane (50 mL) and $Rh_2(OAc)_4$ (9.6 mg, 0.022 mmol, 0.3 mol%). R_f= 0.80 (dichloromethane). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52-7.27 (m, 8H, C_{arom}-H), 7.09 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.06-7.00 (m, 2H, C_{arom}-H), 6.83 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 5.03 (s, 2H, $ArOCH_2$), 4.87 (d, *J* = 12.1 Hz, 1H, COOC**H$_a$**H$_b$), 4.72 (d, *J* = 12.0 Hz, 1H, COOCH$_a$**H$_b$**), 3.24 (app t, *J*= 8.7 Hz, 1H, C**H**CH_2), 2.43 (s, 3H, CH_3C=O), 2.21 (dd, *J* = 8.2, 4.5, Hz, 1H, CHC**H$_a$**H$_b$), 1.74 (dd, *J* = 9.2, 4.6, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.3 (CH_3**C**=O), 168.4 (COO), 158.3 (**C**$_{arom}$-OCH_3), 137.0 (C_{arom}), 135.1 (C_{arom}), 130.1 (2×C_{arom}-H), 128.7 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (C_{arom}-H), 128.1 (C_{arom}-H), 127.6 (2×C_{arom}-H), 127.0 (C_{arom}), 114.7 (2×C_{arom}-H), 70.1 ($ArOCH_2$), 67.3 (COO**C**H_2), 44.9 (**C**CH_2), 35.6 (**C**H_3C=O), 29.8 (**C**HCH_2), 22.0 (CH**C**H_2). **IR** (ATR): 1726 (C=O st), 1689 (C=O st), 1178 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 400.2 (M^+, 3), 91.0 (100), 65.1 (11). **HRMS**: Calculated for $[C_{26}H_{25}O_4]^+$: 401.1753 [M+H]$^+$; found: 401.1758. **M.p.**: 67-70 ºC (petroleum ether/dichloromethane).

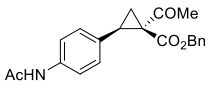


Benzyl 1-acetyl-2-(4-phenoxyphenyl)cyclopropane-1-carboxylate (1c). Following *GP-B*, **1c** (568 mg, 1.5 mmol, 21%, dr > 20:1) was isolated by FC (petroleum ether/dichloromethane, 2:3) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.53 g, 7.0 mmol, 1.0 eq), 4-phenoxystyrene (1.38 g, 7.0 mmol, 1.0 eq), dichloromethane (7 mL) and $Rh_2(OAc)_4$ (9.6 mg, 0.002 mmol, 0.3 mol%). R_f= 0.50 (petroleum ether/dichloromethane, 1:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.27 (m, 5H, C_{arom}-H), 7.19-7.06 (m, 5H, C_{arom}-H), 7.01 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.89 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 4.95 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.81 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.31 (app t, *J*= 8.6 Hz, 1H, C**H**CH_2), 2.47 (s, 3H, CH_3C=O), 2.25 (dd, *J* = 8.1, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.78 (dd, *J* = 9.1, 4.6 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.9 (CH_3**C**=O), 168.1

(COO), 156.9 (C_{arom}-O), 156.6 (C_{arom}-O), 134.9 (C_{arom}), 130.2 (2×C_{arom}-H), 129.8 (2×C_{arom}-H), 129.4 (C_{arom}), 128.5 (2×**C**$_{arom}$-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 123.4 (C_{arom}-H), 119.0 (2×C_{arom}-H), 118.4 (2×C_{arom}-H), 67.1 (OCH_2), 44.7 (**C**CH_2), 35.1 (**C**H_3C=O), 29.6 (**C**HCH_2), 21.8 (CH**C**H_2). **IR** (ATR): 1728 (C=O st), 1689 (C=O st), 1185 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 386.2 (M^+, 4), 356.0 (16), 295.0 (16), 115.0 (16), 91.1 (100), 77.2 (17). **HRMS**: Calculated for $[C_{25}H_{23}O_4]^+$: 387.1596 $[M+H]^+$; found: 387.1592. **M.p.**: 66-69 ºC (petroleum ether/dichloromethane).

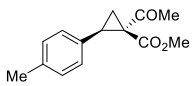


Benzyl 1-acetyl-2-(4-((tert-butyldimethylsilyl)oxy)phenyl)cyclopropane-1-carboxylate (1d). Following *GP-B*, **1d** (845 mg, 2.0 mmol, 30%, dr > 20:1) was isolated by FC (petroleum ether/dichloromethane, 2:3) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.45 g, 6.6 mmol, 1.0 eq), *tert*-butyldimethyl(4-vinylphenoxy)silane (1.56 g, 6.6 mmol, 1.0 eq), dichloromethane (50 mL) and $Rh_2(OAc)_4$ (9.1 mg, 0.021 mmol, 0.3 mol%). R_f= 0.30 (petroleum ether/dichloromethane, 1:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.27 (m, 3H, C_{arom}-H), 7.10-7.06 (m, 2H, C_{arom}-H), 7.04 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.71 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 4.84 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.70 (d, *J* = 12.0 Hz, 1H, OCH$_a$**H$_b$**), 3.23 (app t, *J*= 8.7 Hz, 1H, C**H**CH_2), 2.42 (s, 3H, CH_3C=O), 2.20 (dd, *J* = 8.2, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.73 (dd, *J* = 9.1, 4.6 Hz, 1H, CHCH$_a$**H$_b$**), 0.98 (s, 9H, C(C**H**$_3$)$_3$), 0.18 (s, 6H, Si(C**H**$_3$)$_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.1 (CH_3**C**=O), 168.2 (COO), 155.1 (C_{arom}-O), 133.0 (C_{arom}), 129.9 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 127.4 (C_{arom}), 119.8 (2×C_{arom}-H), 67.1 (OCH_2), 44.8 (**C**CH_2), 35.6 (**C**H_3C=O), 29.7 (**C**HCH_2), 25.7 (SiC(**C**H_3)$_3$), 21.9 (CH**C**H_2), 18.2 (Si**C(**CH_3)$_3$), -4.3 (Si(CH_3)$_2$). **IR** (ATR): 1728 (C=O st), 1690 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 424.3 (M^+, 6), 333.1 (24), 91.1 (100), 73.1 (21), 57.1 (15). **HRMS**: Calculated for $[C_{25}H_{33}O_4Si]^+$: 425.2148 $[M+H]^+$; found: 425.2140. **M.p.**: 58-62 ºC (petroleum ether/dichloromethane).

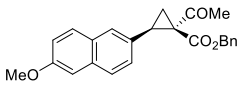


Benzyl 2-(4-acetamidophenyl)-1-acetylcyclopropane-1-carboxylate (1e). Following *GP-B*, **1e** (301.0 mg, 0.86 mmol, 15%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 2:1 to 1:2) on silica gel as an orange solid starting from benzyl 2-diazo-3-oxobutanoate (1.31 g, 6.0 mmol, 1.0 eq), *N*-(4-vinylphenyl)acetamide (1.45 g, 9.0 mmol, 1.5 eq), dichloromethane (25 mL) and $Rh_2(OAc)_4$ (13.3 mg, 0.03 mmol, 0.5 mol%). R_f= 0.20 (petroleum ether/EtOAc, 2:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.96 (br s, 1H, NH), 7.40 (d, *J* = 8.5Hz, 2H, C_{arom}-H), 7.29-7.23 (m, 3H, C_{arom}-H), 7.08 (d, *J* =

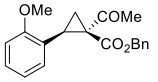
8.4 Hz, 2H, C_{arom}-H), 7.05-6.98 (m, 2H, C_{arom}-H), 4.85 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.73 (d, *J* = 12.0 Hz, 1H, OCH$_a$**H$_b$**), 3.23 (app t, *J* = 8.6 Hz, 1H, C**H**CH$_2$), 2.44 (s, 3H, CH$_3$C(O)-C), 2.20 (dd, *J* = 8.2, 4.7 Hz, 1H, CHC**H$_a$**H$_b$), 2.15 (s, 3H, CH$_3$C(O)-N), 1.72 (dd, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.2 (CH$_3$**C(**O)-C), 168.6 (CH$_3$**C(**O)-N), 168.1 (COO), 137.6 (**C**$_{arom}$-C), 134.9 (C_{arom}), 130.3 (C_{arom}), 129.4 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (C_{arom}-H), 119.5 (2×C_{arom}-H), 67.3 (OCH$_2$), 44.8 (**C**CH$_2$), 35.3 (**C**H$_3$C(O)C), 29.7 (**C**HCH$_2$), 24.6 (**C**H$_3$C(O)-N), 21.8 (CH**C**H$_2$). **IR** (ATR): 3349 (NH st), 1722 (C=O st), 1687 (C=O st), 1664 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 351.2 (M$^+$, 5), 104.9 (15), 91.0 (100), 77.1 (20), 65.0 (18). **HRMS**: Calculated for $[C_{21}H_{22}NO_4]^+$: 352.1549 [M+H]$^+$; found: 352.1559. **M.p.**: 83-86 ºC (petroleum ether/EtOAc).



Benzyl 1-acetyl-2-(p-tolyl)cyclopropane-1-carboxylate (1f). Following *GP-B*, **1f** (673.6 mg, 2.9 mmol, 84%, dr 3.5:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as yellow oil starting from crude methyl 2-diazo-3-oxobutanoate (0.72 g, 3.4 mmol, 1.0 eq), 4-methylstyrene (2.0 g, 16.9 mmol, 5.0 eq), toluene (3.4 mL) and $Rh_2(OAc)_4$ (24.6 mg, 0.05 mmol, 2 mol%). R_f= 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.11-7.06 (m, 4H, C_{arom}-H), 3.80* (s, 3H, OCH$_3$), 3.37 (s, 3H, OCH$_3$), 3.23 (app t, *J* = 8.6 Hz, 1H, C**H**CH$_2$), 2.44 (s, 3H, CH$_3$C=O), 2.30 (s, 3H, C_{arom}-CH$_3$), 2.29* (s, 3H, CH$_3$C=O), 2.21 (dd, *J* = 8.1, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.95* (s, 3H, C_{arom}-CH$_3$), 1.73 (dd, *J* = 9.1, 4.6, 1.1 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.3 (CH$_3$**C**=O), 200.1* (CH$_3$**C**=O), 171.1* (COO), 168.8 (COO), 137.3* (C_{arom}), 137.1 (C_{arom}), 131.8 (C_{arom}), 130.7* (C_{arom}), 129.2* (2×C_{arom}-H), 128.9 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.3* (2×C_{arom}-H), 52.6* (OCH$_3$), 52.0 (OCH$_3$), 44.8 (**C**CH$_2$), 44.2* (**C**CH$_2$), 35.6 (**C**H$_3$C=O), 34.6* (**C**H$_3$C=O), 30.4* (**C**HCH$_2$), 29.7 (**C**HCH$_2$), 21.8 (CH**C**H$_2$), 21.2 (C_{arom}-**C**H$_3$), 21.1* (C_{arom}-**C**H$_3$), 18.0* (CH**C**H$_2$). **IR** (ATR): 1731 (C=O st), 1694 (C=O st), 1166 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 232.1 (M$^+$, 9), 200.1 (50), 190.1 (22), 185.1 (100), 158.1 (21), 130.1 (26), 129.1 (63), 128.1 (42), 127.1 (18), 115.1 (49), 91.1 (21). **HRMS**: Calculated for $[C_{14}H_{17}O_3]^+$: 233.1178 [M+H]$^+$; found: 233.1184.

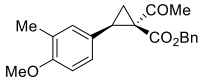


Benzyl 1-acetyl-2-(6-methoxynaphthalen-2-yl)cyclopropane-1-carboxylate (1g). Following *GP-B,* **1g** (676.6 mg, 1.8 mmol, 67%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (0.59 mmol, 2.7 mmol 1.0 eq) and 2-methoxy-6-vinylnaphthalene (1.0 g, 5.4 mmol, 2.0 eq), toluene (2.7 mL) and $Rh_2(OAc)_4$ (23.9 mg, 0.05 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64-7.60 (m, 2H, C_{arom}-H), 7.56 (s, 1H, C_{arom}-H), 7.28 (dd, *J* = 8.6, 1.9 Hz, 1H, C_{arom}-H), 7.22-7.12 (m, 2H, C_{arom}-H), 7.14-7.05 (m, 3H, C_{arom}-H), 6.85-6.81 (m, 2H, C_{arom}-H), 4.80 (d, *J* = 12.0 Hz, 1H, OC**H$_a$**H$_b$), 4.64 (d, *J* = 12.0 Hz, 1H, OCH$_a$**H$_b$**), 3.93 (s, 3H, OCH_3), 3.45 (app t, *J* = 8.5 Hz, 1H, C**H**CH_2), 2.49 (s, 3H, CH_3C=O), 2.39 (dd, *J* = 8.2, 4.7 Hz, 1H, CHC**H$_a$**H$_b$), 1.84 (dd, *J* = 9.1, 4.6 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.1 (CH_3**C**=O), 168.2 (COO), 157.8 (**C**$_{arom}$-OCH_3), 134.8 (C_{arom}), 133.9 (C_{arom}), 129.9 (C_{arom}), 129.4 (C_{arom}-H), 128.6 (C_{arom}), 128.4 (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 128.2 (C_{arom}-H), 127.5 (C_{arom}-H), 127.5 (C_{arom}-H), 126.7 (C_{arom}-H), 119.0 (C_{arom}-H), 105.7 (C_{arom}-H), 67.2 (OCH_2), 55.3 (OCH_3), 44.9 (**C**CH_2), 36.0 (**C**H_3C=O), 29.7 (**C**HCH_2), 21.8 (CH**C**H_2). **IR** (ATR): 1721 (C=O st), 1693 (C=O st), 1189 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 374.0 (M^+, 21), 266.0 (17), 223.1 (21), 206.9 (22), 195.1 (28), 153.2 (19), 152.2 (15), 91.1 (100), 77.0 (24), 51.0 (16). **HRMS**: Calculated for $[C_{24}H_{23}O_4]^+$: 375.1596 $[M+H]^+$; found: 375.1608. **M.p.**: 114-117 ºC (petroleum ether/EtOAc).

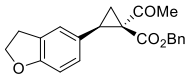


Benzyl 1-acetyl-2-(2-methoxyphenyl)cyclopropane-1-carboxylate (1h). Following *GP-B,* **1h** (1.3 g, 4.1 mmol, 78%, dr 5:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a colorless oil starting from benzyl 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), 2-methoxystyrene (3.6 mL, 26.0 mmol, 5.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.61-7.7.47* (m, 1H, C_{arom}-H), 7.42-7.36 (m, 1H, C_{arom}-H), 7.33-7.20 (m, 3H, C_{arom}-H), 7.10-6.98 (m, 3H, C_{arom}-H), 6.90-6.82 (m, 1H, C_{arom}-H), 6.76 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 5.31* (d, *J* = 12.5 Hz, 1H, OC**H$_a$**H$_b$), 5.25* (d, *J* = 12.4 Hz, 1H, OCH$_a$**H$_b$**), 4.85 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.65 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.82* (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.40* (app t, *J* = 8.7 Hz, 1H, C**H**CH_2), 3.13 (app t, *J* = 8.8 Hz, 1H, C**H**CH_2), 2.52 (s, 3H, CH_3C=O), 2.35* (dd, *J* = 8.6, 4.7 Hz, 1H, CHC**H$_a$**H$_b$), 2.20 (dd, *J* = 8.4, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 2.02* (s, 3H, CH_3C=O), 1.90 (dd, *J* = 9.1, 4.5 Hz, 1H, CHCH$_a$**H$_b$**), 1.72* (dd, *J* = 8.9, 4.7 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.7 (CH_3**C**=O), 200.1* (CH_3**C**=O), 169.9* (COO), 168.5 (COO), 159.0 (**C**$_{arom}$-OCH_3), 158.6* (**C**$_{arom}$-OCH_3), 135.7*

(C_{arom}), 135.3 (C_{arom}), 128.9 (C_{arom}-H), 128.8* (C_{arom}-H), 128.7 (C_{arom}-H), 128.6* (C_{arom}-H), 128.41 (2×C_{arom}-H), 128.39 (2×C_{arom}-H), 128.2 (C_{arom}-H), 128.0* (C_{arom}-H), 123.5 (C_{arom}), 122.4* (C_{arom}), 120.3* (C_{arom}-H), 120.0 (C_{arom}-H), 110.0 (C_{arom}-H), 109.7* (C_{arom}-H), 66.9* (OCH_2), 66.7 (OCH_2), 55.3 (OCH_3), 55.2* (OCH_3), 43.3 (**C**CH_2), 43.0* (**C**CH_2), 32.8 (**C**H_3C=O), 31.4* (**C**H_3C=O), 29.8 (**C**HCH_2), 29.6* (**C**HCH_2), 20.4 (CH**C**H_2), 17.5* (CH**C**H_2). **IR** (ATR): 1721 (C=O st), 1693 (C=O st), 1170 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 324.1 (M^+, 2), 91.1 (100), 77.0 (11), 65.1 (11). **HRMS**: Calculated for $[C_{20}H_{21}O_4]^+$: 325.1440 $[M+H]^+$; found: 325.1449.

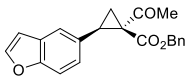


Benzyl 1-acetyl-2-(4-methoxy-3-methylphenyl)cyclopropane-1-carboxylate (1i). Following *GP-B*, **1i** (808.8 mg, 2.4 mmol, 46%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), 3-methyl-4-methoxystyrene (1.5 g, 10.4 mmol, 2.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.70 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.31-7.23 (m, 3H, C_{arom}-H), 7.05-6.85 (m, 4H, C_{arom}-H), 6.65 (d, *J* = 8.6 Hz, 1H, C_{arom}-H), 4.90 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.74 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.80 (s, 3H, OCH_3), 3.23 (app t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.44 (s, 3H, CH_3C=O), 2.22 (dd, *J* = 8.2, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 2.14 (s, 3H, C_{arom}-C**H**$_3$), 1.74 (dd, *J* = 9.2, 4.5 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.3 (CH_3**C**=O), 168.4 (COO), 157.2 (**C**$_{arom}$-OCH_3), 135.2 (C_{arom}), 131.4 (C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 127.1 (C_{arom}-H), 126.4 (C_{arom}), 126.2 (C_{arom}), 109.6 (C_{arom}-H), 67.1 (OCH_2), 55.3 (OCH_3), 44.9 (**C**CH_2), 35.8 (**C**H_3C=O), 29.8 (**C**HCH_2), 21.9 (CH**C**H_2), 16.3 (C_{arom}-**C**H_3). **IR** (ATR): 1728 (C=O st), 1685 (C=O st), 1176 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 338.2 (M^+, 4), 91.1 (100), 77.0 (15). **HRMS**: Calculated for $[C_{21}H_{23}O_4]^+$: 339.1596 $[M+H]^+$; found: 339.1603. **M.p.**: 77-79 ºC (petroleum ether/EtOAc).

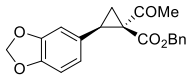


Benzyl 1-acetyl-2-(2,3-dihydrobenzofuran-5-yl)cyclopropane-1-carboxylate (1j). Following *GP-B*, **1j** (437 mg, mmol, 25%, dr 3.5:1) was isolated by FC (petroleum ether/EtOAc, 12:1) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.13 g, 5.2 mmol, 1.0 eq), 5-vinyl-2,3-dihydrobenzofuran (757 mg, 5.2 mmol, 1.0 eq), dichloromethane (50 mL) and $Rh_2(OAc)_4$ (7.1 mg, 0.016 mmol, 0.3 mol%). R_f=0.30 (petroleum ether/EtOAc, 8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.39-7.24 (m, 3H, C_{arom}-H), 7.07-6.85 (m, 4H, C_{arom}-H), 6.62 (d, *J* = 8.1 Hz, 1H, C_{arom}-H), 5.28* (d, *J* = 12.2 Hz, 1H, COOC**H$_a$**H$_b$), 5.17* (d, *J* =

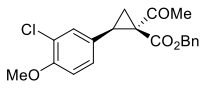
12.0 Hz, 1H, $COOCH_a\mathbf{H_b}$), 4.91 (d, *J* = 12.1 Hz, 1H, $COOC\mathbf{H_a}H_b$), 4.76 (d, *J* = 12.1 Hz, 1H, $COOCH_a\mathbf{H_b}$), 4.52 (t, *J*= 8.7 Hz, 2H, $OC\mathbf{H}_2CH_2$), 3.23 (app t, *J*= 8.9 Hz, 1H, $C\mathbf{H}CH_2$), 3.05 (t, *J* = 8.6 Hz, 2H, $OCH_2C\mathbf{H}_2$), 2.43 (s, 3H, CH_3C=O), 2.24-2.16 (m, 1H, $CHC\mathbf{H_a}H_b$), 1.98* (s, 3H, CH_3C=O), 1.73 (dd, *J* = 9.3, 4.6 Hz, 1H, $CHCH_a\mathbf{H_b}$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.3 ($CH_3\mathbf{C}$=O), 168.4 (COO), 159.7* ($\mathbf{C}_{arom}$-OCH_2), 159.6 ($\mathbf{C}_{arom}$-OCH_2), 135.4* (C_{arom}), 135.2 (C_{arom}), 128.8 (C_{arom}-H), 128.7 (C_{arom}-H), 128.6* (C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 128.0* (C_{arom}-H), 127.2* (C_{arom}), 127.0 (C_{arom}), 126.5 (C_{arom}), 126.4* (C_{arom}), 125.6 (C_{arom}-H), 124.8* (C_{arom}-H), 109.1* (C_{arom}-H), 108.9 (C_{arom}-H), 71.4* (OCH_2), 71.3 (OCH_2), 67.3* ($COO\mathbf{C}H_2$), 67.1 ($COO\mathbf{C}H_2$), 44.9 ($\mathbf{C}CH_2$), 44.3* ($\mathbf{C}CH_2$), 36.1 ($OCH_2\mathbf{C}H_2$), 35.1* ($OCH_2\mathbf{C}H_2$), 30.6* ($\mathbf{C}H_3C$=O), 29.8 ($\mathbf{C}H_3C$=O), 29.6* ($\mathbf{C}HCH_2$), 29.5 ($\mathbf{C}HCH_2$), 22.1 ($CH\mathbf{C}H_2$), 18.3* ($CH\mathbf{C}H_2$). **IR** (ATR): 1725 (C=O st), 1692 (C=O st), 1171 (C-O st as), 981 (C-O-C st as) cm^{-1}. **MS** (EI) m/z (%): 336.2 (M^+, 8), 245.1 (49), 157.1 (15), 91.1 (100), 65.0 (14). **HRMS**: Calculated for $[C_{21}H_{21}O_4]^+$: 337.1440 $[M+H]^+$; found: 337.1450. **M.p.**: 65-68 ºC (petroleum ether/EtOAc).



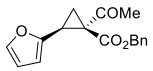
Benzyl 1-acetyl-2-(benzofuran-5-yl)cyclopropane-1-carboxylate (1k). Following *GP-B*, **1k** (115 mg, 0.34 mmol, 15%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 20:1) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (502 mg, 2.3 mmol, 1.0 eq), 5-vinylbenzofuran (332 mg, 2.3 mmol, 1.0 eq), dichloromethane (15 mL) and $Rh_2(OAc)_4$ (3.2 mg, 0.007 mmol, 0.3 mol%). R_f= 0.70 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.2 Hz, 1H, OCH), 7.41-7.37 (m, 1H, C_{arom}-H), 7.32 (d, *J* = 8.5 Hz, 1H, C_{arom}-H), 7.25-7.07 (m, 4H, C_{arom}-H), 6.98-6.82 (m, 2H, C_{arom}-H), 6.67 (dd, *J* = 2.2, 1.0 Hz, 1H, OCHC**H**), 4.82 (d, *J* = 12.0 Hz, 1H, $OC\mathbf{H_a}H_b$), 4.67 (d, *J* = 12.0 Hz, 1H, $OCH_a\mathbf{H_b}$), 3.41 (app t, *J*= 8.7 Hz, 1H, $C\mathbf{H}CH_2$), 2.47 (s, 3H, CH_3C=O), 2.31 (dd, *J* = 8.2, 4.6 Hz, 1H, $CHC\mathbf{H_a}H_b$), 1.79 (dd, *J* = 9.2, 4.6 Hz, 1H, $CHCH_a\mathbf{H_b}$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.2 ($CH_3\mathbf{C}$=O), 168.3 (COO), 154.4 ($\mathbf{C}_{arom}$-OCH), 145.4 (OCH), 134.9 (C_{arom}), 129.2 (C_{arom}), 128.4 (2×C_{arom}-H), 128.32 (2×C_{arom}-H), 128.28 (C_{arom}-H), 127.4 (C_{arom}), 125.5 (C_{arom}-H), 121.4 (C_{arom}-H), 111.1 (C_{arom}-H), 106.6 (C_{arom}-H), 67.2 (OCH_2), 44.9 ($\mathbf{C}CH_2$), 35.9 ($\mathbf{C}H_3C$=O), 29.8 ($\mathbf{C}HCH_2$), 22.1 ($CH\mathbf{C}H_2$). **IR** (ATR): 1726 (C=O st), 1690 (C=O st), 1249 (C-O-C st as), 1171 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 155.0 (35), 91.0 (100), 77.1 (37). **HRMS**: Calculated for $[C_{21}H_{19}O_4]^+$: 335.1283 $[M+H]^+$; found: 335.1292. **M.p.**: 70-73 ºC (petroleum ether/EtOAc).



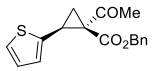
Benzyl 1-acetyl-2-(benzo-1,3-dioxol-5-yl)cyclopropane-1-carboxylate (1l). Following *GP-B,* **1l** (279 mg, 0.83 mmol, 21%, dr > 20:1) was isolated by FC (petroleum ether/dichloromethane, 1:2) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (0.85 g, 3.9 mmol, 1.0 eq), 5-vinylbenzo[d][1,3]dioxole (576 mg, 3.9 mmol, 1.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (5.3 mg, 0.012 mmol, 0.3 mol%) was added. R_f= 0.50 (dichloromethane). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44-7.27 (m, 3H, C_{arom}-H), 7.15-6.98 (m, 2H, C_{arom}-H), 6.64-6.62 (m, 3H, C_{arom}-H), 5.91 (s, 2H, OCH_2O), 4.93 (d, *J* = 12.0 Hz, 1H, OC**H$_a$**H$_b$), 4.81 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.21 (app t, *J*= 8.7 Hz, 1H, C**H**CH$_2$), 2.42 (s, 3H, CH_3C=O), 2.16 (dd, *J* = 8.2, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.70 (dd, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.1 (CH_3**C**=O), 168.2 (COO), 147.5 (**C**$_{arom}$-OCH_2), 147.0 (**C**$_{arom}$-OCH_2), 135.1 (C_{arom}), 128.6 (2×C_{arom}-H), 128.54 (2×C_{arom}-H), 128.49 (C_{arom}), 128.4 (C_{arom}-H), 122.3 (C_{arom}-H), 109.4 (C_{arom}-H), 108.1 (C_{arom}-H), 101.1 (OCH_2O), 67.3 (OCH_2), 44.7 (**C**CH_2), 35.7 (**C**H_3C=O), 29.8 (**C**HCH_2), 22.1 (CH**C**H_2). **IR** (ATR): 1727 (C=O st), 1698 (C=O st), 933 (C-O-C st as) cm^{-1}. **MS** (EI) m/z (%): 338.1 (M^+, 4), 91.1 (100), 77.0 (14), 65.0 (14). **HRMS**: Calculated for $[C_{20}H_{19}O_5]^+$: 339.1233 $[M+H]^+$; found: 339.1241. **M.p.**: 63-65 ºC (petroleum ether/dichloromethane).



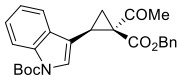
Benzyl 1-acetyl-2-(3-chloro-4-methoxyphenyl)cyclopropane-1-carboxylate (1m). Following *GP-B,* **1m** (196 mg, mmol, 19%, dr > 20:1) was isolated by FC (petroleum ether/dichloromethane, 1:2) on silica gel as white solid starting benzyl 2-diazo-3-oxobutanoate (0.63 g, 2.9 mmol, 1.0 eq), 3-chloro-4-methoxystyrene (0.97 g, 5.7 mmol, 2.0 eq), dichloromethane (25 mL) and $Rh_2(OAc)_4$ (3.9 mg, 0.009 mmol, 0.3 mol%). R_f= 0.85 (dichloromethane). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32-7.27 (m, 3H, C_{arom}-H), 7.19 (d, *J* = 2.5 Hz, 1H, C_{arom}-H), 7.09-7.03 (m, 2H, C_{arom}-H), 6.99 (ddd, *J* = 8.5, 2.3, 0.7 Hz, 1H, C_{arom}-H), 6.70 (d, *J* = 8.5 Hz, 1H, C_{arom}-H), 4.91 (d, *J* = 12.0 Hz, 1H, OC**H$_a$**H$_b$), 4.79 (d, *J* = 12.0 Hz, 1H, OCH$_a$**H$_b$**), 3.86 (s, 3H, OCH_3), 3.20 (app t, *J* = 8.6 Hz, 1H, C**H**CH$_2$), 2.42 (s, 3H, CH_3C=O), 2.16 (dd, *J* = 8.1, 4.7 Hz, 1H, CHC**H$_a$**H$_b$), 1.71 (dd, *J* = 9.2, 4.7 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.0 (CH_3**C**=O), 168.1 (COO), 154.4 (**C**$_{arom}$-OCH_3), 135.0 (C_{arom}), 130.8 (C_{arom}-H), 128.7 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5 (C_{arom}-H), 128.2 (C_{arom}-H), 127.9 (C_{arom}), 122.2 (C_{arom}-Cl), 111.6 (C_{arom}-H), 67.4 (OCH_2), 56.2 (OCH_3), 44.7 (**C**CH_2), 34.6 (**C**H_3C=O), 29.8 (**C**HCH_2), 21.9 (CH**C**H_2). **IR** (ATR): 1725 (C=O st), 1691 (C=O st), 1062 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 358.0 (M^+, 4), 168.9 (13), 91.1 (100). **HRMS**: Calculated for $[C_{20}H_{20}O_4Cl]^+$: 359.1050 $[M+H]^+$; found: 359.1057. **M.p.**: 89-92 ºC (petroleum ether/dichloromethane).



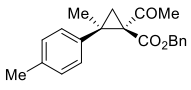
Benzyl 1-acetyl-2-(furan-2-yl)cyclopropane-1-carboxylate (1n). Following *GP-B*, **1n** (99 mg, 0.35 mmol, 10%, dr > 20:1) was isolated by FC (petroleum ether/Et_2O, 2:1) on silica gel as a colorless oil starting from benzyl 2-diazo-3-oxobutanoate (777.0 mg, 3.6 mmol, 1.0 eq), 2-vinylfuran (670 mg, 7.1 mmol, 2.0 eq), dichloromethane (25 mL) and $Rh_2(OAc)_4$ (4.9 mg, 0.011 mmol, 0.3 mol%) was added. R_f= 0.70 (petroleum ether/EtOAc, 5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H, C_{arom}-H), 7.23-7.19 (m, 3H, C_{arom}-H), 6.23 (dd, *J* = 3.3, 1.9 Hz, 1H, C_{arom}-H), 6.09 (dt, *J* = 3.3, 0.8 Hz, 1H, C_{arom}-H), 5.02 (d, *J* = 12.2 Hz, 1H, OC**H$_a$**H$_b$), 4.94 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.11 (app t, *J* = 8.7 Hz, 1H, C**H**CH$_2$), 2.38 (s, 3H, CH_3C=O), 2.13 (dd, *J* = 7.9, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.78 (dd, *J* = 9.4, 4.5 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.4 (CH_3**C**=O), 168.1 (COO), 149.8 (C_{arom}-O), 142.3 (OCH), 135.1 (C_{arom}), 128.7 (4×C_{arom}-H), 128.5 (C_{arom}-H), 110.6 (C_{arom}-H), 108.2 (C_{arom}-H), 67.6 (OCH_2), 44.1 (**C**CH$_2$), 29.6 (**C**H$_3$C=O), 28.5 (**C**HCH$_2$), 21.4 (CH**C**H$_2$). **IR** (ATR): 3120 (C-H st), 1726 (C=O st), 1695 (C=O st), 1172 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 284.1 (M^+, 5), 91.1 (100), 77.1 (16). **HRMS**: Calculated for $[C_{17}H_{17}O_4]^+$: 285.1127 $[M+H]^+$; found: 285.1141.



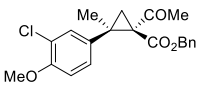
Benzyl 1-acetyl-2-(thiophen-2-yl)cyclopropane-1-carboxylate (1o). Following *GP-B*, **1o** (451.3 mg, 1.5 mmol, 32%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a yellow oil starting from benzyl 2-diazo-3-oxobutanoate (1.02 g, 4.7 mmol, 1.0 eq) 2-vinylthiophene (1.0 g, 9.4 mmol, 2.0 eq), toluene (4.7 mL) and $Rh_2(OAc)_4$ (41.5 mg, 0.09 mmol, 2 mol%) was added. R_f= 0.40 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.34-7.29 (m, 3H, C_{arom}-H), 7.17-7.12 (m, 3H, C_{arom}-H), 6.87 (dd, *J* = 5.1, 3.6 Hz, 1H, C_{arom}-H), 6.85-6.76 (m, 1H, C_{arom}-H), 4.95 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.86 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.33 (app t, *J* = 8.5 Hz, 1H, C**H**CH$_2$), 2.41 (s, 3H, CH_3C=O), 2.20 (dd, *J* = 7.8, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.83 (dd, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.6 (CH_3**C**=O), 167.9 (COO), 138.3 (C_{arom}-S), 135.0 (C_{arom}), 128.64 (2×C_{arom}-H), 128.61 (2×C_{arom}-H), 128.5 (C_{arom}-H), 126.8 (C_{arom}-H), 126.6 (C_{arom}-H), 125.2 (SCH), 67.5 (OCH_2), 45.4 (**C**CH$_2$), 30.2 (**C**H$_3$C=O), 29.8 (**C**HCH$_2$), 23.6 (CH**C**H$_2$). **IR** (ATR): 3099 (C-H st), 1724 (C=O st), 1694 (C=O st), 1176 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 300.1 (M^+, 8), 91.1 (100), 77.0 (18). **HRMS**: Calculated for $[C_{17}H_{17}O_3S]^+$: 301.0898 $[M+H]^+$; found: 301.0905.



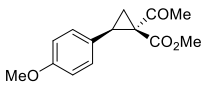
***tert*-Butyl 3-(2-acetyl-2-((benzyloxy)carbonyl)cyclopropyl)-1H-indole-1-carboxylate (1p).** Following *GP-A*, **1p** (653.0 mg, 1.5 mmol, 29%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a yellow oil starting from benzyl 2-diazo-3-oxobutanoate (1.13 g, 5.2 mmol, 1.0 eq), *N*-Boc-3-vinylindole (1.3 g, 5.2 mmol, 1.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.2Hz, 1H, C_{arom}-H), 7.53 (d, *J* = 7.8 Hz, 1H, C_{arom}-H), 7.43-7.33 (m, 2H, C_{arom}-H), 7.25-7.10 (m, 4H, C_{arom}-H), 8.84 (d, *J* = 7.4 Hz, 2H, C_{arom}-H), 4.79 (d, *J* = 12.0 Hz, 1H, OC**H$_a$**H$_b$), 4.71 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.25 (app t, *J* = 8.5 Hz, 1H, C**H**CH$_2$), 2.48 (s, 3H, CH_3C=O), 2.19 (dd, *J* = 8.0, 4.2 Hz, 1H, CHC**H$_a$**H$_b$), 1.84 (dd, *J* = 9.0, 4.2 Hz, 1H, CHCH$_a$**H$_b$**), 1.67 (s, 9H, CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.3 (CH_3**C**=O), 168.3 (**C**OOCH$_2$), 149.5 (N-**C**OO), 135.5 (C_{arom}), 134.5 (C_{arom}), 130.5 (C_{arom}), 128.43 (2×C_{arom}-H), 128.36 (2×C_{arom}-H), 128.3 (C_{arom}-H), 124.8 (C_{arom}-H), 124.3 (C_{arom}-H), 122.8 (C_{arom}-H), 119.3 (C_{arom}-H), 115.5 (C_{arom}), 115.4 (C_{arom}-H), 83.9 (**C**(CH$_3$)$_3$), 67.4 (OCH$_2$), 43.8 (**C**CH$_2$), 29.9 (**C**H$_3$C=O), 28.3 (C(**C**H$_3$)$_3$), 26.6 (**C**HCH$_2$), 21.7 (CH**C**H$_2$). **IR** (ATR): 1729 (C=O st), 1696 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{26}H_{28}NO_5]^+$: 434.1967 $[M+H]^+$; found: 434.1978.



Benzyl 1-acetyl-2-methyl-2-(p-tolyl)cyclopropane-1-carboxylate (1q). Following *GP-B*, **1q** (528.1 mg, 1.6 mmol, 21%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a yellow oil starting from benzyl 2-diazo-3-oxobutanoate (1.7 g, 7.8 mmol, 1.0 eq), 1-methyl-4-(prop-1-en-2-yl)benzene (5.2 g, 39.0 mmol, 5.0 eq), toluene (7.8 mL)and $Rh_2(OAc)_4$ (56.7 mg, 0.12 mmol, 2 mol%). R_f= 0.40 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32-7.22 (m, 3H, C_{arom}-H), 7.07 (d, *J* = 8.1 Hz, 2H, C_{arom}-H), 6.16 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 7.03-6.95 (m, 2H, C_{arom}-H), 4.80 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.57 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 2.61 (s, 3H, C_{arom}-CH_3), 2.34 (s, 3H, CH_3C=O), 2.18 (d, *J* = 5.0 Hz, 1H, CH_3CC**H**$_2$), 1.89 (d, *J* = 5.0 Hz, 1H, CH_3CC**H**$_2$), 1.40 (s, 3H, CH_2CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.5 (CH_3**C**=O), 168.6 (COO), 138.6 (C_{arom}), 136.8 (C_{arom}), 135.2 (C_{arom}), 129.2 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 128.2 (2×C_{arom}-H), 67.0 (OCH$_2$), 47.9 (CH_2**C**C=O), 40.7 (CH_3**C**CH$_2$), 31.7 (**C**H$_3$C=O), 23.5 (CH_3C**C**H$_2$), 23.2 (CH_3), 21.3 (CH_3). **IR** (ATR): 1727 (C=O st), 1703 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 231.1 (M^+-C_7H_7, 12), 187.1 (16), 91.0 (100), 77.1 (15). **HRMS**: Calculated for $[C_{21}H_{23}O_3]^+$: 323.1647 $[M+H]^+$; found: 323.1553.

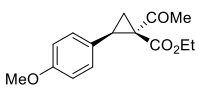


Benzyl 1-acetyl-2-(3-chloro-4-methoxyphenyl)-2-methylcyclopropane-1-carboxylate (1r). Following *GP-B*, **1r** (674.6 mg, 1.8 mmol, 37%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 8:2) on silica gel as a yellow oil starting from benzyl 2-diazo-3-oxobutanoate (1.1 g, 4.9 mmol, 1.0 eq), 2-chloro-1-methoxy-4-(prop-1-en-2-yl)benzene (4.4 mL, 24.4 mmol, 5.0 eq), toluene (4.9 mL) and $Rh_2(OAc)_4$ (35.4 mg, 0.07 mmol, 2 mol%). R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49-7.17 (m, 4H, C_{arom}-H), 7.10-6.97 (m, 3H, C_{arom}-H), 6.72 (d, *J* = 8.5 Hz, 1H, C_{arom}-H), 4.78 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.68 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.82 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3C=O), 2.11 (d, *J* = 5.3 Hz, 1H, CH_3CC**H$_a$**H$_b$), 1.85 (d, *J* = 5.1 Hz, 1H, CH_3CCH_a**H$_b$**), 1.35 (s, 3H, CH_2CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 201.7 (CH_3**C**=O), 168.1 (COO), 153.9 (**C**$_{arom}$-OCH_3), 134.8 (C_{arom}), 134.3 (C_{arom}), 129.9 (C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 128.2 (C_{arom}-H), 127.5 (C_{arom}-H), 122.0 (C_{arom}-Cl), 111.6 (C_{arom}-H), 66.9 (OCH_2), 55.9 (OCH_3), 47.6 (**C**C=O), 39.3 (CH_2**C**CH_3), 31.4 (**C**H_3C=O), 23.3 (**C**H_2CCH_3), 22.8 (CH_2C**C**H_3). **IR** (ATR): 1727 (C=O st), 1704 (C=O st), 1063 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 280.8 (M$^+$-C_7H_7, 5), 91.1 (100). **HRMS**: Calculated for $[C_{21}H_{22}O_4Cl]^+$: 373.1207 $[M+H]^+$; found: 373.1213.

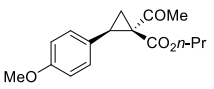


Methyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (5a). Following *GP-B*, **5a** (1.2 g, 4.9 mmol, 57%, dr 3:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 8:2) on silica gel as pale yellow oil starting from methyl acetoacetate (1.0 g, 8.6 mmol, 1.0 eq) and *p*-ABSA (2.5 g, 10.3 mmol, 1.2 eq) in CH_3CN (64 mL) using Et_3N (1.8 mL, 12.9 mmol, 1.5 eq). After dissolving the crude methyl 2-diazo-3-oxobutanoate (1.2 g, 8.6 mmol, 1.0 eq) and 4-methoxystyrene (5.9 mL, 43.0 mmol, 5.0 eq) in toluene (8.6 mL) $Rh_2(OAc)_4$ (78.1 mg, 0.17 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.10 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.05* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.80 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 3.79* (s, 3H, OC**H$_3$**), 3.77 (s, 3H, OC**H$_3$**), 3.38 (s, 3H, OC**H$_3$**), 3.22 (app t, *J* = 8.7 Hz, 1H, C**H**CH_2), 2.44 (s, 3H, CH_3C=O), 2.31-2.23* (m, 1H, CHC**H$_a$**H$_b$), 2.20 (dd, *J* = 8.1, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.96* (s, 3H, CH_3C=O), 1.74 (dd, *J* = 9.1, 4.5 Hz, 1H, $CHCH_a$**H$_b$**), 1.71-1.64* (dd, *J* = 9.1, 4.9 Hz, 1H, $CHCH_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.4 (CH_3**C**=O), 200.2* (CH_3**C**=O), 171.2* (COO), 168.9 (COO), 159.1* (**C**$_{arom}$-OCH_3), 159.0 (**C**$_{arom}$-OCH_3), 129.9 (2×C_{arom}-H), 129.6* (2×C_{arom}-H), 126.8 (C_{arom}),

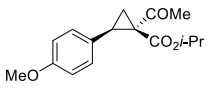
125.6* (C_{arom}), 113.9* (2×C_{arom}-H), 113.6 (2×C_{arom}-H), 55.3 (OCH_3), 52.6* ($COO\mathbf{C}H_3$), 52.1 ($COO\mathbf{C}H_3$), 44.8 ($\mathbf{C}CH_2$), 44.2* ($\mathbf{C}CH_2$), 35.5 ($\mathbf{C}H_3C=O$), 34.5* ($\mathbf{C}H_3C=O$), 30.4* ($\mathbf{C}HCH_2$), 29.7 ($\mathbf{C}HCH_2$), 21.9 ($CH\mathbf{C}H_2$), 18.1* ($CH\mathbf{C}H_2$). **IR** (ATR): 1727 (C=O st), 1693 (C=O st), 1167 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 248.1 (M^+, 37), 217.1 (20), 216.1 (100), 201.0 (85), 198.1 (29), 174.1 (18), 146.1 (24), 145.1 (71), 131.1 (24), 103.1 (22), 77.1 (16). **HRMS**: Calculated for $[C_{14}H_{17}O_4]^+$: 249.1127 $[M+H]^+$; found: 249.1140.



Ethyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (5b). Following *GP-B,* **5b** (1.1 g, 4.1 mmol, 54%, dr 13:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from ethyl acetoacetate (1.0 g, 7.6 mmol, 1.0 eq) and *p*-ABSA (2.2 g, 9.1 mmol, 1.2 eq) in CH_3CN (57 mL) using Et_3N (1.6 mL, 11.4 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-3-oxobutanoate (1.2 g, 7.6 mmol, 1 eq) and 4-methoxystyrene (5.3 mL, 38.0 mmol, 5.0 eq) in toluene (7.6 mL) $Rh_2(OAc)_4$ (70.3 mg, 0.17 mmol, 2 mol%) was added. R_f= 0.70 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.05 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.99* (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.73 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 4.28-4.09* (m, 2H, OCH_2), 3.84-3.73 (m, 2H, OCH_2), 3.69 (s, 3H, OCH_3), 3.15 (app t, *J* = 8.6 Hz, 1H, $C\mathbf{H}CH_2$), 2.38 (s, 3H, $CH_3C=O$), 2.13 (dd, *J* = 8.1, 4.5 Hz, 1H, $CHC\mathbf{H_a}H_b$), 1.90* (s, 3H, $CH_3C=O$), 1.64 (dd, *J* = 9.3, 4.4 Hz, 1H, $CHCH_a\mathbf{H_b}$), 1.24* (t, *J* = 7.1 Hz, 3H, $CH_2C\mathbf{H}_3$), 0.85 (t, *J* = 6.9 Hz, 3H, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.1 ($CH_3\mathbf{C}=O$), 199.9* ($CH_3\mathbf{C}=O$), 170.3* (COO), 168.0 (COO), 158.8 ($\mathbf{C}_{arom}$-OCH_3), 129.9 (2×C_{arom}-H), 129.3* (2×C_{arom}-H), 126.6 (C_{arom}), 125.4* (C_{arom}), 113.6* (2×C_{arom}-H), 113.3 (2×C_{arom}-H), 61.3* (OCH_2), 60.9 (OCH_2), 55.0 (OCH_3), 54.9* (OCH_3), 44.5 ($\mathbf{C}CH_2$), 44.1* ($\mathbf{C}CH_2$), 35.0 ($\mathbf{C}H_3C=O$), 34.0* ($\mathbf{C}H_3C=O$), 30.1* ($\mathbf{C}HCH_2$), 29.4 ($\mathbf{C}HCH_2$), 21.5 ($CH\mathbf{C}H_2$), 17.7* ($CH\mathbf{C}H_2$), 14.0* ($CH_2\mathbf{C}H_3$), 13.6 ($CH_2\mathbf{C}H_3$). **IR** (ATR): 1720 (C=O st), 1693 (C=O st), 1177 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 262.1 (M^+, 32), 217.1 (26), 216.1 (100), 201.0 (88), 198.1 (31), 174.1 (17), 146.1 (26), 145.1 (61), 131.1 (23), 103.1 (24), 77.1 (16). **HRMS**: Calculated for $[C_{15}H_{19}O_4]^+$: 263.1283 $[M+H]^+$; found: 263.1293.

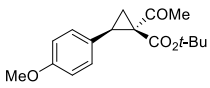


***n*-Propyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (5c).** Following *GP-B*, **5c** (718.5 mg, 2.6 mmol, 52%, dr 16:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from propyl acetoacetate (0.7 g, 5.0 mmol, 1.0 eq) and *p*-ABSA (1.5 g, 6.0 mmol, 1.2 eq) in CH_3CN (37 mL) using Et_3N (1.0 mL, 7.5 mmol, 1.5 eq). After dissolving the crude propyl 2-diazo-3-oxobutanoate (0.7 g, 5.0 mmol, 1.0 eq) and 4-methoxystyrene (3.5 mL, 25.5 mmol, 5.0 eq) in toluene (5.0 mL) $Rh_2(OAc)_4$ (46.0 mg, 0.10 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.08 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.76 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.20-4.05* (m, 2H, OCH_2), 3.82-3.60 (m, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 3.19 (app t, *J*= 8.6 Hz, 1H, C**H**CH_2), 2.42 (s, 3H, CH_3C=O), 2.15 (dd, *J* = 8.2, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.94* (s, 3H, CH_3CH=O), 1.68 (dd, *J* = 9.1, 4.5 Hz, 1H, CHCH_a**H$_b$**), 1.31 (sextet, *J* = 7.1 Hz, 2H, C**H**$_2CH_3$), 0.94* (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$), 0.72 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.5 (CH_3**C**=O), 200.3* (CH_3**C**=O), 170.7* (COO), 168.4 (COO), 159.0 (**C**$_{arom}$-OCH_3), 130.0 (2×C_{arom}-H), 129.5* (2×C_{arom}-H), 126.9 (C_{arom}), 125.7* (C_{arom}), 113.8* (2×C_{arom}-H), 113.6 (2×C_{arom}-H), 67.2* (OCH_2), 66.9 (OCH_2), 55.3 (OCH_3), 55.2* (OCH_3), 44.9 (**C**CH_2), 44.3* (**C**CH_2), 35.3 (**C**H_3C=O), 34.4* (**C**H_3C=O), 30.4* (**C**HCH_2), 29.7 (**C**HCH_2), 22.0* (OCH_2**C**H_2), 21.8 (OCH_2**C**H_2), 21.7 (CH**C**H_2), 18.0* (CH**C**H_2), 10.5* (CH_2**C**H_3), 10.4 (CH_2**C**H_3). **IR** (ATR): 1721 (C=O st), 1693 (C=O st), 1172 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 276.1 (M^+, 23), 217.1 (25), 216.1 (100), 201.0 (90), 198.1 (31), 174.1 (19), 146.0 (26), 145.1 (51), 131.1 (26), 115.1 (17), 103.1 (29), 91.1 (16), 77.1 (20). **HRMS**: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1460.

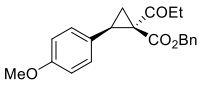


Isopropyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (5d). Following *GP-B*, **5d** (545.5 mg, 2.0 mmol, 47%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from *iso*-propyl acetoacetate (0.6 g, 4.2 mmol, 1.0 eq) and *p*-ABSA (1.2 g, 5.0 mmol, 1.2 eq) in CH_3CN (31 mL) using Et_3N (0.9 mL, 6.3 mmol, 1.5 eq). After dissolving the crude *iso*-propyl 2-diazo-3-oxobutanoate (0.7 g, 4.2 mmol, 1.0 eq) and 4-methoxystyrene (1.7 mL, 12.3 mmol, 5.0 eq) in toluene (4.2 mL) $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.76 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 4.71 (sept, *J* = 6.2 Hz, 1H, OCH), 3.73 (s, 3H, OC**H**$_3$), 3.18 (app t, *J*= 8.6 Hz, 1H, C**H**CH_2), 2.41 (s, 3H, CH_3C=O), 2.13 (dd, *J* = 8.1, 4.5 Hz, 1H, CHC**H**$_2$), 1.64 (dd, *J* = 9.1, 4.5 Hz, 1H, CHC**H**$_2$), 0.94 (d, *J* = 6.3 Hz, 3H, CHC**H**$_3$),

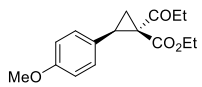
0.83 (d, *J* = 6.2 Hz, 3H, CHC**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.6 (CH_3**C**=O), 167.8 (COO), 159.0 (**C**$_{arom}$-OCH_3), 130.2 (2×C_{arom}-H), 126.9 (C_{arom}), 113.6 (2×C_{arom}-H), 69.0 (OCH), 55.4 (OCH_3), 45.0 (**C**CH_2), 35.1 (**C**H_3C=O), 29.8 (**C**HCH_2), 21.6 (CH**C**H_2), 21.5 (CH**C**H_3), 21.2 (CH**C**H_3). **IR** (ATR): 1716 (C=O st), 1693 (C=O st), 1174 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 262.1 (M^+, 22), 217.1 (28), 216.1 (100), 201.0 (68), 198.1 (26), 174.0 (16), 146.0 (19), 145.1 (36), 131.0 (18), 115.1 (15), 103.1 (25), 77.0 (18). **HRMS**: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1457.



***tert*-Butyl 1-acetyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (5e).** Following *GP-B*, **5e** (1.1 g, 3.6 mmol, 59%, dr 1.2:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as colorless oil starting from *tert*-butyl acetoacetate (1.0 g, 6.1 mmol, 1.0 eq) and *p*-ABSA (1.8 g, 7.3 mmol, 1.2 eq) in CH_3CN (46 mL) using Et_3N (1.3 mL, 9.2 mmol, 1.5 eq). After dissolving the crude *tert*-butyl 2-diazo-3-oxobutanoate (1.1 g, 6.1 mmol, 1.0 eq) and 4-methoxystyrene (4.1 mL, 30.2 mmol, 5.0 eq) in toluene (6.1 mL) $Rh_2(OAc)_4$ (56 mg, 0.17 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.09 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.01* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.77 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.75* (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 3.72 (s, 3H, OCH_3), 3.71* (s, 3H, OCH_3), 3.15 (app t, J = 8.6 Hz, 1H, C**H**CH_2), 3.10* (app t, J = 8.5 Hz, 1H, C**H**CH_2), 2.40 (s, 3H, CH_3C=O), 2.14* (dd, *J* = 8.0, 4.9 Hz, 1H, CHC**H$_a$**H$_b$), 2.07 (dd, *J* = 8.1, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.90* (s, 3H, CH_3C=O), 1.62-1.50 (m, 1H, CHCH$_a$**H$_b$**), 1.47* (s, 9H, C$(CH_3)_3$), 1.09 (s, 9H, C$(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 202.8 (CH_3**C**=O), 200.5* (CH_3**C**=O), 169.5* (COO), 167.2 (COO), 158.9 (**C**$_{arom}$-OCH_3), 158.8* (**C**$_{arom}$-OCH_3), 130.2 (2×C_{arom}-H), 129.4* (2×C_{arom}-H), 126.9 (C_{arom}), 125.9* (C_{arom}), 113.7* (2×C_{arom}-H), 113.4 (2×C_{arom}-H), 82.2* (**C**$(CH_3)_3$), 81.6 (**C**$(CH_3)_3$), 55.3 (OCH_3), 55.1* (OCH_3), 45.6 (**C**CH_2), 45.3* (**C**CH_2), 34.6 (**C**H_3C=O), 33.5* (**C**H_3C=O), 30.2* (**C**HCH_2), 29.6 (**C**HCH_2), 28.0* (C(**C**$H_3)_3$), 27.5 (C(**C**$H_3)_3$), 21.3 (CH**C**H_2), 17.6* (CH**C**H_2). **IR** (ATR): 1719 (C=O st), 1698 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 290.1 (M^+, 2), 234.1 (39), 217.1 (26), 216.1 (100), 201.0 (71), 198.1 (27), 174.1 (20), 147.1 (24), 146.1 (24), 145.1 (38), 137.1 (17) 135.1 (25), 131.1 (24), 115.0 (18), 103.1 (29), 91.1 (19), 77.1 (21). **HRMS**: Calculated for $[C_{17}H_{22}O_4Na]^+$: 313.1416 $[M+Na]^+$; found: 313.1429.

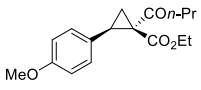


Benzyl 2-(4-methoxyphenyl)-1-propionylcyclopropane-1-carboxylate (7a). Following *GP-B*, **7a** (1.4 g, 4.2 mmol, 44%, dr 5:1) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as pale yellow solid, from benzyl 3-oxopentanoate (2.0 g, 9.5 mmol, 1.0 eq), *p*-ABSA (2.2 g, 11.4 mmol, 2.7 eq), CH_3CN (68 mL) and Et_3N (2.0 mL, 14.2 mmol, 1.5 eq) to obtain crude benzyl 2-diazo-3-oxopentanoate (2.2 g, 9.5 mmol, 1.0 eq), and 4-methoxystyrene (2.6 mL, 18.9 mmol, 2.0 eq), toluene (9.5 mL) and $Rh_2(OAc)_4$ (87.5 mg, 0.19 mmol, 2 mol%) for the cyclopropanation step. R_f = 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.52-7.18 (m, 3H, C_{arom}-H), 7.15-6.99 (m, 4H, C_{arom}-H), 6.84-6.66 (m, 2H, C_{arom}-H), 5.27* (d, *J* = 12.2 Hz, 1H, OC**H**$_a$H$_b$), 5.16* (d, *J* = 12.1 Hz, 1H, OC**H**$_a$H$_b$), 4.87 (d, *J* = 12.2 Hz, 1H, OCH$_a$**H**$_b$), 4.73 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H**$_b$), 3.78 (s, 3H, OCH_3), 3.76* (s, 3H, OCH_3), 3.24 (app t, *J* = 8.6 Hz, 1H, C**H**CH$_a$H$_b$), 3.05-2.85 (m, 1H, C**H**$_a$H$_b$C=O), 2.74-2.53 (m, 1H, CH$_a$**H**$_b$C=O), 2.29* (dd, *J* = 8.1, 5.0 Hz, 1H, C**H**CH$_a$H$_b$), 2.18 (dd, *J* = 8.1, 4.6 Hz, 1H, CHC**H**$_a$H$_b$), 1.90-1.79* (m,1H, CHCH$_a$**H**$_b$), 1.69 (dd, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$**H**$_b$), 1.07 (t, *J* = 7.2 Hz, 3H, $OCH_2C\mathbf{H}_3$), 0.62* (t, *J* = 7.2 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 204.9 ($CH_2\mathbf{C}$=O), 203.5* ($CH_2\mathbf{C}$=O), 170.5* (COO), 168.3 (COO), 158.9* (**C**$_{arom}$-OCH_3), 158.9 (**C**$_{arom}$-OCH_3), 135.3* (C_{arom}), 135.1 (C_{arom}), 129.8 (2×C_{arom}-H), 129.5* (2×C_{arom}-H), 128.8* (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.3 (C_{arom}-H), 126.8 (C_{arom}), 125.7* (C_{arom}), 113.7* (2×C_{arom}-H), 113.6 (2×C_{arom}-H), 67.3* (OCH_2), 67.1 (OCH_2), 55.1 (OCH_3), 44.4 (**C**CH_2), 44.2* (**C**CH_2), 36.1* (**C**H_2C=O), 35.1 (**C**H_2C=O), 34.7 (**C**HCH_2), 34.0* (**C**HCH_2), 21.6 (CH**C**H_2), 17.9* (CH**C**H_2), 8.2 (**C**H_3CH_2C=O), 7.8* (**C**H_3CH_2C=O). IR (ATR): 1703 (C=O st), 1637 (C=O st) cm-1. MS (EI) m/z (%): 338.1 (M^+, 6), 247.1 (15), 91.1 (100), 57.1 (29). HRMS (ESI^+): Calculated for $[C_{21}H_{23}O_4]^+$: 339.1596 $[M+H]^+$; found: 339.1604. **M.p.**: 57-60 ºC (petroleum ether/EtOAc).



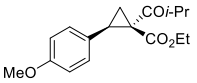
Ethyl 2-(4-methoxyphenyl)cyclopropane-1-propionylcyclopropane-1-carboxylate (7b). Following *GP-B*, **7b** (944.2 mg, 3.4 mmol, 51%, dr 3.4:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from ethyl propionylacetate (1.0 g, 6.7 mmol, 1.0 eq) and *p*-ABSA (2.0 g, 8.0 mmol, 1.2 eq) in CH_3CN (48 mL) using Et_3N (1.4 mL, 10.0 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-3-oxopentanote (1.1 g, 6.7 mmol, 1.0 eq) and 4-methoxystyrene (4.6 mL, 33.5 mmol, 5.0 eq) in toluene (6.7 mL) $Rh_2(OAc)_4$ (61.7 mg, 0.13 mmol, 2 mol%) was added. R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.10 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.02* (d, *J* = 8.6

Hz, 2H, C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.33-4.16* (m, 2H, OCH_2), 3.92-3.79 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.21 (app t, *J* = 8.5 Hz, 1H, C**H**CH_2), 2.99 (dq, *J* = 18.1, 7.3 Hz, 1H, CC**H$_a$**H$_b$$CH_3$), 2.71* (dq, J = 17.5, 7.3 Hz, 1H, CC**H$_a$**H$_b$$CH_3$), 2.65 (dq, *J* = 18.1, 7.2 Hz, 1H, CCH_a**H$_b$**CH_3), 2.25* (dd, *J* = 8.1, 5.0 Hz, 1H, CHC**H**$_2$), 2.15 (dd, *J* = 8.0, 4.6 Hz, 1H, CHC**H$_a$**H$_b$), 1.84* (dq, *J* = 17.5, 7.2 Hz, 1H, CCH_a**H$_b$**CH_3), 1.65 (dd, *J* = 9.1, 4.5 Hz, 1H, $CHCH_a$**H$_b$**), 1.63* (dd, *J* = 9.2, 5.0 Hz, 1H, $CHCH_a$**H$_b$**), 1.29* (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.09 (t, *J* = 7.2 Hz, 3H, OCH_2C**H**$_3$), 0.90 (t, *J* = 7.1 Hz, 3H, CCH_2C**H**$_3$), 0.67* (t, *J* = 7.3 Hz, 3H, CCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 205.2 (CH_2**C**=O), 203.4* (CH_2**C**=O), 170.8* (COO), 168.4 (COO), 159.0* (**C**$_{arom}$-OCH_3), 158.9 (**C**$_{arom}$-OCH_3), 130.2 (2×C_{arom}-H), 129.6* (2×C_{arom}-H), 127.2 (C_{arom}), 126.1* (C_{arom}), 113.8* (2×C_{arom}-H), 113.5 (2×C_{arom}-H), 61.5* (OCH_2), 61.1 (OCH_2), 55.3 (OCH_3), 55.2* (OCH_3), 44.3 (**C**CH_2), 44.2* (**C**CH_2), 36.1* (C**C**H_2CH_3), 35.1 (C**C**H_2CH_3), 34.5 (**C**HCH_2), 33.8* (**C**HCH_2), 21.5 (CH**C**H_2), 17.8* (CH**C**H_2), 14.2* (OCH_2**C**H_3), 13.8 (OCH_2**C**H_3), 8.2 (CCH_2**C**H_3), 7.9* (CCH_2**C**H_3). **IR** (ATR): 1720 (C=O st), 1696 (C=O st), 1177 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 276.1 (M^+, 24), 231.1 (18), 230.1 (54), 202.1 (19), 201.0 (100), 174.0 (17), 146.0 (17), 145.0 (41), 131.1 (17), 103.1 (20), 57.0 (48). **HRMS**: Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1460.

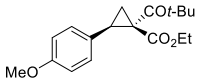


Ethyl 1-butyryl- 2-(4-methoxyphenyl)cyclopropane-1-carboxylate (7c). Following *GP-B*, **7c** (1.16 mg, 4.0 mmol, 64%, dr 3:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from ethyl 3-oxohexanoate (1.0 g, 6.2 mmol, 1.0 eq) and *p*-ABSA (1.8 g, 7.4 mmol, 1.2 eq) in CH_3CN (24 mL) using Et_3N (1.3 mL, 9.3 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-3-oxohexanoate (1.1 g, 6.2 mmol, 1.0 eq) and 4-methoxystyrene (4.1 mL, 31.0mmol, 5.0 eq) in toluene (6.2 mL) $Rh_2(OAc)_4$ (56.5 mg, 0.12 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.10 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.03* (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.39-4.01* (m, 2H, OCH_2), 3.90-3.78 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.35-3.11 (m, 1H, C**H**CH_2), 2.89 (dt, *J* = 17.2, 7.2 Hz, 1H, CC**H$_a$**H$_b$$CH_2$), 2.81-2.57 (m, 1H, CCH_a**H$_b$**CH_2), 2.25* (dd, *J* = 8.1, 4.9 Hz, 1H, CHC**H$_a$**H$_b$), 2.14 (dd, *J* = 8.0, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.91-1.70* (m, 1H, CC**H$_a$**H$_b$$CH_2$), 1.70-1.55 (m, 3H, CH_2C**H**$_2CH_3$ + $CHCH_a$**H$_b$**), 1.30* (t, *J* = 7.2 Hz, 3H, CH_2C**H**$_3$), 1.16-1.04* (m, 2H, CH_2C**H**$_2CH_3$), 0.92 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$), 0.91 (t, *J* = 7.2 Hz, 3H, CH_2C**H**$_3$), 0.61* (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 204.1 (CH_2**C**=O), 202.0* (CH_2**C**=O), 170.5* (COO), 168.1 (COO), 158.8* (**C**$_{arom}$-OCH_3), 158.7 (**C**$_{arom}$-OCH_3), 128.8 (2×C_{arom}-H), 129.3* (2×C_{arom}-H), 126.7

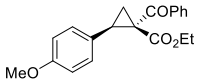
(C_{arom}), 125.6* (C_{arom}), 113.5* (2×C_{arom}-H), 113.3 (2×C_{arom}-H), 61.2* (OCH_2), 60.8 (OCH_2), 54.9 (OCH_3), 44.5* (C**C**H_2CH_2), 44.3 (**C**CH_2), 43.9* (**C**CH_2), 43.5 (C**C**H_2CH_2), 34.1 (**C**HCH_2), 33.6* (**C**HCH_2), 21.0 (CH_2**C**H_2CH_3), 17.5* (CH_2**C**H_2CH_3), 17.3 (CH**C**H_2), 16.7* (CH**C**H_2), 13.9* (CH_2**C**H_3), 13.6 (2×CH_2**C**H_3), 13.3* (CH_2**C**H_3). **IR** (ATR): 1720 (C=O st), 1697 (C=O st), 1177 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 290.2 (M^+, 33), 259.1 (15), 245.1 (21), 244.1 (69), 211.1 (15), 202.1 (17), 201.0 (100), 174.1 (35), 146.0 (19), 145.0 (40), 131.1 (20), 115.0 (16), 103.1 (22), 77.1 (16), 71.0 (29). **HRMS**: Calculated for $[C_{17}H_{23}O_4]^+$: 291.1596 [M+H]$^+$; found: 291.1616.



Ethyl 1-isobutyryl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (7d). Following *GP-B*, **7d** (719.5 mg, 2.5 mmol, 42%, dr 2.5:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from ethyl isobutyrylacetate (1.0 g, 5.9 mmol, 1.0 eq) and *p*-ABSA (1.7 g, 7.1 mmol, 1.2 eq) in CH_3CN (43 mL) using Et_3N (1.2 mL, 8.9 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-4-methyl-3-oxopentanoate (1.1 g, 5.9 mmol, 1.0 eq) and 4-methoxystyrene (4.1 mL, 29.5 mmol, 5.0 eq) in toluene (5.9 mL) $Rh_2(OAc)_4$ (54.3 mg, 0.12 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.10 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.04* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.34-4.14* (m, 2H, OCH_2), 3.92-3.78 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.75* (s, 3H, OCH_3), 3.40-3.19 (m, 2H, C**H**CH_2 + C**H**CH_3), 2.83* (sept, *J* = 6.8 Hz, 1H, C**H**$(CH_3)_2$), 2.31* (dd, *J* = 8.4, 4.8 Hz, 1H, CHC**H$_a$**H$_b$), 2.17 (dd, *J* = 8.0, 4.5 Hz, 1H, CHC**H$_a$**H$_b$), 1.65-1.58* (m, 1H, CHCH$_a$**H$_b$**), 1.57 (dd, *J* = 9.2, 4.5 Hz, 1H, CHCH$_a$**H$_b$**), 1.30* (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$), 1.14 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 1.12 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 0.99-0.86 (m, 3H, CH_2C**H**$_3$), 0.99-0.86* (m, 3H, CHC**H**$_3$), 0.40* (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 208.5 (CH**C**=O), 206.0* (CH**C**=O), 170.8* (COO), 168.4 (COO), 158.9* (**C**$_{arom}$-OCH_3), 158.8 (**C**$_{arom}$-OCH_3), 130.0 (2×C_{arom}-H), 129.7* (2×C_{arom}-H), 126.9 (C_{arom}), 126.1* (C_{arom}), 113.5* (2×C_{arom}-H), 113.4 (2×C_{arom}-H), 61.5* (OCH_2), 61.0 (OCH_2), 55.2 (OCH_3), 44.5* (**C**CH_2), 43.5 (**C**CH_2), 39.9* (**C**HCH_3), 39.0 (**C**HCH_3), 34.8* (**C**HCH_2), 33.4 (**C**HCH_2), 21.5 (CH**C**H_2), 19.6 (CH**C**H_3), 18.8* (CH**C**H_3), 18.7* (CH**C**H_2), 18.1 (CH**C**H_3), 17.7* (CH**C**H_3), 14.1* (CH_2**C**H_3), 13.7 (CH_2**C**H_3). **IR** (ATR): 1720 (C=O st), 1694 (C=O st), 1178 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 290.2 (M^+, 13), 244.1 (47), 211.1 (15), 202.0 (15), 201.0 (100), 174.1 (28), 146.1 (16), 145.0 (41), 131.1 (19), 103.1 (25), 91.1 (16), 77.1 (18), 71.0 (15). **HRMS**: Calculated for $[C_{17}H_{23}O_4]^+$: 291.1596 [M+H]$^+$; found: 291.1612.

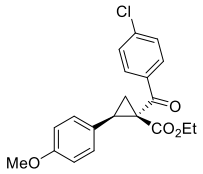


Ethyl 2-(4-methoxyphenyl)-1-pivaloylcyclopropane-1-carboxylate (7e). Following *GP-B*, **7e** (733.0 mg, 2.4 mmol, 43%, dr 6:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as pale yellow oil starting from ethyl 4,4-dimethyl-3-oxovalerate (1.0 g, 5.6 mmol, 1.0 eq) and *p*-ABSA (1.6 g, 6.7 mmol, 1.2 eq) in CH_3CN (40 mL) using Et_3N (1.2 mL, 8.5 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-4,4-dimethyl-3-oxopentanoate (1.1 g, 5.6 mmol, 1.0 eq) and 4-methoxystyrene (3.9 mL, 28.0 mmol, 5.0 eq) in toluene (5.6 mL) $Rh_2(OAc)_4$ (51.6 mg, 0.11 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.15 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.02* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.79 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 4.28-4.14* (m, 2H, OCH_2), 3.91-3.80 (m, 2H, OCH_2), 3.77 (s, 3H, OCH_3), 3.20 (app t, *J* = 8.5 Hz, 1H, C**H**CH_2), 2.35-2.17* (m, 1H, CHC**H$_a$**H$_b$), 2.14 (dd, *J* = 7.9, 5.0 Hz, 1H, CHC**H$_a$**H$_b$), 1.51-1.41* (m, 1H, CHCH$_a$**H$_b$**), 1.38-1.28 (m, 1H, CHCH$_a$**H$_b$**), 1.25 (s, 9H, $C(CH_3)_3$), 0.96 (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$), 0.79* (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 209.5 (C**C**=O), 170.8* (COO), 168.0 (COO), 159.0* (**C**$_{arom}$-OCH_3), 158.6 (**C**$_{arom}$-OCH_3), 130.1 (2×C_{arom}-H), 129.4* (2×C_{arom}-H), 127.0 (C_{arom}), 126.3* (C_{arom}), 113.7* (2×C_{arom}-H), 113.4 (2×C_{arom}-H), 61.6* (OCH_2), 61.1 (OCH_2), 55.3* (OCH_3), 55.2 (OCH_3), 45.2 (**C**$(CH_3)_3$), 44.4* (**C**$(CH_3)_3$), 44.1* (**C**CH_2), 42.7 (**C**CH_2), 28.7* (C(**C**$H_3)_3$), 28.1 (C(**C**$H_3)_3$), 27.2 (**C**HCH_2), 18.1 (CH**C**H_2), 14.1* (CH_2**C**H_3), 13.8 (CH_2**C**H_3). **IR** (ATR): 1726 (C=O st), 1693 (C=O st), 1178 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 304.1 (M^+, 8), 258.1 (34), 202.0 (18), 201.0 (100), 174.1 (36), 173.1 (16), 145.1 (36), 131.1 (17), 103.1 (25), 91.1 (15), 77.1 (18), 57.1 (90). **HRMS**: Calculated for $[C_{18}H_{25}O_4]^+$: 305.1753 $[M+H]^+$; found: 305.1768.



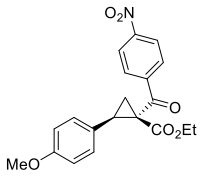
Ethyl 1-benzoyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (7f). Following *GP-B*, **7f** (703.5 mg, 3.2 mmol, 62%, dr 14:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as yellow solid starting from ethyl benzoylacetate (1.0 g, 5.2 mmol, 1.0 eq) and *p*-ABSA (1.5 g, 6.2 mmol, 1.2 eq) in CH_3CN (37 mL) using Et_3N (1.1 mL, 7.8 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-3-oxo-3-phenylpropanoate (1.1 g, 5.2 mmol, 1.0 eq) and 4-methoxystyrene (3.6 mL, 26.0 mmol, 5.0 eq) in toluene (5.2 mL) $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%) was added. R_f= 0.70 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.98-7.86 (m, 2H, C_{arom}-H), 7.87-7.80* (m, 2H, C_{arom}-H), 7.71-7.65* (m, 2H, C_{arom}-

H), 7.59-7.50 (m, 1H, C_{arom}-H), 7.48-7.39 (m, 2H, C_{arom}-H), 7.38-7.28* (m, 2H, C_{arom}-H), 7.23 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.10-6.99* (m, 2H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.65* (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 4.23-3.98* (m, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 3.75-3.63 (m, 2H, OCH_2), 3.53 (app t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.40 (dd, *J* = 8.0, 4.8 Hz, 1H, CHC**H$_a$**H$_b$), 1.80-1.71* (m, 1H, CHC**H$_a$**H$_b$), 1.67 (dd, *J* = 9.1, 4.7 Hz, 1H, CHCH$_a$**H$_b$**), 0.92* (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$), 0.70 (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 195.2 (C_{arom}**C**=O), 190.9* (C_{arom}**C**=O), 171.3* (COO), 168.6 (COO), 158.9 (**C**$_{arom}$-OCH_3), 158.8* (**C**$_{arom}$-OCH_3), 137.7* (**C**$_{arom}$-CO), 137.6 (**C**$_{arom}$-CO), 132.9 (C_{arom}-H), 132.6* (C_{arom}-H), 130.3 (2×C_{arom}-H), 129.2* (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5* (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 128.2* (2×C_{arom}-H), 126.8 (C_{arom}), 125.9* (C_{arom}), 113.7* (2×C_{arom}-H), 113.6 (2×C_{arom}-H), 61.6* (OCH_2), 61.2 (OCH_2), 55.3 (OCH_3), 55.2* (OCH_3), 42.5 (**C**CH_2), 42.0* (**C**CH_2), 33.8* (**C**HCH_2), 30.3 (**C**HCH_2), 20.4 (CH**C**H_2), 18.5* (CH**C**H_2), 13.8* (CH_2**C**H_3), 13.6 (CH_2**C**H_3). **IR** (ATR): 1723 (C=O st), 1671 (C=O st), 1175 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 324.2 (M$^+$, 12), 279.1 (15), 278.1 (42), 277.1 (18), 200.0 (34), 105.0 (100), 77.1 (56). **HRMS**: Calculated for $[C_{20}H_{21}O_4]^+$: 325.1440 $[M+H]^+$; found: 325.1460. **M.p.**: 76-79 ºC (petroleum ether/EtOAc).

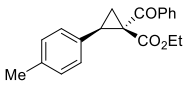


Ethyl 1-(4-chlorobenzoyl)-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (7g). Following *GP-B*, **7g** (2.08 g, 5.8 mmol, 58%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as white solid starting from ethyl 4-chlorobenzoylacetate (2.27 g, 10.0 mmol, 1.0 eq) and *p*-ABSA (2.64 g, 11.0 mmol, 1.1 eq) in CH_3CN (25 mL) using Et_3N (4.2 mL, 30.0 mmol, 3.0 eq). After dissolving the crude ethyl 2-diazo-3-oxo-3-(4-chlorophenyl)propanoate (2.09 g, 8.3 mmol, 1.0 eq) and 4-methoxystyrene (2.8 mL, 20.7 mmol, 2.5 eq) in toluene (8.3 mL) $Rh_2(OAc)_4$ (11.3 mg, 0.026 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.42 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.22 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.78 (s, 3H, OCH_3), 3.77-3.66 (m, 2H, OCH_2), 3.50 (app t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.39 (dd, *J* = 8.1, 4.8 Hz, 1H, CHC**H$_a$**H$_b$), 1.66 (dd, *J* = 9.2, 4.8 Hz, 1H, CHC**H$_a$**H$_b$), 0.74 (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.9 (C_{arom}**C**=O), 168.4 (COO), 158.9 (**C**$_{arom}$-OCH_3), 139.2 (C_{arom}-Cl), 135.9 (**C**$_{arom}$-CO), 130.3 (2×C_{arom}-H), 129.7 (2×C_{arom}-H), 128.9 (2×C_{arom}-H), 126.6 (C_{arom}), 113.6 (2×C_{arom}-H), 61.3 (OCH_2), 55.3 (OCH_3), 42.3 (**C**CH_2), 30.5 (**C**HCH_2), 20.4 (CH**C**H_2), 13.7 (CH_2**C**H_3). **IR** (ATR): 1726 (C=O st), 1673 (C=O st), 1176 (C-O st as), 1086 (C-Cl) cm^{-1}. **MS** (EI) m/z (%): 358.1 (M$^+$, 15), 356.0 (16), 312.0 (24), 200.0 (43), 144.9 (21),

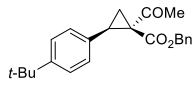
141.0 (32), 139.0 (100), 111.0 (37). **HRMS**: Calculated for $[C_{20}H_{19}O_4ClNa]^+$: 381.0870 $[M+Na]^+$; found: 381.0882. **M.p.**: 89-92 ºC (petroleum ether/EtOAc).



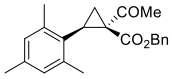
Ethyl 2-(4-methoxyphenyl)-1-(4-nitrobenzoyl)cyclopropane-1-carboxylate (7h). Following *GP-B*, **7h** (2.0 mg, 5.4 mmol, 71%, dr 6:1) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as an orange solid, from ethyl 4-nitrobenzoylacetate (1.8 g, 7.6 mmol, 1.0 eq), p-ABSA (2.2 g, 9.1 mmol, 1.2 eq), CH_3CN (54 mL) and Et_3N (1.6 mL, 11.4 mmol, 1.5 eq) to obtain crude ethyl 2-diazo-3-(4-nitrophenyl)-3-oxopropanoate (2.0 g, 7.6 mmol, 1.0 eq), and 4-methoxystyrene (5.0 mL, 38.0 mmol, 5.0 eq), toluene (7.6 mL) and Rh2(OAc)4 (67.2 mg, 0.15 mmol, 2 mol%) for the cyclopropanation step. Rf = 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 8.30 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 8.15* (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 8.01 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.80* (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.22 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 7.03* (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.84 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.66* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.22-4.07* (m, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.77-3.67 (m, 2H, OCH_2), 3.66* (s, 3H, OCH_3), 3.57 (app t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.47 (dd, *J* = 8.2, 4.9 Hz, 1H, CHC**H$_a$**H$_b$), 1.87* (dd, *J* = 9.3, 5.2 Hz, 1H, CHC**H$_a$**H$_b$), 1.77 (dd, *J* = 9.2, 4.8 Hz, 1H, CHCH$_a$**H$_b$**), 0.97* (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$), 0.71 (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 194.3 (C_{arom}**C**=O), 191.8* (C_{arom}**C**=O), 170.4* (COO), 168.0 (COO), 159.1 (**C**$_{arom}$-OCH_3), 150.1 (C_{arom}-NO_2), 149.9* (C_{arom}-NO_2), 142.8 (**C**$_{arom}$-CO), 142.3* (**C**$_{arom}$-CO), 130.3 (2×C_{arom}-H), 129.3* (2×C_{arom}-H), 129.1* (2×C_{arom}-H), 129.0 (2×C_{arom}-H), 126.1 (C_{arom}), 123.8 (2×C_{arom}-H), 123.5* (2×C_{arom}-H), 113.9* (2×C_{arom}-H), 113.7 (2×C_{arom}-H), 61.9* (OCH_2), 61.5 (OCH_2), 55.3 (OCH_3), 55.2* (OCH_3), 42.7 (**C**CH_2), 42.3* (**C**CH_2), 35.0* (**C**HCH_2), 31.6 (**C**HCH_2), 21.4 (CH**C**H_2), 18.7* (CH**C**H_2), 13.9* (CH_2**C**H_3), 13.7 (CH_2**C**H_3). **IR** (ATR): 1726 (C=O st), 1675 (C=O st), 1177 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 369.1 (M^+, 13), 367.0 (19), 324.0 (23), 323.1 (100), 200.0 (15), 150.0 (54), 145.1 (64), 135.0 (15), 104.0 (34), 103.1 (16), 77.1 (18), 76.0 (25). **HRMS**: Calculated for $[C_{20}H_{20}NO_6]^+$: 370.1291 $[M+H]^+$; found: 370.1294. **M.p.**: 73-76 ºC (petroleum ether/EtOAc).



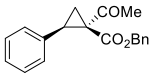
Ethyl 1-benzoyl-2-(p-tolyl)cyclopropane-1-carboxylate (7i). Following *GP-B*, **7i** (1.3 g, 4.2 mmol, 81%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as white solid starting from ethyl benzoylacetate (1.0 g, 5.2 mmol, 1.0 eq) and *p*-ABSA (1.5 g, 6.2 mmol, 1.2 eq) in CH_3CN (37 mL) using Et_3N (1.1 mL, 7.8 mmol, 1.5 eq). After dissolving the crude ethyl 2-diazo-3-oxo-3-phenylpropanoate (1.1 g, 5.2 mmol, 1.0 eq) and 4-methylstyrene (3.4 mL, 26.0 mmol, 5.0 eq) in toluene (5.2 mL) $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 7.2, 1.0 Hz, 2H, C_{arom}-H), 7.62-7.51 (m, 1H, C_{arom}-H), 7.50-7.40 (m, 2H, C_{arom}-H), 7.20 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 7.10 (d, *J* = 7.9 Hz, 2H, C_{arom}-H), 3.82-3.63 (m, 2H, OCH_2), 3.54 (app t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.42 (ddd, *J* = 8.1, 4.7, 0.8 Hz, 1H, CHC**H$_a$**H$_b$), 2.31 (s, 3H, C_{arom}-CH_3), 1.67 (ddd, *J* = 9.1, 4.8, 0.8 Hz, 1H, CHCH$_a$**H$_b$**), 0.69 (t, *J* = 7.1 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.2 (C_{arom}**C**=O), 168.6 (COO), 137.6 (C_{arom}), 136.9 (C_{arom}), 132.9 (C_{arom}-H), 131.8 (C_{arom}), 129.1 (2×C_{arom}-H), 128.9 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 61.2 (OCH_2), 42.5 (**C**C=O), 30.6 (**C**HCH_2), 21.2 (Ca_{rom}-**C**H_3), 20.2 (CH**C**H_2), 13.6 (CH_2**C**H_3). **IR** (ATR): 1730 (C=O st), 1678 (C=O st), 1145 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 203.11 (M^+ - C_7H_5O, 1), 105.0 (100), 77.0 (50). **HRMS**: Calculated for $[C_{20}H_{20}O_3Na]^+$: 331.1210 $[M+Na]^+$; found: 331.1322. **M.p.**: 56-59 ºC (petroleum ether/EtOAc).



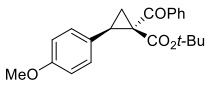
benzyl 1-acetyl-2-(4-(tert-butoxy)phenyl)cyclopropane-1-carboxylate (7j). Following *GP-B*, **7j** (771.0 mg, 2.2 mmol, 42%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a white solid starting from benzyl 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), 4-*tert*-butylstyrene (4.2 g, 26.0 mmol, 5.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.50 (petroleum ether/EtOAc, 8:2)**. ^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5H, C_{arom}-H), 7.19-7.08 (m, 2H, C_{arom}-H), 7.04-6.91 (m, 2H, C_{arom}-H), 4.86 (d, *J* = 12.1 Hz, 1H, OC**H$_a$**H$_b$), 4.68 (d, *J* = 12.1 Hz, 1H, OCH$_a$**H$_b$**), 3.29 (app t, *J* = 8.7 Hz, 1H, C**H**CH_2), 2.46 (s, 3H, CH_3C=O), 2.25 (dd, *J* = 8.4, 4.3 Hz, 1H, CHC**H$_a$**H$_b$), 1.78 (dd, *J* = 8.7, 4.2 Hz, 1H, CHCH$_a$**H$_b$**), 1.33 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.1 (CH_3**C**=O), 168.3 (COO), 150.3 (C_{arom}(CH_3)$_3$)), 135.0 (C_{arom}), 131.8 (C_{arom}), 128.5 (4×C_{arom}-H), 128.4 (2×C_{arom}-H), 128.3 (C_{arom}-H), 125.1 (2×C_{arom}-H), 67.2 (O**C**H_2), 44.7 (**C**CH_2), 35.6 (**C**H_3C=O), 34.5 (**C**$(CH_3)_3$), 31.4 (C(**C**H_3)$_3$), 29.7 (**C**HCH_2), 21.9 (CH**C**H_2). **IR** (ATR): 1728 (C=O st), 1691 (C=O st) cm^{-1}. **HRMS**: Calculated for $[C_{23}H_{27}O_3]^+$: 351.1960 $[M+H]^+$; found: 351.1967. **M.p.**: 48-51 ºC (petroleum ether/EtOAc).



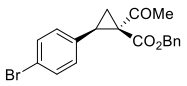
benzyl -1-acetyl-2-mesitylcyclopropane-1-carboxylate (7k). Following *GP-B,* **7k** (522.8 mg, 1.5 mmol, 42%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as yellow oil starting from benzyl 2-diazo-3-oxobutanoate (0.8 g, 3.7 mmol, 1.0 eq), 1,3,5-trimethyl-2-vinylbenzene (1.1 g, 7.4 mmol, 2.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (31.5mg, 0.07 mmol, 2 mol%). R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.16 (m, 3H, C_{arom}-H), 7.09-6.88 (m, 2H, C_{arom}-H), 6.75 (s, 2H, C_{arom}-H), 4.84 (d, *J* = 12.0 Hz, 1H, OC**H**$_a$CH$_b$), 4.59 (d, *J* = 12.0 Hz, 1H, OCH$_a$C**H**$_b$), 3.16 (t, *J* = 9.3 Hz, 1H, C**H**CH$_a$H$_b$), 2.59 (s, 3H, $COCH_3$), 2.45 (dd, *J* = 9.1, 4.3 Hz, 1H, CHC**H**$_a$H$_b$), 2.36-2.05 (m, 9H, 3× C_{arom} -CH_3), 1.99 (dd, *J* = 9.5, 4.3 Hz, 1H, CHCH$_a$**H**$_b$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.4 (CH_3**C**=O), 169.2 (COO), 136.5 (C_{arom}), 135.0 (C_{arom}), 129.3 (2×C_{arom}-H), 129.0 (C_{arom}), 128.7 (2×C_{arom}-H), 128.4 (3×C_{arom}-H + 2×C_{arom}), 67.2 (OCH_2), 42.7 (**C**C=O), 35.7 (**C**HCH$_2$), 30.3 (C**C**H$_3$), 27.1 (3×C_{arom}-**C**H$_3$) 21.0 (CH**C**H$_2$). **IR** (ATR): 1715 (C=O st), 1691 (C=O st), 1176 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 336.2 (M$^+$, 3), 157.1 (21), 143.1 (15), 142.1 (16), 141.1 (19), 128.1 (20), 115.1 (17), 91.1 (100), 77.0 (17). **HRMS**: Calculated for $[C_{22}H_{25}O_3]^+$: 336.1754 $[M+H]^+$; found: 336.1762.



benzyl 1-acetyl-2-phenylcyclopropane-1-carboxylate (7l). Following *GP-B,* **7l** (918.4 mg, 3.1 mmol, 60%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as yellow oil starting from benzyl 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), styrene (1.1 g, 10.4 mmol, 2.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.55 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37-7.12 (m, 8H, C_{arom}-H), 7.09-6.91 (m, 2H, C_{arom}-H), 4.85 (d, *J* = 12.1 Hz, 1H, OC**H**$_a$CH$_b$), 4.70 (d, *J* = 12.1 Hz, 1H, OCH$_a$C**H**$_b$), 3.31 (t, *J* = 8.6 Hz, 1H, C**H**CH$_a$H$_b$), 2.44 (s, 3H, CH_3), 2.25 (dd, *J* = 8.2, 4.6 Hz, 1H, CHC**H**$_a$H$_b$), 1.75 (dd, *J* = 9.2, 4.6 Hz, 1H, CHCH$_a$**H**$_b$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.2 (CH_3**C**=O), 168.3 (COO), 135.0 (C_{arom}), 134.9 (C_{arom}), 128.9 (2×C_{arom}-H), 128.6 (4×C_{arom}-H), 128.4 (C_{arom}-H), 128.3 (2×C_{arom}-H), 127.5 (C_{arom}-H), 67.3 (OCH_2), 44.8 (**C**C=O), 35.7 (**C**HCH$_2$), 29.8 (C**C**H$_3$), 21.8 (CH**C**H$_2$). **IR** (ATR): 1728 (C=O st), 1691 (C=O st), 1166 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 203.0 (M$^+$-C_7H_7, 2), 115.0 (17), 91.1 (100), 77.0 (17). **HRMS**: Calculated for $[C_{19}H_{18}O_3Na]^+$: 317.1154 $[M+Na]^+$; found: 317.1164.



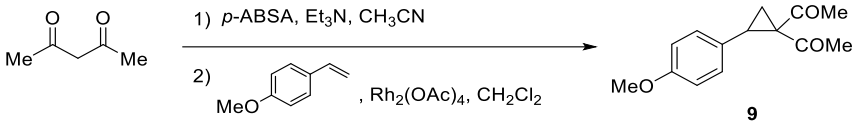
tert-butyl -1-benzoyl-2-(4-methoxyphenyl)cyclopropane-1-carboxylate (7m). Following *GP-B*, **7m** (938.1 mg, 2.7 mmol, 72%, dr 2.5:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as yellow oil starting from *tert*-butyl benzoylacetate (815.0 mg, 3.7 mmol, 1.0 eq) and *p*-ABSA (1.1 g, 4.4 mmol, 1.2 eq) in CH_3CN (26 mL) using Et_3N (0.8 mL, 5.5 mmol, 1.5 eq). After dissolving the crude *tert*-butyl 2-diazo-3-oxo-3-phenylpropanoate (920.0 mg, 3.7 mmol, 1.0 eq) and 4-methoxystyrene (2.5 mL, 18.5 mmol, 5.0 eq) in toluene (3.7 mL) $Rh_2(OAc)_4$ (32.0 mg, 0.07 mmol, 2 mol%) was added. R_f= 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 8.06-7.79 (m, 2H, C_{arom}-H), 7.73-7.62* (m, 2H, C_{arom}-H), 7.59-7.48* (m, 2H, C_{arom}-H), 7.50-7.27 (m, 3H, C_{arom}-H), 7.50-7.27* (m, 1H, C_{arom}-H), 7.34-7.18 (m, 2H, C_{arom}-H), 7.07* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.66* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.77 (s, 3H, OCH_3), 3.65* (s, 3H, OCH_3), 3.52 (t, *J* = 8.6 Hz, 1H, C**H**CH_2), 3.43* (t, *J* = 8.6 Hz, 1H, C**H**CH_2), 2.38* (dd, *J* = 4.9, 3.1 Hz, 1H, C**H**$_a$$CH_b$), 2.33 (dd, *J* = 8.0, 4.7 Hz, 1H, C**H**$_a$$CH_b$), 1.70* (dd, *J* = 9.2, 4.9 Hz, 1H, CH_aC**H**$_b$), 1.59 (dd, *J* = 9.1, 4.7 Hz, 1H, CH_aC**H**$_b$), 1.17* (s, 9H, $C(CH_3)_3$), 0.90 (s, 9H, $C(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 196.1 (C_{arom}-**C**=O), 1936* (C_{arom}-**C**=O), 170.1* (COO), 167.3 (COO), 158.8 (**C**$_{arom}$-OCH_3), 158.7* (**C**$_{arom}$-OCH_3), 138.3 (C_{arom}), 138.3* (C_{arom}), 132.6 (C_{arom}-H), 132.3* (C_{arom}-H), 130.4 (2×C_{arom}-H), 129.2* (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4* (2×C_{arom}-H), 128.1 (2×C_{arom}-H), 128.1* (2×C_{arom}-H), 127.1 (C_{arom}), 126.2* (C_{arom}), 113.7* (2×C_{arom}-H), 113.5 (2×C_{arom}-H), 82.2* (**C**$(CH_3)_3$), 81.6 (**C**$(CH_3)_3$), 55.4 (OCH_3), 55.2* (OCH_3), 43.4 (**C**CH_2), 43.1* (**C**CH_2), 33.6* (**C**HCH_2), 29.8 (**C**HCH_2), 27.7* (C(**C**$H_3)_3$), 27.4 (C(**C**$H_3)_3$), 20.2 (CH**C**H_2), 18.2* (CH**C**H_2). **IR** (ATR): 1720 (C=O st), 1678 (C=O st), 1166 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 352.1 (M^+, 1), 278.0 (33), 277.0 (16), 250.1 (26), 235 (21), 200 (21), 147 (31) 105.0 (100), 77.0 (49), 56.1 (20). **HRMS**: Calculated for $[C_{22}H_{24}O_4Na]^+$: 375.1572 $[M+Na]^+$; found: 375.1569.



benzyl 1-acetyl-2-(4-bromophenyl)cyclopropane-1-carboxylate (7n). Following *GP-B*, **7n** (2.3 g, 6.1 mmol, 59%, dr > 20:1) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as white solid starting from 2-diazo-3-oxobutanoate (1.1 g, 5.2 mmol, 1.0 eq), 4-bromostyrene (1.9 g, 10.4 mmol, 2.0 eq), toluene (5.2 mL) and $Rh_2(OAc)_4$ (37.7 mg, 0.08 mmol, 2 mol%). R_f= 0.40 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61-7.15 (m, 5H, C_{arom}-H), 7.13-6.76 (m, 4H, C_{arom}-H), 4.93 (d, *J* = 11.9 Hz, 1H, OC**H**$_a$$CH_b$), 4.80 (d, *J* = 12.0 Hz, 1H, OCH_aC**H**$_b$), 3.24 (t, *J* = 8.6 Hz, 1H, C**H**CH_aH_b), 2.44 (s, 3H, CH_3), 2.19 (dd, *J* = 8.1, 4.7 Hz, 1H, CHC**H**$_a$$H_b$), 1.73 (dd, *J*

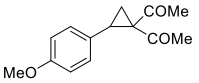
= 9.1, 4.7 Hz, 1H, $CHCH_aH_b$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 210.9 (CH_3**C**=O), 168.0 (COO), 134.9 (C_{arom}), 133.9 (C_{arom}), 131.4 (2×C_{arom}-H), 130.6 (2×C_{arom}-H), 128.8 (2×C_{arom}-H), 128.7 (2×C_{arom}-H), 128.6 (C_{arom}-H), 121.6 (C_{arom}), 67.4 (OCH_2), 44.7 (**C**C=O), 34.6 (**C**HCH_2), 29.8 (C**C**H_3), 21.7 (CH**C**H_2). **IR** (ATR): 1725 (C=O st), 1693 (C=O st), 1166 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 371.9 (M^+, 1), 91.1 (100). **HRMS**: Calculated for $[C_{19}H_{17}BrO_3Na]^+$: 395.0259 $[M+Na]^+$; found: 395.0265. **M.p.**: 103-106 ºC (petroleum ether/EtOAc).

2.3 Synthesis of diacyl-substituted cyclopropane 9



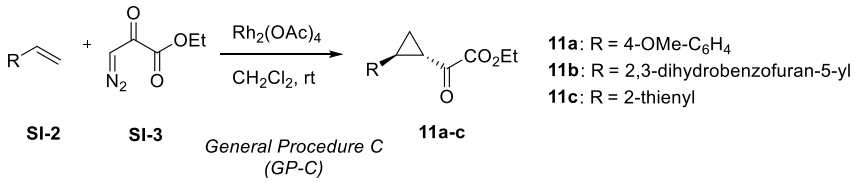
Scheme 4. 3 Synyhesis of cyclopropane **9**

Cyclopropanes **9** was prepared following the General Procedure B.



1,1'-(2-(4-Methoxyphenyl)cyclopropane-1,1-diyl)bis(ethan-1-one) (9). Following *GP-B*, **9** (149 mg, 0.64 mmol, 10%) was isolated by FC (petroleum ether/Et_2O, 3:1 to 2:1) on silica gel as yellow oil starting from pentane-2,4-dione (0.66 mL, 6.4 mmol, 1.0 eq) and *p*-ABSA (1.71 g, 7.1 mmol, 1.2 eq) in CH_3CN (16 mL) using Et_3N (1.3 mL, 9.6 mmol, 1.5 eq). To 3-diazopentane-2,4-dione (810 mg, 6.4 mmol, 1.0 eq) and 4-methoxystyrene (1.7 mL, 13.0 mmol, 2.0 eq) in dichloromethane (30 mL) $Rh_2(OAc)_4$ (14.4 mg, 0.03 mmol, 0.5 mol%) was added. R_f= 0.45 (petroleum ether/Et_2O, 1:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.80 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 3.77 (s, 3H, OCH_3), 3.24 (app t, *J* = 8.5 Hz, 1H, C**H**CH_2), 2.26 (s, 3H, CH_3C=O), 2.22 (dd, *J* = 7.9, 5.3 Hz, 1H, CHC**H$_a$**H_b), 1.83 (s, 3H, CH_3C=O), 1.64 (dd, *J* = 9.1, 5.3 Hz, $CHCH_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 203.0 (C=O), 202.6 (C=O), 159.1 (**C**$_{arom}$-OCH_3), 129.6 (2×C_{arom}-H), 126.0 (C_{arom}), 114.1 (2×C_{arom}-H), 55.3 (OCH_3), 52.8 (**C**C=O), 33.6 (**C**H_3C=O), 30.6 (**C**H_3C=O), 27.8 (**C**HCH_2), 19.4 (CH_2). **IR** (ATR): 1707 (C=O st), 1683 (C=O st), 1178 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 232.1 (M^+, 100), 171.1 (17), 147.1 (22), 121.0 (16), 115.1 (17), 103.0 (16), 91.0 (19), 77.1 (22). **HRMS**: Calculated for $[C_{14}H_{17}O_3]^+$: 233.1178 $[M+H]^+$; found: 233.1190.

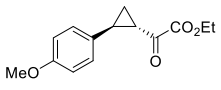
2.4 Synthesis of glyoxyl-substituted cyclopropanes (11a-c)



Scheme 4. 4 General Procedure C for the synthesis of glyoxyl-substituted cyclopropanes **11a-c**

General Procedure C (GP-C) for the Synthesis of trans-α-ketoester substituted Donor-acceptor Cyclopropanes 11a-c.

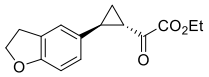
Alkyl 3-diazo-2-oxopropanoate **SI-3** was prepared according to the following modified procedure.[20] Alkyl 2-oxopropanoate (45.0 mmol, 1.0 eq) was dissolved in dry THF (200 mL) and (trimethylsilyl)diazomethane (45 mL, 90.0 mmol, 2 M in Et_2O, 2.0 eq) was added dropwise. The mixture was stirred at room temperature for 12 hours, the volatiles were evaporated under reduced pressure and the crude product was filtered through a short silica plug (petroleum ether/EtOAc 7:3). Cyclopropanes **11a-c** were prepared following a modified literature procedure.[21] To a stirred mixture of alkene **SI-2** (2.0 eq) and $Rh_2(OAc)_4$ (0.31 mol%) in dry CH_2Cl_2 (1 M) was added a solution **SI-3** (1.0 eq) in dry CH_2Cl_2 (0.2 M) via syringe pump for 2 hours at room temperature. The reaction mixture was further stirred for 1 hour. The resulting mixture was quenched with water and extracted with CH_2Cl_2 (2×20 mL). The combined organic phases were washed with brine and dried with Na_2SO_4. Removal of volatiles under reduced pressure, followed by purification by column chromatography on silica gel gave the corresponding ketoester **11a-c**.



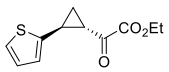
Ethyl *trans-2*-(2-(4-methoxyphenyl)cyclopropyl)-2-oxoacetate (11a). Following *GP-C*, **11a** (1.0 g, 4.0 mmol, 27%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 8:2) on silica gel as a pale yellow solid, from **SI-3** (2.1 g, 15.0 mmol, 1.0 eq), 4-methoxystyrene **SI-2a** (4.0 mL, 30.0 mmol, 2.0 eq) and $Rh_2(OAc)_4$ (22.2 mg, 0.050 mmol, 0.31 mol%) in CH_2Cl_2 (105 mL). R_f= 0.40 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.83 (d, *J* =

[20] Müller, P.; Chappellet, S. *Helv. Chim. Acta* **2005**, *88*, 1010.
[21] Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem. Int. Ed.* **2008**, *47*, 8933.

8.8 Hz, 2H, C_{arom}-H), 4.33 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 2.94 (ddd, *J* = 8.1, 5.2, 3.9 Hz, 1H, CH_2CHC_{arom}), 2.67 (ddd, J = 9.2, 7.0, 3.9 Hz, 1H, C**H**C=O), 1.83 (ddd, *J* = 9.2, 5.2, 4.1 Hz, 1H, C**H**$_a$H$_b$CH), 1.59 (ddd, *J* = 8.1, 7.0, 4.1, 1H, CH$_a$**H**$_b$CH), 1.37 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.3 (CH**C**=O), 161.0 (COO), 158.7 (**C**$_{arom}$-OCH_3), 131.3 (**C**$_{arom}$-CH), 127.5 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 62.6 (OCH_2), 55.3 (OCH_3), 32.4 (C_{arom}-**C**H), 29.6 (**C**HC=O), 21.3 (CH**C**H_2), 14.1 (CH_2**C**H_3). **IR** (ATR): 1726 (C=O st), 1703 (C=O st), 1176 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 248.1 (M^+, 27), 246.1 (27), 175.0 (27), 174.0 (61), 160.0 (19), 147.1 (100), 145.1 (15), 131.0 (26), 115.1 (24), 103.0 (26), 102.0 (15), 91.0 (31), 77.0 (17). **HRMS**: Calculated for $[C_{14}H_{16}O_4Na]^+$: 271.0946 $[M+Na]^+$; found: 271.0953. **M.p.**: 47-50 ºC (petroleum ether/EtOAc).



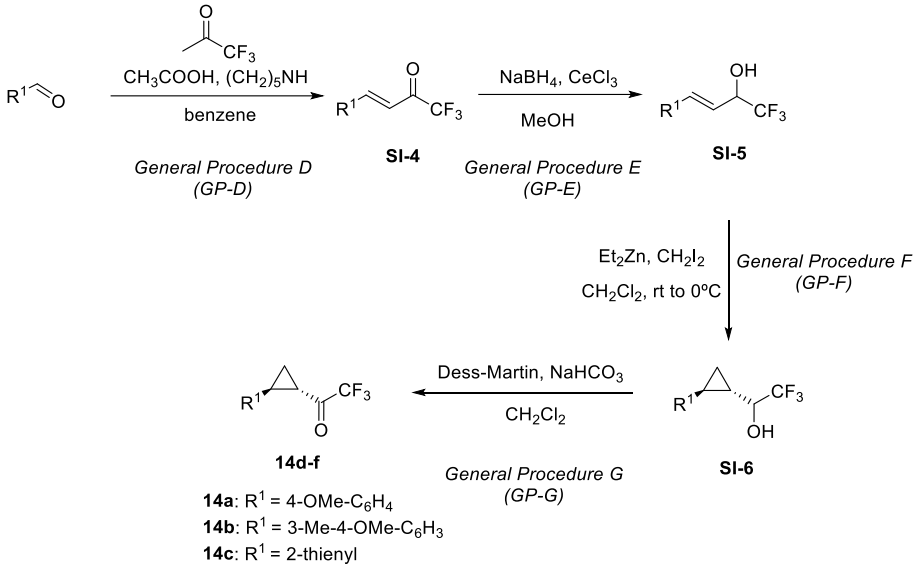
Ethyl 2-(2-(2,3-dihydrobenzofuran-5-yl)cyclopropyl)-2-oxoacetate (11b). Following *GP-C*, **11b** (644.2 mg, 2.5 mmol, 33%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 8:2) on silica gel as a white solid, from **SI-3** (1.0 g, 7.5 mmol, 1.0 eq), 5-vinyl-2,3-dihydrobenzofuran **SI-2t** (2.2 g, 15.0 mmol, 2.0 eq) and $Rh_2(OAc)_4$ (11.6 mg, 0.023 mmol, 0.31 mol%) in CH_2Cl_2 (53 mL). Rf = 0.50 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.97 (s, 1H, C_{arom}-H), 6.88 (d, *J* = 7.9 Hz, 1H, C_{arom}-H), 6.69 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 4.54 (t, *J* = 8.6 Hz, 2H, OC**H**$_2$CH$_2$), 4.33 (q, *J* = 7.1 Hz, 2H, $COOCH_2$), 3.16 (t, *J* = 8.6 Hz, 2H, OCH_2C**H**$_2$), 2.98-2.85 (m, 1H, CH_2CHC_{arom}), 2.70-2.61 (m, 1H, C**H**C=O), 1.82 (dt, *J* = 9.2, 4.7 Hz, 1H, C**H**$_a$H$_b$CH), 1.58 (td, *J* = 7.5, 4.0, 1H, CH$_a$**H**$_b$CH), 1.37 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.4 (CH**C**=O), 161.1 (COO), 159.4 (**C**$_{arom}$-OCH_2), 131.2 (**C**$_{arom}$-CH), 127.5 (**C**$_{arom}$-CH_2), 126.4 (C_{arom}-H), 123.1 (C_{arom}-H), 109.2 (C_{arom}-H), 71.4 (O**C**H_2CH_2), 62.6 (COO**C**H_2), 33.0 (**C**HC_{arom}), 29.7 (OCH_2**C**H_2), 29.7 (**C**HC=O), 21.4 (CH**C**H_2), 14.1 (CH_2**C**H_3). **IR** (ATR): 1724 (C=O st), 1702 (C=O st), 981 (C-O-C st as) cm^{-1}. **MS** (EI) m/z (%): 260.1 (M^+, 34), 258.1 (23), 187.0 (19), 186.1 (42), 160.0 (16), 159.1 (100), 157.0 (15), 131.1 (15), 129.0 (16), 128.0 (20), 115.0 (27), 91.1 (20). **HRMS**: Calculated for $[C_{15}H_{16}O_4Na]^+$: 283.0946 $[M+Na]^+$; found: 283.0952. **M.p.**: 99-101 ºC (petroleum ether/EtOAc).



Ethyl 2-oxo-2-(2-(thiophen-2-yl)cyclopropyl)acetate (11c). Following *GP-C*, **11c** (235.5 mg, 1.0 mmol, 14%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a pale yellow oil, from **SI-3** (1.0 g, 7.5 mmol, 1.0 eq), 2-vinylthiophene **SI-2x** (1.65 g, 15.0 mmol, 2.0 eq) and $Rh_2(OAc)_4$ (11.6 mg, 0.023 mmol, 0.31 mol%) in CH_2Cl_2 (27 mL). Rf = 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.14 (dd, *J* =

5.1, 1.2 Hz, 1H, SCH), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H, C_{arom}-H), 6.88-6.86 (m, 1H, C_{arom}-H), 4.36 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.05 (ddd, *J* = 8.2, 5.3, 3.9 Hz, 1H, $CH_2C\mathbf{H}C_{arom}$), 2.89 (ddd, *J* = 9.1, 6.8, 3.9 Hz, 1H, C**H**C=O), 1.88 (ddd, *J* = 9.1, 5.3, 4.2 Hz, 1H, C$\mathbf{H_a}H_bCH$), 1.64 (ddd, *J* = 8.2, 6.8, 4.2 Hz, 1H, $CH_a\mathbf{H_b}CH$), 1.39 (t, *J* = 7.2 Hz, 3H, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 191.8 (CH**C**=O), 160.8 (COO), 143.4 (C_{arom}), 127.1 (C_{arom}-H), 124.6 (C_{arom}-H), 123.8 (C_{arom}-H), 62.8 (OCH_2), 30.4 (C_{arom}-**C**H), 27.7 (**C**HC=O), 22.4 (CH**C**H_2), 14.2 ($CH_2\mathbf{C}H_3$). **IR** (ATR): 1730 (C=O st), 1708 (C=O st), 1176 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 224.0 (M^+, 12), 222.0 (15), 151.0 (26), 150.0 (56), 123.0 (100), 122 (22), 121.0 (26), 97.0 (17), 79.0 (18), 77.1 (16). **HRMS**: Calculated for $[C_{11}H_{12}O_3SNa]^+$: 247.0405 $[M+Na]^+$; found: 247.0410.

2.5 Synthesis of trifluoroacetyl-derived cyclopropanes (14a-c)

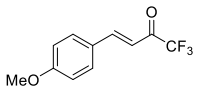


Scheme 4. 5 Synthesis of trifluoroacetyl cyclopropanes 8d-f

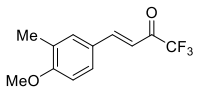
2.5.1 Synthesis of unsaturated trifluoromethyl ketones (SI-4)

General Procedure D (GP-D) for the synthesis of α-β-insaturated trifluoromethyl ketones SI-4.

A solution of trifluoroacetone (4.0 eq) in dry benzene (4M) was added to a stirred solution of the corresponding aldehyde (1.0 eq), acetic acid (1.5 eq), and piperidine (1.0 eq) in benzene (1 M) at 0 ºC, and the mixture was allowed to warm to room temperature overnight. Then, the reaction was quenched with saturated aqueous solution of NH_4Cl and extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the volatile substances under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding α-β-insaturated trifluoromethyl ketones **SI-4**.

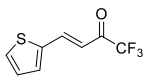


(E)-1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-en-2-one (SI-4a). Following *GP-D*, **SI-4a** (1.3 g, 5.9 mmol, 47%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as white solid, starting from 4-anisaldehyde (1.6 mL, 12.5 mmol, 1.0 eq), acetic acid (1.1 mL, 18.8 mmol, 1.5 eq) and piperidine (1.3 mL, 12.5 mmol, 1 eq) in benzene (12.5 mL), followed by the addition of trifluoroacetone (4.5 mL, 50 mmol, 4.0 eq) in benzene (12.5 mL). R_f= 0.60 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.88 (d, *J* = 15.8 Hz, 1H, C_{arom}C**H**=CH), 7.55 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.92 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.86 (d, *J* = 15.8 Hz, 1H, CHC=O), 3.83 (s, 3H, OCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.8 (q, $^2J_{C\text{-}F}$ = 34.9 Hz, C=O), 163.3 (**C**$_{arom}$-OCH_3), 150.0 (C_{arom}-**C**H=CH), 131.4 (2×C_{arom}-H), 126.2 (**C**$_{arom}$-C), 116.7 (q, $^1J_{C\text{-}F}$ = 291.0 Hz, CF_3), 114.8 (2×C_{arom}-H), 113.9 (**C**HC=O), 55.4 (OCH_3). **IR** (ATR): 1699 (C=O st), 1193 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 230.0 (M^+, 36), 161.0 (100), 133.0 (33), 90.0 (19), 89.1 (21), 69.0 (24), 63.0 (16). **HRMS**: Calculated for $[C_{11}H_{10}O_2F_3]^+$: 231.0633 $[M+H]^+$; found: 231.0630. **M.p.**: 47-50 ºC (petroleum ether/EtOAc).



(E)-1,1,1-Trifluoro-4-(4-methoxy-3-methylphenyl)but-3-en-2-one (SI-4b). Following *GP-D*, **SI-4b** (2.4 g, 9.9 mmol, 79%) was isolated by FC (petroleum ether/EtOAc, 19:1) on silica gel as an orange oil, starting from 4-methoxy-3-methylbenzaldehyde (1.8 mL, 12.5 mmol, 1.0 eq), acetic acid (1.1 mL, 18.8 mmol, 1.5 eq) and piperidine (1.3 mL, 12.5 mmol, 1 eq) in benzene (12.5 mL), followed by the addition

of trifluoroacetone (4.5 mL, 50 mmol, 4.0 eq) in benzene (12.5 mL). R_f= 0.60 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.92 (d, *J* = 15.8 Hz, 1H, C_{arom}C**H**=CH), 7.51-7.43 (m, 2H, C_{arom}-H), 6.92-6.84 (m, 2H, C_{arom}-H + CHC=O), 3.90 (s, 3H, OCH_3), 2.25 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 180.0 (q, $^2J_{C-F}$ = 34.9 Hz, C=O), 161.7 (**C**$_{arom}$-OCH_3), 150.5 (C_{arom}-**C**H=CH), 131.2 (C_{arom}-H), 130.2 (C_{arom}-H), 128.0 (C_{arom}), 125.8 (C_{arom}), 116.8 (q, $^1J_{C-F}$ = 291.0 Hz, CF_3), 113.8 (C_{arom}-H), 110.3 (C_{arom}-H), 55.7 (OCH_3), 16.3 (CH_3). **IR** (ATR): 1709 (C=O st), 1195 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 244.1 (M^+, 54), 229.0 (16), 175.0 (100), 147.1 (17). **HRMS**: Calculated for $[C_{12}H_{12}O_2F_3]^+$: 245.0789 $[M+H]^+$; found: 245.0778.

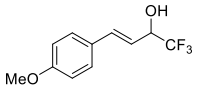


(E)-1,1,1-Trifluoro-4-(thiophen-2-yl)but-3-en-2-one (SI-4c). Following *GP-D*, **SI-4c** (3.0 g, 14.6 mmol, 42%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as orange oil, starting from thiophene-2-carbaldehyde (3.3 mL, 34.9 mmol, 1.0 eq), acetic acid (3.0 mL, 52.3 mmol, 1.5 eq) and piperidine (3.4 mL, 34.9 mmol, 1 eq) in benzene (35 mL), followed by the addition of trifluoroacetone (12.9 mL, 139.6 mmol, 4.0 eq) in benzene (35 mL). R_f= 0.70 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, *J* = 15.5 Hz, 1H, C_{arom}C**H**=CH), 7.57 (d, *J* = 5.0 Hz, 1H, SC_{arom}-H), 7.47 (d, *J* = 3.8 Hz, 1H, C_{arom}-H), 7.14 (dd, *J* = 5.0, 3.7 Hz, 1H, C_{arom}-H), 6.78 (d, *J* = 15.5 Hz, 1H, CHC=O). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 179.8 (q, $^2J_{C-F}$ = 35.3 Hz, C=O), 142.0 (C_{arom}-H), 139.1 (C_{arom}), 134.8 (C_{arom}-H), 132.0 (C_{arom}-H), 129.1 (C_{arom}-H), 116.5 (q, $^1J_{C-F}$ = 290.6 Hz, CF_3), 115.2 (C_{arom}-H). **IR** (ATR): 3113 (C-H st), 1709 (C=O st), 1198 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 206.0 (M^+, 35), 137.0 (100), 109.0 (61), 69.0 (39), 65.0 (38).

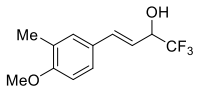
2.5.2 Synthesis of allylic alcohols (SI-5)

General Procedure E (GP-E) for the Synthesis of allylic alcohols SI-5.

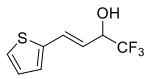
To a solution of the corresponding enone **SI-4** (1.0 eq) in MeOH (0.13 M), $CeCl_3$ (1.05 eq) was added and after stirring the solution for 10 minutes, $NABH_4$ (1.0 eq) was added. After stirring the solution for another 30 minutes, saturated aqueous NH_4Cl was added and the solvent was removed, after wich water was again added and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the volatile substances under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding α-β-insaturated trifluoromethyl substituted alcohols **SI-5**.



(E)-1,1,1-Trifluoro-4-(4-methoxyphenyl)but-3-en-2-ol (SI-5a). Following *GP-E*, **SI-5a** (788.9 mg, 4.4 mmol, 79%) was isolated by FC (petroleum ether/EtOAc, 8:2) on silica gel as a white solid, starting from **SI-4a** (1.0 g, 4.3 mmol, 1.0 eq) followed by the addition of cerium trichloride (1.1 g, 4.6 mmol, 1.05 eq) and $NaBH_4$ (164.0 mg, 4.3 mmol, 1.0 eq) in MeOH (33 mL). R_f= 0.40 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.88 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.76 (d, *J* = 15.9 Hz, 1H, C_{arom}C**H**=CH), 6.07 (dd, *J* = 15.9, 7.0 Hz, 1H, C**H**CHOH), 4.65-4.54 (m, 1H, C**H**OH), 3.82 (s, 3H, OCH_3), 3.38 (d, *J* = 5.7 Hz, 1H, OH). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.0 (**C**$_{arom}$-OCH_3), 136.0 (C_{arom}**C**H=CH), 128.3 (2×C_{arom}-H + C_{arom}), 124.5 (q, $^1J_{C\text{-}F}$ = 281.9 Hz, CF_3), 118.4 (q, $^3J_{C\text{-}F}$ = 1.9 Hz, **C**HCHOH), 114.2 (2×C_{arom}-H), 71.8 (q, $^2J_{C\text{-}F}$ = 32.3 Hz, CHOH), 55.4 (OCH_3). **IR** (ATR): 3288 (OH bs), 1656 (C=C st), 1124 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 232.0 (M^+, 55), 215.0 (18), 163.0 (100), 145.0 (46), 135.0 (26), 121.0 (23), 91.0 (21), 77.1 (33), 69.0 (35), 65.0 (15), 63.0 (27), 55.0 (80), 50.9 (29), 50.1 (19). **HRMS**: Calculated for $[C_{11}H_{12}O_2F_3]^+$: 233.0789 $[M+H]^+$; found: 233.0785. **M.p.**: 53-56 ºC (petroleum ether/EtOAc).



(E)-1,1,1-Trifluoro-4-(4-methoxy-3-methylphenyl)but-3-en-2-ol (SI-5b). Following *GP-E*, **SI-5b** (1.0 g, 4.2 mmol, 93%) was isolated by FC (petroleum ether/EtOAc, 9:1 to 8:2) on silica gel as a white solid, starting from **SI-4b** (1.1 g, 4.5 mmol, 1.0 eq) followed by the addition of cerium trichloride (1.2 g, 4.7 mmol, 1.05 eq) and $NaBH_4$ (246.5 mg, 4.5 mmol, 1.0 eq) in MeOH (34 mL). R_f= 0.40 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25-7.19 (m, 2H, C_{arom}-H), 6.81-6.73 (m, 2H, C_{arom}-H + C_{arom}C**H**=CH), 6.05 (dd, *J* = 15.9, 6.9 Hz, 1H, CHC=O), 4.63-4.56 (m, 1H, C**H**OH), 3.85 (s, 3H, OCH_3), 2.25 (s, 1H, OH), 2.23 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5 (**C**$_{arom}$-OCH_3), 136.4 (C_{arom}**C**H=CH), 129.0 (C_{arom}-H), 127.7 (C_{arom}), 127.1 (C_{arom}), 126.1 (C_{arom}-H), 124.5 (q, $^1J_{C\text{-}F}$ = 281.8 Hz, CF_3), 118.1 (q, $^3J_{C\text{-}F}$ = 2.2 Hz, **C**HCHOH), 110.0 (C_{arom}-H), 72.1 (q, $^2J_{C\text{-}F}$ = 32.4 Hz, CHOH), 55.5 (OCH_3), 16.4 (CH_3). **IR** (ATR): 3289 (OH bs), 1656 (C=C st), 1127 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 246.0 (M^+, 74), 228.2 (17), 177.1 (100), 159.0 (29), 149.0 (27), 135.0 (25), 115.0 (24), 91.1 (27), 78.1 (15), 76.9 (18), 69.0 (29), 55.0 (62), 51.0 (21). **HRMS**: Calculated for $[C_{12}H_{12}OF_3]^+$: 229.0840 $[M\text{-}H_2O+H]^+$; found: 229.0852. **M.p.**: 85-88 ºC (petroleum ether/EtOAc).

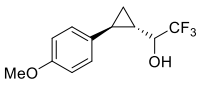


(E)-1,1,1-Trifluoro-4-(thiophen-2-yl)but-3-en-2-ol (SI-5c). Following *GP-E*, **SI-5c** (1.4 g, 6.4 mmol, 88%) was isolated by FC (petroleum ether/EtOAc, 9:1 to 8:2) on silica gel as white crystals, starting from **SI-4c** (1.5 g, 7.3 mmol, 1.0 eq) followed by the addition of cerium trichloride (1.9 g, 7.6 mmol, 1.05 eq) and $NaBH_4$ (280.0 mg, 7.3 mmol, 1.0 eq) in MeOH (55 mL). R_f= 0.40 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.4 Hz, 1H, SC_{arom}-H), 7.16-6.87 (m, 3H, 2×C_{arom}-H + C_{arom}C**H**=CH), 6.03 (dd, *J* = 15.7, 6.5 Hz, 1H, C**H**CHOH), 4.65-4.55 (m, 1H, C**H**OH), 2.42 (d, *J* = 5.7 Hz, 1H, OH). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.4 (C_{arom}), 129.4 (C_{arom}-H), 127.7 (2×C_{arom}-H), 126.0 (C_{arom}-**C**H=CH), 124.3 (q, $^1J_{C\text{-}F}$ = 281.9 Hz, CF_3), 119.8 (q, $^3J_{C\text{-}F}$ = 2.0 Hz, **C**HCHOH), 71.5 (q, $^2J_{C\text{-}F}$ = 32.5 Hz, CHOH). **IR** (ATR): 3375 (OH bs), 1651 (C=C st), 1122 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 208.0 (M^+, 64), 139.0 (100), 137.0 (16), 121.0 (19), 111.0 (32), 109.1 (19), 97.0 (36), 77.1 (18), 69.0 (56), 65.0 (18), 55.0 (91), 51.1 (22). **M.p.**: 39-42 ºC (petroleum ether/EtOAc).

2.5.3 Synthesis of cyclopropyl trifluoroethanols (SI-6)

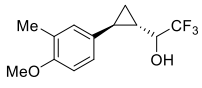
General Procedure F (GP-F) for the synthesis of cyclopropyl trifluoroethanols SI-6.

To a stirred solution of the corresponding allylic alcohol **SI-5** (1.0 eq) in CH_2Cl_2 (0.076 M), diethyl zinc (1.0 M in hexanes, 5.0 eq) was added at -10 ºC, followed by the addition of CH_2I_2 in one portion in absence of light. The solution was then warmed to 0 ºCover a period of 2 hours before being quenched with saturated aqueous Na_2SO_3 solution and stirred for 10 minutes. HCl 1M was then added to dissolve the resultant white precipitate and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the volatile substances under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding cyclopropyl trifluoroethanols **SI-6**.

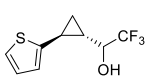


2,2,2-Trifluoro-1-(2-(4-methoxyphenyl)cyclopropyl)ethan-1-ol (SI-6a). Following *GP-F*, **SI-6a** (745.7 mg, 3.0 mmol, 94%) was isolated by FC (petroleum ether/EtOAc, 9:1 to 8:2) on silica gel as a white solid, starting from **SI-5a** (750.0 mg, 3.2 mmol, 1.0 eq) in CH_2Cl_2 (42 mL), followed by the addition of Et_2Zn (1.0 M in hexanes, 16.1 mL, 16.1 mmol, 5.0 eq) and CH_2I_2 (3.3 mL, 16.1 mmol, 5.0 eq). R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.83 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 3.79 (s, 3H, OCH_3), 3.66-3.55 (m, 1H, C**H**OH), 2.30 (d, *J* = 5.7

Hz, 1H, OH), 2.05 (dt, *J* = 9.6, 5.3 Hz, 1H, C_{arom}C**H**CH_2), 1.36-1.28 (m, 1H, C**H**CHOH), 1.16-0.99 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3 (**C**$_{arom}$-OCH_3), 132.8 (C_{arom}), 127.8 (2×C_{arom}-H), 125.1 (q, $^1J_{C\text{-}F}$ = 282.6 Hz, CF_3), 114.0 (2×C_{arom}-H), 73.3 (q, $^2J_{C\text{-}F}$ = 31.0 Hz, CHOH), 55.5 (OCH_3), 21.2 (q, $^3J_{C\text{-}F}$ = 2.2 Hz, **C**HCHOH), 20.0 (C_{arom}**C**HCH_2), 10.9 (CH_2). **IR** (ATR): 3518 (OH bs), 1155 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 246.1 (M^+, 23), 159.0 (19), 147.1 (100), 115.1 (30), 103.0 (16), 91.1 (41), 79.0 (15), 78.0 (16), 77.1 (17), 69.0 (18), 51.0 (24). **HRMS**: Calculated for $[C_{11}H_{13}O_2]^-$: 177.0916 [M-CF_3]$^-$; found: 177.0923. **M.p.**: 79-82 ºC (petroleum ether/EtOAc).



2,2,2-Trifluoro-1-(2-(4-methoxy-3-methylphenyl)cyclopropyl)ethan-1-ol (SI-6b). Following *GP-F*, **SI-6b** (1.0 g, 3.9 mmol, 95%) was isolated by FC (petroleum ether/EtOAc, 9:1 to 8:2) on silica gel as a colorless oil, starting from **SI-5b** (1.0 g, 4.1 mmol, 1.0 eq) in CH_2Cl_2 (52 mL), followed by the addition of Et_2Zn (1.0M in hexanes, 20.5 mL, 20.5 mmol, 5.0 eq) and CH_2I_2 (5.5 mL, 20.5 mmol, 5.0 eq). R_f= 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.07-6.93 (m, 2H, C_{arom}-H), 6.83 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 3.88 (s, 3H, OCH_3), 3.73-3.67 (m, 1H, OH), 3.66-3.53 (m, 1H, C**H**OH), 2.30 (s, 3H, $C_{arom}CH_3$), 2.06 (dt, *J* = 9.3, 5.2 Hz, 1H, C_{arom}C**H**CH_2), 1.46-1.32 (m, 1H, C**H**CHOH), 1.12 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.5 (**C**$_{arom}$-OCH_3), 132.2 (C_{arom}), 129.0 (C_{arom}-H), 126.8 (C_{arom}), 125.1 (q, $^1J_{C\text{-}F}$ = 282.4 Hz, CF_3), 124.8 (C_{arom}-H), 110.1 (C_{arom}-H), 73.3 (q, $^2J_{C\text{-}F}$ = 30.9 Hz, CHOH), 55.6 (OCH_3), 21.2 (q, $^3J_{C\text{-}F}$ = 2.1 Hz, **C**HCHOH), 20.0 (C_{arom}**C**H_3), 16.4 (C_{arom}**C**HCH_2), 11.0 (CH_2). **IR** (ATR): 3420 (OH bs), 1157 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 260.1 (M^+, 34), 173.0 (15), 161.1 (100), 146.0 (23), 115.0 (18), 91.1 (23). **HRMS**: Calculated for $[C_{13}H_{14}OF_3]^+$: 243.0997 [M-H_2O+H]$^+$; found: 243.0992.



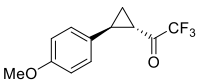
2,2,2-Trifluoro-1-(2-(thiophen-2-yl)cyclopropyl)ethan-1-ol (SI-6c). Following *GP-F*, **SI-6c** (1.3 g, 5.9 mmol, 96%) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a yellow oil, starting from **SI-5c** (1.4 g, 6.2 mmol, 1.0 eq) in CH_2Cl_2 (82 mL), followed by the addition of Et_2Zn (1.0M in hexanes, 31.0 mL, 31.0 mmol, 5.0 eq) and CH_2I_2 (2.4 mL, 31.0 mmol, 5.0 eq). R_f= 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (dd, *J* = 5.1, 1.2 Hz, 1H, SC_{arom}-H), 6.91 (dd, *J* = 5.1, 3.5 Hz, 1H, C_{arom}-H), 6.80 (dt, *J* = 3.5, 1.1 Hz, 1H, C_{arom}-H), 3.74-3.65 (m, 1H, C**H**OH), 2.26 (dt, *J* = 9.5, 5.1 Hz, 1H, C_{arom}C**H**CH_2), 2.13 (br s, 1H, OH), 1.49-1.40 (m, 1H, C**H**CHOH), 1.29-1.02 (m, 2H, CH_2). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.0 (C_{arom}), 127.0 (C_{arom}-H), 125.0 (q, $^1J_{C\text{-}F}$ = 282.7

Hz, CF_3), 123.8 (C_{arom}-H), 123.1 (C_{arom}-H), 72.4 (q, $^2J_{C-F}$ = 31.2 Hz, CHOH), 22.3 (q, $^3J_{C-F}$ = 2.1 Hz, **C**HCHOH), 15.7 (C_{arom}**C**HCH$_2$), 12.3 (CH_2). **IR** (ATR): 3485 (OH bs), 1155 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 221.9 (M^+, 21), 123.0 (100), 97.0 (19), 69.0 (17).

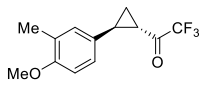
2.5.4 Synthesis of trifluoroacetyl cyclopropanes (14a-c)

General Procedure G (GP-G) for the synthesis of trifluoroacetyl cyclopropanes 14a-c.

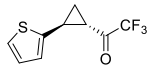
To a stirred solution of the corresponding cyclopropane **SI-6** (1.0 eq) in CH_2Cl_2 (0.1 M) $NaHCO_3$ (4.5 eq) was added at room temperature, followed by the addition of Dess-Martin periodinane (1.5 eq). After sitirring the solution 2 hours, the reaction mixture was quenched by adding saturated aqueous Na_2SO_3 solution and was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried over Na_2SO_4. Removal of the volatile substances under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding trifluoroacetyl cyclopropane **14a-c**.



2,2,2-Trifluoro-1-(2-(4-methoxyphenyl)cyclopropyl)ethan-1-one (14a). Following *GP-G*, **14a** (635.9 mg, 2.6 mmol, 93%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a pale yellow solid, starting from **SI-6a** (700.0 mg, 2.8 mmol, 1.0 eq) in CH_2Cl_2 (28 mL), followed by the addition of $NaHCO_3$ (1.1 g, 12.8 mmol, 4.5 eq) and Dess-Martin periodinane (1.8 g, 4.3 mmol, 1.5 eq). R_f= 0.40 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.87 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.81 (s, 3H, OCH_3), 2.81-2.74 (m, 1H, C_{arom}C**H**CH$_2$), 2.49-2.43 (m, 1H, CHC=O), 1.95-1.89 (m, 1H, C**H$_a$**H$_b$), 1.75-1.69 (m, 1H, CH$_a$**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.1 (q, $^2J_{C-F}$ = 36.0 Hz, C=O), 159.1 (**C**$_{arom}$-OCH_3), 130.3 (C_{arom}), 127.8 (2×C_{arom}-H), 115.9 (q, $^1J_{C-F}$ = 290.9 Hz, CF_3), 114.3 (2×C_{arom}-H), 55.4 (OCH_3), 32.8 (C_{arom}**C**HCH$_2$), 27.5 (**C**HC=O), 20.6 (CH_2). **IR** (ATR): 1734 (C=O st), 1204 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 244.1 (M^+, 25), 175.1 (21), 147.1 (100), 130.9 (15), 115.0 (32), 103.0 (24), 91.0 (41), 78.0 (22), 77.0 (22), 69.0 (32), 51.0 (18). **HRMS**: Calculated for $[C_{12}H_{12}O_2F_3]^+$: 245.0789 $[M+H]^+$; found: 245.0792. **M.p.**: 38-40 ºC (petroleum ether/EtOAc).

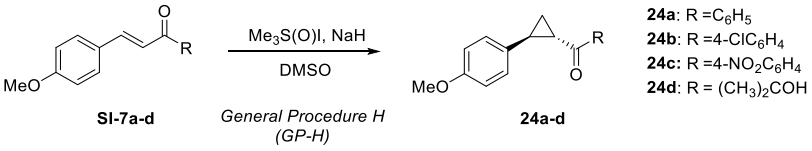


2,2,2-Trifluoro-1-(2-(4-methoxy-3-methylphenyl)cyclopropyl)ethan-1-one (14b). Following *GP-G*, **14b** (932.2 mg, 3.6 mmol, 95%) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a pale yellow oil, starting from **SI-6b** (1.0 g, 3.8 mmol, 1.0 eq) in CH_2Cl_2 (38 mL), followed by the addition of $NaHCO_3$ (1.4 g, 17.2 mmol, 4.5 eq) and Dess-Martin periodinane (2.4 g, 5.7 mmol, 1.5 eq). R_f= 0.40 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.02-6.88 (m, 2H, C_{arom}-H), 6.78 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 3.84 (s, 3H, OCH_3), 2.79-2.70 (m, 1H, $C_{arom}C\mathbf{H}CH_2$), 2.46 (dt, *J* = 8.6, 4.5 Hz, 1H, CHC=O), 2.23 (s, 3H, $C_{arom}CH_3$), 1.95-1.87 (m, 1H, $C\mathbf{H_a}H_b$), 1.77-1.68 (m, 1H, $CH_a\mathbf{H_b}$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 190.2 (q, $^2J_{C\text{-}F}$ = 35.8 Hz, C=O), 157.3 ($\mathbf{C}_{arom}$-OCH_3), 129.8 (C_{arom}), 128.9 (C_{arom}-H), 127.2 (C_{arom}), 125.0 (C_{arom}-H), 116.0 (q, $^1J_{C\text{-}F}$ = 290.9 Hz, CF_3), 110.1 (C_{arom}-H), 55.4 (OCH_3), 33.0 ($C_{arom}\mathbf{C}HCH_2$), 27.6 ($C_{arom}CH_3$), 20.6 (CH_2), 16.3 (**C**HC=O). **IR** (ATR): 1736 (C=O st), 1210 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 258.1 (M^+, 46), 189.1 (22), 161.1 (100), 146.1 (29), 131.0 (17), 115.1 (25), 91.1 (20), 69.0 (15). **HRMS**: Calculated for $[C_{13}H_{14}O_2F_3]^+$: 259.0946 $[M+H]^+$; found: 259.0936.



2,2,2-Trifluoro-1-(2-(thiophen-2-yl)cyclopropyl)ethan-1-one (14c). Following *GP-G*, **14c** (924.9 mg, 4.2 mmol, 73%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a yellow oil, starting from **SI-6c** (1.3 g, 5.8 mmol, 1.0 eq) in CH_2Cl_2 (58 mL), followed by the addition of $NaHCO_3$ (2.2 g, 26.1 mmol, 4.5 eq) and Dess-Martin periodinane (3.7 g, 8.7 mmol, 1.5 eq). R_f= 0.50 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.18 (dd, *J* = 5.1, 1.3 Hz, 1H, SC_{arom}-H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H, C_{arom}-H), 6.90 (dt, *J* = 3.5, 1.0 Hz, 1H, C_{arom}-H), 3.10-2.83 (m, 1H, $C_{arom}C\mathbf{H}CH_2$), 2.60-2.53 (m, 1H, CHC=O), 2.00-1.93 (m, 1H, $C\mathbf{H_a}H_b$), 1.78-1.72 (m, 1H, $CH_a\mathbf{H_b}$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.6 (q, $^2J_{C\text{-}F}$ = 36.2 Hz, C=O), 142.1 (C_{arom}), 127.2 (C_{arom}-H), 125.1 (C_{arom}-H), 124.3 (C_{arom}-H), 115.9 (q, $^1J_{C\text{-}F}$ = 290.4 Hz, CF_3), 28.3 ($C_{arom}\mathbf{C}HCH_2$), 27.9 (**C**HC=O), 21.7 (CH_2). **IR** (ATR): 1737 (C=O st), 1207 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 220.0 (M^+, 32), 151.0 (23), 123.0 (100), 121.0 (16), 97.0 (17), 79.1 (26), 69.0 (31). **HRMS**: Calculated for $[C_8H_7OS]^-$: 151.0218 $[M\text{-}CF_3]^-$; found: 151.0216.

2.6 Synthesis of acyl-substituted donor-acceptor cyclopropanes (24a-d)

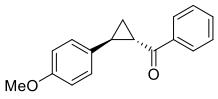


SI-7a-d *General Procedure H (GP-H)* **24a-d**

Scheme 4. 6 General Procedure H for the synthesis of ketone substituted cyclopropanes **24a-d**

Alkenes **SI-7a**,[22] **SI-7b**,[23] **SI-7c**[24] and **SI-7d**[25] are reported compounds and were prepared following the procedures described in the literature.

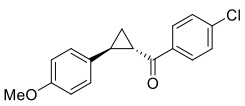
General Procedure H (GP-H) for the synthesis of ketone substituted cyclopropanes 24a-d. To a mixture of trimethylsulfoxonium iodide (1.2 eq) and sodium hydride (1.2 eq) DMSO (0.24M) was added and the mixture was stirred at room temperature for 30 minutes. Then, the corresponding alkene (1.0 eq) in DMSO (0.5M) was added to the solution at 0ºC and the solution was stirred for 2h at 60ºC. The reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with a saturated aqueous solution of NaCl and dried over Na_2SO_4. Removal of the volatile substances under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding cyclopropanes **24a-d**.



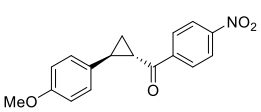
(2-(4-methoxyphenyl)cyclopropyl)(phenyl)methanone (24a). Following *GP-H*, **24a** (378.5 mg, 1.5 mmol, 71%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a colorless oil, starting from **SI-7a** (0.50 g, 2.1 mmol, 1.0 eq) in DMSO (4.2 mL) and the mixture of trimethylsulfoxonium iodide (0.55 g, 2.5 mmol, 1.2 eq) and NaH (60.0 mg, 2.5 mmol, 1.2 eq) in DMSO (10.4 mL). R_f= 0.60 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01

[22] Downey, C. W.; Glist, H. M.; Takashima, A.; Bottum, R. S.; Dixon, G. J. *Tetrahedron Lett.* **2018**, *59*, 3080.
[23] Kumar, R.; Mohanakrishnan, D.; Sharma, A.; Kaushik, N. K.; Kalia, K.; Sinha, A. K.; Sahal, D. *Eur. J. Med. Chem.* **2010**, *45*, 5292.
[24] Gaikwad, S.; Goswami, A.; De, S.; Schmittel, M. *Angew. Chem Int. Ed.* **2016**, *55*, 10512.
[25] Palomo, C.; Oiarbide, M.; García, J. M.; González, A.; Arceo, E. *J. Am. Chem. Soc.* **2003**, *125*, 13942.

(dd, *J* = 8.2, 1.4 Hz, 2H, C_{arom}-H), 7.63-7.53 (m, 1H, C_{arom}-H), 7.51-7.40 (m, 2H, C_{arom}-H), 7.13 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.87 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.81 (s, 3H, OCH_3), 2.85 (ddd, *J* = 7.8, 5.2, 4.0 Hz, 1H, CH-PMP), 2.68 (ddd, *J* = 8.9, 6.6, 4.0 Hz, 1H, CHC=O), 1.92 (ddd, *J* = 9.1, 5.2, 4.0 Hz, 1H, C**H**$_a$CH$_b$), 1.53 (ddd, *J* = 7.8, 6.6, 4.0 Hz, 1H, CH$_a$C**H**$_b$).**^{13}C NMR** (75 MHz, $CDCl_3$) δ 198.7 (C=O), 158.6 (**C**$_{arom}$-OCH_3), 137.9 (C_{arom}), 132.9 (C_{arom}-H), 132.6 (C_{arom}), 128.6 (2×C_{arom}-H), 128.2 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 55.4 (OCH_3), 29.8 (C_{arom}**C**HCH_2), 29.3 (**C**HC=O), 19.0 (CH_2). **IR** (ATR): 2934 (C-H st), 1664 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 252.1 (M^+, 30), 250.1 (29), 147.0 (41), 115.0 (24), 105.0 (70), 103.0 (21), 91.0 (24), 78.0 (29), 77.0 (100), 51.0 (31). **HRMS**: Calculated for $[C_{17}H_{17}O_2]^+$: 253.1229 $[M+H]^+$; found: 253.1228.

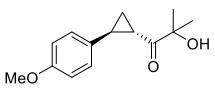


(4-chlorophenyl)(2-(4-methoxyphenyl)cyclopropyl)methanone (24b). Following *GP-H*, **24b** (889.0 mg, 3.1 mmol, 56%) was isolated by FC (petroleum ether/EtOAc, 19:1) on silica gel as a white solid, starting from **SI-7b** (1.5 g, 5.5 mmol, 1.0 eq) in in DMSO (11.0 mL) and the mixture of trimethylsulfoxonium iodide (1.4 g, 6.6 mmol, 1.2 eq) and NaH (158.5 mg, 6.6 mmol, 1.2 eq) in DMSO (27.5 mL). R_f= 0.50 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.42 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.11 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.86 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 3.80 (s, 3H, OCH_3), 2.77 (ddd, *J* = 7.9, 5.2, 4.0 Hz, 1H, CH-PMP), 2.67 (ddd, *J* = 9.0, 6.7, 4.0 Hz, 1H, CHC=O), 1.91 (ddd, *J* = 9.2, 5.2, 4.1 Hz, 1H ,C**H**$_a$CH$_b$), 1.54 (ddd, *J* = 7.9, 6.7, 4.1 Hz, 1H, CH$_a$C**H**$_b$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.5 (C=O), 158.6 (**C**$_{arom}$-OCH_3), 139.4 (C_{arom2}), 136.2 (C_{arom}), 132.3 (C_{arom}), 129.6 (2×C_{arom}-H), 128.9 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 55.4 (OCH_3), 30.0 (C_{arom}**C**HCH_2), 29.3 (**C**HC=O), 19. (CH_2). **IR** (ATR): 2937 (C-H st), 1664 (C=O st), 1032 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 286.0 (M^+, 17), 147.0 (100), 138.9 (60), 115.0 (30), 113.0 (18), 111.0 (48), 103.0 (22), 91.0 (35), 78.0 (35), 78.0 (20), 77.0 (22), 75.0 (27). **HRMS**: Calculated for $[C_{17}H_{16}O_2Cl]^-$: 287.0839 $[M+H]^+$; found: 287.0839. **M.p.**: 71-74 ºC (petroleum ether/EtOAc).



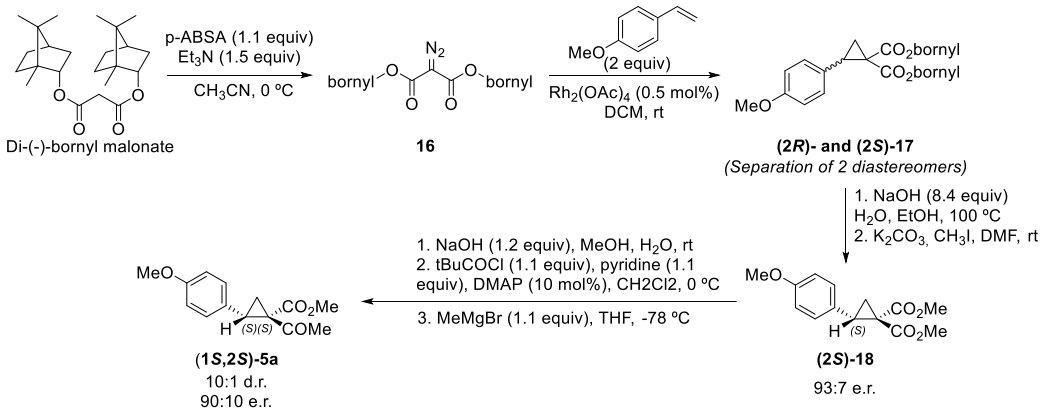
(2-(4-methoxyphenyl)cyclopropyl)(4-nitrophenyl)methanone (24c). Following *GP-H*, **24c** (416.2 mg, 1.4 mmol, 40%) was isolated by FC (petroleum ether/EtOAc, 19:1) on silica gel as a yellow solid, starting from **SI-7c** (1.0 g, 3.5 mmol, 1.0 eq) in DMSO (7.0 mL) and the mixture of trimethylsulfoxonium iodide (0.92 g, 4.2 mmol, 1.2 eq) and NaH (100.0 mg, 4.2

mmol, 1.2 eq) in DMSO (17.5 mL). R_f= 0.50 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H, C_{arom}-H), 8.10 (d, *J* = 9.0 Hz, 2H, C_{arom}-H), 7.11 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.85 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 3.78 (s, 3H, OCH_3), 2.82 (ddd, *J* = 7.9, 5.2, 3.9 Hz, 1H, CH-PMP), 2.72 (ddd, *J* = 8.8, 6.8, 3.9 Hz, 1H, CHC=O), 1.95 (ddd, *J* = 9.1, 5.2, 4.1 Hz, 1H, C**H**$_a$CH$_b$), 1.67-1.56 (m, 1H, CH$_a$C**H**$_b$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.2 (C=O), 158.7 (**C**$_{arom}$-OCH_3), 150.2 (C_{arom}-NO_2), 142.3 (C_{arom}), 131.7 (C_{arom}), 129.1 (2×C_{arom}-H), 127.4 (2×C_{arom}-H), 123.8 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 55.4 (OCH_3), 31.0 (C_{arom}**C**HCH$_2$), 30.1 (**C**HC=O), 19.8 (CH_2). **IR** (ATR): 2934 (C-H st), 1671 (C=O st), 1515 (NO_2 st as), 1341 (NO_2 st sim) cm^{-1}. **HRMS**: Calculated for $[C_{17}H_{16}NO_4]^+$: 298.1079 $[M+H]^+$; found: 298.1084. **M.p.**: 61-63 ºC (petroleum ether/EtOAc).



2-hydroxy-1-((1S,2S)-2-(4-methoxyphenyl)cyclopropyl)-2-methylpropan-1-one (24d). Following *GP-H*, **24d** (103.2 mg, 0.44 mmol, 68%) was isolated by FC (petroleum ether/EtOAc, 19:1 to 9:1) on silica gel as a pale yellow solid, starting from **SI-7d** (162.7 mg, 0.65 mmol, 1.0 eq) in DMSO (1.3 mL) and the mixture of trimethylsulfoxonium iodide (171.6 mg, 0.78 mmol, 1.2 eq) and NaH (18.7 mg, 0.78 mmol, 1.2 eq) in DMSO (3.25 mL). R_f= 0.50 (petroleum ether/EtOAc, 19:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.84 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 3.91 (s, 1H, OH), 3.79 (s, 3H, OCH_3), 2.59-2.45 (m, 1H, C_{arom}C**H**CH$_2$), 2.24 (app dt, *J* = 8.9, 4.6 Hz, 1H, CHC=O), 1.72 (app dt, *J* = 9.3, 4.7 Hz, 1H, C**H**$_a$CH$_b$), 1.53-1.39 (m, 7H, CH$_a$C**H**$_b$ + 2×CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 212.5 (C=O), 158.6 (**C**$_{arom}$-OCH_3), 131.6 (C_{arom}), 127.6 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 76.3 (COH), 55.4 (OCH_3), 30.2 (C_{arom}**C**HCH$_2$), 27.1 (**C**HC=O), 26.5 (CCH_3), 26.4 (CCH_3), 19.0 (CH_2). **IR** (ATR): 3482 (O-H st), 2973 (C-H st), 1686 (C=O st) cm^{-1}. **MS** (EI) m/z (%): 234.1 (M^+, 9), 216.1 (M^+-H_2O, 22), 214.1 (23), 201.1 (24), 199.1 (20), 148.1 (40), 147.1 (100), 134.1 (63), 121.0 (35), 115.0 (26), 91.0 (25), 77.0 (19), 59.1 (51). **HRMS**: Calculated for $[C_{14}H_{19}O_3Na]^+$: 257.1154 $[M+Na]^+$; found: 257.1161. **M.p.**: 35-38 ºC (petroleum ether/EtOAc).

2.7 Synthesis of enantioenriched cyclopropane (1*S*,2*S*)-5a



Scheme 4. 7 Synthesis of enantioenriched cyclopropane **(1S,2S)-5a**

2.7.1 Preparation of cyclopropanes (2*R*)- and (2*S*)-17

Triethylamine (10.2 mL, 73.1 mmol, 1.5 eq.) was added dropwise to a solution of di-(-)-bornyl malonate[26] (18.26 g, 48.8 mmol, 1.0 eq.) and 4-acetamidobenzenesulfonyl azide (*p*-ABSA, 12.89 g, 53.6 mmol, 1.2 eq.) in dry acetonitrile (350 mL) at 0 ºC, and the reaction mixture was allowed to warm to rt and stirred overnight. Volatiles were evaporated, the residue was suspended in CH_2Cl_2, silica gel was added and solvent was evaporated. The resulting solid mixture was loaded onto a pad of silica and eluted with petroleum ether/EtOAc (10:1) to provide the corresponding diazocompound **16** as a yellow solid (18.30 g, 45.4 mmol, 93% yield). Rhodium(II) acetate dimer (100 mg, 0.23 mmol, 0.5 mol%) was added to a solution of **16** and 4-methoxystyrene (12.1 mL, 90.9 mmol, 2 equiv) in CH_2Cl_2 (250 mL), and the resulting green solution was stirred at rt for 1-2 h (TLC shows full consumption of diazocompound). Volatiles were evaporated and the residue was purified by column chromatography (petroleum ether/EtOAc 25:1 to 10:1). A mixture of diastereoisomers **(2*R*)-** and **(2*S*)-17** was isolated (13.86 g, 27.2 mmol, 60% yield). Further

[26] Bagnoli, L.; Scarponi, C.; Testaferri, L.; Tiecco, M. *Tetrahedron: Asymmmetry* **2009**, *20*, 1506.

purification by column chromatography allowed the separation of both diastereomers.[27] Spectroscopic data of both diastereomers match those reported in the literature.[26]

2.7.2 Hydrolysis and esterification ((2*S*)-18)

Following a modified literature procedure,[28] **(2*S*)-17** (1.29 g, 2.5 mmol) was dissolved in EtOH (6.7 mL), a solution of NaOH (21 mmol, 8.4 equiv) in H_2O (3.4 mL) was added and the reaction mixture was heated at 100 ºC for 14 h. When full conversion was achieved (as determined by ^{1}H-NMR of an aliquot[29]), the volatiles were removed below room temperature (by a stream of compressed air). The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL), the phases were separated and the organic layer was washed with H_2O (5 mL). The combined aqueous layers were acidified to pH 2 by dropwise addition of 1 M HCl at 0 ºC (abundant precipitate was observed). The diacid was extracted with Et_2O (4×10 mL), the combined organic layers were dried over Na_2SO_4, filtered and evaporated below room temperature (stream of air). The diacid,[30] obtained as a yellow solid (599 mg, 2.5 mmol, quant.), was dissolved in dry DMF (5 mL) and K_2CO_3 (1.38 g, 10 mmol, 4 equiv) was added. After 30 minutes at rt, iodomethane (0.93 mL, 15 mmol, 6 equiv) was added dropwise,[31] and the heterogeneous mixture was stirred overnight. The reaction mixture was diluted with H_2O (20 mL), and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography to give pure dimethyl ester **(2*S*)-18** (430 mg, 1.6 mmol, 65% yield, 93:7 er). Spectroscopic data match those reported in the literature.[32] The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 7.76 min, τ_{minor} = 8.58 min (93:7).

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[27] Both diastereomers have essentially the same R_f, but partial separation is achieved as judged by ^{1}H-NMR (representative signals are 2 overlapped apparent triplets at 3.18 ppm for **(2*R*)-SI-8** and at 3.15 ppm for **(2*S*)-SI-8**). Iterative purifications by column chromatography (PE/Et_2O 20:1) allowed the progressive enrichment of the diastereomixtures up to dr > 15:1 for both diastereomers.

[28] Yamazaki, S.; Kataoka, H.; Yamabe, S. *J. Org. Chem.* **1999**, *64*, 2367.

[29] An aliquot (0.1 mL) was diluted with H_2O and Et_2O; the ethereal layer was discarded and the aqueous layer was acidified with 1M HCl and extracted with Et_2O for ^{1}H-NMR analysis.

[30] ^{1}H-NMR showed that enantioenriched diacid was pure, but it turned out to be relatively unstable and Cloke-Wilson rearrangement product was observed upon heating or standing, so it was handled cold and immediately esterified.

[31] Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642.

[32] Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689.

2.7.3 Transformation of the *trans* ester into an acetyl group ((1*S*,2*S*)-5a)

Dimethyl ester **(2*S*)-18** (430 mg, 1.6 mmol) was dissolved in MeOH (1.3 mL), a 1.6 M aqueous solution of NaOH (1.2 mL, 1.9 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred at rt for 2h (full conversion was determined by TLC). The volatiles were evaporated, the mixture was diluted with H_2O (5 mL) and 1 M HCl was added at 0 ºC until pH 2. The aqueous phase was extracted with EtOAc (3×10 mL), and the combined organic layers were dried over Na_2SO_4, filtered and evaporated below room temperature (stream of air). The monoester (375 mg, 1.5 mmol, 94% yield), obtained as a single diastereomer, was dissolved in dry CH_2Cl_2 (5 mL) and pyridine (0.24 mL, 3.0 mmol, 2 equiv) and DMAP (18 mg, 0.15 mmol, 10 mol%) were subsequently added. The mixture was cooled to 0 ºC and pivaloyl chloride (0.37 mL, 3.0 mmol, 2 equiv) was added dropwise. The mixture was stirred at 0 ºC for 2h and the volatiles were evaporated. The residue was quickly purified by column chromatography (petroleum ether/EtOAc 10:1). The mixed anhydride (274 mg, 0.82 mmol, 55% yield), obtained as a single diastereomer, was dissolved in dry THF (3 mL) and cooled to -78 ºC. A solution of MeMgBr (1.06 M in Et_2O,[33] 0.81 mL, 0.86 mmol, 1.05 equiv) was added dropwise, and the mixture was stirred at -78 ºC for 3 h (full conversion determined by TLC). The reaction was quenched by addition of aq. NH_4Cl (sat) at -78 ºC, and the aqueous phase was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc 15:1) to afford **(1*S*,2*S*)-5a** (107 mg, 0.43 mmol, 10:1 dr, 90:10 er, 52% yield).[34] The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{minor} = 12.61 min, τ_{major} = 13.44 min (10:90). $[\alpha]_D^{20}$: -222.7 (*c* = 0.59, CH_2Cl_2).

[33] Titrated with salicylaldehyde phenylhydrazone as an indicator, as reported in: Love, B. E.; Jones, E, G. *J. Org. Chem.* **1999**, *64*, 3755.

[34] The addition of the Grignard reagent produced a small amount of **(1*R*,2*S*)-1b**, which was minimized by keeping the reaction at -78 ºC and quenching it after 3h, and can be separated by column chromatography (monitored by ^{1}H-NMR).

2.8 Synthesis of indoles (19a-p)

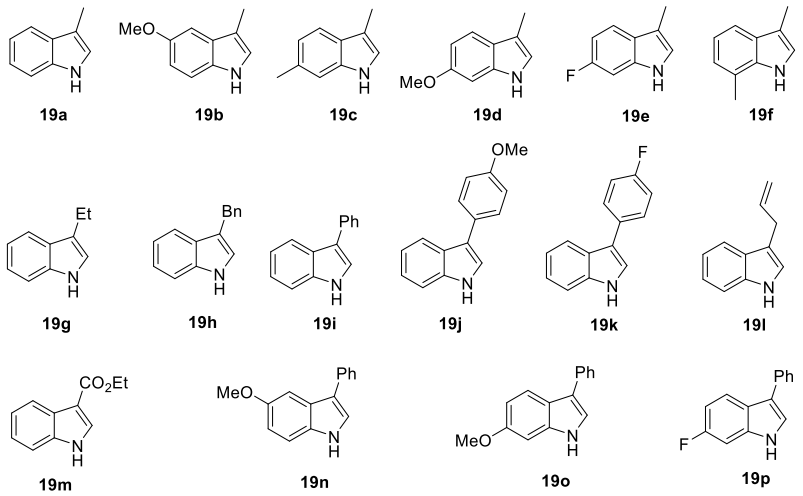


Figure 1. Indoles employed

Indole **18a** was obtained from commercial sources. Indoles **19b**,[35] **19c**,[35] **19d**,[35] **19e**,[36] **19f**,[35] **19g**,[37] **19h**,[38] **19i**,[39] **19j**,[39] **19k**,[39] **19l**,[40] **19m**,[41] **19n**,[39] **19o**,[42] and **19p**[42] and are reported compounds and were prepared following the procedures described in the literature.

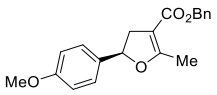
[35] Zhou, Z.; Li, Y.; Gong, L.; Meggers, E. *Org. Lett.* **2017**, *19*, 222.
[36] Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11881.
[37] Song, C.; Dong, X.; Yi, H.; Chiang, C.-W.; Lei, A. *ACS Catal.* **2018**, *8*, 2195.
[38] Karnakanti, S.; Zang, Z.-L.; Zhao, S.; Shao, P.-L.; Hu, P.; He, Y. *Chem. Commun.* **2017**, *53*, 11205.
[39] O´Brien, C.J.; Droege, D. G.; Jiu, A. Y.; Gandhi, S. S.; Paras, N. A.; Olson, S. H.; Conrad, J. *J. Org. Chem.* **2018**, *83*, 8926.
[40] Huchet, Q. A.; Kuhn, B.; Wagner, B.; Kratochwil, N. A.; Fischer, H.; Kansy, M.; Zimmerli, D.; Carreira, E. M.; Müller, K. *J. Med. Chem.* **2015**, *58*, 9041.
[41] Abe, T.; Yamada, K. *Org. Lett.* **2016**, *18*, 6504.
[42] Gattu, R.; Bhattacharjee, S.; Mahato, K.; Khan, A. T. *Org. Biomol. Chem.* **2018**, *16*, 3760.

3. CATALYTIC ENANTIOSELECTIVE CLOKE-WILSON REARRANGEMENT

3.1 Synthesis of dihydrofurans

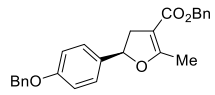
General Procedure I (GP-I) for the enantioselective Cloke-Wilson rearrangement

An oven-dried 5 mL screw-capped test tube containing a stirring bar was charged with the corresponding cyclopropane and dissolved in the appropriate solvent or solvent mixture (0.2 M) under Ar. The mixture was cooled to the desired temperature for 30 minutes, and the catalyst (10 mol%) was quickly added to the mixture. When the reaction was judged complete (monitored by TLC), it was quenched by addition of aq. $NaHCO_3$ (sat) at low temperature and diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel to afford pure dihydrofuran.

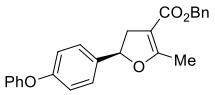


Benzyl 5-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2a). Following *GP-I*, **2a** (116.8 mg, 0.36 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1a** (129.8 mg, 0.4 mmol) and catalyst **3g** (28.0 mg, 0.04 mmol) in 1,2-dichloroethane (0.5 mL) and m-xylene (1.5 mL) at -30 ºC for 48 h.[43] **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.32 (m, 5H, C_{arom}-H), 7.29 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.92 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.56 (dd, *J* = 10.6, 8.6 Hz, 1H, Ar-C**H**-O), 5.21 (s, 2H, OC**H**$_2$Ph), 3.81 (s, 3H, OCH_3), 3.34 (ddq, *J* = 14.5, 10.6, 1.6 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.97 (ddq, *J* = 14.5, 8.6, 1.6 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.30 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (CH_2C=**C**-O), 165.9 (COO), 159.7 (**C**$_{arom}$-OCH_3), 136.8 (C_{arom}), 133.4 (C_{arom}), 128.6 (2×C_{arom}-H), 128.0 (3×C_{arom}-H), 127.4 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 101.6 (CH_2**C**=C-O), 83.4 (CH-O), 65.4 (CO_2**C**H_2), 55.4 (OCH_3), 37.8 (**C**H_2C=C), 14.3 (C=C-**C**H_3). **IR** (ATR): 1696 (C=O st), 1249 (C-O st), 1074 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 324.1 (M+, 9), 233.1 (21), 91.1 (100), 77.1 (15). **HRMS** (ESI^+): Calculated for $[C_{20}H_{21}O_4]^+$: 325.1440 $[M+H]^+$; found: 325.1452. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 7.55 min, τ_{major} = 8.82 min (5:95). $[\alpha]_D^{20}$: -115.0 (*c* = 1.1, CH_2Cl_2).

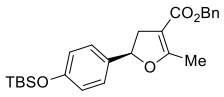
[43] Reaction at 0.05 mmol-scale was complete after 48 h and the yield and e.e. was the same. Reaction with 5 mol% catalyst loading was complete after 96 h and the yield and e.e. was the same.



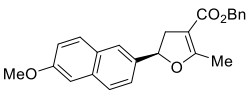
Benzyl 5-(4-(benzyloxy)phenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2b). Following *GP-I*, **2b** (18.2 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1b** (20.0 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 48 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47-7.27 (m, 12H, C_{arom}-H), 6.98 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.55 (dd, *J* = 10.6, 8.5 Hz, 1H, Ar-C**H**-O), 5.19 (s, 2H, $CO_2C\mathbf{H}_2Ph$), 5.07 (s, 2H, $ArOC\mathbf{H}_2Ph$), 3.32 (ddq, *J* = 14.5, 10.6, 1.6 Hz, 1H, $C\mathbf{H}_aH_b$-CH-O), 2.95 (ddq, *J* = 14.6, 8.6, 1.6 Hz, 1H, $CH_a\mathbf{H}_b$-CH-O), 2.27 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (CH_2C=**C**-O), 165.9 (COO), 158.9 (**C**$_{arom}$-OCH_2), 137.0 (C_{arom}), 136.8 (C_{arom}), 133.8 (C_{arom}), 128.7 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.1 (C_{arom}-H), 128.0 (3×C_{arom}-H), 127.6 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 115.2 (2×C_{arom}-H), 101.6 (CH_2**C**=C-O), 83.4 (CH-O), 70.2 ($ArO\mathbf{C}H_2Ph$), 65.5 ($CO_2\mathbf{C}H_2$), 37.8 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1697 (C=O st), 1223 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 400.2 (M+, 3), 309.0 (6), 92.0 (8), 91.0 (100), 65.9 (8). **HRMS** (ESI$^+$): Calculated for $[C_{26}H_{25}O_4]^+$: 401.1753 $[M+H]^+$; found: 401.1758. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 12.11 min, τ_{major} = 14.34 min (10:90). $[\alpha]_D^{20}$: -62.9 (*c* = 0.8, CH_2Cl_2).



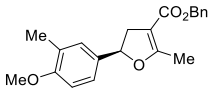
Benzyl 2-methyl-5-(4-phenoxyphenyl)-4,5-dihydrofuran-3-carboxylate (2c). Following *GP-I*, **2c** (12.0 mg, 0.03 mmol, 62%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1c** (19.3 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 120 h. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40-7.29 (m, 9H, C_{arom}-H), 7.15-7.10 (m, 1H, C_{arom}-H), 7.04-6.99 (m, 4H, C_{arom}-H), 5.59 (dd, *J* = 10.7, 8.4 Hz, 1H, Ar-C**H**-O), 5.19 (s, 2H, $OC\mathbf{H}_2Ph$), 3.40-3.32 (m, 1H, C**H**H'-CH-O), 3.00-2.93 (m, 1H, CH**H'**-CH-O), 2.29 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4 (CH_2C=**C**-O), 165.9 (O=**C**-O), 157.4 (C_{arom}-O), 157.1 (C_{arom}-O), 136.8 (C_{arom}), 136.2 (C_{arom}), 129.9 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 127.6 (2×C_{arom}-H), 123.6 (C_{arom}-H), 119.2 (2×C_{arom}-H), 119.1 (2×C_{arom}-H), 101.7 (CH_2**C**=C-O), 83.2 (CH-O), 65.5 ($CO_2\mathbf{C}H_2$), 38.0 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1774 (C=O st), 1244 (C-O st) cm^{-1}. **HRMS**: Calculated for $[C_{25}H_{23}O_4]^+$: 387.1596 $[M+H]^+$; found: 387.1600. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 6.60 min, τ_{major} = 7.46 min, (42:58).



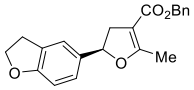
Benzyl 5-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2d). Following *GP-I*, **2d** (12.1 mg, 0.03 mmol, 57%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1d** (21.2 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 120 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H, C_{arom}-H), 7.20 (d, *J* = 8.4 Hz, 2H, C_{arom}-H), 6.83 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 5.54 (dd, *J* = 10.6, 8.6 Hz, 1H, Ar-C**H**-O), 5.19 (s, 2H, OC**H$_2$**Ph), 3.31 (ddq, *J* = 14.6, 10.6, 1.6 Hz, 1H, C**H**H'-CH-O), 2.95 (ddq, *J* = 14.6, 8.7, 1.6 Hz, 1H, CH**H'**-CH-O), 2.28 (t, *J* = 1.6 Hz, 3H, C=C-C**H$_3$**), 0.98 (s, 9H, Si-C$(CH_3)_3$), 0.19 (s, 6H, Si$(CH_3)_2$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (CH_2C=**C**-O), 166.0 (O=**C**-O), 155.9 (C_{arom}-O), 136.8 (C_{arom}), 134.1 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 127.4 (2×C_{arom}-H), 120.4 (2×C_{arom}-H), 101.6 (CH_2**C**=C-O), 83.5 (CH-O), 65.5 (CO_2**C**H_2), 37.9 (**C**H_2C=C), 25.8 (C(**C**$H_3)_3$), 18.4 (**C**$(CH_3)_3$), 14.4 (C=C-**C**H_3), -4.3 (Si$(CH_3)_2$). **IR** (ATR): 1774 (C=O st), 1259 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 424.3 (M+, 8), 333.2 (19), 91.0 (100), 72.9 (17), 57.1 (17). **HRMS**: Calculated for $[C_{25}H_{33}O_4Si]^+$: 425.2146 $[M+H]^+$; found: 425.2148. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 7.41 min, τ_{minor} = 8.25 min (74:26).



Benzyl 5-(6-methoxynaphthalen-2-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2g). Following *GP-I*, **2g** (17.6 mg, 0.05 mmol, 94%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1g** (18.7 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and m-xylene (0.12 mL) at -30 ºC for 60 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81-7.67 (m, 3H, C_{arom}-H), 7.46-7.28 (m, 6H, C_{arom}-H), 7.20-7.11 (m, 2H, C_{arom}-H), 5.74 (dd, *J* = 10.7, 8.5 Hz, 1H, Ar-C**H**-O), 5.20 (s, 2H, OC**H$_2$**Ph), 3.92 (s, 3H, OCH_3), 3.48-3.35 (m, 1H, C**H$_a$**H$_b$-CH-O), 3.11-2.99 (m, 1H, CH$_a$**H$_b$**-CH-O), 2.33 (s, 3H, C=C-C**H$_3$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (CH_2C=**C**-O), 165.9 (COO), 158.1 (**C**$_{arom}$-OCH_3), 136.8 (C_{arom}), 136.4 (C_{arom}), 134.5 (C_{arom}), 129.7 (C_{arom}-H), 128.7 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 127.8 (C_{arom}-H), 124.8 (C_{arom}-H), 124.2 (C_{arom}-H), 119.4 (C_{arom}-H), 105.9 (C_{arom}-H), 101.7 (CH_2**C**=C-O), 83.8 (CH-O), 65.5 (CO_2**C**H_2), 55.5 (OCH_3), 38.0 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1695 (C=O st), 1261 (C-O st), 1072 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 374.2 (M+, 9), 266.0 (15), 195.1 (20), 91.1 (100). **HRMS** (ESI^+): Calculated for $[C_{24}H_{23}O_4]^+$: 375.1596 $[M+H]^+$; found: 375.1595. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (94:6)]; flow rate 1.0 mL/min; τ_{minor} = 13.0 min, τ_{major} = 14.3 min (3:97). $[\alpha]_D^{20}$: -125.4 (*c* = 0.7, CH_2Cl_2).

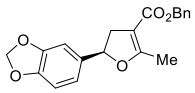


Benzyl 5-(4-methoxy-3-methylphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2i). Following *GP-I*, **2i** (14.5 mg, 0.04 mmol, 86%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1i** (16.9 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 15 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H, C_{arom}-H), 7.18-7.10 (m, 2H, C_{arom}-H), 6.83-6.77 (m, 1H, C_{arom}-H), 5.52 (dd, *J* = 10.6, 8.7 Hz, 1H, Ar-C**H**-O), 5.19 (s, 2H, OC**H**$_2$Ph), 3.83 (s, 3H, OCH_3), 3.30 (ddq, *J* = 14.6, 10.6, 1.6 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.97 (ddq, *J* = 14.6, 8.7, 1.6 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.27 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$), 2.22 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.5 (CH_2C=**C**-O), 166.0 (COO), 158.0 (**C**$_{arom}$-OCH_3), 136.9 (C_{arom}), 132.9 (C_{arom}), 128.62 (2×C_{arom}-H), 128.56 (C_{arom}-H), 128.1 (3×C_{arom}-H), 127.3 (C_{arom}), 124.8 (C_{arom}-H), 110.0 (C_{arom}-H), 101.6 (CH_2**C**=C-O), 83.7 (CH-O), 65.5 (CO_2**C**H_2), 55.6 (OCH_3), 37.8 (**C**H_2C=C), [31.1 (C)], [29.9 (C)], 16.4 (Ar-**C**H_3), 14.4 (C=C-**C**H_3). **IR** (ATR): 1697 (C=O st), 1255 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 338.1 (M+, 6), 247.1 (15), 91.1 (136). **HRMS** (ESI$^+$): Calculated for $[C_{21}H_{19}O_4Na]^+$: 359.1259 $[M\text{-}H_2\text{+Na}]^+$; found: 359.1257. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 5.66 min, τ_{major} = 7.03 min (5:95). $[\alpha]_D^{20}$: -62.2 (*c* = 1.0, CH_2Cl_2).

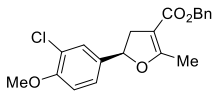


Benzyl 5-(2,3-dihydrobenzofuran-5-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2j). Following *GP-I*, **2j** (15.6 mg, 0.05 mmol, 93%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1j** (16.8 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 36 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H, C_{arom}-H), 7.20 (s, 1H, C_{arom}-H), 7.08 (d, *J* = 8.1 Hz, 1H, C_{arom}-H), 6.76 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 5.53 (dd, *J* = 10.6, 8.6 Hz, 1H, Ar-C**H**-O), 5.19 (s, 2H, OC**H**$_2$Ph), 4.58 (t, *J* = 8.7 Hz, 2H, OC**H**$_2$$CH_2$), 3.38-3.26 (m, 1H, C**H**$_a$H$_b$-CH-O), 3.21 (t, *J* = 8.7 Hz, 2H, OCH_2C**H**$_2$), 3.01-2.89 (m, 1H, CH$_a$**H**$_b$-CH-O), 2.27 (s, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4 (CH_2C=**C**-O), 165.9 (COO), 160.4 (**C**$_{arom}$-OCH_2), 136.8 (C_{arom}), 133.5 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 127.8 (C_{arom}), 126.5 (C_{arom}-H), 122.9 (C_{arom}-H), 109.3 (C_{arom}-H), 101.6 (CH_2**C**=C-O), 83.8 (CH-O), 71.6 (O**C**$H_2$$CH_2$), 65.5 ($CO_2$**C**$H_2$), 37.9 (**C**$H_2$C=C), 29.8 ($OCH_2$**C**$H_2$), 14.4 (C=C-**C**$H_3$). **IR** (ATR): 1714 (C=O st), 1245 (C-O st), 1097 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 335.6 (M+, 1), 91.1 (100), 76.9 (16), 65.0 (18). **HRMS** (ESI$^+$): Calculated for $[C_{21}H_{21}O_4]^+$: 337.1440 $[M+H]^+$; found: 337.1434. The e.e. was determined by HPLC using a *Chiralpak IC*

column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.48 min, τ_{minor} = 13.70 min (91:9). $[\alpha]_D^{20}$: -189.2 (*c* = 0.9, CH_2Cl_2).

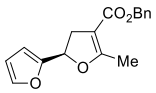


Benzyl 5-(benzo[d][1,3]dioxol-5-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2l). Following *GP-I*, **2l** (15.2 mg, 0.05 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1l** (16.9 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 68 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 5H, C_{arom}-H), 6.83 (s, 1H, C_{arom}-H), 6.79 (s, 2H, C_{arom}-H), 5.96 (s, 2H, OCH_2O), 5.50 (dd, *J* = 10.7, 8.4 Hz, 1H, Ar-C**H**-O), 5.18 (s, 2H, OC**H**$_2$Ph), 3.40-3.25 (m, 1H, C**H**$_a$H$_b$-CH-O), 2.99-2.86 (m, 1H, CH$_a$**H**$_b$-CH-O), 2.27 (s, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3 (CH_2C=**C**-O), 165.8 (COO), 148.2 (**C**$_{arom}$-OCH_2), 147.7 (**C**$_{arom}$-OCH_2), 136.8 (C_{arom}), 135.4 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 119.7 (C_{arom}-H), 108.3 (C_{arom}-H), 106.4 (C_{arom}-H), 101.6 (CH_2**C**=C-O), 101.3 (OCH_2O), 83.5 (CH-O), 65.5 (CO_2**C**H_2), 38.0 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1694 (C=O st), 1220 (C-O st), 1072 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 338.1 (M+, 4), 247.10 (8), 92.1 (8), 91.1 (100), 77.1 (9), 65.1 (9). **HRMS** (ESI^+): Calculated for $[C_{20}H_{18}O_5Na]^+$: 361.1052 $[M+Na]^+$; found: 361.1043. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 11.50 min, τ_{major} = 13.43 min (15:85). $[\alpha]_D^{20}$: -60.6 (*c* = 0.9, CH_2Cl_2).

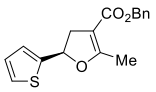


Benzyl 5-(3-chloro-4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (2m). Following *GP-I*, **2m** (8.6 mg, 0.02 mmol, 48%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1m** (17.9 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and m-xylene (0.12 mL) at -30 ºC for 120h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.28 (m, 6H, C_{arom}-H), 7.19 (dd, *J* = 8.5, 2.2 Hz, 1H, C_{arom}-H), 6.91 (d, *J* = 8.5 Hz, 1H, C_{arom}-H), 5.52 (dd, *J* = 10.7, 8.4 Hz, 1H, Ar-C**H**-O), 5.18 (s, 2H, OC**H**$_2$Ph), 3.90 (s, 3H, OCH_3), 3.33 (ddq, *J* = 14.6, 10.7, 1.6 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.91 (ddq, *J* = 14.6, 8.4, 1.6 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.28 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.3 (CH_2C=**C**-O), 165.8 (COO), 155.0 (**C**$_{arom}$-OCH_3), 136.7 (C_{arom}), 134.6 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 128.0 (C_{arom}-H), 125.5 (C_{arom}-H), 122.9 (C_{arom}), 112.2 (C_{arom}-H), 101.6

(CH_2**C**=C-O), 82.5 (CH-O), 65.6 (CO_2**C**H_2), 56.4 (OCH_3), 37.9 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1684 (C=O st), 1261 (C-O st), 1064 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 357.9 (M+, 1), 91.0 (100), 76.9 (14). **HRMS** (ESI^+): Calculated for $[C_{20}H_{20}O_4Cl]^+$: 359.1050 $[M+H]^+$; found: 359.1047. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 7.95 min, τ_{major} = 11.03 min (4:96). $[\alpha]_D^{20}$: -18.7 (*c* = 0.9, CH_2Cl_2).

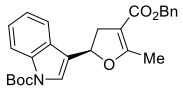


Benzyl 5-methyl-2,3-dihydro-[2,2'-bifuran]-4-carboxylate (2n). Following *GP-I*, **2n** (12.1 mg, 0.04 mmol, 85%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1n** (14.2 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (25 µL) and m-xylene (0.22 mL) at -30 ºC for 88 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (s, 1H, C_{arom}-H), 7.41-7.29 (m, 5H, C_{arom}-H), 6.44-6.33 (m, 2H, C_{arom}-H), 5.58 (t, *J* = 9.8 Hz, 1H, HetAr-C**H**-O), 5.20 (s, 2H, OC**H$_2$**Ph), 3.21 (d, *J* = 9.7 Hz, 2H, C**H$_2$**-CH-O), 2.22 (s, 3H, C=C-C**H$_3$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (CH_2C=**C**-O), 165.7 (O=**C**-O), 152.5 ($C_{heteroarom}$), 143.5 ($C_{heteroarom}$-H), 136.8 (C_{arom}), 128.6 (2×C_{arom}-H), 128.1 (3×C_{arom}-H), 110.5 ($C_{heteroarom}$-H), 108.7 ($C_{heteroarom}$-H), 101.8 (CH_2**C**=C-O), 76.4 (CH-O), 65.6 (CO_2**C**H_2), 34.0 (**C**H_2C=C), 14.3 (C=C-**C**H_3). **IR** (ATR): 1696 (C=O st), 1223 (C-O st), 1074 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 284.1 (M+, 3), 176.0 (9), 91.1 (100), 77.1 (9), 65.1 (9). **HRMS**: Calculated for $[C_{17}H_{17}O_4]^+$: 285.1127 $[M+H]^+$; found: 285.1128. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 9.6 min, τ_{major} = 10.3 min (24:76). $[\alpha]_D^{20}$: -40.6 (*c* = 1.0, CH_2Cl_2).

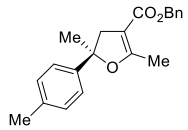


Benzyl 2-methyl-5-(thiophen-2-yl)-4,5-dihydrofuran-3-carboxylate (2o). Following *GP-I*, **2o** (13.6 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1o** (15.0 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (25 µL) and m-xylene (0.22 mL) at -30 ºC for 88 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.28 (m, 6H, C_{arom}-H), 7.08 (d, *J* = 3.6 Hz, 1H, C_{arom}-H), 7.02-6.97 (m, 1H, C_{arom}-H), 5.81 (dd, *J* = 10.4, 8.2 Hz, 1H, HetAr-C**H**-O), 5.20 (s, 2H, OC**H$_2$**Ph), 3.44-3.31 (m, 1H, C**H$_a$**H$_b$-CH-O), 3.17-3.04 (m, 1H, CH$_a$**H$_b$**-CH-O), 2.25 (s, 3H, C=C-C**H$_3$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (CH_2C=**C**-O), 165.7 (COO), 144.1 (C_{arom}), 136.7 (C_{arom}), 128.6 (2×C_{arom}-H), 128.11 (C_{arom}-H), 128.07 (2×C_{arom}-H), 127.0 (C_{arom}-H), 126.0 (C_{arom}-H), 125.5 (C_{arom}-H), 101.7 (CH_2**C**=C-O), 79.2 (CH-O), 65.6 (CO_2**C**H_2), 38.1 (**C**H_2C=C), 14.4 (C=C-**C**H_3). **IR** (ATR): 1698 (C=O st), 1220 (C-O st), 1072 (C-

O st) cm^{-1}. **MS** (EI) m/z (%): 300.1 (M+, 4), 91.1 (100), 77.1 (11), 65.0 (12). **HRMS** (ESI^+): Calculated for $[C_{20}H_{20}O_4Na]^+$: 323.0718 $[M+Na]^+$; found: 323.0728. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 10.25 min, τ_{major} = 11.39 min (15:85). $[\alpha]_D^{20}$: -158.4 (*c* = 0.8, CH_2Cl_2).

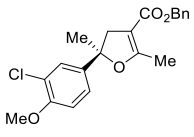


tert-Butyl 3-(4-((benzyloxy)carbonyl)-5-methyl-2,3-dihydrofuran-2-yl)-1H-indole-1-carboxylate (2p). Following *GP-I*, **2p** (15.0 mg, 0.04 mmol, 69%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1p** (21.7 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 5 d. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.3 Hz, 1H, C_{arom}-H), 7.59 (s, 1H, C_{arom}-H), 7.54 (ddd, *J* = 7.7, 1.4, 0.8 Hz, 1H, C_{arom}-H), 7.41-7.30 (m, 5H, C_{arom}-H), 7.28-7.21 (m, 2H, C_{arom}-H), 5.84 (ddd, *J* = 10.8, 8.7, 0.9 Hz, 1H, HetAr-C**H**-O), 5.23 (d, *J* = 12.7 Hz, 1H, OC**H$_a$**H$_b$Ph), 5.19 (d, *J* = 12.7 Hz, 1H, OCH$_a$**H$_b$**Ph), 3.36 (ddq, *J* = 14.4, 10.7, 1.6 Hz, 1H, C**H$_a$**H$_b$-CH-O), 3.17 (ddq, *J* = 14.4, 8.7, 1.6 Hz, 1H, CH$_a$**H$_b$**-CH-O), 2.29 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$), 1.67 (s, 9H, OC(CH$_3$)$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6 (CH_2C=**C**-O), 166.0 (**C**OOCH$_2$), 149.7 (N-**C**=O), 136.8 (C_{arom}), 136.2 (C_{arom}), 128.7 (2×C_{arom}-H), 128.2 (C_{arom}), 128.10 (C_{arom}-H), 128.07 (2×C_{arom}-H), 125.0 (C_{arom}-H), 123.4 (C_{arom}-H), 123.0 (C_{arom}-H), 120.4 (C_{arom}), 119.7 (C_{arom}-H), 115.7 (C_{arom}-H), 101.8 (CH_2**C**=C-O), 84.2 (**C**(CH$_3$)$_3$), 77.7 (CH-O), 65.6 (CO_2**C**H$_2$), 35.7 (**C**H$_2$C=C), 31.1 (C), 28.3 (C(**C**H$_3$)$_3$), 14.4 (C=C-**C**H$_3$). **IR** (ATR): 1735 (C=O st), 1698 (C=O st), 1256 (C-O st), 1154 (C-O st) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{26}H_{28}NO_5]^+$: 434.1967 $[M+H]^+$; found: 434.1967. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{minor} = 7.13 min, τ_{major} = 7.67 min (14:86). $[\alpha]_D^{20}$: -97.8 (*c* = 0.9, CH_2Cl_2).

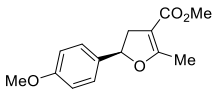


Benzyl 2,5-dimethyl-5-(p-tolyl)-4,5-dihydrofuran-3-carboxylate (2q). Following *GP-I*, **2q** (13.9 mg, 0.04 mmol, 86%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1q** (16.1 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (25 µL) and m-xylene (0.22 mL) at -30 ºC for 12 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H, C_{arom}-H), 7.26 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 7.16 (d, *J* = 8.0 Hz, 2H, C_{arom}-H), 5.15 (s, 2H, OC**H$_2$**Ph), 3.15 (d, *J* = 14.4 Hz, 1H, C**H**H'-C-O), 3.05 (d, *J* = 14.3 Hz, 1H, CH**H'**-C-O), 2.34 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.67 (s, 3H, C**H$_3$**-C-Ar). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (CH_2C=**C**-O), 166.1 (O=**C**-O), 143.5 (C_{arom}), 137.0 (C_{arom}), 136.9 (C_{arom}), 129.2

(2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.1 (2×C_{arom}-H), 128.0 (C_{arom}-H), 124.3 (2×C_{arom}-H), 101.1 (CH_2**C**=C-O), 88.8 (Ar-**C**-CH_3), 65.4 (CO_2**C**H_2), 44.4 (**C**H_2C=C), 29.6 (Ar-C-**C**H_3), 21.1 (Ar-**C**H_3), 14.6 (C=C-**C**H_3). **IR** (ATR): 1698 (C=O st), 1242 (C-O st), 1093 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 322.1 (M+, 2), 231.1 (15), 187.1 (19), 128.1 (16), 91.1 (100). **HRMS**: Calculated for $[C_{21}H_{23}O_3]^+$: 323.1647 $[M+H]^+$; found: 323.1653. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 1.0 mL/min; τ_{minor} = 6.68 min, τ_{major} = 7.14 min (24:76). $[\alpha]_D^{20}$: +146.3 (*c* = 0.5, CH_2Cl_2).

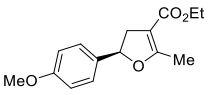


Benzyl 5-(3-chloro-4-methoxyphenyl)-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (2r). Following *GP-I*, **2r** (13.0 mg, 0.04 mmol, 70%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **1r** (18.6 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in toluene (0.25 mL) at -60 ºC for 20 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 6H, C_{arom}-H), 7.21 (dd, *J* = 8.6, 2.3 Hz, 1H, C_{arom}-H), 6.89 (d, *J* = 8.6 Hz, 1H, C_{arom}-H), 5.16 (s, 2H, OC**H**$_2$Ph), 3.89 (s, 3H, OCH_3), 3.11 (dq, *J* = 14.4, 1.6 Hz, 1H, C**H**$_a$H$_b$-C-O), 3.03 (dq, *J* = 14.4, 1.6 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.29 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$), 1.65 (s, 3H, C**H**$_3$-C-Ar). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2 (CH_2C=**C**-O), 165.9 (COO), 154.2 (**C**$_{arom}$-OCH_3), 139.7 (C_{arom}), 136.8 (C_{arom}), 128.6 (2×C_{arom}-H), 128.13 (2×C_{arom}-H), 128.11 (C_{arom}-H), 126.7 (C_{arom}-H), 123.8 (C_{arom}-H), 122.6 (C_{arom}), 112.0 (C_{arom}-H), 101.2 (CH_2**C**=C-O), 88.0 (Ar-**C**-CH_3), 65.5 (CO_2**C**H_2), 56.4 (OCH_3), 44.4 (**C**H_2C=C), 29.5 (Ar-C-**C**H_3), 14.6 (C=C-**C**H_3). **IR** (ATR): 1697 (C=O st), 1270 (C-O st), 1240 (C-O st), 1064 (C-Cl st) cm^{-1}. **MS** (EI) m/z (%): 281.0 (M^+-C_7H_7, 7), 237.0 (9), 91.0 (100), 77.0 (10), 64.9 (10). **HRMS** (ESI^+): Calculated for $[C_{21}H_{22}O_4Cl]^+$: 373.1207 $[M+H]^+$; found: 373.1207. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 7.52 min, τ_{minor} = 8.37 min (78:22). $[\alpha]_D^{20}$: +316.7 (*c* = 0.3, CH_2Cl_2).

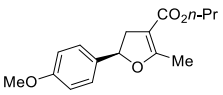


Methyl 5-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (6a). Following *GP-I* **6a** (11.9 mg, 0.05 mmol, 95%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **5a** (12.4 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 84 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.54 (dd, *J* = 10.6, 8.4 Hz, 1H, Ar-C**H**-O), 3.81 (s, 3H, Ar-OCH_3), 3.72 (s, 3H, CO_2CH_3), 3.28 (ddq, *J* = 14.5, 10.6, 1.6 Hz,

1H, C**H**$_a$H$_b$-CH-O), 2.92 (ddq, *J* = 14.5, 8.4, 1.6 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.26 (t, *J* = 1.6 Hz, 3H, C=C-C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (CH_2C=**C**-O), 166.5 (COO), 159.6 (**C**$_{arom}$-OCH_3), 133.5 (C$_{arom}$), 127.3 (2×C$_{arom}$-H), 114.1 (2×C$_{arom}$-H), 101.5 (CH_2**C**=C-O), 83.2 (CH-O), 55.3 (Ar-OCH_3), 50.9 (CO_2**C**H_3), 37.7 (**C**H_2C=C), 14.1 (C=C-**C**H_3). **IR** (ATR): 1703 (C=O st), 1247 (C-O st), 1030 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 248.1 (M+, 33), 217.1 (21), 216.1 (100), 201.0 (87), 198.1 (30), 174.1 (21), 146.1 (32), 145.1 (92), 135.0 (19), 131.0 (33), 115.0 (23), 103.1 (36), 102.1 (21), 91.1 (17), 77.1 (29). **HRMS** (ESI$^+$): Calculated for $[C_{14}H_{17}O_4]^+$: 249.1127 $[M+H]^+$; found: 249.1132. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 6.08 min, τ_{major} = 7.08 min (5:95). $[\alpha]_D^{20}$: -156.1 (*c* = 1.0, CH_2Cl_2).

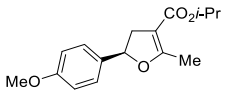


Ethyl 5-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (6b). Following *GP-I*, **6b** (12.1 mg, 0.05 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **5b** (13.1 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 84 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H, C$_{arom}$-H), 6.89 (d, *J* = 8.6 Hz, 2H, C$_{arom}$-H), 5.53 (dd, *J* = 10.6, 8.5 Hz, 1H, Ar-C**H**-O), 4.18 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.80 (s, 3H, OCH_3), 3.35-3.21 (m, 1H, C**H**$_a$H$_b$-CH-O), 2.97-2.86 (m, 1H, CH$_a$**H**$_b$-CH-O), 2.26 (s, 3H, C=C-C**H**$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (CH_2C=**C**-O), 166.3 (COO), 159.7 (**C**$_{arom}$-OCH_3), 133.6 (C$_{arom}$), 127.4 (2×C$_{arom}$-H), 114.2 (2×C$_{arom}$-H), 101.9 (CH_2**C**=C-O), 83.2 (CH-O), 59.6 (CO_2**C**H_2), 55.5 (OCH_3), 37.9 (**C**H_2C=C), 14.6 (CH_3), 14.3 (CH_3). **IR** (ATR): 1697 (C=O st), 1247 (C-O st), 1083 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 262.1 (M+, 29), 217.1 (23), 216.1 (100), 201.1 (87), 198.0 (30), 174.1 (17), 146.1 (28), 145.1 (65), 131.0 (26), 115.1 (19), 103.1 (30), 77.1 (21). **HRMS** (ESI$^+$): Calculated for $[C_{15}H_{19}O_4]^+$: 263.1283 $[M+H]^+$; found: 263.1302. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 5.30 min, τ_{major} = 6.17 min (7:93). $[\alpha]_D^{20}$: -59.5 (*c* = 0.8, CH_2Cl_2).

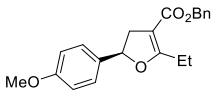


Propyl 5-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (6c). Following *GP-I*, **6c** (12.8 mg, 0.05 mmol, 93%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **5c** (13.8 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 84 h. **^{1}H NMR** (300 MHz, $CDCl_3$)

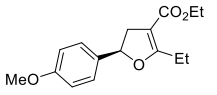
δ 7.28 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.54 (dd, *J* = 10.6, 8.6 Hz, 1H, Ar-C**H**-O), 4.09 (t, *J* = 6.7 Hz, 2H, OC**H**$_2$), 3.81 (s, 3H, OCH_3), 3.36-3.22 (m, 1H, C**H**$_a$H$_b$-CH-O), 2.98-2.86 (m, 1H, CH_a**H**$_b$-CH-O), 2.26 (s, 3H, C=C-C**H**$_3$), 1.68 (sextet, *J* = 7.0 Hz, 2H, C**H**$_2$CH$_3$), 0.96 (t, *J* = 7.4 Hz, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (CH_2C=**C**-O), 166.3 (COO), 159.7 (**C**$_{arom}$-OCH_3), 133.6 (C_{arom}), 127.4 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 101.9 (CH_2**C**=C-O), 83.3 (CH-O), 65.3 (CO_2**C**H_2), 55.5 (OCH_3), 37.9 (**C**H_2C=C), 22.3 (**C**H_2CH_3), 14.3 (C=C-**C**H_3), 10.7 (CH_2**C**H_3). **IR** (ATR): 1697 (C=O st), 1223 (C-O st), 1084 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 276.1 (M+, 27), 217.1 (27), 216.1 (100), 201.0 (84), 198.1 (32), 174.1 (16), 146.1 (24), 145.1 (48), 131.1 (23), 115.0 (15), 103.1 (26), 77.1 (17). **HRMS** (ESI$^+$): Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1454. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 5.28 min, τ_{major} = 6.05 min (6:94). $[\alpha]_D^{20}$: -35.5 (*c* = 0.7, CH_2Cl_2).



Isopropyl 5-(4-methoxyphenyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (6d). Following *GP-I*, **6d** (12.7 mg, 0.05 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **5d** (13.8 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 μL) and m-xylene (0.19 mL) at -40 ºC for 144 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.52 (dd, *J* = 10.6, 8.6 Hz, 1H, Ar-C**H**-O), 5.07 (hept, *J* = 6.2 Hz, 1H, OC**H**$(CH_3)_2$), 3.81 (s, 3H, OCH_3), 3.33-3.21 (m, 1H, C**H**$_a$H$_b$-CH-O), 2.96-2.84 (m, 1H, CH_a**H**$_b$-CH-O), 2.25 (s, 3H, C=C-C**H**$_3$), 1.26 (d, *J* = 6.2 Hz, 3H, CHC**H**$_3$), 1.25 (d, *J* = 6.2 Hz, 3H, CHC**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3 (CH_2C=**C**-O), 165.8 (COO), 159.7 (**C**$_{arom}$-OCH_3), 133.7 (C_{arom}), 127.4 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 102.3 (CH_2**C**=C-O), 83.2 (CH-O), 66.8 (CO_2**C**H), 55.5 (OCH_3), 38.0 (**C**H_2C=C), 22.3 (CH(**C**$H_3)_2$), 14.3 (C=C-**C**H_3). **IR** (ATR): 1685 (C=O st), 1250 (C-O st), 1105 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 276.1 (M+, 21), 217.1 (27), 216.9 (100), 201.0 (67), 198.1 (26), 146.0 (21), 145.1 (36), 135.0 (19), 131.0 (17), 103.0 (21), 77.1 (18). **HRMS** (ESI$^+$): Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1458. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 7.30 min, τ_{major} = 8.90 min (7:93). $[\alpha]_D^{20}$: -140.0 (*c* = 1.0, CH_2Cl_2).

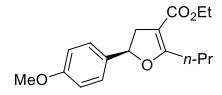


Benzyl 2-ethyl-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (8a). Following *GP-I*, **8a** (15.4 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7a** (16.9 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 15 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H, C_{arom}-H), 7.27 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.55 (dd, *J* = 10.7, 8.4 Hz, 1H, Ar-C**H**-O), 5.18 (s, 2H, OC**H**$_2$Ph), 3.81 (s, 3H, OCH_3), 3.33 (dd, *J* = 14.6, 10.7 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.94 (dd, *J* = 14.6, 8.4 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.75 (q, *J* = 7.6 Hz, 2H, C**H**$_2$CH$_3$), 1.17 (t, *J* = 7.5 Hz, 3H, CH$_2$C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 173.2 (CH_2C=**C**-O), 165.8 (COO), 159.7 (**C**$_{arom}$-OCH_3), 136.9 (C_{arom}), 133.9 (C_{arom}), 128.6 (2×C_{arom}-H), 128.0 (3×C_{arom}-H), 127.3 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 100.4 (CH_2**C**=C-O), 83.2 (CH-O), 65.4 (CO_2**C**H$_2$), 55.5 (OCH_3), 38.1 (**C**H$_2$C=C-O), 21.6 (C=C-**C**H$_2$CH$_3$), 11.4 (CH$_2$**C**H$_3$). **IR** (ATR): 1697 (C=O st), 1248 (C-O st), 1029 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 338.1 (M+, 8), 247.1 (17), 91.1 (100), 57.0 (24). **HRMS** (ESI$^+$): Calculated for $[C_{21}H_{23}O_4]^+$: 339.1596 $[M+H]^+$; found: 339.1600. The e.e. was determined by HPLC using a *Chiralpak AD-H* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 13.12 min, τ_{major} = 16.25 min (7:93). $[\alpha]_D^{20}$: -70.8 (*c* = 0.8, CH_2Cl_2).

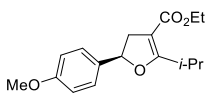


Ethyl 2-ethyl-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (8b). Following *GP-I*, **8b** (12.6 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7b** (13.8 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 108 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.53 (dd, *J* = 10.7, 8.3 Hz, 1H, Ar-C**H**-O), 4.18 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.81 (s, 3H, OCH_3), 3.29 (dd, *J* = 14.6, 10.7 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.90 (dd, *J* = 14.6, 8.3 Hz, 1H, CH$_a$**H**$_b$-CH-O), 2.73 (q, *J* = 7.6 Hz, 2H, C=C-C**H**$_2$CH$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.17 (t, *J* = 7.6 Hz, 3H, C=C-CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.4 (CH_2C=**C**-O), 166.1 (COO), 159.6 (**C**$_{arom}$-OCH_3), 134.0 (C_{arom}), 127.3 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 100.7 (CH_2**C**=C-O), 83.0 (CH-O), 59.5 (CO_2**C**H$_2$), 55.4 (OCH_3), 38.1 (**C**H$_2$C=C-O), 21.5 (C=C-**C**H$_2$CH$_3$), 14.6 (CO_2CH_2**C**H$_3$), 11.4 (C=C-CH_2**C**H$_3$). **IR** (ATR): 1696 (C=O st), 1247 (C-O st), 1032 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 276.1 (M+, 23), 231.1 (18), 230.1 (52), 202.1 (16), 201.0 (100), 174.1 (16), 146.1 (17), 145.1 (39), 131.0 (18),

103.1 (21), 77.1 (15), 57.1 (45). **HRMS** (ESI$^+$): Calculated for $[C_{16}H_{21}O_4]^+$: 277.1440 $[M+H]^+$; found: 277.1456. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 7.05 min, τ_{minor} = 7.50 min (6:94). $[\alpha]_D^{20}$: -79.7 (*c* = 0.6, CH_2Cl_2).

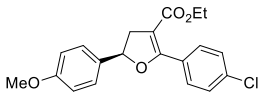


Ethyl 5-(4-methoxyphenyl)-2-propyl-4,5-dihydrofuran-3-carboxylate (8c). Following *GP-I*, **8c** (13.0 mg, 0.04 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7c** (14.5 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 84 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.52 (dd, *J* = 10.6, 8.5 Hz, 1H, Ar-C**H**-O), 4.18 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.81 (s, 3H, OCH_3), 3.29 (dd, *J* = 14.7, 10.6 Hz, 1H, C**H$_a$**H$_b$-CH-O), 2.91 (dd, *J* = 14.6, 8.5 Hz, 1H, CH$_a$**H$_b$**-CH-O), 2.73-2.64 (m, 2H, C=C-CH_2), 1.74-1.55 (m, 2H, CH_2C**H**$_2$CH$_3$), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 0.97 (t, *J* = 7.4 Hz, 3H, CH_2CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.3 (CH_2C=**C**-O), 166.1 (COO), 159.6 (**C**$_{arom}$-OCH_3), 133.9 (C_{arom}), 127.4 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 101.5 (CH_2**C**=C-O), 83.0 (CH-O), 59.6 (CO_2**C**H$_2$), 55.4 (OCH_3), 38.1 (**C**H$_2$C=C), 29.9 (**C**H$_2$CH$_2$CH$_3$), 20.5 (CH_2**C**H$_2$CH$_3$), 14.6 (CO_2CH_2**C**H$_3$), 14.0 (CH_2CH_2**C**H$_3$). **IR** (ATR): 1695 (C=O st), 1248 (C-O st), 1100 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 290.2 (M+, 32), 245.1 (22), 244.1 (70), 211.1 (15), 202.0 (16), 201.0 (100), 174.1 (34), 146.1 (16), 145.1 (36), 131.1 (18), 103.1 (16), 71.1 (17). **HRMS** (ESI$^+$): Calculated for $[C_{17}H_{23}O_4]^+$: 291.1596 $[M+H]^+$; found: 291.1608. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 5.66 min, τ_{major} = 6.12 min (12:88). $[\alpha]_D^{20}$: -121.2 (*c* = 0.6, CH_2Cl_2).

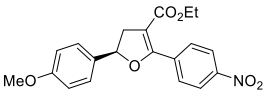


Ethyl 2-isopropyl-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (8d). Following *GP-I*, **8d** (7.4 mg, 0.03 mmol, 51%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7d** (14.5 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -40 ºC for 144 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.90 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.51 (dd, *J* = 10.7, 8.2 Hz, 1H, Ar-C**H**-O), 4.17 (q, *J* = 7.1 Hz, 2H, OC**H**$_2$CH$_3$), 3.81 (s, 3H, OCH_3), 3.70 (hept, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 3.29 (dd, *J* = 14.6, 10.8 Hz, 1H, C**H$_a$**H$_b$-CH-O), 2.86 (dd, *J* = 14.6, 8.2 Hz, 1H, CH$_a$**H$_b$**-CH-O), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$), 1.17 (d, *J* = 6.9 Hz, 3H, CH-C**H**$_3$), 1.16 (d, *J*

= 6.9 Hz, 3H, CH-C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.6 (CH_2C=**C**-O), 166.1 (COO), 159.6 (**C**$_{arom}$-OCH_3), 134.4 (C_{arom}), 127.1 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 99.5 (CH_2**C**=C-O), 82.7 (CH-O), 59.5 (CO_2**C**H_2), 55.5 (OCH_3), 38.4 (**C**H_2C=C), 27.0 (**C**H(CH_3)$_2$), 19.8 (CH(**C**H_3)(CH_3)), 19.7 (CH(CH_3)(**C**H_3)), 14.6 (CO_2CH_2**C**H_3). **IR** (ATR): 1697 (C=O st), 1249 (C-O st), 1048 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 290.1 (M+, 29), 245.1 (16), 244.1 (51), 229.1 (15), 201.9 (18), 201.0 (100), 174.1 (26), 145.0 (37), 135.1 (17), 134.0 (15), 103.0 (17), 91.1 (15). **HRMS** (ESI$^+$): Calculated for $[C_{17}H_{23}O_4]^+$: 291.1596 $[M+H]^+$; found: 291.1603. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 7.65 min, τ_{major} = 8.67 min (17:83). $[\alpha]_D^{20}$: -148.7 (*c* = 0.2, CH_2Cl_2).

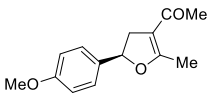


Ethyl 2-(4-chlorophenyl)-5-(4-methoxyphenyl)-4,5-dihydrofuran-3-carboxylate (8g). Following *GP-I*, **8g** (4.5 mg, 0.012 mmol, 25%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7g** (17.9 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 144 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.36 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.33 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.92 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.67 (dd, *J* = 10.6, 8.8 Hz, 1H, Ar-C**H**-O), 4.16 (q, *J* = 7.1 Hz, 2H, OC**H$_2$**CH_3), 3.82 (s, 3H, OCH_3), 3.52 (dd, *J* = 15.4, 10.7 Hz, 1H, C**H**H'-CH-O), 3.16 (dd, *J* = 15.4, 8.8 Hz, 1H, CH**H'**-CH-O), 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2C**H$_3$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2 (O=**C**-O), 163.5 (CH_2C=**C**-O), 159.8 (**C**$_{arom}$-OCH_3), 136.5 (C_{arom}), 133.5 (C_{arom}), 131.0 (2×C_{arom}-H), 128.5 (C_{arom}), 128.0 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 114.3 (2×C_{arom}-H), 102.8 (CH_2**C**=C-O), 82.8 (CH-O), 60.1 (CO_2**C**H_2), 55.5 (OCH_3), 39.8 (**C**H_2C=C), 14.4 (CO_2CH_2**C**H_3). **IR** (ATR): 1697 (C=O st), 1240 (C-O st), 1077 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 357.9 (M+, 10), 311.9 (15), 200 (32), 140.9 (42), 139.0 (100), 135.1 (16), 111.0 (31). **HRMS**: Calculated for $[C_{20}H_{20}O_4Cl]^+$: 359.1050 $[M+H]^+$; found: 359.1046. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 11.27 min, τ_{major} = 11.96 min (12:88).

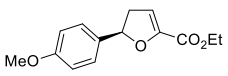


Ethyl 5-(4-methoxyphenyl)-2-(4-nitrophenyl)-4,5-dihydrofuran-3-carboxylate (8h). Following *GP-I*, **8h** (16.8 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **7h** (18.5 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 µL) and m-xylene (0.19 mL) at -30 ºC for 15 h. **^{1}H NMR**

(300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 8.05 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.35 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.94 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.73 (dd, *J* = 10.7, 9.0 Hz, 1H, Ar-C**H**-O), 4.17 (q, *J* = 7.1 Hz, 3H, OC**H**$_2$CH$_3$), 3.82 (s, 3H, OCH_3), 3.56 (dd, *J* = 15.8, 10.7 Hz, 1H, C**H$_a$**H$_b$-CH-O), 3.21 (dd, *J* = 15.8, 9.0 Hz, 1H, CH$_a$**H$_b$**-CH-O), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.8 (COO), 161.8 (CH_2C=**C**-O), 159.9 (**C**$_{arom}$-OCH_3), 148.6 (C_{arom}-NO_2), 136.2 (C_{arom}), 133.0 (C_{arom}), 130.6 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 122.9 (2×C_{arom}-H), 114.3 (2×C_{arom}-H), 105.3 (CH_2**C**=C-O), 83.3 (CH-O), 60.4 (CO_2**C**H_2), 55.5 (OCH_3), 39.8 (**C**H_2C=C), 14.4 (CO_2CH_2**C**H_3). **IR** (ATR): 1697 (C=O st), 1243 (C-O st), 1081 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 369.1 (M+, 15), 367.0 (25), 324.1 (28), 323.1 (100), 200.0 (17), 150.0 (58), 146.1 (18), 145.0 (75), 135.0 (16), 104.0 (35), 103.0 (18), 92.0 (17), 77.0 (17), 76.0 (26). **HRMS** (ESI^+): Calculated for $[C_{20}H_{20}NO_6]^+$: 370.1291 $[M+H]^+$; found: 370.1289. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 22.19 min, τ_{minor} = 29.50 min (92:8). $[\alpha]_D^{20}$: +65.8 (*c* = 1.0, CH_2Cl_2).

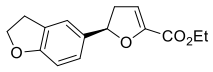


Ethyl 5-(4-methoxyphenyl)-4,5-dihydrofuran-2-carboxylate (10). Following *GP-I*, **10** (7.8 mg, 0.033 mmol, 65%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **9** (11.6 mg, 0.05 mmol) and catalyst **3g** (3.5 mg, 0.005 mmol) in 1,2-dichloroethane (62 μL) and m-xylene (0.19 mL) at -30 ºC for 8h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 1H, C_{arom}-H), 6.91 (d, *J* = 8.7 Hz, 1H, C_{arom}-H), 5.55 (dd, *J* = 10.6, 8.5 Hz, 1H, Ar-C**H**-O), 3.81 (s, 1H, OCH_3), 3.35 (ddd, *J* = 14.2, 10.6, 1.5 Hz, 1H, C**H$_a$**H$_b$-CH-O), 2.98 (ddd, *J* = 14.3, 8.5, 1.6 Hz, 1H, CH$_a$**H$_b$**-CH-O), 2.29 (s, 3H, CCH_3), 2.22 (s, 1H,C CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 194.5 (CH_3**C**=O), 167.5 (COO), 159.8 (**C**$_{arom}$-OCH_3), 133.3 (C_{arom}), 127.4 (2×C_{arom}-H), 114.2 (2×C_{arom}-H), 112.1 (C_{arom}-H), 83.3 (CH-O), 55.5 (OCH_3), 38.7 (**C**H_2C=C), 29.6 (**C**H_3C=O), 15.2 (C=C-**C**H_3). **IR** (ATR): 1719 (C=O st), 1687 (C=O st), 1159 (C-O st as) cm^{-1}. **HRMS**: Calculated for $[C_{14}H_{17}O_3]^+$: 233.1178 $[M+H]^+$; found: 233.1184. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.40 min, τ_{minor} = 10.34 min (54:46).

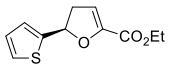


Ethyl 5-(4-methoxyphenyl)-4,5-dihydrofuran-2-carboxylate (12a). Following *GP-I*, **12a** (9.3 mg, 0.04 mmol, 75%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and

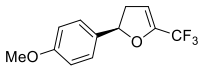
dichloromethane (0.12 mL) at -30 ºC for 96 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.89 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.97 (t, *J* = 3.0 Hz, 1H, C**H**=C), 5.65 (dd, *J* = 10.7, 9.0 Hz, 1H, Ar-C**H**-O), 4.29 (qd, *J* = 7.1, 1.5 Hz, 2H, OC**H**$_2$CH$_3$), 3.80 (s, 3H, OCH_3), 3.20 (ddd, *J* = 17.5, 10.7, 3.0 Hz, 1H, C**H$_a$**H$_b$-CH-O), 2.81 (ddd, *J* = 17.5, 9.0, 3.0 Hz, 1H, CH$_a$**H$_b$**-CH-O), 1.33 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.4 (COO), 159.6 (**C**$_{arom}$-OCH_3), 148.3 (CH_2CH=**C**), 133.9 (C_{arom}), 127.5 (2×C_{arom}-H), 114.1 (2×C_{arom}-H), 110.5 (CH_2**C**H=C), 83.9 (CH-O), 61.3 (**C**H_2CH_3), 55.4 (OCH_3), 38.9 (**C**H_2CH=C), 14.4 (CH_2**C**H_3). **IR** (ATR): 1735 (C=O st), 1253 (C-O st), 1071 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 248.1 (M+, 27), 246.1 (27), 175.0 (27), 174.0 (61), 160.0 (19), 147.1 (100), 145.1 (15), 131.0 (26), 115.1 (24), 103.0 (26), 102.0 (15), 91.0 (31), 77.0 (17). **HRMS** (ESI$^+$): Calculated for $[C_{14}H_{16}O_4Na]^+$: 271.0946 $[M+Na]^+$; found: 271.0952. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 7.58 min, τ_{minor} = 8.86 min (90:10). $[\alpha]_D^{20}$: +107.3 (*c* = 0.5, CH_2Cl_2).



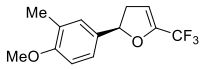
Ethyl 5-(2,3-dihydrobenzofuran-5-yl)-4,5-dihydrofuran-2-carboxylate (12b). Following *GP-I*, **12b** (12.0 mg, 0.05 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **11b** (13.0 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and dichloromethane (0.12 mL) at -60 ºC for 24 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.24 (s, 1H, C_{arom}-H), 7.09 (d, *J* = 8.1 Hz, 1H, C_{arom}-H), 6.74 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 5.97 (t, *J* = 3.0 Hz, 1H, C**H**=C), 5.62 (dd, *J* = 10.7, 9.0 Hz, 1H, Ar-C**H**-O), 4.56 (t, *J* = 8.7 Hz, 2H, Ar-CH_2C**H**$_2$O), 4.29 (qd, *J* = 7.1, 2.1 Hz, 2H, CO_2C**H**$_2$CH$_3$), 3.19 (t, *J* = 8.7 Hz, 2H, Ar-C**H**$_2$CH$_2$O), 3.24-3.12 (m, 1H, C**H$_a$**H$_b$-CH-O), 2.80 (ddd, *J* = 17.5, 9.0, 2.9 Hz, 1H, CH$_a$**H$_b$**-CH-O), 1.33 (t, *J* = 7.1 Hz, 3H, CO_2CH_2C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.4 (COO), 160.2 (**C**$_{arom}$-OCH_2), 148.2 (CH_2CH=**C**), 133.8 (C_{arom}), 127.6 (C_{arom}), 126.4 (C_{arom}-H), 122.9 (C_{arom}-H), 110.5 (CH_2**C**H=C), 109.2 (C_{arom}-H), 84.2 (CH-O), 71.5 (O**C**H_2CH_2), 61.3 (**C**H_2CH_3), 38.9 (**C**H_2CH=C), 29.8 (OCH_2**C**H_2), 14.3 (CH_2**C**H_3). **IR** (ATR): 1731 (C=O st), 1246 (C-O st), 1100 (C-O st) cm^{-1}. **MS** (EI) m/z (%): 260.2 (M+, 44), 258.0 (40), 186.9 (25), 186.1 (44), 159.1 (100), 158.0 (21), 157.2 (22), 144.0 (24), 141.0 (21), 131.0 (19), 129.1 (20), 128.1 (21), 115.0 (21), 91.0 (19), 63.1 (22). **HRMS** (ESI$^+$): Calculated for $[C_{15}H_{17}O_4]^+$: 261.1127 $[M+H]^+$; found: 261.1127. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.19 min, τ_{minor} = 10.47 min (95:5). $[\alpha]_D^{20}$: +11.4 (*c* = 0.7, CH_2Cl_2).



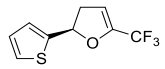
Ethyl 5-(thiophen-2-yl)-4,5-dihydrofuran-2-carboxylate (12c). Following *GP-I*, **12c** (10.3 mg, 0.05 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **11c** (11.2 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and dichloromethane (0.12 mL) at -30 ºC for 96 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 5.1, 1.3 Hz, 1H, C_{arom}-H), 7.11-7.07 (m, 1H, C_{arom}-H), 6.97 (dd, *J* = 5.1, 3.5 Hz, 1H, C_{arom}-H), 6.00 (t, *J* = 3.0 Hz, 1H, C**H**=C), 5.91 (dd, *J* = 10.4, 8.4 Hz, 1H, Ar-C**H**-O), 4.28 (qd, *J* = 7.1, 1.4 Hz, 2H, OC**H**$_2$CH$_3$), 3.25 (ddd, *J* = 17.5, 10.4, 3.0 Hz, 1H, C**H**$_a$H$_b$-CH-O), 2.97 (ddd, *J* = 17.5, 8.4, 3.0 Hz, 1H, CH$_a$**H**$_b$-CH-O), 1.32 (t, *J* = 7.1 Hz, 3H, OCH$_2$C**H**$_3$). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.2 (COO), 147.9 (CH$_2$CH=**C**), 144.3 (C_{arom}), 126.9 (C_{arom}-H), 125.8 (C_{arom}-H), 125.6 (C_{arom}-H), 110.4 (CH$_2$**C**H=C), 79.7 (CH-O), 61.4 (**C**H$_2$CH$_3$), 39.1 (**C**H$_2$CH=C), 14.3 (CH$_2$**C**H$_3$). **IR** (ATR): 1739 (C=O st), 1259 (C-O st), 1036 (C-O st) cm^{-1}. **HRMS** (ESI$^-$): Calculated for [$C_{12}H_{13}O_5S$]$^-$: 269.0484 [M+HCOOH-H]$^-$; found: 269.0470. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 7.11 min, τ_{minor} = 8.33 min (92:8). $[\alpha]_D^{20}$: +16.6 (*c* = 0.5, CH_2Cl_2).



2-(4-Methoxyphenyl)-5-(trifluoromethyl)-2,3-dihydrofuran (15a). Following *GP-I*, **15a** (9.5 mg, 0.04 mmol, 78%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **14a** (12.2 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and dichloromethane (0.12 mL) at -30 ºC for 96 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.70 (dd, *J* = 10.6, 8.5 Hz, 1H, Ar-C**H**-O), 5.54-5.49 (m, 1H, C**H**=C), 3.82 (s, 3H, OCH_3), 3.28-3.12 (m, 1H, C**H**$_a$H$_b$-CH-O), 2.86-2.70 (m, 1H, CH$_a$**H**$_b$-CH-O). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.8 (**C**$_{arom}$-OCH_3), 145.8 (q, $^2J_{C\text{-}F}$ = 37.9 Hz, **C**-CF_3), 133.4 (C_{arom}), 127.2 (2×C_{arom}-H), 119.0 (q, $^1J_{C\text{-}F}$ = 270.0, CF_3), 114.3 (2×C_{arom}-H), 102.7 (q, $^3J_{C\text{-}F}$ = 3.4 Hz, **C**H-C-CF_3), 84.6 (CH-O), 55.5 (OCH_3), 38.2 (CH_2). **IR** (ATR): 1174 (C-O st), 1133 (C-O st), 1083 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 244.0 (M+, 50), 175.1 (23), 147.1 (100), 132.1 (16), 131.1 (16), 115.0 (28), 103.0 (19), 91.0 (38), 77.1 (22), 69.0 (18). **HRMS** (ESI$^+$): Calculated for [$C_{12}H_{12}O_2F_3$]$^+$: 245.0789 [M+H]$^+$; found: 245.0794. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 4.26 min, τ_{minor} = 4.71 min (93:7). $[\alpha]_D^{20}$: +6.5 (*c* = 0.8, CH_2Cl_2).

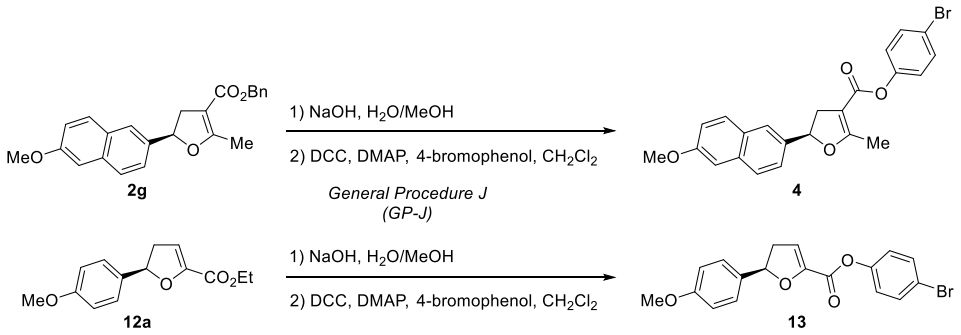


2-(4-Methoxy-3-methylphenyl)-5-(trifluoromethyl)-2,3-dihydrofuran (15b). Following *GP-I*, **15b** (11.7 mg, 0.05 mmol, 91%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **14b** (12.9 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol) in 1,2-dichloroethane (0.12 mL) and dichloromethane (0.12 mL) at -30 ºC for 48 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20-7.10 (m, 2H, C_{arom}-H), 6.82 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 5.67 (dd, *J* = 10.5, 8.7 Hz, 1H, Ar-C**H**-O), 5.53-5.49 (m, 1H, C**H**=C), 3.84 (s, 3H, OCH_3), 3.26-3.08 (m, 1H, C**H$_a$**H$_b$-CH-O), 2.88-2.71 (m, 1H, CH$_a$**H$_b$**-CH-O), 2.23 (s, 3H, Ar-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.0 (**C**$_{arom}$-OCH_3), 145.8 (q, $^{2}J_{C\text{-}F}$ = 38.1 Hz, **C**-CF_3), 132.8 (C_{arom}), 128.3 (C_{arom}-H), 127.3 (C_{arom}), 124.5 (C_{arom}-H), 119.0 (q, $^{1}J_{C\text{-}F}$ = 269.1 Hz, CF_3), 110.0 (C_{arom}-H), 102.7 (q, $^{3}J_{C\text{-}F}$ = 3.5 Hz, **C**H-C-CF_3), 84.8 (CH-O), 55.5 (OCH_3), 38.1 (CH_2), 16.4 (Ar-CH_3). **IR** (ATR): 1175 (C-O st), 1131 (C-O st), 1083 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 258.1 (M+, 50), 189.1 (19), 161.1 (100), 146.1 (30), 131.1 (16), 115.0 (26), 105.1 (16), 91.1 (24), 69.0 (18). **HRMS** (ESI$^+$): Calculated for $[C_{13}H_{14}O_2F_3]^+$: 259.0946 $[M+H]^+$; found: 259.0942. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 3.75 min, τ_{minor} = 4.08 min (95:5). $[\alpha]_D^{20}$: +13.8 (*c* = 1.0, CH_2Cl_2).



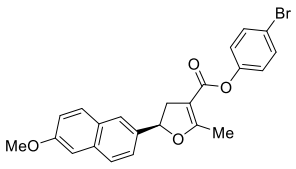
2-(Thiophen-2-yl)-5-(trifluoromethyl)-2,3-dihydrofuran (15c). Following *GP-I*, **15c** (8.8 mg, 0.04 mmol, 80%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow oil, from cyclopropane **14c** (11.0 mg, 0.05 mmol) and catalyst **3f** (3.0 mg, 0.005 mmol in 1,2-dichloroethane (0.25 mL) at -30 ºC for 96 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 5.0, 1.2 Hz, 1H, C_{arom}-H), 7.11-7.07 (m, 1H, C_{arom}-H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H, C_{arom}-H), 5.97 (dd, *J* = 10.3, 7.9 Hz, 1H, Ar-C**H**-O), 5.58-5.51 (m, 1H, C**H**=C), 3.33-3.15 (m, 1H, C**H$_a$**H$_b$-CH-O), 3.03-2.86 (m, 1H, CH$_a$**H$_b$**-CH-O). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 145.4 (q, $^{2}J_{C\text{-}F}$ = 39.0 Hz, **C**-CF_3), 143.8 (C_{arom}), 127.0 (C_{arom}-H), 126.0 (C_{arom}-H), 125.5 (C_{arom}-H), 118.8 (q, $^{1}J_{C\text{-}F}$ = 269.4 Hz, CF_3), 102.8 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, **C**H-C-CF_3), 80.7 (CH-O), 38.3 (CH_2). **IR** (ATR): 1177 (C-O st), 1138 (C-O st), 1083 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 220.0 (M+, 41), 151.0 (20), 123.0 (100), 97.0 (15), 79.1 (24), 69.0 (28). **HRMS** (ESI$^-$): Calculated for $[C_9H_6OSF_3]^-$: 219.0091 $[M-H]^-$; found: 219.0089. The e.e. was determined by HPLC using a *Chiralcel OJ-H* column [*n*-hexane/*i*-PrOH (95:5)]; flow rate 1.0 mL/min; τ_{minor} = 10.27 min, τ_{major} = 13.33 min (4:96). $[\alpha]_D^{20}$: +5.8 (*c* = 0.8, CH_2Cl_2).

3.2 4-Bromophenyl esters (4, 13) for the determination of absolute configuration



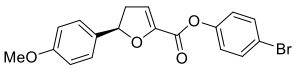
Scheme 4. 8 General Procedure J for the transesterification of representative dihydrofurans

General Procedure J (GP-J) for the transesterification of dihydrofurans. To a solution of the corresponding dihydrofuran (1.0 equiv) in MeOH (1.3 M), a 2 M aqueous solution of NaOH (1.2 equiv) was added and it was stirred for 15 hours for the required temperature. The reaction mixture was acidified to pH 1 with 1 M HCl at 0 ºC and extracted with Et_2O (4 × 10 mL). The combined organic phases were dried over Na_2SO_4 and removal of the volatiles under reduced pressure gave the corresponding acids. Then, DMAP (0.8 equiv), 4-bromophenol (2.0 equiv) and CH_2Cl_2 (0.4 M) were added and stirred for 10 minutes at room temperature. After cooling the solution to 0 ºC, DCC (1.2 equiv) was added in portions and the reaction mixture was stirred for 30 minutes at that temperature and 16 hours at room temperature. Removal of the volatiles under reduced pressure followed by purification by column chromatography on silica gel gave the corresponding 4-bromophenyl esters **6, 10**. Crystals suitable for X-ray analysis were grown by slow evaporation of a solution of 4-bromophenyl derivative in dichloromethane and *n*-hexane.



4-Bromophenyl (R)-5-(6-methoxynaphthalen-2-yl)-2-methyl-4,5-dihydrofuran-3-carboxylate (4). Following *GP-J*, **4** (13.6 mg, 0.031 mmol, 62%) was isolated by FC (petroleum ether/EtOAc, 19:1) on silica gel as a white solid. The intermediate acid was obtained from **2g** (18.0 mg, 0.05 mmol, 1.0 equiv), MeOH (38 μL), NaOH (2.4 mg, 0.06 mmol, 1.2 equiv) in H_2O (30.0 μL) for 15 hours at reflux temperature. The ester was obtained from the crude carboxylic acid (14.2 mg, 0.05 mmol, 1.0

equiv), DMAP (4.9 mg, 0.04 mmol, 0.8 equiv), 4-bromophenol (17.3 mg, 0.1 mmol, 2.0 equiv), CH_2Cl_2 (0.1 mL) and DCC (12.4 mg, 0.06 mmol, 1.2 equiv). R_f = 0.50 (petroleum ether/EtOAc, 9:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82-7.72 (m, 3H, C_{arom}-H), 7.57-7.40 (m, 3H, C_{arom}-H), 7.22-7.11 (m, 2H, C_{arom}-H), 7.03 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 5.83 (dd, *J* = 10.7, 8.5 Hz, 1H, C**H**CH_2), 3.94 (s, 3H, OCH_3), 3.64-3.40 (m, 1H, C**H$_a$**H$_b$), 3.15 (dd, *J* = 14.5, 8.5 Hz, 1H, CH_a**H$_b$**), 2.39 (s, 3H, CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) 171.2 (**C**CH_3), 164.3 (COO), 158.4 (**C**$_{arom}$-OCH_3), 150.2 (COO-**C**$_{arom}$), 136.2 (C_{arom}), 134.8 (C_{arom}), 132.6 (2×C_{arom}-H), 129.9 (C_{arom}-H), 128.9 (C_{arom}), 128.1 (C_{arom}-H), 125.1 (C_{arom}-H), 124.4 (C_{arom}-H), 124.0 (2×C_{arom}-H), 119.7 (C_{arom}-H), 118.8 (**C**$_{arom}$-Br), 106.1 (C_{arom}-H), 101.2 (**C**-COO), 84.5 (OCH), 55.7 (OCH_3), 37.9 (CH_2), 14.8 (**C**CH_3). **IR** (ATR): 1716 (C=O st), 1195 (C-O st as), 1132 (C-Br) cm^{-1}. **MS** (EI) m/z (%): 438 (M^+, 2), 268.1 (19), 267.1 (100), 225.0 (51), 224.0 (29), 153.0 (18), 152.0 (20). **HRMS** (ESI^+): Calculated for $[C_{23}H_{20}O_4Br]^+$: 439.0545 $[M+H]^+$; found: 439.0540. **M.p.**: 133-136 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.18 min, τ_{minor} = 11.41 min (89:11). $[\alpha]_D^{20}$: -91.8 (*c* = 0.43, CH_2Cl_2).



4-Bromophenyl (R)-5-(4-methoxyphenyl)-4,5-dihydrofuran-2-carboxylate (13). Following *GP-J*, **13** (19.6 mg, 0.052 mmol, 87%) was isolated by FC (petroleum ether/EtOAc, 9:1) on silica gel as a white solid. The intermediate acid was obtained from **12a** (14.9 mg, 0.06 mmol, 1.0 equiv), MeOH (46 μL), NaOH (2.9 mg, 0.07 mmol, 1.2 equiv) in H_2O (36.0 μL) for 15 hours at room temperature. The ester was obtained from the crude carboxylic acid (13.2 mg, 0.06 mmol, 1.0 equiv), DMAP (5.9 mg, 0.05 mmol, 0.8 equiv), 4-bromophenol (20.8 mg, 0.12 mmol, 2.0 equiv), CH_2Cl_2 (0.15 mL) and DCC (14.9 mg, 0.07 mmol, 1.2 equiv). R_f = 0.60 (petroleum ether/EtOAc, 8:2). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.35 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.07 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.92 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.22 (t, *J* = 3.1 Hz, 1H, OC**H**CH_2), 5.73 (app t, *J* = 9.9 Hz, 1H, C=C**H**CH_2), 3.82 (s, 3H, OCH_3), 3.28 (ddd, *J* = 17.9, 10.7, 3.1 Hz, 1H, C**H$_a$**H$_b$), 2.91 (ddd, *J* = 17.9, 9.2, 3.0 Hz, 1H, CH_a**H$_b$**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.0 (COO), 158.4 (**C**$_{arom}$-OCH_3), 149.6 (COO-**C**$_{arom}$), 147.5 (CH_2CH=**C**), 133.6 (CH_2**C**H=C), 132.9 (2×C_{arom}-H), 127.8 (2×C_{arom}-H), 123.7 (2×C_{arom}-H), 119.5 (**C**$_{arom}$-$CHCH_2$), 114.4 (2×C_{arom}-H), 113.43 (C_{arom}-Br), 84.4 (OCH), 55.7 (OCH_3), 39.2 (CH_2). **IR** (ATR): 1748 (C=O st), 1197 (C-O st as), 1089 (C-Br) cm^{-1}. **MS** (EI) m/z (%): 374.0 (M^+, 10), 175.0 (100), 160.0 (52), 157.0 (18), 147.0 (81), 131.0 (18), 115.0 (22), 77.0 (15). **HRMS** (ESI^+): Calculated for $[C_{18}H_{16}O_4Br]^+$: 375.0232 $[M+H]^+$; found: 375.0235. **M.p.**: 90-93 ºC (petroleum ether/EtOAc). The e.e. was

determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 11.41 min, τ_{major} = 14.18 min (10:90). $[\alpha]_D^{20}$: +15.1 (*c* = 1.0, CH_2Cl_2).

4. ACID-CATALYZED CYCLOCONDENSATION OF DONOR-ACCEPTOR CYCLOPROPANES WITH 3-SUBSTITUTED INDOLES

4.1 Synthesis of dihydropyridoindoles

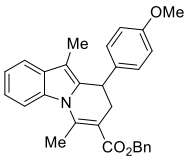
General Procedure K (GP-K) for the intermolecular reaction

An oven-dried 5 mL screw-capped test tube containing a stirring bar was charged with the corresponding cyclopropane (1eq.) and indole (1eq) and dissolved in toluene (0.2 M) under Ar. After adding the catalyst (10 mol%) the mixture was stirred at 100 ºC. When the reaction was judged complete (monitored by TLC), it was warmed to room temperature, quenched by addition of aq. $NaHCO_3$ (sat) and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography on silica gel to afford pure compound.

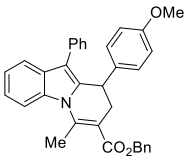
General Procedure L (GP-L) for the intermolecular reaction

An oven-dried 5 mL screw-capped test tube containing a stirring bar was charged with the corresponding cyclopropane (1eq.) and indole (1eq) and dissolved in toluene (0.2 M) under Ar. After adding the catalyst **3c** (10 mol%) the mixture was stirred at 50ºC for 12h. When the starting material was consumed, it was warmed to room temperature, quenched by addition of aq. $NaHCO_3$ (sat) and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. After the combined organic layers were dried over Na_2SO_4, filtered and evaporated, the crude residue was redissolved in toluene (0.2M), added PTSA (1 eq.) and heated to 50ºC for 1h. Finally, after warming to room temperature, the residue was purified by column chromatography on silica gel to afford pure compound.

4.1.1 Dihydropyridoindoles 21

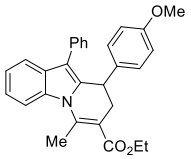


benzyl 9-(4-methoxyphenyl)-6,10-dimethyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21a). Following *GP-K* (carrying out the reaction at 50 ºC), ***rac*-21a** (3.5 mg, 0.008 mmol, 17%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel, as a white solid from cyclopropane **1a** (16.2 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at room temperature for 12h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.77-7.657 (m, 1H, H-1), 7.60-7.51 (m, 1H, H-4), 7.46-7.20 (m, 7H, C_{arom}-H), 7.01 (d, *J* = 8.6 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.80 (d, *J* = 8.6 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.26 (d, *J* = 12.7 Hz, 1H, OC**H**$_a$CH$_b$), 5.15 (d, *J* = 12.7 Hz, 1H, OCH$_a$C**H**$_b$), 4.41 (app t, *J* = 4.7 Hz, 1H, H-9), 3.80 (s, 3H, OCH_3), 3.30 (dd, *J* = 15.5, 4.2 Hz, 1H, H-8a), 2.99 (d, *J* = 1.8 Hz, 3H, C-6-CH_3), 2.89-2.72 (m, 1H, H-8b), 2.12 (s, 3H, C-10-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (COO), 158.3 (**C**$_{arom}$-OCH_3), 146.8 (C-6), 136.7 (C_{arom}), 135.8 (C_{arom}), 134.9 (C_{arom}), 133.3 (C_{arom}), 131.5 (C-10a), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 128.5 (2×C_{arom}-H), 128.0 (C_{arom}-H), 127.8 (2×C_{arom}-H), 122.6 (C-3), 121.3 (C-2), 119.0 (C-1), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.8 (C-4), 110.2 (C-10), 108.4 (C-7), 65.9 (OCH_2), 55.3 (OCH_3), 36.1 (C-9), 30.1 (C-8), 19.5 (C-6-**C**H_3), 8.7 (C-10-**C**H_3). **IR** (ATR): 2942 (C-H st), 1695 (C=O st), 1239 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{29}H_{28}NO_3]^+$: 438.2069 $[M+H]^+$; found: 438.2074. **M.p.**: 65-68 ºC (petroleum ether/EtOAc).

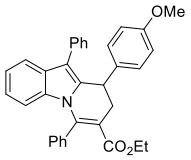


benzyl 9-(4-methoxyphenyl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21b). Following *GP-K*, ***rac*-21b** (20.8 mg, 0.042 mmol, 83%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **1a** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92-7.63 (m, 2H, H-1 + H-4), 7.48-7.09 (m, 12H, C_{arom}-H), 6.95 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.77 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.22 (d, *J* = 12.8 Hz, 1H, OC**H**$_a$H$_b$), 5.09 (d, *J* = 12.8 Hz, 1H, OCH$_a$**H**$_b$), 4.44 (dd, *J* = 5.1, 2.6 Hz, 1H, H-9), 3.79 (s, 3H, OCH_3), 3.33 (dd, *J* = 15.7, 2.6 Hz, 1H, H-8a), 3.01 (d, *J* = 2.1 Hz, 3H, C-6-CH_3), 2.75-2.63 (m, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (COO), 158.3 (**C**$_{arom}$-OCH_3), 146.4 (C-6), 136.6 (C_{arom}), 136.0 (C_{arom}), 135.2 (C_{arom}), 133.9 (C_{arom}), 133.7 (C_{arom}), 129.6 (C-10a), 129.5 (2×C_{arom}-H), 128.6 (4×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.0 (C_{arom}-H), 127.6

(2×C_{arom}-H), 126.8 (C_{arom}-H), 123.0 (C-3), 121.9 (C-2), 120.1 (C-1), 116.3 (C-10), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 110.5 (C-7), 66.0 (OCH_2), 55.3 (OCH_3), 35.6 (C-9), 30.5 (C-8), 19.7 (C-6-**C**H_3). **IR** (ATR): 2976 (C-H st), 1698 (C=O st), 1247 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 438.2 (27), 437.1 (100), 365.1 (27), 364.1 (M^+-$C_8H_7O_2$, 86), 363.1 (20), 349.2 (33), 337.1 (24), 329.1 (18), 301.1 (19). **HRMS** (ESI^+): Calculated for $[C_{34}H_{29}NO_3Na]^+$: 522.2045 $[M+Na]^+$; found: 522.2047. **M.p.**: 60-63 ºC (petroleum ether/EtOAc).



ethyl 9-(4-methoxyphenyl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21c). Following *GP-K*, ***rac*-21c** (19.8 mg, 0.045 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **5b** (13.1 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (m, 2H, H-1 + H-4), 7.41-7.17 (m, 7H, C_{arom}-H), 6.97 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 4.44 (dd, *J* = 5.1, 2.6 Hz, 1H, H-9), 4.15 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.78 (s, 3H, OCH_3), 3.27 (dd, *J* = 15.7, 2.6 Hz, 1H, H-8a), 3.01 (d, *J* = 2.1 Hz, 3H, C-6-CH_3), 2.68 (dd, *J* = 15.8, 5.1 Hz, 1H, H-8b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (COO), 158.2 (**C**$_{arom}$-OCH_3), 145.6 (C-6), 136.0 (C_{arom}), 135.2 (C_{arom}), 133.9 (C_{arom}), 133.7 (C_{arom}), 129.5 (C-10a), 129.4 (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5 (2×C_{arom}-H), 126.8 (C_{arom}-H), 122.9 (C-3), 121.7 (C-2), 120.0 (C-1), 116.1 (C-10), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 111.0 (C-7), 60.4 (OCH_2), 55.3 (OCH_3), 35.6 (C-9), 30.5 (C-8), 19.6 (C-6-**C**H_3), 14.4 (OCH_2**C**H_3). **IR** (ATR): 2980 (C-H st), 1696 (C=O st), 1247 (C-O st as) cm^{-1}. **IR** (ATR): 2980 (C-H st), 1696 (C=O st), 1247 (C-O st as) cm^{-1}. **M.p.**: 138-141 ºC (petroleum ether/EtOAc).

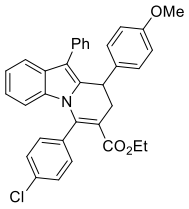


ethyl 9-(4-methoxyphenyl)-6,10-diphenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21d).

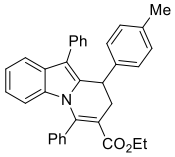
Following *GP-K*, ***rac*-21d** (22.5 mg, 0.045 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min.

Following the modified procedure *GP-L*, **20d** (15.0 mg, 0.030 mmol, 60%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under catalyst **3m** (3.0 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for until full conversion to final product (12h).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.9 Hz, 1H, H-1), 7.61-7.29 (m, 10H, C_{arom}-H), 7.22-7.04 (m, 3H, H-2 + C-9-C_{arom}-C_{arom}-H), 6.93-6.80 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 5.86 (d, *J* = 8.5 Hz, 1H, H-4), 4.58 (dd, *J* = 5.3, 2.4 Hz, 1H, H-9) 4.06-3.65 (m, 5H, OCH_2 + OCH_3), 3.29 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 3.0 (dd, *J* = 15.5, 5,1 Hz, 1H, H-8b), 0.88 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (COO), 158.3 (**C**$_{arom}$-OCH_3), 145.6 (C-6), 136.0 (C-4a), 135.8 (C_{arom}), 135.4 (C_{arom}), 134.1 (C-9a), 133.6 (C_{arom}), 129.5 (3×C_{arom}-H), 129.4 (C_{arom}-H), 128.6 (7×C_{arom}-H + C-10a), 126.9 (C_{arom}-H), 122.7 (C-3), 121.7 (C-2), 119.6 (C-1), 117.2 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 111.0 (C-7), 60.1 (OCH_2), 55.3 (OCH_3), 35.7 (C-9), 31.5 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2926 (C-H st), 1686 (C=O st), 1239 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{34}H_{29}NO_3]^+$: 500.2226 $[M+H]^+$; found: 500.2226. **M.p.**: 179-182 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 4.71 min, τ_{minor} = 6.17 min (63:37).

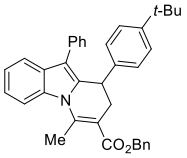


ethyl 6-(4-chlorophenyl)-9-(4-methoxyphenyl)-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21e). Following *GP-K*, ***rac*-21e** (24.0 mg, 0.045 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7g** (17.9 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H, H-1), 7.54-7.28 (m, 9H, C_{arom}-H), 7.17-7.02 (m, 3H, H-2 + C-9-C_{arom}-C_{arom}-H), 6.90 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H, H-3), 6.84 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.95 (d, *J* = 8.5 Hz, 1H, H-4), 4.55 (dd, *J* = 5.3, 2.5 Hz, 1H, H-9) 4.14-3.66 (m, 5H, OCH_2 + OCH_3), 3.28 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.95 (dd, *J* = 15.5, 5,1 Hz, 1H, H-8b), 0.93 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (COO), 158.4 (**C**$_{arom}$-OCH_3), 144.4 (C-6), 135.6 (C-4a), 135.5 (C_{arom}), 135.3 (C_{arom}), 134.1 (C-9a), 133.8 (C_{arom}), 133.4 (C-Cl), 129.5 (C-10a), 129.4 (3×C_{arom}-H), 128.6 (5×C_{arom}-H), 128.4 (2×C_{arom}-H), 127.0 (C_{arom}-H), 122.9 (C-3), 121.9 (C-2), 119.7 (C-1), 117.4 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.5 (C-4), 111.6 (C-7), 60.3 (OCH_2), 55.3 (OCH_3), 35.6 (C-9), 31.4 (C-8), 13.8 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2980 (C-H st), 1686 (C=O st), 1242 (C-O st as), 1088 (C-Cl st) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{34}H_{29}NO_3Cl]^+$: 534.1836 $[M+H]^+$; found: 534.1828. **M.p.**: 175-178 ºC (petroleum ether/EtOAc).

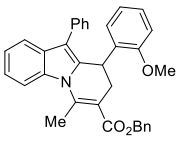


ethyl 6,10-diphenyl-9-(p-tolyl)-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21f). Following *GP-K*, ***rac*-21f** (18.9 mg, 0.039 mmol, 78%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7i** (15.4 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H, H-1), 7.56-7.24 (m, 10H, C_{arom}-H), 7.17-7.01 (m, 5H, C_{arom}-H), 6.84 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H, H-3), 5.83 (d, *J* = 8.5 Hz, 1H, H-4), 4.57 (dd, *J* = 5.3, 2.4 Hz, 1H, H-9) 4.07-3.67 (m, 2H, OCH_2), 3.28 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.99 (dd, *J* = 15.5, 5,2 Hz, 1H, H-8b), 2.33 (s, 3H, C_{arom}-CH_3), 0.86 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (COO), 145.6 (C-6), 138.9 (C_{arom}), 136.2 (C_{arom}), 136.0 (C_{arom}), 135.8 (C_{arom}), 135.3 (C_{arom}), 133.6 (C_{arom}), 129.4 (6×C_{arom}-H + C-10a), 128.6 (5×C_{arom}-H), 127.3 (2×C_{arom}-H), 126.9 (C_{arom}-H), 122.7 (C-3), 121.7 (C-2), 119.6 (C-1), 117.3 (C-10), 113.7 (C-4), 111.0 (C-7), 60.1 (OCH_2), 36.0 (C-9), 31.4 (C-8), 21.2 (C_{arom}-**C**H_3), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2984 (C-H st), 1692 (C=O st), 1237 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 410.2 (M^+-C_3H_5O, 3), 207.0 (21). **HRMS** (ESI$^+$): Calculated

for $[C_{34}H_{30}NO_2]^+$: 484.2277 $[M+H]^+$; found: 484.2279. **M.p.**: 182-185 ºC (petroleum ether/EtOAc).

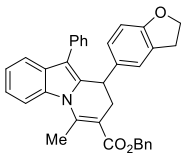


benzyl 9-(4-(tert-butoxy)phenyl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21g). Following *GP-K*, ***rac*-21g** (20.0 mg, 0.038 mmol, 76%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7j** (17.5 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87-7.61 (m, 2H, H-1 + H-4), 7.41-7.13 (m, 14H, C_{arom}-H), 6.96 (d, *J* = 8.3 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.22 (d, *J* = 12.8 Hz, 1H, $OC\mathbf{H}_aH_b$), 5.11 (d, *J* = 12.8 Hz, 1H, $OCH_a\mathbf{H}_b$), 4.47 (dd, *J* = 5.2, 2.9 Hz, 1H, H-9), 3.36 (dd, *J* = 15.8, 2.9 Hz, 1H, H-8a), 3.03 (d, *J* = 2.0 Hz, 3H, C-6-CH_3), 2.74 (dd, *J* = 15.8, 5.2 Hz, 1H, H-8b), 1.30 (s, 9H,$C(CH_3)_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (COO), 149.2 (**C**$_{arom}$-O), 146.5 (C-6), 138.4 (C_{arom}), 136.6 (C_{arom}), 136.0 (C_{arom}), 135.2 (C_{arom}), 133.7 (C_{arom}), 129.7 (C-10a), 129.5 (2×C_{arom}-H), 128.6 (4×C_{arom}-H), 128.0 (C_{arom}-H), 127.7 (2×C_{arom}-H), 127.1 (2×C_{arom}-H), 126.8 (C_{arom}-H), 125.4 (2×C_{arom}-H), 123.0 (C-3), 121.8 (C-2), 120.1 (C-1), 116.5 (C-10), 113.7 (C-4), 110.5 (C-7), 66.0 (OCH_2), 35.9 (C-9), 34.5 (**C**$(CH_3)_3$), 31.5 (C(**C**$H_3)_3$), 30.2 (C-8), 19.7 (C-6-**C**H_3). **IR** (ATR): 2961 (C-H st), 1698 (C=O st), 1243 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{37}H_{35}NO_2Na]^+$: 548.2565 $[M+Na]^+$; found: 548.2569. **M.p.**: 82-85 ºC (petroleum ether/EtOAc).

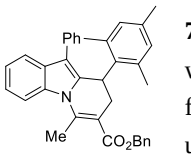


benzyl 9-(2-methoxyphenyl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21h). Following *GP-K*, ***rac*-21h** (20.1 mg, 0.040 mmol, 80%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **1h** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (m, 2H, H-1 + H-4), 7.49-7.05 (m, 13H, C_{arom}-H), 6.88 (dd, *J* = 8.2, 1.1 Hz, 1H, C_{arom}-H), 6.75 (app td, *J* = 7.5, 1.1 Hz, 1H, C_{arom}-H), 6.56 (dd, *J* = 7.6, 1.7 Hz, 1H, C_{arom}-H), 5.17 (d, *J* = 12.9 Hz, 1H, $OC\mathbf{H}_aH_b$), 5.03 (d, *J* = 12.9 Hz, 1H, $OCH_a\mathbf{H}_b$), 4.76 (dd, *J* = 5.5, 2.5 Hz, 1H, H-9), 3.76 (s, 3H, OCH_3), 3.41 (dd, *J* = 15.8, 2.5 Hz, 1H, H-8a), 3.03 (d, *J* = 2.1 Hz, 3H, C-6-CH_3), 2.58 (dd, *J* = 15.7, 5.5 Hz, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (COO), 156.5 (**C**$_{arom}$-OCH_3), 145.8 (C-6), 136.7 (C_{arom}), 136.4 (C_{arom}),

135.3 (C_{arom}), 133.8 (C_{arom}), 130.0 (C_{arom}), 129.7 (C-10a), 129.4 (2×C_{arom}-H), 128.8 (C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (2×C_{arom}-H), 127.9 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 126.6 (C_{arom}-H), 122.9 (C-3), 121.8 (C-2), 120.4 (C_{arom}-H), 120.1 (C-1), 115.9 (C-10), 113.7 (C_{arom}-H), 111.3 (C-4), 110.7 (C-7), 65.8 (OCH_2), 55.4 (OCH_3), 31.6 (C-9), 28.3 (C-8), 19.6 (C-6-**C**H_3). **IR** (ATR): 2934 (C-H st), 1698 (C=O st), 1241 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{34}H_{29}NO_3Na]^+$: 522.2045 $[M+Na]^+$; found: 522.2046. **M.p.**: 74-77 ºC (petroleum ether/EtOAc).

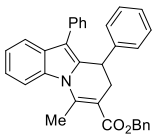


benzyl 9-(2,3-dihydrobenzofuran-5-yl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21i). Following *GP-K*, ***rac*-21i** (23.7 mg, 0.046 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **1j** (16.8 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80-7.75 (m, 2H, H-1 + H-4), 7.52-7.17 (m, 12H, C_{arom}-H), 6.96-6.70 (m, 2H, C_{arom}-H), 6.66 (d, *J* = 8.2 Hz, 1H, C_{arom}-H), 5.24 (d, *J* = 12.8 Hz, 1H, OC**H**$_a$H$_b$), 5.10 (d, *J* = 12.8 Hz, 1H, OCH$_a$**H**$_b$), 4.54 (t, *J* = 8.9 Hz, 2H, OC**H**$_2$CH$_2$), 4.42 (dd, *J* = 5.1, 2.7 Hz, 1H, H-9), 3.31 (dd, *J* = 15.7, 2.7 Hz, 1H, H-8a), 3.17-2.87 (m, 5H, $OCH_2C\mathbf{H}_2$ + CH_3), 2.79-2.56 (m, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5 (COO), 158.8 (**C**$_{arom}$-OCH_2), 146.4 (C-6), 136.6 (C_{arom}), 136.1 (C_{arom}), 135.2 (C_{arom}), 133.8 (C_{arom}), 133.7 (C_{arom}), 129.6 (C_{arom}), 129.4 (2×C_{arom}-H), 128.6 (4×C_{arom}-H), 128.0 (C_{arom}-H), 127.6 (2×C_{arom}-H), 127.2 (C-10a + C_{arom}-H), 126.8 (C_{arom}-H), 123.9 (C_{arom}-H), 123.0 (C-3), 121.9 (C-2), 120.1 (C-1), 116.2 (C-10), 113.7 (C-4), 110.6 (C-7), 109.1 (C_{arom}-H), 71.3 (O**C**H_2CH_2), 66.0 (O**C**H_2C_{arom}), 35.9 (C-9), 30.7 (C-8), 29.9 ($OCH_2\mathbf{C}H_2$), 19.7 (C-6-**C**H_3). **IR** (ATR): 2957 (C-H st), 1698 (C=O st), 1242 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{35}H_{29}NO_3Na]^+$: 534.2045 $[M+Na]^+$; found: 534.2054. **M.p.**: 85-88 ºC (petroleum ether/EtOAc).

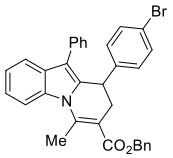


benzyl 9-mesityl-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21j). Following *GP-K*, ***rac*-21j** (15.9 mg, 0.031 mmol, 42%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7k** (16.8 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005

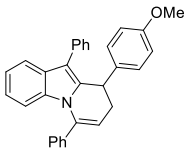
mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 1H, H-1), 7.52 (d, *J* = 7.4 Hz, 1H, H-4), 7.41-7.28 (m, 5H, C_{arom}-H), 7.25-7.12 (m, 2H, C_{arom}-H), 7.08-6.98 (m, 5H, C_{arom}-H), 6.65 (s, 1H, C_{arom}-H), 6.33 (s, 1H, C_{arom}-H), 5.33-5.07 (m, 2H, OCH_2), 4.71 (dd, *J* = 11.3, 6.7 Hz, 1H, H-9), 3.06 (s, 3H, C-6-CH_3), 3.00-2.72 (m, 2H, H-8), 2.34 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.82 (s, 3H, CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (COO), 146.6 (C-6), 136.5 (C_{arom}), 136.0 (2×C_{arom}), 135.8 (C_{arom}), 135.0 (C_{arom}), 133.8 (C_{arom}), 133.4 (C_{arom}), 130.6 (2×C_{arom}), 129.2 (3×C_{arom}-H), 129.0 (C_{arom}-H), 128.7 (3×C_{arom}-H), 128.2 (C_{arom}-H), 128.1 (2×C_{arom}-H), 127.4 (C_{arom}-H), 126.1 (C_{arom}-H), 122.7 (C-3), 121.7 (C-2), 119.8 (C-1), 117.3 (C-10), 114.3 (C-4), 111.0 (C-7), 66.3 (OCH_2), 35.5 (C-9), 28.1 (C-8), 20.6 (CH_3), 19.8 (3×CH_3). **IR** (ATR): 2920 (C-H st), 1699 (C=O st), 1243 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{36}H_{33}NO_2Na]^+$: 534.2409 $[M+Na]^+$; found: 534.2408. **M.p.**: 197-200 ºC (petroleum ether/EtOAc).



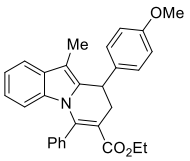
benzyl 6-methyl-9,10-diphenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21k). Following *GP-K*, ***rac*-21k** (17.0 mg, 0.036 mmol, 72%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7l** (14.7 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.00-7.57 (m, 2H, H-1 + H-4), 7.46-7.13 (m, 15H, C_{arom}-H), 7.04 (dd, *J* = 7.5, 2.0 Hz, 2H, C_{arom}-H), 5.20 (d, *J* = 12.8 Hz, 1H, OC**H**$_a$H$_b$), 5.08 (d, *J* = 12.8 Hz, 1H, OCH$_a$**H**$_b$), 4.49 (dd, *J* = 5.1, 2.5 Hz, 1H, H-9), 3.36 (dd, *J* = 15.7, 2.6 Hz, 1H, H-8a), 3.01 (d, *J* = 2.2 Hz, 3H, C-6-CH_3), 2.74 (dd, *J* = 13.4, 5.1 Hz, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.4 (COO), 146.5 (C-6), 141.8 (C_{arom}), 136.6 (C_{arom}), 135.6 (C_{arom}), 135.3 (C_{arom}), 133.6 (C_{arom}), 129.6 (C-10a), 129.5 (2×C_{arom}-H), 128.6 (6×C_{arom}-H), 128.0 (C_{arom}-H), 127.6 (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 126.9 (C_{arom}-H), 126.6 (C_{arom}-H), 123.1 (C-3), 121.9 (C-2), 120.1 (C-1), 116.5 (C-10), 113.8 (C-4), 110.4 (C-7), 66.0 (OCH_2), 36.4 (C-9), 30.5 (C-8), 19.7 (C-6-**C**H$_3$). **IR** (ATR): 2956 (C-H st), 1698 (C=O st), 1248 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{33}H_{27}NO_2Na]^+$: 492.1939 $[M+Na]^+$; found: 492.1944. **M.p.**: 67-70 ºC (petroleum ether/EtOAc).



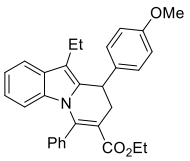
benzyl 9-(4-bromophenyl)-6-methyl-10-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21l). Following *GP-K*, ***rac*-21l** (15.5 mg, 0.031 mmol, 62%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7n** (18.7 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl) sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.78-7.53 (m, 2H, H-1 + H-4), 7.40-6.98 (m, 14H, C_{arom}-H), 6.81 (d, *J* = 8.4 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 5.13 (d, *J* = 12.7 Hz, 1H, OC**H**$_a$CH$_b$), 4.98 (d, *J* = 12.7 Hz, 1H, OCH$_a$C**H**$_b$), 4.33 (dd, *J* = 5.2, 2.6 Hz, 1H, H-9), 3.21 (dd, *J* = 15.7, 2.6 Hz, 1H, H-8a), 2.90 (d, *J* = 2.1 Hz, 3H, CH_3), 2.63 (ddd, *J* = 15.7, 5.1, 2.4 Hz, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3 (COO), 146.4 (C-6), 140.9 (C_{arom}), 136.5 (C_{arom}), 135.2 (C_{arom}), 134.8 (C_{arom}), 133.4 (C_{arom}), 131.7 (2×C_{arom}-H), 129.5 (C-10a), 129.4 (2×C_{arom}-H), 129.3 (2×C_{arom}-H), 128.7 (4×C_{arom}-H), 128.1 (C_{arom}-H), 127.6 (2×C_{arom}-H), 127.0 (C_{arom}-H), 123.3 (C-3), 122.0 (C-2), 120.6 (C-Br), 120.2 (C-1), 116.8 (C-10), 113.8 (C-4), 110.1 (C-7), 66.1 (OCH_2), 36.0 (C-9), 30.4 (C-8), 19.6 (C-6-**C**H_3). **IR** (ATR): 2942 (C-H st), 1698 (C=O st), 1265 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{33}H_{27}BrNO_2]^+$: 548.1225 $[M+H]^+$; found: 548.1219. **M.p.**: 152-155 ºC (petroleum ether/EtOAc).



9-(4-methoxyphenyl)-6,10-diphenyl-8,9-dihydropyrido[1,2-a]indole (21m'). Following *GP-K*, ***rac*-21m'** (15.5 mg, 0.036 mmol, 72%) was isolated by FC (petroleum ether/EtOAc, 99:1) on silica gel as a white solid, from cyclopropane **7m** (17.6 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H, H-1), 7.57-7.28 (m, 10H, C_{arom}-H), 7.21-7.06 (m, 3H, C_{arom}-H), 6.95 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H, H-3), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.42 (d, *J* = 8.4 Hz, 1H, H-4), 5.38 (dd, *J* = 7.2, 3.0 Hz, 1H, H-7), 4.53 (d, *J* = 5.2 Hz, 1H, H-9), 3.78 (s, 3H, OCH_3), 3.04-2.53 (m, 2H, H-8). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.2 (**C**$_{arom}$-OCH_3), 139.1 (C-6), 136.6 (C_{arom}), 135.7 (C_{arom}), 135.3 (C_{arom}), 134.9 (C_{arom}), 129.5 (2×C_{arom}-H), 128.6 (8×C_{arom}-H), 128.2 (C_{arom}), 127.8 (2×C_{arom}-H), 126.4 (C-10a), 121.7 (C-3), 120.6 (C-2), 119.4 (C-1), 115.7 (C-10), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.3 (C-7), 111.5 (C-4), 55.3 (OCH_3), 36.2 (C-9), 30.5 (C-8). **IR** (ATR): 2955 (C-H st), 1650 (arC-C), 1608 (arC-C). cm^{-1}. **IR** (ATR): 2955 (C-H st), 1650 (arC-C), 1608 (arC-C) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{31}H_{26}NO]^+$: 428.2014 $[M+H]^+$; found: 428.2004. **M.p.**: 239-242 ºC (petroleum ether/EtOAc).

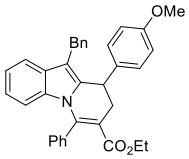


ethyl 9-(4-methoxyphenyl)-10-methyl-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21n). Following *GP-K*, ***rac*-21n** (20.6 mg, 0.047 mmol, 94%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59-7.33 (m, 5H, C_{arom}-H), 7.25-7.20 (m, 1H, C_{arom}-H), 7.18-7.02 (m, 3H, H-2 + C-9-C_{arom}-C_{arom}-H), 6.92-6.63 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 5.70 (d, *J* = 8.5 Hz, 1H, H-4), 4.53 (app t, *J* = 4.7 Hz, 1H, H-9), 4.02-3.77 (m, 5H, OCH_2 + OCH_3), 3.27 (dd, *J* = 15.5, 3.9 Hz, 1H, H-8a), 3.03 (dd, *J* = 15.5, 5.4 Hz, 1H, H-8b), 2.13 (s, 3H, C-10-CH_3), 0.87 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (COO), 158.4 (**C**$_{arom}$-OCH_3), 146.1 (C-6), 136.0 (C_{arom}), 135.5 (C_{arom}), 135.2 (C_{arom}), 133.6 (C_{arom}), 131.3 (C-10a), 129.2 (2×C-9-C_{arom}-**C**$_{arom}$-H), 128.5 (5×C_{arom}-H), 122.3 (C-3), 121.1 (C-2), 118.4 (C-1), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.6 (C-4), 111.1 (C-10), 109.1 (C-7), 60.0 (OCH_2), 55.4 (OCH_3), 36.2 (C-9), 31.0 (C-8), 13.8 ($OCH_2\mathbf{C}H_3$), 8.7 (C-10-**C**H_3). **IR** (ATR): 2980 (C-H st), 1683 (C=O st), 1239 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 438.2 (23), 437.2 (M^+, 74), 365.2 (23), 364.1 (100), 257.1 (19), 256.1 (50), 254.1 (27), 241.1 (21), 204.0 (24), 135.0 (35) 115.0 (52), 108.0 (38), 78.0 (23), 77.0 (48), 21.0 (65). **HRMS** (ESI^+): Calculated for $[C_{29}H_{27}NO_3Na]^+$: 460.1889 $[M+Na]^+$; found: 460.1889. **M.p.**: 121-124 ºC (petroleum ether/EtOAc).

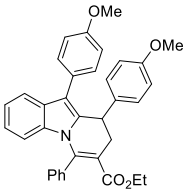


ethyl 10-ethyl-9-(4-methoxyphenyl)-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21o). Following *GP-K*, ***rac*-21o** (20.7 mg, 0.046 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19g** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.59-7.34 (m, 5H, C_{arom}-H), 7.26-7.17 (m, 1H, C_{arom}-H), 7.17-6.99 (m, 3H, H-2 + C-9-C_{arom}-C_{arom}-H), 6.88-6.69 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 5.72 (d, *J* = 8.4 Hz, 1H, H-4), 4.55 (dd, *J* = 5.4, 3.2 Hz, 1H, H-9), 4.02-3.59 (m, 5H, OCH_2 + OCH_3), 3.27 (dd, *J* = 15.4, 3.2 Hz, 1H, H-8a), 3.02 (dd, *J* = 15.4, 5.4 Hz, 1H, H-8b), 2.65 (m, 2H, C-10-CH_2), 1.12 (t, *J* = 7.5 Hz, 3H, C-10-$CH_2C\mathbf{H}_3$), 0.85 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.0 (COO), 158.3 (**C**$_{arom}$-OCH_3), 146.1 (C-6), 136.0 (C-4a), 135.8 (C_{arom}), 134.6 (C_{arom}), 133.9 (C-9a), 130.3 (C-10a), 129.2 (2×C-9-C_{arom}-**C**$_{arom}$-H), 128.4 (5×C_{arom}-H), 122.2 (C-3), 121.1 (C-2), 118.7 (C-1), 117.3 (C-10), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 109.1

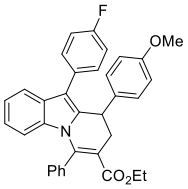
(C-7), 60.0 (OCH_2), 55.4 (OCH_3), 35.8 (C-9), 31.1 (C-8), 17.3 (C-10-**C**H_2), 14.8 (C-10-CH_2**C**H_3), 13.7 (OCH_2**C**H_3). **MS** (EI) m/z (%): 452.2 (30), 451.2 (M^+, 100), 379.1 (31), 378.2 (86), 362.0 (19), 349.1 (24), 330.1 (20), 300.1 (26), 270.1 (31), 256.1 (34), 255.1 (19), 254.1 (43), 241.0 (33), 217.9 (29), 204.0 (36), 121.0 (50), 115.0 (84), 108.0 (87), 92.0 (21), 89.0 (23), 65.0 (29). **IR** (ATR): 2965 (C-H st), 1683 (C=O st), 1246 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{30}H_{29}NO_3Na]^+$: 474.2045 $[M+Na]^+$; found: 474.2053. **M.p.**: 123-126 ºC (petroleum ether/EtOAc).



ethyl 10-benzyl-9-(4-methoxyphenyl)-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21p). Following *GP-K*, ***rac*-21p** (20.8 mg, 0.040 mmol, 81%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19h** (10.4 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57-7.39 (m, 4H, C_{arom}-H), 7.34 (d, *J* = 7.6 Hz, 1H, H-1), 7.23-7.05 (m, 8H, C_{arom}-H), 6.98 (t, *J* = 7.5 Hz, 1H, H-2), 6.83-6.70 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 5.73 (d, *J* = 8.5 Hz, 1H, H-4), 4.57 (dd, *J* = 5.5, 3.3 Hz, 1 H, H-9), 3.99 (s, 1H, C-10-CH_2), 3.93-3.66 (m, 5H, OCH_2 + OCH_3), 3.26 (dd, *J* = 15.5, 3.3 Hz, 1H, H-8a), 3.04 (dd, *J* = 15.5, 5.5 Hz, 1H, H-8b), 0.86 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.9 (COO), 158.4 (**C**$_{arom}$-OCH_3), 145.9 (C-6), 140.1 (C-4a), 136.1 (C_{arom}), 135.9 (C_{arom}), 135.8 (C-9a), 133.5 (C_{arom}), 130.5 (C-10a), 130.2 (C_{arom}-H), 129.3 (C_{arom}-H), 129.0 (C_{arom}-H), 128.5 (5×C_{arom}-H), 128.4 (2×C_{arom}-H), 126.0 (C_{arom}-H), 122.3 (C-3), 121.3 (C-2), 119.2 (C-1), 114.0 (3×C_{arom}-H), 113.7 (C-4), 109.5 (C-7 + C-10), 60.0 (OCH_2), 55.4 (OCH_3), 36.1 (C-9), 31.3 (C-8), 30.1 (C-10-**C**H_2-C_{arom}), 13.7 (OCH_2**C**H_3). **IR** (ATR): 2977 (C-H st), 1683 (C=O st), 1245 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{35}H_{31}NO_3Na]^+$: 536.2202 $[M+Na]^+$; found: 536.2202. **M.p.**: 135-138 ºC (petroleum ether/EtOAc).

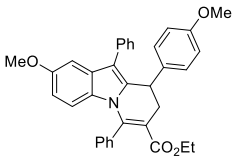


ethyl 9,10-bis(4-methoxyphenyl)-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21q). Following *GP-K*, ***rac*-21q** (22.9 mg, 0.043 mmol, 86%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19k** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H, H-1), 7.56-7.23 (m, 7H, C_{arom}-H), 7.19-7.04 (m, 3H, H-2 + C-9-C_{arom}-C_{arom}-H), 6.93 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.88-6.77 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 5.81 (d, *J* = 8.5 Hz, 1H, H-4), 4.52 (dd, *J* = 5.3, 2.4 Hz, 1H, H-9), 4.06-3.64 (m, 8H, OCH_2 + 2×OCH_3), 3.25 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.97 (dd, *J* = 15.5, 5.2 Hz, 1H, H-8b), 0.84 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (COO), 158.7 (**C**$_{arom}$-OCH_3), 158.3 (**C**$_{arom}$-OCH_3), 145.7 (C-6), 135.9 (C_{arom}), 135.8 (C-4a), 135.0 (C_{arom}), 134.2 (C-9a), 130.5 (3×C_{arom}-H), 129.7 (C_{arom}), 129.4 (C_{arom}-H), 128.5 (5×C_{arom}-H), 125.9 (C-10a), 122.6 (C-3), 121.6 (C-1), 119.5 (C-2), 116.9 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 110.7 (C-7), 60.1 (OCH_2), 55.4 (OCH_3), 55.3 (OCH_3), 35.7 (C-9), 31.5 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2955 (C-H st), 1685 (C=O st), 1263 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{35}H_{32}NO_4]^+$: 530.2331 $[M+H]^+$; found: 530.2325. **M.p.**: 197-200 ºC (petroleum ether/EtOAc).

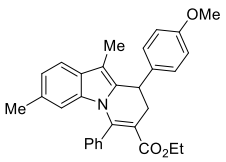


ethyl 10-(4-fluorophenyl)-9-(4-methoxyphenyl)-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21r). Following *GP-K*, ***rac*-21r** (21.4 mg, 0.041 mmol, 82%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19l** (10.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.9 Hz, 1H, H-1), 7.57-7.38 (m, 4H, C_{arom}-H), 7.39-7.20 (m, 3H, C_{arom}-H), 7.19-7.00 (m, 5H, C_{arom}-H), 6.92-6.73 (m, 3H, C_{arom}-H), 5.83 (d, *J* = 8.5 Hz, 1H, H-4), 4.49 (dd, *J* = 5.4, 2.6 Hz, 1H, H-9), 3.95-3.69 (m, 5H, OCH_2 + OCH_3), 3.24 (dd, *J* = 15.5, 2.6 Hz, 1H, H-8a), 2.98 (dd, *J* = 15.5, 5.2 Hz, 1H, H-8b), 0.85 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (COO), 162.0 (d, $^{1}J_{C\text{-}F}$ = 246.2 Hz, C_{arom}-F), 158.4 (**C**$_{arom}$-OCH_3), 145.5 (C-6), 135.9 (C_{arom}), 135.7 (C-4a), 135.4 (C_{arom}), 133.9 (C-9a), 131.2 (d, $^{3}J_{C\text{-}F}$ = 8.0 Hz, 2×C-9-C_{arom}-**C**$_{arom}$-H), 129.6 (C-10a + C_{arom}), 129.4 (2×C_{arom}-H), 128.5 (5×C_{arom}-H), 122.7 (C-3), 121.8 (C-1), 119.3 (C-2), 116.2 (C-10), 115.6 (d, $^{2}J_{C\text{-}F}$ = 21.4 Hz , 2×F-C_{arom}-**C**$_{arom}$-H), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (C-4), 111.0 (C-7), 60.1 (OCH_2), 55.4 (OCH_3),

35.7 (C-9), 31.5 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2980 (C-H st), 1685 (C=O st), 1239 (C-O st as), 1221 (C-F st) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{34}H_{28}NO_3F]^+$: 518.2131 $[M+H]^+$; found: 518.2139. **M.p.**: 175-178 ºC (petroleum ether/EtOAc).

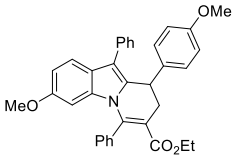


ethyl 2-methoxy-9-(4-methoxyphenyl)-6,10-diphenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21s). Following *GP-K*, ***rac*-21s** (18.8 mg, 0.035 mmol, 71%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19n** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61-7.27 (m, 10H, C_{arom}-H), 7.15-7.05 (m, 3H, H-1 + C-9-C_{arom}-C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.46 (dd, *J* = 9.2, 2.6 Hz, 1H, H-4), 5.67 (d, *J* = 9.2 Hz, 1H, H-3), 4.51 (dd, *J* = 5.3, 2.4 Hz, 1H, H-9), 3.98-3.67 (m, 8H, OCH_2 + (2×OCH_3)), 3.24 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.96 (dd, *J* = 15.5, 5.2 Hz, 1H, H8-b), 0.84 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.8 (COO), 158.3 (**C**$_{arom}$-OCH_3), 155.5 (C-2), 145.7 (C-6), 136.1 (C-4a), 135.8 (C_{arom}), 134.1 (C_{arom}), 133.7 (C_{arom}), 130.8 (C_{arom}), 130.3 (C-10a), 129.4 (4×C_{arom}-H), 128.6 (7×C_{arom}-H), 126.9 (C_{arom}-H), 117.1 (C-10), 114.4 (C-4), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 111.6 (C-3), 110.2 (C-7), 102.1 (C-1), 60.1 (OCH_2), 55.9 (OCH_3), 55.3 (OCH_3), 35.7 (C-9), 31.4 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2951 (C-H st), 1684 (C=O st), 1248 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{35}H_{31}NO_4Na]^+$: 552.2151 $[M+Na]^+$; found: 552.2147. **M.p.**: 157-160 ºC (petroleum ether/EtOAc).

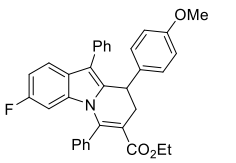


ethyl 9-(4-methoxyphenyl)-3,10-dimethyl-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21t). Following *GP-K*, ***rac*-21t** (21.1 mg, 0.047 mmol, 93%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19c** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56-7.36 (m, 4H, C_{arom}-H), 7.32 (d, *J* = 7.9 Hz, 1H, H-1), 7.25-7.15 (m, 1H, C_{arom}-H), 7.10 (d, *J* = 8.3 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.89 (d, 1H, *J* = 8.0 Hz, H-2), 6.82 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.42 (s, 1H, H-4), 4.50 (app t, *J* = 4.7 Hz, 1H, H-9), 4.10-3.64 (m, 5H, OCH_2 + OCH_3), 3.25 (dd, *J* = 15.4, 3.9 Hz, 1H, H-8a), 3.01 (dd, *J* = 15.5, 5.4 Hz, 1H, H-8b), 2.13-2.0 (m, 6H, C_{arom}-CH_3 + C-10-CH_3), 0.86 (t, *J* = 7.1 Hz, 3H,

$OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1 (COO), 158.4 ($\mathbf{C}_{arom}$-OCH_3), 146.3 (C-6), 136.2 (C_{arom}), 135.9 (C_{arom}), 134.5 (C_{arom}), 133.8 (C_{arom}), 131.8 (C-10a), 130.2 (C_{arom}-H), 129.1 (3×C_{arom}-H), 128.5 (3×C_{arom}-H+ C-3), 122.5 (C-2), 118.0 (C-1), 114.1 (C-4), 114.0 (2×OCH_3-C_{arom}-$\mathbf{C}_{arom}$-H), 111.0 (C-10), 108.6 (C-7), 60.0 (OCH_2), 55.4 (OCH_3), 36.2 (C-9), 31.0 (C-8), 21.9 (C-3-$\mathbf{C}H_3$), 13.8 ($OCH_2\mathbf{C}H_3$), 8.7 (C-10-$\mathbf{C}H_3$). **IR** (ATR): 2980 (C-H st), 1683 (C=O st), 1244 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{30}H_{29}NO_3Na]^+$: 474.2045 $[M+Na]^+$; found: 474.2047. **M.p.**: 111-114 ºC (petroleum ether/EtOAc).

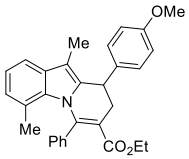


ethyl 3-methoxy-9-(4-methoxyphenyl)-6,10-diphenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21u). Following *GP-K*, ***rac*-21u** (21.0 mg, 0.040 mmol, 79%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19o** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61-7.44 (m, 5H, C_{arom}-H), 7.44-7.28 (m, 6H, C_{arom}-H), 7.12 (d, *J* = 8.6 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.85 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.73 (dd, *J* = 8.7, 2.3 Hz, 1H, H-2), 5.40 (d, *J* = 2.3 Hz, 1H, H-4), 4.52 (dd, *J* = 5.3, 2.5 Hz, 1H, H-9), 4.13-3.63 (m, 5H, OCH_2 + OCH_3), 3.35 (s, 1H, OCH_3), 3.27 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.96 (dd, *J* = 15.5, 5.1 Hz, 1H, H-8b), 0.86 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.7 (COO), 158.3 ($\mathbf{C}_{arom}$-OCH_3), 156.2 (C-3), 145.7 (C-6), 136.7 (C-4a), 136.0 (C_{arom}), 134.3 (C_{arom}), 133.9 (C_{arom}), 133.7 (C_{arom}), 129.3 (5×C_{arom}-H), 128.6 (6×C_{arom}-H), 126.8 (C_{arom}-H), 123.3 (C-10a), 119.9 (C-1), 117.0 (C-10), 114.0 (2×OCH_3-C_{arom}-$\mathbf{C}_{arom}$-H), 111.4 (C-2), 110.8 (C-7), 97.8 (C-4), 60.1 (OCH_2), 55.3 (OCH_3), 55.2 (OCH_3), 35.6 (C-9), 31.5 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2984 (C-H st), 1685 (C=O st), 1246 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{35}H_{31}NO_4Na]^+$: 552.2151 $[M+Na]^+$; found: 552.2148. **M.p.**: 152-155 ºC (petroleum ether/EtOAc).



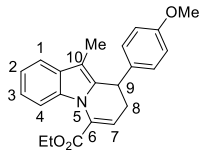
ethyl 3-fluoro-9-(4-methoxyphenyl)-6,10-diphenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21v). Following *GP-K*, ***rac*-21v** (22.6 mg, 0.044 mmol, 87%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19p** (10.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL)

at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67-7.29 (m, 11H, C_{arom}-H), 7.11 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.85 (d, *J* = 8.7 Hz, 3H, H-2 + OCH_3-C_{arom}-C_{arom}-**H**), 5.47 (dd, *J* = 11.4, 2.3 Hz, 1H, H-4), 4.53 (dd, *J* = 5.3, 2.5 Hz, 1H, H-9), 3.94-3.69 (m, 5H, OCH_2 + OCH_3), 3.25 (dd, *J* = 15.5, 2.5 Hz, 1H, H-8a), 2.98 (dd, *J* = 15.6, 5.2 Hz, 1H, H-8b), 0.85 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.6 (COO), 159.5 (d, $^{1}J_{C\text{-}F}$ = 238.2 Hz, C-3), 158.4 (**C**$_{arom}$-OCH_3), 145.2 (C-6), 135.9 (d, $^{3}J_{C\text{-}F}$ = 12.3 Hz, C-4a), 135.6 (d, $^{4}J_{C\text{-}F}$ = 4.0 Hz, C-10a), 135.2(C_{arom}), 134.0 (C_{arom}), 133.3 (C_{arom}), 129.7 (C_{arom}-H), 129.4 (2×C_{arom}-H), 128.5 (8×C_{arom}-H), 127.1 (C_{arom}-H), 125.8 (C-9a), 120.0 (d, $^{3}J_{C\text{-}F}$ = 9.9 Hz, C-1), 117.0 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 111.5 (C-7), 109.9 (d, $^{2}J_{C\text{-}F}$ = 24.4 Hz, C-4), 100.85 (d, $^{2}J_{C\text{-}F}$ = 29.2 Hz, C-2), 60.2 (OCH_2), 55.3 (OCH_3), 35.7 (C-9), 31.5 (C-8), 13.7 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2980 (C-H st), 1688 (C=O st), 1244 (C-O st as), 1143 (C-F st) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{34}H_{28}NO_3FNa]^+$: 540.1951 $[M+Na]^+$; found: 540.1955. **M.p.**: 178-181 ºC (petroleum ether/EtOAc).



ethyl 9-(4-methoxyphenyl)-4,10-dimethyl-6-phenyl-8,9-dihydropyrido[1,2-a]indole-7-carboxylate (21w). Following *GP-K*, ***rac*-21w** (12.1 mg, 0.027 mmol, 54%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19f** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 45 min. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H, C_{arom}-H), 7.26-7.19 (m, 2H, C_{arom}-H), 7.15-7.00 (m, 5H, C_{arom}-H), 6.87-6.67 (m, 3H, H-3 + OCH_3-C_{arom}-C_{arom}-**H**), 4.42 (app t, *J* = 5.2 Hz, 1H, H-9), 3.84 (m, 2H, OCH_2), 3.75 (s, 3H, OCH_3), 3.22-2.79 (m, 2H, H-8), 2.00 (s, 3H, C-10-CH_3), 1.43 (s, 3H, C_{arom}-CH_3), 0.86 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.0 (COO), 158.4 (**C**$_{arom}$-OCH_3), 144.7 (C-6), 139.1 (C_{arom}), 136.4 (C_{arom}), 135.6 (C_{arom}), 133.3 (C_{arom}), 132.6 (C-10a), 129.9 (2×C_{arom}-H), 129.0 (C_{arom}-H), 128.9 (2×C_{arom}-H), 127.6 (2×C_{arom}-H), 125.7 (C-2), 124.5 (C-4), 121.8 (C-3), 115.9 (C-1), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.0 (C-10), 110.9 (C-7), 60.2 (OCH_2), 55.3 (OCH_3), 40.5 (C-9), 34.1 (C-8), 20.6 (C_{arom}-CH_3), 13.8 ($OCH_2\mathbf{C}H_3$), 9.2 (NCH_3). **MS** (EI) m/z (%): 452.1 (27), 451.2 (M^+, 74), 379.1 (22), 378.2 (100), 363.2 (21), 270.0 (44), 254.9 (17), 253.9 (25), 248.0 (17), 218.1 (25), 216.9 (18), 204.1 (23), 135.0 (52), 121.0 (31), 115.9 (18), 115.0 (90), 108.0 (50), 78.0 (24), 77.0 (36). **IR** (ATR): 2926 (C-H st), 1692 (C=O st), 1247 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{30}H_{29}NO_3Na]^+$: 474.2045 $[M+Na]^+$; found: 74.241. **M.p.**: 132-135 ºC (petroleum ether/EtOAc).

4.1.2 Dihydropyridoindoles 22

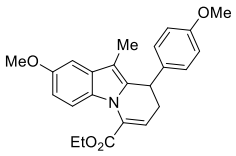


ethyl 9-(4-methoxyphenyl)-10-methyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22a).

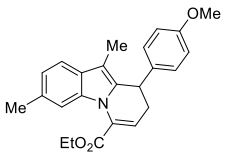
Following *GP-K*, ***rac*-22a** (9.1 mg, 0.025 mmol, 50%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22a** (5.8 mg, 0.016 mmol, 32%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.46 (m, 1H, H-1), 7.26-7.12 (m, 3H, H-2 + H-3 + H-4), 7.05 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.81 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.27 (dd, *J* = 6.6, 3.8 Hz, 1H, H-7), 4.46-4.05 (m, 3H, H-9 + OCH_2), 3.77 (s, 3H, OCH_3), 2.99-2.49 (m, 2H, H-8), 2.15 (s, 3H, C-10-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (COO), 158.4 (**C**$_{arom}$-OCH_3), 134.0 (C-4a + C-9a + C-9-**C**$_{arom}$), 131.3 (C-6), 129.9 (C-10a), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 122.0 (C-3), 120.3 (C-2), 119.9 (C-7), 118.5 (C-1), 114.0 (2× OCH_3-C_{arom}-**C**$_{arom}$-H), 112.0 (C-4), 109.4 (C-10), 61.7 (OCH_2), 55.3 (OCH_3), 35.9 (C-9), 30.5 (C-8), 14.3 ($OCH_2\mathbf{C}H_3$), 8.7 (C-10-**C**H_3). **IR** (ATR): 2987 (C-H st), 1727 (C=O st), 1260 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 362.2 (26), 361.2 (M^+, 100), 289.1 (16), 288.1 (72), 287.1 (23), 286.1 (20), 273.1 (19). **HRMS** (ESI^+): Calculated for $[C_{23}H_{24}NO_3]^+$: 362.1756 $[M+H]^+$; found: 362.1758. **M.p.**: 126-129 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.30 min, τ_{minor} = 6.88 min (84:16).



ethyl 2-methoxy-9-(4-methoxyphenyl)-10-methyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22b). Following *GP-K*, ***rac*-22b** (8.2 mg, 0.021 mmol, 42%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19b** (7.5 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.17-6.92 (m, 4H, C_{arom}-H), 6.91-6.69 (m, 3H, C_{arom}-H), 6.22 (dd, *J* = 6.8, 3.8 Hz, 1H, H-7), 4.55-4.18 (m, 3H, H-9 + OCH_2), 3.88 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.84-2.60 (m, 2H, H-8), 2.10 (s, 3H, C-10-CH_3), 1.36 (t, *J* = 7.2 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (COO), 158.4 ($\mathbf{C}_{arom}$-OCH_3), 154.7 (C-2), 134.7 (C-9-$\mathbf{C}_{arom}$), 134.0 (C-9a), 131.3 (C-6), 130.5 (C-10a), 129.2 (C-4a), 128.6 (2×C-9-C_{arom}-$\mathbf{C}_{arom}$-H), 119.3 (C-7), 114.0 (2×OCH_3-C_{arom}-$\mathbf{C}_{arom}$-H), 112.7 (C-4), 111.3 (C-3), 109.1 (C-10), 101.0 (C-1), 61.7 (OCH_2), 55.9 (OCH_3), 55.3 (OCH_3), 35.9 (C-9), 30.6 (C-8), 14.4 ($OCH_2\mathbf{C}H_3$), 8.7 (C-10-$\mathbf{C}H_3$). **IR** (ATR): 2926 (C-H st), 1728 (C=O st), 1258 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 392.2 (27), 391.2 (M^+, 100), 318.1 (22). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_4]^+$: 392.1862 $[M+H]^+$; found: 392.1857. **M.p.**: 98-101 ºC (petroleum ether/EtOAc).

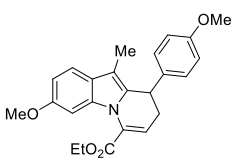


ethyl 9-(4-methoxyphenyl)-3,10-dimethyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22c).

Following *GP-K*, ***rac*-22c** (9.7 mg, 0.026 mmol, 52%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19c** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22c** (8.0 mg, 0.021 mmol, 43%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19c** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.9 Hz, 1H, H-4), 7.10-6.89 (m, 4H, C-9-C_{arom}-C_{arom}-H + H-1 + H-2), 6.79 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.22 (dd, *J* = 6.6, 3.9 Hz, 1H, H-7), 4.49-4.39 (m, 3H, H-9 + OCH_2), 3.76 (s, 3H, OCH_3), 2.85-2.59 (m, 2H, H-8), 2.47 (s, 3H, C-3-CH_3), 2.11 (s, 3H, C-10-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.7 (COO), 158.4 (**C**$_{arom}$-OCH_3), 134.4 (C-4a), 134.2 (C-9-**C**$_{arom}$), 133.3 (C-9a), 131.7 (C-3), 131.4 (C-6), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 127.7 (C-10a), 121.9 (C-2), 119.6 (C-9), 118.2 (C-1), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.1 (C-4), 109.2 (C-10), 61.6 (OCH_2), 55.3 (OCH_3), 35.9 (C-9), 30.5 (C-8), 22.1 (C-3-**C**H_3), 14.3 (OCH_2**C**H_3), 8.7 (C-10-**C**H_3). **MS** (EI) m/z (%): 376.2 (26), 375.2 (M^+, 100), 302.2 (56), 301.1 (16), 287.1 (19). **IR** (ATR): 2925 (C-H st), 1725 (C=O st), 1245 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1911. **M.p.**: 76-79 ºC (petroleum ether/EtOAc).The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.97 min, τ_{minor} = 6.80 min (79:21).



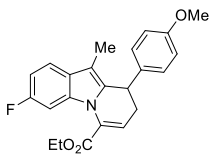
ethyl 3-methoxy-9-(4-methoxyphenyl)-10-methyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22d).

Following *GP-K*, ***rac*-22d** (11.9 mg, 0.030 mmol, 61%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19d** (8.1 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22d** (7.8 mg, 0.02 mmol, 40%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a yellow solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19d** (8.1 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 1H, H-1), 7.05 (d, *J* = 8.6 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.92-6.76 (m, 3H, OCH_3-C_{arom}-C_{arom}-**H** + H-2), 6.73 (d, *J* = 2.2 Hz, 1H, H-4), 6.25 (dd, *J* = 6.7, 3.9 Hz, 1H, H-7), 4.63-4.28 (m, 3H, H-9 + OCH_2), 3.86 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 2.87-2.60 (m, 2H, H-8), 2.11 (s, 3H, C-10-CH_3), 1.38 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (COO), 158.3 (**C**$_{arom}$-OCH_3), 156.3 (**C**$_{arom}$-OCH_3), 134.8 (C-4a),

134.2 (C-9-**C**$_{arom}$), 132.9 (C-9a), 131.3 (C-6), 128.5 (2×C-9-C$_{arom}$-**C**$_{arom}$-H), 124.3 (C-10a), 120.0 (C-7), 118.8 (C-1), 113.9 (2×OCH$_3$-C$_{arom}$-**C**$_{arom}$-H), 109.2 (C-2 + C-10), 97.0 (C-4), 61.7 (OCH$_2$), 55.9 (OCH$_3$), 55.3 (OCH$_3$), 35.9 (C-9), 30.6 (C-8), 14.4 (OCH$_2$**C**H$_3$), 8.7 (C-10-**C**H$_3$). **IR** (ATR): 2936 (C-H st), 1724 (C=O st), 1247 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 392.2 (26), 391.2 (M$^+$, 100), 318.1 (35), 302.1 (13). **HRMS** (ESI$^+$): Calculated for [$C_{24}H_{26}NO_4$]$^+$: 392.1862 [M+H]$^+$; found: 392.1855. **M.p.**: 100-104 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 5.84 min, τ_{minor} = 12.99 min (79:21).



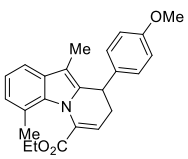
ethyl 3-fluoro-9-(4-methoxyphenyl)-10-methyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22e).

Following *GP-K*, ***rac*-22e** (11.3 mg, 0.030 mmol, 60%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19e** (7.5 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22e** (8.0 mg, 0.021 mmol, 42%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19e** (7.5 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.32 (m, 1H, H-1), 7.03 (d, *J* = 7.9 Hz, 2H, C-9-C$_{arom}$-C$_{arom}$-H), 6.97-6.86 (m, 2H, H-2 + H-4), 6.80 (d, *J* = 8.0 Hz, 2H, OCH$_3$-C$_{arom}$-C$_{arom}$-**H**), 6.41-6.21 (m, 1H, H-7), 4.63-4.07 (m, 3H, H-9 + OCH$_2$), 3.77 (s, 3H, OCH$_3$), 2.91-2.54 (m, 2H, H-8), 2.11 (s, 3H, C-10-CH$_3$), 1.38 (t, *J* = 7.0 Hz, 3H, OCH$_2$C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.1 (COO), 159.8 (d, $^1J_{C\text{-}F}$ = 237.1 Hz, C-3), 158.3 (**C**$_{arom}$-OCH$_3$), 134.3 (d, $^4J_{C\text{-}F}$ = 3.6 Hz, C-4a), 134.1 (d, $^3J_{C\text{-}F}$ = 12.3 Hz, C-4a), 133.8 (C-9-**C**$_{arom}$), 131.0 (C-6), 128.5 (2×C-9-C$_{arom}$-**C**$_{arom}$-H), 126.4 (C-10a), 120.9 (C-7), 118.9 (d, $^3J_{C\text{-}F}$ = 10.0 Hz, C-1), 114.0 (2×OCH$_3$-C$_{arom}$-**C**$_{arom}$-H), 109.3 (C-10), 108.6 (d, $^2J_{C\text{-}F}$ = 24.3 Hz, C-4), 99.2 (d, $^2J_{C\text{-}F}$ = 27.7 Hz, C-2), 61.8 (OCH$_2$), 55.3 (OCH$_3$), 35.9 (C-9), 30.5 (C-8), 14.3 (OCH$_2$**C**H$_3$), 8.7 (C-10-**C**H$_3$). **IR** (ATR): 2933 (C-H st), 1722 (C=O st), 1247 (C-O st as), 1147 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 380.2 (26), 379.2 (M$^+$, 100), 307.2

(17), 306.2 (79), 305.2 (29), 304.2 (22), 291.1 (22), 198.1 (22). **HRMS** (ESI^+): Calculated for $[C_{23}H_{23}NO_3F]^+$: 380.1662 $[M+H]^+$; found: 380.1668. **M.p.**: 123-126 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.87 min, τ_{minor} = 6.51 min (71:29).

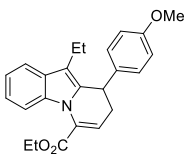


ethyl 9-(4-methoxyphenyl)-4,10-dimethyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22f).

Following *GP-K*, ***rac*-22f** (9.7 mg, 0.026 mmol, 54%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19f** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22f** (6.4 mg, 0.017 mmol, 34%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19f** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.7 Hz, 1H, H-1), 7. 07 (app t, *J* = 7.5 Hz, 1H, H-2), 7.03-6.93 (m, 3H, C-9-C_{arom}-C_{arom}-H + H-3), 6.79 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.32 (dd, *J* = 6.9, 4.8 Hz, 1H, H-7), 4.46-4.07 (m, 3H, H-9 + OCH_2), 3.77 (s, 3H, OCH_3), 2.84-2.61 (m, 2H, H-8), 2.43 (s, 3H, C-4-**C**H_3), 2.04 (s, 3H, C-10-CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.6 (COO), 158.4 (**C**$_{arom}$-OCH_3), 135.9 (C-4a), 134.5 (C-9-**C**$_{arom}$), 133.6 (C-9a), 133.0 (C-6), 130.5 (C-10a), 128.8 (2×C-9-C_{arom}-**C**$_{arom}$-H), 125.3 (C-2), 121.9 (C-4), 121.7 (C-3), 120.6 (C-7), 116.1 (C-1), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 109.2 (C-10), 61.5 (OCH_2), 55.3 (OCH_3), 37.9 (C-9), 31.1 (C-8), 19.4 (C-4-**C**H_3), 14.2 (OCH_2**C**H_3), 9.0 (C-10-**C**H_3). **IR** (ATR): 2958 (C-H st), 1725 (C=O st), 1259 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 376.2 (27), 375.2 (M^+, 100), 302.1 (38), 287.1 (16). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1905. **M.p.**: 138-141 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.27 min, τ_{minor} = 5.99 min (50:50).

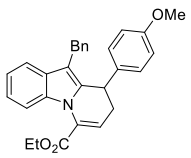


ethyl 10-ethyl-9-(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22g).

Following *GP-K*, ***rac*-22g** (8.6 mg, 0.023 mmol, 46%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19g** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22g** (6.6 mg, 0.018 mmol, 35%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19g** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.53 (m, 1H, H-1), 7.22-7.10 (m, 3H, H-2 + H-3 + H-4), 7.02 (d, *J* = 8.6 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.23 (dd, *J* = 7.0, 3.6 Hz, 1H, H-7), 4.58-4.28 (m, 3H, H-9 + OCH_2), 3.76 (s, 3H, OCH_3), 2.91-2.50 (m, 4H, C-10-CH_2 + H-8), 1.36 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$), 1.09 (t, *J* = 7.5 Hz, 3H, C-10-$CH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (COO), 158.3 (**C**$_{arom}$-OCH_3), 134.3 (C-4a + C-9-**C**$_{arom}$), 133.5 (C-9a), 131.4 (C-6), 128.9 (C-10a), 128.5 (2×C-9-C_{arom}-**C**$_{arom}$-H), 121.9 (C-3), 120.3 (C-2), 119.9 (C-7), 118.7 (C-1), 115.9 (C-10), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.1 (C-4), 61.7 (OCH_2), 55.3 (OCH_3), 35.6 (C-9), 30.6 (C-8), 17.5 (C-10-**C**H_2), 15.3 (C-10-CH_2**C**H_3), 14.4 (OCH_2**C**H_3). **IR** (ATR): 2933 (C-H st), 1724 (C=O st), 1246 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 376.2 (27), 375.2 (M^+, 100), 360.2 (25), 302.1 (40), 286.1 (26), 273.1 (18), 239.1 (16). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1902. **M.p.**: 50-53 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.41 min, τ_{minor} = 5.89 min (69:31).

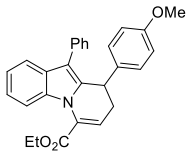


ethyl 10-benzyl-9-(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22h).

Following *GP-K*, ***rac*-22h** (10.4 mg, 0.024 mmol, 47%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19h** (10.4 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22h** (7.0 mg, 0.016 mmol, 32%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19h** (10.4 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.5 Hz, 1H, H-1), 7.22-7.02 (m, 8H, C_{arom}-H), 6.99 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.75 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.27 (dd, *J* = 6.6, 3.8 Hz, 1H, H-7), 4.62-4.26 (m, 3H, H-9 + OCH_2), 4.0 (s, 2H, C-10-CH_2), 3.76 (s, 3H, OCH_3), 2.86-2.58 (m, 2H, H-8), 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.5 (COO), 158.4 (**C**$_{arom}$-OCH_3), 140.5 (C-10-CH_2-**C**$_{arom}$), 134.9 (C-4a), 134.4 (C-9-**C**$_{arom}$), 133.8 (C-9a), 131.4 (C-6), 129.2 (C-10a), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 128.5 (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 125.9 (C_{arom}-H), 122.1 (C-3), 120.5 (C-2), 120.2 (C-7), 119.2 (C-1), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.4 (C-4), 112.0 (C-10), 61.7 (OCH_2), 55.4 (OCH_3), 35.7 (C-9), 30.6 (C-8), 30.3 (C-10-**C**H_2), 14.4 (OCH_2**C**H_3). **IR** (ATR): 2903 (C-H st), 1724 (C=O st), 1247 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{29}H_{28}NO_3]^+$: 438.2069 $[M+H]^+$; found: 438.2065. **M.p.**: 54-57 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.57 min, τ_{minor} = 7.80 min (58:42).

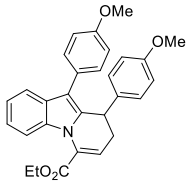


ethyl 9-(4-methoxyphenyl)-10-phenyl-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22i).

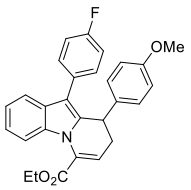
Following *GP-K*, ***rac*-22i** (13.1 mg, 0.031 mmol, 62%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19i** (7.9 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **22i** (8.3 mg, 0.020 mmol, 39%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19i** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 1H, H-1), 7.53-7.20 (m, 8H, C_{arom}-H), 7.14 (d, *J* = 8.1 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.89 (d, *J* = 8.3 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.41 (dd, *J* = 7.0, 3.6 Hz, 1H, H-7), 4.76-4.29 (m, 3H, H-9 + OCH_2), 3.83 (s, 3H, OCH_3), 3.12-2.57 (m, 2H, H-8), 1.45 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.2 (COO), 158.3 (**C**$_{arom}$-OCH_3), 134.5 (C-4a + C-9-**C**$_{arom}$ + C-10-**C**$_{arom}$), 134.1 (C-9a), 131.2 (C-6), 129.4 (2×C_{arom}-H), 128.5 (4×C_{arom}-H), 127.9 (C-10a), 126.5 (C_{arom}-H), 122.4 (C-3), 122.2 (C-2), 121.1 (C-7), 119.5 (C-1), 115.9 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.1 (C-4), 61.7 (OCH_2), 55.2 (OCH_3), 35.6 (C-9), 30.9 (C-8), 14.3 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2981 (C-H st), 1724 (C=O st), 1246 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 424.2 (30), 423.2 (M^+, 100), 351.2 (17), 350.2 (64), 349.2 (24), 348.2 (22). **HRMS** (ESI^+): Calculated for $[C_{28}H_{26}NO_3]^+$: 424.1913 $[M+H]^+$; found: 424.1894. **M.p.**: 80-83 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.11 min, τ_{minor} = 7.60 min (76:24).

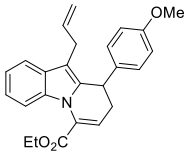


ethyl 9,10-bis(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22j). Following *GP-K*, ***rac*-22j** (18.0 mg, 0.040 mmol, 79%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19j** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 6.9 Hz, 1H, H-1), 7.39-7.17 (m, 5H, C_{arom}-H), 7.07 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.92 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.83 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.33 (dd, *J* = 7.0, 3.4 Hz, 1H, H-7), 4.86-4.28 (m, 3H, H-9 + OCH_2), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.89-2.47 (m, 2H, H-8), 1.39 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (COO), 158.4 (**C**$_{arom}$-OCH_3), 158.3 (**C**$_{arom}$-OCH_3), 134.6 (C-4a), 134.5 (C-9-**C**$_{arom}$), 134.0 (C-9a), 131.3 (C-6), 129.5 (2×C-10-C_{arom}-**C**$_{arom}$-H), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 128.2 (C-10-**C**$_{arom}$), 126.5 (C-10a), 122.4 (C-3), 122.0 (C-2), 121.1 (C-7), 119.5 (C-1), 115.6 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.1 (C-4), 61.8 (OCH_2), 55.4 (OCH_3), 55.3 (OCH_3), 35.7 (C-9), 31.0 (C-8), 14.4 ($OCH_2\mathbf{C}H_3$). **IR** (ATR): 2959 (C-H st), 1724 (C=O st), 1245 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 454.2 (27), 453.2 (M^+, 100), 379.2 (17), 380.2 (69). **HRMS** (ESI^+): Calculated for $[C_{29}H_{28}NO_4]^+$: 454.2018 $[M+H]^+$; found: 454.2016. **M.p.**: 84-87 ºC (petroleum ether/EtOAc).



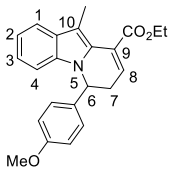
ethyl 10-(4-fluorophenyl)-9-(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22k). Following *GP-K*, ***rac*-22k** (14.6 mg, 0.033 mmol, 73%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19k** (10.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.8 Hz, 1H, H-1), 7.38-7.18 (m, 5H, C_{arom}-H), 7.17-6.97 (m, 4H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.35 (dd, *J* = 7.0, 3.4 Hz, 1H, H-7), 4.73-4.23 (m, 3H, H-9 + OCH_2), 3.79 (s, 3H, OCH_3), 2.93-2.56 (m, 2H, H-8), 1.39 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (COO), 161.8 (d, $^{1}J_{C\text{-}F}$ = 245.5 Hz, C_{arom}-F), 158.4 (**C**$_{arom}$-OCH_3), 134.5 (C-4a), 134.4 (C-9-**C**$_{arom}$), 134.3 (C-9a), 131.3 (C-6), 130.9 (d, $^{3}J_{C\text{-}F}$ = 7.9 Hz, 2×C-10-C_{arom}-**C**$_{arom}$-H), 130.1 (d, $^{4}J_{C\text{-}F}$ = 3.3 Hz, C-10-**C**$_{arom}$), 128.6 (2×C-9-C_{arom}-**C**$_{arom}$-H), 127.9 (C-10a), 122.5 (C-3), 122.1 (C-2), 121.3 (C-7), 119.3 (C-1), 115.5 (d, $^{2}J_{C\text{-}F}$ = 21.3 Hz, 2×F-C_{arom}-**C**$_{arom}$-H), 115.1 (C-10), 114.2 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.2 (C-4), 61.8 (OCH_2), 55.3 (OCH_3), 35.7 (C-9), 30.9 (C-8), 14.4 ($OCH_2\mathbf{C}H_3$).

IR (ATR): 2935 (C-H st), 1724 (C=O st), 1243 (C-O st as), 1225 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 442.2 (30), 441.2 (M^+, 100), 369.1 (18), 368.1 (73), 367.2 (35), 366.1 (33), 324.1 (22), 322.1 (25), 261.0 (34), 260.0 (22), 259.0 (34). **HRMS** (ESI^+): Calculated for $[C_{28}H_{25}NO_3F]^+$: 442.1818 $[M+H]^+$; found: 442.1814. **M.p.**: 90-93 ºC (petroleum ether/EtOAc).



ethyl 10-allyl-9-(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole-6-carboxylate (22l). Following *GP-K*, ***rac*-22l** (7.9 mg, 0.020 mmol, 36%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19l** (7.9 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.56 (d, *J* = 6.7 Hz, 1H, H-1), 7.22-7.11 (m, 3H, H-2 + H-3 + H-4), 7.02 (d, *J* = 8.7 Hz, 2H, C-9-C_{arom}-C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.26 (dd, *J* = 6.9, 3.7 Hz, 1H, H-7), 5.82 (ddt, *J* = 16.4, 10.0, 6.2 Hz, 1H, C**H**=CH_2), 5.01 (dd, *J* = 17.0, 1.8 Hz, 1H, CH=C**H**$_a$H$_b$), 4.93 (dd, *J* = 10.0, 1.7 Hz, 1H, CH=CH$_a$**H**$_b$), 4.51 (dd, *J* = 6.0, 2.9 Hz, 1H, H-9), 4.47-4.32 (m, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 3.38 (d, *J* = 6.2 Hz, 1H, C-10-CH_2), 2.84-2.60 (m, 2H, H-8), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.4 (COO), 158.4 (**C**$_{arom}$-OCH_3), 136.5 (**C**H=CH_2), 134.5 (C-4a), 134.3 (C-9-**C**$_{arom}$), 133.9 (C-9a), 131.4 (C-6), 129.1 (C-10a), 128.5 (2×C-9-C_{arom}-**C**$_{arom}$-H), 122.0 (C-3), 120.4 (C-2), 120.1 (C-7), 118.9 (C1), 115.2 (CH=**C**H_2), 113.9 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.1 (C-4), 111.3 (C-10), 61.7 (OCH_2), 55.3 (OCH_3), 35.6 (C-9), 30.5 (C-8), 28.7 (C-10-**C**H_2), 14.3 (OCH_2**C**H_3). **IR** (ATR): 2930 (C-H st), 1724 (C=O st), 1246 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 388.1 (27), 387.2 (M^+, 93), 314.1 (38), 312.1 (22), 298.0 (20), 273.1 (30), 272.1 (21), 254.0 (25), 242.1 (24), 241.0 (26), 228.0 (20), 206.1 (26), 205.1 (20), 204.0 (55), 180.0 (34), 167.1 (21), 127.9 (22), 127.0 (23), 121.0 (41), 115.1 (25), 108.0 (100), 78.1 (38), 77.0 (36), 65.0 (25). **HRMS** (ESI^+): Calculated for $[C_{25}H_{25}NO_3Na]^+$: 410.1732 $[M+Na]^+$; found: 410.1734. **M.p.**: 79-82 ºC (petroleum ether/EtOAc).

4.1.3 Dihydropyridoindoles 23

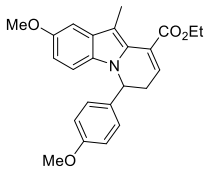


ethyl 6-(4-methoxyphenyl)-10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23a).

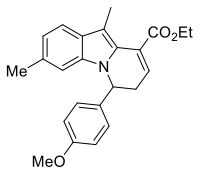
Following *GP-K*, ***rac*-23a** (1.6 mg, 0.004 mmol, 9%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23a** (8.1 mg, 0.022 mmol, 45%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.52 (m, 1H, H-1), 7.18-6.98 (m, 3H, C_{arom}-H), 6.84 (d, *J* = 8.8 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.76 (d, *J* = 8.8 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.57 (dd, *J* = 7.1, 3.0 Hz, 1H, H-8), 5.63 (d, *J* = 6.9 Hz, 1H, H-6), 4.45-4.25 (m, 2H, O**C**$\mathbf{H}_2$$CH_3$), 3.73 (s, 3H, OCH_3), 3.13 (ddd, *J* = 17.1, 7.2, 3.0 Hz, 1H, H-7a), 2.82 (ddd, *J* = 17.1, 7.1, 1.8 Hz, 1H, H-7b), 2.40 (s, 3H, C-10-CH_3), 1.38 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6 (COO), 158.9 (**C**$_{arom}$-OCH_3), 135.6 (C-4a), 133.2 (C_{arom}), 129.4 (C-8), 129.3 (C_{arom}), 128.6 (C_{arom}), 127.4 (C_{arom}), 126.9 (2× C-6-C_{arom}-**C**$_{arom}$-H), 123.1 (C_{arom}-H), 119.5 (2xC_{arom}-H), 114.1 (2x OCH_3-C_{arom}-**C**$_{arom}$-H), 109.9 (C-10), 109.1 (C_{arom}-H), 61.3 (OCH_2), 55.3 (OCH_3), 52.5 (C-6), 33.1 (C-7), 14.4 (OCH_2**C**H_3), 10.5 (C-10-**C**H_3). **IR** (ATR): 2937 (C-H st), 1721 (C=O st), 1250 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 362.2 (26), 361.2 (M^+, 100), 288.1 (39), 287.1 (15), 286.1 (15), 273.1 (21), 121.0 (15). **HRMS** (ESI^+): Calculated for $[C_{23}H_{24}NO_3]^+$: 362.1756 $[M+H]^+$; found: 362.1751. **M.p.**: 64-67 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 7.41 min, τ_{minor} = 18.95 min (71:29).



ethyl 2-methoxy-6-(4-methoxyphenyl)-10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23b). Following *GP-K*, ***rac*-23b** (1.6 mg, 0.004 mmol, 8%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19b** (8.1 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.06-6.95 (m, 1H, C_{arom}-H), 6.95 (d, *J* = 8.9, 1H, C_{arom}-H), 6.86-6.70 (m, 5H, C_{arom}-H), 6.54 (dd, *J* = 7.0, 3.1 Hz, 1H, H-8), 5.56 (d, *J* = 7.1 Hz, 1H, H-6), 4.42-4.18 (m, 2H, OC**H**$_2$CH$_3$), 3.36 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.12 (dd, *J* = 16.8, 6.9 Hz, 1H, H-7a), 2.80 (dd, *J* = 16.7, 7.4 Hz, 1H, H-7b), 2.36 (s, 3H, C-10-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6 (COO), 158.9 (**C**$_{arom}$-OCH_3), 154.1 (C-2-OCH_3), 133.3 (C_{arom}), 131.0 (C_{arom}), 129.5 (C_{arom}), 129.0 (C-8), 128.7 (C_{arom}), 128.0 (C_{arom}), 126.9 (2× C-6-C_{arom}-**C**$_{arom}$-H), 114.0 (2× OCH_3-C_{arom}-**C**$_{arom}$-H), 113.4 (C_{arom}-H), 109.9 (C_{arom}-H), 109.4 (C-10), 101.1 (C_{arom}-H), 61.3 (OCH_2), 56.1 (OCH_3), 55.3 (OCH_3), 52.7 (C-6), 33.1 (C-7), 14.4 (OCH_2**C**H_3), 10.6 (C-10-**C**H_3). **IR** (ATR): 2918 (C-H st), 1724 (C=O st), 1249 (C-O st as) cm^{-1}. **HRMS** (ESI$^+$): Calculated for $[C_{24}H_{26}NO_4]^+$: 392.1862 $[M+H]^+$; found: 392.1864. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.94 min, τ_{minor} = 23.70 min (67:33).

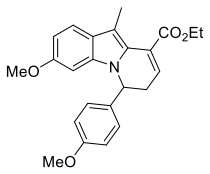


ethyl 6-(4-methoxyphenyl)-3,10-dimethyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23c).

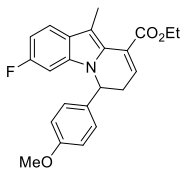
Following *GP-K*, ***rac*-23c** (1.6 mg, 0.004 mmol, 8%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19c** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23c** (3.7 mg, 0.010 mmol, 20%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19c** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.9 Hz, 1H, H-1), 7.02-6.81 (m, 4H, C_{arom}-H), 6.76 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.52 (dd, *J* = 7.2, 2.9 Hz, 1H, H-8), 5.70-5.52 (m, 1H, H-6), 4.50-4.12 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.73 (s, 3H, OCH_3), 3.11 (ddd, *J* = 17.0, 7.2, 3.0 Hz, 1H, H-7a), 2.80 (ddd, *J* = 17.0, 7.2, 1.6 Hz, 1H, H-7b), 2.39 (s, 3H, C_{arom}-CH_3), 2.37 (s, 3H, C_{arom}-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.6 (COO), 158.9 (**C**$_{arom}$-OCH_3), 136.1 (C-4a), 133.4 (C_{arom}), 133.1 (C_{arom}), 128.7 (C-8 + C_{arom}), 127.5 (C_{arom}), 127.3 (C_{arom}), 126.9 (2× C-6-C_{arom}-**C**$_{arom}$-H), 121.3 (C_{arom}-H), 119.2 (C_{arom}-H), 114.1 (2x OCH_3-C_{arom}-**C**$_{arom}$-H), 109.9 (C-10), 108.9 (C_{arom}-H), 61.3 (OCH_2), 55.3 (OCH_3), 52.3 (C-6), 33.1 (C-7), 22.1 (C-3-**C**H_3), 14.4 ($OCH_2\mathbf{C}H_3$), 10.5 (C-10-**C**H_3). **IR** (ATR): 2925 (C-H st), 1721 (C=O st), 1250 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 375.2 (M^+, 36), 281.0 (17), 208.0 (23), 207.0 (100), 96.0 (15). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1908. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.37 min, τ_{minor} = 11.62 min (74:26).



ethyl 3-methoxy-6-(4-methoxyphenyl)-10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23d). Following *GP-L*, **23d** (3.1 mg, 0.008 mmol, 16%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19d** (8.1 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6, 1H, H-1), 6.86 (d, *J* = 8.6, 2H, C-6-C_{arom}-C_{arom}-H), 6.80-6.69 (m, 3H, OCH_3-C_{arom}-C_{arom}-**H** + H-2), 6.52-6.46 (m, 2H, H-4 + H-8), 5.54 (d, *J* = 6.6 Hz, 1H, H-6), 4.40-4.24 (m, 2H, $OC\mathbf{H}_2CH_3$), 3.76 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.11 (ddd, *J* = 16.9, 7.0, 3.1 Hz, 1H, H-7a), 2.80 (ddd, *J* = 17.0, 7.1, 1.8 Hz, 1H, H-7b), 2.36 (s, 3H, C-10-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.7 (COO), 158.9 (**C**$_{arom}$-OCH_3), 157.4 (**C**$_{arom}$-OCH_3), 136.5 (C-4a), 133.2 (C_{arom}), 128.6 (C_{arom}), 128.0 (C-8), 127.0 (2× C-6-C_{arom}-**C**$_{arom}$-H), 126.6 (C_{arom}), 123.9 (C_{arom}), 120.2 (C_{arom}-H), 114.1 (2× OCH_3-C_{arom}-**C**$_{arom}$-H), 110.0 (C-10), 109.2 (C_{arom}-H), 92.8 (C_{arom}-H), 61.2 (OCH_2), 55.7 (OCH_3), 55.7 (OCH_3), 52.5 (C-6), 33.1 (C-7), 14.3 ($OCH_2\mathbf{C}H_3$), 10.5 (C-10-**C**H_3). **IR** (ATR): 2934 (C-H st), 1721 (C=O st), 1249 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 392.2 (27), 391.2 (M^+, 100), 318.1 (23), 303.1 (13). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_4]^+$: 392.1862 $[M+H]^+$; found: 392.1866. **M.p.**: 65-68 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.97 min, τ_{minor} = 16.62 min (85:15).

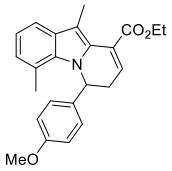


ethyl 3-fluoro-6-(4-methoxyphenyl)-10-methyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23e).

Following *GP-K*, ***rac*-23e** (1.0 mg, 0.003 mmol, 5%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19e** (7.5 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23e** (3.4 mg, 0.009 mmol, 18%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19e** (7.5 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 8.6, 5.3 Hz, 1H, H-1), 6.90-6.80 (m, 3H, C_{arom}-H), 6.80-6.67 (m, 3H, C_{arom}-H), 6.56 (dd, *J* = 7.1, 3.0 Hz, 1H, H-8), 5.51 (d, *J* = 7.1 Hz, 1H, H-6), 4.42-4.22 (m, 2H, OC**H**$_2$CH$_3$), 3.74 (s, 3H, OCH_3), 3.13 (ddd, *J* = 17.1, 7.1, 3.1 Hz, 1H, H-7a), 2.81 (ddd, *J* = 17.2, 7.1, 1.9 Hz, 1H, H-7b), 2.36 (s, 3H, C-10-CH_3), 1.37 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.4 (COO), 160.7 (d, $^{1}J_{C\text{-}F}$ = 239.2 Hz, C-3), 159.1 (**C**$_{arom}$-OCH_3), 135.8 (d, $^{3}J_{C\text{-}F}$ = 12.4 Hz, C-4a), 132.8 (C_{arom}), 129.2 (C-8), 128.5 (C_{arom}), 127.9 (d, $^{4}J_{C\text{-}F}$ = 4.2 Hz, C-10a), 126.9 (2× C-6-C_{arom}-**C**$_{arom}$-H), 126.0 (C_{arom}), 120.4 (d, $^{3}J_{C\text{-}F}$ = 10.3 Hz, C-1), 114.2 (2x OCH_3-C_{arom}-**C**$_{arom}$-H), 110.0 (C-10), 108.2 (d, $^{2}J_{C\text{-}F}$ = 24.7 Hz, C_{arom}-H), 95.6 (d, $^{2}J_{C\text{-}F}$ = 26.5 Hz, C_{arom}-H), 61.4 (OCH_2), 55.4 (OCH_3), 52.8 (C-6), 33.1 (C-7), 14.4 (OCH_2**C**H_3), 10.5 (C-10-**C**H_3). **IR** (ATR): 2930 (C-H st), 1728 (C=O st), 1242 (C-O st as), 1179 (C-F st) cm^{-1}. **MS** (EI) m/z (%): 380.2 (26), 379.2 (M^+, 100), 306.2 (29). **HRMS** (ESI^+): Calculated for $[C_{23}H_{23}NO_3F]^+$: 380.1662 $[M+H]^+$; found: 380.1653. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.56 min, τ_{minor} = 12.68 min (78:22).

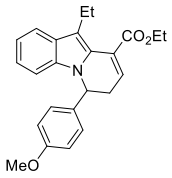


ethyl 6-(4-methoxyphenyl)-4,10-dimethyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23f).

Following *GP-K*, ***rac*-23f** (0.7 mg, 0.002 mmol, 4%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19f** (7.5 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23f** (1.5 mg, 0.004 mmol, 8%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19f** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1H, H-1), 6.97 (app t, *J* = 7.4 Hz, 1H, H-2), 6.86 (d, *J* = 7.4 Hz, 1H, H-3), 6.82-6.69 (m, 4H, C-6-C_{arom}-C_{arom}-H + OCH_3-C_{arom}-C_{arom}-**H**), 6.48 (dd, *J* = 7.3, 2.9 Hz, 1H, H-8), 6.16 (d, *J* = 6.8 Hz, 1H, H-6), 4.41-4.23 (m, 2H, O**C**$\mathbf{H}_2$$CH_3$), 3.73 (s, 3H, OCH_3), 3.14 (ddd, *J* = 16.7, 6.8, 2.6 Hz, 1H, H-7a), 2.81 (dd, *J* = 16.8, 7.3 Hz, 1H, H-7b), 2.49 (s, 3H, C_{arom}-CH_3), 2.34 (s, 3H, C-10-CH_3), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8 (COO), 158.8 (**C**$_{arom}$-OCH_3), 134.6 (C_{arom}), 134.4 (C_{arom}), 129.7 (C_{arom}), 129.0 (C_{arom}), 128.8 (C-8), 127.9 (C_{arom}), 126.7 (2×C-6-C_{arom}-**C**$_{arom}$-H), 126.1 (C_{arom}-H), 120.4 (C_{arom}), 119.4 (C_{arom}-H), 117.4 (C_{arom}-H), 114.1 (2xOCH_3-C_{arom}-**C**$_{arom}$-H), 109.9 (C-10), 61.3 (OCH_2), 55.3 (OCH_3), 54.2 (C-6), 33.4 (C-7), 20.0 (C-4-**C**H_3), 14.4 (OCH_2**C**H_3), 10.5 (C-10-**C**H_3). **IR** (ATR): 2918 (C-H st), 1732 (C=O st), 1248 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 376.2 (27), 375.2 (M^+, 100), 302.1 (48), 301.1 (17), 300.1 (15), 287.1 (28), 286.1 (15), 121.0 (18). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1909. The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 5.83 min, τ_{minor} = 7.43 min (93:7).

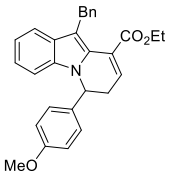


ethyl 10-ethyl-6-(4-methoxyphenyl)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23g).

Following *GP-K*, ***rac*-23g** (1.9 mg, 0.005 mmol, 10%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19g** (7.3 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23g** (6.8 mg, 0.018 mmol, 36%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19g** (7.3 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H, H-1), 7.19-7.01 (m, 3H, H-2 + H-3 + H-4), 6.84 (d, *J* = 8.7 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.76 (d, *J* = 8.8 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.53 (dd, *J* = 7.1, 3.0 Hz, 1H, H-8), 5.63 (d, *J* = 7.0 Hz, 1H, H-6), 4.53-4.19 (m, 2H, O**C**$\mathbf{H}_2CH_3$), 3.73 (s, 3H, OCH_3), 3.13 (ddd, *J* = 17.1, 7.2, 3.0 Hz, 1H, H-7a), 2.85 (m, 3H, C-10-C$\mathbf{H}_2CH_3$ + H-7b), 1.48-1.17 (m, 6H, C-10-CH_2**C**H_3 + OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8 (COO), 158.9 (**C**$_{arom}$-OCH_3), 135.8 (C-4a), 133.3 (C_{arom}), 129.3 (C_{arom}), 129.2 (C-8), 128.9 (C_{arom}), 128.4 (C_{arom}), 126.9 (2×C-6-C_{arom}-**C**$_{arom}$-H), 126.6 (C_{arom}), 123.0 (C_{arom}-H), 119.8 (C_{arom}-H), 119.4 (C_{arom}-H), 116.7 (C-10), 114.1 (2× OCH_3-C_{arom}-**C**$_{arom}$-H), 109.2 (C_{arom}-H), 61.3 (OCH_2), 55.3 (OCH_3), 52.4 (C-6), 33.0 (C-7), 18.5 (C-10-**C**H_2CH_3), 15.0 (CH_2**C**H_3), 14.3 (CH_2**C**H_3). **IR** (ATR): 2923 (C-H st), 1722 (C=O st), 1249 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 376.2 (26), 375.2 (M^+, 100), 360.2 (29), 273.1 (22). **HRMS** (ESI^+): Calculated for $[C_{24}H_{26}NO_3]^+$: 376.1913 $[M+H]^+$; found: 376.1902. **M.p.**: 48-51 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.32 min, τ_{minor} = 14.35 min (65:35).

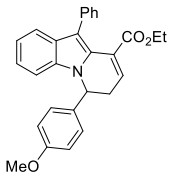


ethyl 10-benzyl-6-(4-methoxyphenyl)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23h).

Following *GP-K*, ***rac*-23h** (2.8 mg, 0.006 mmol, 13%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19h** (10.4 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

Following *GP-L*, **23h** (7.9 mg, 0.018 mmol, 36%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19h** (10.4 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.8, 1H, H-1), 7.25-7.19 (m, 4H, C_{arom}-H), 7.18-7.09 (m, 3H, C_{arom}-H), 7.04-6.95 (m, 1H, C_{arom}-H), 6.88 (d, *J* = 8.8 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.78 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.57 (dd, *J* = 7.2, 2.9 Hz, 1H, H-8), 5.67 (d, *J* = 7.0 Hz, 1H, H-6), 4.30 (s, 2H, C-10-CH_2), 4.23-4.14 (m, 1H, OC**H$_a$**CH_3), 4.13-4.03 (m, 1H, OC**H$_b$**CH_3), 3.74 (s, 3H, OCH_3), 3.16 (ddd, *J* = 17.1, 7.3, 3.0 Hz, 1H, H-7a), 2.84 (ddd, *J* = 17.1, 7.2, 1.7 Hz, 1H, H-7b), 1.16 (t, *J* = 7.1 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.4 (COO), 159.0 (**C**$_{arom}$-OCH_3), 141.7 (C-10-CH_2-**C**$_{arom}$), 135.9 (C-4a), 133.1 (C_{arom}), 130.1 (C-8), 129.0 (C_{arom}), 128.8 (C_{arom}), 128.6 (2×C_{arom}-H), 128.3 (2×C_{arom}-H), 127.9 (C_{arom}), 126.9 (2×C-6-C_{arom}-**C**$_{arom}$-H), 125.7 (C_{arom}-H), 123.1 (C_{arom}-H), 120.1 (C_{arom}-H), 119.7 (C_{arom}-H), 114.1 (2xOCH_3-C_{arom}-**C**$_{arom}$-H), 112.8 (C-10), 109.2 (C_{arom}-H), 61.3 (OCH_2), 55.4 (OCH_3), 52.4 (C-6), 33.0 (C-7), 31.0 (C-10-**C**H_2), 14.1 (OCH_2**C**H_3). **IR** (ATR): 2927 (C-H st), 1720 (C=O st), 1250 (C-O st as) cm^{-1}. **MS** (EI) m/z (%): 438.2 (32), 437.2 (M^+, 100), 364.2 (20), 273.1 (34). **HRMS** (ESI^+): Calculated for $[C_{29}H_{28}NO_3]^+$: 438.2069 $[M+H]^+$; found: 438.2068. **M.p.**: 47-50 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.40 min, τ_{minor} = 18.02 min (66:34).

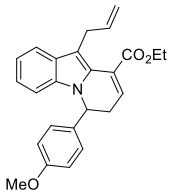


ethyl 6-(4-methoxyphenyl)-10-phenyl-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23i).

Following *GP-K*, ***rac*-23i** (1.6 mg, 0.004 mmol, 7%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

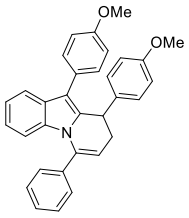
Following *GP-L*, **23i** (7.3 mg, 0.017 mmol, 33%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) using catalyst **3c** (3.5 mg, 0.005 mmol) and PTSA (8.61 mg, 0.05 mmol) in toluene (0.25 mL).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 1H, H-1), 7.63-7.39 (m, 4H, C_{arom}-H), 7.38-7.28 (m, 1H, C_{arom}-H), 7.24-7.07 (m, 3H, C_{arom}-H), 6.93 (d, *J* = 8.3 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.80 (d, *J* = 8.4 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.64 (dd, *J* = 7.2, 2.8 Hz, 1H, H-8), 5.72 (d, *J* = 7.1 Hz, 1H, H-6), 3.82-3.66 (m, 4H, OCH_3 + O**CH_a**CH_3), 3.35-3.16 (m, 2H, H-7a + O**CH_b**CH_3), 2.90 (dd, *J* = 17.0, 7.0 Hz, 1H, H-7b), 0.85 (t, *J* = 7.1 Hz, 3H, OCH_2**CH_3**). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.8 (COO), 159.1 (**C**$_{arom}$-OCH_3), 136.0 (C-4a), 135.7 (C_{arom}), 132.7 (C_{arom}), 130.7 (C-8), 129.6 (2×C_{arom}-H), 129.1 (C_{arom}), 128.6 (2×C_{arom}-H), 127.8 (C_{arom}), 127.6 (C_{arom}), 127.1 (2×C-6-C_{arom}-**C**$_{arom}$-H), 126.4 (C_{arom}-H), 123.4 (C_{arom}-H), 120.5 (C_{arom}-H), 120.2 (C_{arom}-H), 116.1 (C-10), 114.2 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 109.5 (C_{arom}-H), 61.1 (OCH_2), 55.4 (OCH_3), 52.7 (C-6), 33.1 (C-7), 13.7 (OCH_2**C**H_3). **IR** (ATR): 2939 (C-H st), 1726 (C=O st), 1243 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{28}H_{26}NO_3]^+$: 424.1913 $[M+H]^+$; found: 424.1915. **M.p.**: 56-59 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 10.06 min, τ_{minor} = 11.13 min (78:22).



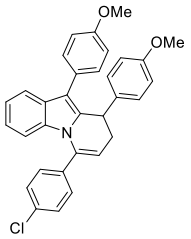
ethyl 10-allyl-6-(4-methoxyphenyl)-6,7-dihydropyrido[1,2-a]indole-9-carboxylate (23l). Following *GP-K*, ***rac*-23l** (2.0 mg, 0.005 mmol, 22%) was isolated by FC (petroleum ether/EtOAc, 95:5) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19l** (7.9 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.7 Hz, 1H, H-1), 7.19-6.93 (m, 3H, H-2 + H-3 + H-4), 6.84 (d, *J* = 8.4 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.76 (d, *J* = 8.5 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 6.59 (d, *J* = 5.9 Hz, 1H, H-8), 6.34-5.76 (m, 1H, C**H**=CH_2), 5.65 (d, *J* = 7.1 Hz, 1H, H-6), 5.31-4.69 (m, 2H, CH=C**H**$_2$), 4.49-4.10 (m, 2H, OCH_2), 3.73 (s, 3H, OCH_3), 3.66 (d, *J* = 6.2 Hz, 2H, C-10-CH_2), 3.28-2.97 (m, 1H, H-7a), 2.83 (dd, *J* = 17.2, 7.1 Hz, 1H, H-7b), 1.35 (t, *J* = 7.2 Hz, 3H, OCH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.3 (COO), 158.8 (**C**$_{arom}$-OCH_3), 138.0 (C-8), 135.8 (C-4a), 133.1 (C_{arom}), 130.0 (C_{arom}-H), 128.8 (C_{arom}), 128.7 (C_{arom}), 127.4 (C_{arom}), 126.9 (2×C-6-C_{arom}-**C**$_{arom}$-H), 123.1 (C_{arom}-H), 120.0 (C_{arom}-H), 119.6 (C_{arom}-H), 114.8 (CH=**C**H_2), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.0 (C-10), 109.2 (C_{arom}-H), 61.3 (OCH_2), 55.3 (OCH_3), 52.4 (C-6), 33.0 (C-7), 29.6 (C-10-**C**H_2), 14.3 (OCH_2**C**H_3). **IR** (ATR): 2945 (C-H st), 1729 (C=O st), 1248 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{25}H_{25}NO_3Na]^+$: 410.1732 $[M+Na]^+$; found: 410.1729. The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (95:05)]; flow rate 1.0 mL/min; τ_{major} = 8.59 min, τ_{minor} = 9.23 min (67:33).

4.1.4 Dihydropyridoindoles 25

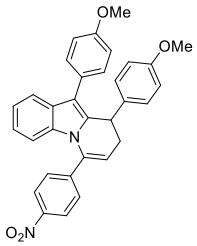


9,10-bis(4-methoxyphenyl)-6-phenyl-8,9-dihydropyrido[1,2-a]indole (25a). Following *GP-K*, ***rac*-25a** (19.5 mg, 0.043 mmol, 85%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24a** (12.6 mg, 0.05 mmol) and indole **19j** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 1H, H-1), 7.57-7.36 (m, 5H, C_{arom}-H), 7.32 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 7.21-7.07 (m, 3H, C_{arom}-H), 6.99-6.90 (m, 3H, C_{arom}-H), 6.83 (d, *J* = 8.6 Hz, 2H, C_{arom}-H), 6.41 (d, *J* = 8.4 Hz, 1H, H-4), 5.36 (dd, *J* = 7.3, 3.0 Hz, 1H, H-7), 4.51 (d, *J* = 5.2 Hz, 1H, H-9), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.80 (ddd, *J* = 15.8, 5.5, 3.1 Hz, 1H, H-8a), 2.66 (ddd, *J* = 15.8, 7.3, 2.1 Hz, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (**C**$_{arom}$-OCH_3), 158.2 (**C**$_{arom}$-OCH_3), 139.1 (C-6), 136.6 (C_{arom}), 135.5 (C_{arom}), 135.3 (C_{arom}), 134.8 (C_{arom}), 130.6

(2×C_{arom}-H), 128.6 (5×C_{arom}-H), 128.4 (C_{arom}), 127.8 (2×C_{arom}-H), 126.8 (C-10a), 121.6 (C-3), 120.5 (C-2), 119.4 (C-1), 115.3 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.3 (C-7), 111.2 (C-4), 55.4 (OCH_3), 55.3 (OCH_3), 36.2 (C-9), 30.5 (C-8). **IR** (ATR): 2950 (C-H st), 1645 (arC-C), 1608 (arC-C) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{32}H_{28}NO_2]^+$: 458.2120 $[M+H]^+$; found: 458.2100. **M.p.**: 89-92 ºC (petroleum ether/EtOAc).

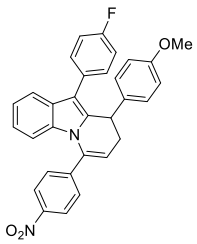


6-(4-chlorophenyl)-9,10-bis(4-methoxyphenyl)-8,9-dihydropyrido[1,2-a]indole (25b). Following *GP-K*, ***rac*-25b** (22.3 mg, 0.045 mmol, 90%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24b** (14.3 mg, 0.05 mmol) and indole **19j** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 1H, H-1), 7.46-7.35 (m, 4H, C_{arom}-H), 7.31 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.18-7.05 (m, 3H, C_{arom}-H), 7.05-6.88 (m, 3H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.45 (d, *J* = 8.3 Hz, 1H, H-4), 5.37 (dd, *J* = 7.2, 3.1 Hz, 1H, H-7), 4.66-4.40 (m, 1H, H-9), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 2.78 (ddd, *J* = 15.8, 5.5, 3.2 Hz, 1H, H-8a), 2.67 (ddd, *J* = 15.9, 7.2, 2.2 Hz, 1H, H-8b). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (**C**$_{arom}$-OCH_3), 158.3 (**C**$_{arom}$-OCH_3), 138.1 (C-6), 135.3 (C_{arom}-Cl), 135.2 (C_{arom}), 135.0 (C_{arom}), 134.7 (C_{arom}), 134.5 (C_{arom}), 130.5 (2×C_{arom}-H), 129.0 (4×C_{arom}-H), 128.5 (2×C_{arom}-H), 128.4 (C_{arom}), 126.7 (C-10a), 121.8 (C-3), 120.6 (C-2), 119.5 (C-1), 115.5 (C-10), 114.1 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.1 (C-7), 112.0 (C-4), 55.4 (OCH_3), 55.3 (OCH_3), 36.2 (C-7), 30.5 (C-8). **IR** (ATR): 2947 (C-H st), 1645 (arC-C), 1608 (arC-C), 1034 (C-Cl st) cm^{-1}. **M.p.**: 100-103 ºC (petroleum ether/EtOAc).

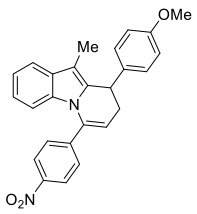


9,10-bis(4-methoxyphenyl)-6-(4-nitrophenyl)-8,9-dihydropyrido[1,2-a]indole (25c). Following *GP-K*, ***rac*-25c** (23.1 mg, 0.046 mmol, 92%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19j** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h**. ^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 2H, NO_2-C_{arom}-C_{arom}-H), 7.79 (d, *J* = 7.8 Hz, 1H, H-1), 7.64 (d, *J* = 8.1 Hz, 2H, C_{arom}-H, C-6-C_{arom}-C_{arom}-H), 7.33 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 7.21-7.09 (m, 3H, C_{arom}-H), 7.06-6.92 (m, 3H, C_{arom}-H), 6.85 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.39

(d, *J* = 8.3 Hz, 1H, H-4), 5.57 (dd, *J* = 6.7, 3.4 Hz, 1H, H-7), 4.55 (dd, *J* = 5.2, 2.4 Hz, 1H, H-9), 3.85 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.96-2.66 (m, 2H, H-8). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.5 (**C**$_{arom}$-OCH_3), 158.3 (**C**$_{arom}$-OCH_3), 147.8 (C_{arom}-NO_2), 142.7 (C-6), 137.4 (C_{arom}), 134.9 (C_{arom}), 134.8 (C_{arom}), 134.4 (C_{arom}), 130.5 (2×C_{arom}-H), 128.5 (C_{arom}), 128.3 (2×C_{arom}-H), 128.2 (2×C_{arom}-H), 126.4 (C-10a), 124.0 (2×C_{arom}-H), 122.0 (C-3), 120.9 (C-2), 119.8 (C-1), 115.9 (C-10), 115.3 (C-7), 114.1 (4×C_{arom}-H), 112.7 (C-4), 55.4 (OCH_3), 55.3 (OCH_3), 36.0 (C-9), 30.8 (C-8). **IR** (ATR): 2940 (C-H st), 1509 (NO_2 st as), 1343 (NO_2 st sim) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{32}H_{27}N_2O_4]^+$: 503.1971 $[M+H]^+$; found: 503.1962. **M.p.**: 122-125 ºC (petroleum ether/EtOAc).



10-(4-fluorophenyl)-9-(4-methoxyphenyl)-6-(4-nitrophenyl)-8,9-dihydropyrido[1,2-a]indole (25d). Following *GP-K*, ***rac*-25d** (19.7 mg, 0.040 mmol, 80%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19k** (10.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.6 Hz, 2H, NO_2-C_{arom}-C_{arom}-H), 7.74 (d, *J* = 7.9 Hz, 1H, H-1), 7.64 (d, *J* = 7.6 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 7.33 (dd, *J* = 8.6, 5.5 Hz, 2H, C_{arom}-H), 7.23-6.92 (m, 6H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.38 (d, *J* = 8.4 Hz, 1H, H-4), 5.58 (dd, *J* = 6.8, 3.6 Hz, 1H, H-7), 4.51 (dd, *J* = 5.3, 2.5 Hz, 1H, H-7), 3.78 (s, 3H, OCH_3), 2.96-2.67 (m, 2H, H-8). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.9 (d, $^1J_{C\text{-}F}$ = 246.0 Hz, C_{arom}-F), 158.5 (**C**$_{arom}$-OCH_3), 147.9 (C_{arom}-NO_2), 142.6 (C-6), 137.3 (C_{arom}), 135.4 (C_{arom}), 134.6 (2×C_{arom}), 134.4 (C_{arom}), 130.9 (d, $^3J_{C\text{-}F}$ = 7.9 Hz, 2×C-10-C_{arom}-**C**$_{arom}$-H), 130.0 (d, $^4J_{C\text{-}F}$ = 3.2 Hz, C-10-**C**$_{arom}$), 128.3 (3×C_{arom}-H), 128.2 (C_{arom}-H), 124.1 (2×C_{arom}-H), 122.3 (C-3), 121.1 (C-2), 119.6 (C-1), 115.5 (d, $^2J_{C\text{-}F}$ = 21.5 Hz, 2×C_{arom}-H), 115.4 (C-7), 115.3 (C-10), 114.2 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.8 (C-4), 55.3 (OCH_3), 36.1 (C-9), 30.8 (C-8). **IR** (ATR): 2951 (C-H st), 1505 (NO_2 st as), 1340 (NO_2 st sim), 1221 (C-F st) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{31}H_{24}N_2O_3F]^+$: 491.1771 $[M+H]^+$; found: 491.1771. **M.p.**: 237-240 ºC (petroleum ether/EtOAc).

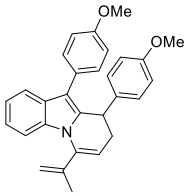


9-(4-methoxyphenyl)-10-methyl-6-(4-nitrophenyl)-8,9-dihydropyrido[1,2-a]indole (25e).

Following *GP-K*, ***rac*-25e** (12.9 mg, 0.031 mmol, 80%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl ((trifluoromethyl)sulfonyl) phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h.

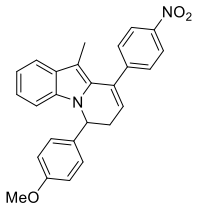
Following *GP-L*, **25a** (7.4 mg, 0.018 mmol, 36%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under catalyst **3c** (3.5 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 72 h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.7 Hz, 2H, NO_2-C_{arom}-C_{arom}-H), 7.64-7.46 (m, 3H, C-6-C_{arom}-C_{arom}-H + H-1), 7.17-7.03 (m, 3H, C-9-C_{arom}-C_{arom}-H + H-2), 6.92 (app t, *J* = 7.7 Hz, 1H, H-3), 6.81 (d, *J* = 8.7 Hz, 2H, OCH_3-C_{arom}-C_{arom}-H), 6.25 (d, *J* = 8.3 Hz, 1H, H-4), 5.48 (dd, *J* = 6.5, 3.9 Hz, 1H, H-7), 4.76-4.41 (m, 1H, H-9), 3.76 (s, 3H, OCH_3), 3.04-2.46 (m, 2H, H-8), 2.21 (s, 3H, NCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.4 (**C**$_{arom}$-OCH_3), 147.7 (C_{arom}-NO_2), 142.9 (C-6), 137.4 (C_{arom}), 135.0 (C_{arom}), 134.2 (C_{arom}), 133.9 (C_{arom}), 130.2 (C-10a), 128.3 (4×C_{arom}-H), 123.9 (2×C_{arom}-H), 121.7 (C-3), 120.2 (C-2), 118.8 (C-1), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.5 (C-7), 112.5 (C-4), 109.6 (C-10), 55.3 (OCH_3), 36.2 (C-9), 30.2 (C-8), 8.7 (C-10-CH_3). **IR** (ATR): 2930 (C-H st), 1510 (NO_2 st as), 1344 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 411.2 (28), 410.2 (M^+, 100), 409.2 (20), 289.1 (14). **HRMS** (ESI^+): Calculated for $[C_{26}H_{23}N_2O_3]^+$: 411.1709 $[M+H]^+$; found: 411.1704. **M.p.**: 110-113 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 6.45 min, τ_{minor} = 7.04 min (83:17).



9,10-bis(4-methoxyphenyl)-6-(prop-1-en-2-yl)-8,9-dihydropyrido[1,2-a]indole (25f'). Following *GP-K*, ***rac*-25f'** (15.8 mg, 0.037 mmol, 75%) was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24d** (11.7 mg, 0.05 mmol) and indole **19j** (11.2 mg, 0.05 mmol) under diphenyl ((trifluoromethyl) sulfonyl)phosphoramidate (1.9 mg, 0.005 mmol) in toluene (0.25 mL) at 100 ºC for 2 h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.81-7.63 (m, 2H, H-1 + H-2), 7.33-7.11 (m, 4H, C_{arom}-H), 7.05 (d, *J* = 8.3 Hz, 2H, C_{arom}-H), 6.91 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 6.82 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.36 (d, *J* = 1.9 Hz, 1H, C=C**H**$_a$H$_b$), 5.27 (dd, *J* = 7.3, 3.0 Hz, 1H, H-7), 5.19 (d, *J* = 1.8 Hz, 1H, C=CH$_a$**H**$_b$), 4.41 (d, *J* = 5.3 Hz, 1H, H-9), 3.83 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.67 (ddd, *J* = 15.8, 5.6, 3.0 Hz, 1H, H-8a), 2.52 (ddd, *J* = 15.8, 7.3, 2.1 Hz, 1H, H-8b), 2.04 (s, 3H, CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.3 (**C**$_{arom}$-OCH_3), 158.2 (**C**$_{arom}$-OCH_3), 140.9 (C-6), 135.3 (2×C_{arom}), 134.9 (C_{arom}), 134.8 (C_{arom}), 130.5 (2×C_{arom}-H), 128.7 (2×C_{arom}-H), 128.1 (C_{arom}), 126.9 (C-10a), 122.2 (C-3), 120.6 (C-2), 119.4 (C-1), 116.3 (C=**C**H_2), 114.8 (C-10), 114.0 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.8 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 112.5 (C-4), 109.0 (C-7), 55.4 (OCH_3), 55.3 (OCH_3), 35.9 (C-9), 30.2 (C-8), 21.8 (C**C**H_3). **IR** (ATR): 2958 (C-H st), 1638 (arC-C), 1609 (arC-C). cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{29}H_{28}NO_2]^+$: 422.2120 $[M+H]^+$; found: 422.2121. **M.p.**: 72-75 ºC (petroleum ether/EtOAc).

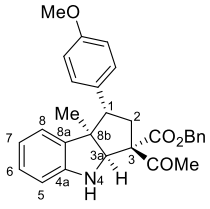
4.1.5 Dihydropyridoindole 31



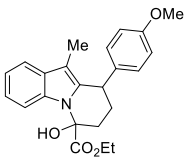
6-(4-methoxyphenyl)-10-methyl-9-(4-nitrophenyl)-6,7-dihydropyrido[1,2-a]indole (31). Following *GP-J*, **31** was isolated by FC (petroleum ether/EtOAc, 93:7) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under catalyst **3c** (0.005 mmol) in toluene (0.25 mL) at 50 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.7 Hz, 2H, NO_2-C_{arom}-C_{arom}-H), 7.65-7.45 (m, 3H, C-9-C_{arom}-C_{arom}-H + H-1), 7.23-7.02 (m, 3H, H-2 + H-3 + H-4), 6.88 (d, *J* = 8.6 Hz, 2H, C-6-C_{arom}-C_{arom}-H), 6.78 (d, *J* = 8.8 Hz, 2H, OCH_3-C_{arom}-C_{arom}-**H**), 5.85 (dd, *J* = 7.0, 2.9 Hz, 1H, H-8), 5.73-5.61 (m, 1H, H-6), 3.73 (s, 3H, OCH_3), 3.22 (ddd, *J* = 16.6, 7.0, 3.0 Hz, 1H, H-7a), 2.90 (ddd, *J* = 16.6, 7.1, 1.8 Hz, 1H, H-7b), 1.89 (s, 3H, CCH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0 (**C**$_{arom}$-OCH_3), 147.4 (C_{arom}-NO_2), 146.8 (C_{arom}), 135.9 (C_{arom}), 134.5 (C_{arom}), 133.4 (C_{arom}), 129.6 (C_{arom}), 129.3 (C_{arom}), 129.1 (2×C-9-C_{arom}-**C**$_{arom}$-H), 126.8 (2×C-6-C_{arom}-**C**$_{arom}$-H), 123.8 (2×NO_2-C_{arom}-**C**$_{arom}$-H), 123.7 (C-8), 123.3 (C_{arom}-H), 119.6 (C_{arom}-H), 119.3 (C_{arom}-H), 114.1 (2×OCH_3-

C_{arom}-**C**$_{arom}$-H), 109.3 (C-10), 109.2 (C_{arom}-H), 55.3 (OCH_3), 52.8 (C-6), 33.2 (C-7), 11.0 (C-10-**C**H_3). **IR** (ATR): 2926 (C-H st), 1512 (NO_2 st as), 1344 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 410.2 (M^+, 28), 298.1 (70), 295.1 (22), 150.0 (92), 147.1 (64), 131.0 (82), 130.0 (100), 104.0 (38), 91.0 (18), 77.0 (26), 76.0 (20). **HRMS** (ESI^+): Calculated for $[C_{26}H_{23}N_2O_3]^+$: 411.1709 $[M+H]^+$; found: 411.1704. **M.p.**: 105-108 ºC (petroleum ether/EtOAc).

4.2 Intermediates and other products



benzyl 3-acetyl-1-(4-methoxyphenyl)-8b-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[b]indole-3-carboxylate (20). Following *GP-J*, **20** (15.5 mg, 0.034 mmol, 68%) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **1a** (16.2 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at r.t. for 12h. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48-7.33 (m, 5H, C_{arom}-H), 7.09-6.87 (m, 3H, H-8 + C-1-C_{arom}-C_{arom}-H), 6.83 (d, *J* = 8.4 Hz, 2H, OCH_3-C_{arom}-C_{arom}-H), 6.64 (app t, *J* = 7.3 Hz, 1H, H-7), 6.55 (d, *J* = 7.3 Hz, 1H, H-6), 6.38 (d, *J* = 7.8 Hz, 1H, H-5), 5.39 (d, *J* = 12.0 Hz, 1H, OC**H**$_a$$CH_b$), 5.17 (d, *J* = 11.9 Hz, 1H, OCH_aC**H**$_b$), 4.92 (s, 1H, H-3a), 3.81 (s, 3H, OCH_3), 3.76 (bs, 1H, NH), 3.45 (dd, *J* = 13.6, 6.1 Hz, 1H, H-1), 2.92 (dd, *J* = 12.8, 6.1 Hz, 1H, H-2a), 2.19 (d, *J* = 17.3 Hz, 1H, H-2b), 2.16 (s, 3H, $COCH_3$), 0.99 (s, 3H, C-8b-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 202.5 (C=O), 170.0 (COO), 158.7 (**C**$_{arom}$-OCH_3), 148.6 (C-4a), 135.5 (2×C_{arom}), 129.9 (C_{arom}), 129.8 (2×C_{arom}-H), 129.2 (2×C_{arom}-H), 128.9 (3×C_{arom}-H), 127.7 (H-6), 123.2 (H-8), 118.4 (H-7), 113.4 (2×C_{arom}-H), 109.8 (H-5), 75.0 (C-3a), 70.1 (C-3), 67.3 (OCH_2), 56.7 (C-8b), 55.4 (OCH_3), 52.8 (C-1), 38.0 (C-2), 27.2 (CO**C**H_3), 18.8 (C-8b-**C**H_3). **IR** (ATR): 3379 (N-H st), 2962 (C-H st), 1747 (C=O st), 1710 (C=O st) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{29}H_{30}NO_4]^+$: 456.2175 $[M+H]^+$; found: 456.2177. **M.p.**: 158-161 ºC (petroleum ether/EtOAc).

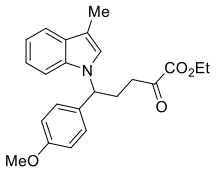


ethyl 6-hydroxy-9-(4-methoxyphenyl)-10-methyl-6,7,8,9-tetrahydropyrido[1,2-a]indole-6-carboxylate (26) dr = 1.7:1**.**

Following *GP-J*, ***rac*-26** (4.8 mg, 0.0.13 mmol, 25%) was isolated by FC (petroleum ether/EtOAc, 90:10) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 12h.

Following *GP-J*, **26** (4.8 mg, 0.0.13 mmol, 25%) was isolated by FC (petroleum ether/EtOAc, 90:10) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under catalyst **3c** (3.5 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 12h.

^{1}H NMR (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 7.58-7.44 (m, 1H, H-1), 7.58-7.44* (m, 1H, H-1), 7.37-7.28* (m, 1H, C_{arom}-H), 7.22-7.01 (m, 5H, C_{arom}-H), 7.22-7.01* (m, 4H, C_{arom}-H), 6.88-6.74 (m, 2H, C_{arom}-H), 6.88-6.74* (m, 2H, C_{arom}-H), 4.53 (s, 1H, OH), 4.50* (s, 1H, OH), 4.43-4.10 (m, 3H, C**H**$_2$CH$_3$ + H-9), 4.43-4.10* (m, 3H, C**H**$_2$CH$_3$ + H-9), 3.69 (s, 3H, OCH_3), 3.69* (s, 3H, OCH_3), 2.68-2.51 (m, 1H, H-7a), 2.45-1.83 (m, H-7b + H-8 + C-10-CH_3), 1.20 (t, *J* = 7.0, 3H, CH_2C**H**$_3$), 1.09* (t, *J* = 7.1, 3H, CH_2C**H**$_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 174.2 (COO), 173.5* (COO), 158.3* (**C**$_{arom}$-OCH_3), 158.2 (**C**$_{arom}$-OCH_3), 135.8* (C_{arom}), 135.5 (C_{arom}), 135.0* (C_{arom}), 134.8* (C_{arom}), 134.5 (C_{arom}), 133.9 (C_{arom}), 130.0* (C_{arom}), 130.0 (C_{arom}), 129.2 (2×C-9-C_{arom}-**C**$_{arom}$-H), 129.1* (2×C-9-C_{arom}-**C**$_{arom}$-H), 121.6 (C-3), 121.6* (C-3), 120.2 (C-2), 120.1* (C-2), 118.5 (C-1), 118.3* (C-1), 113.9* (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 113.7 (2×OCH_3-C_{arom}-**C**$_{arom}$-H), 111.0* (C-4), 110.3 (C-4), 108.4* (C-10), 108.0 (C-10), 82.9* (C-6), 82.3 (C-6), 63.5 (OCH_2), 63.3* (OCH_2), 55.4 (OCH_3), 55.4* (OCH_3), 38.5* (C-9), 37.1 (C-9), 33.7* (C-7), 31.8 (C-7), 28.0* (C-8), 25.9 (C-8), 14.1* (CH_2**C**H_3), 14.0 (CH_2**C**H_3), 8.8* (C-10-CH_3), 8.2 (C-10-CH_3). **IR** (ATR): 3549 (O-H st), 2934 (C-H st), 1730 (C=O st), 1244 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{23}H_{26}NO_4]^+$: 380.1862 $[M+H]^+$; found: 380.1866. **M.p.**: 102-105 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 1.0 mL/min; $\tau_{major\ (1)}$ = 62.76 min, $\tau_{minor\ (1)}$ = 36.31 min (15:85); $\tau_{major\ (2)}$ = 50.52 min, $\tau_{minor\ (2)}$ = 53.79 (93:7).

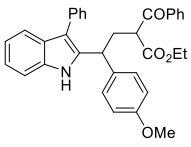


ethyl 5-(4-methoxyphenyl)-5-(3-methyl-1H-indol-1-yl)-2-oxopentanoate (27).

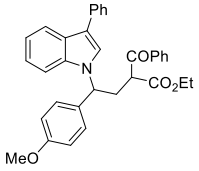
Following *GP-J*, ***rac*-27** (2.1 mg, 0.006 mmol, 11%) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 12h.

Following *GP-J*, **27** (2.1 mg, 0.006 mmol, 11%) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **11a** (12.4 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under catalyst **3c** (3.5 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 12h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (ddd, *J* = 7.6, 1.4, 0.8 Hz, 1H, C_{arom}-H), 7.27 (d, *J* = 8.0 Hz, 1H, C_{arom}-H), 7.20-7.05 (m, 4H, C_{arom}-H), 6.96 (d, *J* = 1.2 Hz, 1H, NC_{arom}-H), 6.82 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.46 (app t, *J* = 7.8 Hz, 1H, H-5), 4.23 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.76 (s, 3H, OCH_3), 2.83 (app t, *J* = 7.0 Hz, 2H, H-3), 2.60 (app q, *J* = 7.1 Hz, 2H, H-4), 2.33 (d, *J* = 1.0 Hz, 3H, C_{arom}-CH_3), 1.31 (t, *J* = 7.1 Hz, 3H, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 193.8 (C-2), 160.7 (C-1), 159.2 ($\mathbf{C}_{arom}$-OCH_3), 136.8 (C_{arom}), 133.0 (C_{arom}), 129.0 (C_{arom}), 127.8 (2×C_{arom}-H), 122.2 (NC_{arom}-H), 121.8 (C_{arom}-H), 119.2 (C_{arom}-H), 119.1 (C_{arom}-H), 114.2 (2×C_{arom}-H), 111.6 (C_{arom}), 109.7 (C_{arom}-H), 62.3 (OCH_2), 57.5 (C-5), 55.4 (OCH_3), 36.4 (C-4), 28.5 (C-3), 14.1 ($CH_2\mathbf{C}H_3$), 9.9 (C_{arom}-$\mathbf{C}H_3$). **IR** (ATR): 2946 (C-H st), 1738 (C=O st), 1705 (C=O st), 1153 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{23}H_{25}NO_4]^+$: 379.1806 $[M+H]^+$; found: 379.1811. **M.p.**: 76-79 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IC* column [*n*-hexane/*i*-PrOH (98:02)]; flow rate 1.0 mL/min; τ_{major} = 13.24 min, τ_{minor} = 24.69 min (73:27).

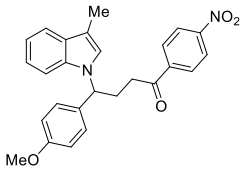


ethyl 2-benzoyl-4-(4-methoxyphenyl)-4-(3-phenyl-1H-indol-2-yl)butanoate (28). Following *GP-J*, ***rac*-28** (18.6 mg, 0.036 mmol, 72%, dr = 1.1:1) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 8h. dr = 1.1:1 **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 8.09* (s, 1H, NH), 7.92 (s, 1H, NH), 7.70-7.04 (m, 16H, C_{arom}-H), 7.70-7.04* (m, 16H, C_{arom}-H), 6.85 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 6.85* (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 4.54 (dd, *J* = 11.0, 5.0 Hz, 1H, H-4), 4.46* (dd, *J* = 10.1, 6.5 Hz, 1H, H-4), 4.29-4.09 (m, 1H, H-2), 4.29-4.09* (m, 1H, H-2), 4.04-3.80 (m, 2H, OCH_2), 4.04-3.80* (m, 2H, OCH_2), 3.79 (s, 3H, OCH_3), 3.79* (s, 3H, OCH_3), 2.96-2.79 (m, 1H, H-3a), 2.96-2.79* (m, 1H, H-3a), 2.67* (ddd, *J* = 14.0, 10.0, 5.8 Hz, 1H, H-3b), 2.50 (ddd, *J* = 13.9, 11.1, 4.6 Hz, 1H, H-3b), 1.04 (t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$), 0.98* (t, *J* = 7.1 Hz, $OCH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) (* indicates minor diastereoisomer resonances) δ 195.4 (C=O), 194.6* (C=O), 169.8 (C-1), 169.6* (C-1), 158.6 ($\mathbf{C}_{arom}$-OCH_3), 158.6* ($\mathbf{C}_{arom}$-OCH_3), 136.0* (C_{arom}), 135.9 (C_{arom}), 135.9* (C_{arom}), 135.7 (C_{arom}), 135.6 (C_{arom}), 135.6* (C_{arom}), 134.6 (C_{arom}), 134.5* (C_{arom}), 134.2* (C_{arom}), 134.0 (C_{arom}), 133.5 (C_{arom}-H), 133.5* (C_{arom}-H), 130.0 (2×C_{arom}-H), 129.9* (2×C_{arom}-H), 128.7 (4×C_{arom}-H), 128.7* (2×C_{arom}-H), 128.6 (2×C_{arom}-H), 128.5* (2×C_{arom}-H), 127.9* (C_{arom}), 127.8 (C_{arom}), 126.6 (C_{arom}-H), 126.4* (C_{arom}-H), 122.5 (C_{arom}-H). 122.3* (C_{arom}-H), 120.3 (C_{arom}-H), 120.1* (C_{arom}-H), 119.6 (C_{arom}-H), 119.4* (C_{arom}-H), 117.4 (C_{arom}), 116.7* (C_{arom}), 114.4 (2×C_{arom}-H), 114.4* (2×C_{arom}-H), 111.0* (C_{arom}-H), 110.9 (2×C_{arom}-H), 61.7* (OCH_2), 61.5 (OCH_2), 55.4 (OCH_3), 55.4* (OCH_3), 52.0* (C-2), 51.9 (C-2), 39.4 (C-4), 39.2* (C-4), 34.7 (C-3), 34.1* (C-3), 14.0 ($CH_2\mathbf{C}H_3$), 13.9* ($CH_2\mathbf{C}H_3$). **IR** (ATR): 3379 (NH st), 2943 (C-H st), 1730 (C=O st), 1681 (C=O st), 1247 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{34}H_{31}NO_4]^+$: 518.2331 $[M+H]^+$; found: 518.2336. **M.p.**: 95-98 ºC (petroleum ether/EtOAc).



ethyl 2-benzoyl-4-(4-methoxyphenyl)-4-(3-phenyl-1H-indol-1-yl)butanoate (29). Following *GP-J*, ***rac*-29** (1.3 mg, 0.002 mmol, 5%, dr = 2.2:1) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **7f** (16.2 mg, 0.05 mmol) and indole **19i** (9.7 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 8h. **^{1}H NMR** (300 MHz, $CDCl_3$) (* indicates minor diastereoisomer

resonances) δ 8.14-7.77 (m, 1H, C_{arom}-H), 8.14-7.77* (m, 1H, C_{arom}-H), 7.81-7.57 (m, 4H, C_{arom}-H), 7.81-7.57* (m, 3H, C_{arom}-H), 7.55-6.99 (m, 12H, C_{arom}-H), 7.55-6.99* (m, 1H, C_{arom}-H), 6.90-6.77 (m, 2H, C_{arom}-H), 6.90-6.77* (m, 2H, C_{arom}-H), 5.73 (dd, *J* = 10.4, 5.3 Hz, 1H, H-4), 5.54* (dd, *J* = 9.8, 6.1 Hz, 1H, H-4), 4.41-3.97 (m, 3H, OCH_2 + H-2), 4.41-3.97* (m, 3H, OCH_2 + H-2), 3.77* (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.17-2.75 (m, 2H, H-3), 3.17-2.75* (m, 2H, H-3), 1.13 (t, *J* = 7.1 Hz, $CH_2C\mathbf{H}_3$), 1.08* (t, *J* = 7.1 Hz, $CH_2C\mathbf{H}_3$). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 195.2 (C=O), 195.0* (C=O), 169.7 (C-1), 169.4* (C-1), 159.4 ($\mathbf{C}_{arom}$-OCH_3), 137.5 (C_{arom}), 137.1* (C_{arom}), 135.6* (C_{arom}), 135.5 (C_{arom}), 135.5* (C_{arom}), 135.4 (C_{arom}), 133.8 (C_{arom}-H), 133.7* (C_{arom}-H), 132.2* (C_{arom}),, 131.9 (C_{arom}), 128.9 (2×C-4-C_{arom}-C_{arom}-H), 128.8* (2×C-4-C_{arom}-C_{arom}-H), 128.8 (4×C_{arom}-H), 128.7* (4×C_{arom}-H), 128.0 (2×C_{arom}-H), 127.9* (2×C_{arom}-H), 127.5 (2×C_{arom}-H), 126.5 (C_{arom}), 126.1 (C_{arom}-H), 126.0* (C_{arom}-H), 123.0 (C_{arom}-H), 122.7* (C_{arom}-H), 122.5 (C_{arom}-H), 122.3* (C_{arom}-H), 120.6 (C_{arom}-H), 120.4* (C_{arom}-H), 120.3 (C_{arom}-H), 120.0* (C_{arom}-H), 118.4 (C_{arom}), 114.4* (2×OCH_3-C_{arom}-C_{arom}-H), 114.3 (2×OCH_3-C_{arom}-C_{arom}-H), 110.5* (C_{arom}-H), 110.4 (C_{arom}-H), 61.9* (OCH_2), 61.8 (OCH_2), 56.9 (C-4), 56.8* (C-4), 55.4 (OCH_3), 50.7* (C-2), 50.6 (C-2), 34.4 (C-3), 34.2* (C-3), 14.1 ($CH_2\mathbf{C}H_3$), 14.0* ($CH_2\mathbf{C}H_3$). **IR** (ATR): 2934 (C-H st), 1736 (C=O st), 1683 (C=O st), 1248 (C-O st as) cm^{-1}. **HRMS** (ESI^+): Calculated for $[C_{34}H_{31}NO_4Na]^+$: 540.2151 $[M+Na]^+$; found: 540.2151. **M.p.**: 83-86 ºC (petroleum ether/EtOAc).



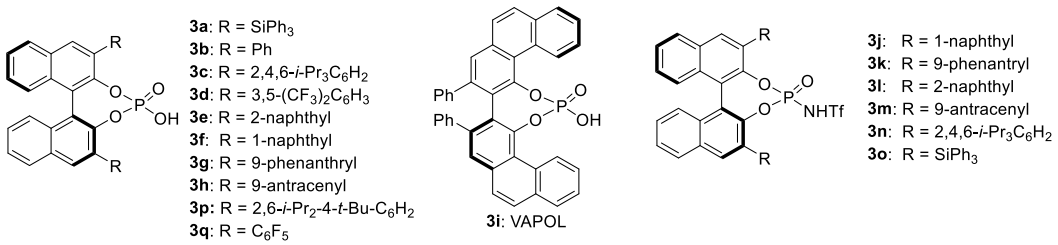
4-(4-methoxyphenyl)-4-(3-methyl-1H-indol-1-yl)-1-(4-nitrophenyl)butan-1-one (30).

Following *GP-J*, ***rac*-30** (7.7 mg, 0.018 mmol, 36%) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under diphenyl phosphoric acid (1.3 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 72h.

Following *GP-J*, **30** (9.8 mg, 0.023 mmol, 47%) was isolated by FC (petroleum ether/EtOAc, 85:15) on silica gel as a white solid, from cyclopropane **24c** (14.9 mg, 0.05 mmol) and indole **19a** (6.6 mg, 0.05 mmol) under catalyst **3c** (3.5 mg, 0.005 mmol) in toluene (0.25 mL) at 50 ºC for 72h.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.87 (d, *J* = 8.8 Hz, 2H, C_{arom}-H), 7.55 (dd, *J* = 7.8, 1.5 Hz, 1H, C_{arom}-H), 7.36-7.05 (m, 5H, C_{arom}-H), 6.99 (s, 1H, C_{arom}-H), 6.83 (d, *J* = 8.7 Hz, 2H, C_{arom}-H), 5.55 (dd, *J* = 9.8, 5.8 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 2.94 (app t, *J* = 6.8 Hz, 2H, H-2), 2.85-2.59 (m, 2H, H-3), 2.33 (s, 3H, C_{arom}-CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 197.9 (C-1), 159.2 (**C**$_{arom}$-OCH_3), 150.4 (C_{arom}-NO_2), 141.1 (C_{arom}), 136.8 (C_{arom}), 133.1 (C_{arom}), 129.0 (2×C_{arom}-H + C_{arom}), 127.7 (2×C_{arom}-H), 123.8 (2×C_{arom}-H), 122.4 (NC_{arom}-H), 121.8 (C_{arom}-H), 119.2 (C_{arom}-H), 119.1 (C_{arom}-H), 114.2 (2×C_{arom}-H), 111.7 (C_{arom}), 109.7 (C_{arom}-H), 57.6 (C-4), 55.4 (OCH_3), 35.8 (C-2), 29.2 (C-3), 9.9 (C_{arom}-**C**H_3). **IR** (ATR): 2932 (C-H st), 1513 (NO_2 st as), 1345 (NO_2 st sim) cm^{-1}. **MS** (EI) m/z (%): 428.2 (M^+, 12), 410.2 (28), 298.1 (70), 295.1 (22), 150.0 (92), 147.1 (64), 131.0 (82), 130.0 (100), 104.0 (38), 77.0 (26), 76.0 (20). **HRMS** (ESI^+): Calculated for $[C_{26}H_{25}N_2O_4]^+$: 429.1814 $[M+H]^+$; found: 429.1805. **M.p.**: 117-120 ºC (petroleum ether/EtOAc). The e.e. was determined by HPLC using a *Chiralpak IA* column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 50.45 min, τ_{minor} = 54.25 min (88:12).

5. PREPARATION OF CATALYSTS 3a-q



Catalysts **3a**, **3c**, **3d**, **3g**, **3h** and **3i** are commercially available. Ctalysts **3b**,[44] **3e**,[44] **3f**,[45] **3j**,[46] **3k**,[46] **3l**,[46] **3m**,[46] **3n**,[47] **3o**,[48] **3p**[49] and **3q**[50] have been previously synthesized and used in the literature.

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Appendix

Abbreviations, acronyms and symbols[1]

Ac	Acetyl group
Ad	Adamanthyl
ADC	1-Adamantanecarboxylate
aq.	Aqueous
Ar	Aryl
ATR	Attenuated total reflectance
BINOL	1,1'-Binaphthalene-2,2'-diol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bs	Broad signal
BOX	Bisoxazoline
***n*-Bu**	*n*-butyl
***t*-Bu**	*tert*-butyl
c	Concentration (measured in g/100 mL)
C_{arom}	Aromatic carbon
Cat.	Catalyst
CI	Chemical Ionization
cod	cyclooctadiene
CSA	10-Camphorsulfonic acid
δ	Chemical shift
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
dd	Double of doublets
d.e.	Diastereomeric excess
DFT	Density functional theory
DMAP	4-dimethyalaminopyridine
DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DPP	Diphenyl phosphoric acid
dr	Diastereomeric ratio
E	Electrophile
EDG	Electron-donating group
e.e.	Enantiomeric excess
EI	Electron Ionization

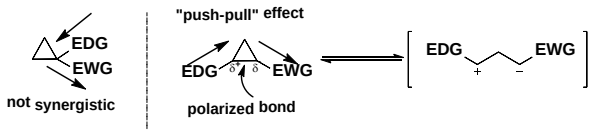
[1] For Standard Abbreviations and Acronyms, see: "Guidelines for Authors" *J. Org. Chem.* **2017**.

ELF	Electron localization function
Ent.	Enantiomer
Eq.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron-withdrawing group
FC	Flash column chromatography
GC	Gas Chromathography
HFIP	Hexafluoroisopropanol
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
J	Coupling constant
L	Ligand
LA	Lewis acid
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m	*meta*
M.p.	Melting point
m/z	Mass-to-charge ratio
M^+	Molecular ion
Me	Methyl
MS	Mass spectrometry or Molecular shieves
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o	*orto*
p	*para*
***p*-ABSA**	*para*-acetamidobenzenesulfonyl azide
Ph	Phenyl
PMP	*para*-methoxyphenyl
ppm	Parts per million
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromathography
Ts	Tosyl
τ_1	Retention time for first enantiomer
τ_2	Retention time for second enantiomer
vs	Versus

Resumen extendido

En el trabajo de investigación recogido en la presente memoria se ha estudiado la diversa reactividad que presentan los ciclopropanos dador-aceptores bajo catálisis de ácido de Brønsted.

En este sentido, los ciclopropanos doblemente sustituidos por un grupo electrón-dador y otro electrón-aceptor se consideran particularmente adecuados para aplicaciones sintéticas, debido a que las propiedades electrónicas de estos sustituyentes garantizan la activación del anillo de tres miembros. En general, los sustituyentes dadores y aceptores pueden estar dispuestos tanto en posición geminal como vecinal en el anillo de ciclopropano (Esquema 1). Cuando los sustituyentes están colocados en posición geminal, no actúan de forma sinérgica, y por lo tanto, no hay una polarización crucial en el enlace C-C. Sin embargo, la disposición vecinal de ambos sustituyentes genera un controlable efecto *push-pull*, el cual induce una alta polarización del enlace C-C que está entre ambos sustituyentes, lo que conlleva a un enlace C-C más débil. Debido a esto, este enlace C-C puede sufrir una fácil escisión que permite que estos ciclopropanos dador-aceptores puedan representarse como 1,3-dipolos, con el carbocatión estabilizado por un grupo dador de electrones y el carbanión por un sustituyente aceptor de electrones.

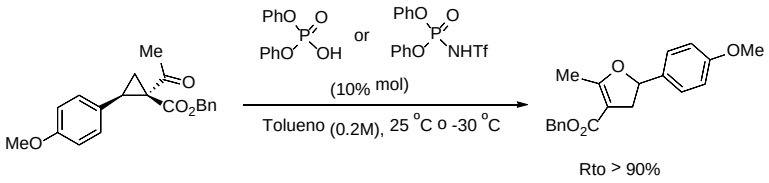


Esquema 1

La polarización del enlace C-C inducida por el efecto *push-pull* permite la apertura del ciclopropano y su posterior empleo en una gran variedad de reacciones, entre las que se encuentra la reacción de reagrupamiento intramolecular, en la que el aceptor polarizado negativamente ataca al átomo de carbono cargado positivamente adyacente al grupo electrón-dador. Por otro lado, el 1,3-dipolo generado tras la apertura del ciclopropano pude participar en una variedad de reacciones de cicloadición con diferentes dipolarófilos.

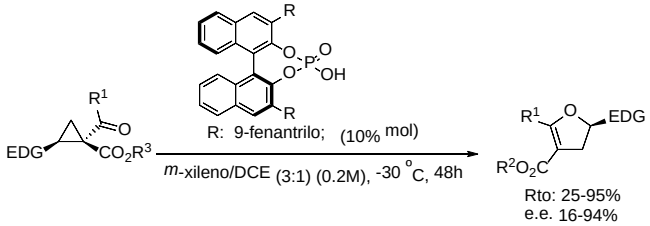
De este modo, después de presentar en un primer capítulo una introducción sobre las características más fundamentales y la reactividad de los ciclopropanos, y más en concreto, los ciclopropanos dadores aceptores, en un segundo capítulo se ha demostrado la capacidad

de estos ciclos tensionados para llevar a cabo un proceso de reagrupamiento formando una variedad de dihidrofuranos. Así, en primer lugar, se estudió el reagrupamiento de Cloke-Wilson en presencia de diferentes ácidos de Brønsted aquirales, tales como el ácido difenilfosfórico y el difenil ((trifluorometil)sulfonil)fosforamidato (Esquema 2). A través de estos experimentos preliminares se observó que el ciclopropano doblemente activado con dos grupos electrón-aceptores en posición geminal, experimentaba un rápido reordenamiento en presencia de ambos catalizadores para producir el correspondiente 2,3-dihidrofurano de manera eficiente.



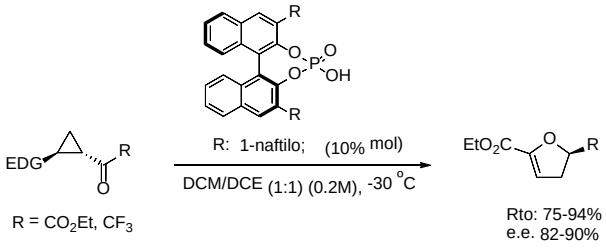
Esquema 2

Una vez demostrada la viabilidad de la reacción y tras un proceso exhaustivo de evaluación de parámetros experimentales, se determinaron las mejores condiciones para llevar a cabo la reacción enantioselectiva, las cuales consistían en el empleo de 10% mol de catalizador de ácido fosfórico quiral derivado del BINOL sustituido por grupos fenantrilo en las posiciones 3y 3', a -30 o -40 ºC en una mezcla de *m*-xileno/DCE (3:1). La reacción se pudo extender de manera eficaz al uso de ciclopropanos sustituidos con diferentes grupos dadores y aceptores (Esquema 3). De esta forma, el reagrupamiento de Cloke-Wilson se llevó a cabo modificando tanto la cetona y el ester del ciclopropano como el grupo dador de electrones, obteniendo los dihidrofuranos correspondientes con muy buenos rendimientos y enantioselectividades en la mayoría de los casos.



Esquema 3

Adicionalmente, también se extendió la metodología al empleo de ciclopropanos dadores-aceptores sustituidos con un único grupo electrón-aceptor (Esquema 4). En este caso, los correspondientes dihidrofuranos se obtuvieron satisfactoriamente, aunque fue necesaria la modificación de algunas condiciones de reacción para conseguir un alto enantiocotrol de la transformación.

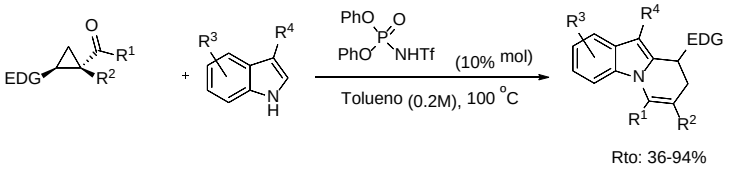


Esquema 4

Los estudios mecanísticos, junto con los análisis experimentales llevados a cabo confirmaron que la reacción procede a través de la formación de un intermedio carbocatiónico transitorio, el cual permite el uso de sustratos racémicos para llevar a cabo una DYKAT de tipo II.

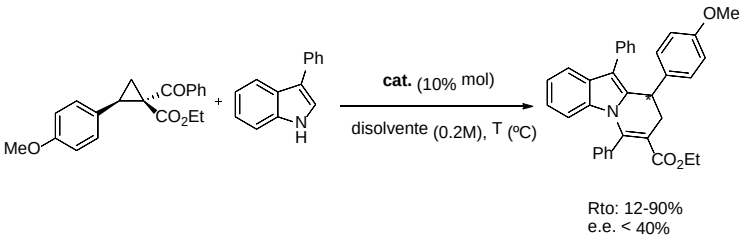
Por otro lado, en el tercer capítulo de la tesis se ha estudiado la reactividad de estos mismos ciclopropanos frente a indoles 3-sustituidos. En este contexto, se ha demostrado la capacidad del catalizador aquiral difenil ((trifluorometil) sulfonil) fosforamidato para actuar como catalizador bifuncional, activando al mismo tiempo el ciclopropano y el derivado de indol. De esta manera, se estudió la síntesis de dihidropiridoindoles a través de la ciclocondensación entre los correspondientes ciclopropanos e indoles. Una vez observada la viabilidad de la reacción y tras un proceso de evaluación de parámetros experimentales, se determinaron las mejores condiciones para llevar a cabo la reacción, las cuales consistían en el empleo de 10% mol de difenil ((trifluorometil) sulfonil)fosforamidato, a 100 ºC en tolueno. La reacción se pudo extender de manera satisfactoria al uso de diferentes ciclopropanos e indoles 3-sustituidos. Respecto al ciclopropano, la reacción procedió satisfactoriamente con una gran variedad de grupos dadores y aceptores, y en lo que al indol se refiere, diferentes sustituyentes en el anillo de benceno como en la posición C3 proporcionaron efectivamente

los derivados de dihidropiridoindol con altos rendimientos y en la mayoría de los casos de manera regioselectiva (Esquema 5).



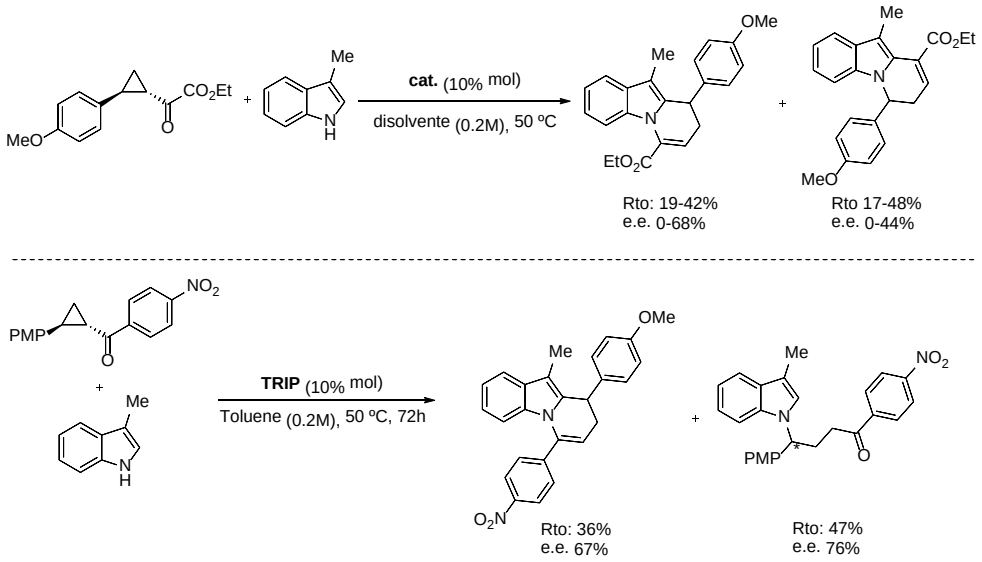
Esquema 5

Tras observar el gran alcance de la reacción, se decidió estudiar la versión asimétrica de la misma a través de la activación de ambos sustratos empleando ácidos de Brønsted quirales derivados de BINOL (Esquema 6). Cuando la reacción se llevó a cabo empleando un ciclopropano con dos sustituyentes aceptores en posición geminal en presencia de un ácido de Brønsted quiral, el correspondiente derivado de dihidropiridoindol se obtuvo con buen rendimiento y regioselectivamente. Sin embargo, la modificación de parámetros experimentales no proporcionaron el enantiocontrol deseado, obteniendo en todos los casos el producto final con pobres excesos enantioméricos.



Esquema 6

En el intento de aumentar la enantioselectividad del proceso, se evaluó el empleo de ciclopropanos dador-aceptores que contienen un único sustituyente electrón-aceptor. Así los catalizadores ensayados proporcionaron los productos deseados con un mayor exceso enantiomérico a pesar de no observar una reacción regioselectiva, dando lugar a mezclas de productos (Esquema 7).



Esquema 7

Teniendo en cuenta estos resultados, deben considerarse modificaciones adicionales en las condiciones de reacción con el objetivo de lograr un proceso totalmente regio- y enantioselectivo.