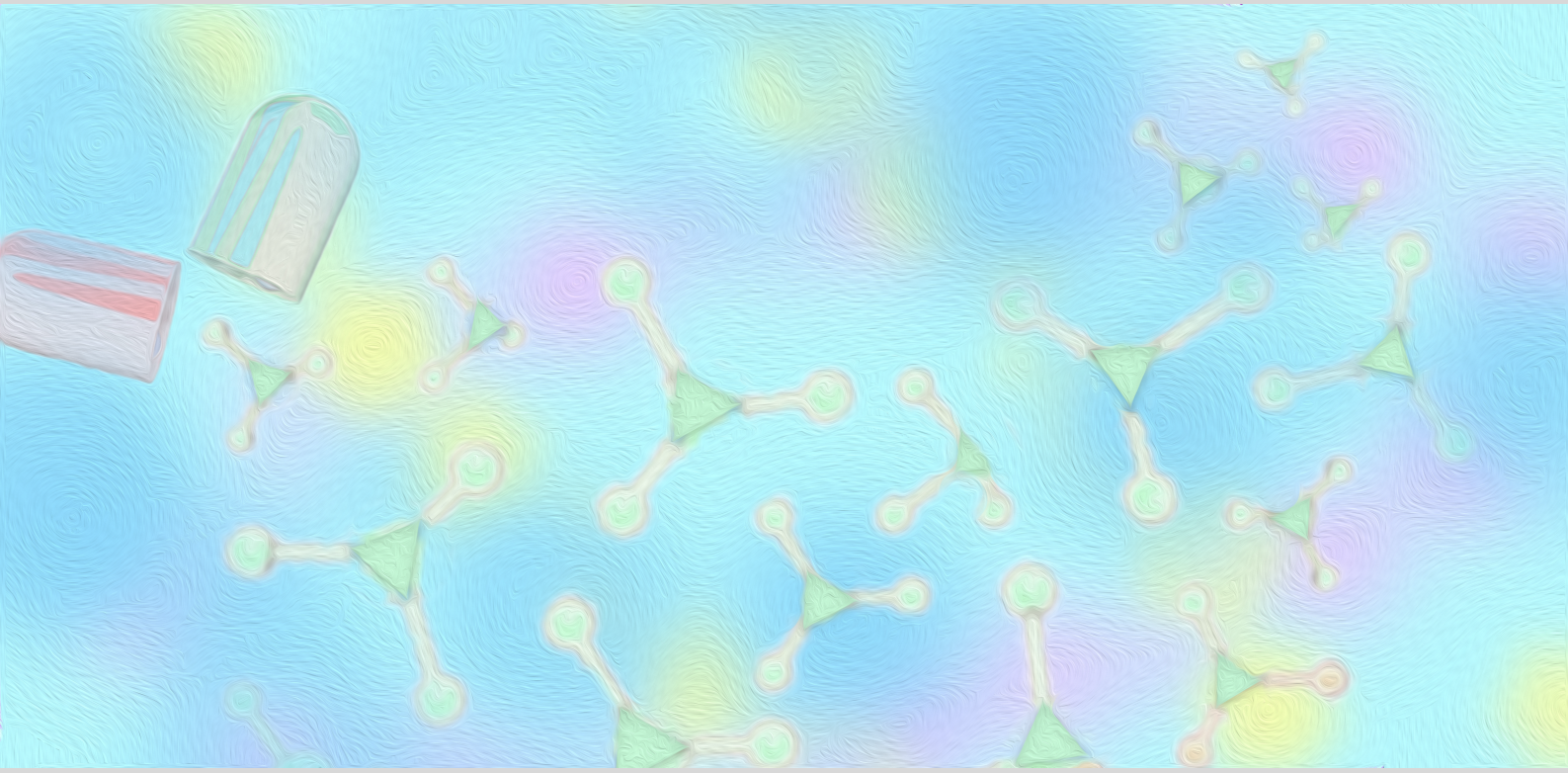
SYNTHESIS OF CYCLOPROPENIUM CATIONS BY CARBYNE TRANSFER CATALYSIS AND APPLICATIONS IN NOVEL CYCLOPROPENE SYNTHESES

Aliénor Celine Renee Jeandin

UNIVERSITAT ROVIRA i VIRGILI

Synthesis of Cyclopropenium Cations by Carbyne Transfer Catalysis and Applications in Novel Cyclopropene Syntheses

Aliénor Jeandin



DOCTORAL THESIS
2023

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Doctoral Thesis

Supervised by Prof. Marcos García Suero

URV – Universitat Rovira i Virgili

ICIQ – Institut Català d'Investigació Química

UNIVERSITAT ROVIRA i VIRGILI

ICIQ Institut Català d'Investigació Química

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Prof. Marcos García Suero, Group Leader of the Institut Català d'Investigació Química (ICIQ)

I STATE that the present study, entitled "*Synthesis of cyclopropenium cations by carbyne transfer catalysis and applications in novel cyclopropene syntheses*", presented by Aliénor Jeandin for the award of the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, August 28th, 2023.

Doctoral Thesis Supervisor
Prof. Marcos García Suero

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Dedicated to the memory of Prof. Kilian Muñiz

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List of Publications

- Hang-Fei Tu, Aliénor Jeandin, Marcos G. Suero*

  "Catalytic Synthesis of Cyclopropenium Cations with Rh-Carbynoids"

  J. Am. Chem. Soc. **2022**, *144*, 16737.

- Hang-Fei Tu, Aliénor Jeandin, Marcos G. Suero*

  "Cyclopropenium compounds, Process for their Preparation and Use"

  European Patent Application EP22382472, May 17th, **2022**.

- Hang-Fei Tu[+], Aliénor Jeandin[+], Corentin Bon, Cara Brocklehurst, Fabio Lima, Marcos G. Suero*

  [+] Authors contributed equally

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  Angew. Chem. Int. Ed. **2023**, *62*, e202308379.

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Prologue

The cyclopropenium cation — smallest member of Hückel's aromatic ring systems — was identified in the upper atmosphere of the Saturnian moon Titan in 2013.[1] Titan is the second largest moon in our solar system and resembles primitive Earth according to astronomers, which makes chemistry in its atmosphere germane to prebiotic organic synthesis.[2] Cyclopropenium cations of formula $C_3H_3^+$ and their cyclic methyl derivatives were later on identified as direct intermediates in the synthesis of complex multicyclic hydrocarbons and organic compounds, formed by ion-molecule reactions happening on Titan's upper atmosphere.[3]

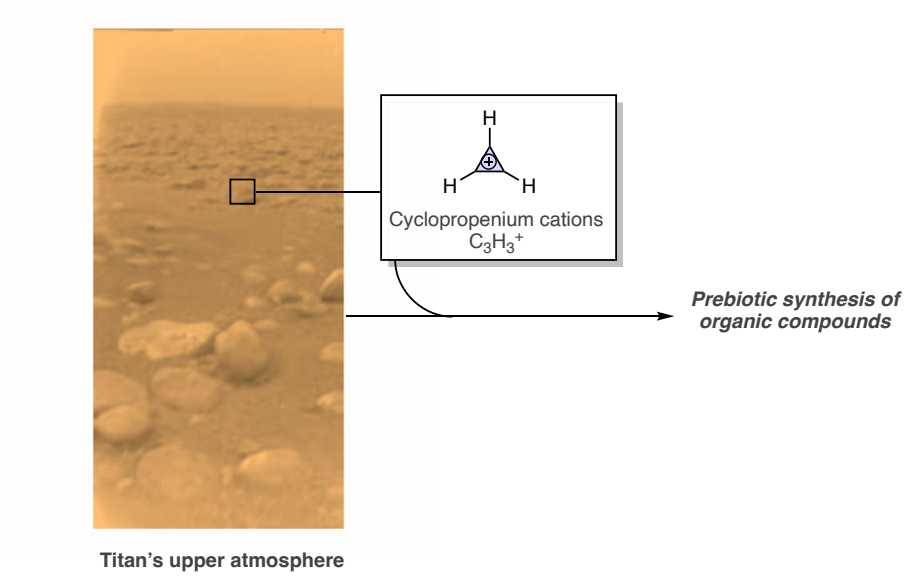

Figure 1 Cyclopropenium cations as intermediates in extraterrestrial syntheses of organic compounds[4]

Coming back to Earth, cyclopropenium cations were isolated in the laboratory for the first time in the late 1950s,[5] and they have attracted great attention as the smallest aromatic system. However, in contrast to the role they play in the prebiotic chemistry of Titan's upper atmosphere, their synthetic potential as three-carbons synthons in modern organic chemistry remains largely uncharted. In this Doctoral Thesis, the reader will find first the discovery and development of a catalytic synthesis of cyclopropenium cations by means of a novel carbyne transfer platform developed in the Suero group. We then set out to reveal the synthetic potential of this new class of cyclopropenium cations with highly selective syntheses of cyclopropenes, thereby accessing a "cyclopropenylated" chemical space and diversifications thereof, relevant to drug discovery and complex natural products synthesis.

---

[1] Ali, A.; Sittler, E. C.; Chornay, D.; Rowe, B. R.; Puzzarini, C. *Planet. Space Sci.* **2013**, *87*, 96.
[2] Trainer, M. G.; Pavlov, A. A.; DeWitt, H. L.; Jimenez, J. L.; McKay, C. P.; Toon, O. B.; Tolbert, M. A. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 18035.
[3] Ali, A.; Sittler, E. C.; Chornay, D.; Rowe, B. R.; Puzzarini, C. *Planet. Space Sci.* **2015**, *109–110*, 46.
[4] Free image from : https://solarsystem.nasa.gov/resources/869/first-color-view-of-titans-surface/; Image credit : NASA/JPL/ESA/University of Arizona.
[5] Breslow, R. *J. Am. Chem. Soc.* **1957**, *79*, 5318.

General objectives and summary

The main objective of this thesis was the discovery and the development of new chemical reactions involving catalytic carbyne transfer with alkynes, and applications of these new reactions to the synthesis of complex molecules.

Our research group demonstrated the first catalytic generation of diazomethyl radicals [N_2=C(·)—R] as carbyne equivalents by means of photoredox catalysis.[1] This work highlighted the under-appreciated ability of neutral carbynes to form three new bonds and provided the fundaments of an "assembly-point" coupling for chiral center construction, through a C-H bond diazomethylation reaction in aromatic feedstocks and drug molecules. Key on this work was the use of stable carbyne sources decorated with a hypervalent iodine moiety [$I^{(III)}$(Ar)(OTf)] and a diazo functionality (=N_2).

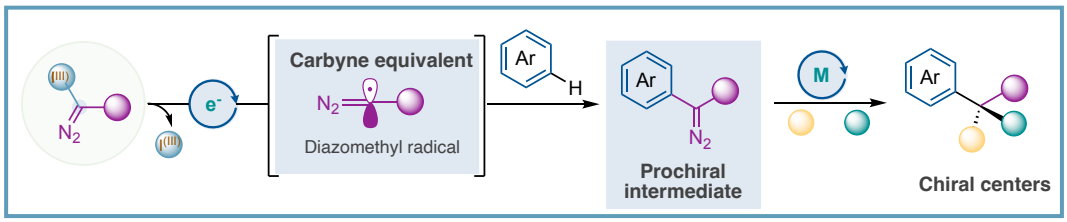

Figure 1 Generation of carbyne equivalents with photoredox catalysis for the diazomethylation of aromatic feedstocks

After this, our group reported a catalytic strategy that generates rhodium-carbynoids by selective diazo activation of the designed carbyne sources.[2] It was found that rhodium-carbynoid species, formally $I^{(III)}$-substituted Rh-carbenes, provoke C(sp^2)—C(sp^2) bond scission in alkenes by inserting a monovalent carbon unit between both sp^2-hybridized carbons. Importantly, the outstanding leaving group ability of the $I^{(III)}$-moiety combined with the weakness of the hypervalent iodine bond emulates the carbene/carbocation behavior of a monovalent cationic carbyne ($:^{+}$C—R). This finding circumvented the long-standing problem involving carbyne or monovalent carbon transfers with a catalytically-generated metal-carbyne (Figure 2).

[1] (a) Wang, Z.; Herraiz, A. G.; Del Hoyo, A. M.; Suero, M. G. *Nature* **2018**, *554*, 86; (b) Herraiz, A.G. Thesis defense, Title: *New carbon reactivity rules with radical carbenoids and carbyne equivalents enabled by photoredox catalysis;* Director: Suero, M. G.; **2019**, ICIQ-Universitat Rovira i Virgili.
[2] (a) Wang, Z.; Jiang, L.; Sarró, P.; Suero, M. G. *J. Am. Chem. Soc.* **2019**, *141*, 15509; (b) Sarró, P. Thesis defense, Title: *The Discovery and Development of a Rh-Catalyzed Carbyne Transfer Platform for the Skeletal Modification of C(sp^2)—C(sp^2) Bonds;* Director: Suero, M. G.; **2022**, ICIQ-Universitat Rovira i Virgili.

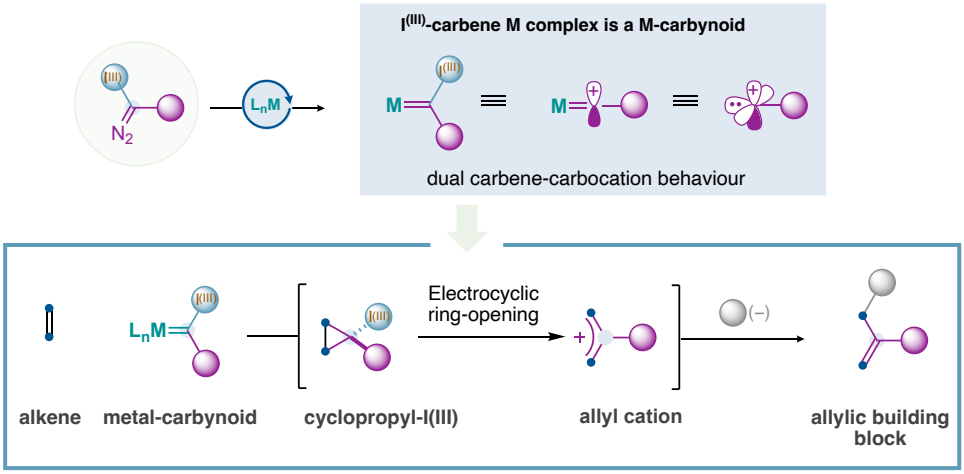

Figure 2 Catalytic cleavage of C(sp^2)—C(sp^2) bonds with metal-carbynoids for the generation of synthetically useful allyl cations

At the outset of this Thesis, we questioned the behavior of metal carbyne equivalents with alkynes. We hypothesized that analogously to their behavior with alkenes, rhodium carbynoid species would mimic the carbene/carbocation behavior of a monovalent cationic carbyne with alkynes. This would result in a process involving the formation of a cyclopropenyl-$I^{(III)}$ primary intermediate, which would, after an ionization process occurring with the departure of the $I^{(III)}$ leaving group, afford cyclopropenium cations as secondary intermediates, and potentially provide access to cyclopropenes upon external nucleophilic attack (Figure 3).

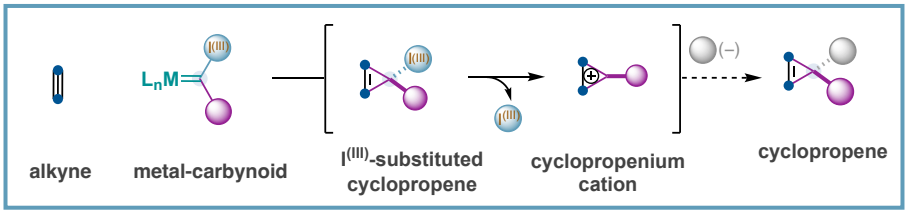

Figure 3 Synthesis of cyclopropenes from alkynes with metal-carbynoids *via* cyclopropenium cations

In Chapter II, we present the development of the first catalytic synthesis of a novel class of ester-substituted cyclopropenium cations (CPCs), smallest member of the Hückel aromatic ring systems. They were obtained by the reaction of readily available alkynes with Rh-carbynoids catalytically generated from Rh(II) paddlewheel carboxylate complexes and bespoke carbyne sources. We demonstrate that the extent of aromatic stability is such that these cationic species, initially expected to remain simple reaction intermediates, could be isolated as stable solids by filtration, and handled under air at room temperature.

We then set out to explore the reactivity of this novel class of CPCs as electrophilic reagents: CPCs could be used as three-carbon synthons and react with different nucleophiles to afford tri- and tetrasubstituted cyclopropenes. Current pathways to cyclopropenes suffer from limitations affecting the available substitution patterns. We hypothesized that the cationic nature of CPCs as reagents could allow for a unique synthetic flexibility. In Chapter

III, we present a novel synthetic route to diverse cyclopropenes from the reactions of CPCs with various carbon- and heteroatom-based nucleophiles. This process is distinguished by an exquisite regioselectivity and simple reaction conditions. Notably, this new synthetic route expands the scope of synthetically accessible cyclopropenes by addressing challenges inherent to preexisting methods (Figure 4).

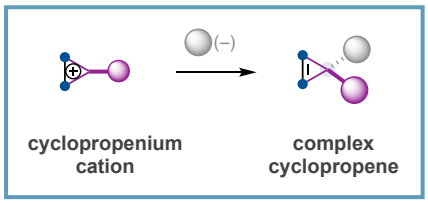

Figure 4 CPCs as three-carbon synthons for the synthesis of diverse cyclopropenes

Considering the selectivity and efficiency of CPCs in the synthesis of complex cyclopropenes with a variety of nucleophiles, we then wondered whether they could undergo an aryl C-H bond cyclopropenylation in densely functionalized settings. Small rings are prevalent in drug design, yet cyclopropenes remain underexplored in medicinal chemistry. Their existing synthetic pathways are hardly amenable in complex architectures: albeit challenging, a suitable methodology for their incorporation into drug molecules remains highly desirable. Moreover, cyclopropenes are well known for their unique potential as versatile building blocks in organic synthesis, and the late-stage installation of a cyclopropene in a drug-molecule would also represent a potential stepping stone to sp^3-rich scaffolds relevant to medicinal chemistry (Figure 5).

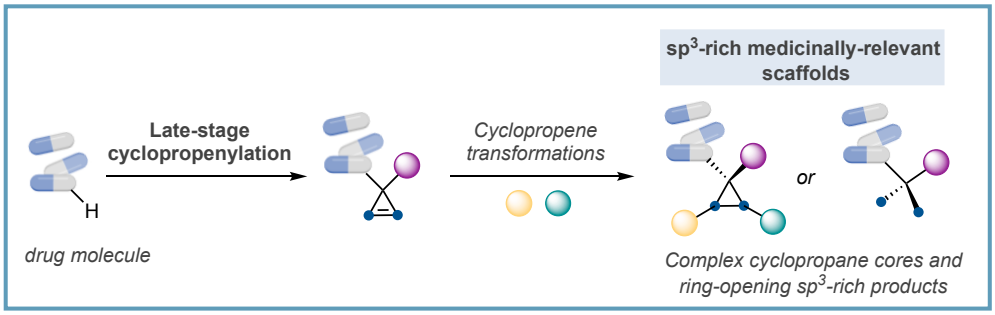

Figure 5 Late-stage cyclopropenylation and cyclopropenes transformations to medicinally-relevant scaffolds

In Chapter IV, we extend the synthetic utility of our CPCs by using aromatic rings as nucleophiles in a Friedel-Crafts-type transformation. The process occurs in a regio-, site- and chemoselective manner in simple settings and in complex architectures. Importantly, this represents the first report of a late-stage incorporation of cyclopropene rings in densely-functionalized drug molecules and natural products. We also explore the versatile reactivity of the cyclopropene scaffold with various reported transformations affording medicinally-relevant motifs. Finally, a collaboration with the Novartis Institute for Biomedial Research allowed to evaluate the impact of the cyclopropene motif on the metabolic stability of the cyclopropenylated drug molecules.

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Chapter I

General Introduction

1.1 Carbene species

1.1.1 Free carbenes

Carbene species are neutral divalent carbon atoms holding six electrons in their valence shell, two of which are non-bonded. The ground state spin multiplicity of carbenes dictates their reactivity. Carbenes can exist in a singlet state, or in a triplet state. In the lowest energy configuration, the singlet state, the electrons are paired in one sp^2 orbital, with a net angular momentum and a spin quantum number equal to zero (S = ½ + (-½) = 0) and a multiplicity of one ($m_s = 2S + 1 = 1$). In the triplet state, the two electrons are unpaired and placed in two different orbitals, a *p* and a σ orbital with an overall spin quantum number equal to one, and a multiplicity of three (Figure 1, left). Singlet carbenes have one filled σ and one vacant *p* orbital, giving them an ambiphilic character. Triplet carbenes, with two singly occupied orbitals, can be considered as diradicals. [1]

The multiplicity of carbenes is governed by electronic and steric effects of their substituents. While the higher spin triplet state should be preferred according to Hund's rule, singlet carbenes can be favored in presence of π-donating substituents, due to a favorable overlap with the carbene empty *p* orbital, allowing for mesomeric stabilization. The parent carbene methylene exists thus in a triplet ground state, favored by 9 kcal/mol over the singlet state, whereas π-donors substituents such as -NR_2, OR, -SR, -F, -Cl, -Br and -I favor the ground singlet state. [1,2]

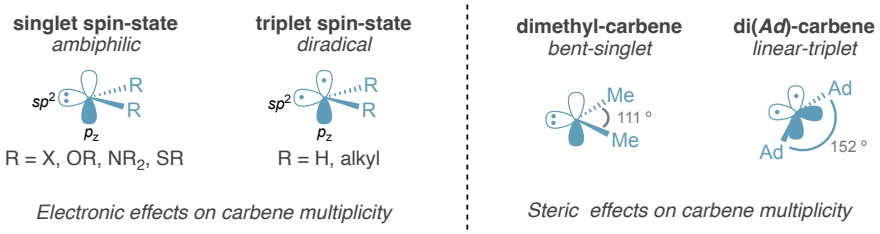


Figure 1 Schematic representation of singlet and triplet carbenes with steric and electronic effects on multiplicity

Steric effects can also play a major role in carbene ground states. A linear geometry, in which the carbene frontier orbitals are close to degeneracy, favors the triplet state: increasing the carbene bond angle with bulky substituents will thus favor a triplet state. In this way, while dimethylcarbenes have a bent ground singlet state (carbene bond angle of 111º), bulkier diadamantylcarbenes are triplet carbenes, with a bond angle of 152º (Figure 1, right). [1,3]

The first stable, free singlet carbenes were isolated for the first time in 1988 by Bertrand as phosphinocarbenes (Figure 2, left).[4] The silicon and phosphorus substituents allowed for stabilization of the carbene carbon atom. A few years later, Arduengo reported the first synthesis of a crystalline *N*-heterocyclic carbene (NHC) by

[1] (a) Bourissou, D. ; Guerret, O.; Gabbaï, P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39; (b) de Frémont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862.
[2] (a) Mueller, P. H.; Rondan, N. G.; Houk, K. N.; Harrison, J. F.; Hooper, D.; Willen, B. H.; Liebman, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 5049; (b) Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109*, 3275.
[3] Myers, D. R.; Senthilnathan, V. P.; Platz, M. S.; Jones, M. *J. Am. Chem. Soc.* **1986**, *108*, 4232.
[4] (a) Igau, A.; Grutzmacher, H.; Baceiredo, A.; Bertrand, G. *J. Am. Chem. Soc.* **1988**, *110*, 6463; (b) Gillette, G. R.; Baceiredo, A.; Bertrand, G. *Angew. Chem. Int. Ed.* **1990**, *29*, 1429.

deprotonation of *N,N'*-diadamantyl imidazolium salt (Figure 2, right). The stability and ease of isolation of this first NHC aroused a tremendous interest in the synthetic community, and NHCs have since then been extensively studied as ligands in organometallic chemistry, showing properties comparable to phosphines.[5]

Phosphinocarbene *Bertrand* **N-heterocyclic carbene (NHC)** *Arduengo*

Figure 2 First stable, isolated free singlet carbenes

1.1.2 Metal carbenes: general considerations

Carbenes coordinated to a transition-metal center are known as metal carbenes ($M{=}CR_2$). The first metal carbene was characterized and reported by Fischer in 1964.[6] Since then, these organometallic species have found broad applications in organic synthesis and catalysis.[7] Metal carbenes can be divided in two classes: Fischer-type[6] and Schrock-type carbenes.[8]

Fischer-type carbenes are usually late-transition metal complexes (groups VI-VIII) in a low oxidation state, containing π-acceptor ligands such as carbon monoxide.[9] Heteroatoms (π-donors) such as oxygen or nitrogen on the carbene center stabilize the carbene carbon atom. The carbene is in a singlet state, and its σ lone electron pair injects electron density into the vacant d_{z2} orbital of the metal. π-back donation from the metal d_{xy} orbital to the carbene p orbital is weaker due to the presence of the π-acidic CO ligand (Figure 3, left). Fischer-type carbenes are therefore highly electrophilic and tend to undergo nucleophilic attacks.[10] Their reactivity is very rich, and Fischer carbene complexes have been used as reagents in numerous transformations[9] among which the Dötz benzannulation,[11] cyclopropanations, and cycloadditions stand out as the most characteristic ones. Methodologies proposing the catalytic generation of Fischer carbenes remain however scarce, and include seminal reports with W(0) catalysts[12] as well as more recent works using Rh(I), Cu(I) and Pd(0) catalysts[13].

[5] For selected reviews on NHCs and their use in organic synthesis, see : (a) Crabtree, R. H. *J. Organomet. Chem.* **2005**, *690*, 5451; (b) Hahn, F. E.; Jahnke, M. C. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122; (c) Nelson, D. J.; Nolan, S. P. *Chem. Soc. Rev.* **2013**, *42*, 6723; (d) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485; (e) Zhao, Q.; Meng, G.; Nolan, S. P.; Szostak, M. *Chem. Rev.* **2020**, *120*, 1981.
[6] Fischer, E. O.; Maasböl, A. *Angew. Chem. Int. Ed.* **1964**, *8*, 580.
[7] Dötz, K. H. (Ed.) Topics in Organometallic Chemistry: Metal Carbenes in Organic Synthesis. *Springer,* **2004**.
[8] Schrock, R. R. *J. Am. Chem. Soc.* **1974**, *96*, 6796.
[9] Dötz, K. H.; Stendel, J. *Chem. Rev.* **2009**, *109*, 3227.
[10] Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810.
[11] Dötz, K. H. *Angew. Chem.* **1975**, *87*, 672.
[12] (a) McDonald, F. E.; Reddy, S. K. ; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304; (b) McDonald, F. E.; Reddy, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 3653 ; (c) Wipf, P. ; Graham, T.H. *J. Org. Chem.* **2003**, *68*, 8798 ; (d) Barluenga, J. ; Diéguez, A. ; Rodríguez, F.; Fañanas, F. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 126.
[13] (a) Takano, S. ; Shiomi, R. ; Morimoto, Y. ; Kochi, T. ; Kakiuchi, F. *Angew. Chem. Int. Ed.* **2020** ; (b) Takeuchi, T. ; Aoyama, T.; Orihara, K. ; Ishida, K. ; Kusama, H. *Org. Lett.* **2021**, *23*, 9490 ; (c) Zheng, L. ; Guo, X. ; Li, Y.-C. ; Wu, Y. ; Xue, X.-S. ; Wang, P. *Angew. Chem. Int. Ed.* **2023**, *62*, e202216373 ; (d) Sakurai, S. ; Inagaki, T. ; Kodama, T. ; Yamanaka, M. ; Tobisu, M. *J. Am. Chem. Soc.* **2022**, *144*, 1099.

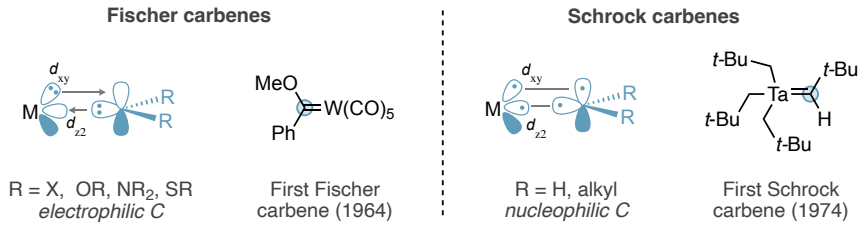


Figure 3 Fischer- and Schrock-type carbenes

Schrock-type carbenes, on the opposite, are found in early transition metals with high oxidation states (Figure 3, right). Substituents on the carbene carbon atom are poorly stabilizing (H or alkyl groups), while the metal ligands are strong electron donors. Such carbene complexes are usually considered to be in a triplet state. The two unpaired electrons of the carbene carbon atom interact with the metal *d* orbitals to form what is considered as a M=C double bond. The carbene complexes formed are nucleophilic and may resemble ylides rather than carbenes in their reactivity.[1b,10] Schrock carbenes are known for their important role in the development of alkene metathesis, awarded with a Nobel prize in 2005.[14]

The quest for stable metal carbene complexes was actively pursued over the last decades, and nowadays, stable metal carbenes play one of their most typical roles as catalysts in olefin metathesis. In particular, Schrock carbenes, first- and second-generation ruthenium carbenes developed by Grubbs, and the Hoveyda-Grubbs catalyst are among the most widely used catalysts for such processes (Figure 4). [15]

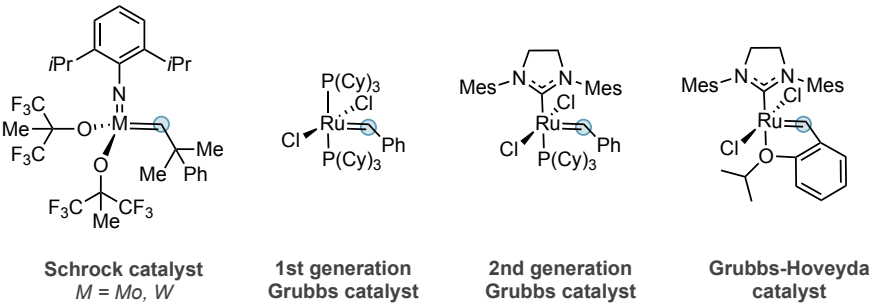


Figure 4 Carbene complexes catalysts for olefin metathesis

1.1.3 Metal carbenes as reactive intermediates

Aside from their role as catalysts, metal carbenes are also crucial intermediates in numerous carbene-related organic reactions, among which the most emblematic ones are X-H insertions (X=C, Si, O, S, N), cyclopropanations and ylide reactions.[16] [10]

[14] Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *43*, 3748.
[15] (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243, (b) Vougioukalakis, G. C. ; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746.
[16] For selected reviews, see : (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911 ; (b) Zhang, Y.; Wang, J. *Chem. Commun.* **2009**, 5350; (c) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704; (d) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981; (e) He, Y.; Huang, Z.; Wu, K.; Ma, J.; Zhou, Y. G.; Yu, Z. *Chem. Soc. Rev.* **2022**, *51*, 2459.

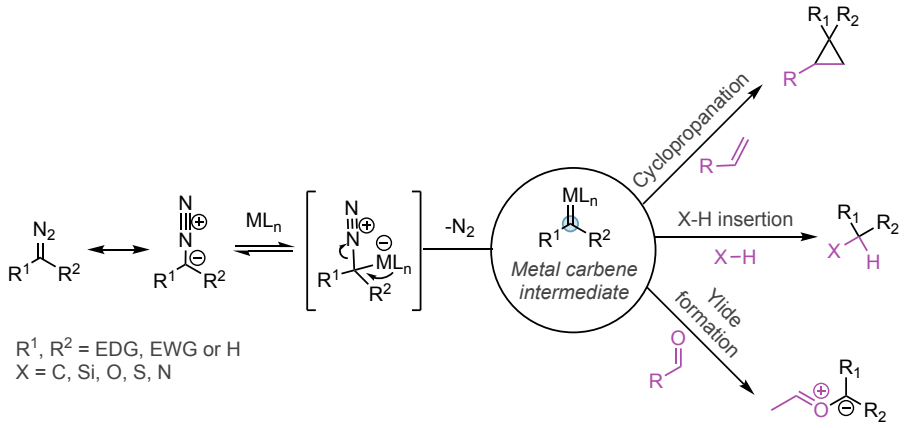


Figure 5 Metal carbenes in representative carbene-related transformations

The catalytic decomposition of diazo compounds, illustrated in Figure 5, is the most employed synthetic pathway to metal carbenes. The reactivity of metal carbenes can be tuned by the choice of the substituents on the diazo compounds, which can be classified as (1) acceptor only, (2) acceptor-acceptor, (3) acceptor-donor and (4) donor-donor, based on the electronic features of the substituents. The electronic properties generate carbene species with different electrophilicities, and can either stabilize or enhance the reactivity of the generated metal carbenes (Figure 6). These metal carbene intermediates have no heteroatom substituent to stabilize of the carbene vacant *p*-orbital, which makes them particularly electrophilic at the metal-carbon bond.[16b]

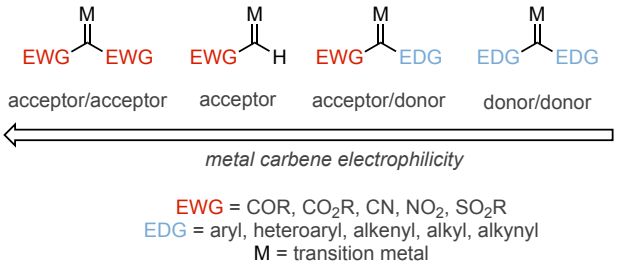


Figure 6 Different types and reactivity of metal carbene intermediates from diazo compounds

The first metal-carbene formation from the decomposition of a diazo compound was catalyzed by copper, as disclosed by Yates in 1952.[17] In the late 1970s, Rh(II) tetracarboxylates were discovered to catalyze the decomposition of ethyl diazoacetate in an intermolecular C-H insertion reaction with alkanes.[18] Their utility was rapidly extended to X-H insertions,[19] cyclopropanations,[20] cyclopropenations[21] and later on to [3+4] annulations[22]

[17] (a) Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 5376; (b) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348.
[18] (a) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *14*, 2233; (b) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *J. Chem. Soc. Chem. Commun.* **1981**, *14*, 688.
[19] (a) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1974**, *7*, 607; (b) Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssié, P. *Tetrahedron* **1982**, *38*, 2733.
[20] Hubert, A. J.; Noels, A.F.; Anciaux, A.J.; Teyssié, P. *Synthesis* **1976**, *600.*
[21] Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, *19*, 1239.
[22] Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203.

or ylide formation.[23] Notably, rhodium (II) paddlewheel bimetallic compounds quickly emerged as the most versatile catalysts for C-H carbene insertion (Figure 7).[24,25]

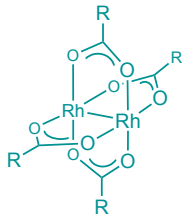


Figure 7 Rh(II) carboxylate paddlewheel catalysts

The dimetallic nature of dirhodium carbenes makes them particularly electrophilic. It was proposed that one rhodium atom served as carbene binding site throughout the carbene transfer, while the second rhodium atom acted as mobile metalloligand, increasing the electrophilicity of the carbene, and its reactivity. [26] Originally, dirhodium tetracarboxylates were used with acceptor diazoacetates, the combination of which led at first to site- or diastereoselectivity challenges in the C-H functionalization reactions and cyclopropanations, respectively, due to the high reactivity of the carbene complex involved. Breakthrough contributions from the group of Davies led to the conclusion that tuning the diazo source allowed to modulate the reactivity of such carbene intermediates.[27,24] Notably, Davies pioneered the use of acceptor/donor diazo compounds as rhodium carbene precursors, which proved crucial to the development of selective carbene-based transformations (Figure 8).[28]

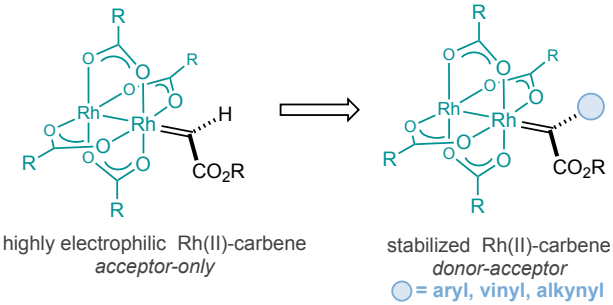


Figure 8 From acceptor-only to donor-acceptor Rh(II)-carbenes

Catalyst design also revealed to be crucial to achieve selective dirhodium catalyzed carbene transfer reactions.[29] Variation of the carboxylate ligands from $[Rh_2(OAc)_4]$ include adamantane-1-carboxylate, pivalate, triphenyl

[23] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
[24] (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861; (b) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857; (c) Davies, H. M. L.; Liao, K. *Nat. Rev. Chem.* **2019**, *3*, 347.
[25] Wu, R.; Zhu, D.; Zhu, S. *Org. Chem. Front.* **2023**, *10*, 2849.
[26] (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181; (b) Powers, I. G.; Uyeda, C. *ACS Catal.* **2017**, *7*, 936.
[27] Davies, H. M. L. *J. Org. Chem.* **2019**, *84*, 12722.
[28] For the initial report, see: Davies, H. M.L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.
[29] Padwa, A.; Austin, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 1797.

acetate, mandelate or salicylate.[30] Perfluorinated substituents such as trifluoroacetate [$Rh_2(tfa)_4$] or perfluorobutyrate [$Rh_2(pbf)_4$] showed to influence most the reactivity due to their distinct electronic properties, enhancing the electrophilicity of the rhodium carbene.[31] Dirhodium carboxamidates catalysts have also been designed, showing lower reactivity yet increased selectivity (Figure 9).[32]

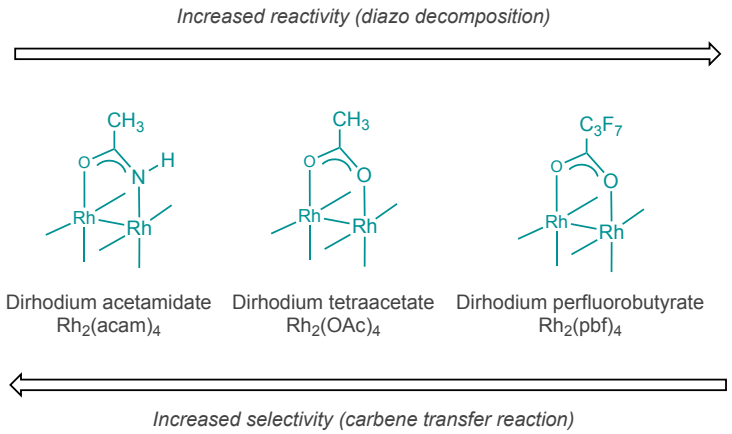


Figure 9 Reactivity trends in dirhodium paddlewheel complexes

$Rh_2(esp)_2$, a tethered dicarboxylate catalyst reported by Dubois in 2004 also showed considerable reactivity and selectivity, especially in amination reactions (Figure 10).[33]

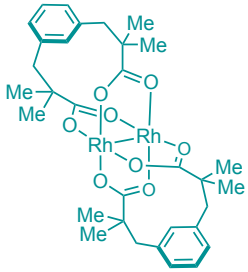
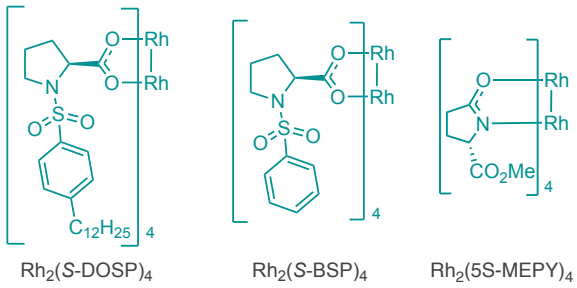


Figure 10 $Rh_2(esp)_2$ structure

All the abovementioned dirhodium complexes share a highly symmetric bimetallic paddlewheel scaffold (Figure 7), which plays a major role in chiral catalyst design as it allows more control in the asymmetric induction.[34]

[30] (a) Cotton, F.A.; Felthouse, T.R. *Inorg. Chem.* **1980**, *19*, 323; (b) Cotton, F.A.; Thompson, J.L. *Inorg. Chim. Acta* **1984**, *81*, 193; (c) Agaskar, P.A.; Cotton, F.A.; Falvello, L.R.; Han, S. *23*, 2408; (d) Bancroft, D.P.; Cotton, F.A.; Han, S. *Inorg. Chem.* **1984**, *23*, 2408.
[31] Doyle, M.P.; Shanklin, M.S. *Organometallics*, **1994**, *13*, 1081.
[32] Doyle, M. P.; Westrum , L.J.; Wolthuis, W. N. E.; See, M. M.; Boone, W.P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115,* 958.
[33] (a) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378; (b) Zalatan, D. N.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 7558.
[34] Hansen, J.; Davies, H. M. L. *Coord. Chem. Rev.* **2008**, *252*, 545.

Chiral dirhodium carboxylates were initially developed by McKervey,[35] Ikegami and Hashimoto,[36] and Davies.[37] They are constructed upon N-protected amino acid templates, holding four carboxylates symmetrically positioned aroud the dirhodium center, and show even greater reactivity than many achiral Rh(II) tetracarboxylates.[29c] The prolinate complex $Rh_2(DOSP)_4$, a dirhodium tetracarboxylate developed in the 1990s by Davies[38] allowed asymmetric induction in cyclopropanation reactions first[39] and then in [3+4] cycloadditions.[40] Chiral Rh(II) carboxamidates, constructed from amino acids-derived lactams such as $Rh_2(5S\text{-MEPY})_4$, were developed by Doyle.[41] These catalysts showed outstanding versatility, in particular in reaction involving acceptor-only carbenoids (Figure 10).[27]



$Rh_2(S\text{-DOSP})_4$ $Rh_2(S\text{-BSP})_4$ $Rh_2(5S\text{-MEPY})_4$

Figure 11 Examples of chiral dirhodium catalysts

Dirhodium (II) complexes form highly reactive carbenoid intermediates, however, the group of Davies succeeded first to characterize them in 2013 using vibrational and nuclear magnetic resonance spectroscopy.[42] Two years later, Fürstner and co-workers reported the first crystal structure of a dirhodium carbene complex.[43]

1.3 Carbyne species

1.3.1 Theoretical considerations

A carbyne is an electronically neutral monovalent carbon species with five valence electrons, three of which are non-bonded. The five valence electrons can be arranged in two different spin states. In the doublet spin-state, four electrons are paired in two σ-orbitals, of which one is bonding and the other one is non-bonding, and one unpaired electron is alone in a π orbital. The three non-bonding electrons are arranged as a in a carbene/radical species. In

[35] Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Roos, G. H. P. *J. Chem. Soc. Chem. Commun.* **1990**, 361.
[36] Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173.
[37] Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243.
[38] Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.
[39] (a) Davies, H. M. L.; Rusiniak, L. *Tetrahedron Lett.* **1998**, *39*, 8811; (b) Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett.* **2000**, *41*, 8189; (c) Davies, H. M. L.; Nagashima, T.; Klino, J. L., Org. Lett. **2000**, *2*, 823; (d) Davies, H. M. L.; Townsend, R. J. J. Org. Chem. **2001**, *66*, 6595; (e) Ventura, D. L.; Li, Z.; Coleman, M. G.; Davies, H. M. L. *Tetrahedron* **2009**, *65*, 3052; (f) Fu, L.; Mighion, J. D.; Voight, E. A.; Davies, H. M. L. *Chem. Eur. J.* **2017**, *23*, 3272.
[40] (a) Reddy, R. P.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 10312; (b) Olson, J. P.; Davies, H. M. L. *Org. Lett.* **2008**, *10*, 573; (c) Davies, H. M. L.; Stafford, D. G.; Doan, B. D.; Houser, J. H. *J. Am. Chem. Soc.* **1998**, *120*, 3326.
[41] Doyle, M. P.; Brandes, B. D.; Kazala, A. P.; Pieters, R. J.; Jarstfer, M. B.; Watkins, L. M.; Eagle, C. T. *Tetrahedron Lett.* **1990**, *31*, 6613.
[42] Kornecki K.P. ; Briones J.F. ; Boyarskikh V. ; Fullilove F. ; Autschbach J. ; Schrote K.E. ; Lancaster K.M. ; Davies H.M. ; Berry J.F. ; *Science* **2013**, *342*,351.
[43] Werlé, C.; Goddard, R.; Fürstner, A. *Angew. Chem.* **2015**, *127*, 15672.

the quartet spin-state, two electrons are paired in a bonding σ orbital, and each of the three unbonded electrons are allocated in singly occupied orbitals, respectively one σ and two degenerate π orbitals, forming overall a triradical species. In the case of the parent carbyne methylidyne (:Ċ-H), the doublet spin-state is the ground-state and lies below the quartet spin-state by 17 kcal/mol.[44] Its hypovalent character endows methylidyne with a high reactivity and electrophilicity, as shown by its heat of formation of 141 kcal/mol, versus 92 kcal/mol for divalent methylidene and 35 kcal/mol for the trivalent methyl radical (Figure 12).[45]

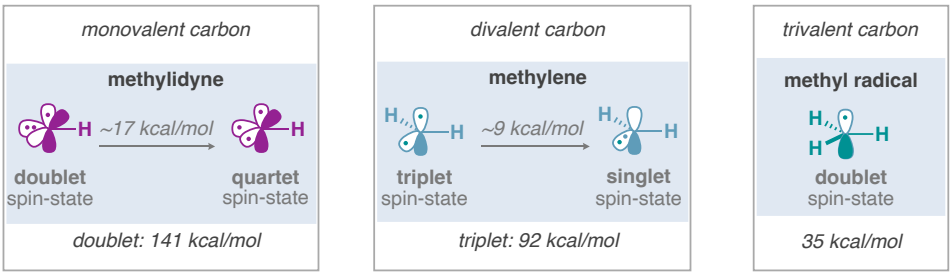


Figure 12 Hypovalent carbon species and their electronic ground states

Tuning the electronic ground state is however a non-trivial challenge, first due to the high energy difference between the doublet and the quartet spin state, and also to the presence of only one substituent on carbyne compounds, which decreases the tunability of carbynes. Computational studies have however shown that the quartet spin-state can become the ground state in the case where an electropositive substituent X such as Li, Na or K is present on the carbyne.[46] The C-X bond becomes ionic, and C^- is then isoelectronic to a N or P atom which do have a quartet ground-state. In this way, in the hypothetical compound [C^-Li^+], the quartet ground-state is lower than the doublet spin-state by 33 kcal/mol. Additional theoretical studies by Hoffman and co-workers[44] showed that π-accepting substituents, as a secondary parameter, also allow to stabilize the two degenerate π orbitals which then lie closer to the non-bonding σ orbital and favors the quartet spin-state as ground electronic state. Ultimately, electronegative, π-donating substituents such as halogens led to a doublet spin-state as ground electronic state (Figure 13). In this way, in the theoretical compound CF, the doublet spin-state was calculated to lie lower than the quartet spin-state by 78 kcal/mol. [44]

[44] Zeng, T.; Wang, H.; Lu, Y.; Xie, Y.; Wang, H.; Schaefer, H. F.; Ananth, N.; Hoffmann, R. *J. Am. Chem. Soc.* **2014**, *136*, 13388.
[45] Shelvin, P. B. Atomic Carbon In *Reactive Intermediate Chemistry* Moss, R. A.; Platz, M. S.; Jones M. J., Eds.; Wiley&Sons: New Jersey, **2004**; pp. 465.
[46] (a) Mavridis, A.; Harrison, J. F. *J. Phys. Chem.* **1982**, *86*, 1979; (b) Boldyrev, A. I.; Simons, J. *J. Phys. Chem.* **1993**, *97*, 1526.

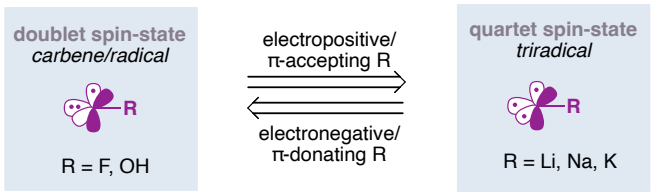


Figure 13 Carbyne species and doublet *vs* quartet state

1.3.2 Free carbyne generation

Methylidyne, the parent carbene of formula :ĊH, was one of the first molecules to be identified in the interstellar space, first at visible wavelengths in the late 1930s,[47] and later in radio[48] and far-ultraviolet wavelengths.[49] Methylidyne is among the most abundant molecules in the interstellar space, produced in the sequences of ion-molecules reactions governing interstellar chemistry. Interestingly, its deuterated isotopologue, :ĊD, was also identified in the interstellar medium for the first time in 2023.[50]

Different carbyne species were also generated in the gas phase in the laboratory, using high-energy processes, producing carbynes among other reactive radicals in overall complex reaction mixtures.[51] :ĊH was for example obtained from methane by flash[52] or laser[53] photolysis and pulsed radiolysis.[54] $CHBr_3$[55] or CH_3NH_2[56] were also used as methylidyne sources with laser photolysis. Halomethylidynes such as :ĊBr, :ĊCl and :ĊF have also been generated by flash photolysis of $CHBr_3$, $CHClBr_2$ or $CHFBr_2$, respectively.[57]

Strausz and co-workers reported the solution phase generation of ethyl ester carbyne (:Ċ-CO_2Et) by the *in situ* UV light photolysis in ether of the Buchner reagent,[58] diethyl mercury-*bis*diazoacetate, in the late 1960s.[59] A single, symmetrical electron paramagnetic resonance (EPR) signal at -196 ºC indicated the presence of a doublet ground-state radical species with no adjacent protons. When the photolysis was performed in cyclohexene, products of C-H insertion, cyclopropanation and hydrogen atom transfer (HAT) were observed, pointing to the presence of ethyl ester carbyne intermediate, with a dual carbene/radical behavior, among other reactive species (Figure 14). Additional studies led to the conclusion that cyclopropanation and C-H insertion take place before the HAT, discarding a HAT-generated carbene as reactive intermediate. The nature and ground state electronic configuration of the intermediate formed was further studied by performing the reaction in *trans* and *cis* 2-butene. The cyclopropanation occurred in a highly stereospecific manner, with conservation of the stereochemical

[47] Swings, P.; Rosenfeld, L. *Astrophys. J.* **1937**, *86*, 483.
[48] Rydbeck, O. E. H.; Elldér, J.; Irvine, W.M. *Nature*, **1973**, *246*, 466.
[49] Sheffer, Y.; Federman, S. R. *Astrophys. J.* **2007**, *659*, 1352.
[50] Jacob, A. M.; Menten, K. M.; Wyrowski, F.; Sipilä, O *Astron. Astrophys.* **2023**, *675*, 1.
[51] James, F.C.; Choi, H. K. J.; Ruzsicska, B.; Strausz, O. P.; Bell, T.N. The Gas Phase Chemistry of Carbynes In *Frontiers of Free Radical Chemistry* Pryor, W. A., Ed.; Academic Press, Inc: New-York, **1980**; pp. 139-169.
[52] Braun, W.; McNesby, J.R.; Bass, A.M. *J. Chem. Phys.* **1967**, *46*, 2071.
[53] Kasdan, A.; Herbst, E. *Chem. Phys. Lett.* **1975**, *31*, 78.
[54] Bosnali, M. W.; Perner, D. *Naturforsch.* **1971**, *26a*, 1768.
[55] Butler, J. E.; Goss, L. P.; Lin, M. C.; Hudgens, J. W *Chem. Phys. Lett.* **1979**, *63*, 104.
[56] Messing, I.; Sadowski, C. M.; Filseth, S. V. *Chem. Phys. Lett.* **1979**, *66*, 95.
[57] Ruzsicska, B. P.; Jodhan, A.; Choi, H. K. J.; Strausz, O. P. *J. Am. Chem. Soc.* **1983**, *105*, 2489.
[58] Buchner, E. *Berichte der Dtsch. Chem. Gesellschaft* **1985**, *28*, 215.
[59] (a) DoMinh, T.; Gunning, H. E.; Strausz, O. P. *J. Am. Chem. Soc.* **1967**, *89*, 6785; (b) Strausz, O. P.; DoMinh, T.; Font, J. *J. Am. Chem. Soc.* **1968**, *90*, 1930.

information of the starting material. These experiments pointed to a concerted addition of ethyl ester carbyne in a doublet ground state, in a spin multiplicity-based analogy with singlet carbene.[60]

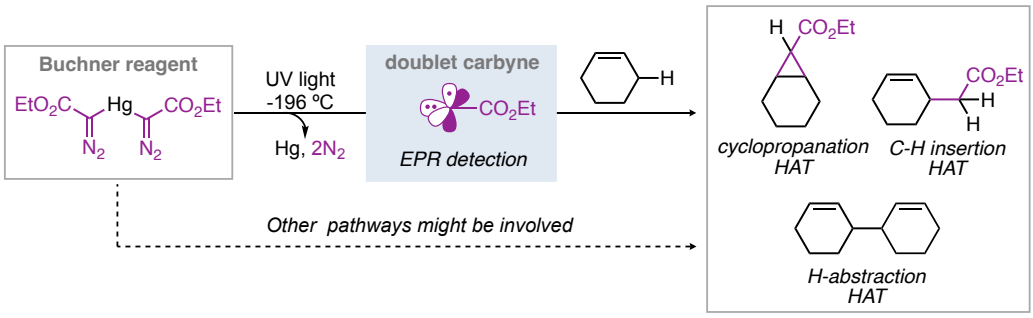


Figure 14 Generation of a doublet state carbyne equivalent from diethyl mercury-*bis*diazoacetate

Additional studies on the photolysis of diethyl mercury-*bis*diazoacetate with chloroalkanes and heterocyclic systems were performed by Patrick and co-workers.[61] Regioselective carbyne insertion was observed into the C-Cl bond[61a] and into the C-H bond α to the heteroatom[61b] again indicated the generation of the doublet carbyne :Ċ-CO_2Et.

In 2005, Bino and co-workers reported the formation of 2-butyne from the decomposition of a trimolybdenum cluster containing two bridging ethylidyne ligands.[62] The presence of the paramagnetic molybdenum metal clusters impeded the use of EPR to detect the formation of a carbyne species. Nonetheless, isotope-labeling experiments performed later on excluded the possibility of an intramolecular mechanism and demonstrated the formation of free methyl carbyne radicals in aqueous solution, reacting together to afford 2-butyne. Pseudo-homolytic dissociation of the metallic system was proposed to generate quartet carbynes which further dimerized to form alkynes (Figure 18).[63] Additional theoretical studies and calculations led to the conclusion that the free carbyne species generated by the decomposition of the metal complex had a quartet spin-state as ground state.[64]

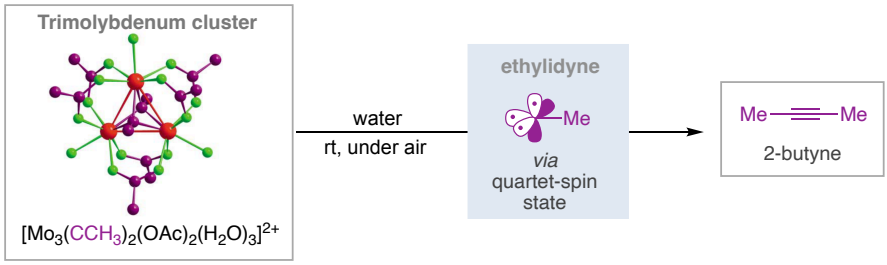


Figure 15 Quartet state carbyne from the decomposition of a molybdenum cluster

[60] Strausz, O. P.; Kennepohl, G. J. A.; Garneau, F. X.; DoMinh, T.; Kim, B.; Valenty, S.; Skell, P. S. *J. Am. Chem. Soc.* **1974**, *96*, 5723.
[61] (a) Patrick, T. B.; Kovitch, G. H. *J. Org. Chem.* **1975**, *40*, 1527; (b) Patrick, T. B.; Wu, T. *J. Org. Chem.* **1978**, *43*, 1506.
[62] Bino, A.; Ardon, M.; Shirman, E. *Science* **2005**, *308*, 234.
[63] Bogoslavsky, B.; Levy, O.; Kotlyar, A.; Salem, M.; Gelman, F.; Bino, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 90.
[64] Danovich, D.; Bino, A.; Shaik, S. *J. Phys. Chem. Lett.* **2013**, *4*, 58.

A similar observation to the abovementioned Bino experiment[62] was made by Falck and Mioskwski in 2007, when they reported the formation of alkynes from the reaction between 1,1,1-trichloroalkyls and low-valent Cr^{2+}.[65] Their mechanistic proposal involved the formation of chromium-carbyne complexes as key intermediates, a theory discarded by subsequent theoretical studies of Bino. Free carbyne radicals, formed from the reduction of 1,1,1-trihaloalkyls by low-valent Cr^{2+} metal ions, were identified as key intermediates instead.[66] Another experimental observation of a quartet-spin state carbyne was reported by Zhou and Li in 2020.[67] The carbonyl complex BeBeCO was first formed through reaction of beryllium dimers with carbon monoxide. Photorearrangement of the latter species then afforded a BeCOBe isomer first, followed by the lower energy BeOBeC multiple radical under UV-visible light excitation. Quantum calculations led to the conclusion that the carbyne present on the most stable BeOBeC isomer existed in a quartet spin-state with three unpaired electrons (Figure 16).

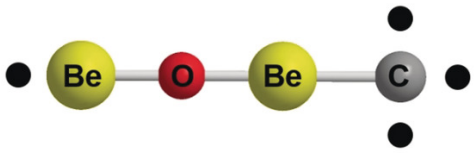


Figure 16 BeOBeC multiple radical featuring a quartet carbyne moiety

1.3.3 Metal carbynes

Metallacarbynes, or alkylidyne complexes, are organometallic compounds containing a metal-carbon triple bond. They were reported first by Fischer in 1973,[68] and shortly after by Schrock,[69] and have been extensively studied since their discovery.[70] In analogy with metal carbenes, metallacarbynes are also classified as Fischer or Schrock-type carbynes. Fischer are formed with low valent transition metals and are generally stabilized by π-acceptor ligands such as CO. They display an electrophilic behavior. Schrock complexes tend to show a nucleophilic reactivity, and are formed with metals in the highest possible oxidation state, such as W, Ta, Re or Mo. This dual classification of metallacarbynes is however more of a formalism, and their distinct reactivity is less obvious than in the case of metal carbenes. Alkylidyne complexes are usually obtained from transformations of the parent carbenes, by elimination processes (Figure 17).

[65] Bejot, R.; He, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem. Int. Ed.* **2007**, *119*, 1749.
[66] Levy, O.; Bino, A. *Chem. Eur. J.* **2012**, *18*, 15944.
[67] Li, W. L.; Zhang, Q.; Chen, M.; Hu, H. S.; Li, J.; Zhou, M. *Angew. Chem. Int. Ed.* **2020**, *59*, 6923.
[68] Fischer, E. O.; Kreis, G.; Kreiter, C. G.; Müller, J.; Huttner, G.; Lorenz, H. *Angew. Chem. Int. Ed.* **1973**, *12*, 564.
[69] Guggenberger, L. J.; Schrock, R. R. *J. Am. Chem. Soc.* **1975**, *97*, 2935.
[70] For selected reviews, see : (a) Fischer, E. O.; Schubert, U.; Fischer, H. *Pure Appl. Chem.* **1978**, *50*, 857; (b) Kim, H. P.; Angelici, R. J. *Adv. Organomet. Chem.* **1987**, *27*, 51; (c) Mayr, A.; Hoffmeister, H. *Adv. Organomet. Chem.* **1991**, *32*, 227; (d) Yyboishchikov, S. F.; Frenking, G. *Chem Eur. J.* **1998**, *4*, 1439; (e) Schrock, R. R. *J. Chem. Soc. Dalt. Trans.* **2001**, 2541, (f) Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145.

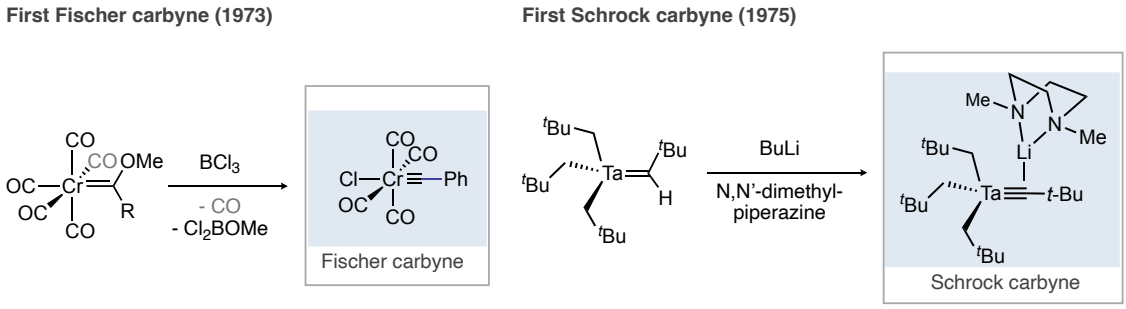


Figure 17 First Fischer and Schrock carbynes

The most well studied application of alkylidyne complexes is their role in alkyne metathesis. Fischer-type carbynes revealed inefficient at catalysing such process, but Schrock alkylidynes can undergo and mediate ring-closing and ring-opening alkyne metathesis, and have been extensively used for this purpose.[71] An example of the use of alkylidyne complexes is shown in Figure 18, with a ring-closing alkyne metathesis in the total synthesis of Ecklonialactones A and B.[72] Fischer-type carbynes, however, have shown to successfully induce polymerization in alkynes.[73]

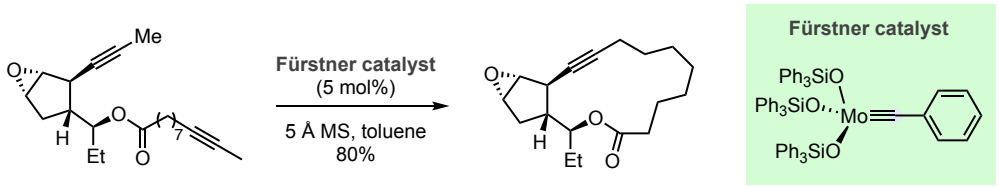


Figure 18 Alkylidyne complexes for alkyne metathesis

Alkylidyne complexes have found applications in organic synthesis. Nonetheless, if alkyne metathesis might be considered as a type of carbyne transfer, this process is limited to alkynes. Alkylidynes complexes were thus never used as general carbyne precursors for the catalytic transfer of monovalent carbon units into organic molecules, due to the lack of suitable monovalent carbon species (Figure 19).

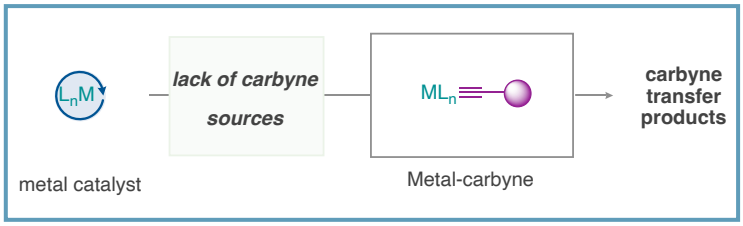


Figure 19 Long-standing issue : catalytic generation of metal-carbynes

[71] For reviews, see (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794; (b) Cui, M.; Jia, G. *J. Am. Chem. Soc.* **2022**, *144*, 12546.
[72] Hickmann, V.; Alcarazo, M.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, *132*, 11042.
[73] Katz, T. J.; Ho, T. H.; Shih, N.-Y.; Ying, Y.-C.; Stuart, V. I. W. *J. Am. Chem. Soc.* **1984**, *106*, 2659.

1.4 Hypervalent iodine reagents

1.4.1 General considerations

Iodine is the heaviest nonmetallic element and belongs to group XVII of the Periodic Table. Iodine stands out as the least electronegative and most polarizable among the halogens, and may resemble transition metals due to its variety of oxidation states, structural features and reactivity patterns in organic transformations.[74] As opposed to lighter main group elements, iodine is able to form hypervalent compounds, the first of which, iodobenzene dichloride was reported by C. Willgerodt in 1886.[75]

1.4.2 Structure and bonding

The term hypervalent was introduced by Musher in 1969, for the description of compounds in groups XV-XVIII of the periodic table that do not follow the classical 2 center-2 electrons (2c-2e) bonding described by Lewis.[76] Hypervalent iodine reagents are classified by their oxidation state in two different classes: (1) Iodine (III), or λ^3-iodanes, and (2) Iodine (V), or λ^5-iodanes (Figure 20).

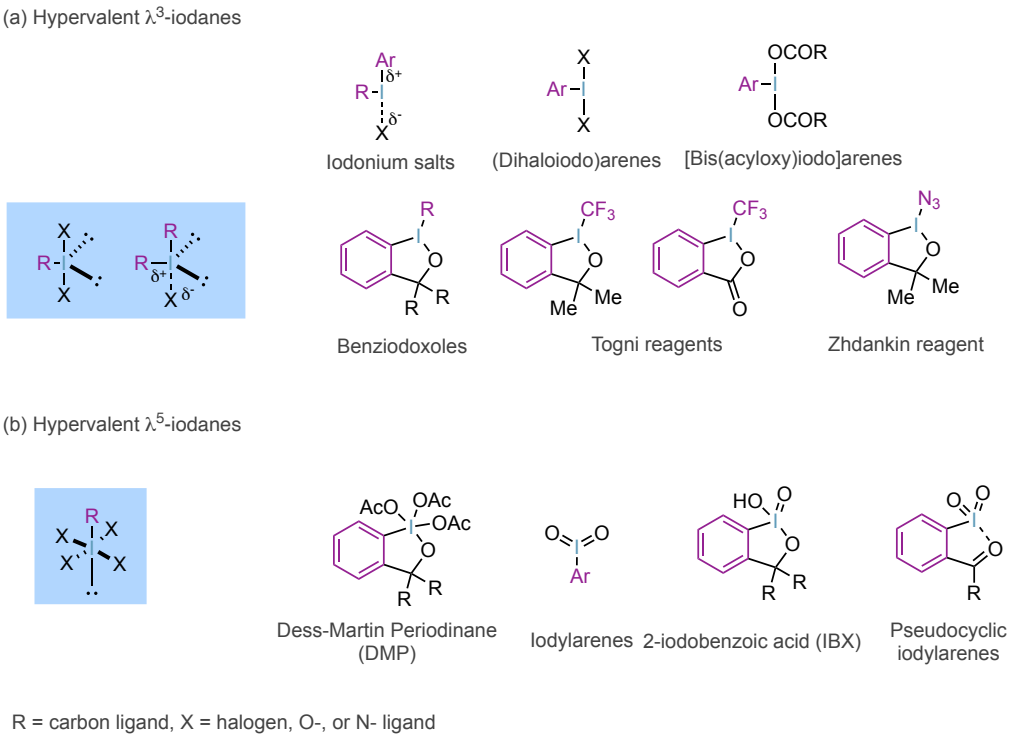


Figure 20 Structures of hypervalent iodine reagents and selected examples

[74] (a) Yoshimura, A.; V. V. Zhdankin *Chem. Rev.* **2016**, *116,* 3328; (b) Wirth, T. (Ed.) Hypervalent Iodine Chemistry. *Springer International Publishing,* Topics in Current Chemistry, **2016**, *373*; (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299; (d) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893; (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.
[75] Wilgerodt, C. *J. Prakt. Chem.* **1886**, *33*, 154.
[76] (a) Musher, J. *Angew. Chem. Int. Ed.* **1969**, *8*, 54; (b) Noury, S.; Silvi, B.; Gillespie, R. J. *Inorg. Chem.* **2002**, *41*, 2164.

λ^3-iodanes have 10 electrons at the iodine atom, in a RIX_2 docet structure where X are heteroatom ligands. Such compounds have a trigonal (pseudo)bipyramidal geometry, with the ligands placed along the axis in the apical position, and the two lone pairs of the iodine atom and the carbon substituent are placed in equatorial positions, in a T-shaped structure. (Figure 20, a). λ^5-iodanes, of the formula RIX_4, have a dodecet structure and show a square bipyramidal geometry with the organic substituent R and a lone pair in the apical positions, and the four electronegative substituents in the basal positions (Figure 20, b).

The hypervalent molecular orbitals of λ^3-iodanes involve the unhybridized 5*p* orbitals of iodine, and the ligand orbitals a linear X-I-X bond. This results in a linear three-center, four-electrons electronic distribution (3c-4e), the "hypervalent bond" (Figure 21). Such bonds are longer and weaker than regular covalent bonds, as well as highly polarized, due to the delocalization of the electrons of the bonding pairs into the more electronegative atoms. This confers to the central iodine atom a highly electrophilic character, central to its reactivity. The least electronegative carbon substituent is linked with a normal covalent bond. In the case of λ^5-iodanes, two orthogonal 3c-4e hypervalent bonds connect the four ligands across the plane, and the carbon substituent is linked with a regular covalent bond.[74]

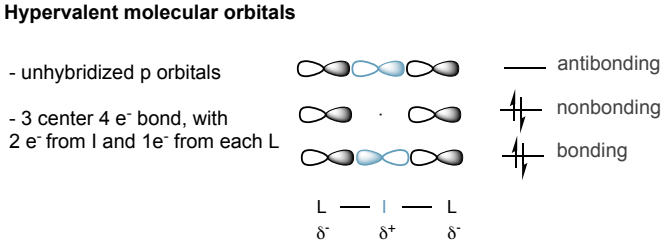


Figure 21 Molecular Orbital diagram for λ^3-iodanes

1.4.3 Reactivity of hypervalent iodine compounds

Hypervalent iodine chemistry has witnessed an exponential growth over the last years. Hypervalent iodine compounds share with transition metals a similar structure and reactivity, yet they are environmentally benign, cheaper, readily available and easier to handle, which explains their increasing popularity. Numerous λ^3-iodanes and λ^5-iodanes are now routinely used in organic synthesis.[74] The core of their reactivity lies in the following principles: (1) the iodine atom is highly electrophilic due to the abovementioned nature of the hypervalent bonding, (2) the aryliodo group Ar-I(X) is an excellent nucleofuge, owing to the favorable entropy of the hypervalent compound split into three, and (3) a return to normal valency favors the reductive elimination of iodine. The spectra of transformations enabled by hypervalent iodine compounds goes from bond formations (C-C, C-X and X-X bonds, with X= heteroatom), to oxidations and rearrangements. Sets of hypervalent iodine reagents have been judiciously designed to serve different kinds of purposes, such as oxidations,[77] aminations,[78]

[77] (a) Uyanik, M.; Ishihara, K. *Chem. Comm.* **2009**, 2086; (b) Singh, F. V.; Wirth, T. *Chem. Asian J.* **2014**, *9*, 972.
[78] Muñiz, K. *Acc. Chem. Res.* **2018**, *51*, 1507.

trifluoromethylations,[79] alkynylations[80] or arylation[81] reactions. A special mention goes to Togni's reagent, extensively exploited for trifluoromethylation reactions, [82] as well as Dess-Martin periodinane (DMP), a well-known mild oxidant (Figure 20).[83]

Hypervalent iodine reagents decorated with a diazo moiety were reported for the first time in 1994 by Weiss.[84] α-aryl iodonodiazo compounds were synthesized by S_N2 on the α-carbon of diazo esters with phenyliodine (III) diacetate (PIDA), with the retention of the diazo functionality (Figure 22). This resulted in an "umpolung" of the α-carbon of diazo compound, and afforded a highly electrophilic reagent.[85] This reactivity was then exploited with various nucleophiles, such as tertiary amines, pyridines, arsines, stibines and dialkyl sulfides. Notably, the use of triphenylphosphine led to the formation of a phosphazine, whose reactivity was further studied by Podrugina in 2019.[86]

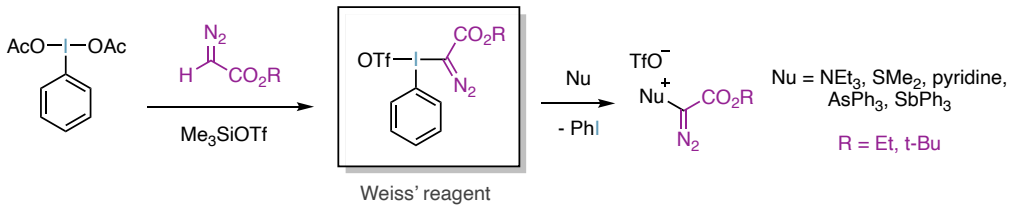


Figure 22 First synthesis of a α-aryl iodonodiazo compound

The group of Bonge-Hansen exploited Weiss' reagents in 2013 with a nucleophilic halogenation using tetrabutylammonium or potassium halides, leading to thermally unstable α-halodiazoacetate compounds.[87] Subsequent dirhodium(II) catalyzed intermolecular cyclopropanation of the *in situ* generated halodiazo compounds gave access to halocyclopropylesters and halocyclopropylphosphonates. (Figure 23, a)

A set of various linear aryliodonium reagents was optimized by the Gaunt group in 2018 and applied to the development of the first selective bioconjugation of proteins native at methionine residues, in a two-step protocol.[88] The S-Me group of the methionine side chain was successfully functionalized with a highly electrophilic linear λ^3–iodonio diazo reagent (Figure 23, b). The resulting protein-sulfonium conjugate, endowed with a new reactivity, served as platform for further biorthogonal protein functionalization by exploiting the inherent reactivity of the diazo compound. Fine-tuning of the hypervalent iodine reagent proved crucial to the obtention of high yields and selectivity to the methionine thioether residue.

[79] Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650.
[80] Hari, D. P.; Caramenti, P.; Waser, J. *Acc. Chem. Res.* **2018**, *51*, 3212.
[81] Beringer, F. M.; Daniel, W. J.; Galton, S. A.; Rubin, G. *J. Org. Chem.* **1966**, *31*, 4315.
[82] (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. Eur. J.* **2006**, *12*, 2579; (b) Kieltsch, I.; Eisenberger, P.; Togni, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 754.
[83] Dess, D. B.; Martin, J. C. *J. Org. Chem.*, **1983**, *48*, 4155.
[84] Weiss, R.; Seubert, J.; Hampel, F. *Angew. Chem. Int. Ed.* **1994**, *33*, 1952.
[85] Zhao, R.; Shi, L. *Angew. Chem. Int. Ed.* **2020**, *59*, 12282.
[86] Podrugina, T. A.; Pavlova, A. S.; Vinogradov, D. S.; Shuvalov, M. V; Potapov, I. D.; Levina, I. I.; Mironov, A. V; Gleiter, R. *Russ. Chem. Bull.* **2019**, *68*, 284.
[87] Schnaars, C.; Hennum, M.; Bonge-Hansen, T. *J. Org. Chem.* **2013**, *78*, 7488.
[88] Taylor, M. T.; Nelson, J. E.; Suero, M. G.; Gaunt, M. J. *Nature* **2018**, *562*, 563.

In 2021, our group further exploited Weiss' linear reagents as electrophilic diazomethyl source.[89] The hypervalent iodine reagents were decorated with electron-withdrawing groups other than esters, such as acetates, ketones, phosphonates, trifluoromethyl or sulfonate groups. Their reactivity was studied with ketone silyl enol ethers as nucleophiles, in a synthesis of elusive β-diazocarbonyl compounds. The utility of the latter compounds was demonstrated with the discovery of a rare Rh-catalyzed intramolecular 1,3 C-H carbene insertion, yielding complex cyclopropanes with excellent stereocontrol (Figure 23, c).

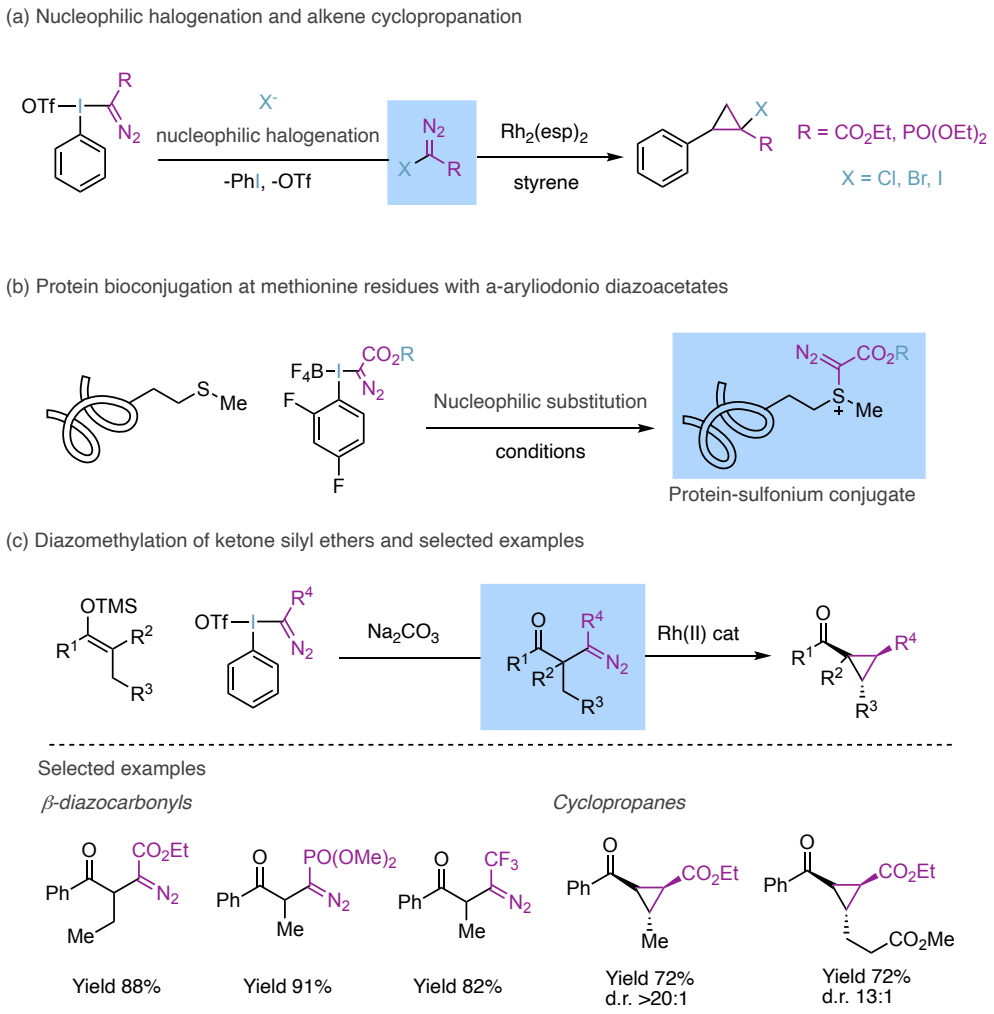


Figure 23 Synthetic uses of α-aryliodono diazo reagents

Recently, the reactivity of α-aryliodonio acetates has also been exploited in the synthesis of different hetereocycles, such as 1,3,4-oxadiazoles,[90] diazirines,[91] azaareenes[92] and isoquinolines.[93]

[89] Jiang, L.; Wang, Z.; Armstrong, M.; Suero, M. G. *Angew. Chem. Int. Ed.* **2021**, *133*, 6242.
[90] Huang, H.; Zou, X.; Cao, S.; Peng, Z.; Peng, Y.; Wang, X. *Org. Lett.* **2021**, *23*, 4185.
[91] Ansari, M. A.; Kumar, G.; Singh, M. S. *Org. Lett.* **2022**, *24*, 2815.
[92] Devi, L.; Kumar, P.; Kant, R.; Rastogi, N. *Chem. Commun.* **2022**, *58*, 7062.
[93] Ansari, M. A.; Khan, S.; Ray, S.; Shukla, G.; Singh, M. S. *Org. Lett.* **2022**, *24*, 6078.

1.4.4 Novel cyclic and pseudo-cyclic iodine (III) reagents

Linear hypervalent iodine reagents are highly reactive, and in consequence, poorly stable. In comparison, the cyclic reagent developed by Togni is more stable due to the presence of benziodoxolone backbone (Figure 19, a). Based on these two considerations, our group set out to develop new, more stable hypervalent iodine (III) cyclic and pseudo-cyclic reagents, of which we were able to tune the reactivity. In cyclic reagents, stability is increased by the presence of the acetate arm, whereas in pseudo-cyclic reagents, the lone pair of the oxygen interacts with the empty σ* C-I orbital, injecting electron density. Cyclic reagents are therefore more stable, which allowed for the introduction of different electron-withdrawing groups such as trifluoromethyl, sulfonate, or phosphonate. They were obtained by the Lewis-acid mediated reaction of 1-acetoxy-1,2-benziodoxolo-3(1H)-one with pyridine, generating a pyridinium salt which was further treated with ethyl diazoacetate to afford the corresponding cyclic reagent (Figure 24).

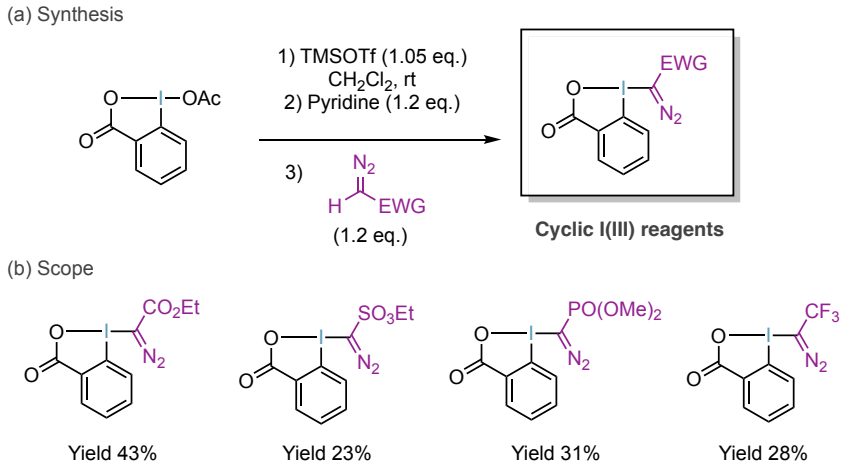


Figure 24 Synthesis and scope of novel $I^{(III)}$ cyclic reagents

The triflate-substituted pseudo-cyclic reagents were obtained from methoxy-iodaxolone by treating it first with TMSOTf, followed by addition of the corresponding diazo compound, in the absence of base. A simple anion-exchange procedure with a saturated solution of the potassium salt of the desired cation (KPF_6 or KBF_4) afforded the corresponding salt. Different ester groups could be used (Figure 25).

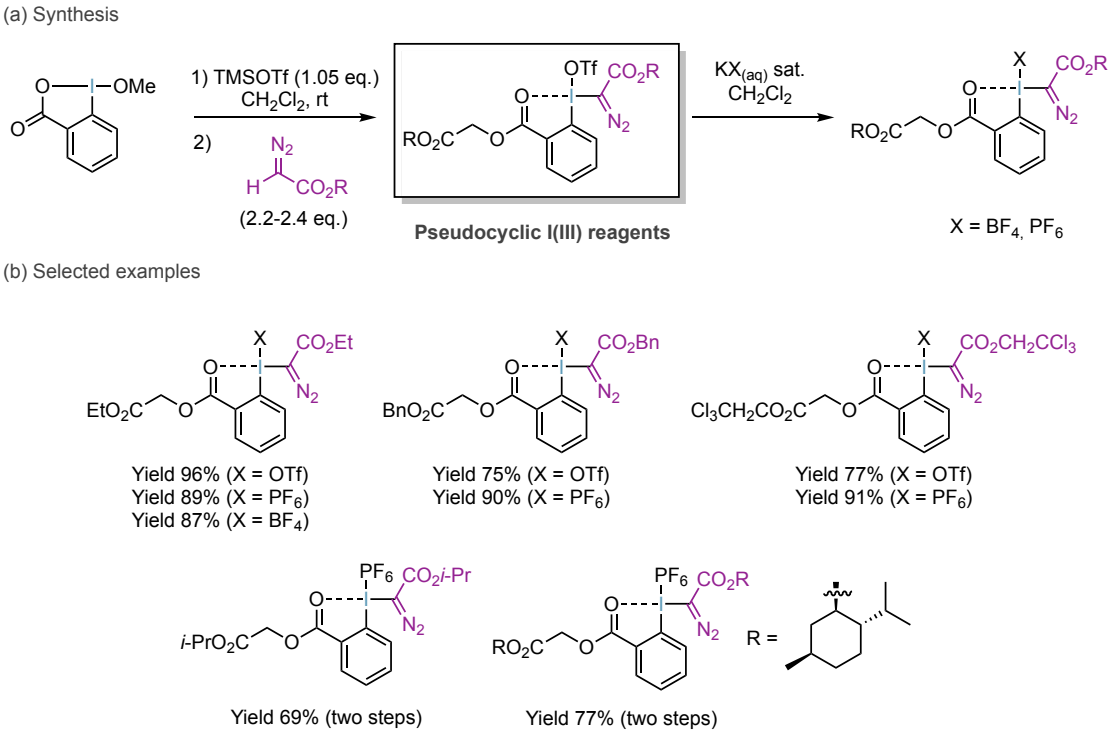


Figure 25 Novel pseudo-cyclic hypervalent iodine reagents

1.5 Development of a carbyne transfer platform

Our research group recognized that the diazo susbstituted-hypervalent iodine reagents represented an outstanding opportunity for the development of a catalytic carbyne transfer platform. (Photo)catalytic activation of such dual reagents had the potential to lead to departure of both the hypervalent iodine moiety and diazo functionality, generating carbyne equivalent species with dual radical/carbocation reactivities (Figure 26).

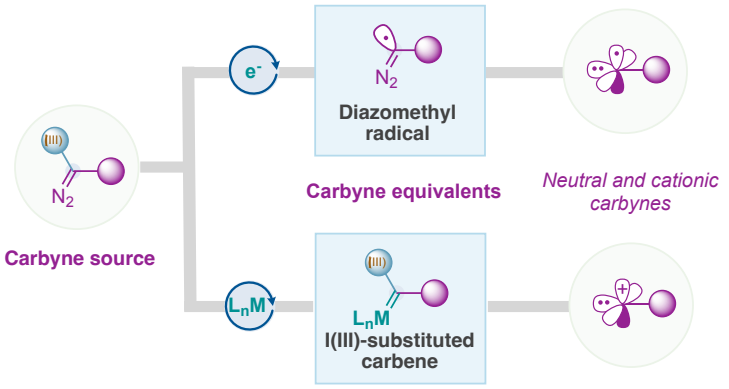


Figure 26 Diazo-substituted $I^{(III)}$ reagents for the development of a catalytic transfer platform

Strausz generated free carbynes in solution by photoactivation of diethyl mercury-*bis*diazoacetate.[59] Inspired by these findings, we pioneered the generation of diazomethyl radicals as neutral carbyne equivalents by means of photoredox catalysis. This led to the development of the first aromatic C-H bond diazomethylation reaction in a

broad range of simple aromatic feedstocks, natural products and drug molecules.[94] The dual radical/carbene character of diazomethyl radicals was further exploited in the "assembly point" construction of chiral centers using aromatic C-H bonds in simple and complex settings (Figure 27).

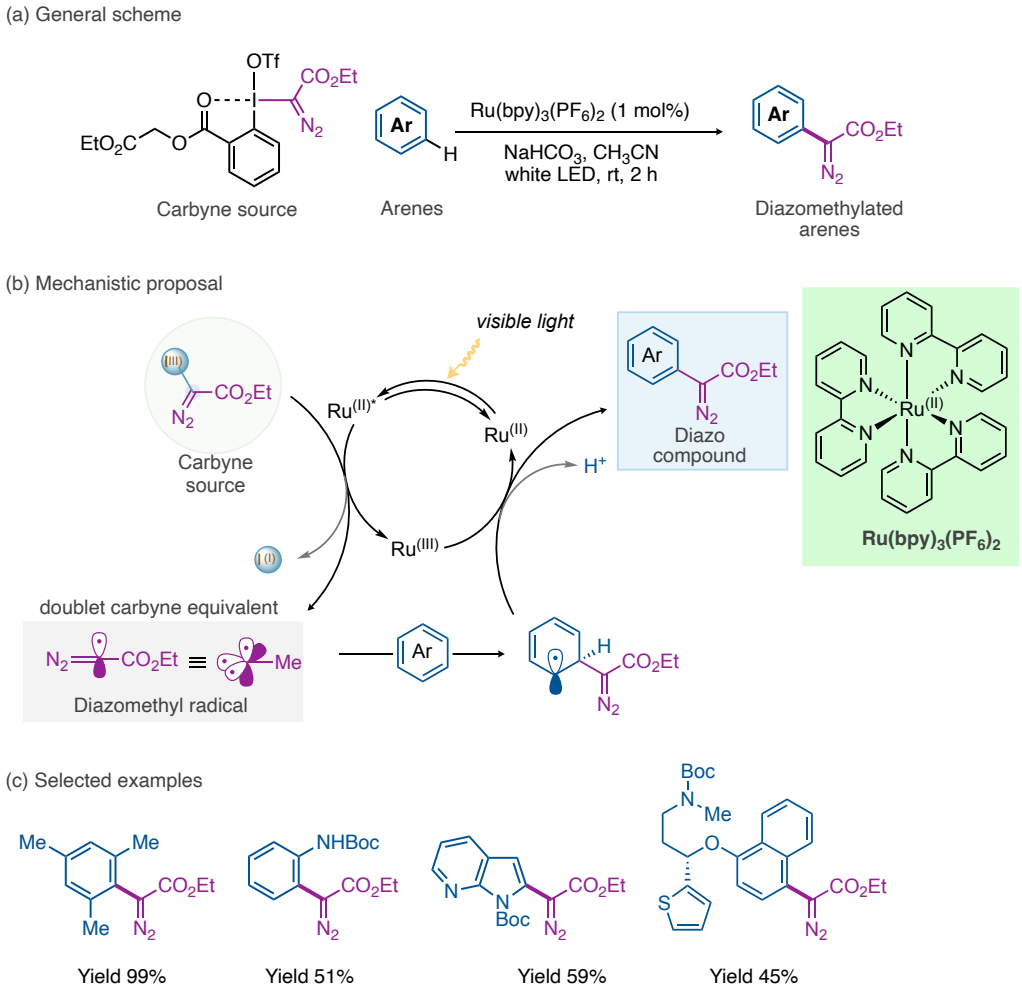


Figure 27 Generation of carbyne equivalents with photoredox catalysis

This methodology was utilized in different ways in the following years:

[94] Wang, Z.; Herraiz, A. G.; Del Hoyo, A. M.; Suero, M. G. *Nature* **2018**, *554*, 86.

On one hand, the diazo-methyl radical formed from such hypervalent iodine reagents was exploited with different radical acceptors. This led to the synthesis of various heterocycles, such as 1,3,4-oxadiazoles,[95] 1,2,3-triazoles,[96] 6-phenanthridines[97] and acridines.[98]

On the other hand, alternative sources of transferable diazomethyl groups were developed. Alcarazo reported the use of α-diazo sulfonium salts instead of hypervalent iodine reagents, which under photochemical conditions allowed for the synthesis of 1,2,3-triazoles after addition of the diazomethyl radical to hydrazones.[99] α-diazo sulfonium salts were also used by Wang and co-workers in 2022, in a coupling with alkynes and water under photoredox catalysis, ultimately yielding 1,4-dicarbonyl Z-alkenes.[100] A cyclopropenium cation was identified as intermediate of the three component reaction. (Figure 28)

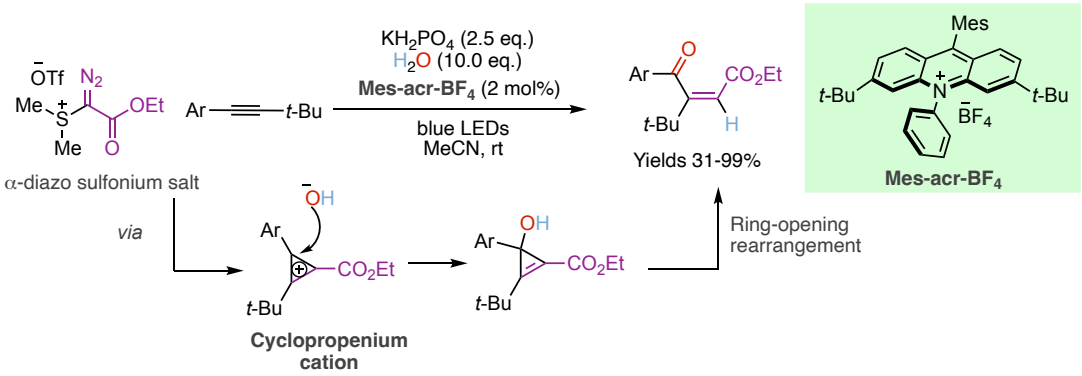


Figure 28 1,4-dicarbonyl synthesis through three-component coupling

Doyle reported the generation of diazomethyl radicals by a HAT process from α-diazo compounds. The intermediates generated further reacted in a cycloaddition with unactivated alkenes, yielding pyrazoline products.[101] At last, during the redaction of this Thesis, a non-peer-reviewed report disclosed the use of phosphorus ylides as carbyne equivalent sources in a three-component cycloaddition with electron-rich olefins and α,β-unsaturated carbonyl compounds.[102]

[95] (a) Li, J.; Lu, X. C.; Xu, Y.; Wen, J. X.; Hou, G. Q.; Liu, L. *Org. Lett.* **2020**, *22*, 9621; (b) Zhao, W. W.; Shao, Y. C.; Wang, A. N.; Huang, J. L.; He, C. Y.; Cui, B. D.; Wan, N. W.; Chen, Y. Z.; Han, W. Y. *Org. Lett.* **2021**, *23*, 9256; (c) Li, J.; Wen, J. X.; Lu, X. C.; Hou, G. Q.; Gao, X.; Li, Y.; Liu, L. *ACS Omega* **2021**, *6*, 26699.
[96] (a) Dong, J. Y.; Wang, H.; Mao, S.; Wang, X.; Zhou, M. D.; Li, L. *Adv. Synth. Catal.* **2021**, *363*, 2133; (b) Wen, J.; Zhao, W.; Gao, X.; Ren, X.; Dong, C.; Wang, C.; Liu, L.; Li, J. *J. Org. Chem.* **2022**, *87*, 4415; (c) Wen, J.; Zhao, W.; Gao, X.; Ren, X.; Dong, C.; Wang, C.; Liu, L.; Li, J. *J. Org. Chem.* **2022**, *87*, 4415.
[97] Ma, X.; Sun, A.; Wang, K. K. *New J. Chem.* **2022**, *46*, 6856.
[98] Liu, L.; Zhang, Y.; Zhao, W.; Wen, J.; Dong, C.; Hu, C.; Li, J. *Org. Lett.* **2023**, *25*, 592.
[99] Li, X.; Golz, C.; Alcarazo, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 6943.
[100] Wang, X.; Tong, W. Y.; Huang, B.; Cao, S.; Li, Y.; Jiao, J.; Huang, H.; Yi, Q.; Qu, S.; Wang, X. *J. Am. Chem. Soc.* **2022**, *144*, 4952.
[101] Su, Y.; Dong, K.; Zheng, H.; Doyle, M. P. *Angew. Chem.* **2021**, *133*, 18632.
[102] Suzuki, R. ; Ando, T. ; Deufel, F. ; Ohmatsu, K. ; Ooi, T. *ChemRxiv*, August 9th, 2023. DOI : 10.26434/chemrxiv-2023-mx0vg (accessed August 9th, 2023).

Finally, alternative uses of these reagents in material science or photocatalysis have also been reported.[103]

It is well-known that diazo compounds can be activated by transition metal catalysts.[104] In addition, as mentioned in Section 1.3.3., if alkylidyne complexes are broadly used in alkyne metathesis, they have never been used as carbyne precursors for the catalytic transfer of monovalent carbon units into organic molecules (Figure 19, Section 1.3.3.). With this in mind, we exploited further the reactivity of hypervalent $I^{(III)}$ reagents by activation with Rh(II) paddlewheel carboxylate complexes for the generation of metal-carbynoids.[105] The latter species, formally $I^{(III)}$-substituted Rh-carbenes, emulated the carbene/carbocation behavior of a monovalent cationic carbyne ($:^{+}C—R$) due to the outstanding leaving group ability of the $I^{(III)}$ moiety[106] and the weakness of the hypervalent bond. This strategy enabled a novel route to allylic building blocks from alkenes and styrenes by the insertion of a monovalent carbon unit into the $C(sp^2)—C(sp^2)$ bond and subsequent trapping by a broad range of nucleophiles (Figure 29).

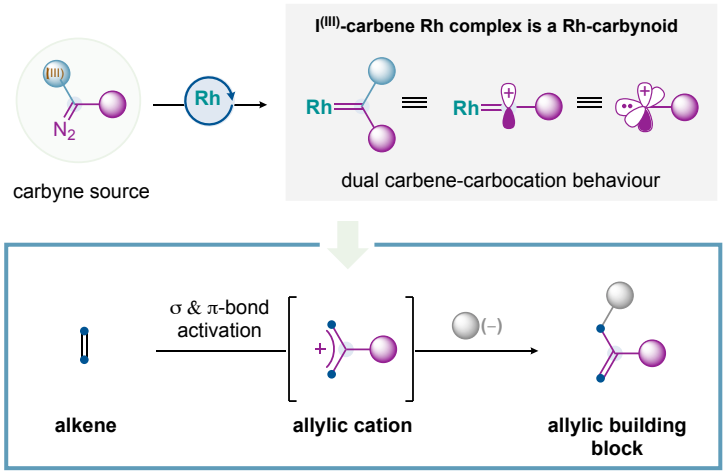


Figure 29 Catalytic cleavage of $C(sp^2)$–$C(sp^2)$ bonds

This skeletal modification involved a catalytic cyclopropanation to a transient cyclopropyl-$I^{(III)}$ intermediate by the Rh-carbynoid intermediate generated. Subsequent electrocyclic ring opening through a disrotatory mode according to the Woodward-Hoffman-Dupuy rules, and concomittant departure of the $I^{(III)}$ leaving group led to an allylic cation first, which could be intercepted by different nucleophiles to form allylic building blocks (Figure 30).

[103] (a) Gao, Z. Z.; Xu, Y. Y.; Wang, Z. K.; Wang, H.; Zhang, D. W.; Li, Z. T. *ACS Appl. Polym. Mater.* **2020**, *2*, 4885; (b) Yip, W. M.; Yu, Q.; Tantipanjaporn, A.; Chan, W. C.; Deng, J. R.; Ko, B. C. B.; Wong, M. K. *Org. Biomol. Chem.* **2021**, *19*, 8507.
[104] See section 1.1.3.
[105] Wang, Z.; Jiang, L.; Sarró, P.; Suero, M. G. *J. Am. Chem. Soc.* **2019**, *141*, 15509.
[106] Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360.

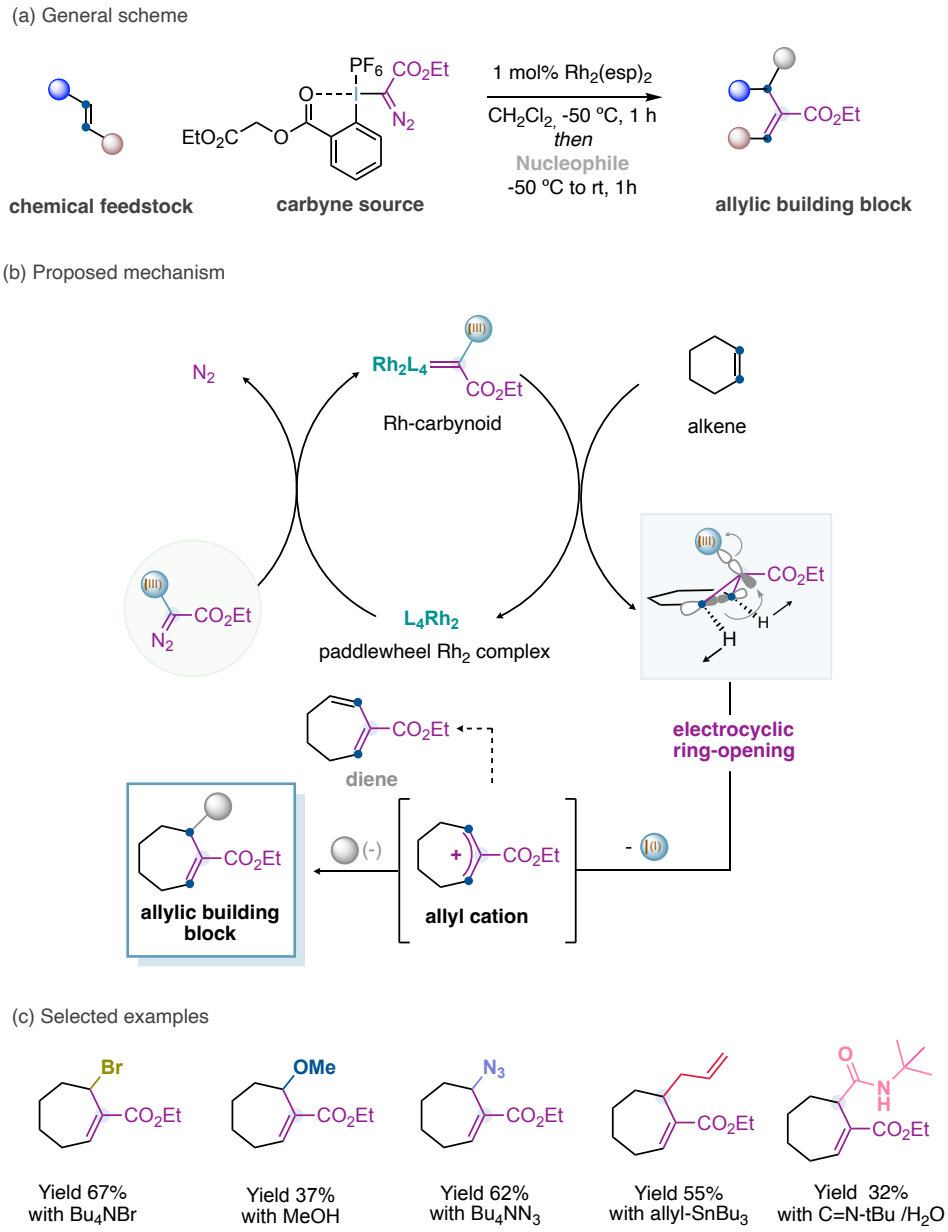


Figure 30 Catalytic cleavage of C(sp^2) – C(sp^2) bonds for allylic building block synthesis

This methodology was further utilized for the catalytic conversion of 1,1-disubstituted alkenes into fluorinated tertiary allylic fluorides, a class of fluorinated compounds challenging to attain with current methods.[107] Considering that both the charge and the highest LUMO coefficient of the allyl cation may be centered at the α-position, the fluoride nucleophilic attack proceeded with high branched selectivity (Figure 31, a).

[107] Jiang, L.; Sarró, P.; Teo, W. J.; Llop, J.; Suero, M. G. *Chem. Sci.* **2022**, *13*, 4327.

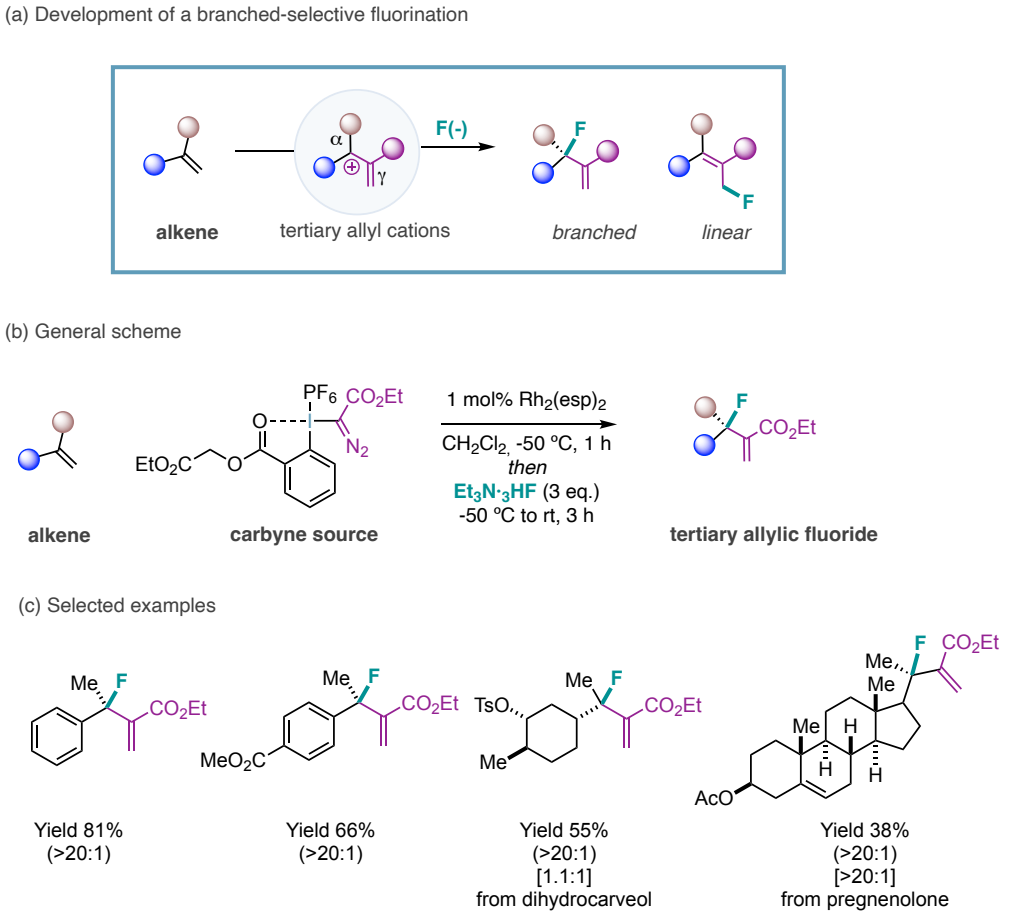


Figure 31 Development of a branched selective fluorination

Notably, the process included a wide scope including natural products, drug molecule derivatives and the adaptability to fluorination (Figure 27, b and c). Finally, a novel catalytic methodology for the synthesis of 1,3-dienes from alkenes using a suitable proton acceptor is under development (Figure 32).[108]

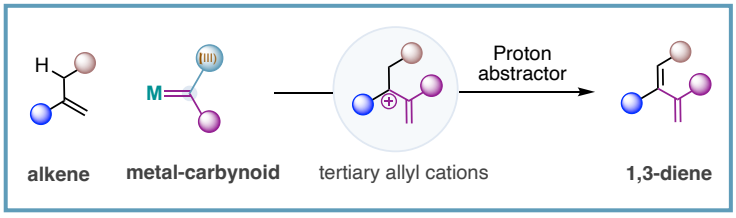


Figure 32 Catalytic synthesis of 1,3-dienes from alkenes

Finally, in a collaboration with the Maseras group, we also utilized the synthetic potential of our Rh-carbynoids with alkenyl carboxylic acids, in the generation of a new class of donor-acceptor Rh(II)-carbenes substituted with

[108] Unpublished results, see Sarró, P. Thesis defense, Title: *The Discovery and Development of a Rh-catalyzed Carbyne Transfer Platform the the Skeletal Modification of C(sp^2)—C(sp^2) bonds*; Director: Suero, M. G.; **2022**, ICIQ-Universitat Rovira i Virgili.

an acyloxy group (Figure 33, a).[109] Importantly, the latter species can be considered as Fischer-type carbenes, of which the catalytic generation has been elusive for many years. The combination of the metal carbynoid electrophilicity with the nucleofuge ability of the hypervalent iodine (III) allowed for the alkenyl carboxylic acids to displace the iodine (III) group and provide a Fischer-type acyloxy carbene. Intramolecular alkene cyclopropanation led to cyclopropyl-fused δ-lactones with excellent diastereoselectivity (Figure 33, b and c).

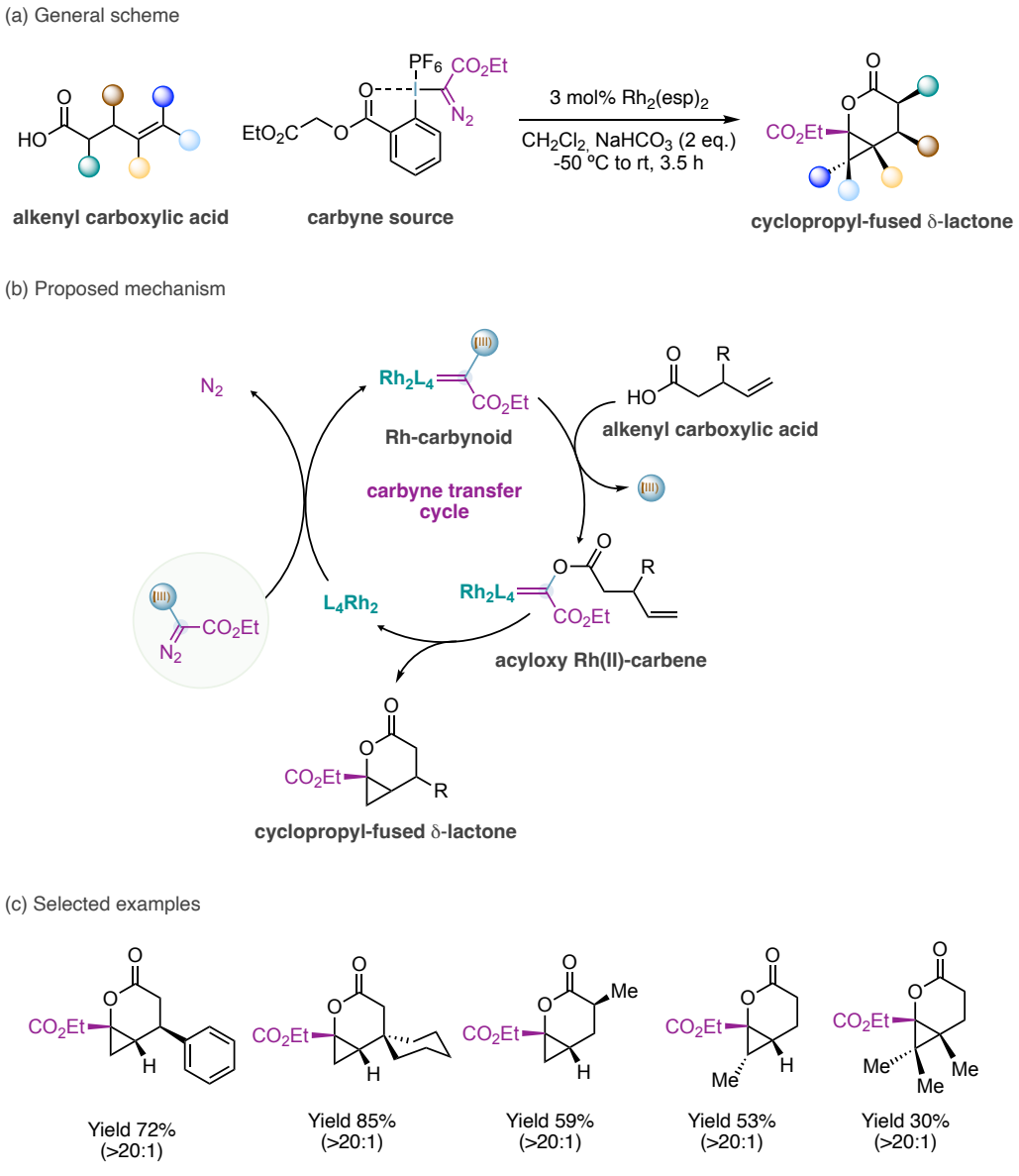


Figure 33 Catalytic carbyne transfer with alkenyl carboxylic acids

Importantly, DFT calculations were also performed in order to compare the properties of the Rh(II)-carbynoid generated and a donor/acceptor Rh(II)-carbene. (Figure 34). Rh(II)-carbynoids, according to the calculations

[109] Palomo, E.; Sharma, A. K.; Wang, Z.; Jiang, L.; Maseras, F.; Suero, M. G. *J. Am. Chem. Soc.* **2023**, *145*, 4975.

performed, revealed to be the most electrophilic species, with a lower LUMO mainly consisting in the *p*-orbital of the carbon atom. This is rationalized by the presence of the cationic hypervalent iodine atom on the carbon. In contrast, the presence of the phenyl ring as π–donor substituent on the donor /acceptor carbene shows a LUMO distributed onto the phenyl ring. This results in a higher LUMO energy.

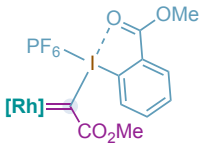
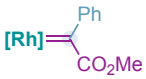
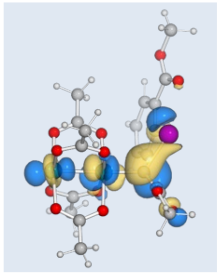
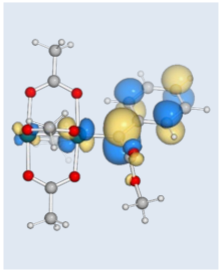
	Rh(II)-carbynoid	Rh(II)-donor/acceptor carbene
		
donation (d)	0.245	0.275
back donation (b)	0.123	0.037
d-b	0.122	0.238
ε_{LUMO} (eV)	-4.083	-3.496
ω	5.78	4.68
		

Figure 34 Comparison of the properties of a Rh(II) carbynoid and a donor/acceptor Rh-carbene

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF CYCLOPROPENIUM CATIONS BY CARBYNE TRANSFER CATALYSIS AND APPLICATIONS IN NOVEL CYCLOPROPENE SYNTHESES
Aliénor Celine Renee Jeandin

Chapter II

Catalytic synthesis of cyclopropenium cations with Rh-carbynoids

*The work described in this chapter was performed in collaboration with **Dr. Hang-Fei Tu**. Part of the work has been published, see:* Hang-Fei Tu, Aliénor Jeandin, Marcos G. Suero *"Catalytic Synthesis of Cyclopropenium Cations with Rh-carbynoids" J. Am. Chem. Soc.,* **2022***, 144,* 16737.

2.1 Introduction

Cyclopropenium cations (CPC) were reported for the first time by Ronald Breslow in 1957.[1] They are the smallest member of the Hückel aromatic ring systems, and show considerable thermodynamic stability in spite of their high ring strain. Although they possess indisputable potential as three-carbon synthons, CPCs have however been poorly explored in synthetic organic chemistry. This can be partly attributed to the reported synthetic methods, which are limited in number and in scope. In this Chapter, we describe the development of the first catalytic one-step synthesis of cyclopropenium cations (CPCs) with readily available alkynes and hypervalent iodine reagents as neutral carbyne sources. Key to the process was the catalytic generation of a Rh-carbynoid able to transfer a monovalent cationic carbyne (:$^{+}$C-R) to the alkyne *via* a formal [2+1] cycloaddition process. Through this strategy, we were able to access a new class of CPCs substituted with an ester group from a broad range of internal aryl- and alkyl- substituted alkynes. To contextualize this work, we will first give an overview of cyclopropenium cations in organic chemistry, from their discovery, properties and synthetic routes to their practical applications. This work represents a fundamentally different approach to CPC syntheses and paves the way to a resurgence of their utility as building blocks in organic synthesis.

2.2 Cyclopropenium cations : theoretical considerations

Aromaticity is the particular stability of compounds obeying to Hückel's rule, which are namely planar, cyclically conjugated molecules holding (4n+2) π electrons, where n is an integer. These systems have a closed shell of electrons all allocated in bonding orbitals. If carbocyclic aromatic compounds have long been confined to neutral benzenoid derivatives, the successive isolation of the cyclopentadienyl,[2] tropylium,[3] and cyclopropenium[1] ions widened the concept of aromatic character (Figure 1).[4] Among non-benzenoid aromatic species, the cyclopropenium cation, isolated in 1957 by Breslow, not only stands out as the simplest aromatic system with only two π electrons delocalized in three *p* orbitals (n=0), but also as synthetic demonstration of aromatic stabilization, significant enough to compensate for the high ring strain of the cyclopropenyl ring. This unique duality between high ring strain and aromatic stability has fascinated chemists ever since the seminal report of Breslow, and CPCs have been subject to numerous theoretical and synthetic studies and applications.[5]

[1] Breslow, R. *J. Am. Chem. Soc*. **1957**, *79*, 5318.
[2] Thiele, J. *Chem. Ber.* **1901**, *34*, 68.
[3] Doering von Eggers, W.; Knox, L. H. *J. Am. Chem. Soc.* **1954**, *76,* 3203.
[4] Hafner, K. *Angew. Chem. Int. Ed.* **1964**, *3,* 165.
[5] For reviews on cyclopropenium cations, see: (a) Krebs, A. *Angew. Chem. Int. Ed.* **1965**, *4*, 10; (b) Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371; (c) Lyons, D.; Crocker, M.; Blümel, M.; Nguyen, T.V. *Angew. Chem. Int. Ed.* **2017**, *56*, 1466; (d) Ranga, P. K.; Ahmad, F.; Singh, G.; Tyagi, A.; Vijaya Anand, R. *Org. Biomol. Chem.* **2021**, *19*, 9541; (e) Wilson, R. M.; Lambert, T. H. *Acc. Chem. Res.* **2022**, *55*, 3057.

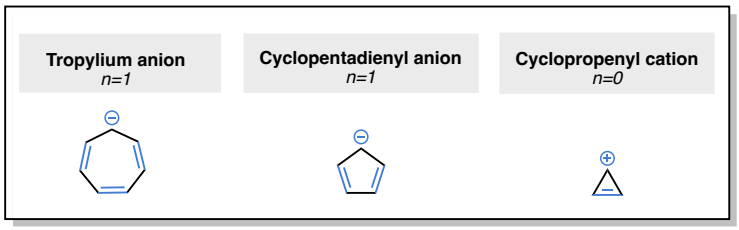


Figure 1: Non-benzenoid aromatic systems

The σ-bonds of the cyclopropenium system were described as "bent bonds", characteristic of strained rings which cannot reach the 109.5º angle of the sp^3 hybridization, such as cyclopropanes, aziridines, or oxiranes. As a response to the geometrical constraints imposed by the small cyclic system, the *s* character of the carbon atoms increases or decreases according to the type of bond formed. This accommodation of the molecular geometry results in overall non-equivalent carbon σ-orbitals.[6] In the case of the unsubstituted cyclopropenium cation, the established relationship between ^{13}C-^{1}H coupling constants and the amount of *s* character[7] revealed that the C-H exocyclic bond had a 53% *s* character, and therefore used an approximatively *sp* orbital for bonding.[8] This led Breslow to propose a description of the bonding in the parent cation as illustrated in Figure 2: each ring carbon holds 2 sp^3 orbitals for the bent cyclic bonds and one *sp* orbital for the exocyclic bond, along with the *p* orbital for the π system.

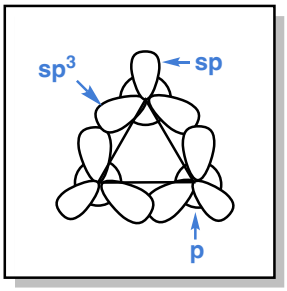


Figure 2: C-C bond hybridization of the unsubstituted cyclopropenium cation

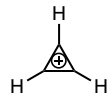
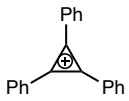
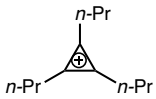
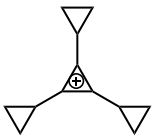
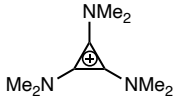
The first crystallographic studies on CPCs were performed on the perchlorate salt of the triphenylcyclopropenium ion.[9] They revealed the same C-C bond length for all three bonds of the cyclopropenium ring, 1.373 Å, somewhat shorter than the benzene aromatic C-C bond of 1.390 Å.[10] This was rationalized either as a possible consequence of the electrostatic interaction between the formally positive charge and the π electrons of the cyclopropenium ring, or as a secondary effect of the particular bonding scheme of the cyclopropenium system. The average C-C exocyclic bonds of the triphenylcyclopropenium cation of 1.436 Å also revealed to be shorter than the standard

[6] (a) Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys.* **1947**, *15*, 151; (b) Flygare, W. H. *Science* **1963**, *140*, 1179; (c) Wiberg, K.B. *Acc. Chem. Res.* **1996**, *29*, 229.
[7] Muller, N.; Pritchard, D.E. *J. Chem. Phys.***1959**, *31*, 768.
[8] Breslow, R.; Groves, J. T. *J. Am. Chem. Soc.* **1970**, *92*, 984.
[9] Sundaralingam, M.; Jensen, L. H. *J. Am. Chem. Soc.* **1966**, *88*, 198.
[10] Pauling, L.; Brockway, L. O. *J. Chem. Phys.* **1934**, *2*, 867.

single bond between C(sp^2)-C(sp^2) hybridized carbons,[11] which was interpretated as potential manifestation of an increased amount of *s* character of the exocyclic orbitals of the cyclopropenium system. Notably, the crystal structure revealed a twisted arrangement of the three phenyl groups with angles of 7.6, 12.1, and 21.2 º to the cyclopropenium ring plane. Numerous X-ray structures of cyclopropenium salts have been elucidated since this first report, but the bond length values overall fall in the same range as this first study.[12]

Aromaticity confers a high thermodynamical stability to CPCs, yet this inherent stability ranges on a wide spectrum, depending on the nature of the substituents. The thermodynamical constant used to describe the stability of a standard carbonium ion is the pK_{R+}, which measures the equilibrium between the cation and its derived alcohol resulting from hydrolysis: the greater the pK_{R+}, the more stable the cation. The pK_{R+} corresponds to the pH of the solution when half of the cation is neutralized, and is most commonly measured by potentiometric titration. Alternative solutions have been designed however for the cations at both ends of the stability spectrum. Especially unstable cations (pK_{R+} <0) have been titrated by NMR spectroscopy, and pK_{R+} values of amino-substituted cations have been extrapolated from vibrational spectra. Different pK_{R+} values are summarized in Table 1.

Table 1: pK_{R+} of selected CPCs

Entry	Cation	pK_{R+}
1[a]		-7.4[8]
2[b]		3.1[13]
3[b]		7.2[13]
4[b]		10.0[14]
5[c]		13[15]

[a] Determined by NMR spectroscopy titration, H_2SO_4 – EtOH. [b] Determined by potentiometric titration H_2O – ACN 1:1. [c] Extrapolated by vibrational spectroscopy.

[11] Dewar, M. J. S.; Schmeising, H. N. *Tetrahedron* **1960**, *11*, 96.
[12] For a summary of crystallographic data on cyclopropenium cations, see reference 5 b, pp. 1384.
[13] Breslow, R.; Höver, H.; Chang, H. W. *J. Am. Chem. Soc.* **1962**, *84*, 3168.
[14] Komatsu, K.; Tomioka, I.; Okamoto, K. *Tetrahedron Lett.* **1980**, *21*, 947.
[15] Yoshida, Z.; Tawara, Y.; Hirota, S.; Ogoshi, H. *Bull. Chem. Soc. Jap.* **1974,** *47,* 797.

Electronic effects have shown to have an uncommon influence on the stability in the case of CPCs. Standard carbonium ions are known to highly benefit from π-conjugation effects of a phenyl ring: in the case of the CPC, the planar, three-carbon cyclic system is pivotal. As revealed by the crystal structure of the triphenylcyclopropenium ion,[9] phenyl substituents accommodate themselves in a "propeller-like" structure (Figure 3, left) when placed around the cyclopropenium ring. The resulting lack of planarity prevents any effective conjugation from taking place (Table 1, entry 2).[16] In contrast, the σ-inducing effect from alkyl substituents has a higher influence on the cyclopropenium stability compared with the poorly effective π-conjugation of phenyl rings (entry 3).[13] The greatest stabilization from alkyl substituents is however found with cyclopropyl substituents, which adopt a bisected conformation around the ring (Figure 3, middle), allowing for a highly effective hyperconjugation with the carbon atoms of the cyclopropenium ring (entry 4).[16] The most stable cations known are the tris(dialkylamino)cyclopropenium cations (TACs): the positive charge on the aromatic ring is delocalized onto the *p* orbitals of the nitrogen, allowing for extra-resonance structures and greater stability (Table 1, entry 5, and Figure 3, right).[17]

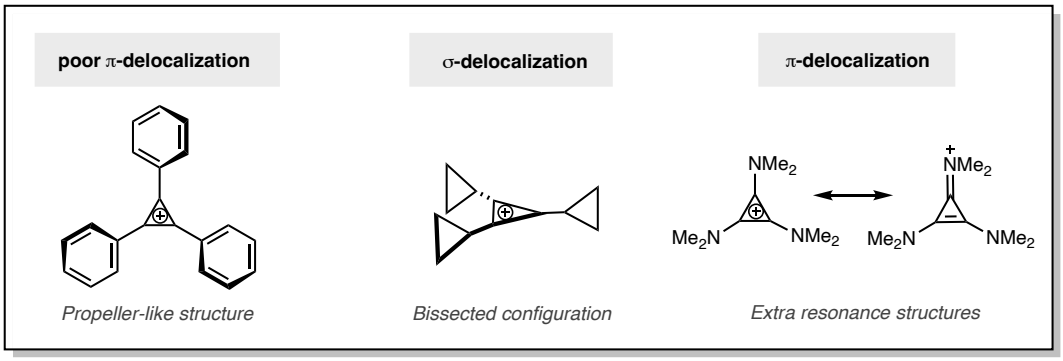


Figure 3 : Electronic effects on CPC stabilization

2.3 Synthetic routes to cyclopropenium cations

2.3.1 From cyclopropenes

Since the seminal report of Breslow in 1957,[1] cyclopropenes remain the most common starting material for the synthesis of CPCs by ionization. Approaches to ionize cyclopropenes are mainly based on Lewis or Brønsted acid-mediated (a) (pseudo)halide, (b) carbonyl, or (c) hydride abstraction. The CPCs are most commonly obtained as solids and isolated by precipitation.

[16] Moss, R. A.; Shen, S.; Krogh-Jespersen, K.; Potenza, J. A.; Schugar, H. J.; Munjal, R. C. *J. Am. Chem. Soc.* **1986**, *13*, 134.
[17] Yoshida, Z. I.; Tawara, Y. *J. Am. Chem. Soc.* **1971**, *93*, 2573.

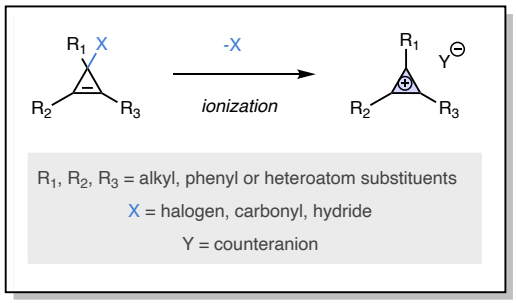


Figure 4: Syntheses of CPCs from cyclopropenes

Early syntheses of Breslow were focused on diversifying the substitution patterns of CPCs with various combinations of substituted triaryl[18], diphenyl[19], and alkyl[13] substitution. The first triphenyl CPC was obtained by reacting first phenylacetylene with phenyldiazoacetonitrile to yield the corresponding cyclopropene, and abstraction of the cyano group with a Lewis acid gave access to the desired cation (Figure 5, a).[1] An alternative, more general method for aryl-substituted cations was reported in 1961. After reacting phenylchlorocarbene with phenylacetylene in the presence of potassium *tert*-butoxide, the *tert*-butyl ether of the corresponding chlorocyclopropene was obtained, which was hydrolyzed to the cyclopropenyl symmetrical ether during the work-up. Treatment of the latter species with hydrogen bromide afforded the triphenylcyclopropenium cation as the bromide salt. This protocol has shown to be efficient for tri-phenyl, diphenyl-*p*-anysil, di-*p*-anysilphenyl, tri-*p*-anysil and diphenylcyclopropenium cations (Figure 5, b).[18,19] As for alkyl-substituted species, decarbonylation of the corresponding cyclopropene carboxylic acid in strongly acidic conditions allowed for the synthesis of dipropyl-substituted cations. Subsequent reaction of the obtained dialkyl cation with *n*-propyl lithium gave access to the corresponding trialkylcyclopropene, from which hydride abstraction with the triphenylmethyl cation afforded the trialkyl substituted cation (Figure 5, c).[13] Finally, Breslow reported the synthesis of the parent cation in 1967 by reduction of tetrachlorocyclopropene to 3-chlorocyclopropene with tributyltin hydride. Subsequent chloride abstraction yielded the unsubstituted CPC as the chloride salt (Figure 5, d).[20]

[18] Breslow, R.; Chang, H. W. *J. Am. Chem. Soc.* **1961**, *83*, 2367.
[19] Breslow, R.; Lockhart, J.; Chang, H. W. **1961**, *3*, 2375.
[20] (a) Breslow, R.; Groves, J. T.; Ryan, G. *J. Am. Chem. Soc.* **1967**, *89*, 5048; (b) reference 8.

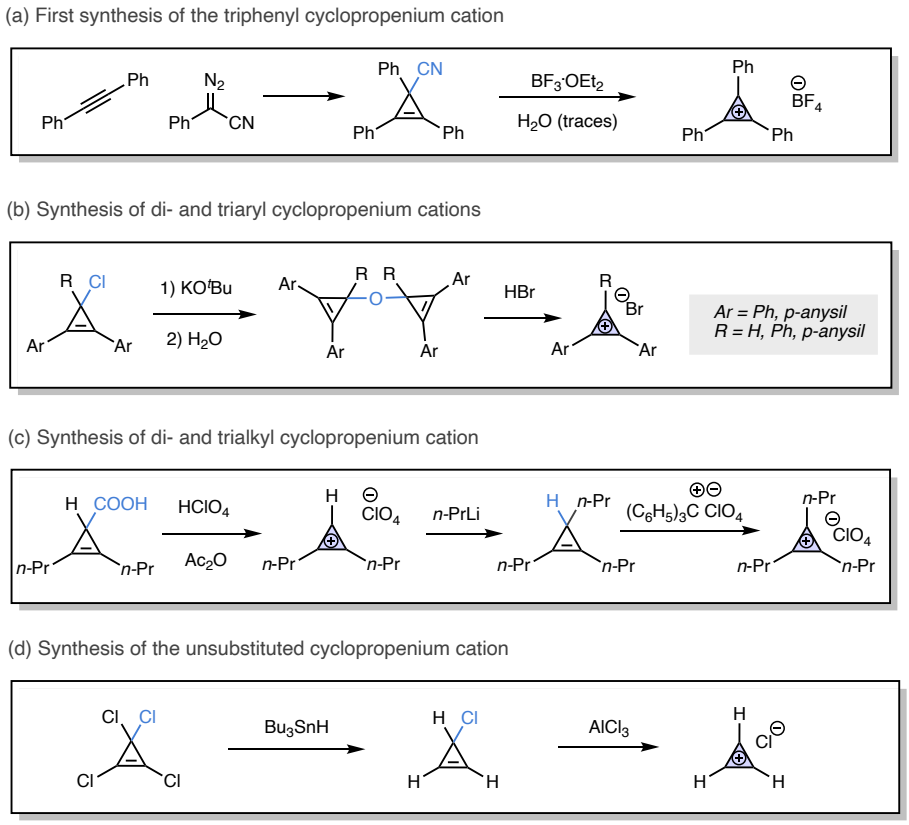


Figure 5: Breslow's early syntheses of CPCs

Another seminal contribution by West in 1964 reported a halide abstraction process for the synthesis of trihalogenocyclopropenium cations from tetrahalogenocyclopropenes. Trichlorocyclopropenyl salts were reported first (Figure 6, a),[21] followed by tribromocyclopropenyl salts in 1966[22] and the trifluorocyclopropenyl salt in 1969.[23] Interestingly, tetraiodocyclopropene was found to exist as ionic species by itself, not requiring any Lewis acid for its ionization.[24]

The trichlorocyclopropenium ion in particular served as multifunctional electrophile in the synthesis of mono-, di- and trisubstituted CPCs and cyclopropenones by reacting in a Friedel-Crafts manner with aromatic rings (Figure 6, b).[25] Addition-elimination with unsaturated compounds also gave access to new CPCs (Figure 6, c).[26] Importantly, the use of trichlorocyclopropenium salts as synthetic intermediates allowed for the expansion of the cyclopropenium cation scope by offering an alternative route from the early syntheses.

[21] Tobey, S. W.; West, R. *J. Am. Chem. Soc.* **1964**, *86*, 1459.
[22] West, R.; Sadô, A.; Tobey, S. W. *J. Am. Chem. Soc.* **1966**, *88*, 2488.
[23] (a) Sargeant, P. B.; Krespan, C. G. *J. Am. Chem. Soc.* **1969**, *91*, 415; (b) Craig, N. C.; Fleming, G. F.; Pranata, J. *J. Am. Chem. Soc.* **1985**, *107*, 7324.
[24] Weiss, R.; Miess, G.-E.; Haller, A.; Reinhardt, W. *Angew. Chem. Int. Ed.* **1986**, *25*, 103.
[25] (a) West, R.; Zecher, D. C.; Goyert, W. *J. Am. Chem. Soc.* **1970**, *92*, 149; (b) West, R. *Acc. Chem. Res.* **1970**, *3*, 130; (c) Tobey, S. W.; West, R. *J. Am. Chem. Soc.* **1964**, *86*, 4215.
[26] (a) Weiss, R.; Kölbl, H.; Schlierf, C. *J. Org. Chem.* **1976**, *41*, 2258; (b) Musigmann, K.; Mayr, H.; de Meijere, A. *Tetrahedron Lett.* **1987**, *28*, 4517.

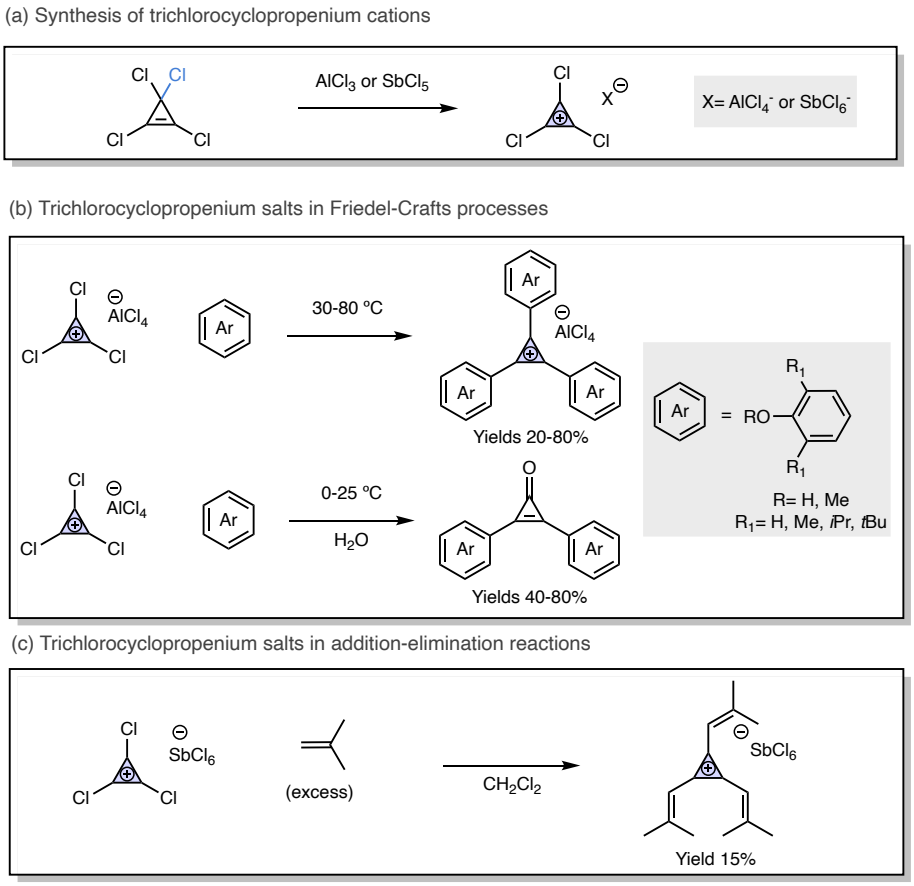


Figure 6: Trichlorocyclopropenium cation synthesis and use as synthetic intermediates

In 1971, Yoshida reported a new class of CPCs, uncovering a different reactivity mode of tetrachlorocyclopropene: successive S_N2' in excess dimethylamine followed by ionization gave access to the first tris(dialkylamino)substituted cyclopropenium cations (TACs) (Figure 7).[27] Although dimethylamine, piperidine or morpholine lead to the trisubstituted cations quantitatively, more hindered amines such as isopropylamine or dicyclohexylamine stopped at the "bis" aminated product (Figure 8, a).[28]

[27] Yoshida, Z. I.; Tawara, Y. *J. Am. Chem. Soc.* **1971**, *93*, 2573.
[28] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 5552.

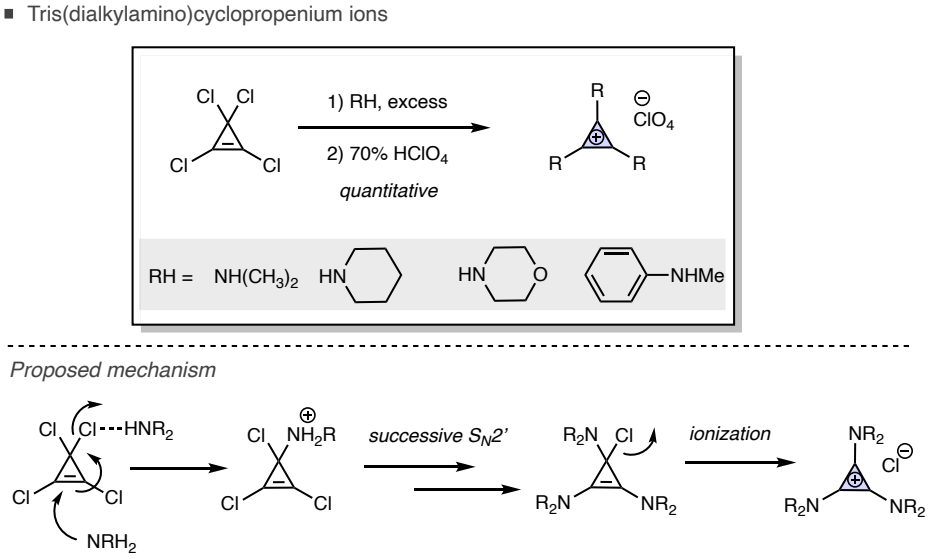


Figure 7: Synthesis of tris(dialkylamino)cyclopropenium cations

It is worth highlighting here that bis(dialkylamino)cyclopropenium cations have been of particular interest as synthetic intermediates to cyclopropylidene equivalents. Cyclopropylidene (C_3H_2) is a singlet carbene that has been detected in the interstellar space, and was long presumed to be too unstable to be isolated in the laboratory. The tremendous stability of amino-substituted CPCs allowed for its isolation as bis(dialkylamino)cyclopropylidene in 2006.[29] The reduced bis(diisopropylamino)cyclopropenium cation was obtained first from an adapted procedure reported by Weiss in 1978: triphenylphosphine addition to the chlorobis(diisopropylamino)cyclopropenium cation followed by hydrolysis afforded the unsubstituted corresponding cation (Figure 8, b).[30] Deprotonation with a strong, non-nucleophilic base allowed for the obtention of the bis(dialkylamino)cyclopropylidene as the first equivalent of cyclopropylidene isolated as the neutral equivalent of a CPC (Figure 8, c).

[29] Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science.* **2006**, *312*, 722.
[30] Weiss, R.; Priesner, C. *Angew. Chem. Int. Ed.* **1978**, *17*, 445.

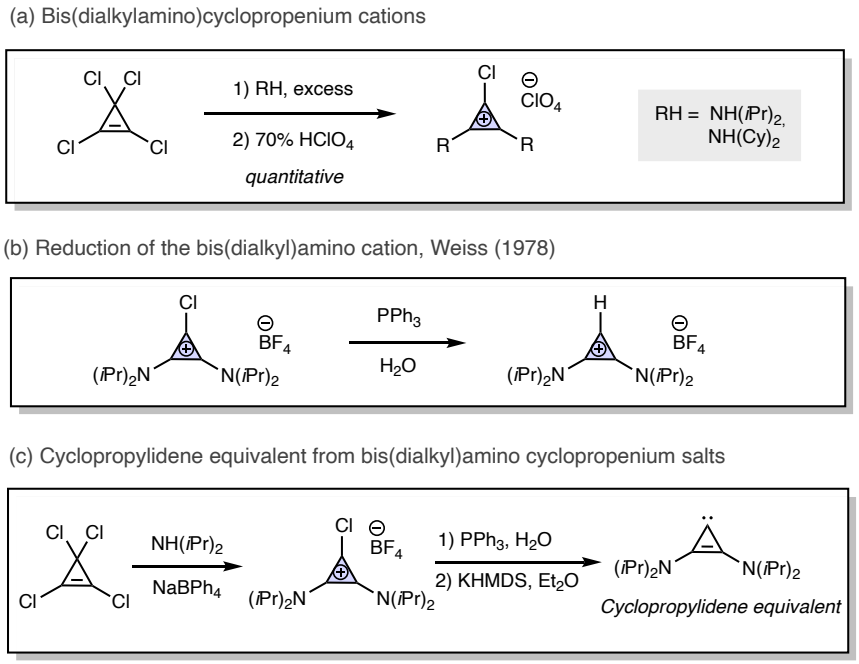


Figure 8: Synthesis of a cyclopropylidene equivalent from bis(dialkyl)amino cyclopropenium salts

Weiss reported an elegant alternative to the Yoshida procedure to TACs in 1975, sparing the need for excess amine.[31] By adding *N*-(trimethylsilyl)amines to tetrachlorocyclopropene, an exchange reaction afforded TACs instantaneously and quantitatively (Figure 9, a). Later on, in 1979, a modified procedure allowed for a selective access to mono-, bis-, and trisaminocyclopropenium ions by using the corresponding equivalents of the silylated amine.[32] Interestingly, the latter procedure revealed to be highly dependent on the counteranion and worked effectively only with the hexachloroantimonate salt.

[31] Weiss, R.; Schloter, K. *Tetrahedron Lett.* **1975**, *40*, 3491.
[32] Weiss, R. *Tetrahedron Lett.* **1979**, *67*, 3295.

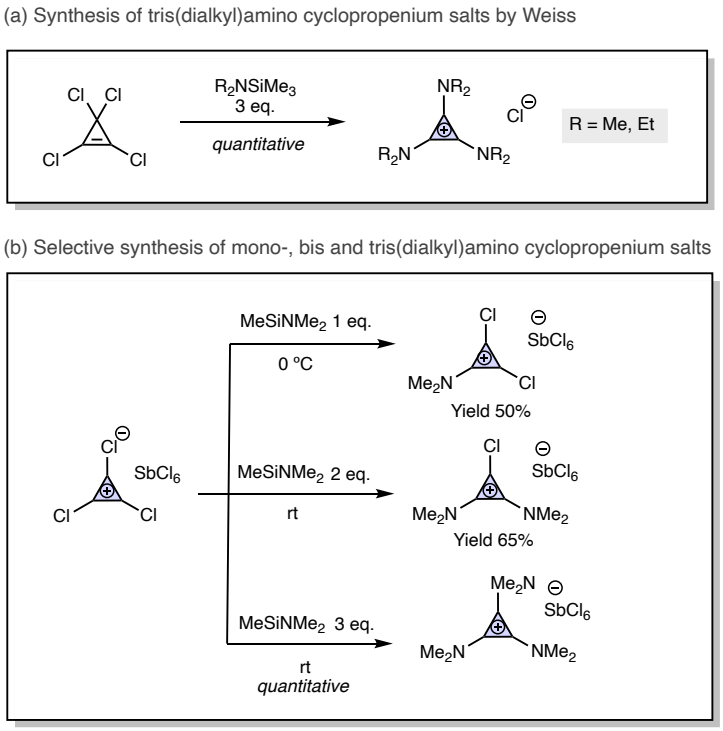


Figure 9: Weiss modifications to the Yoshida procedure

From the 1980s, only limited developments on CPC synthesis were reported, most frequently involving hydride abstraction processes. An electrochemical reduction of tetracyclopropene reported by Olah in 1999 afforded a trisilylated cyclopropene, from which hydride abstraction with nitronium tetrafluoroborate yielded the tris(*tert*-butyldimethylsilyl)cyclopropenium tetrafluoroborate quantitatively (Figure 10, a).[33] In 2000, the first report of an alkynylcyclopropenium salt involved the use triphenylmethyl hexachloroantimonate as hydride abstractor on an alkynylated cyclopropene (Figure 10, b).[34]

[33] Buchholz, H. A.; Prakash, G. K. S.; Deffieux, D.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 10003.
[34] Gilbertson, R. D.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2000**, *65*, 1422.

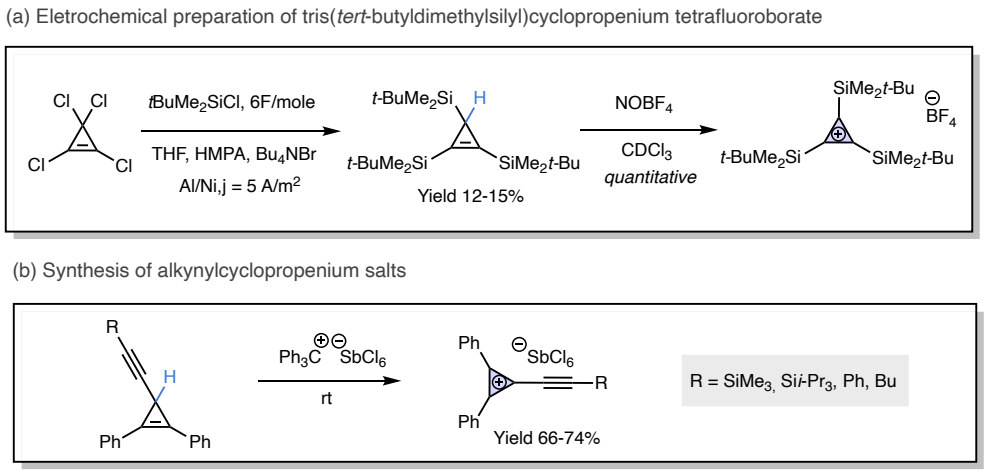


Figure 10: Latest developments in cyclopropenium salts synthesis from cyclopropenes

2.3.2 Alternative strategies

Synthetic reports of CPCs independent from cyclopropenes are scarce and show extremely limited scope, nonetheless, a couple of examples reported the use of alkynes as building blocks. The tricyclopropylcyclopropenium cation, highly stable, was synthesized simultaneously by Okamoto[14] and Moss[35] in two distinct reports in 1980. Chlorocarbenes were generated by photolysis of diazirines first. Their subsequent addition to cyclopropyl-substituted alkynes resulted in the spontaneous ionic dissociation of the chloro-substituent, precipitating the corresponding tricyclopropylcyclopropenyl salt. Ultimately, the transfer of a cationic metal carbyne to diamino substituted alkynes led to cyclopropenium cations in a formal [2+1] cycloaddition process, as reported by Troll in 1994 (Figure 11, b).[36]

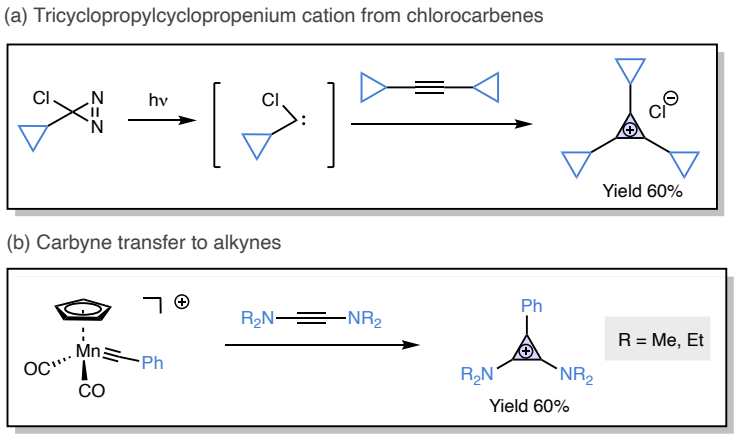


Figure 11: Synthesis of cyclopropenium cations from alkynes

[35] Moss, R. A.; Munjal, R. C. *Tetrahedron Lett.* **1980**, *21*, 1221.
[36] Fischer, H.; Troll, C. *J. Chem. Soc., Chem. Commun.*, **1994**, 457.

2.4 Applications of cyclopropenium cations

2.4.1. Cyclopropenium cations in synthesis

The synthetic potential of CPCs as three-carbon building blocks has been largely explored, with applications ranging from nucleophilic additions to ring-opening reactions, reduction and oxidations, or formation of metal complexes.[37]

Carbon nucleophiles

The major application of CPCs as synthons remains their reaction with nucleophiles to form cyclopropenes. Carbon nucleophiles were the most extensively studied, and CPCs showed excellent reactivity with organometallic species, forming cyclopropenes in a highly efficient manner. Special attention was given to the reaction of unsymmetrical cations with Grignard reagents, which gave rise to different regioisomers, depending on the type of Grignard reagent used.[38] While alkyl Grignard gave almost exclusive access to symmetrical cyclopropenes, allyl and benzyl reagents allowed for a higher percentage of the formation of the unsymmetrical cyclopropene instead (Figure 12, a). This was attributed to the stability of the radical center generated from the Grignard reagent, determining the single electron transfer (SET) character of the reaction. The varying SET character of the reaction was presumed to give rise to different intermediates (Figure 12b, A and B) and to ultimately determine the regioselectivity of the final product. Enolates have shown to be competent substrates for cyclopropene formation, too (Figure 12, b).[39]

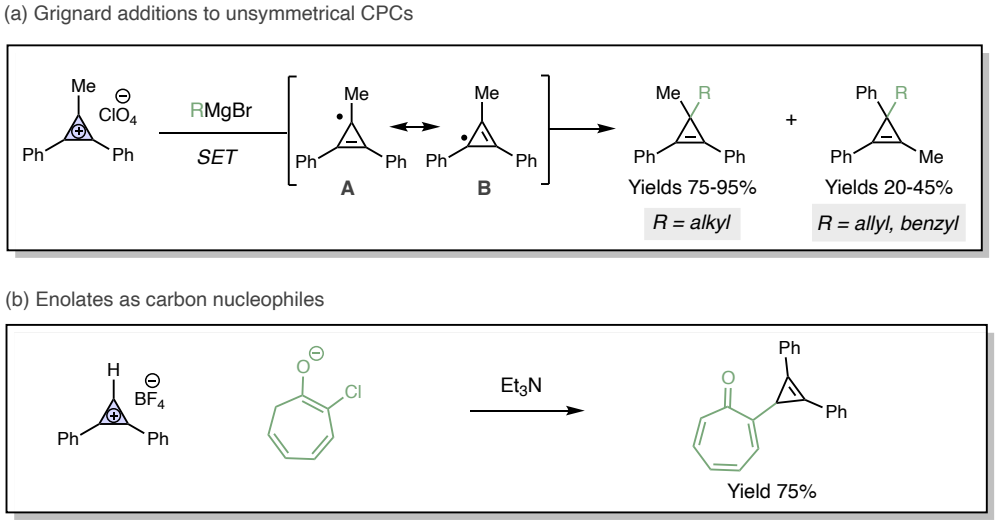


Figure 12: Reactivity of CPCs with carbon nucleophiles

[37] For a review of the applications of CPCs in organic synthesis, see reference 5 (e).
[38] Padwa, A.; Goldstein, S. I.; Rosenthal, R. J. *J. Org. Chem.* **1987**, *52*, 3278.
[39] Miyano, H.; Nitta, M. *Tetrahedron Lett.* **1988**, *29*, 4723.

Heteroatom nucleophiles

CPCs bearing no heteroatom substituent also react with diverse heteroatomic nucleophiles, such as alkoxide or hydroxide ions,[40] sodium nitrite[41] or triphenylphosphine[42] to afford the corresponding cyclopropenes (Figure 13, a and b). Diphenyl-,[43] amino- and alkylthiocyclopropenium salts[44] however, have shown to react efficiently with hetereoatoms to form ring-expansion products. In particular, Yoshida reported the use of trithiocyclopropenium salts, obtained from tetrachlorocyclopropenes and mercaptane, as building blocks for the synthesis of diverse 5- and 6-membered heterocycles.[45]

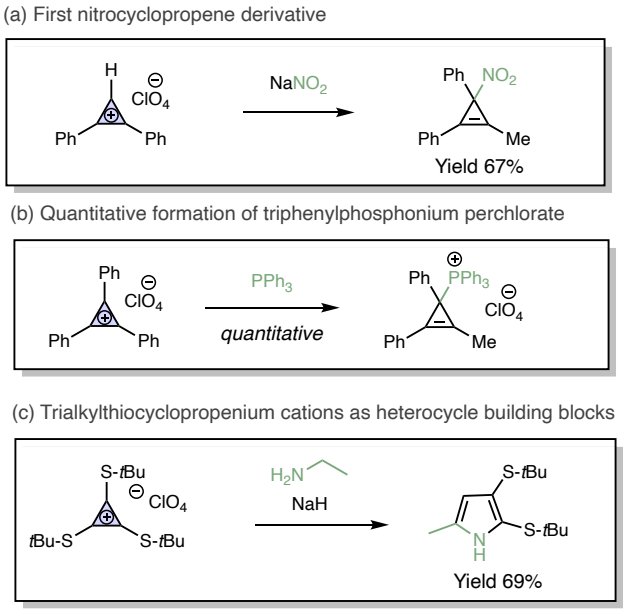


Figure 13: Reactivity of CPCs with heteroatom nucleophiles

Oxidations and reductions

Reductions of CPCs have been known for a long time: Breslow reported the dimerization and thermal isomerization of the tri-phenylcyclopropenium cation to hexaphenylbenzene when reacted with zinc dust in benzene in 1958 already (Figure 14, a),[46] and related studies were performed by Padwa in the context of the evaluation of the reactivity of Grignard reagents.[38] Oxidations of CPCs remain scarce, and so far only the high-lying HOMO of the aminocyclopropenium cation could be successfully oxidized to the radical dication (Figure 14, b).[47]

[40] Föhlisch, B.; Bürgle, P. *Liebigs Ann.* **1967**, *705*, 164.
[41] Jones, W. M.; Kobzina, J. W. *J. Org. Chem.* **1965**, *30*, 4389.
[42] Kojima, H.; Ozaki, K.; Matsumura, N.; Inoue, H. *J. Chem, Res.* **1991**, *324*.
[43] (a) Chandross, E. A.; Smolinsky, G. *Tetrahedron Lett.* **1960**, 19; (b) Breslow, R.; Boikess, R.; Battiste, M. *Tetrahedron Lett.* **1960**, *19*, 42.
[44] Yoshida, Z. *Top. Curr. Chem.* **1973**, *40*, 47.
[45] Yoshida, Z.; Hirai, H.; Miki, H.; Yoneda, S. **1989**, *45*, 3217.
[46] Breslow, R.; Gal, P. *J. Am. Chem. Soc.* **1958**, *81*, 4747.
[47] Gerson, F.; Plattner, G.; Yoshida, Z. *Mol. Phys.* **1971**, *21*, 1027.

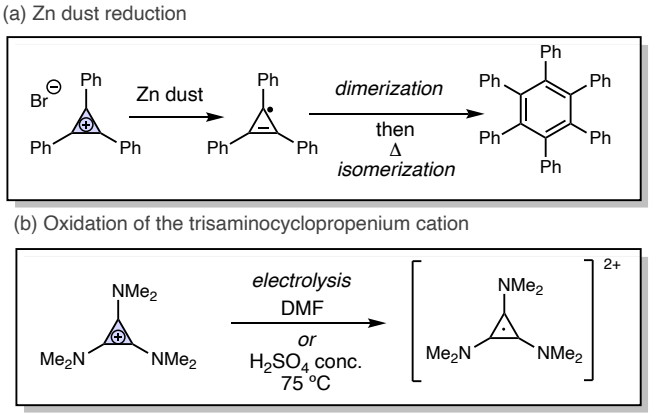


Figure 14: Reductions and oxidations of CPCs

Synthesis of metal complexes

Finally, cyclopropenium salts have also been studied in organometallic chemistry and found synthetic utility in the synthesis of different metal complexes. π-complexes, in particular η^3-cyclopropenyl complexes involving coordination of the metal center to the three carbons of the cyclopropenyl ring were the most extensively studied (Figure 15, a).[48] Interestingly, σ-complexes, where the cyclopropenium ring is directly linked to a metal center, were also reported (Figure 15, b).[49]

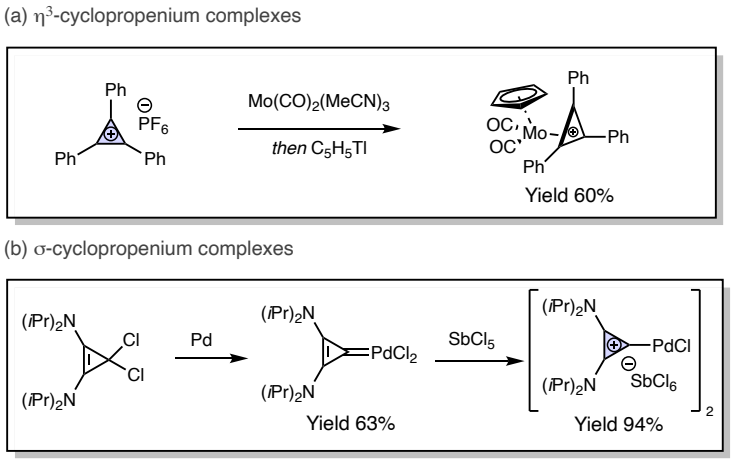


Figure 15: Reactions of CPCs to form metal complexes

[48] (a) Hughes, R. P.; Reisch, J. W.; Rheingold, A. L. *Organometallics* **1985**, *4*, 1754; (b) Hughes, R. P.; Tucker, D.S.;Rheingold, A. L. *Organometallics* **1993**, *12*, 3069; (c) Lichtenberger, D. L.; Hoppe, M. L.; Subramanian, L.; Kober, E. M.; Hughes, R. P.; Hubbard, J. L.; Tucker, D. S. *Organometallics* **1993**, *12*, 2025.
[49] Weiss, R.; Priesner, C. *Angew. Chem. Int. Ed.* **1978**, *17*, 457.

2.4.2 Cyclopropenium cations in catalysis

Cyclopropenium activation

CPCs and their unique aromatic and cationic duality have been used as central design elements for catalysis. Neutral precursors to CPCs are particularly prone to ionize, the aromaticity compensating for the cost of achieving the cationic state. CPCs have therefore the ability to exist in equilibrium between charged and neutral species upon association with an anion or a halogen lone pair. This natural propensity was exploited extensively by the Lambert group for the activation of different substrates towards nucleophilic substitutions, eliminations or rearrangements (Figure 16, a).[50]

A seminal contribution from the group of Lambert, in 2009, reported the conversion of alcohols to alkyl chlorides with 1,1-dichloro-2,3-diphenylcyclopropene as stoichiometric activator in a formal ligand exchange process (Figure 16, b).[51] Subsequent nucleophilic attack by the chloride ion afforded the corresponding chloride adduct. Interestingly, when an enantioenriched secondary alcohol was used as substrate for the reaction, the corresponding chloride adduct was obtained in 93% *ee,* confirming a S_N2 pathway. Similar activation strategies were applied for different transformations, such as the activation of carboxylic acids towards nucleophilic substitutions,[52] or Beckmann rearrangements.[53]

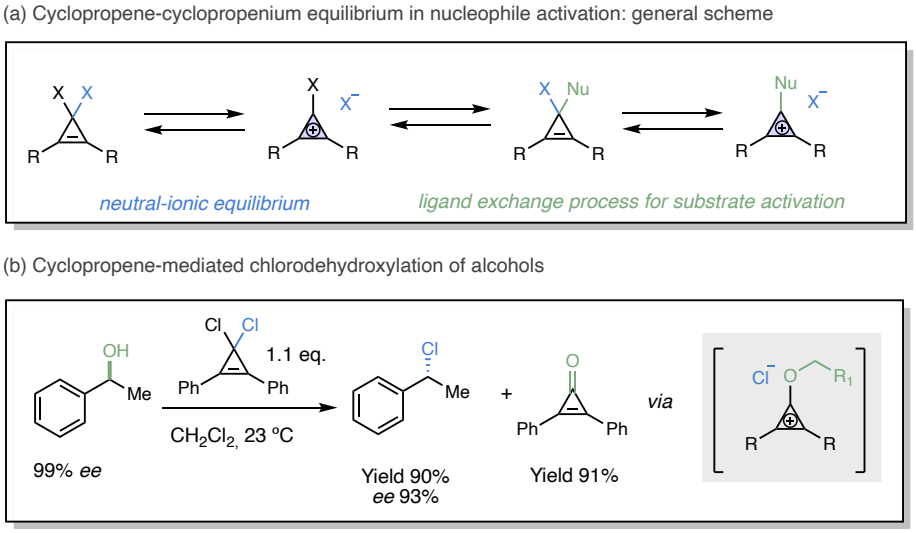


Figure 16: Cyclopropenium activation: principle and selected example

Later on, catalytic cyclopropenium activation strategies were developed by taking advantage of the common byproduct of these transformations, cyclopropenone (Figure 17, a). In the presence of a stoichiometric activator,

[50] For reviews on cyclopropenium cations in synthesis, see: references 5 (c), (d) and (e).
[51] Kelly, B. D.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 13930.
[52] Hardee, D. J.; Kovalchuke, L.; Lambert, T. H. *J. Am. Chem. Soc.* **2010**, *132*, 5002.
[53] (a) Srivastava, V. P.; Patel, R.; Garima; Yadav, L. D. S. *Chem. Commun.* **2010**, *46*, 5808; (b) Vanos, C. M.; Lambert, T. H. *Chem. Sci.* **2010**, *1*, 705.

cyclopropenone could be used as catalyst first in the chlorodehydration of alcohols,[54] and then in a Mitsunobu-type reaction (Figure 17).[55]

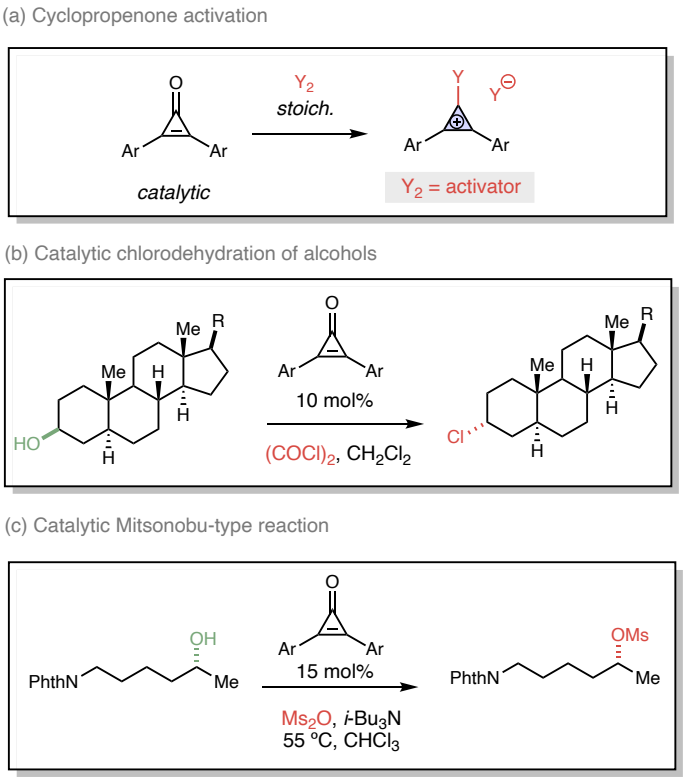


Figure 17: Catalytic cyclopropenium activation and selected examples

Cyclopropenimines as superbases

Cyclopropenimines are latent cyclopropenium ions, revealed upon reaction with an electrophile. This characteristic makes them very strong Brønsted bases, the conjugated acid being stabilized by the combination of the aromaticity of the cyclopropenium cation with the conjugation of the lone pairs of the nitrogen substituents. The pK_{BH^+} of a cyclopropenimine was evaluated first in 2012 by the Lambert group, and the obtained value of 26.9 confirmed their potential as strong bases (Figure 18 a). Chiral cyclopropenimines were developed, and then used in different Brønsted-base catalyzed transformations, including enantioselective Michael additions[56] or Mannich reactions (Figure 18 b).[57]

[54] Vanos, C. M.; Lambert, T. H. *Angew. Chem. Int. Ed.* **2011**, *50,* 12222.
[55] Nacsa, E. D.; Lambert, T. H.. *Org. Lett.* **2013**, *15*, 38.
[56] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 5552.
[57] Bandar, J. S.; Lambert, T. H. *J. Am. Chem. Soc.* **2013**, *135*, 11799.

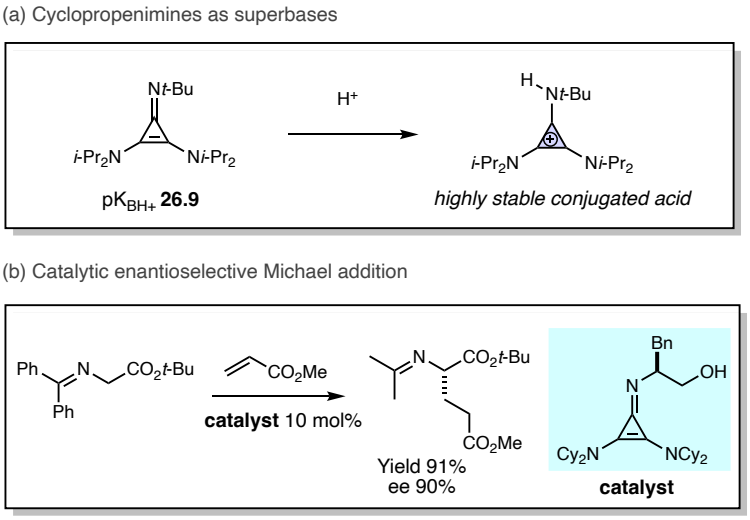


Figure 18: Cyclopropenimines as superbases and selected enantioselective example

CPCs as phase-transfer catalysts

Phase-transfer catalysts have long been limited to ammonium and phosphonium salts. In 2015, a study by Lambert expanded the field of phase-transfer catalysis by playing on the stability and tunability of TACs.[58] TACs revealed to be stable in the strongly basic and nucleophilic conditions inherent to phase-transfer reactions, conveniently and modularly synthesized on large-scale as illustrated on Figure 19 and most importantly, they proved to be competent catalysts in a wide repertoire of typical transformations involving phase-transfer catalysis.

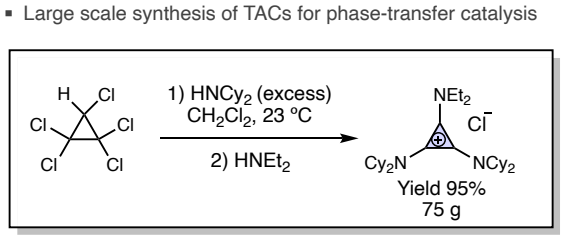


Figure 19 TACs as phase-transfer catalysts

Electrophotocatalysts

Aside from their stability, TACs show an ability to undergo reversible oxidation to form stable radical dications, an observation made in the early 70s already by Yoshida and Weiss.[59] This was not exploited until 2019, when a seminal study by the Lambert group showed that the TAC radical dication could also undergo photoexcitation with visible light.[60] The photoexcited species showed a great oxidizing ability, sufficient to promote oxidative coupling of unactivated arenes via single electron transfer (E_{red} = 3.33 V vs SCE). The process merged for the

[58] Bandar, J. S.; Tanaset, A.; Lambert, T. H. *Chem. Eur. J.* **2015**, *21*, 7365.
[59] (a) Gerson, F.; Plattner, G.; Yoshida, Z. *Mol. Phys.* **1971**, *21*, 1027; (b) Weiss, R.; Schloter, K. *Tetrahedron Lett.* **1975**, *40*, 3491.
[60] Huang, H.; Strater, Z. M.; Lambert, T. H. *J. Am. Chem. Soc.* **2020**, *142*, 1698.

first time electro- and photocatalysis with a single component, and pioneered the use of TACs as "electrophotocatalysts" (Figure 20). This strategy has since then been explored for multiple oxidative transformations, ranging from Minisci-type reactions[60] to Ritter-type functionalizations,[61] or vicinal C-H diaminations.[62]

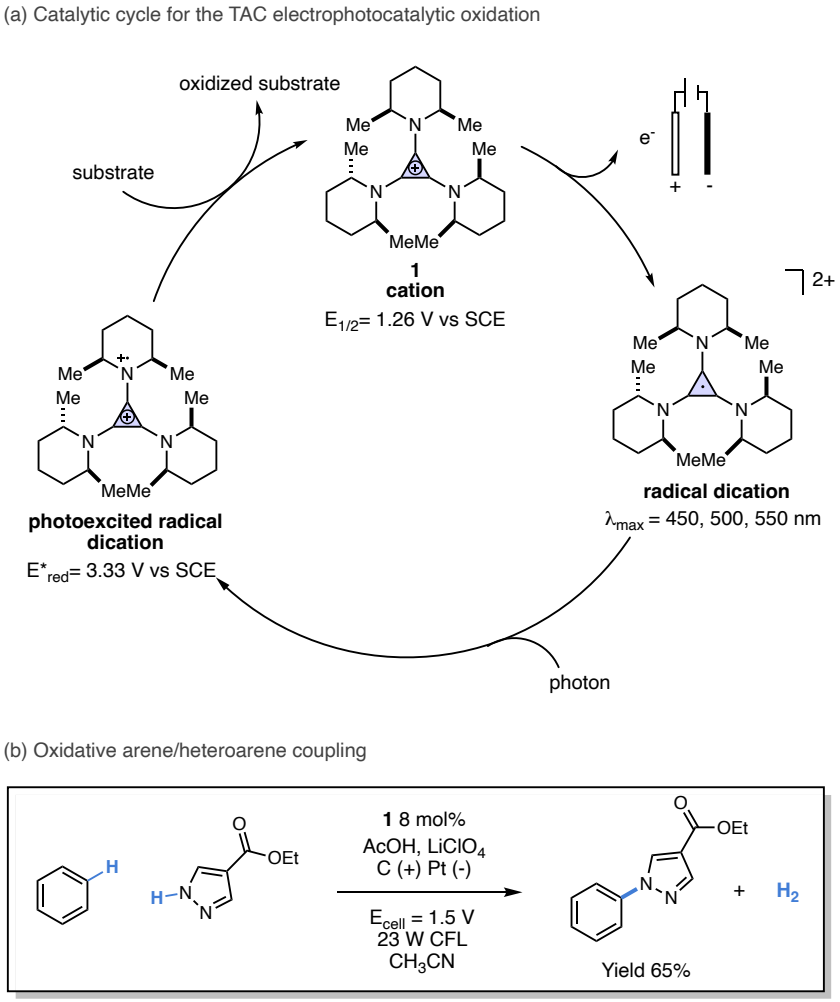


Figure 20: Electrophotocatalytic cycle of the TACs and selected example

2.4.3 Cyclopropenium cations outside of method development

TAC salts, highly stable and tunable, have been widely exploited in material science. A class of TACs was reported in 2011 as a new family of ionic liquids.[63] In 2015, a study of TACs as functional polyelectrolytes reported a class of new materials with high modularity,[64] which later translated to a wide array of applications in

[61] Shen, T.; Lambert, T. H. *J. Am. Chem. Soc.* **2021**, *143*, 8597.
[62] Shen, T.; Lambert, T. H. *Science* **2021**, *371*, 620.
[63] Curnow, O. J.; MacFarlane, D. R.; Walst, K. J. *Chem. Comm.* **2011**, *47*, 10248.
[64] Jiang, Y.; Freyer, J. L.; Cotanda, P.; Brucks, S. D.; Killops, K. L.; Bandar, J. S.; Torsitano, C.; Balsara, N. P.; Lambert, T. H.; Campos, L. M. *Nat. Commun.* **2015**, *6*, 1.

material science, including gene transfection[65] or ionic liquid crystals[66]. Notably, Sanford uncovered and explored the potential of monomeric TAC derivatives as a new class of organic catholytes for non-aqueous redox-flow batteries from 2017 on,[67] which also paved the way to the applications of TACs oligomers for energy storage.[68]

2.5 Catalytic synthesis of cyclopropenium cations

2.5.1 Hypothesis of the project

Our research group is focused on the development of a carbyne transfer platform in organic synthesis using tailored hypervalent iodine reagents as carbyne synthons. We discovered that stable carbyne sources decorated with a hypervalent iodine moiety [I^{III}(Ar)(OTf)] and a diazo functionality (=N_2) were catalytically activated with dirhodium catalysts. The outstanding leaving group ability of the $I^{(III)}$ combined with the weakness of the hypervalent bond emulated the carbene/carbocation behavior of a monovalent cationic carbyne ($:^{+}$C-R). Upon reaction with alkenes, this resulted in the development of a new route to allylic building blocks by the formal insertion of a monovalent carbon unit into C(sp^2)-C(sp^2) bonds.[69] Inspired by the reactivity of alkenes with Rh-carbynoids, we wondered about the reactivity of alkynes with our carbyne transfer platform. We hypothesized that such a reaction would involve the formation of a cyclopropenium cation through a formal [2+1] cycloaddition between the alkyne and the carbyne synthon. The reported CPCs are isolated as solids by filtration:[70] this cation could then either be directly isolated, or exploited as intermediate in the development of a synthesis of cyclopropenes upon external nucleophilic attack (Figure 21). In the case of a successful CPC isolation, the developed process would represent the first catalytic synthesis of cyclopropenium cations from readily available alkynes.

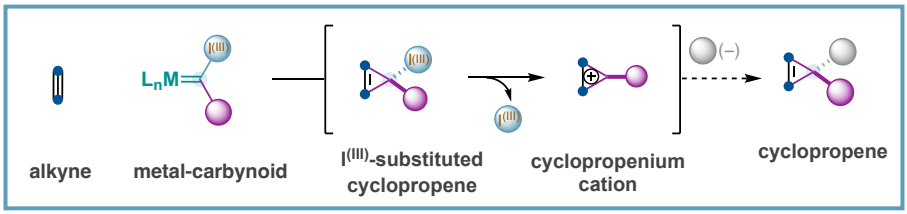


Figure 21 Synthesis of cyclopropenes from alkynes with metal-carbynoids *via* cyclopropenium cations

[65] Freyer, J. L.; Brucks, S. D.; Gobieski, G. S.; Russell, S. T.; Yozwiak, C. E.; Sun, M.; Chen, Z.; Jiang, Y.; Bandar, J. S.; Stockwell, B. R.; Lambert, T. H.; Campos, L. M. *Angew. Chem. Int. Ed.* **2016**, *55*, 12382.
[66] Litterscheidt, J.; Bandar, J. S.; Ebert, M.; Forschner, R.; Bader, K.; Lambert, T. H.; Frey, W.; Bühlmeyer, A.; Brändle, M.; Schulz, F.; Laschat, S. *Angew. Chem. Int. Ed.* **2020**, *59*, 10557.
[67] (a) Sevov, C. S.; Samaroo, S. K.; Sanford, M. S. *Adv. Energy Mater.* **2017**, *7,* 1602027; (b) Yan, Y.; Vaid, T.P.; Sanford, M.S. *J. Am. Chem Soc.* **2020**, *142,* 17564; (c) Yan, Y.; Vogt, D.B.; Vaid, T.P.; Sigman, M.S.; Sanford, M.S. *Angew. Chem. Int. Ed.* **2021**, *60*, 27039.
[68] Hendriks, K. H.; Robinson, S. G.; Braten, M. N.; Sevov, C. S.; Helms, B. A.; Sigman, M. S.; Minteer, S. D.; Sanford, M. S. *ACS Cent. Sci.* **2018**, *4*, 189.
[69] Wang, Z.; Jiang, L.; Sarró, P.; Suero, M. G. *J. Am. Chem. Soc.* **2019**, *141*, 15509.
[70] See Section 2.3.

2.5.2 Proposed mechanism

Rh_2-paddlewheel catalysts showed to successfully activate the carbyne sources **2** to provide the $I^{(III)}$-substituted carbene ***int-1***. In analogy to the formation of the cyclopropyl-$I^{(III)}$ intermediate upon alkene cyclopropanation, we hypothesized that the catalytically generated Rh-carbynoid (***int-1***) could intercept alkynes and provide cyclopropenyl-$I^{(III)}$ intermediate (***int-2***). Upon an ionization process that occurs with the departure of the $I^{(III)}$ leaving group,[71] the process would lead to a new class of CPCs **3**, which could either be directly isolated or used as secondary intermediates in a cyclopropene synthesis, upon addition of an external nucleophile (Figure 22).

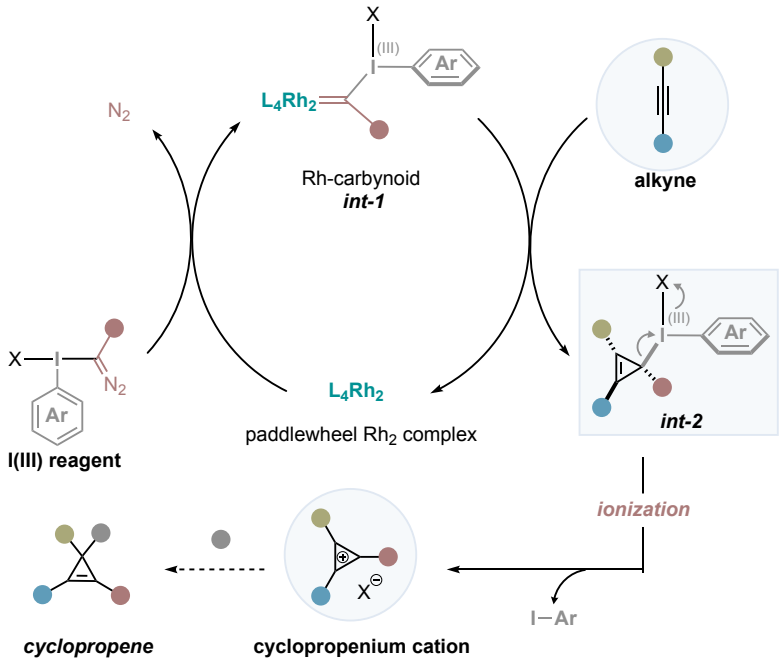


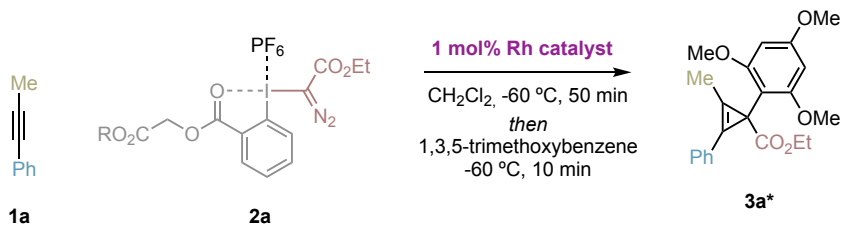
Figure 22: Proposed mechanism for the generation of a new class of ester-substituted CPCs

2.5.3 Reaction optimization

Optimization studies started with the commercially available 1-phenyl-1-propyne **1a**, a broad range of commercial Rh_2 catalysts and diazomethyl-based hypervalent iodine reagents **2**. Taking into account the possible instability and reactivity of the desired CPC, we first employed 1,3,5-trimethoxybenzene as external nucleophile to quantify the efficiency of the transformation.

[71] Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360.

Table 2: Rh catalyst evaluation[a,b]



Entry	Rh catalyst	NMR yield **3a***(%)
1	$Rh_2(OAc)_4$	4
2	$Rh_2(OPiv)_4$	93
3	$Rh_2(TPA)_4$	0
4	$Rh_2(Oct)_4$	76
5	$Rh_2(TFA)_4$	0
6	$Rh_2(hfb)_4$	0
7	$Rh_2(esp)_2$	>99
8	$Rh_2(Adc)_4$	90

[a] Reactions performed with alkyne **1a** (0.2 mmol, 2.0 eq.), reagents **2** (0.1 mmol, 1 eq.), Rh catalyst (1 mol%) and 1,3,5-trimethoxybenzene (4 eq.) in CH_2Cl_2 (0.067 M). [b] Yields are reported on the basis of ^{1}H-NMR analysis using CH_2Br_2 as the internal standard.

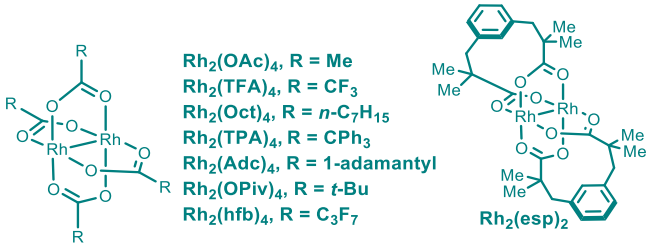


Figure 23: Rh catalysts

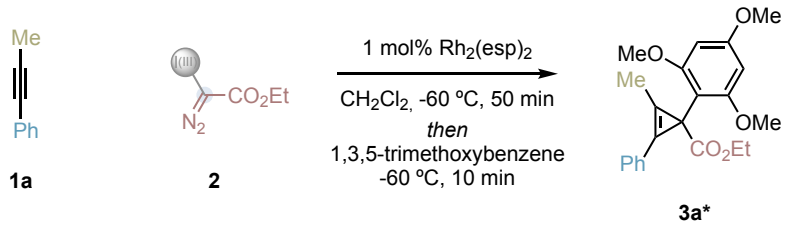
Among the catalysts evaluated with pseudo-cyclic reagent **2a**, $Rh_2(esp)_2$ (DuBois catalyst)[72] performed best, leading to cyclopropene **3a*** with excellent efficiency (94% isolated yield, >20:1 r.r.), (Table 2, entry 7). While other sterically demanding catalysts such as $Rh_2(OPiv)_4$, $Rh_2(Oct)_4$ or $Rh_2(Adc)_4$ worked well (entries 2, 4, 8), $Rh_2(OAc)_4$ and $Rh_2(TPA)_4$, or the more electrophilic $Rh_2(hfb)_4$ and $Rh_2(TFA)_4$ were not competent (entries 1, 3, 5, 6). Importantly, the only regioisomer of **3a*** observed comes from the selective attack of the nucleophile to the cyclopropenium carbon atom substituted with the ester group.

After identifying the most adequate catalyst, we evaluated the type of carbyne source employed. While the use of triflate as counterion provided a moderate yield (Table 3, entry 2), no conversion to the final product was observed with linear reagent **2c** although full consumption of the salt was achieved (entry 3). The cyclic reagent **2d** showed

[72] Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

to be inert to catalytic diazo activation (entry 4). Finally, the combination of **2d** and $Zn(OTf)_2$, a well-known activator of cyclic $I^{(III)}$ reagents, provided a moderate yield (entry 5).

Table 3: Carbyne sources evaluation[a,b]



Entry	reagent **2**	NMR yield **3a*** (%)
1	**2a**	>99
2	**2b**	50
3	**2c**	0
4	**2d**	0
5	**2c**	60[c]

[a] Reactions performed with alkyne **1a** (0.2 mmol, 2.0 eq.), reagents **2** (0.1 mmol, 1 eq.), Rh catalyst (1 mol%) and 1,3,5-trimethoxybenzene (4 eq.) in CH_2Cl_2 (0.067 M). [b] Yields are reported on the basis of ^{1}H-NMR analysis using CH_2Br_2 as the internal standard. [c] 0.5 equiv. of $Zn(OTf)_2$ was added.

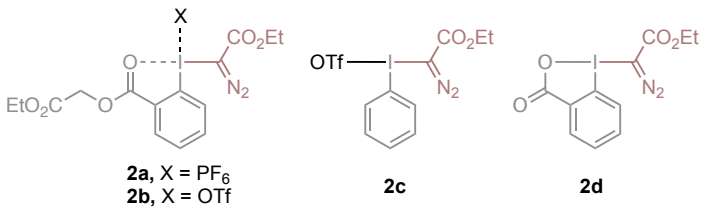
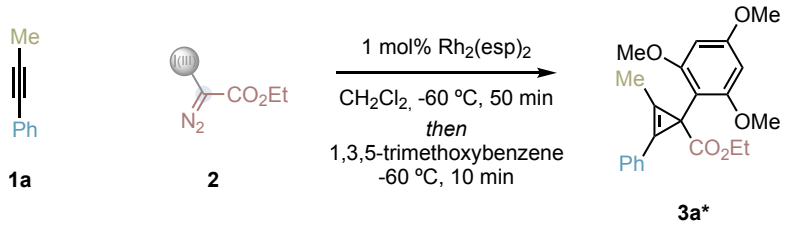


Figure 24: Carbyne sources **2** studied for the optimization

Ultimately, we set out to study the impact of alkynes equivalents and temperature. A slight excess of alkyne (1.3 eq.) confirmed to be necessary (Table 3, entries 3, 4 and 5). Higher reaction temperatures provided the product with less efficiency (entries 1, 2). Leaving the reaction mixture warming up to room temperature after the addition of 1,3,5-trimethoxybenzene revealed to be detrimental to the reaction (entry 6).

Table 4: Alkyne equivalents and temperature evaluation [a,b]



Entry	alkyne **1a** (equiv.)	reagent **2**	NMR yield **3a*** (%)
1	2.0	**2a**	81[c]
2	2.0	**2b**	14[c]
3	1.5	**2a**	>99
4	1.3	**2a**	>99
5	1.1	**2a**	94
6	2.0	**2a**	38[d]

[a] Reactions performed with reagents **2** (0.1 mmol, 1 eq.), Rh catalyst (1 mol%) and 1,3,5-trimethoxybenzene (4 eq.) in CH_2Cl_2 (0.067 M). [b] Yields are reported on the basis of ^{1}H-NMR analysis using CH_2Br_2 as the internal standard. [c] Reaction carried out at -50 ºC. [d] After the addition of **2a**, the reaction mixture was allowed to warm to room temperature during 2 hours.

During the optimization process, we observed that the addition of **2a** to **1a** and $Rh_2(esp)_2$ at –60 ºC provided the formation of a slurry, that quickly turned into a clear solution after the addition of 1,3,5-trimethoxybenzene (Figure 25).

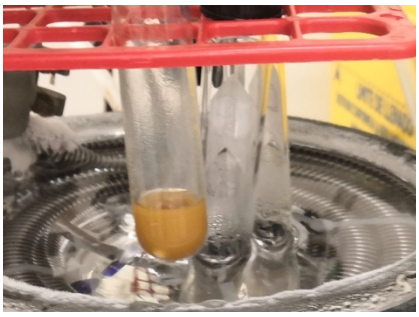


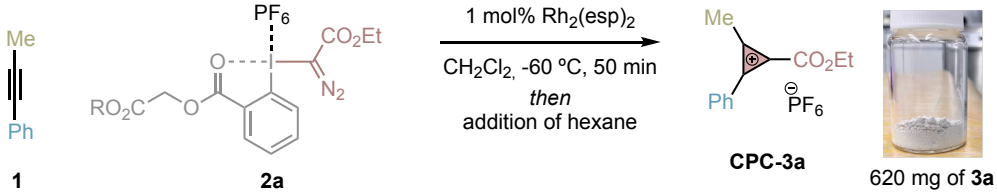
Figure 25: Slurry formed in the reaction tube after dropwise addition of reagent **2a** to alkyne **1a**

To our eyes, this observation suggested the potential formation of either intermediate ***int-2*** or CPC **3a** (Figure 22). Initial experiments performed to isolate the intermediate at room temperature were unsuccessful, however, slow addition of dry hexane at –60 ºC and quick filtration provided a white solid that was subjected to spectroscopic analysis using mono and bidimensional nuclear magnetic resonance (^{1}H, ^{13}C, ^{19}F, ^{31}P, ^{1}H-^{13}C NMR, CD_3NO_2 as solvent), IR and HRMS. The three deshielded signals at 171.5, 166.7 and 156.0 ppm observed in the ^{13}C NMR spectra clearly referred to the cyclopropenium carbon atoms, thus confirming the formation of **3a** (86% yield). The IR spectra was also consistent with previously characterized CPCs: the characteristic band of the

cyclopropenium ring vibration observed around 1400 cm^{-1}, was identified at 1448 cm^{-1}.[73] As for the stability of the isolated CPC, **3a** could be stored at –20 ºC under argon for at least 1 month without detectable decomposition and can be handled at room temperature without the need of a glovebox.

After the isolation of **3a**, foreseeing potential synthetic applications of CPCs, we performed an ultimate round of optimization of the reaction conditions for the gram-scale synthesis of CPCs. A scale of 2.0 mmol was found to be higher yielding, as the slurry formed on higher scale (4.0 mmol) prevented an efficient stirring of the reaction (Table 4, entries 1 and 2). The catalyst loading could also be decreased to 0.5 mol% (entry 3). Shorter or longer addition times were evaluated, both leading to decreased synthetic outcome (entries 4, 5).

Table 5 : Optimization studies of the scale-up synthesis of CPC **3a**[a]



Entry	Deviation of reaction conditions	Isolated yield 3a (%)
1	-	90
2	4 mmol instead of 2 mmol	78
3	0.5 mol% $Rh_2(esp)_2$	84
4	30 min addition time	78
5	60 min addition time	66

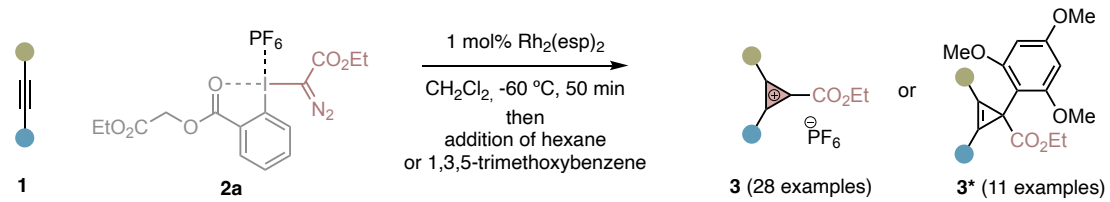
[a] Reactions performed with alkyne **1a** (2.6 mmol, 1.3 eq.), reagents **2** (2 mmol, 1 eq.), Rh catalyst (1 mol%).

2.5.4 Cyclopropenium cation scope

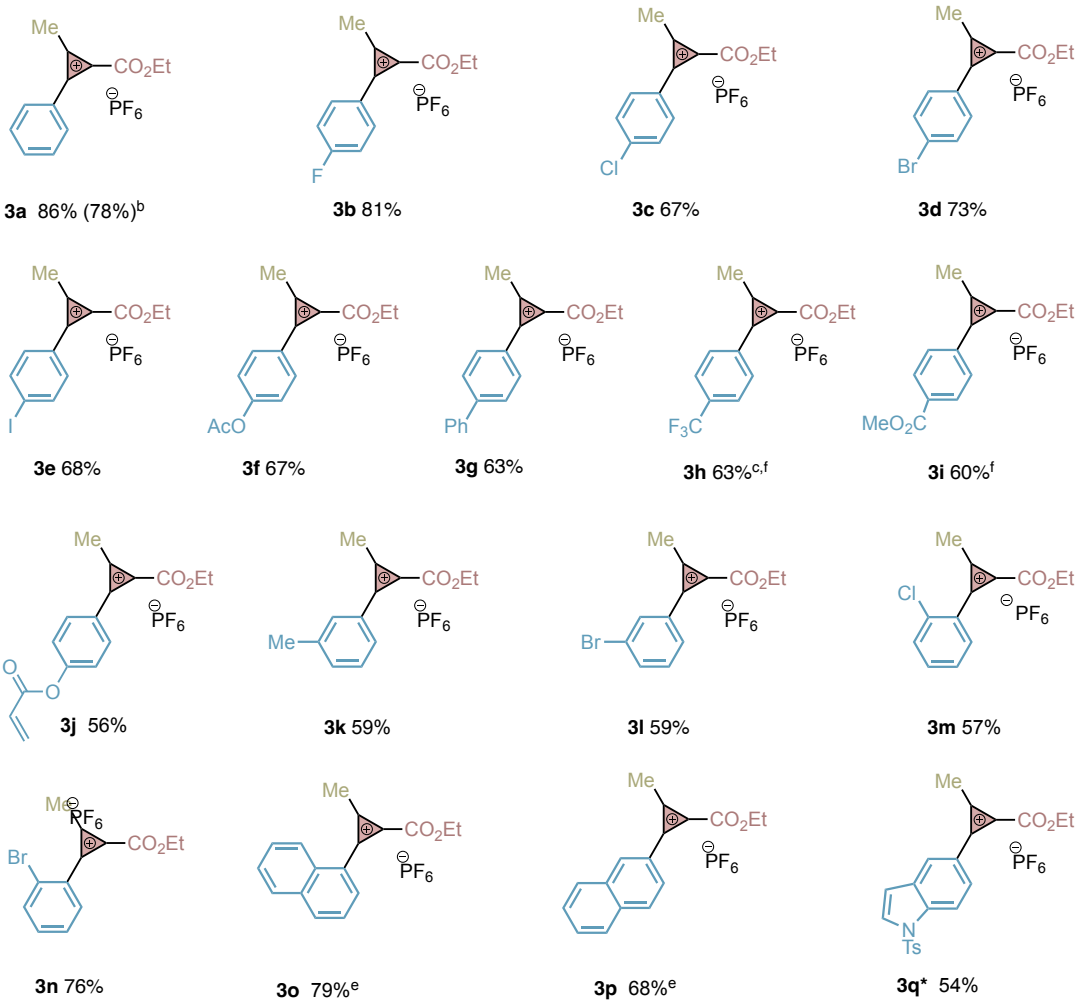
We next aimed to develop the scope of our catalytic protocol for the synthesis of CPCs **3** by examining a wide range of alkynes. CPCs difficult or impossible to precipitate were transformed to the corresponding cyclopropene **3*** with 1,3,5-trimethoxybenzene. Our process worked well for alkynes with aryl rings substituted with synthetically useful functionalities such as halogens (**3b–e, 3l–n**), acetoxy (**3f**), phenyl (**3g**), CF_3 (**3h**), ester (**3i**), alkene (**3j**) and methyl (**3k**) in *para*, *meta* and *ortho* positions as well as naphthalene (**3o-p**) and heterocycle cores (**3q***).

[73] For details on the characteristic bands on IR spectras of selected CPCs, see references 13, 14, and 16.

Table 6 CPC scope for methyl-aryl cations[a]



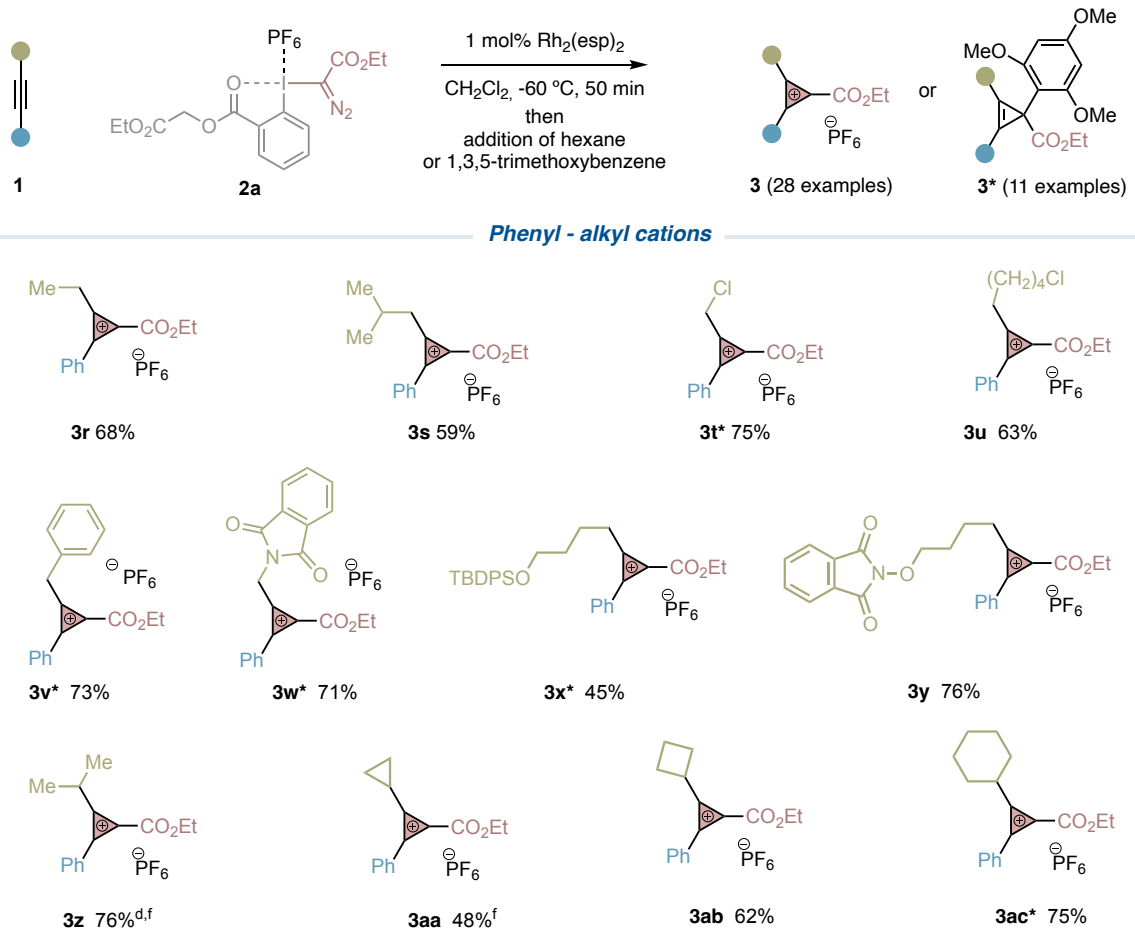
Methyl - aryl cations



[a] Reaction conditions for Tables 6-9: alkyne **1** (0.26 mmol, 1.3 eq.), hypervalent iodine reagents **2** (0.2 mmol 1.0 eq.). CH_2Cl_2 -60 ºC, 50 min, 1,3,5-trimethoxybenzene (0.8 mmol, 4.0 eq.) was added for the synthesis of **3***. [b] Yield of the reaction to give 1.08 g of **3a** and 1.10 g of **3add** [c] 1.5 mol % catalyst. [d] 2 mol % catalyst. [e] Reaction carried out at -63ºC. [f] 1.5 equiv. of alkyne. [g] 2.0 equiv of alkyne.

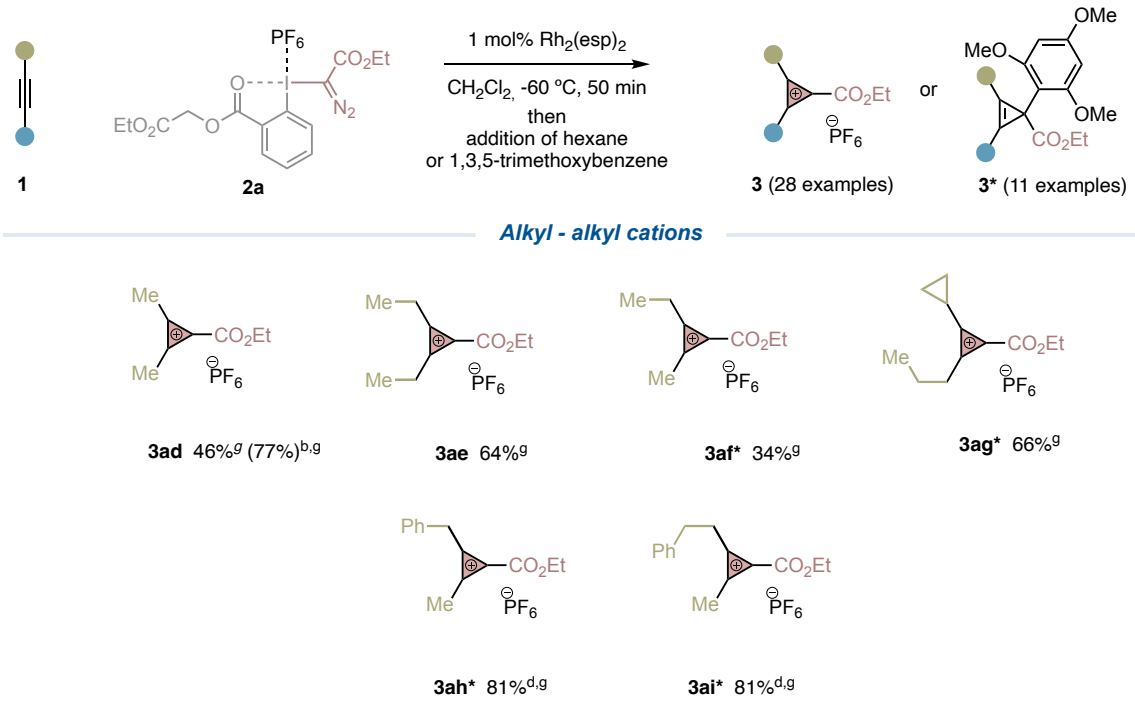
Alternative primary alkyl groups such as ethyl (**3r**), *sec*-butyl (**3s**), chloroalkyls (**3t*, 3u**), benzyl (**3v***) as well as alkyl groups functionalized with protected amines (**3w***) or alcohols (**3x*, 3y**) were well tolerated. Secondary alkyl substituents like *iso*-propyl required an increment on the catalyst loading (2 mol%) and alkyne (1.5 eq.), however, cyclic derivatives such as cyclopropyl (**3aa**), cyclobutyl (**3ab**) and cyclohexyl (**3ac***) worked well under the standard conditions. Alkynes substituted with tertiary groups like *tert*-butyl or trimethylsilyl provided traces of the desired CPCs.

Table 7 CPC scope for phenyl-alkyl cations[a] (see Table 6 for reaction conditions)



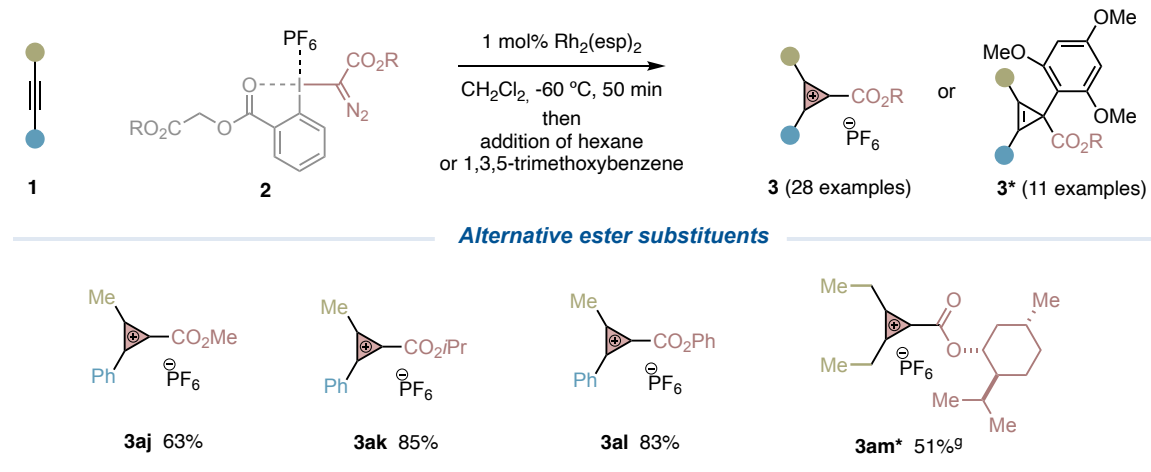
On the other hand, while alkynes substituted with two alkyl groups were well tolerated (**3ad-ai***), terminal alkynes such as phenylacetylene provided mixtures of products difficult to identify. Strong electron-donating functionalities in the aryl substituent of the alkyne such as methoxy, or electron-rich heterocyclic substituents such as thiophene and unprotected indole were not tolerated. Cyclooctyne did not allow for the CPC formation, and alkynes substituted with heteroatomic functionalities (Cl, Br, I, NMeTs) did not afford the desired CPC either, but instead complex mixtures of products were observed.

Table 8 CPC scope for dialkyl cations (see Table 6 for reaction conditions)



We also demonstrated that alternative ester substituents at the hypervalent iodine reagents were possible (**3aj-al, 3am***). Finally, CPC **3a** and **3ad** were prepared in >1 gram without compromising the efficiency of the process.

Table 9 CPC scope for alternative ester substituents (see Table 6 for reaction conditions)



A crystal structure was obtained for **3ad**. The cyclic C-C bonds lengths of 1.36 Å, are all equal, and fall in the average reported for such compounds.[9, 12]

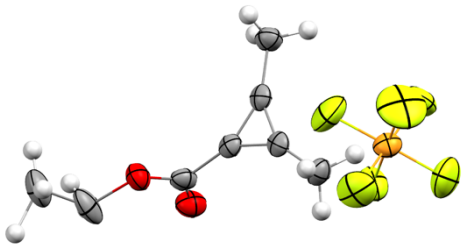


Figure 26: ORTEP diagram of **3ad**

2.6 Conclusions

Our studies led to the development of the first catalytic synthesis of CPCs based on the formal transfer of monovalent cationic carbynes to alkynes. This represents a fundamentally different approach for the synthesis of CPCs. Notably, this type of group transfer is uncommon for carbyne complexes, which mainly evolve via [2+2] cycloadditions with alkynes.[74]. CPCs are largely under-explored in organic synthesis in spite of their potential as three-carbon building blocks: this new class of bench-stable, ester-substituted CPCs hold the promise to open new synthetic potentialities in the construction of complex architectures.

[74] (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794. (b) reference 36.

2.7 Experimental section

General information. All reagents were used as purchased and used with no further purification. Ethyl diazoacetate, (≥13 wt.% dichloromethane) was purchased from Aldrich (Ref. E22201) and used without further purification. Anhydrous solvents were dried by passing through an activated alumina column on a PureSolvTM solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography (TLC) was carried out using aluminum sheets with 0.2 mm of silica gel (Merck GF234). Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of potassium permanganate or vanillin stain followed by heating. Flash column chromatography was performed on silica gel (Aldrich, 230-400 mesh) or neutral silica gel (Material Harvest Ltd., 230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. Unless otherwise stated, reactions were carried out under argon atmosphere. Yields refer to purified compounds unless otherwise noted. NMR spectra were recorded at 298 K on Bruker Avance 300, Bruker Avance 400 Ultrashield or Bruker Avance 500 Ultrashield apparatuses. Coupling constants (*J*) are quoted in hertz (Hz). Multiplicity is reported with the following abbreviations: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, sp = septet, m = multiplet, app = apparent. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) analysis were carried out in Agilent 1260 Infinity – 6130 Quadrupole and Agilent 7890B - 5977A MSD, respectively.

Synthesis of alkynes.

1a, **1r**, **1t**, **1ad**, **1ae, 1af** were commercially available and used directly as received. **1b-1d**, **1f-1p**, **1s-1z**, **1aa-1ac** were prepared with the Sonogashira reaction with the corresponding iodo/bromoarene and terminal alkynes.[75] **1e** was synthesized from 4-iodobenzaldehyde according to a reported procedure.[76] **1q** was synthesized by following a reported protocol based on a decarboxylative cross-coupling reaction.[77] **1ag**, **1ah**, **1ai** were prepared by alkylation of the corresponding lithium acetylide derived from cyclopropylacetylene, 1-phenyl-2-propyne and 4-phenyl-1-butyne based on a reported procedure.[78]

[75] (a) Gao, S.; Liu, H.; Wu, Z.; Yao, H.; Lin, A. *Green Chem.* **2017**, *19*, 1861. (b) Berthold, D.; Breit, B. *Org. Lett.* **2018**, *20*, 598.
[76] An, D.-L.; Zhang, Z.; Orita, A.; Mineyama, H.; Otera, J. *Synlett* **2007**, *12*, 1909.
[77] Cruz, F. A.; Dong, V. M. *J. Am. Chem. Soc.* **2017**, *139*, 1029.
[78] (a) Deponti, M.; Kozhushkov, S. I.; Yufit, D. S.; Ackermann, L. *Org. Biomol. Chem.* **2013**, *11*, 142. (b) Tan, E. H. P.; Lloyd-Jones, G. C.; Harvey, J. N.; Lennox, A. J. J.; Mills, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 9602.

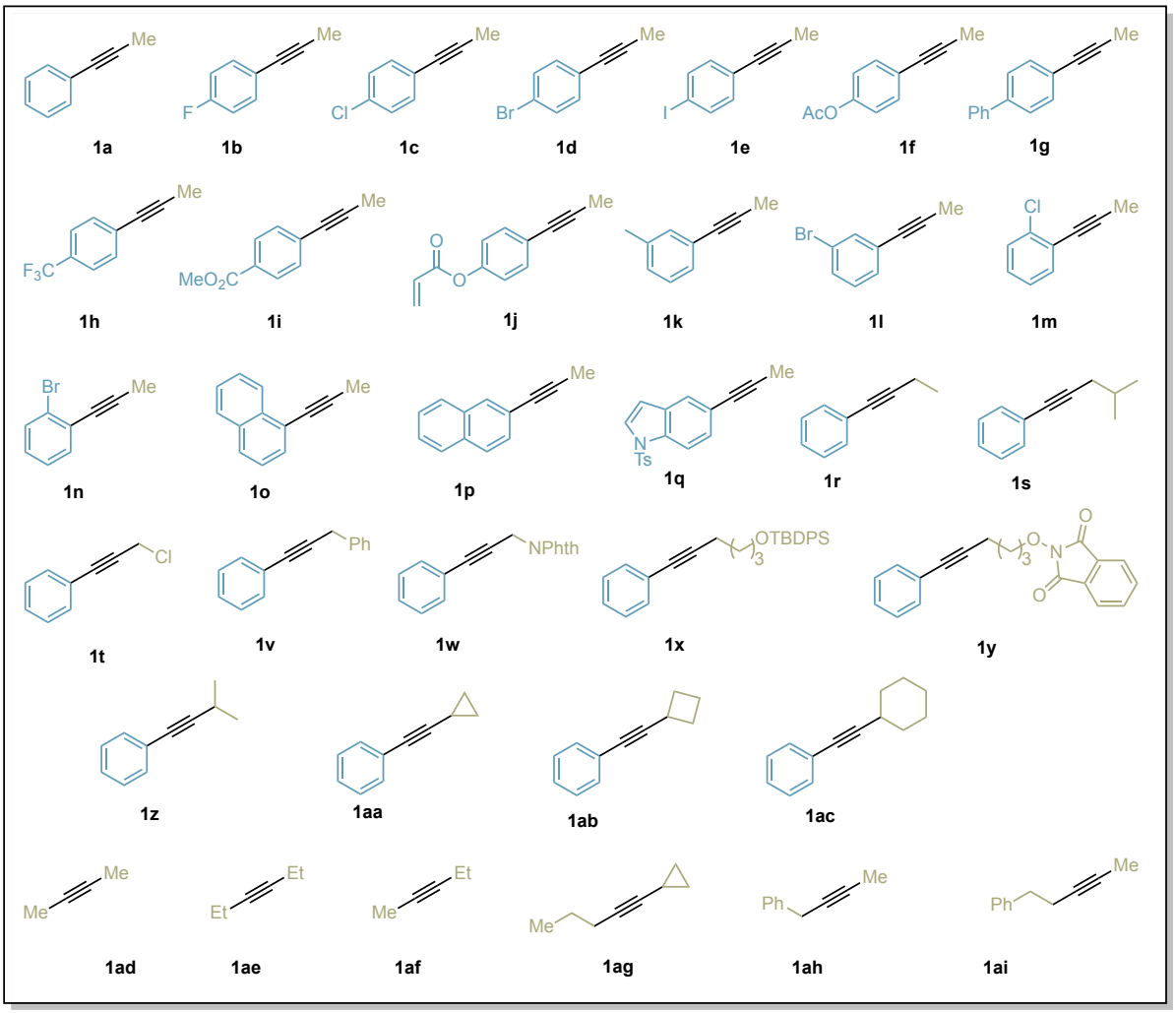


Figure 27: Alkyne synthesis

Synthesis of hypervalent iodine reagents.

The hypervalent iodine reagents **2a-2d** indicated below are known compounds, reagents **2e-2h** are new and were prepared following a modified procedure of reported protocols.[79]

[79] (a) Wang, Z.; Jiang, L.; Sarró, P.; Suero, M. G. *J. Am. Chem. Soc.* **2019**, *141*, 15509. (b) Jiang, L.; Sarró, P.; Teo, W. J.; Llop, J.; Suero, M. G. *Chem. Sci.* **2022**, *13*, 4327

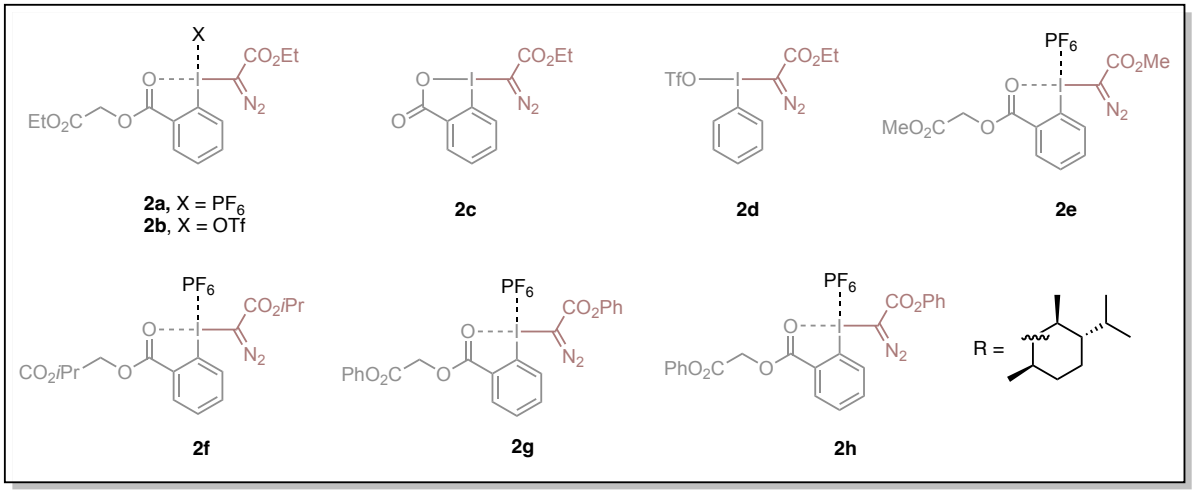


Figure 28 : Hypervalent iodine reagents

Modified procedure of reported protocols for the synthesis of reagents 2e-2h:

A solution of 1-methoxy-1,2-benziodoxol-3(1H)-one (1.0 eq.) in dichloromethane (0.5 M) was treated with trimethylsilyl trifluoromethanesulfonate (1.0 eq.) at room temperature. After 30 minutes, a cloudy suspension was observed and the corresponding diazo compound (2.2 eq.) was added dropwise during 10 minutes. Nitrogen evolution was observed and the resulting reaction mixture was stirred at room temperature until a clear yellow solution was observed (1 hour). Solvent was removed under vacuum and the crude was recrystallized from a mixture of diethyl ether/dichloromethane (5/1) during 12 hours at -20 °C (Note: the recrystallization process may be repeated if impurities are observed). The desired product **2-OTf** was collected by filtration, washed with cold diethyl ether, dried under high vacuum and stored a -20 °C.

A solution of **2-OTf** in dichloromethane (0.2 M) was added to a separation funnel and then washed with a saturated aqueous solution of KPF_6. The combined organic layers were dried over Na_2SO_4 and solvent was removed under vacuum to give **2e-2h** as yellow solid.

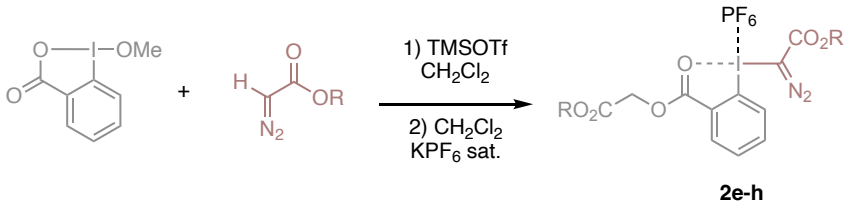
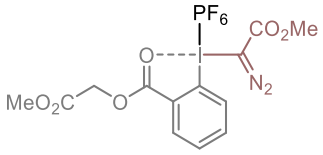


Figure 29: Modified procedure for the synthesis of hypervalent iodine reagents **2e-h**

(1-diazo-2-methyloxy-2-oxoethyl)(2-(2-methyloxy-2-oxoethoxyl)carbonylphenyl)iodonium hexafluorophosphate (2e)



Prepared according to the modified procedure using methyl diazoacetate. The title compound was obtained as yellow solid (1.5 g, 48% yield for two steps).

^{1}H NMR (400 MHz, CD_3CN) δ 8.48 – 8.43 (m, 1H), 8.10 – 8.03 (m, 2H), 7.98 – 7.93 (m, 1H), 5.12 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, CD_3CN) δ 170.6, 167.6, 162.5, 139.4, 134.2, 133.5, 130.2, 126.0, 116.6, 65.0, 55.4, 53.3.

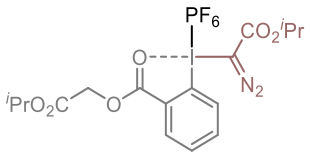
^{19}F NMR (376 MHz, CD_3CN) δ -72.6 (d, J = 706.6 Hz).

^{31}P NMR (162 MHz, CD_3CN) δ -141.5 (sp, J = 706.3 Hz).

HRMS (MALDI): calculated for $C_{13}H_{12}IN_2O_6$ $[M\text{-}PF_6]^+$ m/z: 418.9740, found: 418.9739.

IR ν max (film, cm^{-1}): 2123, 1707, 1659, 1557, 1437, 1384, 1278, 1151, 837, 745.

(1-diazo-2-isopropyloxy-2-oxoethyl)(2-(2-isopropyloxy-2-oxoethoxyl)carbonylphenyl)iodonium hexafluorophosphate (2f)



Prepared according to the modified procedure using isopropyl diazoacetate. The title compound was obtained as yellow solid (1.1 g, 69% yield for two steps).

^{1}H NMR (500 MHz, CD_3CN) δ 8.46 (d, J = 7.7 Hz, 1H), 8.09 – 8.04 (m, 2H), 7.98 – 7.93 (m, 1H), 5.21 – 5.10 (m, 2H), 5.06 (s, 2H), 1.30 (d, J = 6.3 Hz, 12H).

^{13}C NMR (126 MHz, CD_3CN) δ 170.6, 166.6, 161.5, 139.4, 134.2, 133.5, 130.1, 126.1, 116.6, 73.9, 71.0, 65.3, 21.9, 21.8.

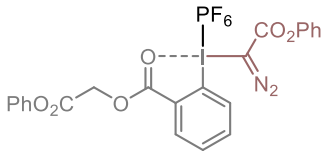
^{19}F NMR (376 MHz, CD_3CN) δ -72.7 (d, J = 707.2 Hz).

^{31}P NMR (162 MHz, CD_3CN) δ -141.5 (sp, J = 707.3 Hz).

HRMS (MALDI): calculated for $C_{17}H_{20}IN_2O_6$ $[M\text{-}PF_6]^+$ m/z: 475.0366, found: 475.0380.

IR ν max (film, cm^{-1}): 2119, 1699, 1657, 1588, 1428, 1386, 1323, 1270, 1223, 1151, 1099, 1028, 827.

(1-diazo-2-phenyloxy-2-oxoethyl)(2-(2-phenyloxy-2-oxoethoxyl)carbonylphenyl)iodonium hexafluorophosphate (2g)



Prepared according to the modified procedure using phenyl diazoacetate. The title compound was obtained as yellow solid (0.9 g, 73% yield for two steps).

^{1}H NMR (400 MHz, CD_3CN) δ 8.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 8.13 – 8.06 (m, 1H), 7.98 – 7.92 (m, 1H), 7.50 – 7.41 (m, 4H), 7.37 – 7.30 (m, 2H), 7.25 – 7.17 (m, 4H), 5.36 (s, 2H).

^{13}C NMR (101 MHz, CD_3CN) δ 170.8, 166.2, 161.2, 151.5, 151.0, 142.4, 139.7, 134.4, 133.6, 130.74, 130.73, 130.3, 127.8, 127.5, 122.5, 122.34, 122.26, 65.2.

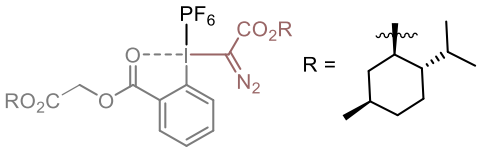
^{19}F NMR (376 MHz, CD_3CN) δ -72.8 (d, *J* = 707.0 Hz).

^{31}P NMR (162 MHz, CD_3CN) δ -141.6 (sp, *J* = 707.9 Hz).

HRMS (MALDI): calculated for $C_{23}H_{16}IN_2O_6$ $[M\text{-}PF_6]^+$ m/z: 543.0053, found: 543.0077.

IR ν max (film, cm^{-1}): 2121, 1772, 1717, 1654, 1587, 1425, 1383, 1328, 1262, 1185, 1147, 829, 769.

(1-diazo-2-(*R*)-menthyloxy-2-oxoethyl)(2-(2-(*R*)-menthyloxy-2-oxoethoxyl)carbonylphenyl)iodonium hexafluorophosphate (2h)



Prepared according to the modified procedure using (*R*)-menthyl diazoacetate. The title compound was obtained as yellow solid (2.4 g, 77% yield for two steps).

^{1}H NMR (400 MHz, CD_3CN) δ 8.51 – 8.41 (m, 1H), 8.12 – 8.02 (m, 2H), 7.96 (ddd, *J* = 8.0, 5.9, 2.4 Hz, 1H), 5.09 (s, 2H), 4.90 – 4.80 (m, 2H), 2.09 – 1.82 (m, 4H), 1.74 – 1.66 (m, 5H), 1.62 – 1.27 (m, 5H), 1.18 – 1.03 (m, 4H), 0.92 (dd, *J* = 6.9, 3.2 Hz, 9H), 0.81 (d, *J* = 7.0 Hz, 6H), 0.76 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, CD_3CN) δ 170.7, 166.8, 161.4, 139.3, 134.2, 133.5, 130.2, 126.1, 116.6, 79.8, 77.0, 65.3, 47.8, 47.7, 41.4, 41.3, 34.7, 34.6, 32.1, 32.0, 27.01, 26.98, 24.0, 23.9, 22.2, 22.1, 21.0, 20.8, 16.6, 16.5.

^{19}F NMR (376 MHz, CD_3CN) δ -72.8 (d, *J* = 706.1 Hz).

^{31}P NMR (162 Hz, CD_3CN), δ -141.5 (sp, *J* = 706.3 Hz).

HRMS (MALDI): calculated for $C_{31}H_{44}IN_2O_6$ $[M\text{-}PF_6]^+$ m/z: 667.2244, found: 667.2247.

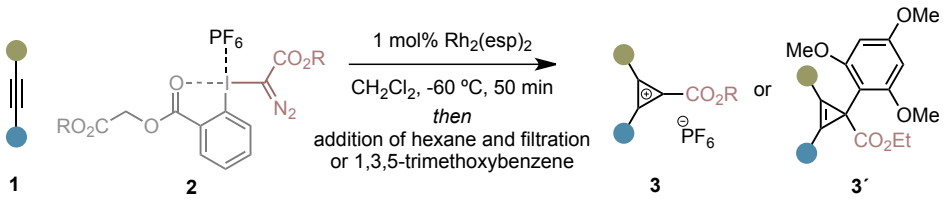
IR ν max (film, cm^{-1}): 2954, 2926, 2868, 2121, 1751, 1700, 1662, 1220, 1026, 746.

Synthesis of cyclopropenium cations (CPCs) 3: reaction optimization and scope.

General Procedure for reaction optimization:

To a 10 mL oven-dried tube equipped with a stirring bar was added the corresponding Rh catalyst (0.001 mmol, 1 mol%). The tube was sealed before being evacuated and backfilled with argon. 1-Phenyl-1-propyne **1a** (23.2 mg, 25 µL, 0.2 mmol) and degassed dichloromethane (0.5 mL) were added and the resulting mixture was placed into a cooling bath at -60 ºC. Then, a solution of the corresponding reagent **2** (0.1 mmol, 1.0 eq.) in degassed dichloromethane (1.0 mL) was added dropwise during 40 min using a syringe pump and a precipitate was generally observed (Figure 25, Section 2.5.3). The reaction mixture was stirred for additional 10 min at -60 ºC. After this, 1,3,5-trimethoxybenzene (0.4 mmol, 4.0 eq.) was added as solid at -60 ºC and the precipitate disappeared almost instantaneously. The reaction mixture was then quenched with triethylamine (0.5 mL) and the solvent was removed under *vacuum*. The resulting reaction crude mixture was analyzed by ^{1}H NMR using dibromomethane as internal standard.

General procedure A: Synthesis of the CPCs



To a 10 mL oven-dried tube equipped with a stirring bar was added $Rh_2(esp)_2$ (2.0 mg, 0.002 mmol, 1 mol%). The tube was sealed before being evacuated and backfilled with argon. The corresponding alkyne (0.26 mmol, 1.3 eq.) and degassed dichloromethane (0.5 mL) were added and the resulting mixture was cooled to -60 ºC. Then, a solution of reagent **2** (0.20 mmol, 1.0 eq.) in degassed dichloromethane (2.0 mL) was added dropwise during 40 min using a syringe pump. The reaction mixture was stirred for additional 10 min at -60 ºC. After this, dry hexane (3.0 mL) was added slowly to the reaction mixture and the precipitate **3** was collected by quick filtration, washed with dry hexane (2.0 mL x 3) and dried under *vacuum* at room temperature. *Note: compounds **3** could be stored at –20 ºC under argon for at least 1 month without detectable decomposition and can be handled at room temperature without the need of a glovebox. No detectable decompositions were observed for compound **3ak** for over 1 year.*

In some cases, the precipitate was not observed probably due to a higher solubility of the corresponding **CPC**. In order to quantify its formation, 1,3,5-trimethoxybenzene was used as nucleophile employing the following modification of the **General Procedure A**: After the solution of reagent **2** in degassed dichloromethane was added dropwise, 1,3,5-trimethoxybenzene (0.8 mmol, 4.0 eq.) was added as solid at -60 ºC. Then, the reaction mixture was quenched with triethylamine (0.5 mL) and the solvent was removed under *vacuum.* The crude residue was purified by flash column chromatography on neutral silica gel to give the corresponding cyclopropene **3***.

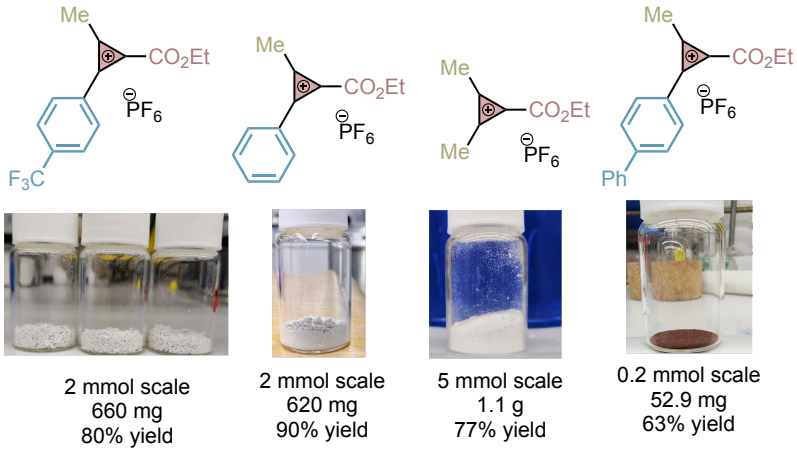
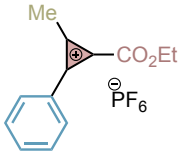


Figure 30 Pictures of **CPCs**.

1-(ethoxycarbonyl)-2-phenyl-3-methylcyclopropenium hexafluorophosphate (CPC 3a)



Prepared according to the **general procedure A** using 1-phenyl-1-propyne (30.2 mg, 32 µL, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (59.5 mg, 86% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.52 (d, *J* = 7.3 Hz, 2H), 8.22 – 8.15 (m, 1H), 7.97 – 7.90 (m, 2H), 4.71 (q, *J* = 7.1 Hz, 2H), 3.38 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.5, 166.7, 156.0, 153.1, 141.2, 137.8, 130.6, 118.2, 65.9, 13.1, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.4 (d, *J* = 707.4 Hz).

^{31}P NMR (203 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 708.7 Hz).

IR ν max (film, cm^{-1}): 2121, 1858, 1739, 1594, 1508, 1448, 1396, 1311, 1229, 1150, 1120, 1010, 819, 757.

HRMS (ESI) calculated for $C_{13}H_{13}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 201.0910, found: 201.0909.

m.p. 95 ºC (decomp).

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

^{1}H and ^{13} C NMR were also measured in methanol-d_4.

^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 6.9 Hz, 2H), 7.48 – 7.35 (m, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 174.1, 130.5, 130.3, 130.0, 127.2, 115.2, 114.8, 64.8, 62.2, 14.5, 9.3.

Procedure for a 4.0 mmol-scale reaction with 1-phenyl-1-propyne:

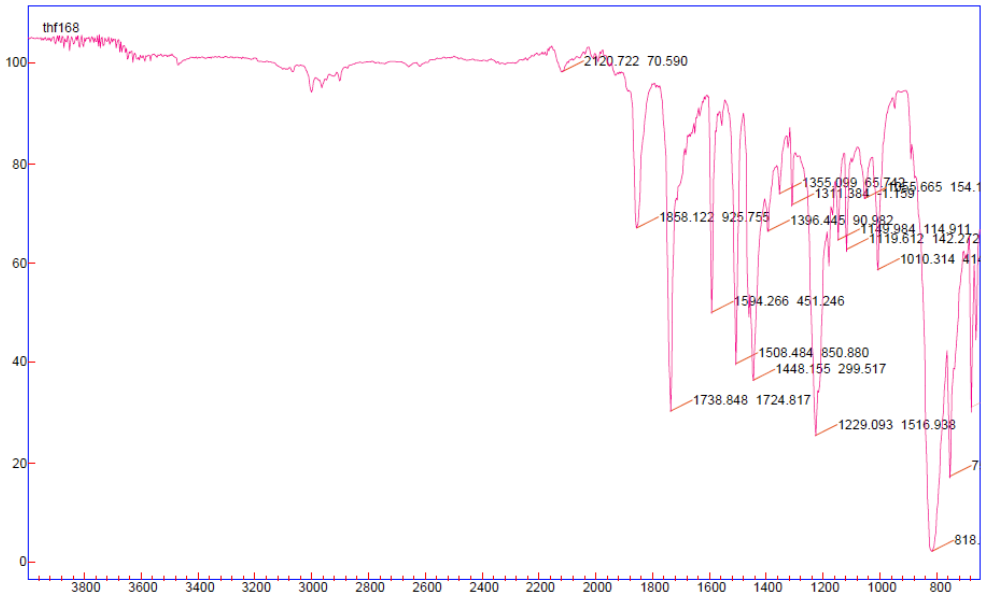
To a 100 mL oven-dried flask equipped with a stirring bar was added $Rh_2(esp)_2$ (32.0 mg, 1 mol%). The flask was sealed before being evacuated and backfilled with nitrogen. 1-Phenyl-1-propyne (604 mg, 640 µL, 5.2 mmol) and degassed dichloromethane (35 mL) were added and the resulting mixture was cooled to -60 ºC. Then, a solution of reagent **2a** (2.4 g, 4.0 mmol, 1.0 eq.) in degassed dichloromethane (20 mL) was added dropwise during 40 minutes using a syringe pump. After the addition, the reaction was kept stirring at -60 ºC until the reaction was complete (monitored by TLC, 10 minutes). Then dry hexane (9 mL) was added to the reaction mixture slowly. The product was collected by quick filtration, washed with dry hexane (6 mL x 3), dried under high *vacuum* to give **CPC 3a** (1.08 g, 78% yield).

Notes:

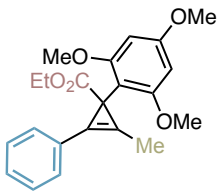
(a) Upon scaling up, efficient stirring is important to get a clean reaction and high yield.

(b) **CPC 3a** is soluble in ACN, EtOAc, THF, DMF, DMSO or acetone but decomposes quickly with time. **CPC 3a** is soluble in alcoholic solvents (methanol, ethanol, 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-2-propanol) but its decomposition is slow. The cation is also soluble in CD_3NO_2 and stable for around one hour.

IR spectra of 3a



ethyl 2-methyl-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3a*)



Prepared according to the **general procedure A** using 1-phenyl-1-propyne (30.2 mg, 16 µL, 0.13 mmol) and **2a** (60.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the corresponding cyclopropene as a white solid (34.6 mg, 94% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.39 – 7.32 (m, 2H), 7.29 – 7.22 (m, 1H), 6.10 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.68 (s, 6H), 2.37 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 160.4, 160.2, 129.8, 128.9, 128.3, 128.0, 113.2, 111.7, 111.2, 90.8, 60.5, 55.6, 55.5, 29.1, 14.9, 10.6.

IR ν max (film, cm^{-1}): 2994, 2839, 1874, 1711, 1587, 1456, 1410, 1337, 1228, 1190, 1153, 1116, 1022, 955, 802.

HRMS (ESI) calculated for $C_{22}H_{24}NaO_5^+$ $[M+Na]^+$ m/z: 391.1516, found: 391.1512.

m.p. 89-90 ºC.

A crystal of **3a*** was grown by slow evaporation of a solution of **3a*** in dichloromethane and hexane at room temperature. It has been deposited at the Cambridge Cristallographic Data Center, CCDC No: 2191637.

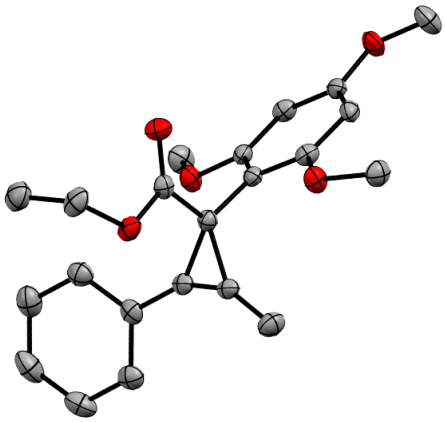
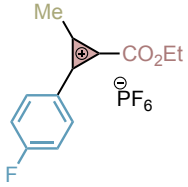


Figure 31 ORTEP diagram of **3a***

1-(ethoxycarbonyl)-2-(4-fluorophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3b)



Prepared according to the **general procedure A** using 1-(4-fluorophenyl)-1-propyne (34.8 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (59.1 mg, 81% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.72 – 8.53 (m, 2H), 7.73 – 7.57 (m, 2H), 4.70 (q, *J* = 7.1 Hz, 2H), 3.35 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.5, 170.7, 169.4, 165.3, 154.1 (d, *J* = 257.3 Hz), 141.6 (d, *J* = 12.1 Hz), 118.4 (d, *J* = 23.3 Hz), 115.0 (d, *J* = 1.8 Hz), 65.9, 13.0, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -75.8 (d, *J* = 707.3 Hz), -93.2.

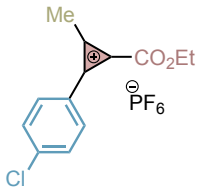
^{31}P NMR (203 MHz, CD_3NO_2) δ -144.1 (sp, *J* = 707.5 Hz).

IR ν max (film, cm^{-1}): 2995, 1852, 1740, 1593, 1523, 1444, 1314, 1218, 1163, 1116, 1006, 826, 766.

HRMS (ESI) calculated for $C_{13}H_{12}FO_2^+$ $[M\text{-}PF_6]^+$ m/z: 219.0816, found: 219.0815.

m.p. 97 °C (decomp).

1-(ethoxycarbonyl)-2-(4-chlorophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3c)



Prepared according to the **general procedure A** using 1-(4-chlorophenyl)-1-propyne (39.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (51.1 mg, 67% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.49 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 4.70 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CD_3NO_2) δ 171.4, 165.8, 155.9, 153.0, 148.1, 139.0, 131.0, 116.8, 65.9, 13.1, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.5 (d, *J* = 707.3 Hz).

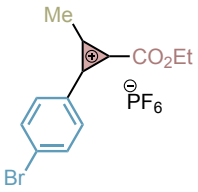
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.1 Hz).

IR ν max (film, cm^{-1}): 2996, 1858, 1747, 1580, 1506, 1451, 1283, 1217, 1178, 1110, 1069, 1009, 828, 764.

HRMS (ESI) calculated for $C_{13}H_{12}ClO_2^+$ $[M\text{-}PF_6]^+$ m/z: 235.0520, found: 235.0530.

m.p. 115 °C (decomp).

1-(ethoxycarbonyl)-2-(4-bromophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3d)



Prepared according to the **general procedure A** using 1-(4-bromophenyl)-1-propyne (50.4 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (61.9 mg, 73% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.39 (d, *J* = 8.4 Hz, 2H), 8.11 (d, *J* = 8.5 Hz, 2H), 4.70 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.6, 166.1, 156.0, 153.0, 138.7, 137.6, 134.1, 117.2, 66.0, 13.2, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.4 (d, *J* = 707.3 Hz).

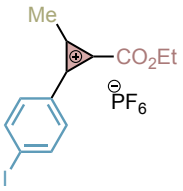
^{31}P NMR (203 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2997, 1859, 1747, 1580, 1506, 1452, 1398, 1218, 1069, 1009, 835, 764.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_2^+$ $[M\text{-}PF_6]^+$ m/z: 279.0015, found: 279.0006.

m.p. 125 °C (decomp).

1-(ethoxycarbonyl)-2-(4-iodophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3e)



Prepared according to the **general procedure A** using 1-(4-iodophenyl)-1-propyne (63.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (64.2 mg, 68% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.35 (d, *J* = 8.2 Hz, 2H), 8.19 (d, *J* = 8.1 Hz, 2H), 4.69 (q, *J* = 7.0 Hz, 2H), 3.36 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 171.6, 166.4, 156.0, 153.0, 140.3, 137.9, 117.5, 111.9, 65.9, 13.2, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.4 (d, *J* = 707.4 Hz).

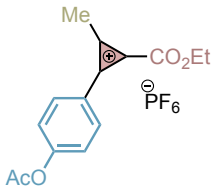
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 708.9 Hz).

IR ν max (film, cm^{-1}): 2987, 1855, 1745, 1575, 1503, 1450, 1394, 1367, 1214, 1056, 1006, 820, 764.

HRMS (ESI) calculated for $C_{13}H_{12}IO_2^+$ $[M\text{-}PF_6]^+$ m/z: 326.9877, found: 326.9861.

m.p. 108 °C (decomp).

1-(ethoxycarbonyl)-2-(4-acetoxyphenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3f)



Prepared according to the **general procedure A** using 1-(4-acetoxyphenyl)-1-propyne (45.2 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a brown solid (54.1 mg, 67% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.58 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 4.70 (q, *J* = 7.1 Hz, 2H), 3.36 (s, 3H), 2.41 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 170.8, 168.8, 165.4, 160.9, 155.1, 153.1, 140.0, 124.1, 115.5, 65.8, 19.8, 13.0, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -75.8 (d, *J* = 707.2 Hz).

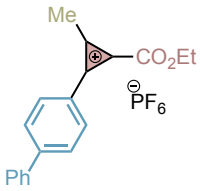
^{31}P NMR (203 MHz, CD_3NO_2) δ -144.1 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2930, 1849, 1746, 1597, 1515, 1457, 1372, 1305, 1233, 1182, 1160, 1057, 1007, 906, 825, 766.

HRMS (ESI) calculated for $C_{15}H_{15}O_4^+$ $[M\text{-}PF_6]^+$ m/z: 259.0965, found: 259.0953.

m.p. 88 °C (decomp).

1-(ethoxycarbonyl)-2-(4-phenyphenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3g)



Prepared according to the **general procedure A** using 1-(4-phenylphenyl)-1-propyne (50.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a dark brown solid (52.9 mg, 63% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.67 – 7.63 (m, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.42 (m, 2H), 7.39 – 7.34 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.39 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD) δ 174.2, 143.6, 141.4, 130.9, 130.0, 128.9, 128.5, 128.0, 126.1, 115.0, 114.9, 64.9, 62.3, 14.6, 9.5.

^{19}F NMR (376 MHz, CD_3OD) δ -75.0 (d, *J* = 707.4 Hz).

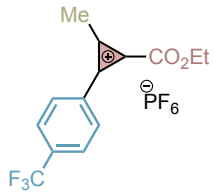
^{31}P NMR (162 MHz, CD_3OD) δ -141.5 (sp, *J* = 707.5 Hz).

IR ν max (film, cm^{-1}): 2988, 1846, 1743, 1600, 1520, 1453, 1406, 1223, 1006, 831, 765.

HRMS (ESI) calculated for $C_{19}H_{17}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 277.1223, found: 277.1223.

m.p. 88 °C (decomp).

1-(ethoxycarbonyl)-2-(4-trifluoromethylphenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3h)



Prepared according to the **general procedure A** using 1-(4-trifluoromethylphenyl)-1-propyne (55.2 mg, 0.30 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mol% of $Rh_2(esp)_2$ (3.0 mg) instead of 1 mol%. Filtration of the reaction mixture provided the title compound as a white solid (52.0 mg, 63% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.72 (d, *J* = 8.1 Hz, 2H), 8.21 (d, *J* = 8.1 Hz, 2H), 4.73 (q, *J* = 7.1 Hz, 2H), 3.44 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 173.4, 167.0, 158.2, 152.8, 139.6 (q, *J* = 32.8 Hz), 138.2, 127.2 (q, *J* = 4.1 Hz), 123.1 (q, *J* = 273.4 Hz), 121.4, 66.2, 13.5, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -64.4, -75.0 (d, *J* = 707.4 Hz).

^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 3000, 1864, 1745, 1618, 1520, 1473, 1410, 1318, 1237, 1177, 1141, 1114, 1064, 1010, 827, 769.

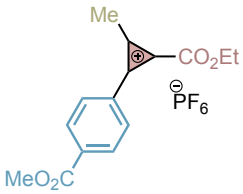
HRMS (ESI) calculated for $C_{14}H_{12}F_3O_2^+$ $[M\text{-}PF_6]^+$ m/z: 269.0784, found: 269.0785.

m.p. 106 °C (decomp).

Procedure for a 2.0 mmol-scale reaction with 1-(4-trifluoromethylphenyl)-1-propyne:

To a 100 mL oven-dried flask equipped with a stirring bar was added $Rh_2(esp)_2$ (24.0 mg, 1.5 mol%). The flask was sealed before being evacuated and backfilled with nitrogen. 1-(4-trifluorophenyl)-1-propyne (736.0 mg, 4.0 mmol) and degassed dichloromethane (5 mL) were added and the resulting mixture was cooled to -60 ºC. Then, a solution of reagent **2a** (1.2 g, 2.0 mmol, 1.0 eq.) in degassed dichloromethane (15 mL) was added dropwise during 40 minutes using a syringe pump. After the addition, the reaction was kept stirring at -60 ºC until the reaction was complete (monitored by TLC, 10 minutes). Then dry hexane (7 mL) was added to the reaction mixture slowly. The product was collected by quick filtration, washed with dry hexane (6 mL x 3) and dried under high *vacuum* to give **CPC 3h** (0.66 g, 80% yield).

1-(ethoxycarbonyl)-2-(4-(methoxycarbonyl)phenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3i)



Prepared according to the **general procedure A** using 1-(4-(methoxycarbonyl)phenyl)-1-propyne (52.2 mg, 0.30 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (48.4 mg, 60% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 8.09 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 2.41 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 173.7, 167.7, 131.8, 131.6, 131.1, 130.3, 118.6, 114.6, 64.6, 62.3, 52.8, 14.5, 9.5.

^{19}F NMR (471 MHz, CD_3OD) δ -75.4 (d, *J* = 707.4 Hz).

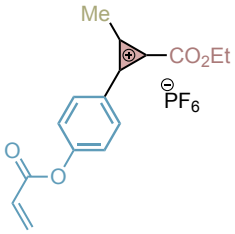
^{31}P NMR (203 MHz, CD_3OD) δ -142.1 (sp, *J* = 708.9 Hz).

IR ν max (film, cm^{-1}): 1862, 1724, 1608, 1513, 1467, 1437, 1279, 1212, 1108, 1016, 829, 774.

HRMS (ESI) calculated for $C_{15}H_{15}O_4^+$ $[M\text{-}PF_6]^+$ m/z: 259.0965, found: 259.0959.

m.p. 57 °C (decomp).

1-(ethoxycarbonyl)-2-(4-acrylatephenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3j)



Prepared according to the **general procedure A** using 1-(4-acrylatephenyl)-1-propyne (48.4 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a brown solid sticked to the wall of the reaction tube (46.5 mg, 56% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.60 (d, *J* = 8.7 Hz, 2H), 7.75 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 18.1 Hz, 1H), 6.45 (dd, *J* = 17.2, 10.5 Hz, 1H), 6.25 (d, *J* = 10.5 Hz, 1H), 4.70 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 1.53 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 170.8, 165.4, 163.5, 160.7, 155.2, 153.1, 140.0, 134.3, 126.7, 124.0, 115.5, 65.9, 13.1, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -75.9 (d, J = 707.1 Hz).

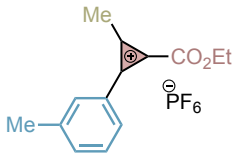
^{31}P NMR (203 MHz, CD_3NO_2) δ -144.1 (sp, J = 708.5 Hz).

IR ν max (film, cm^{-1}): 1849, 1741, 1596, 1505, 1449, 1407, 1294, 1215, 1127, 1009, 902, 825.

HRMS (ESI) calculated for $C_{16}H_{15}O_4^+$ $[M\text{-}PF_6]^+$ m/z: 271.0965, found: 271.0962.

m.p. 64-65 °C (decomp).

1-(ethoxycarbonyl)-2-(3-methylphenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3k)



Prepared according to the **general procedure A** using 1-(3-methylphenyl)-1-propyne (33.5 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (42.7 mg, 59% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.38 – 8.25 (m, 2H), 8.01 (d, J = 7.6 Hz, 1H), 7.87 – 7.76 (m, 1H), 4.70 (q, J = 7.1 Hz, 2H), 3.36 (s, 3H), 2.58 (s, 3H), 1.53 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.2, 166.6, 155.7, 153.2, 142.2, 141.5, 137.8, 135.1, 130.4, 118.1, 65.8, 19.7, 13.1, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.2 (d, J = 707.1 Hz).

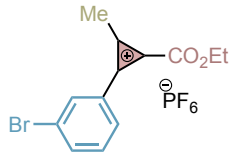
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.6 (sp, J = 707.1 Hz).

IR ν max (film, cm^{-1}): 1854, 1738, 1603, 1580, 1504, 1467, 1397, 1300, 1234, 1119, 1009, 830, 766.

HRMS (ESI) calculated for $C_{14}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 215.1067, found: 215.1070.

m.p. 98 °C (decomp).

1-(ethoxycarbonyl)-2-(3-bromophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3l)



Prepared according to the **general procedure A** using 1-(3-bromophenyl)-1-propyne (50.4 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (49.9 mg, 59% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.63 (s, 1H), 8.50 (d, *J* = 7.7 Hz, 1H), 8.30 (d, *J* = 8.2 Hz, 1H), 7.89 – 7.82 (m, 1H), 4.71 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 172.3, 166.3, 157.0, 152.9, 143.5, 139.4, 136.5, 132.1, 123.4, 119.9, 66.1, 13.3, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.5 (d, *J* = 707.0 Hz).

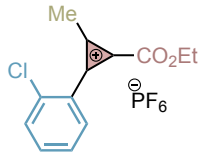
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.6 (sp, *J* = 707.1 Hz).

IR ν max (film, cm^{-1}): 2987, 1851, 1732, 1588, 1560, 1496, 1446, 1240, 1217, 1156, 1007, 826.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_2^+$ $[M\text{-}PF_6]^+$ m/z: 279.0015, found: 279.0017.

m.p. 78 °C (decomp).

1-(ethoxycarbonyl)-2-(2-chlorophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3m)



Prepared according to the **general procedure A** using 1-(2-chlorophenyl)-1-propyne (39.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (43.6 mg, 57% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.58 (dd, *J* = 7.8, 1.6 Hz, 1H), 8.19 – 8.10 (m, 1H), 7.95 (dd, *J* = 10.0, 1.0 Hz, 1H), 7.89 – 7.82 (m, 1H), 4.72 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 3H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.1, 164.1, 156.6, 153.4, 142.6, 141.9, 140.5, 131.6, 129.0, 118.1, 66.1, 13.9, 12.9.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.5 (d, *J* = 707.3 Hz).

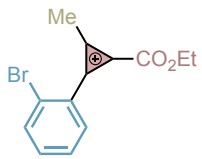
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 708.4 Hz).

IR ν max (film, cm^{-1}): 2989, 1858, 1753, 1587, 1492, 1223, 1302, 1215, 1137, 1046, 832, 760.

HRMS (ESI) calculated for $C_{13}H_{12}ClO_2^+$ $[M\text{-}PF_6]^+$ m/z: 235.0520, found: 235.0514.

m.p. 68 °C (decomp).

1-(ethoxycarbonyl)-2-(2-bromophenyl)-3-methylcyclopropenium hexafluorophosphate (CPC 3n)



Prepared according to the **general procedure A** using 1-(2-bromophenyl)-1-propyne (50.4 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (64.2 mg, 76% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.59 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.08 – 8.00 (m, 1H), 7.93 – 7.86 (m, 1H), 4.72 (q, *J* = 6.9 Hz, 2H), 3.45 (s, 3H), 1.52 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.0, 165.6, 157.1, 153.5, 142.2, 141.2, 135.1, 131.1, 129.4, 120.3, 66.1, 14.3, 12.9.

^{19}F NMR (471 MHz, CD_3NO_2) δ -75.9 (d, *J* = 707.2 Hz).

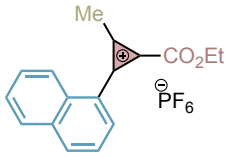
^{31}P NMR (203 MHz, CD_3NO_2) δ -144.1 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2983, 1696, 1467, 1369, 1261, 1160, 1065, 1025, 838, 757.

HRMS (ESI) calculated for $C_{13}H_{12}BrO_2^+$ $[M\text{-}PF_6]^+$ m/z: 279.0015, found: 279.0016.

m.p. 81 °C (decomp).

1-(ethoxycarbonyl)-2-(1-naphthalene)-3-methylcyclopropenium hexafluorophosphate (CPC 3o)



Prepared according to the **general procedure A** using 1-naphthalene-1-propyne (43.2 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed at -63 ºC instead of -60 ºC. Filtration of the reaction mixture provided the title compound as a brown solid (62.4 mg, 79% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.94 (dd, *J* = 7.3, 1.1 Hz, 1H), 8.82 (d, *J* = 8.4 Hz, 1H), 8.76 (d, *J* = 8.2 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.12 – 8.05 (m, 1H), 8.05 – 7.99 (m, 1H), 7.95 – 7.88 (m, 1H), 4.78 (q, *J* = 7.1 Hz, 2H), 3.53 (s, 3H), 1.59 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 170.5, 163.3, 154.0, 153.7, 144.1, 143.9, 133.7, 132.8, 131.4, 130.1, 128.6, 126.3, 123.7, 115.5, 66.0, 13.5, 12.9.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.5 (d, *J* = 707.3 Hz).

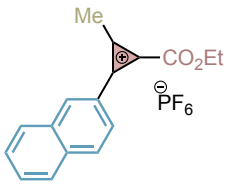
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2981, 2925, 1836, 1735, 1569, 1514, 1474, 1366, 1203, 1012, 829, 773.

HRMS (ESI) calculated for $C_{17}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 251.1067, found: 251.1072.

m.p. 69 °C (decomp).

1-(ethoxycarbonyl)-2-(2-naphthalene)-3-methylcyclopropenium hexafluorophosphate (CPC 3p)



Prepared according to the **general procedure A** using 2-naphthalene-1-propyne (43.2 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed at -63 ºC instead of -60 ºC. Filtration of the reaction mixture provided the title compound as a brown solid (54.1 mg, 68% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 9.26 (s, 1H), 8.38 – 8.27 (m, 3H), 8.19 (d, *J* = 8.2 Hz, 1H), 8.05 – 7.96 (m, 1H), 7.90 – 7.83 (m, 1H), 4.74 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 3H), 1.56 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 170.9, 166.2, 155.2, 153.3, 143.6, 138.8, 133.4, 132.5, 131.1, 130.4, 128.7, 128.6, 128.5, 115.3, 65.8, 13.1, 12.9.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.4 (d, *J* = 707.3 Hz).

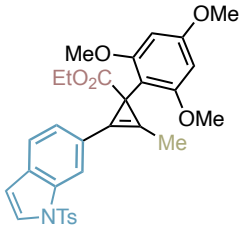
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 707.3 Hz).

IR ν max (film, cm^{-1}): 2924, 1842, 1739, 1622, 1486, 1446, 1411, 1301, 1221, 1155, 1009, 917, 831, 764.

HRMS (ESI) calculated for $C_{17}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 251.1067, found: 251.1064.

m.p. 80 °C (decomp).

ethyl 2-methyl-3-(1-tosyl-1*H*-indol-5-yl)-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3q')



Prepared according to the **general procedure A** using 5-(prop-1-yn-1-yl)-1-tosyl-1*H*-indole (60.0 mg, 0.20 mmol) and **2a** (90 mg, 0.15 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 2/1) provided the title compound as a yellow oil (45.5 mg, 54% yield).

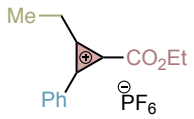
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.6 Hz, 1H), 7.81 – 7.70 (m, 3H), 7.60 – 7.54 (m, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 6.67 (d, *J* = 3.3 Hz, 1H), 6.11 (s, 2H), 4.21 – 4.08 (m, 2H), 3.80 (s, 3H), 3.69 (s, 6H), 2.39 (s, 3H), 2.36 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 160.0, 159.8, 145.0, 135.2, 134.3, 130.7, 129.8, 126.8, 126.7, 126.3, 123.8, 122.4, 113.2, 112.0, 111.3, 110.7, 109.4, 90.5, 60.2, 55.3, 55.1, 28.9, 21.5, 14.5, 10.2.

IR ν max (film, cm^{-1}): 2930, 2837, 1707, 1587, 1455, 1367, 1286, 1202, 1154, 1122, 1033, 991, 907, 810.

HRMS (ESI) calculated for $C_{31}H_{31}NNaO_7S^+$ $[M+Na]^+$ m/z: 584.1713, found: 584.1708.

1-(ethoxycarbonyl)-2-phenyl-3-ethylcyclopropenium hexafluorophosphate (CPC 3r)



Prepared according to the **general procedure A** using 1-phenyl-1-butyne (33.9 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (49.0 mg, 68% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.51 (dd, *J* = 8.3, 1.4 Hz, 2H), 8.23 – 8.15 (m, 1H), 7.98 – 7.89 (m, 2H), 4.71 (q, *J* = 7.1 Hz, 2H), 3.72 (q, *J* = 7.2 Hz, 2H), 1.76 (t, *J* = 7.3 Hz, 3H), 1.54 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 175.2, 166.6, 156.0, 152.9, 141.3, 137.9, 130.6, 118.2, 65.9, 22.4, 12.8, 9.2.

^{19}F NMR (471 MHz, CD_3NO_2) δ -75.9 (d, *J* = 707.2 Hz).

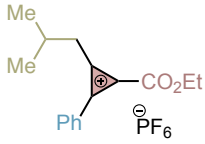
^{31}P NMR (203 MHz, CD_3NO_2) δ -144.1 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2992, 1856, 1743, 1593, 1506, 1447, 1380, 1301, 1215, 1117, 1019, 830, 777.

HRMS (ESI) calculated for $C_{14}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 215.1067, found: 215.1065.

m.p. 96 °C (decomp).

1-(ethoxycarbonyl)-2-phenyl-3-(2-methyl)propylcyclopropenium hexafluorophosphate (CPC 3s)



Prepared according to the **general procedure A** using (4-methylpent-1-yn-1-yl)benzene (41.1 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (45.5 mg, 59% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.52 (dd, *J* = 8.2, 1.3 Hz, 2H), 8.24 – 8.16 (m, 1H), 7.98 – 7.89 (m, 2H), 4.73 (q, *J* = 7.1 Hz, 2H), 3.65 (d, *J* = 6.8 Hz, 2H), 2.72 – 2.54 (m, 1H), 1.55 (t, *J* = 7.1 Hz, 3H), 1.25 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 173.2, 167.4, 156.0, 153.0, 141.4, 137.9, 130.6, 118.2, 66.0, 36.4, 26.9, 21.1, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.4 (d, *J* = 707.3 Hz).

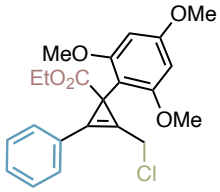
^{31}P NMR (203 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.3 Hz).

IR ν max (film, cm^{-1}): 2966, 1854, 1747, 1596, 1507, 1450, 1371, 1309, 1221, 1181, 1116, 823, 757.

HRMS (ESI) calculated for $C_{16}H_{19}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 243.1380, found: 243.1391.

m.p. 88 °C (decomp).

ethyl 2-(chloromethyl)-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3t')



Prepared according to the **general procedure A** using (3-chloroprop-1-yn-1-yl)benzene (39.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow solid (60.7 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 2H), 7.46 – 7.39 (m, 2H), 7.38 – 7.32 (m, 1H), 6.13 (s, 2H), 4.79 (s, 2H), 4.25 – 4.04 (m, 2H), 3.81 (s, 3H), 3.74 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H).

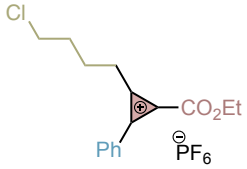
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 160.3, 159.8, 130.4, 128.7, 128.0, 126.8, 115.1, 111.3, 110.1, 90.5, 60.5, 55.3, 55.2, 38.0, 31.2, 14.4.

IR ν max (film, cm^{-1}): 2937, 2837, 1710, 1586, 1455, 1410, 1337, 1230, 1201, 1154, 1123, 1059, 1026, 954, 837, 805.

HRMS (ESI) calculated for $C_{22}H_{23}ClNaO_5^+$ $[M+Na]^+$ m/z: 425.1126, found: 425.1122.

m.p. 95-97 ºC.

1-(ethoxycarbonyl)-2-phenyl-3-(4-chloro)butylcyclopropenium hexafluorophosphate (CPC 3u)



Prepared according to the **general procedure A** using 1-phenyl-1-(6-chlorohexyne) (49.9 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (53.4 mg, 63% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.52 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.24 – 8.16 (m, 1H), 7.99 – 7.90 (m, 2H), 4.72 (q, *J* = 7.1 Hz, 2H), 3.83 – 3.74 (m, 4H), 2.44 – 2.30 (m, 2H), 2.18 – 2.04 (m, 2H), 1.54 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 173.6, 166.8, 156.0, 152.9, 141.4, 138.0, 130.6, 118.2, 66.0, 44.3, 31.3, 27.6, 22.9, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.5 (d, *J* = 707.3 Hz).

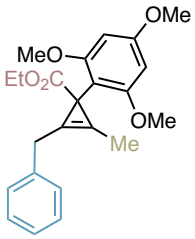
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 707.3 Hz).

IR ν max (film, cm^{-1}): 2955, 1850, 1740, 1594, 1504, 1446, 1304, 1229, 1111, 1010, 828, 756.

HRMS (ESI) calculated for $C_{16}H_{18}ClO_2^+$ $[M\text{-}PF_6]^+$ m/z: 277.0990, found: 277.0983.

m.p. 75 °C (decomp).

ethyl 2-benzyl-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3v')



Prepared according to the **general procedure A** using prop-1-yne-1,3-diyldibenzene (25.0 mg, 0.13 mmol) and **2a** (60 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (32.4 mg, 73% yield).

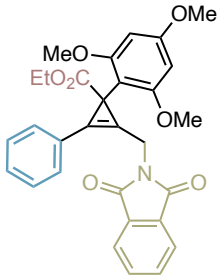
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 7.26 – 7.20 (m, 5H), 6.15 (s, 2H), 4.20 – 4.01 (m, 4H), 3.83 (s, 3H), 3.73 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 160.1, 160.0, 138.2, 129.8, 129.1, 128.5, 127.9, 127.73, 127.67, 126.5, 115.5, 111.8, 111.2, 90.5, 60.2, 55.3, 55.1, 32.3, 29.4, 14.5.

IR ν max (film, cm^{-1}): 2935, 2835, 1711, 1586, 1491, 1452, 1412, 1333, 1202, 1152, 1123, 1029, 810, 751.

HRMS (ESI) calculated for $C_{28}H_{28}NaO_5^+$ $[M+Na]^+$ m/z: 467.1829, found: 467.1826.

ethyl 2-((1,3-dioxoisoindolin-2-yl)methyl)-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3w')



Prepared according to the **general procedure A** using 2-(3-phenylprop-2-yn-1-yl)isoindoline-1,3-dione (68.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow foam (73.3 mg, 71% yield).

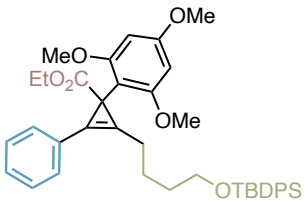
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 2H), 7.75 – 7.71 (m, 2H), 7.59 – 7.54 (m, 2H), 7.34 – 7.23 (m, 3H), 6.09 (s, 2H), 5.06 (d, *J* = 1.9 Hz, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.71 (s, 6H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 167.4, 160.1, 159.9, 134.0, 132.2, 130.1, 128.4, 128.0, 127.4, 123.3, 114.4, 110.4, 110.1, 90.5, 60.4, 55.3, 55.2, 33.3, 29.6, 14.3.

IR ν max (film, cm^{-1}): 2937, 2837, 1772, 1716, 1606, 1465, 1416, 1388, 1335, 1225, 1204, 1155, 1127, 1036, 954.

HRMS (ESI) calculated for $C_{30}H_{27}NNaO_7^+$ $[M+Na]^+$ m/z: 536.1680, found: 536.1669.

ethyl 2-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3x')



Prepared according to the **general procedure A** using *tert*-butyldiphenyl((6-phenylhex-5-yn-1-yl)oxy)silane (107.1 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (59.1 mg, 45% yield).

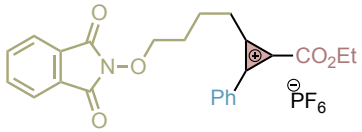
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.9, 1.6 Hz, 4H), 7.64 – 7.58 (m, 2H), 7.48 – 7.34 (m, 8H), 7.32 – 7.25 (m, 1H), 6.12 (s, 2H), 4.19 – 4.08 (m, 2H), 3.81 (s, 3H), 3.75 (t, *J* = 6.2 Hz, 2H), 3.67 (s, 6H), 2.90 – 2.68 (m, 2H), 2.03 – 1.85 (m, 2H), 1.82 – 1.68 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 160.1, 159.8, 135.6, 134.0, 129.6, 129.5, 128.6, 127.9, 127.62, 127.57, 116.5, 111.5, 110.5, 90.5, 63.8, 60.1, 55.3, 55.0, 32.6, 28.8, 26.9, 25.6, 24.2, 19.3, 14.5.

IR ν max (film, cm^{-1}): 2931, 2855, 1713, 1666, 1457, 1426, 1202, 1153, 1127, 1105, 1034, 964, 810, 775.

HRMS (ESI) calculated for $C_{41}H_{48}NaO_6Si^+$ $[M+Na]^+$ m/z: 687.3112, found: 687.3103.

1-(ethoxycarbonyl)-2-phenyl-3-(4-((1,3-dioxoisoindolin-2-yl)oxy)butyl)-cyclopropenium hexafluorophosphate (CPC 3y)



Prepared according to the **general procedure A** using 2-((6-phenylhex-5-yn-1-yl)oxy)isoindoline-1,3-dione (83.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL

dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (83.6 mg, 76% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.55 (dd, *J* = 8.3, 1.2 Hz, 2H), 8.22 – 8.13 (m, 1H), 7.97 – 7.91 (m, 2H), 7.90 – 7.85 (m, 4H), 4.72 (q, *J* = 7.1 Hz, 2H), 4.39 (t, *J* = 5.9 Hz, 2H), 3.90 (t, *J* = 7.2 Hz, 2H), 2.58 – 2.45 (m, 2H), 2.19 – 2.07 (m, 2H), 1.54 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 173.9, 166.8, 164.0, 156.0, 152.9, 141.3, 138.0, 134.7, 130.6, 128.8, 123.1, 118.2, 77.5, 66.0, 27.9, 27.0, 22.2, 12.8.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.4 (d, *J* = 707.4 Hz).

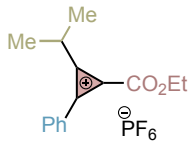
^{31}P NMR (203 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 708.8 Hz).

IR ν max (film, cm^{-1}): 2948, 1853, 1786, 1726, 1595, 1505, 1448, 1375, 1267, 1216, 1186, 1127, 1081, 981, 829, 756.

HRMS (ESI) calculated for $C_{24}H_{22}NO_5^+$ $[M\text{-}PF_6]^+$ m/z: 404.1492, found: 404.1497.

m.p. 78 °C (decomp).

1-(ethoxycarbonyl)-2-phenyl-3-isopropylcyclopropenium hexafluorophosphate (CPC 3z)



Prepared according to the **general procedure A** using 1-phenyl-1-isopentyne (55.2 mg, 0.30 mmol) and **2a** (120 mg, 0.20 mmol) with 2 mol% $Rh_2(esp)_2$ (4.0 mg). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. After the addition of **2a**, the reaction mixture was stirred for 20 min. Filtration of the reaction mixture provided the title compound as a white solid (57.1 mg, 76% yield).

^{1}H NMR (500 MHz, CD_3NO_2) δ 8.51 (d, *J* = 7.6 Hz, 2H), 8.24 – 8.17 (m, 1H), 7.99 – 7.89 (m, 2H), 4.71 (q, *J* = 7.1 Hz, 2H), 4.01 – 3.93 (m, 1H), 1.77 (d, *J* = 7.1 Hz, 6H), 1.54 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 177.0, 166.6, 156.0, 152.8, 141.4, 138.1, 130.7, 118.2, 66.0, 30.0, 17.9, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.6 (d, *J* = 707.0 Hz).

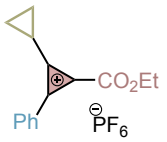
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 706.9 Hz).

IR ν max (film, cm^{-1}): 2976, 1854, 1741, 1596, 1506, 1445, 1387, 1219, 1112, 828, 761.

HRMS (ESI) calculated for $C_{15}H_{17}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 229.1223, found: 229.1226.

m.p. 71 °C (decomp).

1-(ethoxycarbonyl)-2-phenyl-3-cyclopropylcyclopropenium hexafluorophosphate (CPC 3aa)



Prepared according to the **general procedure A** using (cyclopropylethynyl)benzene (42.6 mg, 0.30 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (35.8 mg, 48% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.44 (dd, *J* = 8.3, 1.3 Hz, 2H), 8.17 – 8.11 (m, 1H), 7.95 – 7.88 (m, 2H), 4.66 (q, *J* = 7.1 Hz, 2H), 3.19 – 3.09 (m, 1H), 2.40 – 2.31 (m, 2H), 2.28 – 2.18 (m, 2H), 1.52 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 175.6, 160.9, 152.6, 147.1, 140.4, 137.1, 130.5, 118.5, 65.6, 20.4, 12.8, 11.7.

^{19}F NMR (471 MHz, CD_3NO_2) δ -72.5 (d, *J* = 707.1 Hz).

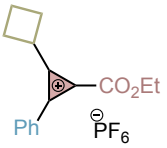
^{31}P NMR (203 MHz, CD_3NO_2) δ -140.7 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 1852, 1741, 1595, 1504, 1471, 1443, 1309, 1218, 1133, 1012, 909, 827, 755.

HRMS (ESI) calculated for $C_{15}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 227.1067, found: 227.1062.

m.p. 110 °C (decomp).

1-(ethoxycarbonyl)-2-phenyl-3-cyclobutylcyclopropenium hexafluorophosphate (CPC 3ab)



Prepared according to the **general procedure A** using (cyclobutylethynyl)benzene (40.6 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). The dropwise addition of **2a** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (48.1 mg, 62% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.48 (d, *J* = 7.2 Hz, 2H), 8.24 – 8.14 (m, 1H), 7.99 – 7.89 (m, 2H), 4.72 (q, *J* = 7.1 Hz, 2H), 4.66 – 4.56 (m, 1H), 2.96 – 2.84 (m, 2H), 2.84 – 2.73 (m, 2H), 2.48 – 2.30 (m, 2H), 1.55 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 174.3, 165.4, 154.0, 152.9, 141.2, 137.9, 130.6, 118.3, 65.9, 32.7, 27.4, 18.8, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.6 (d, *J* = 707.2 Hz).

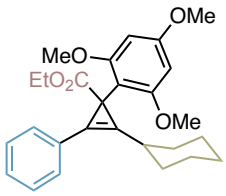
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.1 Hz).

IR ν max (film, cm^{-1}): 1848, 1707, 1594, 1505, 1444, 1213, 1016, 833, 761.

HRMS (ESI) calculated for $C_{16}H_{17}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 241.1223, found: 241.1221.

m.p. 61 °C (decomp).

ethyl 2-cyclohexyl-3-phenyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3ac')



Prepared according to the **general procedure A** using (cyclohexylethynyl)benzene (48.0 mg, 0.26 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a yellow solid (65.2 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.58 (m, 2H), 7.43 – 7.34 (m, 2H), 7.32 – 7.26 (m, 1H), 6.11 (s, 2H), 4.20 – 4.09 (m, 2H), 3.81 (s, 3H), 3.66 (s, 6H), 2.86 – 2.73 (m, 1H), 2.23 – 2.08 (m, 2H), 1.88 – 1.78 (m, 2H), 1.78 – 1.64 (m, 2H), 1.55 – 1.28 (m, 4H), 1.19 (t, *J* = 7.1 Hz, 3H).

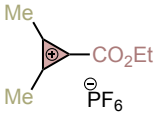
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 160.0, 159.8, 129.7, 128.7, 127.8, 127.5, 119.8, 111.7, 109.4, 90.4, 60.0, 55.3, 54.9, 36.0, 31.9, 30.2, 28.6, 26.3, 26.03, 25.99, 14.5.

IR ν max (film, cm^{-1}): 2928, 2848, 1704, 1496, 1456, 1411, 1338, 1276, 1226, 1193, 1152, 1126, 1032, 956, 808.

HRMS (ESI) calculated for $C_{27}H_{32}NaO_5^+$ $[M+Na]^+$ m/z: 459.2142, found: 459.2126.

m.p. 92-94 ºC.

1-(ethoxycarbonyl)-2,3-dimethylcyclopropenium hexafluorophosphate (CPC 3ad)



Prepared according to the **general procedure A** using 2-butyne (32 µL, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (26.0 mg, 46% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 4.62 (q, *J* = 7.1 Hz, 2H), 3.17 (s, 6H), 1.45 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 178.8, 166.4, 153.8, 65.9, 12.9, 12.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.6 (d, *J* = 706.9 Hz).

^{31}P NMR (162 MHz, CD_3 NO_2) δ -141.6 (sp, *J* = 706.3 Hz).

IR ν max (film, cm^{-1}): 2998, 2944, 1856, 1758, 1471, 1413, 1221, 1055, 1007, 825, 725, 556, 497.

HRMS (ESI) calculated for $C_8H_{11}O_2^+$ $[M-PF_6]^+$m/z: 139.0754, found: 139.0750.

m.p. 50 ºC (decomp).

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

Single crystal X-Ray diffraction analysis: A single crystal of **3ad** was obtained through slow crystallization at -30ºC under argon of its solution in dichloromethane and hexane. The crystal structure of **3ad** has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2151106.

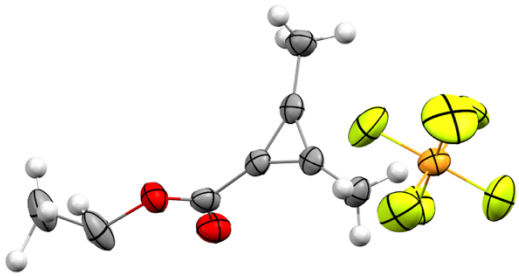
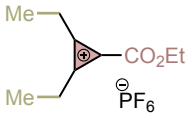


Figure 32 ORTEP diagram of **3ad**

Procedure for a 5.0 mmol-scale reaction with 2-butyne:

To a 100 mL oven-dried flask equipped with a stirring bar was added $Rh_2(esp)_2$ (60.0 mg, 1.5 mol%). The flask was sealed before being evacuated and backfilled with nitrogen. After being cooled to -60 ºC, 2-butyne (783 µL, 10.0 mmol) and degassed dichloromethane (25 mL) were added. Then, a solution of reagent **2a** (3.0 g, 5.0 mmol, 1.0 eq.) in degassed dichloromethane (20 mL) was added dropwise during 40 minutes using a syringe pump. After the addition, the reaction was kept stirring at -60 ºC until the reaction was complete (monitored by TLC, 20 minutes). Then dry hexane (7 mL) was added to the reaction mixture slowly. The product was collected by quick filtration, washed with dry hexane (6 mL x 3), dried under high *vacuum* to give **CPC 3ad** (1.10 g, 77% yield).

1-(ethoxycarbonyl)-2,3-diethylcyclopropenium hexafluorophosphate (CPC 3ae)



Prepared according to the general procedure using 3-hexyne (46 µL, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (40.1 mg, 64% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 4.61 (q, *J* = 7.1 Hz, 2H), 3.50 (q, *J* = 7.2 Hz, 4H), 1.59 (t, *J* = 7.2 Hz, 6H), 1.44 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 182.1, 165.7, 153.2, 65.9, 22.3, 12.7, 8.8.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.8 (d, *J* = 706.9 Hz).

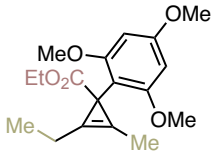
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.9 Hz).

IR ν max (film, cm^{-1}): 2953, 1842, 1748, 1465, 1381, 1287, 1214, 1009, 826, 752, 555.

HRMS (ESI) calculated for $C_{10}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 167.1067, found: 167.1064.

m.p. 56 ºC (decomp).

ethyl 2-ethyl-3-methyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3af')



Prepared according to the **general procedure A** using pent-2-yne (40 µL, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a beige oil (22.2 mg, 34% yield).

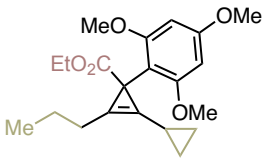
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 6H), 2.59 – 2.41 (m, 2H), 2.11 (t, *J* = 1.5 Hz, 3H), 1.20 – 1.13 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 160.2, 159.9, 113.1, 112.6, 107.5, 90.6, 60.0, 55.5, 55.4, 27.7, 18.4, 14.6, 11.7, 9.4.

IR ν max (film, cm^{-1}): 2933, 1712, 1606, 1599, 1456, 1204, 1154, 1128.

HRMS (ESI) calculated for $C_{18}H_{24}NaO_5^+$ $[M+Na]^+$m/z: 343.1516, found: 343.1511.

ethyl 3-propyl-2-(2,4,6-trimethoxyphenyl)-[1,1'-bi(cyclopropan)]-3-ene-2-carboxylate (3ag')



Prepared according to the **general procedure A** using pent-1-yn-1-ylcyclopropane (43.0 mg, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a yellow oil (47.2 mg, 66% yield).

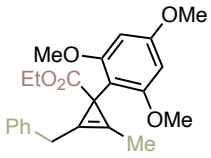
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (s, 2H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 2.56 – 2.36 (m, 2H), 1.82 – 1.71 (m, 1H), 1.69 – 1.49 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.98 (t, *J* = 7.4 Hz, 3H), 0.92 – 0.69 (m, 3H), 0.69 – 0.61 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 160.4, 160.2, 114.5, 112.7, 109.7, 90.8, 60.3, 55.7, 55.6, 30.2, 27.6, 21.4, 14.9, 14.6, 7.4, 7.1, 6.0.

IR ν max (film, cm^{-1}): 2926, 2853, 1711, 1588, 1496, 1456, 1414, 1334, 1203, 1153, 1126, 1037, 966, 811.

HRMS (ESI) calculated for $C_{21}H_{28}NaO_5^+$ $[M+Na]^+$m/z: 383.1829, found: 383.1819.

ethyl 2-benzyl-3-methyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3ah')



Prepared according to the **general procedure A** using but-2-yn-1-ylbenzene (52.0 mg, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). The catalyst loading was increased to 2 mol% (4.0 mg, 0.004 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 9/1 to 3/1) provided the title compound as a brown oil (61.8 mg, 81% yield).

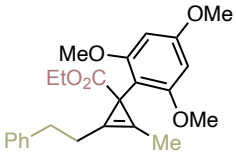
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 4H), 7.22 – 7.18 (m, 1H), 6.11 (s, 2H), 4.08 – 4.04 (m, 2H), 3.87 – 3.84 (m, 2H), 3.81 (s, 3H), 3.76, (s, 6H), 2.05 (t, J = 1.6 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.4, 160.3, 160.0, 138.5, 128.7, 128.4, 126.3, 112.3, 110.9, 109.8, 90.6, 60.1, 55.5, 55.4, 31.4, 28.2, 14.6, 9.4.

IR ν max (film, cm^{-1}): 2936, 1711, 1605, 1589, 1455, 1204, 1154, 1127.

HRMS (ESI) calculated for $C_{23}H_{26}NaO_5^+$ $[M+Na]^+$m/z: 405.1672, found: 405.1690.

ethyl 2-methyl-3-phenethyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3ai')



Prepared according to the **general procedure A** using pent-3-yn-1-ylbenzene (57.6 mg, 0.40 mmol) and **2a** (120 mg, 0.20 mmol). The catalyst loading was increased to 2 mol% (4.0 mg, 0.004 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 9/1 to 3/1) provided the title compound as a brown oil (56.2 mg, 71% yield).

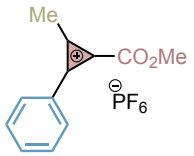
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 6.12 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.77 (s, 6H), 3.04 – 2.78 (m, 4H), 2.05 (t, J = 1.4 Hz, 3H), 1.16 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.8, 160.2, 159.9, 142.0, 128.4, 126.0, 112.4, 111.3, 108.6, 90.6, 60.1, 55.5, 55.4, 33.4, 27.8, 26.7, 14.6, 9.5.

IR ν max (film, cm^{-1}): 2934, 1709, 1588, 1454, 1413, 1203, 1152, 1125, 1043.

HRMS (ESI) calculated for $C_{24}H_{28}NaO_5^+$ $[M+Na]^+$m/z: 419.1841, found: 419.1829.

1-(methoxycarbonyl)-2-phenyl-3-methylcyclopropenium hexafluorophosphate (CPC 3aj)



Prepared according to the **general procedure A** using 1-phenyl-1-propyne (30.2 mg, 0.26 mmol) and **2e** (113 mg, 0.20 mmol). Filtration of the reaction mixture provided the title compound as a white solid (41.9 mg, 63% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.52 (d, *J* = 7.2 Hz, 2H), 8.24 – 8.15 (m, 1H), 7.98 – 7.90 (m, 2H), 4.25 (s, 3H), 3.38 (s, 3H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.6, 166.8, 155.6, 153.7, 141.3, 137.8, 130.6, 118.2, 55.1, 13.1.

^{19}F NMR (376 MHz, CD_3NO_2) δ -73.6 (d, *J* = 707.1 Hz).

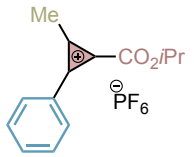
^{31}P NMR (162 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.2 Hz).

IR ν max (film, cm^{-1}): 2983, 1712, 1492, 1446, 1372, 1205, 1132, 1096, 1022, 924, 840, 744, 693, 557.

HRMS (ESI) calculated for $C_{12}H_{11}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 187.0754, found: 187.0758.

m.p. 85 °C (decomp).

1-(isopropoxycarbonyl)-2-phenyl-3-methylcyclopropenium hexafluorophosphate (CPC 3ak)



Prepared according to the **general procedure A** using 1-phenyl-1-propyne (30.2 mg, 0.26 mmol) and **2f** (124 mg, 0.20 mmol). The dropwise addition of **2f** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a white solid (61.1 mg, 85% yield).

^{1}H NMR (400 MHz, CD_3NO_2) δ 8.51 (d, *J* = 7.3 Hz, 2H), 8.23 – 8.14 (m, 1H), 7.99 – 7.88 (m, 2H), 5.57 – 5.42 (m, 1H), 3.37 (s, 3H), 1.53 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (126 MHz, CD_3NO_2) δ 171.4, 166.7, 156.3, 152.6, 141.2, 137.8, 130.5, 118.3, 75.3, 20.4, 13.1.

^{19}F NMR (471 MHz, CD_3NO_2) δ -73.4 (d, *J* = 707.2 Hz).

^{31}P NMR (203 MHz, CD_3NO_2) δ -141.7 (sp, *J* = 707.3 Hz).

IR ν max (film, cm^{-1}): 2990, 1857, 1742, 1592, 1506, 1448, 1375, 1306, 1239, 1147, 1096, 831, 754.

HRMS (ESI) calculated for $C_{14}H_{15}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 215.1067, found: 215.1067.

m.p. 113 °C (decomp).

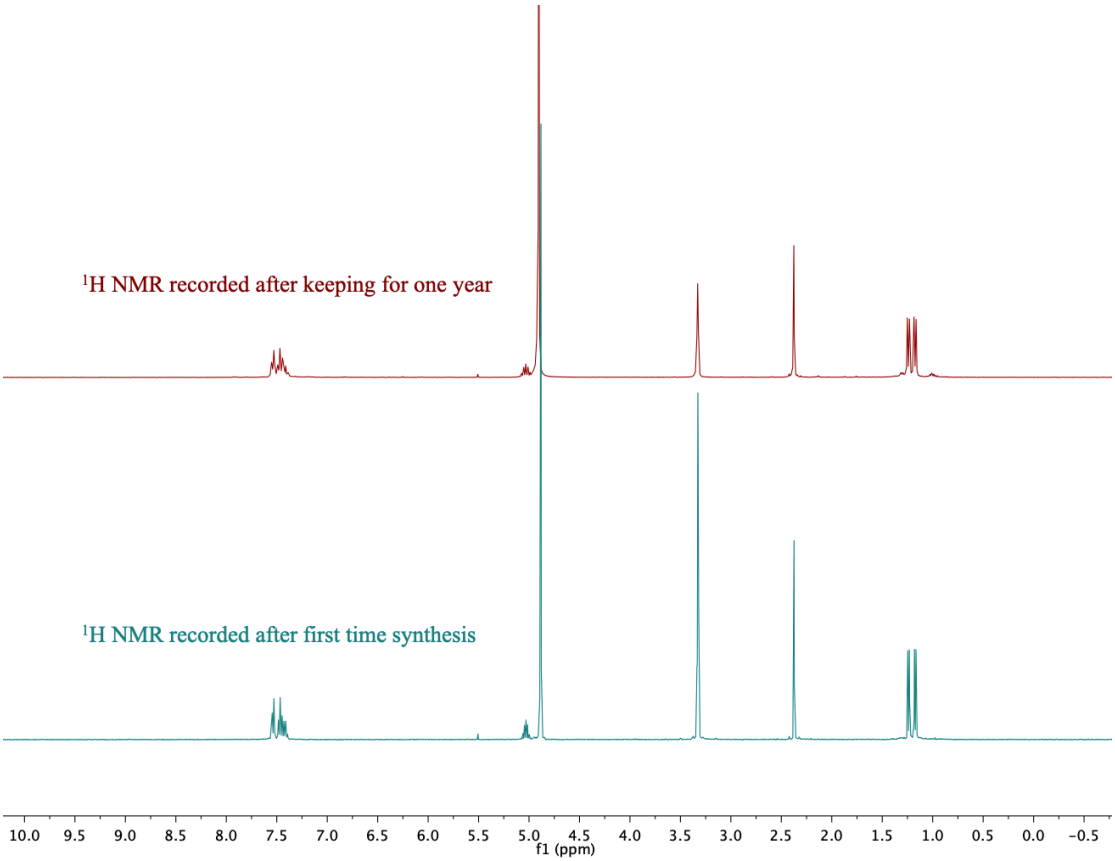
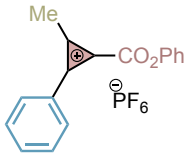


Figure 33 ^{1}H NMR spectra of **CPC 3ak** in CD_3OD, the **CPC** is stable for at least 1 year without detectable decomposition.

1-(phenoxycarbonyl)-2-phenyl-3-methylcyclopropenium hexafluorophosphate (CPC 3al)



Prepared according to the **general procedure A** using 1-phenyl-1-propyne (30.2 mg, 0.26 mmol) and **2g** (138 mg, 0.20 mmol). The dropwise addition of **2g** was performed with 1.5 mL dichloromethane instead of 2.0 mL. Filtration of the reaction mixture provided the title compound as a dark brown solid (65.6 mg, 83% yield).

^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (d, J = 7.3 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 7.40 – 7.33 (m, 2H), 7.26 – 7.19 (m, 1H), 7.02 (d, J = 8.4 Hz, 2H), 2.47 (s, 3H).

^{13}C NMR (126 MHz, CD_3OD) δ 172.9, 152.4, 130.8, 130.5, 130.4, 130.1, 127.0, 126.8, 122.6, 115.2, 114.7, 64.7, 9.5.

^{19}F NMR (471 MHz, CD_3OD) δ -74.8 (d, J = 707.5 Hz).

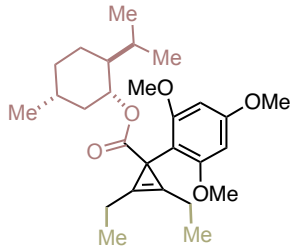
^{31}P NMR (203 MHz, CD_3OD) δ -141.5 (sp, J = 707.6 Hz).

IR ν max (film, cm^{-1}): 1853, 1759, 1596, 1506, 1467, 1202, 1140, 1070, 881, 835, 752.

HRMS (ESI) calculated for $C_{17}H_{13}O_2^+$ $[M\text{-}PF_6]^+$ m/z: 249.0910, found: 249.0907.

m.p. 63 °C (decomp).

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2,3-diethyl-1-(2,4,6-trimethoxyphenyl)cycloprop-2-ene-1-carboxylate (3am')



Prepared according to the **general procedure A** using 3-hexyne (33.0 mg, 0.4 mmol) and **2h** (162 mg, 0.20 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless solid (45.1 mg, 51% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (s, 2H), 4.70 – 4.51 (m, 1H), 3.82 (s, 3H), 3.76 (s, 6H), 2.66 – 2.39 (m, 4H), 2.02 – 1.91 (m, 1H), 1.90 – 1.79 (m, 1H), 1.71 – 1.57 (m, 3H), 1.51 – 1.40 (m, 1H), 1.25 – 1.17 (m, 7H), 1.10 – 0.96 (m, 1H), 0.92 – 0.82 (m, 7H), 0.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 160.2, 159.8, 113.1, 112.9, 112.7, 90.6, 73.5, 55.43, 55.36, 47.4, 41.1, 34.6, 31.5, 28.1, 26.0, 23.6, 22.3, 21.0, 18.50, 18.45, 16.5, 12.3, 12.2.

IR ν max (film, cm^{-1}): 2935, 2863, 1701, 1582, 1449, 1408, 1280, 1196, 1147, 1117, 1036, 988, 810.

HRMS (ESI) calculated for $C_{27}H_{40}NaO_5^+$ $[M+Na]^+$ m/z: 467.2768, found: 467.2754.

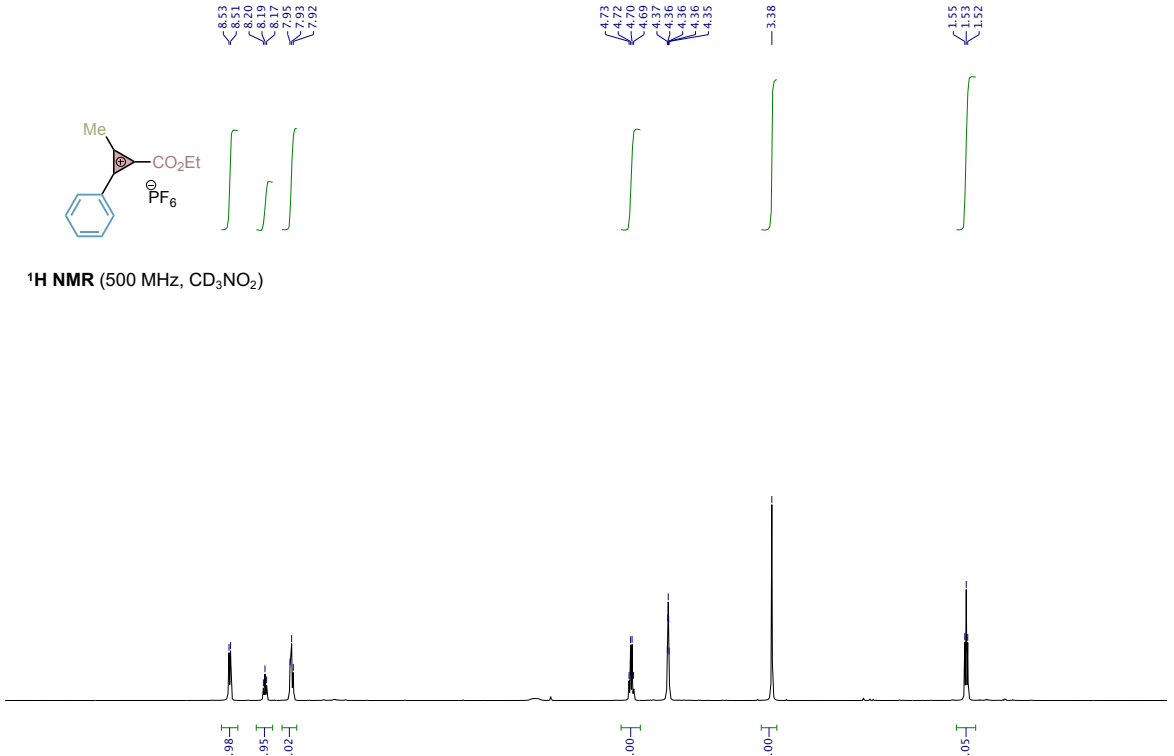
m.p. 72-73 ºC.

$[\alpha]^{25}_D$ = -7.9 (*c* = 1.0, $CHCl_3$).

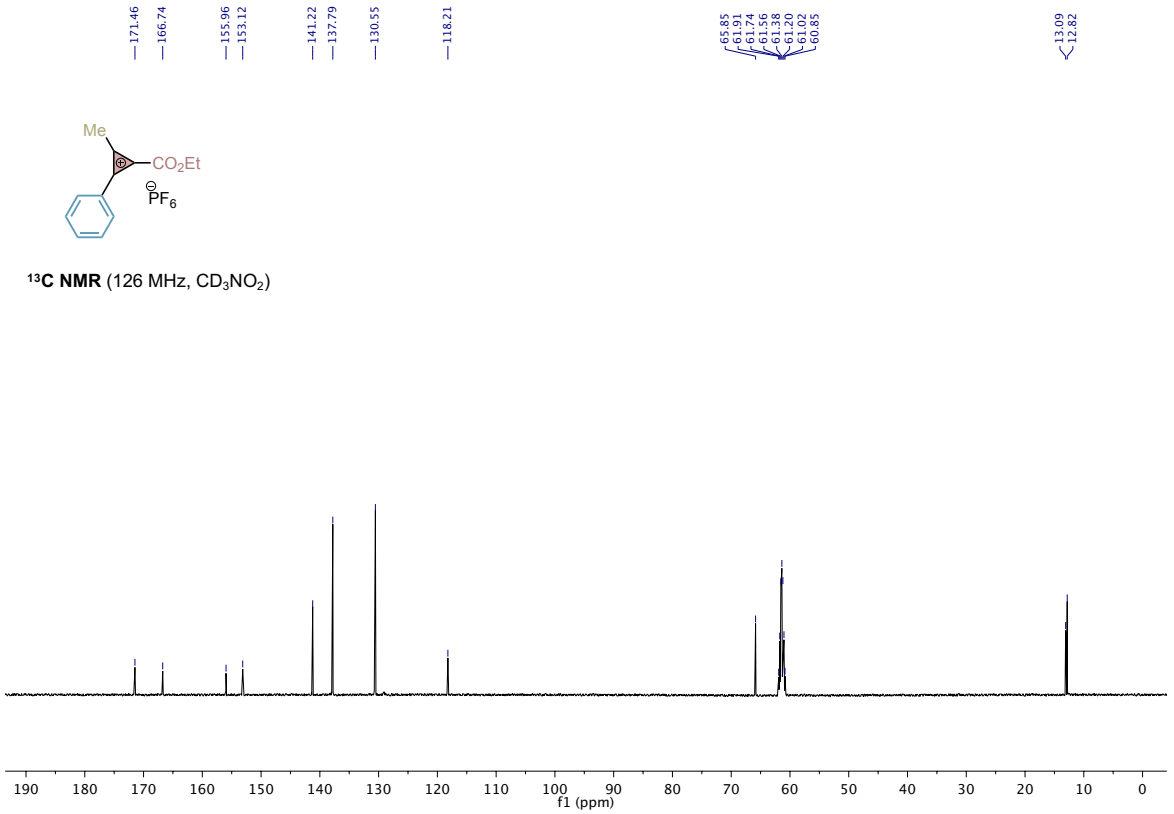
Cyclic voltammetry and p*Kr*$^+$ measurements

Attempts on additional constants measurements such as pK_R^+ or cyclic voltammetry failed. The CPCs are too sensitive to air and moisture to allow for an appropriate measurement, and their high reactivity makes the majority of solvents unsuitable for such studies.

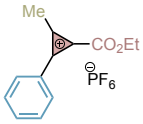
Selected NMR spectra



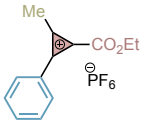
^{1}H NMR (500 MHz, CD_3NO_2)



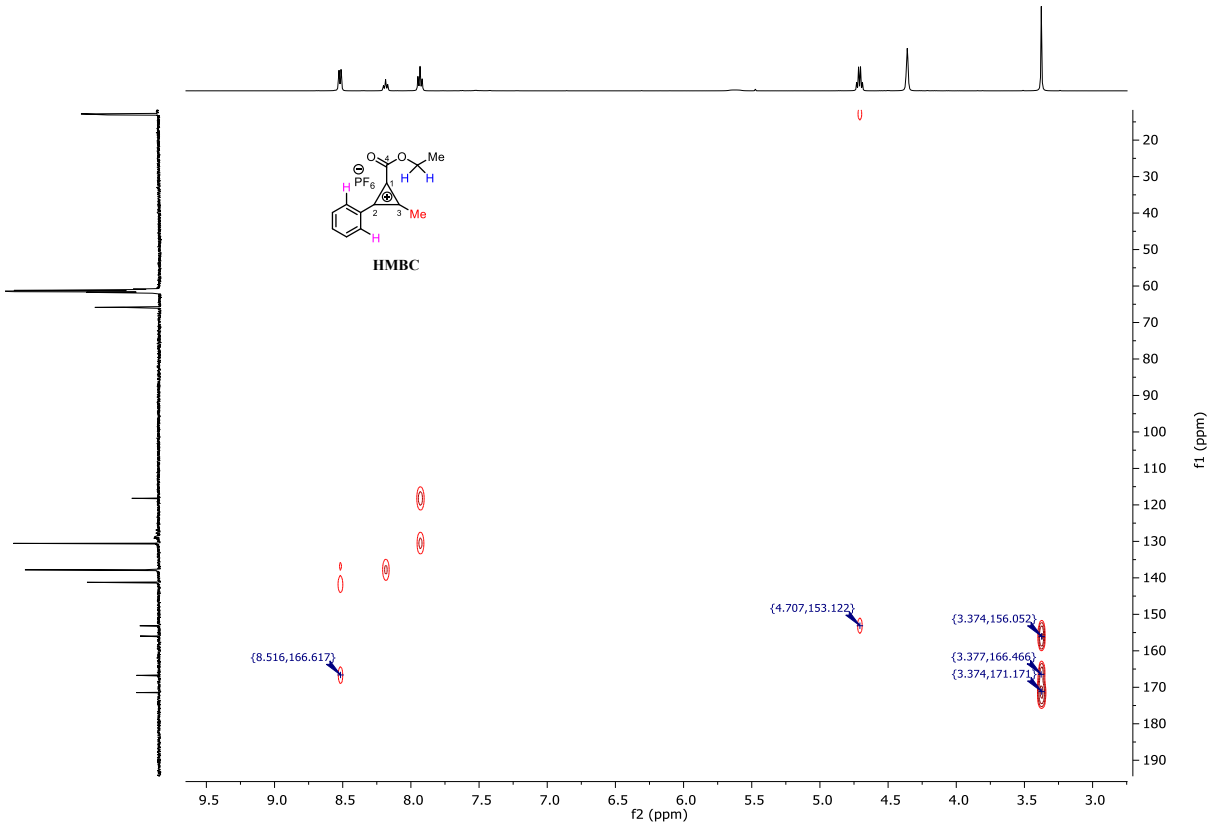
^{13}C NMR (126 MHz, CD_3NO_2)

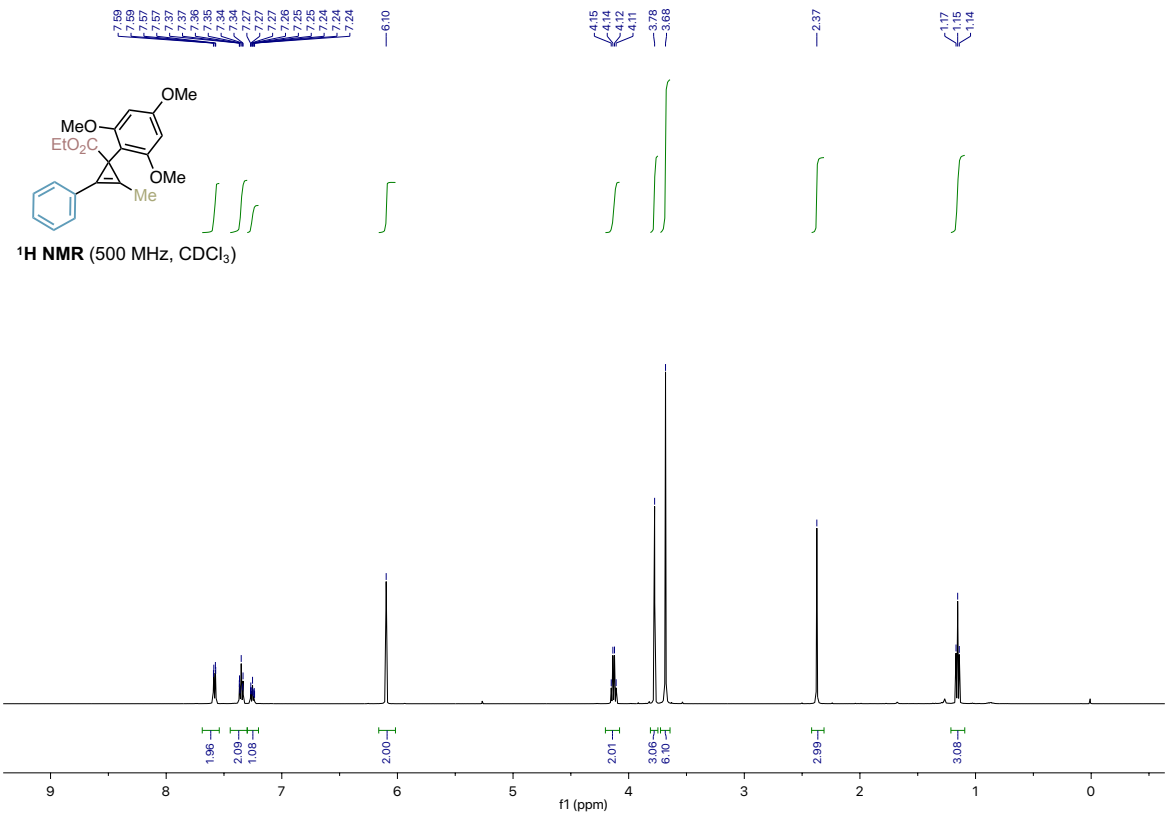


^{19}F NMR (471 MHz, CD_3NO_2)

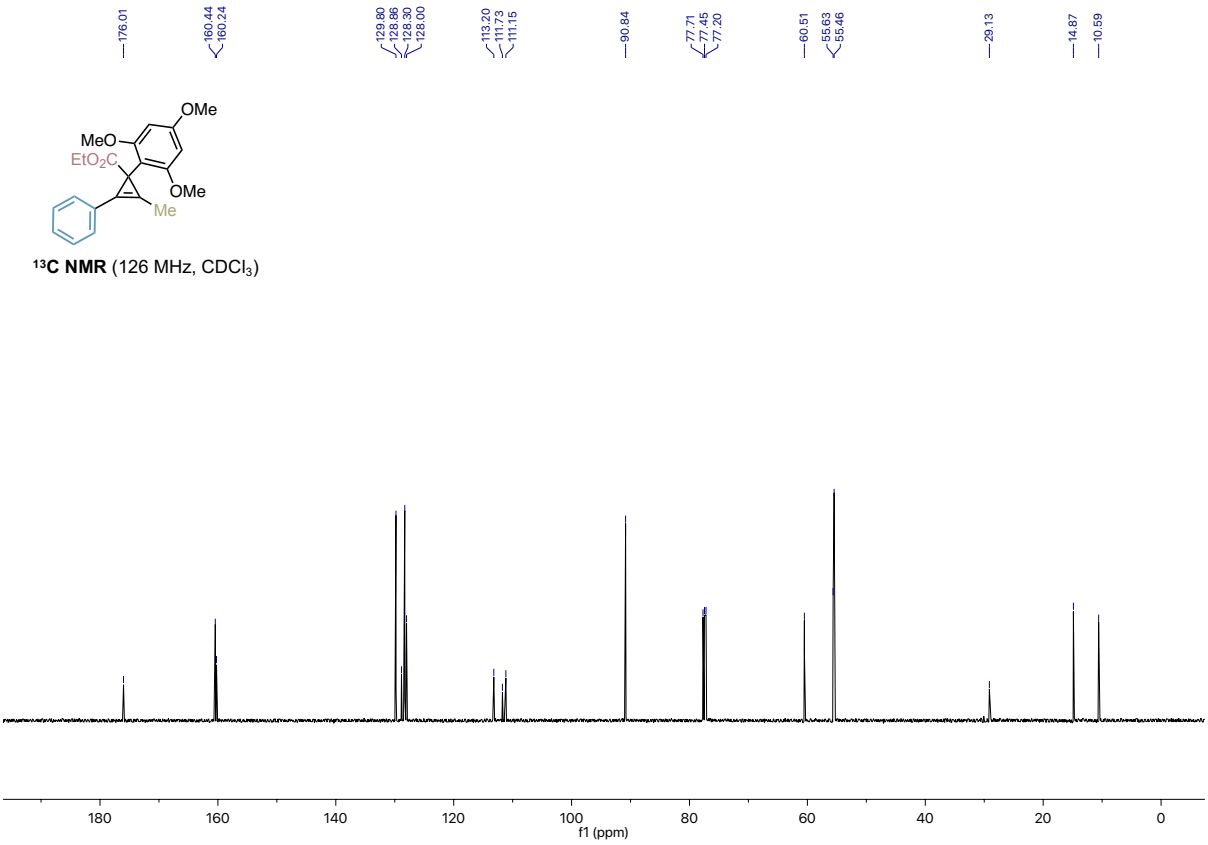


^{31}P NMR (203 MHz, CD_3NO_2)


HMBC
{4.707,153.122}
{3.374,156.052}
{8.516,166.617}
{3.377,166.466}
{3.374,171.171}
f2 (ppm)
f1 (ppm)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (126 MHz, $CDCl_3$)

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF CYCLOPROPENIUM CATIONS BY CARBYNE TRANSFER CATALYSIS AND APPLICATIONS IN NOVEL CYCLOPROPENE SYNTHESES
Aliénor Celine Renee Jeandin

Chapter III

Regioselective synthesis of diverse cyclopropenes with cyclopropenium cations

The work described in this chapter was performed in collaboration with **Dr. Hang-Fei Tu**. *Part of the work has been published, see*: Hang-Fei Tu, Aliénor Jeandin, Marcos G. Suero "*Catalytic Synthesis of Cyclopropenium Cations with Rh-Carbynoids*" *J. Am. Chem. Soc*., **2022**, *144*, 16737.

3.1 Introduction

In Chapter II, we described the first catalytic synthesis of a novel class of cyclopropenium cations (CPCs) substituted with an ester group. In this Chapter, we demonstrate the synthetic utility of these CPCs, which underpin the regioselective attack of a broad range of carbon- and heteroatom-based nucleophiles in simple reaction conditions. This provides a platform for the synthesis of various diverse cyclopropenes, some of which are difficult or not possible to attain with current methodologies. Cyclopropenes show unique features and reactivity. To gain some perspective, we will first cover the characteristics, synthetic routes and derivatizations of the cyclopropene ring.

3.2 The cyclopropene ring

The cyclopropene is the smallest unsaturated carbocycle. Its inherent planarity results in a significant ring strain: 54.5 kcal/mol for cyclopropene, versus 28.1 kcal/mol for cyclopropane.[1] The molecular geometry of cyclopropenes was first rationalized using X-ray and gas-phase data in a study disclosed by Allen in 1982.[2] At the time, it was most accurately described using the bent-bond model, in which the *p* and *s* characters of ordinary hybridizations are increased or decreased to accommodate the molecular geometry.[3] Although the data on cyclopropenes remained then scarce, the resulting picture of the cyclopropene ring geometry is illustrated in Figure 1, as follows: (1) the vinylic carbons C1 and C2 use $sp^{1.19}$ hybrids to form exocyclic bonds while the ring s-hybrids are $sp^{2.68}$, and (2) at C3, the *p*-character of the carbon atom orbital is increased to $sp^{4.26}$ while the *s*-character of the exocyclic orbitals increases to $sp^{2.22}$. Importantly, the increased *s*-character of the vinylic carbons to form exocyclic bonds reflects the observed "alkyne-like" reactivity of cyclopropenes.

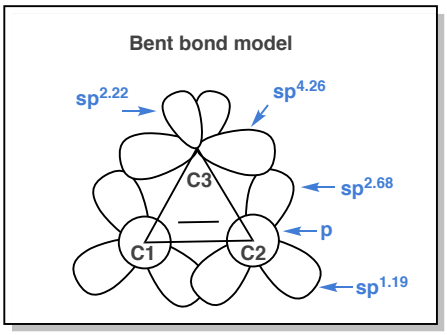


Figure 1 Bent bond model for cyclopropene

This acetylenic character of the vinylic carbons is an essential element to the exceptionally rich chemistry of cyclopropenes. Overall, the complex combination of bonding effects and ring strain—intrinsically related—create

[1] Schleyer, P. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 2377.
[2] Allen, F. H. *Tetrahedron* **1982**, *38*, 645.
[3] (a) Coulson, C. A.; Moffitt, W. E. *J. Chem. Phys*. **1947**, *15*, 151; (b) Flygare, W. H. *Science* **1963**, *140*, 1179; (c) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229.

a unique reactivity pattern, characteristic to cyclopropenes and ranging from typical alkyne reactions to alkene or specific transformations originating from this peculiar structure. [4]

3.3 Synthetic routes to cyclopropenes

The parent cyclopropene was isolated for the first time in 1922 by Doyarenko and co-workers by pyrolyzing trimethylcyclopropylammonium hydroxide on platinized clay, forming cyclopropylamine and methylacetylene,[5] a synthetic route optimized in1941, and ultimately affording cyclopropene in 45% yield (Figure 2).[6]

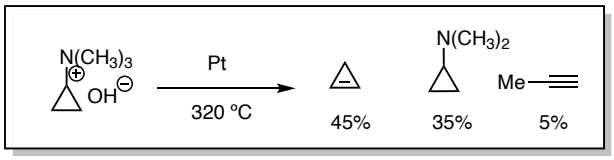


Figure 2 Historical synthesis of cyclopropene

The mid-fifties witnessed a growing interest from the synthetic community for the smallest unsaturated carbocycle. First pathways to substituted cyclopropenes involved 1,2-eliminations from adequately functionalized cyclopropanes.[7] As progresses in carbene chemistry were made, [2+1] cycloadditions between alkynes and metal or free carbenes stood out as a resourceful route to cyclopropenes, too. While other accesses to cyclopropenes have also been reported over the years,[8] 1,2-eliminations from cyclopropanes and [2+1] cycloadditions between alkynes and carbenes remain the two most common synthetic routes to cyclopropenes (Figure 3).

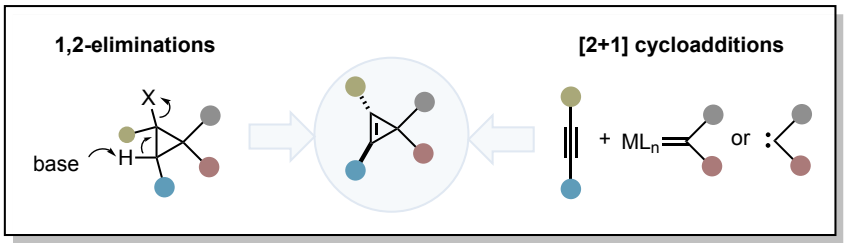


Figure 3 Main pathways to cyclopropenes

3.3.1 1,2-eliminations

1,2-elimination pathways in the synthesis of cyclopropenes can be divided in two classes: dehalogenations (from trihalogenocyclopropanes), and dehydrohalogenations (from dihalogenocyclopropanes). These two categories share the same first step, namely the construction of the corresponding halocyclopropane, as illustrated in Figure

[4] The detailed electronic structure of cyclopropenes is very complex. For additional studies, see: (a) Fattahi, A.; McCarthy, R. E.; Ahmad, M. R.; Kass, S. R. *J. Am. Chem. Soc.* **2003**, *125*, 11746; (b) Bach, R. D.; Dmitrenko, O. *J. Am. Chem. Soc.* **2004**, *126*, 4444. For a review, see: Rademacher, P. *Chem. Rev.* **2003**, *103*, 933.
[5] Dem'yanov, N.Y.; Doyarenko, M.N. *Bull. Acad. Sci. Russ.* **1922**, *16,* 297.
[6] Schlatter, M. J. *J. Am. Chem. Soc.* **1941**, *63*, 1733.
[7] For a review on early syntheses of cyclopropenes, see: Baird, M. S. *Top. Curr. Chem.* **1988**, *144*, 137.
[8] For a detailed perspective on synthetic pathways to cyclopropenes, see: Rubin, M.; Rubina, M.; Gevorgyan, V. *Synthesis* **2006**, 1221.

4. Bromoform acts as dihalocarbene upon addition to either a vinyl halide (in the case of dehalogenation) or a disubstituted olefin (in the case of a dehydrohalogenation) in the presence of a phase-transfer catalyst such as cetrimide. This yields the corresponding 1,1,2-trihalogenocyclopropane or 1,1-dihalocyclopropane, respectively, as first intermediate.[9]

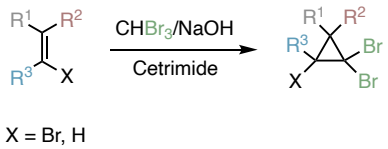


Figure 4 Synthesis of halocyclopropanes for subsequent1,2-eliminations

In the case of a 1,2-dehalogenation, the second step consists in treating the 1,1,2-trihalocyclopropane with two equivalents of an alkyl lithium. The first equivalent yields the 1-halogenocyclopropene after a first 1,2-dehalogenation (-LiX) and the second equivalent enables a halogen-lithium exchange reaction to yield a lithiocyclopropene. Subsequent addition of an electrophile yields the desired final cyclopropene (Figure 5, top).[10] This methodology has proven to be useful in the synthesis of diverse tri- and tetrasubstituted cyclopropenes, of which a few examples are represented in Figure 5.[11]

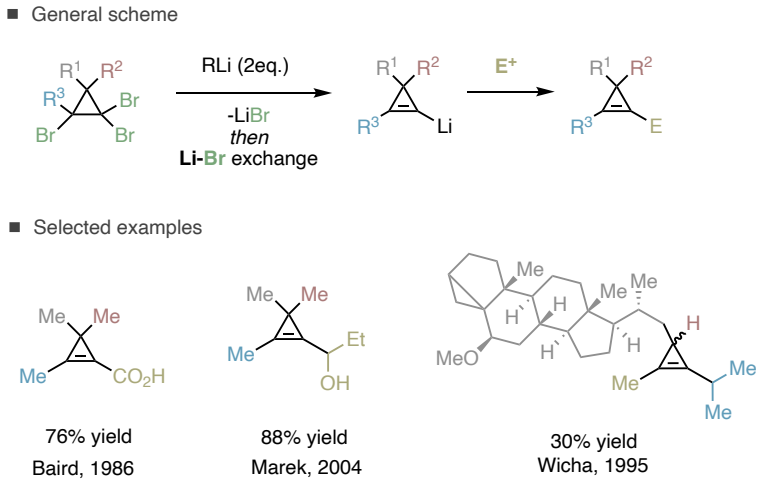


Figure 5 Synthesis of cyclopropenes from 1,1,2-halogenocyclopropanes

1,2-dehydrohalogenations are particularly convenient for the synthesis of 3,3-disubstituted cyclopropenes, key building blocks in cyclopropene chemistry. As shown in Figure 6, the second step here consists in a selective partial reduction of the 1,1-dihalocyclopropane with ethyl magnesium bromide and catalytic titanium isopropoxide, to afford the monohalogenocyclopropane first.[12] The remaining halogen is then eliminated in

[9] (a) Bertrand, M.; Monti, H. C. R. *Seances Acad. Sci., Ser. C* **1967**, *264*, 998; (b) Bolesov, I. G.; Ignatchenko, A. V.; Bovin, N. V.; Prudchenko, I. A.; Surmina, L. S.; Plemenkov, V. V.; Petrovskii, P. V.; Romanov, I. V.; Mel'nik, I. I. *Zh. Org. Khim.* **1990**, *26*, 102; *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *26*, 89.
[10] (a) Baird, M. S.; Nethercott, W. *Tetrahedron Lett.* **1983**, *24*, 605; (b) Baird, M. S.; Hussain, H. H.; Nethercott, W. *J. Chem. Soc. Perkin Trans. 1* **1986**, 1845.
[11] For examples of the use of this strategy, see: (a) Kurek-Tyrlik, A.; Minksztym, K.; Wicha, J. *J. Am. Chem. Soc.* **1995**, *117*, 1849; (b) Zohar, E.; Marek, I. *Org. Lett.* **2004**, *6*, 341; (c) reference 10b.
[12] Al Dulayymi, J.; Baird, M.S.; Bolesov, I.G.; Tveresovsky, V.; Rubin, M. *Tetrahedron Lett.* **1996**, *31*, 8933.

strongly basic conditions (*t*-BuOK in DMSO) to afford the final 3,3-disubstituted cyclopropene. An alternative to the use of DMSO, enabling the synthesis of hydrophilic cyclopropenes, was proposed in 2008 by Rubin *et al.,* who reported the use of THF as solvent with 18-crown-6 ether.[13] In spite of requiring harsh reaction conditions, the 1,2-dehydrohalogenation of cyclopropanes remains a reference protocol for the synthesis of 3,3-disubstituted cyclopropenes.[14]

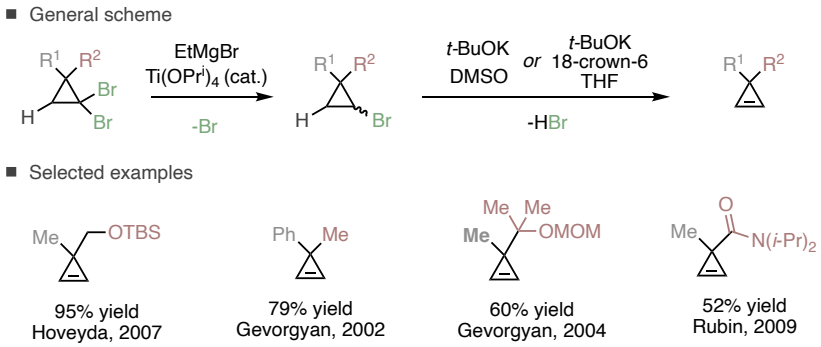


Figure 6 Synthesis of 3,3-disubstituted cyclopropenes by 1,2-elimination

3.3.2 [2+1] cycloadditions

If 1,2-eliminations from cyclopropanes remain useful for some substitution patterns in cyclopropenes, the most versatile approach to synthesize cyclopropenes are [2+1] cycloadditions of alkynes to metal carbenes, generated from diazo compounds.

[2+1] cycloaddition of metal carbenes to terminal alkynes

Historically, early reports of [2+1] cycloadditions for the synthesis of cyclopropenes relied on the use of Cu as well as Cu(I) and Cu(II) salts as catalyst for the decomposition of alkyl diazoacetates under elevated temperatures (90-140 ºC).[15,16] However, if copper-based techniques were improved over the years,[17] dirhodium catalysts took over copper catalysts early on, as they allowed for milder reaction conditions. A seminal report in 1978 by Teyssié and co-workers disclosed the use of Rh(II) carboxylates for the cyclopropenation of terminal alkynes by the [2+1] cycloaddition of methyl diazoacetate with alkynes.[18] A few years later in 1994, Doyle, Müller and Shapiro

[13] Sherrill, W. M.; Kim, R.; Rubin, M. *Synthesis* **2009**, *9*, 1477.
[14] For selected examples, illustrated in Figure 6, see: (a) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824; (b) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2002**, *124*, 11566; (c) Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688; (c) reference 13.

[15] Seminal report : D'jakonov, I. A.; Komendantov, M. I. *Vestnik Leningrad. Univ.,* **1956**, *22*, 166.
[16] Protopopova, M. N.; Shapiro, E. A. *Russ. Chem. Rev.* **1989**, *58*, 667.
[17] For recent examples of Cu-catalyzed cyclopropenation, see: (a) Díaz-Requejo, M. M.; Mairena, M. A.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Chem. Commun.* **2001**, *1*, 1804; (b) Rodríguez, P.; Caballero, A.; Díaz-Requejo, M. M.; Nicasio, M. C.; Pérez, P. J. *Org. Lett.* **2006**, *8*, 557; (c) Park, E. J.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 17268; (d) Swenson, A. K.; Higgins, K. E.; Brewer, M. G.; Brennessel, W. W.; Coleman, M. G. *Org. Biomol. Chem.* **2012**, *10*, 7483.
[18] Petiniot, N.; Anciaux, A. J.; Noels, A. F.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1978**, *19*, 1239.

reported Rh_2(5*S*-MEPY)$_4$ and Rh_2(5*R*-MEPY)$_4$ as competent catalysts for the enantioselective synthesis of cyclopropenes from alkynes and ethyldiazoacetate (Figure 7).[19]

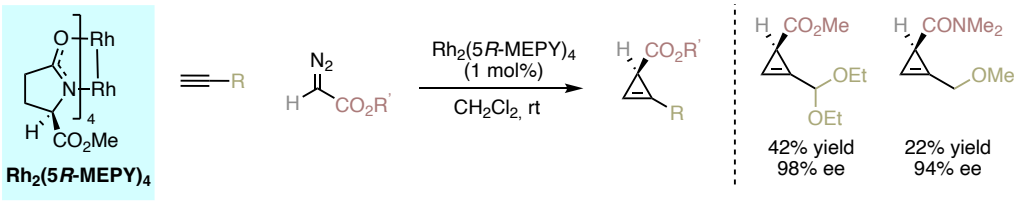


Figure 7 First Rh(II)-catalyzed asymmetric synthesis of cyclopropenes

Rh_2(5*S*-MEPY)$_4$ in particular revealed to be effective for various terminal alkynes, including alkynes bearing alkoxy groups or protected amines.[20]

The following years witnessed the development of numerous catalytic systems, unlocking access to various substitution patterns in chiral cyclopropenes from terminal alkynes. In 2004, Doyle disclosed the use of Rh_2(*S*-DOSP)$_4$ to obtain high enantioselectivities for cyclopropenes obtained from donor/acceptor diazoacetates for the first time,[21] substituted with aryl,[21a] and later on with styryl groups,[21b] the use of which gave access to the first chiral cyclopropenes fully substituted at C3 (Figure 8).

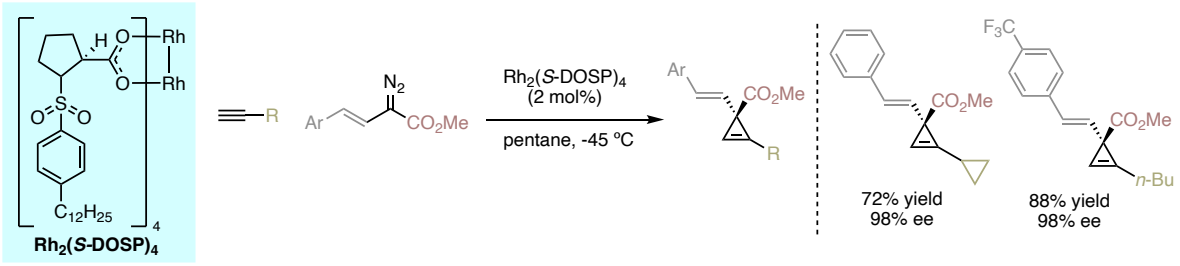


Figure 8 Rh_2(*S*-DOSP)-catalyzed asymmetric synthesis of cyclopropenes with vinyldonor/acceptor diazoacetates

The same year, Corey reported a mixed carboxylate/carboxamidate paddlewheel catalyst [Rh_2(OAc)(dpti)$_3$] allowing to reach exquisite enantiomeric excesses and yields with ethyl diazoacetate as carbene source.[22] Hashimoto also reported the use of [Rh_2(*S*-TBPTTL)$_4$] for the enantioselective synthesis of cyclopropenes in

[19] (a) Protopopova, M. N.; Doyle, M. P.; Müller, P.; Ene, D. *J. Am. Chem. Soc.* **1992**, *114*, 2755. (b) Doyle, M. P.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492.
[20] (a) Müller, P.; Imogaï, H. *Tetrahedron Asymmetry* **1998**, *9*, 4419; (b) Imogaï, H.; Bernardinelli, G.; Gränicher, C.; Moran, M.; Rossier, J. C.; Müller, P. *Helv. Chim. Acta* **1998**, *81*, 1754.
[21] (a) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233; (b) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211.
[22] Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

2011, which however required the use of isobutyl diazo esters to minimize the formation of the β-hydride elimination product (Figure 9).[23]

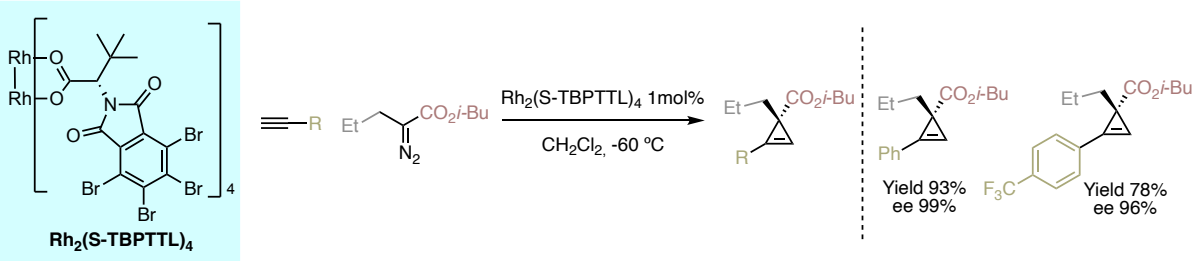


Figure 9: Rh_2(*S*-TBPTTL)$_4$-catalyzed enantioselective synthesis of cyclopropenes with *iso*-butyl diazo esters

Aside from Rh(II) catalysts, cobalt-[24] and iridium-based[25] catalytic systems were developed in 2011 for the asymmetric cyclopropenation of alkynes by Zhang and Katsuki, respectively (Figure 10). Both of these strategies allowed for the unprecedented use of acceptor/acceptor diazoacetates in cyclopropenation reactions. Notably, the chiral Ir(salen) complex also gave access to trifluoromethyl-substituted cyclopropenes by metal-catalyzed cyclopropenation of alkynes with trifluoromethyl-substituted diazoalkanes for the first time. [26]

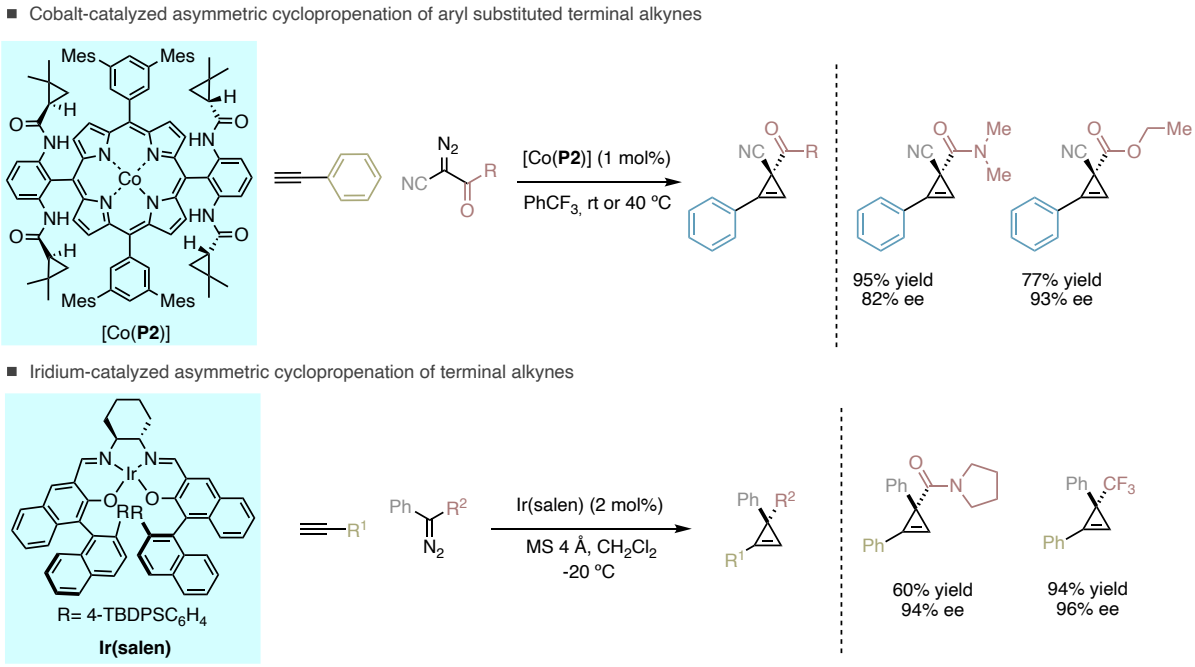


Figure 10 Cobalt- and iridium-catalyzed asymmetric cyclopropenation of terminal alkynes

[23] Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 6803.
[24] Cui, X.; Xu, X.; Lu, H.; Zhu, S.; Wojtas, L.; Zhang, X. P. *J. Am. Chem. Soc.* **2011**, *133*, 3307.
[25] Uehara, M.; Suematsu, H.; Yasutomi, Y.; Katsuki, T. *J. Am. Chem. Soc.* **2011**, *133*, 170.
[26] Cyclopropenylations had been previously reported under metal-free conditions with difluorocarbene, for a review see: Dolbier, W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071.

Fluorinated cyclopropenes are particularly sought-after, as the introduction of a fluorine atom in a molecule is known to impact its physical, chemical and biological properties. The first racemic procedure for the synthesis of trifluorosubstituted cyclopropenes was reported by Carreira in 2010. $Rh_2(esp)_2$ served as catalyst in aqueous media, where trifluoroethylamine hydrochloride was converted *in situ* to trifluoromethyldiazomethane in the presence of sodium nitrite and sulfuric acid for the cyclopropenation of alkynes, the scope of which included interestingly two products obtained from internal alkynes (Figure 11).[27]

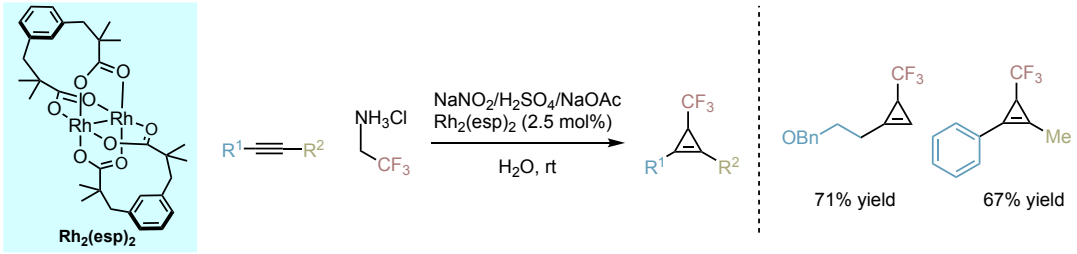


Figure 11 Rh(II)-catalyzed racemic synthesis of trifluoromethylated cyclopropenes

A few years later in 2019, a general methodology to chiral trifluoromethyl-substituted cyclopropenes from terminal alkynes was reported by Koenigs using trifluoromethylated donor/acceptor diazoalkanes and Rh_2(*S*-BTPCP)$_4$ as catalyst (Figure 12).[28]

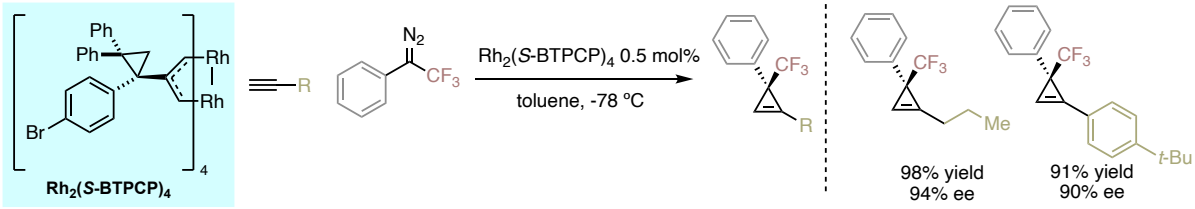


Figure 12 Asymmetric synthesis of trifluoromethylated cyclopropenes with terminal alkynes

[2+1] cycloaddition of metal carbenes to internal alkynes

In spite of the achievements they represent, the abovementioned catalytic systems have in common an efficiency restricted to terminal alkynes. Davies proposed a rationalization to this limitation by invoking the manner by which the alkyne approaches the catalyst.[21] Two scenarios were considered to explain the Rh catalyst efficiency: a side-on approach of the alkyne to the catalyst, or an end-on approach (Figure 13, left and right, respectively). The fact that Rh(II)-catalyzed cyclopropenations are only effective with terminal alkynes was thought to favor the end-on approach scenario. Indeed, disubstituted alkynes would be impeded to successfully approach the

[27] Morandi, B.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *122*, 4390.
[28] Tran, U. P. N.; Hommelsheim, R.; Yang, Z.; Empel, C.; Hock, K. J.; Nguyen, T. V.; Koenigs, R. M. *Chem. Eur. J.* **2020**, *26*, 1254.

catalyst due to steric effects and would collide on the surface instead. The presence of a terminal hydrogen proves in this way crucial to the stereocontrol and success of the enantioselective cyclopropenation with Rh(II) paddlewheel catalysts. The use of internal alkynes in cyclopropenation reactions required thus the design of alternative catalytic systems.

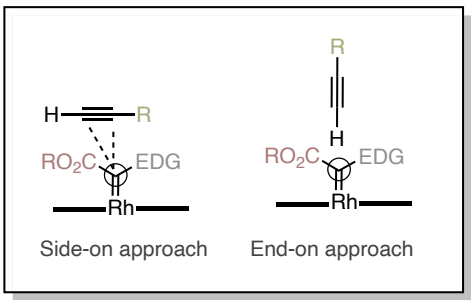


Figure 13 Extreme orientations of alkynes in Rh(II) catalyzed cyclopropenations

The first general route to achiral cyclopropenes from internal alkynes relied on silver catalysis, as disclosed by Davies in 2011.[29,30] The ability of silver to react with highly substituted alkenes in a chemoselective manner in cyclopropanation reactions was utilized to successfully access a wide scope of diversely substituted cyclopropenes (Figure 14).

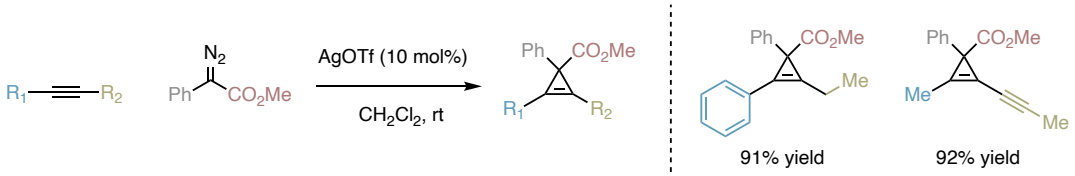


Figure 14 Silver triflate-catalyzed cyclopropenation of internal alkynes

The catalytic process was finely-tuned in 2012 to a dual system involving a silver-activated gold(I) chiral complex, accessing new substitution patterns in chiral cyclopropenes using from donor/acceptor carbenoids and internal alkynes.[31]

[29] Briones, J. F.; Davies, H. M. L. *Org. Lett.* **2011**, *13*, 3984.
[30] The use of the achiral paddlewheel catalyst $Rh_2(esp)_2$ allowed for the obtention of one racemic cyclopropene from 1-phenylpropyne in 2008, see: González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813. The scope of reference 27 also includes two internal alkynes.
[31] Briones, J. F.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 11916.

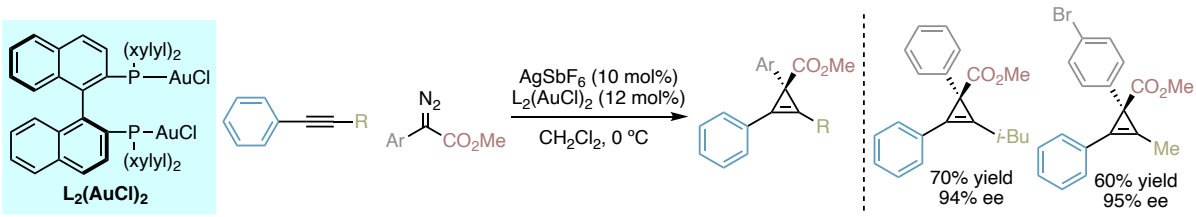


Figure 15 Davies dual gold-silver asymmetric cyclopropenation and selected examples

A few years later, in 2019, a seminal report from Marek, Zhang and Ma disclosed the first Rh(II)-catalyzed cyclopropenation of internal alkynes with an acceptor-only fluorinated diazo compound as carbene source (Figure 16, top).[32] This unprecedented strategy allowed access to a new class of enantioenriched cyclopropenes substituted with a valuable fluorine equivalent, and fully substituted at the vinylic carbons. The stereochemical mode proposed involved a "tilted side-on" approach of the alkyne to the Rh-carbenoid, rationalizing the origin of the enantioselectivity induced with disubstituted alkynes. In 2023, the same authors reported the first use of trifluorodiazoethane as acceptor-only carbene surrogate in a long sought-after enantioselective synthesis of trifluoromethyl group-substituted cyclopropenes from internal alkynes (Figure 16, bottom).[33]

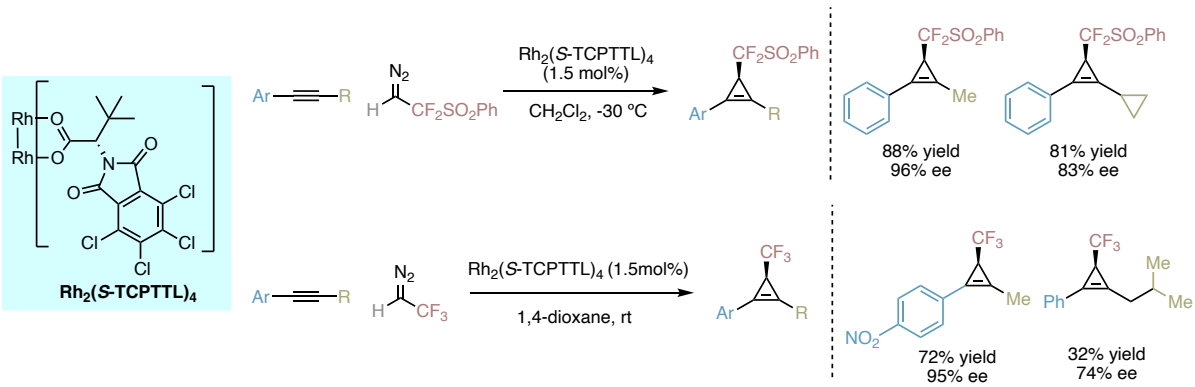


Figure 16 Rh(II)-catalyzed asymmetric cyclopropenation of internal alkynes with acceptor only fluorinated carbenes

Alternative [2+1] cycloadditions

Alternative [2+1] cycloaddition protocols, diazo- or metal-free, were also reported for the synthesis of cyclopropenes.

Diazo surrogates were, for example, found in conjugated enynones and applied to the synthesis of cyclopropenes, as reported by Vicente in 2014. Zinc catalysis allowed for substrate activation and cyclization to a furyl intermediate first, which afforded the cyclopropene after [2+1] addition with an alkyne (Figure 17).[34]

[32] Zhang, Z.; Zheng, M.; Xue, X.; Marek, I.; Zhang, F.; Ma, J. *Angew. Chem. Int. Ed.* **2019**, *131*, 18359.
[33] Cui, X.; Zheng, M.; Tang, X.; Zhang, Z.; Xue, X.; Marek, I.; Ma, J.; Zhang, F. *Chem Catal.* **2023**, *3*, 100637.
[34] González, M. J.; López, L. A.; Vicente, R. *Org. Lett.* **2014**, *16*, 5780.

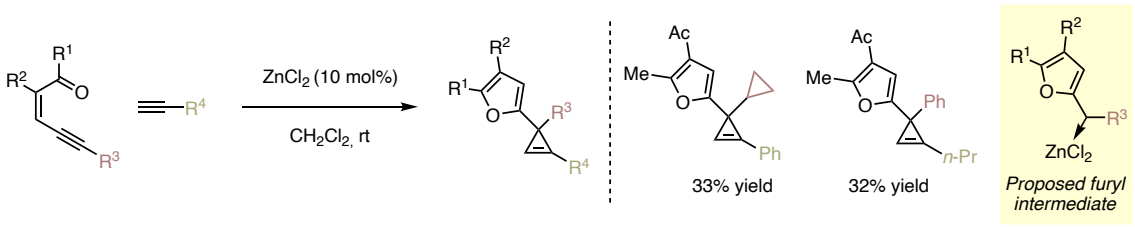


Figure 17 Enynones as carbene surrogates for the Zn-catalyzed synthesis of cyclopropenes

Different metal-free approaches were also reported. An $I^{(III)}$-mediated cyclopropenation was reported by Zhang in 2014. Hypervalent iodine reagents were used as electrophiles to activate internal and terminal alkynes in a protocol where malonitrile acted as C1 synthon, ultimately affording a wide range of cyclopropenes under mild reaction conditions and in good yields (Figure 18).[35]

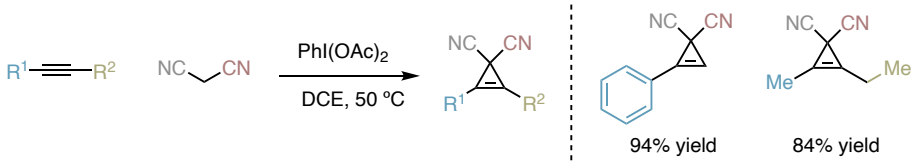


Figure 18 $I^{(III)}$-mediated cyclopropenation of alkynes

Valdés disclosed in 2016 the use of trifluoromethylated tosylhydrazones as carbene equivalents, in a transformation effective with both terminal and internal alkynes upon heating (Figure 19).[36] Notably, chiral fluoroalkyl cyclopropenes were also obtained from tosylhydrazones in 2021 by Bi and co-workers using Rh_2(*R*-BTPCP)$_4$ as catalyst.[37]

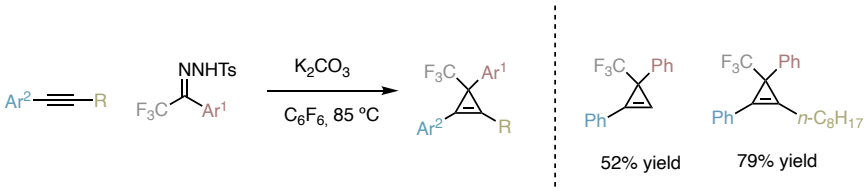


Figure 19 Tosylhydrazones as carbene equivalents in the synthesis of trifluoromethylated cyclopropenes and selected examples

Another metal-free approach from Koenigs in 2020 reported the use of donor/acceptors diazoalkanes. Blue-light photolysis of the latter afforded carbenes, ultimately yielding tri- and tetrasubstituted cyclopropenes (Figure 20).[38]

[35] Lin, S.; Li, M.; Dong, Z.; Liang, F.; Zhang, J. *Org. Biomol. Chem.* **2014**, *12*, 1341.
[36] Barroso, R.; Jiménez, A.; Carmen Pérez-Aguilar, M.; Cabal, M. P.; Valdés, C. *Chem. Commun.* **2016**, *52*, 3677.
[37] Bi, X.; Zhang, X.; Tian, C.; Wang, Z.; Sivaguru, P.; Nolan, S. P.; Bi, X. *ACS Catal.* **2021**, *11*, 8527.
[38] Hommelsheim, R.; Guo, Y.; Yang, Z.; Empel, C.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 1203.

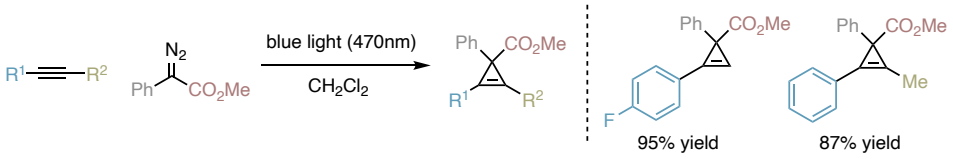


Figure 20 Photolytic generation of carbenes for the cyclopropenation of terminal and internal alkynes

In 2021, a continuous flow photochemical process using trifluoromethylated diazirines as carbene sources was also reported as efficient for the cyclopropenation of both terminal and internal alkynes.[39]

Ultimately, a biocatalytic method was designed by Arnold and co-workers.[40] An engineered P450 enzyme, namely the variant P411-C10, generated a lineage of different enzymes (P411-C10-WIRF, P411-C10WIRF_G, P411-C10WIRF_GAK). These enzymes successfully cyclopropenated internal alkynes with unprecedented enantiomeric excesses (>99.9% in all examples of the scope) (Figure 21).

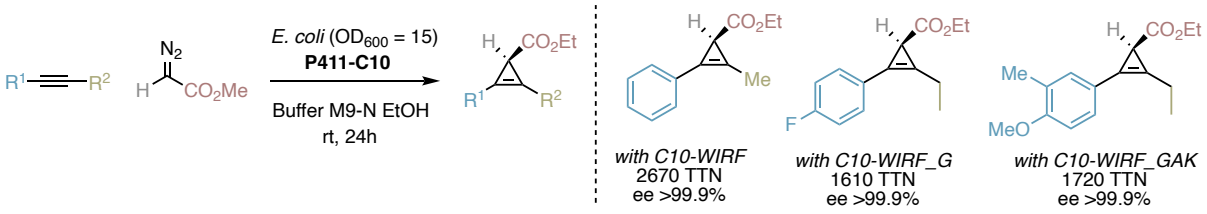


Figure 21 Directed evolution catalysis for the enantioselective synthesis of cyclopropenes

In spite of the progress made in [2+1] cycloadditions between alkynes and metal carbenes, presented in this Section, some limitations are still to be overcome. These methodologies indeed fail to access cyclopropenes (1) with aromatic rings substituted with electron-rich groups, because of dimerizations of the metal-carbene; (2) with alkyl groups, because the metal-carbene undergoes β-hydride migration;[41] (3) with allyl groups, because the metal-carbene undergoes intramolecular cyclopropanation.[42]

3.4 Derivatizations of cyclopropenes

As introduced in part 3.2, the chemistry of cyclopropenes is tremendously rich. It has been comprehensively and regularly reviewed.[43] For the sake of conciseness, the reactivity described in this section will be limited to the

[39] Tanbouza, N.; Carreras, V.; Ollevier, T. *Org. Lett.* **2021**, *23*, 5420.
[40] Chen, K.; Arnold, F. H. *J. Am. Chem. Soc.* **2020**, *142*, 6891.
[41] Panne, P.; Fox, J. M. *J. Am. Chem. Soc.* **2007**, *129*, 22.
[42] (a) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M. *J. Am. Chem. Soc.* **2013**, *135*, 9283, (b) Qin, C.; Davies, H. M. L. *Org. Lett.* **2013**, *15*, 310.
[43] For reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77; (b) reference 7; (c) reference 8; (b) Rubin, M.; Rubina, M.; Gevorgyan, V., *Chem. Rev.* **2007**, *107*, 3117; (c) Zhu, Z. Bin; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534; (d) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J *Acc. Chem. Res.* **2015**, *48*, 1021; (e) Vicente, R. *Synthesis* **2016**, *48*, 2343; (f) Dian, L.; Marek, I. *Chem. Rev.* **2018**, *118*, 8415; (g) Li, P.; Zhang, X.; Shi, M. *Chem. Commun.* **2020**, *56*, 5457; (h) Vicente, R. *Chem. Rev.* **2021**, *121*, 162; (i) Cohen, Y.; Marek, I. *Acc. Chem. Res.* **2022**, *55*, 2848; (j) Huo, H.; Gong, Y. *Org. Biomol. Chem.* **2022**, 3847.

main pathways. Derivatizations with retention of the three-carbon rings will be discussed first—namely syntheses of complex cyclopropanes—before exploring different pathways involving the opening of the cyclopropene ring: reactions where metal vinyl carbenes are proposed as main intermediates, as well as cycloisomerization reactions and metathesis reactions of cyclopropenes will be then discussed. Ultimately, in the last category of transformations covered, an overview of cycloadditions involving cyclopropenes will be presented.[44] Reactions involving cyclopropenes are somewhat challenging to uniformize in a single way, which might explain the presence of what can be regarded as overlaps between some sections.

3.4.1 Carbometalations and related reactions

Cyclopropene carbometalations represent a powerful approach for the synthesis of highly functionalized, diastereo- and enantiomerically enriched cyclopropanes. These are much sought-after compounds, both for their biological activity and own reactivity. Carbometalation and related reactions are therefore among the most widely used and studied functionalizations of cyclopropenes. The high π-density of the double bond makes cyclopropene a starting material of choice for π-philic transition metals, enabling a rich coordination chemistry. Subsequent electrophile trapping of the cyclopropyl metal compound allows for the functionalization of both vinylic carbons (Figure 22). The control and fine-tuning of the diastereo- and enantioselectivity is made possible by the rational design of substrates or transition-metal catalysts.

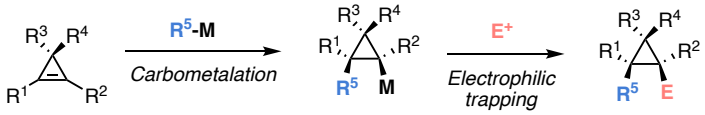


Figure 22 Carbometalations of cyclopropenes and subsequent electrophilic trapping

As for catalytic asymmetric carbometalations, Nakamura was the first to report, in 2000, a catalytic asymmetric Fe-catalyzed carbozincation on cyclopropenone ketals with chiral phosphine ligands.[45] In the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), $FeCl_3$/(R)-Tol-BINAP as catalytic system allowed to reach high enantioselectivities from these stereochemically biased substrates (Figure 23).

[44] For a detailed review on ring-opening reactions of cyclopropenes, see reference 43h.
[45] Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978.

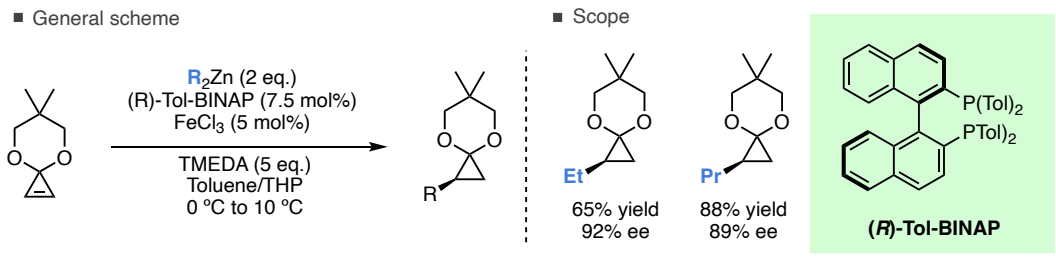


Figure 23 First asymmetric carbozincation of cyclopropenyl ketals

Facial selectivity of the addition was also achieved by taking advantage of the installation of a polar functional group substituent on the cyclopropene. This was disclosed first by Fox in 2002, with a copper-catalyzed directed carbomagnesiation of hydroxymethylcyclopropenes, in which the hydroxy group gave access to stereodefined cyclopropanes with an outstanding *syn* selectivity.[46] As for the regioselectivity, the control was achieved by the presence of a sp^2 group on the cyclopropene double bond, allowing for the formation of the least hindered carbometalated intermediate (Figure 24).

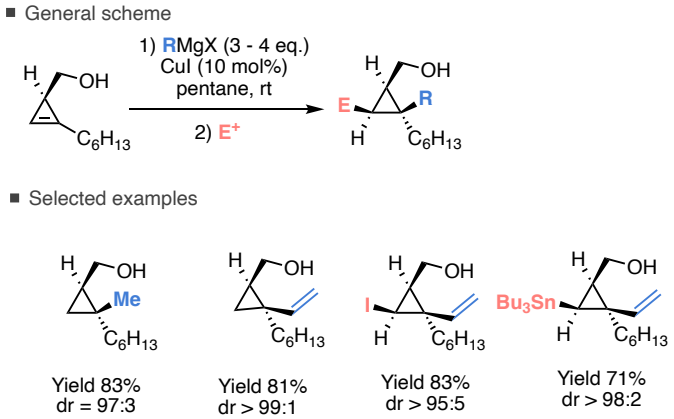


Figure 24 Directed copper-catalyzed carbometalation of hydroxomethyl cyclopropenyl derivatives

A significant extension of this protocol in 2006 afforded single diastereoisomers by using *N*-methylprolinol as chiral additive (Figure 25). [47] Interestingly, methoxide ions proved to be essential to reproduce the high enantioselectivities obtained.

[46] Liao, L. A.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322
[47] Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600.

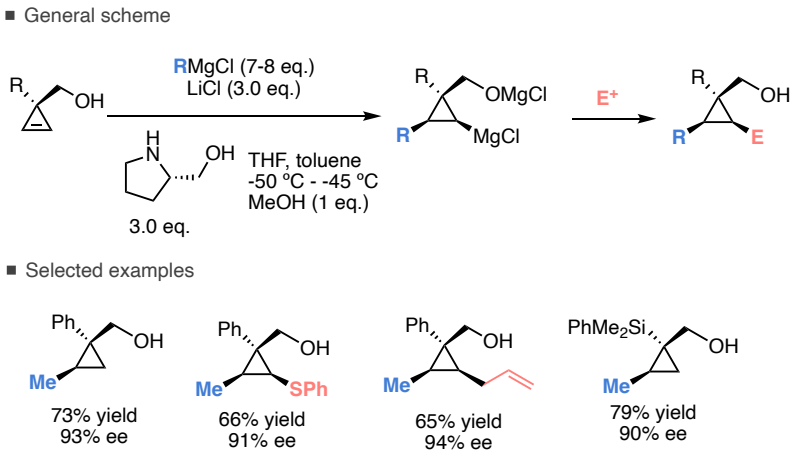


Figure 25 Directed enantioselective carbomagnesiation of cyclopropenes

The use of directing groups for asymmetric cyclopropene carbometalations revealed to be a powerful tool to achieve facial selectivity, and various catalytic systems were reported over the years mainly by the groups of Fox and Marek.[48] Notably, ester-substituted cyclopropenes were also compatible with Grignard reagents at low temperatures, as demonstrated by Marek with a directed copper-catalyzed carbomagnesiation leading to various substituted cyclopropanes species with excellent diastereoselectivities.[49]

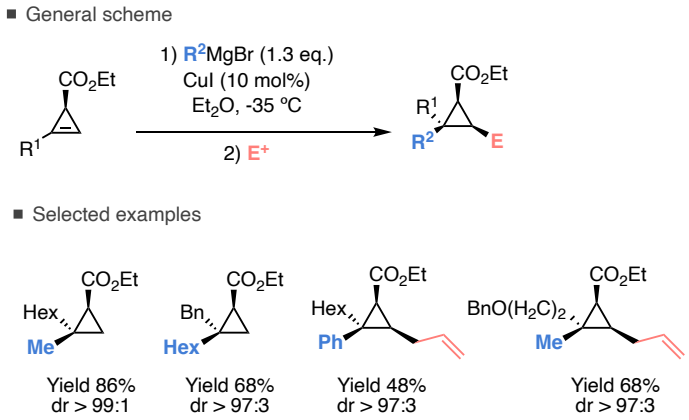


Figure 26 Copper-catalyzed diastereoselective carbomagnesiation of cyclopropenes

[48] For examples of the use of directing groups in asymmetric cyclopropene carbometalation, see: (d) Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569; (b) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563; (c) Levin, A.; Marek, I. *Chem. Commun.* **2008**, 4300; (d) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382; (e) Simaan, S.; Masarwa, A.; Zohar, E.; Stanger, A.; Bertus, P.; Marek, I. *Chem. Eur. J.* **2009**, *15*, 8449; (f) Simaan, M.; Delaye, P.-O.; Shi, M.; Marek, I. *Angew. Chem. Int. Ed.* **2015**, *127*, 12522; (g) Simaan, M.; Marek, I. *Beilstein J. Org. Chem.* **2019**, *15*, 752.
[49] Didier, D.; Delaye, P. O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. Eur. J.* **2014**, *20*, 1038

As for unfunctionalized cyclopropenes, the first enantioselective Pd-catalyzed carbozincation of spirocyclopropenes was reported by Lautens in 2011.[50] Subsequent copper-mediated electrophilic functionalization provided enantioenriched cyclopropyl derivatives (Figure 27).

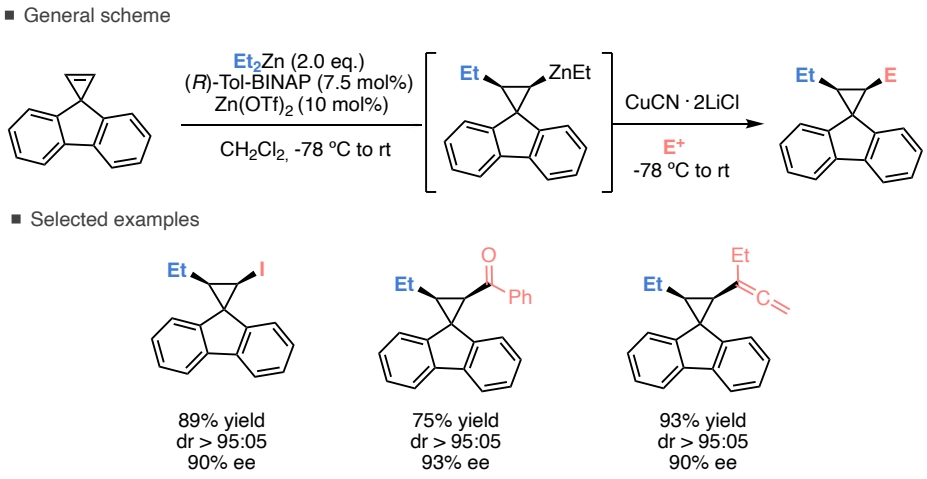


Figure 27 First asymmetric Pd-catalyzed carbozincation

Unbiased achiral cyclopropenes were enantioselectively functionalized for the first time by Marek in 2015.[51] This versatile carbozincation used Cu(I) catalysis with (R)-DTBM-Segphos to afford single diastereoisomers cyclopropanes in high diastereo- and enantioselectivities.

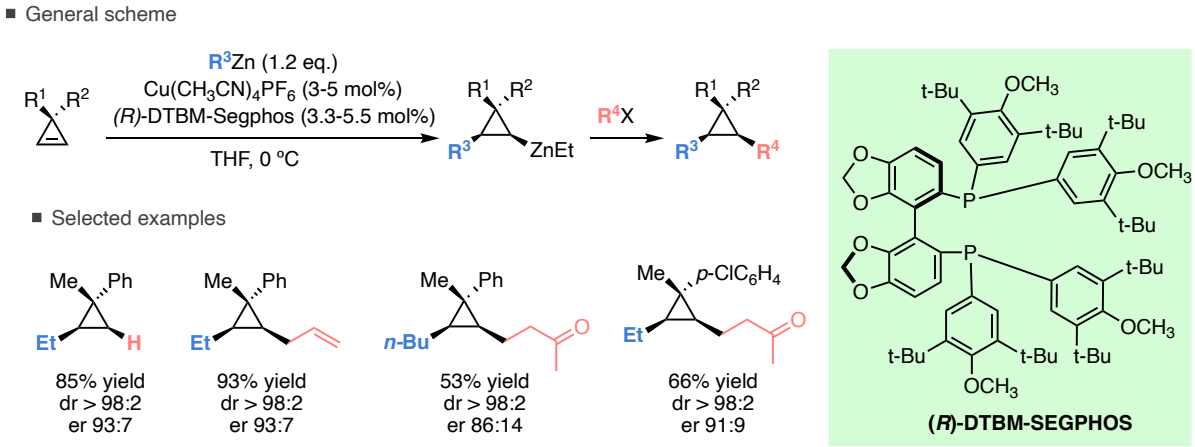


Figure 28 Cu-catalyzed diastereo- and enantioselective synthesis of polysubstituted cyclopropanes

Lower enantiomeric ratios were however observed when using dialkyl zinc derivatives other than diethyl zinc. To address this limitation, the strategy was strengthened a few years later with the development of an asymmetric

[50] Krämer, K.; Leong, P.; Lautens, M. *Org. Lett.* **2011**, *13*, 819.
[51] Müller, D. S.; Marek, I. *J. Am. Chem. Soc.* **2015**, *137*, 15414.

Cu(I)/(*R, S*)-Josiphos catalyzed carbomagnesiation tolerating the use of a wide range of Grignard reagents in the first carbometalation step, affording a broad range of products with both excellent diastereo- and enantioselectivities (Figure 29).[52]

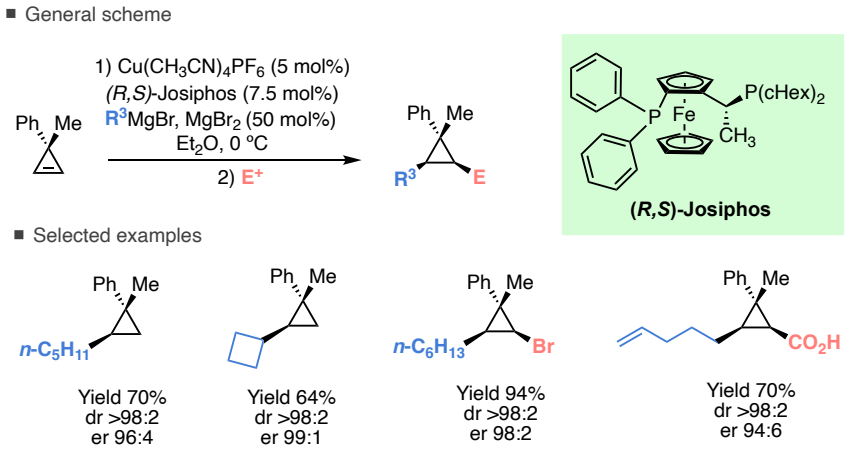


Figure 29 Asymmetric copper-catalyzed carbomagnesiation of unfunctionalized cyclopropenes

Latest developments in the quest for highly functionalized cyclopropanes were disclosed in 2021 by Marek, with an elegant protocol disclosing the first copper-catalyzed carbomagnesiation of highly-strained persubstituted cyclopropenes.[53] Penta- and hexa-substituted cyclopropanes bearing three vicinal stereogenic centers were accessed as single diastereoisomers from electronically-biased polysubstituted cyclopropenes. The presence of an ester substituent on the sp^3 carbon, as well as a sp^2 hybridized carbon center on the disubstituted cyclopropene sp^2 carbon allowed for a complete diastereoselectivity, and regioselectivity (Figure 30).

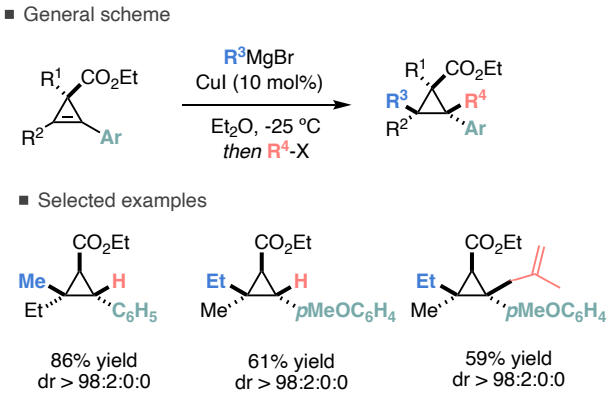


Figure 30 Synthesis of penta- and hexa-substituted cyclopropanes from persubstituted cyclopropenes

[52] Dian, L.; Müller, D. S.; Marek, I. *Angew. Chem. Int. Ed.* **2017**, *56*, 6783.
[53] Cohen, Y.; Augustin, A. U.; Levy, L.; Jones, P. G.; Werz, D. B.; Marek, I. *Angew. Chem. Int. Ed.* **2021**, *60*, 11804.

Highly functionalized and stereodefined cyclopropanes are also of the highest interest as substrates in the synthesis of acyclic compounds with several stereogenic centers. Carbometalated cyclopropenyl species can undergo a C-C bond cleavage under cleverly designed reaction conditions, with transfer of chiral information from the diastereoselective carbometalation step. Significant contributions were reported in the past years.[54]

One representative design, of the most impressive, is a one-pot cascade sequence for the synthesis of δ-ketoamides containing a quaternary stereocenter. Starting from enantiomerically enriched cyclopropenecarboxamides, the carbomagnesiation step was followed by the addition of an acylsilane. Subsequent [1,2]-Brook rearrangement, β C-C fragmentation and hydrolysis afforded the final products with complete overall stereocontrol (Figure 31).[55]

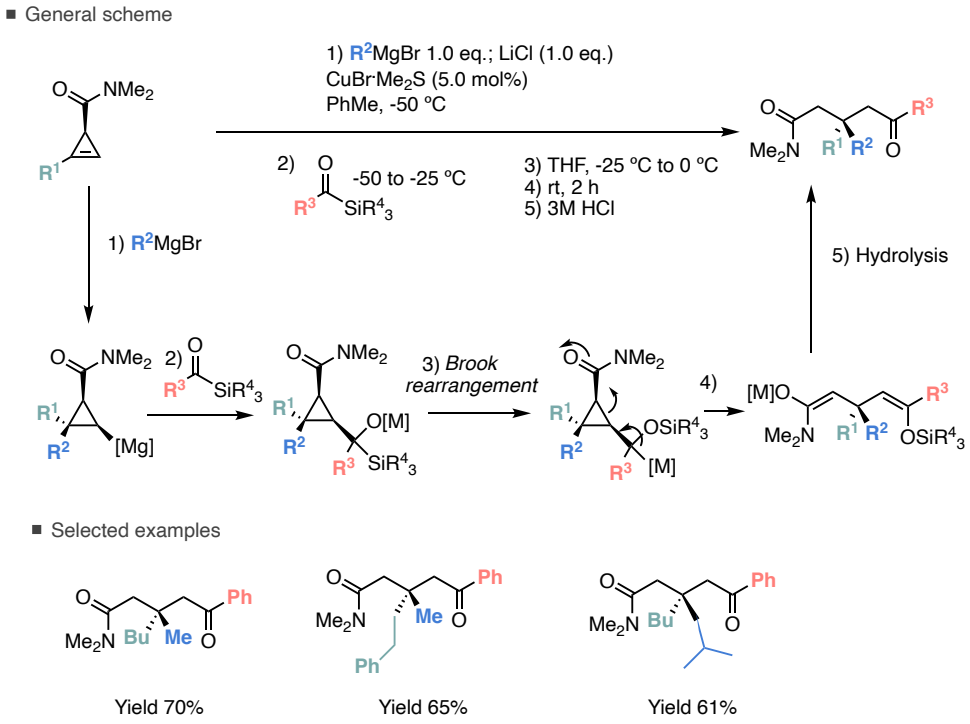


Figure 31 One-pot stereocontrolled synthesis of δ-ketoamides from non-racemic cyclopropenes

Hydrofunctionalizations

Related to carbometalations, hydrofunctionalizations of cyclopropenes by asymmetric addition on the double bond also represent a powerful access to a plethora of functionalized cyclopropanes.

[54] For examples of ring-opening processes, see: (a) Liu, Y.; Ma, S. *Chem. Sci.* **2011**, *2*, 811; (b) Delaye, P. O.; Didier, D.; Marek, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 5333; (c) Didier, D.; Delaye, P. O.; Simaan, M.; Island, B.; Eppe, G.; Eijsberg, H.; Kleiner, A.; Knochel, P.; Marek, I. *Chem. Eur. J.* **2014**, *20*, 1038; (d) reference 48f; (e) Zhang, F. G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714; (f) Tugny, C.; Zhang, F. G.; Marek, I. *Chem. Eur. J.* **2019**, *25*, 205. For a synthesis of cyclobutenes, see: Zhang, F. G.; Marek, I. *J. Am. Chem. Soc.* **2017**, *139*, 8364.

[55] Zhang, F. G.; Eppe, G.; Marek, I. *Angew. Chem. Int. Ed.* **2016**, *55*, 714

The first asymmetric hydroboration of cyclopropenes substituted with an ester moiety as directing group was reported by Gevorgyan in 2003.[56] Cyclopropyl boronates were accessed by Rh-catalysis with excellent diastereo- and enantioselectivities (Figure 32).[57]

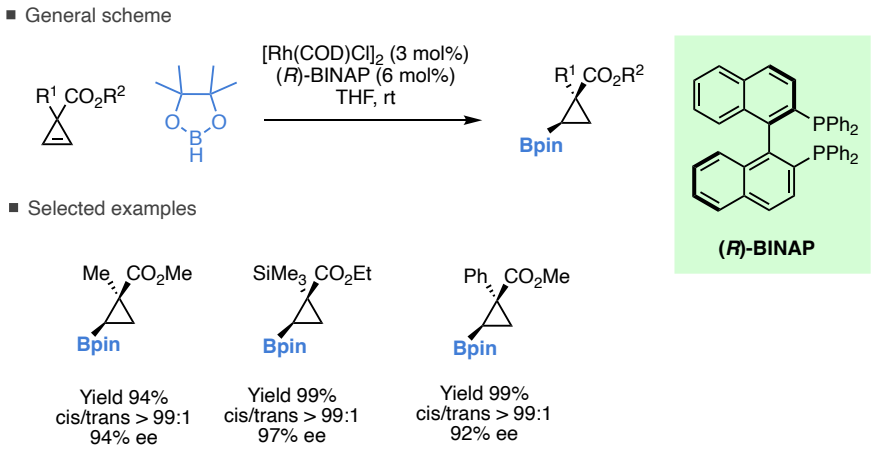


Figure 32 Rh-catalyzed directed enantioselective hydroboration of cyclopropenes

A few years later in 2014, Tortosa reported a powerful protocol for unbiased cyclopropenes bearing various aromatic rings.[58] Copper chloride in catalytic amounts, combined with (*R*)-DTBM-Segphos allowed for the addition of B_2pin_2 across the cyclopropene double bond in excellent diastereo- and enantiomeric ratios (Figure 33).

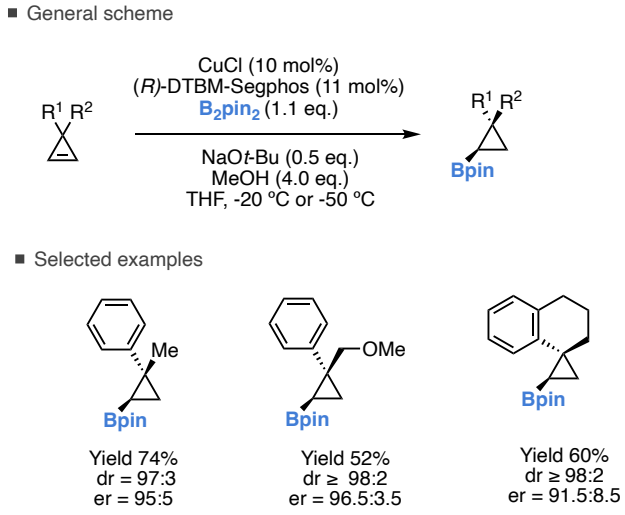


Figure 33 Cu-catalyzed enantioselective hydroboration of cyclopropenes

[56] Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198.
[57] For recent studies on directed hydroboration of cyclopropenes, see: (a) Tian, B.; Liu, Q.; Tong, X.; Tian, P.; Lin, G. Q. *Org. Chem. Front.* **2014**, *1*, 1116; (b) Edwards, A.; Rubina, M.; Rubin, M. *Chem. Eur. J.* **2018**, *24*, 1394.
[58] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833.

A diastero- and enantioselective hydroformylation of cyclopropenes using Rh-catalysis and (*R*)-C3-Tunephos was reported in 2003 by Rubin.[59] Optically active cyclopropylcarboxaldehydes were obtained from unfunctionalized cyclopropenes in good yields and diastereoselectivities, albeit with limited enantiomeric excesses (Figure 34).[60]

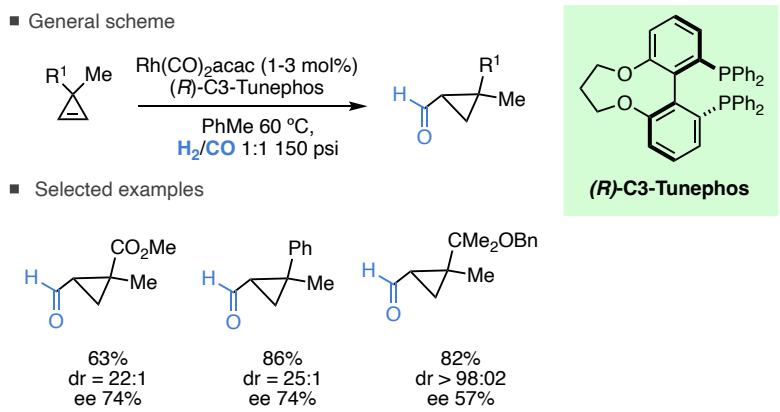


Figure 34 Rh-catalyzed asymmetric hydroformylation of cyclopropenes

The first asymmetric hydrostannation of a C-C double bond was reported by Gevorgyan in 2004.[61] Rh-catalysis together with a chiral stilbene-derived ligand afforded cyclopropylstannanes in high yields and enantiomeric excesses (Figure 35).

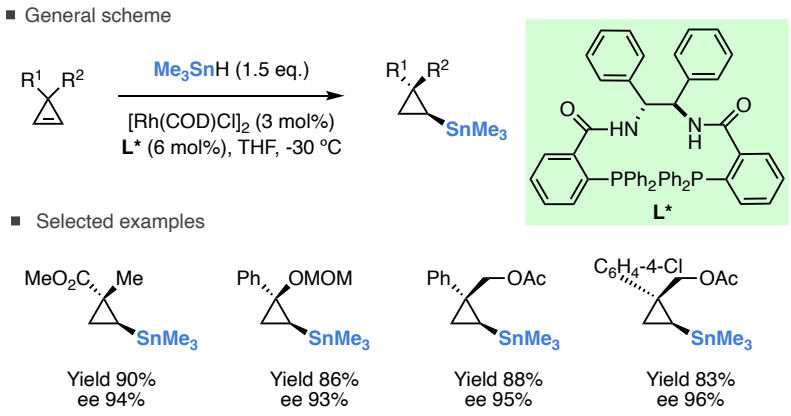


Figure 35 Rh-catalyzed enantioselective hydrostannation of cyclopropenes

[59] Sherrill, W. M.; Rubin, M. *J. Am. Chem. Soc.* **2008**, *130*, 13804.
[60] For a related synthesis of cyclopropylketones, see Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132,* 16330.
[61] Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2004**, *126*, 3688.

Interestingly, various half sandwich rare-earth metal complexes have been reported as catalytic systems for the hydrofunctionalization of cyclopropenes.[62] The first catalytic hydroamination of cyclopropenes was, for example, enabled by a chiral half-sandwich samarium dialkyl complex with morpholines as substrates, as reported by the group of Hou in 2016 (Figure 36).[62a]

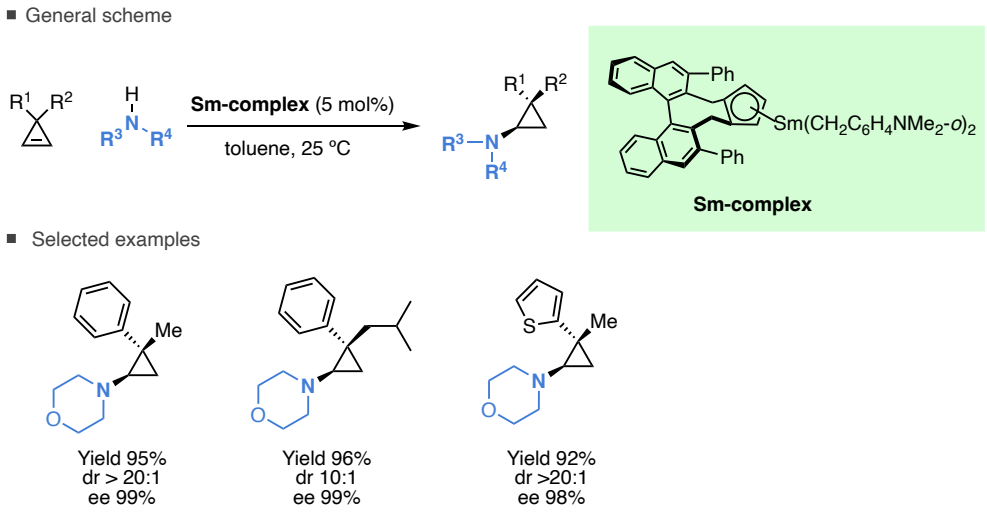


Figure 36 Sm-catalyzed hydroamination of cyclopropenes

Some transformations are however not limited to the use of chiral rare earth metal complexes as catalytic systems. Indeed, the first hydroalkynylation of cyclopropenes was reported first by Hou in 2018[62d] and relied on a half-sandwich gadolinium complex to reach high diastero- and enantioselectivities. These valuable enantiomerically enriched alkynyl cyclopropanes were alternatively accessed by Pd-catalysis in a mild approach disclosed by Marek shortly after (Figure 37).[63]

[62] For examples of half-sandwich rare-earth metal complexes catalysts in cyclopropenes hydrometalations see: (a) Teng, H. L.; Luo, Y.; Wang, B.; Zhang, L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2016**, *55*, 15406; (b) Luo, Y.; Teng, H. L.; Nishiura, M.; Hou, Z. *Angew. Chem. Int. Ed.* **2017**, *56*, 9207; (c) Teng, H.-L.; Luo, Y.; Nishiura, M.; Hou, Z. *J. Am. Chem. Soc.* **2017**, *139*, 16506; (d) Teng, H. L.; Ma, Y.; Zhan, G.; Nishiura, M.; Hou, Z. *ACS Catal.* **2018**, *8*, 4705.
[63] Dian, L.; Marek, I. *ACS Catal.* **2020**, *10*, 1289.

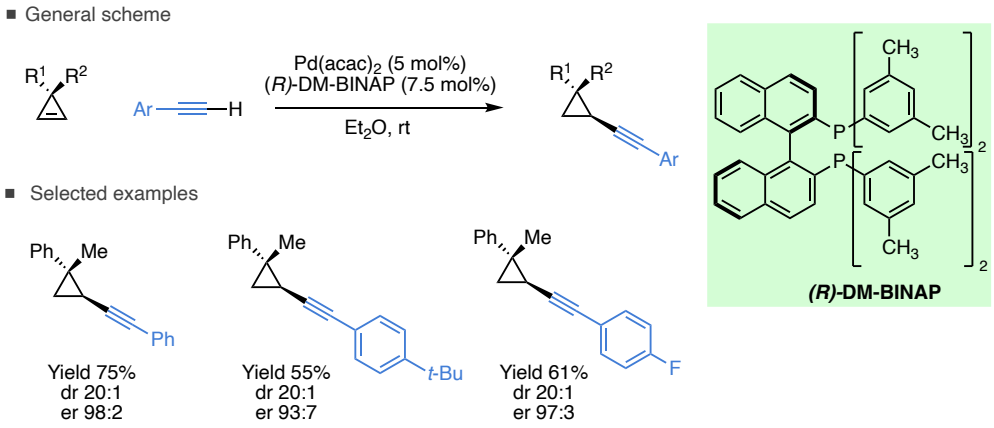


Figure 37 Pd-catalyzed enantioselective hydroalkynylation of cyclopropenes

Enantiomerically enriched cyclopropylsilanes have also been accessed from cyclopropenes in different approaches.[64] A copper-based catalytic system reported by Oestreich in 2019 afforded cyclopropylsilanes from unbiased cyclopropenes in an enantio- and diastereoselective manner (Figure 38).[64a]

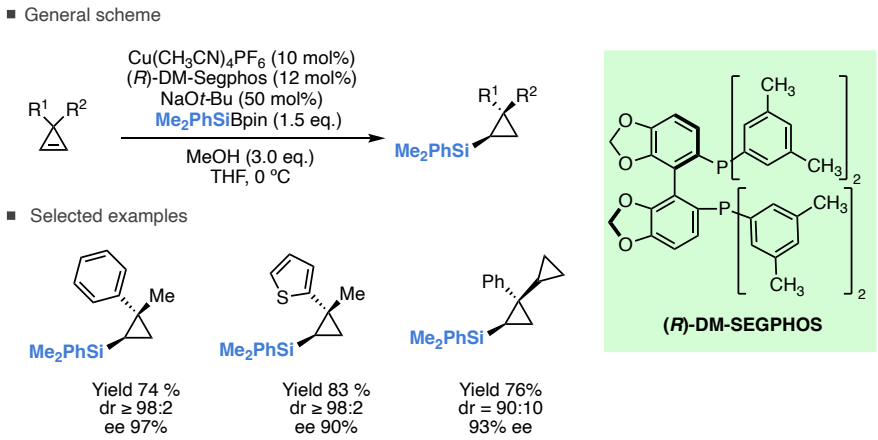


Figure 38 Cu-catalyzed enantioselective hydrosilylation of cyclopropenes

A complementary approach was notably reported by Marek and co-workers in 2020, with the development of a mild Co-based catalytic system reaching high enantio- and diastereoselectivities (Figure 39).[64e]

[64] For reports on the asymmetric hydrosilylation of cyclopropenes, see: (a) Zhang, L.; Oestreich, M. *Chem. Eur. J.* **2019**, *25*, 14304; (b) Wang, H.; Zhang, G.; Zhang, Q.; Wang, Y.; Li, Y.; Xiong, T.; Zhang, Q. *Chem. Commun.* **2020**, *56*, 1819 ; (c) Zhao, Z. Y.; Nie, Y. X.; Tang, R. H.; Yin, G. W.; Cao, J.; Xu, Z.; Cui, Y. M.; Zheng, Z. J.; Xu, L. W. *ACS Catal.* **2019**, *9*, 9110; (e) Dian, L.; Marek, I. *Org. Lett.* **2020**, *22*, 4914.

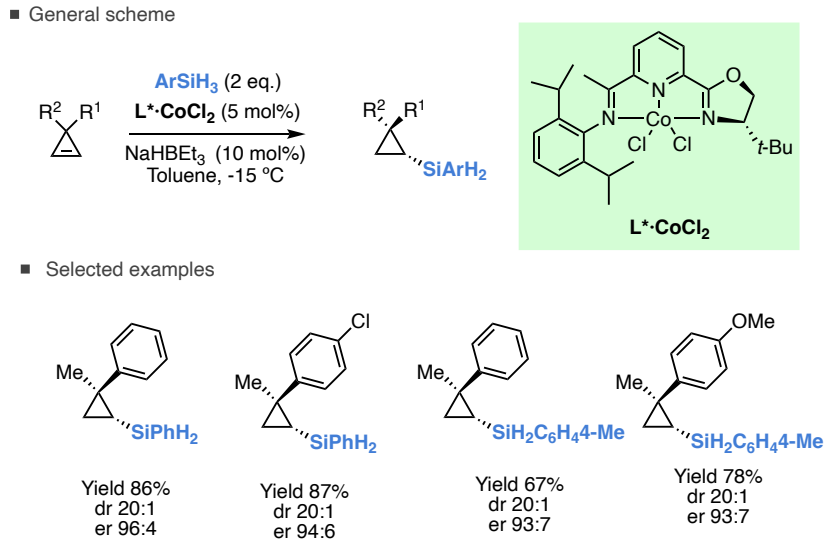


Figure 39 Co-catalyzed diastereo- and enantioselective hydrosilylation of cyclopropenes

Lastly, Gevorgyan and co-workers reported in 2022 the first light-induced, Pd-catalyzed hydroalkenylation of cyclopropenes by merging traditional Pd(II) chemistry with photo-induced Pd(I) chemistry (Figure 40). Importantly, this combination uncovered a new reactivity mode of cyclopropenes. A regio- and chemoselective hydropalladation first step was followed by the photoinduced generation of a hybrid C (sp^3)-centered radical (Figure 40, bottom right). Subsequent Heck-type coupling yielded a broad scope of alkenylated cyclopropanes with high functional group tolerance.[65]

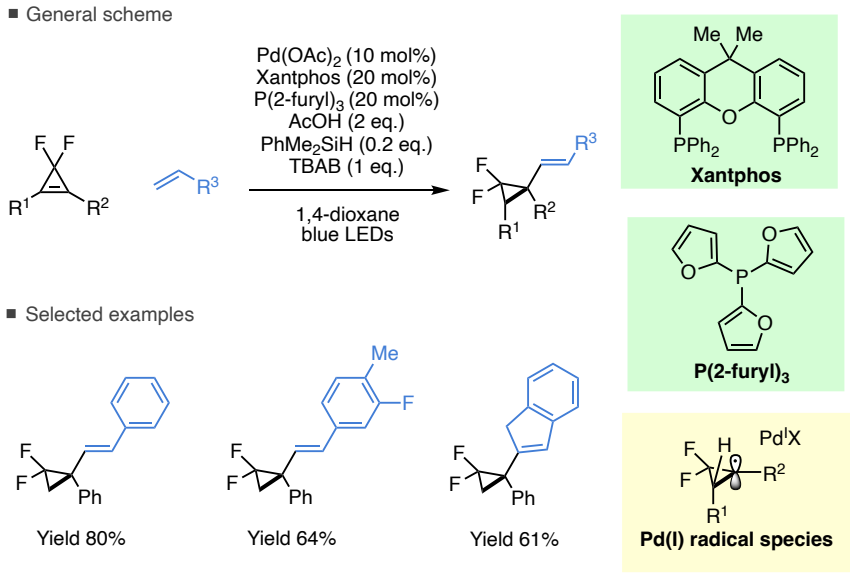


Figure 40 Palladium hydride-enabled hydroalkenylation of cyclopropenes

[65] Zhang, Z.; Gevorgyan, V. *J. Am. Chem. Soc.* **2022**, *144*, 20875.

3.4.2 Cyclopropenes as vinyl carbene equivalents

The transition-metal chemistry of cyclopropenes goes beyond carbometalations: transition-metal catalyzed ring-opening reactions of cyclopropenes can also generate vinyl metal carbene species (Figure 41). They have been proposed as synthetic intermediates in different reactions, either subsequently trapped by alkenes as an access to vinyl cyclopropanes derivatives, or trapped by nucleophiles in an inter- or intramolecular manner.

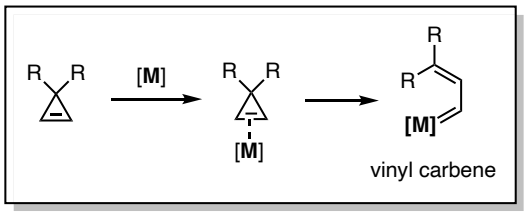


Figure 41 Generation of vinyl metal carbenes from cyclopropenes

Cyclopropanations

Cyclopropenes have been identified as vinyl carbenes equivalents for the synthesis of vinyl cyclopropanes already in the early 1970s,[66] and this transformation was revisited later on through the advent of gold catalysis.[67] As a representative example, complex bicyclic scaffolds were achieved through alkene intramolecular cyclopropanation, as reported by Cossy in 2010.[68] 1,6-cyclopropene-enes, in which an alkene was tethered to a cyclopropene, were successfully converted to 3-oxa or 3-azabicyclo[4.1.0]heptane derivatives in high yields and diastereoselectivities by the generation of a gold carbene intermediate (Figure 42).

[66] For early reports, see: (a) Binger, P.; McMeeking, J. *Angew. Chem. Int. Ed.* **1974**, *13*, 466; (b) Tomilov, Y. V.; Bordakov, V. G.; Tsvetkova, N. M.; Dolgii, I. E.; Nefedov, O. M. *Russ. Chem. Bull,* **1982**, *31*, 2129; (c) Padwa, A.; Blacklock, T. J.; Loza, R. *J. Am. Chem. Soc.* **1981**, *103*, 2404.
[67] For a review, see reference 43d.
[68] Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12,* 4144.

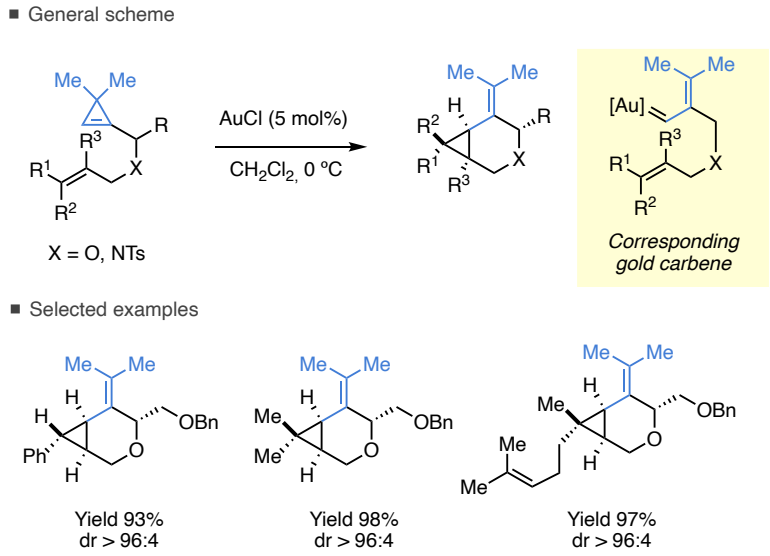


Figure 42 Intramolecular cyclopropanation through gold-catalyzed cycloisomerization of cyclopropenes

Carbenoids generated by ring-opening of cyclopropenes are however not limited to gold species, and examples of rhodium and ruthenium generated carbenoids in intramolecular cyclopropanations have been disclosed as well.[69] Notably, aside from precious metal catalysts, Vicente and co-workers reported the use of inexpensive $ZnCl_2$ for π-activation, for an intermolecular synthesis of vinyl cyclopropanes.[70] The procedure showed a broad scope and high efficiency, performing better than standard gold catalysts in some cases (Figure 43).[71]

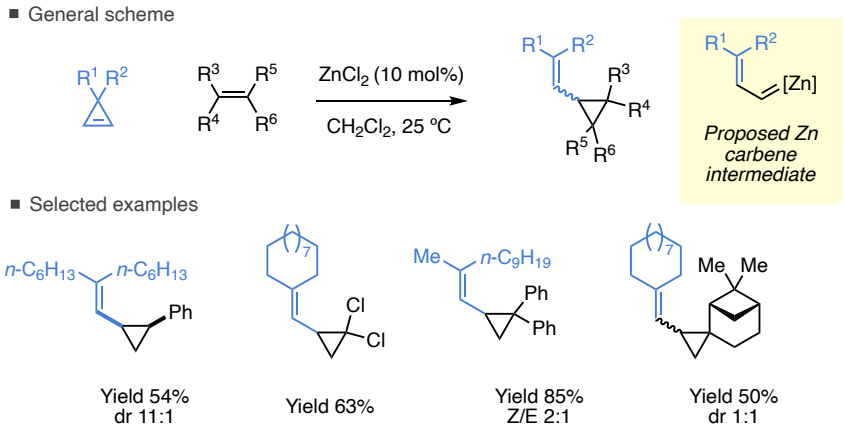


Figure 43 Intermolecular cyclopropanation by generation of zinc vinyl carbenoids

[69] For an intramolecular Rh-catalyzed cyclopropanation, see: Miege, F.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 5932. For an intramolecular Ru-catalyzed cyclopropanation, see: López-Rodríguez, A.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2019**, *84*, 924.
[70] González, M. J.; González, J.; López, L. A.; Vicente, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 12139.
[71] González, J.; de la Fuente, A.; González, M. J.; de Tejada, L. D.; López, L. A.; Vicente, R. *Beilstein J. Org. Chem.* **2019**, *15*, 285.

C-H and Si-H insertions

Cyclopropenes as precursors of metal carbenoids have also been used in C-H and Si-H insertion reactions. As for recent reports,[72] Cossy *et al.* described a diastereoselective C(sp^3)-H intramolecular insertion of donor-only rhodium carbenoids generated from 3,3-dimethylcyclopropenylcarbinols in 2012.[73] Products of 1,6 C-H insertions were obtained in good yields and high diastereoselectivities, tolerating the presence of a hydroxy group (Figure 44).

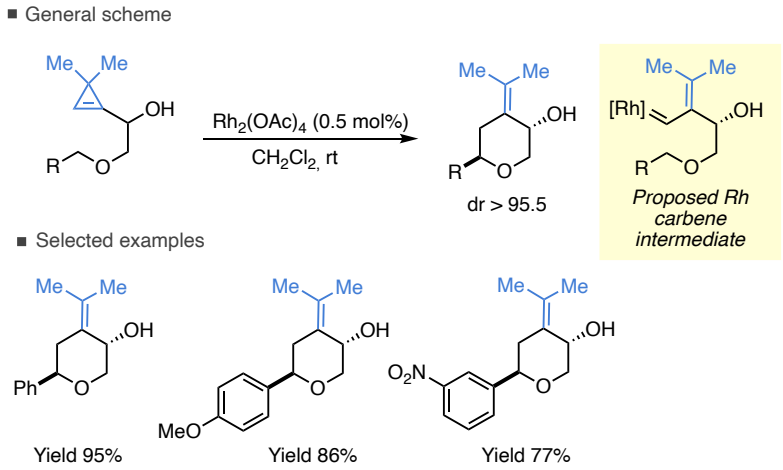


Figure 44 Synthesis of oxygen heterocycles by 1,6-C-H insertions

Allylsilanes, useful building blocks in organic synthesis, were also accessed from hydrosilanes and 3,3-disubstituted cyclopropenes, as reported by Vicente in 2017.[74] $ZnBr_2$ revealed to be a competent, inexpensive catalyst. It allowed for the generation of the vinyl zinc carbenoid intermediates, further inserted into the Si-H bond of various hydrosilanes (Figure 45, left). A broad scope of bifunctional silane/alcohol allylic derivatives was also accessed under rhodium catalysis from cyclopropenyl alcohols as allylic fragment source in 2018, by the generation of the corresponding rhodium vinyl carbene intermediate (Figure 45, right). [75]

[72] For early studies, see: (a) Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1993**, *76*, 521; (b) Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1995**, *78*, 129.
[73] Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 11540.
[74] Mata, S.; López, L. A.; Vicente, R. *Angew. Chem. Int. Ed.* **2017**, *56*, 7930.
[75] Mata, S.; López, L. A.; Vicente, R. *Angew. Chem. Int. Ed.* **2018**, *57*, 11422.

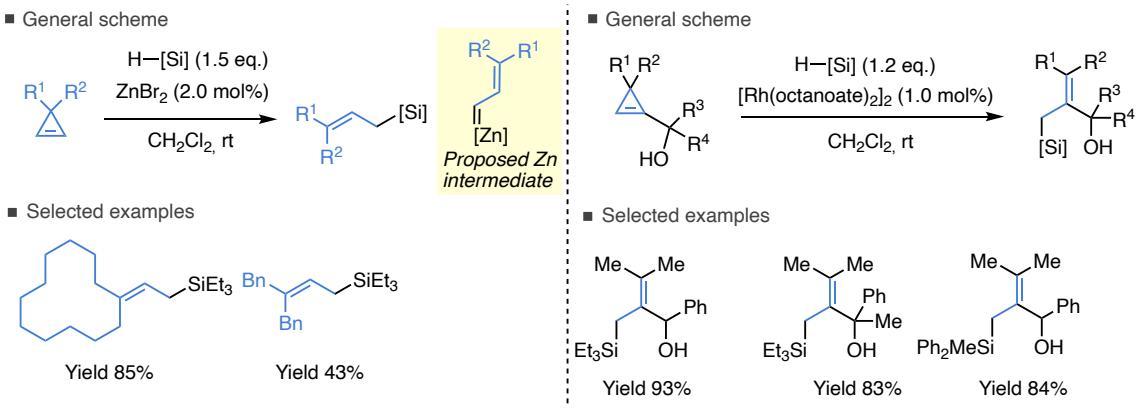


Figure 45 Si-H bond insertions from cyclopropene-generated metal vinyl carbenoids

3.4.3 Cycloisomerizations

Cyclopropenes can undergo metal-catalyzed cycloisomerizations, of which different types can be distinguished. First, 3-carbonylcyclopropenes can cycloisomerize to furans under metal-catalysis. They were identified early on by Padwa as by-products of metal-catalyzed syntheses of cyclopropenes from alkynes and diazoacetates, occurring upon rearrangement of 3-carbonylcyclopropenes.[76] The full synthetic potential and scope of this transformation were exploited by Ma and co-workers in 2003. They disclosed the thorough study of a palladium-copper complementary regiodivergent cycloisomerization of 3-carbonylcyclopropenes to 2,3,4- or 2,3,5-trisubstituted furans (Figure 46).[77]

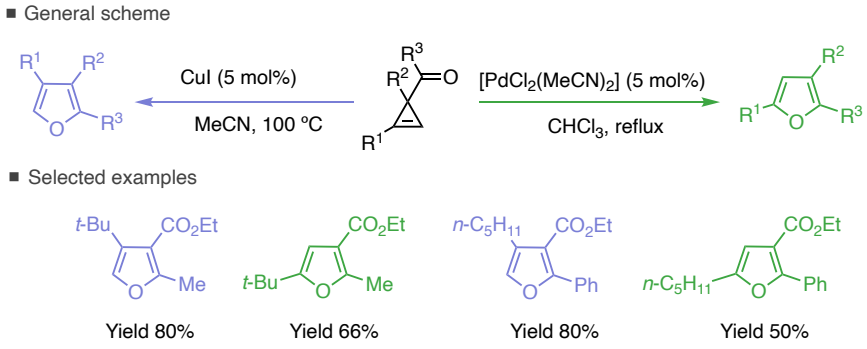


Figure 46: Regiodivergent synthesis of furans from 3-alkoxycarbonylcyclopropenes

Various regiodivergent protocols were reported from this point on, for the synthesis of 2-alkoxyfurans[78] or polycyclic furans.[79] A regiodivergent – although not complementary – synthesis of pyrrole derivatives under Cu(I) or Rh(I) from 3-(pyridin-2-yl) cyclopropenes was also described by Gevorgyan in 2007 (Figure 47). [80] Other examples of 3-iminocyclopropenes cycloisomerizations to N-fused heterocycles have also been reported.[81]

[76] Padwa, A.; Kassir, J. M.; Xu, S. L. *J. Org. Chem.* **1991**, *56*, 6971. See also reference 21b for a more recent example.
[77] Ma, S.; Zhang, J. *J. Am. Chem. Soc.* **2003**, 125, 12386.
[78] Chen, J.; Ma, S. *Chem. Asian J.* **2010**, *5*, 2415.
[79] Gong, J.; Zhao, Z.; Zhang, F.; Wu, S.; Yan, G.; Quan, Y.; Ma, B. *Org. Lett.* **2014**, *16*, 5524.
[80] Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463.
[81] Konishi, K.; Takeda, N.; Yasui, M.; Matsuzaki, H.; Miyata, O.; Ueda, M. *J. Org. Chem.* **2019**, *84*, 14320.

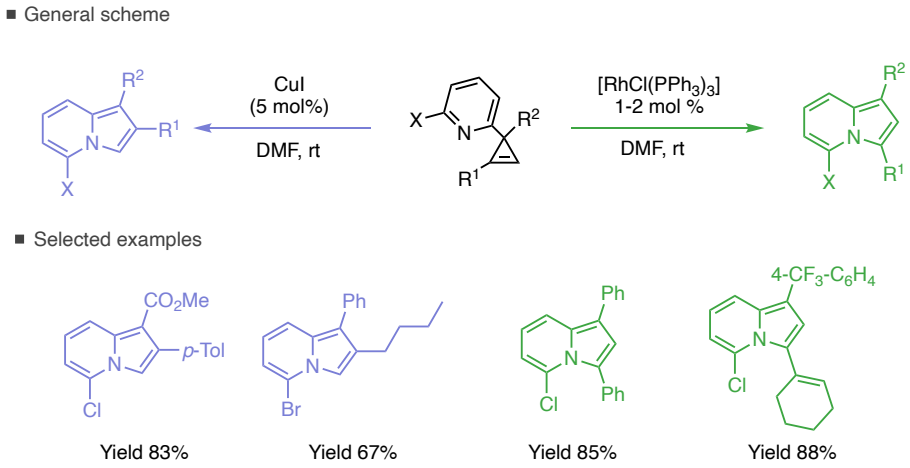


Figure 47 Regiodivergent synthesis of N-fused pyrroles from 3-(pyridin-2-yl) cyclopropenes

A second type of what can be regarded as a cyclopropene cycloisomerization resides in the transformation of 3-aryl cyclopropenes into a variety of indene derivatives.[82] Formally, *d*-metals, acting as Lewis acids, coordinate to the double bond of cyclopropenes, forming first a carbocationic cyclopropane which is then transformed into an allylic carbocation intermediate upon C-C bond cleavage. The allylic carbocation further reacts as electrophile with arenes tethered to the cyclopropene core, in a Friedel-Crafts-type process. Regioselectivity is governed by the stability of the allylic carbocation intermediate formed upon cleavage of the carbocationic cyclopropane. Gold catalysis allowed for the in-depth study of this transformation, and a representative example of this transformation—one of the first—was reported by the group of Wang in 2009.[83] In this specific case, acetyl-substituted cyclopropenes were used as substrates, and acetic acid elimination with a strong base afforded benzofulvene derivatives (Figure 48).[84] Other reports by Endo[85] and Shi[86] in the following years addressed the full scope of this transformation.

[82] For a seminal report, see: Walker, A.; Orchin, M. *Chem. Commun.* **1968**, 1239.
[83] Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956.
[84] Interestingly, a related transformation using propargyl cyclopropenes was reported by Wang in 2010. In that case, gold catalysis revealed to activate preferentially the alkyne, affording benzynes upon rearrangements. See: Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413.
[85] Nakano, T.; Endo, K.; Ukaji, Y. *Chem. Asian J.* **2016**, *11*, 713.
[86] (a) Zhu, Z. Bin; Wei, Y.; Shi, M. *Chem. Eur. J.* **2009**, *15*, 7543; (b) Zhu, Z. Bin; Shi, M. *J. Org. Chem.* **2009**, *74*, 2481; (c) Zhu, Z. Bin; Shi, M. *Org. Lett.* **2009**, *11*, 5278.

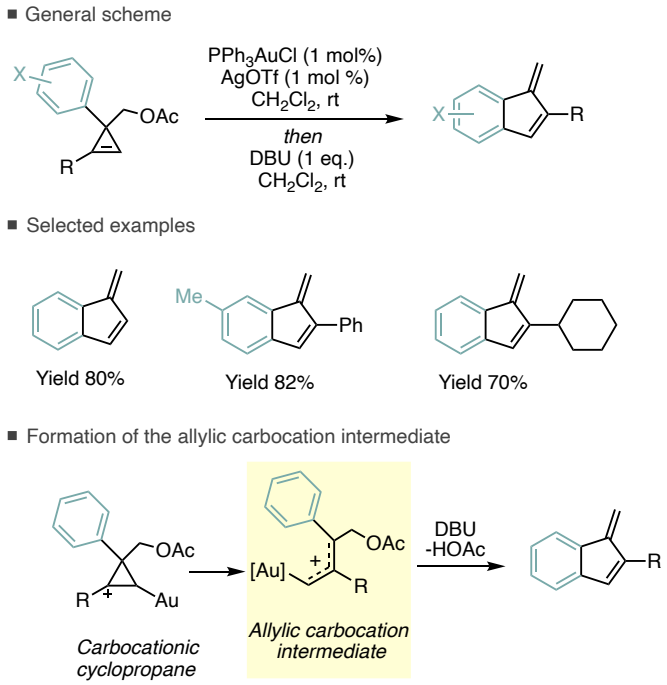


Figure 48 Au-catalyzed synthesis of indene derivatives from acetyl-substituted cyclopropenes

3.4.4 Metathesis reactions

Cyclopropenes, as strained cycloalkenes, are also involved in different variants of metathesis reactions.

To start, they have been pivotal in gaining mechanistic insights in ruthenium-catalyzed metathesis reactions. 3,3-diphenylcyclopropene allowed for the synthesis of the first ruthenium carbene complex with metathesis activity by Grubbs and co-workers, in 1992 (Figure 49).[87]

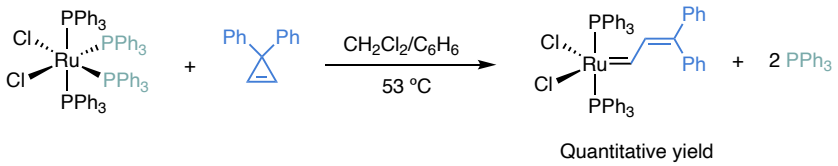


Figure 49 First well-defined ruthenium carbene complex synthesis with metathesis activity

Regarding their use as substrates, the early 2000s saw the development of different protocols using cyclopropenes in ring-opening / cross-metathesis (ROM/CM) reactions, first by Michaut, Parrain and Santelli in the synthesis of protected divinyl ketones in high *E* selectivities, using the first-generation Grubbs ruthenium complex catalyst (Figure 50, a).[88] A chiral ruthenium catalyst was used by Hoveyda and co-workers for the first asymmetric directed ROM/CM between cyclopropenes and cross partners holding enoate or ynoate groups, providing products with high enantioselectivities (Figure 50, b).[89] Shortly after, the same authors reported a stereoselective Ru-catalyzed

[87] Nguyen, S.T.; Johnson, L.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **1992**, *114*, 3974.
[88] Michaut, M.; Parrain, J. L.; Santelli, M. *Chem. Commun.* **1998**, 2567.
[89] Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824

using this time chiral allyl alcohols derivatives as cross partners. Intramolecular H-bonding interactions were exploited to increase the stereochemical control, affording skipped dienes with high diastereoselectivity in the presence of the Hoveyda-Grubbs catalyst (Figure 50, c). [90] ROM/CM were also used in the total syntheses of Bistramide A, Spirofungin A, and Routiennocin using cyclopropene acetal and terminal alkenes.[91]

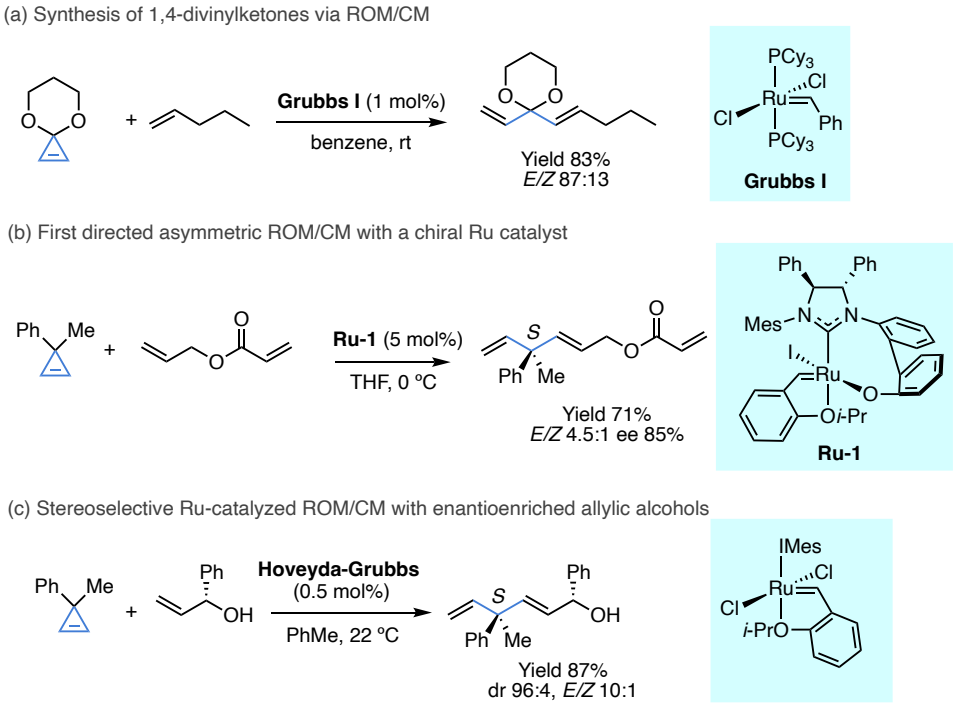


Figure 50 ROM/CM reactions involving cyclopropenes

More complex architectures have also been accessed by ring rearrangement metathesis (RRM), a sequential combination of ROM and ring-closing metathesis (RCM). An elegant transformation reported by Cossy in 2010 involved tethered 1,7- and 1,6-cyclopropenes substituted with an unsaturated side chain leading to different heterocyclic compounds (Figure 51).[92]

[90] Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378.
[91] (a) Statsuk, A.V.; Liu, D.; Kozmin, S.A. *J. Am. Chem. Soc*., **2004**, *126*, 9546; (b) Marjanovic, J.; Kozmin, S.A. *Angew. Chem. Int. Ed.,* **2007**, *46*, 8854; (c) Matsumoto, K.; Kozmin, S.A. *Adv. Synth. Catal.,* **2008**, *350*, 557.
[92] Miège, F.; Meyer, C.; Cossy, J. *Org. Lett.* **2010**, *12*, 248.

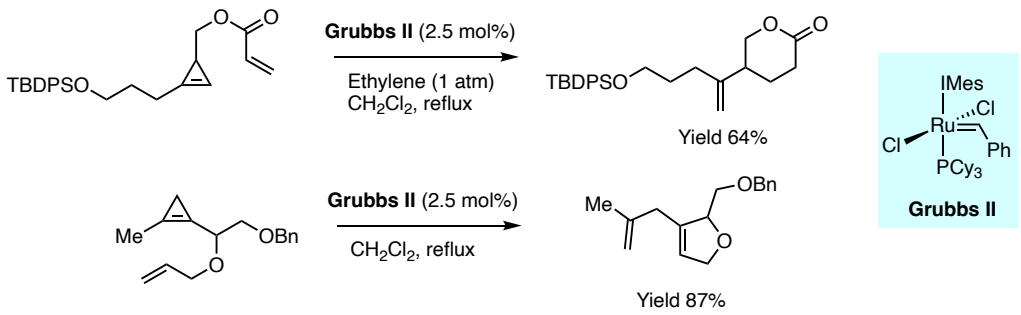


Figure 51 Ring-rearrangement metathesis with cyclopropene-enes

Ultimately, the high ring strain of cyclopropenes makes them useful susbtrates for the synthesis of functionalized polymers by ring-opening metathesis reaction (ROMP), as demonstrated first in various contributions by Schrock, Binder, and Mauduit using 1,1-disubstituted polymers.[93] An impactful contribution to the use of cyclopropenes as polymer building blocks was made by the group of Xia in 2015, by designing 1,1-disubstituted cyclopropenes to selectively undergo a living alternating ring-opening metathesis (AROMP) with cyclic alkenes. This controlled synthesis of block copolymers by the alternate addition of single monomers resulted in products with highly regular microstructures, low dispersities and controllable molecular weight (Figure 52).[94,95]

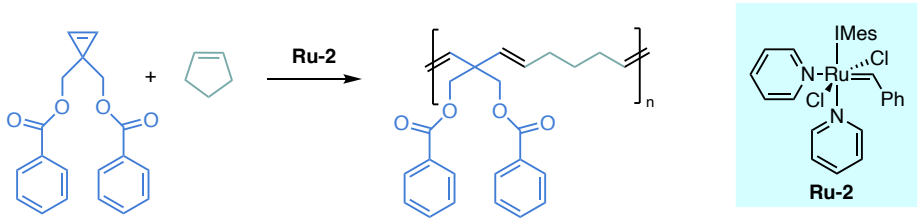


Figure 52 Living AROMP with cyclopropenes designed for a single addition

3.4.3 Cycloadditions

Unsurprisingly, cyclopropenes are ideal substrates for [2+1], [2+2], [2+4], [2+3] and [2+2+1] cycloadditions, offering an atom-economical access to multiple polycyclic scaffolds.[96]

Diels-Alder reactions are the most elaborated cycloadditions involving cyclopropenes, and their high strain energy makes them excellent dienophiles. The first Diels-Alder reaction between cyclopropene and cyclopentadiene was reported in 1960 already,[97] and cyclopropene cycloadditions were reviewed as early as 1972.[98]

The most impactful Diels-Alder involving cyclopropenes to date is the inverse electron-demand Diels-Alder (IED-DA) involving tetrazine. Sauer demonstrated in 1990 that the cycloaddition between unsubstituted cyclopropene

[93] (a) Singh, R.; Czekelius, C.; Schrock, R. R. *Macromolecules* **2006**, *39*, 1316; (b) Binder, W. H.; Kurzhals, S.; Pulamagatta, B.; Decker, U.; Pawar, G. M.; Wang, D.; Ku, C.; Buchmeiser, M. R. *Macromolecules* **2008**, *41*, 8405; (c) Dumas, A.; Tarrieu, R.; Vives, T.; Roisnel, T.; Dorcet, V.; Baslé, O.; Mauduit, M. *ACS Catal.* **2018**, *8*, 3257.
[94] Elling, B. R.; Xia, Y. *J. Am. Chem. Soc.* **2015**, *137*, 9922,
[95] For a further improvement of the methodology, see: Elling, B. R.; Su, J. K.; Feist, J. D.; Xia, Y. *Chem* **2019**, *5*, 2691.
[96] See references 43b, c, e, g, h for a more complete overview of cyclopropene cycloadditions.
[97] Wiberg, K. B.; Bartley, W. J. *J. Am. Chem. Soc.* **1960**, *82*, 6375
[98] Deem, M. L. *Synthesis* **1972**, *4*, 675.

and tetrazine proceeded extremely rapidly and afforded, after loss of nitrogen, a stable diazanorcaradiene (Figure 53, a).[99] The potential of this discovery was uncovered first by Devaraj and co-workers in the design of a cyclopropene tag for cycloadditions with fluorogenic tetrazines.[100] The small size of cyclopropenes, combined with the right design, resulted in an ideal dienophile for a rapid tetrazine cycloaddition. Quenched BODIPY-tetrazine fluorescent probes in phosphate buffer reacted efficiently with the designed cyclopropenes, and the cycloaddition elicited a strong fluorogenic response from the final product (Figure 53, b). The process was adapted in human cells containing cyclopropene-modified phospholipids for live-cell imaging (Figure 53, c). In the following years, the abovementioned [4+2]-cycloadditions with cyclopropenes unveiled the use of cyclopropenes as biorthogonal handles, strongly impacting the biological research field.[101,102]

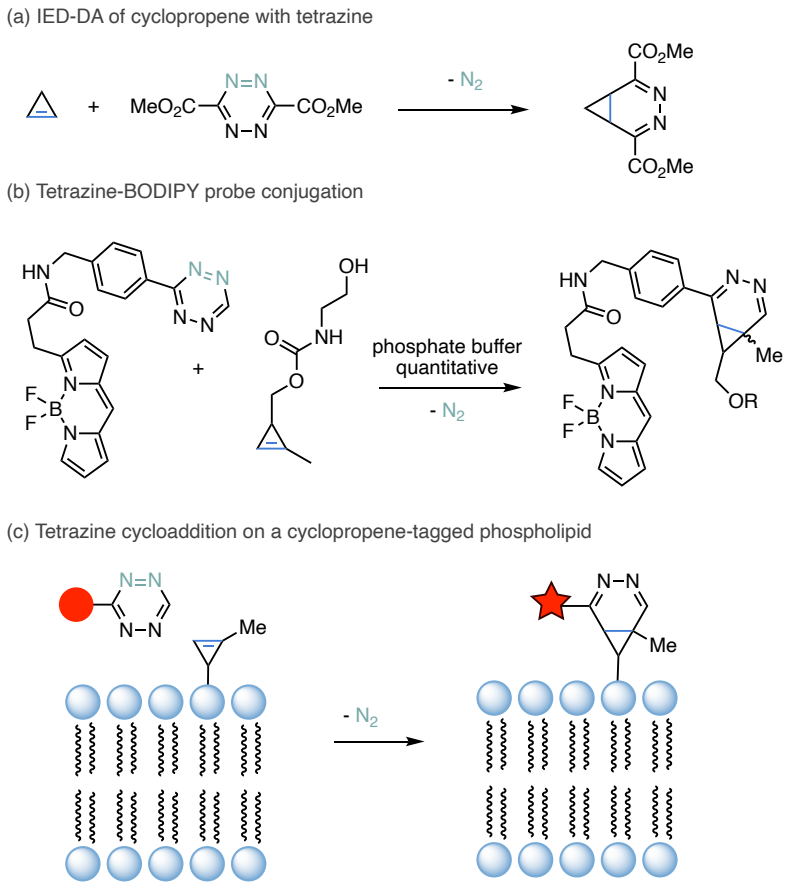


Figure 53 Cyclopropene Diels-Alder reactions and application in live-cell imaging

[99] Thalhammer, F.; Wallfahrer, U.; Sauer, J. *Tetrahedron Letters* **1990**, *31*, 6851.
[100] Yang, J.; Šečkute, J.; Cole, C. M.; Devaraj, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 7476.
[101] (a) Ravasco, J. M. J. M.; Monteiro, C. M.; Trindade, A. F. *Org. Chem. Front.* **2017**, *4*, 1167. (b) Oller-Salvia, B.; Kym, G.; Chin, J. W. *Angew. Chem. Int. Ed.* **2018**, *57*, 2831; (c) Wu, H.; Devaraj, N. K. *Acc. Chem. Res.* **2018**, *51*, 1249; (d) Row, R. D.; Prescher, J. A. *Acc. Chem. Res.* **2018**, *51*, 1073. (e) Hassenrück, J.; Wittmann, V. *Beilstein J. Org. Chem.* **2019**, *15*, 584.
[102] The use of cyclopropenes as biorthogonal agents is covered in Chapter 4.

Another representative example of cyclopropene cycloadditions is the Pauson-Khand reaction.[103] A first general scope for unsubstituted cyclopropenes in intermolecular Pauson-Khand reactions with terminal alkynes was described in 2001 by Pericàs and co-workers, affording cycloaddition products in good yields (Figure 54, a).[104] Fox later on expanded the scope and utility of intermolecular Pauson-Khand reactions by disclosing a study of the reactivity of chiral cyclopropenes in a highly diastereoselective, intermolecular Pauson-Khand reaction providing a single isomer of the cyclopentanone product (Figure 54, b).[105] In all these protocols, the cycloaddition took place at low temperatures (-30 or -35 ºC), highlighting the ease with which cyclopropene undergo such cycloadditions.

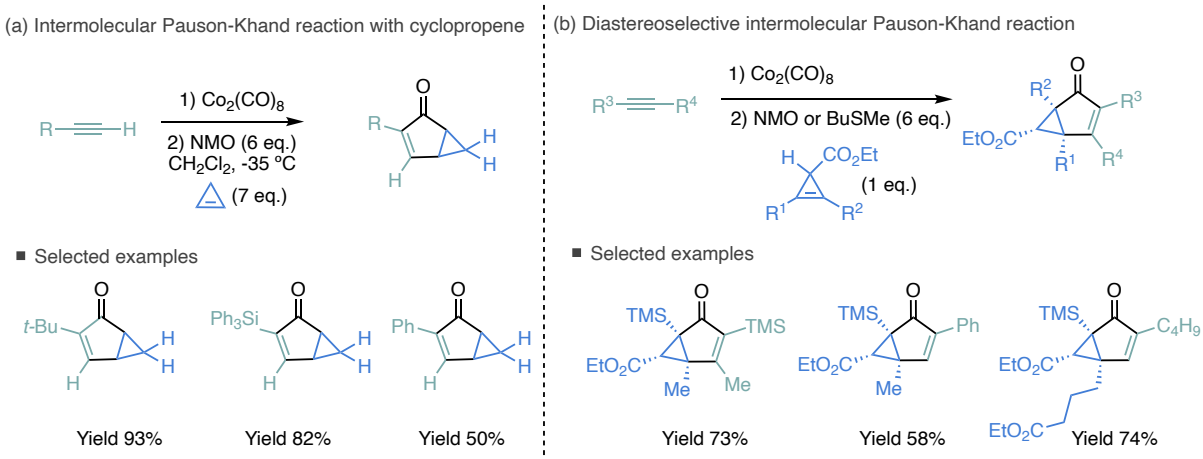


Figure 54 Pauson-Khand reactions with cyclopropenes

[103] For first reports, see: (a) Nuske, H.; Brase, S.; De Meijere, A. *Synlett* **2000**, *17*, 1467. (b) Witulski, B.; Gossmann, M. *Synlett* **2000**, *12*, 1793.
[104] Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2001**, *3*, 3193.
[105] Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2005**, *7*, 3593.

3.5 Regioselective synthesis of diverse cyclopropenes with cyclopropenium cations

3.5.1 Hypothesis of the project

Inspired by the reactivity of our novel class of CPCs with 1,3,5-trimethoxybenzene (see Chapter II), affording a tetrasubstituted cyclopropene with complete regioselectivity, we wondered if alternative nucleophiles could behave analogously. Reactions with nucleophiles are the most basic reactions with carbocations, and different examples have been reported previously with CPCs and carbon- and heteroatom-based nucleophiles.[106] If successful with carbon-based nucleophiles, the development of this novel synthetic route to cyclopropenes would provide solutions to problems observed in metal-catalyzed carbene transfer with diazo acetates.[107] In addition, if the synthetic route is efficient with hetereoatom-based nucleophiles too, this would provide access to new tetrasubstituted cyclopropenes not possible to make by any reaction currently available, because of the lack of heteroatom-substituted diazoacetates or alternative carbene sources.

3.5.2 Reaction optimization

Initial successful results were found when a solution of phenylmagnesium chloride (1.5 eq.) was added dropwise to a solution of CPC **3a** in dichloromethane at -50 ºC. With this protocol, the formation of the corresponding cyclopropene was almost quantitative (NMR yield 93%). A further practical improvement was implemented by increasing the reaction temperature to 0 ºC, affording the product in 95% NMR yield (Figure 55).

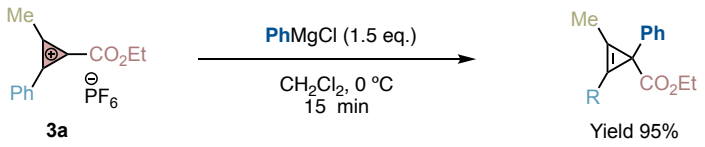


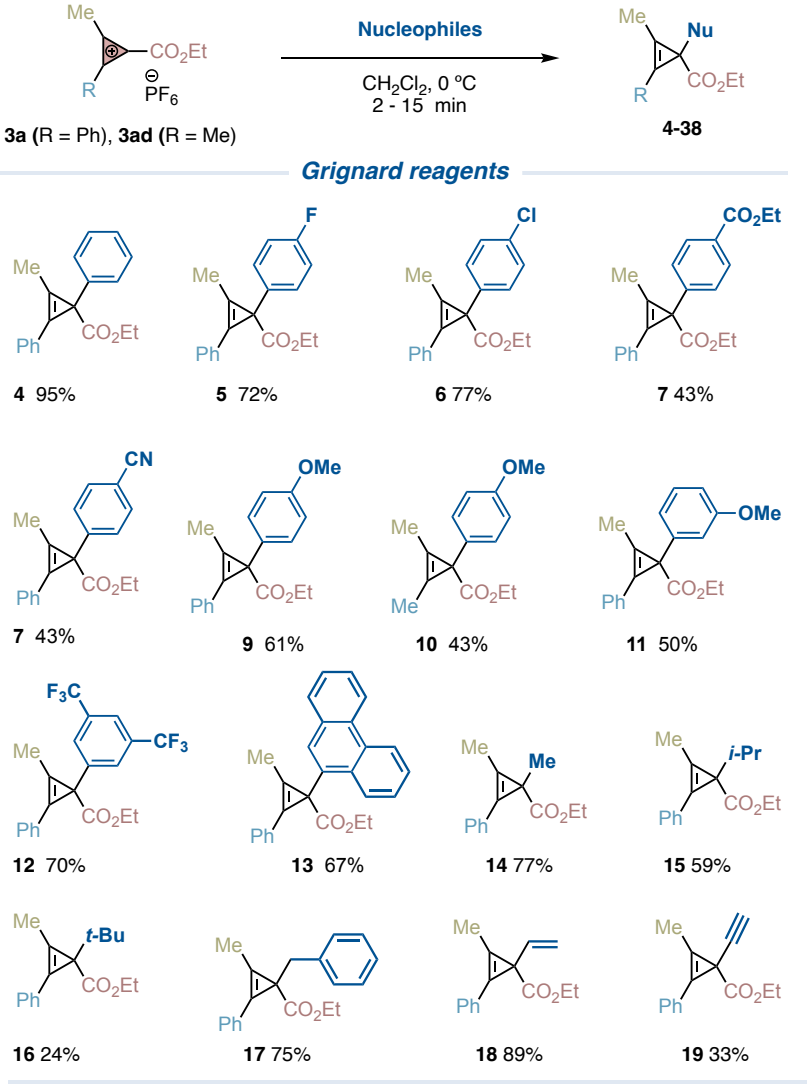
Figure 55 Optimized reaction conditions

3.5.3 Cyclopropene scope

We first focused our efforts on evaluating the reactivity of our cyclopropenium cations with carbon nucleophiles. We were delighted to observe that a variety of commercial or readily available aryl, alkyl, vinyl and alkynyl Grignard reagents provided instantaneous access to cyclopropenes **4-19** as single regioisomers and in high efficiency (Table 1).

[106] For examples, see Chapter II, Section 2.4.1. See also : Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371, pp 1385.
[107] See Section 3.3.2.

Table 1 Substrate scope: Grignard reagents[a]



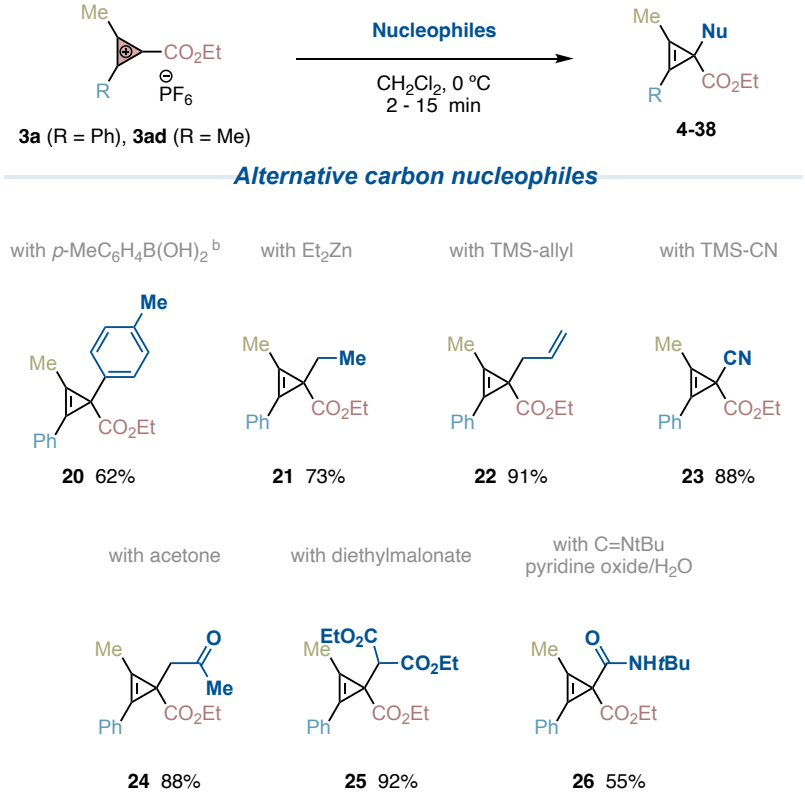
[a] Performed with **3** (0.1 mmol), nucleophile (0.15-0.2 mmol) CH_2Cl_2, 0 °C, 2-15 min.

Yields are reported on the basis of isolated products.

We then extended the scope to alternative carbon nucleophiles. Boronic acid (**20**), organozinc (**21**), organosilicon (**22**, **23**) as well as carbonyl (**24**, **25**) and isocyanide nucleophiles (**26**) performed well and in many cases, no chromatographic column was needed to obtain the corresponding cyclopropene product (Table 2).[108]

[108] The choice of Cs_2CO_3 as base in the reactions releasing a proton originates from preliminary screenings with aromatic substrates as nucleophiles, not relevant here. No re-optimization was performed for the carbon- and heteroatom-based nucleophiles presented in this section, as the choice of base did not appear crucial to the success of the reaction.

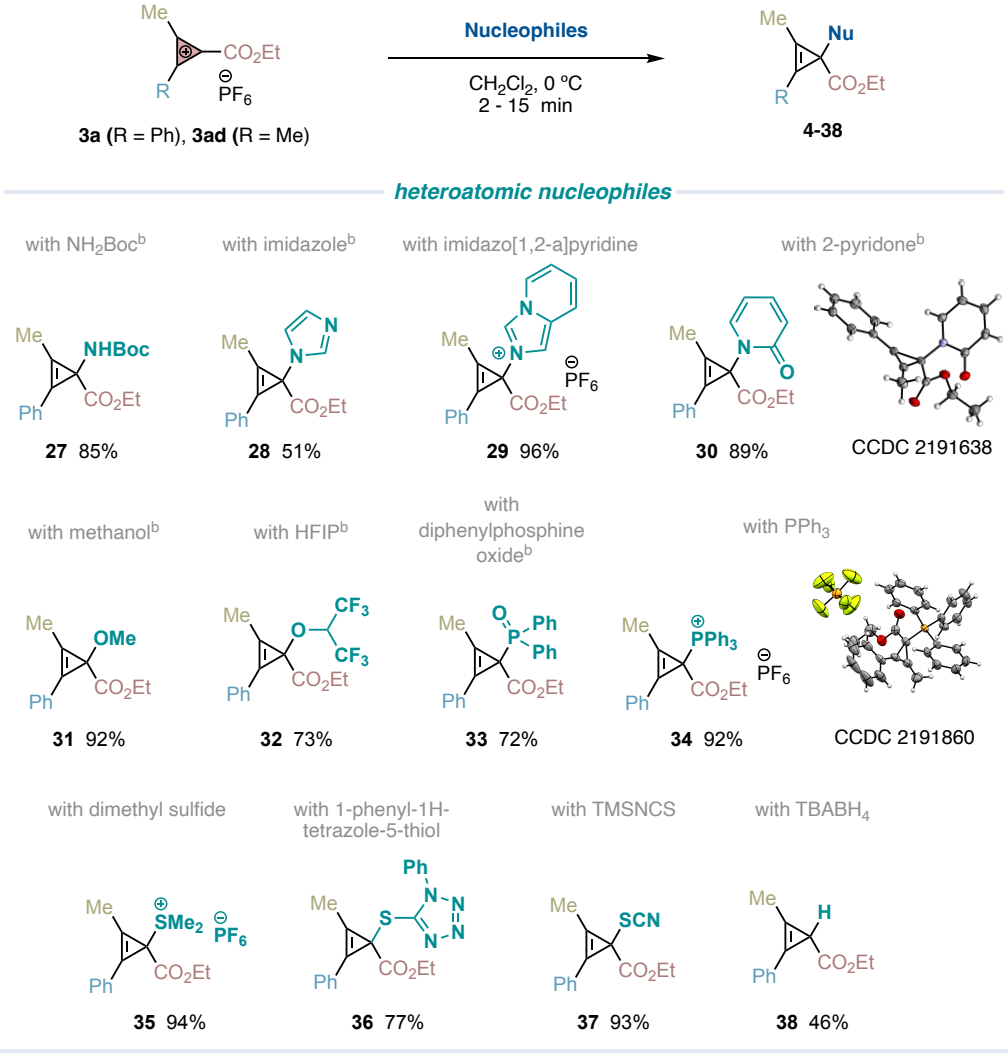
Table 2 Substrate scope: Alternative carbon nucleophiles[a]



[a] Performed with **3** (0.1 mmol), nucleophile (0.15-0.2 mmol) CH_2Cl_2, 0 °C, 2-15 min. Yields are reported on the basis of isolated products. [b] Cs_2CO_3 (0.1 mmol) was added as base.

The remarkable promiscuity observed of our CPCs to react with carbon nucleophiles encouraged us to question whether heteroatomic nucleophiles could work. A selection of commercial nitrogen, oxygen, phosphorous and sulfur nucleophiles provided cyclopropenes **27**-**37** with high efficiency (Table 3). In addition, a reaction carried out with tetrabutylammonium borohydride provided trisubstituted cyclopropene derivative **38** by the regioselective hydride attack to **3a**.

Table 3 Substrate scope: Heteroaromatic nucleophiles[a]



Performed with **3** (0.1 mmol), nucleophile (0.15-0.2 mmol), CH_2Cl_2, 0 °C, 2-15 min.
Yields are reported on the basis of isolated products.[b] Cs_2CO_3 (0.1 mmol) was added as base.

Notably, all kinds of nucleophiles underwent regioselective attack to the cyclopropenium carbon atom substituted with the ester group. In order to provide an explanation of the outstanding and intriguing regiocontrol observed in the nucleophilic addition to CPCs **3**, we calculated the geometry optimization and LUMO map using SPARTAN 20 at ωb97xd/6-31G(d) level. In Figure 56, it can clearly be appreciated that the carbon atom substituted with the ester group has the highest LUMO coefficient among the cyclopropenium carbon sites, thus suggesting that nucleophilic attack occurs under orbital control.

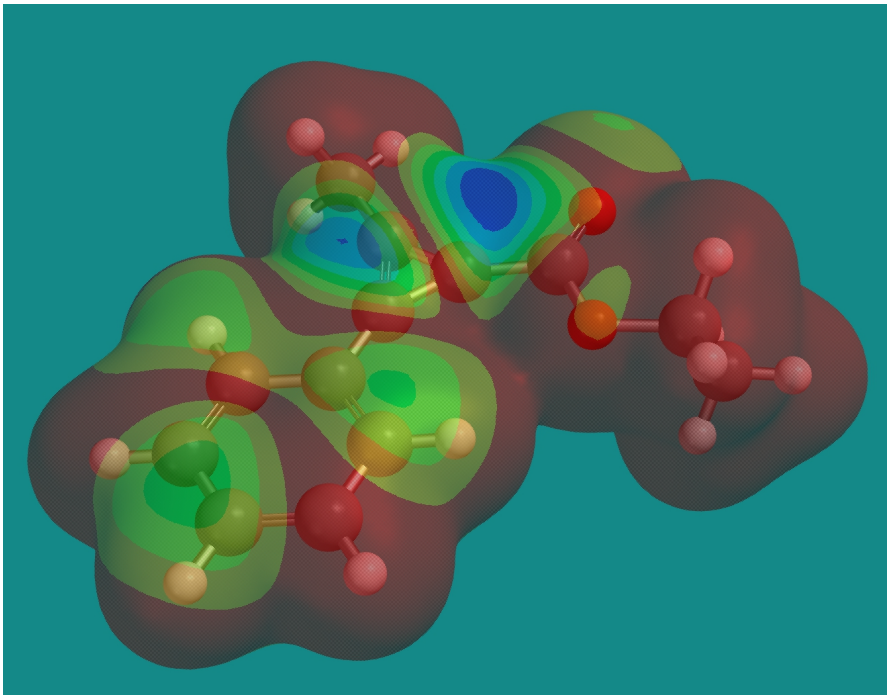


Figure 56 LUMO map of **3a** (Method: ωB97X-D, Basis set: 6-31G(D))

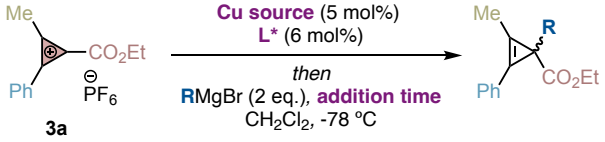
3.5.4 Attempts on an enantioselective synthesis of cyclopropenes [109]

Considering the outstanding efficiency of Grignard reagents with CPCs, initial attempts on an enantioselective version of our newly developed cyclopropenes synthesis were inspired by the reports of asymmetric copper-catalyzed Grignard additions developed by Feringa, Minaard and Harutyunyan.[110]

[109] Only the attempts to the asymmetric synthesis of cyclopropenes that involved the use of Grignard reagents as nucleophiles, and isolated CPCs as starting material are presented below. Alternative strategies as well as attempts not performed by the author of this Thesis are not discussed. No strategy for an asymmetric version of the cyclopropene synthesis from CPCs was discovered to date. This Section essentially aims at summarizing issues encountered and at presenting possible rationalizations.

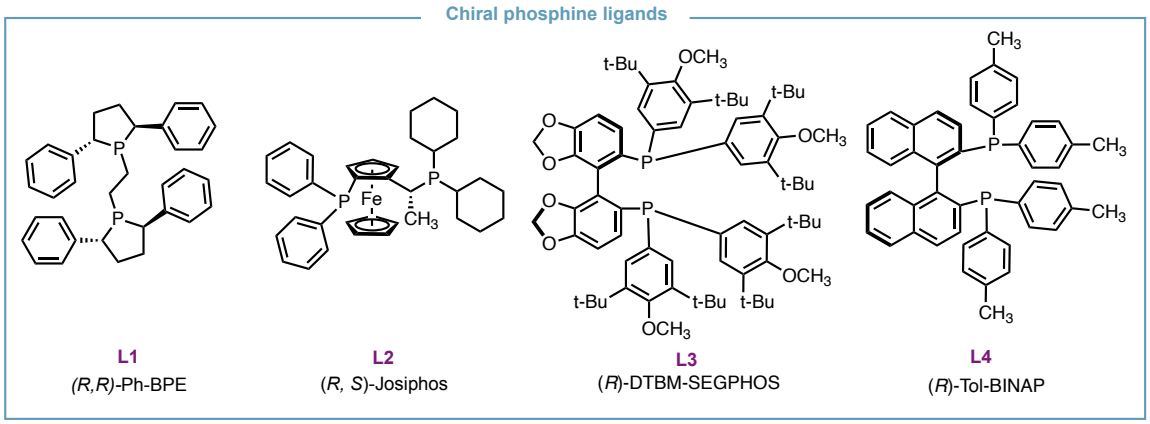
[110] For selected examples, see: (a) López, F.; Harutyunyan, S. R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 2752; (b) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Chem. Commun.* **2012**, *48*, 1478; (c) Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R. *Science* **2016**, *352*, 433; (d) Rong, J.; Collados, J. F.; Ortiz, P.; Jumde, R. P.; Otten, E.; Harutyunyan, S. R. *Nat. Commun.* **2016**, *7*, 1; (e) Guo, Y.; Harutyunyan, S. R. *Angew. Chem. Int. Ed.* **2019**, *58*, 12950.

Table 4 Attempts on the copper-catalyzed asymmetric Grignard addition with CPCs



entry	Cu source	L*	RMgBr	addition time (min)	NMR yield (%)	ee (%)
1	CuBr•SMe_2	L1	PhMgBr	5	90	0
2	CuBr•SMe_2	L2	PhMgBr	5	38	0
3	CuBr•SMe_2	L3	PhMgBr	5	65	0
4	CuBr•SMe_2	L4	PhMgBr	5	57	0
5	CuBr•SMe_2	L1	PhMgBr	30	37	0
6	CuBr•SMe_2	L2	PhMgBr	30	61	0
7	CuBr•SMe_2	L3	PhMgBr	30	70	0
8	CuBr•SMe_2	L4	PhMgBr	30	40	0
9	CuBr•SMe_2	L4	PhMgBr	30	78	0[a]
10	CuTc	L4	PhMgBr	30	n.d.	n.d.[a]
11	CuBr•SMe_2	L4	BnMgBr	30	n.d.	n.d[a]

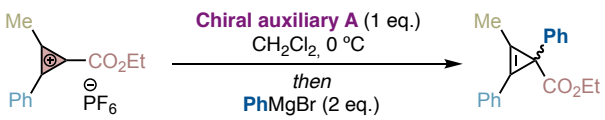
[a] Reaction performed with a stoechiometric amount of ligand.



It became rapidly clear that the high reactivity of the CPC impeded an efficient induction of chirality by copper catalysis. Either the background reaction was taking place, affording the racemic product (Table 1, entries 1-9), or side-reactions with copper sources or ligands afforded mixtures of products instead (entries 10-11).

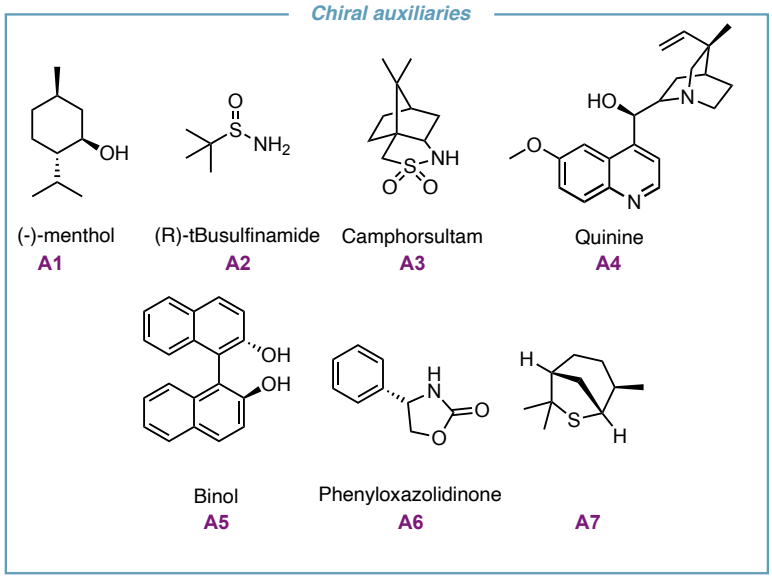
We also turned our attention to the use of chiral auxiliaries as a way to stoichiometrically harness the reactivity of the CPC. Selected examples are shown in Table 5.

Table 5 Selected examples of attempts with chiral auxiliaries



entry	Chiral auxiliary A	NMR yield (%)[a]	ee (%)
1	A1	0	n.d
2	A2	0	n.d
3	A3	n.d. (31)	0
4	A4	n.d. (20)	0
5	A5	n.d.(42)	0
6	A6	0	n.d.
7[b,c]	A7	n.d.	0

[a] Isolated yields are shown in brackets. [b] A 1 :1 mixture of PhCl : DCM was used as solvent. [c] The reaction was run at -50 °C.



Here again, two scenarios were distinguished. In the first case, no reaction was observed between the chiral auxiliary and the CPC, which allowed only for the background reaction to occur upon addition of the Grignard reagent (Table 5, entries 3-5). Alternatively, a reaction did occur between the CPC and the chiral auxiliary, which later prevented further reaction and addition of the Grignard reagent and successful chiral induction upon (entries 1, 2 and 6, 7).

As general—yet temporary—conclusion, the cationic nature of the CPC represents so far a major hurdle in the development of an asymmetric cyclopropene synthesis from CPCs. Overall, the efficiency with which diverse racemic cyclopropenes are synthesized, presented in Section 3.5.3, acts here as a double-edged sword: the reactivity of the cyclopropenium salt revealed to be challenging to harness for a successful asymmetric induction until now. A conceivable strategy could reside in synthesizing stereochemically biased CPCs and use them as synthons. The introduction of a chiral auxiliary on the alkyne prior to the synthesis of the CPC would represent a first access to stereochemically biased CPCs. Alternatively, replacing PF_6^- with a chiral counteranion in the $I^{(III)}$ salt used as carbyne synthon could also access CPCs containing chiral information. Such anions could be found

in the conjugated bases of chiral carboxylic and sulfonic acids, issued or derived from the chiral pool (Figure 57).[111] Chiral borate or phosphate anions could also be envisaged.[112]

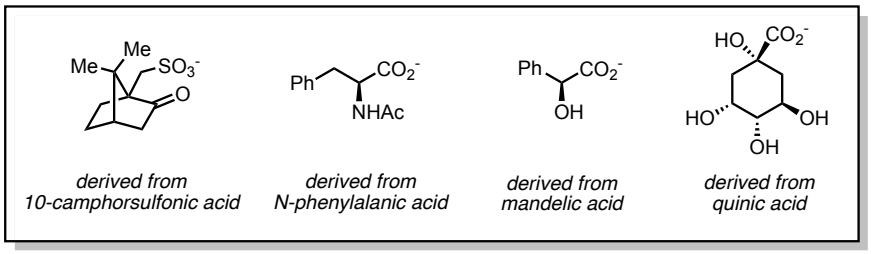


Figure 57 Chiral anions derived from the chiral pool

3.6 Conclusions

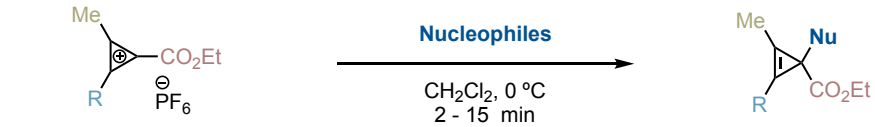
Herein, we have demonstrated the synthetic utility of our CPCs with the regioselective attack of a broad range of carbon and heteroatomic nucleophiles that provided valuable persubstituted cyclopropenes. The reaction occurs in simple conditions and provides an almost instantaneous access to a plethora of novel cyclopropene derivatives with unknown reactivity, which promise applications in reaction discovery and in the construction of complex skeletons. The outstanding regioselectivity of the reaction is corroborated by the LUMO map of the CPC, showing that the carbon atom substituted with the ester group holds the highest LUMO coefficient and confirming that the reaction happens under orbital control. Importantly, our novel class of ester-substituted CPCs allows to circumvent issues previously reported in nucleophilic additions of Grignard reagents to asymmetric CPCs, giving rise to mixtures of regioisomers.[113]

[111] Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935.
[112] For reviews on chiral anions and their use in catalysis, see: (a) Lacour, J.; Moraleda, D. *Chem. Commun.* **2009**, 7073; (b) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603.
[113] See Chapter II, Section 2.4.1.

3.7 Experimental section

General information. All reagents were used as purchased and used with no further purification. Ethyl diazoacetate, (≥13 wt.% dichloromethane) was purchased from Aldrich (Ref. E22201) and used without further purification. Anhydrous solvents were dried by passing through an activated alumina column on a PureSolvTM solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography (TLC) was carried out using aluminum sheets with 0.2 mm of silica gel (Merck GF234). Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of potassium permanganate or vanillin stain followed by heating. Flash column chromatography was performed on silica gel (Aldrich, 230-400 mesh) or neutral silica gel (Material Harvest Ltd., 230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. Unless otherwise stated, reactions were carried out under argon atmosphere. Yields refer to purified compounds unless otherwise noted. NMR spectra were recorded at 298 K on Bruker Avance 300, Bruker Avance 400 Ultrashield or Bruker Avance 500 Ultrashield apparatuses. Coupling constants (*J*) are quoted in hertz (Hz). Multiplicity is reported with the following abbreviations: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, sp = septet, m = multiplet, app = apparent. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Liquid chromatography-mass spectrometry (LC-MS) and gas chromatography-mass spectrometry (GC-MS) analysis were carried out in Agilent 1260 Infinity – 6130 Quadrupole and Agilent 7890B - 5977A MSD, respectively.

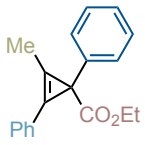
General procedure : Synthesis of cyclopropenes



3a (R = Ph), **3ad** (R = Me) **4-38**

To a 10 mL oven-dried tube equipped with a stirring bar was added the corresponding **CPC 3** (0.10 mmol, 35.0 mg for **3a** and 29.0 mg for **3ad**). For nucleophiles that generated acid, 1.0 equiv of Cs_2CO_3 (34.0 mg, 0.10 mmol) was added as base (cyclopropenes **27**, **28**, **30**, **31**, **32**, **33**). The tube was sealed before being evacuated and backfilled with argon. Then 0.5 mL of dry dichloromethane was added and the reaction was cooled to 0 °C. A solution of the corresponding nucleophile (0.15 - 0.20 mmol) in dichloromethane (0.5 mL) was added and the resulting mixture was stirred at 0 °C. For Grignard reagents, dropwise addition was needed. When the reaction was complete (no cation solid could be observed), the reaction mixture was quenched by sat. NH_4Cl. The resulting mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate, analyzed by ^1H NMR after removing the solvent. The crude residue was purified by column chromatography on silica gel to give the corresponding cyclopropene.

ethyl 2-methyl-1,3-diphenylcycloprop-2-ene-1-carboxylate (4)



Prepared according to the **general procedure B** using phenyl magnesium chloride (2 M solution in THF, 75 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a white solid (26.4 mg, 95% yield).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.46 – 7.26 (m, 7H), 7.24 – 7.16 (m, 1H), 4.21 (qd, *J* = 7.1, 1.9 Hz, 2H), 2.41 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

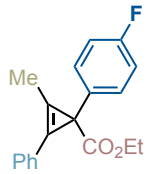
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 141.4, 129.4, 128.9, 128.8, 128.3, 128.1, 126.9, 126.3, 111.5, 108.6, 60.7, 35.6, 14.5, 9.7.

IR ν max (film, cm^{-1}) 2984, 2953, 1707, 1491, 1445, 1282, 1193, 1094, 1075, 1039, 1023, 760, 736, 693.

HRMS (ESI): m/z calculated for $C_{19}H_{19}O_2^+$ [M+H$^+$] m/z: 279.1380, found: 279.1379.

Note: A one pot procedure according to the **general procedure A** delivered the title compound in 82% and 78% NMR yield by employing Ph_2Zn or PhMgBr as the nucleophile.

ethyl 1-(4-fluorophenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (5)



Prepared according to the **general procedure B** using 4-fluorophenylmagnesium bromide (0.6 M solution in THF, 250 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by filtration with dichloromethane on a silica gel plug provided the title compound as a yellow oil (21.5 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.44 – 7.39 (m, 2H), 7.38 – 7.29 (m, 3H), 6.99 – 6.90 (m, 2H), 4.24 – 4.12 (m, 2H), 2.38 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

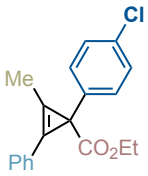
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 161.5 (d, *J* = 244.1 Hz), 137.2 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 7.9 Hz), 129.3, 128.98, 128.96, 114.9 (d, *J* = 21.2 Hz), 111.5, 108.5, 60.7, 34.9, 14.5, 9.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ -116.9.

IR ν max (film, cm^{-1}): 2980, 1712, 1602, 1507, 1446, 1216, 1158, 1095, 1034, 841, 759, 691, 580.

HRMS (ESI): m/z calculated for $C_{19}H_{18}FO_2^+$ [M+H$^+$] m/z: 297.1285, found: 297.1271.

ethyl 1-(4-chlorophenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (6)



Prepared according to the **general procedure B** using 4-chlorophenylmagnesium bromide (0.8 M solution in THF, 180 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by filtration with dichloromethane on a silica gel plug provided the title compound as a yellow oil (23.9 mg, 77% yield).

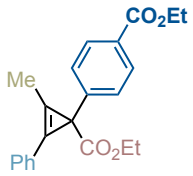
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.49 (m, 2H), 7.46 – 7.27 (m, 5H), 7.25 – 7.16 (m, 2H), 4.23 – 4.13 (m, 2H), 2.37 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 139.9, 132.0, 129.7, 129.3, 129.03, 128.99, 128.2, 126.5, 111.1, 108.2, 60.8, 35.0, 14.5, 9.6.

IR ν max (film, cm^{-1}): 2979, 1713, 1490, 1446, 1280, 1202, 1091, 1035, 1013, 841, 761, 692.

HRMS (ESI): m/z calculated for $C_{19}H_{18}ClO_2^+$ [M+H$^+$] m/z: 313.0990, found: 313.0996.

ethyl 4-(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)benzoate (7)



Prepared according to the **general procedure B** using 4-ethyl benzoate magnesium chloride (prepared from *i*PrMgCl·LiCl and ethyl 4-iodobenzoate, 0.5 M solution in THF, 300 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colorless oil (14.9 mg, 43% yield).

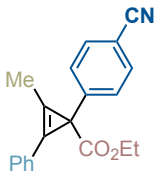
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.88 (m, 2H), 7.56 – 7.49 (m, 2H), 7.46 – 7.31 (m, 5H), 4.35 (q, *J* = 7.1 Hz, 2H), 4.18 (qd, *J* = 7.2, 3.7 Hz, 2H), 2.38 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 166.7, 146.7, 129.43, 129.39, 129.1, 129.0, 128.4, 128.2, 126.4, 110.8, 108.0, 60.9, 35.7, 14.5(2C), 9.6 (2C).

IR ν max (film, cm^{-1}): 2979, 1710, 1608, 1446, 1366, 1269, 1198, 1101, 1019, 760, 692.

HRMS (ESI): m/z calculated for $C_{22}H_{23}O_4^+$ [M+H$^+$] m/z: 351.1591, found: 351.1592.

ethyl 1-(4-cyanophenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (8)



Prepared according to the **general procedure B** using benzonitrile magnesium chloride (prepared from *i*PrMgCl·LiCl and 4-bromobenzonitrile, 1 M solution in THF, 150 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (21.9 mg, 72% yield).

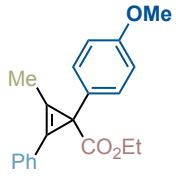
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.45 (m, 6H), 7.45 – 7.32 (m, 3H), 4.25 – 4.12 (m, 2H), 2.37 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 147.1, 131.9, 129.4 (2C), 129.1, 128.9, 125.9, 119.3, 110.4, 109.8, 107.5, 61.0, 35.6, 14.5, 9.6.

IR ν max (film, cm^{-1}): 2979, 2226, 1711, 1606, 1504, 1490, 1446, 1281, 1201, 1033, 849, 761, 691.

HRMS (ESI): m/z calculated for $C_{20}H_{18}NO_2^+$ [M+H$^+$] m/z: 304.1332, found: 304.1325.

ethyl 1-(4-methoxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (9)



Prepared according to the **general procedure B** using 4-methoxyphenylmagnesium bromide (0.5 M solution in THF, 300 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a yellow oil (18.8 mg, 61% yield).

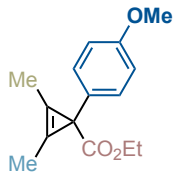
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.49 (m, 2H), 7.45 – 7.22 (m, 5H), 6.86 – 6.73 (m, 2H), 4.25 – 4.07 (m, 2H), 3.77 (s, 3H), 2.38 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 158.1, 133.6, 129.4, 129.3, 128.9, 128.8, 127.0, 113.6, 111.8, 108.8, 60.6, 55.4, 34.9, 14.6, 9.7.

IR ν max (film, cm^{-1}): 2937, 2839, 1709, 1606, 1510, 1488, 1445, 1270, 1247, 1201, 1176, 1031, 961, 841, 759, 690, 563.

HRMS (ESI): m/z calculated for $C_{20}H_{21}O_3^+$ [M+H$^+$] m/z: 309.1485, found: 309.1472.

ethyl 1-(4-methoxyphenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (10)



Prepared according to the **general procedure B** using 4-methoxyphenylmagnesium bromide (0.5 M solution in THF, 300 µL, 0.15 mmol) and **3ad** (29.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (10.5 mg, 43% yield).

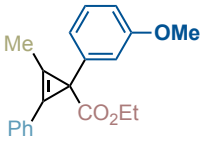
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 – 7.15 (m, 2H), 6.87 – 6.74 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.12 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 157.9, 134.9, 129.4, 113.6, 106.9, 60.4, 55.4, 34.2, 14.6, 8.9.

IR ν max (film, cm^{-1}): 2917, 1709, 1610, 1510, 1440, 1281, 1244, 1198, 1172, 1035, 840.

HRMS (ESI) calculated for $C_{15}H_{18}NaO_3^+$ $[M+Na]^+$ m/z: 269.1148, found: 269.1143.

ethyl 1-(3-methoxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (11)



Prepared according to the **general procedure B** using 3-methoxyphenylmagnesium bromide (0.8 M solution in THF, 180 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colorless oil (15.3 mg, 50% yield).

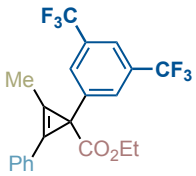
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.44 – 7.36 (m, 2H), 7.36 – 7.30 (m, 1H), 7.22 – 7.13 (m, 1H), 7.00 – 6.89 (m, 2H), 6.77 – 6.69 (m, 1H), 4.23 – 4.13 (m, 2H), 3.76 (s, 3H), 2.38 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 159.5, 143.1, 129.4, 129.1, 128.9, 128.8, 126.8, 120.8, 114.4, 113.6, 111.4, 108.6, 60.7, 55.3, 35.6, 14.6, 9.7.

IR ν max (film, cm^{-1}): 2979, 1712, 1607, 1580, 1488, 1446, 1289, 1229, 1034, 762, 693.

HRMS (ESI): m/z calculated for $C_{20}H_{21}O_2^+$ $[M+H^+]$ m/z: 309.1485, found: 309.1496.

ethyl 1-(3,5-bis(trifluoromethyl)phenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (12)



Prepared according to the **general procedure B** using 3,5-bis(trifluoromethyl)phenylmagnesium bromide (0.8 M solution in THF, 180 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a yellow oil (28.8 mg, 70% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 2H), 7.70 (s, 1H), 7.54 – 7.48 (m, 2H), 7.48 – 7.31 (m, 3H), 4.20 (qd, *J* = 7.1, 1.1 Hz, 2H), 2.41 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

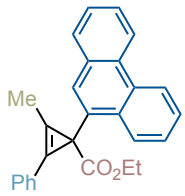
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 144.2, 131.3 (q, *J* = 33.0 Hz), 129.6, 129.4, 129.2, 128.4 (q, *J* = 3.0 Hz), 125.6, 123.6 (q, *J* = 273.7 Hz), 120.2 (q, *J* = 4.0 Hz), 110.0, 107.7, 61.2, 35.2, 14.4, 9.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6.

IR ν max (film, cm^{-1}): 2983, 1716, 1447, 1376, 1274, 1168, 1124, 896, 846, 761, 681.

HRMS (ESI): m/z calculated for $C_{21}H_{17}F_6O_2^+$ [M+H$^+$] m/z: 415.1127, found: 415.1134

ethyl 2-methyl-1-(phenanthren-9-yl)-3-phenylcycloprop-2-ene-1-carboxylate (13)



Prepared according to the **general procedure B** using phenanthrene magnesium chloride (prepared from *i*PrMgCl·LiCl and 9-bromophenantrene, 0.5 M solution in THF, 300 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (25.3 mg, 67% yield).

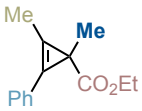
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 – 8.70 (m, 1H), 8.68 – 8.63 (m, 1H), 8.20 – 8.11 (m, 1H), 7.79 – 7.55 (m, 7H), 7.54 – 7.47 (m, 3H), 7.46 – 7.37 (m, 1H), 4.23 – 4.05 (m, 2H), 2.50 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 138.4, 132.5, 132.1, 130.7, 130.2, 129.3, 129.1, 129.0, 128.6, 127.7, 126.60, 126.56, 126.4, 126.31, 126.28, 125.6, 123.2, 122.6, 114.7, 109.8, 60.9, 34.8, 14.4, 10.3.

IR ν max (film, cm^{-1}): 2978, 1713, 1491, 1446, 1215, 1054, 745, 727.

HRMS (ESI): m/z calculated for $C_{27}H_{23}O_2^+$ [M+H$^+$] m/z: 379.1693, found: 379.1696.

ethyl 1,2-dimethyl-3-phenylcycloprop-2-ene-1-carboxylate (14)



Prepared according to the **general procedure B** using methyl magnesium bromide (3 M solution in Et_2O, 50.0 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by filtration with dichloromethane on a silica gel plug provided the title compound as a yellow oil (16.7 mg, 77% yield).

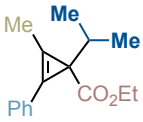
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 4H), 7.33 – 7.27 (m, 1H), 4.16 – 4.04 (m, 2H), 2.27 (s, 3H), 1.47 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.1, 129.1, 128.8, 128.4, 127.5, 111.9, 110.8, 60.3, 26.8, 18.3, 14.6, 9.5.

IR ν max (film, cm^{-1}): 2925, 1709, 1491, 1445, 1367, 1246, 1107, 1026, 802, 760, 692.

HRMS (ESI): m/z calculated for $C_{14}H_{17}O_2^+$ [M+H$^+$] m/z: 217.1223, found: 217.1216.

ethyl 1-isopropyl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (15)



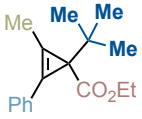
Prepared according to the **general procedure B** using the corresponding isopropylmagnesium chloride lithium chloride (1.3 M solution in THF, 116 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (14.5 mg, 59% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.39 (m, 2H), 7.40 – 7.33 (m, 2H), 7.32 – 7.27 (m, 1H), 4.14 – 4.05 (m, 2H), 2.91 – 2.65 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H), 0.88 (d, J = 6.7 Hz, 4H), 0.81 (d, J = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.2, 129.2, 128.6, 128.34, 128.25, 109.8, 109.3, 60.1, 37.5, 29.0, 21.2, 14.6, 10.8.

IR ν max (film, cm^{-1}): 2957, 1711, 1242, 1055.

HRMS (ESI): m/z calculated for $C_{16}H_{21}O_2^+$ [M+H$^+$] m/z: 245.1536, found: 245.1531.

ethyl 1-(*tert*-butyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (16)



Prepared according to the **general procedure B** using *tert*-butyl magnesium bromide (2 M solution in THF, 75 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude

reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (6.1 mg, 24% yield).

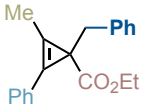
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.41 – 7.27 (m, 3H), 4.11 – 4.00 (m, 2H), 2.33 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.08 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 129.8, 129.2, 128.7, 128.1, 112.0, 111.3, 59.7, 40.0, 34.9, 29.6, 14.5, 10.7.

IR ν max (film, cm^{-1}): 2923, 2854, 1716, 1462, 1214.

HRMS (ESI): m/z calculated for $C_{17}H_{23}O_2^+$ [M+H$^+$] m/z: 259.1693, found: 259.1698.

ethyl 1-benzyl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (17)



Prepared according to the **general procedure B** using benzylmagnesium bromide (1 M solution in THF, 150 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colorless oil (21.9 mg, 75% yield).

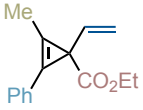
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 5H), 7.19 – 7.10 (m, 5H), 4.12 (qd, *J* = 7.1, 2.0 Hz, 2H), 3.55 (d, *J* = 14.2 Hz, 1H), 3.09 (d, *J* = 14.3 Hz, 1H), 2.12 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 140.5, 129.7, 129.2, 128.7, 128.5, 128.1, 127.4, 125.9, 110.7, 109.6, 60.5, 38.6, 32.8, 14.5, 10.1.

IR ν max (film, cm^{-1}): 3027, 2915, 1708, 1492, 1446, 1255, 1144, 1076, 1048, 756, 691.

HRMS (ESI): m/z calculated for $C_{20}H_{21}O_2^+$ [M+H$^+$] m/z: 293.1536, found: 293.1525.

ethyl 2-methyl-3-phenyl-1-vinylcycloprop-2-ene-1-carboxylate (18)



Prepared according to the **general procedure B** using vinyl magnesium bromide (0.8 M solution in Et_2O, 190 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by filtration with dichloromethane on a neutral silica gel plug provided the title compound as a yellow oil (20.3 mg, 89% yield).

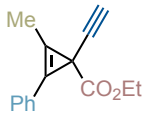
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 2H), 7.41 – 7.35 (m, 2H), 7.35 – 7.27 (m, 1H), 6.82 (dd, *J* = 17.4, 10.7 Hz, 1H), 4.94 (dd, *J* = 10.7, 1.4 Hz, 1H), 4.80 (dd, *J* = 17.5, 1.5 Hz, 1H), 4.23 – 4.05 (m, 2H), 2.29 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 137.4, 129.5, 128.83, 128.76, 125.9, 112.5, 107.5, 105.3, 60.6, 33.4, 14.6, 8.6.

IR ν max (film, cm^{-1}): 2979, 1714, 1491, 1446, 1367, 1253, 1063, 905, 761, 692.

HRMS (ESI): m/z calculated for $C_{15}H_{17}O_2^+$ [M+H$^+$] m/z: 229.1223, found: 229.1213.

ethyl 1-ethynyl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (19)



Prepared according to the **general procedure B** using ethynylmagnesium bromide (0.5 M solution in THF, 300 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by column chromatography on neutral silica gel provided the title compound as a colorless oil (7.5 mg, 33% yield).

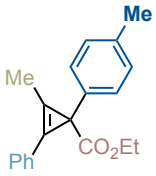
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.45 – 7.34 (m, 3H), 4.26 – 4.16 (m, 2H), 2.35 (s, 3H), 2.12 (s, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 172.7, 129.5, 129.0, 126.9, 125.0, 107.0, 106.3, 83.7, 67.1, 61.6, 23.5, 14.5, 9.2.

IR ν max (film, cm^{-1}): 3286, 2981, 1721, 1447, 1367, 1246, 1082, 1053, 762, 692.

HRMS (ESI): m/z calculated for $C_{15}H_{14}NaO_2^+$ [M+Na$^+$] m/z: 249.0886, found: 249.0882.

ethyl 2-methyl-3-phenyl-1-(*p*-tolyl)cycloprop-2-ene-1-carboxylate (20)



Prepared according to the **general procedure B** using *p*-tolylboronic acid (27.2 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol) with Cs_2CO_3. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (18.2 mg, 62% yield).

This compound was also prepared according to the **general procedure B** using *p*-toluylmagnesium bromide (0.5 M solution in THF, 300 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (22.0 mg, 75% yield).

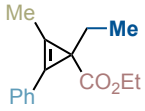
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.53 (m, 2H), 7.45 – 7.38 (m, 2H), 7.37 – 7.31 (m, 1H), 7.30 – 7.25 (m, 2H), 7.14 – 7.04 (m, 2H), 4.25 – 4.15 (m, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 138.3, 135.8, 129.4, 128.9, 128.9, 128.8, 128.2, 127.0, 111.7, 108.7, 60.6, 35.3, 21.2, 14.6, 9.7.

IR ν max (film, cm^{-1}): 2920, 1711, 1511, 1444, 1267, 1204, 1180, 1055, 759, 691.

HRMS (ESI): m/z calculated for $C_{20}H_{21}O_2^+$ [M+H$^+$] m/z: 293.1536, found: 293.1535

ethyl 1-ethyl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (21)



Prepared according to the **general procedure B** using diethylzinc (0.85 M solution in THF, 180 µL, 0.15 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by filtration with dichloromethane on a silica gel plug provided the title compound as a yellow oil (16.8 mg, 73% yield).

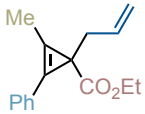
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.33 (m, 4H), 7.32 – 7.26 (m, 1H), 4.16 – 4.04 (m, 2H), 2.30 (s, 3H), 2.09 – 1.94 (m, 2H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 129.1, 128.7, 128.4, 128.0, 110.8, 109.7, 60.2, 32.6, 24.6, 14.6, 11.9, 10.3.

IR ν max (film, cm^{-1}): 2961, 2930, 1711, 1446, 1232, 1125, 1088, 1036, 760, 692.

HRMS (ESI): m/z calculated for $C_{15}H_{19}O_2^+$ [M+H$^+$] m/z: 231.1380, found: 231.1377.

ethyl 1-allyl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (22)



Prepared according to the **general procedure B** using allyltrimethylsilane (23.0 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (22.1 mg, 91% yield).

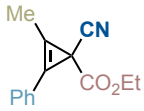
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.42 – 7.36 (m, 2H), 7.35 – 7.29 (m, 1H), 5.82 (ddt, *J* = 17.2, 10.1, 7.1 Hz, 1H), 5.07 – 4.98 (m, 1H), 4.98 – 4.90 (m, 1H), 4.20 – 4.05 (m, 2H), 2.85 (dd, *J* = 13.6, 7.2 Hz, 1H), 2.62 (dd, *J* = 14.6, 7.0 Hz, 1H), 2.31 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 136.7, 129.1, 128.6, 128.4, 127.5, 115.9, 110.9, 109.7, 60.2, 37.0, 31.0, 14.4, 10.1.

IR ν max (film, cm^{-1}): 2976, 1876, 1708, 1637, 1489, 1445, 1269, 1220, 1169, 1121, 912, 760.

HRMS (ESI) calculated for $C_{16}H_{19}O_2^+$ [M+H]$^+$ m/z: 243.1380, found: 243.1372.

ethyl 1-cyano-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (23)



Prepared according to the **general procedure B** using trimethylsilyl cyanide (19.8 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). The reaction was quenched with sat. $NaHCO_3$. Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (20.0 mg, 88% yield).

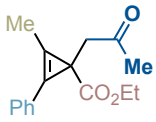
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.38 (m, 5H), 4.37 – 4.14 (m, 2H), 2.36 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 130.5, 129.6, 129.1, 123.1, 119.2, 103.7, 103.5, 62.4, 21.7, 14.3, 9.2.

IR ν max (film, cm^{-1}): 2982, 2233, 1731, 1367, 1251, 1084, 1057, 814, 762.

HRMS (ESI) calculated for $C_{14}H_{14}NO_2^+$ $[M+H]^+$ m/z: 228.1019, found: 228.1016.

ethyl 2-methyl-1-(2-oxopropyl)-3-phenylcycloprop-2-ene-1-carboxylate (24)



Prepared according to the **general procedure B** using acetone (1.0 mL) and **3a** (35.0 mg, 0.10 mmol) without Cs_2CO_3. Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (22.8 mg, 88% yield).

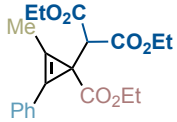
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.36 – 7.30 (m, 1H), 4.17 – 4.04 (m, 2H), 3.27 (d, *J* = 17.2 Hz, 1H), 2.58 (d, *J* = 17.2 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 175.5, 129.2, 128.7, 128.6, 127.0, 111.3, 110.0, 60.5, 48.0, 30.3, 28.4, 14.3, 10.1.

IR ν max (film, cm^{-1}): 2979, 1879, 1706, 1490, 1445, 1359, 1269, 1222, 1152, 1098, 1072, 1026, 876.

HRMS (ESI) calculated for $C_{16}H_{19}O_3^+$ $[M+H]^+$ m/z: 259.1329, found: 259.1323.

diethyl 2-(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)malonate (25)



Prepared according to the **general procedure B** using sodium diethyl malonate (0.30 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (33.1 mg, 92% yield).

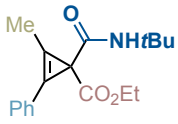
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.31 (m, 1H), 4.48 (s, 1H), 4.24 – 4.09 (m, 4H), 4.06 – 3.98 (m, 1H), 3.93 – 3.84 (m, 1H), 2.38 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 168.8, 168.5, 129.4, 128.7, 128.5, 126.6, 109.5, 107.6, 61.3, 61.1, 60.9, 55.4, 31.7, 14.3, 14.0, 13.6, 9.8.

IR ν max (film, cm^{-1}): 2979, 1728, 1446, 1367, 1317, 1253, 1175, 1033, 762.

HRMS (ESI) calculated for $C_{20}H_{24}NaO_6^+$ $[M+Na]^+$ m/z: 383.1465, found: 383.1469.

ethyl 1-(tert-butylcarbamoyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (26)



Prepared according to the **general procedure B** using *tert*-butyl isocyanide (19.6 mg, 0.20 mmol), pyridine 1-oxide (18.8 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Once the reaction finished and warmed to room temperature, 3.0 mL of water were added and the mixture was stirred for 10 min. The reaction mixture was then extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 4/1) provided the title compound as a colourless oil (16.6 mg, 55% yield).

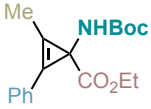
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (br, 1H), 7.51 – 7.31 (m, 5H), 4.21 – 4.00 (m, 2H), 2.36 (s, 3H), 1.42 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 168.6, 129.3, 128.9, 128.7, 125.6, 103.3, 102.3, 60.9, 51.1, 35.5, 29.0, 14.2, 9.3.

IR ν max (film, cm^{-1}): 3344, 2962, 1697, 1653, 1539, 1456, 1363, 1290, 1077, 841.

HRMS (ESI) calculated for $C_{18}H_{24}NO_3^+$ $[M+H]^+$ m/z: 302.1751, found: 302.1744.

ethyl 1-((tert-butoxycarbonyl)amino)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (27)



Prepared according to the **general procedure B** using *tert*-butyl carbamate (23.4 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 2/1) provided the title compound as a colourless oil (27.1 mg, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 5.9 Hz, 2H), 7.45 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 5.52 (br, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 1.47 (s, 9H), 1.23 (t, *J* = 6.6 Hz, 3H).

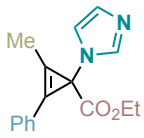
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 156.4, 129.3, 129.1, 128.8, 125.8, 111.2, 110.5, 79.3, 61.1, 40.1, 28.4, 14.3, 9.9.

IR ν max (film, cm^{-1}): 2974, 1705, 1489, 1364, 1255, 1166, 1049, 919.

HRMS (ESI) calculated for $C_{18}H_{23}NNaO_4^+$ $[M+Na]^+$ m/z: 340.1519, found: 340.1522.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(1H-imidazol-1-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (28)



Prepared according to the **general procedure B** using imidazole (13.6 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 1/1 to 1/10) provided the title compound as a yellow oil (13.8 mg, 51% yield).

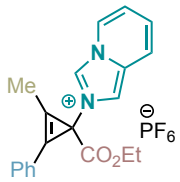
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.58 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.53 – 7.43 (m, 3H), 7.05 – 7.00 (m, 2H), 4.28 – 4.16 (m, 2H), 2.46 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 137.1, 130.2, 129.32, 129.25, 128.4, 124.6, 119.1, 110.6, 110.4, 61.9, 44.0, 14.2, 9.5.

IR ν max (film, cm^{-1}): 2920, 1727, 1490, 1447, 1252, 1221, 1078, 1012, 840.

HRMS (ESI) calculated for $C_{16}H_{17}N_2O_2^+$ $[M+H]^+$ m/z: 269.1285, found: 269.1286.

1-(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)imidazo[1,2-a]pyridin-1-ium hexafluorophosphate (29)



Prepared according to the **general procedure B** using imidazo[1,2-a]pyridine (14.2 mg, 0.12 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 20/1) provided the title compound as a white solid (44.5 mg, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 6.7 Hz, 1H), 8.04 (d, *J* = 2.0 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.53 – 7.48 (m, 1H), 7.42 – 7.33 (m, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 2.59 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 140.1, 135.1, 131.1, 129.9, 129.8, 129.3, 124.5, 123.3, 118.1, 115.5, 111.3, 110.9, 108.9, 63.0, 46.3, 14.1, 9.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.6 (d, *J* = 712.0 Hz).

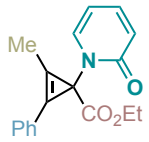
^{31}P NMR (162 MHz, $CDCl_3$) δ -141.2 (sp, *J* = 712.3 Hz).

IR ν max (film, cm^{-1}): 1725, 1645, 1515, 1448, 1262, 1207, 1067, 1019, 827, 755.

HRMS (ESI) calculated for $C_{20}H_{19}N_2O_2^+$ $[M\text{-}PF_6]^+$ m/z: 319.1441, found: 319.1437.

m.p. 70 ºC (decomp).

ethyl 2-methyl-1-(2-oxopyridin-1(2H)-yl)-3-phenylcycloprop-2-ene-1-carboxylate (30)



Prepared according to the **general procedure B** using 2-pyridone (19.0 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 2/5) provided the title compound as a yellow solid (26.4 mg, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.51 – 7.45 (m, 2H), 7.45 – 7.40 (m, 1H), 7.34 – 7.30 (m, 2H), 6.59 – 6.52 (m, 1H), 6.11 – 6.04 (m, 1H), 4.23 (qd, *J* = 7.1, 2.4 Hz, 2H), 2.53 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.4, 163.7, 139.7, 136.4, 129.8, 129.4, 129.1, 125.4, 121.3, 113.1, 110.7, 105.8, 61.6, 48.8, 14.2, 9.8.

IR ν max (film, cm^{-1}): 2922, 1724, 1648, 1586, 1534, 1443, 1363, 1284, 1246, 1169, 1149, 1062, 1009, 958, 918, 849.

HRMS (ESI) calculated for $C_{18}H_{17}NNaO_3^+$ $[M+Na]^+$ m/z: 318.1101, found: 318.1098.

m.p. 141-142 ºC.

A crystal of **30** was grown by slow evaporation of a solution of **30** in ethyl acetate and hexane at room temperature. The crystal structure was deposited at the Cambrige Cristallographic Data Center, CCDC No 2191638.

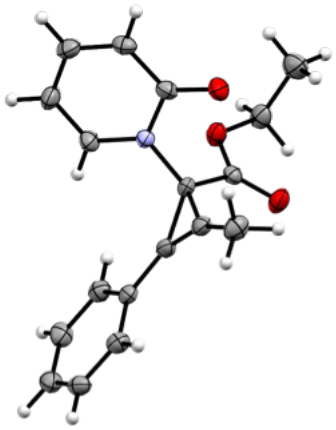
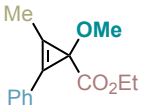


Figure 58 ORTEP diagram of **30**

ethyl 1-methoxy-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (31)



Prepared according to the **general procedure B** using methanol (0.2 mL) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (21.4 mg, 92% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.38 – 7.33 (m, 1H), 4.27 – 4.16 (m, 2H), 3.40 (s, 3H), 2.37 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

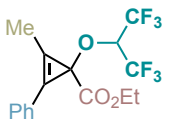
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 129.4, 129.3, 128.8, 126.2, 114.4, 114.1, 63.7, 61.0, 55.7, 14.4, 9.8.

IR ν max (film, cm^{-1}): 2978, 1718, 1490, 1445, 1245, 1165, 1092, 1064, 1034.

HRMS (ESI) calculated for $C_{14}H_{16}NaO_3^+$ $[M+Na]^+$ m/z: 255.0992, found: 255.0988.

Note: A one pot procedure according to the **general procedure A** delivered the title compound in 65% yield by employing methanol as the nucleophile and PhCOONa (1.5 equiv) as the base.

ethyl 1-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (32)



Prepared according to the **general procedure B** using HFIP (0.2 mL) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy.

Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (26.8 mg, 73% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.51 – 7.41 (m, 3H), 4.35 – 4.08 (m, 3H), 2.37 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

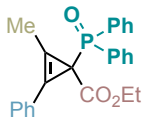
^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6, 130.3, 129.5, 129.1, 124.6, 121.3 (q, *J* = 279.1 Hz), 114.0, 113.2, 71.1 (q, *J* = 33.3 Hz), 67.4, 61.6, 14.2, 9.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.9 (m), -73.4 (m).

IR ν max (film, cm^{-1}): 1725, 1367, 1287, 1218, 1188, 1101, 1047, 891, 763.

HRMS (ESI) calculated for $C_{16}H_{14}F_6NaO_3^+$ $[M+Na]^+$ m/z: 391.0739, found: 391.0736.

ethyl 1-(diphenylphosphoryl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (33)



Prepared according to the **general procedure B** using diphenylphosphine oxide (40.4 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (ethyl acetate to dichloromethane/methanol = 20/1) provided the title compound as a colourless oil (29.0 mg, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.70 – 7.64 (m, 2H), 7.59 – 7.54 (m, 1H), 7.52 – 7.44 (m, 3H), 7.42 – 7.36 (m, 4H), 7.35 – 7.31 (m, 3H), 4.10 – 3.97 (m, 2H), 2.39 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H).

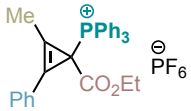
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 133.4, 132.9, 132.0, 131.6, 131.4, 131.3, 129.8, 129.3, 128.6, 128.3, 128.2, 125.4, 105.6, 103.9, 61.0, 34.0, 13.8, 10.4.

^{31}P NMR (202 MHz, $CDCl_3$) δ 36.0.

IR ν max (film, cm^{-1}): 2978, 1713, 1436, 1232, 1183, 1117, 1049, 754.

HRMS (ESI) calculated for $C_{25}H_{24}O_3P^+$ $[M+H]^+$ m/z: 403.1458, found: 403.1467.

(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)triphenylphosphonium hexafluorophosphate (34)



Prepared according to the **general procedure B** using triphenylphosphine (26.0 mg, 0.10 mmol) and **3a** (44.0 mg, 0.12 mmol). After removing the solvent, the residue was washed with diethyl ether (3 mL x 3). The title compound was provided as a white solid (56.2 mg, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 3H), 7.73 – 7.65 (m, 6H), 7.61 – 7.52 (m, 6H), 7.45 – 7.38 (m, 3H), 7.33 – 7.26 (m, 2H), 4.19 (q, *J* = 8.0 Hz, 2H), 2.26 (d, *J* = 1.2 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8 (d, *J* = 33.8 Hz), 135.2 (d, *J* = 3.0 Hz), 134.0 (d, *J* = 10.0 Hz), 131.2, 130.5, 130.3, 129.4 (d, *J* = 33.7 Hz), 123.0 (d, *J* = 3.3 Hz), 118.4 (d, *J* = 86.9 Hz), 106.8, 103.7, 63.4, 32.3 (d, *J* = 84.3 Hz), 13.8, 9.8 (d, *J* = 2.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.1 (d, *J* = 712.1 Hz).

^{31}P NMR (162 MHz, $CDCl_3$) δ 33.5, -141.2 (sp, *J* = 712.1 Hz).

IR ν max (film, cm^{-1}): 1711, 1438, 1259, 1109, 836.

HRMS (ESI) calculated for $C_{31}H_{28}O_2P^+$ $[M\text{-}PF_6]^+$ m/z: 463.1821, found: 463.1815.

m.p. 195-197 ºC.

Note: A one pot procedure according to the **general procedure A** delivered the title compound in >90% NMR yield by employing PPh_3 as the nucleophile.

A crystal of **34**was grown by slow evaporation of a solution of **34** in dichloromethane at room temperature. The crystal structure was deposited at the Cambrige Cristallographic Data Center, CCDC No 2191860.

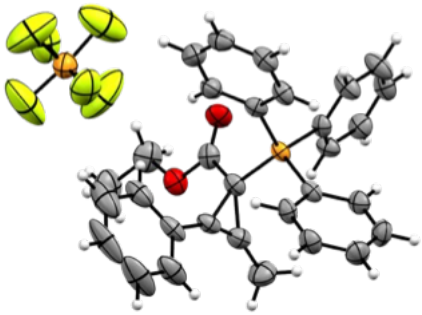
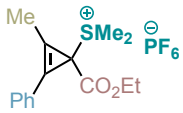


Figure 59 ORTEP diagram of **34**

(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)dimethylsulfonium hexafluorophosphate (35)



Prepared according to the **general procedure B** using dimethyl sulfide (14.9 mg, 0.24 mmol) and **3a** (70.0 mg, 0.20 mmol). After removing the solvent, the residue was washed with diethyl ether (3 mL x 3). The title compound was provided as a colourless foam (76.7 mg, 94% yield). *Note: the compound is very unstable at room temperature to collect high quality ^{13}C NMR and HRMS.*

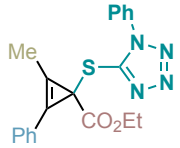
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.46 (m, 5H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.62 (s, 6H), 2.60 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 132.1, 129.9, 129.8, 121.9, 109.34, 109.28, 66.2, 64.1, 23.1, 14.0, 9.8.

^{19}F NMR (471 MHz, $CDCl_3$) δ -71.6 (d, *J* = 712.4 Hz).

^{31}P NMR (202 MHz, $CDCl_3$) δ -141.4 (sp, *J* = 712.2 Hz).

ethyl 2-methyl-3-phenyl-1-((1-phenyl-1H-tetrazol-5-yl)thio)cycloprop-2-ene-1-carboxylate (36)



Prepared according to the **general procedure B** using 1-phenyl-1H-tetrazole-5-thiol sodium salt (0.20 mmol, prepared from 1-phenyl-1H-tetrazole-5-thiol and NaH in 0.5 mL THF) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (29.0 mg, 77% yield).

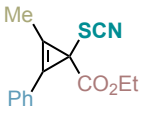
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 – 7.96 (m, 2H), 7.87 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.61 – 7.42 (m, 6H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.68 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 164.7, 135.0, 130.3, 130.2, 129.4, 129.2, 128.9, 124.2, 123.7, 110.2, 109.5, 62.2, 46.9, 14.3, 10.7.

IR ν max (film, cm^{-1}): 2978, 1731, 1594, 1494, 1446, 1347, 1298, 1245, 1058, 1032, 1021, 951, 836, 757.

HRMS (ESI) calculated for $C_{20}H_{18}N_4NaO_2S^+$ $[M+Na]^+$ m/z: 401.1043, found: 401.1042.

ethyl 2-methyl-3-phenyl-1-thiocyanatocycloprop-2-ene-1-carboxylate (37)



Prepared according to the **general procedure B** using trimethylsilyl isothiocyanate (26.3 mg, 0.20 mmol) and **3a** (35.0 mg, 0.10 mmol). Filtration through a pad of celite, followed by removal of the solvents gave the title compound as a colourless oil (24.2 mg, 93% yield).

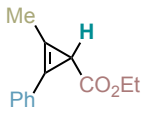
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 – 7.40 (m, 5H), 4.35 – 4.20 (m, 2H), 2.36 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 130.2, 129.5, 129.1, 123.9, 109.7, 109.1, 62.4, 44.8, 14.3, 8.9.

IR ν max (film, cm^{-1}): 2978, 2045, 1728, 1445, 1367, 1246, 1096, 1064, 1014, 918, 762.

HRMS (ESI) calculated for $C_{13}H_{13}O_2^+$ $[M-SCN]^+$ m/z: 201.0910, found: 201.0922.

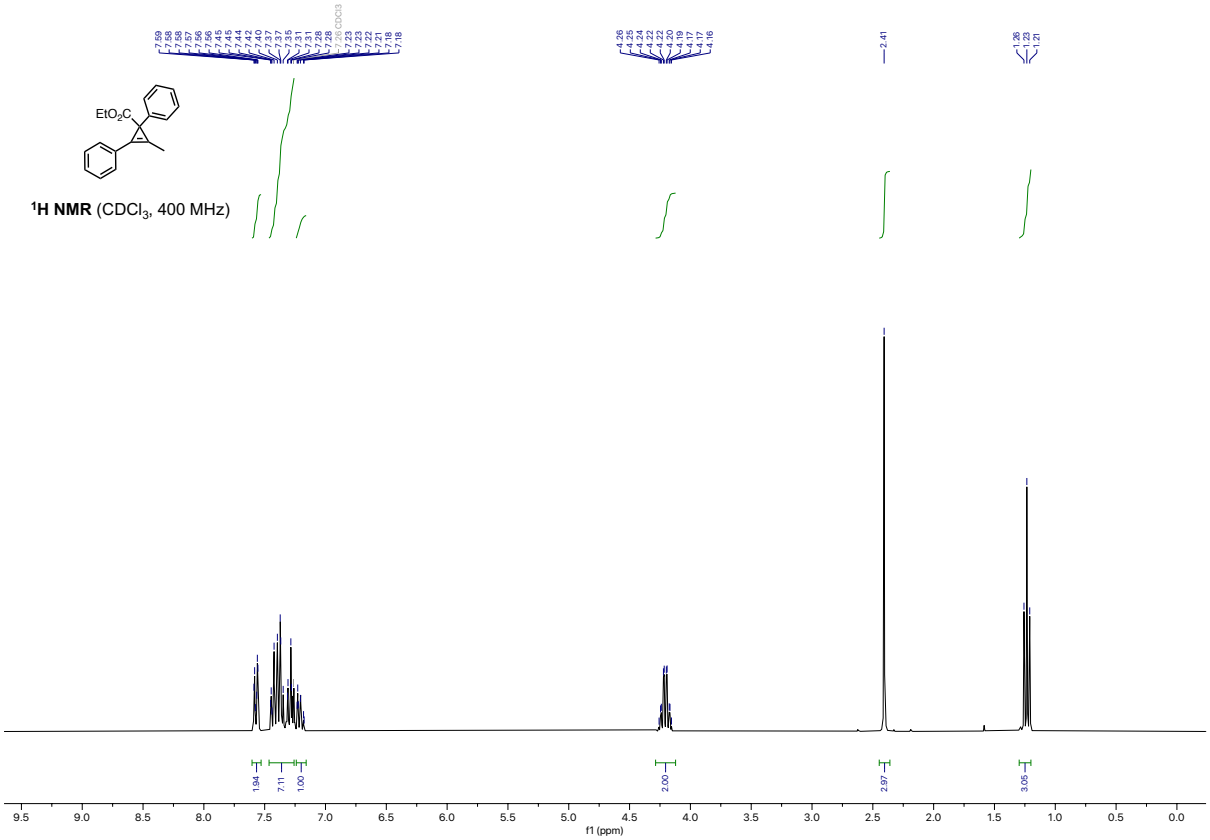
ethyl 2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (38)



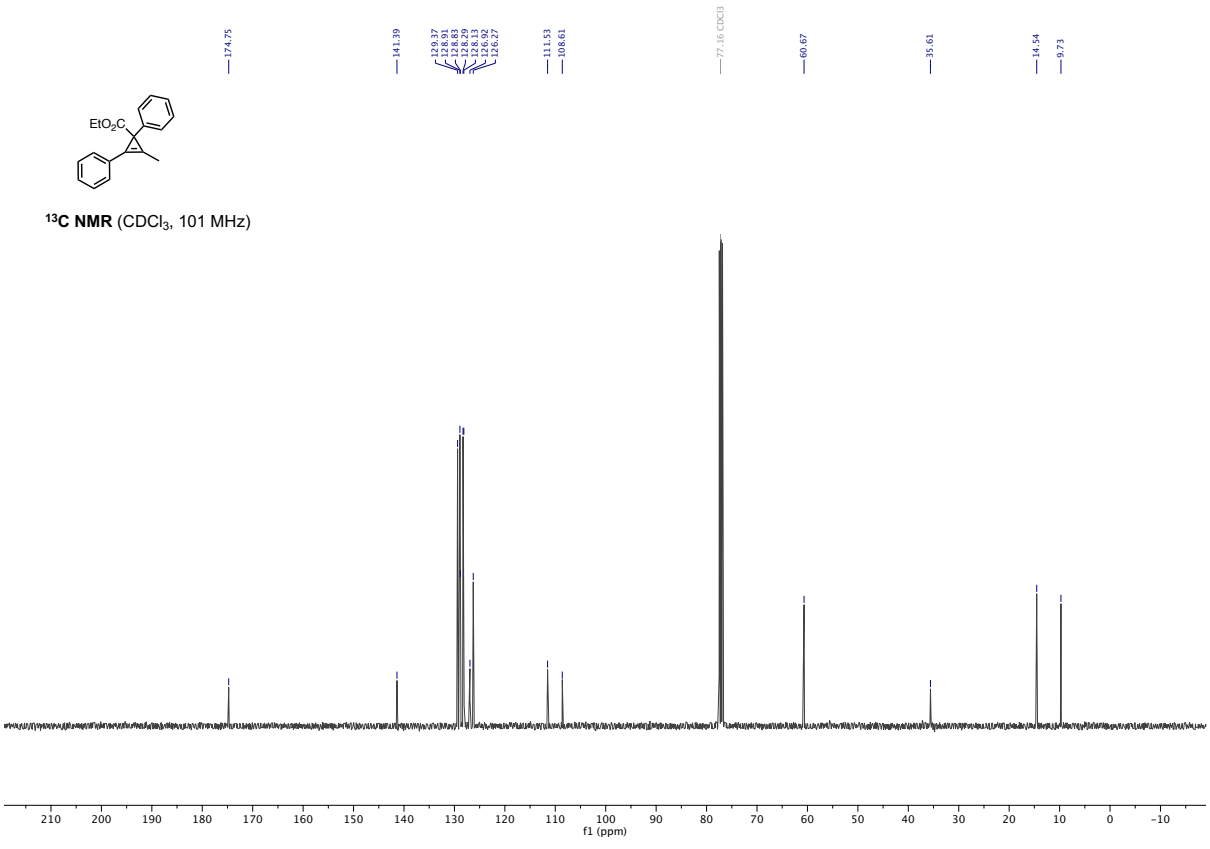
Prepared according to the **general procedure B** using tetrabutylammonium borohydride (78.0 mg, 0.30 mmol) and **3a** (35.0 mg, 0.10 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (9.3 mg, 46% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.36 – 7.30 (m, 1H), 4.23 – 4.10 (m, 2H), 2.45 (s, 1H), 2.35 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

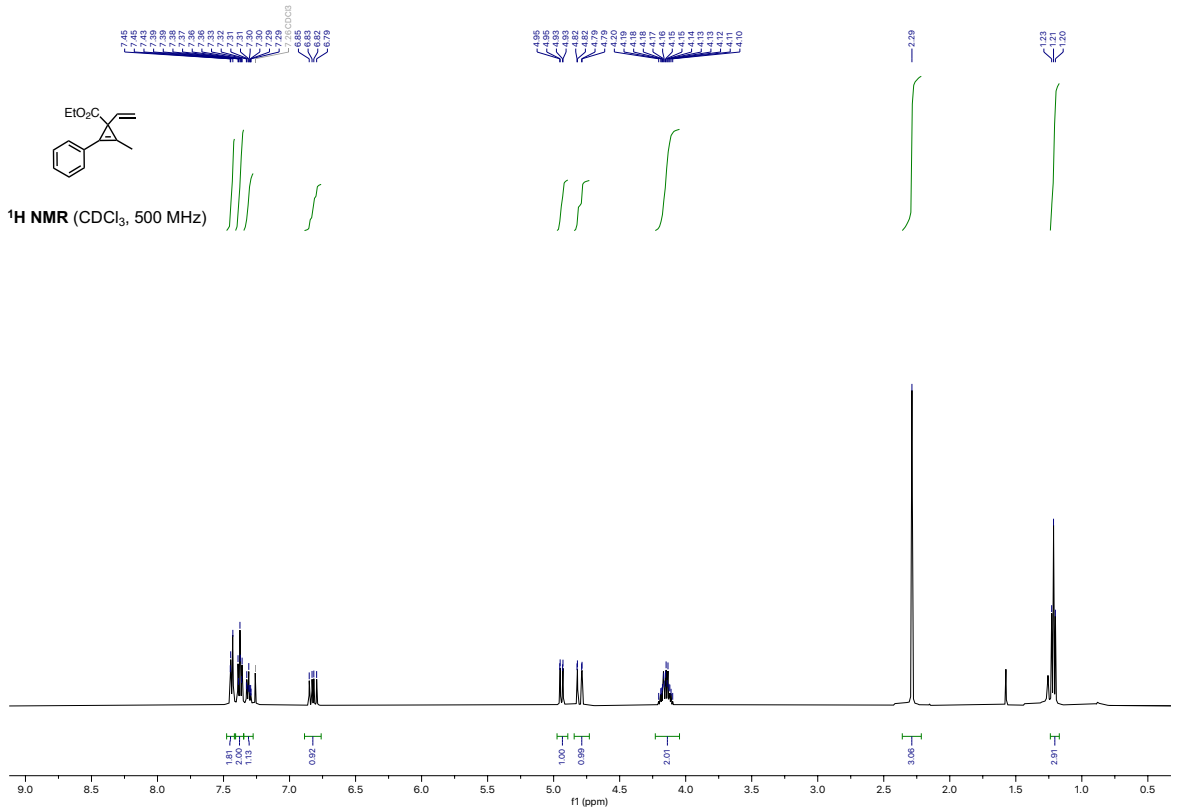
Selected NMR spectra

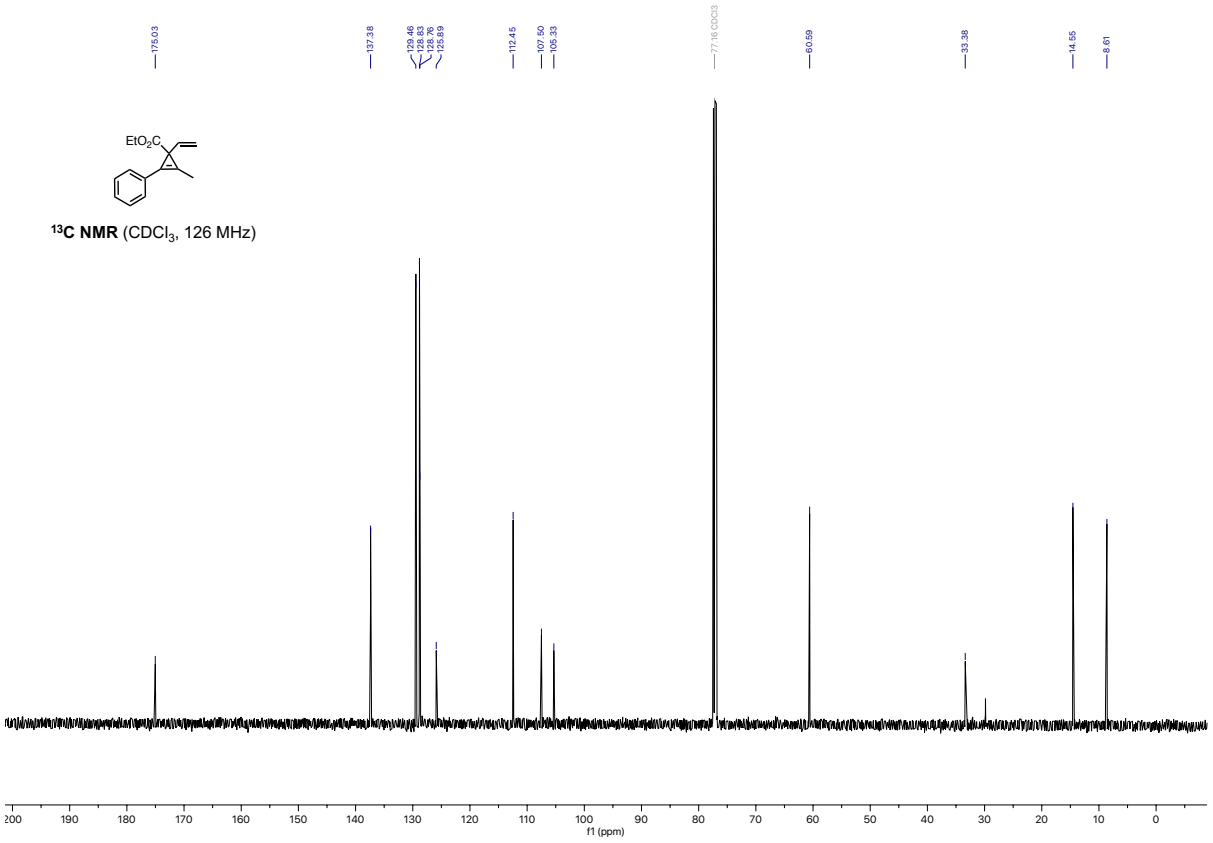


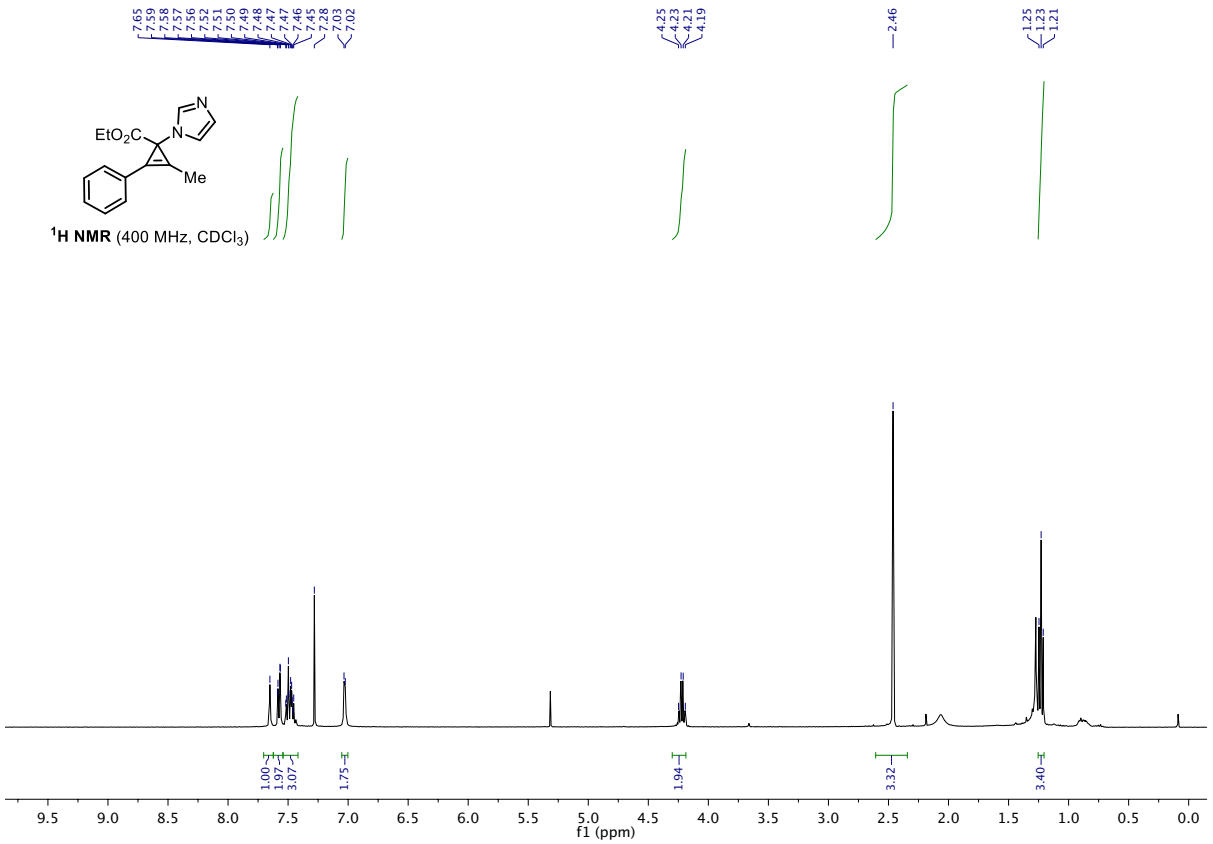
^{1}H NMR ($CDCl_3$, 400 MHz)

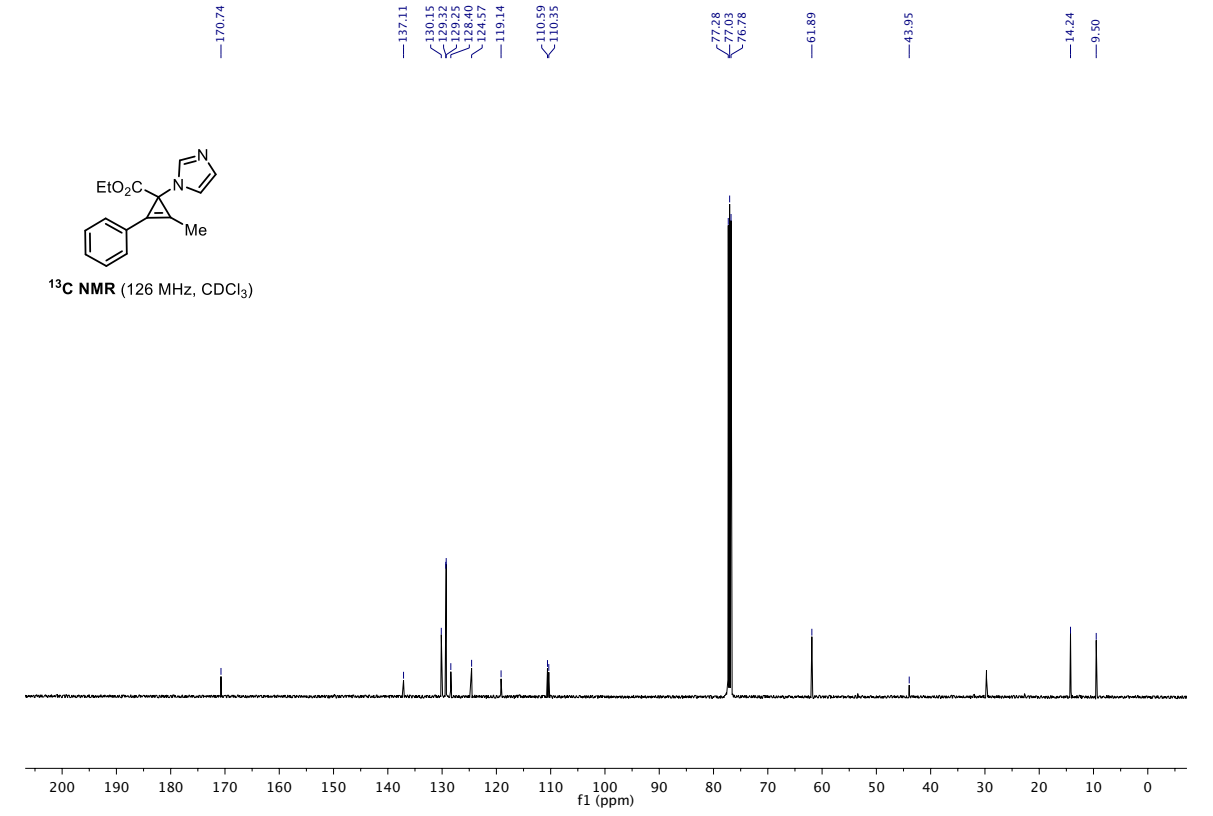


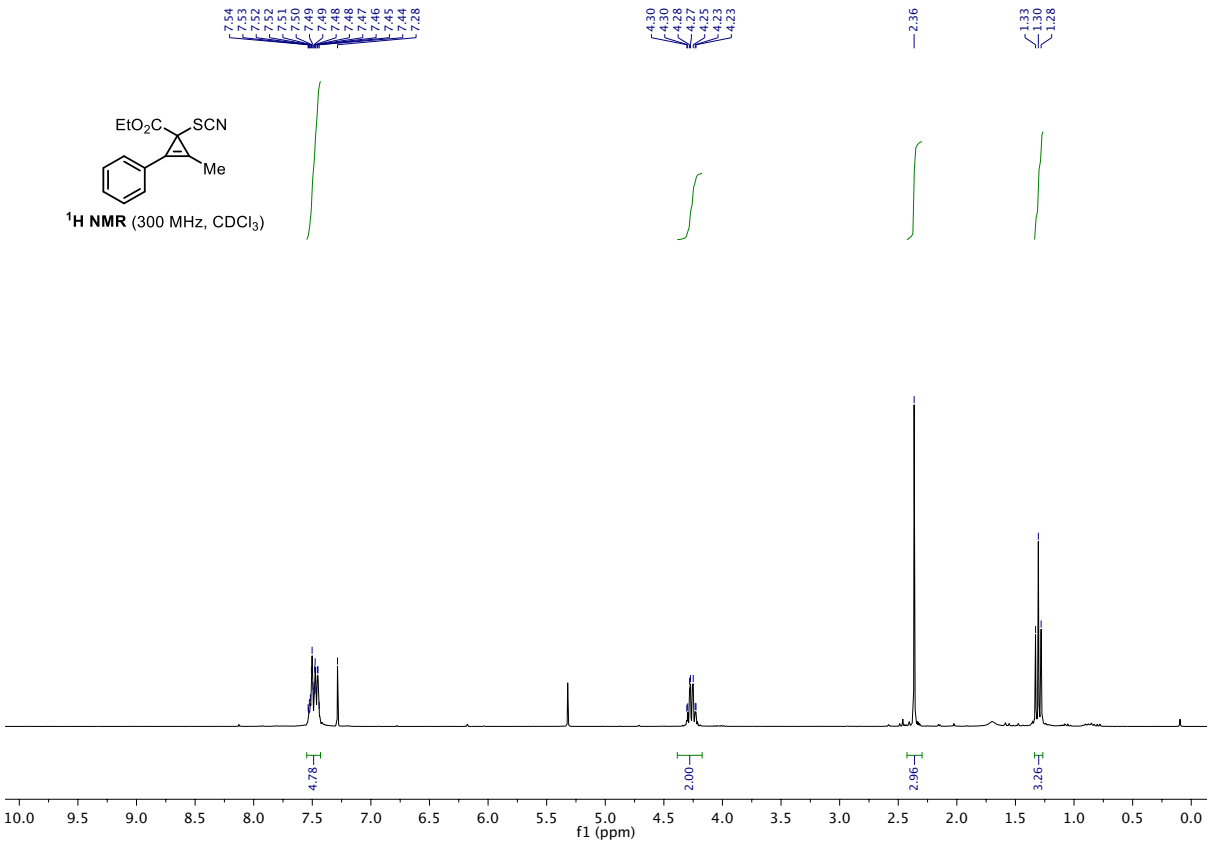
^{13}C NMR ($CDCl_3$, 101 MHz)


EtO2C
1H NMR (CDCl3, 500 MHz)
f1 (ppm)


EtO2C
13C NMR (CDCl3, 126 MHz)
f1 (ppm)


7.65
7.59
7.58
7.57
7.56
7.52
7.51
7.50
7.49
7.48
7.47
7.47
7.46
7.45
7.28
7.03
7.02
4.25
4.23
4.21
4.19
2.46
1.25
1.23
1.21
EtO2C
N
N
Me
1H NMR (400 MHz, CDCl3)
1.00
1.97
3.07
1.75
1.94
3.32
3.40
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


170.74
137.11
130.15
130.32
129.25
128.40
124.57
119.14
110.59
110.35
77.28
77.03
76.78
61.89
43.95
14.24
9.50
EtO2C
N
N
Me
13C NMR (126 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.54
7.53
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7.48
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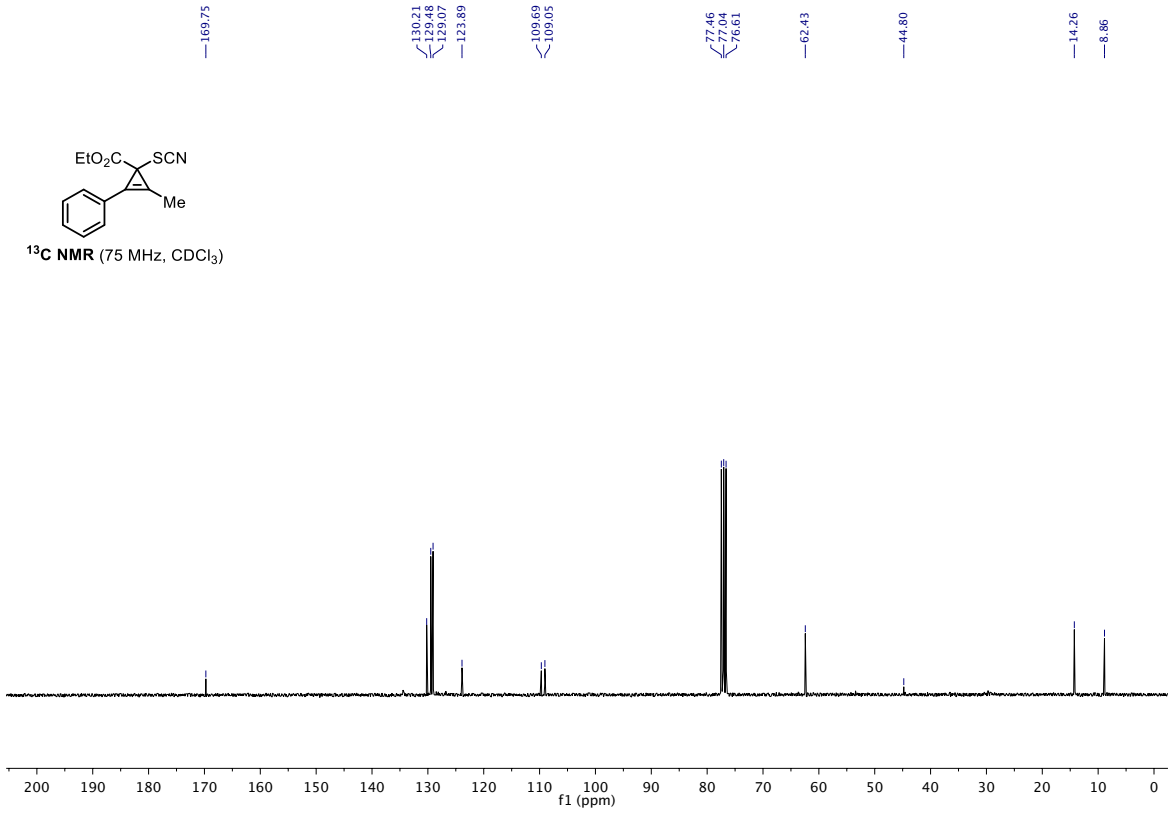
7.46
7.45
7.44
7.28
4.30
4.30
4.28
4.27
4.25
4.23
4.23
2.36
1.33
1.30
1.28
EtO2C
SCN
Me
1H NMR (300 MHz, CDCl3)
4.78
2.00
2.96
3.26
f1 (ppm)


169.75
130.21
129.48
129.07
123.89
109.69
109.05
77.46
77.04
76.61
62.43
44.80
14.26
8.86
EtO2C
SCN
Me
13C NMR (75 MHz, CDCl3)
f1 (ppm)

UNIVERSITAT ROVIRA I VIRGILI
SYNTHESIS OF CYCLOPROPENIUM CATIONS BY CARBYNE TRANSFER CATALYSIS AND APPLICATIONS IN NOVEL CYCLOPROPENE SYNTHESES
Aliénor Celine Renee Jeandin

Chapter IV

Late-stage aryl C-H bond cyclopropenylation with cyclopropenium cations

The work described in this chapter was performed in collaboration with **Dr. Hang-Fei Tu**, *as well as with* **Dr. Corentin Bon**, **Dr. Cara Brocklehurst**, and **Dr. Fabio Lima**. *Part of the work has been published, see*: Hang-Fei Tu, Aliénor Jeandin, Corentin Bon, Cara Brocklehurst, Fabio Lima, Marcos G. Suero "*Late-Stage Aryl C-H Bond Cyclopropenylation with Cyclopropenium Cations*" *Angew. Chem. Int. Ed.*, **2023**, *62*, e202308379.

4.1 Introduction

In Chapter III, we have described a regioselective synthesis of cyclopropenes by using a novel class of ester-substituted CPCs. The reaction occurred with an excellent regioselectivity and accessed a broad scope of diverse cyclopropenes. In this Chapter, we explore further the reactivity of CPCs by disclosing a methodology for a novel late-stage aryl C-H bond cyclopropenylation with CPCs. Small rings are common place in drug design, nonetheless, cyclopropenes remain overall largely underexplored in medicinal chemistry. This can be explained by a lack of general methods for their installation in complex settings. Cyclopropenes are however found in natural products and used as biorthogonal reporters in living systems. The developed platform gives access to previously unknown cyclopropenylated (hetero)arenes, drug molecules, agrochemicals, natural products and fluorescent dyes. Furthermore, we capitalize on the versatile nature of cyclopropenes in organic synthesis to derivatize our cyclopropenylated compounds with known transformations. In this way, the cyclopropene ring also serves as synthetic tool to access medicinally-relevant sp^3-rich scaffolds, difficult or not possible to attain with known methodologies.

4.2 Cyclopropenes in natural products

The cyclopropene motif is found in only a handful of natural products.

Cyclopropene-containing fatty acids (CPFAs) were the first natural products holding a cyclopropene moiety to be identified. Sterculic acid was isolated and characterized by Nun in 1952 from the kernel oil of the plant *Stercolia fœtida.*[1] A few years later, a related fatty acid, one carbon atom shorter, was identified in related plants and referred to as malvalic acid.[2] It was rapidly established that sterculic and malvalic acids are commonly present together in different percentages in the seeds and leaves of plants of the order *Malvaceae* (Figure 1, left).[3] Notably, it was observed early on that animals fed with such malvaceous plants suffered a hardening of their fat, namely an increase in the stearic acid content and a decrease in the oleic acid content. This was rapidly linked to the presence of CPFAs in the ingested food, and studies in the late 1960s already attributed these effects to the inhibitory action of CPFAs on Δ^9 stearoyl-CoA desaturase, the enzyme catalyzing the biodesaturation of stearic acid to oleic acid (Figure 1, right).[4]

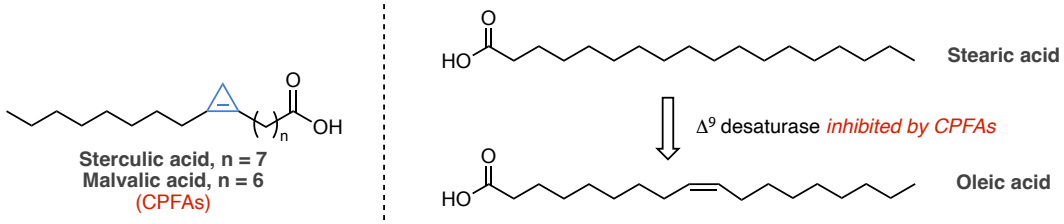


Figure 1 Cyclopropene-containing fatty acids and inhibition of the Δ^9 desaturase

[1] Nunn, J. R. *J. Chem. Soc.* **1952**, 313.
[2] (a) Shenstone, F. S.; Vickery, J. R. *Nature* **1956**, *177*, 94, (b) MacFarlane, J. J.; Shenstone, F. S.; Vickery, J. R. *Nature* **1957**, *179*, 830.
[3] (a) Wilson, T. L.; Smith, C. R.; Mikolajczak, K. L. *J. Am. Oil. Chem. Soc* **1961**, *38*, 696, (b) Shenstone, F. S.; Vickery, J. R. *Nature* **1961**, *190*, 168, (c) Lyn Carter, F.; Frampton, V. L. *Chem. Rev.* **1964**, *64*, 497.
[4] Johnson, A. R.; Pearson, J. A.; Shenstone, F. S.; Fogerty, A. C. *Nature* **1967**, *214*, 1244.

Cyclopropenes were also identified in living systems (Figure 2). A sterol from a rare marine species, calysterol, was isolated from the Mediterranean marine sponge *Calyx niceaensis* for the first time in 1975.[5] Related compounds were characterized and studied in the following years, from the same sponge,[6] or from the Caribbean sponge *Calyx podatypa.*[7] Polyandrocarpidines I and II, cyclopropene-containing bioactive components isolated from the marine tunicate *Polyandrocarpa,* were reported in 1978.[8] Interestingly, these extracts showed a cytotoxic and antibacterial activity. In 2009, the toxin of the toxic fungus *R. Subnigricans*, responsible for a type of mushroom poisoning, was isolated and characterized as a cyclopropene carboxylic acid.

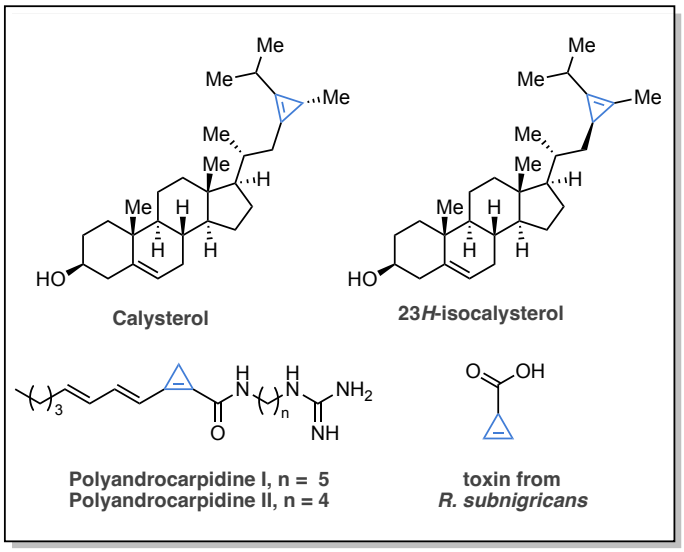


Figure 2: Cyclopropene-containing natural products from living systems

4.3 Cyclopropenes as chemical reporters

Bioorthogonal chemical reporters, as defined by Jennifer Prescher and Carolyn Bertozzi, are "non-native, non-perturbing chemical handles that can be modified in living systems through highly selective reactions with exogenously delivered probes".[9] They are commonly used to visualize the biomolecules they are tagged to. As described in Chapter III, cyclopropenes are highly reactive towards inverse-electron demand Diels-Alder reactions (IED-DA) with tetrazine. This reaction has been exploited in biological systems *in vitro* first,[10] then extended to living systems, where the use of cyclopropenes as chemical reporters was described for the first time.[11] An appropriate design combined with their small size allowed a set of cyclopropenes to be metabolically introduced

[5] Fattorusso, E.; Magno, S.; Mayol, L.; Santacroce, C.; Sica, D. *Tetrahedron* **1975**, *31*, 1715.
[6] (a) Li, L. N.; Li, H.-T.; Lang, R. W.; Itoh, T.; Sica, D.; Djerassi, C. *J. Am. Chem. Soc.* **1982**, *104*, 6726, (b) Itoh, T.; Djerassi, C. *J. Am. Chem. Soc.* **1983**, *105*, 4407, (c) Margot, C.; Catalan, C. A. N.; Proudfoot, J. R.; Sodano, G.; Sica, D. *J. Chem. Soc., Chem. Commun.* **1987**, *19*, 1441.
[7] Doss, G. A.; Djerassi, C. *J. Am. Chem. Soc.* **1988**, *110*, 8124.
[8] Cheng, M. T.; Rinehart, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7409.
[9] Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13.
[10] This reaction has been presented in Chapter III, Section 3.4.3 : Yang, J.; Šečkute, J.; Cole, C. M.; Devaraj, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 7476.
[11] Patterson, D. M.; Nazarova, L. A.; Xie, B.; Kamber, D. N.; Prescher, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 18638.

into cell surface glycans and subsequently detected with probes generated upon IED-DA with tetrazine (Figure 3). Since then, alternative designs of cyclopropenes sets allowed for the labelling of various biomolecules.[12]

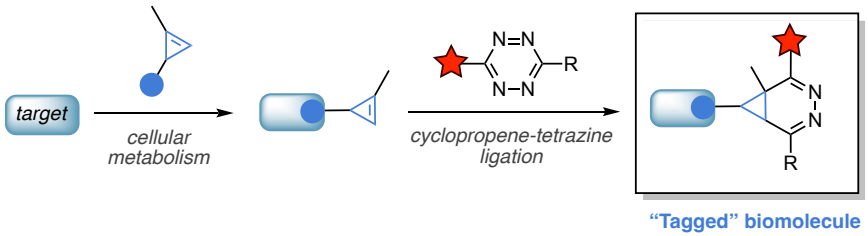


Figure 3 Cyclopropenes as chemical reporters in living systems

4.4 Cyclopropenes as bioactive compounds

4.4.1 Desaturase inhibitors

As mentioned in Section 4.2, CPFAs were identified early on as potent inhibitors of Δ^9 stearoyl-CoA desaturase.[4] The inhibitory effect of sterculic acid in particular was extended to Δ^9 desaturases of various aliphatic acids, independently from their chain length.[13] In 2001, the inhibitory activity of CPFAs on desaturases was used as starting point for the design of a cyclopropene-containing ceramide as potential inhibitor of dihydroceramide desaturase.[14] The *de novo* biosynthesis of ceramide was successfully stopped at dihydroceramide by the compound *erythro*-1 (Figure 4). Ceramide accumulation is at the origin of different diseases,[15] and *erythro*-1 was identified as potential therapeutic agent for such malfunctions, among other analogs developed later on.[16] The therapeutic potential of the inhibitory activity of sterculic acid on desaturases was also the subject of various scientific studies.[17]

[12] For a review on chemical reporters, see: (a) Patterson, D. M.; Nazarova, L. A.; Xie, B.; Kamber, D. N.; Prescher, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 18638. For selected references on the use of cyclopropenes as chemical reporters, see: (b) Patterson, D. M.; Jones, K. A.; Prescher, J. A. *Mol. Biosyst.* **2014**, *10*, 1693, (c) Cole, C. M.; Yang, J.; ŠečkuteC, J.; Devaraj, N. K. *ChemBioChem* **2013**, *14*, 205, (d) Späte, A. K.; Bußkamp, H.; Niederwieser, A.; Schart, V. F.; Marx, A.; Wittmann, V. *Bioconjug. Chem.* **2014**, *25*, 147, (e) Xiong, D. C.; Zhu, J.; Han, M. J.; Luo, H. X.; Wang, C.; Yu, Y.; Ye, Y.; Tai, G.; Ye, X. S. *Org. Biomol. Chem.* **2015**, *13*, 3911, (f) Hassenrück, J.; Wittmann, V. *Beilstein J. Org. Chem.* **2019**, *15*, 584.
[13] (a) Johnson, A. R.; Fogerty, A. C.; Pearson, J. A.; Shenstone, F. S.; Bersten, A. M. *Lipids* **1969**, *4*, 265, (b) Quintana, J.; Barrot, M.; Fabrias, G.; Camps, F. *Tetrahedron* **1998**, *54*, 10187.
[14] Triola, G.; Fabriàs, G.; Llebaria, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 1960.
[15] Unger, R. H.; Orci, L. *Int. J. Obes.* **2000**, *24*, S28–S32.
[16] (a) Triola, G.; Fabriàs, G.; Casas, J.; Llebaria, A. *J. Org. Chem.* **2003**, *68*, 9924, (b) Bedia, C.; Triola, G.; Casas, J.; Llebaria, A.; Fabriàs, G. *Org. Biomol. Chem.* **2005**, *3*, 3707.
[17] Peláez, R.; Pariente, A.; Pérez-Sala, Á.; Larráyoz, I. M. *Cells* **2020**, *9*, 140.

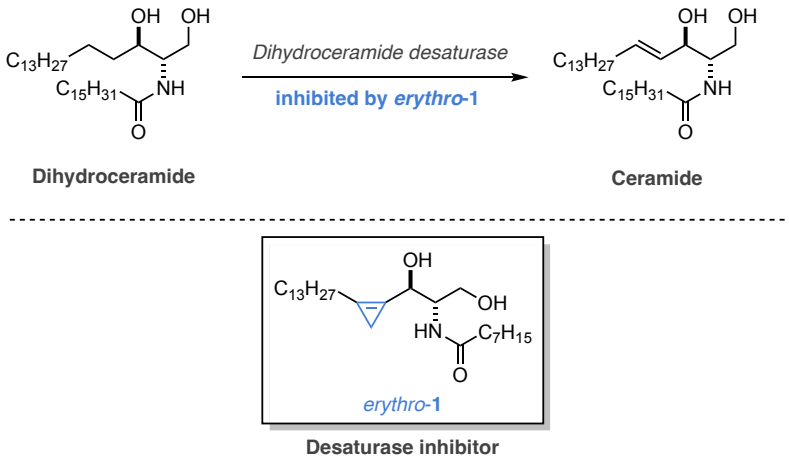


Figure 4 Last step of the biosynthesis of ceramide and desaturase inhibitor *erythro*-**1**

4.4.2 Cyclopropenes in postharvest science

Ethylene controls numerous physiological processes in plants by binding a membrane-bound receptor, the most important one being the ripening process. Controlling ethylene perception, and thus ripening, in horticultural products is highly desirable. 1-Methylcyclopropene (1-MCP), represented in Figure 5, was identified as an inhibitor of ethylene perception in plants by interacting with the membrane-bound receptors and patented in 1996.[18] It is now extensively used in postharvest science to maintain the ripeness level of fruits, and to conserve cut flowers.[19] The inherent strain of the cyclopropene double bond proved key to the efficiency of the inhibition process.[20] Recently, carboxylate-substituted cyclopropenes were also identified as chemical biology tools for the determination of molecular targets for herbicides or plant growth regulators.[21]

Figure 5 1-Methylcyclopropene (MCP)

4.4.3 Cyclopropenes as small drug molecules

N-(2-aminocyclohexyl)arylacetamides, in particular U-50488 and CI-977, have been identified as potent selective agonists of the kappa opioid receptor (Figure 6, top). Kappa opioid receptors modulate numerous physiological pathways in the central nervous systems, yet the development of agonists as therapeutics remains arduous due to the multiple undesirable side effects associated with such agents.[22] In 1997, some potential structural analogues

[18] Sisler, E.C.; Blankenship, S.M. Method of counteracting an ethylene response in plants, US Patent No. 5518988A, **1996**.
[19] Watkins, C. B. *Biotechnol. Adv.* **2006**, *24*, 389.
[20] Pirrung, M. C.; Bleecker, A. B.; Inoue, Y.; Rodríguez, F. I.; Sugawara, N.; Wada, T.; Zou, Y.; Binder, B. M. *Chem. Biol.* **2008**, *15*, 313.
[21] Koyama, T.; Takahashi, I.; Asami, T. *J. Pestic. Sci.* **2023**, *48*, 61.
[22] For a review on the kappa opioid receptor as therapeutic target, see : Dalefield, M. L.; Scouller, B.; Bibi, R.; Kivell, B. M. *Front. Pharmacol.* **2022**, *13*, 837671.

of U-50488 and CI-977 were synthesized and studied.[23] Among the screened compounds, a diphenylcyclopropene compound, more precisely a cyclopropene-3-carboxamide, was distinguished as chemically novel and potent lipophilic analogue to CI-977. The planarity of the aromatic portion stood out as decisive requirement for such analogues, and the incorporation of a cyclopropene moiety upon analogue design and synthesis represented a way to fulfill this criterion (Figure 6, bottom).

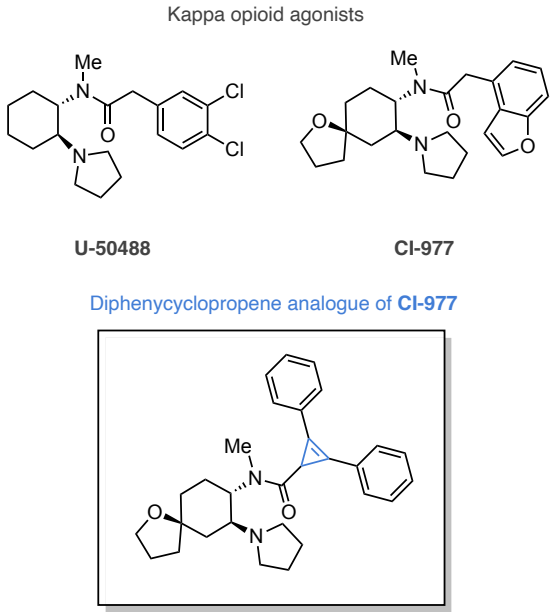


Figure 6 Kappa opioid receptor agonists U-50488 and CI-977 and analogues

4.5 Small rings in medicinal chemistry

The small size and rigidity of aliphatic small rings such as cyclopropanes, cyclobutanes, oxetanes, azetidines and bicyclo[1.1.1.]pentanes (BCPs) has been continuously more utilized in medicinal chemistry.[24] Their structural features often improve physicochemical properties of drug candidates compared to larger, planar aromatic rings, while also positively impacting metabolism and solubility, notably by increasing the fraction of sp^3 carbons.[25] Each aliphatic small ring has different medicinal chemistry attributes.[26] The rigidity of cyclopropanes has, for example, been used to constrain aliphatic systems, in the development of a series of phosphodiesterase 2 (PDE 2) inhibitors. It allowed for the stabilization the conformation of the drug candidate while maintaining physicochemical properties (Figure 7, a).[27] The use of azetidines could, in some cases, improve the solubility in the replacement of unsaturated ring systems, such as in the design of a selective phosphodiesterase 10A (PDE10A)

[23] Sabin, V.; Horwell, D. C.; McKnight, A. T.; Broqua, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 291.
[24] Bauer, M. R.; Di Fruscia, P.; Lucas, S. C. C.; Michaelides, I. N.; Nelson, J. E.; Storer, R. I.; Whitehurst, B. C. *RSC Med. Chem.* **2021**, *12*, 448.
[25] Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.
[26] Only a few examples will be covered here. For reviews on the use of rings in medicinal chemistry, see: (a) reference 24, (b) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845, (c) Shearer, J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D. *J. Med. Chem.* **2022**, *65*, 8699.
[27] Forster, A. B.; Abeywickrema, P.; Bunda, J.; Cox, C. D.; Cabalu, T. D.; Egbertson, M.; Fay, J.; Getty, K.; Hall, D.; Kornienko, M.; Lu, J.; Parthasarathy, G.; Reid, J.; Sharma, S.; Shipe, W. D.; Smith, S. M.; Soisson, S.; Stachel, S. J.; Su, H. P.; Wang, D.; Berger, R. *Bioorganic Med. Chem. Lett.* **2017**, *27*, 5167.

(Figure 7, b). Small rings can also be exploited as functional group bioisosteres.[28] A well-known case is the application of BCP as phenyl group bioisostere, for example in the design of a γ-secretase inhibitor.[29] The small, aliphatic ring improved solubility by increasing saturation compared to a fluorophenyl group, and reduced lipophilicity (Figure 7, c).

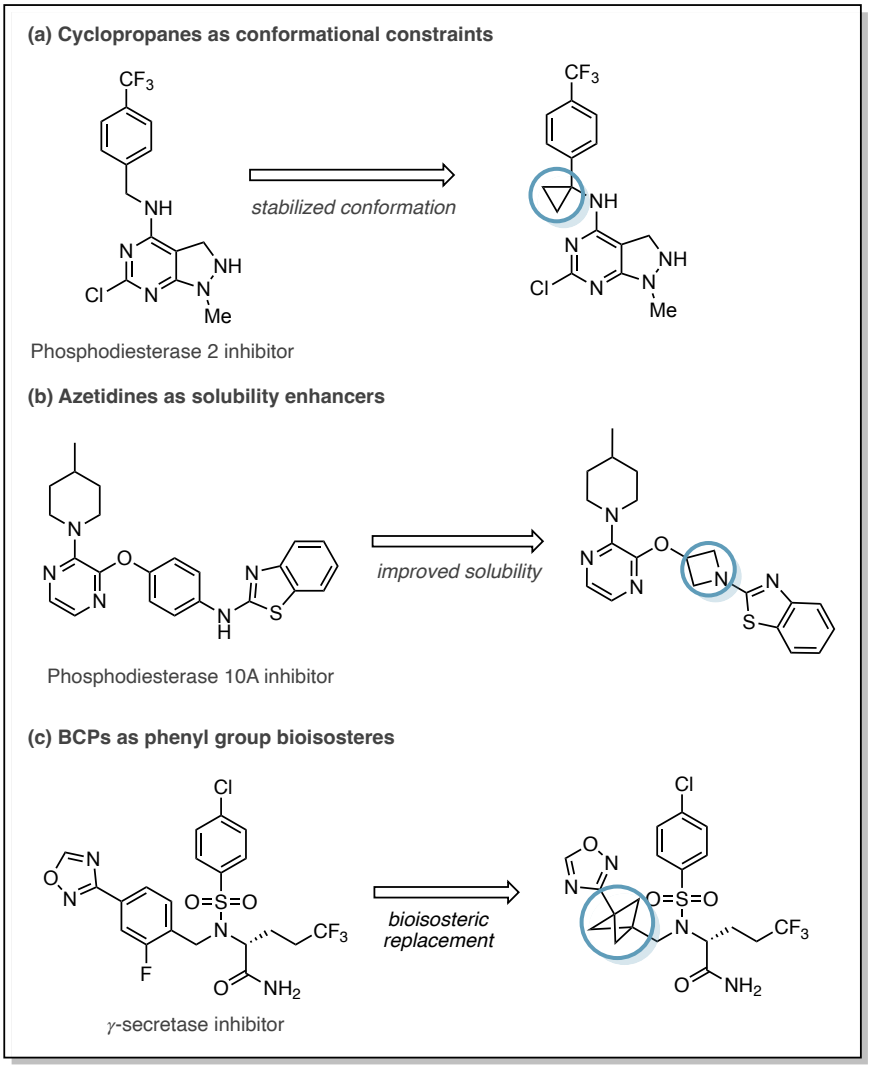


Figure 7 Some examples of the uses of small rings in medicinal chemistry

4.6 Late-stage C-H bond functionalization

Late-stage functionalization (LSF), as defined by Ritter in 2020, is "a desired chemoselective transformation on a complex molecule to provide at least one analog in sufficient quantity and purity for a given purpose without

[28] For reviews on bioisosteres, see: (a) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147, (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.
[29] Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; Dirico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J. *J. Med. Chem.* **2012**, *55*, 3414.

the necessity for installation of a functional group that exclusively serves the purpose to enable said transformation".[30] While chemoselectivity is essential to LSF, site-selectivity is highly desirable too when working with complex architectures. LSF is a vast field, and the concerned reactions can be catalytic or non-catalytic, C-H bond functionalizations or functional-group manipulations.[31] They all have in common an ability to quickly access derivatives of complex molecules, which is highly beneficial in drug discovery. C-H bond functionalization in particular can be challenging in the frame of complex organic molecules, as the transformation needs to be selective for C-H bonds over various functional groups. Aryl C-H bond functionalization constitutes another subclass of LSF, and the most common manner to functionalize arenes is through electrophilic aromatic substitution (S_EAr).[32] Yet, in the case of complex molecules, the harsh reaction conditions required drastically decrease the applicability of such transformations, negatively impacting the chemoselectivity, and, to an even higher extent, site-selectivity. Although a few examples of S_EAr via direct attack, electrophilic metal species, or charge-transfer (CT) complexes have been disclosed,[32] the most versatile protocol for aromatic C-H bond LSF to date was reported by Ritter in 2019 with the development of a highly site-selective thiantrenation (Figure 8).[33] The aryl thiantrenium salt obtained served then as linchpin for multiple further transformations, which made this S_EAr the most versatile and useful platform for aryl C-H bond LSF. Nonetheless, all the latter transformations share the limitation of a scope excluding electron-poor arenes due to the electrophilic nature of the reaction.

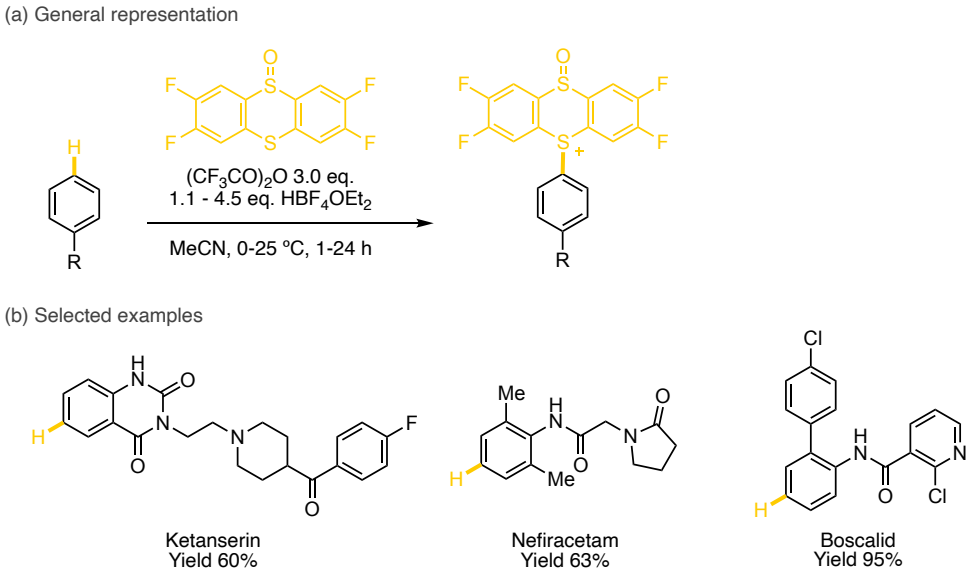


Figure 8 Late-stage aromatic C-H bond functionalization *via* aryl thianthrenium salts

[30] Börgel, J.; Ritter, T. *Chem* **2020**, *6*, 1877.
[31] Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546.
[32] For a review on late-stage arene C-H functionalization, see: Zhang, L.; Ritter, T. *J. Am. Chem. Soc.* **2022**, *144*, 2399.
[33] Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. *Nature* **2019**, *567*, 223.

4.7 Late-stage aryl C-H bond cyclopropenylation with cyclopropenium cations

4.7.1 Hypothesis of the project

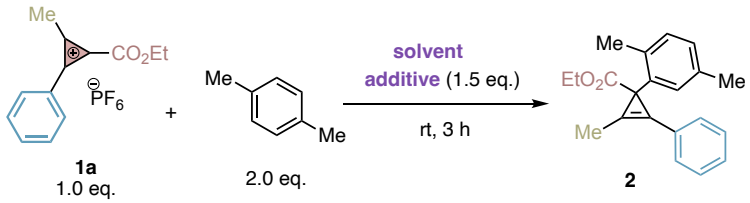
Encouraged by the reactivity of our ester-substituted CPCs to react with a broad range of carbon- and heteroatom-based nucleophiles in a highly regioselective manner (Chapter III), we questioned whether they could undergo an aryl C-H bond cyclopropenylation in complex settings. Such an electrophilic aromatic substitution (S_EAr) with CPCs has mainly been reported between the reactive trichlorocyclopropenium cation and simple aromatics, in a process providing aryl-substituted cyclopropenium cations upon replacement of the chloride ion. More stable CPCs such as amino-, alkyl- or aryl- substituted CPCs tend to remain unreactive towards S_EAr.[34] The potential utility of this Friedel-Crafts type reaction would be conditioned to achieving excellent site- and chemoselectivity levels, a potential major challenge in drug molecules or natural products often displaying great density of heteronucleophiles and multiple aromatic rings. Importantly, the development of a methodology allowing for the installation of a cyclopropene ring in a late-stage fashion would be highly valued and would permit further derivatizations to other complex scaffolds.

4.7.2 Reaction optimization

The feasibility of the envisaged electrophilic cyclopropenylation reaction was initially evaluated with *p*-xylene (2 eq.) and CPC **1a** (1 eq.). Initially, we tested organic solvents with low polarity such as CH_2Cl_2 at room temperature. CH_2Cl_2 was previously successful with strong nucleophiles,[35] but in this case only traces of the desired cyclopropene product **2** were obtained and instead, decomposition of **1a** was observed (Table 1, entry 1). 1,4-dioxane gave similar results (entry 2). Non-protic polar solvents such as dimethylformamide (DMF), acetonitrile, or nitromethane (entries 3-5) and protic polar solvents with low acidity such as MeOH, EtOH, or *i*-PrOH were ineffective (entries 6-8). However, 2,2,2-trifluoroethanol (TFE) and hexafluoroisopropanol (HFIP) provided promising yields of **2** (entries 9 and 10; 16 and 20% yield respectively).

[34] The reactivity of trichlorocyclopropenium cations in Friedel-Crafts type transformations has been described in Chapter II. For selected references on the lack of reactivity with more stable CPCs, see: (a) Tobey, S. W.; West, R. *J. Am. Chem. Soc.* **1964**, *86*, 4215; (b) West, R.; Sadô, A.; Tobey, S. W. *J. Am. Chem. Soc.* **1966**, *88*, 2488; (c) Komatsu, K.; Tomioka, I.; Okamoto, K. *Tetrahedron Lett.* **1980**, *21*, 947; (d) Yoshida, Z. I.; Tawara, Y. *J. Am. Chem. Soc.* **1971**, *93*, 2573. For a review on the reactivity of cyclopropenium cations, see: (e) Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371.
[35] This reaction was disclosed in Chapter III.

Table 1 Solvent and additive screening for **1a**



Entry	Solvent	Additive	NMR yield **2** (%)
1	CH_2Cl_2	none	traces
2	1,4-dioxane	none	0
3	DMF	none	0
4	CH_3CN	none	0
5	CH_3NO_2	none	0
6	MeOH	none	traces
7	EtOH	none	traces
8	*i*-PrOH	none	traces
9	TFE	none	16
10	HFIP	none	20
11	HFIP	15-Crown-5	26[a]
12	HFIP	4 Å MS	26[b]
13	HFIP	$NaHCO_3$	25
14	HFIP	$KHCO_3$	10
15	HFIP	2,6-Lutidine	trace
16	HFIP	$Zn(OTf)_2$	17[c]

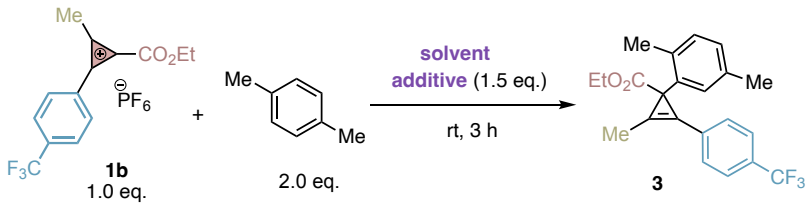
[a] 1.0 eq.of 15-C-5 was used. [b] 30 mg 4 Å MS were used. [c] 0.2 eq. of $Zn(OTf)_2$ was used.

We pursued our efforts by screening the effect of different additives. We hypothesized that 15-Crown-5 could eventually chelate the CPC as cationic species and improve the efficiency of the reaction, but no improvement was observed (entry 11). We observed the water attack product as major side-product and attempted to impede its formation. The addition of 4Å molecular sieves to remove any traces of water (entry 12) had no effect on the obtained yield, neither did the addition of $Zn(OTf)_2$ as Lewis acid, initially intended to weaken the C-O bond formed by the water attack, and allow for the attack of *p*-xylene instead (entry 16). Considering that HPF_6 was formed in the course of the reaction, we also considered various proton abstractors as a way to improve the yield. However, neither inorganic bases such as $NaHCO_3$ or $KHCO_3$ (entries 13 and 14) nor an organic base such as 2,6-lutidine revealed effective (entry 15). Further optimization for *p*-xylene did not afford better yields with **1a**.

We then hypothesized that a more electrophilic CPC might provide better results, and we were indeed pleased to see that CPC **1b**, substituted with a 4-CF_3-C_6H_4 group, provided the desired cyclopropene with a 46% yield (Table 2, entry 1). Additional solvent screening confirmed that HFIP was the most suitable solvent for this transformation (entries 2-4). Another evaluation of proton abstractors revealed that while Na_2CO_3, did improve the yield to 68%

(entry 6), neither Na_2CO_3 nor K_2CO_3 significantly improved the reaction outcome (entries 5, 7). However, CsF enabled the formation of **3** in 92%. Less soluble LiF or NaF bases, or CsBr, gave poor yields (entries 10-12).

Table 2 Solvent and additive screening for **1b**

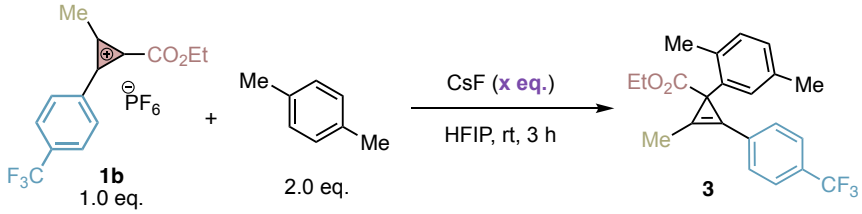


Entry	Solvent	Additive	NMR yield **3** (%)
1	HFIP	none	46
2	CH_2Cl_2	none	38
3	TFE	none	16
4	MeOH	none	0
5	HFIP	$NaHCO_3$	50
6	HFIP	Na_2CO_3	68
7	HFIP	K_2CO_3	35
8	HFIP	2,6-Lutidine	0
9	HFIP	CsF	92
10	HFIP	NaF	22
11	HFIP	LiF	30
12	HFIP	CsBr	13

Evaluation of the stoichiometry of the reaction confirmed that 1.5 equivalents of CsF was optimal for the reaction, while adding 0.5 equivalents resulted in a lower yield, and 1.9 equivalents provided only the HFIP attack product[36] instead of the cyclopropenylated arene (Table 3, entries 1-3). The reaction also worked well when using *p*-xylene as limiting reagent (entry 4). With the optimized conditions in hand, we performed a last round of solvent evaluation, which confirmed that the combination of both HFIP and CsF was essential to the success of the reaction (entries 5-8).

[36] See the corresponding structure in Figure 9, Section 4.7.3

Table 3 Optimization of the CsF equivalents

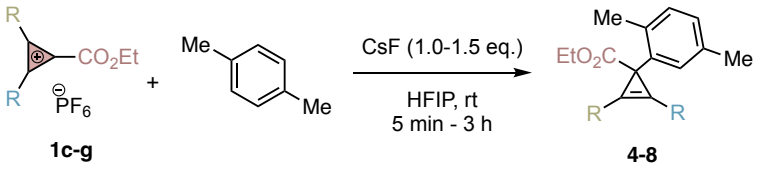


Entry	Solvent	CsF (eq.)	NMR yield **3** (%)
1	HFIP	1.0	83
2	HFIP	0.5	32
3	HFIP	1.9	0
4	HFIP	1.5	93[a]
5	DCM	1.5	7
6	MeOH	1.5	n.d.
7	CH_3NO_2	1.5	n.d.

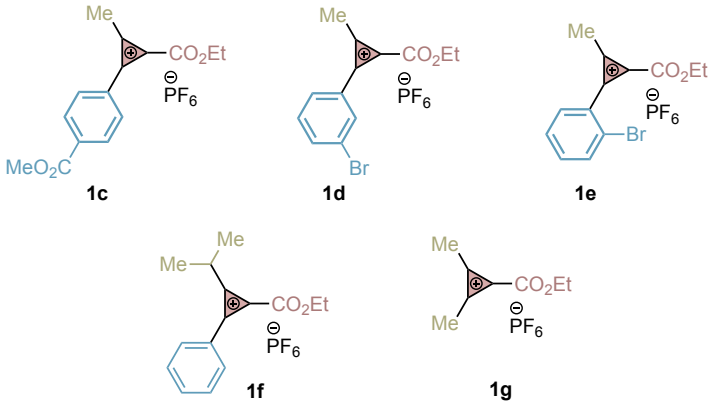
n.d. = not determined. [a] 1.2 eq. of CPC **1b** was used.

Finally, alternative classes of CPCs substituted in *para* (**1c**), *meta* (**1d**) and *ortho* (**1e**) positions of the phenyl ring provided cyclopropenes **4-6** in good efficiencies (Table 4, entries 1-3). CPCs substituted with a secondary alkyl group (entry 4, **1f**) or with two methyl groups (entry 5, **1g**) were also tolerated.

Table 4 CPC scope with *p*-xylene as coupling partner



Entry	CPC	Cyclopropene	Yield (%)
1	**1c**	**4**	77
2	**1d**	**5**	47
3	**1e**	**6**	47
4	**1f**	**7**	44
5	**1g**	**8**	67



4.7.3 Mechanistic insights of the reaction

It became rapidly clear that HFIP as solvent was essential to the efficiency of the reaction. We first supposed that its high ionizing ability conferred by the presence of trifluoromethyl groups stabilized the ionic species during the S_EAr event, or allowed to form a solvent-separated ion pair between the cyclopropenium cation and [PF_6^-].[37] Nonetheless, we decided to further investigate its exact role by performing a reaction with **1g** and *p*-xylene under the standard conditions and to monitor it by GC-MS. To our surprise, we detected the transient formation of ***int-1*** (Figure 9).

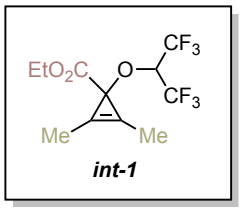


Figure 9 ***Int-1***

An aliquot of the reaction mixture collected after 2 min showed a mixture of *p*-xylene, ***int-1*** and cyclopropene **8** (Figure 10). After 90 min, another aliquot was analyzed by GC-MS and showed the absence of ***int-1*** (Figure 11). Such an intermediate, resulting from the attack of HFIP to **1g**, could be serving as a cyclopropenium cation reservoir, keeping low concentrations of the reactive CPCs and preventing side reactions. Independent synthesis of ***int-1*** confirmed its involvement in the process.[38]

[37] For a review: (a) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood, V. M.; Aubé, J. *Chem. Rev.* **2022**, *122*, 12544. For selected examples of the use of HFIP in S_EAr reactions, see: (b) Li, G. X.; Qu, J. *Chem. Commun.* **2010**, *46*, 2653, (c) Ricardo, C. L.; Mo, X.; McCubbin, J. A.; Hall, D. G. *Chem. Eur. J.* **2015**, *21*, 4218, (d) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajooei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. *Chem* **2021**, *7*, 3425.

[38] See experimental section for detailed reaction conditions.

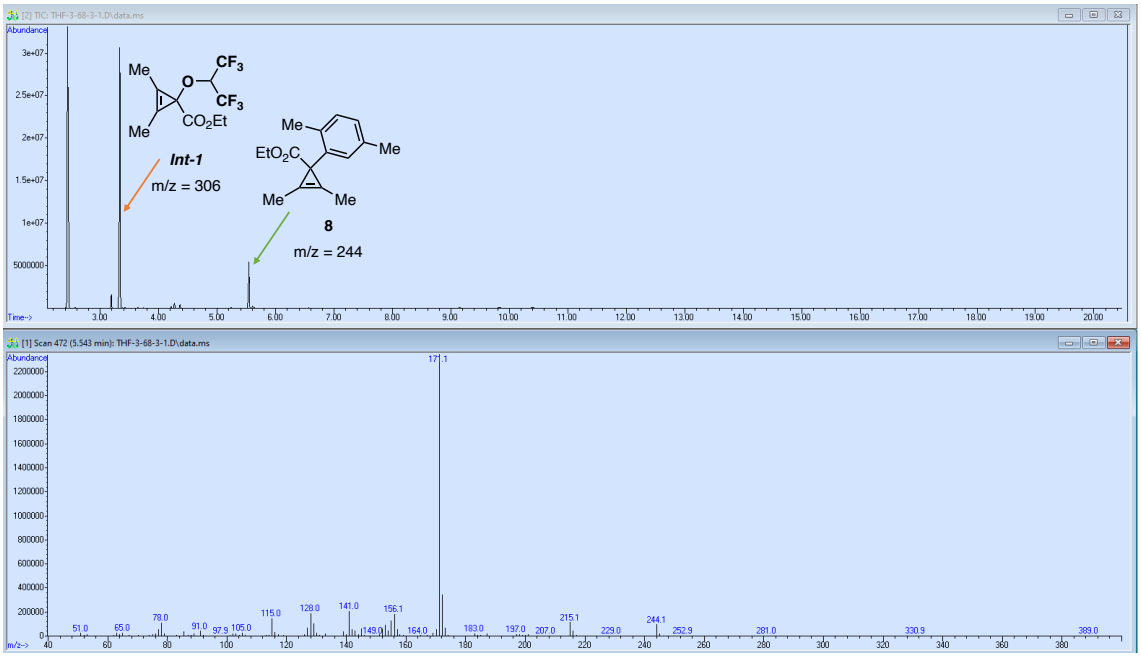


Figure 10 GC chromatogram of the reaction at 2 min (top), and MS traces of **8** (bottom).

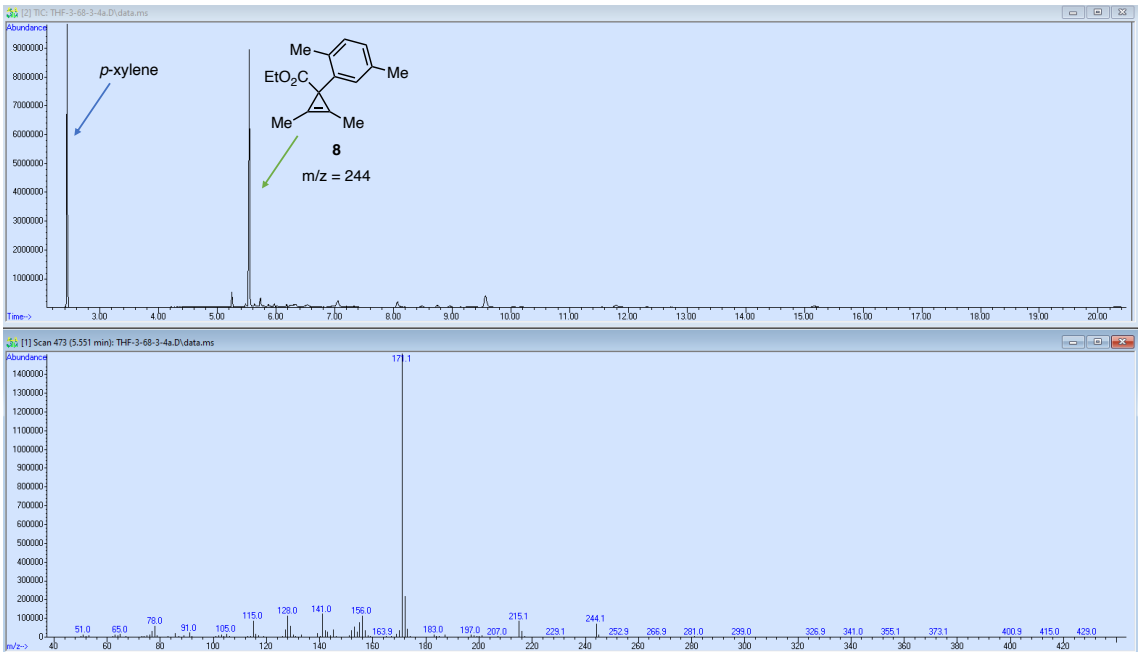


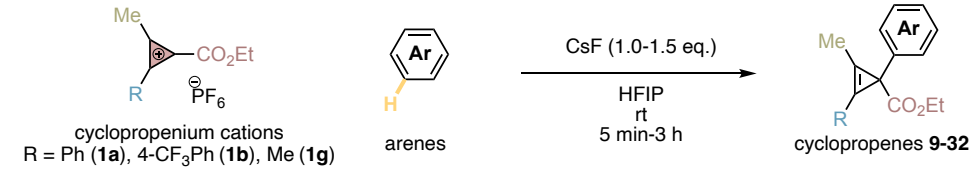
Figure 11 GC-MS traces of the reaction at 90 min (top), and MS traces of **8** (bottom).

4.7.4 Scope

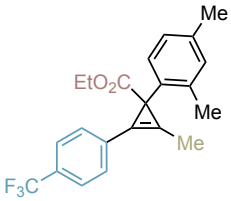
We next turned our attention to evaluating the scope of the C–H bond cyclopropenylation reaction using CPCs **1a, b, g** and an array of simple aromatics, natural products, drug molecules, agrochemicals and fluorescent dyes. We observed that C–H bond cyclopropenylations of di-, trisubstituted arenes generally occurred at the least hindered and electron-rich aromatic site and provided cyclopropenes **9**–**19** with high efficiencies (Table 4). Mono-substituted arenes with strong and moderate electron-donating groups provided the desired cyclopropenes with

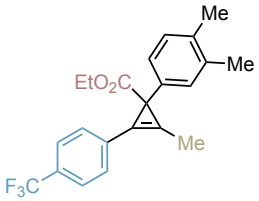
excellent para-selectivity (**20**–**24**). Bulky and weak electron-donating groups were also effective substituents in directing the CPC to the para position (**25**), however, small groups such as methyl provided the cyclopropene with moderate regioselectivity (**26**, **27**). On the other hand, while arenes substituted with strong or moderate electron-withdrawing groups like nitro or ester were unsuccessful, weak electron-withdrawing groups or simple benzene ring gave modest conversion (**28**, **29**). Naphtalenes (**30**–**32**) also allowed for the obtention of the cyclopropenylated products in good yields.

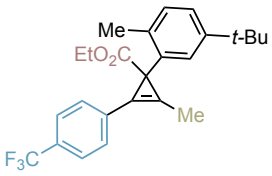
Table 5 Reaction scope for arenes

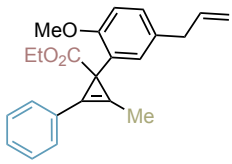


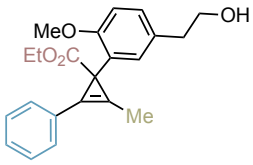
arenes

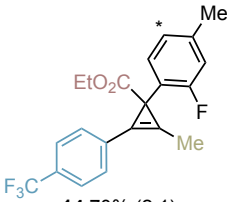

9 81% (>20:1)

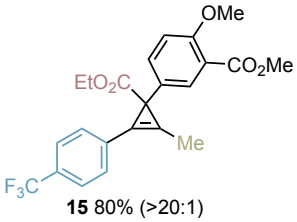

10 82% (12:1)

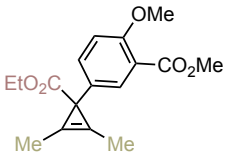

11 93% (>20:1)

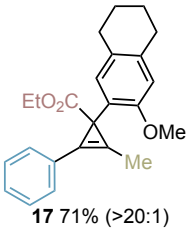

12 51% (>20:1)

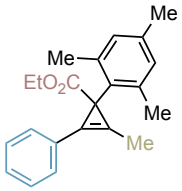

13 51% (>20:1)

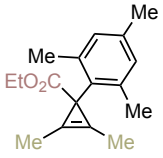

14 70% (2:1)

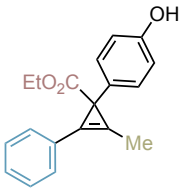

15 80% (>20:1)

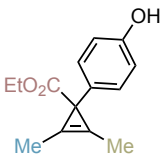

16 52% (>20:1)

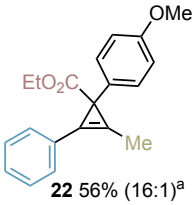

17 71% (>20:1)

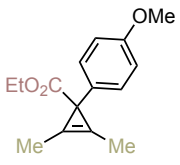

18 71%

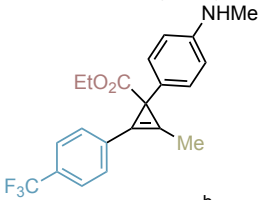

19 55%

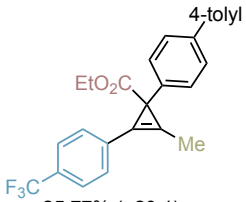

20 51% (>20:1)

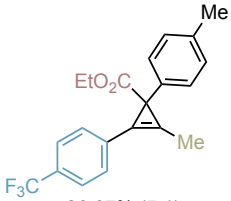

21 56% (>20:1)

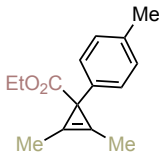

22 56% (16:1)[a]

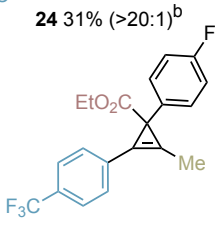

23 65% (>20:1)

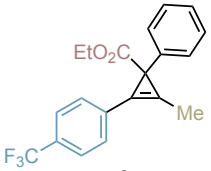

24 31% (>20:1)[b]

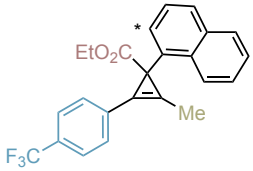

25 77% (>20:1)

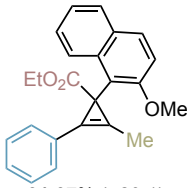

26 67% (5:1)

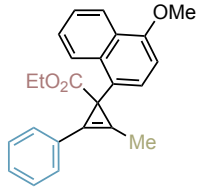

27 51% (5:1)


28 10% (6:1)[c]


29 24%[c]


30 72% (3:1)

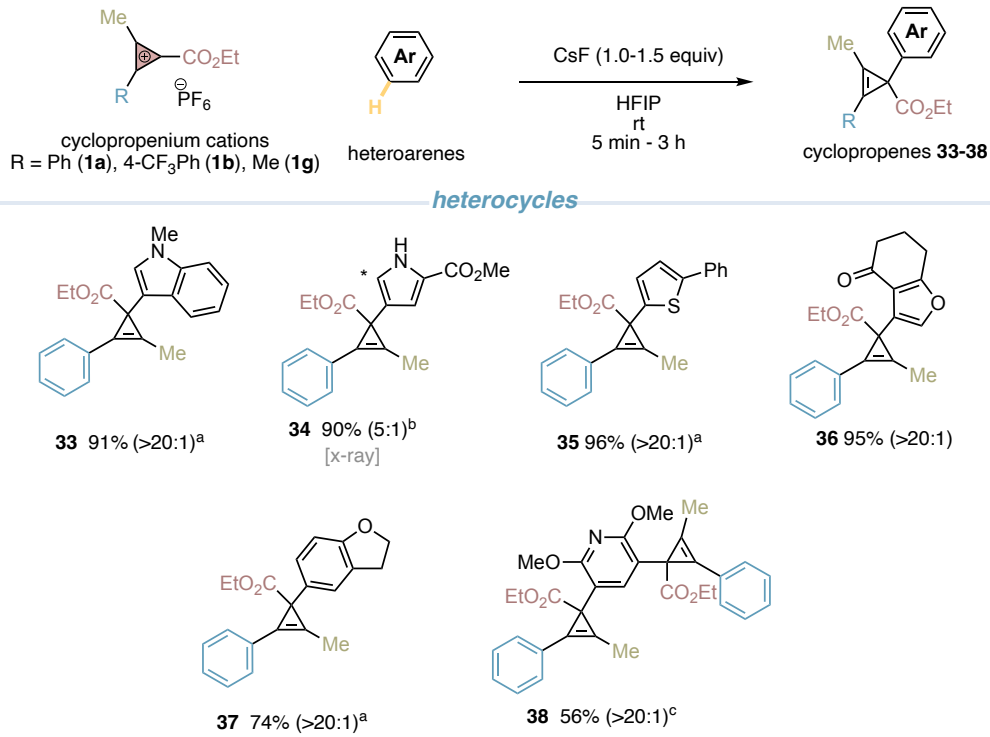

31 87% (>20:1)
[x-ray]


32 76% (>20:1)

Reaction conditions: arene (0.10 mmol), CPC 1 (0.12 mmol), CsF (0.10-0.15 mmol), HFIP (2 mL), room temperature. In parenthesis ratio of regioisomers is indicated. [a]2,2,2-trifluoroethanol was used as solvent. [b]*N*-Boc-*N*-methylaniline was used. [c]Arene was used as cosolvent with HFIP in 3:7 ratio.

Heterocycles such as indole (**33**), pyrrole (**34**), thiophene (**35**), furan (**36**) and dihydrobenzofuran (**37**) worked with excellent efficiencies and regioselectivity. Interestingly, 2,6-dimethoxypyridine provided exclusively the bis-cyclopropenylation product (**38**) (Table 6).

Table 6 Reaction scope for heteroarenes



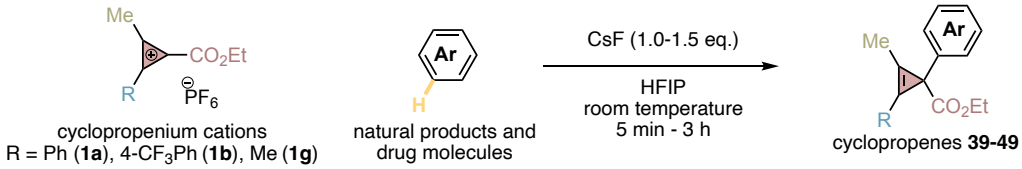
Reaction conditions: arene (0.10 mmol), CPC 1 (0.12 mmol), CsF (0.10-0.15 mmol), HFIP (2 mL), room temperature. In parenthesis ratio of regioisomers is indicated. [a] 2,2,2-trifluoroethanol was used as solvent. [b] Conducted at 0 ºC. [c] Exclusive bis-cyclopropenylation was observed.

After this, we demonstrated that our C–H bond cyclopropenylation reaction was effective in complex settings (**39**–**58**) (Tables 7 and 8). The CPC preference to react chemoselectively at aryl C–H bonds with excellent positional selectivity over other functionalities such as carboxylic acids, esters, ketones, amides, alcohols, alkenes, ureas, ethers, anilines, or hindered secondary amines was striking. Although the formation of kinetic products from O-H or N-H cyclopropenylations cannot be excluded, these showed to evolve over time to the thermodynamical C-H bond cyclopropenylation products.[39] Less sterically-hindered amines, as well as pyridines were not tolerated, however, the use of the hydrochloric salt derivatives (**44**, **54**) or the addition of $Et_2O{\cdot}HBF_4$ beforehand (**48**–**50**) provided the desired "cyclopropenylated" drug molecules with high efficiency. In addition, we demonstrated our protocol was amenable for the functionalization of BODIPY dyes (**58**) and could be scaled

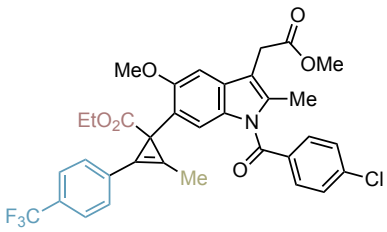
[39] A reaction carried out with 2-(4-methoxyphenyl)ethan-1-ol under the optimized reaction conditions and quenched after 10 min instead of 2.5 h provided a mixture of C-H and O-H bond cyclopropenylation (**13** + **13'**65% yield 2.2:1). **13'** could be converted to **13** in the presence of BF_3. See experimental section for details, compound **13**.

up to 1.5 gram under air without the need of chromatography (**51**, **52**). However, no diastereoselectivity was observed when using **1a** and enantiopure molecules (**51**, diastereomeric ratio = 1:1).

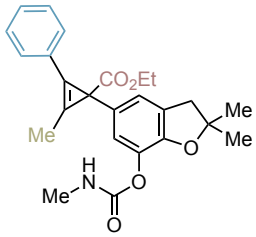
Table 7 Reaction scope for natural products and drug molecules (1)



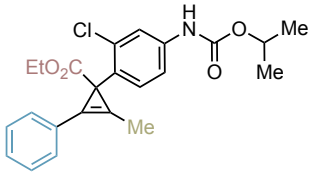
natural products and drug molecules



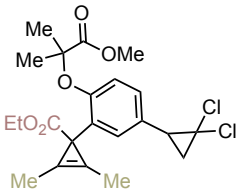
39 82% (>20:1)



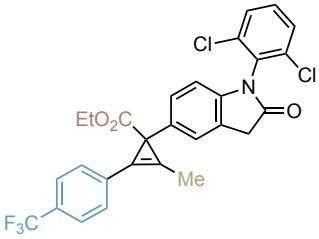
40 94% (>20:1)



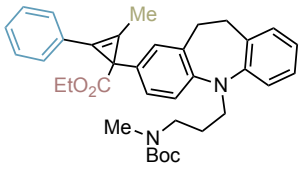
41 75% (>20:1)[a,b]



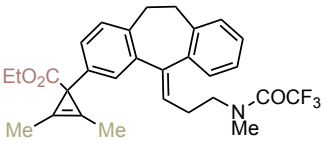
42 39% (>20:1)



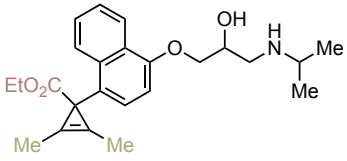
43 68% (>20:1)



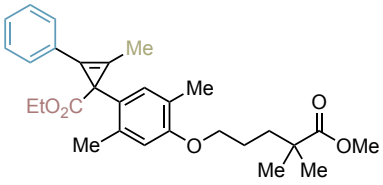
44 75% (>20:1)[c]{2:1}



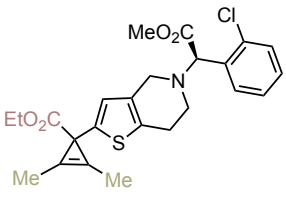
45 24% (1.5:1)



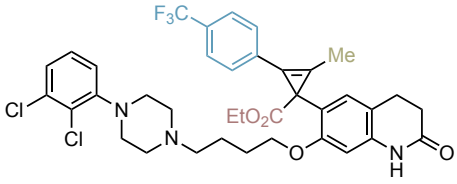
46 79% (>20:1)



47 95% (>20:1)[d]



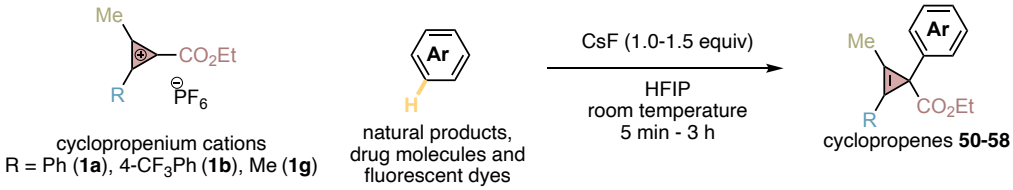
48 66% (>20:1)[e]



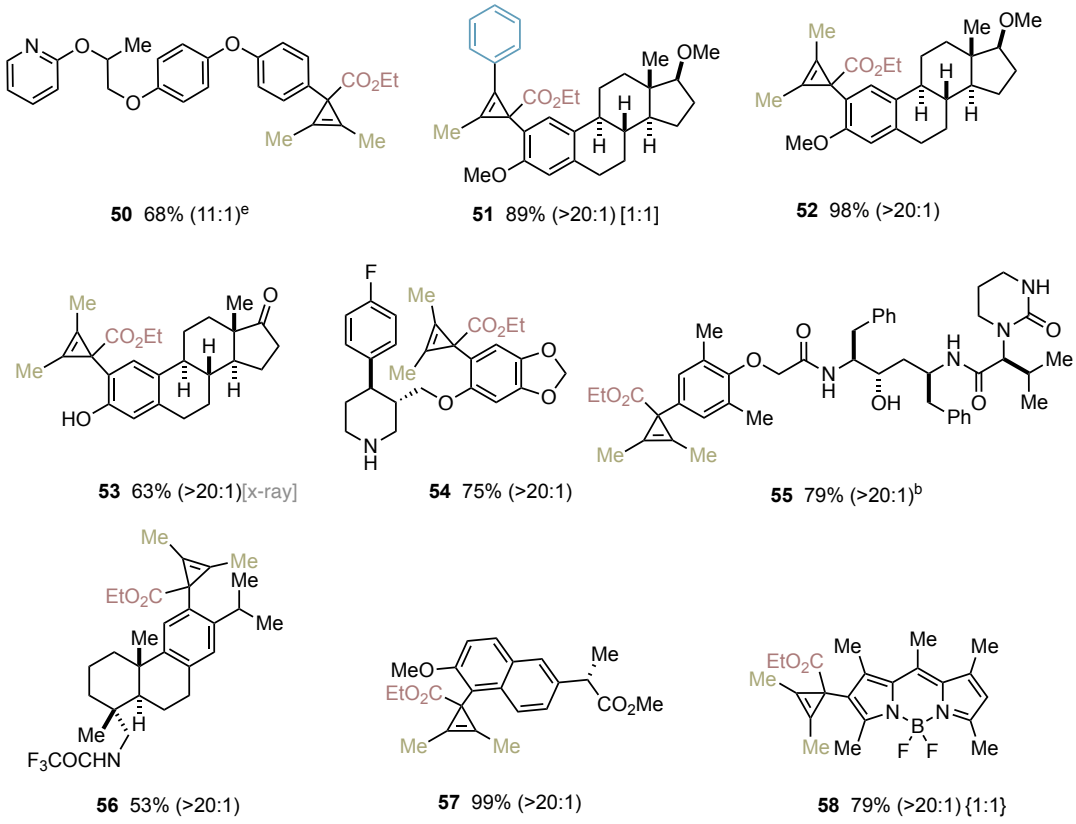
49 81% (>20:1)[e]

See Table 8 for reaction conditions

Table 8 Reaction scope for natural products, drug molecules and fluorescent dyes (2)



natural products, drug molecules and fluorescent dyes



Reaction conditions: arene (0.10 mmol), CPC 1 (0.12 mmol), CsF (0.10-0.15 mmol), HFIP (2 mL), room temperature. In parenthesis ratio of regioisomers is indicated. In brackets ratio of diastereoisomers is indicated. In curly brackets ratio of mono/bis-cyclopropenylation is indicated. [a] 2,2,2-trifluoroethanol was used as solvent. [b] Conducted without CsF. [c] Desipramine hydrochloride was used as starting material. [d] Starting material with free carboxylic acid was used, for purification purpose the final acid was treated with $TMSCHN_2$ to provide methyl ester derivative **47**. [e] HBF_4 (50-55% w/w solution in Et_2O) was added.

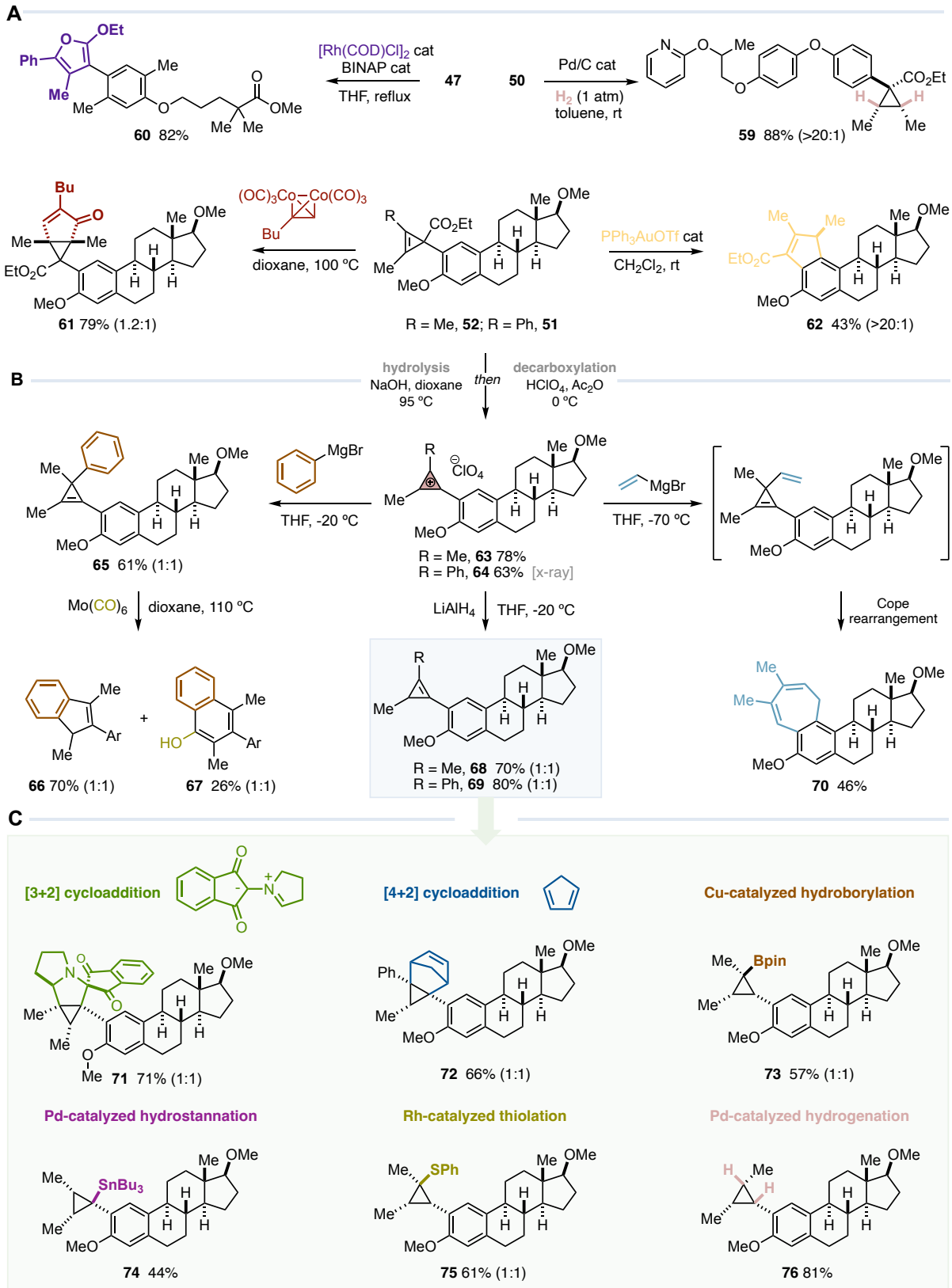
4.7.5 Cyclopropene derivatizations

To increase the synthetic potential of our C–H bond cyclopropenylation process, we took advantage of the broad and diverse variety of known transformations of cyclopropenes (Table 8). We demonstrated that the Pd-catalyzed hydrogenation of **50** and Pauson-Khand reaction of **52** with hexacarbonyldicobalt(1-hexyne) complex were amenable to the selective construction of tetra and hexa-substituted cyclopropane cores (**59**, **61**) (Table 9A). While the Rh(I)-catalyzed cycloisomerization of **47** delivered tetrasubstituted furan **60**, the Au(I)-catalyzed rearrangement of **52** provided the formation of indene **62** with excellent stereoselectivity. The latter example highlights a rare example of a two-step late-stage C–H bond cyclopentannulation.

We then wondered whether we could expand the synthetic potential of our late-stage C–H bond cyclopropenylation by transforming the cyclopropenyl ester derivative into a new cyclopropenium cation that could undergo nucleophilic additions (Table 9B).[40, 41] We were pleased to synthesize new CPCs **63** and **64** as stable solids from **52** and **51** by a two-step protocol involving hydrolysis with NaOH and oxidative decarboxylation with $HClO_4$ in Ac_2O. Site-selective attack of phenylmagnesium bromide provided **65**, that upon treatment with $Mo(CO)_6$ led predominantly to indene **66** and, upon CO insertion, to naphthol **67**. Reduction with $LiAlH_4$ provided cyclopropenes **68** and **69**. In addition, attack of vinylmagnesium bromide to **63** at low temperature provided the formation of cycloheptadiene **70** *via* a spontaneous Cope rearrangement of the corresponding vinylcyclopropene intermediate. **68** and **69** could successfully undergo [3+2] and [4+2] cycloaddition reactions (**71**, **72**). The synthetic utility of cyclopropenes as precursors of highly functionalized cyclopropanes was finally confirmed by the well-known hydrometalation/electrophile trapping sequence in a protoborylation (**73**), a hydrostannation (**74**), and a hydrothiolation (**75**) or by a simple hydrogenation (**76**) (Table 9C). Notably, these densely functionalized sp^3-rich cyclopropane cores are hard to introduce by other approaches and, in the cases of **73** and **74**, provide the opportunity for further functionalization by cross-coupling, increasing the potential utility of our cyclopropenylation process.

[40] Breslow, R.; Höver, H.; Chang, H. W. *J. Am. Chem. Soc.* **1962**, *84*, 3168.
[41] For examples of nucleophilic additions with cyclopropenium cations, see (a) Padwa, A.; Blacklock, C.S.; Chou, N.; Hatanaka, *J. Am. Chem. Soc.* **1979**, *101*, 5743, (b) Padwa, A.; Rieker, W. F.; Rosenthal, R. J. *J. Am. Chem. Soc.* **1983**, *105,* 4446, (c) Padwa, A.; Rieker, W. F.; Rosenthal, R. J. *J. Org. Chem.* **1984**, *49*, 1353 (d) Padwa, A.; Rieker, W. F.; Rosenthal, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 1710, (e) Padwa, A.; Goldstein, S. I.; Rosenthal, R. J. *J. Org. Chem.* **1987**, *52*, 3278.

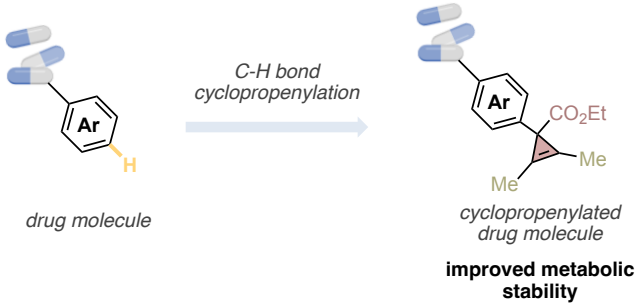
Table 9 Cyclopropene derivatizations



4.7.6 Bioassays on cyclopropenylated molecules[42]

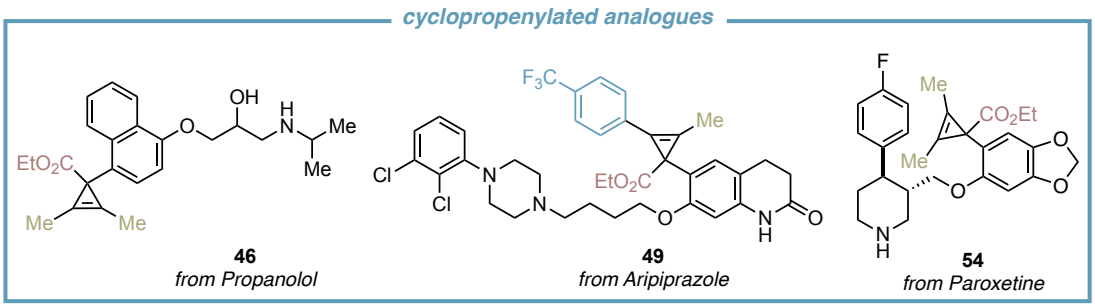
The described late-stage cyclopropenylation occurs at the most electron-rich aromatic positions of drug molecules. Such positions are common sites of metabolic instability through hydroxylation in the liver, which can be at the origin of low *in vivo* metabolic stability of drug molecules.[43] This led us to explore the possible use of the cyclopropene ring as tool to shield bioactive compounds from metabolic instability. The physicochemical (solubility and lipophilicity) and ADME (Absorption, Distribution, Metabolism and Excretion) properties of selected cyclopropenylated drug molecules were measured in order to test our hypothesis. Selected examples are shown in Table 10.

Table 10 Physiochemical and ADME properties for bioactive compounds and cyclopropenylated analogues



Entry	Compound	Solubility (mM, pH = 6.8)	LogP	Permeability (% FA)	CYP rat ($t_{1/2}$) (min^{-1})
1	Propanolol	0.71	2.80	94.9	<1.98
2	**46**	0.75	3.65	90.3	6.11
3	Aripiprazole	0.001	4.70	96.5	2.00
4	**49**	0.013	4.70	91.4	4.29
5	Paroxetine	0.75	3.60	94.1	4.9
6	**54**	0.75	4.70	93.2	14.4

FA = Fraction absorbed. CYP = Cytochrome P.



[42] The work presented in this Section was performed by the Novartis Institutes of Biomedical Research. For the full study, please see : Tu, H.-F. ; Jeandin, A. ; Suero, M.G. *Angew. Chem. Int. Ed.* **2023**, *62*, e202308379 and the corresponding Section in the Supporting Information.
[43] (a) Bathelt, C. M.; Ridder, L.; Mulholland, A. J.; Harvey, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 15004; (b) Bathelt, C. M.; Ridder, L.; Mulholland, A. J.; Harvey, J. N. *Org. Biomol. Chem.* **2004**, *2*, 2998.

The introduction of the cyclopropene resulted to have only a limited influence on the solubility and passive penetration properties, and an improved metabolic stability was generally observed in the cyclopropenylated analogues (Table 10, entries 1, 3, 5 *vs.* 2, 4, 6, respectively). The presence of the 2,3-dimethyl-2-cyclopropene moiety resulted in an improved metabolic stability of the drug molecules, blocking arene hydroxylation in rat liver cells.[44]

4.8 Conclusions

We have developed a novel late-stage C-H bond functionalization reaction allowing for the introduction of cyclopropene rings into a broad range of simple aromatics and complex molecules. The reaction occurs in simple conditions and with excellent selectivity and efficiency. Preliminary mechanistic investigations suggested the formation of an intermediate generated by the solvent attack to the CPC, which might act as cyclopropenium cation reservoir. The newly installed cyclopropene scaffold was further derivatized in diverse ways by taking advantage of the inherent versatility of the smallest unsaturated carbocycle. These transformations allowed to reach unique molecular architectures, difficult or not possible to attain with known methodologies for late-stage functionalization. Additionally, the cyclopropene motif revealed to be a shield against metabolic instability in rat liver cells. This C-H bond cyclopropenylation may pave the way for cyclopropenes to become common place in drug discovery, not only as small rings but also as stepping stones to complex, sp^3-rich molecular scaffolds.

4.9 Experimental section

General information. All reagents were used as purchased and used with no further purification. Ethyl diazoacetate, (≥13 wt. % dichloromethane) was purchased from Aldrich (Ref. E22201) and used without further purification. Anhydrous solvents were dried by passing through an activated alumina column on a PureSolvTM solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography (TLC) was carried out using aluminum sheets with 0.2 mm of silica gel (Merck GF234). Visualization of the developed chromatogram was performed by irradiation with UV light or treatment with a solution of potassium permanganate or vanillin stain followed by heating. Flash column chromatography was performed on silica gel (Aldrich, 230-400 mesh) or neutral silica gel (Material Harvest Ltd., 230-400 mesh). Organic solutions were concentrated under reduced pressure on a Büchi rotatory evaporator. Unless otherwise stated, reactions were carried out under argon atmosphere. Yields refer to purified compounds unless otherwise noted. NMR spectra were recorded at 298 K on Bruker Avance 300, Bruker Avance 400 Ultrashield or Bruker Avance 500 Ultrashield apparatuses. Coupling constants (*J*) are quoted in hertz (Hz). Multiplicity is reported with the following abbreviations: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dt = doublet of triplets, td = triplet of doublets, tt = triplet of triplets, sp = septet, m = multiplet, app = apparent. Melting points were measured using open glass capillaries in a Büchi B540 apparatus. Infrared spectra were recorded on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Liquid chromatography-mass spectrometry

[44] For an example of a structural replacement increasing metabolic stability, see: Barnes-Seeman, D.; Jain, M.; Bell, L.; Ferreira, S.; Cohen, S.; Chen, X. H.; Amin, J.; Snodgrass, B.; Hatsis, P. *ACS Med. Chem. Lett.* **2013**, *4*, 514.

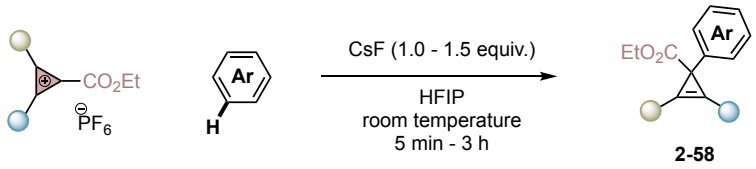
(LC-MS) and gas chromatography-mass spectrometry (GC-MS) analysis were carried out in Agilent 1260 Infinity – 6130 Quadrupole and Agilent 7890B - 5977A MSD, respectively.

Late-stage aryl C–H bond cyclopropenylation.

General procedure for reaction optimization:

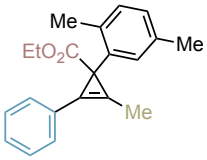
To a 10 mL oven-dried tube equipped with a stirring bar was added the corresponding **CPC** (0.05 mmol, 18.0 mg for **1a** and 22.0 mg for **1b**) and the additive (0.075 mmol, 1.5 equiv.). The tube was sealed before being evacuated and backfilled with argon. *p*-Xylene (10.6 mg, 13 µL, 0.1 mmol) and dry solvent (1.0 mL) were added and the resulting mixture was stirred at room temperature for 3 h. Then, the reaction mixture was filtered through a pad of celite, and the solvent was removed under *vacuum*. The resulting reaction mixture was analyzed by ^{1}H NMR using dibromomethane as internal standard.

General procedure A for late-stage aryl C–H bond cyclopropenylation.



To a 10 mL oven-dried tube equipped with a stirring bar was added the corresponding CPC (**1a-g** 0.10-0.12 mmol) and CsF (23.0 mg, 0.15 mmol). The tube was sealed before being evacuated and backfilled with argon. A solution of the corresponding arene/heteroarene (0.1 mmol, 1.0 equiv.) in HFIP (2.0 mL) was added and the resulting mixture was stirred at room temperature. For the substrates bearing nucleophilic amine or pyridine groups, the corresponding arenes/heteroarenes (0.10 mmol, 1.0 equiv.) were treated with HBF_4 (50-55% w/w solution in Et_2O, 21 µL, 1.4 equiv.) before being added to the reaction tube. When the reaction was complete, the reaction mixture was quenched by aq. sat. $NaHCO_3$. After removing the solvent, the resulting mixture was extracted with dichloromethane, dried over anhydrous sodium sulfate, analyzed by ^{1}H NMR. The crude residue was purified by column chromatography on silica gel to give the corresponding cyclopropene.

ethyl 1-(2,5-dimethylphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (2)



Prepared according to the **general procedure A** using *p*-xylene (0.6 mL) and **1a** (35.0 mg, 0.10 mmol, 1.0 equiv.) in HFIP (1.4 mL). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (10.2 mg, 33% yield).

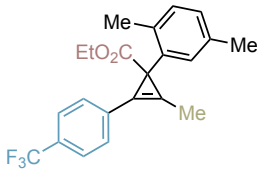
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 2H), 7.50 – 7.41 (m, 2H), 7.41 – 7.34 (m, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.02 (s, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 2.37 (s, 3H), 2.20 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 140.8, 135.3, 134.4, 129.9, 128.99, 128.96, 128.8, 128.6, 127.72, 127.70, 114.4, 109.9, 60.6, 35.2, 21.1, 19.3, 14.5, 10.0.

IR ν max (film, cm^{-1}): 2921, 1871, 1712, 1490, 1444, 1221, 1167, 1054, 810, 760.

HRMS (ESI) calculated for $C_{21}H_{22}NaO_2^+$ $[M+Na]^+$ m/z: 329.1512, found: 329.1510.

ethyl 1-(2,5-dimethylphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (3)



Prepared according to the **general procedure A** using *p*-xylene (10.4 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (31.5 mg, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.60 (m, 4H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 7.00 (s, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 2.42 (s, 3H), 2.25 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6, 140.2, 135.5, 134.4, 131.3, 130.3 (q, *J* = 32.7 Hz), 130.2, 129.1, 128.8, 128.0, 125.9 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 118.0, 109.3, 60.9, 35.5, 21.1, 19.3, 14.4, 10.2.

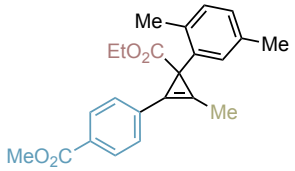
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7.

IR ν max (film, cm^{-1}): 2979, 2930, 1872, 1714, 1613, 1405, 1320, 1223, 1164, 1117, 1056, 1013, 844, 807, 759.

HRMS (ESI) calculated for $C_{22}H_{21}F_3NaO_2^+$ $[M+Na]^+$ m/z: 397.1386, found: 397.1371.

m.p. 134-135 ºC.

methyl 4-(3-(2,5-dimethylphenyl)-3-(ethoxycarbonyl)-2-methylcycloprop-1-en-1-yl)benzoate (4)



Prepared according to the **general procedure A** using *p*-xylene (37.0 μL, 0.30 mmol), **1c** (41.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using

^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (28.2 mg, 77% yield).

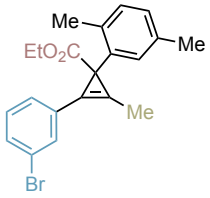
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 – 8.05 (m, 2H), 7.71 – 7.61 (m, 2H), 7.12 – 7.02 (m, 1H), 7.00 – 6.88 (m, 2H), 4.18 (qd, J = 7.1, 0.7 Hz, 2H), 3.95 (s, 3H), 2.45 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 166.8, 140.4, 135.6, 134.5, 132.2, 130.23, 130.21, 130.0, 129.0, 128.9, 128.1, 118.1, 109.7, 61.0, 52.4, 35.6, 21.2, 19.4, 14.6, 10.4.

IR ν max (film, cm^{-1}): 2952, 1714, 1606, 1435, 1274, 1223, 1172, 1109, 771.

HRMS (ESI) calculated for $C_{23}H_{25}O_4^+$ $[M+H]^+$ m/z: 365.1747, found 365.1753.

ethyl 2-(3-bromophenyl)-1-(2,5-dimethylphenyl)-3-methylcycloprop-2-ene-1-carboxylate (5)



Prepared according to the **general procedure A** using *p*-xylene (18.4 μL, 0.15 mmol), **1d** (43.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 4/1) provided the title compound as a colourless oil (18.2 mg, 47% yield).

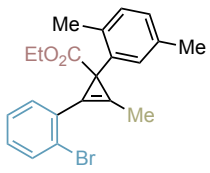
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (t, J = 1.8 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.31 (m, 1H), 7.08 – 7.01 (m, 1H), 6.98 – 6.90 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.34 (s, 3H), 2.20 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 140.4, 135.5, 134.5, 131.8, 131.7, 130.5, 130.2, 129.9, 129.0, 128.0, 127.5, 122.9, 116.7, 109.1, 60.9, 35.6, 21.2, 19.4, 14.6, 10.2.

IR ν max (film, cm^{-1}): 2979, 1716, 1589, 1558, 1471, 1225, 1058, 786.

HRMS (ESI) calculated for $C_{21}H_{22}BrO_2^+$ $[M+H]^+$ m/z: 385.0798, found 385.0797.

ethyl 2-(2-bromophenyl)-1-(2,5-dimethylphenyl)-3-methylcycloprop-2-ene-1-carboxylate (6)



Prepared according to the **general procedure A** using *p*-xylene (37.0 μL, 0.30 mmol), **1e** (43.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (18.1 mg, 47% yield).

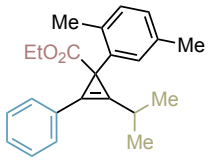
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.28 – 7.23 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.94 (s, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 2.38 (s, 3H), 2.20 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 140.3, 135.3, 134.5, 133.3, 130.8, 130.00, 129.98, 129.1, 128.7, 127.8, 127.5, 123.7, 118.3, 108.3, 60.8, 34.5, 21.1, 19.3, 14.5, 11.2.

IR ν max (film, cm^{-1}): 2922, 1871, 1714, 1416, 1223, 1168, 1064, 759.

HRMS (ESI) calculated for $C_{21}H_{21}BrNaO_2^+$ $[M+Na]^+$ m/z: 407.0617, found: 407.0609.

ethyl 1-(2,5-dimethylphenyl)-2-isopropyl-3-phenylcycloprop-2-ene-1-carboxylate (7)



Prepared according to the **general procedure A** using *p*-xylene (123.0 µL, 10.0 equiv.), **1f** (38.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 10/1) provided the title compound as a colourless oil (14.7 mg, 44% yield).

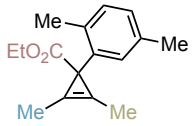
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.1 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.32 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.95 – 6.91 (m, 2H), 4.24 – 4.07 (m, 2H), 3.11 – 3.02 (m, 1H), 2.36 (s, 3H), 2.17 (s, 3H), 1.35 (d, *J* = 6.9 Hz, 6H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 140.9, 135.1, 134.2, 130.0, 129.3, 128.80, 128.78, 128.6, 127.60, 127.56, 122.9, 108.7, 60.6, 35.8, 26.7, 21.6, 21.1, 21.0, 19.6, 14.4.

IR ν max (film, cm^{-1}): 2967, 1715, 1496, 1445, 1222, 1166, 1094, 1040, 810.

HRMS (ESI) calculated for $C_{23}H_{26}NaO_2^+$ $[M+Na]^+$ m/z: 357.1825, found: 357.1825.

ethyl 1-(2,5-dimethylphenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (8)



Prepared according to the **general procedure A** using *p*-xylene (37.0 µL, 0.30 mmol), **1g** (29.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (16.4 mg, 67% yield).

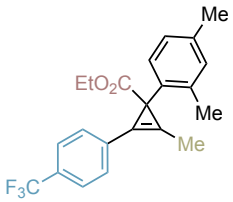
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.6 Hz, 1H), 6.96 – 6.91 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 6H), 2.19 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 142.1, 135.2, 134.5, 129.9, 129.2, 127.4, 108.5, 60.4, 34.0, 21.1, 19.1, 14.5, 9.4.

IR ν max (film, cm^{-1}): 2918, 2849, 1714, 1222, 1043.

HRMS (ESI) calculated for $C_{16}H_{20}NaO_2^+$ $[M+Na]^+$ m/z: 267.1356, found: 267.1357.

ethyl 1-(2,4-dimethylphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (9)



Prepared according to the **general procedure A** using *m*-xylene (10.4 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (30.3 mg, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4H), 7.06 (d, *J* = 7.7 Hz, 1H), 7.03 (s, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.48 (s, 3H), 2.40 (s, 3H), 2.31 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7, 137.5, 137.3, 136.8, 131.3, 131.0, 130.3 (q, *J* = 32.6 Hz), 129.1, 128.2, 126.7, 125.8 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 272.2 Hz), 118.0, 109.2, 60.8, 35.1, 21.0, 19.7, 14.4, 10.2.

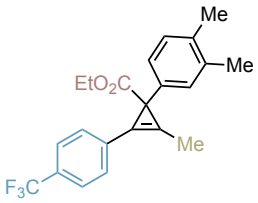
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8.

IR ν max (film, cm^{-1}): 2977, 2924, 1874, 1711, 1613, 1405, 1320, 1213, 1168, 1108, 1055, 1010, 839, 754.

HRMS (ESI) calculated for $C_{22}H_{21}F_3NaO_2^+$ $[M+Na]^+$ m/z: 397.1386, found: 397.1393.

m.p. 121 ºC.

ethyl 1-(3,4-dimethylphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (10)



Prepared according to the **general procedure A** using *o*-xylene (10.4 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be 12:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (30.7 mg, 82% yield).

major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.13 (s, 1H), 7.10 – 7.05 (m, 2H), 4.28 – 4.16 (m, 2H), 2.45 (s, 3H), 2.25 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 138.0, 136.3, 134.8, 130.5, 130.3 (q, *J* = 32.5 Hz), 129.5, 129.3, 129.2, 125.8 (q, *J* = 3.9 Hz), 125.4, 124.0 (q, *J* = 272.2 Hz), 115.1, 108.0, 60.7, 35.3, 20.0, 19.4, 14.4, 9.8.

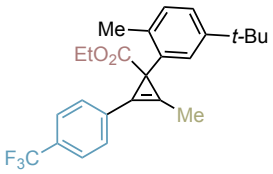
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

IR ν max (film, cm^{-1}): 2977, 2921, 1875, 1713, 1613, 1499, 1446, 1406, 1320, 1221, 1164, 1104, 1066, 1013, 844, 747.

HRMS (ESI) calculated for $C_{22}H_{21}F_3NaO_2^+$ $[M+Na]^+$ m/z: 397.1386, found: 397.1375.

m.p. 68-69 ºC.

ethyl 1-(5-(*tert*-butyl)-2-methylphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (11)



Prepared according to the **general procedure A** using 1-(*tert*-butyl)-4-methylbenzene (14.8 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (38.6 mg, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 4H), 7.24 – 7.18 (m, 2H), 7.15 – 7.10 (m, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.49 (s, 3H), 2.39 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 148.7, 139.8, 134.3, 131.4, 130.2 (q, *J* = 32.6 Hz), 129.8, 129.0, 125.7 (q, *J* = 3.7 Hz), 125.3, 124.2, 124.0 (q, *J* = 272.9 Hz), 117.9, 109.3, 60.8, 35.9, 34.2, 31.3, 19.3, 14.4, 10.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

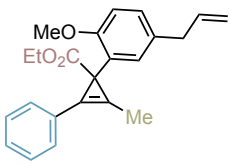
IR ν max (film, cm^{-1}): 2967, 1868, 1713, 1612, 1362, 1321, 1248, 1214, 1160, 1119, 1054, 1012, 950, 846, 820.

HRMS (ESI) calculated for $C_{25}H_{27}F_3NaO_2^+$ $[M+Na]^+$ m/z: 439.1855, found: 439.1865.

m.p. 104 ºC.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(5-allyl-2-methoxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (12)



Prepared according to the **general procedure A** using estragole (14.8 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (17.7 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.36 – 7.31 (m, 1H), 7.03 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.00 (d, *J* = 2.2 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 5.91 (ddt, *J* = 16.9, 10.0, 6.8 Hz, 1H), 5.06 – 4.97 (m, 2H), 4.17 (qd, *J* = 7.1, 0.7 Hz, 2H), 3.85 (s, 3H), 3.27 (d, *J* = 6.8 Hz, 2H), 2.45 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

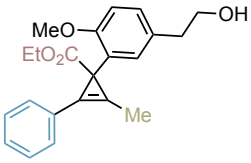
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 157.0, 137.8, 131.8, 131.2, 129.31, 129.29, 128.6, 128.4, 127.7, 127.5, 115.4, 112.5, 110.7, 110.5, 60.3, 55.4, 39.4, 32.8, 14.5, 10.2.

IR ν max (film, cm^{-1}): 2974, 2833, 1868, 1771, 1715, 1606, 1495, 1444, 1363, 1217, 1170, 1030, 912, 811, 758.

HRMS (ESI) calculated for $C_{23}H_{24}NaO_3^+$ $[M+Na]^+$ m/z: 371.1618, found: 371.1617.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(5-(2-hydroxyethyl)-2-methoxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (13)



Prepared according to the **general procedure A** using 2-(4-methoxyphenyl)ethan-1-ol (15.2 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol) for 2.5 h. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 3/1) provided the title compound as a colourless oil (17.8 mg, 51% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.2 Hz, 2H), 7.45 – 7.40 (m, 2H), 7.36 – 7.31 (m, 1H), 7.07 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 3.78 (t, *J* = 6.6 Hz, 2H), 2.75 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H).

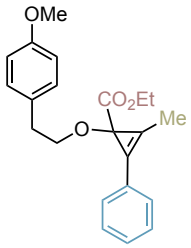
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 157.3, 131.5, 130.0, 129.7, 129.2, 128.6, 128.5, 128.3, 127.4, 112.6, 110.7, 110.5, 63.7, 60.3, 55.4, 38.4, 32.8, 14.5, 10.2.

IR ν max (film, cm^{-1}): 2935, 1712, 1491, 1444, 1262, 1218, 1169, 1024, 811.

HRMS (ESI) calculated for $C_{22}H_{25}O_4^+$ $[M+H]^+$ m/z: 353.1747, found: 353.1758.

An additional experiment carried out using 2-(4-methoxyphenyl)ethan-1-ol (7.6 mg, 0.05 mmol) and **1a** (21.0 mg, 0.06 mmol) was quenched after 10 min of reaction. **13** (45% yield) and **13'** (20% yield) were obtained by ^{1}H NMR analysis using dibromomethane as internal standard.

ethyl 1-(4-methoxyphenethoxy)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (13')



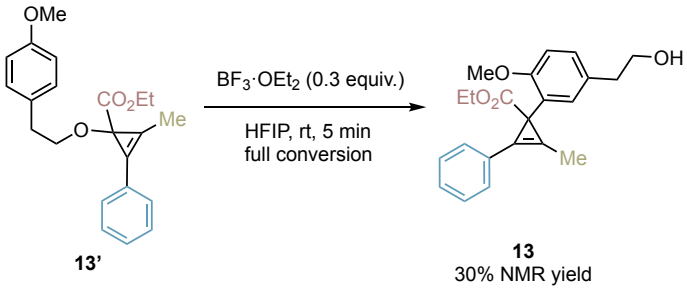
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.46 – 7.34 (m, 3H), 7.13 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.28 – 4.14 (m, 2H), 3.79 (s, 3H), 3.87 – 3.67 (m, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 158.0, 130.9, 129.9, 129.4, 129.2, 128.8, 126.2, 114.5, 114.2, 113.7, 70.0, 63.0, 61.0, 55.3, 35.8, 14.4, 9.7.

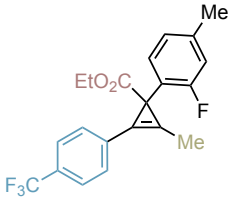
IR ν max (film, cm^{-1}): 2928, 1723, 1611, 1512, 1445, 1246, 1176, 1093, 1035, 763.

HRMS (ESI) calculated for $C_{22}H_{24}NaO_4^+$ $[M+Na]^+$ m/z: 375.1567, found: 375.1578.

A control experiment with product **13'** (4.6 mg), $BF_3{\cdot}OEt_2$ (30 mol%) and HFIP (0.5 mL) was performed. After 5 min, full conversion of **13'** was observed and formation of **13** was detected by ^{1}H NMR (30% yield) using dibromomethane as internal standard.



ethyl 1-(2-fluoro-4-methylphenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (major, 14)



Prepared according to the **general procedure A** using 1-fluoro-3-methylbenzene (11.0 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be 1.5:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the

mixture of two isomers **14** and **14'** as a white solid (26.3 mg, 70% yield). Attempts for the separation of both regioisomers were unsuccessful using preparative layer chromatography or column chromatography. The minor isomer was confirmed by an authentic sample.

major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.65 (m, 4H), 7.14 – 7.07 (m, 1H), 6.93 – 6.83 (m, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 2.34 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

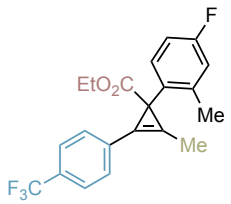
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 161.6 (d, *J* = 244.9 Hz), 139.2 (d, *J* = 7.9 Hz), 130.4 (q, *J* = 32.6 Hz), 129.5 (d, *J* = 5.2 Hz), 129.30, 129.29, 125.7 (q, *J* = 3.7 Hz), 125.6 (d, *J* = 17.0 Hz), 124.7 (d, *J* = 3.0 Hz), 123.9 (q, *J* = 272.8 Hz), 116.0 (d, *J* = 22.0 Hz), 114.8, 109.2, 61.0, 31.5, 21.0, 14.3, 10.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8, -116.0 (m).

IR ν max (film, cm^{-1}): 2980, 2926, 1870, 1713, 1613, 1318, 1264, 1221, 1116, 1057, 1012, 932, 867, 845, 763.

HRMS (ESI) calculated for $C_{21}H_{18}F_4NaO_2^+$ $[M+Na]^+$ m/z: 401.1135, found: 401.1132.

ethyl 1-(4-fluorophenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (minor, 14')



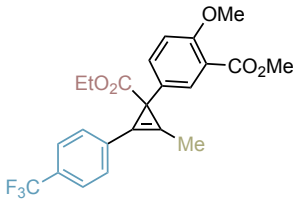
minor isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 – 7.67 (m, 4H), 7.09 (dd, *J* = 8.5, 5.9 Hz, 1H), 6.89 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.78 – 6.71 (m, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.47 (s, 3H), 2.40 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 161.7 (d, *J* = 244.9 Hz), 139.9 (d, *J* = 7.8 Hz), 136.3 (d, *J* = 3.0 Hz), 130.9, 130.5 (q, *J* = 32.9 Hz), 129.7 (d, *J* = 8.4 Hz), 129.0, 125.9 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 271.9 Hz), 117.7, 116.8 (d, *J* = 21.0 Hz), 112.6 (d, *J* = 20.7 Hz), 108.9, 61.0, 34.7, 19.8, 14.4, 10.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8, -116.2 (m).

m.p. 87-88 ºC.

methyl 5-(1-(ethoxycarbonyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-en-1-yl)-2-methoxybenzoate (15)



Prepared according to the **general procedure A** using methyl 2-methoxybenzoate (16.6 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 4/1) provided the title compound as a yellow oil (34.9 mg, 80% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.5 Hz, 1H), 7.71 – 7.62 (m, 4H), 7.46 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 4.20 (qd, *J* = 7.1, 3.2 Hz, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 2.45 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

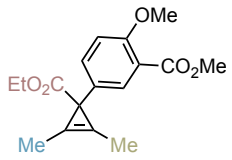
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 166.8, 157.7, 133.1, 132.5, 131.3, 130.5 (q, *J* = 32.5 Hz), 130.1, 129.3, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.4 Hz), 119.7, 114.5, 111.9, 107.7, 60.9, 56.1, 52.1, 34.7, 14.4, 9.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8.

IR ν max (film, cm^{-1}): 2951, 2839, 1877, 1711, 1613, 1576, 1499, 1435, 1407, 1321, 1236, 1162, 1121, 1065, 1015, 842, 787.

HRMS (ESI) calculated for $C_{23}H_{21}F_3NaO_5^+$ $[M+Na]^+$ m/z: 457.1233, found: 457.1223.

methyl 5-(1-(ethoxycarbonyl)-2,3-dimethylcycloprop-2-en-1-yl)-2-methoxybenzoate (16)



Prepared according to the **general procedure A** using methyl 2-methoxybenzoate (25.0 mg, 0.15 mmol), **1g** (29.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 7/1) provided the title compound as a colourless oil (15.7 mg, 52% yield).

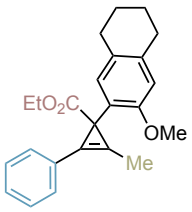
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 2.4 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 3.89 (s, 3H), 2.13 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 166.9, 157.4, 134.4, 133.5, 131.4, 119.5, 111.8, 106.5, 60.4, 56.1, 52.0, 33.8, 14.4, 8.7.

IR ν max (film, cm^{-1}): 2842, 1707, 1498, 1435, 1308, 1238, 1197, 1082, 1044, 956, 834.

HRMS (ESI) calculated for $C_{17}H_{20}NaO_5^+$ $[M+Na]^+$ m/z: 327.1203, found: 327.1206.

ethyl 1-(3-methoxy-5,6,7,8-tetrahydronaphthalen-2-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (17)



Prepared according to the **general procedure A** using 6-methoxy-1,2,3,4-tetrahydronaphthalene (16.2 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (25.8 mg, 71% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.60 (m, 2H), 7.45 – 7.37 (m, 2H), 7.36 – 7.29 (m, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 2.79 – 2.71 (m, 2H), 2.66 – 2.56 (m, 2H), 2.45 (s, 3H), 1.83 – 1.68 (m, 4H), 1.21 (t, *J* = 7.1 Hz, 3H).

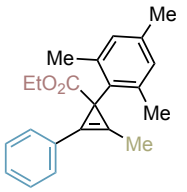
^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 156.3, 136.5, 129.4, 129.3, 128.70, 128.67, 128.6, 128.3, 127.6, 112.9, 110.9, 110.6, 60.3, 55.3, 32.5, 29.7, 28.6, 23.4, 23.2, 14.5, 10.2.

IR ν max (film, cm^{-1}): 2925, 1869, 1714, 1611, 1498, 1444, 1408, 1310, 1214, 1106, 1055, 1034, 915, 846, 757.

HRMS (ESI) calculated for $C_{24}H_{26}NaO_3^+$ $[M+Na]^+$ m/z: 385.1774, found: 385.1780.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured

ethyl 1-mesityl-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (18)



Prepared according to the **general procedure A** using mesitylene (12.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (22.7 mg, 71% yield).

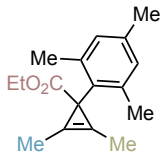
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.38 (m, 4H), 7.37 – 7.32 (m, 1H), 6.84 (s, 2H), 4.23 (q, *J* = 7.4 Hz, 2H), 2.43 (s, 3H), 2.27 (s, 3H), 2.26 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 137.9, 136.4, 135.8, 129.4, 129.1, 128.5, 128.4, 128.1, 115.8, 112.5, 60.7, 35.2, 21.7, 20.8, 14.5, 10.1.

IR ν max (film, cm^{-1}): 3062, 1868, 1709, 1610, 1462, 1318, 1209, 1162, 1056, 1013, 930, 839, 754.

HRMS (ESI) calculated for $C_{22}H_{24}NaO_2^+$ $[M+Na]^+$ m/z: 343.1669, found: 343.1667.

m.p. 75-76 ºC.

ethyl 1-mesityl-2,3-dimethylcycloprop-2-ene-1-carboxylate (19)



Prepared according to the **general procedure A** using mesitylene (12.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 9/1 to 4/1) provided the title compound as a colourless oil (14.2 mg, 55% yield).

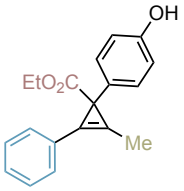
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (s, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.31 (s, 6H), 2.25 (s, 3H), 2.19 (s, 6H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0, 137.9, 137.4, 135.8, 128.9, 110.6, 60.5, 33.5, 21.0 (2C), 14.7, 9.9.

IR ν max (film, cm^{-1}): 2974, 2921, 1712, 1206, 1040.

HRMS (ESI) calculated for $C_{17}H_{22}NaO_2^+$ $[M+Na]^+$m/z: 281.1512, found: 281.1516.

ethyl 1-(4-hydroxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (20)



Prepared according to the **general procedure A** using phenol (9.4 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 4/1) provided the title compound as a yellow foam (14.9 mg, 51% yield).

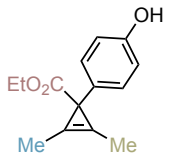
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.25 – 7.20 (m, 2H), 6.75 – 6.68 (m, 2H), 4.23 – 4.13 (m, 2H), 2.39 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 154.1, 133.4, 129.5, 129.2, 128.8, 128.7, 126.8, 115.0, 111.7, 108.7, 60.6, 34.8, 14.4, 9.6.

IR ν max (film, cm^{-1}): 3400, 2977, 2922, 1792, 1711, 1684, 1611, 1511, 1444, 1365, 1204, 1031, 838, 758.

HRMS (ESI) calculated for $C_{19}H_{18}NaO_3^+$ $[M+Na]^+$ m/z: 317.1148, found: 317.1161.

ethyl 1-(4-hydroxyphenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (21)



Prepared according to the **general procedure A** using phenol (9.4 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 20/1 to 2/1) provided the title compound as a colourless oil (13.0 mg, 56% yield).

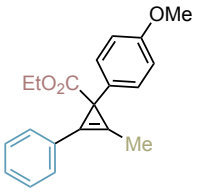
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.7 Hz, 2H), 4.85 (s, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.11 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 153.9, 134.9, 129.6, 115.1, 106.9, 60.5, 34.2, 14.6, 8.9.

IR ν max (film, cm^{-1}): 3388, 2981, 2918, 1792, 1712, 1688, 1515, 1436, 1266, 1219, 1042.

HRMS (ESI) calculated for $C_{14}H_{16}NaO_3^+$ $[M+Na]^+$ m/z: 255.0992, found: 255.0992.

ethyl 1-(4-methoxyphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (22)



Prepared according to the **general procedure A** using anisole (11.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Instead of HFIP, TFE was used as solvent. Ratio of isomers was determined to be 16:1 (*p:o*) from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow solid (17.1 mg, 56% yield).

An additional experiment carried out with HFIP provided the title compound with better yield (74% yield) and lower *para*:*ortho* ratio (5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H), 7.46 – 7.40 (m, 2H), 7.38 – 7.33 (m, 1H), 7.33 – 7.29 (m, 2H), 6.86 – 6.81 (m, 2H), 4.26 – 4.15 (m, 2H), 3.80 (s, 3H), 2.41 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

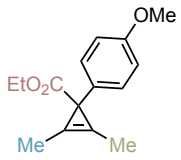
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 158.0, 133.5, 129.3, 129.2, 128.8, 128.6, 126.9, 113.5, 111.7, 108.7, 60.5, 55.2, 34.8, 14.4, 9.6.

IR ν max (film, cm^{-1}): 2971, 2837, 1874, 1708, 1605, 1508, 1444, 1246, 1200, 1174, 1030, 960, 840.

HRMS (ESI) calculated for $C_{20}H_{20}NaO_3^+$ $[M+Na]^+$ m/z: 331.1305, found: 331.1295.

m.p. 51-52 ºC.

ethyl 1-(4-methoxyphenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (23)



Prepared according to the **general procedure A** using anisole (11.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 99/1 to 9/1) provided the title compound as a colourless oil (16.0 mg, 65% yield).

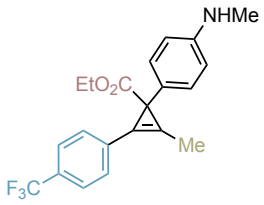
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.17 (m, 2H), 6.84 – 6.80 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.12 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 157.9, 134.9, 129.4, 113.6, 106.9, 60.4, 55.4, 34.2, 14.6, 8.9.

IR ν max (film, cm^{-1}): 2917, 1709, 1610, 1510, 1440, 1281, 1244, 1198, 1172, 1035, 840.

HRMS (ESI) calculated for $C_{15}H_{18}NaO_3^+$ $[M+Na]^+$ m/z: 269.1148, found: 269.1143.

ethyl 2-methyl-1-(4-(methylamino)phenyl)-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (24)



Prepared according to the **general procedure A** using *tert*-butyl methyl(phenyl)carbamate (20.7 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a green oil (11.5 mg, 31% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, 4H), 7.22 – 7.16 (m, 2H), 6.66 – 6.60 (m, 2H), 4.26 – 4.14 (m, 2H), 2.84 (s, 3H), 2.43 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

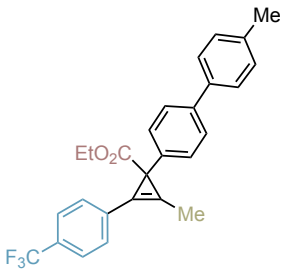
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 147.0, 130.6, 130.21, 130.20 (q, *J* = 32.8 Hz), 129.3, 129.0, 125.7 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.2 Hz), 115.5, 113.0, 108.1, 60.7, 35.0, 31.4, 14.4, 9.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

IR ν max (film, cm^{-1}): 3403, 2916, 1868, 1707, 1613, 1521, 1407, 1319, 1206, 1163, 1120, 1064, 1015, 841.

HRMS (ESI) calculated for $C_{21}H_{21}F_3NO_2^+$ $[M+H]^+$ m/z: 376.1519, found: 376.1521.

ethyl 2-methyl-1-(4'-methyl-[1,1'-biphenyl]-4-yl)-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (25)



Prepared according to the **general procedure A** using 4-methyl-1,1'-biphenyl (16.8 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (33.7 mg, 77% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, 4H), 7.56 – 7.51 (m, 2H), 7.52 – 7.48 (m, 2H), 7.45 – 7.41 (m, 2H), 7.26 (d, *J* = 7.9 Hz, 2H), 4.25 (qd, *J* = 7.1, 2.6 Hz, 2H), 2.49 (s, 3H), 2.42 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 139.33, 139.31, 138.1, 136.9, 130.5 (q, *J* = 32.5 Hz), 130.3, 129.5, 129.4, 128.4, 126.9, 126.8, 125.9 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.1 Hz), 114.8, 107.7, 60.8, 35.4, 21.1, 14.4, 9.8.

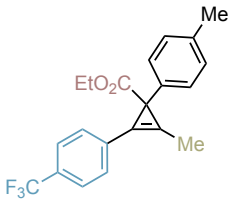
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8.

IR ν max (film, cm^{-1}): 2973, 2924, 1871, 1712, 1613, 1513, 1407, 1321, 1219, 1163, 1119, 1065, 1012, 946, 847, 747.

HRMS (ESI) calculated for $C_{27}H_{23}F_3NaO_2^+$ $[M+Na]^+$ m/z: 459.1542, found: 459.1537.

m.p. 110-112 ºC.

ethyl 2-methyl-1-(*p*-tolyl)-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (26)



Prepared according to the **general procedure A** using toluene (9.2 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be 5.2:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the mixture of two isomers as a white solid (24.2 mg, 67% yield).

major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 4H), 7.28 – 7.23 (m, 2H), 7.15 – 7.08 (m, 2H), 4.27 – 4.17 (m, 2H), 2.45 (s, 3H), 2.34 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 137.5, 136.1, 130.3 (q, *J* = 27.0 Hz), 129.3, 129.1, 128.9, 127.9, 125.8 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.2 Hz), 115.0, 107.9, 60.7, 35.3, 21.1, 14.4, 9.8.

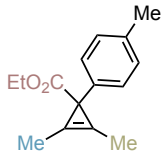
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

IR ν max (film, cm^{-1}): 2973, 2924, 1871, 1712, 1613, 1513, 1407, 1321, 1219, 1163, 1119, 1065, 1012, 946, 847, 747.

HRMS (ESI) calculated for $C_{21}H_{19}F_3NaO_2^+$ $[M+Na]^+$ m/z: 383.1229, found: 383.1231.

m.p. 60-62 ºC.

ethyl 2,3-dimethyl-1-(*p*-tolyl)cycloprop-2-ene-1-carboxylate (27)



Prepared according to the **general procedure A** using toluene (27.6 mg, 0.30 mmol), **1g** (29.0 mg, 0.10 mmol) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be 4.8:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the mixture of two isomers as a yellow oil (11.7 mg, 51% yield).

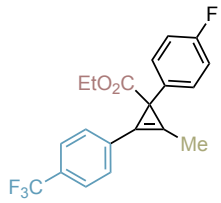
major isomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 2.14 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 139.5, 135.4, 128.7, 128.1, 106.7, 60.3, 34.4, 21.1, 14.5, 8.7.

IR ν max (film, cm^{-1}): 2917, 2851, 1712, 1508, 1436, 1280, 1204, 1041, 838.

HRMS (ESI) calculated for $C_{15}H_{18}NaO_2^+$ $[M+Na]^+$ m/z: 253.1199, found: 253.1194.

ethyl 1-(4-fluorophenyl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (28)



Prepared according to the **general procedure A** using fluorobenzene (0.3 mL) and **1b** (42.0 mg, 0.10 mmol, 1.0 equiv.) in HFIP (0.7 mL). Ratio of isomers was determined to be 6:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (3.5 mg, 10% yield).

major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 4H), 7.35 – 7.29 (m, 2H), 7.02 – 6.94 (m, 2H), 4.25 – 4.15 (m, 2H), 2.44 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 161.5 (d, *J* = 244.6 Hz), 136.3 (d, *J* = 3.2 Hz), 130.5 (q, *J* = 32.6 Hz), 130.1, 129.6 (d, *J* = 7.9 Hz), 129.3, 125.9 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 273.4 Hz), 115.0 (d, *J* = 21.4 Hz), 114.8, 107.7, 60.9, 34.9, 14.4, 9.7.

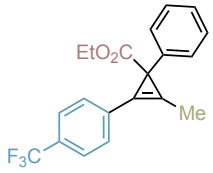
^{19}F NMR (471 MHz, $CDCl_3$) δ -62.7, -116.4 (m).

IR ν max (film, cm^{-1}): 2967, 2924, 1879, 1713, 1613, 1507, 1407, 1318, 1199, 1166, 1123, 1103, 1065, 1032, 948, 842, 749.

HRMS (ESI) calculated for $C_{20}H_{16}F_4NaO_2^+$ $[M+Na]^+$ m/z: 387.0979, found: 387.0985.

m.p. 61-62 ºC.

ethyl 2-methyl-1-phenyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (29)



Prepared according to the **general procedure A** using benzene (0.6 mL) and **1b** (42.0 mg, 0.10 mmol, 1.0 equiv.) in HFIP (1.4 mL). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (8.2 mg, 24% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.38 – 7.33 (m, 2H), 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 1H), 4.22 (qd, *J* = 7.1, 1.8 Hz, 2H), 2.45 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 140.6, 130.4 (q, *J* = 32.4 Hz), 130.3, 129.3, 128.1, 128.0, 126.4, 125.8 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.2 Hz), 114.9, 107.7, 60.8, 35.6, 14.4, 9.8.

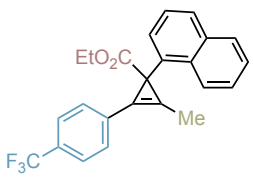
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8.

IR ν max (film, cm^{-1}): 2917, 1879, 1715, 1611, 1406, 1318, 1216, 1159, 1105, 1055, 1011, 846.

HRMS (ESI) calculated for $C_{20}H_{17}F_3NaO_2^+$ $[M+Na]^+$ m/z: 369.1073, found: 369.1071.

m.p. 104 ºC.

ethyl 2-methyl-1-(naphthalen-1-yl)-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (major, 30)



Prepared according to the **general procedure A** using naphthalene (13.0 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be 2.8:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the mixture of two isomers **30** and **30'** as a white solid (28.4 mg, 72% yield). Attempts for the separation of both regioisomers were unsuccessful using preparative layer chromatography or column chromatography. The two regioisomers were confirmed by authentic sample.

major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.83 – 7.77 (m, 3H), 7.76 – 7.73 (m, 2H), 7.57 (ddd, *J* = 8.4, 6.8, 1.5 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.43 (dd, *J* = 7.0, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.1, 7.1 Hz, 1H), 4.26 – 4.12 (m, 2H), 2.54 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 139.0, 133.8, 133.1, 131.1, 130.5 (q, *J* = 32.7 Hz), 129.2, 128.7, 127.8, 126.0, 125.9 (q, *J* = 3.8 Hz), 125.7, 125.6, 125.5, 124.7, 124.0 (q, *J* = 272.1 Hz), 118.1, 109.1, 61.0, 34.8, 14.3, 10.4.

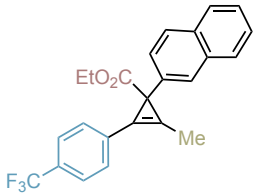
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

IR ν max (film, cm^{-1}): 2986, 1877, 1715, 1610, 1457, 1363, 1316, 1217, 1170, 1133, 1108, 1013, 942, 872, 850, 785.

HRMS (ESI) calculated for $C_{24}H_{19}F_3NaO_2^+$ $[M+Na]^+$ m/z: 419.1229, found: 419.1224.

m.p. 179-180 ºC.

ethyl 2-methyl-1-(naphthalen-2-yl)-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (minor, 30')



minor isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 4H), 7.75 – 7.69 (m, 4H), 7.51 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.48 – 7.43 (m, 2H), 4.31 – 4.22 (m, 2H), 2.51 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 138.3, 133.4, 132.2, 130.5 (q, *J* = 32.6 Hz), 130.3, 129.4, 127.8, 127.7, 127.6, 126.5, 126.4, 126.0, 125.9 (q, *J* = 3.8 Hz), 125.6, 124.0 (q, *J* = 272.3 Hz), 115.0, 107.9, 60.9, 35.8, 14.4, 9.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4.

IR ν max (film, cm^{-1}): 3003, 1868, 1716, 1506, 1405, 1318, 1236, 1214, 1159, 1125, 1065, 1011, 865, 843, 778, 757.

HRMS (ESI) calculated for $C_{24}H_{19}F_3NaO_2^+$ $[M+Na]^+$ m/z: 419.1229, found: 419.1224.

m.p. 92-93 ºC.

ethyl 1-(2-methoxynaphthalen-1-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (31)

Prepared according to the **general procedure A** using 2-methoxynaphthalene (15.8 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (31.2 mg, 87% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.1 Hz, 1H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.46 – 7.37 (m, 3H), 7.34 – 7.28 (m, 2H), 7.21 (d, *J* = 9.0 Hz, 1H), 4.21 – 4.08 (m, 2H), 3.57 (s, 3H), 2.43 (s, 3H), 1.12 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 156.1, 135.0, 129.7, 129.5, 129.2, 128.8, 128.7, 128.4, 128.2, 126.5, 124.9, 123.8, 123.4, 114.0, 113.8, 111.4, 60.9, 55.7, 31.1, 14.8, 10.5.

IR ν max (film, cm^{-1}): 2978, 2936, 1701, 1659, 1458, 1257, 1233, 1199, 1092, 1044, 813, 768.

HRMS (ESI) calculated for $C_{24}H_{22}NaO_3^+$ $[M+Na]^+$ m/z: 381.1461, found: 381.1451.

m.p. 162 ºC.

A single crystal of **31** was obtained through slow evaporation from its solution in ethyl acetate and hexane. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2150954.

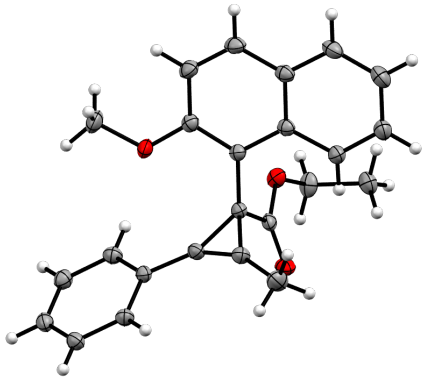
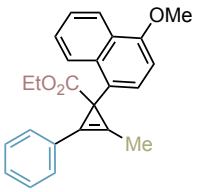


Figure 12 ORTEP diagram of **31**

ethyl 1-(4-methoxynaphthalen-1-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (32)



Prepared according to the **general procedure A** using 1-methoxynaphthalene (15.8 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow solid (27.2 mg, 76% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.53 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.49 – 7.41 (m, 3H), 7.39 – 7.33 (m, 2H), 6.64 (d, *J* = 7.9 Hz, 1H), 4.22 – 4.08 (m, 2H), 3.93 (s, 3H), 2.45 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H).

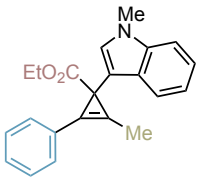
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 155.1, 134.4, 132.2, 129.5, 129.2, 129.0, 128.1, 126.7, 126.1, 125.9, 125.2, 125.0, 122.8, 115.3, 110.1, 103.9, 61.1, 55.8, 34.4, 14.7, 10.5.

IR ν max (film, cm^{-1}): 2834, 1876, 1702, 1653, 1584, 1423, 1374, 1289, 1217, 1093, 1048, 1026, 864, 812, 764.

HRMS (ESI) calculated for $C_{24}H_{22}NaO_3^+$ $[M+Na]^+$ m/z: 381.1461, found: 381.1457.

m.p. 105-107 ºC.

ethyl 2-methyl-1-(1-methyl-1*H*-indol-3-yl)-3-phenylcycloprop-2-ene-1-carboxylate (33)



Prepared according to the **general procedure A** using 1-methyl-1*H*-indole (13.1 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Instead of HFIP, TFE was used as solvent. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a brown solid (30.0 mg, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.57 (m, 3H), 7.47 – 7.42 (m, 2H), 7.39 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 7.24 – 7.19 (m, 2H), 7.08 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.24 (qd, *J* = 7.1, 0.9 Hz, 2H), 3.74 (s, 3H), 2.47 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

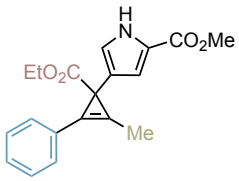
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 136.7, 129.2, 128.8, 128.5, 127.9, 127.7, 127.4, 121.2, 120.3, 118.8, 115.0, 112.6, 109.3, 109.2, 60.6, 32.7, 29.1, 14.5, 10.2.

IR ν max (film, cm^{-1}): 3053, 2931, 1877, 1711, 1465, 1444, 1374, 1327, 1231, 1206, 1092, 1049, 1001, 923, 869, 826, 760, 733.

HRMS (ESI) calculated for $C_{22}H_{21}NNaO_2^+$ $[M+Na]^+$ m/z: 354.1464, found: 354.1463.

m.p. 112-114 ºC.

methyl 4-(1-(ethoxycarbonyl)-2-methyl-3-phenylcycloprop-2-en-1-yl)-1*H*-pyrrole-2-carboxylate (34)



Prepared according to the **general procedure A** using methyl 1*H*-pyrrole-2-carboxylate (13.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol) with HFIP (1.0 mL) as the solvent at 0 ºC. Ratio of isomers was determined to be 4.8:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless solid (29.3 mg, 90% yield).

When the reaction was conducted in HFIP (2.0 mL) at 0 ºC, a slightly lower yield (91% NMR yield) was obtained but with enhanced regioselectivity (6.5:1).

major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.99 (brs, 1H), 7.51 – 7.46 (m, 2H), 7.42 – 7.37 (m, 2H), 7.36 – 7.31 (m, 1H), 7.30 – 7.27 (m, 1H), 6.71 (dd, *J* = 2.7, 1.6 Hz, 1H), 4.26 – 4.11 (m, 2H), 3.81 (s, 3H), 2.35 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 161.6, 129.3, 128.8, 128.7, 126.2, 126.0, 122.4, 121.5, 114.3, 109.1, 107.2, 60.5, 51.3, 29.4, 14.4, 8.9.

IR ν max (film, cm^{-1}): 3291, 2952, 1884, 1684, 1568, 1485, 1435, 1383, 1241, 1199, 1101, 1038, 984, 911, 842, 761, 733.

HRMS (ESI) calculated for $C_{19}H_{19}NNaO_4^+$ $[M+Na]^+$ m/z: 348.1206, found: 348.1199.

m.p. 126 ºC.

A single crystal of **34** was obtained through slow crystallization at room temperature of its solution in ethyl acetate and hexane. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2150953.

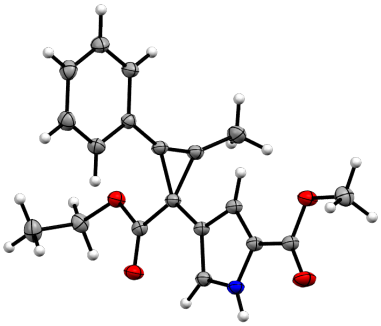
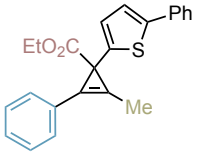


Figure 13 ORTEP diagram of **34**

ethyl 2-methyl-3-phenyl-1-(5-phenylthiophen-2-yl)cycloprop-2-ene-1-carboxylate (35)



Prepared according to the **general procedure A** using 2-phenylthiophene (16.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Instead of HFIP, TFE was used as solvent. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (34.5 mg, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 2H), 7.57 – 7.53 (m, 2H), 7.46 – 7.40 (m, 2H), 7.40 – 7.33 (m, 3H), 7.27 – 7.22 (m, 1H), 7.15 (d, *J* = 3.7 Hz, 1H), 6.94 (d, *J* = 3.7 Hz, 1H), 4.31 – 4.19 (m, 2H), 2.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

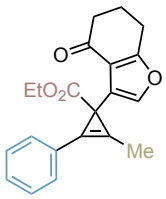
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 145.1, 142.3, 134.8, 129.4, 129.0, 128.9, 128.8, 126.9, 125.6, 125.5, 125.3, 122.5, 109.0, 107.8, 61.0, 32.2, 14.4, 9.0.

IR ν max (film, cm^{-1}): 2976, 1881, 1708, 1596, 1490, 1444, 1365, 1276, 1240, 1171, 1050, 1027, 957, 822, 753.

HRMS (ESI) calculated for $C_{23}H_{20}NaO_2S^+$ $[M+Na]^+$ m/z: 383.1076, found: 383.1068.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 2-methyl-1-(4-oxo-4,5,6,7-tetrahydrobenzofuran-3-yl)-3-phenylcycloprop-2-ene-1-carboxylate (36)



Prepared according to the **general procedure A** using 6,7-dihydrobenzofuran-4(5*H*)-one (14.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 4/1) provided the title compound as a yellow oil (32.0 mg, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 2H), 7.45 – 7.39 (m, 2H), 7.39 – 7.33 (m, 1H), 6.61 (s, 1H), 4.27 – 4.13 (m, 2H), 2.86 – 2.76 (m, 2H), 2.49 – 2.43 (m, 2H), 2.41 (s, 3H), 2.18 – 2.09 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H).

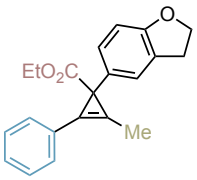
^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 172.8, 165.8, 155.6, 129.3, 129.2, 128.8, 125.6, 122.0, 107.6, 107.1, 103.4, 61.0, 37.6, 29.6, 23.4, 22.6, 14.4, 9.7.

IR ν max (film, cm^{-1}): 2952, 1716, 1670, 1569, 1446, 1363, 1235, 1172, 1113, 1054, 1003, 941, 830, 761.

HRMS (ESI) calculated for $C_{21}H_{20}NaO_4^+$ $[M+Na]^+$ m/z: 359.1254, found: 359.1249.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(2,3-dihydrobenzofuran-5-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (37)



Prepared according to the **general procedure A** using 2,3-dihydrobenzofuran (12.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Instead of HFIP, TFE was used as solvent. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (23.7 mg, 74% yield).

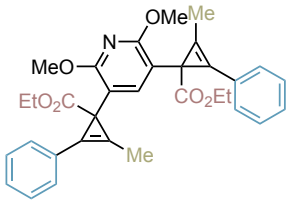
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.38 – 7.34 (m, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 7.10 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 4.59 – 4.50 (m, 2H), 4.26 – 4.14 (m, 2H), 3.22 – 3.15 (m, 2H), 2.41 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 158.6, 133.4, 129.2, 128.8, 128.6, 127.9, 127.0, 126.7, 124.9, 112.0, 109.0, 108.8, 71.2, 60.5, 35.0, 29.9, 14.4, 9.7.

IR ν max (film, cm^{-1}): 2974, 2898, 1877, 1708, 1613, 1489, 1444, 1362, 1225, 1097, 1053, 1032, 981, 941, 829, 759.

HRMS (ESI) calculated for $C_{21}H_{20}NaO_3^+$ $[M+Na]^+$ m/z: 343.1305, found: 343.1301.

diethyl 1,1'-(2,6-dimethoxypyridine-3,5-diyl)bis(2-methyl-3-phenylcycloprop-2-ene-1-carboxylate) (38)



Prepared according to the **general procedure A** using 2,6-dimethoxypyridine (14.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 4/1) provided a mixture of two diastereoisomers (1:1) as a yellow foam (30.1 mg, 56% yield).

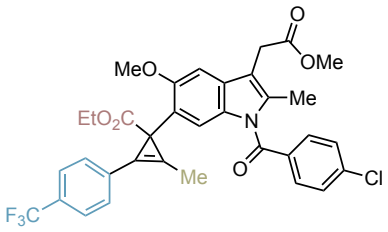
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.51 (m, 2H), 7.50 – 7.45 (m, 2H), 7.37 – 7.26 (m, 6H), 7.24 – 7.21 (m, 1H), 4.17 – 4.09 (m, 4H), 3.97 (s, 6H), 2.30 (s, 3H), 2.30 (s, 3H), 1.22 – 1.13 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.00, 174.97, 160.1, 160.0, 139.91, 139.87, 129.2, 129.1, 128.56, 128.54, 128.4, 128.3, 127.2, 127.1, 115.31, 115.27, 112.4, 111.9, 110.2, 109.8, 60.32, 60.30, 53.17, 53.15, 31.3, 31.2, 14.4, 9.93, 9.87.

IR ν max (film, cm^{-1}): 2947, 1868, 1714, 1577, 1457, 1396, 1324, 1217, 1193, 1055, 1018, 786, 757.

HRMS (ESI) calculated for $C_{33}H_{33}NNaO_6^+$ $[M+Na]^+$ m/z: 562.2200, found: 562.2186.

ethyl 1-(1-(4-chlorobenzoyl)-5-methoxy-3-(2-methoxy-2-oxoethyl)-2-methyl-1*H*-indol-6-yl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (39)



Prepared according to the **general procedure A** using indomethacin methyl ester (37.1 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 3/1) provided the title compound as a yellow foam (52.2 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.97 (s, 1H), 6.65 (s, 1H), 4.18 – 4.10 (m, 2H), 3.94 (s, 3H), 3.73 (s, 3H), 3.70 (s, 2H), 2.45 (s, 3H), 2.31 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H).

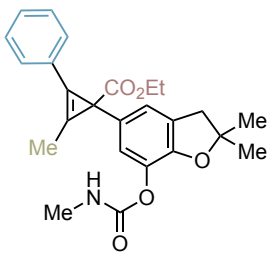
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 171.5, 168.0, 155.2, 139.2, 135.9, 133.7, 131.3, 130.6, 130.1, 130.0 (q, *J* = 31.5 Hz), 129.6, 129.0, 128.8, 127.2, 125.7 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.0 Hz), 116.3, 114.5, 112.4, 109.9, 99.3, 60.6, 55.7, 52.2, 33.4, 30.2, 14.4, 13.0, 9.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7.

IR ν max (film, cm^{-1}): 2986, 1876, 1716, 1684, 1612, 1463, 1352, 1318, 1216, 1164, 1124, 1061, 1013, 839, 786, 754.

HRMS (ESI) calculated for $C_{34}H_{29}ClF_3NNaO_6^+$ $[M+Na]^+$ m/z: 662.1528, found: 662.1531.

ethyl 1-(2,2-dimethyl-7-((methylcarbamoyl)oxy)-2,3-dihydrobenzofuran-5-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (40)



Prepared according to the **general procedure A** using carbofuran (22.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy.

Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow foam (39.4 mg, 94% yield).

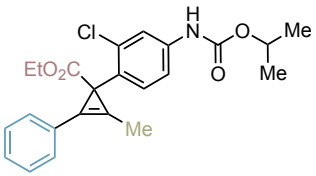
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.51 (m, 2H), 7.45 – 7.39 (m, 2H), 7.37 – 7.32 (m, 1H), 7.02 – 6.99 (m, 1H), 6.94 (s, 1H), 5.03 (brs, 1H), 4.24 – 4.07 (m, 2H), 2.99 (s, 2H), 2.88 – 2.79 (m, 3H), 2.38 (s, 3H), 1.48 (s, 3H), 1.48 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 154.6, 148.8, 134.1, 133.4, 129.2, 129.0, 128.8, 128.6, 126.8, 122.0, 121.7, 111.9, 108.5, 88.2, 60.5, 43.2, 34.9, 28.24, 28.24, 27.8, 14.4, 9.6.

IR ν max (film, cm^{-1}): 3363, 2973, 2247, 1716, 1487, 1445, 1336, 1222, 1131, 910, 867, 761.

HRMS (ESI) calculated for $C_{25}H_{27}NNaO_5^+$ $[M+Na]^+$ m/z: 444.1781, found: 444.1771.

ethyl 1-(2-chloro-4-((isopropoxycarbonyl)amino)phenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (41)



Prepared according to the **general procedure A** using chlorpropham (21.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol) without CsF. Instead of HFIP, TFE was used as solvent. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a white solid (31.1 mg, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.59 (m, 2H), 7.55 (s, 1H), 7.48 – 7.42 (m, 2H), 7.39 – 7.34 (m, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.03 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.74 (s, 1H), 5.06 – 4.96 (m, 1H), 4.27 – 4.16 (m, 2H), 2.45 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 153.0, 137.9, 135.6, 135.5, 130.0, 129.1, 128.9, 128.8, 127.1, 119.2, 117.0, 114.0, 109.0, 68.9, 60.9, 34.7, 22.1, 14.4, 9.9.

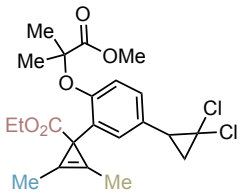
IR ν max (film, cm^{-1}): 3301, 2975, 2930, 1719, 1691, 1580, 1507, 1444, 1386, 1264, 1215, 1178, 1110, 1046, 906, 764.

HRMS (ESI) calculated for $C_{23}H_{24}ClNNaO_4^+$ $[M+Na]^+$ m/z: 436.1286, found: 436.1274.

m.p. 142-144 ºC.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(5-(2,2-dichlorocyclopropyl)-2-((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (42)



Prepared according to the **general procedure A** using ciprofibrate methyl ester (30.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a colourless oil (17.2 mg, 39% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 2.80 (dd, *J* = 10.8, 8.3 Hz, 1H), 2.22 – 2.19 (m, 6H), 1.94 (dd, *J* = 10.7, 7.3 Hz, 1H), 1.74 (dd, *J* = 8.3, 7.4 Hz, 1H), 1.63 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H).

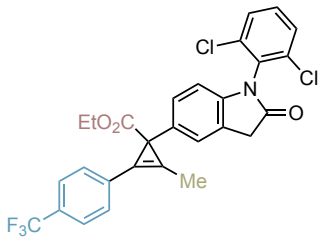
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 175.2, 154.0, 134.1, 130.4, 127.2, 126.8, 113.7, 108.0, 107.8, 78.2, 61.1, 60.2, 52.5, 34.9, 31.7, 26.2, 25.4, 25.3, 14.5, 9.39, 9.37.

IR ν max (film, cm^{-1}): 2981, 1713, 1491, 1435, 1269, 1211, 1171, 1137, 1042, 964, 818, 756.

HRMS (ESI) calculated for $C_{22}H_{26}Cl_2NaO_5^+$ $[M+Na]^+$ m/z: 463.1049, found: 463.1047.

NOESY spectrum was measured.

ethyl 1-(1-(2,6-dichlorophenyl)-2-oxoindolin-5-yl)-2-methyl-3-(4-(trifluoromethyl)phenyl)cycloprop-2-ene-1-carboxylate (43)



Prepared according to the **general procedure A** using the lactam derivative of diclofenac (27.8 mg, 0.10 mmol) and **1b** (50.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow solid (37.1 mg, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.61 (m, 4H), 7.52 – 7.48 (m, 2H), 7.40 – 7.37 (m, 1H), 7.36 (d, *J* = 1.1 Hz, 1H), 7.17 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.33 (d, *J* = 8.2 Hz, 1H), 4.21 (qd, *J* = 7.1, 3.1 Hz, 2H), 3.76 (s, 2H), 2.46 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 173.7, 141.8, 135.6, 135.5, 130.7, 130.49 (q, *J* = 32.8 Hz), 130.47, 130.2, 129.3, 129.0, 127.6, 125.9 (q, *J* = 3.7 Hz), 124.7, 124.2, 123.9 (q, *J* = 272.2 Hz), 115.1, 108.8, 107.9, 60.9, 35.9, 35.3, 14.4, 9.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8.

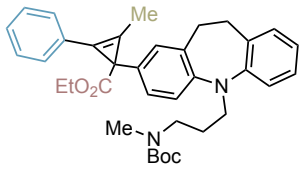
IR ν max (film, cm^{-1}): 2975, 2255, 1876, 1701, 1615, 1566, 1491, 1465, 1438, 1358, 1322, 1237, 1213, 1161, 1100, 1065, 917, 831, 792.

HRMS (ESI) calculated for $C_{28}H_{20}Cl_2F_3NNaO_3^+$ $[M+Na]^+$ m/z: 568.0665, found: 568.0652.

m.p. 85-86 ºC.

^1H-^{13}C HSQC, ^1H-^{13}C HMBC, NOESY spectra were measured.

ethyl 1-(5-(3-((*tert*-butoxycarbonyl)(methyl)amino)propyl)-10,11-dihydro-5*H*-dibenzo[b,f]azepin-2-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (44)



Prepared according to the **general procedure A** using desipramine hydrochloride (30.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). After removing the solvent, the crude product was dissolved in 2.0 mL of dichloromethane. Then 3.0 mL of sat. $NaHCO_3$ solution and $(Boc)_2O$ (65.5 mg, 0.30 mmol) were added sequentially to the mixture at 0 ºC. Progress of the reaction was followed by TLC. After 2 hours, the reaction mixture was extracted with dichloromethane. The solvent was removed under *vacuum* and purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the corresponding cyclopropenes **44** (28.7 mg, 51% yield) and **44'** (18.5 mg, 24% yield) as a yellow oil.

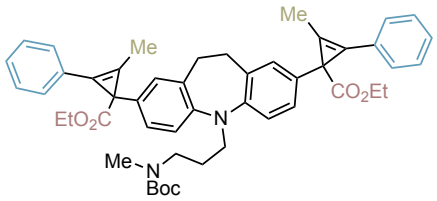
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 – 7.51 (m, 2H), 7.44 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 7.16 – 7.08 (m, 4H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.94 – 6.89 (m, 1H), 4.25 – 4.10 (m, 2H), 3.72 (t, *J* = 6.8 Hz, 2H), 3.33 – 3.20 (m, 2H), 3.19 – 3.05 (m, 4H), 2.75 (s, 3H), 2.38 (s, 3H), 1.84 – 1.74 (m, 2H), 1.39 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 155.8, 148.3, 146.3, 135.1, 134.6, 133.3, 129.7, 129.6, 129.2, 128.7, 128.6, 126.9, 126.3, 126.2, 122.5, 119.8, 119.2, 111.5, 108.5, 79.2, 60.5, 48.0, 47.1, 34.9, 34.2, 32.4, 32.1, 28.4, 26.4, 14.4, 9.6.

IR ν max (film, cm^{-1}): 2972, 2918, 1685, 1488, 1394, 1363, 1212, 1168, 1146, 1043, 910, 760.

HRMS (ESI) calculated for $C_{36}H_{42}N_2NaO_4^+$ $[M+Na]^+$ m/z: 589.3037, found: 589.3024.

diethyl 1,1'-(5-(3-((*tert*-butoxycarbonyl)(methyl)amino)propyl)-10,11-dihydro-5*H*-dibenzo[b,f]azepine-2,8-diyl)bis(2-methyl-3-phenylcycloprop-2-ene-1-carboxylate) (44')



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 4H), 7.44 – 7.37 (m, 4H), 7.36 – 7.30 (m, 2H), 7.12 – 7.04 (m, 4H), 6.93 (d, *J* = 8.7 Hz, 2H), 4.24 – 4.12 (m, 4H), 3.68 (t, *J* = 6.8 Hz, 2H), 3.30 – 3.16 (m, 2H), 3.13 – 3.00 (m, 4H), 2.73 (s, 3H), 2.37 (s, 6H), 1.82 – 1.70 (m, 2H), 1.36 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 6H).

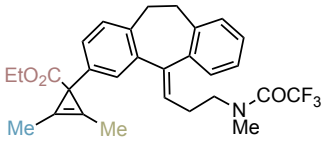
^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 155.8, 146.5, 135.1, 133.6, 129.4, 129.2, 128.7, 128.6, 126.9, 126.1, 119.2, 111.5, 108.5, 79.2, 60.5, 47.9, 47.2, 34.9, 34.2, 32.3, 28.4, 26.4, 14.4, 9.6.

IR ν max (film, cm^{-1}): 2972, 2919, 1877, 1685, 1490, 1445, 1394, 1363, 1209, 1147, 1044, 895, 830, 760.

HRMS (ESI) calculated for $C_{49}H_{54}N_2NaO_6^+$ $[M+Na]^+$ m/z: 789.3874, found: 789.3860.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl (2,3-dimethyl-1-(5-(3-(2,2,2-trifluoro-*N*-methylacetamido)propylidene)-10,11-dihydro-5H-dibenzo[a,d][7]annulen-3-yl)cycloprop-2-ene-1-carboxylate (45)



Prepared according to the **general procedure A** using nortriptyline trifluoroacetamide (36.0 mg, 0.10 mmol), **1g** (0.12 mmol, 35.0 mg) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 7/1) provided the title compound as a mixture of diastereoisomers (12.1 mg, 24% yield, E/Z ratio = 1.5:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.21 – 7.16 (m, 2H), 7.13 – 7.05 (m, 2H), 6.99 – 6.92 (m, 1H), 5.88 – 5.74 (m, 1H), 4.24 – 4.10 (m, 2H), 3.63 – 3.42 (m, 2H), 3.37 – 3.20 (m, 2H), 3.01 (s, 2H), 2.98 – 2.90 (m, 1H), 2.87 (s, 1H), 2.82 – 2.73 (m, 1H), 2.55 – 2.37 (m, 2H), 2.15 & 2.14 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H).

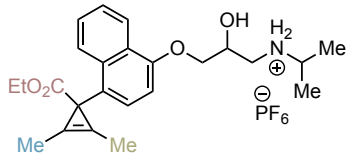
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.52, 175.47, 156.8 (q, *J* = 35.7 Hz), 146.8, 145.9, 140.2, 140.1, 139.8, 139.7, 139.5, 139.44, 139.41, 134.5, 129.9, 129.8, 128.23, 128.15, 128.12, 128.05, 127.9, 127.8, 127.7, 127.6, 127.32, 127.26, 126.1, 125.9, 125.8, 125.0, 116.5 (q, *J* = 287.9 Hz), 106.7, 106.2, 60.3, 49.0, 34.7 (q, *J* = 3.9 Hz), 34.34, 34.25, 33.5, 32.0, 31.9, 29.7, 28.2, 26.8, 24.91, 24.87, 14.5, 8.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -68.6, -69.8.

IR ν max (film, cm^{-1}): 2917, 1694, 1652, 1368, 1192, 1105, 1046, 756.

HRMS (ESI) calculated for $C_{29}H_{31}F_3NO_3^+$ $[M+H]^+$ m/z: 498.2240, found: 498.2251.

3-((4-(1-(ethoxycarbonyl)-2,3-dimethylcycloprop-2-en-1-yl)naphthalen-1-yl)oxy)-2-hydroxy-N-isopropylpropan-1-aminium hexafluorophosphate (46)



Prepared according to the **general procedure A** using propanolol (26.0 mg, 0.10 mmol) and **1g** (0.12 mmol, 35.0 mg). The reaction was not quenched by sat. $NaHCO_3$. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 50/1 to 4/1) provided the title compound as a yellow solid (38.9 mg, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.23 (m, 1H), 7.92 – 7.88 (m, 1H), 7.48 – 7.40 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 4.55 – 4.53 (m, 1H), 4.14 – 4.03 (m, 4H), 3.34 (q, *J* = 6.5 Hz, 1H), 3.27 – 3.23 (m, 1H), 3.19 – 3.13 (m, 1H), 2.21 (s, 6H), 1.35 – 1.32 (m, 6H), 1.07 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8, 152.9, 134.0, 133.7, 126.8, 126.2, 125.64, 125.55, 124.9, 122.5, 108.3, 108.2, 105.2, 69.2, 65.9, 61.1, 52.2, 50.9, 48.0, 32.8, 18.9, 18.8, 14.4, 9.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -70.9 (d, *J* = 710.6 Hz).

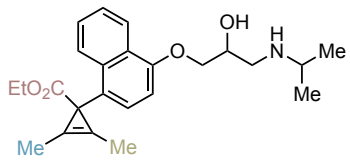
^{31}P NMR (162 MHz, $CDCl_3$) δ -141.0 (sp, *J* = 714.4 Hz).

IR ν max (film, cm^{-1}): 2977, 1707, 1584, 1426, 1376, 1295, 1215, 1173, 1094, 1061, 1034, 840, 767.

HRMS (ESI) calculated for $C_{24}H_{32}NO_4$ $[M\text{-}PF_6]^+$ m/z: 398.2326, found: 398.2323.

m.p. 69-70 ºC.

ethyl 1-(4-(2-hydroxy-3-(isopropylamino)propoxy)naphthalen-1-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (46')



Prepared according to the **general procedure A** using propranolol hydrochloride (30.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 20/1 to 15/1) provided the title compound as a yellow oil (31.3 mg, 79% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.96 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 4.24 – 4.17 (m, 2H), 4.16 – 4.12 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.07 – 2.99 (m, 1H), 2.95 – 2.83 (m, 2H), 2.43 (brs, 2H), 2.26 (s, 6H), 1.14 (d, *J* = 6.3 Hz, 6H), 1.10 (t, *J* = 7.1 Hz, 3H).

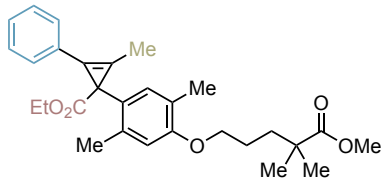
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 153.3, 134.2, 133.6, 126.2, 125.7, 125.5, 125.0, 124.9, 122.2, 108.4, 104.6, 70.6, 68.5, 60.5, 49.5, 49.0, 32.7, 23.1, 23.0, 14.4, 9.5.

IR ν max (film, cm^{-1}): 3067, 2917, 2962, 1706, 1583, 1508, 1458, 1424, 1374, 1292, 1212, 1170, 1090, 1060, 908, 765.

HRMS (ESI) calculated for $C_{24}H_{32}NO_4^+$ $[M+H]^+$ m/z: 398.2326, found: 398.2318.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(4-((5-methoxy-4,4-dimethyl-5-oxopentyl)oxy)-2,5-dimethylphenyl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (47)



Prepared according to the **general procedure A** using gemfibrozil (130.0 mg, 0.52 mmol) and **1a** (210.0 mg, 0.61 mmol) in HFIP (7.0 mL). After removing the solvent, the crude acid was dissolved in a mixed solvent containing 2.0 mL of methanol and 3.0 mL of toluene. Then trimethylsilyldiazomethane (1.3 mL, 2.0 M in hexanes, 2.6 mmol) was added to the mixture at 0 °C slowly. After 1 hour, the reaction mixture was filtered through a short pad of silica gel and washed with dichloromethane. The solvent was removed under vacuum and ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (230.0 mg, 95% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.59 (m, 2H), 7.51 – 7.42 (m, 2H), 7.41 – 7.34 (m, 1H), 6.99 (s, 1H), 6.63 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.94 (t, J = 4.8 Hz, 2H), 3.69 (s, 3H), 2.44 (s, 3H), 2.39 (s, 3H), 2.09 (s, 3H), 1.77 – 1.70 (m, 4H), 1.26 (s, 6H), 1.23 (t, J = 8.0 Hz, 3H).

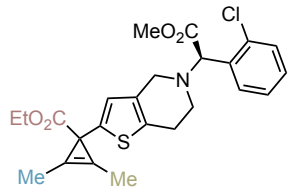
^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 175.4, 155.9, 135.8, 132.6, 130.6, 129.0, 128.8, 128.5, 127.8, 124.0, 114.5, 112.8, 110.0, 68.0, 60.6, 51.7, 42.1, 37.2, 34.6, 25.3, 25.2, 19.8, 15.9, 14.5, 10.0.

IR ν max (film, cm^{-1}): 2926, 1752, 1726, 1609, 1506, 1447, 1338, 1279, 1242, 1142, 1053, 967, 858, 771.

HRMS (ESI) calculated for $C_{29}H_{36}NaO_5^+$ $[M+Na]^+$ m/z: 487.2455, found: 487.2444.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, NOESY spectra were measured.

ethyl (*R*)-1-(5-(1-(2-chlorophenyl)-2-methoxy-2-oxoethyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin-2-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (48)



Prepared according to the **general procedure A** using clopidrogrel (32.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol) with HBF_4 (50-55% w/w solution in Et_2O, 21 µL, 1.4 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^1H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a yellow oil (30.5 mg, 66% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.34 – 7.22 (m, 2H), 6.51 (s, 1H), 4.92 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.72 – 3.66 (m, 1H), 3.58 (d, *J* = 14.1 Hz, 1H), 2.93 – 2.85 (m, 2H), 2.85 – 2.78 (m, 2H), 2.07 (s, 6H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 171.3, 144.2, 134.7, 133.9, 130.9, 130.0, 129.7, 129.4, 127.1, 122.1, 105.34, 105.27, 68.0, 60.6, 52.2, 50.7, 48.4, 31.5, 25.4, 14.5, 7.8.

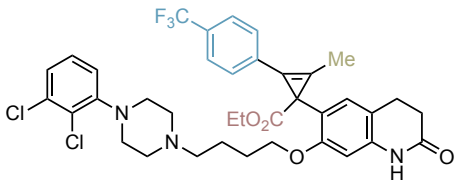
IR ν max (film, cm^{-1}): 2916, 1740, 1707, 1653, 1435, 1373, 1260, 1213, 1174, 1099, 1036, 892, 836, 751.

HRMS (ESI) calculated for $C_{24}H_{27}ClNO_4S^+$ $[M+H]^+$ m/z: 460.1344, found: 460.1334.

$[\alpha]^{25}_D$ = +12.2 (*c* = 1.0, $CHCl_3$).

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC spectra were measured.

ethyl 1-(7-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)butoxy)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (49)



Prepared according to the **general procedure A** using aripiprazole (44.7 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol) with HBF_4 (50-55% w/w solution in Et_2O, 40 µL, 2.8 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^1H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 20/1) provided the title compound as a yellow solid (52.6 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (brs, 1H), 7.66 – 7.60 (m, 2H), 7.48 – 7.40 (m, 2H), 7.39 – 7.32 (m, 1H), 7.22 – 7.12 (m, 2H), 6.99 (dd, *J* = 7.3, 2.2 Hz, 1H), 6.93 (s, 1H), 6.31 (s, 1H), 4.21 – 4.13 (m, 2H), 4.08 – 3.97 (m,

2H), 3.25 – 3.05 (m, 4H), 2.87 – 2.72 (m, 6H), 2.68 – 2.53 (m, 4H), 2.44 (s, 3H), 1.94 – 1.85 (m, 2H), 1.85 – 1.75 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

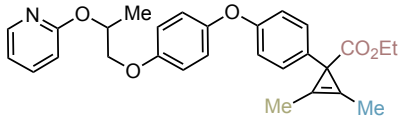
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.1, 172.0, 157.3, 150.8, 136.8, 134.0, 129.1, 128.7, 128.6, 128.3, 127.53, 127.51, 127.46, 126.0, 124.8, 118.7, 114.9, 113.2, 110.2, 99.4, 67.8, 60.5, 58.1, 53.2, 50.7, 32.4, 31.0, 27.3, 24.6, 22.8, 14.5, 10.2.

IR ν max (film, cm^{-1}): 2929, 1675, 1621, 1506, 1445, 1362, 1265, 1239, 1192, 1154, 1113, 1055, 952, 848, 760, 735.

HRMS (ESI) calculated for $C_{36}H_{39}Cl_2N_3NaO_4^+$ $[M+Na]^+$ m/z: 670.2210, found: 670.2212.

m.p. 75-77 ºC

ethyl 2,3-dimethyl-1-(4-(4-(2-(pyridin-2-yloxy)propoxy)phenoxy)phenyl)cycloprop-2-ene-1-carboxylate (50)



Prepared according to the **general procedure A** using pyriproxyfen (32.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol) with with HBF_4 (50-55% w/w solution in Et_2O, 21 µL, 1.4 equiv.). Ratio of isomers was determined to be 11:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the title compound as a colourless oil (31.1 mg, 68% yield).

major isomer: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.17 (dd, J = 5.0, 1.3 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.24 – 7.18 (m, 2H), 7.01 – 6.95 (m, 2H), 6.95 – 6.91 (m, 2H), 6.90 – 6.84 (m, 3H), 6.77 (d, J = 8.4 Hz, 1H), 5.65 – 5.54 (m, 1H), 4.20 (dd, J = 9.9, 5.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 4.12 – 4.05 (m, 1H), 2.14 (s, 6H), 1.50 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 163.1, 156.5, 155.0, 150.6, 146.7, 138.8, 136.7, 129.4, 120.6, 117.3, 116.8, 115.7, 111.7, 106.6, 71.1, 69.5, 60.3, 34.1, 17.0, 14.5, 8.7.

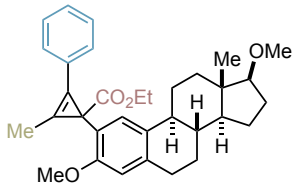
IR ν max (film, cm^{-1}): 2976, 2916, 1708, 1594, 1569, 1496, 1469, 1430, 1272, 1211, 1166, 1038, 988, 955, 836, 777.

HRMS (ESI) calculated for $C_{28}H_{29}NNaO_5^+$ $[M+Na]^+$ m/z: 482.1938, found: 482.1931.

Procedure for a 2.0 mmol-scale reaction:

Following the **general procedure A**, the reaction was carried out with pyriproxyfen (642.0 mg, 2.0 mmol), **CPC 1g** (720.0 mg, 2.5 mmol, 1.3 equiv.), CsF (540.0 g, 3.0 mmol), HBF_4 (50-55% w/w solution in Et_2O, 400 µL, 1.4 equiv.) and HFIP (20.0 mL). The crude residue was purified by column chromatography to afford **50** (562.0 mg, 61% yield).

ethyl 1-((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)-2-methyl-3-phenylcycloprop-2-ene-1-carboxylate (51)



Prepared according to the **general procedure A** using estradiol dimethyl ether (30.0 mg, 0.10 mmol) and **1a** (42.0 mg, 0.12 mmol). Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white foam (44.6 mg, 89% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

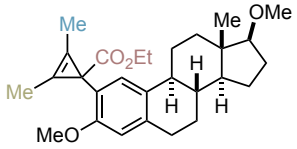
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 – 7.60 (m, 2H), 7.46 – 7.38 (m, 2H), 7.36 – 7.30 (m, 1H), 7.15 – 7.09 (m, 1H), 6.60 (s, 1H), 4.25 – 4.12 (m, 2H), 3.84 & 3.83 (s, 3H), 3.39 & 3.38 (s, 3H), 3.33 – 3.29 (m, 1H), 2.94 – 2.78 (m, 2H), 2.46 (s, 3H), 2.20 – 1.95 (m, 4H), 1.92 – 1.82 (m, 1H), 1.74 – 1.65 (m, 1H), 1.58 – 1.49 (m, 1H), 1.46 – 1.28 (m, 5H), 1.21 (t, *J* = 7.5 Hz, 3H) 1.25 – 1.13 (m, 1H), 0.80 & 0.76 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 175.3, 156.30, 156.29, 136.3, 132.03, 132.01, 129.3, 129.2, 128.53, 128.51, 128.3, 127.6, 126.1, 112.6, 112.5, 110.9, 110.84, 110.83, 90.9, 90.8, 60.3, 57.9, 55.29, 55.28, 50.31, 50.28, 43.9, 43.3, 43.2, 38.5, 38.2, 38.1, 32.77, 32.76, 29.88, 29.85, 27.8, 27.3, 26.3, 26.2, 23.0, 14.5, 11.6, 11.5, 10.3.

IR ν max (film, cm^{-1}): 2925, 1870, 1714, 1611, 1499, 1445, 1410, 1219, 1103, 1036, 908, 862, 829.

HRMS (ESI) calculated for $C_{33}H_{40}NaO_4^+$ $[M+Na]^+$ m/z: 523.2819, found: 523.2818.

ethyl 1-((8*R*,9*S*,13*S*,14*S*,17*S*)-3,17-dimethoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-2-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (52)



Prepared according to the **general procedure A** using estradiol dimethyl ether (62.0 mg, 0.21 mmol) and **1g** (76.0 mg, 0.25 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a yellow oil (91.1 mg, 98% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.57 (s, 1H), 4.23 – 4.05 (m, 2H), 3.78 (s, 3H), 3.40 (s, 3H), 3.37 – 3.30 (m, 1H), 2.95 – 2.75 (m, 2H), 2.30 – 2.22 (m, 1H), 2.21 – 2.14 (m, 7H), 2.12 – 2.03 (m, 2H), 1.93 – 1.84 (m, 1H), 1.76 – 1.65 (m, 1H), 1.59 – 1.49 (m, 2H), 1.46 – 1.29 (m, 4H), 1.28 – 1.14 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 156.4, 136.0, 132.0, 129.5, 126.6, 110.9, 108.3, 107.6, 90.8, 60.1, 57.9, 55.3, 50.3, 43.9, 43.3, 38.5, 38.1, 31.5, 29.9, 27.8, 27.3, 26.4, 23.1, 14.6, 11.6, 9.4, 9.3.

IR ν max (film, cm^{-1}): 2925, 1869, 1715, 1611, 1499, 1445, 1363, 1310, 1218, 1105, 1033, 914, 759.

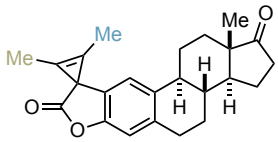
HRMS (ESI) calculated for $C_{28}H_{38}NaO_4^+$ $[M+Na]^+$ m/z: 461.2662, found: 461.2653.

$[\alpha]^{25}_D$ = +58.6 (*c* = 1.0, $CHCl_3$).

Procedure for a 3.5 mmol-scale reaction:

Following the **general procedure A**, the reaction was carried out with estradiol dimethyl ether (1.0 g, 3.45 mmol), **CPC 1g** (1.1 g, 3.8 mmol, 1.1 equiv.), CsF (0.79 g, 5.2 mmol) and HFIP (52.0 mL) under air. After working up, the crude residue was purified by column chromatography to give 1.45 g of **52**, 95% yield. *It was noticeable the reaction finished in 30 minutes and was not sensitive to air.*

(3a*S*,3b*R*,10b*S*,12a*S*)-2',3',12a-trimethyl-2,3,3a,3b,4,5,10b,11,12,12a-decahydro-1*H*,8*H*-spiro[cyclopenta[7,8]phenanthro[2,3-b]furan-9,1'-cyclopropan]-2'-ene-1,8-dione (53)



Prepared according to the **general procedure A** using estrone (27.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol) in HFIP (1.4 mL) for 1.5 h. Ratio of regioisomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the corresponding cyclopropene **53** (14.0 mg, 39% yield) and **53'** (9.8 mg, 24% yield) as white solid.

When the reaction was conducted for a longer time (3 h), the yields of **53** and **53'** were 52% and 8% respectively.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.80 (s, 1H), 3.02 – 2.94 (m, 2H), 2.57 – 2.49 (m, 1H), 2.44 – 2.37 (m, 1H), 2.35 – 2.26 (m, 1H), 2.23 – 2.15 (m, 1H), 2.13 (d, *J* = 1.4 Hz, 3H), 2.12 (d, *J* = 1.4 Hz, 3H), 2.11 – 2.02 (m, 2H), 2.01 – 1.95 (m, 1H), 1.71 – 1.64 (m, 1H), 1.63 – 1.59 (m, 1H), 1.58 – 1.45 (m, 4H), 0.94 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 151.8, 135.8, 135.2, 126.9, 116.6, 110.8, 101.7, 101.5, 50.5, 48.0, 44.3, 38.2, 35.9, 34.3, 31.6, 29.9, 26.5, 26.2, 21.6, 13.8, 8.09, 8.06.

IR ν max (film, cm^{-1}): 2923, 2848, 1922, 1782, 1734, 1479, 1428, 1370, 1259, 1222, 1137, 1097, 1058, 928, 881, 820, 795.

HRMS (ESI) calculated for $C_{24}H_{26}NaO_3^+$ $[M+Na]^+$ m/z: 385.1774, found: 385.1770.

m.p. 188 ºC.

$[\alpha]^{25}_D$ = -190.7 (*c* = 1.0, $CHCl_3$).

A single crystal of **53** was obtained through slow crystallization at room temperature of its solution in dichloromethane and hexane. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2150952.

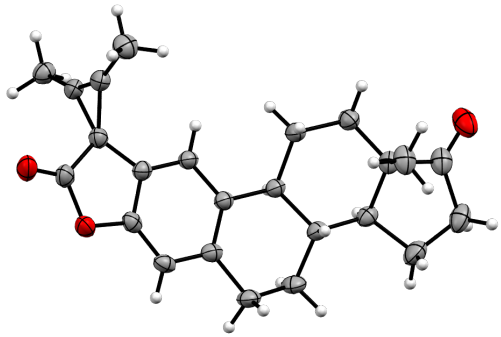
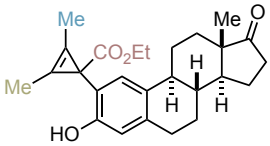


Figure 14 ORTEP diagram of 53

ethyl 1-((8*R*,9*S*,13*S*,14*S*)-3-hydroxy-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-2-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (53')



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.70 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.91 – 2.82 (m, 2H), 2.52 (dd, *J* = 18.8, 8.5 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.22 (d, *J* = 1.4 Hz, 3H), 2.20 (d, *J* = 1.4 Hz, 3H), 2.20 – 2.04 (m, 3H), 2.04 – 1.93 (m, 2H), 1.69 – 1.52 (m, 4H), 1.49 – 1.36 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 153.6, 136.6, 131.9, 127.7, 125.8, 117.8, 108.4, 108.1, 61.2, 50.4, 48.0, 43.9, 38.3, 35.9, 32.0, 31.6, 29.1, 26.6, 25.9, 21.6, 14.3, 13.9, 9.54, 9.49.

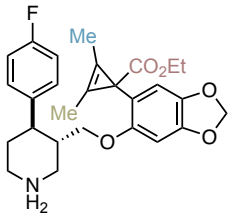
IR ν max (film, cm^{-1}): 3447, 2921, 1791, 1718, 1615, 1507, 1414, 1373, 1215, 1169, 1095, 1037, 930, 890, 828.

HRMS (ESI) calculated for $C_{26}H_{32}NaO_4^+$ $[M+Na]^+$ m/z: 431.2193, found: 431.2189.

m.p. 191-192 ºC.

$[\alpha]^{25}_D$ = +96.1 (*c* = 0.2, $CHCl_3$).

ethyl 1-(6-(((3*S*,4*R*)-4-(4-fluorophenyl)piperidin-3-yl)methoxy)benzo[d][1,3]dioxol-4-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (54)



Prepared according to the **general procedure A** using paroxetine hydrochloride hemihydrate (37.3 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture

using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 20/1 to 2/1) provided the title compound as a yellow oil (35.2 mg, 75% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H), 7.02 – 6.96 (m, 2H), 6.54 (s, 1H), 6.17 (s, 1H), 5.83 – 5.82 (m, 2H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.55 – 3.44 (m, 4H), 3.27 – 3.22 (m, 1H), 2.77 – 2.65 (m, 2H), 2.60 – 2.53 (m, 1H), 2.16 – 2.15 (m, 3H), 2.13 – 2.12 (m, 3H), 1.84 – 1.79 (m, 2H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 161.7 (d, *J* = 244.7 Hz), 152.9, 146.6, 140.8, 139.7 (d, *J* = 3.3 Hz), 128.9 (d, *J* = 7.8 Hz), 124.8, 115.7 (d, *J* = 21.1 Hz), 109.2, 108.6, 108.0, 101.1, 95.3, 69.5, 60.4, 50.1, 46.9, 44.3, 42.9, 34.8, 31.8, 14.7, 9.6, 9.5.

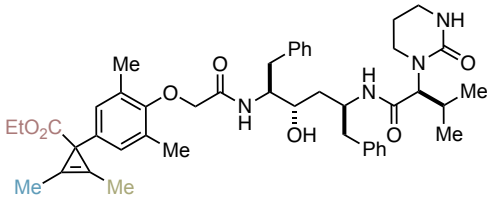
^{19}F NMR (376 MHz, $CDCl_3$) δ -116.4.

IR ν max (film, cm^{-1}): 2918, 1709, 1509, 1483, 1435, 1221, 1174, 1038.

HRMS (ESI) calculated for $C_{27}H_{31}FNO_5^+$ $[M+H]^+$ m/z: 468.2181, found: 468.2190.

$[\alpha]^{25}_D$ = -41.4 (*c* = 0.1, $CHCl_3$).

ethyl 1-(4-(2-(((2*S*,3*S*,5*S*)-3-hydroxy-5-((*S*)-3-methyl-2-(2-oxotetrahydropyrimidin-1(2H)-yl)butanamido)-1,6-diphenylhexan-2-yl)amino)-2-oxoethoxy)-3,5-dimethylphenyl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (55)



Prepared according to the **general procedure A** using lopinavir (6.3 mg, 10 μmol) and **1g** (3.5 mg, 12 μmol) in HFIP (0.5 mL). No CsF was used. Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (dichloromethane/methanol = 20/1 to 2/1) provided the title compound as a colourless oil (6.0 mg, 79% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.26 (m, 2H), 7.24 – 7.08 (m, 7H), 7.04 – 6.98 (m, 2H), 6.97 – 6.91 (m, 1H), 4.29 – 4.20 (m, 1H), 4.21 – 4.12 (m, 2H), 4.13 – 4.03 (m, 3H), 3.75 – 3.65 (m, 1H), 3.27 – 3.16 (m, 2H), 3.11 – 3.02 (m, 1H), 3.00 – 2.92 (m, 3H), 2.86 – 2.78 (m, 1H), 2.78 – 2.66 (m, 1H), 2.18 (s, 6H), 2.14 (s, 6H), 1.86 – 1.61 (m, 4H), 1.32 – 1.23 (m, 2H), 1.20 – 1.17 (m, 4H), 0.84 (d, *J* = 6.6 Hz, 6H).

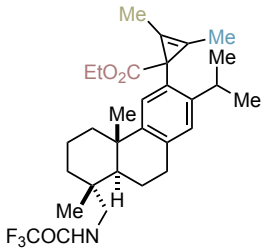
^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 171.4, 168.6, 157.4, 154.4, 138.2, 138.0, 130.5, 129.4, 129.3, 129.0, 128.42, 128.35, 126.4, 126.2, 124.6, 70.3, 70.0, 60.9, 54.3, 49.5, 47.0, 45.2, 41.7, 40.9, 38.4, 22.0, 19.9, 18.8, 16.3, 14.4, 8.9, 8.8.

IR ν max (film, cm^{-1}): 3415, 2959, 2924, 2855, 1722, 1672, 1497, 1444, 1305, 1264, 1198, 1059.

HRMS (ESI) calculated for $C_{45}H_{58}N_4NaO_7^+$ $[M+Na]^+$ m/z: 789.4198, found: 789.4169.

$[\alpha]^{25}_D$ = -44.3 (*c* = 0.1, $CHCl_3$).

ethyl 1-((4b*S*,8*R*,8a*R*)-2-isopropyl-4b,8-dimethyl-8-((2,2,2-trifluoroacetamido)methyl)-4b,5,6,7,8,8a,9,10-octahydrophenanthren-3-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (56)



Prepared according to the **general procedure A** using (+)-dehydroabietylamine trifluoroacetamide (28.0 mg, 0.10 mmol), **1g** (0.12 mmol, 35.0 mg) and CsF (15.2 mg, 1.0 equiv.). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 7/1) provided the title compound as a white solid (27.7 mg, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.92 (s, 1H), 6.26 (t, *J* = 5.5 Hz, 1H), 4.11 (qd, *J* = 7.1, 1.7 Hz, 2H), 3.29 (qd, *J* = 13.7, 6.5 Hz, 2H), 3.11 – 3.01 (m, 1H), 2.93 (dd, *J* = 16.7, 5.6 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.30 – 2.24 (m, 1H), 2.21 (d, *J* = 1.3 Hz, 3H), 2.18 (d, *J* = 1.3 Hz, 3H), 1.87 – 1.68 (m, 4H), 1.54 – 1.40 (m, 4H), 1.24 (s, 6H), 1.23 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 157.5 (q, *J* = 36.5 Hz), 146.5, 145.3, 138.3, 133.2, 125.9, 124.9, 116.0 (q, *J* = 288.5 Hz), 109.0, 108.7, 60.4, 50.4, 45.8, 38.1, 37.5, 37.4, 36.1, 33.7, 29.9, 29.3, 25.4, 24.8, 24.7, 19.1, 18.5, 18.4, 14.5, 9.5, 9.4.

^{19}F NMR (471 MHz, $CDCl_3$) δ -75.6.

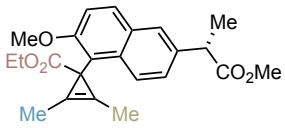
IR ν max (film, cm^{-1}): 3319, 2923, 1720, 1685, 1557, 1448, 1362, 1202, 1150, 1037.

HRMS (ESI) calculated for $C_{30}H_{41}F_3NO_3^+$ $[M+H]^+$ m/z: 520.3033, found: 520.3041.

m.p. 151-153 ºC.

$[\alpha]^{25}_D$ = +35.8 (*c* = 0.3, CH_2Cl_2).

ethyl (*S*)-1-(2-methoxy-6-(1-methoxy-1-oxopropan-2-yl)naphthalen-1-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (57)



Prepared according to the **general procedure A** using (*S*)-naproxen methyl ester (25.0 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1) provided the title compound as a white solid (37.8 mg, 99% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 7.67 (d, *J* = 1.6 Hz, 1H), 7.41 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 3.87 (q, *J* = 7.1 Hz, 1H), 3.69 (s, 3H), 2.23 (s, 6H), 1.59 (d, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 175.2, 155.8, 135.1, 133.8, 129.2, 128.1, 126.4, 125.9, 125.2, 124.7, 114.0, 108.7, 60.3, 56.1, 52.0, 45.2, 29.3, 18.5, 14.5, 9.5.

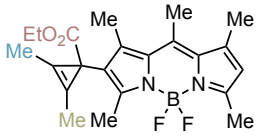
IR ν max (film, cm^{-1}): 2917, 2848, 1706, 1577, 1457, 1397, 1327, 1218, 1192, 1101, 1023, 921, 834, 759.

HRMS (ESI) calculated for $C_{23}H_{26}NaO_5^+$ $[M+Na]^+$ m/z: 405.1672, found: 405.1671.

m.p. 83-84 ºC.

$[\alpha]^{25}_D$ = +47.1 (*c* = 1.0, $CHCl_3$)

ethyl 1-(5,5-difluoro-1,3,7,9,10-pentamethyl-5*H*-5λ4,6λ4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-2-yl)-2,3-dimethylcycloprop-2-ene-1-carboxylate (58)



Prepared according to the **general procedure A** using 5,5-difluoro-1,3,7,9,10-pentamethyl-5*H*-4λ^4,5λ^4-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinine (26.2 mg, 0.10 mmol) and **1g** (35.0 mg, 0.12 mmol). Ratio of isomers was determined to be >20:1 from the crude reaction mixture using ^{1}H NMR spectroscopy. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 9/1 to 2/1) provided cyclopropenes **58** (15.7 mg, 39% yield) and **58'** (21.5 mg, 40% yield) as bright pink-orange solids.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 2.52 (s, 3H), 2.50 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H), 2.18 (s, 6H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 154.8, 152.7, 141.0, 140.1, 139.7, 133.5, 132.1, 120.9, 108.2, 60.7, 29.9, 27.1, 17.5, 16.8, 16.0, 14.6, 14.5, 13.9, 9.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -146.6 (q, *J* = 32.5 Hz).

^{11}B NMR (128 MHz, $CDCl_3$) δ 0.6 (t, *J* = 33.2 Hz).

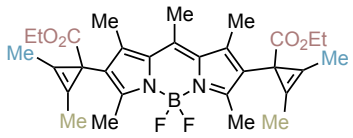
IR ν max (film, cm^{-1}): 2920, 1706, 1552, 1517, 1469, 1398, 1312, 1257, 1180, 989.

HRMS (ESI) calculated for $C_{22}H_{27}F_2N_2NaO_2{}^{10}B^+$ $[M+Na]^+$ m/z: 422.2062, found: 422.2070

m.p. 200 °C (decomp).

UV/Vis (CH_3OH): λ_{abs} = 504 nm (1.3 x 10^{-5} $M^{-1}cm^{-1}$); λ_{em} = 520 nm (λ_{ex} = 480 nm).

diethyl 1,1'-(5,5-difluoro-1,3,7,9,10-pentamethyl-5H-4λ4,5λ4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine-2,8-diyl)bis(2,3-dimethylcycloprop-2-ene-1-carboxylate) (58')



^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (q, *J* = 7.1 Hz, 4H), 2.58 (s, 3H), 2.50 (s, 6H), 2.37 (s, 6H), 2.17 (s, 12H), 1.18 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 153.7, 140.5, 138.8, 132.9, 131.9, 108.2, 60.7, 27.1, 17.1, 16.0, 14.6, 13.8, 9.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ -146.2 (q, *J* = 33.0 Hz).

^{11}B NMR (160 MHz, $CDCl_3$) δ 0.6 (t, *J* = 33.6 Hz).

IR ν max (film, cm^{-1}): 2921, 1707, 1546, 1469, 1387, 1318, 1207, 1177, 1134, 1040, 996, 846.

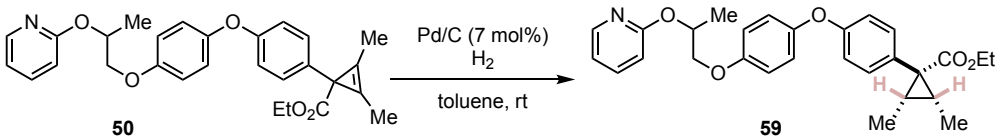
HRMS (ESI) calculated for $C_{30}H_{37}F_2N_2NaO_4{}^{10}B^+$ $[M+Na]^+$ m/z: 560.2743, found: 560.2745.

m.p. 220 °C (decomp).

UV/Vis (CH_3OH): λ_{abs} = 515 nm (1.84 x 10^{-6} $M^{-1}cm^{-1}$); λ_{em} = 531 nm (λ_{ex} = 500 nm).

Diversification of cyclopropenylated drug molecules.

Pd-catalyzed hydrogenation.



50 **59**

7% Pd/C (7.4 mg, 0.007 mmol) was added to a solution of cyclopropene **50** (46.0 mg, 0.10 mmol) in toluene (3.0 mL). After being purged with hydrogen, the suspension was stirred vigorously under hydrogen atmosphere overnight. The reaction mixture was then filtered through a short plug of celite and concentrated *in vacuo*. The residue was purified with column chromatography (hexane/ethyl acetate = 6/1) to give the desired cyclopropane **59** as a colourless oil (40.5 mg, 88% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 4.7, 1.6 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.27 – 7.22 (m, 2H), 6.99 – 6.92 (m, 4H), 6.91 – 6.87 (m, 1H), 6.87 – 6.83 (m, 2H), 6.79 – 6.75 (m, 1H), 5.65 – 5.57 (m, 1H), 4.21 (dd, *J* = 9.9, 5.4 Hz, 1H), 4.13 – 4.08 (m, 3H), 1.58 – 1.52 (m, 2H), 1.51 (d, *J* = 6.4 Hz, 3H), 1.31 (d, *J* = 2.0 Hz, 3H), 1.30 (d, *J* = 2.0 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H).

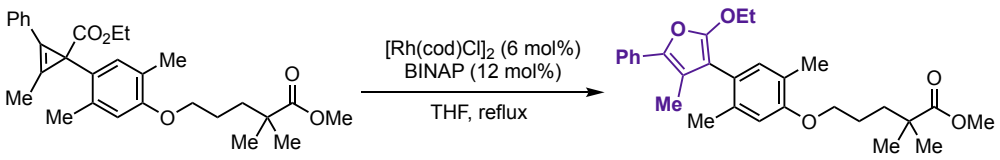
^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 163.1, 157.0, 155.2, 150.3, 146.6, 138.9, 137.2, 130.4, 120.7, 117.1, 116.8, 115.8, 111.8, 71.1, 69.5, 60.3, 36.4, 25.2, 17.0, 14.3, 8.9.

IR ν max (film, cm^{-1}): 2929, 1716, 1594, 1497, 1469, 1431, 1306, 1285, 1217, 1186, 1123, 1034, 956, 832, 778.

HRMS (ESI) calculated for $C_{28}H_{31}NNaO_5^+$ $[M+Na]^+$ m/z: 484.2094, found: 484.2099.

NOESY spectrum was measured.

Rh(I)-catalyzed cycloisomerization.



47 **60**

To a 10 mL oven-dried tube equipped with a stirring bar was added $[Rh(cod)Cl]_2$ (1.5 mg, 6 mol%) and (*rac*)-BINAP (3.8 mg, 12 mol%). After being evacuated and backfilled with argon, 0.5 mL of dry THF was added and the mixture was stirred at room temperature for 20 minutes. Then a solution of the corresponding cyclopropene **47** (23.0 mg, 0.05 mmol) in THF (1.0 mL) was added and the resulting mixture was heated at 70 ºC. When the reaction was complete (monitored by TLC), the reaction mixture was passed through a short pad of celite and washed with dichloromethane. The solvent was removed and the resulting reaction mixture was analyzed by ^{1}H NMR. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 8/1 to 4/1) provided the corresponding furan **60** as a yellow oil (19.1 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.44 – 7.38 (m, 2H), 7.24 – 7.19 (m, 1H), 6.98 (s, 1H), 6.72 (s, 1H), 4.21 – 4.12 (m, 2H), 4.01 – 3.95 (m, 2H), 3.70 (s, 3H), 2.23 (s, 3H), 2.22 (s, 3H), 2.07 (s, 3H), 1.82 – 1.71 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 156.3, 154.3, 138.8, 136.4, 133.3, 132.0, 128.5, 125.6, 124.3, 123.6, 122.6, 118.9, 112.4, 103.4, 67.9, 67.8, 51.8, 42.1, 37.2, 25.24, 25.21, 20.1, 15.8, 15.2, 10.9.

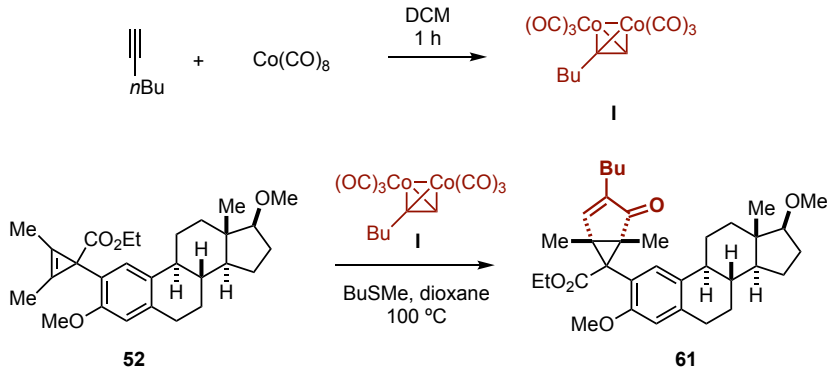
IR ν max (film, cm^{-1}): 2948, 2924, 2868, 1730, 1636, 1601, 1506, 1566, 1472, 1386, 1331, 1249, 1196, 1144, 1122, 1061, 1012, 761.

HRMS (ESI) calculated for $C_{29}H_{36}NaO_5^+$ $[M+Na]^+$ m/z: 487.2455, found: 487.2469.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, NOESY, COSY spectra were measured.

Intermolecular Pauson−Khand reaction.[45,46]

[45] Marchueta, I.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2001**, *3*, 3193.
[46] Zhang, Z.; Zheng, M.; Xue, X.; Marek, I.; Zhang, F.; Ma, J. *Angew. Chem. Int. Ed.* **2019**, *131*, 18359.



I was synthesized according to a reported methodology. To a 25 mL Schlenk tube containing the compound **52** (39.0 mg, 0.09 mmol) was added **I** (110.0 mg, 0.30 mmol), *n*-butyl methyl sulfide (416 mg, 4.00 mmol), and 1,4-dioxane (3.0 mL). The reaction was carried out at 100 °C for 2 h, and chromatographed over silica gel (hexane/ethyl acetate = 6/1) to give the title compound **61** as a white solid (38.5 mg, 79% yield, 1.2:1 mixture of diastereoisomers as determined by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.73 – 6.67 (m, 1H), 6.43 (s, 1H), 4.11 – 3.99 (m, 2H), 3.80 (s, 3H), 3.39 (s, 3H), 3.34 – 3.28 (m, 1H), 2.90 – 2.65 (m, 2H), 2.30 – 2.17 (m, 1H), 2.15 – 1.99 (m, 3H), 1.89 – 1.80 (m, 1H), 1.79 – 1.65 (m, 2H), 1.64 (s, 3H), 1.58 – 1.46 (m, 4H), 1.43 – 1.20 (m, 6H), 1.20 – 1.11 (m, 4H), 1.01 – 0.86 (m, 2H), 0.80 – 0.75 (m, 3H), 0.75 – 0.66 (m, 4H), 0.51 – 0.37 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 207.0, 206.9, 168.3, 168.2, 156.4, 156.3, 155.1, 154.8, 142.0, 141.9, 137.1, 131.9, 131.6, 130.5, 130.4, 121.54, 121.47, 110.23, 110.19, 90.83, 90.79, 60.56, 60.55, 57.93, 57.91, 57.8, 57.7, 55.6, 50.3, 50.2, 44.1, 43.7, 43.3, 43.2, 39.6, 39.53, 39.47, 39.4, 38.8, 38.5, 38.1, 38.0, 30.0, 29.9, 29.8, 29.6, 27.9, 27.8, 27.2, 27.1, 26.4, 26.1, 24.0, 23.9, 23.1, 23.0, 22.4, 22.3, 14.20, 14.17, 14.0, 11.6, 11.5, 10.77, 10.75, 8.54, 8.47.

IR ν max (film, cm^{-1}): 2921, 2852, 1718, 1695, 1504, 1456, 1379, 1288, 1234, 1194, 1104, 1036, 893, 862.

HRMS (ESI) calculated for $C_{35}H_{48}NaO_5^+$ $[M+Na]^+$ m/z: 571.3394, found: 571.3393.

$[\alpha]^{25}_D$ = +27.6 (*c* = 1.0, $CHCl_3$).

A single crystal of **61** was obtained through slow evaporation from its solution in acetonitrile and hexane. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2150949.

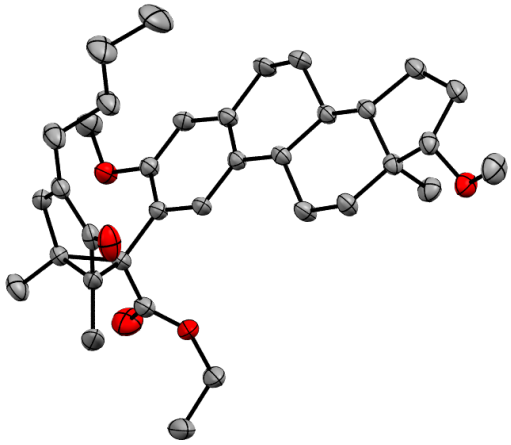
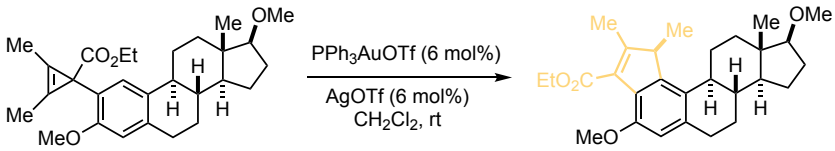


Figure 15 ORTEP diagram of **61**

Au(I)-catalyzed cycloisomerization.[47]



52 **62**

To a 10 mL oven-dried tube equipped with a stirring bar was added $AuClPPh_3$ (1.6 mg, 6 mol%) and AgOTf (0.8 mg, 6 mol%). After being evacuated and backfilled with argon, 0.5 mL of dry dichloromethane was added and the mixture was stirred at room temperature for 5 minutes. Then a solution of the corresponding cyclopropene **52** (22.0 mg, 0.05 mmol) in dichloromethane (1.0 mL) was added. The solution turned yellow immediately. The reaction was monitored with TLC. After the substrate was consumed, the solvent was removed *in vacuo* and the crude product was purified by preparative TLC (hexane/diethyl ether = 3/2) to give the corresponding indene **62** as a yellow oil (9.4 mg, 43% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.70 (q, J = 7.5 Hz, 1H), 3.40 (s, 3H), 3.38 – 3.33 (m, 1H), 3.02 – 2.91 (m, 1H), 2.85 – 2.78 (m, 1H), 2.64 – 2.48 (m, 2H), 2.15 – 2.03 (m, 2H), 2.06 (s, 3H), 1.86 – 1.79 (m, 1H), 1.75 – 1.66 (m, 1H), 1.56 – 1.41 (m, 4H), 1.41 – 1.35 (m, 1H), 1.38 (t, J = 7.1 Hz, 3H), 1.34 – 1.30 (m, 1H), 1.26 (d, J = 7.5 Hz, 3H), 1.30 – 1.19 (m, 1H), 0.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 150.4, 147.6, 147.2, 136.3, 129.0, 128.6, 128.5, 111.0, 90.9, 60.6, 57.9, 55.5, 50.4, 49.7, 45.4, 43.5, 40.3, 39.0, 32.0, 27.8, 26.1, 25.9, 23.2, 14.4, 12.8, 12.6, 11.9.

IR ν max (film, cm^{-1}): 2922, 2849, 1724, 1583, 1464, 1366, 1314, 1288, 1222, 1130, 1102, 1049, 1017, 864, 803.

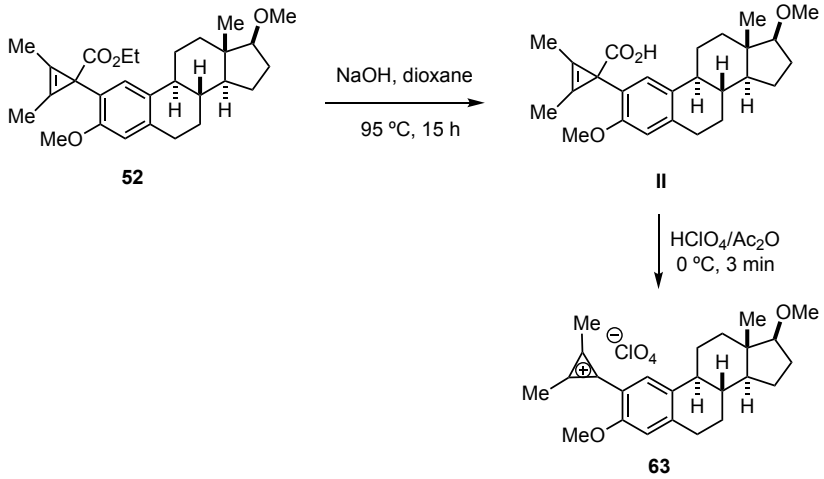
HRMS (ESI) calculated for $C_{28}H_{38}NaO_4^+$ $[M+Na]^+$ m/z: 461.2662, found: 461.2656.

$[\alpha]^{25}_D$ = +116.2 (c = 0.5, $CHCl_3$).

[47] Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956.

NOESY spectrum was measured.

Synthesis of CPC 63.[48]



Aqueous NaOH (34 mL of 1N solution) was added to a 200 mL flask containing **52** (1.3 g, 3.0 mmol), 150 mL dioxane and 21 mL water. The mixture was stirred at 95 ºC until full conversion of the starting material. Dioxane was removed *in vacuo* and the residue was acidified to pH 1-3 with 2N HCl solution. The resulting mixture was extracted with dichloromethane (20 mL x 4) and dried over Na_2SO_4. After removing the solvent, the crude residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 2/1 to 1/1) to afford the corresponding acid **II** as a white foam (1.2 g, 95% yield).

4.0 g of freshly prepared $HClO_4$ solution in acetic anhydride (0.2 g of 70% $HClO_4$ in 5.6 g acetic anhydride) was added slowly to a reaction flask containing the acid **II** (410 mg, 1.0 mmol) at 0 ºC. The mixture turned red immediately and gas evolution was observed. After 3 minutes, diethyl ether (3 mL) and hexane (3 mL) were added, and the mixture was stirred vigorously for additional 1 minute. Two layers appeared after standing still for 1 minute, and the upper layer was removed carefully. Then the residue was washed with diethyl ether (3 mL x 4), dried under vacuum to give the CPC **63** as a red foam (380 mg, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.84 (s, 1H), 4.02 (s, 3H), 3.40 (s, 3H), 3.39 – 3.33 (m, 1H), 3.12 – 2.92 (m, 8H), 2.42 – 2.30 (m, 1H), 2.27 – 2.17 (m, 1H), 2.16 – 2.04 (m, 2H), 1.98 – 1.88 (m, 1H), 1.77 – 1.66 (m, 1H), 1.64 – 1.49 (m, 2H), 1.49 – 1.32 (m, 4H), 1.29 – 1.17 (m, 1H), 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 162.6, 160.9, 153.9, 135.0, 133.4, 112.3, 106.2, 90.7, 57.9, 56.6, 50.1, 43.1, 43.0, 37.9, 37.5, 31.2, 27.6, 26.4, 26.1, 23.0, 13.1, 11.5.

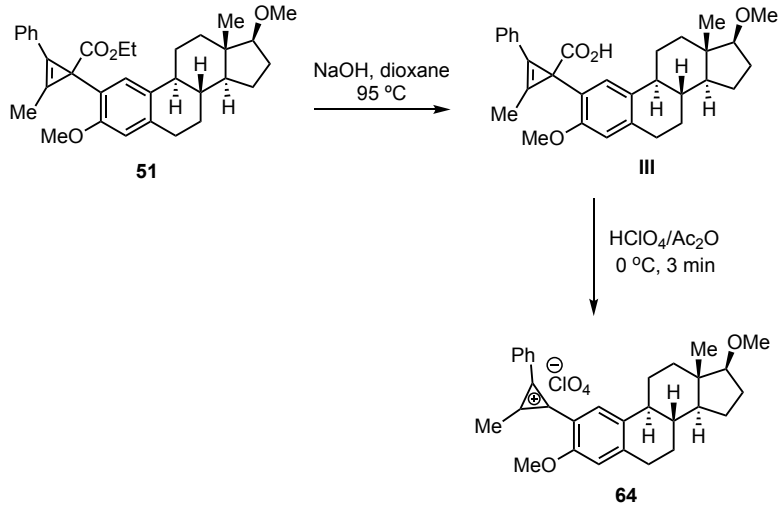
IR ν max (film, cm^{-1}): 2924, 2865, 1861, 1716, 1609, 1558, 1472, 1440,1383, 1271, 1072, 1022, 980, 865.

HRMS (ESI) calculated for $C_{25}H_{33}O_2^+$ $[M\text{-}ClO_4]^+$ m/z: 365.2475, found: 365.2480.

$[\alpha]^{25}_D$ = +54.6 (*c* = 0.1, $CHCl_3$).

48 Breslow, R; Hover, H.; Chang, H.W. *J. Am. Chem. Soc.* **1962**, *84*, 3168.

Synthesis of CPC 64.



Cyclopropene **51** was prepared according to the **general procedure A** using estradiol dimethyl ether (520 mg, 1.7 mmol) and **1a** (660 mg, 1.9 mmol). After the removal of HFIP under reduced pressure, the crude residue was filtered through a short pad of silica gel to give NMR pure **51** (854 mg, 98% yield) as 1:1 mixture of diastereoisomers, which was used directly for the next step.

Aqueous NaOH (19 mL of 1N solution) was added to a 200 mL flask containing **51** (810 mg, 1.6 mmol), 81 mL dioxane and 10 mL water. The mixture was stirred at 95 ºC until full conversion of the starting material. Dioxane was removed *in vacuo* and the residue was acidified to pH 1-3 with 2N HCl solution. The resulting mixture was extracted with dichloromethane (20 mL x 4) and dried over Na_2SO_4. After removing the solvent, the corresponding acid **III** was obtained as a white foam (704 mg, 92% yield).

6.0 g of freshly prepared $HClO_4$ solution in acetic anhydride (0.25 g of 70% $HClO_4$ in 7.0 g acetic anhydride) was added slowly to a reaction flask containing the acid **III** (704 mg, 1.5 mmol) at 0 ºC. The mixture turned yellow immediately and gas evolution was observed. After 3 minutes, diethyl ether (4 mL) was added, and the mixture was stirred vigorously for additional 1 minute. The product was collected by filtration, washed with diethyl ether (4 mL x 4), dried under high vacuum to give the CPC **64** as a yellow solid (540 mg, 69% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.3 Hz, 2H), 7.98 (s, 1H), 7.92 – 7.86 (m, 1H), 7.83 – 7.75 (m, 2H), 6.92 (s, 1H), 4.11 (s, 3H), 3.42 (s, 3H), 3.40 – 3.34 (m, 1H), 3.32 (s, 3H), 3.14 – 2.97 (m, 2H), 2.47 – 2.36 (m, 1H), 2.35 – 2.25 (m, 1H), 2.22 – 2.08 (m, 2H), 2.03 – 1.96 (m, 1H), 1.80 – 1.69 (m, 1H), 1.69 – 1.59 (m, 1H), 1.59 – 1.36 (m, 5H), 1.32 – 1.23 (m, 1H), 0.84 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 162.5, 161.0, 157.3, 155.6, 154.1, 137.4, 135.3, 135.2, 133.6, 130.3, 120.2, 112.6, 106.6, 90.5, 58.0, 56.6, 50.1, 43.2, 43.1, 37.9, 37.7, 31.3, 27.7, 26.5, 26.3 23.0, 13.7, 11.5.

IR ν max (film, cm^{-1}): 2930, 2867, 1741, 1607, 1495, 1436, 1404, 1270, 1181, 1083, 1005, 864, 779.

HRMS (ESI) calculated for $C_{30}H_{35}O_2^+$ $[M\text{-}ClO_4]^+$ m/z: 427.2632, found: 427.2631.

m.p. >200 ºC.

$[\alpha]^{25}_{D}$ = +107.3 (c = 0.3, $CHCl_3$).

A single crystal of **64** was obtained through slow crystallization at room temperature of its solution in dichloromethane and hexane. The crystal structure of **64** has been deposited at the Cambridge Crystallographic Data Centre, CCDC No. 2150951.

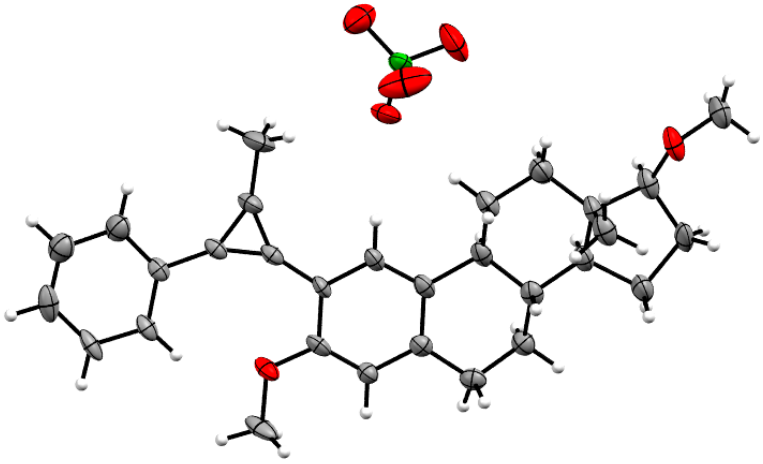


Figure 16 ORTEP diagram of **64**

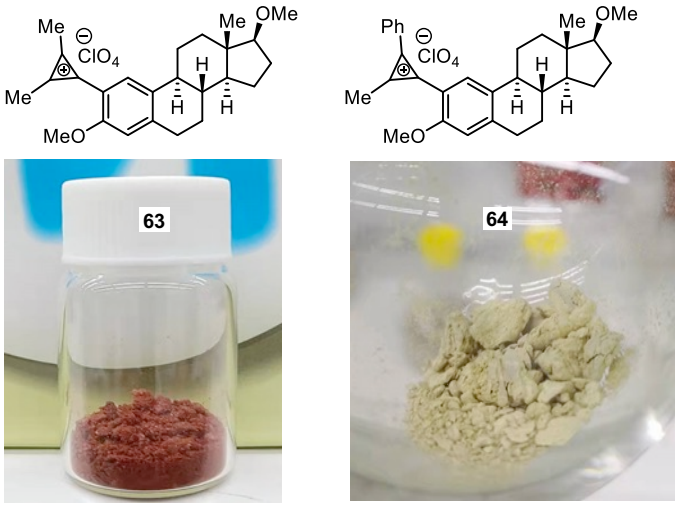
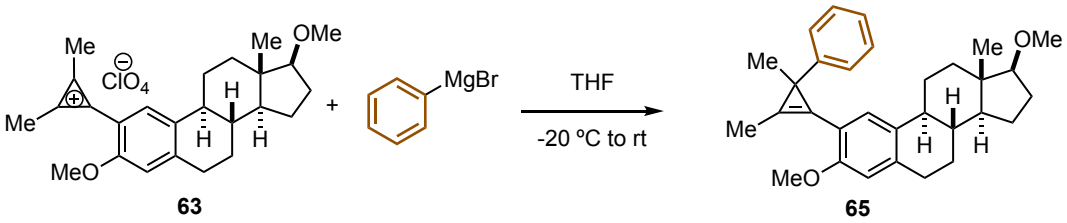


Figure S1. (a) Left, picture of **CPC 63** as a red foam. (b) Right, picture of **CPC 64** as a yellow solid.

Addition of phenylmagensium bromide to CPC 63.



63 **65**

To a 25 mL oven-dried flask equipped with a stirring bar was added **CPC 63** (78.5 mg, 0.17 mmol). After being evacuated and backfilled with argon, 3.0 mL of dry THF was added and the reaction was cooled to -20 °C. Then phenylmagnesium bromide (0.34 mL, 1M in THF) was added slowly. The mixture turned from red to yellow in 20 minutes. The reaction mixture was passed through a short pad of celite and washed with dichloromethane. The solvent was removed and the resulting reaction mixture was analyzed by ^{1}H NMR. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 25/1 to 15/1) provided the corresponding cyclopropene **65** as a white foam (46.1 mg, 61% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

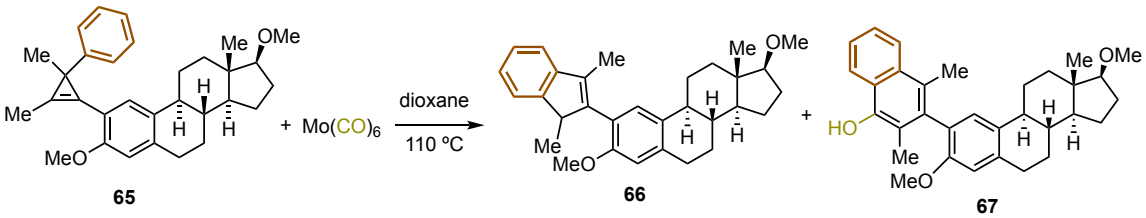
^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.28 – 7.22 (m, 4H), 7.13 – 7.06 (m, 2H), 6.68 (s, 1H), 3.93 & 3.92 (s, 3H), 3.35 (s, 3H), 3.33 – 3.28 (m, 1H), 2.93 – 2.87 (m, 2H), 2.28 (s, 3H), 2.22 – 2.05 (m, 3H), 2.02 – 1.95 (m, 1H), 1.94 – 1.87 (m, 1H), 1.71 & 1.70 (s, 3H), 1.55 – 1.30 (m, 7H), 1.26 – 1.17 (m, 1H), 0.79 & 0.75 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 155.9, 155.8, 149.2, 138.5, 138.4, 132.4, 132.3, 127.69, 127.68, 126.33, 126.30, 125.97, 125.95, 124.21, 124.16, 118.1, 117.6, 115.1, 115.0, 111.9, 111.6, 110.83, 110.81, 90.60, 90.59, 57.5, 55.5, 50.21, 50.16, 43.72, 43.66, 43.2, 38.6, 38.5, 37.9, 30.1, 27.7, 27.2, 27.1, 26.4, 26.2, 25.4, 25.2, 22.9, 21.5, 21.4, 11.4, 11.3, 9.24, 9.18.

IR ν max (film, cm^{-1}): 2854, 1603, 1563, 1497, 1456, 1400, 1285, 1228, 1130, 1105, 1031, 892, 773.

HRMS (ESI) calculated for $C_{31}H_{38}NaO_2^+$ $[M+Na]^+$ m/z: 465.2764, found: 465.2758.

Synthesis of indene 66 and naphthol 67 with molybdenum hexacarbonyl.[49]



65 **66** **67**

A screw capped reaction tube equipped with a magnetic bar was charged with cyclopropene **65** (21.0 mg, 0.05 mmol, 1.0 equiv.), $Mo(CO)_6$ (64.6 mg, 0.06 mmol, 1.2 equiv.) and flushed with argon. Subsequently, 1,4-dioxane (1.0 mL) was added. The tube was sealed with a Teflon-lined screw cap, and stirred vigorously at 110 °C for 2 h. After cooling to room temperature, the solvent was concentrated *in vacuo*. Purification of the resulting crude residue by column chromatography on silica gel (hexane/ethyl acetate = 4/1 to 2/1) provided indene **66** (colourless

[49] Semmelhack, M. F.; Ho, S.; Steigerwald, M.; Lee, M. C. *J. Am. Chem. Soc.* **1987**, *109*, 4397.

oil, 15.4 mg, 70% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR) and naphthol **67** (colourless oil, 5.9 mg, 26% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

Indene 66:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.3, 1.0 Hz, 1H), 7.36 – 7.27 (m, 2H), 7.24 – 7.14 (m, 1H), 7.10 & 7.07 (s, 1H), 6.67 (s, 1H), 4.07 & 3.99 (q, *J* = 8.2 Hz, 1H), 3.76 & 3.76 (s, 3H), 3.38 & 3.38 (s, 3H), 3.34 – 3.31 (m, 1H), 2.96 – 2.88 (m, 2H), 2.30 – 2.20 (m, 2H), 2.11 & 2.07 (d, *J* = 2.0 Hz, 3H), 2.06 – 2.00 (m, 1H), 1.98 – 1.83 (m, 2H), 1.75 – 1.67 (m, 1H), 1.56 – 1.48 (m, 3H), 1.43 – 1.36 (m, 3H), 1.25 – 1.20 (m, 1H), 1.17 – 1.10 (m, 3H), 0.83 & 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.24, 155.22, 148.99, 148.95, 145.91, 145.88, 145.7, 145.4, 136.8, 136.7, 133.7, 133.6, 132.07, 132.05, 128.7, 128.3, 126.22, 126.20, 124.44, 124.42, 123.1, 123.0, 122.3, 122.2, 118.80, 118.78, 111.3, 90.8, 57.9, 55.5, 50.4, 50.3, 46.3, 46.1, 43.99, 43.97, 43.30, 43.28, 38.70, 38.66, 38.12, 38.10, 29.94, 29.88, 27.8, 27.4, 27.3, 26.6, 26.5, 23.1, 16.1, 16.0, 11.77, 11.75, 11.64, 11.60.

IR ν max (film, cm^{-1}): 2925, 2866, 1606, 1499, 1465, 1381, 1314, 1256, 1223, 1105, 1033, 759, 738.

HRMS (ESI) calculated for $C_{31}H_{39}O_2^+$ $[M+H]^+$ m/z: 443.2945, found: 443.2957.

Naphthol 67:

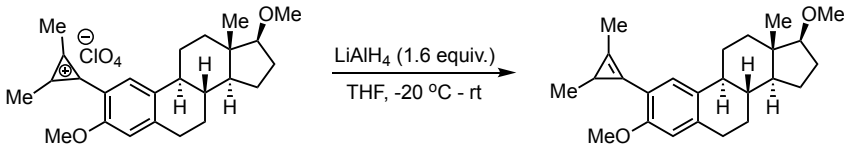
^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.20 (dd, *J* = 7.1, 2.1 Hz, 1H), 8.09 – 7.98 (m, 1H), 7.58 – 7.50 (m, 2H), 6.98 (s, 1H), 6.77 (s, 1H), 5.17 & 5.16 (s, 1H), 3.72 (s, 3H), 3.36 (s, 3H), 3.35 – 3.31 (m, 1H), 3.05 – 2.92 (m, 2H), 2.33 & 2.30 (s, 3H), 2.29 – 2.19 (m, 2H), 2.13 – 2.08 (m, 1H), 2.07 & 2.05 (s, 3H), 2.03 – 1.95 (m, 2H), 1.80 – 1.71 (m, 1H), 1.57 – 1.48 (m, 3H), 1.47 – 1.36 (m, 3H), 1.29 – 1.24 (m, 1H), 0.83 & 0.82 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2) δ 154.6, 146.54, 146.50, 137.47, 137.45, 137.0, 132.5, 131.80, 131.75, 128.1, 128.0, 127.1, 125.31, 125.30, 124.6, 124.41, 124.36, 124.33, 123.7, 121.23, 121.20, 116.63, 116.61, 111.1, 90.7, 57.5, 55.4, 50.3, 44.04, 44.02, 43.2, 38.8, 38.0, 29.9, 27.7, 27.4, 26.6, 23.0, 15.84, 15.81, 13.3, 13.2, 11.4.

IR ν max (film, cm^{-1}): 3048, 2916, 2848, 1733, 1646, 1504, 1468, 1373, 1264, 1102, 1031, 967.

HRMS (ESI) calculated for $C_{32}H_{38}NaO_3^+$ $[M+Na]^+$ m/z: 493.2713, found: 493.2701.

Addition of $LiAlH_4$ to CPC 63.



63 **68**

To a 25 mL oven-dried flask equipped with a stirring bar was added **CPC 63** (400.0 mg, 0.86 mmol). After being evacuated and backfilled with argon, 9.0 mL of dry THF was added and the reaction was cooled to -20 ºC. Then lithium aluminum hydride (52.0 mg, 1.40 mmol) was added in one portion. The mixture turned from red to yellow in 20 minutes. The reaction mixture was passed through a short pad of celite and washed with dichloromethane. The solvent was removed and the resulting reaction mixture was analyzed by ^{1}H NMR. Purification by flash

chromatography on neutral silica gel (hexane/ethyl acetate = 25/1 to 15/1) provided the corresponding cyclopropene **68** as a white foam (221.0 mg, 70% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

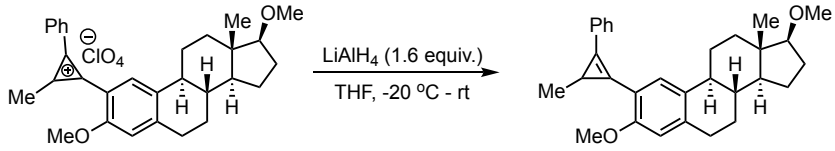
^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.25 (s, 1H), 6.64 (s, 1H), 3.89 (s, 3H), 3.38 (s, 3H), 3.36 – 3.30 (m, 1H), 2.97 – 2.84 (m, 2H), 2.43 – 2.33 (m, 1H), 2.29 (s, 3H), 2.27 – 2.17 (m, 1H), 2.14 – 2.04 (m, 2H), 1.97 – 1.88 (m, 1H), 1.79 – 1.66 (m, 2H), 1.58 – 1.44 (m, 4H), 1.43 – 1.30 (m, 2H), 1.30 – 1.20 (m, 1H), 1.18 & 1.17 (d, *J* = 2.4 Hz, 3H), 0.82 (s, 3H).

^{13}C NMR (101 MHz, CD_2Cl_2) δ 155.3, 137.9, 132.37, 132.35, 126.70, 126.68, 118.39, 118.38, 116.9, 112.39, 112.38, 110.55,110.55, 90.7, 57.5, 55.4, 50.3, 43.84, 43.76, 43.2, 38.7, 38.0, 30.02, 30.00, 27.7, 27.3, 27.2, 26.52, 26.45, 23.0, 19.50, 19.47, 13.6, 13.5, 11.4, 11.3.

IR ν max (film, cm^{-1}): 2926, 2866, 1604, 1566, 1497, 1456, 1399, 1362, 1285, 1228, 1126, 1103, 1030, 892, 860.

HRMS (ESI) calculated for $C_{25}H_{35}O_2^+$ $[M+H]^+$ m/z: 367.2632, found: 367.2636.

Addition of $LiAlH_4$ to CPC 64.



64 **69**

To a 25 mL oven-dried flask equipped with a stirring bar was added **CPC 64** (53.0 mg, 0.10 mmol). After being evacuated and backfilled with argon, 2.0 mL of dry THF was added and the suspension was cooled to -20 ºC. Then lithium aluminum hydride (6.0 mg, 0.16 mmol) was added in one portion. The resulting reaction mixture was stirred until a clear yellow solution was obtained (30 minutes). The reaction mixture was passed through a short pad of celite and washed with dichloromethane. The solvent was removed and the resulting reaction mixture was analyzed by ^{1}H NMR. Purification by flash chromatography on neutral silica gel (hexane/ethyl acetate = 25/1 to 15/1) provided the corresponding cyclopropene **69** as a white foam (34.1 mg, 80% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

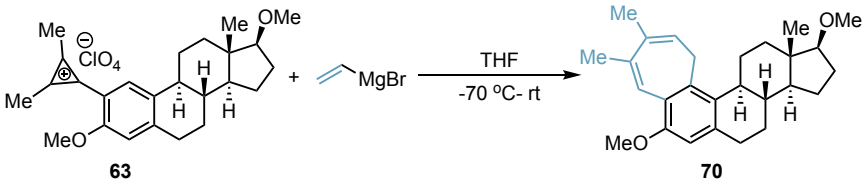
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.50 – 7.42 (m, 3H), 7.36 – 7.30 (m, 1H), 6.69 (s, 1H), 3.98 (s, 3H), 3.43 & 3.42 (s, 3H), 3.40 – 3.33 (m, 1H), 3.01 – 2.86 (m, 2H), 2.46 – 2.37 (m, 1H), 2.31 – 2.20 (m, 1H), 2.17 – 2.07 (m, 2H), 2.05 (q, *J* = 4.8 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.78 – 1.69 (m, 1H), 1.63 – 1.39 (m, 6H), 1.39 & 1.38 (d, *J* = 2.0 Hz, 3H), 1.32 – 1.21 (m, 1H), 0.85 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.59, 155.57, 139.0, 132.64, 132.63, 131.21, 131.19, 129.8, 128.50, 128.46, 128.4, 127.5, 117.3, 116.9, 116.8, 114.31, 114.28, 111.0, 90.8, 57.9, 55.3, 50.3, 43.79, 43.75, 43.3, 38.6, 38.07, 38.05, 30.20, 30.18, 27.82, 27.80, 27.25, 27.23, 26.5, 26.4, 23.10, 23.09, 19.3, 19.2, 12.3, 11.6.

IR ν max (film, cm^{-1}): 2926, 2868, 1810, 1593, 1499, 1456, 1399, 1307, 1237, 1104, 1030, 991, 893, 861, 761.

HRMS (ESI) calculated for $C_{30}H_{36}NaO_2^+$ $[M+Na]^+$ m/z: 451.2608, found: 451.2614.

Addition of vinylmagnesium bromide to CPC 59.



63 70

To a 25 mL oven-dried flask equipped with a stirring bar was added **CPC 63** (46.4 mg, 0.10 mmol). After being evacuated and backfilled with argon, 2.0 mL of dry THF was added and the reaction was cooled to -70 °C. Then vinylmagnesium bromide (0.17 mL, 1M in THF) was added slowly. The mixture turned from red to yellow in 20 minutes. Then neutral silica gel was added to the reaction mixture. The solvent was removed and the crude residue was purified by column chromatography on neutral silica gel (hexane/ethyl acetate = 25/1 to 15/1) to give the corresponding compound **70** as a colourless oil (18.0 mg, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.66 (s, 1H), 6.14 – 6.06 (m, 1H), 3.79 (s, 3H), 3.40 (s, 3H), 3.37 – 3.32 (m, 1H), 3.30 – 3.26 (m, 2H), 2.99 – 2.83 (m, 2H), 2.33 – 2.19 (m, 2H), 2.14 – 2.08 (m, 1H), 2.07 – 2.05 (m, 1H), 2.02 (q, J = 1.8 Hz, 3H), 1.93 (q, J = 1.7 Hz, 3H), 1.76 – 1.68 (m, 1H), 1.56 – 1.48 (m, 3H), 1.47 – 1.34 (m, 4H), 1.26 – 1.21 (m, 1H), 0.82 (s, 3H).

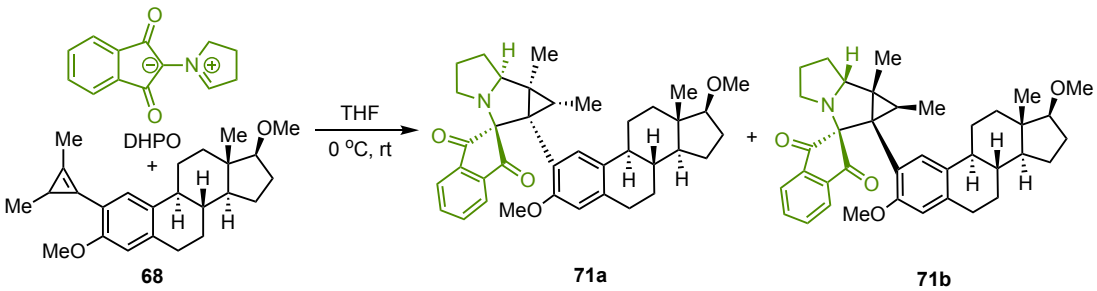
^{13}C NMR (126 MHz, $CDCl_3$) δ 154.8, 144.1, 139.1, 138.0, 136.1, 131.9, 127.9, 126.1, 124.7, 111.3, 90.8, 57.9, 55.4, 50.3, 44.0, 43.3 (2 C), 38.7, 38.1, 29.8, 27.8, 27.3, 26.5, 23.1, 14.3, 12.5, 11.6.

IR ν max (film, cm^{-1}): 1732, 1656, 1558, 1497, 1457, 1398, 1252, 1102, 1029, 862.

HRMS (ESI) calculated for $C_{27}H_{36}NaO_2^+$ $[M+Na]^+$ m/z: 415.2608, found: 415.2614.

$[\alpha]^{25}_D$ = +47.3 (c = 0.5, $CHCl_3$).

1,3-Dipolar cycloaddition.[50]



68 71a 71b

To a 10 mL oven-dried tube equipped with a stirring bar was added **68** (15.0 mg, 0.04 mmol) and DHPO (13.0 mg, 0.06 mmol). After being evacuated and backfilled with argon, 1.0 mL of dry THF was added at 0 °C. The mixture was warmed to room temperature slowly. When the reaction was complete (monitored with TLC), the

[50] Filatov, A. S.; Knyazev, N. A.; Molchanov, A. P.; Panikorovsky, T. L.; Kostikov, R. R.; Larina, A. G.; Boitsov, V. M.; Stepakov, A. V. *J. Org. Chem.* **2017**, *82*, 959.

solvent was removed *in vacuo*. The residue was analyzed by ^{1}H NMR as a 1:1 mixture of diastereoisomers. The crude product was purified by preparative TLC (dichloromethane/ethyl acetate = 7/1) to give the corresponding **71** (16.5 mg, 71% yield).

Diastereoisomer 1 (71a):

Yellow foam, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.70 – 7.64 (m, 1H), 7.57 – 7.51 (m, 1H), 7.41 (d, *J* = 7.6 Hz, 1H), 6.91 (s, 1H), 5.90 (s, 1H), 4.36 – 4.29 (m, 1H), 3.69 – 3.61 (m, 1H), 3.41 (s, 3H), 3.37 – 3.31 (m, 1H), 3.26 (s, 3H), 2.72 – 2.62 (m, 2H), 2.53 (dd, *J* = 17.0, 5.5 Hz, 1H), 2.34 – 2.25 (m, 1H), 2.18 – 2.11 (m, 1H), 2.09 – 1.91 (m, 4H), 1.81 (q, *J* = 6.4 Hz, 1H), 1.79 – 1.74 (m, 1H), 1.71 – 1.60 (m, 3H), 1.56 – 1.47 (m, 1H), 1.44 – 1.29 (m, 5H), 1.22 (s, 3H), 1.20 – 1.13 (m, 1H), 0.78 (s, 3H), 0.73 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.3, 198.4, 156.5, 142.5, 139.8, 136.6, 134.7, 134.4, 132.8, 131.6, 122.1, 121.7, 118.5, 108.8, 90.8, 74.2, 57.9, 53.6, 50.24, 50.17, 47.9, 43.6, 43.3, 38.6, 38.1, 36.6, 29.73, 29.70, 28.2, 27.9, 27.8, 27.1, 26.6, 23.0, 19.6, 13.7, 11.6, 9.7.

IR ν max (film, cm^{-1}): 2921, 2863, 1741, 1704, 1597, 1506, 1457, 1255, 1212, 1131, 1102, 1070, 1029, 861, 793.

HRMS (ESI) calculated for $C_{38}H_{46}NO_4^+$ $[M+H]^+$ m/z: 580.3421, found: 580.3413.

$[\alpha]^{25}_D$ = -15.8 (*c* = 0.4, $CHCl_3$).

NOESY spectrum was measured.

Diastereoisomer 2 (71b):

Brown foam, **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.56 – 7.50 (m, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 6.88 (s, 1H), 5.90 (s, 1H), 4.36 – 4.28 (m, 1H), 3.69 – 3.62 (m, 1H), 3.42 (s, 3H), 3.37 – 3.31 (m, 1H), 3.28 (s, 3H), 2.73 – 2.67 (m, 1H), 2.62 – 2.56 (m, 2H), 2.33 – 2.24 (m, 1H), 2.18 – 2.12 (m, 1H), 2.12 – 2.05 (m, 2H), 2.04 – 1.92 (m, 2H), 1.79 (q, *J* = 6.5 Hz, 1H), 1.71 – 1.65 (m, 2H), 1.65 – 1.59 (m, 2H), 1.58 – 1.48 (m, 2H), 1.45 – 1.31 (m, 3H), 1.27 – 1.19 (m, 2H), 1.18 (s, 3H), 0.88 (s, 3H), 0.74 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0, 198.5, 156.6, 142.2, 139.9, 136.6, 134.6, 134.2, 132.5, 131.7, 121.7, 121.6, 118.4, 108.8, 90.9, 74.0, 57.9, 53.6, 50.4, 50.3, 47.7, 43.8, 43.3, 38.7, 38.0, 36.2, 29.7, 29.5, 28.2, 27.9, 27.8, 27.0, 26.5, 23.1, 19.7, 13.4, 11.8, 9.7.

IR ν max (film, cm^{-1}): 2922, 2864, 1745, 1705, 1596, 1506, 1456, 1237, 1212, 1132, 1103, 1071, 1030, 861, 767.

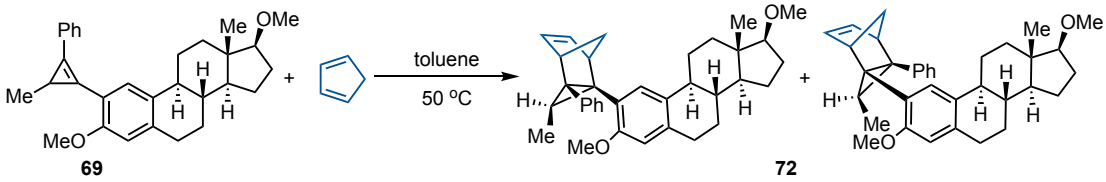
HRMS (ESI) calculated for $C_{38}H_{46}NO_4^+$ $[M+H]^+$ m/z: 580.3421, found: 580.3426.

$[\alpha]^{25}_D$ = +58.4 (*c* = 0.4, $CHCl_3$).

NOESY spectra was measured.

Diels-Alder reaction with cyclopentadiene.[51, 52]

[51] Binger, P.; Wedemann, P.; Goddard, R.; Blinker, U. H. *J. Org. Chem.* **1996**, *61*, 6462
[52] Lou, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. A. *J. Am. Chem. Soc.* **2004**, *126*, 8916.



A solution of cyclopropene **69** (8.0 mg, 0.02 mmol) and cyclopentadiene (22.0 mg, 0.30 mmol) in toluene (1 mL) was stirred at 50 °C for 12 h. The residue after rotary evaporation was purified by column chromatography (hexane/ethyl acetate = 16/1 to 10/1) to afford the desired cycloadduct **72** as a yellow oil (7.1 mg, 66% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.35 – 7.29 (m, 2H), 7.27 – 7.16 (m, 2H), 6.56 & 6.55 (s, 1H), 6.23 – 6.18 (m, 1H), 6.11 – 6.06 (m, 1H), 3.80 & 3.79 (s, 3H), 3.41 & 3.40 (s, 3H), 3.33 – 3.27 (m, 1H), 2.99 – 2.87 (m, 1H), 2.87 – 2.74 (m, 3H), 2.56 – 2.49 (m, 1H), 2.15 – 2.01 (m, 2H), 2.00 – 1.94 (m, 1H), 1.93 – 1.77 (m, 2H), 1.69 (q, J = 7.2 Hz, 1H), 1.54 – 1.44 (m, 3H), 1.39 – 1.29 (m, 5H), 1.22 – 1.09 (m, 1H), 0.81 & 0.71 (s, 3H), 0.79 & 0.74 (d, J = 6.5 Hz, 3H).

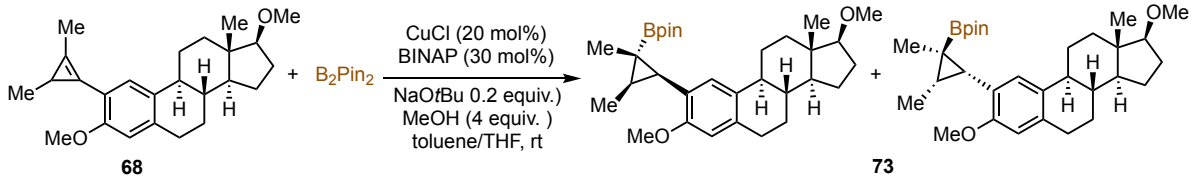
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 156.9, 142.2, 135.13, 135.06, 134.73, 134.67, 133.0, 132.8, 131.3, 131.2, 130.8, 130.5, 128.1, 127.83, 127.79, 127.5, 126.9, 126.6, 125.5, 125.3, 110.49, 110.46, 90.87, 90.85, 59.8, 59.7, 57.94, 57.90, 55.9, 55.5, 55.3, 52.3, 50.3, 50.2, 44.1, 43.9, 43.22, 43.20, 38.6, 38.5, 38.1, 38.0, 37.2, 37.0, 36.6, 36.1, 31.3, 30.9, 29.7, 29.6, 27.8, 27.7, 27.4, 27.3, 26.4, 26.2, 23.1, 23.0, 13.93, 13.86, 11.6, 11.5.

IR ν max (film, cm^{-1}): 3053, 2926, 1599, 1500, 1450, 1406, 1251, 1226, 1128, 1104, 1033, 990, 861, 755.

HRMS (ESI) calculated for $C_{35}H_{42}NaO_2^+$ $[M+Na]^+$ m/z: 517.3077, found: 517.3076.

NOESY spectrum was measured.

Cu(I)-catalyzed protoborylation.[53, 54]



A dried Schlenk flask was charged with CuCl (1.0 mg, 20 mol%), (*rac*)-BINAP (9.3 mg, 30 mol%), B_2Pin_2 (26.0 mg, 0.10 mmol, 2.0 equiv.), NaO*t*Bu (1.2 mg, 25 mol%) and anhydrous toluene (1.0 mL) under argon atmosphere. After the mixture was stirred at room temperature for 40 minutes, a solution of cyclopropene **68** (18.0 mg, 0.05 mmol) in anhydrous THF (1.0 mL) was added, followed by anhydrous methanol (8.0 µL, 4.0 equiv.). The resulting mixture was stirred at room temperature until full consumption of the starting material (monitored with TLC), then filtered through celite, concentrated *in vacuo,* analyzed by ^{1}H NMR. The residue was purified by column

[53] Tian, B.; Liu, Q.; Tong, X.; Tian, P.; Lin, G. Q. *Org. Chem. Front.* **2014**, *1*, 1116.
[54] Parra, A.; Amenós, L.; Guisán-Ceinos, M.; López, A.; García Ruano, J. L.; Tortosa, M. *J. Am. Chem. Soc.* **2014**, *136*, 15833.

chromatography (hexane/ethyl acetate = 15/1 to 9/1) to afford the desired product **73** as a yellow oil (14.1 mg, 57% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 6.59 – 6.55 (m, 1H), 3.77 (s, 3H), 3.40 (s, 3H), 3.36 – 3.31 (m, 1H), 2.94 – 2.78 (m, 2H), 2.32 – 2.24 (m, 1H), 2.23 – 2.15 (m, 1H), 2.13 – 2.04 (m, 2H), 2.01 (d, *J* = 8.6 Hz, 1H), 1.92 – 1.85 (m, 1H), 1.76 – 1.65 (m, 1H), 1.58 – 1.31 (m, 7H), 1.28 (d, *J* = 1.7 Hz, 6H), 1.27 (d, *J* = 3.7 Hz, 6H), 1.24 – 1.16 (m, 1H), 1.07 & 1.04 (d, *J* = 6.6 Hz, 3H), 0.84 & 0.81 (s, 3H), 0.810 & 0.806 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.47, 157.46, 135.13, 135.11, 131.27, 131.25, 129.07, 129.05, 123.25, 123.23, 110.52, 110.50, 90.9, 82.8, 57.9, 55.25, 55.23, 50.3, 44.0, 43.3, 38.7, 38.2, 29.80, 29.77, 27.8, 27.3, 26.6, 26.5, 25.44, 25.42, 24.77, 24.72, 24.67, 24.63, 23.1, 19.8, 11.6, 10.16, 10.15, 10.02, 9.99.

^{11}B NMR (160 MHz, $CDCl_3$) δ 33.9, -3.6.

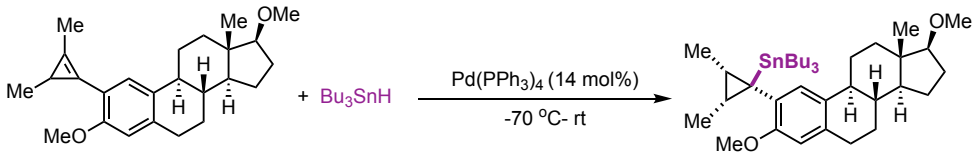
IR ν max (film, cm^{-1}): 2973, 2925, 1611, 1501, 1464, 1362, 1301, 1235, 1143, 1120, 1031, 970, 904, 853, 755.

HRMS (ESI) calculated for $C_{31}H_{48}O_4$^$^{10}B^+$ $[M+H]^+$ m/z: 494.3676, found: 494.3676.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, NOESY spectra were measured.

Relative stereochemistry was also corroborated by the value of the coupling constant (J_{cis}: 7-11 Hz and J_{trans}: 4-7 Hz) in the cyclopropane ring.

Pd-catalyzed hydrostannation.[55]



68 **74**

To a 10 mL oven-dried tube equipped with a stirring bar was added $Pd(PPh_3)_4$ (4.0 mg, 14 mol %). After being evacuated and backfilled with argon, 0.5 mL of dry THF was added. The resulting mixture was stirred for 10 minutes. The solution was cooled to -70 °C, and tributyltin hydride (10 µL, 0.04 mmol) was added. The reaction mixture was stirred at -70 °C for 1 minute, after which cyclopropene **68** (9.0 mg, 0.025 mmol) in THF (0.5 mL) was added, and the mixture was warmed to -30 °C slowly. When the reaction was complete (monitored with TLC), the solvent was removed *in vacuo* and the resulting reaction mixture was analyzed by ^{1}H NMR. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate = 16/1 to 10/1) to yield the corresponding cyclopropane **74** as a colourless oil (7.1 mg, 44% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.46 (s, 1H), 3.72 (s, 3H), 3.40 (s, 3H), 3.37 – 3.31 (m, 1H), 2.91 – 2.74 (m, 2H), 2.31 – 2.24 (m, 1H), 2.21 – 2.13 (m, 1H), 2.13 – 2.03 (m, 2H), 1.91 – 1.83 (m, 1H), 1.75 – 1.66 (m, 1H), 1.57 – 1.48 (m, 2H), 1.48 – 1.41 (m, 3H), 1.39 – 1.32 (m, 7H), 1.26 – 1.20 (m, 9H), 0.97 – 0.90 (m, 6H), 0.86 (t, *J* = 7.3 Hz, 9H), 0.81 (s, 3H), 0.70 – 0.65 (m, 6H).

[55] Trofimov, A.; Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Org. Chem.* **2007**, *72*, 8910.

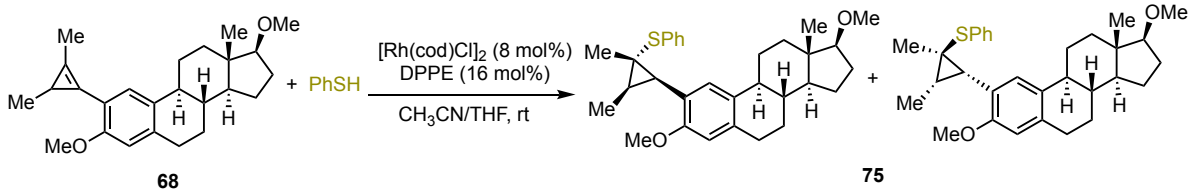
^{13}C NMR (126 MHz, $CDCl_3$) δ 156.1, 132.4, 131.1, 128.17, 128.16, 109.5, 90.9, 57.9, 54.4, 50.3, 44.0, 43.3, 38.8, 38.2, 29.7, 29.0, 27.8, 27.6, 27.5, 26.6, 23.1, 19.8, 18.3, 18.2, 13.8, 11.6, 10.7, 10.6, 9.2.

IR ν max (film, cm^{-1}): 2920, 2850, 1497, 1458, 1376, 1231, 1106, 1068, 1030, 860, 803, 771.

HRMS (ESI) calculated for $C_{37}H_{62}NaO_2{}^{\wedge120}Sn^+$ $[M+Na]^+$ m/z: 681.3664, found: 681.3668.

$[\alpha]^{25}_D$ = +22.3 (*c* = 0.5, $CHCl_3$).

Rh(I)-catalyzed hydrothiolation.[56]



68 **75**

To a 10 mL oven-dried tube equipped with a stirring bar was added $[Rh(cod)Cl]_2$ (2.0 mg, 8 mol%), DPPE (3.3 mg, 16 mol%). After being evacuated and backfilled with argon, 1.0 mL of dry MeCN was added. The resulting mixture was stirred for 10 minutes. Thiophenol (11.0 mg, 0.10 mmol) was added followed by cyclopropene **68** (18.0 mg, 0.05 mmol) in THF (1.0 mL). When the reaction was complete (monitored with TLC), the solvent was removed *in vacuo* and the resulting reaction mixture was analyzed by ^{1}H NMR. The crude product was purified by preparative TLC (hexane/acetonitrile = 7/1) to give the corresponding **75** as a yellow oil (14.4 mg, 61% yield, 1:1 mixture of diastereoisomers as determined by ^{1}H NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.35 – 7.30 (m, 2H), 7.25 – 7.18 (m, 1H), 7.06 & 7.05 (s, 1H), 6.59 (s, 1H), 3.76 (s, 3H), 3.41 & 3.40 (s, 3H), 3.37 – 3.31 (m, 1H), 2.95 – 2.78 (m, 2H), 2.37 (dd, *J* = 9.6, 4.9 Hz, 1H), 2.25 – 2.14 (m, 2H), 2.13 – 2.02 (m, 2H), 1.93 – 1.86 (m, 1H), 1.77 – 1.66 (m, 2H), 1.56 – 1.31 (m, 6H), 1.28 & 1.27 (s, 3H), 1.26 – 1.18 (m, 1H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.82 & 0.80 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.11, 157.09, 136.92, 136.90, 136.1, 136.0, 131.63, 131.62, 129.6, 129.5, 128.9, 128.7, 128.69, 125.8, 125.7, 121.7, 110.6, 90.8, 57.9, 55.1, 50.27, 50.25, 43.91, 43.87, 43.27, 43.25, 38.7, 38.6, 38.09, 38.07, 29.81, 29.77, 29.7, 29.6, 28.9, 28.8, 27.8, 27.29, 27.27, 26.53, 26.49, 24.9, 24.7, 23.0, 16.7, 11.60, 11.55, 11.1, 11.0.

IR ν max (film, cm^{-1}): 3055, 2923, 1611, 1583, 1503, 1463, 1406, 1383, 1315, 1251, 1206, 1122, 1105, 1071, 1030, 992, 900, 862, 736.

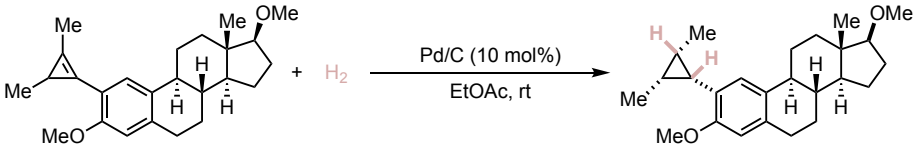
HRMS (ESI) calculated for $C_{31}H_{40}NaO_2S^+$ $[M+Na]^+$ m/z: 499.2641, found: 499.2637.

^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, NOESY spectra were measured.

Relative stereochemistry was also corroborated by the value of the coupling constant (J_{cis}: 7-11 Hz and J_{trans}: 4-7 Hz) in the cyclopropane ring.

[56] Nie, S.; Lu, A.; Kuker, E. L.; Dong, V. M. *J. Am. Chem. Soc.* **2021**, *143*, 6176.

Pd-catalyzed hydrogenation.



68 **76**

10% Pd/C (7.4 mg, 0.007 mmol) was added to a solution of cyclopropene **68** (27.0 mg, 0.07 mmol) in ethyl acetate (2.0 mL). After being purged with hydrogen, the suspension was stirred vigorously under hydrogen atmosphere overnight. The reaction mixture was then filtered through a short plug of celite, and concentrated *in vacuo*. The residue was analyzed by ^{1}H NMR as a 16:3:1 mixture of diastereoisomers. Purification by flash chromatography on silica gel (hexane/ethyl acetate = 6/1) provided the desired cyclopropane **76** as a colourless oil (22.1 mg, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.60 (s, 1H), 3.82 (s, 3H), 3.41 (s, 3H), 3.37 – 3.30 (m, 1H), 2.95 – 2.79 (m, 2H), 2.34 – 2.26 (m, 1H), 2.24 – 2.17 (m, 1H), 2.14 – 2.03 (m, 2H), 1.93 – 1.87 (m, 1H), 1.84 – 1.77 (m, 1H), 1.75 – 1.67 (m, 1H), 1.59 – 1.31 (m, 6H), 1.29 – 1.15 (m, 3H), 1.00 – 0.90 (m, 6H), 0.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6, 135.2, 131.5, 129.7, 123.2, 110.6, 90.9, 57.9, 55.3, 50.3, 44.0, 43.3, 38.7, 38.2, 29.8, 27.8, 27.4, 26.6, 23.1, 18.9, 13.48, 13.46, 11.6, 9.6, 9.5.

IR ν max (film, cm^{-1}): 2869, 1611, 1503, 1463, 1406, 1383, 1256, 1231, 1203, 1121, 1067, 1031, 861.

HRMS (ESI) calculated for $C_{25}H_{36}NaO_2^+$ $[M+Na]^+$ m/z: 391.2608, found: 391.2604.

$[\alpha]^{25}_D$ = +60.6 (*c* = 0.4, $CHCl_3$).

Mechanistic insights of the reaction.

Detection of *int-1* by GC-MS

A reaction was performed with **1g** (18.0 mg, 0.06 mmol), *p*-xylene (10.6 mg, 0.10 mmol) and CsF (9.1 mg, 0.06 mmol) under the standard reaction conditions (**general procedure A**). At 2 min and at 90 min, an aliquot of the reaction mixture was analyzed by GC-MS. GC-MS conditions: 75 °C, isothermal for 1.0 min; 90 °C to 250 °C, 50 °C/min gradient, 16 min.

Synthesis of *int-1*

Note: ***Int-1*** is unstable toward column chromatography. It was synthesized from CPC **1g** and CsF (1.6 equiv.) in HFIP (0.1 M) at rt. After the reaction was finished, the solvent was removed. Then the mixture was dissolved in dichloromethane and filtered through a pad of celite. The solvent was removed under vacuum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 4.12 (m, 3H), 2.09 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{19}F NMR (282 MHz, $CDCl_3$) δ -73.5 (m).

HRMS (APCI) calculated for $C_{11}H_{13}F_6O_3^+$ $[M+H]^+$ m/z: 307.0763, found: 307.0765.

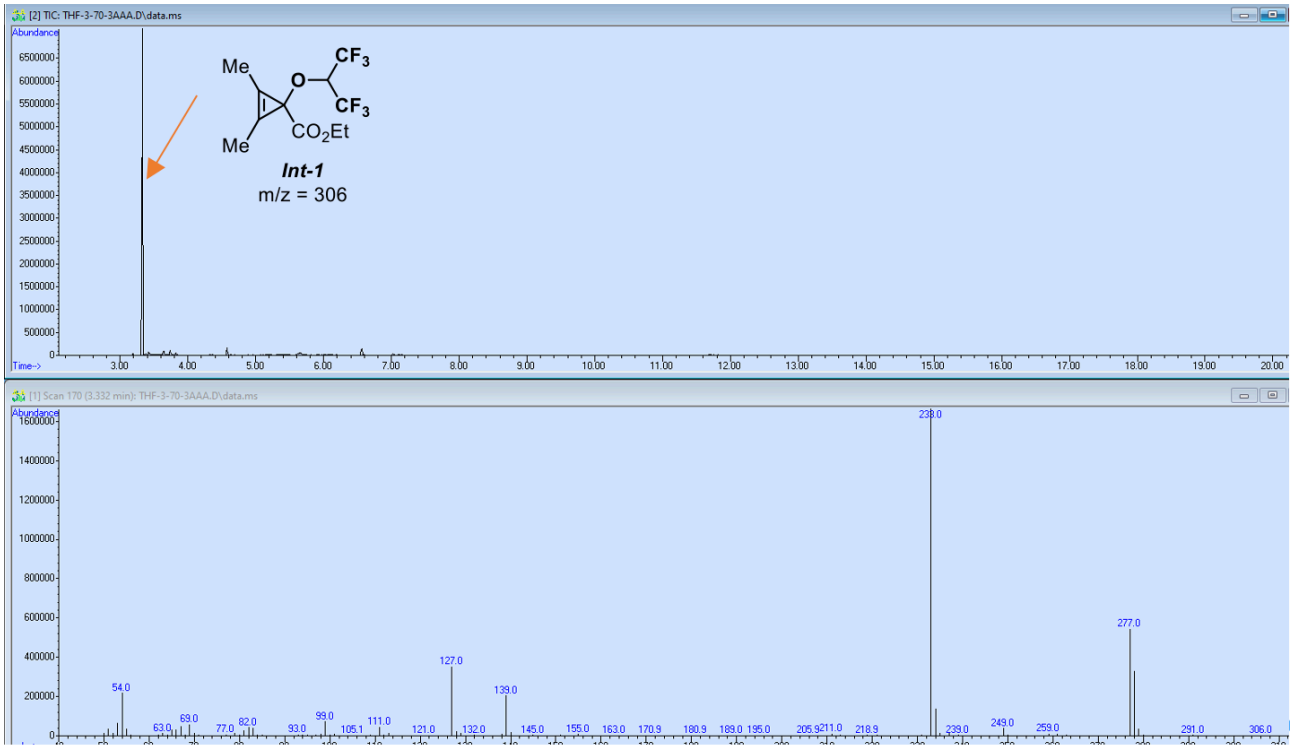
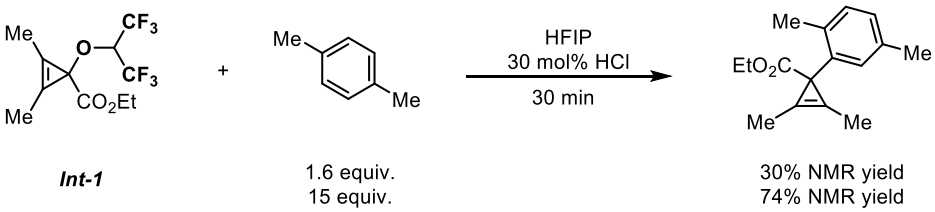


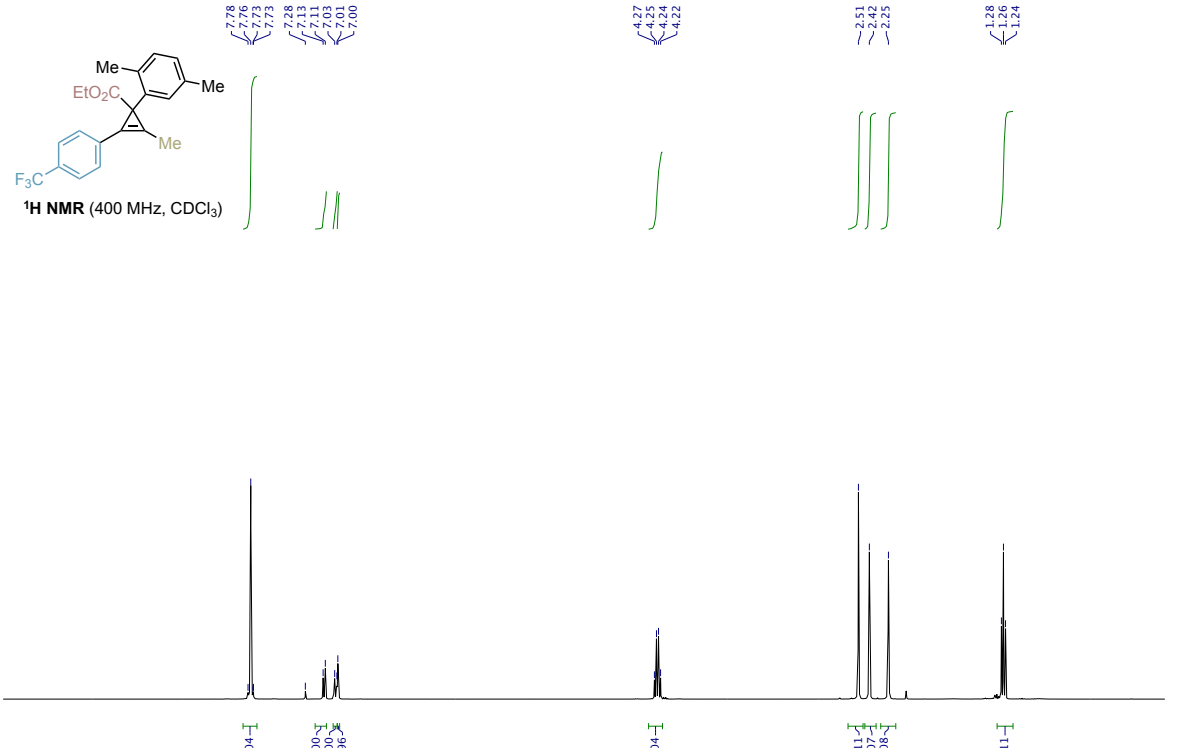
Figure 17 GC-MS traces of ***Int-1***

Synthesis of cyclopropene 8 with *int-1*

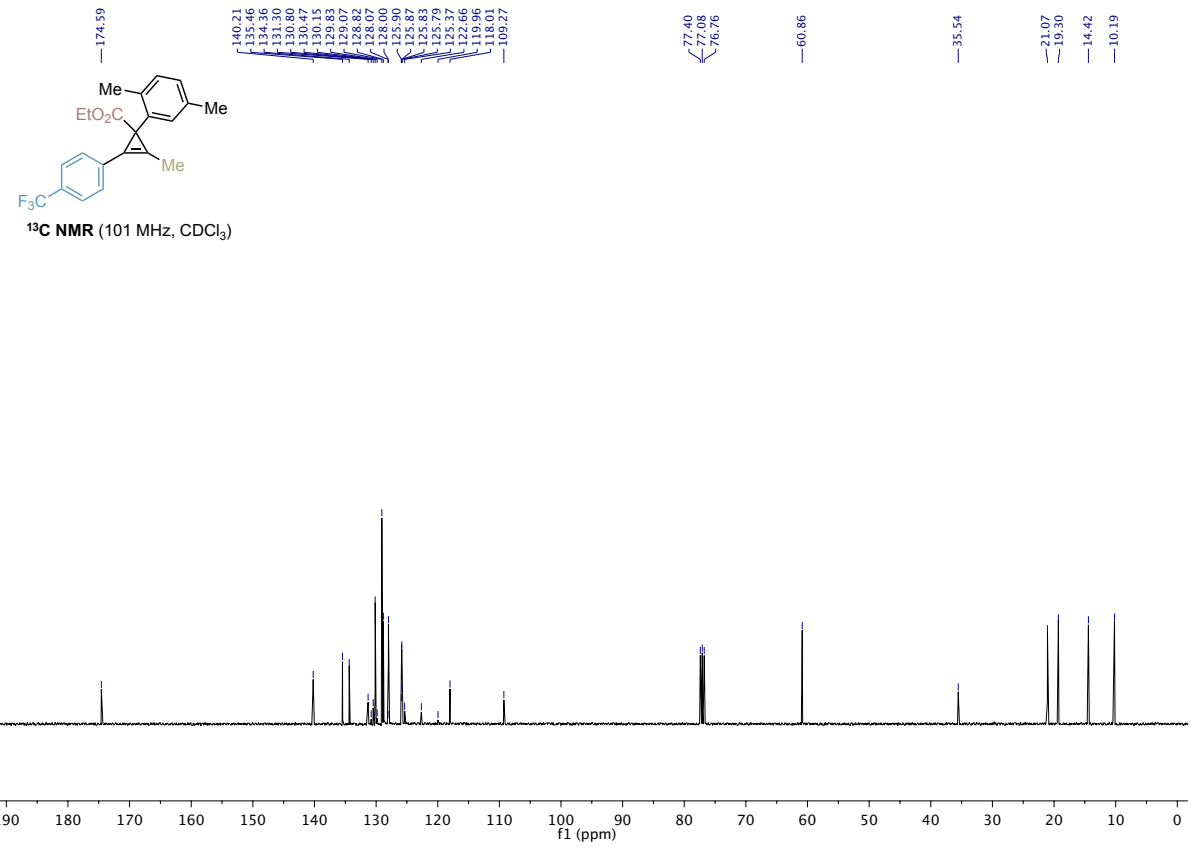
A reaction was performed with ***int-1*** (10.1 mg, 0.03 mmol), *p*-xylene (53.0 mg, 0.50 mmol, 15 equiv.) and HCl (0.01 mmol, 1 M in Et_2O) in HFIP (0.5 mL). The desired cyclopropene **8** was obtained in 74% NMR yield. Using 1.6 equiv. of *p*-xylene afforded the cyclopropene **8** in 30% NMR yield.



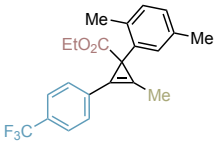
Selected NMR spectra



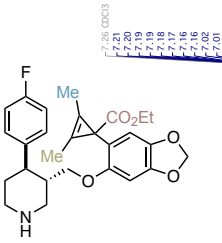
^{1}H NMR (400 MHz, $CDCl_3$)



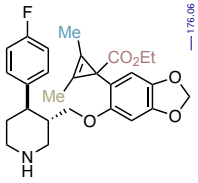
^{13}C NMR (101 MHz, $CDCl_3$)



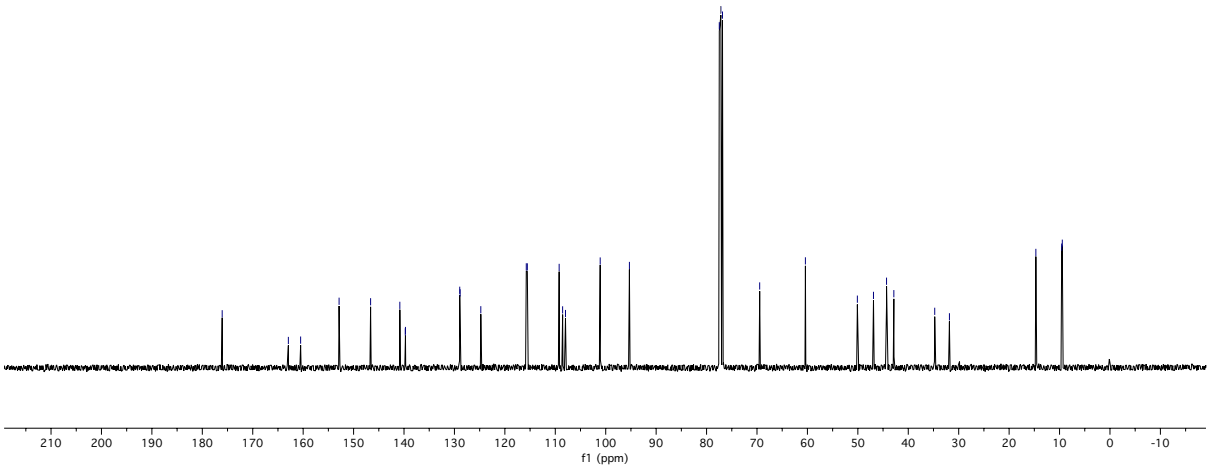
^{19}F NMR (376 MHz, $CDCl_3$)

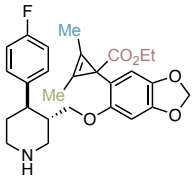


^{1}H NMR (400 MHz, $CDCl_3$)

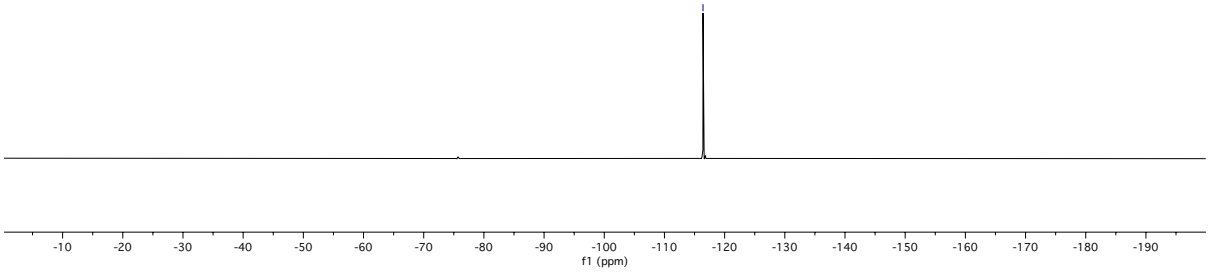


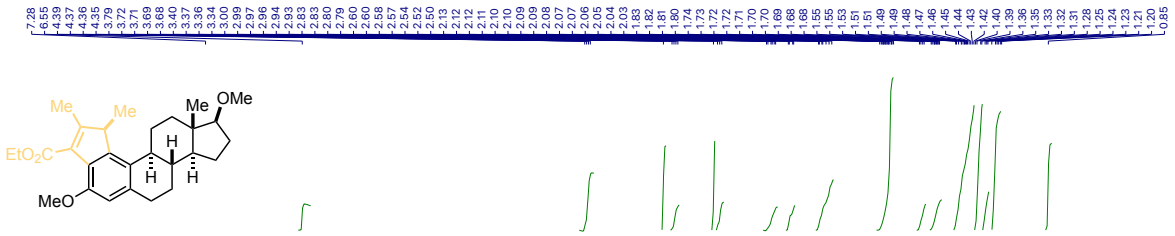
^{13}C NMR (101 MHz, $CDCl_3$)



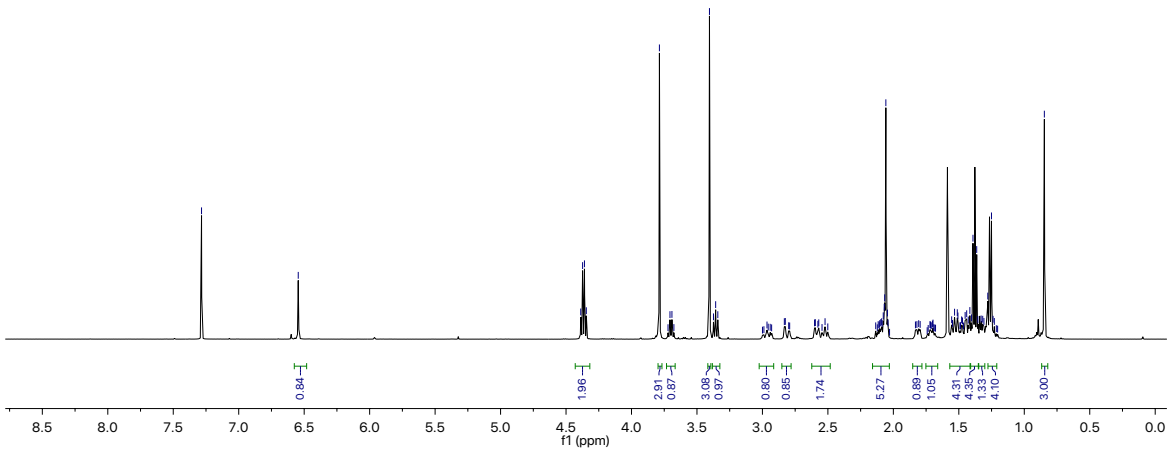


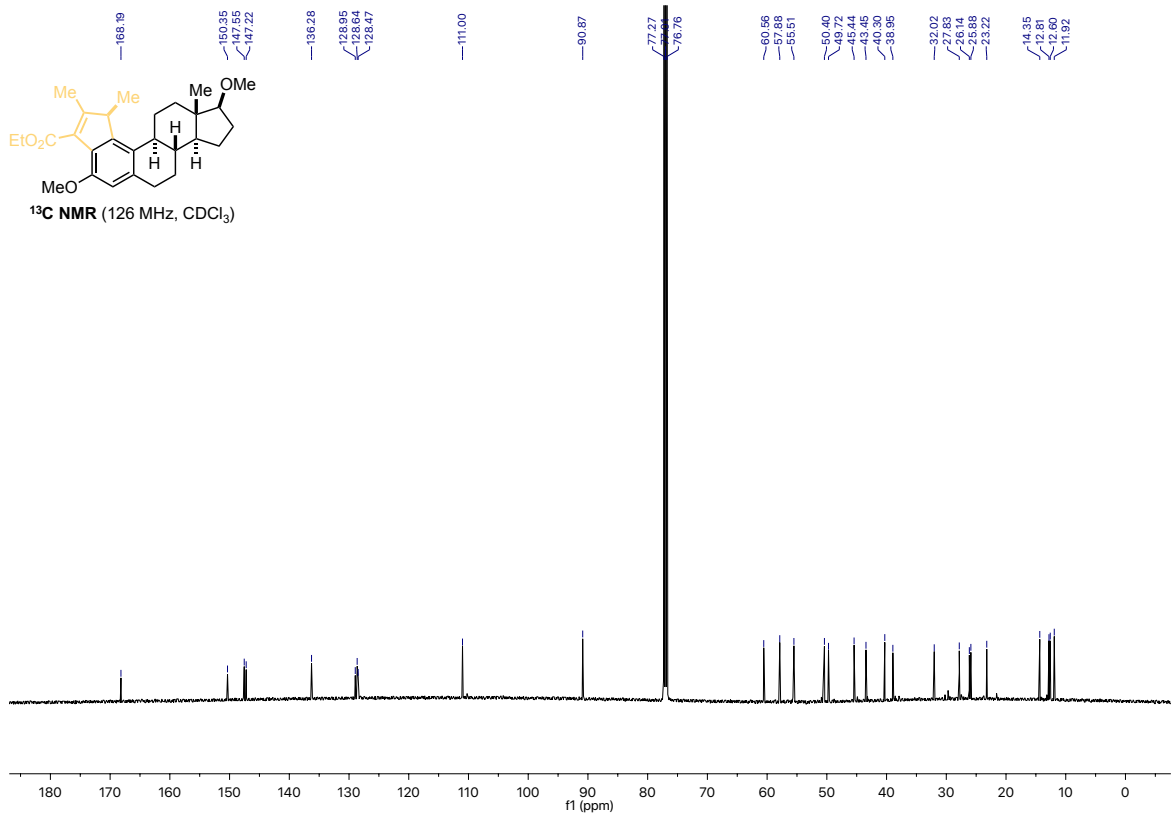
^{19}F NMR (376 MHz, $CDCl_3$)



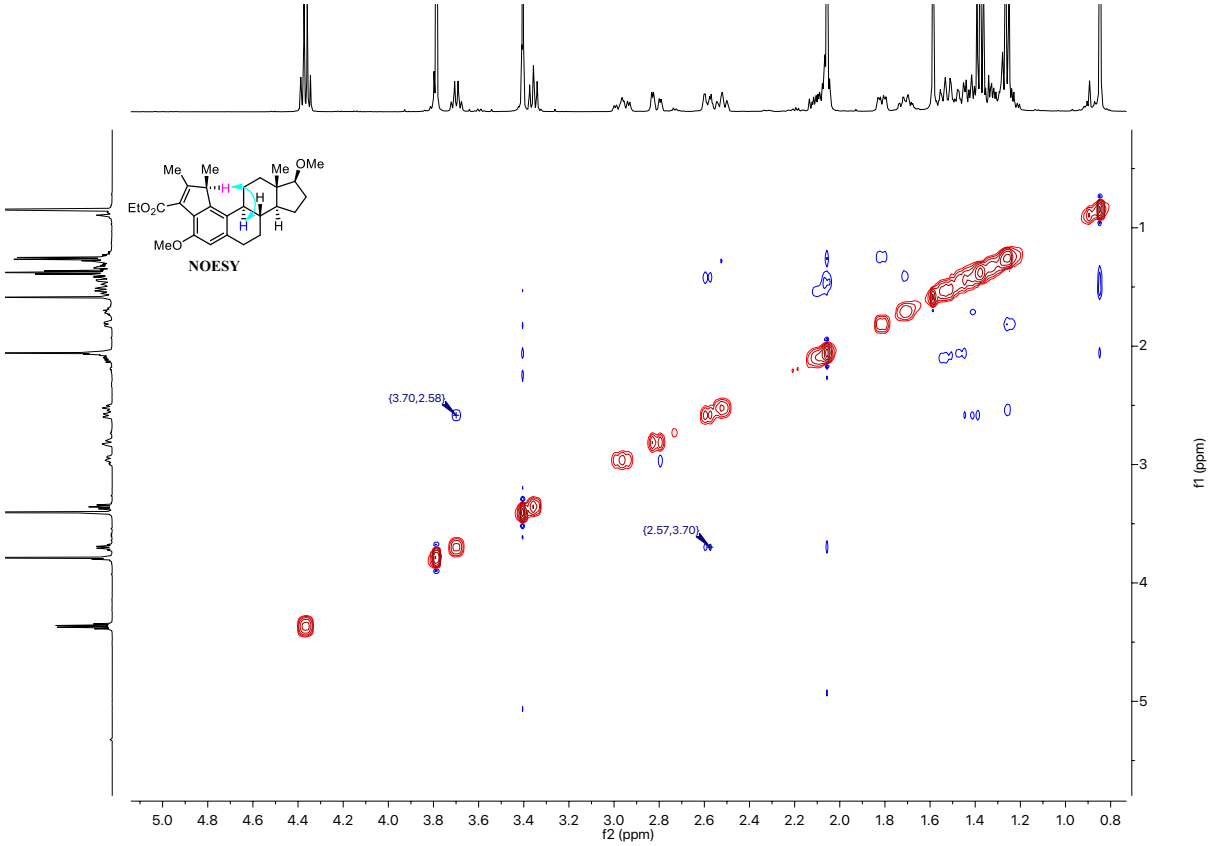


^{1}H NMR (500 MHz, $CDCl_3$)





^{13}C NMR (126 MHz, $CDCl_3$)


Me
Me
Me
OMe
EtO2C
MeO
H
H
H
H
NOESY
{3.70,2.58}
{2.57,3.70}
f2 (ppm)
f1 (ppm)

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SYNTHESIS OF CYCLOPROPENIUM CATIONS BY CARBYNE TRANSFER CATALYSIS AND APPLICATIONS IN NOVEL CYCLOPROPENE SYNTHESES
Aliénor Celine Renee Jeandin

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General conclusion

In this Doctoral Thesis, we have developed further the potential of our metal-catalyzed carbyne transfer platform by exploring its reactivity with alkynes, which resulted in the development of a novel and efficient synthesis of cyclopropenium cations (CPCs). Overall, new synthetic possibilities enabled by carbyne transfer have been unveiled, and this in a multifold manner.

First, in Chapter II, we have developed the first catalytic synthesis of cyclopropenium cations (CPCs) from Rh-carbynoids and readily available alkynes, and we reported a novel class of ester-substituted CPCs. By using carbyne transfer catalysis with alkynes, we have introduced a fundamentally different approach to the synthesis of CPCs compared to preexisting methods. This report is also an additional synthetic demonstration of the extent of aromatic stabilization: CPCs are isolated as stable solids, handled at room temperature outside of a glovebox.

In Chapter III, we have started to uncover the synthetic potential of our new class of ester-substituted CPCs with a highly regioselective synthesis of complex cyclopropenes. CPCs have little precedency as three-carbon building blocks in organic synthesis due to either a lack of reactivity, or regioselectivity issues observed in previous attempts, depending on the substitution pattern of CPCs. We demonstrate that carbon and heteroatom-based nucleophiles reacted exclusively at the carbon substituted with the ester group in a reaction happening under orbital control. Moreover, existing methods for the synthesis of cyclopropenes suffer from limitations related to the availability of carbene sources and efficient catalytic systems: the use of CPCs as synthons allows us to overcome these constraints affording previously inaccessible persubstituted cyclopropenes.

Finally, in Chapter IV, we report the application of CPCs in a late-stage aryl C-H bond cyclopropenylation of simple aromatics as well as natural products, drug molecules and fluorescent dyes. In contrast to other small rings, cyclopropenes have been underexplored in medicinal chemistry, most certainly due to the lack of existing methods for their incorporation in a late-stage manner. Here, the use of CPCs as building blocks allows the installation of cyclopropenes in densely-functionalized settings with outstanding regio-, chemo-, and site-selectivities. We also expand the synthetically accessible space in medicinal chemistry by utilizing the cyclopropene ring as scaffold to reach various sp^3-rich motifs. Additionally, the cyclopropene motif also acts as tool to shield against metabolic instability. This late-stage cyclopropenylation, originally enabled by our carbyne transfer catalysis platform, represents overall an unprecedented tool that simultaneously offers various synthetic possibilities in medicinal chemistry.

The application of carbyne catalysis to alkynes for the generation of CPCs, as well as the subsequent use of CPCs as synthons for the synthesis of highly versatile cyclopropenes, are valuable additions to the synthetic toolbox of organic and medicinal chemists. Importantly, a broader array of medicinally-relevant motifs is now available for further study, with potential impacts on drug design. We envisage that the novel class of CPCs will find further synthetic applications in organic synthesis, medicinal chemistry, and bioconjugation strategies.

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Acknowledgments

This Ph.D. has been a four-year journey along which I encountered many people who have been crucial to the course of my thesis, while also shaping me as a scientist and as a person. This work would be incomplete without the acknowledgment of their influence and the expression of my heartfelt gratitude to them all.

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This leads me to express my deepest gratitude to **Prof. Kilian Muñiz**, who gave me the opportunity to start my Ph.D. in ICIQ four years ago. While our paths diverged earlier than one could have imagined, I have been truly fortunate to work with a brilliant mind like his even for just a few months. There is no doubt what I learned in this short time also impacted the rest of my thesis.

Importantly, I would like to sincerely thank **Prof. Elena Fernández**, **Prof. Rubén Vicente** and **Prof. Ilan Marek** for accepting to be part of my thesis defense committee.

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Coming back to ICIQ, I am truly thankful to **Sorania Jiménez Ávila**, for administrative and everyday life support already before, during, and after my moving to Spain. Your presence and your help throughout these years have truly been so precious to me, thank you. Quiero dar las gracias también a **Paula Segovia**, por su ayuda y apoyo en todo lo relacionado con el laboratorio y su mantenimiento, y a **Eva Casco**, por el valioso soporte administrativo durante la redacción de esta tesis.

I sincerely thank all the **research support units** of ICIQ, as well as the **IT unit**, for their efficiency, professionalism and dedication.

Uncommonly, I have been part of two research groups during my Ph.D., which gave me the opportunity to meet and work with many great scientists and people. All the members of the Muñiz research group when I joined in September 2019—**Dr. Anna Sib**, **Dr. Kang Chen**, **Dr. Thomas Duhamel**, **Dr. Daniel Bafaluy**, **Dr. Estefanía del Castillo**, **Dr. Alexandra Bosnidou**, **Dr. Èric Cots**, **Dr. Eleni Georgiou**, **Dr. Anastasia Tkacheva**, **Ana Mateos** and **Jiayu Zhang**— have been a true family to me since the very first day I started in ICIQ. In particular **Èric**, **Bafa**, **Thomas**, **Estefi**, **Anda** and **Ana**: thank you for your discreet and caring presence always.

Moving on, I have been very fortunate to share all my Ph.D. projects with **Dr. Hang-Fei Tu**. I am infinitely thankful for all the knowledge you shared with me, your precious guidance, and the scientific rigor you taught me. I have learnt so much from you, thank you.

I wish to extend my gratitude to all the past and present postdocs of the Suero group, too—**Dr. Liyin Jiang**, **Dr. Wei-Jie Teo**, **Dr. Leonardo Nannini**, **Dr. Karen de la Vega Hernández**, **Dr. Èric Cots**, and later on **Dr**. **Qiyuan He**, **Dr**. **Bowen Li** and **Dr**. **Adriana Faraone**—who have been present throughout the past years. **Karen**, gracias por tu disponibilidad y tus consejos y correcciones siempre tan valiosos en redacciones o preparaciones de presentaciones. **Èric**, has estado presente desde el principio, muchísimas gracias por considerarme como tu propia hermana desde el primer día. My gratitude also goes to the Ph.D. students, in chronological order: **Dr. Pau Sarró**, **Eric Palomo**, **Valero Gimeno**, **Alessio Puggioli**, **Josep Esteve**, **Guillaume Mollaert**, and **Quan Zhang**. In particular **Pau**, thank you so much for welcoming me in the group, guiding me during the first months and afterwards. Your constant good mood has been priceless and very much missed since you graduated. **Eric**, me llevo a un amigo de toda la vida sin ninguna duda. Siempre agradeceré tu presencia y tu amistad tan sólida desde el primer día. Mención especial merecen también los chicos del laboratorio 1.4, **Alessio**, **Valero** y **Josep**. No hubiera podido esperar trabajar en mejor compañía, y me llevo a tres amigos fantásticos con una infinidad de buenos recuerdos. Muchísimas gracias por todo.

Over the past few years, I have been fortunate to meet and to be surrounded by extraordinary people in ICIQ, too. For the sake of conciseness, I will keep this paragraph short, but this doesn't make me any less thankful to each and every one who came along my path. These friendships formed over time undoubtedly contributed to make my Ph.D. an unforgettable life experience as well.

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