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Transition metal-catalyzed diazo compounds decomposition for the catalytic enantioselective synthesis of new cyclopropanic scaffolds

Chengtao Zhao

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Normandie Université

THÈSE

Pour obtenir le diplôme de doctorat

Spécialité **CHIMIE**

Préparée au sein de l'**INSA Rouen Normandie**

Transition metal-catalyzed diazo compounds decomposition for the catalytic enantioselective synthesis of new cyclopropanic scaffolds

Présentée et soutenue par

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Thèse soutenue le 15/03/2024

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Abstract

Cyclopropane, a significant organic motif featuring the smallest carbocycle and the highest ring strain, exhibits distinctive properties in comparison to other cycloalkanes. This scaffold is prevalent in natural products and finds extensive applications in medicinal research programs aiming at enhancing the pharmaceutical features of drug candidates. With the continuous advancement of organic and pharmaceutical chemistry, there is a growing interest for versatile molecules incorporating cyclopropane skeleton, particularly those with optical activity or fluorine atom.

The first part (chapter II) of this Ph.D. thesis focuses on the use of chiral transition metal complexes in decomposed diazo compounds [2+1] asymmetric cycloaddition strategies. A catalytic asymmetric synthesis of highly functionalized cyclopropanes from 2-substituted allylic derivatives is reported. Using ethyl diazoacetate and a chiral ruthenium complex (Ru(II)-Pheox), the reaction provides easily separable *cis* and *trans* cyclopropanes in moderate to high yields (32-97%) and excellent *ee* (86-99%). DFT calculations suggest an operative outer-sphere mechanism.

In chapter III, this thesis further discloses a groundbreaking protocol for the catalytic synthesis of enantiopure 1,2-disubstituted α,α -difluoroalkyl cyclopropanes using metallocarbene and alkenes [2+1] ring addition strategy. The catalyst, Ru(II)-Pheox, facilitates the synthesis of target products with yields ranging from 17-94%, exceptional diastereoselectivity (often >20:1 *dr*), and enantioselectivity (up to 98.5:1.5 *er*). The methodology is applicable to diverse transformations, providing opportunities for stereocontrolled versatile α,α -difluoroalkyl cyclopropane frameworks.

In chapter IV, this thesis then presents optimization studies for the synthesis of enantiomerically pure alkynylcyclopropanes. While Rh(II)-complexes have shown success in achieving high yields and diastereoselectivity, low to moderate enantioselectivity remains a challenge. Despite the limitations encountered, alternative solutions will be sought for future exploration.

In chapter V, an efficient methodology for accessing 1,2,3-polysubstituted fluorinated cyclopropanes is outlined. The use of Pd(II)-catalyzed C–C bond formation by C–H bond activation enables the functionalization of diverse fluorinated cyclopropanes, including those bearing -F, -

CH₂F, -CF₂H, and -CF₃ groups. The method proved to be tolerant to a wide range of iodide/bromide electrophiles, offering a practical pathway for preparing both racemic and enantiomeric 1,2,3-polysubstituted fluorinated cyclopropane scaffolds.

Résumé

Le cyclopropane, un motif organique significatif présentant le plus petit carbocycle et la plus grande contrainte de cycle, présente des propriétés distinctives par rapport aux autres cycloalcanes. Ce motif est répandu dans les produits naturels et trouve des applications étendues dans les programmes de recherche médicinale visant à améliorer les caractéristiques pharmaceutiques des candidats médicamenteux. Avec l'avancement continu de la chimie organique et pharmaceutique, un intérêt croissant se manifeste pour les molécules polyvalentes incorporant le squelette cyclopropane, en particulier celles avec une activité optique ou un atome de fluor.

La première partie (chapitre II) de cette thèse de doctorat se concentre sur l'utilisation de complexes métalliques de transition chiraux dans des composés diazo décomposés pour des stratégies de cycloaddition asymétrique [2+1]. Une synthèse asymétrique catalytique de cyclopropanes hautement fonctionnalisés à partir de dérivés allyliques 2-substitués est rapportée. En utilisant le diazoacétate d'éthyle et un complexe de ruthénium chiral (Ru(II)-Pheox), la réaction fournit des cyclopropanes cis et trans facilement séparables avec des rendements modérés à élevés (32-97%) et une excellente énantiomérisation (86-99%). Les calculs DFT suggèrent un mécanisme opératoire de type "outer-sphere".

Dans le chapitre III, cette thèse révèle en outre un protocole novateur pour la synthèse catalytique de cyclopropanes α,α -difluoroalkyl 1,2-disubstitués énantio-purs en utilisant un métallocarbène et des alcènes dans une stratégie d'addition de cycle [2+1]. Le catalyseur, Ru(II)-Pheox, facilite la synthèse des produits cibles avec des rendements variant de 17 à 94%, une diastéréosélectivité exceptionnelle (souvent >20:1 dr) et une énantiosélectivité (jusqu'à 98.5:1.5 er). La méthodologie est applicable à diverses transformations, offrant des opportunités pour des cadres de cyclopropanes α,α -difluoroalkyl stéréocontrôlés.

Dans le chapitre IV, cette thèse présente ensuite des études d'optimisation pour la synthèse d'alkynylcyclopropanes énantiomériquement purs. Bien que les complexes de Rh(II) aient montré un succès dans l'obtention de rendements élevés et de diastéréosélectivité, une énantiosélectivité faible à modérée reste un défi. Malgré les limitations rencontrées, des solutions alternatives seront recherchées pour des explorations futures.

Dans le chapitre V, une méthodologie efficace pour l'accès à des cyclopropanes fluorés 1,2,3-polysubstitués est exposée. L'utilisation d'une formation de liaison C–C catalysée par Pd(II) par activation de la liaison C–H permet la fonctionnalisation de divers cyclopropanes fluorés, y compris ceux portant des groupes -F, -CH₂F, -CF₂H et -CF₃. La méthode s'est révélée tolérante à une large gamme d'électrophiles iodés/bromés, offrant une voie pratique pour la préparation de cadres de cyclopropanes fluorés 1,2,3-polysubstitués tant racémiques qu'énantiomériques.

Abbreviations and Acronyms

A

Ac acetyl

AIBN azobisisobutyronitrile

B

Bn benzyl

Boc *tert*-butyloxycarbonyl

bpy bipyridine

Bz benzoyl

C

CAN ceric ammonium nitrate

Cp cyclopentadienyl

Cy cyclohexanyl

D

DABCO 1,4-diazabicyclo[2.2.2]octane

DCC *N,N*-dicyclohexylcarbodiimide

DEC 1,2-dichloroethane

DCM dichloromethane

DEAD diethyl azodicarboxylate

de diastereomeric excess

DFT density functional theory

DIAD diisopropyl azodicarboxylate

DIBAL-H diisobutylaluminium hydride

DIPA diisopropylamine

DMA *N,N*-dimethylacetamide

DMAP *N,N*-(4-dimethylamino)pyridine

DMF *N,N*-dimethylformamide

DMSO dimethylsulfoxide

<i>dr</i>	diastereomeric ratio
E	
EDG	electron-donating group
<i>ee</i>	enantiomeric excess
EEDQ	<i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
equiv.	equivalent
<i>er</i>	enantiomeric ratio
Et	ethyl
EWG	electron-withdrawing group
H	
HATU	hexafluorophosphate azabenzotriazole tetramethyl uronium
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
HOESY	heteronuclear overhauser effect spectroscopy
HRMS	high resolution mass spectroscopy
K	
KHMDS	potassium bis(trimethylsilyl)amide
L	
LA	Lewis acid
LB	Lewis base
LiHMDS	lithium bis(trimethylsilyl)amide
M	
<i>m</i> CPBA	3-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MOMCl	chloromethyl methyl ether
m.p.	melting point
Ms	mesyl
N	
NBS	<i>N</i> -bromosuccinimide
<i>n</i> Bu	<i>n</i> butyl

NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMP	<i>N</i> -methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NS	2-nitrophenyl sulfonyl
Nu	nucleophile
P	
PCC	pyridinium chlorochromate
PE	petroleum ether
Ph	phenyl
PMB	<i>para</i> -methoxybenzyl
PMP	<i>para</i> -methoxyphenyl
R	
r.t.	room temperature
T	
T	temperature
t	time
<i>t</i> -AmylOH	2-methylbutan-2-ol
TBAB	<i>tetra-n</i> butylammonium bromide
TBAF	<i>tetra-n</i> butylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBME	<i>tert</i> -butyl methyl ether
TBS	<i>tert</i> -butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethyl sulfonyl
TFA	trifluoroacetate
Tfs	2-trifluoromethyl benzylsulfonyl
TFT	trifluoromethyl toluene
THF	tetrahydrofuran
TIPS	triisopropylsilyl

TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
t_R	retention time
Ts	tosyl
<i>t</i> Bu	<i>tert</i> -butyl

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Chapter I – Introduction

1.1. The properties of cyclopropanes and their applications

Cyclopropanes are the smallest and most strained cycloalkanes, which exhibit unique structural features. These distinctive properties come from the non-linear arrangement of the three carbon atoms within the cyclopropane ring. As a result, cyclopropanes are characterized by shorter C–C and C–H bonds compared to typical alkanes.¹ This deviation in bond length arises from the specific geometry of the cyclopropane ring. The significant ring strain in cyclopropanes is a direct consequence of the narrow 60° bond angles present within the ring structure (Figure 1).² These bond angles deviate considerably from the ideal tetrahedral bond angles of 109.5° that are commonly found in sp³ hybridized carbon atoms.³ The combined effect of shorter bonds and pronounced ring strain results in cyclopropane's distinctive chemical properties, which include highly reactive bonds and a propensity for engaging in unique chemical reactions.⁴

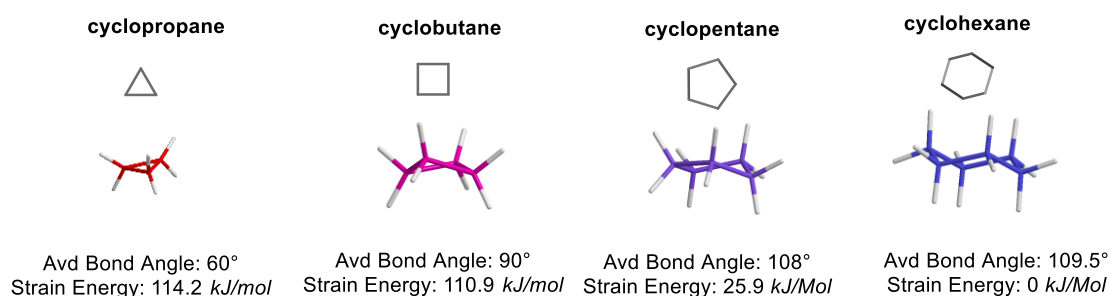


Figure 1. The properties of cycloalkanes.

As one of the most attractive subunits, cyclopropane is present in a large number of nature products.⁵ In the early 20th century, (±)-*trans*-chrysanthemic acid was isolated from pyrethrum petals and its plants by Staudinger and Ruzicka.⁶ This natural cyclopropanic acid is extensively used in the

¹ a) P. B. Karadakov, J. Gerratt, D. L. Cooper, M. Raimondi, *J. Am. Chem. Soc.* **1994**, *116*, 7714–7721. b) J. A. Boatz, M. S. Gordon, R. L. Hilderbrandt, *J. Am. Chem. Soc.* **1988**, *110*, 352–358.

² K. B. Wiberg, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312–322.

³ A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 809–826.

⁴ a) O. G. Kulinkovich, *Cyclopropanes in organic synthesis*, John Wiley & Sons, **2015**. b) J. Liu, R. Liu, Y. Wei, M. Shi, *Trends in Chemistry* **2019**, *1*, 779–793. c) Y. Cohen, A. Cohen, I. Marek, *Chem. Rev.* **2021**, *121*, 140–161. d) H. N. C. Wong, M. Y. Hon, C. W. Tse, Y. C. Yip, J. Tanko, T. Hudlicky, *Chem. Rev.* **2002**, *89*, 165–198.

⁵ a) R. Faust, *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 2251–2253. b) S. Ma, D. Mandalapu, S. Wang, Q. Zhang, *Nat. Prod. Rep.* **2022**, *39*, 926–945.

⁶ H. Staudinger, L. Ruzicka, *Helv. Chim. Acta.* **1924**, *7*, 177–235.

synthesis of industrial insecticides intermediates. Since then, vast quantities of cyclopropane-containing compounds in nature have been disclosed by chemists, such as Echinopine A from *enoplomischus spinosus*, Hypocoprin A from *heliconia rostrata*, and Sarcanolide B from *streptomyces hainanensis*, among others.⁷ On the other hand, the three member carbon rings were explored to divert preclinical and clinical drug molecules.⁸ For example, Tasimelteon is known as a dual melatonin receptor agonist, Lesinurad is selected for hyperuricemia inhibitor with potential to treat gout, and Finafloxacin is a marketed anti-bacteria drug and so on. These attractively promising applications drive scientists make great efforts for synthesis and bioactivity examination of cyclopropane building blocks (Figure 2).⁹

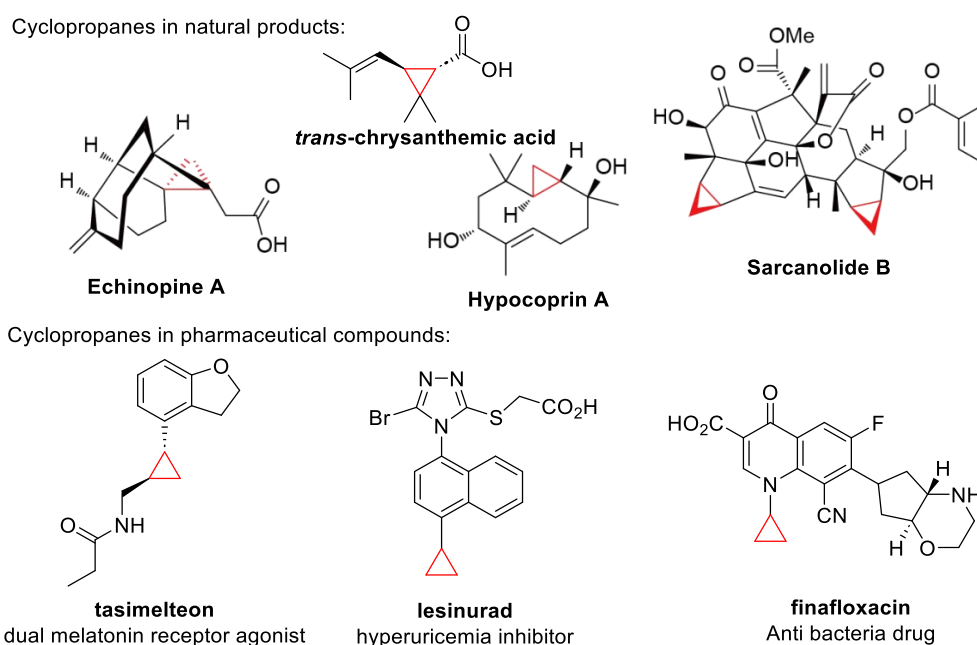


Figure 2. Natural and synthetic Cyclopropane-containing compounds.

⁷ Y.-Y. Fan, X.-H. Gao, J.-M. Yue, *Sci. Chin. Chem.* **2016**, *59*, 1126–1141.

⁸ a) M.-R. Sun, H.-L. Li, M.-Y. Ba, W. Cheng, H.-L. Zhu, Y.-T. Duan, *Mini Rev. Med. Chem.* **2021**, *21*, 150–170.

b) T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.

⁹ a) W. Wu, Z. Lin, H. Jiang, *Org. Bio. Chem.* **2018**, *16*, 7315–7329. b) Y. Qin, P. Tang, *Synthesis* **2012**, *44*, 2969–2984. c) D. Y. Chen, R. H. Pouwer, J. A. Richard, *Chem. Soc. Rev.* **2012**, *41*, 4631–4642. d) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651–11679.

1.2. Transition metal-catalyzed diazo compounds decomposition for intermolecular cyclopropanation

The first synthesis of cyclopropane in a laboratory, using 1,3-dibromopropane and alkali-metal sodium, can be traced back to 1882 and is attributed to August Freund.¹⁰ This low-boiling-point cycloalkane was employed as an anesthetic for a period of time. In 1884,¹¹ William Henry Perkin and Adolf von Baeyer made unprecedented syntheses of cyclopropane derivatives, opening up possibilities for incorporating this fascinating motif into various molecules. Following that, several simple structure cyclopropanes were developed subsequently, for instance, cyclopropanol¹², hexafluorocyclopropane¹³, and *gem*-dichlorocyclopropane¹⁴. It was not until 1958 that an organozinc carbenoid cyclopropanation reaction was reported by Simmons and Smith, marking the beginning of the stereospecific cyclopropanation area.¹⁵ Building upon previous researches, organic chemists have to date successfully pioneered more than ten methods for generating cyclopropane derivatives (Scheme 1).¹⁶ Among these, we will focus on transition metal-catalyzed diazo compound decomposition in the context of cyclopropanation in my forthcoming studies.

¹⁰ A. Freund and U. Trimethylen, *J. Prakt. Chem.* **1882**, *26*, 367–377.

¹¹ W. H. Perkin, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 54–59.

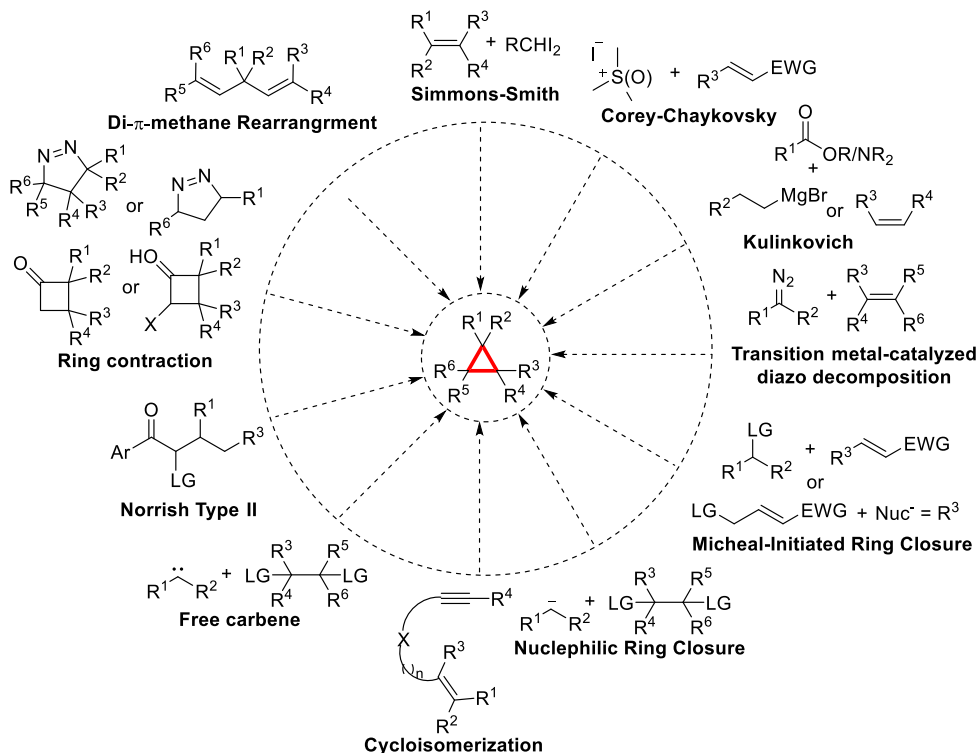
¹² J. K. Magrane, D. L. Cottle, *J. Am. Chem. Soc.* **1942**, *64*, 484–487.

¹³ Atkinson, B. *J. Chem. Soc.* **1952**, 2684–2694.

¹⁴ Doering, W. E.; Hoffmann, A. K. *J. Am. Chem. Soc.* **1954**, *76*, 6162–6165.

¹⁵ H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc.* **1956**, *80*, 5323–5324.

¹⁶ a) A. B. Charette, A. Beauchemin, *Org. React.* **2004**, *58*, 1–415. b) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364. c) O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789–2834. d) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–936. e) Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539. f) M. Mato, A. Franchino, C. García-Morales, A. M. Echavarren, *Chem. Rev.* **2021**, *121*, 8613–8684. g) M. Fedoryński, *Chem. Rev.* **2003**, *103*, 1099–1132. h) C. Hui, L. Craggs, A. P. Antonchick, *Chem. Soc. Rev.* **2022**, *51*, 8652–8675. i) P. Wessig, O. Mühlring, *Angew. Chem. Int. Ed.* **2001**, *40*, 1064–1065. j) H. E. Zimmerman, D. Armesto, *Chem. Rev.* **1996**, *96*, 3065–3112.

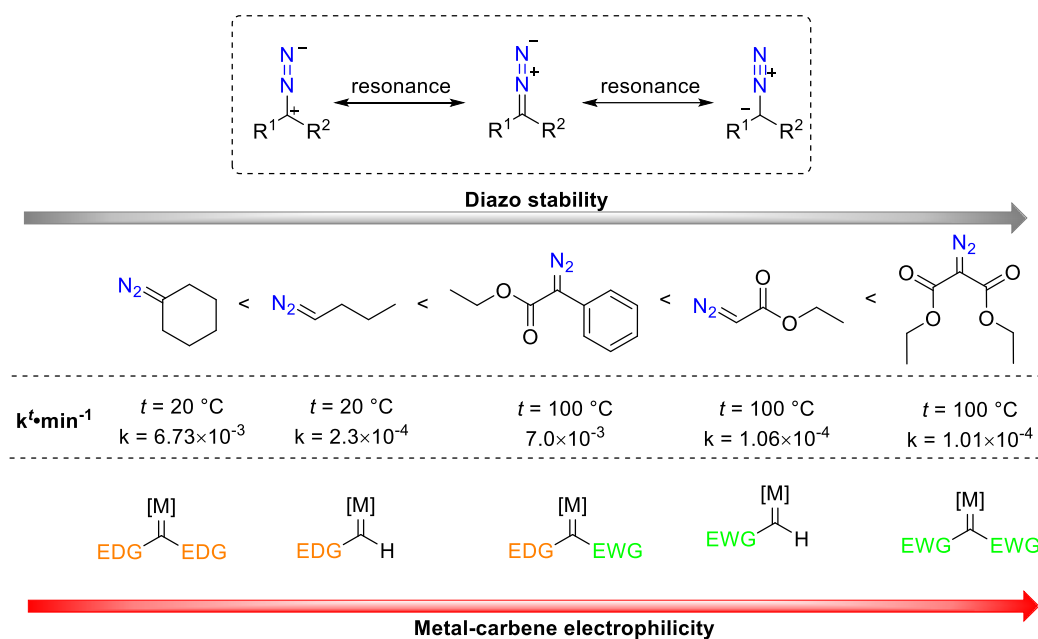


Scheme 1. General methods for the synthesis of cyclopropanes.

Diazo compounds, a remarkable series of potent reagents in the realm of organic synthesis, particularly renowned for their pivotal role in the cyclopropanation field, were initially discovered in 1858 by Peter Griess.¹⁷ Those electronic neutrally charged compounds bearing two nitrogen atoms were considered by three resonance structures. The rate constant for thermolysis decomposition experiments were investigated to compare the stabilities of several diazo compound bearing diverse electronic substituents. In general, the stabilities of diazo compounds are increasing due to delocalization of negative charge by electronic-withdrawing groups (*e.g.*, ester, cyano, or trifluoromethyl), resulting in an increase of the corresponding metal-carbene electrophilicity (Scheme 2).¹⁸

¹⁷ R. Maty'a's, J. Šeleš'ovsk'y, T. Musil, *J. Hazard. Mater.*, **2012**, 213, 236–241.

¹⁸ a) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, 40, 1857–1869. b) B. D. Bergstrom, L. A. Nickerson, J. T. Shaw, L. W. Souza, *Angew. Chem. Int. Ed.* **2021**, 60, 6864–6878. c) M. Regitz, G. Maas, in *Diazo Compounds* (Eds.: M. Regitz, G. Maas), Academic Press, **1986**, pp. 65–95.



Scheme 2. Diazo compounds features. k is the rate constant for decomposition at giving temperature; t = temperature.

The history of transition metal-catalyzed decomposition of diazo compounds dated back to the early 20th century¹⁹, coinciding with the emergence of asymmetric cyclopropanation reactions.²⁰ The mechanism investigation was primitively studied by Yates²¹ who proposed a copper-catalyzed addition of diazoalkanes to organic substrates via the formation of a carbene-metal complex. This formulation assumes that the carbene is bound to the metal surface, completing the octet of valence electrons around the methine carbons with copper. This is a rudimental mechanism for transition metal-mediated diazo compounds decomposition for cyclopropanation albeit it was defective. Nowadays, the most commonly used catalysts for cyclopropanation reactions between alkenes and diazo compounds include Rhodium (Rh(II)), Copper (Cu(I)/Cu(II)), Ruthenium (Ru(II)), Palladium (Pd(0)), and Silver (Ag(I)). However, examples also exist where Cobalt (Co(II)), Iron (Fe(II)/Fe(III)) and Gold (Au(I)) for example been employed as catalysts.²² To address the mechanism for above

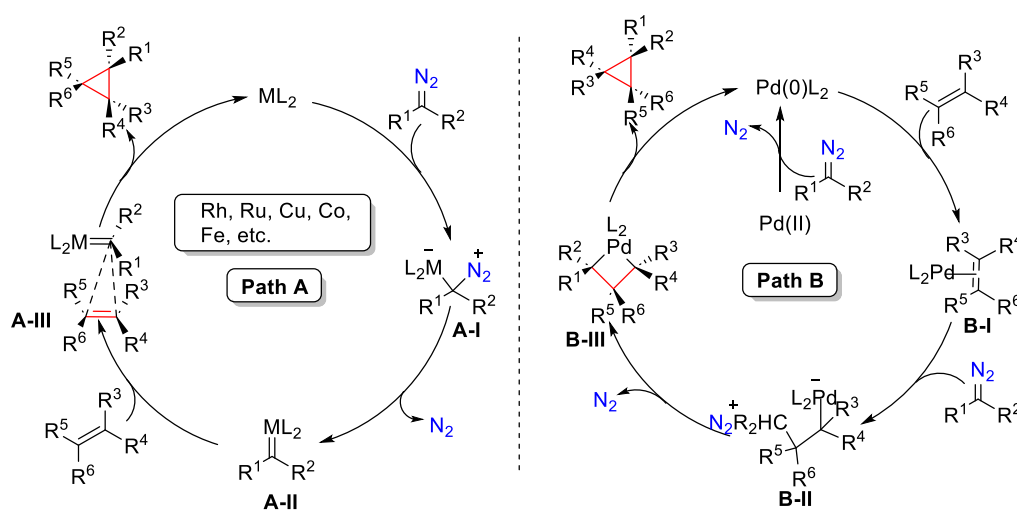
¹⁹ a) A. Loose, *Journ. f. prakt.* **1909**, 79, 507–510. b) F. Kaplan, G. K. Meloy, *J. Am. Chem. Soc.* **1966**, 88, 950–956.

²⁰ a) H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, 7, 5239–5244. b) H. Nozaki, T. Aratani, R. Noyori, *Tetrahedron Lett.* **1968**, 9, 2087–2090. c) G. Stork, J. Ficini, *J. Am. Chem. Soc.* **1961**, 83, 4678–4678.

²¹ P. Yates, *J. Am. Chem. Soc.* **1952**, 74, 5376–5381.

²² a) H. Pellissier, *Tetrahedron* **2008**, 64, 7041–7095. b) V. Carreras, T. Ollevier, *Chiral Building Blocks in Asymmetric Synthesis: Synthesis and Applications* **2022**, 1–20. c) P. Jubault, T. Poisson, Y. Hasegawa, T. Cantin, *Olefin Difunctionalization with the Same Atoms; Cyclopropanation of Olefins. In book: Reference Module in Chemistry, Molecular Sciences and Chemical Engineering.* **2022**.

metals, two main catalytic cycles were revealed alongside the development of metal-carbene chemistry (Scheme 3). The Path A represents mechanism of transition metal Rh(II), Ru(II), Cu(II), Co(II), Fe(II)-based catalysts etc.²³ Firstly, metal complexes reacted with the diazo compound to generate intermediate **A-I**, after releasing nitrogen gas to deliver a coordinated metal-carbenoid **A-II**. Followed by addition of alkene and went through a [2+1] cycloaddition species **A-III** to build up the expected three-member ring and regenerate metal catalyst. For palladium, however, an alternative mechanism was identified as depicted in Path B.²⁴ In the course of this catalytic cycle, initially, the palladium (II) catalyst underwent a reduction to low-valent palladium complex due to the dimerization influence of diazo compound. Then, this low-valent palladium catalyst coordinated with alkene to form species **B-I**, followed by engaging with diazo compound to offer species **B-II**. A metallacyclobutane intermediate **B-III** was given along with nitrogen gas extrusion and finally converted to the cyclopropane product. Additionally, engineered enzymes have demonstrated the ability to facilitate these reactions.²⁵ In general, biosynthetic enzymes for cyclopropane rings fall into two classes of mechanism: carbocationic intermediates and carbanionic intermediates.²⁶



Scheme 3. Catalytic cycles of transition metal-catalyzed cyclopropanation.

²³ a) H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977–1050. b) M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911–935; c) Z. Zhang, J. Wang, *Tetrahedron* **2008**, *64*, 6577–6605.

²⁴ a) Y. V. Tomilov, V. A. Dokichev, U. M. Dzhemilev, O. M. Nefedov, *Russ. Chem. Rev.* **1993**, *62*, 799–838. b) C. Rodriguez–García, A. Oliva, R. M. Ortuno, V. Branchadell, *J. Am. Chem. Soc.* **2001**, *123*, 6157–6163. c) B. F. Straub, *J. Am. Chem. Soc.* **2002**, *124*, 14195–14201.

²⁵ a) G. Roelfes, *J. Inorg. Biochem.* **2021**, *222*, 111523. b) R. Fasan, M. G. Siriboe, *Bull. Chem. Soc. Jpn.* **2022**, *80*, 4–13.

²⁶ C. J. Thibodeaux, W.–C. Chang, H.–W. Liu, *Chem. Rev.* **2012**, *112*, 1681–1709.

1.2.1. Diazomethane

Among versatile diazo compounds have emerged to construct cyclopropanic motifs over several decades, diazomethane, the simplest organic diazo reagent, was safely introduced [2+1] cycloaddition reaction catalyzed by transition metal in 1992.²⁷ That because diazomethane is known as toxic and explosive²⁸ gas (b.p. -23 °C) since it was first synthesized from *N*-methyl-*N*-nitrosocarbamate by Pechmann.²⁹ Subsequently, the most commonly used sources for *in situ* generation of diazomethane were developed, for example, *N*-methyl-*N*-nitrosourea (MNU),³⁰ *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald),³¹ *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)³² and temozolomide (TMZ) (Figure 3).³³ The use of diazomethane and its precursors in the context of cyclopropanation reactions involving batch and flow conditions were commendably summarized in two dedicated reviews³⁴ and several separated chapters of review publications.³⁵ Therefore, this topic will be continually stated only regarding different transition metals.

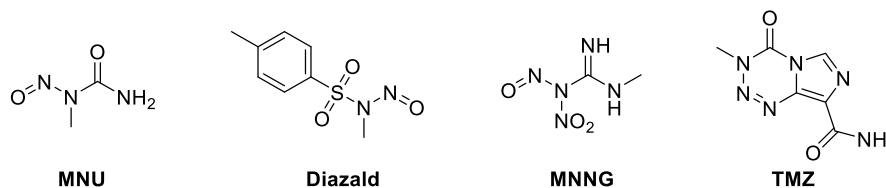


Figure 3. Most commonly diazomethane sources.

In view of massive works were published by pioneers, palladium complexes were frequently used

²⁷ O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, V. A. Dokitchev, *Mendeleev Commun.* **1992**, 2, 13–15.

²⁸ a) G.W.Cowell, A.Ledwith. *Quarterly Rev. Chem. Soc.* **1970**, 24, 119–167. b) L. D. Proctor, A. J. Warr, *Org. Process Res. Dev.* **2002**, 6, 884–892. c) M. Regitz, *Diazo compounds: properties and synthesis*, Elsevier, **2012**.

²⁹ H. V. Pechmann, *Ber. Dtsch. Chem. Ges.* **1894**, 27, 1888–1891.

³⁰ H. Lehmann, *Green Chem.* **2017**, 19, 1449–1453.

³¹ a) B. Morandi, E. M. Carreira, *Science* **2012**, 335, 1471–1474. b) F. Ngan, M. Toofan, *J. Chromatogr. Sci.* **1991**, 29, 8–10.

³² J. A. Montgomery, Nitrosoureas: current status and new developments **1981**, 3–8.

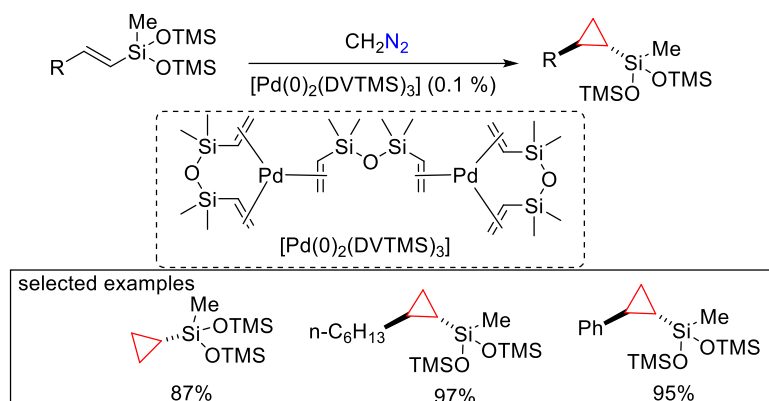
³³ R. L. Svec, P. J. Hergenrother, *Angew. Chem. Ent. Ed.* **2019**, 132, 1873–1878.

³⁴ a) V. T. Yury, V. A. Dokitchev, M. D. Usein, M. N. Oleg, *Russ. Chem. Rev.* **1993**, 62, 799–835. b) L. G. Menchikov, E. V. Shulishov, Y. V. Tomilov, *Russ. Chem. Rev.* **2021**, 90, 199–230.

³⁵ a) M. Roy, V. Lindsay, A. Charette, *Science of Synthesis: Stereoselective Synthesis*. Thieme Chemistry, **2011**. b) A. de Meijere, S. I. Kozhushkov, H. Schill, *Chem. Rev.* **2006**, 106, 4926–4996. c) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, 46, 979–1029. d) V. A. D'yakonov, O. g. A. Trapeznikova, A. de Meijere, U. M. Dzhemilev, *Chem. Rev.* **2014**, 114, 5775–5814. e) Y. Zhang, J. Wang, *Eur. J. Org. Chem.* **2011**, 2011, 1015–1026.

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catalysts incorporation of diazomethane to promote the fuse of cyclopropanic moieties. As the catalytic cycles exhibited, Pd(0) complexes serve as catalytically active species was first reported in 1984.³⁶ Subsequently, the involvement of Pd(0) complexes as catalytically active species in the catalytic circulation was confirmed. This revelation emerged during the catalytic cyclopropanation of alkynylsilanes with diazomethane in the presence of Pd(OAc)₂. Exactly as a previously prepared and separable [Pd(0)₂(DVTMS)₃] complex was employed in the cyclopropanation of vinylsilane substrates at -35 °C within one hour, yielding satisfactory results (Scheme 4).³⁷ Although Palladium complexes are excellent catalysts in CH₂N₂-cyclopropanation with alkenes, but are rarely used for stereoconvergent cyclopropanic derivatives. The strategy is effective with sterically demanding groups³⁸ but less so with linear alkenes,³⁹ while Pd-catalyzed diazo compound decomposition for asymmetric cyclopropanation relies heavily on a chiral auxiliary.⁴⁰



Scheme 4. [Pd(0)₂(DVTMS)₃] catalyzed vinyl silane cyclopropanation.

Unlike Pd-catalysts, Cu-complexes have been infrequently utilized for cyclopropanation reactions between diazomethane and unsaturated compounds. This is primarily due to the rapid decomposition of diazomethane, low reaction selectivity, typically low yields of cyclopropane products, the necessity for a significant excess of diazomethane, and consequently, the generation

³⁶ Y. V. Tomilov, V. G. Bordakov, I. E. Dolgii, O. M. Nefedov, *Russ. Chem. Bull.* **1984**, *33*, 533–538.

³⁷ G. Berthon–Gelloz, M. Marchant, B. F. Straub, I. E. Marko, *Chem. Eur. J.* **2009**, *15*, 2923–2931.

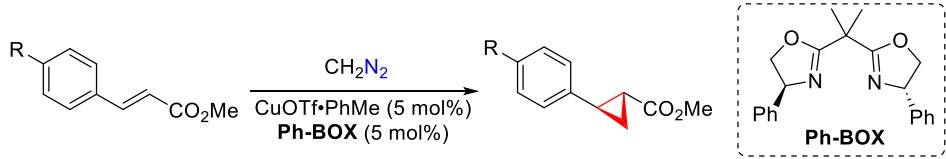
³⁸ a) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfuné, *The Journal of Organic Chemistry* **1991**, *56*, 4167–4176.

b) K. Shimamoto, Y. Ohfuné, *Tetrahedron Lett.* **1989**, *30*, 3802–3804.

³⁹ A. Davletbakova, I. Maidanova, N. Baibulatova, V. Dokichev, Y. V. Tomilov, M. Yunusov, O. Nefedov, *Russ. J. Org. Chem.* **2001**, *37*, 608–611.

⁴⁰ a) J. Pietruszka, A. Witt, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293–4300. b) A. Alami, M. Calmes, J. Daunis, F. Escalé, R. Jacquier, M.–L. Roumestant, P. Viallefont, *Tetrahedron: Asymmetry* **1991**, *2*, 175–178. c) S. E. Denmark, R. A. Stavenger, A.–M. Faucher, J. P. Edwards, *J. Org. Chem.* **1997**, *62*, 3375–3389.

of substantial amounts of polymethylene by-products.⁴¹ Nevertheless, Cu-catalysts demonstrated favorable stereocontrol when employed in limited applications for the synthesis of optically active compounds in the presence of chiral ligand. For instance, in 2003, Charette and co-workers developed a 1:1 ratio of phenyl bis(oxazoline)-CuOTf•PhMe (5 mol%) methodology for the cyclopropanation of cinnamic ester derivatives and diazomethane.⁴² The yields and stereoselectivities depend on electronic effects: electron rich alkenes afforded better yields and lower stereoselectivities while electron poor alkenes afforded lower yields and better stereoselectivities (Table 1).



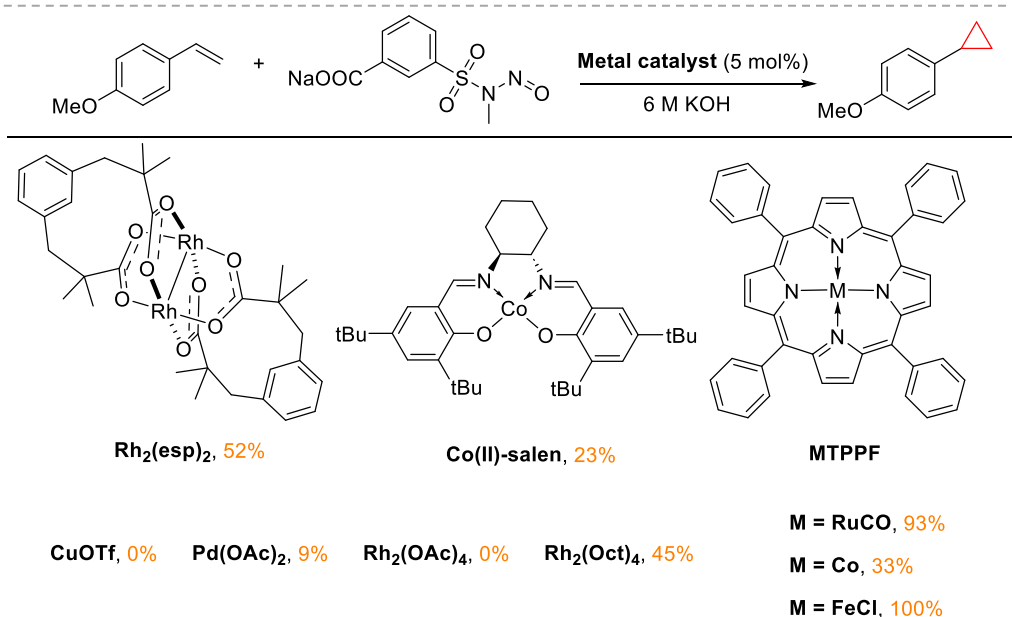
R	yield/(%)	ee/(%)
OMe	81	50
Me	79	60
H	80	72
NO ₂	62	80

Table 1. Cu(I)-mediated cyclopropanation of cinnamic ester derivatives and diazomethane.

Iron-based complex catalysis for the decomposition of diazomethane and cyclopropanation with unsaturated compounds was relatively unexplored until 2012, when the iron 5,10,15,20-tetraphenylporphyrin (FeTPPCl) complex was first proposed as an efficient catalyst for diazomethane cyclopropanation.^{31a} During the cyclopropanation process, several different metal catalysts were screened, and the results are summarized in Scheme 5. Within the category of metal complexes with the same ligand, FeTPPCl achieved a 100% conversion rate, while RuCOTPP exhibited the second-best conversion at 93%, and CoTPP showed significantly lower reactivity. Additionally, other metal complexes with different structures displayed varying levels of conversion: Rh₂(esp)₂ (52%), Co(II)-salen (23%), Rh₂(Oct)₄ (45%), Pd(OAc)₂ (9%) CuOTf (0%), and Rh₂(OAc)₄ (0%) (Scheme 5).

⁴¹ O. Nefedov, A. Ioffe, L. Menchikov, *Moscow: Khimiya* **1990**, 177–183.

⁴² A. B. Charette, M. K. Janes, H. Lebel, *Tetrahedron: Asymmetry* **2003**, *14*, 867–872.



Scheme 5. Catalyst screening for the cyclopropanation reaction.

Efforts to discover efficient catalysts for diazomethane cyclopropanation have spanned a considerable duration. Notably, the exploration has extended beyond the conventional use of copper and palladium compounds traditionally employed in this reaction. In an early and comprehensive investigation, a range of metals, including but not limited to Co, Ni, Zr, Cr, Rh, Dy, and others, were subjected to testing as effective catalysts.⁴³ However, most of the tested metal catalysts exhibited low conversion rates in the cyclopropanation of unsaturated compounds with diazomethane. As a result, only a few transition metals have been confirmed as effective catalysts in the field of diazomethane decomposition cyclopropanation to date.

1.2.2. Mono-acceptor and di-acceptor diazo derivatives

As stated before, the electronic deficient diazo compounds, either with one or two electron withdrawing groups, display excellent stabilities but lower reactivities. Nonetheless, those diverse pre-functionalized carbene precursors have been extensively studied in cyclopropanation reactions. It should be noted that some diazoalkanes bearing a fluorinated or a cyano group are still quite sensitive in particular to temperature and air, so that those diazo compounds were *in situ* generated

⁴³ U. M. Dzhemilev, V. A. Dokichev, S. Z. Sultanov, R. I. Khusnutdinov, Y. V. Tomilov, O. M. Nefedov, G. A. Tolstikov. *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, **1989**, 38, 1707–1714.

during the carbene formation process (Figure 4).⁴⁴

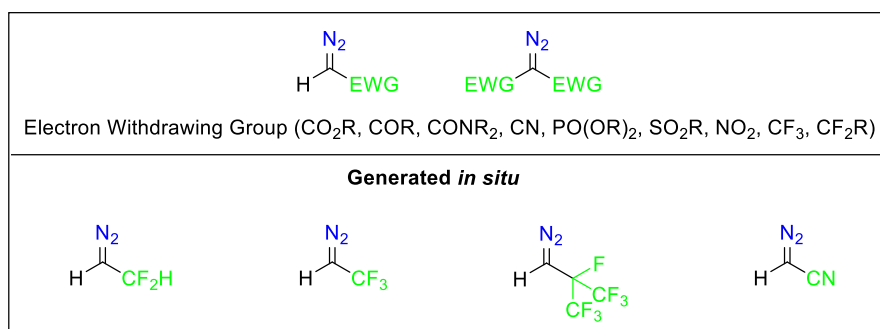


Figure 4. Diazoalkanes with an electron withdrawing group and examples of *in situ* generated mono-acceptor diazo derivatives.

Certainly, the synthesis of racemic cyclopropanes with mono-acceptor diazo compounds has been a focus of considerable efforts. For example, Carreira *et al.* described a practical procedure for the diastereoselective synthesis of trifluoromethyl-substituted cyclopropane building blocks using trifluoromethyl diazomethane and styrene derivatives with eight examples. (Scheme 6a).⁴⁵

Later, an *in situ* generated cyano-diazomethane was identified as a good metallocarbene precursor for the cyclopropanation of styrenes. This approach afforded 30 examples with good to excellent yields (Scheme 6b).⁴⁶

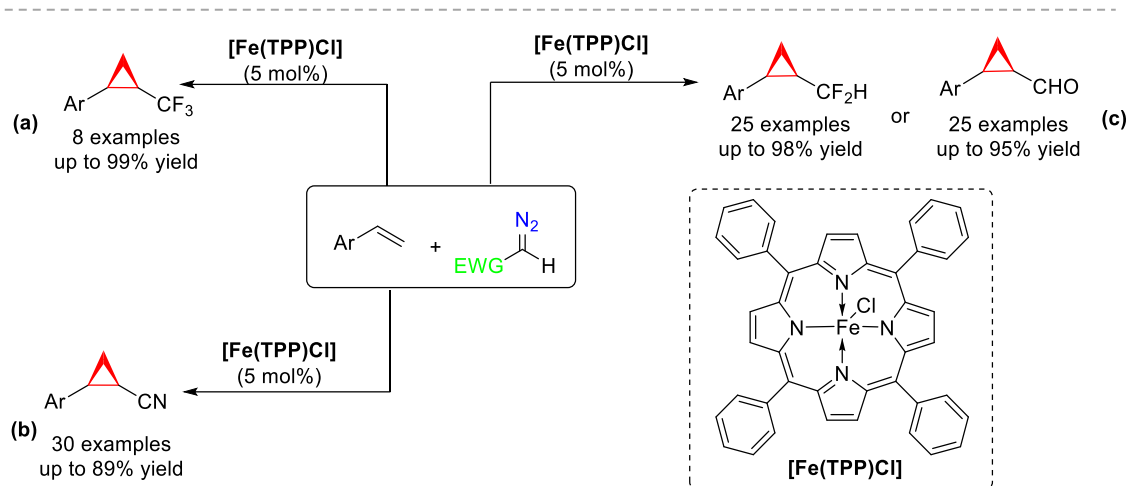
Recently, Bi and co-workers explored a difluoro-reagent (difluoroacetaldehyde *N*-Trifosylhydrazone) which is a difluoro-diazomethane precursor. Cyclopropanation reactions were carried out in the presence of [Fe(PPP)Cl] and have proved that this difluoro reagent was well tolerated for a large scope of alkenes. Interestingly, the formation of cyclopropane adducts depends on the reaction conditions. Indeed, the use of aqueous conditions led to the cyclopropyl aldehydes whereas the use of organic solvents led the difluoromethyl cyclopropanes. (Scheme 6c).⁴⁷

⁴⁴ a) S. A. Künzi, B. Morandi, E. M. Carreira, *Org. Lett.* **2012**, *14*, 1900–1901. b) P. K. Mykhailiuk, *Org. Biomol. Chem.* **2017**, *15*, 7296–7301. c) P. K. Mykhailiuk, I. Kishko, V. Kubyshkin, N. Budisa, J. Cossy, *Chem. Eur. J.* **2017**, *23*, 13279–13283. d) A. L. Chandgude, R. Fasan, *Angew. Chem. Int. Ed.* **2018**, *57*, 15852–15856.

⁴⁵ B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938–941.

⁴⁶ K. J. Hock, R. Spitzner, R. M. Koenigs, *Green Chem.* **2017**, *19*, 2118–2122.

⁴⁷ Y. Ning, X. Zhang, Y. Gai, Y. Dong, P. Sivaguru, Y. Wang, B. R. P. Reddy, G. Zanoni, X. Bi, *Angew. Chem. Int. Ed.* **2020**, *132*, 6535–6543.



Scheme 6. Racemic cyclopropanation reactions with mono-acceptor diazo derivatives.

Enantiomerically pure cyclopropanes have been synthesized using diazo derivatives bearing one or two electron-withdrawing groups since the seminal work of Nozaki in 1966.⁴⁸ They engaged styrene with Ethyl Diazo Acetate (EDA) in the presence of a chiral catalyst (chiral Cu-complex coordinated with a salicylamine ligand). This pioneering work led to the expected cyclopropane in 72% yield. However, the enantiomeric excess (6%) and the diastereoisomeric ratio (1:2) were very modest (Scheme 7a).

Two decades later, a novel C_2 -symmetry ligand known as 'semicorrin' was developed by Pfaltz to improve the stereocontrol during the Cu(II)-mediated EDA cyclopropanation. Using this ligand, diastereo- and enantio-selectivity were improved (22:78 *dr*, 85% *ee*, 68% *ee* respectively), but with a slight decrease in yield (65%) (Scheme 7b).⁴⁹

Furthermore, Boseny and colleagues introduced a highly sterically hindered Cu(I)-*gluco* BOX complex that, when employed in the presence of EDA, produced enantiomerically pure cyclopropanes with very respectable yields. The only drawback was the moderate diastereoselectivity (Scheme 7c).⁵⁰

Additionally, several other transition metal complexes were introduced to decompose EDA in order to access cyclopropanes in the presence of styrenes. For instance, Doyle *et al.* designed an “all up”

⁴⁸ H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, 7, 5239–5244.

⁴⁹ H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed. Engl.* **1986**, 25, 1005–1006.

⁵⁰ T. Minuth, M. M. K. Boseny, *Beilstein J. Org. Chem.* **2010**, 6, 23–29.

(all substituents oriented in the same direction) Rh₂(II)-(MEPY)₄ chiral catalyst in 1990.⁵¹ The use of this dirhodium catalyst resulted in an almost 1:1 diastereomer ratio and poor enantioselectivity (33% *ee*, 58% *ee* respectively) for both diastereoisomers. However, it is important noting that when the diazo compound was changed to *d*-menthyl diazoester, this approach led to improved stereocontrol demonstrating the importance to generate a quite hindered Rh carbene for this process (Scheme 7d).

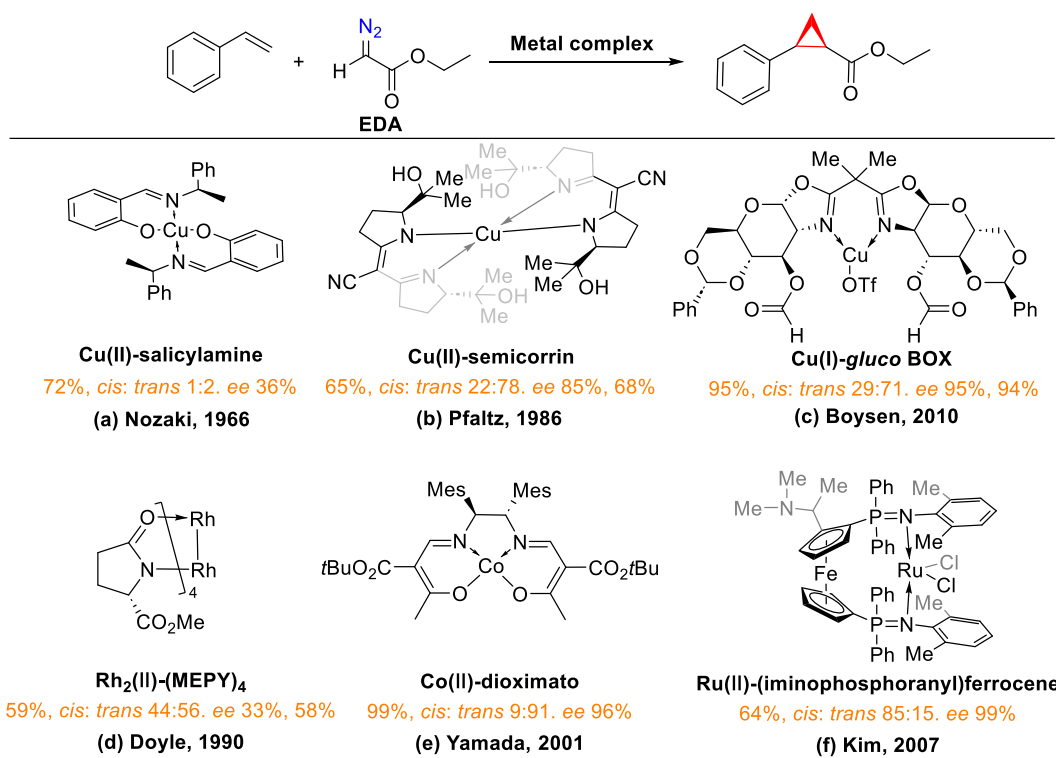
Few years later, an outstanding protocol was reported to produce both high diastereo- and enantio-pure cyclopropanes from styrene and EDA.⁵² The enantioselectivity of the cyclopropanation process using Co(II)-dioximato complexes was significantly influenced by the steric requirements of the diamine unit, while the presence of ester groups on their side chains modestly enhanced the *trans*-selectivity. Consequently, this approach led to 99% yield, the ratio of *cis:trans* as 9:91 and 96% *ee* for the major diastereoisomer (Scheme 7e).

Furthermore, Kim *et al.* demonstrated that chiral Ru(II)-complex generated from (iminophosphoranyl)ferrocene ligand is very powerful catalyst for asymmetric cyclopropanation of styrene with EDA.⁵³ High *cis*-selectivity as well as enantioselectivity (up to 99% *dr* and *ee*) were obtained and this protocol also applied to aliphatic alkenes (Scheme 7f).

⁵¹ M. P. Doyle, B. D. Brandes, A. P. Kazala, R. J. Pieters, M. B. Jarstfer, L. M. Watkins, C. T. Eagle, *Tetrahedron Lett.* **1990**, *31*, 6613–6616.

⁵² T. Ikeno, M. Sato, H. Sekino, A. Nishizuka, T. Yamada, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2139–2150.

⁵³ V. D. Hoang, P. A. Reddy, T.-J. Kim, *Tetrahedron Lett.* **2007**, *48*, 8014–8017.



Scheme 7. Diversity of transition metal-catalyzed asymmetric cyclopropanation of EDA with styrene.

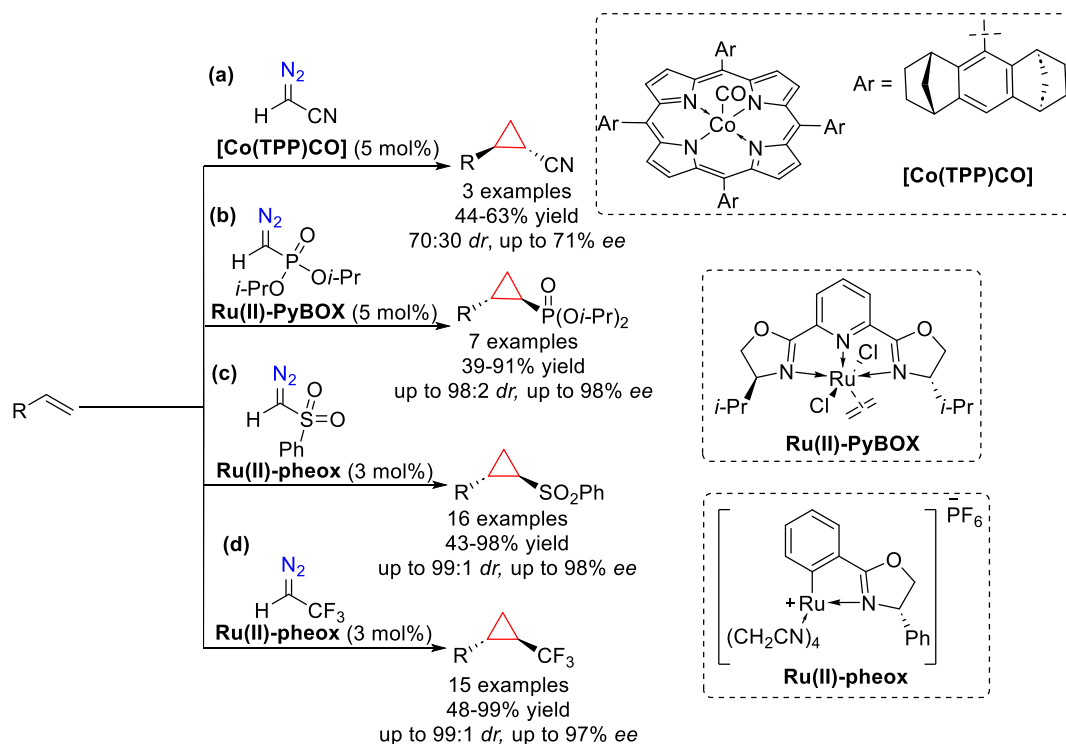
Generally, diazo derivatives bearing one carbonyl group, such as ketone, amide, and ester, exhibit important discrepancies in terms of reactivity and stereoselectivities. Therefore, we will not delve further into extensively documented massive cases in my discussion. Besides, there are three different diazo compounds bearing one electron-withdrawing group, which were used in asymmetric cyclopropanation as well. In 2005, Simonneaux *et al.* described the use of cyano diazomethane for the synthesis of enantiopure cyclopropyl nitriles using a *D₄*-symmetric [Co(TPP)CO] catalyst.⁵⁴ Unfortunately, the [Co(TPP)CO] complex led to poor diastereoselectivity (70:30 *dr*) and modest enantioselectivity ($\leq 71\%$ *ee*) for the three reported examples (Scheme 8a). It is important to mention that, afterwards, Fasan *et al.* successfully controlled either diastereo- or enantioselectivities by the use of engineered myoglobin.⁵⁵ This process benefits from the chiral induction imposed by myoglobin which ensured conservation of stereoselectivity.

The use of diazo derivatives bearing a phosphonate group was examined by Charette *et al.* to

⁵⁴ Y. Ferrand, P. Le Maux, G. Simonneaux, *Tetrahedron: Asymmetry* **2005**, *16*, 3829–3836.

⁵⁵ A. L. Chandgude, R. Fasan, *Angew. Chem. Int. Ed.* **2018**, *57*, 15852–15856.

generate enantioenriched cyclopropanes using chiral catalyst Ru(II)-PyBOX.⁵⁶ This approach afforded very good yields (39-91%) with excellent stereoselectivities (up to 92:8 *dr*, 98% *ee*) in most cases (Scheme 8b). Furthermore, the substitution of the diazo derivative by a sulfonyl group was examined by Iwasa *et al.* in 2012.⁵⁷ Their study demonstrated that diazosulfones are highly efficient carbene precursors in the presence of Ru(II)-Pheox complexes. This asymmetric cyclopropanation method led to sulfonylated cyclopropanes in high stereoselectivities (up to 99:1 *dr*, 98% *ee*) and moderate to excellent yields, for a large scope of alkenes including vinyl ethers, vinyl amines, and vinyl carbamates (Scheme 8c). Finally, Ru(II)-Pheox, was also used to decompose 1,1,1-trifluoroethyl diazomethane in cyclopropanation reactions in the presence of a wide range of olefins.⁵⁸ With this methodology, a series of functionalized trifluoromethyl cyclopropanes were synthesized in high yields (48-99%) with excellent diastereo- (up to 99:1 *dr*) and enantioselectivity (up to 97% *ee*).



Scheme 8. Asymmetric cyclopropanation reactions with cyano, phosphonyl and sulfonyl diazomethane.

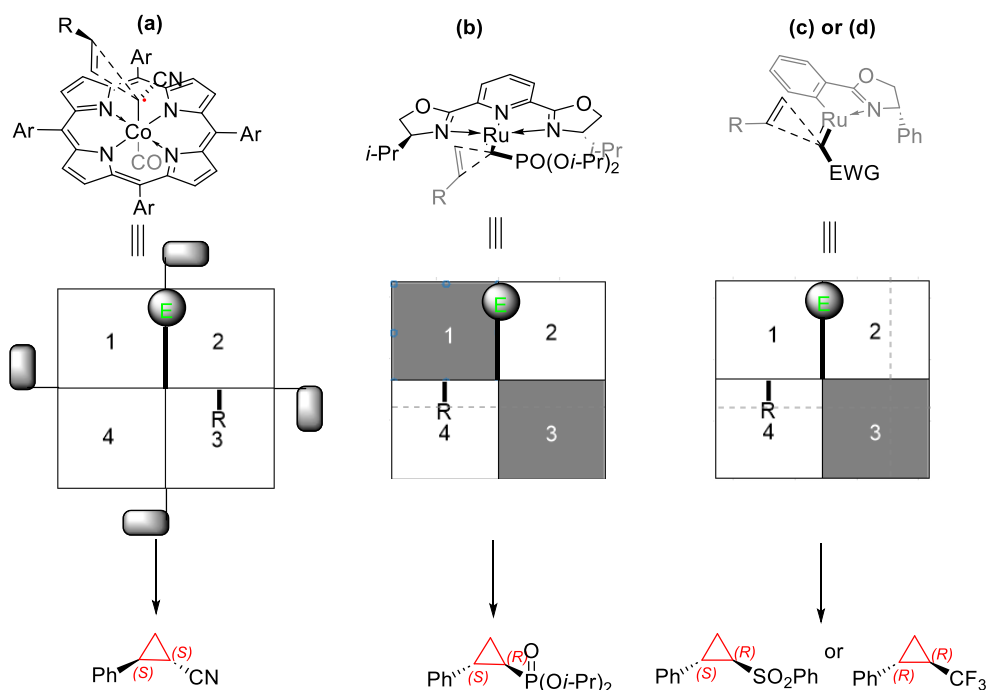
⁵⁶ A. B. Charette, J.-E. Bouchard, *Can. J. Chem.* **2005**, *83*, 533–542.

⁵⁷ M. Kotozaki, S. Chanthamath, I. Fujisawa, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2017**, *53*, 12193–12196.

⁵⁸ M. Kotozaki, S. Chanthamath, T. Fujii, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2018**, *54*, 5110–5113.

Chapter I – Introduction

According to metal complex symmetry theory,⁵⁹ we utilized three quadrant models to explain the stereoselectivities in the metallocarbene to cyclopropane fusion process for the three aforementioned protocols. (Scheme 9). The dark area represents sterically more hindered space than the lighter one. Concerning the *D_{4h}*-symmetric [Co(TPP)CO] catalyst, the ligand, porphyrin, is a more planar and less steric hindered moiety. As a consequence, poor diastereoisomeric ratio and enantiomeric excess were observed. In contrast, PyBOX and Pheox Ru catalysts exhibited outstanding stereocontrol abilities, thanks to bulky carbenoid intermediates coming from the reaction between Ru complexes and diazo compounds.



Scheme 9. Metal complex symmetry models regarding carbenoid intermediates.

In transition metal-catalyzed diazo decomposition reactions, diazo compounds that incorporate two electron-withdrawing groups are observed to exhibit the lowest reactivity, while their corresponding metal carbenoids are highly reactive species. Consequently, cyclopropanation reactions carried out with di-acceptors diazo derivatives led generally to modest stereoselectivity.⁶⁰ However, significant efforts have been devoted to solve this problem and optically pure cyclopropanes bearing two electron-withdrawing groups on the same carbon atom have been obtained using several transition

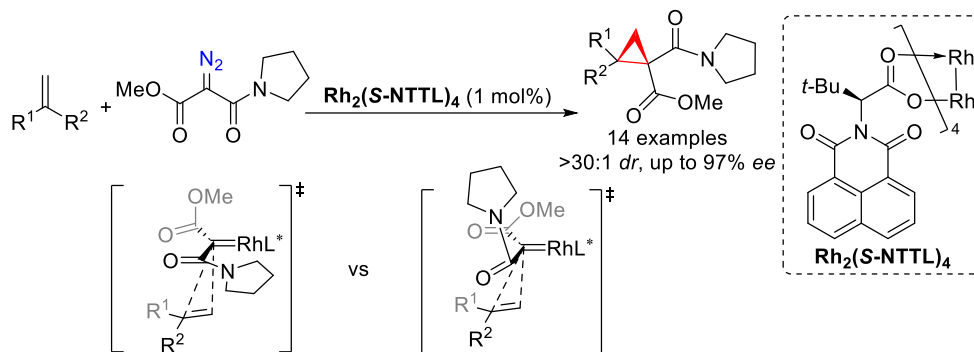
⁵⁹ A. Roy, S. Goswami, A. Sarkar, *Synth. Commun.* **2018**, *48*, 2003–2036.

⁶⁰ a) Doyle, M.P. *J. Org. Chem.* **2006**, *71*, 9253–9260. b) Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* **1996**, *37*, 4133–4136.

metal complexes, including for example Rhodium and Cobalt.

Among these Rh complexes, dirhodium paddlewheel catalysts, which are dimetallic complexes with four bidentate ligands bridging two rhodium atoms, have proven to be powerful mediators in the cyclopropanation process. The catalytic cycle responsible for the transformation of a di-acceptor diazo compound into a sterically hindered dirhodium-stabilized carbene, followed by the subsequent transfer of this carbene, is widely believed to possess robust stereocontrol capabilities.⁶¹

Charette *et al.* investigated the chiral Rh-complexes decomposition of di-acceptor diazo derivatives to form chiral cyclopropanes. For example, in 2008, they developed a highly enantio- and diastereoselective synthesis of cyclopropane 1,1-dicarboxylic derivatives.⁶² This process involved the use of a α -diazodicarboxy derivative containing two carboxy groups with different *trans*-directing abilities to distinguish two transition states, as shown below (Scheme 10). This proposal explained why α -diazomalonate⁶³ had previously led to low enantioselectivities in cyclopropanation reactions. Additionally, a chiral catalyst $\text{Rh}_2(\text{S-NTTL})_4$ was employed to effectively block one proteogenic face of the metal carbene. One year after, they published the cyclopropanation of a large scope of alkenes in the presence of the same diazo compound.⁶⁴



Scheme 10. $\text{Rh}_2(\text{S-NTTL})_4$ catalyzed α -diazodicarboxy derivative cyclopropanation.

Furthermore, Charette *et al.* exploited a couple of dirhodium complex catalysis strategies of di-acceptor diazoalkanes asymmetric cyclopropanation (Scheme 11). They used the "all-up" structured $\text{Rh}_2(\text{S-NTTL})_4$ and $\text{Rh}_2(\text{S-TCPTTL})_4$ catalysts separately to decompose diazoalkanes, both of which

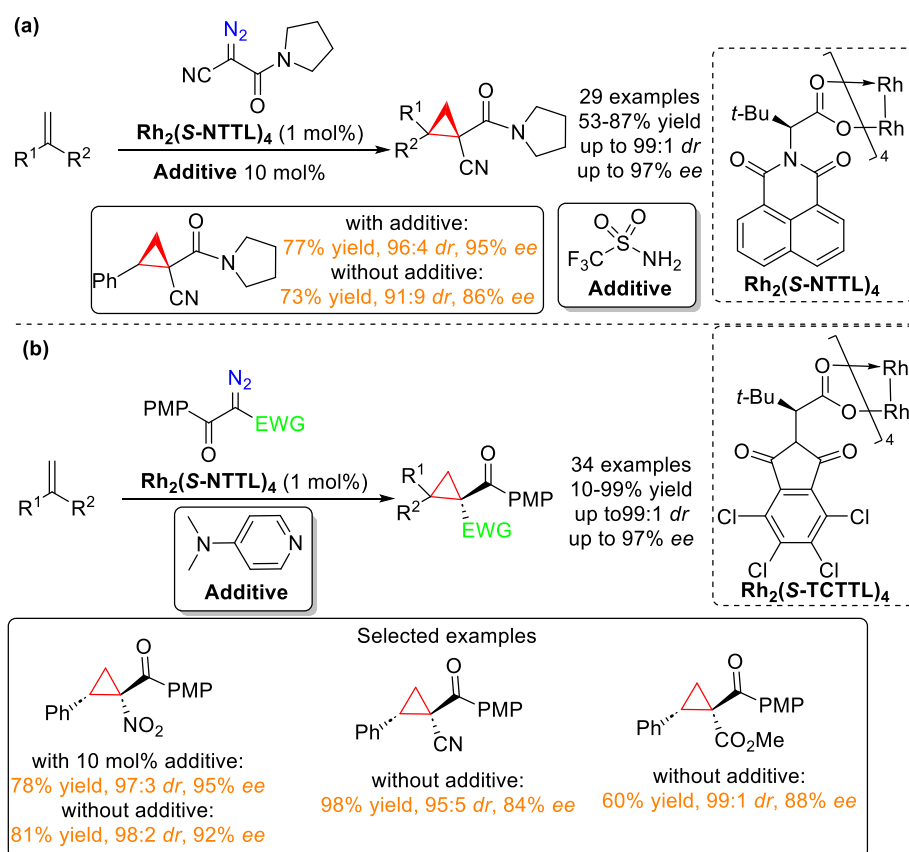
⁶¹ Y. Deng, H. Qiu, H. D Srinivas, M. P Doyle, *Curr. Org. Chem.* **2016**, *20*, 61–81.

⁶² D. Marcoux, A. B. Charette, *Angew. Chem. Int. Ed.* **2008**, *120*, 10309–10312.

⁶³ Doyle, M.P.; Hu, W. *ARKIVOC*, **2003**, *7*, 15–22.

⁶⁴ D. Marcoux, S. R. Goudreau, A. B. Charette, *J. Org. Chem.* **2009**, *74*, 8939–8955.

demonstrated superior stereocontrol abilities. To enhance selectivity, they unprecedentedly introduced an achiral hydrogen-bond donor, trifluoromethyl sulfonamide, as an additive, exploiting the strong *trans*-directing ability of the amide substrates (Scheme 11a).⁶⁵ Unlikely, for the $\text{Rh}_2(\text{S-TCTTL})_4$ complex, they employed a DMAP additive as a ligand, resulting in improved enantioselectivity but slightly reduced *trans*-directing ability. Ultimately, this protocol was demonstrated to be effective with three distinct diazo compounds, each bearing two electron-withdrawing groups (Scheme 11b).⁶⁶



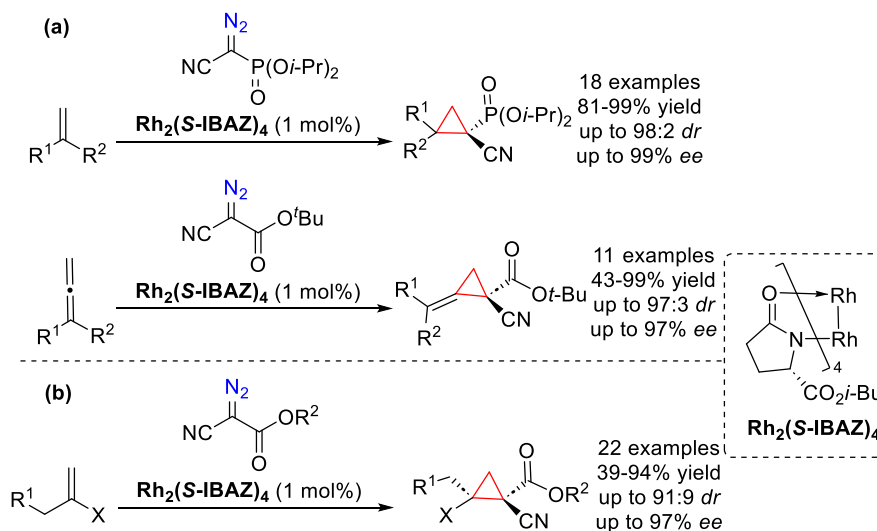
Scheme 11. Rh(II)-catalyzed versatile di-acceptor diazoalkanes cyclopropanations.

Following the aforementioned developments, two α -cyano diazo derivatives were used to access cyclopropane and methylenecyclopropane scaffolds by Charette and coworkers. The use of $\text{Rh}_2(\text{S-IBAZ})_4$ as catalyst induced the formation of the electrophilic cyano phosphonate carbene intermediate, which was able to react with allenes and alkenes. The expected cyano cyclopropyl phosphonates and the corresponding methylene cyclopropanes were obtained excellent yields and

⁶⁵ D. Marcoux, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 6970–6972.

⁶⁶ V. N. Lindsay, C. Nicolas, A. B. Charette, *J. Am. Chem. Soc.* **2011**, *133*, 8972–8981.

stereoselectivities. This approach was the first catalytic asymmetric alkylidene cyclopropanation reaction using di-acceptor diazo compounds (Scheme 12a).⁶⁷ A groundbreaking study is reported by our group, focusing on the $\text{Rh}_2(\text{S-IBAZ})_4$ -catalyzed asymmetric cyclopropanation of donor-acceptor diazo compounds with α -halogenated allylic substrates.⁶⁸ The method produced enantiomeric pure halogenated cyclopropanes in moderate to excellent yields and high *ee*, but in most cases with moderate diastereoselectivities (Scheme 12b).



Scheme 12. $\text{Rh}_2(\text{S-IBAZ})_4$ -catalyzed asymmetric cyclopropanation reactions regarding alkene, allene and allylic substrates.

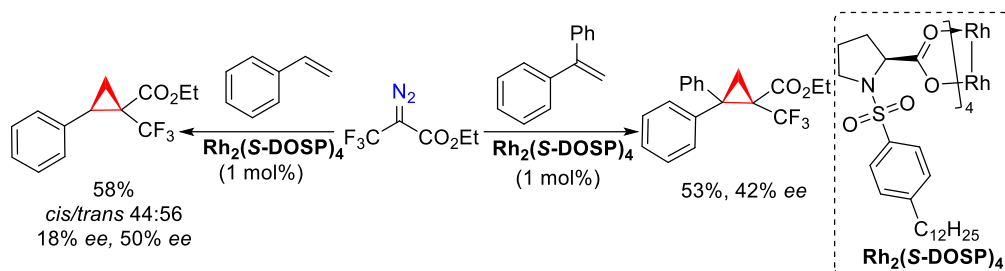
While dirhodium tetracarboxylate complexes have demonstrated impressive abilities in terms of reactivity and stereoselectivity for asymmetric cyclopropanations, challenges still persist. For instance, as shown below (Scheme 13), Müller *et al.* subjected ethyl 2-diazo-3,3,3-trifluoropropanoate in the cyclopropanation reaction with styrene or 1,1-diphenylethylene in the presence of a Rh(II)-catalyst, but only moderate yields and low stereocontrol were received.⁶⁹ Recently, our group reported an efficient catalytic enantioselective cyclopropanation of ethyl 2-diazo-3,3,3-trifluoropropanoate in the presence of sulfonyl allylic olefins with a 1 mol% loading of the catalyst $\text{Rh}_2(\text{S-BTPCP})_4$.⁷⁰

⁶⁷ V. N. Lindsay, D. Fiset, P. J. Gritsch, S. Azzi, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 1463–1470.

⁶⁸ A. Pons, P. Ivashkin, T. Poisson, A. B. Charette, X. Pannecoucke, P. Jubault, *Chem. Eur. J.* **2016**, *22*, 6239–6242.

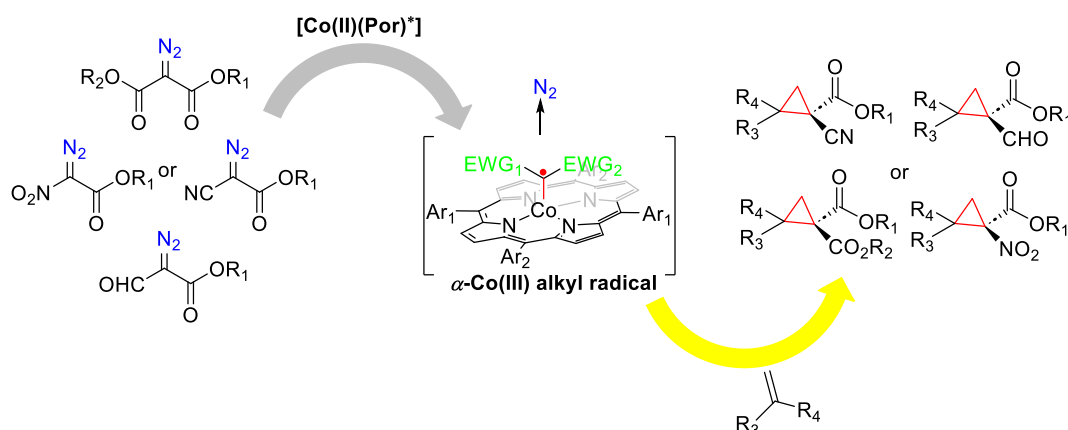
⁶⁹ P. Müller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755–4763.

⁷⁰ L. Chen, T. Minh Thi Le, J. P. Bouillon, T. Poisson, P. Jubault, *Chem. Eur. J.* **2022**, *28*, e202201254.



Scheme 13. $\text{Rh}_2(\text{S-DOSP})_4$ catalyzed 2-diazo-3,3,3-trifluoropropanoate cyclopropanation.

Metalloradical catalysis (MRC), an effective approach utilizing metal-centered free radicals to cooperatively cleave diazo substrates and generate stable organic free radicals as key intermediates, has emerged as an innovative method for controlling the reactivity and stereoselectivity of free radical reactions. In a pioneering application of MRC, the Co(II) complex of chiral porphyrins, serving as stable metal radicals, has proven to be an effective catalysts for the cyclopropanation of asymmetric olefins with diazo compounds. This achievement is carried out through a stepwise radical mechanism (Scheme 14).⁷¹



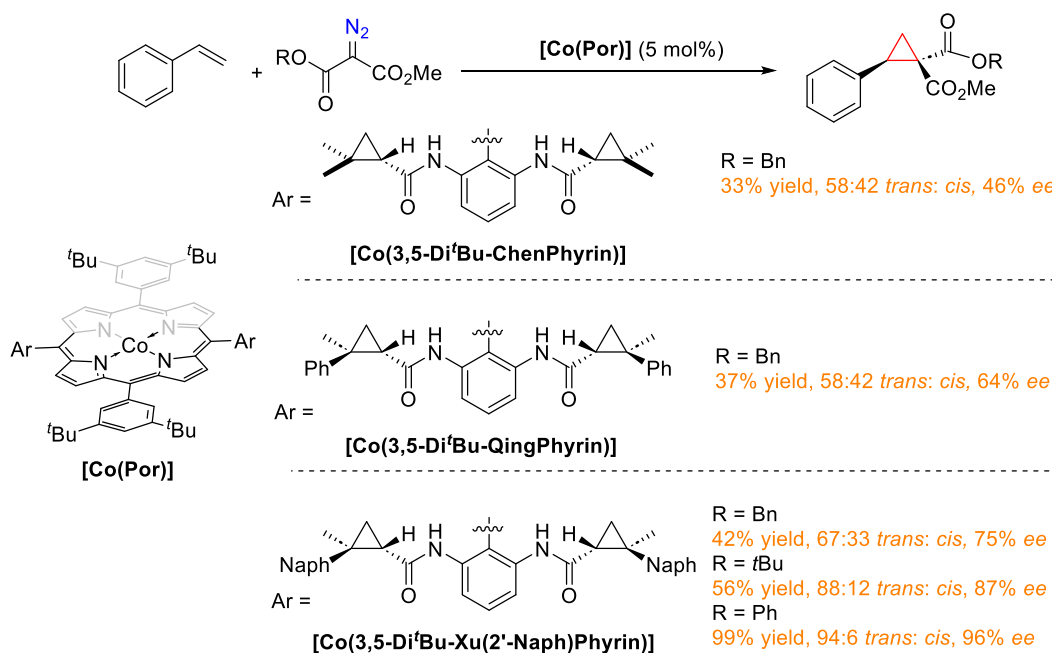
Scheme 14. $[\text{Co}(\text{Por})]$ -mediated diaceptor diazoalkanes cyclopropanations undergo metalloradical pathway.

For instance, in recent work, Zhang and co-workers introduced a homolog of α -diazomanolate as a carbene precursor mediated by chiral $[\text{Co}(\text{Por})^*]$ complexes to achieve highly reactive, diastereoselective, and enantioselective cyclopropanation of alkenes (Scheme 15). Ligand screening results demonstrated that as the barrier of the ligand increased, the reaction process exhibited greater

⁷¹ a) X. Wang, X. P. Zhang, *Transition Metal–Catalyzed Carbene Transformations* **2021**. b) W.-C. C. Lee, X. P. Zhang, *Trends in chemistry* **2022**, *4*, 850–851. c) D. D. Snabilić, E. J. Meeus, R. F. Epping, Z. He, M. Zhou, B. de Bruin, *Chem. Eur. J.* **2023**, e202300336.

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stereocontrol ability. Furthermore, the reactivity and stereoselectivity were found to be influenced by the R group. In addition to conformational rigidification, noncovalent attractive interactions played a crucial role in cooperatively lowering the activation barriers of transition states, potentially enhancing catalytic reactivity and improving the stereoselectivity of the product. This rationalizes why the *tert*-butyl substituted substrate exhibited not only lower reactivity but also reduced stereoselectivity compared to the phenyl-substituted one.⁷²



Scheme 15. The effects of substrates and catalysts in [Co(Por)] catalyzed cyclopropanation.

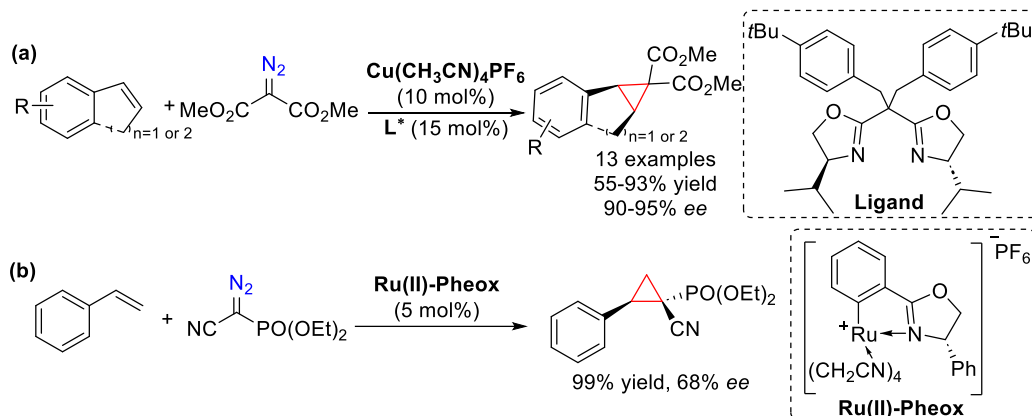
A Cu(I)-complex catalyzed decomposition of dimethyl diazomalonate to synthesize enantiomeric pure cyclopropanes was first investigated by Tang *et al.* in 2017.⁷³ Compared to more classical alkenes generally used in cyclopropanation process, they employed internal alkenes such as, indene, dihydronaphthalene and *Z*- β -methyl styrene. The reaction performed remarkably well with chiral bi-side arm bisoxazoline–copper(I) complex, to give the desired products in excellent yields (up to 93%) and enantioselectivities (up to 95% *ee*) (Scheme 16a). In fact, styrene was engaged with diazomanolate in a cyclopropanation reaction mediated by Cu(I) complex in 2000 but unfortunately, only moderate *ee* was reported.⁷⁴

⁷² J. Wang, J. Xie, W.-C. C. Lee, D.-S. Wang, X. P. Zhang, *Chem Catal.* **2022**, *2*, 330–344.

⁷³ C. Deng, H.-K. Liu, Z.-B. Zheng, L. Wang, X. Yu, W. Zhang, Y. Tang, *Org. Lett.* **2017**, *19*, 5717–5719.

⁷⁴ D. S. Masterson, D. T. Glatzhofer, *J. Mol. Catal. A: Chem.* **2000**, *161*, 65–68.

Iwasa *et al.* have also attempted to assess the cyclopropanation with di-acceptor diazo compounds in the presence of Ru(II)-Pheox complex. However, despite excellent yields, enantioselectivity remains modest (Scheme 16b).⁷⁵



Scheme 16. Cu(I) and Ru(II) catalyzed cyclopropanation of di-acceptor diazo derivatives.

1.2.3. Donor-acceptor diazo derivatives

Donor-acceptor diazo compounds are diazo derivatives bearing a donor and an acceptor group as shown below (Figure 5). The acceptor group enhances the electrophilic nature of this class of carbenoids, while the donor group finely modulates their reactivity, facilitating the occurrence of highly regio- and stereoselective reactions.⁷⁶

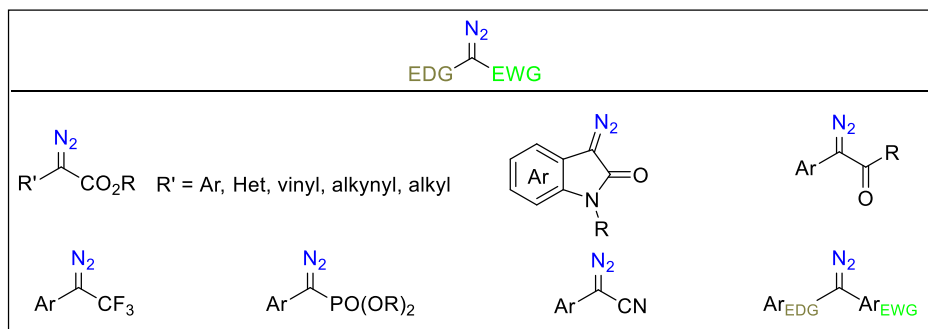


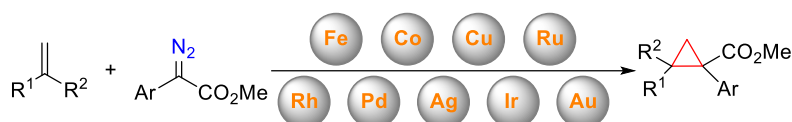
Figure 5. Donor-acceptor diazo compounds.

While the predominant developments in the field of cyclopropanation reactions are essentially

⁷⁵ L. T. L. Chi, S. Chanthamath, K. Shibatomi, S. Iwasa, in *AIP Conference Proceedings, Vol. 1954*, AIP Publishing, **2018**.

⁷⁶ J. R. Denton, H. M. Davies, *Org. Lett.* **2009**, *11*, 787–790.

dedicated to enantioselective strategies, it is important to note the access of racemic cyclopropanes have been also synthesized efficiently. For example, Paulini and Reissig reported the use of a rhodium acetate dimer for the catalytic cyclopropanation between methyl aryldiazoacetate and alkenes, demonstrating the *in situ* generation of an unprecedented donor-acceptor metal-carbene intermediate for the synthesis of cyclopropanes.⁷⁷ Based on this report, subsequently, miscellaneous metal complexes, such as Fe,⁷⁸ Ru,⁷⁹ Au,⁸⁰ Pd⁸¹ and others,⁸² have been proposed as carbene transfer agents for this [2+1] cycloaddition reaction (Scheme 17).



Scheme 17. Alkene non-asymmetric cyclopropanation *via* metals decompose aryldiazoacetate.

Different rhodium complexes have been proposed to carry out asymmetric cyclopropanation reactions with donor-acceptor diazo compounds over the two last decades. The rational design of rhodium complexes is crucial for the construction of enantiomerically pure cyclopropane skeletons. For instance, Fox *et al.* have subsequently described dirhodium paddlewheel catalysts Rh₂(S-PTTL)₄⁸³ and Rh₂(S-PTTL)₃•TPA⁸⁴ as carbene transfers from α -alkyldiazoesters. Even though the Rh₂(S-PTTL)₄ have shown great capabilities within a series of α -alkyldiazoesters and styrenes, the modified Rh₂(S-PTTL)₃•TPA catalyst led to better results. It is owing to the introduction of the triphenylacetate ligand with large aromatic surface could have a positive effect on the yield and enantioselectivity (Scheme 18).

⁷⁷ K. Paulini, H.–U. Reissig, *J. Prakt. Chem.* **1995**, 337, 55–59.

⁷⁸ a) B. Wang, I. G. Howard, J. W. Pope, E. D. Conte, Y. Deng, *Chem. Sci.* **2019**, 10, 7958–7963. b) Y. Li, J.–S. Huang, Z.–Y. Zhou, C.–M. Che, X.–Z. You, *J. Am. Chem. Soc.* **2002**, 124, 13185–13193.

⁷⁹ C. del Pozo, A. Corma, M. Iglesias, F. Sánchez, *Green Chem.* **2011**, 13, 2471–2481.

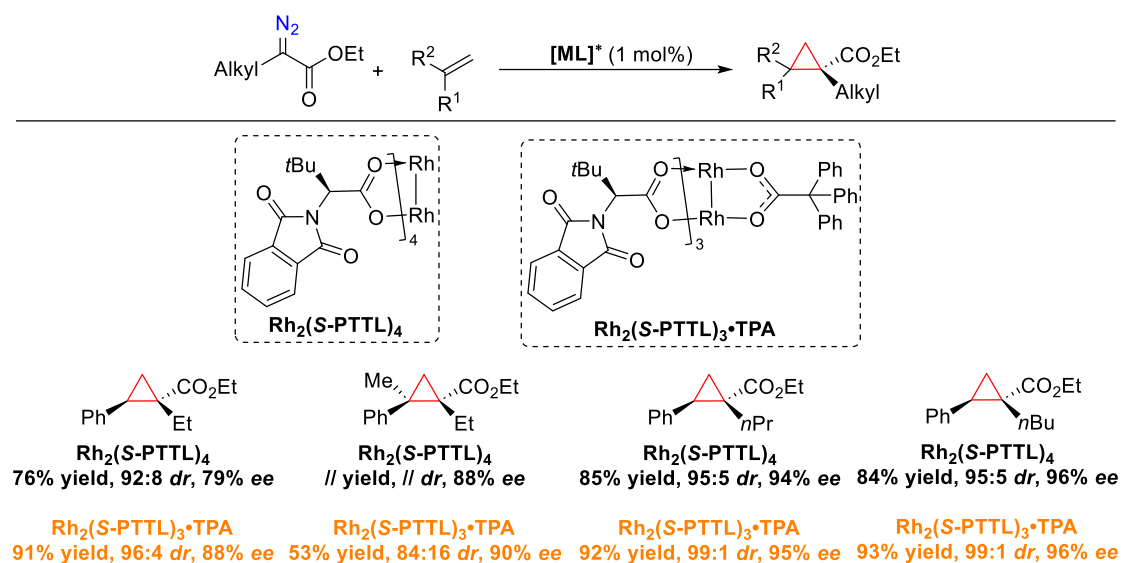
⁸⁰ A. Zeineddine, F. Rekhroukh, E. D. Sosa Carrizo, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2018**, 57, 1306–1310.

⁸¹ S. G. Rull, E. Álvarez, M. R. Fructos, T. R. Belderrain, P. J. Pérez, *Chem. Eur. J.* **2017**, 23, 7667–7671.

⁸² a) C. Tubaro, A. Biffis, R. Gava, E. Scatolin, A. Volpe, M. Basato, M. M. Díaz–Requejo, P. J. Perez, *Eur. J. Org. Chem.* **2012**, 2012, 1367–1372. b) R. J. Pakula, A. M. Martinez, E. A. Noten, C. F. Harris, J. F. Berry, *Polyhedron* **2019**, 161, 93–103. c) B. J. Anding, A. Ellern, L. K. Woo, *Organometallics* **2012**, 31, 3628–3635. d) L. Chen, M. O. Bovee, B. E. Lemma, K. S. M. Keithley, S. L. Pilson, M. G. Coleman, J. Mack, *Angew. Chem. Int. Ed.* **2015**, 54, 11084–11087.

⁸³ A. DeAngelis, O. Dmitrenko, G. P. Yap, J. M. Fox, *J. Am. Chem. Soc.* **2009**, 131, 7230–7231.

⁸⁴ D. T. Boruta, O. Dmitrenko, G. P. Yap, J. M. Fox, *Chem. Sci.* **2012**, 3, 1589–1593.



Scheme 18. Asymmetric cyclopropanation of α -alkyldiazoesters mediated by dirhodium complexes.

Indeed, asymmetric cyclopropanation reaction using rhodium catalysts, have been efficiently developed from donor-acceptor diazo compounds such as phenyldiazoacetates,⁸⁵ heteroaryldiazoacetates,⁸⁶ vinyldiazoacetates,⁸⁷ and alkynyl diazoacetates⁸⁸. Here, we exemplify the evolution of dirhodium catalysts in the construction of versatile enantiomerically pure cyclopropyl scaffolds. In 1996, Davies *et al.* disclosed the first Rh₂(S-DOSP)₄ catalyzed asymmetric cyclopropanation of donor-acceptor diazo compounds. This methodology was applied to both methyl phenyldiazoacetate and methyl phenylvinyl-diazoacetate, leading to good to excellent yields, and moderate to excellent enantiomeric excesses (Scheme 19a).^{87a} Several years later, this approach was extended for the synthesis of optically pure diaryl cyclopropanes which are key intermediates of Tamoxifen derivatives (Scheme 19b).^{87b}

In order to achieve highly enantioselective cyclopropanes with electronic deficient olefins, Davies and co-workers introduced Rh₂(S-TCPTAD)₄ to decompose aryldiazoacetates and vinyldiazoacetates to generate reactive Rh-carbenes species (Scheme 19c). The outcome of reaction

⁸⁵ a) H. M. L. Davies, P. R. Bruzinski, M. J. Fall, *Tetrahedron Lett.* **1996**, *37*, 4133–4136. b) T. Nagashima, H. M. Davies, *Org. Lett.* **2002**, *4*, 1989–1992. c) H. M. L. Davies, T. Nagashima, J. L. Klino, *Org. Lett.* **2000**, *2*, 823–826.

⁸⁶ H. M. L. Davies, R. J. Townsend, *J. Org. Chem.* **2001**, *66*, 6595–6603.

⁸⁷ a) H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall, *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

b) C. Qin, V. Boyarskikh, J. H. Hansen, K. I. Hardcastle, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc.* **2011**, *133*, 19198–19204.

⁸⁸ H. M. L. Davies, T. A. Boebel, *Tetrahedron Lett.* **2000**, *41*, 8189–8192.

process is dependent on the nature of the carbonyl substrates, indeed acrylates and acrylamides led yield cyclopropanes adducts, whereas the use of unsaturated aldehydes and ketones results in the formation of epoxides.⁸⁹

In 2014, Ball and co-workers studied an axial-binding component in ligand design to control Rh (II) diazo chemistry (Scheme 19d). This unprecedented peptide ligand for Rh(II) complex led to seven examples including aryl, ethyl, amino and hetero cyclopropane motifs with very decent yields, diastereo- and enantioselectivities.⁹⁰

In 2021, Davies and his co-workers described a set of versatile methodologies for synthesizing cyclopropanes substituted with heterocycles (Scheme 19e). When *para*- or *meta*-substituted aryldiazoacetates were engaged, the use of Rh₂(*R-p*-Ph-TPCP)₄ as a catalyst led to important to exceptional selectivity. This reaction was also successfully extended to a range of heteroaryldiazoacetates, allowing for the synthesis of 1,2-diheteroarylcyclopropane carboxylates. However, in the case *ortho*-substituted aryldiazoacetates, the use of a distinct chiral catalyst, Rh₂(*S*-TPPTTL)₄ was preferred.⁹¹

More recently, our group has depicted a Rh-catalyzed enantioselective cyclopropanation protocol with allylic substrates involving donor-acceptor diazo compound.⁷⁰ The Rh₂(*S*-BTPCP)₄ complex was selected to furnish a board range of cyclopropanes in moderate to excellent yields, high diastereo- and enantioselectivity (Scheme 19f). Additionally, the exploration of asymmetric cyclopropanation between arylallenes and donor-acceptor diazo compounds under the catalysis of Rh₂(*S*-TCPTAD)₄ was reported by our group.⁹² To further demonstrate the versatility to the methodology, we had investigated this successful application to over 18 arylallene homologs with high stereocontrol, as well as outstanding yields (Scheme 19g). These advancements hold promise for further developments in asymmetric synthesis and the construction of substituted methyldiene cyclopropane architectures.

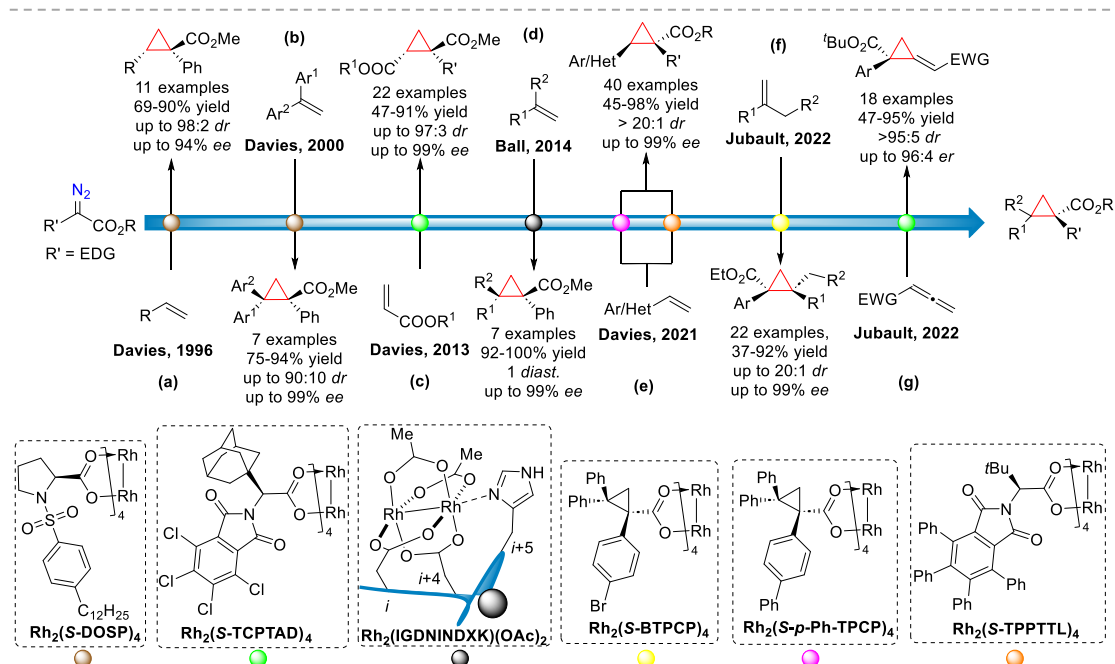
⁸⁹ H. Wang, D. M. Guptill, A. Varela–Alvarez, D. G. Musaev, H. M. Davies, *Chem. Sci.* **2013**, *4*, 2844–2850.

⁹⁰ R. Sambasivan, W. Zheng, S. J. Burya, B. V. Popp, C. Turro, C. Clementi, Z. T. Ball, *Chem. Sci.* **2014**, *5*, 1401–1407.

⁹¹ J. Sharland, B. Wei, D. Hardee, T. Hodges, W. Gong, E. Voight, H. Davies, Role of Additives to Overcome Limitations of Intermolecular Rhodium–Catalyzed Asymmetric Cyclopropanation. ChemRxiv, **2021**.

⁹² Y. Hasegawa, T. Cantin, J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson, P. Jubault, *Chem. Eur. J.* **2022**, *28*, e202201438.

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Scheme 19. The Rh(II) complexes development regarding alkene substrates.

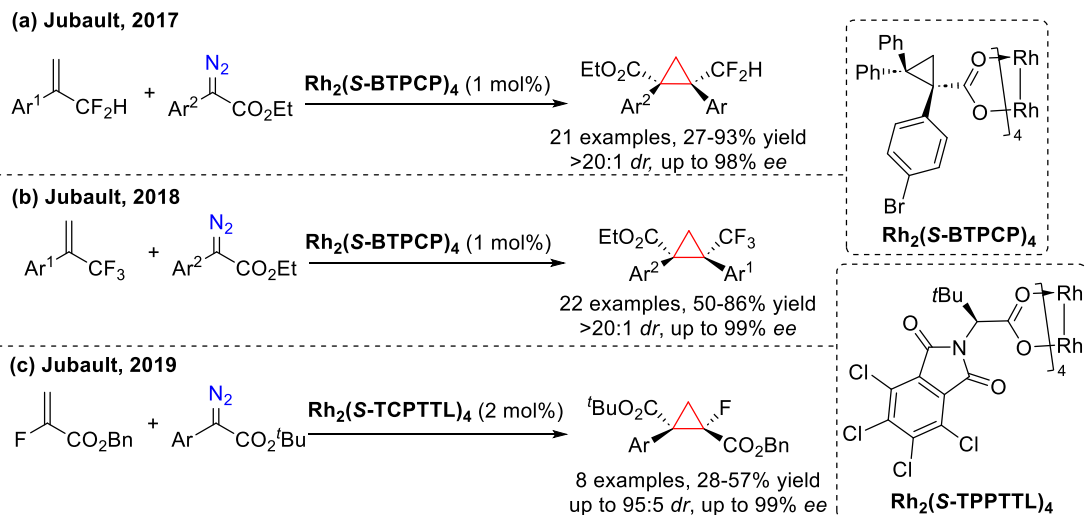
As the importance of fluorinated skeletons in organic and medical chemistry, it is fascinating to note the recent advancements from our group, particularly the Rh-catalyzed enantioselective cyclopropanation methodologies involving fluorinated alkene substrates and donor-acceptor diazo compounds. In 2017, our group developed an efficient protocol for the catalytic enantioselective synthesis of difluoromethyl cyclopropanes.⁹³ This method tolerates a large number of difluoromethyl olefins and aryldiazoacetates by use of a unique $\text{Rh}_2(\text{S-BTPCP})_4$ catalyst (Scheme 20a). Subsequently, our focus shifted to the asymmetric cyclopropanation of α -trifluoromethyl styrenes.⁹⁴ Introducing the $\text{Rh}_2(\text{S-BTPCP})_4$ complex to the cyclopropanation process, we achieved a series of trifluorocyclopropane products with high stereocontrol ability (Scheme 20b). Moreover, the enantiocontrolled synthesis of monofluorinated cyclopropanes, utilizing the $\text{Rh}_2(\text{S-TCPTTL})_4$ catalyst, represents another important approach.⁹⁵ Despite the reactivity of the cyclopropanation reactions was moderate, achieving examples of monofluorinated cyclopropanes with up to 95:5 *dr* and 99% *ee* is commendable (Scheme 20c). Notably, in these reported methodologies, several

⁹³ M. Bos, W. S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *129*, 13504–13508.

⁹⁴ W. S. Huang, C. Schlinquer, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2018**, *24*, 10339–10343.

⁹⁵ A. Pons, V. Tognetti, L. Joubert, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *ACS Catal.* **2019**, *9*, 2594–2598.

acceptor-acceptor diazo reagents were also employed and exhibited great tolerance. These methodologies contribute significantly to the synthesis of fluorinated cyclopropane skeletons, which is crucial in the fields of organic and medical chemistry.

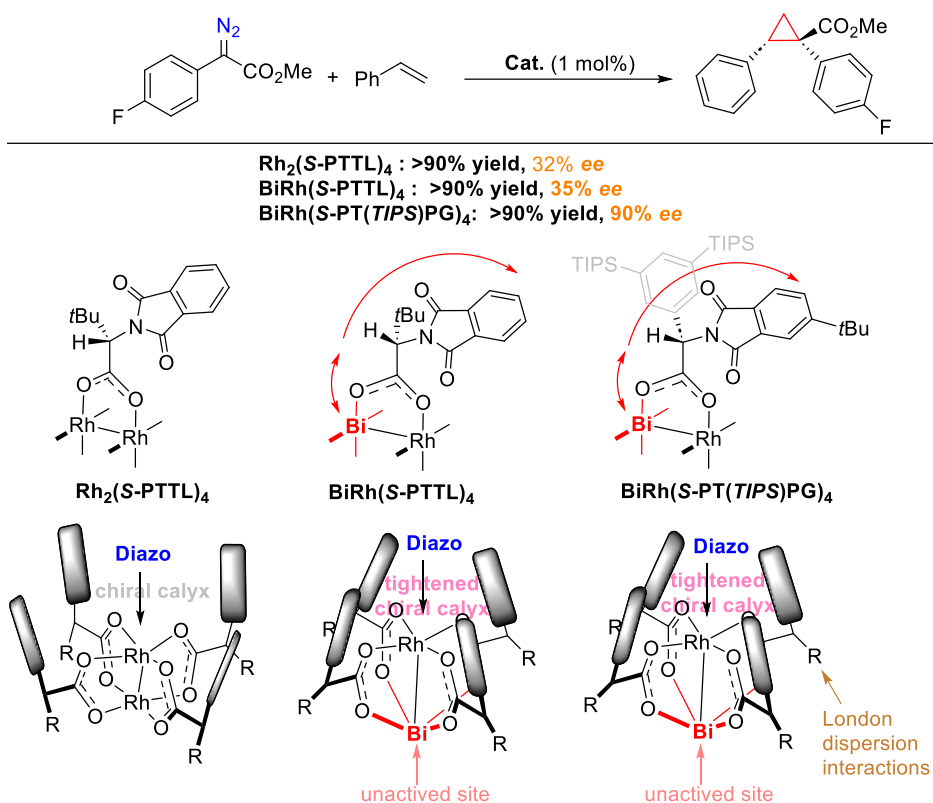


Scheme 20. Asymmetric cyclopropanation of fluorinated alkenes and donor-acceptor diazo compounds.

Alternatively, a heterobimetallic bismuth–rhodium paddlewheel complex with phenylglycine ligands bearing TIPS-groups at the two *meta*-positions of the aromatic ring has been reported, by Fürstner *et al.*, and lead to outstanding levels of selectivity in asymmetric cyclopropanation reactions with donor-acceptor carbenes (Scheme 21).⁹⁶ Simultaneously, the reaction rates are significantly faster, and the substrate scope is considerably broader compared to previous generation of chiral $\text{BiRh}(\text{S-PTTL})_4$ ⁹⁷ catalysts. This $\text{BiRh}(\text{S-PT}(\text{TIPS})\text{PG})_4$ catalyst owe their excellent application profile largely to the stabilization of the chiral ligand sphere through London dispersion interactions with the peripheral silyl substituents.

⁹⁶ S. Singha, M. Buchsteiner, G. Bistoni, R. Goddard, A. Fürstner, *J. Am. Chem. Soc.* **2021**, *143*, 5666–5673.

⁹⁷ L. R. Collins, S. Auris, R. Goddard, A. Fürstner, *Angew. Chem. Int. Ed.* **2019**, *131*, 3595–3599.



Scheme 21. The features of BiRh(S-PT(TIPS)PG)₄ when it was employed in asymmetric cyclopropanation.

While aryldiazoacetate type diazo compounds have attracted significant attention for the synthesis of optically rich cyclopropanes, donor-acceptor diazoalkanes containing other electron-withdrawing groups, such as difluoroalkyl,⁹⁸ phosphonyl,⁹⁹ cyano,¹⁰⁰ aryl_{EWD}-aryl_{EDG},¹⁰¹ trifluoromethyl,¹⁰² and carbonyl¹⁰³ have also been explored. A dirhodium paddlewheel complex with adamantly glycine derivatives, Rh₂(S-PTAD)₄, was designed⁹⁹ and has demonstrated remarkable properties during the catalytic enantioselective cyclopropanation with these donor-acceptor diazo compounds. In spite of various of dirhodium complexes have been tested as well,¹⁰⁴ Rh₂(S-PTAD)₄ remains the

⁹⁸ X. Zhang, Y. Ning, C. Tian, G. Zanoni, X. Bi, *iScience* **2023**, 26.

⁹⁹ R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett.* **2006**, 8, 3437–3440.

¹⁰⁰ J. R. Denton, K. Cheng, H. M. Davies, *Chem. Commun.* **2008**, 1238–1240.

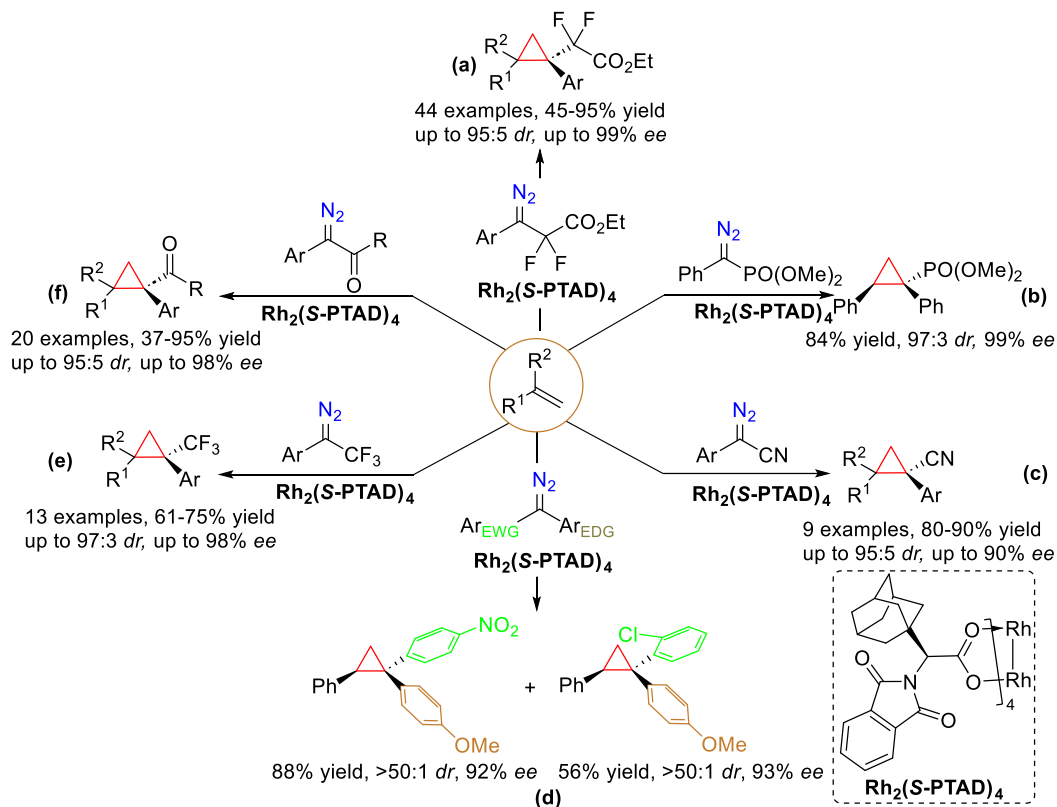
¹⁰¹ M. Lee, Z. Ren, D. G. Musaev, H. M. L. Davies, *ACS Catal.* **2020**, 10, 6240–6247.

¹⁰² a) J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett.* **2007**, 9, 2625–2628. b) X. Zhang, C. Tian, Z. Wang, P. Sivaguru, S. P. Nolan, X. Bi, *ACS Catal.* **2021**, 11, 8527–8537.

¹⁰³ J. R. Denton, H. M. L. Davies, *Org. Lett.* **2009**, 11, 787–790.

¹⁰⁴ a) F. G. Adly, J. Maddalena, A. Ghanem, *Chirality* **2014**, 26, 764–774. b) F. G. Adly, M. G. Gardiner, A. Ghanem, *Chem. Eur. J.* **2016**, 22, 3447–3461. c) H. M. Davies, G. H. Lee, *Org. Lett.* **2004**, 6, 2117–2120.

optimal catalyst for these donor-acceptor diazo compounds (Scheme 22). It can be rationalized the use of sterically blocking group adamantyl limits the number of reasonable orientations of the substrates as they interact with dirhodium catalyst, leading to high diastereo- and enantioselectivities.



Scheme 22. Asymmetric cyclopropanation of $\text{Rh}_2(\text{S-PTAD})_4$ catalyzed versatile donor-acceptor diazo compounds.

The oxindole scaffold is widely present in natural products and drugs,¹⁰⁵ and as a consequence diazo-oxindoles derivatives are interesting substrates for asymmetric synthesis of spiro cyclopropyl structures. In 2013, Zhou *et al.* depicted the first enantioselective cyclopropanation with diazo-oxindoles by use of $\text{Hg}(\text{OTf})_2$ coordinated to (*R*)-difluorophos (Scheme 23a).¹⁰⁶ This reaction could tolerate 16 terminal styrene substrates with moderate to excellent yield. In most cases, diastereoisomeric ratio is high (20:1) and high enantiomeric excesses (up to 99%) are obtained.

Meanwhile, Ding and coworkers reported an asymmetric cyclopropanation of this cyclic diazo compound mediated by a gold(I) complex (Scheme 23b).¹⁰⁷ The spiroketal bisphosphine ligand-

¹⁰⁵ a) F. Zhou, Y. L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, 352, 1381–1407. b) X. Huang, J. Peng, L. Dong, Y.-C. Chen, *Chem. Commun.* **2012**, 48, 2439–2441.

¹⁰⁶ Z.-Y. Cao, F. Zhou, Y.-H. Yu, J. Zhou, *Org. Lett.* **2013**, 15, 42–45.

¹⁰⁷ Z.-Y. Cao, X. Wang, C. Tan, X.-L. Zhao, J. Zhou, K. Ding, *J. Am. Chem. Soc.* **2013**, 135, 8197–8200.

engaged digold catalyst exhibited outstanding stereocontrol ability and reactivity, which produced spirocyclopropyloxindole products from a broad range of internal and external styrenes. This gold(I) catalysis of asymmetric cyclopropanation strategy was introduced to synthesis of optically pure fluorinated cyclopropyl moieties as well.¹⁰⁸

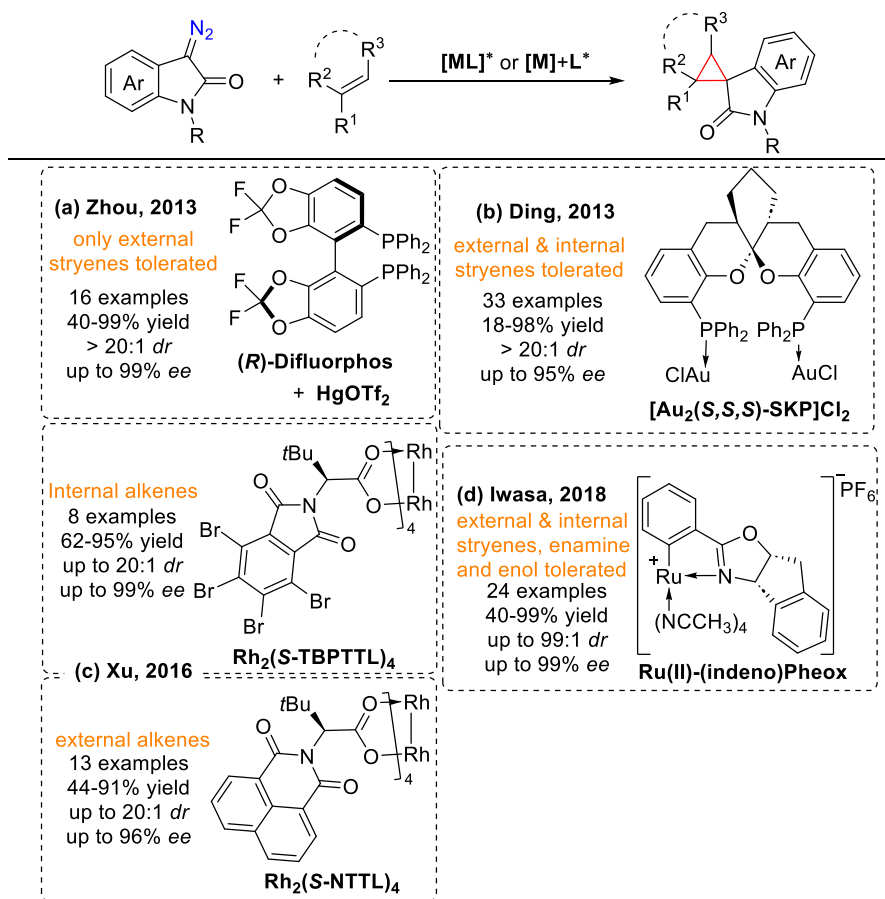
Furthermore, conventional dirhodium complexes were also employed to decompose diazo-oxindoles for construction of enantiomeric pure spirocyclopropanes as reported by Xu *et al.* (Scheme 23c).¹⁰⁹ In their procedures, two different Rh catalysts were used depending on the structure of the alkene partner. In other words, Rh₂(S-TBPTTL)₄-engaged carbenoid generated cyclopropanes from internal alkenes, while Rh₂(S-NTTL)₄-engaged carbenoid afforded cyclopropanes from external alkenes. Both of these catalysts led to the formation of the expected spirocyclopropanes with a very high stereocontrol.

More recently, Iwasa *et al.* described Ru(II)-(indeno)Pheox as a highly effective catalyst for an asymmetric spirocyclopropanation from diazo-oxindoles (Scheme 23d).¹¹⁰ This method was carried out in the presence of various olefins, including styrenes, enamines and enols, leading to the expected cyclopropanes in high yields, high diastereo- and enantioselectivities.

¹⁰⁸ Z.-Y. Cao, W. Wang, K. Liao, X. Wang, J. Zhou, J. Ma, *Org. Chem. Front.* **2018**, *5*, 2960–2968.

¹⁰⁹ Y. Chi, L. Qiu, X. Xu, *Org. Biomol. Chem.* **2016**, *14*, 10357–10361.

¹¹⁰ M. Tone, Y. Nakagawa, S. Chanthamath, I. Fujisawa, N. Nakayama, H. Goto, K. Shibatomi, S. Iwasa, *RSC Adv.* **2018**, *8*, 39865–39869.



Scheme 23. Versatile metal complexes catalyzed asymmetric cyclopropanations with diazoindoles.

1.2.4. Mono-donor and di-donor diazo derivatives

Mono-donor and di-donor diazo compounds that only bear one or two electron-donating groups are known to be the most reactive but the less stable diazoalkanes due to the presence of two electron-donating groups onto the same carbon atom. Consequently, metallocarbenes generated from mono-donor and di-donor diazo compounds exhibit slothful reactivity. In addition, to overcome their inherent toxicity and instability, *in situ* generation strategies are usually required for the efficient use of this type of starting materials.¹¹¹ Generally, three methods are commonly applied to *in situ* generate mono-donor and di-donor diazoalkanes: oxidation of hydrazones,¹¹² conversion of sulfonylhydrazone sodium salts with a phase transfer catalyst,¹¹³ and dissociation of

¹¹¹ E. M. Allouche, A. B. Charette, *Synthesis* **2019**, 51, 3947–3963.

¹¹² H. Liu, Y. Wei, C. Cai, *New J. Chem.* **2016**, 40, 674–678.

¹¹³ V. Aggarwal, H. Smith, R. H. Jones, *Chem. Commun.* **1997**, 1785–1786.

sulfonylhydrazones under alkaline conditions (Figure 6).¹¹⁴

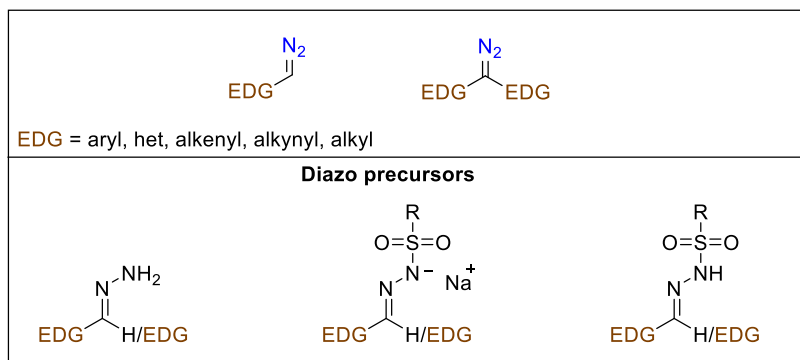


Figure 6. The precursors of H-donor and donor-donor diazoalkanes.

In 2011, a D_2 -symmetric $\text{Rh}_2(R\text{-(perfluoro)DOSP})_4$ was reported to decompose aryldiazomethane and provided *cis*-selective cyclopropanes in the presence of styrenes (Scheme 24a).¹¹⁵ Although dirhodium catalysts offered a board range of scope and slight improvement in the conversion rate of diazo compounds compared to $\text{Rh}_2(\text{OAc})_4$,¹¹⁶ the yields remained lower than 60% in most cases. Furthermore, various metals^{104,117} have been proven to be effective as carbene transfer agents for the synthesis of 1,2-diphenyl cyclopropanes.

Aggarwal *et al.* developed an efficient strategy for the *in situ* generation of mono-donor diazo compounds to synthesize protected cyclopropyl amino acids.¹¹⁸ Interestingly, this reaction underwent a thermal 1,3-dipolar cycloaddition process as well as providing a good *trans* selectivity to access cyclopropyl amino acid derivatives, while the presence of $\text{Fe}(\text{TPP})\text{Cl}$ predominantly afforded the corresponding products in *cis* isomers.

Moreover, the *meso*-tetraphenylporphyrin (TPP) ligand was proposed in combination with Cobalt, generating $\text{Co}(\text{TPP})$ complex, which catalyzed the cyclopropanation of α -pyryldiazomethane with alkenes in good to excellent yields.¹¹⁹

¹¹⁴ W.-H. Cheung, S.-L. Zheng, W.-Y. Yu, G.-C. Zhou, C.-M. Che, *Org. Lett.* **2003**, *5*, 2535–2538.

¹¹⁵ M. Verdecchia, C. Tubaro, A. Biffis, *Tetrahedron Lett.* **2011**, *52*, 1136–1139.

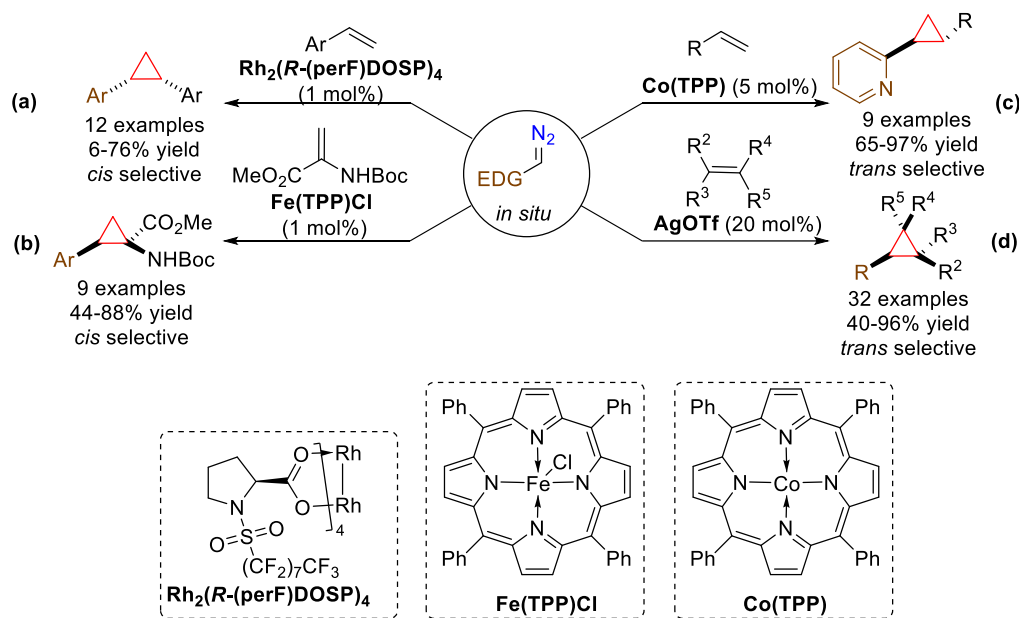
¹¹⁶ V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785–2788.

¹¹⁷ a) Y. Li, J.-S. Huang, Z.-Y. Zhou, C.-M. Che, *J. Am. Chem. Soc.* **2001**, *123*, 4843–4844. b) Y. Zhou, B. G. Trewyn, R. J. Angelici, L. K. Woo, *J. Am. Chem. Soc.* **2009**, *131*, 11734–11743. c) S. Priya, M. S. Balakrishna, S. M. Mobin, R. McDonald, *J. Organomet. Chem.* **2003**, *688*, 227–235. d) X. Dai, T. H. Warren, *J. Am. Chem. Soc.* **2004**, *126*, 10085–10094.

¹¹⁸ L. A. Adams, V. K. Aggarwal, R. V. Bonnert, B. Bressel, R. J. Cox, J. Shepherd, J. de Vicente, M. Walter, W. G. Whittingham, C. L. Winn, *J. Org. Chem.* **2003**, *68*, 9433–9440.

¹¹⁹ S. Roy, S. K. Das, B. Chattopadhyay, *Angew. Chem. Int. Ed.* **2018**, *130*, 2260–2265.

While metal complex catalysis in cyclopropanation strategies often require expensive and less accessible ligands, Bi and coworkers proposed a more cost-effective approach using silver salt catalysis in the cyclopropanation of mono-donor diazo derivatives. The AgOTf catalyst serves a dual function as a Lewis acid and a transition metal, yielding the desired cyclopropanes with high stereoselectivity for a broad substrate scope (Scheme 24c).¹²⁰



Scheme 24. Non-asymmetric cyclopropanation of mono electron-donating diazomethane catalyzed by several metals.

Alongside mono-donor diazo compounds, donor-donor diazo compounds have been also investigated in cyclopropanation reactions but for a minor part. To develop a cyclopropanation portfolio of donor-donor diazo compounds catalyzed by transition metal, Jiang *et al.* showcased palladium-catalyzed cyclopropanation of internal alkenes maleimides with α -aryl- α -alkyldiazomethane.¹²¹ In the study, they used Pd(OAc)₂ as an effective catalyst, which provided a wide spectrum of 3-azabicyclo[3.1.0]hexane derivatives in high yields and diastereoselectivities. This strategy was also used for the cyclopropanation of *N*-alkylacrylamide substrates.¹²²

More recently, Cai *et al.* described a Nickel-mediated non-asymmetric cyclopropanation methodology involving either α -aryl- α -alkyldiazomethane or α -diaryldiazomethane.¹²³ This

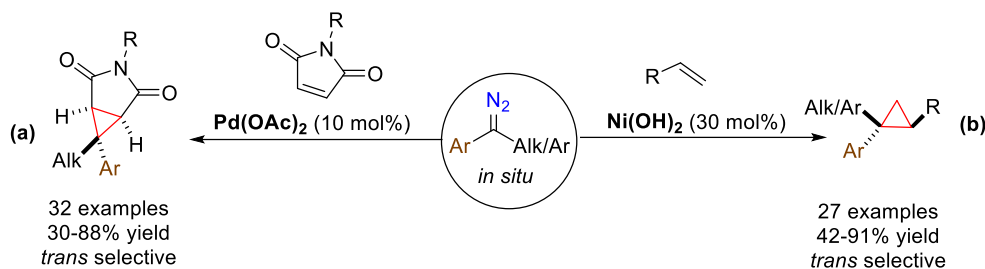
¹²⁰ Z. Liu, X. Zhang, G. Zanoni, X. Bi, *Org. Lett.* **2017**, *19*, 6646–6649.

¹²¹ P. Chen, C. Zhu, R. Zhu, Z. Lin, W. Wu, H. Jiang, *Org. Biomol. Chem.* **2017**, *15*, 1228–1235.

¹²² H. Jiang, W. Fu, H. Chen, *Chem. Eur. J.* **2012**, *18*, 11884–11888.

¹²³ H. Liu, Y. Wei, C. Cai, *New J. Chem.* **2016**, *40*, 674–678.

mild protocol was applied to a large scope of aryl alkenes with various substituents, aliphatic alkenes bearing halogens and alkyl acrylates.



Scheme 25. Cyclopropanation reactions of donor-donor diazo compounds catalyzed by metal Pd(II) or Ni(II).

While significant progresses have been achieved in harnessing diverse types of diazo reagents, the advancement of asymmetric cyclopropanation using donor-substituted diazo reagents remains relatively limited. Aggarwal¹²⁴ and Charette¹²⁵ have independently succeed introducing donor type diazo compound in construction of optical active cyclopropanes, but neither of their approaches involved a metal stereogenic center pathway. Until 2017, Zhang *et al.* introduced the first chiral Cobalt radical complex-catalyzed α -aryldiazomethane decomposition for cyclopropanation with alkenes. This method is applicable to a wide range of alkenes, resulting in high yields and relative stereoisomer ratios. Notably, only highly sterically hindered α -aryldiazomethanes led to excellent enantioselectivities (Scheme 26a).¹²⁶

Furthermore, the asymmetric cyclopropanation strategy mentioned above has proven to be an effective process for synthesizing enantiomer-enriched cyclopropyl amino acid homologs.¹²⁷ As shown in the selected examples below (Scheme 26b), they tested several diazo substrates with lower barriers, and both diastereoselectivity and enantioselectivity dropped dramatically. These results validate the hypothesis put forth in previous work.

Moreover, a new generation of Co(II)-complex (Co(2,6-DiPhO-Hu(C6)Phyrin)) was explored by Zhang and coworkers.¹²⁸ This bridged *D*₂-symmetric complex was demonstrated to serve as a

¹²⁴ V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem. Int. Ed.* **2001**, *40*, 1433–1436.

¹²⁵ S. R. Goudreau, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131*, 15633–15635.

¹²⁶ Y. Wang, X. Wen, X. Cui, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2017**, *139*, 1049–1052.

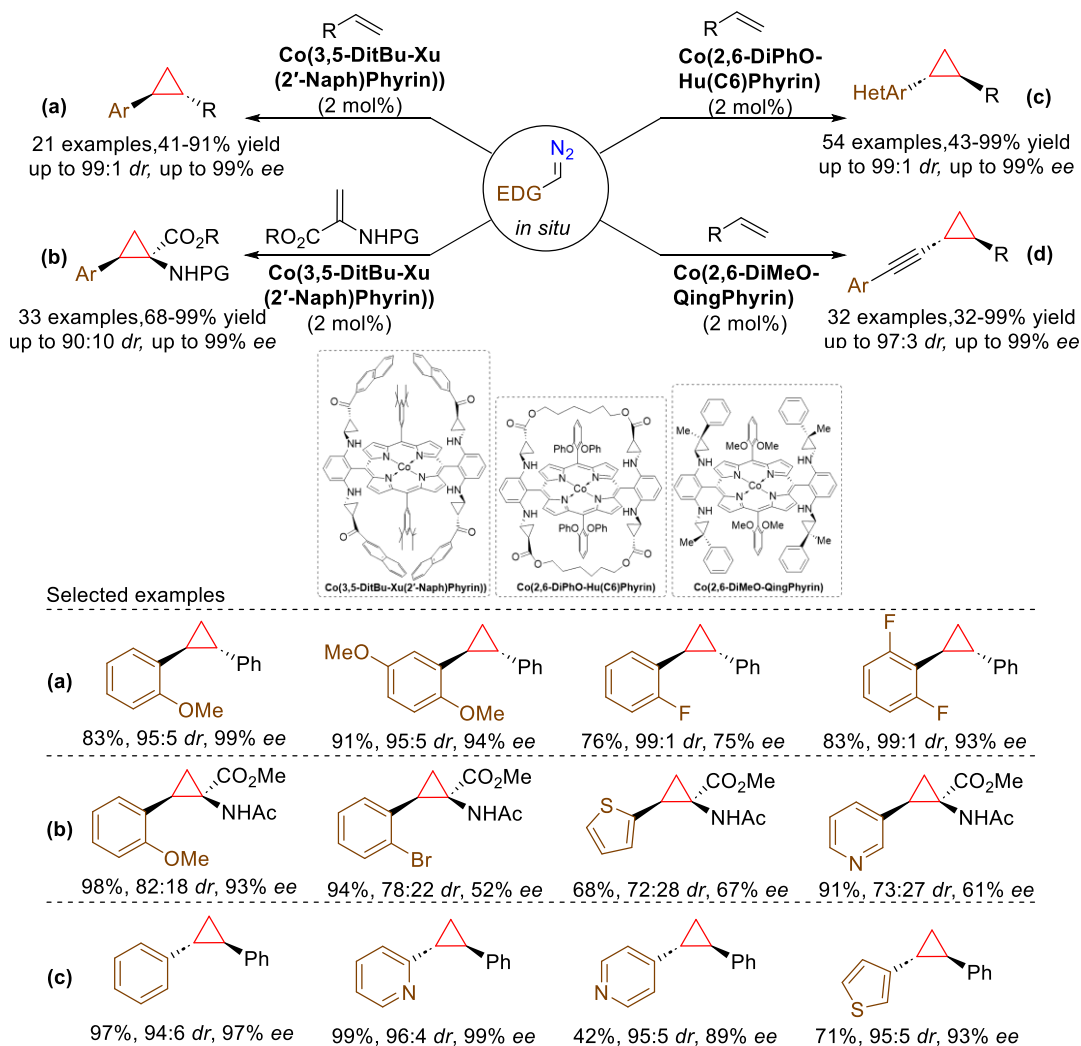
¹²⁷ W.-C. C. Lee, D.-S. Wang, C. Zhang, J. Xie, B. Li, X. P. Zhang, *Chem* **2021**, *7*, 1588–1601.

¹²⁸ X. Wang, J. Ke, Y. Zhu, A. Deb, Y. Xu, X. P. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 11121–11129.

remarkable effective chiral catalyst in activating various types of heteroaryldiazomethanes as well as aryldiazomethanes. This versatile approach for the stereoselective synthesis of chiral heteroaryl cyclopropanes with outstanding yields, diastereoselectivities and enantioselectivities, showcases an exceptionally wide range of applicability across diverse alkenes, including several challenging substrates (Scheme 26c).

More recently, Zhang and his colleagues have pioneered the development of the first asymmetric catalytic system allowing the use of *in situ* generated α -alkynyldiazomethanes for the direct cyclopropanation of alkenes through Co(III)-based metalloradical catalysis.¹²⁹ The use of Co(2,6-DiMeO-QingPhyrin) catalyst facilitates the cyclopropanation process of different alkynyldiazomethanes with diverse alkenes possessing varied electronic and steric properties (Scheme 26d).

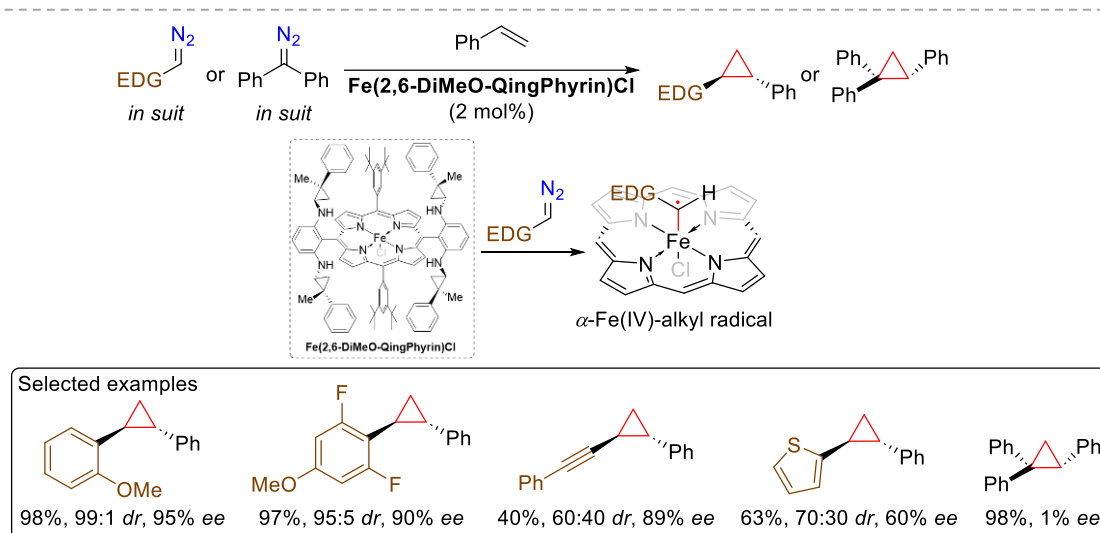
¹²⁹ J. Ke, W.-C. C. Lee, X. Wang, Y. Wang, X. Wen, X. P. Zhang, *J. Am. Chem. Soc.* **2022**, *144*, 2368–2378.



Scheme 26. Chiral Co(II)-complexes catalyzed donor-substitute diazo reagents cyclopropanations.

Exceptionally, Zhang and his team have focused on developing iron-based chiral catalysts for the decomposition of diazo compounds, leading to the production of enantiomerically pure cyclopropanes. In a recent breakthrough, they conducted systematic studies on five-coordinate Fe(III) complexes of porphyrins with an axial ligand.¹³⁰ These complexes act as potent metalloradical catalysts, enabling olefin cyclopropanation through a stepwise radical mechanism. This versatile protocol was applied to a broad range of diazo compounds, including both H-donor and donor-donor diazo compounds. Notably, diazo reagents with donor substituents yielded products with medium to excellent stereoselectivity, although diphenyldiazomethane led to the racemate (Scheme 27).

¹³⁰ W.-C. C. Lee, D.-S. Wang, Y. Zhu, X. P. Zhang, *Nat. Chem.* **2023**, *15*, 1569–1580.



Scheme 27. Chiral Fe(III)-complex catalyzed donor-substitute diazo compounds cyclopropanation.

1.3. General introduction on transition metal-catalyzed C–H bond activation on cyclopropanes

During the past decades, transition metal-catalyzed functionalization of carbon–hydrogen [C(sp³)–H, C(sp²)–H, and C(sp)–H] bonds has become an essential and straightforward strategy in organic chemistry.¹³¹ In recent years, it has become increasingly evident that the direct formation of carbon–carbon and carbon–heteroatom bonds from unactivated C–H bonds via C–H bond activation has tremendous potential for advancing the field of medicinal compounds¹³² or natural products¹³³

¹³¹ a) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169. b) K. M. Engle, T.–S. Mei, M. Wasa, J.–Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788–802. c) A. R. Dick, M. S. Sanford, *Tetrahedron* **2006**, *62*, 2439–2463. d) T. A. Ramirez, B. Zhao, Y. Shi, *Chem. Soc. Rev.* **2012**, *41*, 931–942. e) Z. Huang, H. N. Lim, F. Mo, M.–C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764–7786. f) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009. g) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375. h) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. S. Vachal, W. Krska, *Chem. Soc. Rev.* **2016**, *45*, 546–576. i) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155–1171. g) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254. h) D. Wang, A. B. Weinstein, P. B. White, S. S. Stahl, *Chem. Rev.* **2018**, *118*, 2636–2679. i) T. Rogge, N. Kaplaneris, N. Chatani, J. Kim, S. Chang, B. Punji, L. L. Schafer, D. G. Musaev, J. Wencel-Delord, C. A. Roberts, *Nat. Rev. Methods Primers* **2021**, *1*, 43.

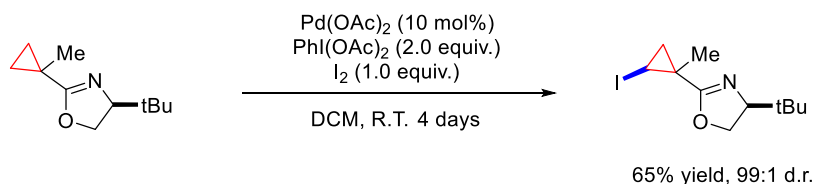
¹³² a) D. Basu, S. Kumar, S. S. V, R. Bandichhor, *J. Chem. Sci.* **2018**, *130*, 1–11. b) R. Jana, H. M. Begam, E. Dinda, *Chem. Commun.* **2021**, *57*, 10842–10866.

¹³³ a) S. K. Sinha, G. Zanoni, D. Maiti, *Asian J. Org. Chem.* **2018**, *7*, 1178–1192. b) S. K. Sinha, P. Ghosh, S. Jain, S. Maiti, S. A. Al–Thabati, A. A. Alshehri, M. Mokhtar, D. Maiti, *Chem. Soc. Rev.* **2023**, *52*, 7461–7503.

synthesis. However, despite all the advances made in the field, the direct functionalization of C(sp³) centers remain a key challenge.¹³⁴ Recently, the palladium catalyzed C–H bond functionalization of cyclopropanes appeared as an efficient method.¹³⁵ In order to promote such transformations, different types of directing groups¹³⁶ have been developed for the transition metal-catalyzed C–H bond activation processes in cyclopropane scaffolds.

1.3.1. Monodentate directing groups

In 2005, the first example of transition metal-catalyzed cyclopropane C–H bond functionalization was reported by Yu's group.¹³⁷ An oxazoline auxiliary was used for the iodination of secondary C(sp³)–H bond, affording the corresponding iodinated cyclopropane products (Scheme 28).



Scheme 28. Oxazoline directed iodination on cyclopropane.

Three years later, Yu's group described a Pd-catalyzed alkylation of cyclopropanes bearing an *O*-methyl hydroxamic acid as a directing group with aliphatic boronic acids.¹³⁸ Phenethyl and *iso*-butyl boronic acids were employed as coupling partners providing the expected compounds in 58% yield and 72% yield, respectively. It is necessary to use 2,2,5,5-tetramethyltetrahydrofuran as solvent which serves as a sterically bulky ligand to prevent homocoupling of the boronic acid as

¹³⁴ a) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X. F. Wu, *ACS Catal.* **2014**, *4*, 2977–2989. b) X. Yang, G. Shan, L. Wang, Y. Rao, *Tetrahedron Lett.* **2016**, *57*, 819–836. c) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911. d) R. Giri, B.–F. Shi, K. M. Engle, N. Mangel, J.–Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. e) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.

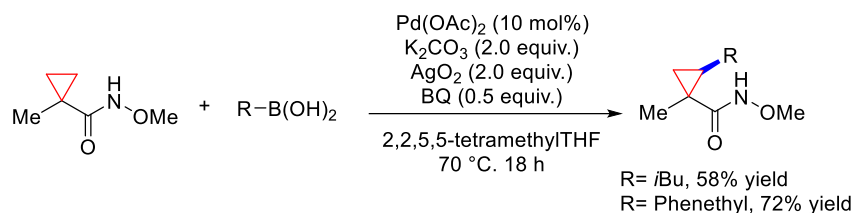
¹³⁵ a) R. D. Sustac, A. B. Charette, In P. Dixneuf, H. Doucet, (eds) *C–H Bond Activation and Catalytic Functionalization II* **2015**, 91–113. b) A. L. Gabbey, K. Scotchburn, S. A. L. Rousseaux, *Nat. Rev. Chem.* **2023**, *7*, 548–560. c) B. Liu, A. M. Romine, C. Z. Rubel, K. M. Engle, B.–F. Shi, *Chem. Rev.* **2021**, *121*, 14957–15074.

¹³⁶ a) S. Rej, A. Das, N. Chatani, *Coord. Chem. Rev.* **2021**, *431*, 213683. b) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107–1295. c) M. J. Wu, J. H. Chu, *J. Chin. Chem. Soc.* **2020**, *67*, 399–421. d) K. Wang, F. Hu, Y. Zhang, J. Wang, *Sci. Chin. Chem.* **2015**, *58*, 1252–1265.

¹³⁷ R. Giri, X. Chen, J.–Q. Yu, *Angew. Chem. Int. Ed.* **2005**, *44*, 2112–2115.

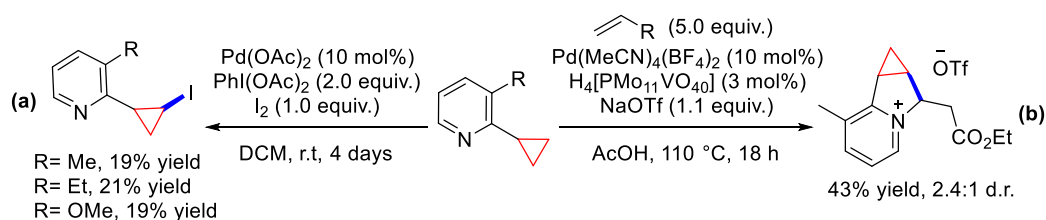
¹³⁸ D. Wang, M. Wasa, R. Giri, J.–Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.

well as β -hydride elimination (Scheme 29).



Scheme 29. *O*-methyl hydroxamic acid directed functionalization on cyclopropanes.

Pyridine was also employed as a directing group towards a palladium catalytic C–H bond activation strategy by Sanford and co-workers in 2011.¹³⁹ The iodination reaction took place with various substituted pyridines leading to the expected products in low yields, even if the reactions were performed for longer reaction time (Scheme 30a). Then, they described the use of ethyl acrylate as coupling partner in a C–H activation process catalyzed by $\text{Pd}[\text{MeCN}]_2\text{BF}_4$. In this case, a cyclized pyridinium salt was obtained in moderate yield and diastereoisomeric ratio (Scheme 30b).¹⁴⁰



Scheme 30. Pyridine directed functionalization on cyclopropanes.

Notably, electronic deficient amides turned out to be very efficient as directing groups for the Pd-catalyzed functionalization of cyclopropanes by C–H bond activation. Since 2010 Yu *et al.* disclosed the first use of pentafluorophenyl amide as a directing group in an olefination reaction and the corresponding product underwent a 1,4-conjugate addition to deliver the corresponding lactam derivative (Scheme 31).¹⁴¹ A large number of electronic deficient amides as directing groups have been reported in the literature regarding cyclopropanes C–H bond activation such as *para*-cyanotetrafluorophenyl amide,¹⁴² tetrafluoro-4-(trifluoromethyl)phenyl amide¹⁴³ and *ortho*-

¹³⁹ A. Kubota, M. S. Sanford, *Synthesis* **2011**, 2579–2589.

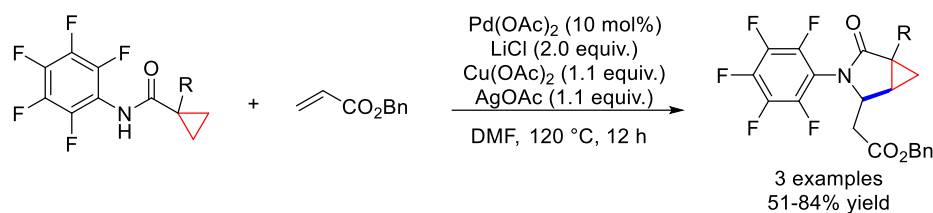
¹⁴⁰ K. J. Stowers, K. C. Fortner, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 6541–6544.

¹⁴¹ M. Wasa, K. M. Engle, J.–Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681.

¹⁴² M. Wasa, K. M. Engle, D.–W. Lin, E.–J. Yoo, J.–Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 19598–19601.

¹⁴³ a) E.–J. Yoo, M. Wasa, J.–Q. Yu, *J. Am. Chem. Soc.* **2010**, *132*, 17378–17380. b) M. Wasa, K.–S. Chan, X.–G.

sulfinylphenyl amide.¹⁴⁴



Scheme 31. Aromatic amide directed functionalization on cyclopropanes.

It is interesting to note that in the presence of a chiral ligand in the cyclopropanation process, chiral cyclopropanes are obtained. For example, cyclopropanes C–H bond activation followed by an intramolecular cyclization reaction was mainly investigated by the groups of Cramer,¹⁴⁵ and Charette.¹⁴⁶ *N*-protected anilines and amides with a halide in an *ortho* position were used as directing groups. The six-membered functionalization products were generated *via* a seven-membered palladacycle intermediate. (Scheme 32).

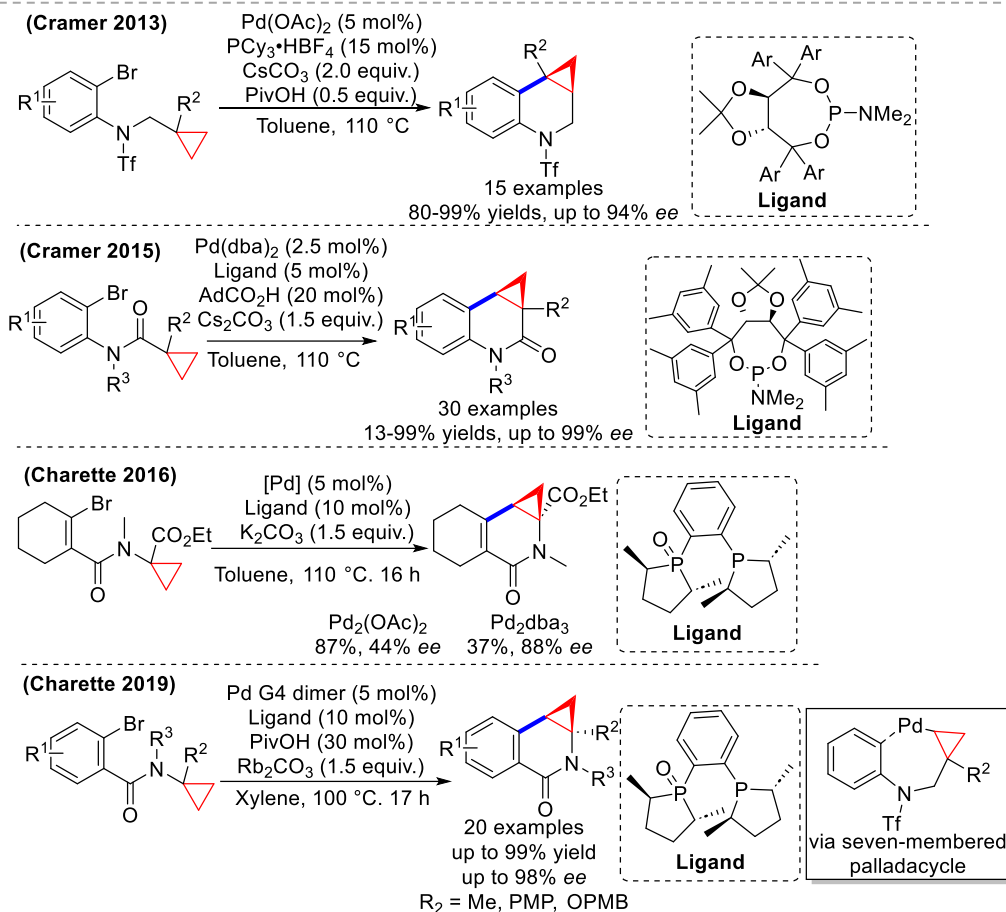
Zhang, J. He, M. Miura, J.-Q. Yu, *J. Am. Chem. Soc.* **2012**, *134*, 18570–18572. c) J. He, S. Li, Y. Deng, H. Fu, B. N. Laforteza, J. E. Spangler, A. Homs, J.-Q. Yu, *Science* **2014**, *343*, 1216–1220. d) J. He, H. Jiang, R. Takise, R.-Y. Zhu, G. Chen, H.-X. Dai, T. G. Dhar, J. Shi, H. Zhang, P. T. Cheng, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 785–789.

¹⁴⁴ a) S. Jerhaoui, F. Chahdoura, C. Rose, J. P. Djukic, J. Wencel-Delord, F. Colobert, *Chem. Eur. J.* **2016**, *22*, 17397–17406. b) R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238–3241.

¹⁴⁵ a) T. Saget, D. Perez, N. Cramer, *Org. Lett.* **2013**, *15*, 1354–1357. b) J. Pedroni, T. Saget, P. A. Donets, N. Cramer, *Chem. Sci.* **2015**, *6*, 5164–5171.

¹⁴⁶ a) C. L. Ladd, A. B. Charette, *Org. Lett.* **2016**, *18*, 6046–6049. b) C. Mayer, C. L. Ladd, A. B. Charette, *Org. Lett.* **2019**, *21*, 2639–2644.

Chapter I – Introduction

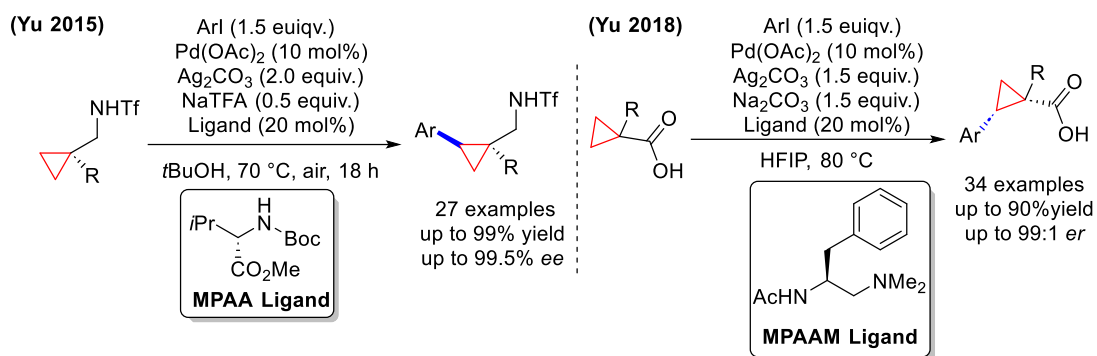


Scheme 32. *N*-protected anilines and amides directed functionalization on cyclopropanes.

Aliphatic amines and carboxylic acids can act as directing groups for cyclopropanes C–H bond activation protocols as established by Yu and co-workers. In 2015, they reported a Pd(II)-catalyzed highly enantioselective arylation of cyclopropyl C–H bonds with aryl iodides, assisted by mono-*N*-protected amino acid (MPAA) ligands.¹⁴⁷ This approach provided a new route for the synthesis of chiral *cis*-aryl-cyclopropyl methylamines. After that, in 2018, a Pd-catalyzed enantioselective C(sp³)-H arylation of cyclopropylcarboxylic and 2-amino *iso*-butyric acids without using exogenous directing groups was disclosed.¹⁴⁸ The presence of monoprotected aminoethyl amine chiral ligand based on an ethylenediamine backbone (MPAAM) led to enantiomerically pure carboxylic acids (Scheme 33).

¹⁴⁷ K.-S. Chan, H.-Y. Fu, J.-Q. Yu, *J. Am. Chem. Soc.* **2015**, *137*, 2042–2046.

¹⁴⁸ P.-X. Shen, L. Hu, Q. Shao, K. Hong, J.-Q. Yu, *J. Am. Chem. Soc.* **2018**, *140*, 6545–6549.

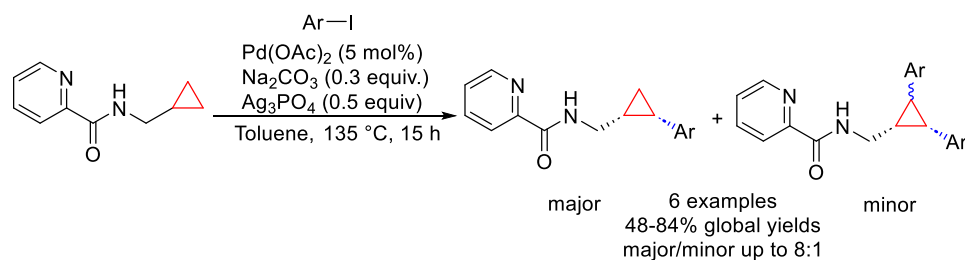


Scheme 33. Amine and acid directed functionalization on cyclopropanes.

1.3.2. Bidentate directing groups

The bidentate directing groups are one of the most efficient auxiliary for the selective C–H bond functionalization of certain positions among numerous directing group strategies.¹⁴⁹ Since 2005, Daugulis reported the arylation of unactivated C(sp³)–H bonds by using the amide derived from 8-aminoquinoline and picolinamide as bidentate directing groups, with Pd(OAc)₂ as the catalyst.¹⁵⁰ There are a number of transformations of C–H bonds which have been developed by using of bidentate directing groups.¹⁵¹

In 2013, Charette and co-workers reported the first palladium catalyzed cyclopropane C–H bond functionalization with the picolinamide directing group.¹⁵² A series of exclusive *cis* arylated cyclopropane products were obtained in moderate to good yields. (Scheme 34).



Scheme 34. Picolinamide directed functionalization on cyclopropanes.

Another directing group, the 2-(pyridin-2-yl)propane-2-yl (PIP) amide was exploited by Shi and co-

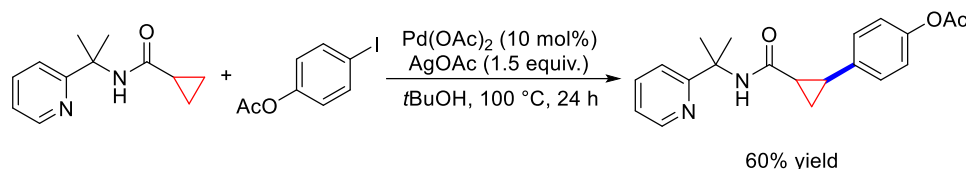
¹⁴⁹ a) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788–1887. a) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743. c) H. Tang, X.–R. Huang, J. Yao, H. Chen, *J. Org. Chem.* **2015**, *80*, 4672–4682.

¹⁵⁰ O. Daugulis, V. G. Zaitsev, *Angew. Chem. Int. Ed.* **2005**, *44*, 4046–4048.

¹⁵¹ O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053–1064.

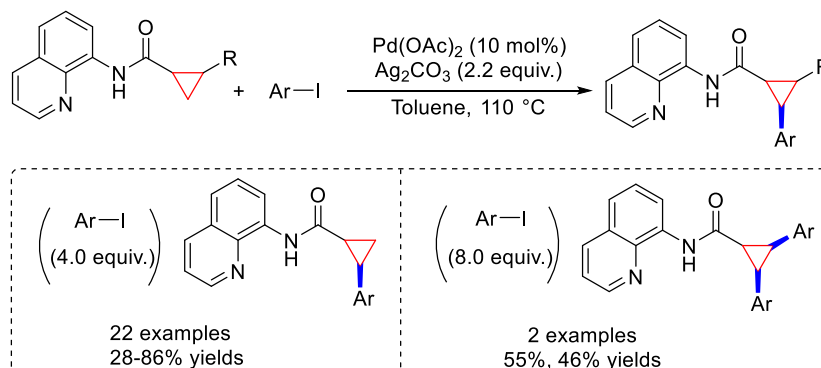
¹⁵² D. S. Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 4394–4397.

workers in 2014.¹⁵³ This Pd(II)-catalyzed arylation of methylene C(sp³)-H bonds activation directed by newly developed PIP directing group following with aryl iodides/bromides enabled to construct C(sp³)-C(sp²) bond with high efficiency. Nevertheless, only one example in the cyclopropane series was presented in 60% yield (Scheme 35).



Scheme 35. PIP directed functionalization on cyclopropanes.

Another study was conducted by Babu, reported that the amide derived from 8-aminoquinoline could be used as a directing group for C-H bond activation with cyclopropanes.¹⁵⁴ Depending on the number of equivalents of iodoarenes, mono- or di-substituted products were obtained using 10 mol% Pd(OAc)₂ as the catalyst (Scheme 36). Because of its high efficiency, the amide derived from 8-aminoquinoline was largely used for the functionalization of cyclopropanes through C-H bond activation.¹⁵⁵



Scheme 36. 8-aminoquinoline amide directed functionalization on cyclopropanes.

The group of Yu reported a very elegant work about the use of bidentate directing group for palladium catalyzed C-H arylation of cyclopropanes in 2014.¹⁵⁶ In this work, they disclosed a site-selective functionalization of C(sp³)-H bonds in cyclopropyl peptides at the *N*-terminal part. Di-

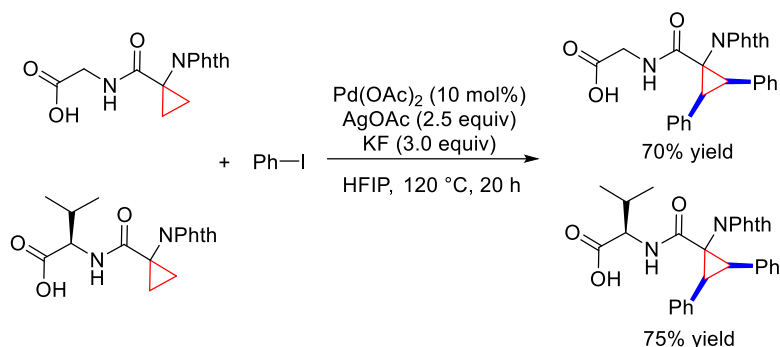
¹⁵³ Q. Zhang, X.-S. Yin, S. Zhao, S.-L. Fang, B.-F. Shi, *Chem. Commun.* **2014**, 50, 8353–8355.

¹⁵⁴ R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, 15, 3238–3241.

¹⁵⁵ M. Corbet, F. De Campo, *Angew. Chem. Int. Ed.* **2013**, 52, 9896–9898.

¹⁵⁶ W. Gong, G. Zhang, T. Liu, R. Giri, J. Q. Yu, *J. Am. Chem. Soc.* **2014**, 136, 16940–16946.

tri-, and tetra-peptides have been arylated with a broad range of arylating reagents to provide cyclopropyl peptides with modified phenylalanine residues (Scheme 37).

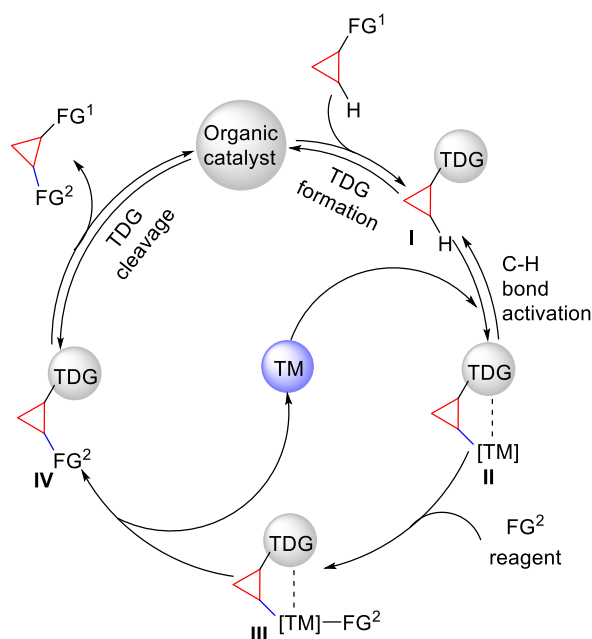


Scheme 37. Amino acids directed functionalization on cyclopropanes.

1.3.3. Transient directing groups

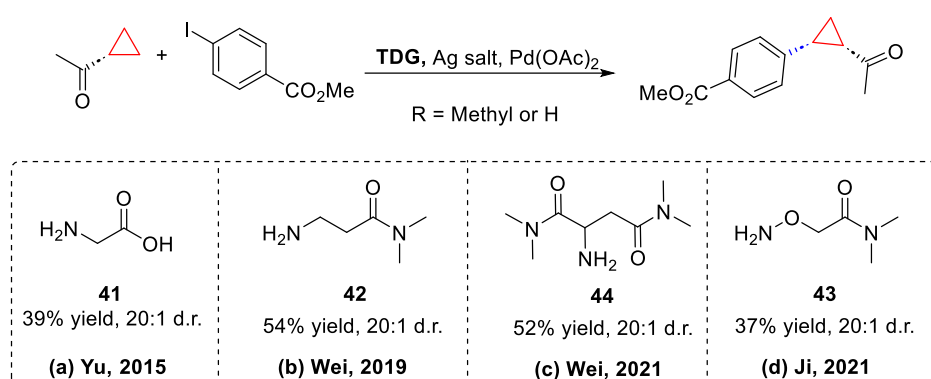
The pre-installed directing groups used in C–H bond activation needs several steps for the introduction and its removal. In comparison to above referred mono- or bidentate directing groups, the transient directing group (TDG) has some disparities for synthetic applications. In a general concept,¹⁵⁷ an organic catalyst react with the substrate to generate a temporary and reversible transient directing group (species **I**). This latter will act as a monodentate or a bidentate directing group. This transient directing group will then coordinate the transition metal to form corresponding metallacycle (intermediate **II**). Afterward, the coupling partner interacted with the intermediate **II** to generate the downstream species **III**, along with the regeneration of transition metal catalyst, the intermediate **IV** was furnished. Finally, the desired product was produced with the cleavage of transient directing group and the regeneration of organic catalyst (Scheme 38).

¹⁵⁷ a) T. Besset, Zhao, Q. T. Poisson, X. Pannecoucke, *Synthesis* **2017**, *49*, 4808–4826. b) P. Gandeepan, L. Ackermann, *Chem* **2018**, *4*, 199–222. c) M. I. Lapuh, S. Mazeh, T. Besset, *ACS Catal.* **2020**, *10*, 12898–12919.



Scheme 38. Mechanism of transient directing group engaged palladium catalyzed functionalization on cyclopropane.

The first application of TDG for cyclopropane C–H bond activation was reported by Yu and co-workers in 2015.¹⁵⁸ They developed the use of a catalytic amount of glycine, which reversibly *in situ* reacts with aldehydes and ketones *via* imine formation to serve as a TDG for activation of inert C–H bonds in the presence of a palladium catalyst. Subsequently, this TDG assisted cyclopropane C–H bond activation approach was further explored with diverse amino acids by Wei¹⁵⁹ and Ji¹⁶⁰ (Scheme 39).



Scheme 39. Transient directing groups involved functionalization on cyclopropanes.

¹⁵⁸ F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, *Science* **2016**, *351*, 252–256.

¹⁵⁹ a) C. Dong, L. Wu, J. Yao, K. Wei, *Org. Lett.* **2019**, *21*, 2085–2089. b) L.-F. Wu, J.-W. Yao, X. Zhang, S.-Y. Liu, Z.-N. Zhuang, K. Wei, *Org. Lett.* **2021**, *23*, 6237–6241.

¹⁶⁰ Y. Wang, G. Wu, X. Xu, B. Pang, S. Liao, Y. Ji, *J. Org. Chem.* **2021**, *86*, 7296–7303.

1.4. Conclusion

The cyclopropane moiety is of significant importance not only because it is widespread in natural products but also due to its unique chemical characteristics. This has fueled the enthusiasm of chemists to synthesize cyclopropanes with diverse substituents. As discussed in the earlier part of this chapter, the strategy of using diazo compounds with various electron-influence groups as carbene precursors, with transition metals as catalysts, to generate a wide array of cyclopropane derivatives by reacting with alkenes, has garnered significant attention over the past decades.

However, challenges persist in the field of metallocarbene [2+1] annulation reactions with olefins. For example, fluorinated cyclopropyl molecules possess unique properties, and there is a high demand for the synthesis of their variants, especially through enantioenriched procedures. Furthermore, when it comes to the cyclopropanation of donor-substituted diazo compounds, only cobalt or iron complexes chelated with complex chiral ligands have exhibited enantiocontrol ability. These multi-step accessible complexes, while effective, are not cost-effective, albeit the use of non-noble metals as catalysts remains an area of interest.

The unique nature of the cyclopropane ring is evident in the varying C–H bond dissociation energy it exhibits, differing from typical C(sp³)–H and C(sp²)–H bond. As a result, the C–H bonds in cyclopropane can be considered to possess both C(sp³)–H and C(sp²)–H characteristics. This intriguing feature has drawn the attention of many research groups toward the functionalization of cyclopropane C–H bond.

In the second part of this chapter, we discussed how various directing groups have been explored to facilitate the functionalization of cyclopropane skeletons when catalyzed by palladium. However, it is important to note that, to the best of our knowledge, there have been no discoveries of functionalizing fluorinated cyclopropanes, whether in enantiomerically pure or racemic forms.

Hence, based on these fundamental insights and encouraged by previous outcomes from our research group, the central focus of the current thesis is the development of a novel methodology for achieving highly stereocontrolled fluorinated cyclopropanes using ruthenium complexes as catalysts. Additionally, we aim to explore the decomposition of donor-substituted diazo compounds

Chapter I – Introduction

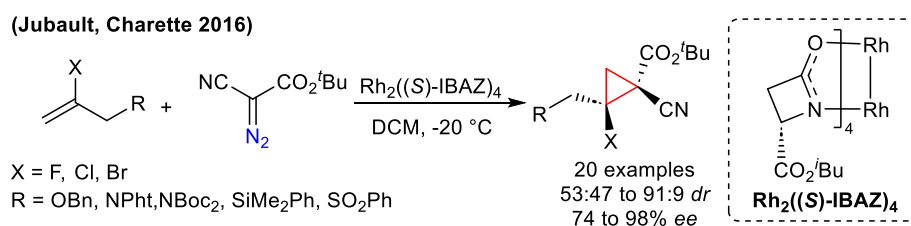
to construct highly diastereo- and enantio-selective cyclopropanes through the use of dirhodium complexes. Simultaneously, we have accomplished a project focused on the palladium-catalyzed functionalization of C–H bond in fluorinated cyclopropanes.

Chapter II – Experimental and computational studies for the catalytic enantioselective synthesis of functionalized cyclopropanes from α -substituted allylic derivatives with ethyl diazoacetate

2.1. State of the art

In the previous chapter, we illustrated the importance of the cyclopropane moiety in natural products and pharmaceutical compounds, as well as the versatility of methods involving metallic carbenes generated from diazo reagents for the synthesis of cyclopropanes. Furthermore, the cyclopropanes, which combine α -allyl functionalized compounds with mono-acceptor diazo derivatives in an asymmetric cyclopropanation process, offer a unique opportunity to access chiral cyclopropanes with two possible post-functionalization sites. As a consequence, enantiopure functionalized cyclopropanes are highly demanded in the field of synthesis chemistry. However, in contrast to the numerous existing methods for styrene derivatives, phenyl vinyl sulfides, and phenyl vinyl ethers, there are only a few pioneering methodologies documented for the asymmetric catalytic synthesis of functionalized cyclopropanic frameworks from 2-allyl functionalized compounds.

As part of our research program, our group has successfully developed two protocols for the catalytic asymmetric synthesis of functionalized cyclopropanes using Rh(II)-complexes to decompose diazo compounds. In 2016, we introduced the first protocol,¹⁶¹ which involved the catalytic enantioselective synthesis of halocyclopropanes from haloalkenes and *tert*-butyl α -cyano- α -diazoacetate, leading to the corresponding functionalized cyclopropanes with good yields, moderate diastereoselectivity, and excellent enantiomeric ratios. This methodology was applied to a wide range of allylic substrates bearing a halogen atom at α position of alkene (Scheme 2. 1).



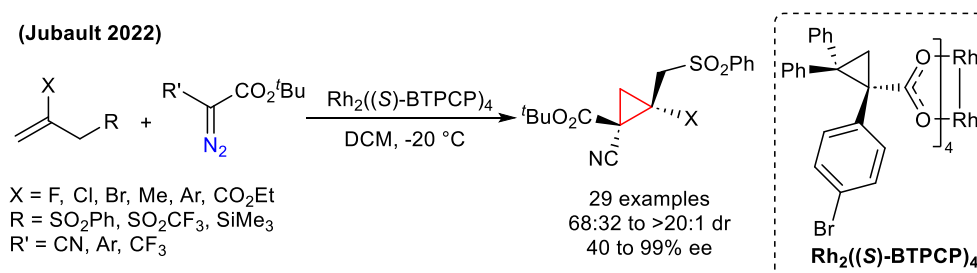
Scheme 2. 1. Rh₂((S)-IBAZ)₄-catalyzed α -haloalkenes asymmetric cyclopropanation.

The second approach depicted by our group on the catalytic enantioselective cyclopropanation of allylic derivatives using Rh(II) chiral catalysts has been recently reported.⁷⁰ The combination of

¹⁶¹ A. Pons, P. Ivashkin, T. Poisson, A. B. Charette, X. Pannecoucke, P. Jubault, *Chem. Eur. J.* **2016**, *22*, 6239–6242.

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$\text{Rh}_2((S)\text{-BTPCP})_4$ and α -substituted allylic substrates, such as allylic sulfones or allylic silanes, in the cyclopropanation process led to the chiral cyclopropanes with moderate to excellent diastereo- and enantio-selectivities. It is worth noting that the metallic carbene precursors can be generated not only from donor-acceptor diazo reagents but also from acceptor-acceptor diazo reagents (Scheme 2. 2).



Scheme 2. 2. $\text{Rh}_2((S)\text{-BTPCP})_4$ and α -substituted allylic substrates in asymmetric cyclopropanation.

Ru(II)-complexes catalyzed asymmetric cyclopropanation strategies of allylic substrates have emerged along with Rh(II)-catalysis methodologies were reported. In 1995, Nishiyama documented a seminal intramolecular cyclopropanation of cinnamyl diazoacetate by mediate of Phebox-Ru(II),¹⁶² resulting in the formation of the bicyclic adduct with high yield and 99% *ee* (Scheme 2. 3a).

In 2019, Mendoza and coworkers disclosed the use of a new mono-acceptor diazo compound with alkenes in asymmetric cyclopropanation to give a large number of enantiopure cyclopropane derivatives using Ru(II)-Pheox complex.¹⁶³ The allylic and cyclic alkene substrates have been beardedly scoped and exhibited great tolerance with this protocol (Scheme 2. 3b).

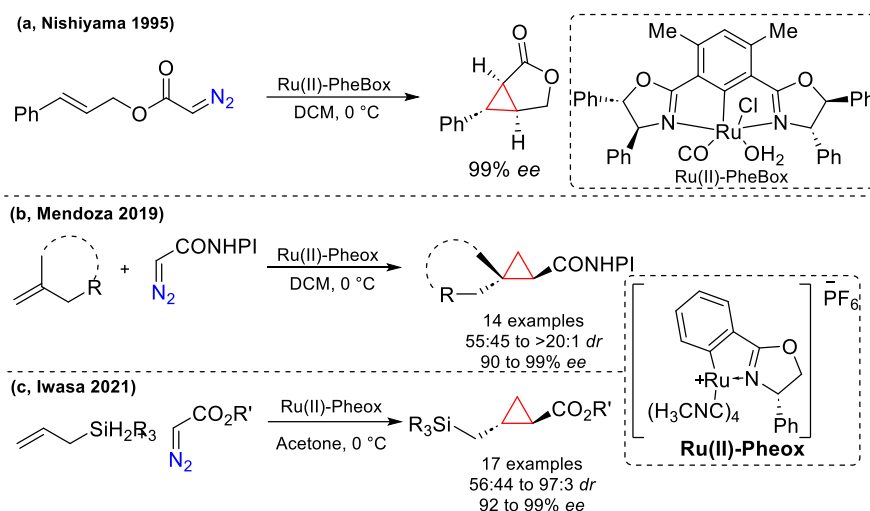
Two years later, using the same Ru(II)-complex, Iwasa reported the first general catalytic enantioselective cyclopropanation of allyl silanes, mostly non-substituted ones, with methyl (diazoacetoxy)acetate giving the expected cyclopropanes in high yields, good *dr* and excellent *ee* (Scheme 2. 3c).¹⁶⁴

¹⁶² a) J. i. Ito, S. Ujiie, H. Nishiyama, *Chem. Eur. J.* **2010**, *16*, 4986–4990. b) S.–B. Park, K. Murata, H. Matsumoto, H. Nishiyama, *Tetrahedron: Asymmetry* **1995**, *6*, 2487–2494.

¹⁶³ M. Montesinos-Magraner, M. Costantini, R. Ramírez-Contreras, M. E. Muratore, M. J. Johansson, A. Mendoza, *Angew. Chem. Int. Ed.* **2019**, *58*, 5930–5935.

¹⁶⁴ N. Otog, H. Inoue, D. T. T. Trinh, Z. Batgerel, N. M. Langendorf, I. Fujisawa, S. Iwasa, *ChemCatChem* **2021**, *13*, 328–337.

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Scheme 2. 3. Ru(II)-Pheox catalyzed allylic substrates asymmetric cyclopropanation.

Ethyl diazo acetate (EDA), an easily accessible diazo reagent commercially available, is known for its safety and relative stability. It has been widely used in asymmetric cyclopropanation with the aid of various chiral metallic catalysts, including Ru,¹⁶⁵ Cu,¹⁶⁶ Fe,¹⁶⁷ Co¹⁶⁸ and Rh.¹⁶⁹ Typically, styrene derivatives are used as the alkene partner to achieve good reactivity and stereoselectivity (Scheme 2. 4). Notably, biocatalytic approaches in the presence of EDA for enantioselective [2+1]

¹⁶⁵ a) I. J. Munslow, K. M. Gillespie, R. J. Deeth, P. Scott, *Chem. Commun.* **2001**, 1638–1639. b) K. H. Chan, X. Guan, V. K. Y. Lo, C. M. Che, *Angew. Chem. Int. Ed.* **2014**, *126*, 3026–3031. c) S. Chanthamath, S. Iwasa, *Acc. Chem. Res.* **2016**, *49*, 2080–2090. d) Y. Nakagawa, Y. Imokawa, I. Fujisawa, N. Nakayama, H. Goto, S. Chanthamath, K. Shibatomi, S. Iwasa, *ACS omega* **2018**, *3*, 11286–11289. e) Y. Nakagawa, N. Nakayama, H. Goto, I. Fujisawa, S. Chanthamath, K. Shibatomi, S. Iwasa, *Chirality* **2019**, *31*, 561.

¹⁶⁶ a) J. M. Brunel, O. Legrand, S. Reymond, G. Buono, *J. Am. Chem. Soc.* **1999**, *121*, 5807–5808. b) O. G. Meyer, R. Fröhlich, G. Haufe, *Synthesis* **2000**, *2000*, 1479–1490.

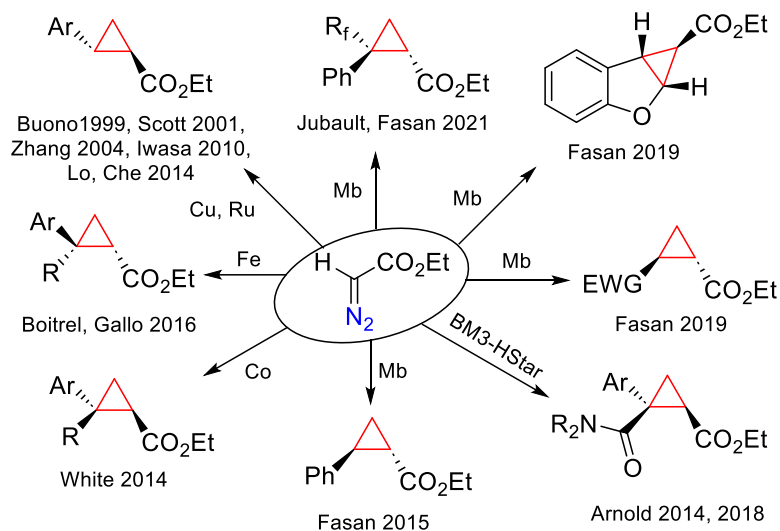
¹⁶⁷ D. M. Carminati, D. Intrieri, A. Caselli, S. Le Gac, B. Boitrel, L. Toma, L. Legnani, E. Gallo, *Chem. Eur. J.* **2016**, *22*, 13599–13612.

¹⁶⁸ a) Y. Chen, K. B. Fields, X. P. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 14718–14719. b) J. D. White, S. Shaw, *Org. Lett.* **2014**, *16*, 3880–3883. c) M. P. Doyle, W. R. Winchester, M. N. Protopopova, P. Müller, G. Bernardinelli, D. Ene, S. Motallebi, *Helv. Chim. Acta* **1993**, *76*, 2227–2235.

¹⁶⁹ a) M. P. Doyle, Q.-L. Zhou, S. H. Simonsen, V. Lynch, *Synlett* **1996**, *1996*, 697–698. b) M. Barberis, P. Lahuerta, J. Pérez-Prieto, M. Sanaú, *Chem. Commun.* **2001**, 439–440.

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cycloaddition reactions have been reported by Arnold¹⁷⁰ and Fasan¹⁷¹ since 2014. Interestingly, a boarder range of alkenes can serve as carbene acceptors, leading to the synthesis of versatile, high optically pure cyclopropane homologs (Scheme 2. 4).



Scheme 2. 4. Metallo- or bio- catalytic approaches lead EDA to asymmetric cyclopropanations.

2.2. Objective

Despite the various methods developed by our group^{70,161} and other chemists^{163,164} for asymmetric cyclopropanation of allylic substrates, as discussed above, there are still some challenges associated with these approaches. For instance:

- 1) As only acceptor-acceptor and donor-acceptor diazoalkanes have been demonstrated as effective carbene precursors to access cyclopropanes with good enantioselective control, the use of Rh(II)-complexes and α -halogeno or α -electron-withdrawing group (EWG)

¹⁷⁰ a) P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold, *Science* **2013**, 339, 307–310. b) P. S. Coelho, Z. J. Wang, M. E. Ener, S. A. Baril, A. Kannan, F. H. Arnold, E. M. Brustad, *Nature chemical biology* **2013**, 9, 485–487. c) A. M. Knight, S. J. Kan, R. D. Lewis, O. F. Brandenburg, K. Chen, F. H. Arnold, *ACS Central Science* **2018**, 4, 37377. d) O. F. Brandenburg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu, F. H. Arnold, *ACS Catal.* **2018**, 8, 2629–2634.

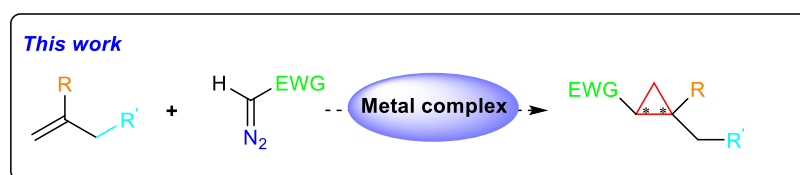
¹⁷¹ a) M. Bordeaux, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2015**, 127, 1764–1768. b) P. Bajaj, G. Sreenilayam, V. Tyagi, R. Fasan, *Angew. Chem. Int. Ed.* **2016**, 128, 16344–16348. c) D. A. Vargas, R. L. Khade, Y. Zhang, R. Fasan, *Angew. Chem. Int. Ed.* **2019**, 58, 10148–10152. d) D. M. Carminati, J. Decaens, S. Couve-Bonnaire, P. Jubault, R. Fasan, *Angew. Chem. Int. Ed.* **2021**, 133, 7148–7152. e) D. M. Carminati, R. Fasan, *ACS Catal.* **2019**, 9, 9683–9697.

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allylic substrates remain a synthetic challenge.

- 2) Although Ru(II)-Pheox has proved to be an excellent carbene transfer catalyst for mono-acceptor diazo reagents, the procedures have primarily focused on allylic silanes or aliphatic alkenes.

Therefore, in the chapter II, we conceived a novel straightforward strategy to furnish diverse cyclopropane derivatives in the presence of allylic compounds and a metal complex catalysis from mono-acceptor diazoalkanes (Scheme 2. 5).



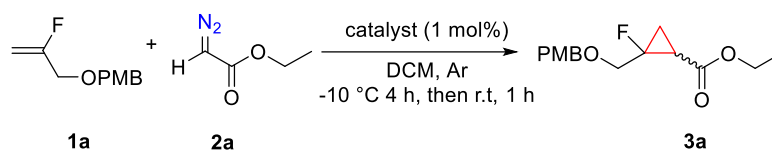
Scheme 2. 5. Objectives of the chapter II: Asymmetric cyclopropanation between mono-acceptor diazoalkanes and allylic derivatives.

2.3. Optimization study

At the outset of the project, we initially investigated the reaction between the α -fluoro-allylic substrate **1a** and the commercially available diazo reagent EDA (**2a**) in the presence of a metal catalyst (Table 2. 1). When Rh₂(OPiv)₄ was employed for this reaction, it exhibited good reactivity, allowing us to obtain the racemic product as flash column-separable diastereoisomers (entry 1). After, chiral Ru(II)(*S*)-Pheox catalysts I and II were screened and in the case of Ru(II)(*S*)-Pheox I, the expected cyclopropane **3a** was observed in modest conversion (32%) as a 1:1 mixture of diastereoisomers, albeit with high enantioselectivity for the *cis* and *trans* cyclopropane **3a** (entry 2). Using the Ru(II)(*S*)-Pheox II, a better enantioselectivity for each diastereoisomer was obtained (96% and 92%, respectively, entry 3) but with a lower conversion (13%). Furthermore, several copper catalysts with chiral bis(oxazolines) as ligands (entries 4-7) turned out to be detrimental to the reaction, as only traces of the expected cyclopropane **3a** were observed by ¹⁹F NMR when Cu(MeCN)₄PF₆ was used. Rhodium catalysts were tested for this reaction as well, such as Rh₂((*S*)-BTPCP)₄ (entry 8) and Rh₂((*S*)-TCPTTL)₄ (entry 9), and **3a** was obtained in good conversions (70-76%) but with poor enantiomeric excesses (<20%). Therefore, Ru(II)(*S*)-Pheox I was selected to

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pursue the optimization of the cyclopropanation process (Table 2. 2). Note that as fluorinated alkene **1a** is quite expensive¹⁷², an excess of EDA was used.



entry	catalysis	<i>trans</i>		<i>cis</i>	
		conv. (%) ^b	<i>ee</i> ^c	conv. (%) ^b	<i>ee</i> ^c
1	Rh ₂ (OPiv) ₄	47	0	39	0
2	Ru(II)(<i>S</i>)-Pheox I	14	92	18	94
3	Ru(II)(<i>S</i>)-Pheox II	6	96	7	94
4 ^d	CuI/ BOX	n.r	-	n.r	-
5 ^d	CuOAc/ BOX	n.r	-	n.r	-
6 ^d	Cu(MeCN) ₄ PF ₆ / BOX	trace	-	trace	-
7 ^d	Cu(OTf)(PhH)/ BOX	n.r	-	n.r	-
8	Rh ₂ ((<i>S</i>)-BTPCP) ₄	43	6	33	6
9	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	27	16	43	10

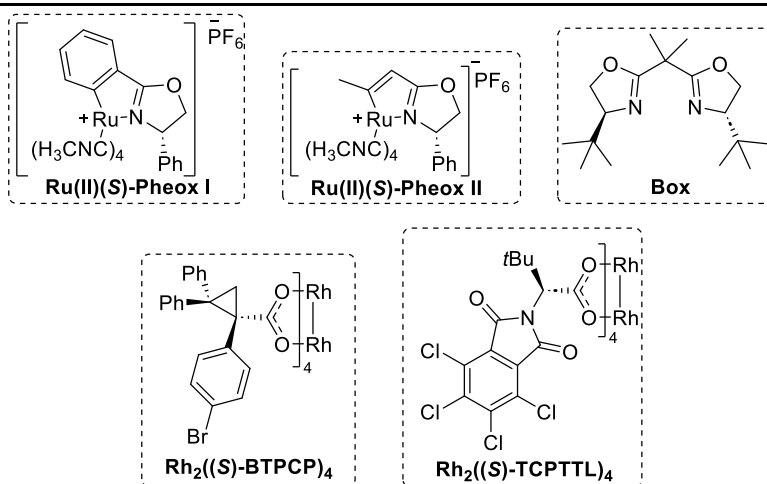
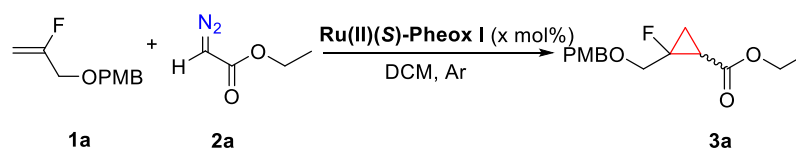


Table 2. 1. Optimization of metal catalysts. ^a To a mixture of olefin **1a** (1 mmol, 5 equiv.) and catalyst (1 mol%) in DCM (0.5 mL), was added dropwise EDA (0.2 mol, 1 equiv.) in 1 mL DCM over a period of 4 h. ^b Conversion was determined on the crude mixture by ¹⁹F NMR. ^c Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase. ^d 5 mol% Cu catalyst and 10 mol% Box ligand were employed. n.r = no reaction.

¹⁷² 165.4€/1g, Sigma–Aldrich. Dec. 31, 2023.

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Firstly, we examined the reaction temperature. The addition of EDA at -10°C over a period of 4 h delivered cyclopropane **3a** with low conversion (entry 1). Similar results were obtained when the addition time was increased (entry 2) or when the temperature was decreased to -20°C (entry 3). When the reaction was carried out using 3 equiv. of EDA at 0°C with a 4 h addition, we observed a good conversion (73%) into **3a** (entry 4) but with a slight decrease in enantioselectivity for both diastereoisomers. To ensure complete conversion of **1a** into **3a**, we tested the addition of EDA (5 equiv.) for a longer time (6.7 h), resulting in **3a** being isolated in 93% yield (entry 6). These optimized reaction conditions produced a 57:43 diastereoisomeric ratio and good to excellent enantioselectivities for both diastereoisomers (76% and 91%, entry 6). Finally, using 2 mol% of the Ru(II)(*S*)-Pheox I, we obtained the best conditions, resulting in **3a** as separable mixture of diastereoisomers in 43% and 51% isolated yields, 92% *ee* for *trans*-**3a** and 86% *ee* for *cis*-**3a** (entry 7). Note, the (*trans/cis*) isomers were determined by ^1H - ^{19}F HOSEY NMR (see Experimental Part).



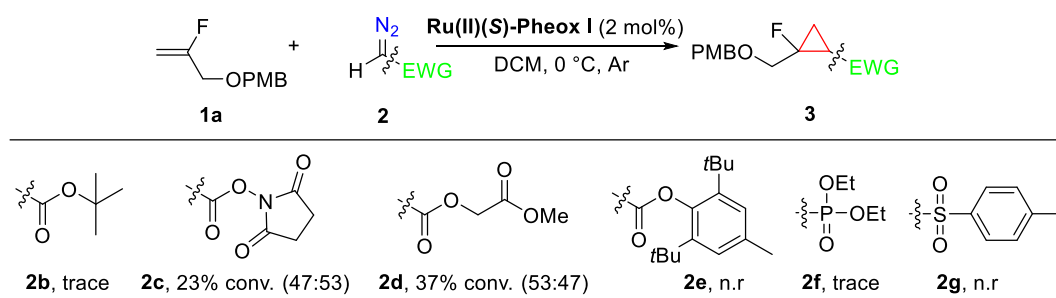
entry	equiv. EDA	T/ ($^{\circ}\text{C}$)	t/ (h)	<i>trans</i>		<i>cis</i>	
				conv. (%) ^b	<i>ee</i> ^c	conv. (%) ^b	<i>ee</i> ^c
1	3	-10	4	13	96	15	92
2	3	-10	10	3	-	4	-
3	3	-20	4	trace	-	trace	-
4	3	0	4	33 (30)	94	40 (37)	85
5	3	r.t	4	trace	-	trace	-
6	5	0	4	38(37)	90	49(48)	69
7	5	0	6.7	42(39)	91	54(54)	76
8^d	5	0	6.7	46(43)	92	53(51)	86

Table 2. 2. Parameters optimization. ^a To a mixture of olefin **1a** (0.2 mmol, 1 equiv.) and Ru(II)(*S*)-Pheox I (1 mol%) in DCM (0.5 mL), was added dropwise EDA in 1 mL DCM over a period of x h. ^b conversion was determined on the crude mixture by ^{19}F NMR. ^c Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase. ^d 2 mol% of Ru(II)(*S*)-Pheox I was used.

In view of the EDA-engaged cyclopropanation process in this procedure exhibited low

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diastereoselectivity (44:55), we aimed to improve the diastereoselectivity of this reaction by introducing several other mono-acceptor diazoalkanes (Scheme 2. 6). Unfortunately, when ester-type diazo reagents were screened, those with bulky groups (**2b**, **2e**) showed low or no reactivity. Even with diazo reagents **2c** and **2d** containing less bulky groups, conversions of 23% and 37%, respectively, were achieved, but the ratio of diastereoisomers remained close to 50:50. Phosphoryl diazoalkane **2f** and sulfonyl diazoalkane **2g** were also tested in this protocol, but the results were unpromising.



Scheme 2. 6. Diazo reagents screening. ^a To a mixture of olefin **1a** (0.2 mmol, 1 equiv.) and Ru(II)(S)-Pheox I (2 mol%) in DCM (0.5 mL), was added dropwise **2** (1.0 mmol, 5 equiv.) in 1 mL DCM over a period of 6.7 h. ^b Conversion and diastereoisomer ratio were determined on the crude mixture by ¹⁹F NMR. n.r = no reaction

To check if a modification of the diastereomeric ratio occurs during the cyclopropanation reaction, the diastereomeric ratio of **3a** was monitored every two hours by ¹⁹F NMR (Chart 2. 1), and it was observed that the diastereomeric ratio of **3a** remained unchanged from the beginning to the end of the reaction. This outcome demonstrated that an excess of diazo reagent did not have a negative effect on Ru(II)(S)-Pheox I, leading to a decrease of the diastereomeric ratio.

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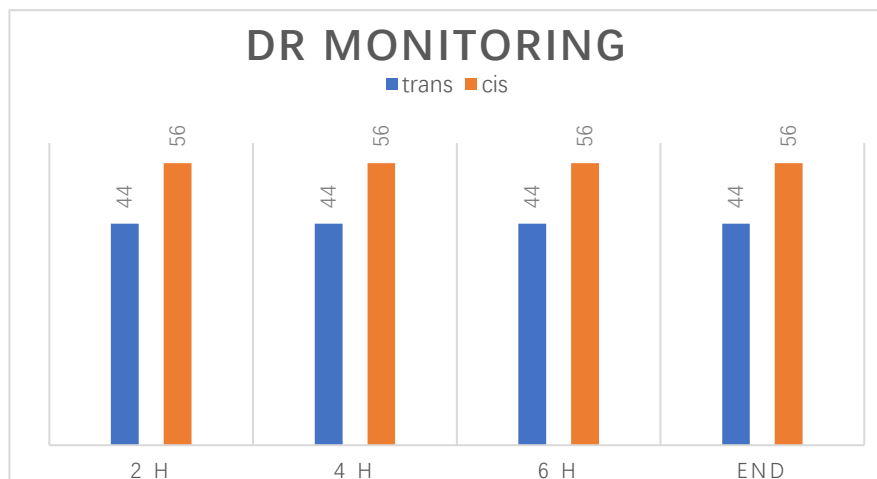
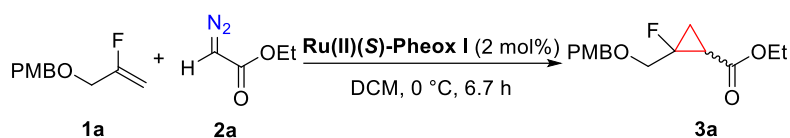


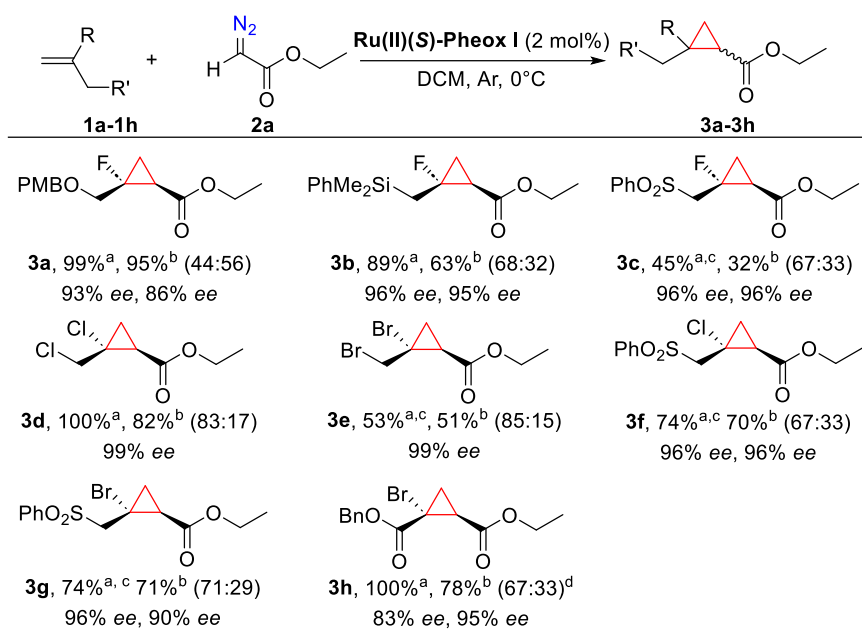
Chart 2. 1. Diastereomeric ratio monitoring. *dr* was analyzed by crude ^{19}F NMR, C_6D_6 was used as solvent.

2.4. Scope of α -substituted allylic derivatives

With the optimal reaction conditions in hand (Table 2. 2, entry 8), we systematically examined a series of α -halogenated allylic derivatives for the scope of the reaction (Scheme 2. 7). Initially, an array of α -fluoro allylic compounds (**1a-1c**) were tested with EDA (**2a**). Notably, alkene **1a**, bearing an OPMB substituent, and alkene **1b**, which included a dimethylphenyl silyl group, were found to be well-tolerated within this cyclopropanation process. As a result, the expected products, **3a** and **3b**, were achieved in good to excellent yields, showcasing excellent control of enantioselectivity on both diastereoisomers (93% and 86%, respectively). Worth mentioning that despite a modest diastereomeric ratio was observed, both diastereoisomers were readily separated through column chromatography on silica-gel. In the case of alkene **1c**, the use of 5 mol% of the chiral Ru(II)(S)-Pheox I was required to access the expected cyclopropane **3c** in a decent yield (32%) and a moderate 68/32 *dr* ratio. Yet, the enantiomeric excesses remained excellent at 96%. Subsequently, we extended our investigation to the catalytic enantioselective cyclopropanation of other α -halogenated allylic derivatives, including 2-chloro-3-chloropropene **1d** and 2-bromo-3-bromopropene **1e**. For both, the corresponding cyclopropanes, **3d** and **3e**, were obtained with remarkable enantiomeric excesses of 99%, an improved *dr* ratio of approximately 85/15, and proceeded good to very good

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isolated product yields from 51% to 82%. Additionally, α -chloro and α -bromo allylic sulfones **1f** and **1g** were engaged in the reaction, successfully afforded the targeted cyclopropanes **3f** and **3g**, characterized by high enantiomeric excess (from 90% to 96%), moderate *dr*, and very satisfactory yields. We finally applied this catalytic enantioselective cyclopropanation process with α -bromo benzyl acrylate leading to the expected cyclopropane **3h** in 85% yield, a moderate *dr* ratio (67/33) and good to excellent enantioselectivities for each diastereoisomer (83% and 95%, respectively).

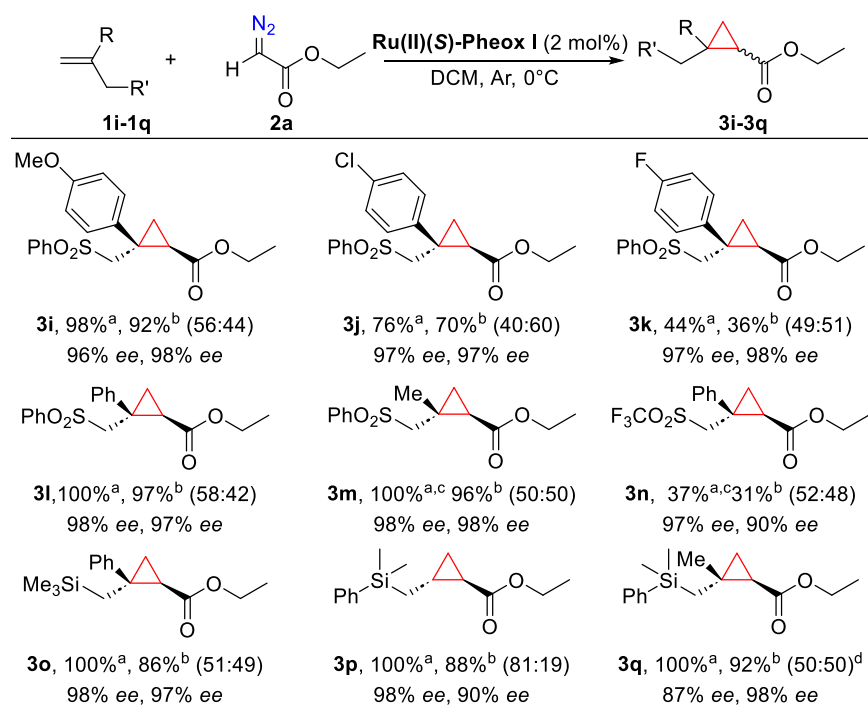


Scheme 2.7. Scope of α -haloalkenes. Reaction conditions: To a mixture of olefin **1a-1h** (0.2 mmol, 1 equiv.) and Ru(II)(S)-Pheox I (2 mol%) in DCM (0.5 mL), was added dropwise **2a** (1 mmol, 5 equiv.) in 1 mL DCM over a period of 6.7 h. ^a conversion was determined on the crude mixture by ¹H NMR. ^b isolated yield. ^c 5 mol% of Ru(II)(S)-Pheox I was used. ^d inseparable mixture of diastereoisomers. Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase.

Next, our investigation was extended to the catalytic enantioselective synthesis of cyclopropanes using EDA (**2a**) in conjunction with various allylic compounds. This scope included α -arylated allylic sulfones, α -methyl allylic sulfones, α -substituted allylic trifluoromethyl sulfones, and allylic silanes (Scheme 2. 8). Firstly, α -arylated allylic sulfones bearing a methoxy group at the *para* position (**1i**), a halogen atom (**1j**: Cl, **1k**: F) or an unsubstituted phenyl group (**1l**) were engaged in the asymmetric cyclopropanation reaction and the desired cyclopropanes **3i-3l** were obtained in moderate to excellent yields. In the presence of electron-withdrawing groups such as halogens, the conversion into the expected cyclopropane significantly decreased especially in the case of a

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fluorine atom (44% for **3k**). On the other hand, it is worth noting that both diastereoisomers of the cyclopropanes **3i-3l** have been achieved with remarkable enantioselectivity, from 96% to 98% *ee*. The reaction went smoothly when the phenyl substituent at the α -position was replaced by a methyl group leading to the cyclopropane **3m** in excellent yield and *ee*. For less activated allyl derivatives such as α -phenyl allylic trifluoromethyl sulfone **1n**, again a modest reactivity was observed even when 5 mol% of Ru(II)(*S*)-Pheox I was employed. Indeed, cyclopropane **3n** was isolated in a decent 31% yield, a 52:48 *dr* ratio but with excellent *ee* (97% and 90%, respectively). We finally engaged allyl dimethylphenylsilane **1p** and two α -substituted allyl silanes **1o**, **1q**, the corresponding cyclopropanes **3o-3q** were obtained in excellent yields (86-92%) and *ee* (87-98%), 50/50 *dr* ratios except for **3p** (81/19 *dr*). As previously mentioned, the *dr* remained modest but, in most cases, the two diastereomers were easily separated (exception **3q**).

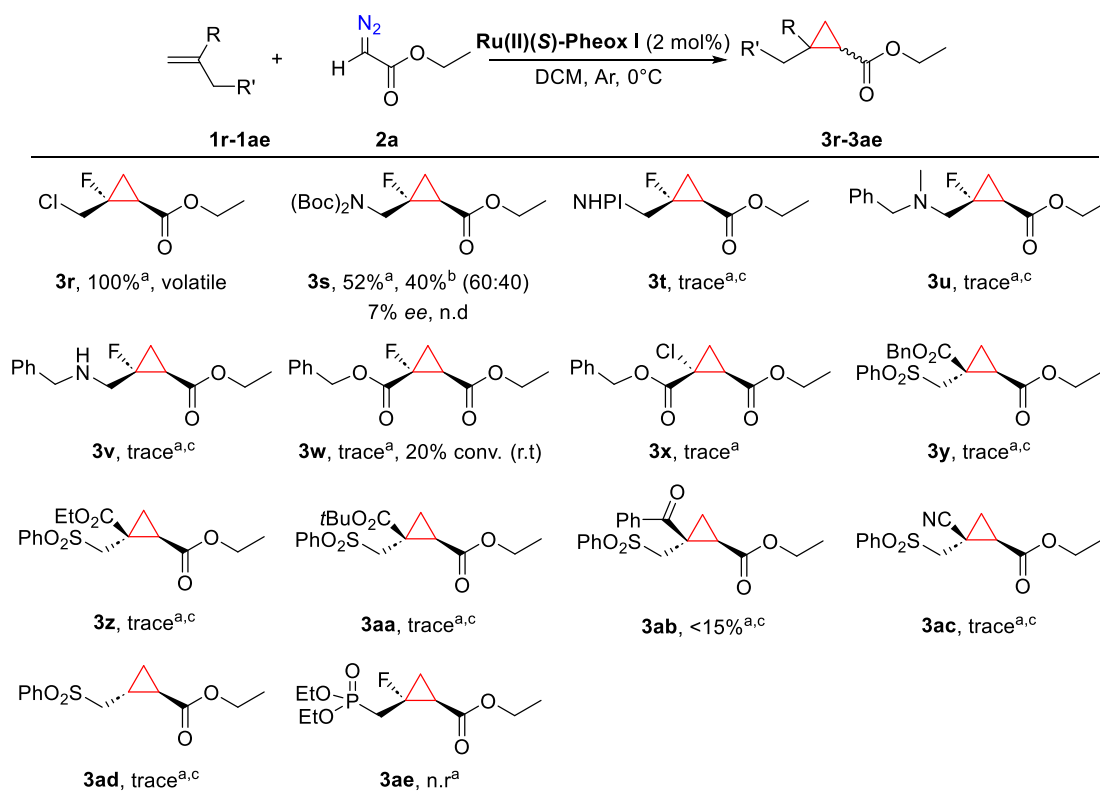


Scheme 2. 8. Scope of allylic sulfones and silanes. To a mixture of olefin **1i-1q** (0.2 mmol, 1 equiv.) and Ru(II)(*S*)-Pheox I (2 mol%) in DCM (0.5 mL), was added dropwise **2a** (1 mmol, 5 equiv.) in 1 mL DCM over a period of 6.7 h. ^a Conversion was determined on the crude mixture by ¹H NMR. ^b Isolated yield. ^c 5 mol% of Ru(II)(*S*)-Pheox I was used. ^d inseparable mixture of diastereoisomers. Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase.

Despite this enantioselective cyclopropanation process was applied to a large range of alkenes, we still observed some limitations (Scheme 2. 9). For example, α -fluorinated allylic chloride substrate

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1r was tested and the reaction proceeded well to full conversion of the desired cyclopropane **3r**. However, the purification of this product was unsuccessful because of its volatility, even after careful evaporation at room temperature. Then we examined several α -fluorinated allylic amides (**1s**, **1t**) or amines (**1u**, **1v**) Unfortunately, only product **3s** was formed with a decent conversion but modest diastereoselectivity and unpromising *ee* (7%) for the major diastereoisomer. Benzyl acrylate substrates with a halogen atom at the α -position such as **1w** (F) and **1x** (Cl) were tested in the cyclopropanation process but only traces of the expected cyclopropanes **3w** and **3x** were observed on ^1H NMR spectra of the crude mixture. When the reaction was carried out with **1w** at room temperature, the conversion of product **3w** was slightly increased to 20%. Furthermore, α -substituted allylic sulfone compounds **1y-1ad** were investigated as well. These substrates were hardly tolerated in this enantioselective cyclopropanation process, except for **3ab** (15% conversion). We finally engaged α -fluoro-allylic phosphonate **1ea**, but this substrate showcased reluctant reactivity.



Scheme 2.9. Unsuccessful scope examples. To a mixture of olefin **1r-1ae** (0.2 mmol, 1 equiv.) and Ru(II)(S)-Pheox I (2 mol%) in DCM (0.5 mL), was added dropwise **2a** (1 mmol, 5 equiv.) in 1 mL DCM over a period of 6.7 h. ^a Conversion was determined on the crude mixture by ^1H NMR. ^b Isolated yield. ^c 5 mol% of Ru(II)(S)-Pheox I was used. Enantiomeric excess (*trans/cis*) determined

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by HPLC analysis on a chiral stationary phase. n.r = no reaction.

2.5. Computational studies, stereochemistry and mechanism

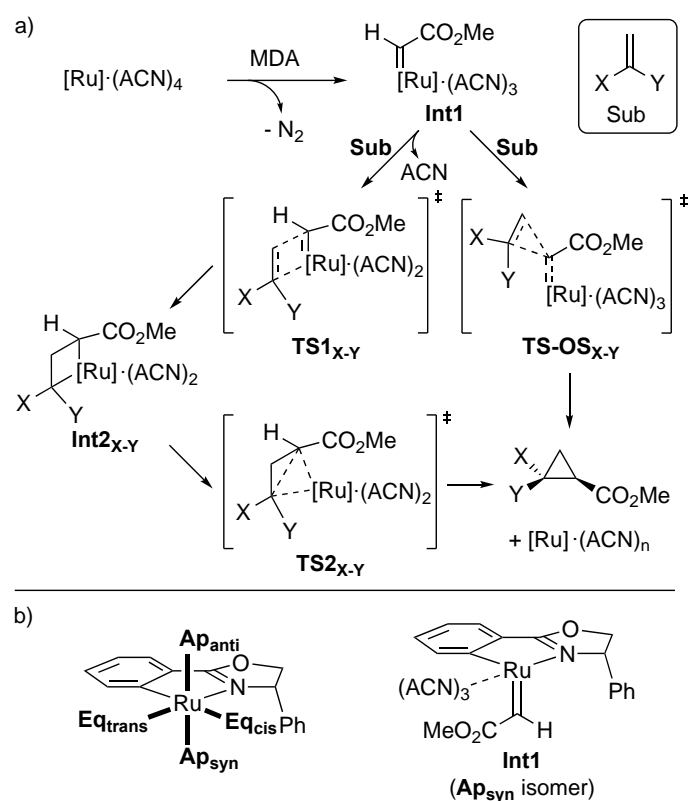
2.5.1. Computational studies (conducted thanks to a collaboration with Claude Legault)

As recently studied by Mendoza, Himo and co-workers, Ru(II)-catalyzed cyclopropanations have multiple possible mechanistic manifolds (Scheme 2. 10a, inner-sphere *vs* outer-sphere mechanisms).¹⁷³ They have investigated the cyclopropanation reaction of *N*-hydroxy phthalimide diazoacetate (NHPI-DA) with propene and styrene, using Ru(II)(S)-Pheox **I**.¹⁷³ Their calculations suggest that the reaction proceeds preferentially *via* an outer-sphere mechanism, in which three acetonitrile (ACN) molecules remain bound as ligands. Due the unique nature of alkenes **1a-1h** used in our study, we turned to computational chemistry to gain insight into the process and evaluate the influence of the haloalkene on the mechanistic outcome. Due to the good correlation between their calculations and experiments, we elected to use the same computational protocol as Mendoza, Himo and co-workers (see Experimental Part for full computational details), but using methyl diazoacetate (MDA) as an ethyl diazoacetate (EDA) surrogate model. For the substrates, we elected to use the 2-halopropenes (X = F, Cl, Br, Y = CH₃) as model alkenes. There are four sites for possible carbene formation on Ru(II)(S)-Pheox **I**, as illustrated in Scheme 2. 10b.

The previous computational study has suggested their formation to be extremely closed in energies, except for position **Eq_{cis}**, which was found to be disfavored kinetically. Nonetheless, it also suggests that the most probable pathway occurs through isomer **Ap_{syn}**. To simplify analysis, we have thus focused solely on the pathways involving this isomer, which is simply denoted **Int1** (Scheme 2. 10b).

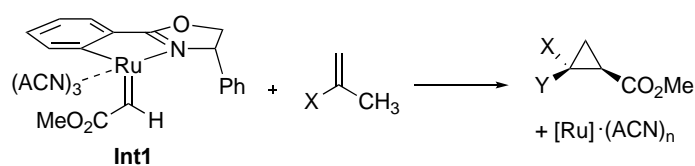
¹⁷³ F. Planas, M. Costantini, M. Montesinos-Magraner, F. Himo, A. Mendoza *ACS Catal.* **2021**, *11*, 10950–10963.

Experimental and computational studies for the catalytic enantioselective synthesis of functionalized cyclopropanes from α -substituted allylic derivatives with ethyl diazoacetate



Scheme 2. 10. a) Inner-sphere and Outer-sphere mechanisms; b) Carbene isomers depiction.

We investigated both inner-sphere and outer-sphere mechanisms for the three 2-haloalkene substrates, as well as propene as a reference point with respect to classical substrates and the study of Mendoza, Himo and co-workers. The results are summarized in Table 2. 3. The barriers found for MDA and propene are coherent with the barriers computed for NHPI-DA and propene, but slightly higher due to the difference in nucleophilicity of the carbene of MDA vs. NHPI-DA. The $TS2_{X-CH_3}$ barriers computed for the 2-halopropene series are very similar to the one found for propene, with the exception for $TS1_{X-CH_3}$, which are systematically higher by almost ca. 5 kcal/mol, in line with a detrimental effect of induction from the electronegative halogen atoms, resulting in electrophilic olefin substrates. In analogy to the propene substrate, the outer-sphere mechanism seems to be clearly operative for the 2-halopropene series, with kinetic preferences ranging from 8.0 to 8.9 kcal/mol.



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Entry	X	TS1 _{X-CH3}	Int2 _{X-CH3}	TS2 _{X-CH3}	TS-OS _(X-CH3)	$\Delta\Delta G^\ddagger_{(OS-IS)}$
1	H	10.5	8.1	23.7	15.7	-8.0
2	F	14.2	8.1	23.4	14.5	-8.9
3	Cl	15.2	11.0	23.4	15.0	-8.4
4	Br	15.2	11.3	23.4	15.1	-8.3

Table 2. 3. Cyclopropanation pathways of propene and 2-halopropenes. Gibbs energies reported in kcal/mol.

Further inspection of the transition structures **TS2_{X-CH3}** did provide however very interesting insight. Indeed, IRC calculations unearthed that **TS2_{X-CH3}** (X = F, Cl, Br), which was initially considered to be a reductive elimination process leading to the product, was instead a κ^1 to κ^2 isomerization toward the unreported intermediate **Int3_{X-CH3}** (Figure 2. 1). This clear two-step mechanism was found to be common for the whole halopropene series, as illustrated in Figure 2. 1.

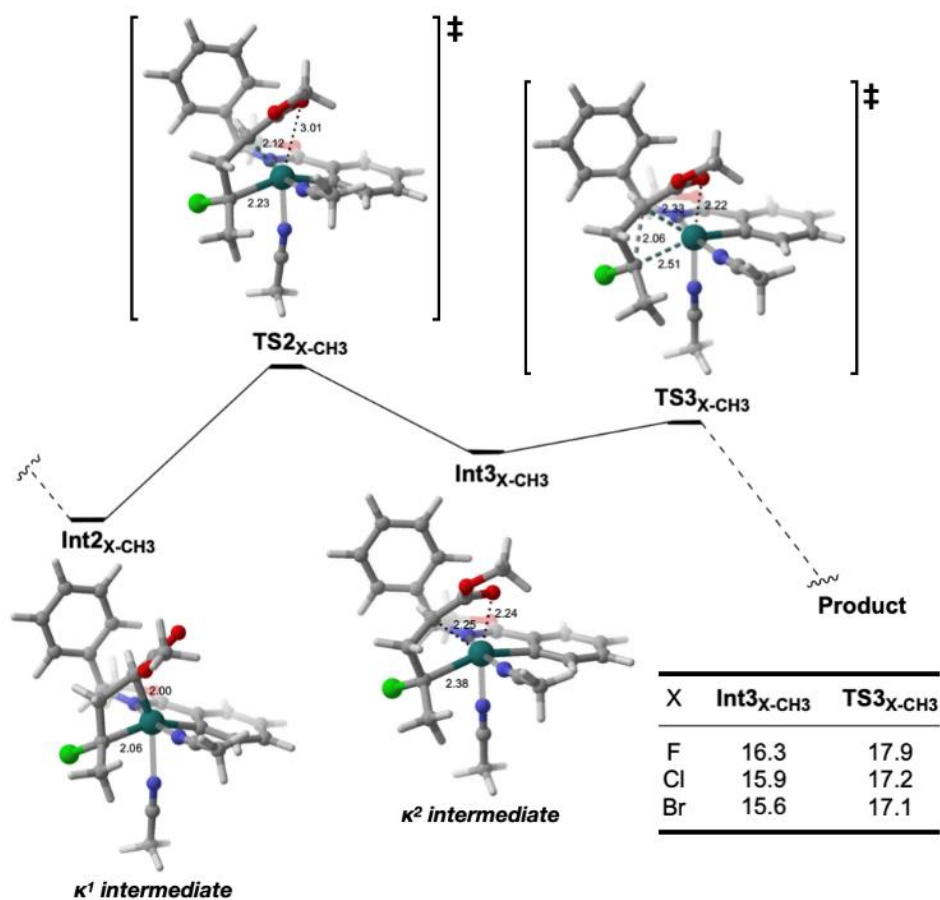


Figure 2. 1. Discovery of a hidden κ^2 intermediate (**Int3_{X-CH3}**) in the inner-sphere mechanism. Gibbs energies are reported in kcal/mol. The structures optimized for 2-chloropropene are illustrated (See EP for other derivatives).

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The structural features and barriers of isomerization are mostly similar for the whole series. This newfound intermediate could have further implications, and intrinsic reaction coordinate (IRC) calculations were performed on **TS2_{H-CH3}** to ensure that this isomerization process had not been missed for classical substrates such as propene. The IRC path of **TS2_{H-CH3}** is illustrated in Figure 2. 2 (blue line). In this case, no intermediate could be found, and **TS2_{H-CH3}** truly connects **Int2_{H-CH3}** to the final cyclopropane product, but interestingly does proceed through a two-steps/no-intermediate process.¹⁷⁴

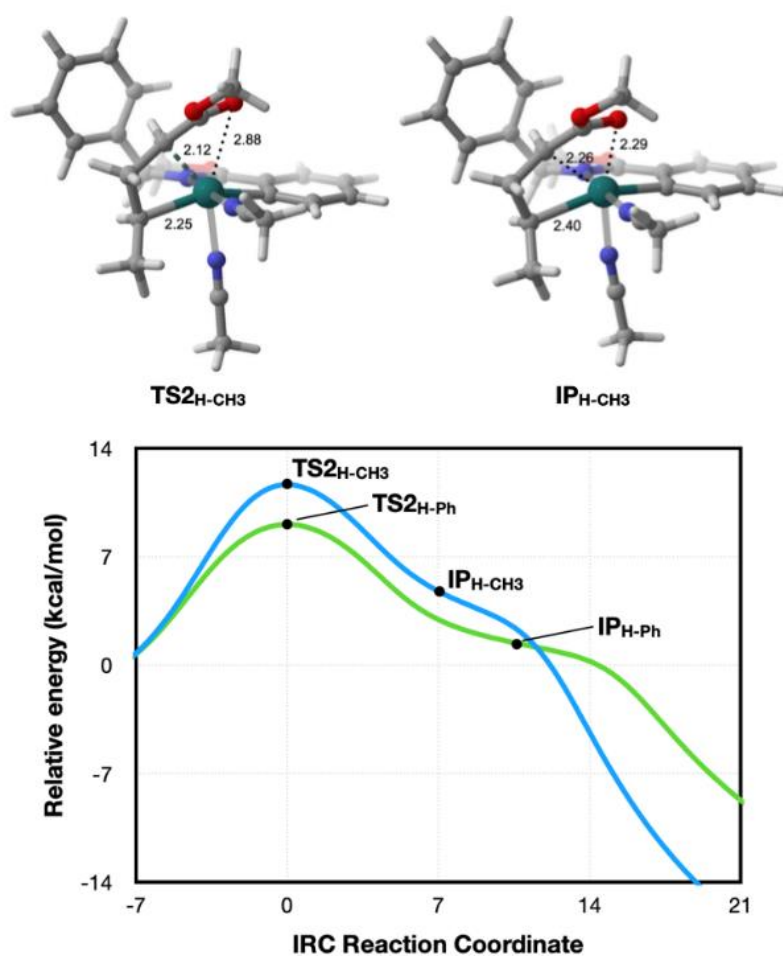


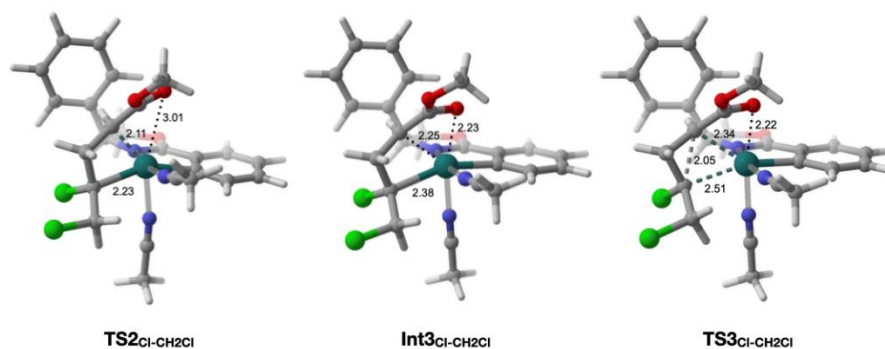
Figure 2. 2. IRC paths of **TS2_{H-CH3}** and **TS2_{H-Ph}** and relevant structures.

Inspection of the inflection point (**IP_{H-CH3}**) on that IRC provides a structure that closely resembles the stable intermediates (**Int3_{X-CH3}**) found for the halopropene series, as illustrated by a comparison

¹⁷⁴ D. A. Singleton, C. Hang, M. J. Szymanski, M. P. Meyer, A. G. Leach, K. T. Kuwata, J. S. Chen, A. Greer, C. S. Foote, K. N. Houk *J. Am. Chem. Soc.* **2003**, *125*, 1319–1328.

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of **Int3**_{Cl-CH₃} (Figure 2. 1) and **IP**_{H-CH₃} (Figure 2. 2). The unique behavior of the 2-halopropene series might thus be due to a stabilization of an excess electronic density on the carbon bearing the halogen atom. Consequently, it could be envisioned that substrates like styrene could also provide access to such intermediate. We computed **TS2**_{H-Ph} for styrene and performed IRC calculations on the latter. In analogy to propene, **TS2**_{H-Ph} connects directly **Int2**_{H-Ph} to the final cyclopropanation product, again with a two-steps/no-intermediate profile (Figure 2. 2, green line). The stabilization required to form the **Int3**_{X-Y} intermediates thus seems to be mostly inductive in nature. There is a slight increase in stabilization for **Int3**_{X-CH₃} as we move from X = F, to Cl, and to Br, suggesting a potential $d_{Ru} \rightarrow \sigma^*_{C-X}$ back donation, although it difficult to draw a clear conclusion on such small variations. With this assumption in hand, we envisioned that substrates with an electrophilic moiety on the allylic position might provide an even stronger stabilization for **Int3**_{X-Y}, through delocalization of the C-Ru bond into a low lying σ^*_{C-X} orbital.



Y	TS1 _{Cl-Y}	Int2 _{Cl-Y}	TS2 _{Cl-Y}	Int3 _{Cl-Y}	TS3 _{Cl-Y}	TS-OS _(Cl-Y)	$\Delta\Delta G^\ddagger_{(OS-IS)}$
H	15.2	11.0	23.4	15.9	17.2	15.0	-8.4
CH ₂ Cl	14.2	10.3	20.6	12.2	14.2	16.5	-4.1

Table 2. 4. Energetics of the cyclopropanation pathways with substrate **1d**. Gibbs energies reported in kcal/mol.

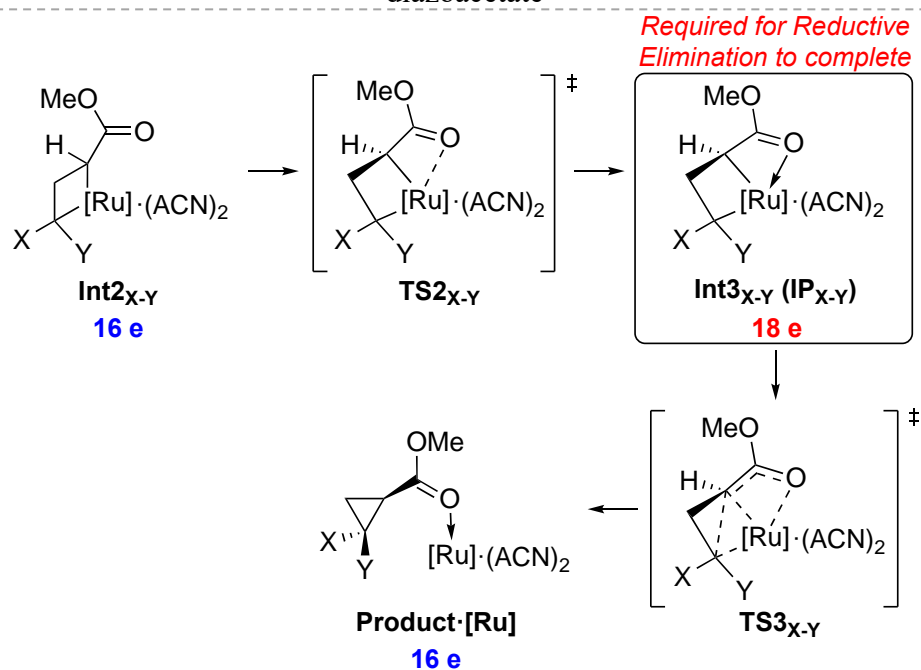
Consequently, we elected to study the different reaction pathways of cyclopropanation with substrate **2d**, as the latter provided the best-combined reactivity (full conversion), yield, and selectivities, and possesses an electrophilic allyl chloride moiety. Again, the reductive elimination process was found to be non-concerted, proceeding through intermediate **Int3**_{Cl-CH₂Cl}. With this substrate we computed **Int3**_{Cl-CH₂Cl} and **TS3**_{Cl-CH₂Cl} for the other carbene isomers (**Ap**_{syn}, **Ap**_{anti}, **Eq**_{trans}), to ensure that this behavior was not unique to the **Ap**_{syn} pathway (See Experimental Part).

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The energetics of the **Ap_{syn}** pathway were compared to 2-chloropropene, the results are illustrated in Table 2. 4. **TS2_{Cl-CH₂Cl}** was found to be only slightly lower in energy, but larger differences were found for **Int3_{Cl-CH₂Cl}** and **TS3_{Cl-CH₂Cl}**. In structures **Int3_{Cl-CH₂Cl}** and **TS3_{Cl-CH₂Cl}**, the allylic chloride atom is antiperiplanar to the C–Ru bond, in line with stabilization from $d_{\text{Ru}} \rightarrow \sigma^*_{\text{C-Cl}}$ delocalization. Interestingly, the allylic chloride did have a detrimental effect on **TS-OS_{Cl-CH₂Cl}**, increasing the barrier to 16.5 kcal/mol. Overall, the contrasting effect of the allylic chloride on the IS and OS mechanism resulted in a smaller preference for the IS mechanism, down to 4.0 kcal/mol compared to 8.0 kcal/mol for 2-chloropropene. These computational results provide interesting insight into this useful cyclopropanation methodology and raise the importance of the influence of the substrate on the outcome. Indeed, while the substrates used in this study are expected to react through an outer-sphere mechanism, one could envision that allylic substituents (X) that provide a low-lying $\sigma^*_{\text{C-X}}$ could provide selective access to a non-concerted inner-sphere mechanism, which could be leveraged to access different reactivity and selectivity profiles.

Finally, what is the cause of the presence of this hidden intermediate with propene, and clear formation of **Int3_{X-Y}** for the 2-halopropene series and substrate **1d**? The electronic configuration of **Int2_{X-Y}** can shed some light on this question. Indeed, **Int2_{X-Y}** possesses 16 valence electrons, and its passage through **TS2_{X-Y}** would result in the release of the cyclopropane product and a 14 valence electrons Ru(II)-complex. The κ^1 to κ^2 shift thus provides a pathway in which **Int3_{X-Y}** (or **IP_{H-Y}**) valence count can increase from 16 to 18 electrons, which then proceeds through reductive elimination and release a Ru(II)-complex with 16 valence electrons, with the carbonyl-oxygen of the cyclopropane product acting as a ligand (Scheme 2. 11). Inspection of the reductive elimination transition structures computed by Mendoza, Himo and co-workers further support this rationale, as in all cases the *N*-hydroxy phthalimide moiety acts as an additional ligand in **TS2** to increase the valence electron count to 18.¹⁷³ This indicates that achieving an 18 valence electrons complex is necessary for the reductive elimination to complete, either through denticity shift, or additional ligand association/chelation.

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Scheme 2.11. Mechanistic rationale for the requirement of the κ^2 intermediate.

2.5.2. Stereochemistry

The absolute configurations of cyclopropanes *trans*-**3g**, *cis*-**3g**, and *trans*-**3i** were determined through single crystal X-ray diffraction analysis (Figure 2.3). The major product, *trans*-**3g**, derived from the α -bromoalkene **1g**, was confirmed to have an absolute configuration of **1S**, **2R**. The corresponding diastereoisomer, *cis*-**3g** (minor product), was determined to possess an absolute configuration of **1S**, **2S**. On the other hand, when an aromatic group was present instead of a halogenated group, the major product, *trans*-**3i**, was determined to have an absolute configuration of **1R**, **2R**. These results provide clarity regarding the absolute configurations of all the cyclopropane products presented in Scheme 2.7 and Scheme 2.8.

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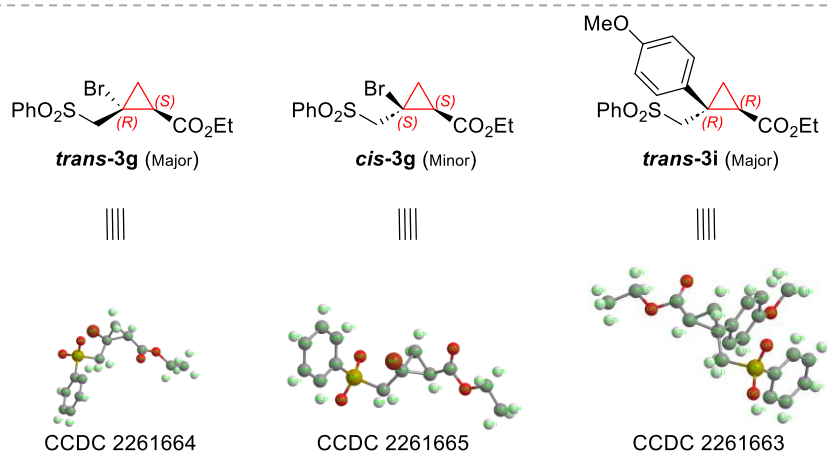
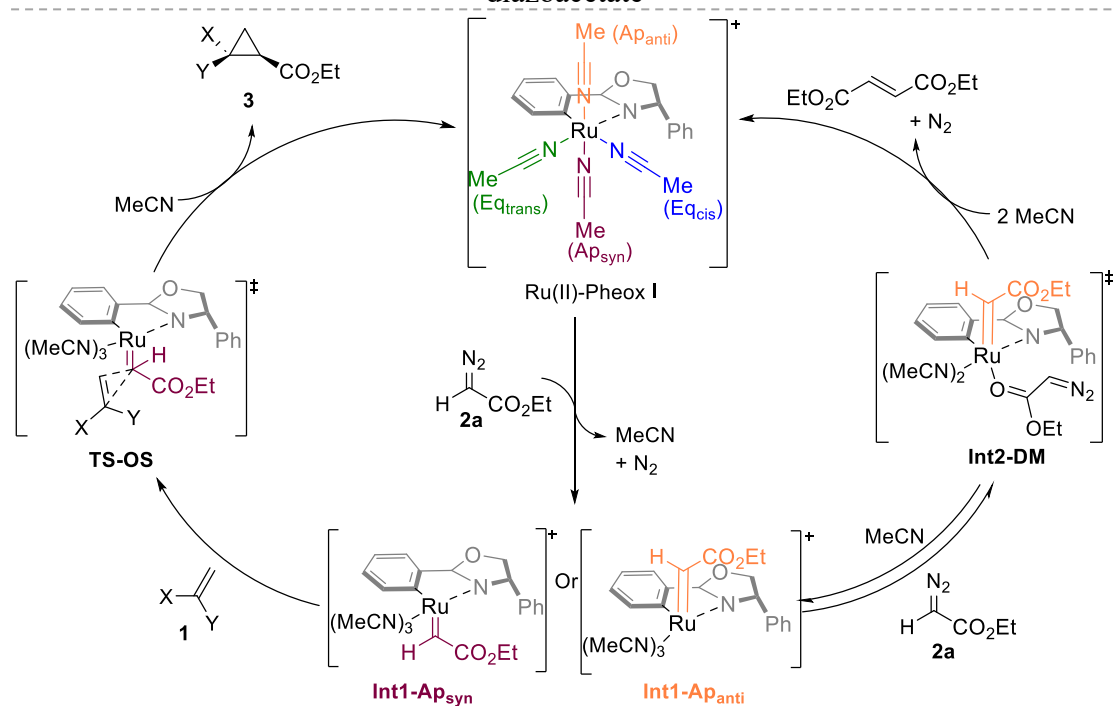


Figure 2. 3. X-ray diffraction analysis of cyclopropanes *trans-3g*, *cis-3g*, and *trans-3i*.

2.5.3. Proposed plausible mechanism

Based on the DFT calculations and stereochemical outcomes, we propose the plausible mechanism for this Ru(II)-catalyzed asymmetric cyclopropanation process (Scheme 2. 12). Initially, Ru(II)(*S*)-Pheox I reacts with ethyl diazoacetate (**2a**) through ligand dissociation, leading to two viable carbene complexes (**Int1-*Ap*_{syn}** and **Int1-*Ap*_{anti}**). Further more, the **Int1-*Ap*_{syn}** complex engages with alkene **1** to form the **TS-OS** species through an outer-sphere mechanism. This **TS-OS** species then combines with a ligand MeCN to generate product **3** and regenerate the catalyst Ru(II)(*S*)-Pheox I. Alternatively, the **Int1-*Ap*_{anti}** metal carbene has a higher affinity for **2a**, resulting in ligand exchange to form **Int2-DM** species through an inner-sphere mechanism. This is followed by the addition of two equivalent MeCN ligand, leading to a dimerization process.

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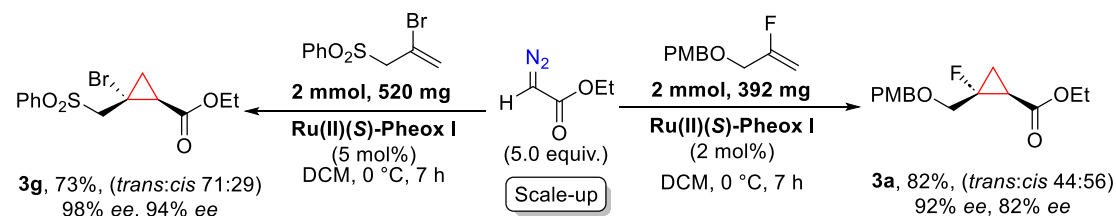


Scheme 2. 12. The plausible mechanism of Ru(II)-catalyzed asymmetric cyclopropanation process.

2.6. Scale-up and post-functionalization reactions

2.6.1. Scale-up reactions

It is important to note that a scale-up of the reactions (Scheme 2. 13) with **1a** and **1g** on 2 mmol was carried out leading to the expected cyclopropanes **3a** and **3g** in 82% and 73% isolated yields, respectively, with the same excellent enantioselectivities, demonstrating the robustness of the process.



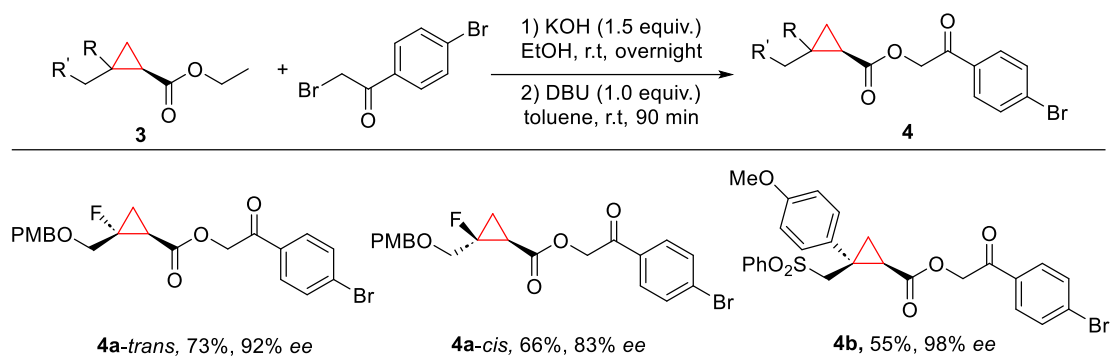
Scheme 2. 13. Scale-up reactions of product **3a** and **3g**.

2.6.2. Post-functionalization reactions

In order to demonstrate the utility and the easy functional groups interconversion of chiral

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cyclopropanes **3**, further functionalization reactions were tested. Saponification of pure *trans*-**3a**, *cis*-**3a** and *cis*-**3i** were carried out under basic conditions, then followed by a coupling reaction with 4-bromophenylacetyl bromide to afford the desired cyclopropanes *trans*-**4a**, *cis*-**4a** and **4b** in 73%, 74% and 55% yields, respectively (Scheme 2. 14).¹⁷⁵ The enantiomeric excesses of the products were checked and no erosion of the *ee* was detected.



Scheme 2. 14. Saponification and further coupling reactions of cyclopropanes *trans*-**3a**, *cis*-**3a** and *cis*-**3i**.

In addition, we conducted several post-functionalization reactions on enantiopure cyclopropane *cis*-**3g**. Initially, we attempted hydrolysis of the ester group of *cis*-**3g** under basic conditions (Scheme 2. 15a, A),¹⁷⁵ but this reaction did not yield any trace of the expected product, even though the starting material was fully consumed. Subsequently, we employed TMSI, a reagent known for ester hydrolysis,¹⁷⁶ which resulted in a moderate overall yield (41%) of undesired cyclopropane opening products **5a**, **5b**, and **5b'** through bromine atom elimination (Scheme 2. 15a, B). Furthermore, an elimination reaction was carried out with compound *cis*-**3g** (Scheme 2. 15b),¹⁷⁷ while an excellent isolated global yield (94%) and good *Z/E* ratio (83/17) were given by use of triethylamine as the base, the enantiomeric excesses were decreased to 55% and 7% respectively. We next attempted to transform the cyclopropyl ester compound *cis*-**3g** to a cyclopropyl amide product incorporation with *para*-chloroaniline (Scheme 2. 15c).¹⁷⁸ However, the six-membered lactam **7** was achieved with decent yield instead of expected cyclopropyl amide product. Finally, under reductive conditions,¹⁷⁹

¹⁷⁵ P. Müller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755–4763.

¹⁷⁶ G. A. Olah, S. C. Narang, *Tetrahedron* **1982**, *38*, 2225–2277.

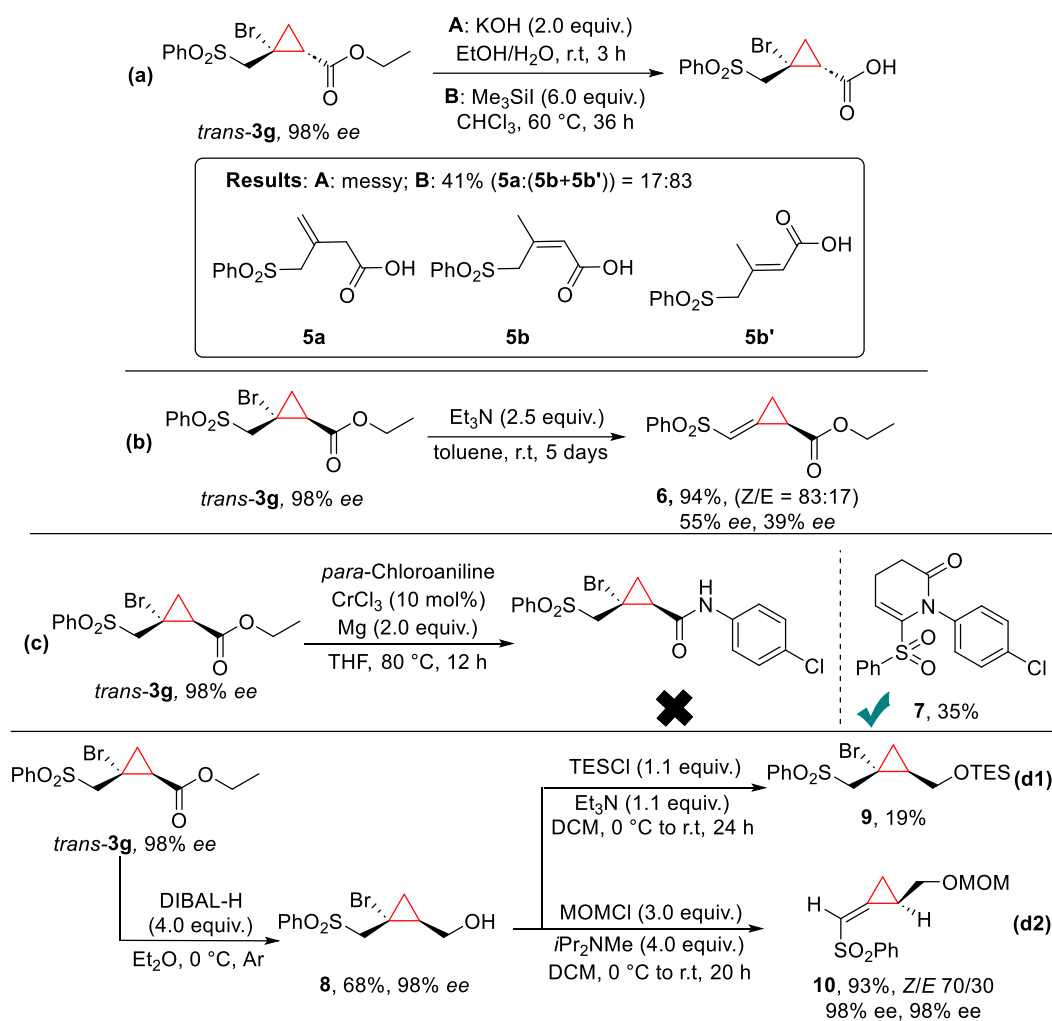
¹⁷⁷ L. Volta, C. J. Stirling, *Phosphorus, Sulfur, and Silicon* **2009**, *184*, 1508–1522.

¹⁷⁸ C. Chen, L. Ling, M. Luo, X. Zeng, *Bull. Chem. Soc. Jpn.* **2021**, *94*, 762–766.

¹⁷⁹ S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055–2068.

Experimental and computational studies for the catalytic enantioselective synthesis of functionalized cyclopropanes from α -substituted allylic derivatives with ethyl diazoacetate

compound *cis*-**3g** was reduced to cyclopropyl alcohol **8** in 68% yield (98% *ee*). Further protection of the primary alcohol was conducted with triethylsilyl chloride,¹⁸⁰ nonetheless it resulted in low yield (19%) (Scheme 2. 15d1). Another reaction was performed using MOMCl (chloromethoxymethane) and a base *i*Pr₂NMe (Scheme 2. 15d2).¹⁸¹ Surprisingly, this reaction went through a two-step process and afforded product **10** in an outstanding global yield (93%, *Z/E* 70/30) without *ee* erosion.



Scheme 2. 15. Functionalization of product *cis*-**3g**.

¹⁸⁰ H. Kondo, S. Miyamura, K. Matsushita, H. Kato, C. Kobayashi, Arifin, K. Itami, D. Yokogawa, J. Yamaguchi, *J. Am. Chem. Soc.* **2020**, *142*, 11306–11313.

¹⁸¹ T. Minami, K. Fukuda, N. Hoshiya, H. Fukuda, M. Watanabe, S. Shuto, *Org. Lett.* **2019**, *21*, 656–659.

2.7. Conclusion

In summary, we have successfully developed a catalytic enantioselective synthesis of highly functionalized cyclopropanes using α -substituted allyl derivatives and ethyl diazoacetate. Employing a chiral Ru(II)-catalyst, specifically Ru(II)(*S*)-Pheox I, we achieved high yields (31-97%) and enantioselectivities (up to 99%), along with separable diastereomers albeit moderate diastereomeric ratios. This reaction manifold provides access to unprecedented enantioenriched versatile building-blocks. Furthermore, we have unearthed a hidden intermediate in the inner-sphere mechanism, using DFT calculations. While the IS mechanism does not seem operative in this specific methodology, the mechanistic findings raise the possibility to exploit the electronic properties of substrates to affect a switch in the mechanistic control. It also emphasizes the significance of the complexing moiety on the carbene precursor, which, once again, can lead to significant variations in the mechanistic outcome. We anticipate that this methodology will be highly valuable for the scientific community as it paves the way for the synthesis of functionalized enantiopure cyclopropanes.

**Chapter III – Ru(II)-Pheox-catalyzed synthesis of enantio-
merically convergent phenylsulfonyl α,α -difluoromethyl
cyclopropanes**

3.1. State of the art

In the field of organic synthesis for bioactive and pharmaceutical molecules, the fluorine atom, the most electronegative element, has garnered significant attention from chemists seeking to modify and enhance physico-chemical properties of active molecules.¹⁸² These consequences arise from the introduction of a fluorine atom or fluorinated groups onto a molecule, which impacts factors such as lipophilicity, metabolic stability, and the acidity/basicity of neighboring functional groups.¹⁸³ Moreover, to date, there is a growing interest for the incorporation of the difluoromethyl group onto organic molecules, because of its propensity to be used as bioisoster for the methyl, thiophenol, aniline or amine group,¹⁸⁴ as well as ketone or ester fragment.¹⁸⁵ In addition, the α,α -difluoromethylcyclopropane motif is present in several bioactive organic structures (Figure 3. 1), for example Voxilaprevir and Glecaprevir for the treatment of chronic hepatitis C,¹⁸⁶ and also the recently developed HIV-1 capsid inhibitor Lenacapavir.¹⁸⁷

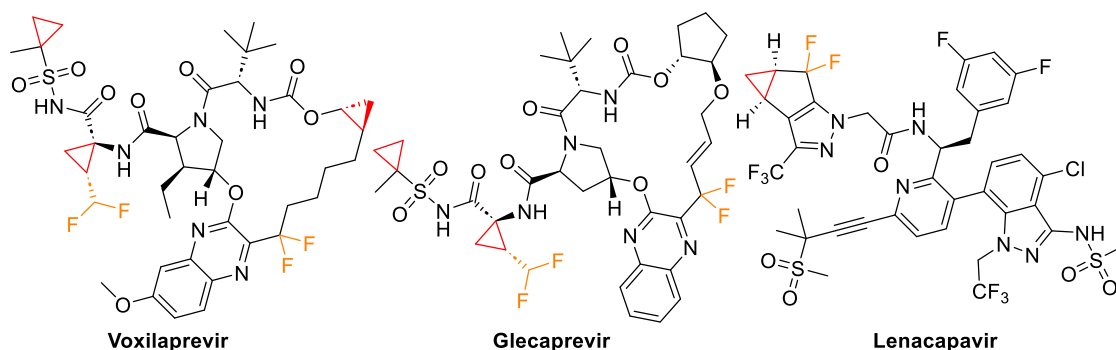


Figure 3. 1. Bioactive compounds containing α,α -difluoromethyl cyclopropane motif.

¹⁸² a) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308–319. b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470–477. c) G. Landelle, A. Panossian, F. R. Leroux, *Curr. Top. Med. Chem.* **2014**, *14*, 941–951. d) M.–C. Belhomme, T. Besset, T. Poisson, X. Pannecoucke, *Chem. Eur. J.* **2015**, *21*, 12836–12865.

¹⁸³ a) H.–J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst–Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637–643. b) M. Bos, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2017**, *23*, 4950–4961.

¹⁸⁴ Y. Zafrani, D. Yeffet, G. Sod–Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2017**, *60*, 797–804.

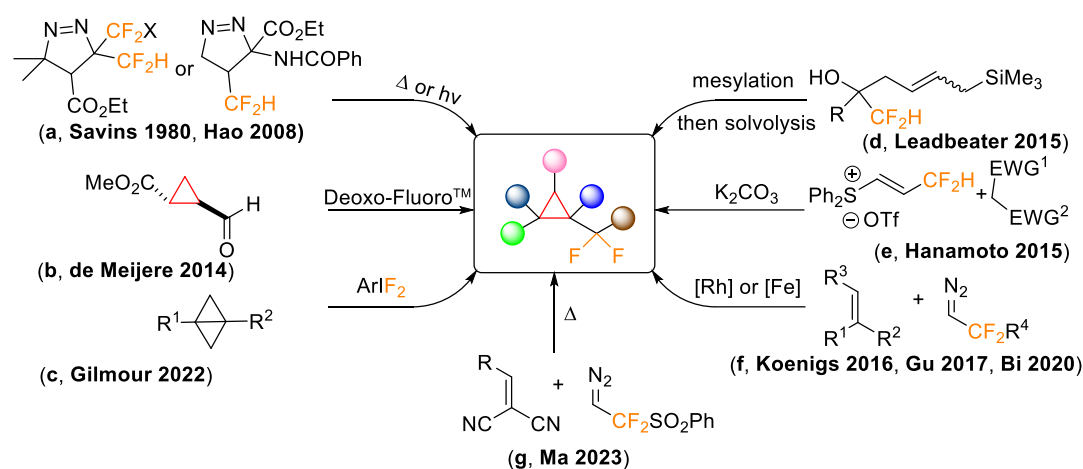
¹⁸⁵ N. A. Meanwell, *J. Med. Chem.* **2011**, *54*, 2529–2591.

¹⁸⁶ A. N. Matthew, J. Zephyr, C. J. Hill, M. Jahangir, A. Newton, C. J. Petropoulos, W. Huang, N. Kurt–Yilmaz, C. A. Schiffer, A. Ali, *J. Med. Chem.* **2017**, *60*, 5699–5716.

¹⁸⁷ S. M. Bester, G. Wei, H. Zhao, D. Adu–Ampratwum, N. Iqbal, V. V. Courouble, A. C. Francis, A. S. Annamalai, P. K. Singh, N. Shkriabai, *Science* **2020**, *370*, 360–364.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes

Because of the advantages mentioned above, the synthesis of α,α -difluoromethylcyclopropane building blocks has become a hot research topic in the scientific community.^{183b,188} Pioneering works regarding non-asymmetric approaches for example ring contraction (Scheme 3. 1a)¹⁸⁹ deoxofluorination (Scheme 3. 1b),¹⁹⁰ ring contraction fluorination (Scheme 3. 1c),¹⁹¹ Michael-Initiated Ring Closure (Scheme 3. 1d),¹⁹² nucleophilic [2+1] ring addition (Scheme 3. 1e),¹⁹³ metalcarbene [2+1] ring addition (Scheme 3. 1f)¹⁹⁴ and free carbene [2+1] ring addition¹⁹⁵ reactions were conducted by chemists in the previous several decades.



Scheme 3. 1. Non-asymmetric approaches regarding synthesis of α,α -difluoroalkylcyclopropanes.

¹⁸⁸ a) J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson, P. Jubault, *Chem. Eur. J.* **2021**, *27*, 2935–2962. b) W. F. Wu, J. H. Lin, J. C. Xiao, Y. C. Cao, Y. Ma, *Asian J. Org. Chem.* **2021**, *10*, 485–495.

¹⁸⁹ a) R. K. Huff, E. G. Savins, *J. Chem. Soc., Chem. Commun.* **1980**, 742–743. b) W. Wan, Y. Gao, H. Jiang, J. Hao, *J. Fluorine Chem.* **2008**, *129*, 510–514. c) W.–Y. Han, J. Zhao, J.–S. Wang, B.–D. Cui, N.–W. Wan, Y.–Z. Chen, *Tetrahedron* **2017**, *73*, 5806–5812. d) Y. Zheng, X. Yu, S. Lv, P. K. Mykhailiuk, Q. Ma, L. Hai, Y. Wu, *RSC Adv.* **2018**, *8*, 5114–5118.

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¹⁹¹ K. Livingstone, K. Siebold, S. Meyer, V. Martín-Heras, C. G. Daniliuc, R. Gilmour, *ACS Catal.* **2022**, *12*, 14507–14516.

¹⁹² C. B. Kelly, M. A. Mercadante, E. R. Carnaghan, M. J. Doherty, D. C. Fager, J. J. Hauck, A. E. MacInnis, L. J. Tilley, N. E. Leadbeater, *Eur. J. Org. Chem.* **2015**, *2015*, 4071–4076.

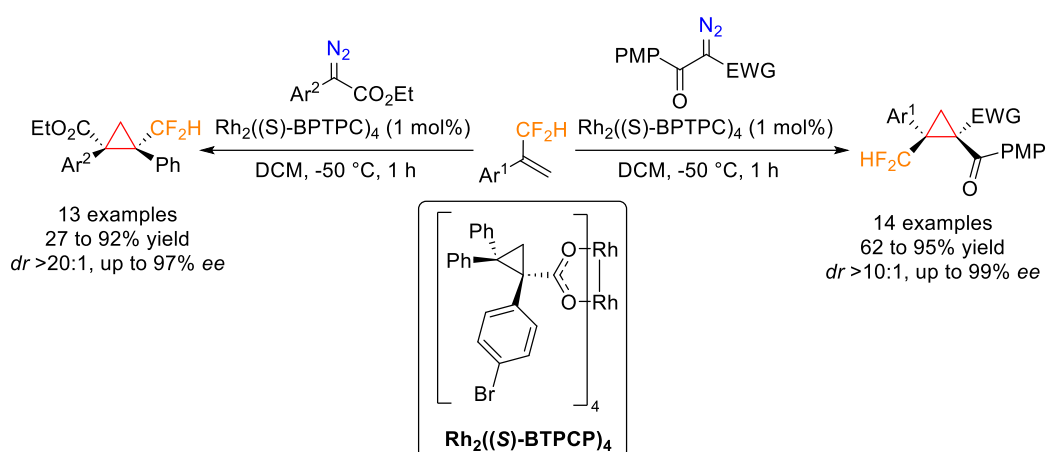
¹⁹³ T. Ishikawa, N. Kasai, Y. Yamada, T. Hanamoto, *Tetrahedron* **2015**, *71*, 1254–1260.

¹⁹⁴ a) Y. Duan, J.–H. Lin, J.–C. Xiao, Y.–C. Gu, *Chem. Commun.* **2017**, *53*, 3870–3873. b) K. J. Hock, L. Mertens, R. M. Koenigs, *Chem. Commun.* **2016**, *52*, 13783–13786. c) Y. Ning, X. Zhang, Y. Gai, Y. Dong, P. Sivaguru, Y. Wang, B. R. P. Reddy, G. Zanoni, X. Bi, *Angew. Chem. Int. Ed.* **2020**, *132*, 6535–6543.

¹⁹⁵ C.–F. Gao, Y.–J. Chen, J. Nie, F.–G. Zhang, C. W. Cheung, J.–A. Ma, *Chem. Commun.* **2023**, *59*, 11664–11667.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes

Asymmetric synthesis of α,α -difluorocyclopropane scaffolds remained undiscovered until the first catalytic methodology was reported by our group in 2017.¹⁹⁶ Under the catalysis of the dirhodium paddlewheel complex $\text{Rh}_2((S)\text{-BTPCP})_4$, a large number of α -difluoromethyl styrenes were converted into the corresponding α,α -difluorocyclopropanes with donor-acceptor or acceptor-acceptor diazo compounds, providing moderate to very good yields (27-95%), high diastereoselectivities (all cases > 10:1), and an excellent enantioselectivity (up to 99% *ee*) (Scheme 3. 2).



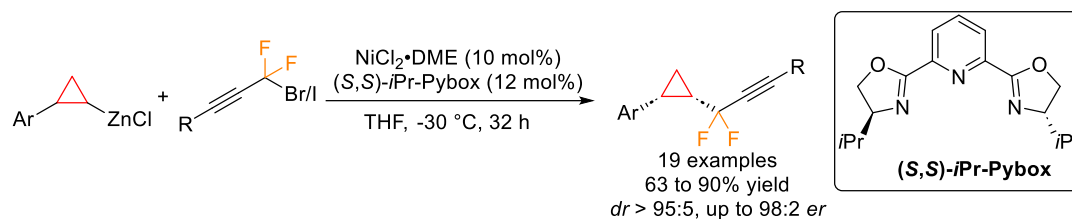
Scheme 3. 2. $\text{Rh}_2((S)\text{-BTPCP})_4$ catalyzed the asymmetric synthesis of α,α -difluoromethylcyclopropanes.

In 2020, Zhang and colleagues reported a straightforward transition metal-catalyzed enantioconvergent coupling protocol that involves widely available difluoromethyl electrophiles and organometallic nucleophiles.¹⁹⁷ The resulting enantiomerically pure α,α -difluorocyclopropane products were obtained with excellent diastereoisomeric ratios (>95:5) and yields from 64% to 90%, up to 98:2 *er* using $\text{NiCl}_2\cdot\text{DME}$ as catalyst in combination with the chiral ligand (*S,S*)-*i*Pr-PyBox (Scheme 3. 3).

¹⁹⁶ M. Bos, W. S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *129*, 13504–13508.

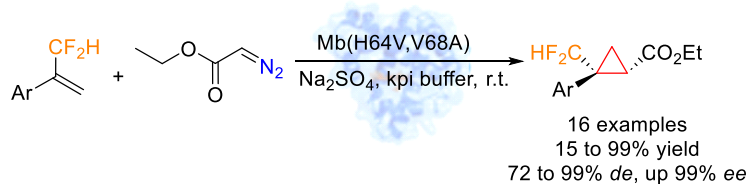
¹⁹⁷ L. An, F.-F. Tong, S. Zhang, X. Zhang, *J. Am. Chem. Soc.* **2020**, *142*, 11884–11892.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes



Scheme 3. 3. Nickel-catalyzed the asymmetric synthesis of α,α -difluoromethylcyclopropanes.

Subsequently, our group in collaboration with Prof. R. Fasan's group disclosed an enzyme-mediated cyclopropanation strategy for the synthesis of α,α -difluoromethylcyclopropanes.^{171d} This innovative approach utilized engineered myoglobin catalysts, enabling the incorporation of α -difluoromethyl styrenes and ethyl diazoacetate to yield a diverse array of CHF₂-containing cyclopropanes. The method exhibited high yields (up to >99%) and exceptional stereoselectivity (up to >99% de and ee), with turnover numbers (TON) reaching up to 3000 (Scheme 3. 4).

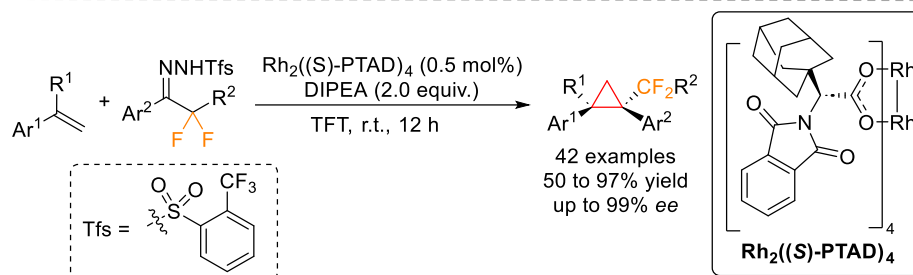


Scheme 3. 4. Enzyme-catalyzed the asymmetric synthesis of α,α -difluoromethylcyclopropanes.

Very recently, the α,α -difluoro- β -carbonyl ketone N -triflylhydrazones reagents acting as diazo precursors, have been exploited by Bi and co-workers to access α,α -difluoromethylcyclopropane building blocks with α,α -disubstituted alkenes.¹⁹⁸ In the presence of the chiral catalyst Rh₂((S)-PTAD)₄, this methodology delivered a series of 1,1,2,2-tetra-functionalized cyclopropanes bearing difluoroalkyl groups, in high yields (50-97% yield), high enantioselectivities (up to 99%), and demonstrated a broad substrate scope (Scheme 3. 5).

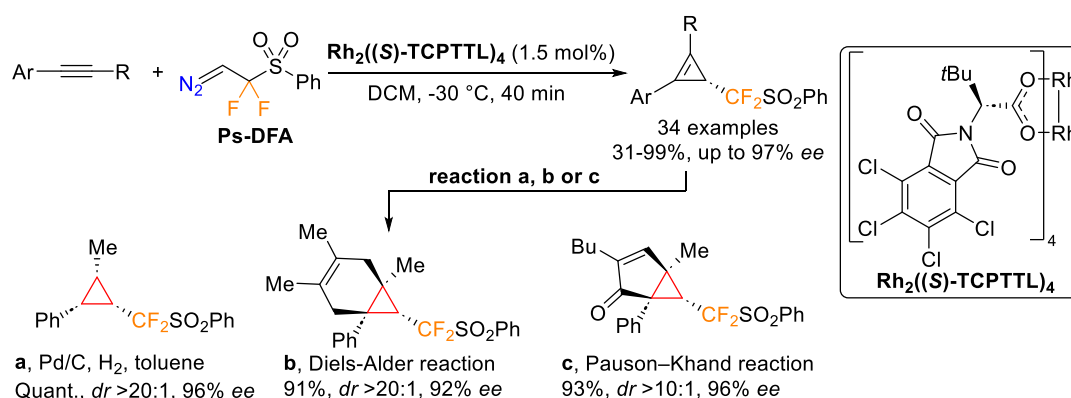
¹⁹⁸ X. Zhang, Y. Ning, C. Tian, G. Zanoni, X. Bi, *iScience* **2023**, 26. 105896.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes



Scheme 3. 5. $\text{Rh}_2((S)\text{-PTAD})_4$ the asymmetric synthesis of α,α -difluoroalkylcyclopropanes.

It should be mentioned that Ma *et al.* depicted a newly designed difluoro diazo compound, phenylsulfonyl difluorodiazomethane (Ps-DFA), in 2018.¹⁹⁹ Subsequently, this Ps-DFA reagent was found to be a crucial component in catalytic asymmetric synthesis of difluoromethylcyclopropanes using chiral Rh(II)-complexes and followed by an additional step (Pd/C reduction, Diels-Alder reaction or Pauson-Khand reaction) to generate difluoromethylcyclopropane frameworks with high yields (91% to quant.) and high *ee* (92-96%) (Scheme 3. 6).²⁰⁰



Scheme 3. 6. Synthesis of enantiopure α,α -difluoroalkyl cyclopropanes and cyclopropanes.

3.2. Objective

In the field of synthesizing usable difluorosubstituted cyclopropane moieties, we have showcased achievements over the past several decades, encompassing both non-asymmetric and asymmetric approaches. However, only four publications have demonstrated the direct access to enantiopure

¹⁹⁹ J.-L. Zeng, Z. Chen, F.-G. Zhang, J.-A. Ma, *Org. Lett.* **2018**, *20*, 4562–4565.

²⁰⁰ Z. Q. Zhang, M. M. Zheng, X. S. Xue, I. Marek, F. G. Zhang, J. A. Ma, *Angew. Chem. Int. Ed.* **2019**, *131*, 18359–18364.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes

difluoromethyl substituted cyclopropanes. Additionally, to the best of our knowledge, the production of optically pure 1,2-disubstituted difluoromethyl substituted cyclopropanes is still relatively unexplored. Therefore, our goal in this chapter is to establish a methodology for synthesizing optically pure 1,2-disubstituted difluoromethyl cyclopropane scaffolds.

Furthermore, inspired by Ma's previous work²⁰⁰ on asymmetric cyclopropanation, we recognized that the Ps-DFA reagent could serve as an excellent metallocarbene precursor for generating difluoromethyl substituted (with a SO₂Ph in this case) three-membered rings in transition metal-catalyzed [2+1] cycloaddition reactions. Hence, we propose the following hypothesis for this project: under the mediation of chiral metal complexes, the asymmetric cyclopropanation reaction will occur between Ps-DFA and versatile alkenes, leading to the construction of enantiopure difluoromethylphenylsulfonyl cyclopropanes (Scheme 3. 7).

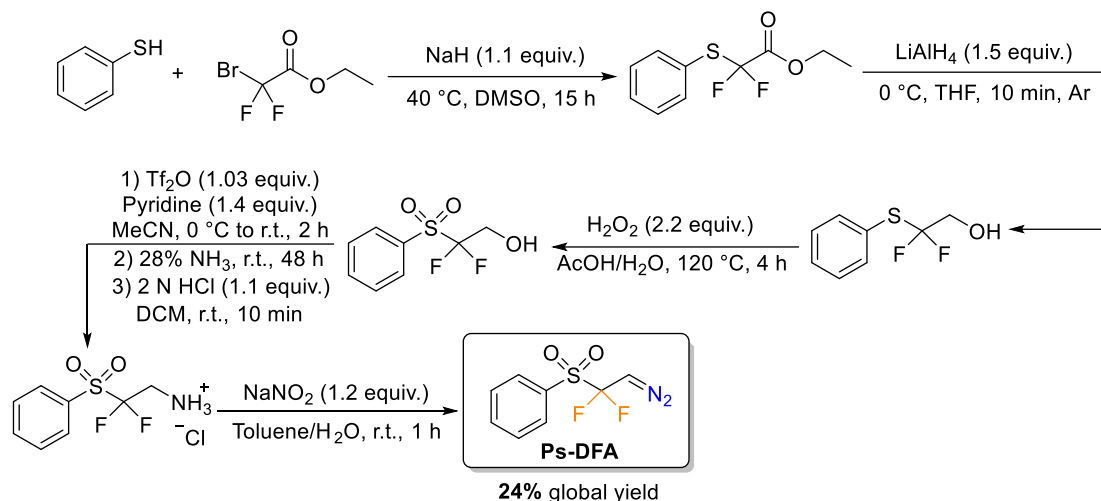


Scheme 3. 7. Project proposal.

3.3. Optimization of the reaction conditions

When we proposed our project, we prepared the Ps-DFA reagent according to Ma's procedure¹⁹⁹ (Scheme 3. 8). Unlike their reported global yield of 65% for 7 steps, our following preparation process resulted in a 24% global yield. Besides, although the diazo reagent Ps-DFA was described as a bench-stable compound, we recognized that it is sensitive to light and heat from our manipulations.

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes



Scheme 3. 8. The synthesis procedure of diazo reagent Ps-DFA.

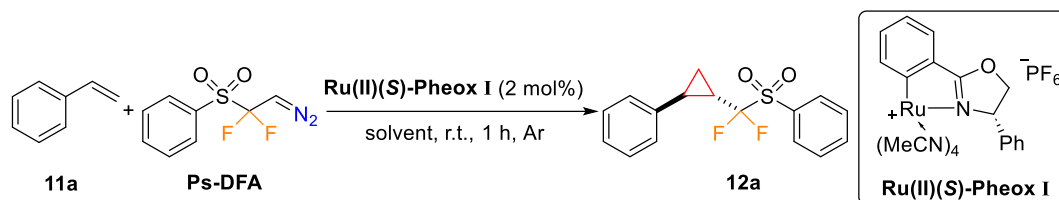
At the beginning of this project, the reactions were performed between styrene **11a** and the diazo reagent Ps-DFA. In the first attempt, a Ru(II)(*S*)-Pheox I catalyzed reaction was carried out using 5 equiv. of styrene **11a** and 1.0 equiv. of the Ps-DFA. To our delight, this reaction provided difluoroSO₂Ph cyclopropane **12a** with 49% NMR yield, 95:5 enantiomeric ratio, and diastereoisomeric ratio greater than 20:1 (Table 3. 1, entry 1). The relative configuration of the product **12a** was determined as a *trans* isomer by ¹H-¹⁹F 2D NMR (see Experimental Part). When an excess of Ps-DFA was used (entries 2-3), the cyclopropane **12a** was obtained with lower yields (37% and 46% respectively), albeit with almost the same stereoselectivity. Therefore, the conditions depicted in entry 1 was selected for further optimization.

entry	equiv. (11a)	equiv. (Ps-DFA)	yield/ (%) ^a	<i>dr</i> ^a	<i>er</i> ^b
1	5.0	1.0	49	>20:1	95:5
2	1.0	1.5	37	>20:1	94.5:5.5
3	1.0	2.0	46	>20:1	94.5:5.5

Table 3. 1. Optimization of the stoichiometry. Reaction conditions: Ps-DFA in DCM (1 mL) was added to solution of **11a** and Ru(II)(*S*)-Pheox I (2 mol%) in DCM (0.5 mL) within 1 h. ^a Yield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromomethane as internal standard. ^b*er* was determined by HPLC chromatography using a chiral IC column.

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As we optimized the ratio between **11a** and Ps-DFA, we next examined the effect of the solvent on the course of this reaction (Table 3. 2). Initially, toluene was tested, but cyclopropane **12a** was produced with a lower yield (24%) and enantiomeric ratio (90:10) (entry 1). Two other solvents were tested individually (entries 2-3); THF afforded difluoroSO₂Ph cyclopropane **12a** in a decent yield (37%) and good enantiomeric ratio (93:7), while Et₂O gave a 16% yield and a 92:8 enantiomeric ratio. Surprisingly, when MeCN was used in this reaction (entry 4), product **12a** was not detected by ¹H NMR, possibly due to the deactivation of the Ru(II)-complex by acetonitrile. We then examined three halogenated solvents (entries 5-7); a moderate yield (52%) was obtained in PhCF₃, CHCl₃ was determined to be a less efficient solvent, yielding **12a** in 39% yield, while DCE afforded **12a** with a higher yield (70%). These three reactions showcased great enantiocontrol abilities (93.5:6.5 to 95:5 *er*). Besides, dioxane (entry 8), EtOAc (entry 9), and acetone (entry 10) were screened as well. However, none of them led to satisfactory results, yielding cyclopropane **12a** in low to moderate yields (54%, 12%, 32%, respectively) and lower enantiomeric ratios (92.5:7.5, 93:7, 94:6, respectively). It is worth to note that in all reaction conditions, that the diastereoselectivities remained excellent (> 20:1).

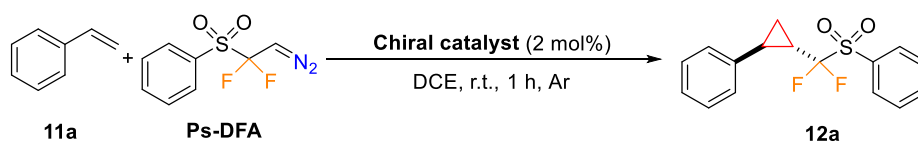


entry	solvent	yield/ (%) ^a	<i>dr</i> ^a	<i>er</i> ^b
1	toluene	24	>20:1	90:10
2	THF	37	>20:1	93:7
3	Et ₂ O	16	>20:1	92:8
4	MeCN	0	-	-
5	PhCF ₃	52	>20:1	94.5:5.5
6	CHCl ₃	39	>20:1	93.5:6.5
7	DCE	70	>20:1	95:5
8	Dioxane	54	>20:1	92.5:7.5
9	EtOAc	12	>20:1	93:7
10	Acetone	32	>20:1	94:6

Table 3. 2. The screening of solvents. Reaction conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in solvent (1 mL) was added to solution of **11a** (0.5 mmol, 5.0 equiv.) and Ru(II)(S)-Pheox I (2 mol%) in solvent (0.5 mL) within 1 h. ^aYield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromomethane as internal standard. ^b*er* was determined by HPLC chromatography using a chiral IC column.

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We further optimized the reaction by investigating the effect of different chiral metal complexes (Table 3. 3). Since we demonstrated that Ru(II)(*S*)-Pheox I was an efficient catalyst in this cyclopropanation process (entry 1), several Ru(II)-complexes chelated with oxazoline ligands were employed. The catalyst Ru(II)(*S*)-Pheox II was used in this reaction (entry 2), and the product **12a** was observed in 33% yield, 91:9 *er*, and over 20:1 *dr*. When Ru(II)(*S*)-Pheox III was tested (entry 3), the cyclopropanation reaction delivered the expected product **12a** in high *er* (95:5) and excellent *dr* (>20:1), but the yield was modest (45%). The cyclopropane product **12a** was afforded with excellent stereocontrol (>20:1 *dr*, 3:97 *er*) in the presence of the catalyst Ru(II)(*R*)-Pheox IV (entry 4). However, the yield still remained moderate (52%). Afterwards, two chiral rhodium catalysts ($\text{Rh}_2((S)\text{-phTCP})_4$ and $\text{Rh}_2((S)\text{-TCPTTL})_4$) were examined in the cyclopropanation reaction (entries 5-6). Although both of them produced **12a** in decent yields (28%, 57%, respectively), the diastereoselectivity (38:62 *dr*, 30:70 *dr*, respectively) and enantioselectivity (78:22 *er*, 80:20 *er*, respectively) were not satisfactory.



 Ru(II)(<i>S</i>)-Pheox I	 Ru(II)(<i>S</i>)-Pheox II	 Ru(II)(<i>S</i>)-Pheox III
(1) 70%, >20:1 <i>dr</i> , 95:5 <i>er</i>	(2) 33%, >20:1 <i>dr</i> , 91:9 <i>er</i>	(3) 45%, >20:1 <i>dr</i> , 95:5 <i>er</i>
 Ru(II)(<i>R</i>)-Pheox IV	 $\text{Rh}_2((S)\text{-phTCP})_4$	 $\text{Rh}_2((S)\text{-TCPTTL})_4$
(4) 52%, >20:1 <i>dr</i> , 3:97 <i>er</i>	(5) 28%, 38:62 <i>dr</i> , 78:22 <i>er</i>	(6) 57%, 30:70 <i>dr</i> , 80:20 <i>er</i>

Table 3. 3. The investigation of different chiral metal complex. Ps-DFA (0.1 mmol, 1.0 equiv.) in DCE (1 mL) was added to solution of **11a** (0.5 mmol, 5.0 equiv.) and chiral catalyst (2 mol%) in DCE (0.5 mL) within 1 h. Yield and *dr* (*trans/cis*) were determined on the crude product by ^1H NMR, dibromomethane as internal standard. *er* was determined by HPLC chromatography using a chiral IC column.

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After selecting Ru(II)(S)-Pheox I as the optimal catalyst for this asymmetric cyclopropanation process, we continued to optimize the parameters of this reaction (Table 3. 4). The addition time of Ps-DFA solution was examined, with 4 h (entry 1) and 10 h (entry 2) additions showing no obvious differences from 1 h, giving 69% and 70% NMR yields, 95:5 and 94:6 *er*. Next, two temperatures (0 °C, entry 3 and -10 °C, entry 4) of reactions were examined respectively; however, the product **12a** was obtained in lower yields (59%, 37%, respectively) and without any improvement for the *er* (95:5 in each case). Furthermore, the catalyst loading was also screened. However, when we used a higher amount of catalyst (3 and 5 mol%) (entries 5-7), the yields of **12a** were much lower than 70%. Finally, we found out that the Ps-DFA reagent easily decomposed, even though this reagent was stored below 4 °C under argon. With freshly prepared Ps-DFA, three reactions were independently performed with 2, 3, or 5 mol% catalyst Ru(II)(S)-Pheox I (entries 8-10). Fortunately, the yields of **12a** were improved with increasing catalyst loading. The optimal condition was found to employ 5% Ru(II)(S)-Pheox I, affording (96:4 *er*) cyclopropane **12a** in 83% ¹H NMR yield (isolated yield: 74%) and excellent *er* (96:4). It is important to notice that for all the reactions, the *dr* was excellent (> 20:1).

entry	cat. (x mol%)	T/(°C)	t/(h)	yield/(%) ^a	<i>dr</i> ^a	<i>er</i> ^b
1	2	r.t.	4	69	>20:1	95:5
2	2	r.t.	10	70	>20:1	94:6
3	2	0	1	59	>20:1	95:5
4	2	-10	1	37	>20:1	95:5
5	3	r.t.	1	43	>20:1	95:5
6	5	r.t.	1	39	>20:1	96:4
7	2	r.t.	1	42	>20:1	n.d
8	2	r.t.	1	68	>20:1	94.5:5.5
9	3	r.t.	1	70	>20:1	95:5
10	5	r.t.	1	83(74)	>20:1	96:4

Table 3. 4. Optimization of reaction addition time, temperature and catalyst loading. Reaction

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conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in DCE (1 mL) was added to solution of **11a** (0.5 mmol, 5.0 equiv.) and Ru(II)(*S*)-Pheox I (x mol%) in DCE (0.5 mL) within 1 h. ^a Yield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromomethane as internal standard. ^b *er* was determined by HPLC chromatography using a chiral IC column. Isolated yield was given in parathesis. n.d. = no detected.

3.4. Scope of the reaction

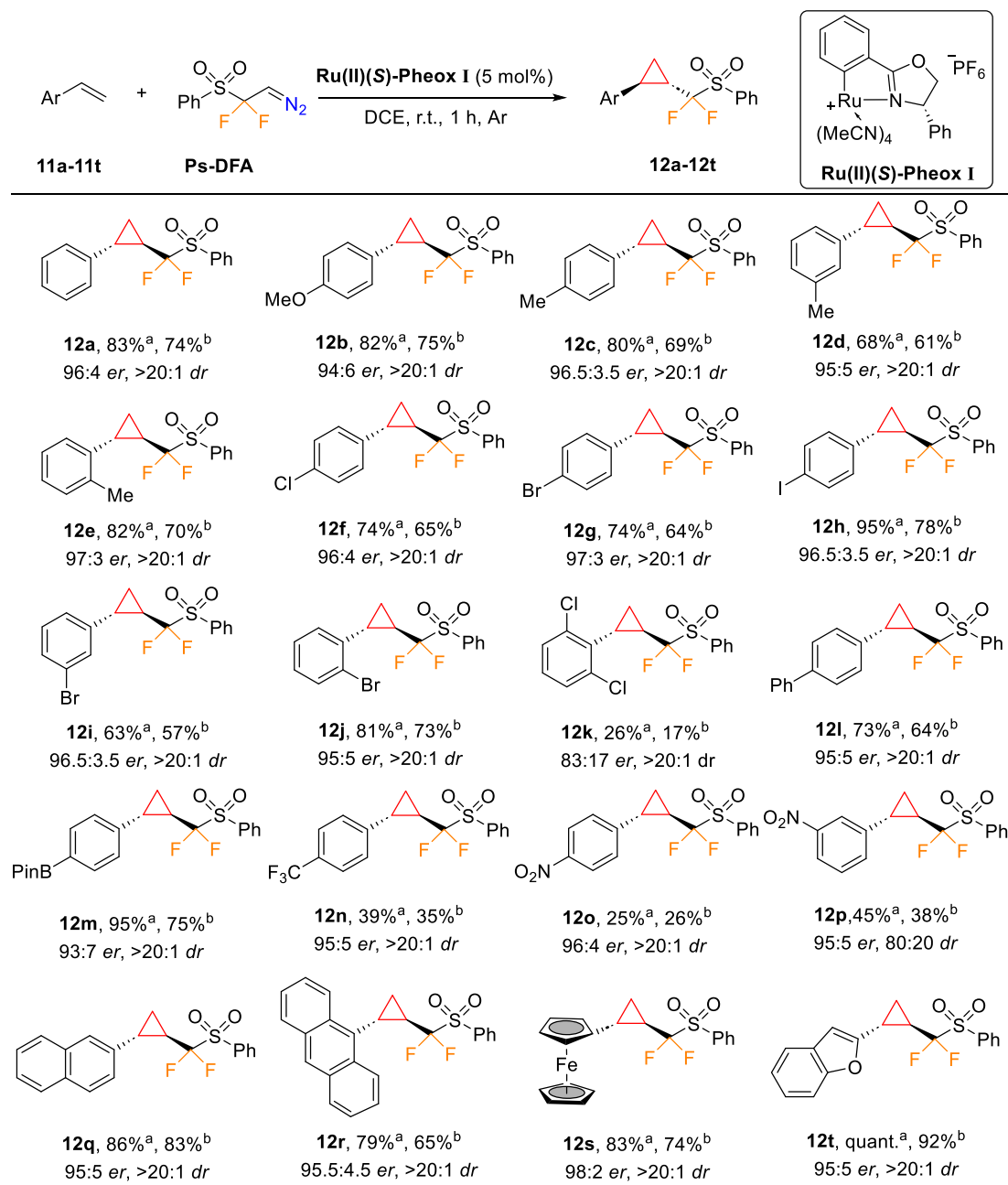
With the optimal reaction conditions in hand (Table 3. 4, entry 10), we turned to examine the feasibility of this approach with different aromatic alkenes (Scheme 3. 9). First, the enantioenriched cyclopropane **12a** generated from styrene was obtained in a 74% isolated yield and 96:4 *er*. *Para*-methoxy substituted styrene led to the corresponding difluoroSO₂Ph cyclopropane **12b** in very good isolated yield (75%) and high *er* (94:6). Methyl groups at different positions (*para*, *meta*, *ortho*) on the aromatic ring were also well tolerated in all cases, generating high enantiomeric pure (95:5 to 97:3 *er*) products **12c** to **12e** in good yields (61-70%).

Subsequently, a series of styrenes bearing halogens in different positions (**11f-11k**) were similarly screened. Regarding the substitution on the *para* position Cl, Br, and I was found to be compatible under the cyclopropanation process, and the corresponding products (**12f-12h**) were isolated in good yields (64%-78%) as well as excellent *er* (96:4 to 93:7). The *meta*-bromo styrene substrate led to the expected cyclopropane **12i** in 57% yield and 96.5:3.5 *er*, whereas the *ortho*-bromo substrate afforded to **12j** in 73% yield and 95:5 *er*. However, when 2,6-dichlorostyrene was tested, the corresponding product **12k** was obtained in low yield (17%) and *er* decreased to 83:13, probably because of steric hindrance effects.

Notably, the current method also exhibits high reactivity and stereocontrol for *para*-phenyl and *para*-boronic pinacol ester group styrenes, leading to cyclopropanes **12l** and **12m** in good yields (64%, 75% respectively) and high enantioselectivities (95:5, 93:7 *er* respectively). It was found that styrenes bearing strong electron-withdrawing groups (CF₃ and NO₂) were also tolerated but the corresponding difluoroalkyl cyclopropanes **12n-12p** were obtained in moderate yields (26-38%), high *er* (95:5 to 96:4). In the case of **12p**, we observed lower *dr* (80:20). Interestingly, the cyclopropanation process proceeded smoothly with other aromatic alkenes such 2-vinyl naphthalene, vinylanthracene, vinylferrocene, and vinylbenzofuran leading to the expected cyclopropanes **12q-**

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12t in good to excellent isolated yields (65-92%) and excellent *er* (95:5 to 98:2). It is worth mentioning that the diastereoselectivity for each reaction remains excellent except for **12p** as mentioned before.

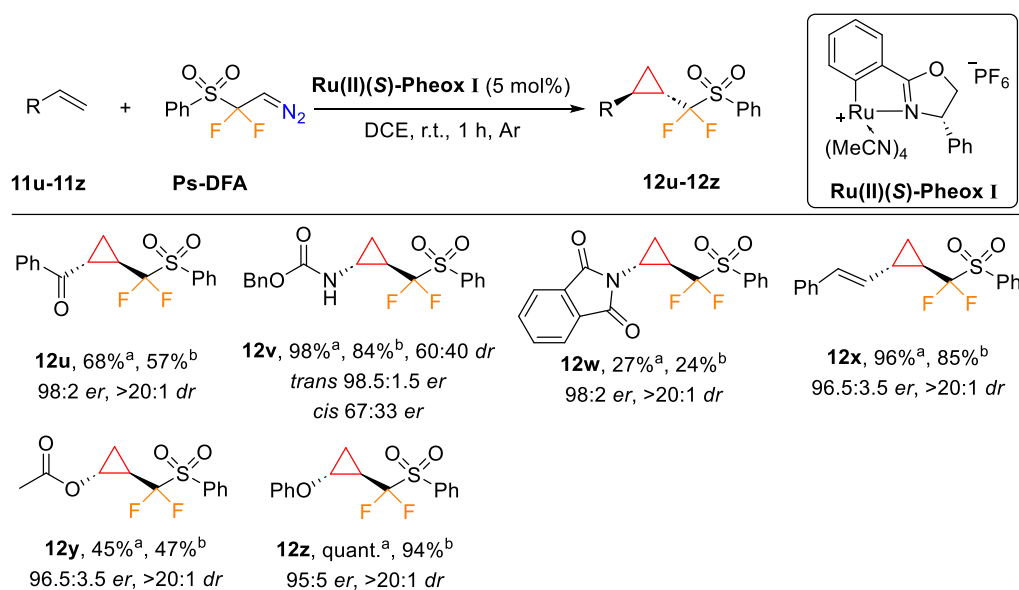


Scheme 3. 9. Scope of aromatic alkenes. Reaction conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in solvent (1 mL) was added to the solution of **11** (0.5 mmol, 5.0 equiv.) and Ru(II)(S)-Pheox I (5 mol%) in DCE (0.5 mL) within 1 h. ^aNMR yield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromomethane as internal standard. ^b Isolated yield. *er* was determined by HPLC chromatography using a chiral column.

After exploring the scope of aromatic alkenes, we tried to extend the protocol to others types of

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alkenes (Scheme 3. 10). Electron-deficient alkene such as an unsaturated ketone was tested and we were very pleased to obtain the expected cyclopropane **12u** in 57% yield, 98:2 *er*, and greater than 20:1 *dr*. Then, an alkene with a carbamate group were tested as well. Unexpectedly, the cyclopropanation product **12v** was as a separable mixture of diastereoisomers (60:40 *dr*) in a high yield (84%), and the *er* was determined as 98.5:1.5 for the *trans* and 67:33 for the *cis*. The difluoroalkyl cyclopropane **12w** from vinylphthalimide was observed in a moderate yield (24%), but with excellent enantio- (98:2 *er*) and diastereo-selectivities (>20:1 *dr*). The use of a diene substrate was then evaluated, resulting in the formation of the expected cyclopropane **12x** in 85% yield and excellent stereocontrol (96.5:3.5 *er* and >20:1 *dr*) and regioselectivity. Finally, in the presence of vinyl acetate and vinyloxybenzene, the cyclopropanation reactions were successfully carried out to afford the corresponding products **12y** and **12z** in 47% and 94% yields, respectively, either enantiopurity (96.5:3.5, 95:5, respectively) or diastereomeric ratio (>20:1) are excellent.

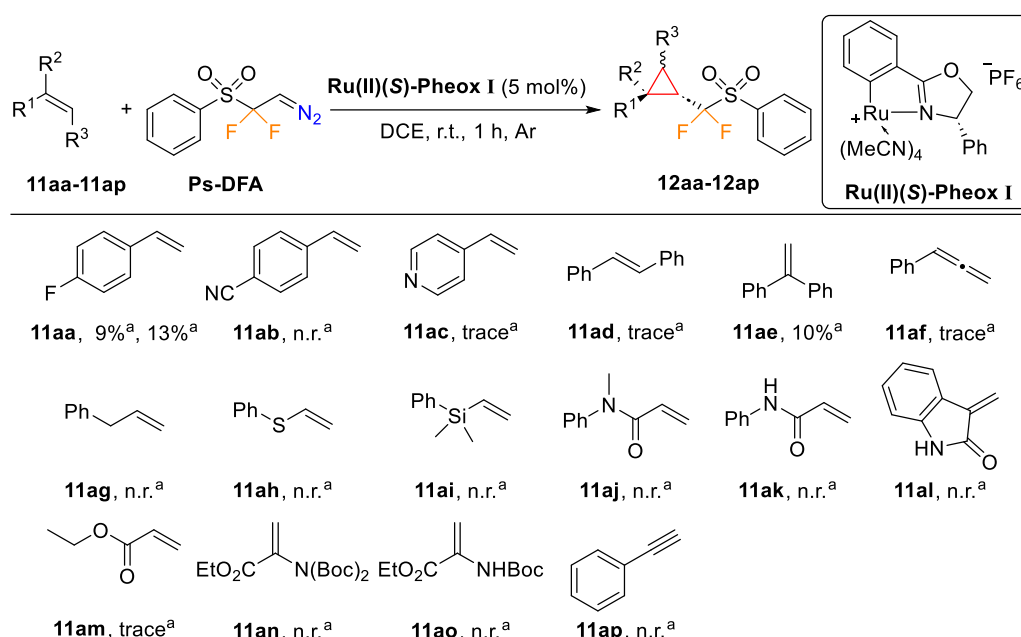


Scheme 3. 10. Scope of alternative alkenes. Reaction conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in DCE (1 mL) was added to solution of alkene **11** (0.5 mmol, 5.0 equiv.) and Ru(II)(*S*)-Pheox I (5 mol%) in DCE (0.5 mL) within 1 h. ^aNMR yield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromethane as internal standard. ^b Isolated yield. *er* was determined by HPLC chromatography using a chiral column.

Although the method has been demonstrated as a powerful protocol for a large scope of alkenes, some reluctant substrates were also identified (Scheme 3. 11). For example, when styrene derivatives **11aa-11ae** were employed, the cyclopropanation processes yielded unpromising

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outcomes, with only 9% or 13% observed for 4-F styrene (**11aa**) and 10% for α -diphenyl alkene (**11ae**), respectively. Furthermore, allene (**11af**), benzyl alkene (**11ag**), vinyl sulfide (**11ah**), and vinyl silane (**11ai**) substrates were reluctant. Additionally, substrates bearing in α position a carbonyl function such as an amide (**11aj-11al**) or an ester group (**11am**) were identified as reluctant partners. Michael acceptors with a masked amino-acid function such as **11an** and **11ao** remained unreactive. Finally, a cyclopropanation reaction was attempted with phenylacetylene (**11ap**), but the reaction did not provide any product.

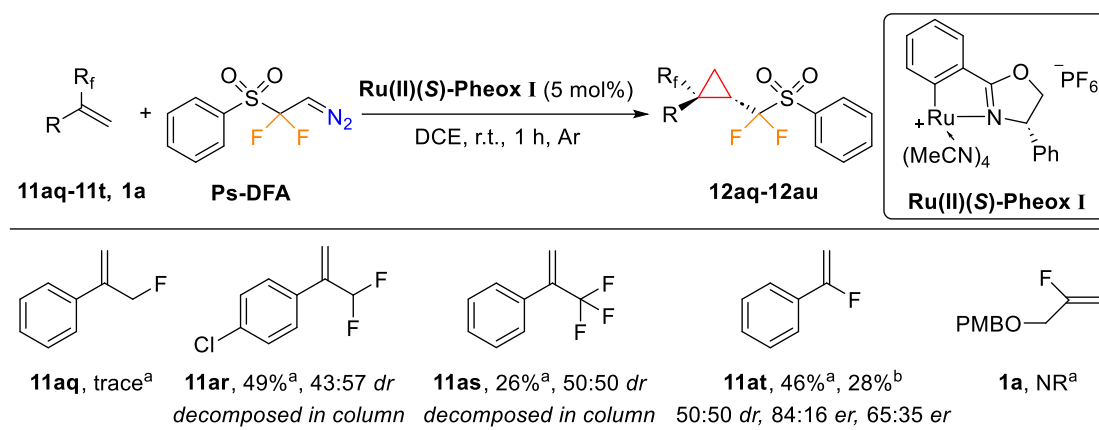


Scheme 3.11. Reluctant substrates of scope. Reaction conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in DCE (1 mL) was added to the solution of **11** (0.5 mmol, 5.0 equiv.) and Ru(II)(S)-Pheox I (5 mol%) in DCE (0.5 mL) within 1 h. ^aNMR yield was determined on the crude product by ¹H NMR, dibromomethane as internal standard. n.r. = no reaction.

The development of this asymmetric cyclopropanation strategy was then examined using fluorinated alkenes (Scheme 3. 12). The α -fluoro, monofluoromethyl, difluoromethyl, and trifluoromethyl styrene derivatives were engaged in the reaction. The use of **11aq** led to only traces of the expected cyclopropane. When **11ar** and **11as** were employed, the targeted cyclopropane products were observed with 49% yield and 43:57 *dr*, and 26% yield and 50:50 *dr*, respectively, upon analysis of the crude mixture by ¹H NMR. However, both decomposed during the purification process (silica-gel column chromatography). α -Monofluoroalkene **11at** and **1a** were also tested; the corresponding product **12at** was isolated in 28% yield, with a 50:50 *dr* and 84:16 *er*, 65:35 *er*, while no reaction

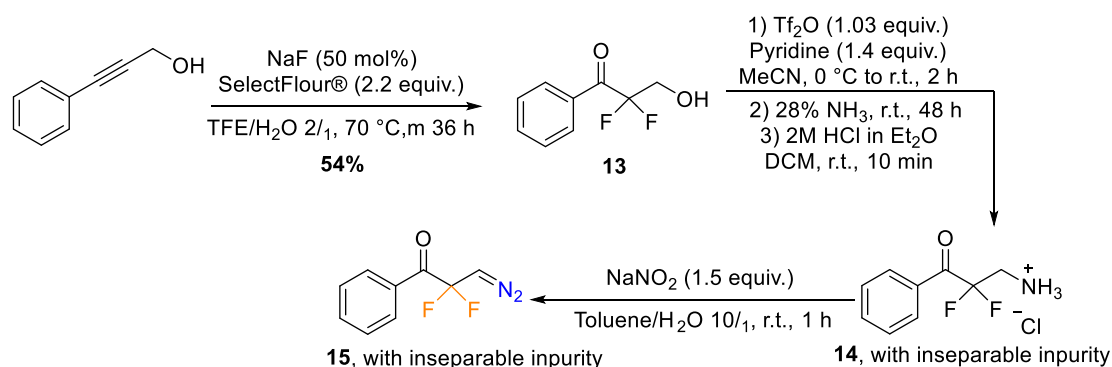
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occurred with **1a**.



Scheme 3. 12. Scope of fluorinated alkenes. Reaction conditions: Ps-DFA (0.1 mmol, 1.0 equiv.) in DCE (1 mL) was added to the solution of fluorinated alkene **11** (0.5 mmol, 5.0 equiv.) and Ru(II)(S)-Pheox I (5 mol%) in DCE (0.5 mL) within 1 h. ^aNMR yield and *dr* (*trans/cis*) were determined on the crude product by ¹H NMR, dibromomethane as internal standard. ^b Isolated yield. *er* was determined by HPLC chromatography using a chiral IE column.

After completing the investigation on alkenes, we planned to examine a scope for the diazo derivatives by modifying the functional group next to the difluoromethylene. Unfortunately, for the preparation of others difluoro substituted diazomethane analogs, we faced unprecedented synthetic challenges. For instance, difluoro alcohol **13** could be easily prepared from the starting material 3-phenylprop-2-yn-1-ol, in 54% yield. However, subsequent steps only produced products **14** or **15** with inseparable impurities (Scheme 3. 13).

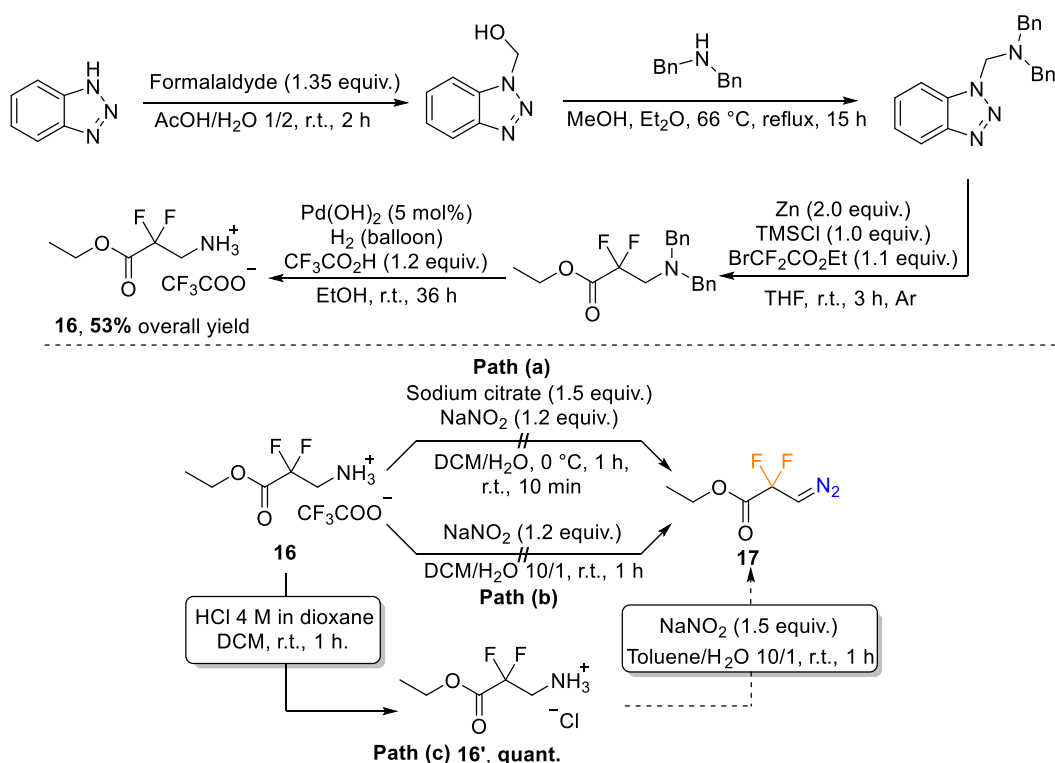


Scheme 3. 13. Synthesis of benzoyl difluoromethyl diazomethane **15**.

Another difluoro diazo compound **17** was also considered for its use in the asymmetric cyclopropanation process. The synthesis route started with benzotriazole, upon treatment with formaldehyde and dibenzylamine, 1-(dibenzylaminomethyl)benzotriazole was generated, which

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underwent a nucleophilic addition with $\text{BrCF}_2\text{CO}_2\text{Et}$, along with the cleavage of benzisotriazole. Subsequently, reductive conditions in the presence of $\text{Pd}(\text{OH})_2$, H_2 , and $\text{CF}_3\text{CO}_2\text{H}$ were conducted, resulting in the diazo precursor **16** with a 53% overall yield for these four steps of reactions. (Scheme 3. 14). However, subsequent operation by employment of either sodium citrate and sodium nitrite (path a) or only sodium nitrite (path b) in mixed solvent (DCM/ H_2O) did not provide the desired product **17**. As an attempt to overcome this issue, path c was proposed; The first step successfully produced the ammonium chloride compound **16'** in quantitative conversion when compound **16** was treated with 4 M HCl, but as of now, the second step has not been carried out.



Scheme 3. 14. Synthesis of difluorodiazo ester **17**.

3.5. Stereochemistry and mechanism

3.5.1. Stereochemistry

The absolute configuration of phenyl sulfonyl difluoroalkyl cyclopropane was determined through single crystal X-ray diffraction analysis. The product **12a**, derived from the formal styrene and Ps-DFA, was confirmed to have an absolute configuration of **1R**, **2R** (Figure 3. 2). This result provides

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insights regarding the absolute configurations of all the phenyl sulfonyl difluoroalkyl cyclopropane products presented in Scheme 3. 9 and Scheme 3. 10.

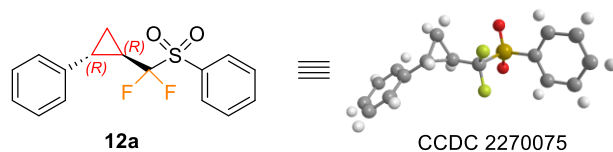
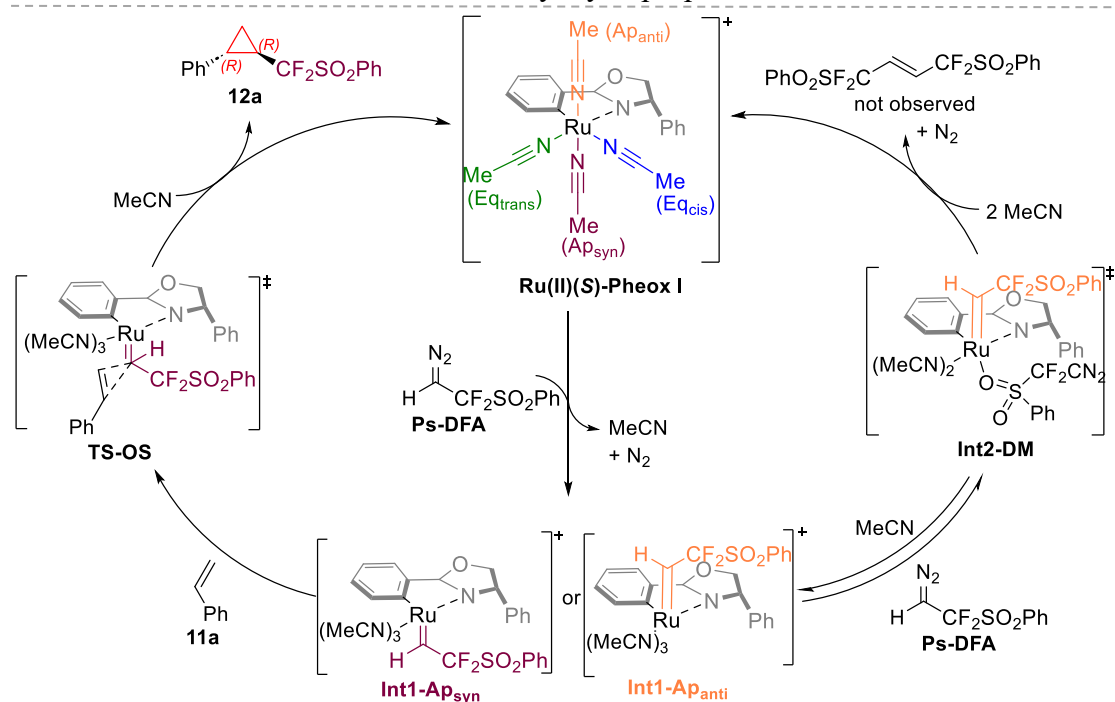


Figure 3. 2. X-ray diffraction analysis of difluoroalkyl cyclopropane **12a**.

3.5.2. Proposed mechanism

Based on the stereochemical outcome of compound **12a**, we propose a plausible mechanism for this Ru(II)-catalyzed Ps-DFA asymmetric cyclopropanation process (Scheme 3. 15), similar to the one discussed in Chapter 2. Initially, two viable carbene complexes (**Int1- A_{syn}** and **Int1- A_{anti}**) are formed through ligand dissociation of Ru(II)-Pheox I in the presence of the Ps-DFA reagent. Furthermore, the **Int1- A_{syn}** intermediate engages with alkene **11a** to generate the **TS-OS** species through an outer-sphere mechanism. Finally, the product **12a** is released by recombination with a MeCN ligand, along with the regeneration of the catalyst Ru(II)-Pheox I. On the other hand, the **Int1- A_{anti}** intermediate would lead to a dimerization product of the diazo reagent in the previous study. However, the dimerization product of Ps-DFA isn't observed in the cyclopropanation process. This suggests that the formation of the **Int2-DM** species is disfavored through the inner-sphere mechanism.

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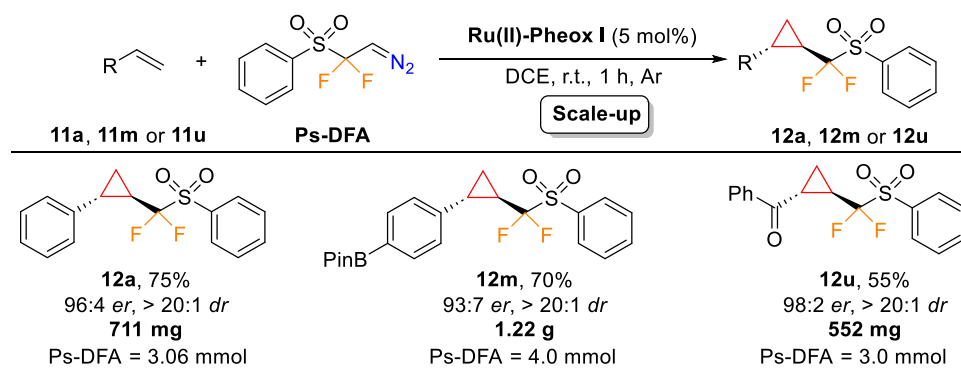


Scheme 3. 15. The plausible mechanism of Ru(II)-catalyzed Ps-DFA asymmetric cyclopropanation process.

3.6. Scale-up and post-functionalization reactions

3.6.1. Scale-up reactions

To demonstrate the robustness and applicability of the asymmetric synthetic approach, the reaction was scaled up with several alkenes (**11a**, **11m**, **11u**, Scheme 3. 16). The cyclopropanation products **12a**, **12m**, and **12u** were obtained in yields of 75% (711 mg), 70% (1.22 g), and 55% (552 mg), respectively. Stereochemical analyses (*er* and *dr*) were found to be consistent with the 0.1 mmol scale reactions.



Scheme 3. 16. Scale-up reactions. Reaction conditions: Ps-DFA (1.0 equiv.) in DCE was added to

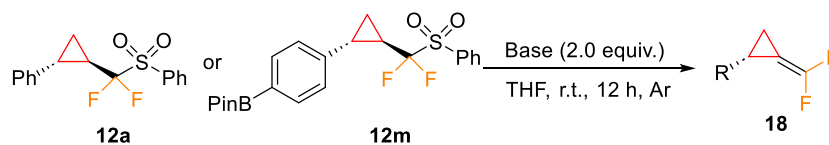
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 solution of alkene **11** (5.0 equiv.) and Ru(II)(*S*)-Pheox I (5 mol%) in DCE within 1 h.

3.6.2. Post-functionalization reactions

Thanks to the developed approach, the products can be converted into high value added diversely functionalized cyclopropanes with enantioenriched difluoroalkyl carbon stereogenic centers. These hold significant promise as valuable chiral building blocks for various applications in stereoselective organic syntheses. Therefore, a number of reactions were carried out for the transformation of compounds **12**.

The first attempt was to convert cyclopropane **12** into methylene cyclopropane **18** through the removal of the phenylsulfonyl group (Table 3. 5). Unfortunately, the use of LiHMDS²⁰¹ as a base did not yield the desired products, for either substrate **12a** or **12m** (entries 1 and 2). Despite the introduction of a stronger base (*n*BuLi), the reaction with substrate **12a** showed no reaction (entry 3).



entry	substrate	base	result
1	12a	LiHMDS	n.r.
2	12m	LiHMDS	no desired product
3	12a	<i>n</i> BuLi	n.r.

Table 3. 5. Elimination reaction of cyclopropane **12a** and **12m**. n.r. = no reaction.

Additionally, the phenylsulfonyl group can be considered as a leaving group to generate a carbon anion²⁰² or a carbon radical.²⁰³ Hence, several electrophiles and radical acceptors were employed to replace this phenylsulfonyl group and synthesize a variety of new stereospecific difluoroalkyl cyclopropanes **19** (Table 3. 6). However, when electrophiles such as trimethylsilyl chloride^{202b}

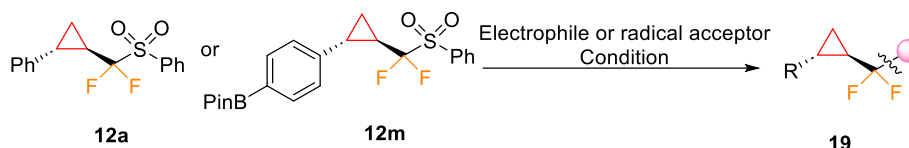
²⁰¹ Z. He, M. Hu, T. Luo, L. Li, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11545–11547.

²⁰² a) P. Xiao, J. Rong, C. Ni, J. Guo, X. Li, D. Chen, J. Hu, *Org. Lett.* **2016**, *18*, 5912–5915. b) G. S. Prakash, J. Hu, G. A. Olah, *J. Org. Chem.* **2003**, *68*, 4457–4463.

²⁰³ V. Reutrakul, T. Thongpaisanwong, P. Tuchinda, C. Kuhakarn, M. Pohmakotr, *J. Org. Chem.* **2004**, *69*, 6913–6915.

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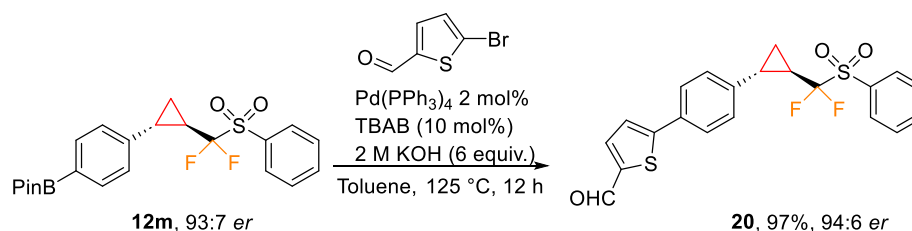
(entry 1) and tolyl disulfide^{202a} (entry 2) were used, none of them exhibited reactivity towards substrate **12a**. Similar reaction was attempted with substrate **12m** using diphenyl selenide and NaH in DMF,²⁰⁴ but still, no conversion was observed (entry 3). The radical acceptor (styrene) was tested with substrate **12a** under the conditions of Sm, CH₂I₂, and *i*PrOH,²⁰³ however, the reaction remained unresponsive (entry 4).



entry	substrate	reagents	condition	result
1	12a	TMSCl (4.6 equiv.)	Mg (2.0 equiv.), DMF, r.t.	n.r.
2	12a	Tolyl disulfide (2.0 equiv.)	<i>t</i> BuOK (2.0 equiv.) DMF, r.t.	n.r.
3	12m	diphenyl selenide (2.0 equiv.)	NaH (8.0 equiv.) DMF, r.t.	n.r.
4	12a	Styrene (5.0 equiv.)	Sm (8.3 equiv.), CH ₂ I ₂ (5.0 equiv.) <i>i</i> PrOH (5.0 equiv.), THF, HMPA, r.t.	n.r.

Table 3. 6. Electrophilic substitution reactions of substrate **12a** and **12m**. n.r. = no reaction.

Moreover, a Suzuki-Miyaura reaction was conducted on cyclopropane **12m** using 5-bromothiophene-2-carbaldehyde²⁰⁵ as coupling partner (Scheme 3. 17). This reaction provided the new compound **20** in an excellent yield of 97%, and no epimerization was observed during the coupling process.



Scheme 3. 17. Suzuki-Miyaura reaction on cyclopropane **12m**.

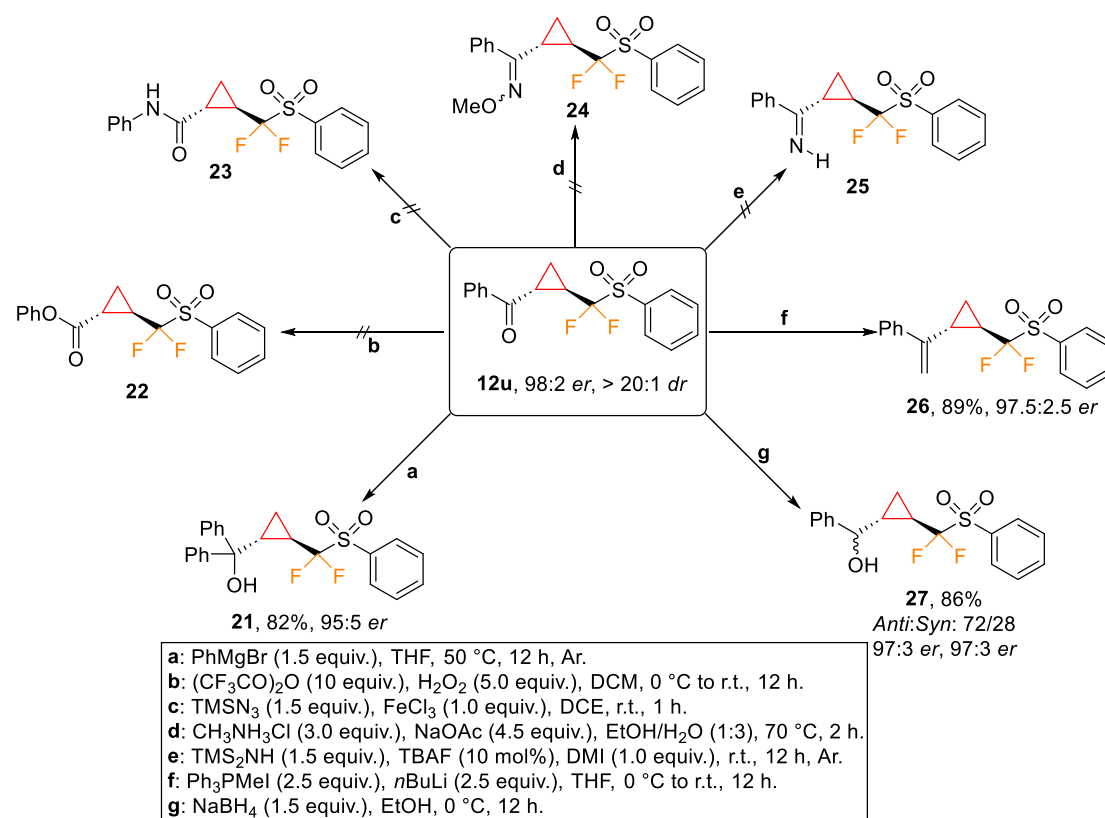
Furthermore, we next examined some post-functionalization starting from cyclopropane **12u**

²⁰⁴ P. Xiao, C. Ni, W. Miao, M. Zhou, J. Hu, D. Chen, J. Hu, *J. Org. Chem.* **2019**, *84*, 8345–8359.

²⁰⁵ Z. Song, C. Luo, (**2021**) *Compound with aggregation-induced emission property, and application thereof in field of surgical navigation* (CN113105441A).

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(Scheme 3. 18). First, the addition of Grignard reagent PhMgBr²⁰⁶ was tested and the corresponding tertiary alcohol was obtained efficiently, after 12 h heating at 50°C in THF, in 82% isolated yield. A slight erosion of the enantiomeric ratio (95:5) was observed (Scheme 3. 18a). Subsequent attempts, including oxidation,²⁰⁷ amide,²⁰⁸ oxime,²⁰⁹ imine²¹⁰ formation was tested but no interesting results were obtained up to date. (Scheme 3. 18b-e). Next, we attempted a Wittig reaction with substrate **12u** in the presence of Ph₃P⁺MeI⁻ reagent and *n*BuLi as a base, resulting in the corresponding product **26** obtained in an 89% yield with an excellent *er* (97.5:2.5) (Scheme 3. 18f). Compound **12u** can also be converted into a secondary alcohol by the use of NaBH₄ in EtOH,²¹¹ offering a mixture of products (*anti/syn* 72:28) in an 86% yield. The enantiomeric ratio of each isomer remained very good as 97:3 (Scheme 3. 18g).



Scheme 3. 18. Transformation reactions of compound **12u**.

²⁰⁶ X. Y. Tang, M. Shi, *Eur. J. Org. Chem.* **2010**, 21, 4106–4110.

²⁰⁷ T. D. Avery, B. W. Greatrex, D. S. Pedersen, D. K. Taylor, E. R. Tiekink, *J. Org. Chem.* **2008**, 73, 2633–2640.

²⁰⁸ J. Yadav, B. S. Reddy, U. S. Reddy, K. Praneeth, *Tetrahedron Lett.* **2008**, 49, 4742–4745.

²⁰⁹ L. Da Ho, N. Otag, I. Fujisawa, S. Iwasa, *Org. Lett.* **2019**, 21, 7470–7474.

²¹⁰ Y. Kondo, Y. Hirazawa, T. Kadota, K. Yamada, K. Morisaki, H. Morimoto, T. Ohshima, *Org. Lett.* **2022**, 24, 6594–6598.

²¹¹ X.-F. Tan, F.-G. Zhang, J.-A. Ma, *Beilstein J. Org. Chem.* **2020**, 16, 638–644.

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Finally, we turned our attention to the reduction of the sulfonyl group present in our chiral cyclopropanic scaffolds **12** in order to obtain chiral 1,2-disubstituted difluoromethyl cyclopropanes **28** (Table 3. 7). Indeed, the cleavage of the sulfonyl group is generally carried out using reductive conditions as it was reported in the literature.²¹² Initially, an excess of magnesium turnings was employed to achieve this reaction from cyclopropane **12a** (entries 1-3). However, all attempts, including the use of a mixture of solvents, additional catalytic amounts of HgCl₂²¹³ or the use of HOAc-NaOAc buffer,²⁰¹ failed. The following reductive conditions employing SmI₂ and MeOH in THF,²¹⁴ was also unsuccessful from **12a** (entry 4). To our delight, using 30.0 equiv. of magnesium and a catalytic amount of I₂ in MeOH²¹⁵ provided the expected product **28a** in 62% isolated yield (entry 5). A better result was obtained using a home-made reductive reagent, 3% Na-Hg,²¹⁶ delivering the expected cyclopropane in an excellent 88% yield of **28a** without any erosion of the *er* (entry 6). The reduction of sulfonyl group reactions was also tested on cyclopropanes **12m**, **20**, and **12u** using magnesium and HOAc/NaOAc buffer (entries 7-9), but the corresponding products weren't observed. For **12u**, the use of Na-Hg reagent or magnesium and catalytic I₂ was unsuccessful (entries 10, 11). Finally, the use of Na-Hg amalgam for substrates **26** and **12z** was very efficient leading to the expected difluoromethyl cyclopropanes in 74% for **28b** and 83% for **28c** without any erosion of the *er* (entries 12, 13).

²¹² a) C. Nájera, M. Yus, *Tetrahedron* **1999**, *55*, 10547–10658. b) D. A. Alonso, C. N. Ájera, *Desulfonylation Reactions. In Organic Reactions*; S. E. Denmark, Ed.; **2008**, Vol 72. c) R. Jia, X. Wang, J. Hu, *Tetrahedron Lett.* **2021**, *75*, 153182. d) E. Ismalaj, D. Le Bars, T. Billard, *Angew. Chem. Int. Ed.* **2016**, *55*, 4790–4793.

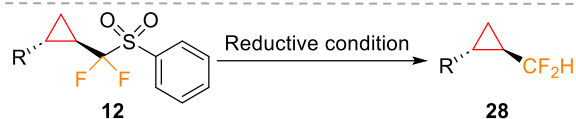
²¹³ J. Zhu, F. Wang, W. Huang, Y. Zhao, W. Ye, J. Hu, *Synlett* **2011**, *2011*, 899–902.

²¹⁴ M. Nambo, J. C.-H. Yim, L. B. Freitas, Y. Tahara, Z. T. Ariki, Y. Maekawa, D. Yokogawa, C. M. Crudden, *Nat. Commun.* **2019**, *10*, 4528.

²¹⁵ C. Batisse, M. F. C. Davila, M. Castello, A. Messara, B. Vivet, G. Marciniak, A. Panossian, G. Hanquet, F. R. Leroux, *Tetrahedron* **2019**, *75*, 3063–3079.

²¹⁶ C. Ni, L. Zhang, J. Hu, *J. Org. Chem.* **2008**, *73*, 5699–5713.

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entry	substrate	conditions	result
1	12a R = Ph	Mg (2.5 equiv.), HOAC/H ₂ O (v/v 1:1), DMSO, r.t., 36 h	trace
2	12a R = Ph	Mg (2.0 equiv.), HgCl ₂ (5 mol%), DMF, - 10 °C to r.t., 3 h	n.r.
3	12a R = Ph	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	trace
4	12a R = Ph	SmI ₂ (3.0 equiv.), MeOH (2.0 equiv.), THF, r.t., 14 h, Ar	n.r.
5	12a R = Ph	Mg (30 equiv.), I ₂ (cat.), MeOH, r.t., 16 h	28a, 62% yield (n.d. <i>er</i>)
6	12a R = Ph	3% Na-Hg (5.0 equiv.), Na ₂ HPO ₄ (7.0 equiv.), MeOH, -30 °C to r.t., 1 h	28a, 88% yield (96:4 <i>er</i>)
7	12m R = 4-BpinPh	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	no desired product
8	20 R = 4-(2-CHO- thiophen-5-yl)Ph	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	n.r.
9	12u R = benzoxyl	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	n.r.
10	12u R = benzoxyl	3% Na-Hg (5.0 equiv.), Na ₂ HPO ₄ (7.0 equiv.), MeOH, -30 °C to r.t., 1 h	messy
11	12u R = benzoxyl	Mg (30 equiv.), I ₂ (cat.), MeOH, r.t., 16 h	messy
12	26 R = α -styryl	3% Na-Hg (5.0 equiv.), Na ₂ HPO ₄ (7.0 equiv.), MeOH, -30 °C to r.t., 1 h	28b, 74% yield (97:3 <i>er</i>)
13	12z R = phenyloxyl	3% Na-Hg (5.0 equiv.), Na ₂ HPO ₄ (7.0 equiv.), MeOH, -30 °C to r.t., 1 h	28c, 83% yield (95:5 <i>er</i>)

Table 3. 7. Reduction of sulfonyl group of phenylsulfonyl difluoroalkyl cyclopropanes. n.r. = no reaction.

3.7. Conclusion

To summarize, in this chapter, we have disclosed the first protocol in the catalytic synthesis of versatile enantiopure 1,2-disubstituted α,α -difluoroalkyl cyclopropanes using metalcarbene and alkenes [2+1] ring addition strategy. The metal complex Ru(II)(S)-Pheox I was introduced as efficient catalyst, which led to target α,α -difluoroalkyl cyclopropane products in a range of yield

Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes

from 17-94%, excellent diastereoselectivity (in most cases $>20:1$ *dr*) and enantioselectivity (up to 98.5:1.5 *er*). Further transformation reactions demonstrate the applicability of this unprecedented protocol, as well as provide unique opportunities to access to stereocontrolled versatile α,α -difluoroalkyl cyclopropane frameworks.

**Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones
decomposition for the synthesis of enantiopure alkynyl-
cyclopropanes**

4.1. State of the art

Alkynes represent a large number of organic molecules containing a carbon-carbon triple bond fragment.²¹⁷ This class of chemicals plays an essential role in organic chemistry due to its various applications, including for medicine and the conception of industrial materials.²¹⁸ For instance, in synthetic chemistry, alkynes, owing to their reactivity and versatility, can be used as building blocks in combination with various chemicals in many types of reactions.²¹⁹ Furthermore, the alkynylcyclopropane unit is widespread in natural products and medical compounds. For example, Phorbosides A and its congeneric derivatives²²⁰ exhibit significant cytotoxicity against the HCT 116 (human colon cancer) cell line, Cipralisant²²¹ was discovered as the lead H₃ receptor antagonist for treatment of cognitive deficiencies and other disorders of the central nervous system, and Efavirenz,²²² a commercially available antiretroviral drug, is used for HIV treatment and prevention (Figure 4. 1). For these reasons, the synthetic processes of the alkynylcyclopropane framework have received considerable attention from the organic chemistry community.

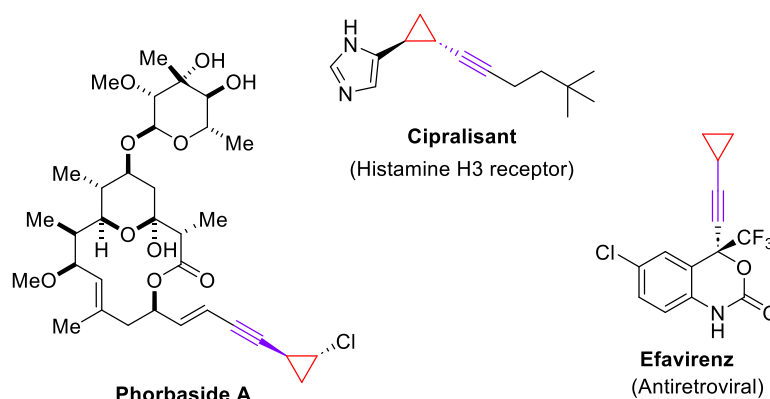


Figure 4. 1. The alkynylcyclopropane unit in natural products and medicinal compounds.

²¹⁷ M. Simonetta, A. Gavezzotti, J. Hencher, R. Shaw, A. Hopkinson, K. Connors, C. Lifshitz, A. Mandelbaum, P. F. Hudrlik, A. M. Hudrlik. (Saul E. Patai, ed.) *The Carbon–Carbon Triple Bond. Vol. 1.* John Wiley & Sons. **1978**.

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²¹⁹ a) R. K. Kumar, X. Bi, *Chem. Commun.* **2016**, *52*, 853–868. b) H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128–1137. c) D. Garayalde, C. Nevado, *Beilstein J. Org. Chem.* **2011**, *7*, 767–780. d) A. Ramani, B. Desai, M. Patel, T. Naveen, *Asian J. Org. Chem.* **2022**, *11*, e202200047.

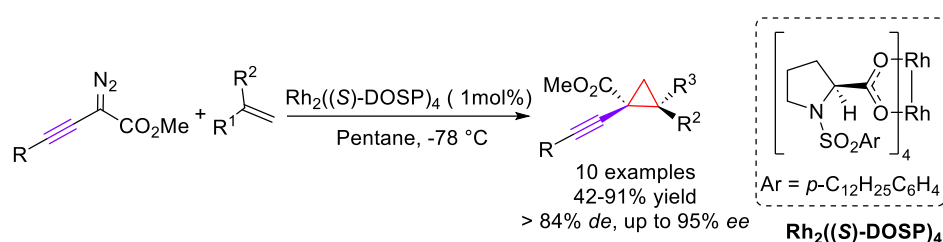
²²⁰ a) I. Paterson, T. Paquet, *Org. Lett.* **2010**, *12*, 2158–2161. b) C. K. Skepper, J. B. MacMillan, G.–X. Zhou, M. N. Masuno, T. F. Molinski, *J. Am. Chem. Soc.* **2007**, *129*, 4150–4151.

²²¹ J. Witkin, D. Nelson, *Pharmacol. Ther.* **2004**, *103*, 1–20.

²²² N. Y. Rakhmanina, J. N. Van den Anker, *Expert Opin. Drug Metab. Toxicol.* **2010**, *6*, 95–103.

Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

Despite several reported works in recent years that provide efficient access to alkynylcyclopropanes *via* either diastereo-²²³ or enantio-selective¹⁹⁷ approaches, the strategy of transition metal-catalyzed cyclopropanation of alkenes with diazo compounds or other carbene precursors remained straightforward and robust in this field. In 2000, a pioneering study by Davies and Boebel involved the synthesis of alkynyldiazoacetates and their subsequent use for the asymmetric cyclopropanation with alkenes under the catalysis of the $\text{Rh}_2((S)\text{-DOSP})_4$ complex.²²⁴ This work demonstrated that alkynyldiazoacetates could participate in the cyclopropanation process similar to aryl- and vinyl-diazoacetates, resulting in high yields and stereoselectivity of alkynylcyclopropanes (Scheme 4. 1).



Scheme 4. 1. $\text{Rh}_2((S)\text{-DOSP})_4$ -catalyzed the formation of alkynylcyclopropanes from alkynyl diazo reagents.

However, over the last two decades, the synthesis of alkynylcyclopropanes was limited to few examples involving mono-acceptor (*i.e.*, $-\text{CF}_3$, $-\text{CF}_2\text{H}$ or $-\text{CO}_2\text{Et}$) diazo reagents and substituted phenyl enynes, diastereoselectivity was achieved using $\text{Fe}[\text{TPP}]\text{Cl}$,^{225,194c} while Ir-salen²²⁶ and Co-complexes²²⁷ were employed for enantioselective approaches. Until 2021, Echavarren *et al.* described a unprecedented two-step alkynylcarbene transfer reaction.²²⁸ This method facilitated the construction of alkynylcyclopropanes from alkenes and terminal alkynes from readily available 7-alkynyl cycloheptatriene. Utilizing $\text{Rh}_2(\text{TFA})_4$ catalyst enabled the efficient synthesis of diverse *cis*-

²²³ a) A. Tenaglia, K. Le Jeune, L. Giordano, G. Buono, *Org. Lett.* **2011**, *13*, 636–639. b) S. Munnuri, J. R. Falck, *J. Am. Chem. Soc.* **2022**, *144*, 17989–17998. c) K. Komeyama, N. Saigo, M. Miyagi, K. Takaki, *Angew. Chem. Int. Ed.* **2009**, *48*, 9875–9878.

²²⁴ H. M. Davies, T. A. Boebel, *Tetrahedron Lett.* **2000**, *41*, 8189–8192.

²²⁵ a) B. Morandi, J. Cheang, E. M. Carreira, *Org. Lett.* **2011**, *13*, 3080–3081. b) X. Zhang, Z. Liu, X. Yang, Y. Dong, M. Virelli, G. Zanoni, E. A. Anderson, X. Bi, *Nat. Commun.* **2019**, *10*, 284.

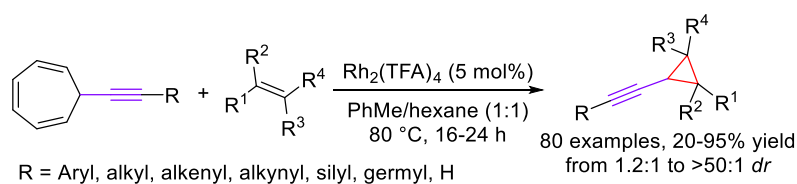
²²⁶ H. Suematsu, S. Kanchiku, T. Uchida, T. Katsuki, *J. Am. Chem. Soc.* **2008**, *130*, 10327–10337.

²²⁷ X. Wang, J. Ke, Y. Zhu, A. Deb, Y. Xu, X. P. Zhang, *J. Am. Chem. Soc.* **2021**, *143*, 11121–11129.

²²⁸ M. Mato, M. Montesinos-Magraner, A. R. Sugranyes, A. M. Echavarren, *J. Am. Chem. Soc.* **2021**, *143*, 10760–10769.

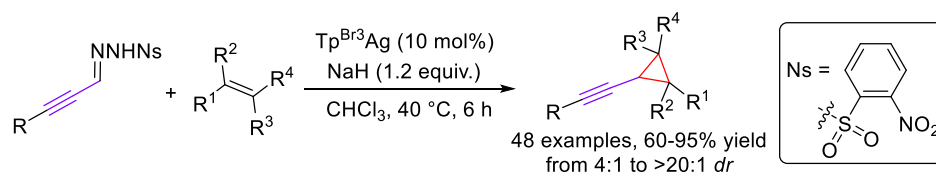
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alkynylcyclopropanes, featuring substituents such as C(sp³)-, C(sp²)-, C(sp)-, H-, Si-, or Ge-substituents in the alkyne part (Scheme 4. 2).



Scheme 4. 2. Rh(II)-catalyzed the formation of alkynylcyclopropanes from alkynyl cycloheptatrienes.

Subsequently, Bi and co-workers explored an alternative class of alkynyl carbene precursors—*N*-nosylhydrazones, which underwent *in situ* diazo reagent generation in the presence of a base.²²⁹ They harnessed this approach for the synthesis of multi-substituted alkynylcyclopropanes. The method employed a silver-based complex (TP^{Br3}Ag) as the optimal catalyst, leading in high yields and stereoselectivity to diverse alkynylcyclopropanes by mediating the reaction between alkenes and alkynyl *N*-nosylhydrazones (Scheme 4. 3).



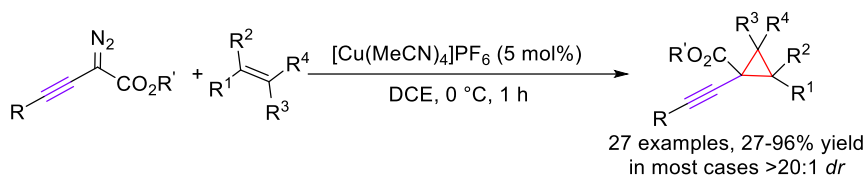
Scheme 4. 3. Silver(I)-catalyzed the formation of alkynylcyclopropanes from alkynyl hydrazone.

While diazo compounds bearing alkynyl and ester groups have been shown to efficiently participate in cyclopropanation reactions using Rh-catalysts,²²⁴ Gurubrahamam *et al.* described an alternative very efficient catalysts: Cu(I)-complexes.²³⁰ This unprecedented [Cu(MeCN)₄]PF₆ catalyzed alkynylcarbene transfer reaction and demonstrates its superior efficiency for the synthesis of alkynylcyclopropanes from diazo compounds combining alkynyl and ester groups, in the presence of alkenes. The non-asymmetric process provided alkynylcyclopropane carboxylates in good yields and excellent diastereoselectivity. (Scheme 4. 4).

²²⁹ Y. Ning, M. Huo, L. Wu, X. Bi, *Chem. Commun.* **2022**, 58, 3485–3488.

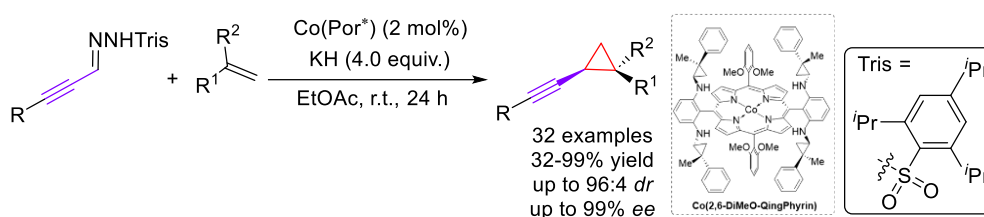
²³⁰ A. Sharma, P. Jamwal, H. Vaid, R. Gurubrahamam, *Org. Lett.* **2023**, 25, 1889–1894.

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Scheme 4. 4. Cu(I)-catalyzed the formation of alkynylcyclopropanes from alkynyl diazo reagents.

In contrast to the metallocarbene process introducing Rh(II), Ag(I), and Cu(I) catalysts, Zhang and co-workers have attributed the generation of alkynylcyclopropane moieties to a Co(II)-based metalloradical catalysis (MRC) process.²³¹ A crucial aspect of their asymmetric catalytic synthesis of alkynylcyclopropanes involves the use of a *D*₂-symmetric supporting ligand, namely amidoporphyrin 2,6-DiMeO-QingPhyrin. This chiral Co(II)-based metalloradical system efficiently activates various α -alkynyl diazomethanes, enabling highly enantioselective cyclopropanation across a diverse array of alkenes (Scheme 4. 5).



Scheme 4. 5. Co(II)-based metalloradical catalysis of alkynyl hydrazone and alkenes asymmetric alkynylcyclopropanation.

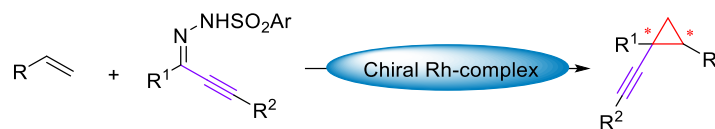
4.2. Objectives

The investigation of both racemic and enantioselective approaches to alkynylcyclopropane moieties has spanned a considerable period. However, upon inspecting previous works, only two reports exist for the direct enantioselective alkynylcyclopropanation. While the Co(II)-based metalloradical catalysis (MRC) process has delivered elegant asymmetric alkynylcyclopropanation results, the use of diazo precursors has been confined to the mono-donor type. On the other hand, the Rh(II)-catalyzed metallocarbene [2+1] strategy has been demonstrated as an accessible pathway in the construction of enantiomerically pure alkynylcyclopropanes. Nevertheless, the application of the

²³¹ J. Ke, W.-C. C. Lee, X. Wang, Y. Wang, X. Wen, X. P. Zhang, *J. Am. Chem. Soc.* **2022**, *144*, 2368–2378.

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protocol is limited to a small range of alkenes. Therefore, there is a high demand to develop new strategies to access versatile, enantioenriched alkynylcyclopropanes. Herein, the goal of the chapter IV is to develop a methodology enabling the enantioselective cyclopropanation of alkenes with donor diazo precursors in the presence of Rh(II)-chiral catalysts. (Scheme 4. 6).



Scheme 4. 6. Enantioselective access to alkynylcyclopropanes.

4.3. Optimization of the reaction conditions with phenyl alkynyl sulfonylhydrazones

At the beginning of this project, we have prepared a series of phenyl alkynyl hydrazone compounds bearing either electron donating or withdrawing groups (Figure 4. 2). In order to unambiguously understand the use of chiral catalysts in this chapter, all of the chemical structures are depicted in Figure 4. 3.

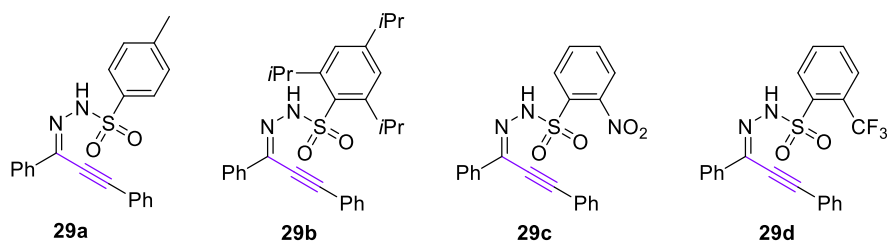


Figure 4. 2. Phenyl alkynyl hydrazone compounds.

Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

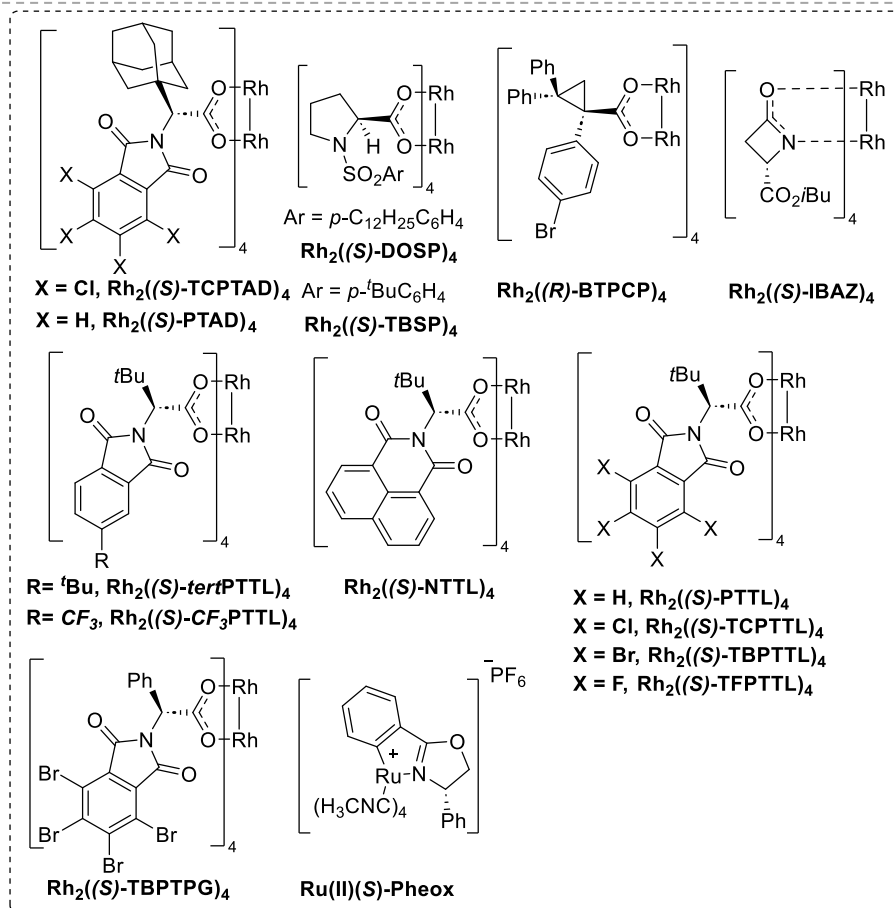
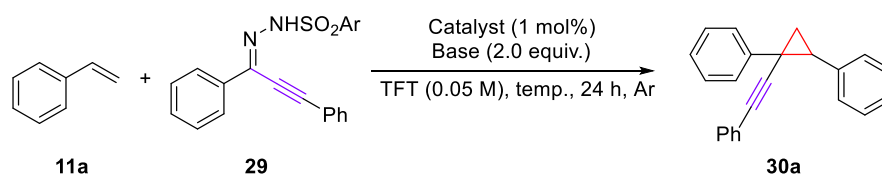


Figure 4. 3. Chiral catalysts used during this study

At first, reactions using styrene **11a** and different phenyl alkynylhydrazones **29** in the presence of $\text{Rh}_2((S)\text{-PTAD})_4$ as chiral catalyst were carried out. Unfortunately, the reactions did not yield the desired product **30a** at either room temperature (Table 4. 1, entries 1-4) or 40 °C (Table 4. 1, entries 5-8) in the presence of DIPEA. This is likely due to DIPEA's inability to induced the diazo formation. Consequently, we screened various bases to facilitate the dissociation of the sulfonylhydrazone group to generate phenyl alkynyl diazomethane. When $\text{Rh}_2((S)\text{-DOSP})_4$ was employed as catalyst, substrates **11a** and **29d** were converted into the expected alkynylcyclopropane **30a** in yields ranging from 11-72%, with moderated diastereomeric ratios (35:65 to 33:67) using different bases (Table 4. 1, entries 9-14). However, only racemic mixtures were obtained indicating that $\text{Rh}_2((S)\text{-DOSP})_4$ catalyst was totally inefficient for the transfer of chirality. Furthermore, additional bases (Table 4. 1, entries 15-20) were tested in the cyclopropanation reaction but did not lead to the formation of **30a**. With the optimal base, sodium hydride (Table 4.1 entry 13) for the cyclopropanation process, several Rh(II)-complexes and Ru(II)(S)-Pheox I were investigated to improve the enantiomeric

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excess of product **30a**. Initially, the use of Rh₂((*S*)-TCPTTL)₄ led to an excellent yield (96%) and slightly improved *dr* (27:73), but only 33% *ee* was observed (Table 4. 1, entry 21). Subsequent optimization reactions with various Rh(II)-catalysts (Table 4. 1, entries 22-28) yielded alkynylcyclopropane **30a** in moderate to excellent yields (51-96%) and *dr* (35:65 to 26:74), but with low *ee* (< 33%). A cyclopropanation reaction attempted with Ru(II)(*S*)-Pheox I resulted in only 12% yield with a 42:58 *dr*. The effect of temperature was also evaluated (Table 4. 1, entries 30-31), with reactions performed at 0 °C or -20 °C independently in the presence of Rh₂((*S*)-TCPTTL)₄ and NaH. Despite improvements in both diastereoselectivity (22:78, 20:80 *dr*) and enantioselectivity (49%, 50% *ee*, respectively), the yield of product **30a** decreased dramatically (38%, 30%, respectively). Finally, a cyclopropanation reaction was proceeded without any metal catalyst (Table 4. 1, entry 32), the outcome demonstrated that the metal catalysts are crucial to the formation of the expected alkynylcyclopropane.



entry	29	cat. (1 mol%)	base	temp./(^o C)	yield ^a	<i>dr</i> ^b	<i>ee</i> ^c
1	29a	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	r.t	n.r	-	-
2	29b	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	r.t	n.r	-	-
3	29c	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	r.t	n.r	-	-
4	29d	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	r.t	n.r	-	-
5	29a	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	40	n.r	-	-
6	29b	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	40	n.r	-	-
7	29c	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	40	n.r	-	-
8	29d	Rh ₂ ((<i>S</i>)-PTAD) ₄	DIPEA	40	n.r	-	-
9	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	Cs ₂ CO ₃	40	26%	33:67	0%
10	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	K ₂ CO ₃	40	11%	33:67	0%
11	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	^t BuOK	40	27%	35:65	0%
12	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	KHMDS	40	17%	35:65	0%
13	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	NaH	40	72% (65)	33:67	0%

Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

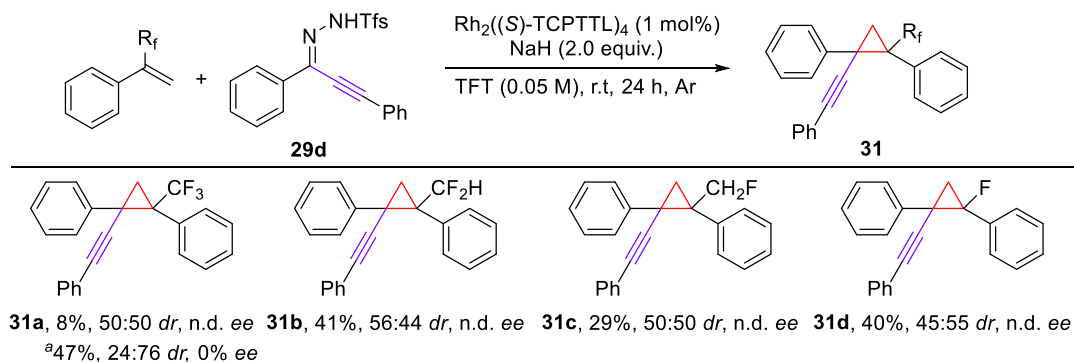
14	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	KH	40	55%	33:67	0%
15	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	NaOAc	40	n.r	-	-
16	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	Na ₂ CO ₃	40	n.r	-	-
17	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	NaTFA	40	n.r	-	-
18	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	CsOAc	40	trace	-	-
19	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	DBU	40	n.r	-	-
20	29d	Rh ₂ ((<i>S</i>)-DOSP) ₄	KOH	40	trace	-	-
21	29d	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	NaH	40	96%	27:73	33%
22	29d	Rh ₂ ((<i>S</i>)-TCPTAD) ₄	NaH	40	96%	30:70	13%
23	29d	Rh ₂ ((<i>R</i>)-BTPCP) ₄	NaH	40	96%	35:65	-19%
24	29d	Rh ₂ ((<i>R</i>)-PTAD) ₄	NaH	40	95%	30:70	-4%
25	29d	Rh ₂ ((<i>S</i>)-IBAZ) ₄	NaH	40	96%	35:65	0%
26	29d	Rh ₂ ((<i>S</i>)-NTTL) ₄	NaH	40	70%	27:73	3%
27	29d	Rh ₂ ((<i>S</i>)-TFPTTL) ₄	NaH	40	51%	26:74	30%
28	29d	Rh ₂ ((<i>S</i>)- <i>tert</i> TP TTL) ₄	NaH	40	78%	26:74	3%
29	29d	Ru(II)(<i>S</i>)-Pheox I	NaH	40	12%	42:58	-
30	29d	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	NaH	0	38%	22:78	49%
31	29d	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	NaH	-20	30%	20:80	50%
32	29d		NaH	40	n.r	-	-

Table 4. 1. Optimization studies for the synthesis of alkynylcyclopropane **30a** from substrates **11a** and **29**. Reaction conditions: **11a** (0.1 mmol, 1.0 equiv.), and **29** (0.2 mmol, 2.0 equiv.) were employed. ^a NMR yield, 1,3,5-trimethoxyl benzene as internal standard. ^b *dr* (*trans/cis*) ratio was determined by ¹H NMR on the crude mixture. ^c *ee* (major isomer) was determined using chiral HPLC analysis. Isolated yield has shown in parenthesis. TFT = trifluoromethyl benzene.

To circumvent the unpromising stereocontrol abilities issue in the asymmetric cyclopropanation process with styrene **11a**, our focus shifted to investigating fluorinated styrenes with diazo precursor **29d**, aiming to generate enantiomerically pure fluorinated alkynylcyclopropanes **31** (Scheme 4. 7). For these reactions, the initially tested chiral catalyst Rh₂((*S*)-TCPTTL)₄ was introduced to decompose the diazo reagent derived from **29d** in the presence of NaH. However, fluorinated styrenes, including -CF₃, -CF₂H, -CH₂F and -F, afforded the corresponding product **31a** to **31d** with

Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

low to moderate yields (8-41%) and *dr* (around 50:50). Consequently, the enantiomeric excess values were not determined. Additionally, the -CF₃ alkynylcyclopropane **31a** was obtained under the catalysis of Rh₂((*S*)-DOSP)₄ at 40 °C. Although both yield (47%) and *dr* (24:76) were improved, enantioselectivity was not observed.



Scheme 4. 7. Asymmetric alkynyl cyclopropanation with fluorinated styrenes. Reaction conditions: fluorinated styrenes (0.1 mmol, 1.0 equiv.), and **29d** (0.2 mmol, 2.0 equiv.) were employed. NMR yield, 1,3,5-trimethoxy benzene as the internal standard, *dr* ratio was determined by ¹H NMR on the crude mixture, *ee* (major isomer) was determined with chiral HPLC analysis. TFT = trifluoromethyl benzene. ^aRh₂((*S*)-DOSP)₄ (1 mol%) was employed at 40 °C.

4.4. Optimization of the reaction conditions with phenyl sulfonylhydrazones

Due to the discouraging outcomes observed when using phenyl alkynyl hydrazone **29** in alkynyl cyclopropanation reactions, we altered our strategy by employing phenyl hydrazone **32a** and alkynyl styrene **33** to synthesize the enantioenriched desired product **30a** (Chart 4. 1). It was discovered that when Rh₂((*R*)-BTPCP)₄ was used, the catalytic reaction provided alkynylcyclopropane **30a** in a 69% yield with a modest 20% diastereomeric excess and 52% enantiomeric excess. The cyclopropane **30a** was also synthesized using Rh₂((*S*)-TCPTTL)₄ and Rh₂((*S*)-TFPTTL)₄ in 67% and 55%, respectively, but with low *de* (28%, 10%, respectively) and enantioselectivity (37%, 35% *ee*, respectively). Similarly, when Rh₂((*R*)-TCPTAD)₄ and Rh₂((*S*)-NTTL)₄ were employed, the reactions afforded alkynylcyclopropane **30a** in good yields (74%, 63%) but modest stereocontrol (around 40% *ee*).

Chapter IV – Rh(II)-catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

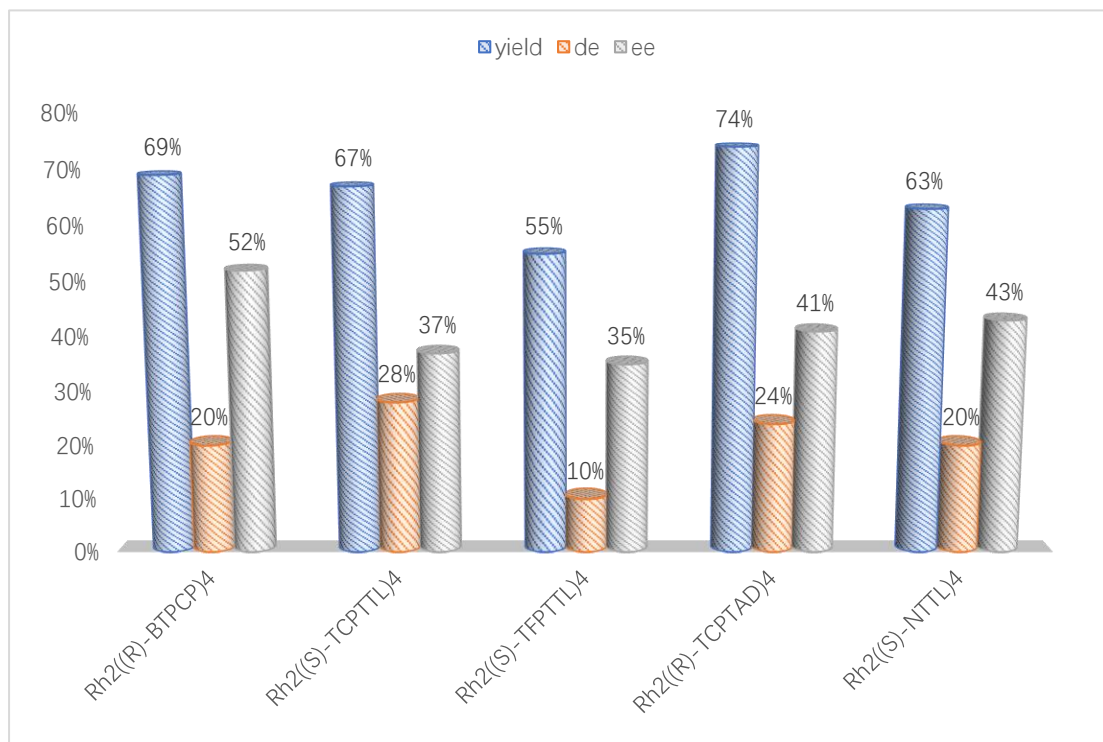
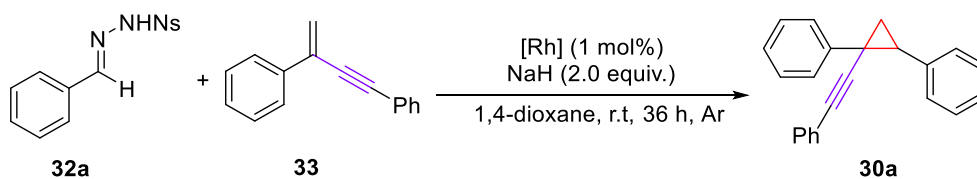
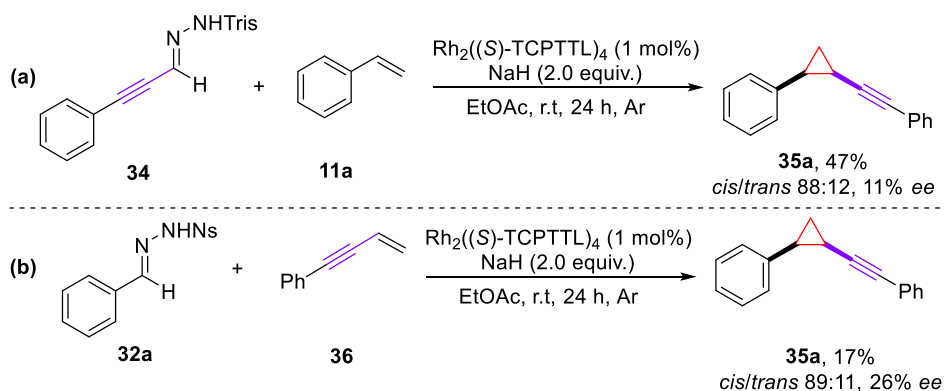


Chart 4. 1. Asymmetric cyclopropanation with phenyl hydrazone **32a** and alkynyl styrene **33** using different chiral Rh(II)-complexes. Reaction conditions: **32a** (0.2 mmol, 2.0 equiv.), **33** (0.1 mmol, 1.0 equiv.), NMR yield, *de* was determined by ¹H NMR on the crude mixture, 1,3,5-trimethoxy benzene as the internal standard, *ee* was determined using chiral HPLC analysis.

Because of the numerous difficulties for the identification of optimal reaction conditions to access to enantioenriched alkynylcyclopropane **30a** in good yield and stereoselectivities, we turned our attention to the synthesis of alkynyl phenyl cyclopropane **35a**. Initially, two different Rh(II)-catalyzed strategies were tested. While the reaction of alkynyl diazomethane precursor **34** with styrene **11a** afforded cyclopropane **35a** in 47% yield, 88:12 *dr*, and 11% *ee* (Scheme 4. 8a), the reaction of phenyl diazomethane precursor with alkynyl alkene **36** provided **35a** in 17% yield, 89:11 *dr*, and 26% *ee* (Scheme 4. 8b). Hence, Scheme 4. 8b was selected for further optimization due to the slightly higher *ee*. It is important to mention that, in contrast to Zhang's work²²⁷, the product **35a** was determined to have a *cis* relative configuration which reinforce the importance of our approach.

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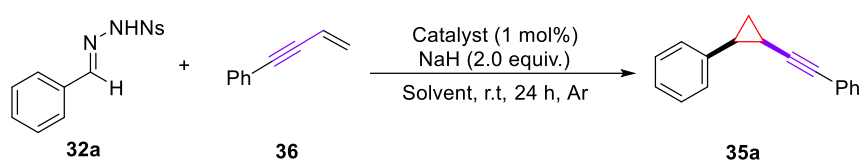


Scheme 4. 8. Rh(II)-catalyzed the asymmetric synthesis of **35a**.

Upon the preliminary outset in hand, various solvents were screened. THF, Et₂O, toluene, PhCF₃, and CH₃CN were found to be inefficient for the increasing of the yield for **35a** (13-21%) which was obtained in good diastereomeric ratios (85:15 to 90:10) and enantioselectivity ranging from 9-43% (Table 4. 2, entries 1-5). MeOH, DCE, and hexane were also tested but totally inhibited the cyclopropanation reaction (Table 4. 2, entries 6-8). The use of DCM led to an interesting 45% yield of alkynylcyclopropane **35a** with 89:11 *dr* and 40% *ee* (Table 4. 2, entry 9), while when 1,4-dioxane was employed, product **35a** was obtained in 81% yield, 89:11 *dr*, and 43% *ee* (Table 4. 2, entry 10). Subsequently, several Rh(II)-complexes were investigated in the presence of 1,4-dioxane as the solvent; The new generation catalysts Rh₂((*R*)-BTPCP)₄ and Rh₂((*R*)-*ph*TPCP)₄ afforded great yields at 96% and 84%, respectively, with good diastereomeric ratios (88:12 for each), but lower enantioselectivity (Table 4. 2, entries 11-12). Furthermore, the asymmetric cyclopropanation reactions were carried out with Rh₂((*R*)-PTAD)₄, Rh₂((*S*)-TCPTAD)₄, and Rh₂((*S*)-NTTL)₄, but lower yields and stereoselectivity were obtained (Table 4. 2, entries 13-15). Moreover, Rh₂((*S*)-IBAZ)₄, generated from β-lactam, exhibited inactivity (Table 4. 2, entries 16), while Rh₂((*S*)-DOSP)₄ and Rh₂((*S*)-TBSP)₄ derived from proline showed undesired cyclopropanation results (Table 4. 2, entries 17-18). Other catalysts based on PTTL skeleton, such as Rh₂((*S*)-*tert*PTTL)₄, Rh₂((*S*)-TFPTTL)₄, and Rh₂((*S*)-PTTL)₄, were also tested but the expected cyclopropane **35a** was obtained in low yields (35-44%), moderated to good *dr* (50:50 to 90:10), and low enantioselectivity (29-35% *ee*) (Table 4. 2, entries 19-21). The reactions were examined at 40°C and 0°C, but both were incapable of affording **35a** with promising outcomes (Table 4. 2, entries 22-23). Finally, a reaction was proceeded with lower concentration of **32a**, but it neither enhanced the yield nor the

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enantioselectivity (Table 4. 2, entry 24).



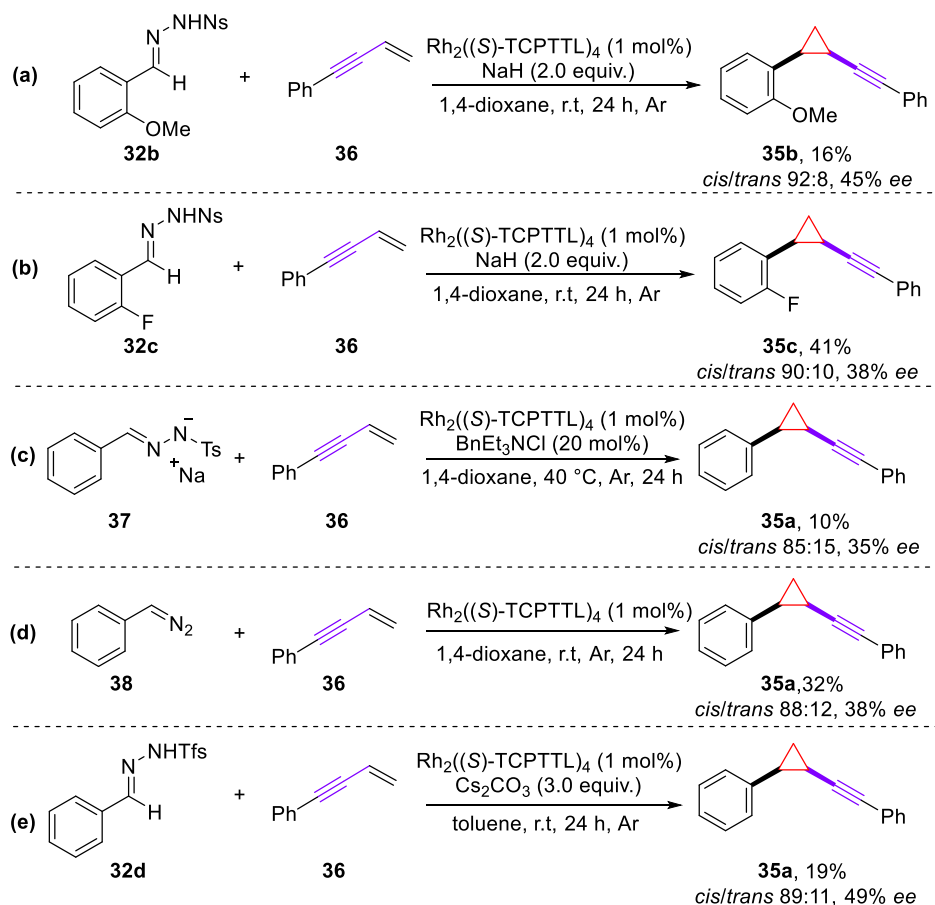
entry	catalyst	solvent	yield ^a	<i>dr</i> ^b	<i>ee</i> ^c
1	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	THF	20	88:12	9
2	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	Et ₂ O	21	88:12	38
3	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	Toluene	18	90:10	43
4	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	PhCF ₃	13	90:10	31
5	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	CH ₃ CN	15	85:15	34
6	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	MeOH	n.r.	-	-
7	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	DCE	trace	-	-
8	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	Hexane	trace	-	-
9	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	DCM	45	89:11	40
10	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	1,4-dioxane	81	89:11	43
11	Rh ₂ ((<i>R</i>)-BTPCP) ₄	1,4-dioxane	96	88:12	-18
12	Rh ₂ ((<i>R</i>)- <i>ph</i> TPCP) ₄	1,4-dioxane	84	88:12	-23
13	Rh ₂ ((<i>R</i>)-PTAD) ₄	1,4-dioxane	59	80:20	-36
14	Rh ₂ ((<i>S</i>)-TCPTAD) ₄	1,4-dioxane	67	76:24	42
15	Rh ₂ ((<i>S</i>)-NTTL) ₄	1,4-dioxane	62	82:18	24
16	Rh ₂ ((<i>S</i>)-IBAZ) ₄	1,4-dioxane	n.r.	-	-
17	Rh ₂ ((<i>S</i>)-DOSP) ₄	1,4-dioxane	13	-	-
18	Rh ₂ ((<i>S</i>)-TBSP) ₄	1,4-dioxane	59	34:66	4
19	Rh ₂ ((<i>S</i>)- <i>tert</i> PTTL) ₄	1,4-dioxane	37	80:20	29
20	Rh ₂ ((<i>S</i>)-TFPTTL) ₄	1,4-dioxane	35	50:50	30
21	Rh ₂ ((<i>S</i>)-PTTL) ₄	1,4-dioxane	44	90:10	35
22 ^d	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	1,4-dioxane	48	62:38	35
23 ^e	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	DCM	7	-	-
24 ^f	Rh ₂ ((<i>S</i>)-TCPTTL) ₄	1,4-dioxane	50	92:8	40

Table 4. 2. Condition optimization of asymmetric synthesis of **35a**. Reaction conditions: **32a** (0.2

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mmol, 2.0 equiv.) and **36** (0.1 mmol, 1.0 equiv.) were employed with 2 mL solvent. ^a NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. ^b *dr* (*cis/trans*) ratio was determined by ¹H NMR on the crude mixture. ^c *ee* (*cis*) was determined using chiral HPLC analysis. ^d 40 °C. ^e 0 °C. ^f 5.5 mL of solvent was used.

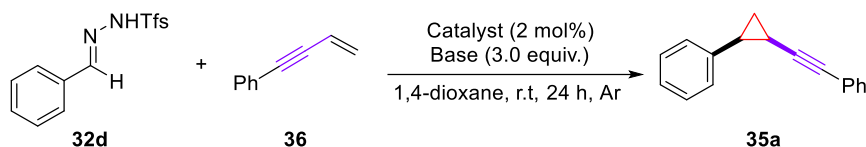
To test the influence of the steric hindrance of the diazo precursor for controlling cyclopropanation stereoselectivity, substrates **32b** and **32c** were tested with enyne **36** in the presence of Rh₂((*S*)-TCPTTL)₄. Unfortunately, when *ortho*-methoxy phenyl hydrazone **32b** was introduced, although the alkynyl cyclopropane **35b** was obtained with better stereoselectivities (92:8 *dr*, 45% *ee*), the yield dropped to only 16% (Scheme 4. 9a). On the other hand, the use of *ortho*-fluoro phenyl hydrazone **32c** led to a 41% yield with 90:10 *dr* and 38% *ee* of **35c** (Scheme 4. 9b). We then assumed that employing a different diazo source might improve the outcomes of the enantioselective cyclopropanation. However, alkynylcyclopropane **35a** was obtained in low yields either from different diazo precursors such as **37**, **38**, and **32d**, albeit the stereoselectivity was slightly improved. (Scheme 4. 9 c-e).



Scheme 4. 9. Asymmetric cyclopropanation from different diazo precursors.

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Our further investigation focused on the use of several Rh(II)-complexes which were proposed recently in the literature. First of all, 1 mol% and 2 mol% Rh₂((*S*)-TBPTTL)₄ were tested individually with substrates **32d** and **36**. To our delight, the utilization of 2 mol% Rh₂((*S*)-TBPTTL)₄ offered alkylcyclopropane **35a** in 77% yield with 91:9 *dr* and 68% *ee* (Table 4. 3, entry 1), while 1 mol% Rh₂((*S*)-TBPTTL)₄ provided a lower yield (41%), diastereo- (98:2 *dr*), and enantio-selectivity (51% *ee*) (Table 4. 3, entry 2). Rh₂((*S*)-CF₃PTTL)₄ and Rh₂((*S*)-TBPTPG)₄ were also tested. Nonetheless, each of them demonstrated less efficiency either in yield or stereocontrol ability (Table 4. 3, entries 3-4). On the other hand, various bases were screened to promote the asymmetric cyclopropanation process. When common carbonated bases such as K₂CO₃, Na₂CO₃, and Li₂CO₃ were tested (Table 4. 3, entries 5-7), only the reaction with K₂CO₃ provided a 50% yield but a reduced *ee* to 50% was observed. The bases with a cesium cation gave a range of yields from 6% to 78%, consistent *dr* (91:9) value, and *ee* reached 61% (Table 4. 3, entries 8-11). Other bases, *i.e.*, LiOMe, LiHMDS, and K₃PO₄, were also tested but did not lead to any improvement in the cyclopropanation process (Table 4. 3, entries 12-14).



entry	catalyst	base	yield ^a	<i>dr</i> ^b	<i>ee</i> ^c
1 ^d	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	Cs ₂ CO ₃	41	92:8	51
2	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	Cs ₂ CO ₃	77	91:9	68
3	Rh ₂ ((<i>S</i>)-CF ₃ PTTL) ₄	Cs ₂ CO ₃	61	84:16	61
4	Rh ₂ ((<i>S</i>)-TBPTPG) ₄	Cs ₂ CO ₃	70	82:18	60
5	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	K ₂ CO ₃	58	91:9	50
6	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	Na ₂ CO ₃	trace	-	-
7	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	Li ₂ CO ₃	n.r.	-	-
8	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	CsF	66	91:9	53
9	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	CsOPiv	75	91:9	57
10	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	CsOAc	78	91:9	61
11	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	CsOH	6	-	-
12	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	LiOMe	32	91:9	50
13	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	LiHMDS	49	91:9	52
14	Rh ₂ ((<i>S</i>)-TBPTTL) ₄	K ₃ PO ₄	trace	-	-

Table 4. 3. Condition optimization for generating **35a** with new synthesized Rh(II)-complexes. Reaction conditions: **32d** (0.2 mmol, 2.0 equiv.), **36** (0.1 mmol, 1.0 equiv.) and 1.5 mL 1,4-dioxane were employed. ^a NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. ^b *dr* (*cis/trans*) ratio was determined by ¹H NMR on the crude mixture. ^c *ee* (*cis*) was determined using chiral HPLC

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analysis. ^d 1 mol% catalyst.

It is noteworthy that the HRMS analysis attested to the excellence purity of the optimal catalyst, Rh₂((*S*)-TBPTTL)₄, presenting an elegant form with a toluene adduct. This catalyst, employed by Hashimoto in enantioselective cyclopropanation reactions,²³² was replicated using our home-made Rh₂((*S*)-TBPTTL)₄ catalyst, yielding 86% with 94% enantiomeric excess, these results are very close to the ones reported in Hashimoto's publication. These experiments offer robust confirmation of the excellent quality of our home-made Rh₂((*S*)-TBPTTL)₄ complex (Figure 4. 4).

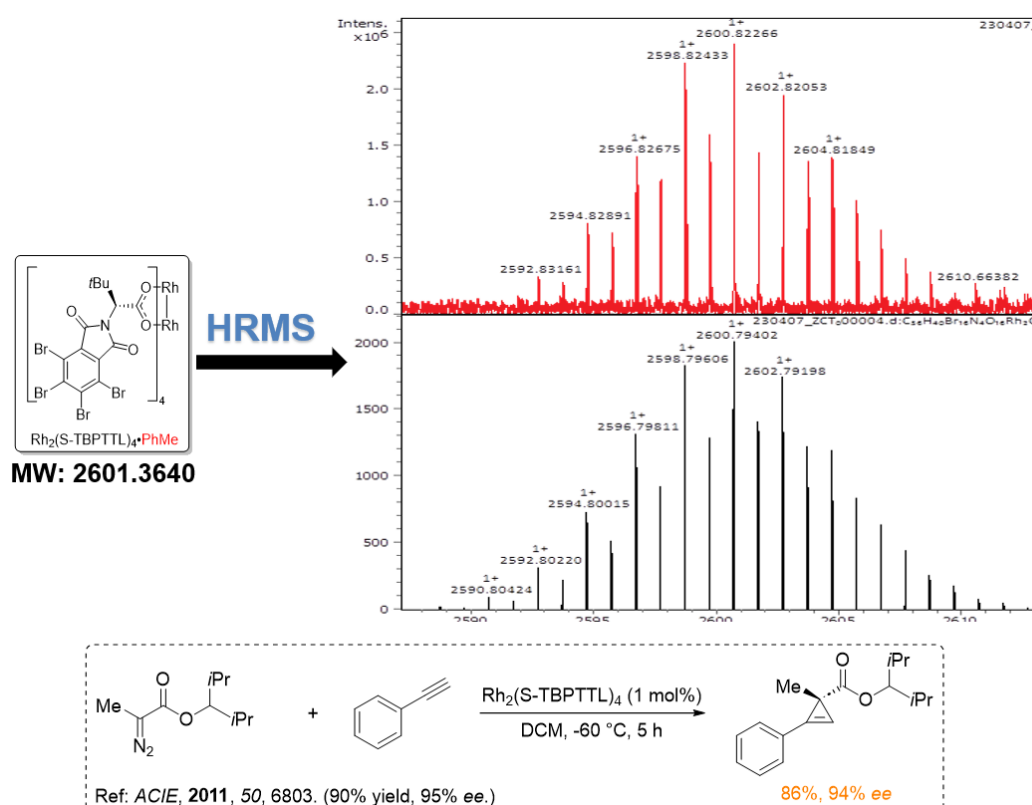


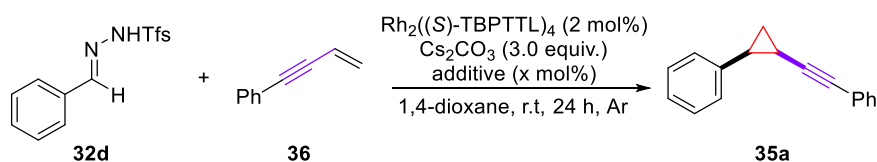
Figure 4. 4. Control experiments using Rh₂((*S*)-TBPTTL)₄.

In terms of the optimal reaction conditions, until now, a good yield (77%) and *dr* (91:9) and a promising 68% *ee* were obtained. We subsequently investigated the influence of a 'cooperative' additive (Table 4. 4), which could either coordinate with alkynyl substrates (Lewis acid) or interact with the Rh(II)-catalyst (Lewis base) to enhance enantioselectivity. Initially, we tried three Lewis acids, namely SnCl₂, ZnCl₂, and AlCl₃ (entries 1-3). These reactions generated **35a** in yields ranging

²³² T. Goto, K. Takeda, N. Shimada, H. Nambu, M. Anada, M. Shiro, K. Ando, S. Hashimoto, *Angew. Chem. Int. Ed.* **2011**, 50, 6803–6808.

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from 71% to 76%, with a mild decrease in stereoselectivity. Similarly, cyclopropanation reactions were conducted with Lewis acid additives $\text{Sc}(\text{OTf})_3$ and BBr_3 , resulting in 78% and 73% yields, respectively, with an 89:11 *dr* for each and a moderate *ee* (57% in each case) (entries 4-5). Several Lewis bases were also investigated in the enantioselective synthesis of alkynylcyclopropane **35a**. The sulfonylamides TfNH_2 , TfsNH_2 , and MeSO_2NH_2 were individually added to the reactions, leading to moderate yields (58-69%) with nearly the same *dr* (88:12 to 92:8), and the *ee* were determined to be 56% to 58% (entries 6-8). Finally, the cyclopropanation was explored using 5 mol% DMAP or pyridine (entries 9-10). However, the reaction with DMAP produced **35a** only in a 20% yield with an 80:20 *dr* and 49% *ee*, while the reaction with pyridine afforded a 66% yield, 91:1 *dr*, and 52% *ee*.



entry	additive	yield (%) ^a	<i>dr</i> ^b	<i>ee</i> (%) ^c
1	SnCl_2 (20 mol%)	76	89:11	60
2	ZnCl_2 (20 mol%)	71	90:10	62
3	AlCl_3 (20 mol%)	75	89:11	56
4	$\text{Sc}(\text{OTf})_3$ (20 mol%)	78	89:11	59
5	BBr_3 (20 mol%)	73	89:11	57
6	TfNH_2 (10 mol%)	66	92:8	58
7	TfsNH_2 (10 mol%)	69	88:12	56
8	MeSO_2NH_2 (10 mol%)	58	90:10	56
9	DMAP (5 mol%)	20	80:20	49
10	Pyridine (5 mol%)	66	91:9	52

Table 4. 4. Additive effects of asymmetric synthesis of alkynylcyclopropane **35a**. Reaction conditions: **32d** (0.2 mmol, 2.0 equiv.), **36** (0.1 mmol, 1.0 equiv.) and 1.5 mL 1,4-dioxane were employed. ^a NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. ^b *dr* (*cis/trans*) ratio was determined by ¹H NMR on the crude mixture. ^c *ee* (*cis*) was determined using chiral HPLC analysis.

4.5. Conclusion and perspective

In this chapter, we have presented the optimization studies for the synthesis of enantiomerically pure alkynylcyclopropanes. While a diverse array of Rh(II)-complexes has been explored in cyclopropanation reactions, leading to high yields and diastereoselectivity, achieving low to moderate enantioselectivity has remained a challenge. Additionally, the modification of substrates has yielded bleak results, as has the use of various additives. Looking forward, a prospective avenue involves designing new dirhodium paddlewheel complexes for the asymmetric synthesis of alkynylcyclopropanes from alkenes and hydrazone compounds. Moreover, there is potential in exploring a low-temperature one-pot approach to generate alkynylcyclopropanes with high diastereo- or enantio-selectivity.

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of enantiopure alkynylcyclopropanes

**Chapter V – Access to 1,2,3-polysubstituted fluorinated
cyclopropanes by Pd(II)-catalyzed C–H bond activation**

5.1. State of the art

Since the introduction of the first fluorinated drug, fludrocortisone²³³, on the market in 1954, there has been a growing interest in fluorinated compounds in many fields for example materials, drugs and agrochemicals, as well as for the advancement of food, healthcare, and agrochemical industries.²³⁴ In the last few years, the FDA has approved 71 novel inventions for market release, spanning the period from 2015 to 2022.²³⁵ These fluorinated drugs exhibit diverse biological properties, including antitumor, antimicrobial, and anti-inflammatory activities. Furthermore, the cyclopropyl fragment emerged as a versatile scaffold frequently found in both preclinical and clinical drug molecules.²³⁶ Combining a cyclopropane and a fluorinated group has been demonstrated to significantly alter the electronic, physical, and biological properties, as well as the reactivity, of crucial structural features in modern drug discovery.²³⁷ For instance, the introduction of a fluorine atom improved the potency of the EC₅₀ of the NTR1 allosteric modulator (Figure 5. 1, top, left) and the K_i of the TYK2 inhibitor (Figure 5. 1, top, right). Notably, the relative and absolute stereochemistries of fluorinated cyclopropanes have demonstrated slightly modified bioactivities when they are used toward a nAChR ligand (Figure 5. 1, bottom).

²³³ R. M. Hussain, S. J. McIntosh, J. Lawson, R. A. Kenny, *Heart* **1996**, *76*, 507–509.

²³⁴ a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640. b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *Isience* **2020**, *23*, 101467. c) V. P. Reddy, *Organofluorine compounds in biology and medicine*, Newnes, **2015**.

²³⁵ N. Sheikhi, M. Bahraminejad, M. Saeedi, S. S. Mirfazli, *Eur. J. Med. Chem.* **2023**, 115758.

²³⁶ T. T. Talele, *J. Med. Chem.* **2016**, *59*, 8712–8756.

²³⁷ O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.

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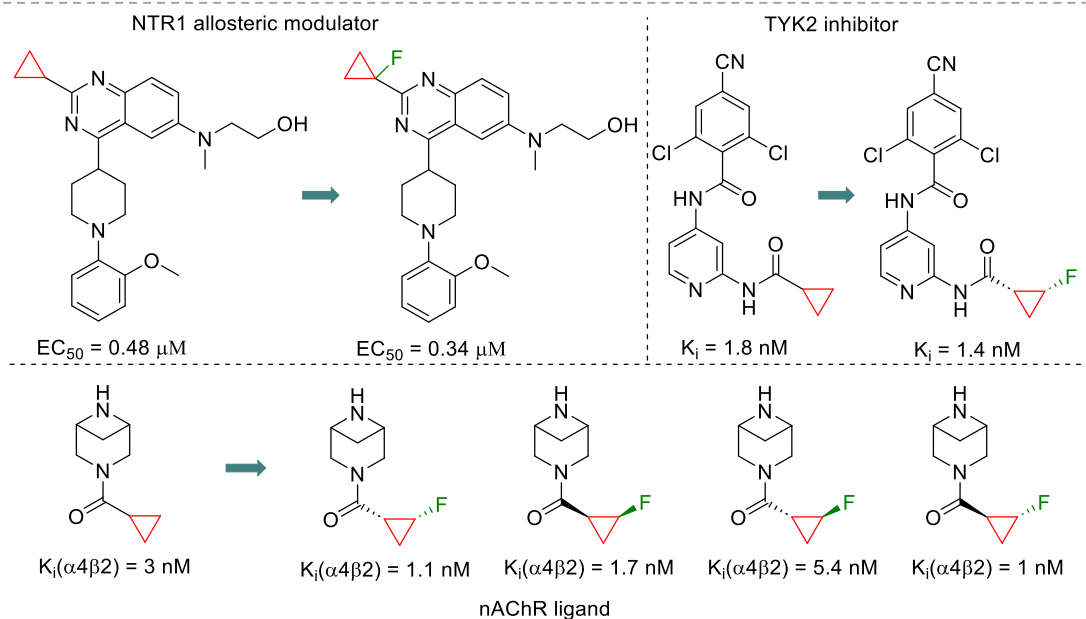


Figure 5. 1. The influence of biological properties induced by the presence a fluorinated cyclopropane. EC_{50} = half maximal effective concentration. K_i = inhibitor constant.

To address the challenging task that represents the synthesis of 1,2,3-polysubstituted fluorinated cyclopropane scaffolds, well-established catalytic protocols exist relying on [2+1] cycloaddition reactions for racemic^{166a,238} and enantiomeric²³⁹ pathways. However, these methods are highly dependent on substrates.

Alternatively, Pd-catalyzed C–H activation is a straightforward strategy widely applied in the functionalization of $C(sp^2)$ –H or $C(sp^3)$ –H bonds.²⁴⁰ Furthermore, the amide derived from 8-aminoquinoline turned out to be a privileged bidentate directing group in transition metal-catalyzed C–H bond functionalization reactions.²⁴¹ This directing group has been already successfully used

²³⁸ a) P. Ivashkin, S. Couve–Bonnaire, P. Jubault, X. Pannecoucke, *Org. Lett.* **2012**, *14*, 2270–2273. b) T. Ferrary, E. David, G. Milanole, T. Besset, P. Jubault, X. Pannecoucke, *Org. Lett.* **2013**, *15*, 5598–5601. c) V. Myronova, D. Cahard, I. Marek, *Org. Lett.* **2022**, *24*, 9076–9080.

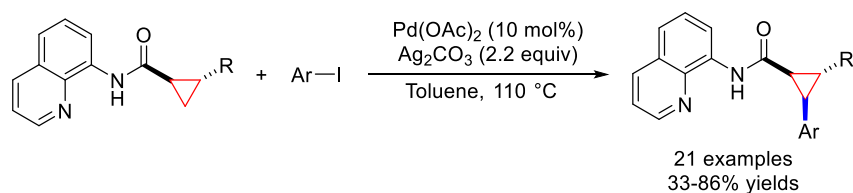
²³⁹ a) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 6966–6970. b) L.–P. B. Beaulieu, J. F. Schneider, A. B. Charette, *J. Am. Chem. Soc.* **2013**, *135*, 7819–7822. c) C. Navuluri, A. B. Charette, *Org. Lett.* **2015**, *17*, 4288–4291.

²⁴⁰ a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. Q. Yu, *Chem. Rev.* **2017**, *117*, 8754–8786. b) N. Dastbaravardeh, M. Christakakou, M. Haider, M. Schnürch, *Synthesis* **2014**, *46*, 1421–1439. c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169. d) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.

²⁴¹ a) R. K. Rit, M. R. Yadav, K. Ghosh, A. K. Sahoo, *Tetrahedron* **2015**, *71*, 4450–4459. b) S. Rej, Y. Ano, N. Chatani, *Chem. Rev.* **2020**, *120*, 1788–1887.

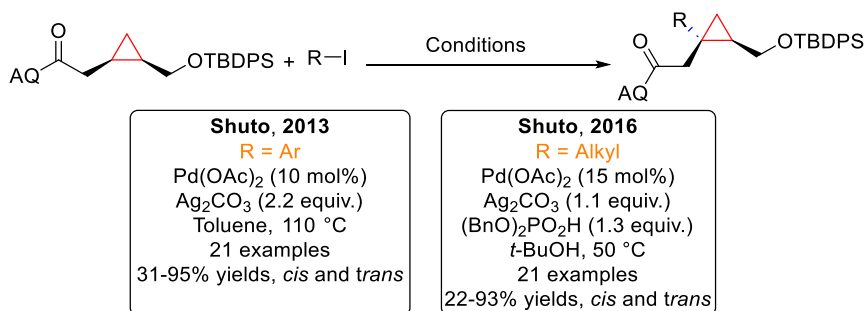
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for the functionalization of cyclopropanes by Pd-catalysis. Indeed, Babu and co-workers first investigated the directed Pd-catalyzed arylation of cyclopropanes by C–H bond activation in 2013.²⁴² Aryl iodides were employed as electrophiles and 21 examples were reported from 33% to 86% isolated yields (Scheme 5. 1). Worth noting that using an excess of iodobenzene furnished the respective diarylated cyclopropane.



Scheme 5. 1. Pd-catalyzed arylation of cyclopropanes by C-H bond activation

Using a similar approach, Shuto *et al.* have developed a Pd(II)-catalyzed arylation²⁴³ and alkylation²⁴⁴ of enantiomerically pure cyclopropanes using the amide derived from 8-aminoquinoline. These methods enabled the formation of a quaternary carbon center onto chiral cyclopropanes by employing aryl/alkyl iodides as coupling partners. The β -selective functionalization process demonstrated broad substrate compatibility with (hetero)aryl/alkyl iodides, providing diverse chiral cyclopropanes featuring both *cis*- and *trans*-1,1,2-trisubstituted structures (Scheme 5. 2).



Scheme 5. 2. Pd(II)-catalyzed arylation and alkylation to access quaternary carbon center on cyclopropanes.

In subsequent years, Pd-catalyzed C–H functionalization of cyclopropanes has featured in various

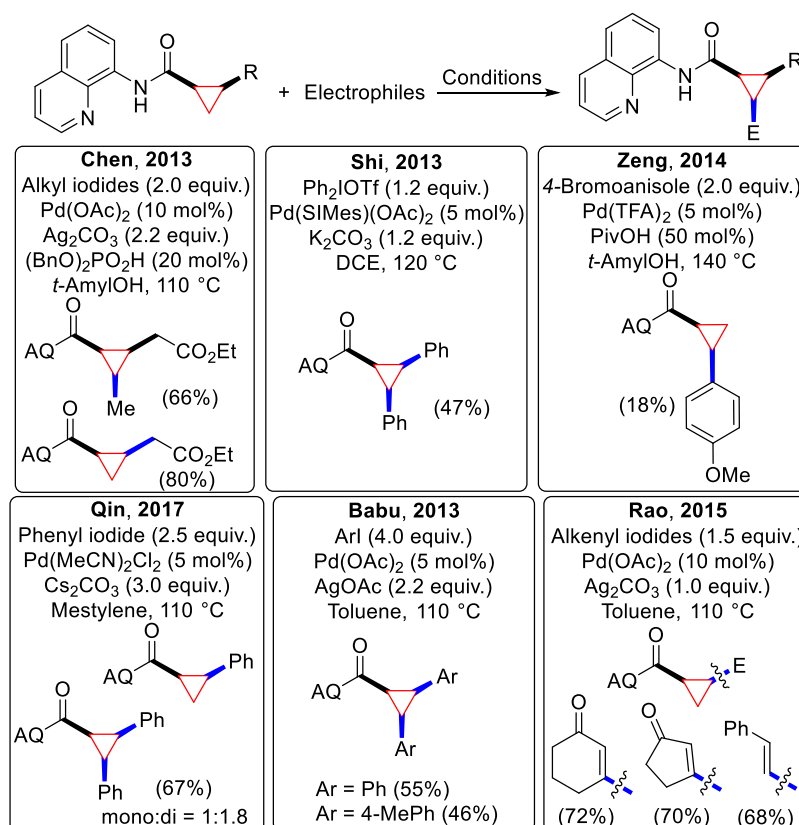
²⁴² R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238–3241.

²⁴³ N. Hoshiya, T. Kobayashi, M. Arisawa, S. Shuto, *Org. Lett.* **2013**, *15*, 6202–6205.

²⁴⁴ N. Hoshiya, K. Takenaka, S. Shuto, J. I. Uenishi, *Org. Lett.* **2016**, *18*, 48–51.

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protocols (Scheme 5. 3). For instance, Chen and co-workers successfully employed electrophiles such as iodomethane and ethyl-2-iodoacetate, leading to the corresponding functionalized cyclopropanes in 66% and 80%, respectively.²⁴⁵ Similarly, Shi, Zeng, and Qin have explored the arylation of cyclopropanes using different electrophiles. When Ph₂IOTf was employed, the cyclopropane substrate exclusively afforded the difunctionalization adduct in 47% yield.²⁴⁶ Conversely, the introduction of 4-bromoanisole resulted in the mono-arylation exclusively, albeit with a low yield (18%).²⁴⁷ The excess of phenyl iodide produced a mixture of mono- and di-arylated products, as indicated in Babu's work.²⁴² Additionally, an unprecedented study on C–H alkenylation of cyclopropanes was conducted by Rao and colleagues, leading to cyclopropanic coupling products with cyclohexanone, cyclopentenone, and styrene in 68-72% yields.²⁴⁸



Scheme 5. 3. Pd(II)-catalyzed the functionalization methodologies with different electrophiles.

More recently, Volla and Nair reported a significant contribution dealing with a Pd(II)-catalyzed

²⁴⁵ S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135–12141.

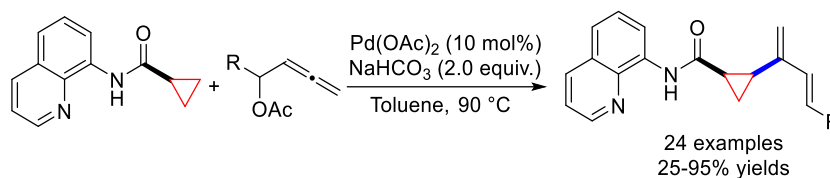
²⁴⁶ F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang, Z.-J. Shi, *Org. Lett.* **2013**, *15*, 4758–4761.

²⁴⁷ Y. Wei, H. Tang, X. Cong, B. Rao, C. Wu, X. Zeng, *Org. Lett.* **2014**, *16*, 2248–2251.

²⁴⁸ G. Shan, G. Huang, Y. Rao, *Org. Biomol. Chem.* **2015**, *13*, 697–701.

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directed aliphatic C(sp³)–H dienylation employing allenyl acetates as coupling partners.²⁴⁹ In this methodology, a diverse range of 1,3-dienes was efficiently used, leading to the corresponding products in moderate to excellent yields from 25% to 95% (Scheme 5. 4).



Scheme 5. 4. Pd(II)-catalyzed functionalization of cyclopropanes with dienes.

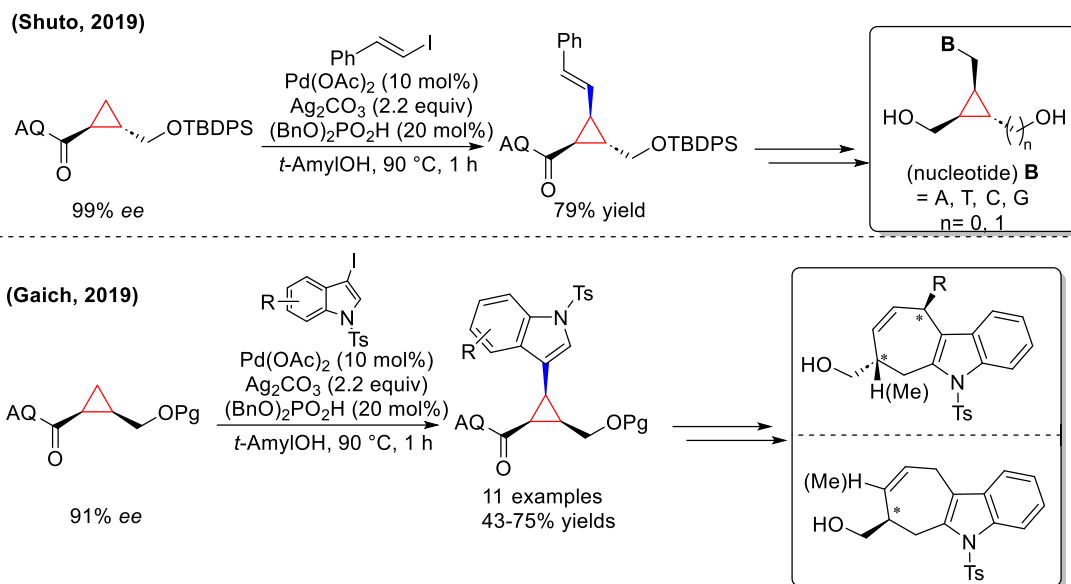
In addition, the synthetic applications of poly-substituted cyclopropanes have been explored extensively,^{4a,250} with recent studies emphasizing the significance of the Pd(II)-catalyzed /directed strategy in the synthesis of 1,2,3-trisubstituted cyclopropanes using bidentate directing group. To name, a few examples, Shuto *et al.* reported the alkenylation of cyclopropanes, subsequently generating bioactive cyclopropane-containing molecules fused with nucleotides (Scheme 5. 5, top).¹⁸¹ Gaich and co-workers applied C–H activation for the synthesis of indolylcyclopropanes, followed by olefination and an indole–vinylcyclopropane rearrangement to access functionalized cyclohepta[b]indoles.²⁵¹ Notably, both studies used enantiomerically pure cyclopropanes as substrates and achieved their targeted products without epimerization (Scheme 5. 5, bottom).

²⁴⁹ R. K. Shukla, A. M. Nair, C. M. Volla, *Chem. Sci.* **2023**, *14*, 955–962.

²⁵⁰ a) H.–U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196. b) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969–2984.

²⁵¹ M. Häfner, Y. M. Sokolenko, P. Gamerdinger, E. Stempel, T. Gaich, *Org. Lett.* **2019**, *21*, 7370–7374.

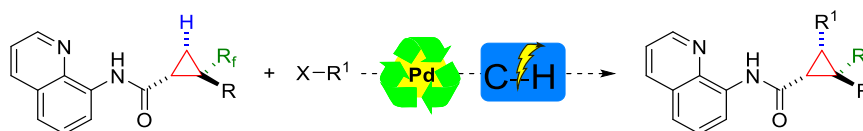
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Scheme 5. 5. Synthetic applications of poly-substituted cyclopropanes obtained *via* a C–H activation strategy.

5.2. Objectives

Despite the major advances made for the Pd-catalyzed C–H functionalization of cyclopropanes, none of them was applied to decorate fluorinated cyclopropanes. Having the knowledge and expertise in the preparation of fluorinated cyclopropanes, we aim at developing a new synthetic strategy to access 1,2,3-polysubstituted fluorinated cyclopropanes using a Pd-catalyzed C–H activation approach (Scheme 5. 6). It is important to highlight that such structure, namely a polysubstituted cyclopropanes bearing a fluorinated group, with an additional substituent on each carbon on the skeleton, is up to our knowledge, unknown in the literature.



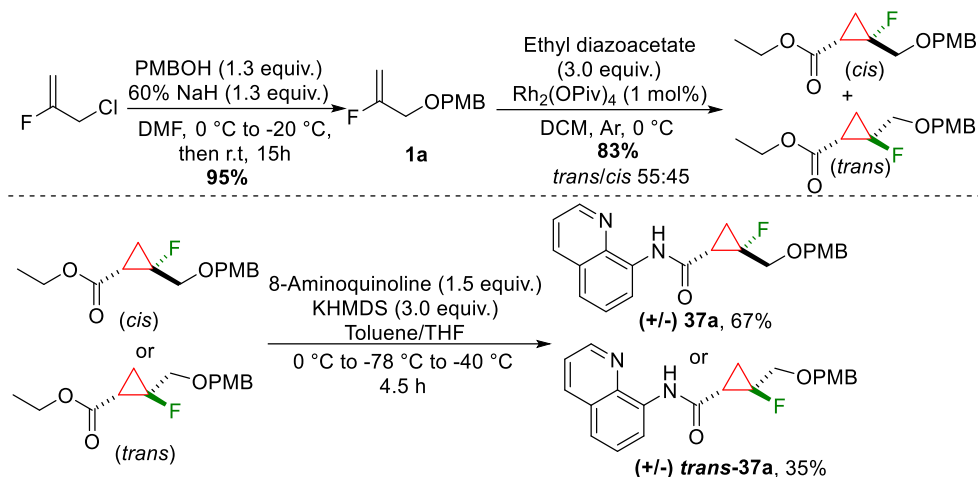
Scheme 5. 6. Project proposal.

5.3. Optimization of the reaction conditions

First, racemic materials, *cis*-**37a** and *trans*-**37a**, were synthesized from a commercially available

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compound, 3-chloro-2-fluoroprop-1-ene (Scheme 5. 7). The allylic compound **1a** was generated in a 95% yield when 3-chloro-2-fluoroprop-1-ene was treated with NaH and PMBOH.²⁵² Subsequently, upon reacting with ethyl diazoacetate under the catalysis of Rh₂(OPiv)₄,²⁵³ the fluorinated cyclopropyl ester was produced in an 83% yield with a 55:45 *dr*. Following this, in the presence of 8-aminoquinoline,¹⁸¹ the two separable diastereoisomers were individually subjected to form our desired product, *cis*-**37a** in a 67% yield, or *trans*-**37a** in a 35% yield.



Scheme 5. 7. Synthesis of racemic fluorinated cyclopropane substrate **37a** and *trans*-**37a**.

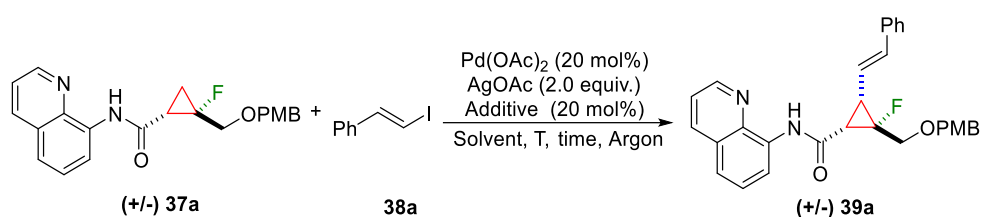
The optimization reactions were carried out between the racemic fluorinated cyclopropane **37a** and β -iodostyrene **38a** (Table 5. 1). Initially, inspired by Shuto's protocol,¹⁸¹ a coupling reaction was set out under the conditions of 20% Pd(OAc)₂, 2.0 equiv. AgOAc, and 20 mol% (BnO)₂PO₂H at 90 °C within 1 h (entry 1). To our delight, the reaction afforded the desired product **39a** in a 32% isolated yield. Lowering the reaction temperature to 60 °C provided a consistent yield compared to 90 °C, but the starting material **37a** was still observed by TLC analysis (entry 2). Subsequently, the reactions were conducted at different temperatures (90 °C, 60 °C, and r.t) without any additive; 90 °C and 60 °C gave similar moderate yields (39%, 38%, respectively) (entries 3-4), while the reaction at room temperature did not produce any product even after extending the time to 18 h (entry 5). Furthermore, the coupling reaction was carried out at 60 °C for 3 h with (BnO)₂POH, and the product was obtained in a high yield (74%) (entry 6). By switching the additive to PivOH, the product **39a**

²⁵² A. Pons, H. Beucher, P. Ivashkin, G. Lemonnier, T. Poisson, A. B. Charette, P. Jubault, X. Pannecoucke, *Org. Lett.* **2015**, *17*, 1790–1793.

²⁵³ C. Zhao, T. Besset, C. Legault, P. Jubault, *Chem. Eur. J.*, **2023**, e202303070.

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was obtained in a better yield of 77% (entry 7). Unfortunately, when these reaction conditions were applied to the coupling reaction of trifluoromethyl cyclopropane *trans*-**41c**, we observed a drastic decrease of the yield (40%) for the corresponding product *trans*-**42c** due to solubility issues. Thus, in order to develop a general strategy from different types of fluorinated cyclopropanes, a co-solvent solution was considered for this first optimization; however, when the reaction was proceeded with a mixed *t*-AmylOH/DCE (1:1), the coupling process was suppressed (entry 8). Finally, the use of a mixture of *t*-AmylOH/EtOAc (9:1) promoted the reaction, leading to the expected product **39a** in a 74% isolated yield (entry 9).



entry	solvent	additive	T/ (°C)	t/ (h)	yield/ (%) ^a
1	<i>t</i> -AmylOH	(BnO) ₂ PO ₂ H	90	1	32
2	<i>t</i> -AmylOH	(BnO) ₂ PO ₂ H	60	1	32
3	<i>t</i> -AmylOH	-	90	1	39
4	<i>t</i> -AmylOH	-	60	1	38
5	<i>t</i> -AmylOH	-	r.t	18	-
6	<i>t</i> -AmylOH	(BnO) ₂ POH	60	3	74
7	<i>t</i> -AmylOH	PivOH	60	3	77
8	<i>t</i> -AmylOH/DCE (1:1)	PivOH	60	3	n.r.
9	<i>t</i> -AmylOH/EtOAc (9:1)	PivOH	60	3	74

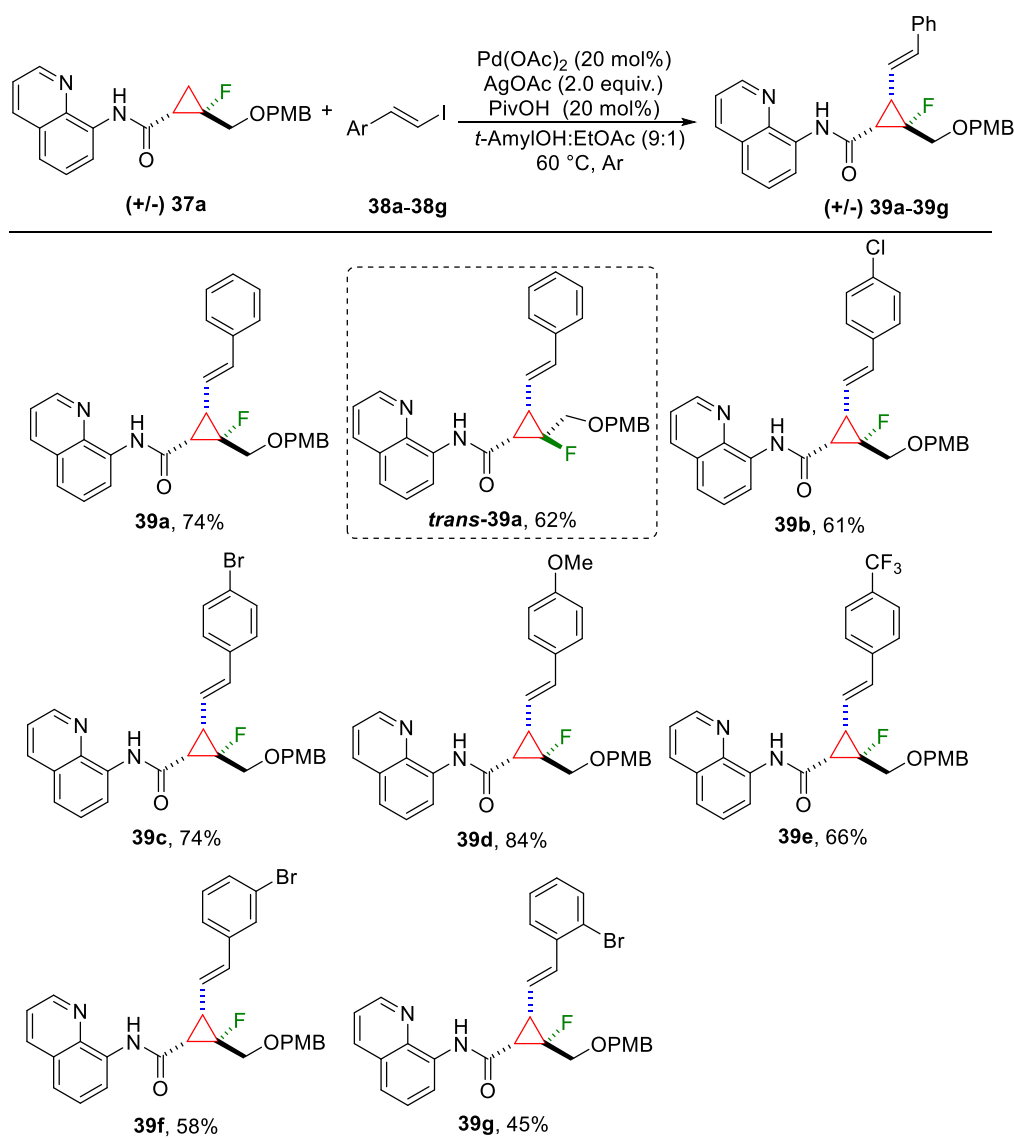
Table 5. 1. Conditions optimization. Reaction conditions: Cyclopropane **37a** (0.2 mmol, 1.0 equiv.), iodostyrene **38a** (0.6 mmol, 3.0 equiv.), Pd(OAc)₂ (20 mol%), AgOAc (2.0 equiv.) and solvent (1 mL) were employed. Argon. ^a Isolated yield.

5.4. Scope of the reaction

With the optimal conditions in hand (Table 5. 1, entry 9), our attention turned to study the applicability of this protocol (Scheme 5. 8). Firstly, the non-substituted β -iodostyrene **38a** was well-tolerated, giving a 74% yield of product **39a**. The use of the same reaction conditions to *trans*-**37a**

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also well proceeded, giving product *trans*-**39a** in a 62% yield. Afterwards, a series of *para*-substituted β -iodostyrenes were screened; *para*-halosubstituted substrates **38b** (Cl) and **38c** (Br) were employed as efficient coupling partners, affording the corresponding products in high yields (61%, 74%, respectively). When the *para*-methoxy substrate **39d** was introduced, the reaction provided the highest yield (84%). The β -iodostyrene with a strong electron-withdrawing group (-CF₃) on the *para* position was also suitable and the product **39e** was isolated in 66% yield. We next examined two coupling partners with bromo group at the *meta* and *ortho* positions. To our pleasure, both of these coupling reactions exhibited good capabilities to offer corresponding products **39f** and **39g** in 58% and 45%, respectively. Albeit the steric hindrance of bromo-substituted β -iodostyrenes arising from *para* to *ortho*, the yield was reduced in a small range.



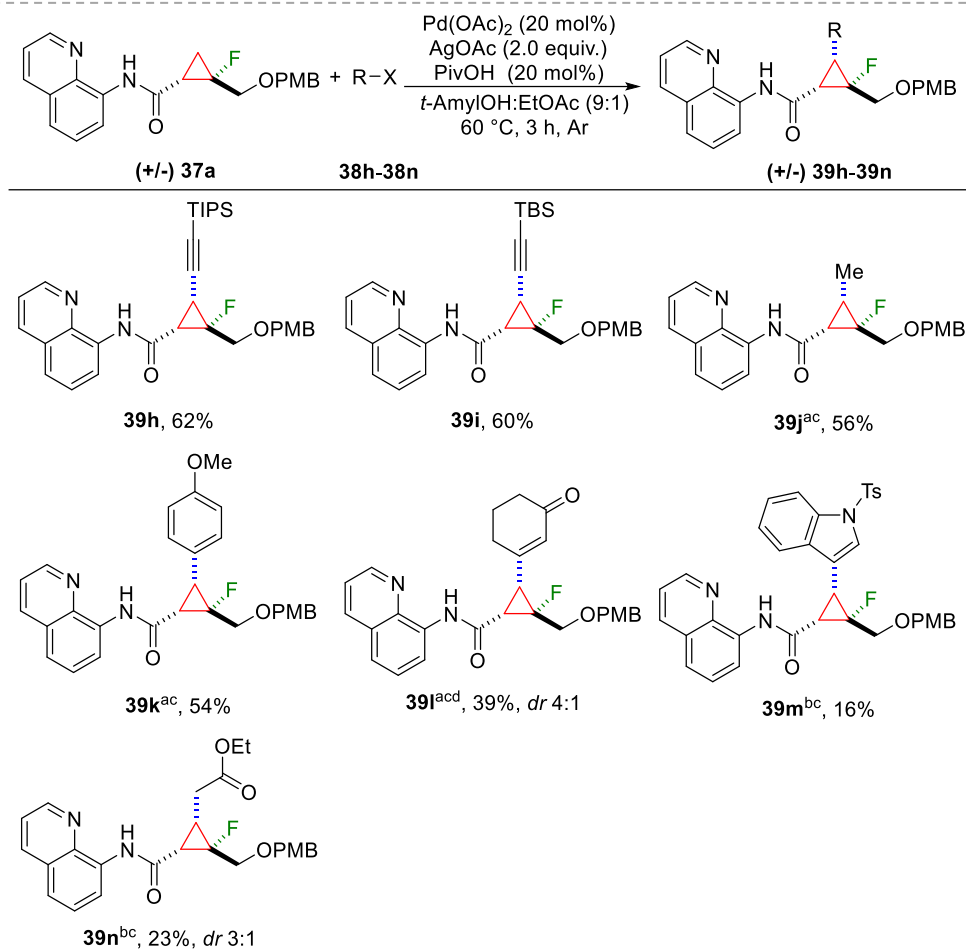
Scheme 5. 8. Scope of iodostyrenes **38a-38g** with substrate **37a**. Reaction conditions: Cyclopropane

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37a (0.2 mmol, 1.0 equiv.), iodostyrene **38** (0.6 mmol, 3.0 equiv.) and solvent (1 mL) were employed. Isolated yield.

With these interesting results obtained with β -iodostyrenes, we have devoted ourselves to seeking other versatile electrophiles in the transformation with the fluorinated cyclopropane **37a** (Scheme 5.9). Initially, alkynyl substrates bearing iodo (**38h**) or bromo (**38i**) groups were tested to generate alkynyl fluorinated cyclopropanes **39h** or **39i**. The reactions went smoothly for both **38h** and **38i**, providing the corresponding products in good yields (62%, 60% respectively). Furthermore, when iodomethane and *para*-iodoanisole were used, 1,2,3-polysubstituted fluorocyclopropanes **39j** and **39k** were obtained in good yields (around 55%), with modification of the oxidant (Ag_2CO_3) and additive ($(\text{BnO})_2\text{PO}_2\text{H}$) at 110 °C. Additionally, 3-iodocyclohexenone (**38l**) was found to be a suitable coupling partner when toluene was employed as the solvent, under the conditions of 2.0 equiv. Ag_2CO_3 and 20 mol% $(\text{BnO})_2\text{PO}_2\text{H}$ at 110 °C, producing a 39% yield of **39l** with a good *dr* (4:1). We then examined the use of 3-iodoindole (**38m**) and iodoethyl acetate (**38n**); however, in both cases, higher temperature (130 °C) was needed, and the functionalized fluorocyclopropanes **39m** and **39n** were isolated in moderate yields (16-23%) in the presence of Ag_2CO_3 and $(\text{BnO})_2\text{PO}_2\text{H}$. It should be mentioned that a moderated *dr* (3:1) of **39n** was observed in the ^{19}F NMR spectra.

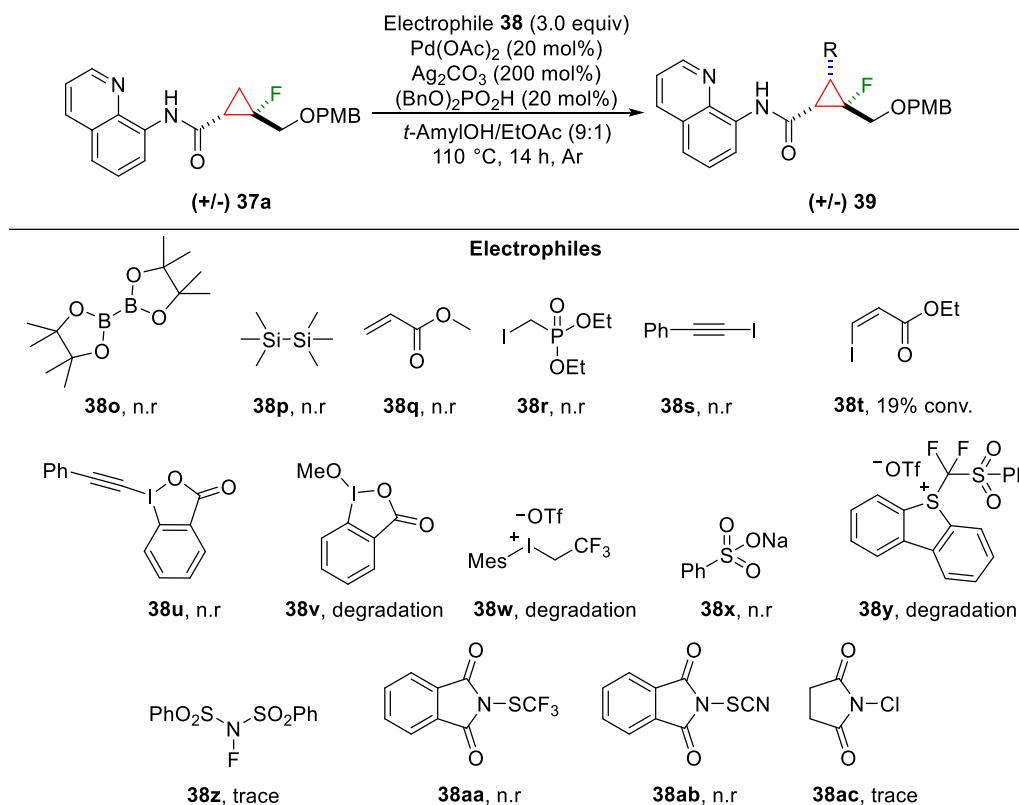
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Scheme 5.9. Scope of electrophiles **38h-38n** with substrate **37a**. Reaction conditions: Cyclopropane **37a** (0.2 mmol, 1.0 equiv.), electrophile **38** (0.6 mmol, 3.0 equiv.) and solvent (1 mL) were employed. Isolated yield. ^a 110 °C. ^b 130 °C. ^c Ag₂CO₃ (2.0 equiv.) as oxidant, (BnO)₂PO₂H (20 mol%) as additive. ^d Toluene as solvent. *dr* was determined by ¹⁹F NMR. **38i** X = Br, otherwise X = I.

Despite the successful engagement of the C–H activation protocol with a wide range of electrophiles, we still encountered some limitations (Scheme 5. 10). For example, when a hetero-functionalization was tested using reagents like B₂Pin₂ (**38o**), HMDS (**38p**) and methyl acrylate (**38q**), the coupling reactions exhibited no reactivity. Other coupling partners (**38r-38t**) containing an iodine atom were screened as well, and only **38t** showed 19% conversion; however, the corresponding product was obtained with impossible-to-separate impurities. Hypervalent iodine compounds **38u-38w** were introduced to the reaction, and no reaction occurred. Sulfonic sodium **38x** and sulfonium **38y** were found to be reluctant to form sulfonyl fluorocyclopropane. Besides, NFSI (**38z**), reagent **38aa** (-SCF₃) or **38ab** (-SCN), and NCS (**38ac**) were tested. Unfortunately, none of them provided a positive result.

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Scheme 5. 10. The limitations of scope. Reaction conditions: Cyclopropane **37a** (0.2 mmol, 1.0 equiv.), electrophile **38** (0.6 mmol, 3.0 equiv.) and solvent (1 mL) were employed. Conversion was determined by ¹⁹F NMR. n.r = no reaction.

In order to obtain the fluorinated cyclopropanes **39** with our desired functional groups (*i.e.*, -Bpin, -SiMe₃, -SCF₃), we examined these coupling reactions with the conditions from reported protocols (Scheme 5. 11). The borylation reactions were conducted following the method reported by Yu's group.²⁵⁴ However, even with the substrate (**37b**) bearing the same directing group, neither at 80 °C nor 100 °C could promote the reaction to synthesize the product **39o'** (Scheme 5. 11a). Next, a silylation reaction was subjected to generate the corresponding silyl fluorocyclopropane **39p** with Zhang's approach;²⁵⁵ similarly, the reaction failed (Scheme 5. 11b). Finally, our group has reported two elegant methodologies for the functionalization of C(sp²)-H and C(sp³)-H by introducing SCF₃ reagents **38aa**²⁵⁶ and **38ae**²⁵⁷ independently. It is unpleasant that when we tried the functional

²⁵⁴ J. He, H. Jiang, R. Takise, R. Y. Zhu, G. Chen, H. X. Dai, T. M. Dhar, J. Shi, H. Zhang, P. T. Cheng, *Angew. Chem. Int. Ed.* **2016**, *128*, 795–799.

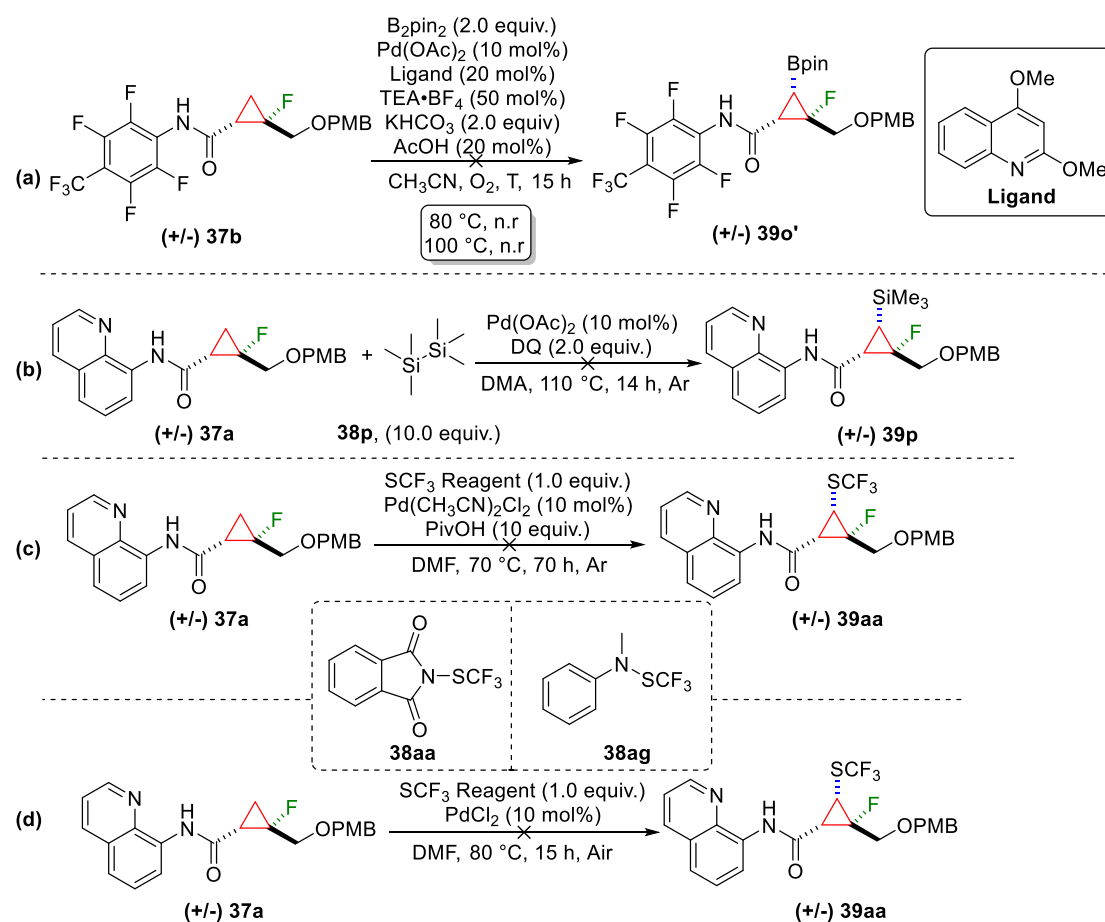
²⁵⁵ J.-L. Pan, Q.-Z. Li, T.-Y. Zhang, S.-H. Hou, J.-C. Kang, S.-Y. Zhang, *Chem. Commun.* **2016**, *52*, 13151–13154.

²⁵⁶ Q. Zhao, T. Poisson, X. Pannecoucke, J.-P. Bouillon, T. Besset, *Org. Lett.* **2017**, *19*, 5106–5109.

²⁵⁷ H.-Y. Xiong, T. Besset, D. Cahard, X. Pannecoucke, *J. Org. Chem.* **2015**, *80*, 4204–4212.

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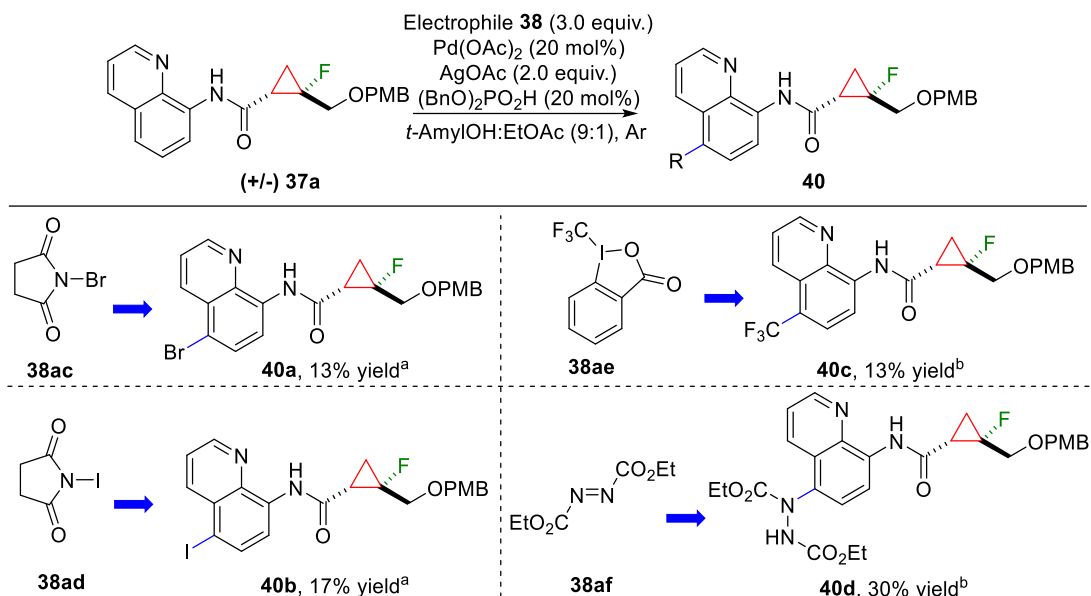
reagents individually in the presence of Pd(CH₃CN)₂Cl₂ or PdCl₂, none of the reactions provided any product **39aa** (Scheme 5. 11c-d).



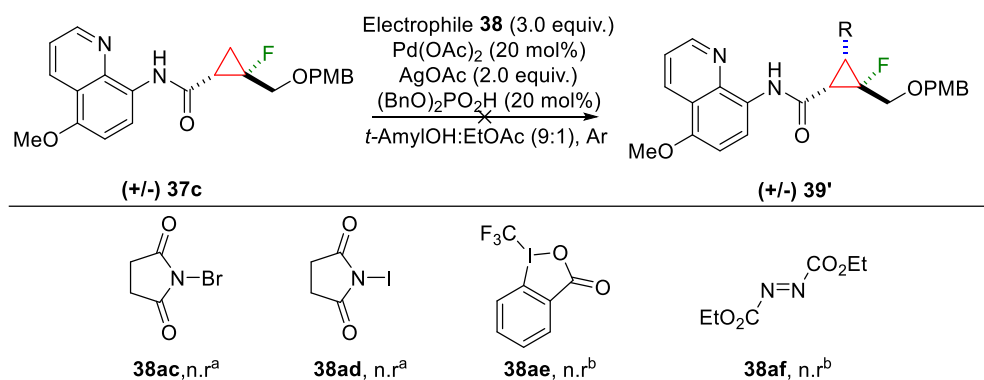
Scheme 5. 11. The functionalization reactions of fluorocyclopropane with reported methods.

During the screening of electrophiles, side reaction was observed with the functionalization of the quinoline moiety at the C5 position (Scheme 5. 12). For instance, the reaction in the presence of NBS (**38ac**) afforded product **40a** in a 13% yield at 130 °C, while NIS (**38ad**) provided iodoquinoline compound in a 17% yield. Consistently, the formation of 5-substituted quinoline product **40c** was isolated in a 13 % yield in the presence of the Togni reagent at 110 °C. Under the same reaction conditions but with the coupling partner DEAD (**38af**), the side product **40d** was observed in a 30% yield. The results indicated that when those four electrophiles were used, the reactions did not undergo C(sp³)–H activation; instead, the 5-position of quinoline showed a more important reactivity. To overcome this issue, we then prepared a C5-position blocked (5-OMe) quinoline fluorocyclopropane **37c** and further carried out coupling reactions with those four electrophiles; unfortunately, each of them exhibited no reactivity (Scheme 5. 13).

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Scheme 5.12. Side reactions with several electrophiles. ^a130 °C, 15 h. ^b110 °C, 12 h.

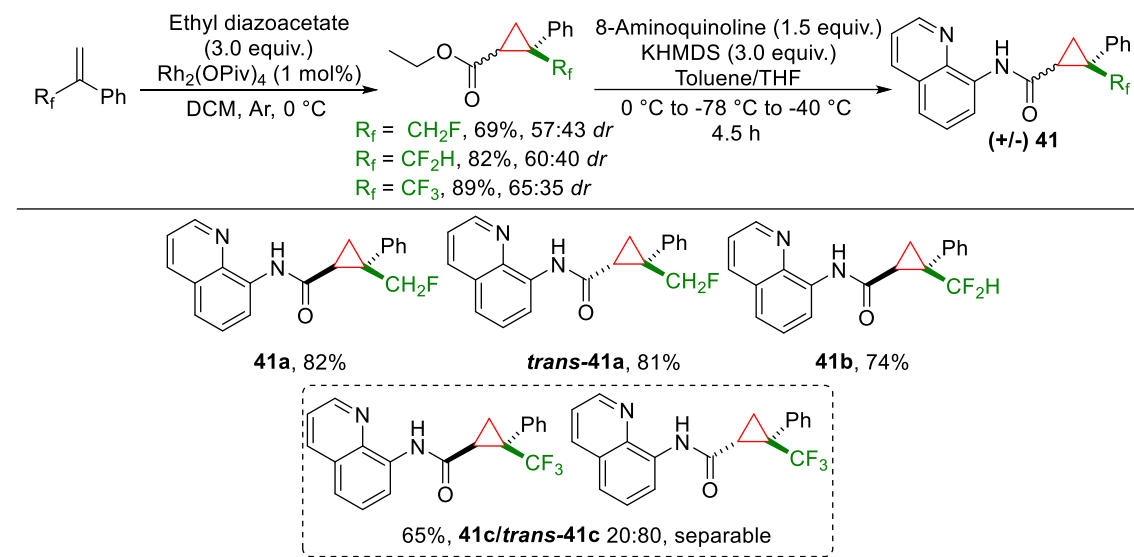


Scheme 5.13. Coupling reaction with fluorocyclopropane **37c**. ^a130 °C, 15 h. ^b110 °C, 12 h.

For the second stage of our scope study, we shifted our focus to the functionalization of several racemic cyclopropanes bearing fluoromethyl, difluoromethyl and trifluoromethyl groups (*i.e.*, -CH₂F, -CHF₂, -CF₃). Similar to the synthesis of compound **37a**, fluoromethyl cyclopropyl amide **41** was synthesized through a cyclopropanation reaction with its α -fluoromethyl styrene precursor (Scheme 5.14). The use of ethyl diazoacetate and Rh₂(OPiv)₄, we obtained the cyclopropyl ester with monofluoromethyl in a 69% yield with two separable diastereoisomers (57:43 *dr*). Similarly, the cyclopropyl ester with difluoromethyl was produced in an 82% yield and 60:40 *dr* (separable), while the cyclopropyl ester with trifluoromethyl was obtained in an 89% yield with 65:35 *dr* (inseparable). The subsequent amidation process provided the corresponding products **41a-41c** in yields ranging from 65% to 82%. Notably, the two diastereoisomers (**41c/trans-41c**) could be

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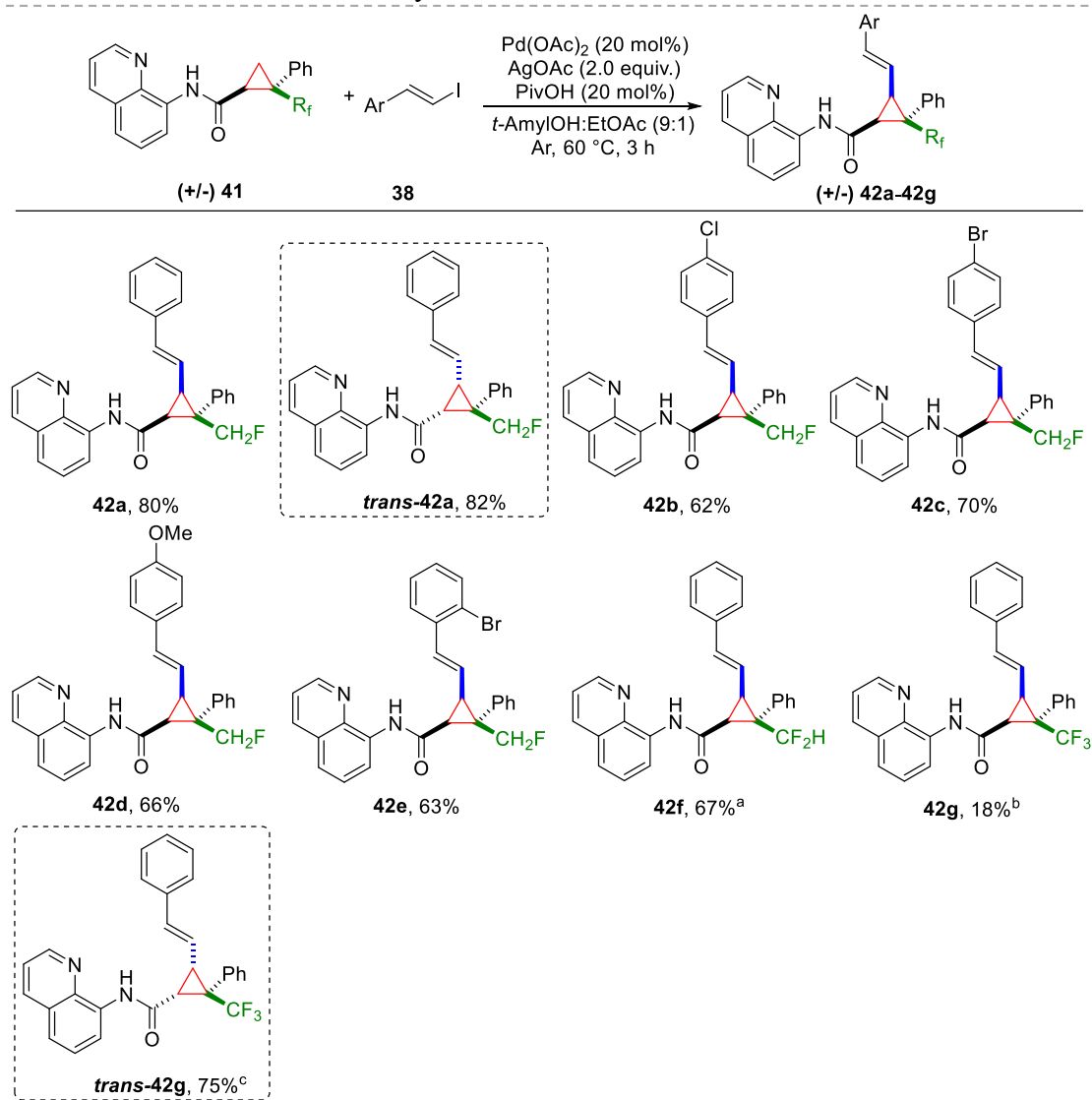
separated by silica-gel chromatography. However, we observed a different *dr* between trifluoromethyl cyclopropyl ester and amide through ^{19}F NMR inspection, indicating epimerization occurred during the amidation process.



Scheme 5. 14. Synthesis of racemic fluoromethyl cyclopropyl amide **41**.

The C-H functionalization of racemic cyclopropanes bearing fluoromethyl, difluoromethyl and trifluoromethyl groups was investigated using β -iodostyrenes as coupling partners under standard conditions (Scheme 5. 15). Firstly, we obtained the product **42a** and *trans*-**42a** in high yields (80%, 82%, respectively) from formal β -iodostyrene **38a** and monofluoromethyl cyclopropanes **41a** and *trans*-**41a**. *Para*-substituted β -iodostyrenes (**38b-38d**) were introduced to functionalize cyclopropane **41a**, offering corresponding 1,2,3-substituted monofluoromethyl cyclopropanes **42b-42d** in a range of yields from 62-70%. The bulkier *ortho*-bromo β -iodostyrene (**38g**) was tested; interestingly, unlike when engaging with substrate **37a**, this reaction proceeded smoothly and afforded product **42e** in good yield (63%). Furthermore, the reactions were carried out with racemic difluoromethyl cyclopropane **41b** and formal β -iodostyrene **38a**, with slightly modified conditions (90°C, 6 h), and the functionalized product **42f** was obtained in a 67% yield. Additionally, the trifluoromethyl cyclopropanes **41g** and *trans*-**41g** were tested for feasibility in the coupling reaction in the presence of **38a**. The *trans*-**41g** was well-tolerated, giving the corresponding product *trans*-**42g** in a 75% yield over a period of 20 h, whereas **42g** was obtained in an 18% yield even without additive (PivOH) and after 48 h of stirring. Thus, we realized that the reactivity of **41g** (*cis*) is much lower than *trans*-**41g** in this Pd(II)-catalyzed C(sp³)-H activation approach.

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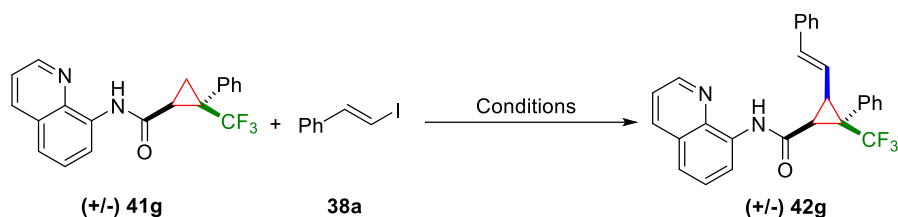


Scheme 5.15. Scope of iodostyrenes with substrate **41**. Reaction conditions: Cyclopropane **41** (0.2 mmol, 1.0 equiv.), iodostyrene **38** (0.6 mmol, 3.0 equiv.) and solvent (1 mL) were employed. Isolated yield. ^a 90 °C, 6 h. ^b Without PivOH, 48 h. ^c 20 h.

In light of the low yield obtained for the trifluoromethyl cyclopropane product **42g**, the conditions were optimized to enhance the reactivity of **41g** in the presence of electrophile **38a** (Table 5. 2). Initially, when standard conditions were used with an extended reaction time (20 h) (entry 1), the reaction showed only an 18% conversion of **42g** as observed by ¹⁹F NMR. Subsequently, the reaction temperature was increased to 90 °C (entry 2); however, the starting material **41g** decomposed during the heating process. When the reaction was carried out without PivOH and over a 48-hour stirring period at 60 °C (entry 3), the product **42g** was detected with a 25% conversion, and a 18% isolated yield was obtained (presented in Scheme 5. 15). Finally, the addition of 20 mol% (BnO)₂PO₂H with a 60-hour reaction time slightly promoted the coupling process (entry 4),

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resulting in a 23% conversion of **42g**.

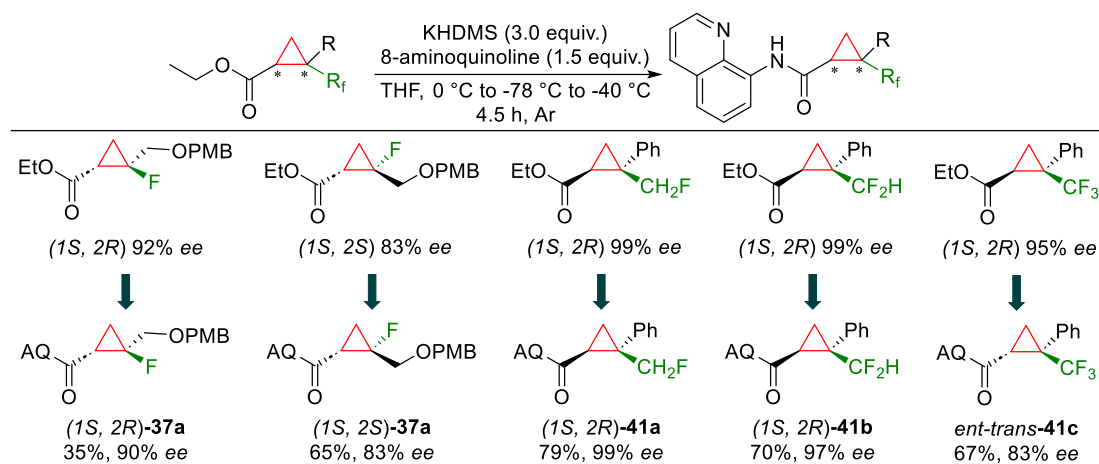


entry	reaction conditions	result
1	Pd(OAc) ₂ (20 mol%), AgOAc (2.0 equiv.), PivOH (20 mol%), <i>t</i> -AmylOH/EtOAc (9:1), 60 °C, 20 h, Ar	18% conv.
2	Pd(OAc) ₂ (20 mol%), AgOAc (2.0 equiv.), PivOH (20 mol%) <i>t</i> -AmylOH/EtOAc (9:1), 90 °C, 20 h, Ar	decomposed
3	Pd(OAc) ₂ (20 mol%), AgOAc (2.0 equiv.), <i>t</i> -AmylOH/EtOAc (9:1), 60 °C, 48 h, Ar	25% conv., 18% yield
4	Pd(OAc) ₂ (20 mol%), AgOAc (2.0 equiv.), (BnO) ₂ PO ₂ H (20 mol%), <i>t</i> -AmylOH/EtOAc (9:1), 60 °C, 60 h, Ar	23% conv.

Table 5. 2. Optimization of coupling reaction between **41g** and **38a**. Conversion was determined by ¹⁹F NMR.

To further explore the scope of this methodology on optically pure substrates, enantiomerically pure fluorinated cyclopropanes engaged with 8-aminoquinoline (AQ) were prepared from their cyclopropyl ester precursors (Scheme 5. 16). These ester precursors were synthesized following the reported methods from our group²⁵³ and in collaboration with Fasan's group^{171d}. The (*1S*, *2R*)-**37a** and (*1S*, *2R*)-**37a** were produced from amidation reactions with decent to good yields (35%, 65% respectively), albeit a slight decrease in *ee* was observed for compound (*1S*, *2R*)-**37a**. Monofluoromethyl cyclopropane (*1S*, *2R*)-**41a** could be generated from its ester precursor in a 79% yield without *ee* erosion, while difluoromethyl cyclopropane (*1S*, *2R*)-**41b** was delivered in a 70% yield with a 2 mol% *ee* loss. Surprisingly, the use of *cis* enantiopure trifluoromethyl cyclopropyl ester did not primarily lead to the corresponding *cis* product; instead, a product with a contrary relative configuration, *trans*-**41c**, was obtained as a major product in good yield (67%), but the *ee* dropped to 83%. It demonstrated that epimerization occurred during the amidation process.

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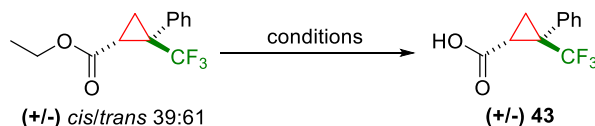


Scheme 5. 16. Synthesis of enantiopure fluorinated cyclopropane with directing group (AQ). Relative configuration was determined by HOESY 2D NMR. *ee* was determined by a chiral HPLC stationary.

When we encountered the epimerization problem in the synthesis of *cis* enantiopure trifluoromethyl cyclopropane **41c**, a two-step solution (hydrolysis-condensation) was considered to address this issue. For the hydrolysis step, numerous reactions were attempted using various reagents (Table 5. 3). Saponification reactions were conducted with KOH or Me₃SnOH (entries 1-2); however, despite the product **43** being obtained in decent yields (58%, 37% respectively), epimerization could not be avoided. Hydrolysis reactions carried out in the presence of acetic acid and zinc as an activator did not yield any product (entry 3). Similarly, transformation reactions from ester to carboxylic acid **43** using LiOOH were inefficient (entries 4-6), regardless of whether LiOOH was commercially available or *in situ* generated. Fortunately, TMSI (trimethylsilyl iodide) was identified as a suitable reagent that could deliver the expected product **43** with a consistent diastereomeric ratio compared to its ester precursor.

To optimize the TMSI-hydrolysis conditions, three solvents were attempted for the reaction: CDCl₃ and CHCl₃ proved to be feasible (entries 7-8), offering carboxylic acid **43** in 61% and 41% conversion, respectively, while MeCN caused the hydrolysis reaction to become messy (entry 9). Due to cost considerations, CHCl₃ was selected for further optimization. The reaction conducted in distilled CHCl₃ resulted in better conversion (48%) of product **43** (entry 10). Additionally, the addition of 6.0 equiv. TMSI improved the hydrolysis reaction, reaching 69% conversion (entry 11). Finally, the best result (84% conversion and 65% isolated yield of **43**) was obtained with an extended reaction time of 36 h (entry 12).

Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation

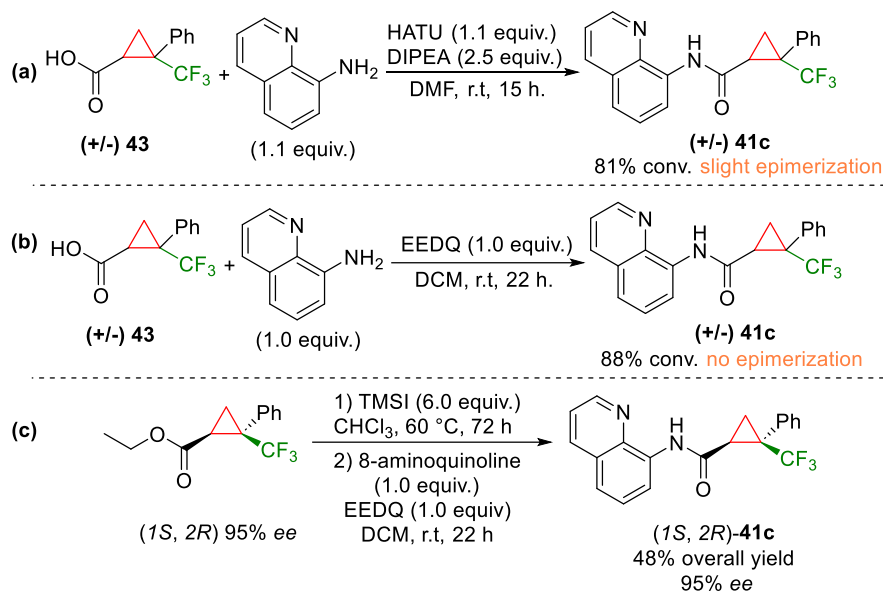


entry	reaction conditions	conv. (%)	<i>dr</i>
1	KOH (2.0 equiv.), EtOH, r.t, 2 h	72 (58)	19:81
2	Me ₃ SnOH (3.0 equiv.), DCE, 80 °C, 72 h	44 (37)	47:53
3	Zinc (5.0 equiv.), AcOH, r.t	n.r	-
4	LiOOH (4.0 equiv.), MeOH, 0 °C to r.t	n.r	-
5	LiOH (2.0 equiv.), H ₂ O ₂ (3.0 equiv.), THF/H ₂ O (3:1), r.t	n.r	-
6	LiOH (2.0 equiv.), H ₂ O ₂ (3.0 equiv.), THF/H ₂ O (3:1), 40 °C	n.r	-
7	TMSI (3.0 equiv.), CDCl ₃ , 50 °C, 24 h	61 (37)	39:61
8	TMSI (3.0 equiv.), CHCl ₃ , 50 °C, 24 h	41	39:61
9	TMSI (3.0 equiv.), MeCN, 50 °C, 24 h	messy	-
10 ^a	TMSI (3.0 equiv.), CHCl ₃ , 50 °C, 24 h, Ar	48	39:61
11 ^a	TMSI (6.0 equiv.), CHCl ₃ , 50 °C, 24 h, Ar	69	39:61
12 ^a	TMSI (6.0 equiv.), CHCl ₃ , 50 °C, 36 h, Ar	84(65)	39:61

Table 5. 3. Optimization of the hydrolysis from trifluoromethyl cyclopropyl ester to carboxylic acid **43**. Isolated yield was presented in parenthesis. Conversion and *dr* were determined by ¹⁹F NMR. n.r = no reaction. ^a Fresh distilled.

With the successful progress of the hydrolysis step, we then continued the investigation of the condensation step in the presence of compound **43** and 8-aminoquinoline. The coupling reagent HATU was firstly used to initiate the reaction (Scheme 5. 17a), but this reaction required an additional base (DIPEA) to deprotonate the amino group, and the base also induced slight epimerization during the condensation process, even with a high conversion (81%). Alternatively, a reaction was performed with the reagent EEDQ (2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) to produce the target product **41c** in 88% conversion without epimerization during the condensation process (Scheme 5. 17b). Therefore, our desired enantiopure product (*1S*, *2R*)-**41c** could be synthesized in a 48% overall yield within the combined two-step procedure, while maintaining a high level of enantiomeric excess (95%) (Scheme 5. 17b).

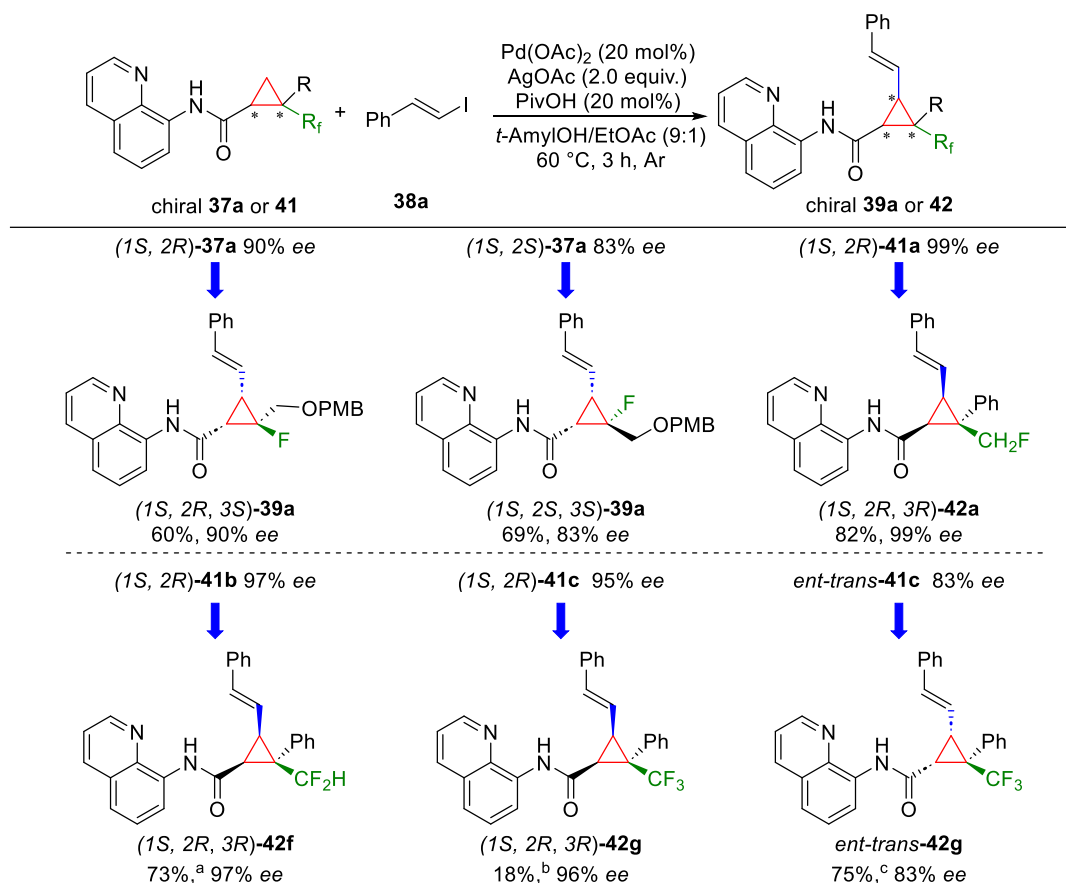
Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation



Scheme 5. 17. Condensation step investigation and synthesis of enantiopure trifluoromethyl cyclopropane (*1S, 2R*)-**41c**.

With all the desired enantiomerically pure fluorinated cyclopropane substrates in hand, a series of reactions were performed to functionalize these chiral compounds with the coupling partner **38a** (Scheme 5. 18). It began with the fluorocyclopropanes (*1S, 2R*)-**37a** and (*1S, 2S*)-**37a**. Under standard conditions, the corresponding products (*1S, 2R, 3S*)-**39a** and (*1S, 2S, 3S*)-**39a** were isolated in 60% and 69% yields, respectively, along with unchanged enantiomeric excess values (90% and 83%). (*1S, 2R*)-**41a** was examined within the methodology, and the coupling product (*1S, 2R, 3R*)-**42a** was delivered in 82% yield with excellent *ee* (99%). Similar to its racemate, the reaction involving (*1S, 2R*)-**41b** needed a higher temperature (90 °C) and longer time (6 h) to achieve a good yield (73%) of (*1S, 2R, 3R*)-**42b** with a very good optical purity (97% *ee*). (*1S, 2R*)-**41c** and *trans*-**41c** were also investigated as substrates with slightly modified reaction conditions. (*1S, 2R, 3R*)-**42c** was obtained in 18% yield, while *trans*-**42c** was generated in a 75% yield. To our delight, both enantioselectivities (96%, 83%, respectively) of the products were determined to be consistent with those of the starting materials.

Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation

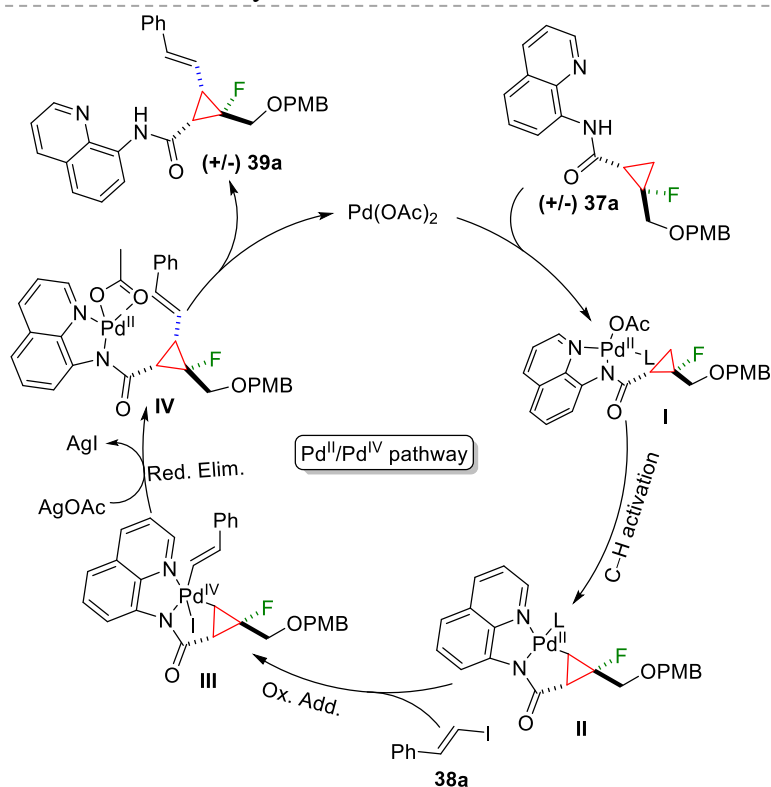


Scheme 5. 18. The formation of enantiopure 1,2,3-polysubstituted fluorinated cyclopropanes. Reaction conditions: Chiral cyclopropane **37a** or **41** (0.2 mmol, 1.0 equiv.), iodostyrene **38a** (0.6 mmol, 3.0 equiv.) and solvent (1 mL) were employed. Isolated yield. ^a 90 °C, 6 h. ^b without PivOH, 48 h. ^c 20 h.

5.5. Propose plausible mechanism

Based on the previous advances in Pd(II)-catalyzed C(sp³) activation,^{258,247} we propose a plausible Pd(II)/Pd(IV)-mechanism for this project (Scheme 5. 19). Initially, bidentate coordination of the catalyst Pd(OAc)₂ with substrate **37a** will generate the organometallic species **I**. After formation of the metallacycle (intermediate **II**), the latter will undergo an oxidative addition with the electrophile **38a**, resulting in a Pd^{IV} species **III**. After reductive elimination and reprotonation the expected product **39a** will be obtained and regenerate the catalyst.

²⁵⁸ a) D. Antermite, A. J. P. White, L. Casarrubios, J. A. Bull, *ACS Catal.* **2023**, *13*, 9597–9615. b) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.



Scheme 5.19. Plausible mechanism of this project.

5.6. Post-functionalization reactions

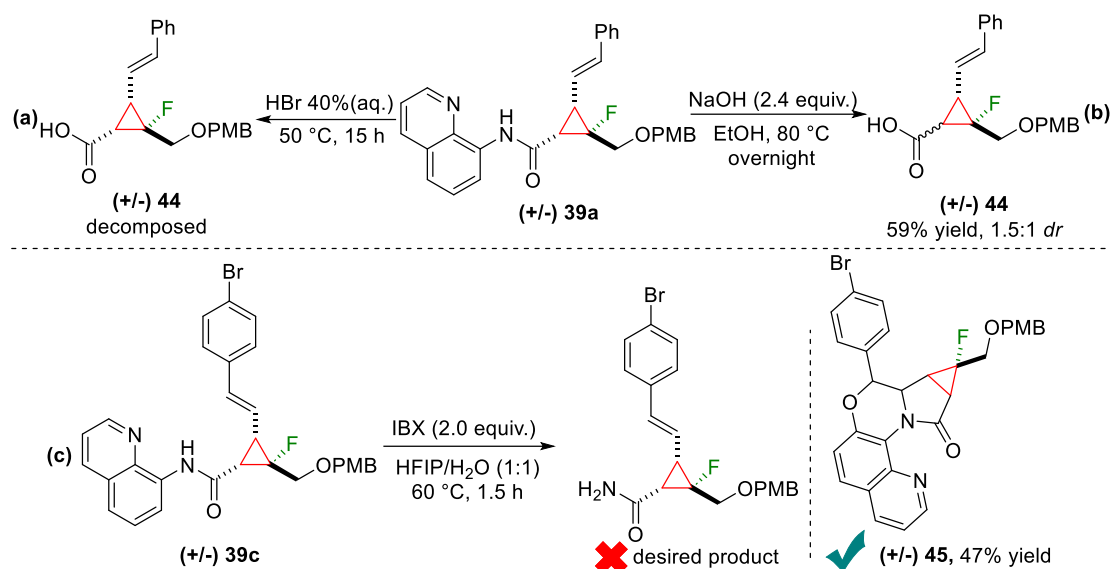
After successfully developing an effective method for synthesizing either racemic or enantioenriched 1,2,3-polysubstituted fluorinated cyclopropane products, we next examined some post-functionalization reactions to demonstrate the robustness of our protocol. With this purpose, the cleavage of the directing group was first carried out with different methods. At the beginning, racemate **39a** was treated with a 40% HBr²⁵⁹ solution in H₂O aiming to produce the carboxylic acid product **44**; unfortunately, we only observed the starting material **39a** decomposed (Scheme 5. 20a). While a saponification reaction was carried out by use of NaOH in EtOH,²⁴² the desired product **44** was offered in a 59% yield, but epimerization was observed (Scheme 5. 20b). In addition, compound **39c** was subjected to an oxidation reaction with the oxidant reagent IBX (2-iodoxybenzoic acid);²⁶⁰ surprisingly, the isolated product was determined to be the polycyclic compound **45** instead of our

²⁵⁹ Q. Zhu, D. Ji, T. Liang, X. Wang, Y. Xu, *Org. Lett.* **2015**, *17*, 3798–3801.

²⁶⁰ L. Ruyet, M. I. Lapuh, V. S. Koshti, T. Földesi, P. Jubault, T. Poisson, Z. Novák, T. Besset, *Chem. Commun.* **2021**, *57*, 6241–6244.

Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation

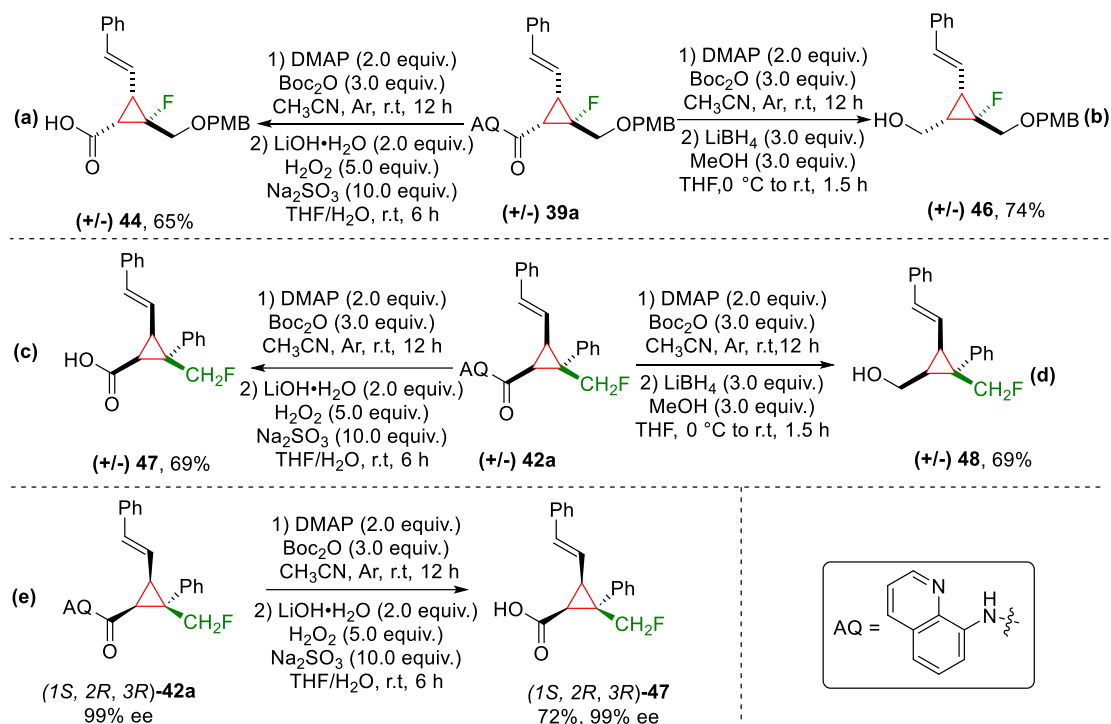
desired primary amide (Scheme 5. 20c).



Scheme 5. 20. Tests for the cleavage of 8-aminoquinoline group.

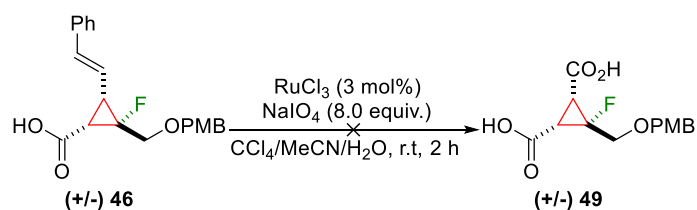
Then, a two-steps strategy was examined for the removal of this group. With a base (DMAP) and Boc_2O ,²⁴³ compound **39a** could be transformed into a tertiary amide, followed by treatment with LiOOH (*in situ* generated),²⁴³ the desired carboxylic acid product **44** was produced in a 65% yield (Scheme 5. 21a). On the other hand, under reductive reaction conditions (LiBH_4 with MeOH),¹⁸¹ the primary alcohol product **46** was synthesized in a 74% yield (Scheme 5. 21b). Similarly, by employing the protection/hydrolysis process, the transformation of compound **42a** led to the corresponding carboxylic acid product **47** in a 69% yield (Scheme 5. 21c) while using the protection/reduction process, the corresponding primary alcohol product **48** was obtained in a 69% yield (Scheme 5. 21d). Starting from the enantiopure difluoromethyl cyclopropane (*1S, 2R, 3R*)-**42a**, the corresponding enantiopure product (*1S, 2R, 3R*)-**47** was afforded in a high yield (72%) and without *ee* erosion (Scheme 5. 21e).

Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation



Scheme 5.21. The cleavage of 8-aminoquinoline reactions in two-step strategies.

In addition to our previous efforts in the transformation of C–H activation products, an oxidation reaction involving compound **46** was tested to obtain cyclopropyl dicarboxylic acid **49**. However, the reaction could not be initiated when employed reagents RuCl_3 and NaIO_4 (Scheme 5.22).^{225a} This consequence has proven the substrate **46** lack of reactivity to $\text{RuCl}_3/\text{NaIO}_4$ oxidation system up to date.



Scheme 5.22. Attempt of oxidizing compound **46** to form cyclopropyl dicarboxylic acid **49**.

5.7. Conclusion

In summary, we have enclosed an efficient methodology for accessing 1,2,3-polysubstituted fluorinated cyclopropanes. The use of Pd(II)-catalyzed C–H bond activation strategy enabled the functionalization of diverse fluorinated cyclopropanes in moderated to high yields, including those

Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation

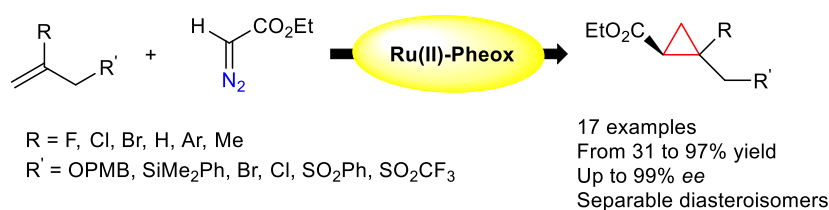
with -F, -CH₂F, -CF₂H, and -CF₃ groups, as well as demonstrating good tolerance to a wide range of iodide/bromide electrophiles. Additionally, removal of the directing group allowed the coupling products to be further transformed into carboxylic acid and primary alcohol derivatives, showcasing the versatility of the products obtained with our protocol. We believe that this method represents a significant and practical pathway for the preparation of both racemic and enantiomeric 1,2,3-polysubstituted fluorinated cyclopropane scaffolds.

Chapter VI – Conclusion and perspectives

6.1. Conclusion

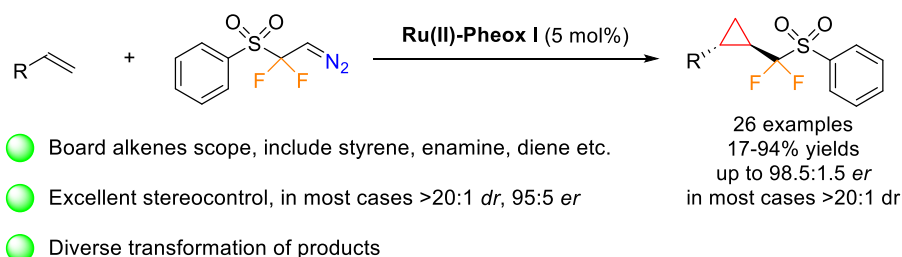
Based on the previous works developed in our group over the past five years, in the first part of this thesis, we focused on the chiral metal-complex-catalyzed enantioselective synthesis of functionalized cyclopropanes from 2-substituted allylic compounds, as well as enantioenriched alkynyl or α,α -difluoroalkyl cyclopropanes.

We initially reported the catalytic asymmetric synthesis of highly functionalized cyclopropanes from 2-substituted allylic derivatives (Scheme 6. 1). Using ethyl diazoacetate, the reaction, catalyzed by a chiral ruthenium complex (Ru(II)-Pheox), furnished the corresponding easily separable *cis* and *trans* cyclopropanes in moderate to high yields (32-97%) and excellent *ee* (86-99%). This approach significantly extends the portfolio of accessible enantioenriched cyclopropanes from an underexplored class of olefins. In collaboration with Prof. Claude Legault, A DFT calculations was conducted and suggest that an outer-sphere mechanism is operative in this system.



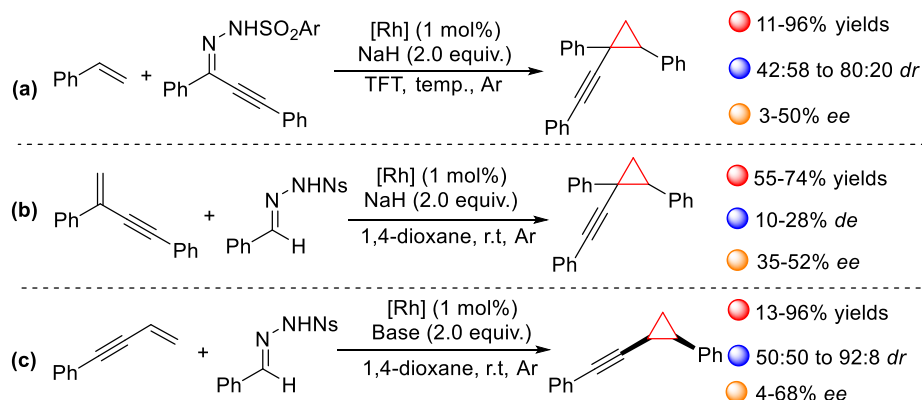
Scheme 6. 1. Ru(II)-Pheox-catalyzed 2-substituted allylic derivatives with EDA asymmetric cyclopropanation.

Subsequently, we have disclosed the first protocol in the catalytic synthesis of versatile enantiopure 1,2-disubstituted α,α -difluoroalkyl cyclopropanes using metallocarbene and alkenes [2+1] ring addition strategy (Scheme 6. 2). The metal complex Ru(II)(*S*)-Pheox I was introduced as efficient catalyst, which afforded α,α -difluoroalkyl cyclopropane products in a range of yield from 17-94%, excellent diastereoselectivity (in most cases >20:1 *dr*) and enantioselectivity (up to 98.5:1.5 *er*). Further post-functionalization reactions demonstrate the synthetic utility of the products providing an unique opportunities to access to stereocontrolled versatile α,α -difluoroalkyl cyclopropane frameworks.



Scheme 6. 2. Ru(II)-Pheox-catalyzed synthesis of enantiomeric convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes.

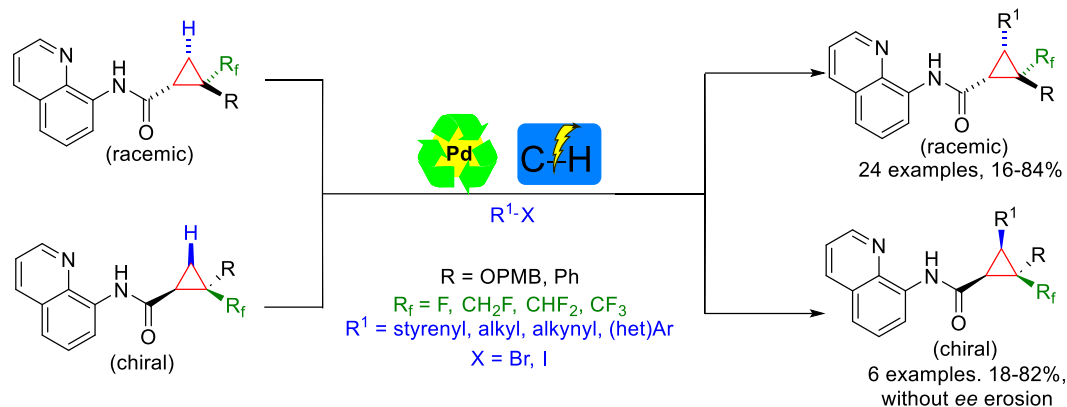
In chapter IV, we have presented the optimization studies for the synthesis of enantiomerically pure alkynylcyclopropanes (Scheme 6. 3). While a diverse array of Rh(II)-complexes has been explored in cyclopropanation reactions, leading to high yields and diastereoselectivity, low to moderate enantioselectivity has been obtained and the transformation remained a synthetic challenge. Additionally, attempts to modify substrates and use various additives have offered unsatisfactory results. Given these limitations in the project, we have set it aside and are actively exploring alternative solutions for the near future.



Scheme 6. 3. Rh(II)-complex-catalyzed synthesis of enantiomerically pure alkynylcyclopropanes.

As part of our group's research, the Pd-catalyzed 8-aminoquinoline amide-directed strategy has proven to be a widely employed and potent approach for C(sp³)-H or C(sp²)-H activation. Based on our previous efforts, a novel synthetic strategy for the synthesis of unexplored 1,2,3-polysubstituted fluorinated cyclopropanes, employing a Pd-catalyzed directed C-C bond formation by C(sp³)-H bond activation was developed using the privileged amide derived from 8-aminoquinoline as a directing group (chapter V, Scheme 6. 4). By employing this Pd(II)-catalyzed C-H bond activation strategy, we achieved the functionalization of various fluorinated

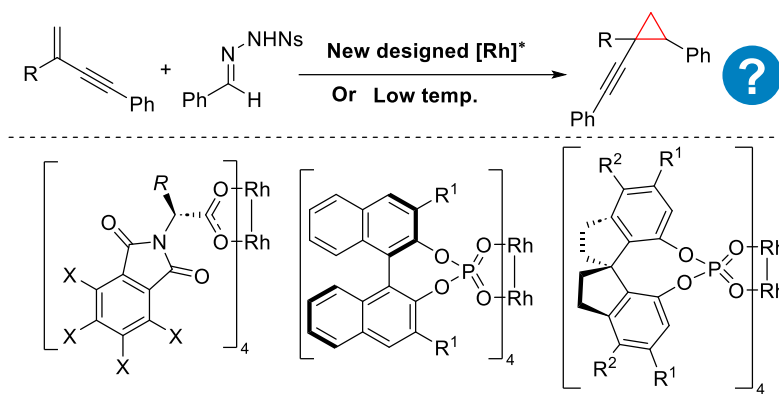
cyclopropanes in moderate to high yields, encompassing those with -F, -CH₂F, -CF₂H, and -CF₃ groups, starting with racemic or chiral substrates. In addition, the protocol also exhibited good tolerance to a wide array of iodide/bromide electrophiles to forge interesting C(sp³)-C(sp), C(sp³)-C(sp²) and C(sp³)-C(sp³) bond. This method is particularly valuable for constructing diverse fluorinated cyclopropanes, given their synthetic significance and potential medicinal applications.



Scheme 6. 4. Palladium-catalyzed C-H bond activation onto fluorinated cyclopropane.

6.2. Perspectives

In order to tackle the difficulties, we met to control the enantioselectivity in the case of our study related the synthesis of enantiomeric pure alkynyl cyclopropanes (low to moderate *ee*, Chapter IV), we would like to investigate a promising direction, involving the design of new dirhodium paddlewheel complexes for the asymmetric synthesis of alkynylcyclopropanes from alkenes and hydrazone compounds (Scheme 6. 5). Additionally, there is potential for exploring a low-temperature, one-pot approach to generate alkynylcyclopropanes with high diastereo- or enantio-selectivity.



Scheme 6. 5. Plausible solutions for enantiomeric excess optimization for construction of enantiopure alkynyl cyclopropanes.

Experimental Part

General information and materials

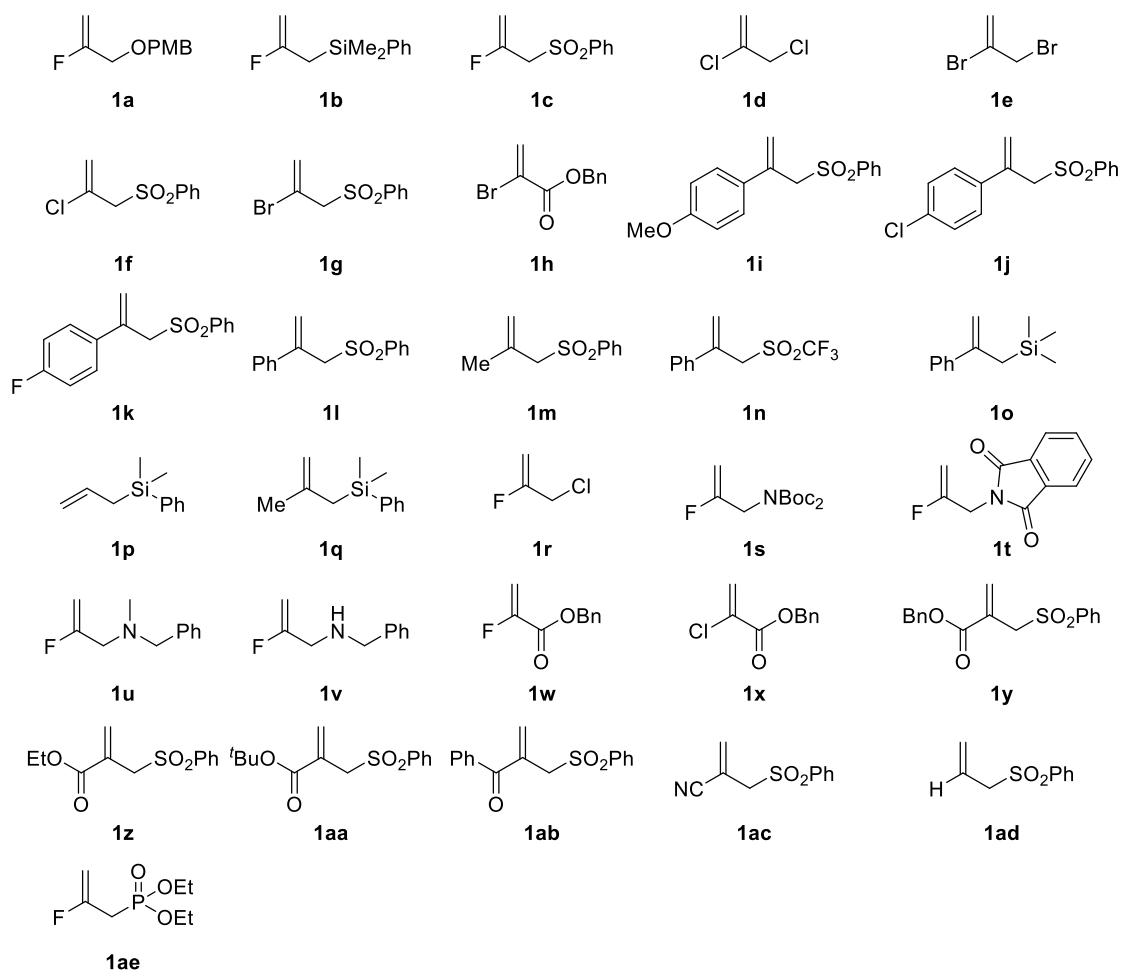
General information: All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of air unless otherwise stated. Reaction temperatures are reported as the temperature of the oil bath surrounding the vessel. Analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a KMnO₄ solution, *p*-anisaldehyde or a phosphomolybdic acid solution. Silica gel column chromatography was performed using 0.040-0.063 mm silica gel. ¹H NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer at 300.1 MHz, ¹³C NMR spectra at 75.5 MHz and ¹⁹F NMR spectra at 282.4 MHz. HOESY or NOESY were recorded on a Bruker DXP 300 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) relative to residual solvent peak for CDCl₃ ($\delta_{\text{H}} = 7.26$ ppm, $\delta_{\text{C}} = 77.00$ ppm) and relative to external CFCl₃ ($\delta_{\text{F}} = 0$ ppm). Coupling constants (J) are quoted in Hz. The following abbreviations were used to show the multiplicities: s: singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, qd: quartet of doublets, m: multiplet. High-Resolution Mass Spectra (HRMS) were recorded with a Waters LCT Premier mass spectrometer with a micro-TOF analyzer. IR spectra were recorded on a PerkinElmer Spectrometer Pargon 100 (ATR). The wave numbers (ν) of recorded IR-signals are quoted in cm⁻¹. Melting points were recorded on a Heizbank system Kofler WME and were uncorrected. Enantiomeric excesses (*ee*) or Enantiomeric ratio (*er*) were determined by high-performance liquid chromatography (HPLC) and gas chromatography (GC).

Materials: Dichloromethane (DCM), Dichloroethane (DCE), diethyl ether (Et₂O) Ethyl acetate (EtOAc), 2-methyl-2-butanol (*tert*-AmylOH) tetrahydrofuran (THF) and toluene were distilled over CaH₂ prior to use. Anhydrous acetonitrile (MeCN), dimethyl sulfoxide (DMSO), 1,4-dioxane, *N,N*-dimethylformamide (DMF) and over molecular sieve from Acros Organics (Solvent extra dry over molecular sieves, Acroseal®) were used. Analytical reagent grade solvents and others chemical reagents were purchased from Acros Organics, Sigma Aldrich or Apollo Scientific.

Chapter II – Experimental and computational studies for the catalytic enantioselective synthesis of functionalized cyclopropanes from α -substituted allylic derivatives with ethyl diazoacetate

1. General procedures for the preparation of starting materials.

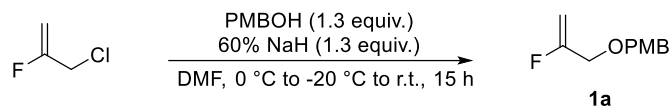
1.1. Synthesis of allylic and acrylate alkenes 1.



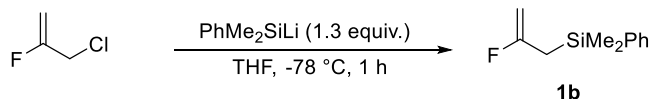
The known alkene starting materials **1a**, **1b**, **1c**, **1f**, **1g**, **1s**, **1t** were synthesized according to reported literature,¹⁶¹ **1i**, **1j**, **1k**, **1l**, **1m**, **1n**, **1o**, **1y** were synthesized according to reported literature,⁷⁰ **1h**, **1w**, **1x** was synthesized according to reported literature,⁹⁵ **1p**, **1q** was synthesized according to

Experimental Part

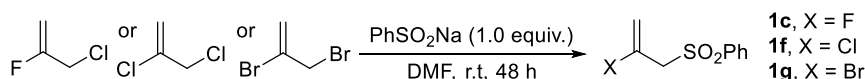
reported literature,²⁶¹ **1u**, **1v** was synthesized according to reported literature,²⁶² **1ae** was synthesized according to reported literature,²⁵² the characterization data is consistent with reported literatures. **1d**, **1e**, **1r**, **1ad** were purchased from standard chemical supplier (Sigma-Aldrich).



A solution of PMBOH (1.8 g, 13 mmol, 1.3 equiv.) in DMF (8 mL) was slowly added to a solution of NaH 60% (520 mg, 13 mmol, 1.3 equiv.) in DMF (5 mL) at 0 °C. The mixture was stirred at 0 °C for 30 minutes, then cooled to -20 °C and a solution of 3-chloro-2-fluoroprop-1-ene (0.87 mL, 10 mmol, 1.0 equiv.) in DMF (3 mL) was slowly added. The mixture was allowed to warm to room temperature, stirred for 15 hours and water was added. The aqueous layer was extracted with Et₂O (3×15 mL), and combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated. The crude product was purified by silica-gel flash column chromatography (petroleum ether /EtOAc 98:2) to afford 1.86 g (95% yield) of olefin **1a** as a colorless oil.



Under argon atmosphere, a 0.5 M solution of PhMe₂SiLi in THF²⁶³ (5.2 mL, 2.6 mmol, 1.3 equiv.) was added dropwise to a solution of 3-chloro-2-fluoroprop-1-ene (1.0 equiv., 2 mmol, 174 μL) in THF (6 mL) at -78 °C. The mixture was stirred at -78 °C for 1 hour, then quenched at -78 °C with saturated aqueous NH₄Cl (5 mL) and extracted with Et₂O (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude was purified by silica-gel flash column chromatography (petroleum ether) to afford 252 mg (65% yield) of olefin **1b** as a colorless oil.



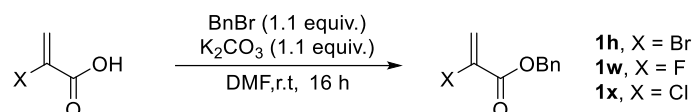
²⁶¹ C. Chen, T. R. Dugan, W. W. Brennessel, D. J. Weix, P. L. Holland, *J. Am. Chem. Soc.* **2014**, *136*, 945–955.

²⁶² S. S. Salim, R. K. Bellingham, V. Satcharoen, R. C. D. Brown, *Org. Lett.* **2003**, *5*, 3403–3406.

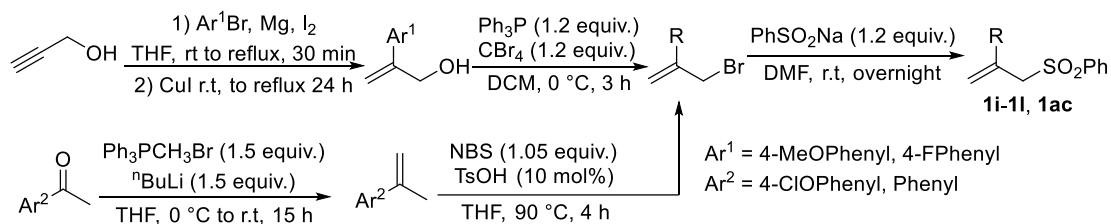
²⁶³ I. Fleming, R. S. Roberts, S. C. Smith, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209–1214.

Experimental Part

2,3-dihaloalkene (2 mmol, 1.0 equiv.) was added to a stirred suspension of sodium benzenesulfinate (328 mg, 2 mmol, 1.0 equiv.) in 2 mL DMF and was stirred at room temperature for 48 hours. This reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were successively washed with water (5 mL) and brine (5 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether/ EtOAc 85:15 to 80:20) to afford corresponding olefin **1c**, **1f** or **1g**.



K_2CO_3 (1.52 g, 11 mmol, 1.1 equiv.) and BnBr (1.2 mL, 11 mmol, 1.1 equiv.) were successively added to a solution of 2-haloacrylic acid (10 mmol, 1.0 equiv.) in DMF (6 mL). The mixture was stirred at room temperature for 16 hours, then EtOAc (20 mL) was added to dilute the reaction. The organic layer was separated and successively washed with water (10 mL), saturated NaHCO_3 (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether/EtOAc 98:2) to afford corresponding olefine **1h**, **1w** or **1x**.



Synthesis of allylic bromide bearing Ar^1 : a) A solution of aryl bromide (2.6 equiv.) in dry THF (1.0 M) was added dropwise to a two-neck flask charged with activated magnesium turnings (2.7 equiv.) and a crystal of iodine in THF (5 mL) at room temperature. The mixture was refluxed until magnesium turnings were completely reacted. After cooling to room temperature, CuI (0.5 equiv.) was added and the mixture was then allowed to stir for 30 min. Propargyl alcohol (1.0 equiv.) in THF (1.0 M) was added dropwise at room temperature. The reaction mixture was then heated to reflux for 24 h. After cooling down to room temperature, saturated aqueous NH_4Cl was added dropwise carefully. The organic phase was separated and the aqueous phase was extracted with Et_2O

Experimental Part

three times. The combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure. The crude product was purified by silica-gel flash column chromatography (petroleum ether/EtOAc 80:20 to 70:30) to give the corresponding allylic alcohol.

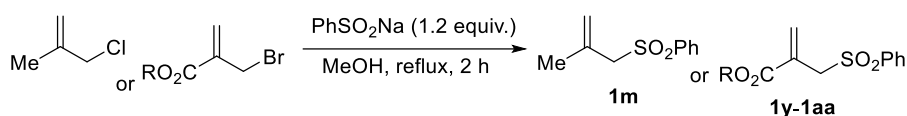
b) To a solution of allylic alcohol (1.0 equiv.) in CH₂Cl₂ (0.4 M), PPh₃ (1.2 equiv.) was added at 0 °C, and the mixture was stirred for 10 min. CBr₄ (1.1 equiv.) was added portion-wise and the mixture was stirred for 3 h at 0 °C. The solvent was concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether) to give the corresponding allyl bromide.

Synthesis of allylic bromide bearing Ar²: a) A solution of methyltriphenylphosphonium bromide (1.5 equiv.) in dry THF (0.15 M) under argon atmosphere was cooled to 0 °C. Then, *n*BuLi (2.5 M solution in hexane, 1.5 equiv.) was added dropwise. After the resulting orange mixture was stirred at 0 °C for 1 h, a solution of the corresponding ketone (1.0 equiv.) in dry THF (1.0 M) was added dropwise at 0 °C. The reaction was allowed to warm up to room temperature, stirred overnight, and finally quenched with a saturated aqueous solution of NaCl. The resulting mixture was extracted with DCM. The combined organic phases were washed with brine, dried over Na₂SO₄, and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether) to give the corresponding styrene.

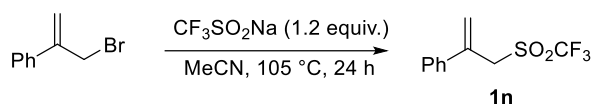
b) To a solution of NBS (1.05 equiv.) and TsOH (0.1 equiv.) in dry THF (0.5 M) under argon atmosphere was added the corresponding styrene (1.0 equiv.). The reaction solution was heated to 90 °C and stirred for 4 h, then cooled down to room temperature. The mixture was quenched with water, extracted with EtOAc. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether) to afford the corresponding allyl bromide.

Synthesis of allylic sulfones: To a solution of the allyl bromide (2 mmol, 1.0 equiv.) in dry DMF (4 mL) was added sodium phenylsulfinate (394 mg, 2.4 mmol, 1.2 equiv.) at room temperature. The mixture was stirred overnight, and finally quenched with a saturated aqueous solution of NaCl (10 mL). The mixture was extracted with DCM (3×10 mL). The combined organic phases were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography (petroleum ether/EtOAc 90:10 to 87:13) to afford corresponding allylic sulfone **1i-1l**, **1ac**.

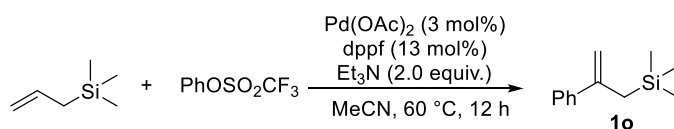
Experimental Part



To a solution of allyl chloride or bromide (2 mmol, 1.0 equiv.) in dry methanol (4 mL) was added sodium phenylsulfinate (394 mg, 2.4 mmol, 1.2 equiv.). After 2 h of reflux, the mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc (10 mL) and the mixture was washed with brine (5 mL), dried with Na₂SO₄, filtered and concentrated under reduced pressure. The resulting crude was purified by silica-gel flash column chromatography to give corresponding allylic sulfone **1m**, or **1y-1aa**.



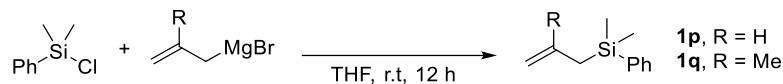
Under argon atmosphere, to a solution of NaSO₂CF₃ (1.48g, 7.5 mmol, 1.5 equiv.) in MeCN (5 mL), (3-bromoprop-1-en-2-yl)benzene (980 mg, 5 mmol, 1.0 equiv.) was added. The solution was heated to 105 °C and stirred in this temperature for 24 h. After the completion of the reaction, the mixture was filtered and extracted with EtOAc (3×10mL). The combined organic phase was evaporated under reduced pressure, and the residue was purified by silica-gel flash column chromatography (petroleum ether/EtOAc 95:5 to 90:10) to provide 300 mg (24% yield) of desired product **1n** a light-yellow oil.



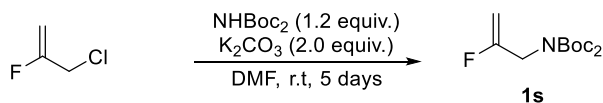
A oven-dried reaction vial equipped with a magnetic stirring bar was charged with triflate (2.26 g, 10 mmol, 1.0 equiv.), Pd(OAc)₂ (68 mg, 0.3 mmol, 3 mol%), dppf (1,1'-ferrocenediyl-bis(diphenylphosphine), 0.73 g, 1.33 mmol, 13 mol%), allyltrimethylsilane (5.7 g, 50 mmol, 5.0 equiv.), Et₃N (2.8 mL, 20 mmol, 2.0 equiv.), and anhydrous MeCN (40 mL), heated at 60 °C for 12 h, then quenched with water (20 mL) and extracted with Et₂O (3×20mL). The organic layers were combined and dried over Na₂SO₄. The residue was purified by silica-gel flash column

Experimental Part

chromatography (petroleum ether) to provide 1.44 g (76% yield) of desired product **1o** as a colorless oil.



To a flame dried round bottom flask equipped with a stir bar, dimethylphenylchlorosilane (834 μL , 5 mmol, 1.0 equiv.) was added dropwise to a solution of allylmagnesium bromide (5 mL, 1.0 M solution in THF, 12 mmol, 1.0 equiv.) under argon at 0 $^\circ\text{C}$. The resulting mixture was stirred at 0 $^\circ\text{C}$ for 15 min and then stirred at room temperature for 1 h. The reaction was then quenched with saturated NH_4Cl (15 mL) and extracted with Et_2O (3×10 mL). The organic layers were washed with brine (20 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure. The desired product **1p** or **1q** was isolated via silica-gel flash column chromatography (hexanes) as a colorless oil.



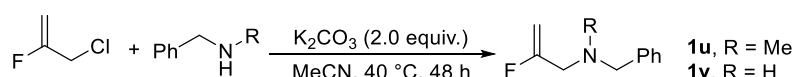
3-Chloro-2-fluoroprop-1-ene (174 μL , 2 mmol, 1.0 equiv.) was added to a stirred solution of NHBoc_2 (521 mg, 2.4 mmol, 1.2 equiv.) and K_2CO_3 (553 mg, 4 mmol, 2.0 equiv.) in DMF (2 mL) at room temperature. The mixture was stirred at room temperature for 5 days, then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3×5 mL). The combined organic layers were successively washed with water (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by silica-gel flash column chromatography (petroleum ether/ EtOAc 98:2) to afford 442 mg (80% yield) of olefin **1s** as a white solid.



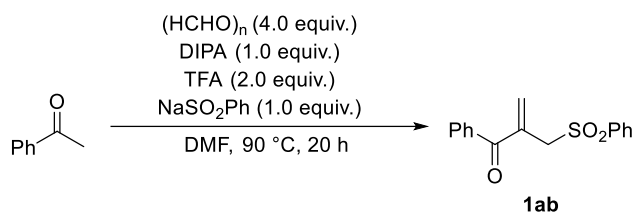
Potassium phthalimide (507 mg, 3 mmol, 1.5 equiv.) was added to a solution of 3-chloro-2-fluoroprop-1-ene (174 μL , 2 mmol, 1 equiv.) in DMF (4 mL) at room temperature. The resulting

Experimental Part

mixture was stirred for 16 hours. Dichloromethane (10 mL) was added and the mixture poured onto water (10 mL). The aqueous phase was separated and extracted with dichloromethane (2x5 mL). The combined organic extract was then washed with 0.2 M NaOH aq. (10 mL) and dried with anhydrous sodium sulfate. The dichloromethane was removed in vacuo and the residue was purified by silica-gel flash column chromatography (heptane/EtOAc 1:1) to afford 234 mg (57%) of protected product **1t** as a white solid.



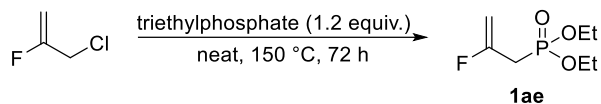
A 25 mL two-neck flask was equipped with a stir bar, a reflux condenser and flushed with argon. A solution of 3-chloro-2-fluoroprop-1-ene (174 μL , 2.0 mmol, 1.0 equiv.) in acetonitrile (2 mL) was prepared. K_2CO_3 (2.0 equiv., 552 mg, 4 mmol) and benzyl amine (2 mmol, 1.0 equiv.) were then added in order. The mixture was heated to 40 $^\circ\text{C}$ and stirred for 20 hours. The reaction was monitored by ^{19}F NMR. When full consumption of starting material was observed, the reaction was stopped by adding water (2 mL) and extracted with DCM (3x5 mL). The organic layers were combined and dried over MgSO_4 . After filtration and concentrated under reduced pressure, the crude was purified by silica-gel flash column chromatography (cyclohexane/EtOAc 9:1) to afford desired product **1u** or **1v**.



A mixture of acetophenone (240 mg, 2 mmol, 1.0 equiv.), DIPA (280 μL , 2 mmol, 1.0 equiv.), TFA (306 μL , 4 mmol, 2.0 equiv.), sodium benzenesulfinate (326 mg, 2 mmol, 1.0 equiv.) and *para*-formaldehyde (242 mg, 8 mmol, 4.0 equiv.) in DMF (4 mL) was heated to 90 $^\circ\text{C}$ in a sealed vessel for 20 h. The reaction was cooled to room temperature, diluted with ethyl acetate (10 mL), washed with aqueous LiCl (5wt%, 10 mL) and dried over MgSO_4 . The solid was filtered off and the organic solvent was evaporated under reduced pressure. The crude was purified by silica-gel flash column

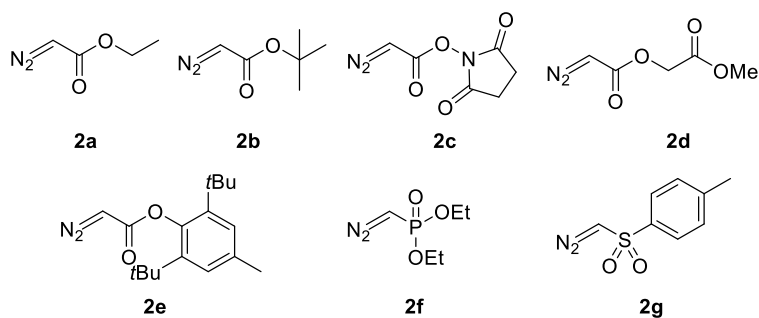
Experimental Part

chromatography (petroleum ether/EtOAc 90:10 to 85:15) to give desired product **1ab** as a white solid.

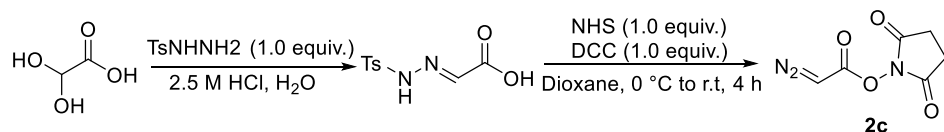


A mixture of 3-chloro-2-fluoroprop-1-ene (174 μ L, 2 mmol, 1 equiv.) and triethylphosphite (420 μ L, 2.4 mmol, 1.2 equiv.) was stirred at 150 °C for 3 days and directly purified by silica-gel flash column chromatography (petroleum ether/EtOAc 1:2 to 0:1) to afford 274 mg (70% yield) of olefin **1ae**.

1.2. Synthesis of mono-acceptor diazo compounds **2**.



Ethyl diazo acetate (**2a**) and tert-butyl diazo acetate (**2b**) were purchased from standard chemical suppliers (Sigma-Aldrich), **2c**,²⁶⁴ **2d**,²⁶⁵ **2e**,²⁶⁶ **2f**,²⁶⁷ **2g**²⁶⁸ were prepared according to reported literatures. the characterization data is consistent with reported literatures.



Glyoxylic acid monohydrate (2.32 g, 25 mmol, 1.0 equiv.) was dissolved in water (25 mL) and heated to 65 °C until it was dissolved fully. In a separate round bottom flask, *p*-toluenesulfonylhydrazide (4.66 g, 25 mmol, 1.0 equiv.) in 2.5 M aqueous hydrochloric acid (15 mL)

²⁶⁴ J. V. Jun, R. T. Raines, *Org. Lett.*, **2021**, *23*, 3110–3114.

²⁶⁵ S. Chanthamath, S. Takaki, K. Shibatomi, S. Iwasa *Angew. Chem. Int. Ed.*, **2013**, *52*, 5818–5821.

²⁶⁶ G. Pisella, A. Gagnebin, J. Waser, *Org. Lett.*, **2020**, *22*, 3884–3889.

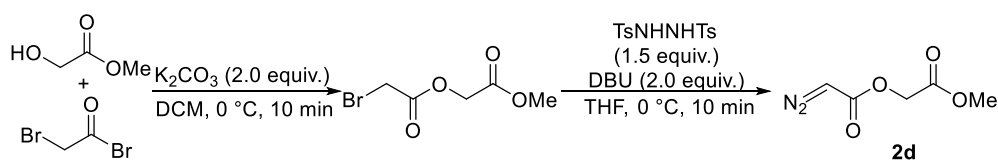
²⁶⁷ S. Chanthamath, S. Ozaki, K. Shibatomi, S. Iwasa, *Org. Lett.* **2014**, *16*, 3012–3015.

²⁶⁸ X. Zhao, J.-Y. Shou, J. J. Newton, F.-L. Qing, *Org. Lett.* **2022**, *24*, 8412–8416.

Experimental Part

was heated at 65 °C. The resulting solution of *p*-toluenesulfonylhydrazide was then added to the glyoxylic acid solution, and the reaction mixture was heated at 65 °C for 15 min. The reaction mixture was allowed to cool to room temperature and was kept in the refrigerator overnight to induce precipitation. The precipitated crude product was collected by filtration, washed with cold water (10 mL), and dried in the open air for 2 days to remove water. The crude product was then recrystallized using hot EtOAc and hexanes. The product was filtered and washed with ice-cold 33% v/v EtOAc in hexanes to afford compound 2-(2-tosylhydrazono) acetic acid as a white solid (4.8 g, 79%).

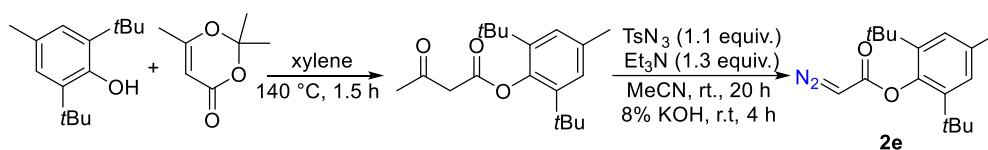
2-(2-tosylhydrazono) acetic acid (0.97 g, 4 mmol, 1.0 equiv.) and *N*-hydroxysuccinimide (510 mg, 4.4 mmol, 1.1 equiv.) were dissolved in anhydrous DCM (40 mL), and the reaction mixture was cooled to 0 °C. A solution of *N,N'*-dicyclohexylcarbodiimide (DCC) (1.24 g, 6 mmol, 1.5 equiv.) in anhydrous DCM (1.0 M solution) was then added dropwise to the reaction mixture, and stirred at 0 °C for 1 h. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by filtering out the byproduct, dicyclohexylurea, and the filtrate was concentrated under reduced pressure. The reaction mixture was then extracted with EtOAc (3×2 mL) and washed with saturated aqueous NaHCO₃ (3×200 mL), followed by brine (20 mL). The organic layer was separated, dried over Na₂SO₄, and filtered. The solvent was removed under reduced pressure, and the crude product was purified by silica-gel flash column chromatography (6:4:1 hexanes/EtOAc/DCM) to yield the product as a pale yellow crystalline solid (305 mg, 42%).



To a suspension of K_2CO_3 (2.77 g, 20 mmol, 2.0 equiv.) and methyl glycolate (0.76 mL, 10 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) was added dropwise bromoacetyl bromide (1.3 mL, 15 mmol, 1.5 equiv.) at 0 °C. The reaction mixture was stirred during 2 hours followed by addition of 1 mL of H_2O . The mixture was then extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4 , and filtered. After evaporation of the solvent, the residue was obtained and used in the next step without purification.

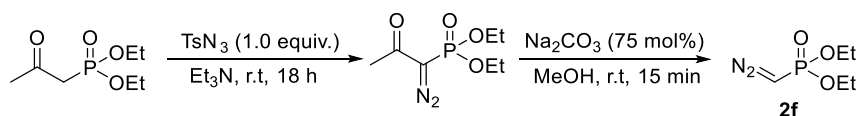
Experimental Part

The resulting bromoacetate and *N,N'*-ditosylhydrazine²⁶⁹ (5.1 g, 15 mmol, 1.5 equiv.) were dissolved in THF (20 mL) and cooled down to 0 °C, then DBU (3 mL, 20 mmol, 2.0 equiv.) was added drop wise and stirred at 0 °C for 10 min. After quenched with NaHCO₃ aq. and extracted with Et₂O (3×20 mL), the organic phase was dried over Na₂SO₄ and evaporated under reduced pressure. The crude was purified by silica-gel flash column chromatography (EtOAc/*n*Hexane 1:4) to give methyl (diazoacetoxyl)acetate **2d** (750 mg, 58% overall yield) as a yellow oil.



A mixture of 2,6-di-tert-butyl-4-methylphenol (2.2 g, 10 mmol, 1.0 equiv.), 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.42 g, 10 mmol, 1.0 equiv.), and xylene (2 mL) was stirred at 140 °C for 1.5 h. After cooling to room temperature, the reaction mixture was directly loaded on silica and was purified by column chromatography (EtOAc/pentane 2:98) to afford 2,6-di-tert-butyl-4-methylphenyl 3-oxobutanoate (2.16 g, 71%) as a white solid.

To a solution of 2,6-di-tert-butyl-4-methylphenyl 3-oxobutanoate (1.52 g, 5 mmol, 1.0 equiv.) in MeCN (6 mL) was added triethylamine (906 μL, 6.5 mmol, 1.30 equiv.). The reaction mixture was cooled in an ice bath and a solution of tosyl azide (1.09 g, 5.5 mmol, 1.1 equiv.) in MeCN (6 mL) was added slowly. The reaction mixture was allowed to warm to room temperature and stirred for 20 h. 8% aqueous KOH solution (25 mL) was added and stirred vigorously for 4 h. The reaction mixture was diluted with water (15 mL), extracted with diethyl ether (3×30 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by silica-gel flash column chromatography (Et₂O/pentane 2:98) to afford desired product **2e** (1.25 g, 87%) as a yellow solid.

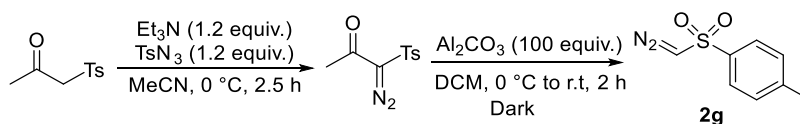


²⁶⁹ T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2007**, *9*, 3195–3197.

Experimental Part

A mixture of crude diethyl (2-oxopropyl)phosphonate (3.88 g, 20 mmol, 1.0 equiv.), tosyl azide (996.0 mg, 20 mmol, 1.0 equiv.) and triethylamine (20 ml) was stirred at room temperature for 18 h. After evaporation of triethylamine under reduced pressure the residue was dissolved in diethyl ether. The precipitate was filtered off, the filtrate was evaporated and the residue was purified by silica-gel flash column chromatography (EtOAc/n-Hexane 70:30) to give the desired product diethyl (1-diazo-2-oxopropyl)phosphonate as a yellow liquid.

To a solution of diethyl (1-diazo-2-oxopropyl)phosphonate (3.04, 13.8 mmol, 1.0 equiv.) in 40 ml of MeOH was added Na₂CO₃ (1.1 g, 10.4 mmol, 0.75 equiv.). The mixture was stirred at room temperature for 15 min. The precipitate was filtered off. The filtrate was purified by silica-gel flash column chromatography (EtOAc/n-Hexane 50:50) to give the desired product **2f** (1.4 g, 41% overall yield) as yellow liquid.

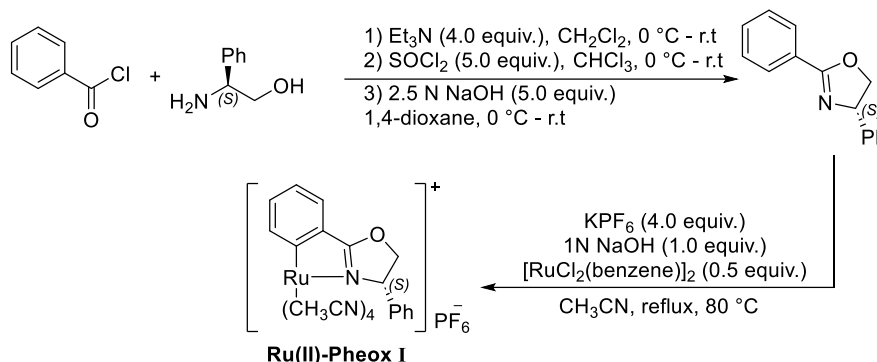


A solution of *p*-toluenesulfonyl azide (1.42 g, 6 mmol, 1.2 equiv.) in anhydrous CH₃CN (10 mL) was added dropwise to a stirred solution 1-(phenylsulfonyl)-2-propanone (0.99 g, 5 mmol, 1.0 equiv.) in anhydrous CH₃CN (15 ml). Triethylamine (1 mL, 6 mmol, 1.2 equiv.) was added dropwise to the reaction and the reaction was stirred for 2.5 h at 0 °C under argon atmosphere. The solvent was evaporated and the crude 1-diazo-1-(phenylsulfonyl)-2-propanone was obtained as a yellow solid.

To a well-stirred suspension of Al₂O₃ (37 g, 370 mmol, 100 equiv.) in anhydrous methylene chloride (35 mL) at 0 °C protected from light by aluminum foil, 1-diazo-1-(toluene-4-sulfonyl)-propan-2-one (830 mg, 3.7 mmol, 1.0 equiv.) was added under 0 °C and left in the ice bath to slowly rise to room temperature. The reaction was monitored by TLC every half hour until all the starting material had been consumed. The reaction mixture was then poured into an empty flash chromatography column and the alumina was washed with DCM until all the product was washed out. The product was collected and concentrated by rotary evaporation at room temperature to give the compound **2g** (616 mg, 85%) as a yellow oil.

Experimental Part

2. General procedure for the preparation Ru(II)-Pheox I (Iwasa's procedure)²⁷⁰



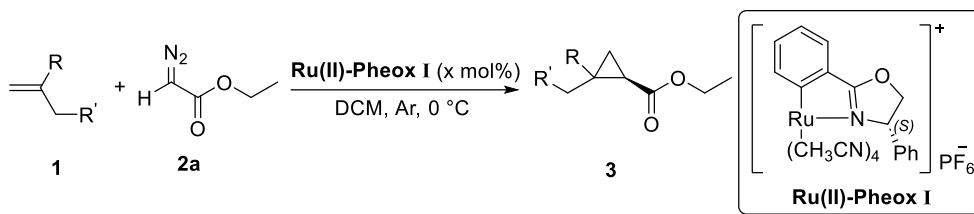
To a mixture of (*S*)-(+)-2-phenylglycinol (1.51 g, 11.0 mmol) and triethylamine (5.6 mL, 40.0 mmol) in CH₂Cl₂ (20.0 mL), a solution of benzoyl chloride (1.4 g, 10.0 mmol) in CH₂Cl₂ (5.0 mL) was added at 0 °C. After stirring for 10 h at room temperature, the mixture was concentrated under reduced pressure. A solution of the residue in CHCl₃ (20.0 mL) was treated with SOCl₂ (3.8 mL, 50.0 mmol) at 0 °C. After stirring for 24 h at room temperature, the solvent and excess SOCl₂ was removed under reduced pressure. A saturated NaHCO₃ aqueous solution (50.0 mL) was added to the residue with stirring for 5 min. The organic product was extracted with CH₂Cl₂ (3×30 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. By using a sonicator, the solid residue was dissolved in 1,4-dioxane (20.0 mL) and 2.5 N NaOH in water (40.0 mL, 100.0 mmol) was added slowly at 0 °C, then the reaction mixture was stirred for 4 h at room temperature. The solvent was removed under vacuo, followed by addition of water (25.0 mL) and extracted with CH₂Cl₂ (3×25 mL). The solvent was evaporated under vacuum and the crude product was purified by silica-gel flash column chromatography (EtOAc/hexane 1:10) to afford (*S*)-4,5-dihydro-2,4-diphenyloxazole in 80% yield as a yellow oil.

A mixture of (*S*)-4,5-dihydro-2,4-diphenyloxazole (67.0 mg, 0.30 mmol), [RuCl₂(benzene)]₂ (75.0 mg, 0.15 mmol), KPF₆ (220.9 mg, 1.2 mmol), and NaOH (aqua.) (0.3 mL, 0.30 mmol, ca. 1.0 M) in CH₃CN (5.0 mL, degassed) was stirred for 48 h at 80 °C. The reaction mixture was extracted with CH₂Cl₂ (3×20 mL) and was dried over Na₂SO₄. After concentration, the residue was purified by silica-gel flash column chromatography (CH₃CN/CH₂Cl₂ 1:20) to give the desired complex Ru(II)-Pheox I in 77% yield as a light yellow solid.

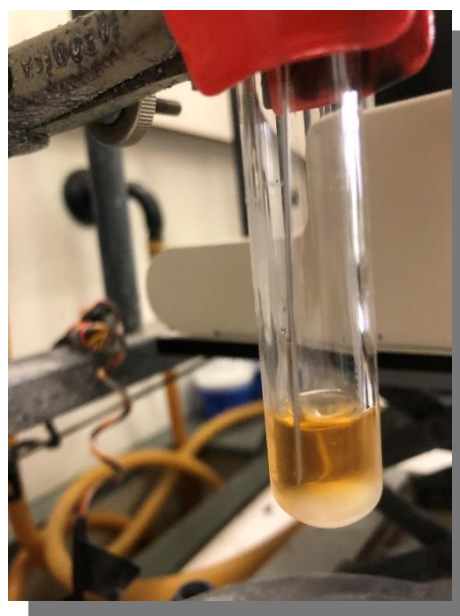
The NMR data of Ru(II)-Pheox I is consistent with reported literature.

²⁷⁰ A.-M. Abu-Elfotouh, K. Phomkeona, K. Shibatomi S. Iwasa *Angew. Chem. Int. Ed.*, **2010**, *49*, 8439–8443.

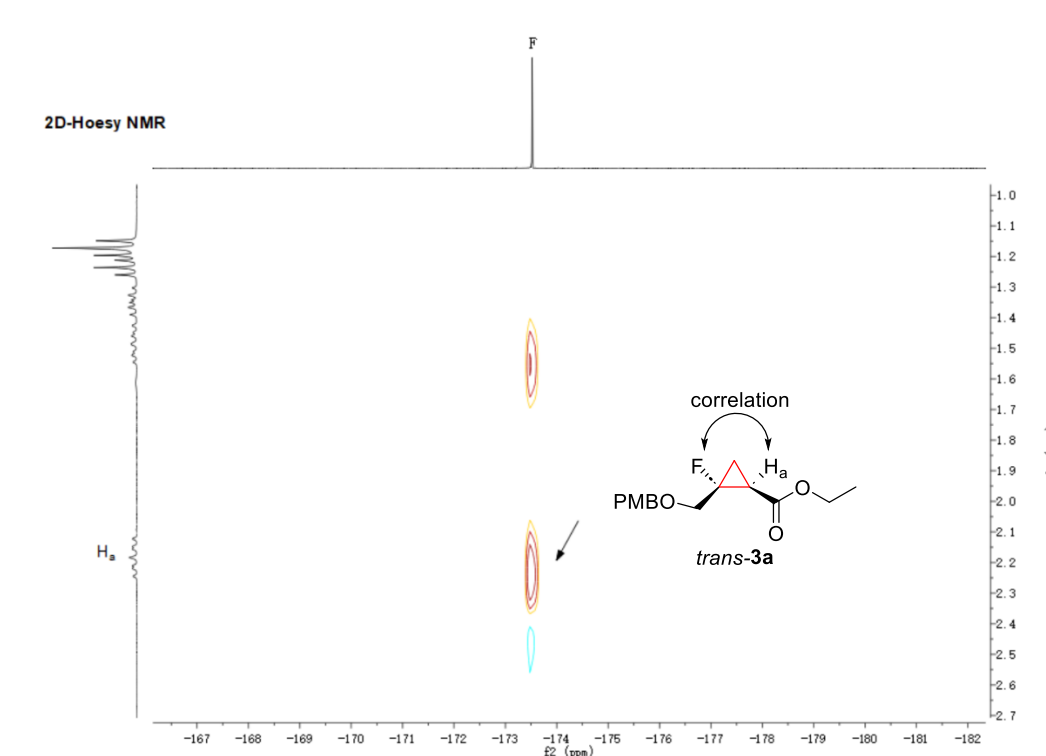
3. General procedure of ruthenium catalyzed enantioselective cyclopropanation of allyl derivatives with ethyl diazoacetate



An oven-dried 10 mL reaction tube contained a stir bar, Ru(II)-Pheox I which was stored in a glovebox was introduced to the reaction tube in this glovebox, followed by allylic substrates **1** (0.2 mmol, 1.0 equiv.). This tube was evacuated under vacuum and backfill argon three times, and this reaction tube should be protected with an argon balloon during the process. Fresh distilled DCM 0.5 mL was added via a syringe, and this solution was placed at 0 °C for 15 min. Diazo compound **2a** (1.0 mmol, 5.0 equiv.) was dissolved in 1.0 mL fresh distilled DCM and added to the former solution with 0.15 mL/h rate by use of microinjection pump. (Note: the needle of syringe should be immersed into the solution and without any contact with the stir bar.). After the addition of diazo compound, this solution was stirred at this temperature for another 5 h. The conversion and diastereomeric ratio were detected with ¹H NMR at the end of this reaction. The reaction mixture was evaporated under reduced pressure and purified by silica gel chromatography leading to the corresponding enantiopure cyclopropanes **3**.



Experimental Part

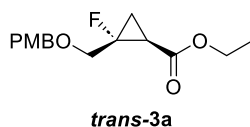


The corresponding racemic cyclopropanes were prepared using $\text{Rh}_2(\text{Opiv})_4$ or $\text{Rh}_2(\text{esp})_2$ catalysts among the following procedure: To an oven-dried 10 mL reaction tube contained a stir bar, $\text{Rh}_2(\text{Opiv})_4$ (0.002 mmol, 0.01 equiv.) was introduced, followed by the allylic substrate **1** (0.2 mmol, 1.0 equiv.). This tube was evacuated under vacuum and backfill argon three times, and this reaction tube should be protected with an argon balloon during the process. Freshly distilled DCM (0.5 mL) was added via a syringe, and this solution was placed at 0 °C for 15 min. Diazo compound **2a** (0.6 mmol, 3.0 equiv.) was dissolved in 1.0 mL fresh distilled DCM and added to the former solution (0.25 mL/h) using a syringe pump. After the addition of diazo compound, this solution was stirred at room temperature for another 1 h. The solution was then evaporated under reduced pressure and purified by silica gel chromatography leading to the corresponding racemic cyclopropanes **3a-3g** and **3i-3q**.

The racemate **3h** was prepared using $\text{Rh}_2(\text{esp})_2$.

Experimental Part

3a. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox **I**, (*trans* 23.1 mg, *cis* 30.4 mg, 95% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 80:20). The diastereomeric ratio (44:56) was determined by ^{19}F NMR on the crude mixture.



ethyl (1*S*,2*R*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropane-1-carboxylate

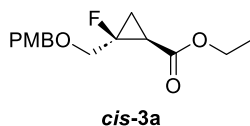
trans-3a (minor isomer) Colorless oil. $R_f = 0.63$ (PE/EtOAc = 5:1). $[\alpha]_D^{20} = -37.8$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 93%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 6.6$ min, $t_R = 7.4$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 4.52 (d, $J = 11.8$ Hz, 1H), 4.48 (d, $J = 11.8$ Hz, 1H), 4.22 – 3.95 (m, 3H), 3.86 – 3.71 (m, 4H), 2.32 – 2.19 (m, 1H), 1.69 – 1.48 (m, 1H), 1.47 – 1.34 (m, 1H), 1.24 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 170.3 (d, $J = 2.0$ Hz), 159.3, 130.1, 129.4, 113.8, 82.1 (d, $J = 227.8$ Hz), 72.9, 68.3 (d, $J = 19.7$ Hz), 61.1, 55.3, 24.3 (d, $J = 13.7$ Hz), 17.5 (d, $J = 9.7$ Hz), 14.2.

^{19}F NMR (282.4 MHz, CDCl_3) δ -196.4 - -196.6 (m, 1 F).



ethyl (1*S*,2*S*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropane-1-carboxylate

cis-3a (major isomer) Colorless oil. $R_f = 0.55$ (PE/EtOAc = 5:1). $[\alpha]_D^{20} = -46.4$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 86%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 11.1$ min, $t_R = 12.4$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.27 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 4.55 (s, 2H), 4.24 – 4.13 (m, 2H), 3.79 (s, 3H), 3.71 (dd, $J = 18.4, 1.4$ Hz, 2H), 1.96 – 1.83 (m, 2H), 1.30 – 1.17 (m, 4H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.2 (d, $J = 2.4$ Hz), 159.4, 129.6, 129.4, 113.9, 80.6 (d, $J = 232.5$ Hz), 72.8, 70.8 (d, $J = 24.0$ Hz), 61.1, 55.2, 23.8 (d, $J = 10.6$ Hz), 15.6 (d, $J = 11.5$ Hz), 14.2.

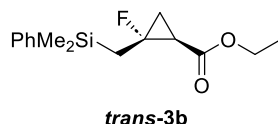
^{19}F NMR (282.4 MHz, CDCl_3) δ -178.4 --178.8 (m, 1 F).

HRMS (AP^+) calcd for $\text{C}_{15}\text{H}_{19}\text{O}_4\text{F}$ ($[\text{M}+\text{H}]^+$) 282.1267, found: 282.1260 (Δ -0.6 ppm).

Experimental Part

IR (Neat) 2292, 2853, 1732, 1612, 1513, 1247, 1173, 1092, 1032, 819 cm^{-1} .

3b. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox **I**, (*trans* 23.4 mg, *cis* 12.0 mg, 63% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/Et₂O 95:5 to 85:15). The diastereomeric ratio (68:32) was determined by ¹⁹F NMR on the crude mixture.



ethyl (1*S*,2*R*)-2-((dimethyl(phenyl)silyl)methyl)-2-fluorocyclopropane-1-carboxylate

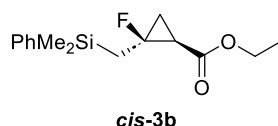
trans-3b (major isomer) Colorless oil. $R_f = 0.60$ (PE/Et₂O = 5:1). $[\alpha]_D^{20} = -14.5$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), $t_R = 6.4$ min, $t_R = 7.7$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.58 – 7.51 (m, 2H), 7.39 – 7.34 (m, 3H), 4.19 – 3.99 (m, 2H), 2.09 (ddd, $J = 19.1, 10.4, 7.5$ Hz, 1H), 1.63 – 1.40 (m, 3H), 1.28 – 1.22 (t, $J = 7.1$ Hz, 3H), 1.13 (ddd, $J = 13.5, 7.4, 6.6$ Hz, 1H), 0.40 (s, 3H), 0.37 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 171.1 (d, $J = 2.3$ Hz), 138.6, 133.7, 129.2, 127.9, 82.5 (d, $J = 218.4$ Hz), 60.9, 25.9 (d, $J = 14.9$ Hz), 19.8 (d, $J = 10.5$ Hz), 17.8 (d, $J = 27.4$ Hz), 14.4, -2.1, -2.2.

¹⁹F NMR (282.4 MHz, CDCl₃) δ -156.5 - -156.8 (m, 1 F).



ethyl (1*S*,2*S*)-2-((dimethyl(phenyl)silyl)methyl)-2-fluorocyclopropane-1-carboxylate

cis-3b (minor isomer) Colorless oil. $R_f = 0.48$ (PE/Et₂O = 5:1). $[\alpha]_D^{20} = -31.4$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 9.8$ min, $t_R = 12.5$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.64 – 7.48 (m, 2H), 7.43 – 7.28 (m, 3H), 4.17 (q, $J = 7.1$ Hz, 2H), 1.85 (dt, $J = 19.9, 7.4$ Hz, 1H), 1.70 – 1.33 (m, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.00 – 0.90 (m, 1H), 0.42 (s, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 168.9 (d, $J = 2.3$ Hz), 138.4, 133.7, 129.3, 128.0, 80.9 (d, $J = 225.4$ Hz), 60.9, 27.1 (d, $J = 11.2$ Hz), 24.5 (d, $J = 28.1$ Hz), 19.2 (d, $J = 12.6$ Hz), 14.4, -2.2, -2.3.

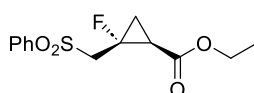
Experimental Part

^{19}F NMR (282.4 MHz, CDCl_3) δ -178.9 - -179.2 (m, 1 F).

HRMS (AP^+) calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2\text{FSi}$ ($[\text{M}+\text{H}]^+$) 281.1373, found: 281.1371 (Δ -0.7 ppm).

IR (Neat) 3070, 2958, 1723, 1379, 1247, 1160, 1113, 891, 727, 697 cm^{-1} .

3c. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 12.6 mg, *cis* 6.0 mg, 32% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). The diastereomeric ratio (68:32) was determined by ^{19}F NMR of the crude mixture.



trans-3c

ethyl (1*S*,2*R*)-2-fluoro-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

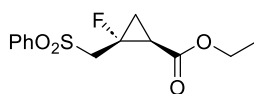
trans-3c (major isomer) Colorless oil. R_f = 0.40 (PE/EtOAc = 3:1). $[\alpha]_D^{20}$ = -43.8 (c = 1.0, CHCl_3).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 29.3 min, t_R = 33.6 min.

^1H NMR (300.1 MHz, CDCl_3) δ 8.03 – 7.90 (m, 2H), 7.70 – 7.62 (m, 1H), 7.61 – 7.51 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 4.02 – 3.77 (m, 2H), 2.28 (ddd, J = 18.5, 10.6, 7.8 Hz, 1H), 1.68 – 1.55 (m, 1H), 1.43 – 1.33 (m, 1H), 1.32 – 1.26 (m, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 170.3 (d, J = 1.9 Hz), 140.02 (s), 134.0, 129.3, 128.5, 77.3 (d, J = 226.3 Hz), 61.7, 56.2 (d, J = 20.6 Hz), 24.4 (d, J = 13.7 Hz), 18.1 (d, J = 9.7 Hz), 14.3.

^{19}F NMR (282.4 MHz, CDCl_3) δ -171.2 - -171.5 (m, 1 F).



cis-3c

ethyl (1*S*,2*R*)-2-fluoro-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

cis-3c (minor isomer) Colorless oil. R_f = 0.24 (PE/EtOAc = 3:1). $[\alpha]_D^{20}$ = -8.0 (c = 1.0, CHCl_3).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 47.2 min, t_R = 51.9min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.97 (d, J = 7.5 Hz, 2H), 7.70 – 7.65 (m, 1H), 7.59 – 7.54 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.77 – 3.65 (m, 1H), 3.48 (dd, J = 22.3, 15.3 Hz, 1H), 2.08 – 1.86 (m, 2H), 1.43 – 1.34 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.2 (d, J = 2.4 Hz), 139.2, 134.3, 129.4, 128.7, 75.9 (d, J = 232.4

Experimental Part

Hz), 61.7 (d, $J = 23.3$ Hz), 61.6, 25.1 (d, $J = 10.8$ Hz), 16.6 (d, $J = 11.5$ Hz), 14.4.

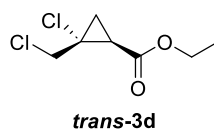
^{19}F NMR (282.4 MHz, CDCl_3) δ -189.2 - -189.5 (m, 1 F).

HRMS (AP^+) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{FS}$ ($[\text{M}+\text{H}]^+$) 287.0753, found: 287.0742 (Δ -3.8 ppm).

IR (Neat) 2983, 2931, 1727, 1447, 1380, 1153, 1084, 989, 749, 530 cm^{-1} .

3d. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 26.8 mg, *cis* 5.3 mg, 82% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/Et₂O 95:5 to 85:15). The diastereomeric ratio (83:17) was determined by ^1H NMR on the crude mixture.

Only the major diastereoisomer was fully characterized.



ethyl (1*S*,2*R*)-2-chloro-2-(chloromethyl)cyclopropane-1-carboxylate

***trans*-3d** (major isomer) Colorless oil. $R_f = 0.60$ (PE/Et₂O = 5:1). $[\alpha]_D^{20} = -165.1$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by GC with a Chiralcel Rt-bDEXsm column, $t_R = 3.56$ min, $t_R = 3.71$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 4.29 – 4.12 (m, 2H), 4.08 (d, $J = 12.3$ Hz, 1H), 3.98 (d, $J = 12.3$ Hz, 1H), 2.36 (t, $J = 8.2$ Hz, 1H), 1.72 (d, $J = 8.0$ Hz, 2H), 1.30 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 169.9, 61.8, 48.8, 48.6, 30.0, 24.6, 14.3.

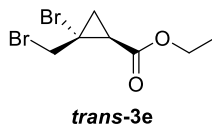
HRMS (EI^+) calcd for $\text{C}_7\text{H}_{10}\text{Cl}_2\text{O}_2$ ($[\text{M}+\text{H}]^+$) 196.0058, found: 196.00578 (Δ 0 ppm).

IR (Neat) 2983, 1723, 1380, 1440, 1229, 1179, 1032, 728, 600 cm^{-1} .

3e. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 24.6 mg, *cis* 4.3 mg, 51% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/Et₂O 95:5 to 85:15). The diastereomeric ratio (85:15) was determined by ^1H NMR on the crude mixture.

Only the major diastereoisomer was fully characterized.

Experimental Part



ethyl (1*S*,2*R*)-2-bromo-2-(bromomethyl)cyclopropane-1-carboxylate

trans-3e (major isomer) Colorless oil. $R_f = 0.60$ (PE/Et₂O = 5:1). $[\alpha]_D^{20} = -153.0$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by GC with a Chiralcel Rt-bDEXsm column, $t_R = 13.94$ min, $t_R = 14.22$ min.

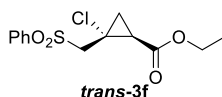
¹H NMR (300.1 MHz, CDCl₃) δ 4.31 – 4.11 (m, 2H), 4.02 (d, $J = 11.5$ Hz, 1H), 3.93 (d, $J = 11.5$ Hz, 1H), 2.48 (dd, $J = 9.0, 7.1$ Hz, 1H), 1.86 (dd, $J = 9.0, 6.6$ Hz, 1H), 1.74 (t, $J = 6.8$ Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.5, 61.8, 39.1, 37.4, 31.6, 26.6, 14.3.

HRMS (EI⁺) calcd for C₅H₆Br₂O₂ ([*(M-ethyl)+H*]⁺) 255.8735, found: 255.8740 ($\Delta 2.24$ ppm).

IR (Neat) 2981, 1720, 1379, 1232, 1161, 1026, 857, 649 cm⁻¹.

3f. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 29.0 mg, *cis* 13.1 mg, 70% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 80:20). The diastereomeric ratio (67:33) was determined by ¹H NMR on the crude mixture.



ethyl (1*S*,2*R*)-2-chloro-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

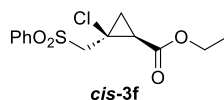
trans-3f (major isomer) White solid, m.p. = 62 - 64 °C. $R_f = 0.57$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -61.8$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 16.0$ min, $t_R = 19.7$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.98 – 7.90 (m, 2H), 7.69 – 7.61 (m, 1H), 7.58 – 7.53 (m, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.92 (d, $J = 14.9$ Hz, 1H), 3.82 (d, $J = 14.9$ Hz, 1H), 2.34 (dd, $J = 9.4, 7.4$ Hz, 1H), 1.57 (ddd, $J = 18.5, 11.6, 6.7$ Hz, 2H), 1.31 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 170.3, 140.2, 134.0, 129.4, 128.6, 61.9, 59.3, 40.4, 29.1, 23.4, 14.3.

Experimental Part



ethyl (1*S*,2*S*)-2-chloro-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

cis-3f (minor isomer) White solid, m.p. = 66 - 68 °C. $R_f = 0.42$ (PE/EtOAc = 3:1). $[\alpha]^{20}_D = -9.4$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IA column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), $t_R = 14.0$ min, $t_R = 15.2$ min.

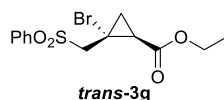
^1H NMR (300.1 MHz, CDCl_3) δ 8.04 – 7.95 (m, 2H), 7.73 – 7.65 (m, 1H), 7.62 – 7.53 (m, 2H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.60 (dd, $J = 15.2, 0.9$ Hz, 1H), 3.48 (d, $J = 15.2$ Hz, 1H) 2.26 (dd, $J = 9.2, 7.5$ Hz, 1H), 1.78 (dt, $J = 0.9, 7.5$ Hz, 1H), 1.55 (dd, $J = 9.2, 7.0$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.6, 139.1, 134.4, 129.4, 129.1, 66.1, 61.7, 39.5, 28.1, 21.0, 14.5.

HRMS (AP⁺) calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4\text{SCl}$ ($[\text{M}+\text{H}]^+$) 305.0428, found: 305.0425 (Δ -1.0 ppm).

IR (Neat) 2288, 2922, 2852, 1719, 1318, 1182, 1148, 1083, 731, 519 cm^{-1} .

3g. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 37.1 mg, *cis* 12.2 mg, 70% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 78:22). The diastereomeric ratio (71:29) was determined by ^1H NMR on the crude mixture.



ethyl (1*S*,2*R*)-2-bromo-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

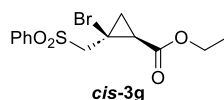
trans-3g (major isomer) White solid, m.p. = 73 - 75 °C. $R_f = 0.52$ (PE/EtOAc = 3:1). $[\alpha]^{20}_D = -77.8$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 17.3$ min, $t_R = 21.5$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.99 – 7.90 (m, 2H), 7.69 – 7.62 (m, 1H), 7.60 – 7.52 (m, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.98 (d, $J = 15.0$ Hz, 1H), 3.88 (d, $J = 15.0$ Hz, 1H), 2.43 (dd, $J = 9.3, 7.2$ Hz, 1H), 1.66 (dd, $J = 9.3, 6.8$ Hz, 1H), 1.56 (t, $J = 6.9$ Hz, 1H), 1.31 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 170.4, 140.1, 134.0, 129.4, 128.6, 61.9, 60.2, 29.5, 26.2, 24.3, 14.3.

Experimental Part



ethyl (1*S*,2*S*)-2-bromo-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

cis-3g (minor isomer) White solid, m.p. = 73 - 75 °C. $R_f = 0.33$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -14.3$ ($c = 1.0$, CHCl₃).

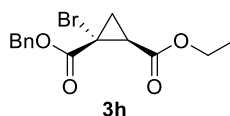
Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 60:40, 220 nm, 1 mL/min), $t_R = 15.8$ min, $t_R = 20.4$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.00 (d, $J = 7.7$ Hz, 2H), 7.72 – 7.68 (m, 1H), 7.62 – 7.56 (m, 2H), 4.27 – 4.16 (m, 2H), 3.66 (d, $J = 15.3$ Hz, 1H), 3.58 (d, $J = 15.3$ Hz, 1H), 2.24 (dd, $J = 8.8, 7.7$ Hz, 1H), 1.78 (t, $J = 7.2$ Hz, 1H), 1.60 (dd, $J = 9.1, 7.1$ Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 168.0, 139.1, 134.5, 129.5, 129.2, 67.2, 61.8, 27.9, 26.5, 21.7, 14.5.

HRMS (AP⁺) calcd for C₁₃H₁₆O₄SBr ([M+H]⁺) 348.9923, found: 348.9937 ($\Delta 1.4$ ppm).

IR (Neat) 2921, 2851, 1719, 1382, 1181, 1146, 1083, 746, 514 cm⁻¹.



1-benzyl 2-ethyl-1-bromocyclopropane-1,2-dicarboxylate

3h. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (50.6 mg, 78% yield) were obtained as an inseparable mixture of diastereoisomers after silica gel column chromatography (PE/EtOAc 99:1 to 90:10). $R_f = 0.3$ (PE/EtOAc = 10:1). The diastereomeric ratio (74:26) was determined by ¹H NMR on the crude mixture. Pale yellow oil.

trans-3h (major isomer)

Enantiomeric Excess: 83%. The enantiomeric excess was determined by HPLC with a Chiralcel Luxcell4 column (*n*-heptane: *i*-PrOH = 95:5, 210nm, 1 mL/min), $t_R = 9.4$ min, $t_R = 10.7$ min.

cis-3h (minor isomer)

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with a Chiralcel Luxcell4 column (*n*-heptane: *i*-PrOH = 95:5, 210 nm, 1 mL/min), $t_R = 7.7$ min, $t_R = 7.9$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.37 (s, 5H), 5.20 (s, 1.48H, *trans*), 5.18 (s, 0.52H, *cis*) 4.24 (q, $J = 6.8$ Hz, 1.48H, *trans*), 4.04 (q, $J = 7.1$ Hz, 0.52H, *cis*), 2.63 (t, $J = 8.6$ Hz, 0.74H, *trans*), 2.45 (t, $J = 8.6$ Hz, 0.26H, *cis*), 2.17 (t, $J = 7.0$ Hz, 0.26H, *cis*), 2.03 – 1.87 (m, 1.48H, *trans*), 1.69 (dd, $J =$

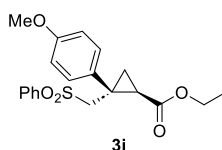
Experimental Part

9.1, 7.0 Hz, 0.26H, *cis*), 1.30 (t, $J = 7.1$ Hz, 2.22H, *trans*), 1.19 (t, $J = 7.1$ Hz, 0.78H, *cis*).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.6 (*cis*), 168.2 (*trans*), 167.4 (*trans*), 166.2 (*cis*), 135.1 (*cis*), 135.0 (*trans*), 128.8 (*trans*), 128.7 (*cis*), 128.6 (*trans*), 128.5 (*cis*), 128.4 (*cis*), 128.2 (*trans*), 68.8 (*trans*), 68.2 (*cis*), 61.9 (*trans*), 61.6 (*cis*), 31.2 (*cis*), 30.6 (*trans*), 30.8 (*trans*), 29.8 (*cis*), 23.5 (*trans*), 22.5 (*cis*), 14.4 (*trans*), 14.1 (*cis*).

HRMS (AP^+) calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{Br}$ ($[\text{M}+\text{H}]^+$) 327.0232, found: 327.0228 (Δ -1.2 ppm).

IR (Neat) 2982, 1723, 1376, 1266, 1180, 1118, 1030, 747, 696 cm^{-1} .



ethyl-2-(4-methoxyphenyl)-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

3i. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 40.0 mg, *cis* 28.5 mg, 92% overall yield) were obtained as separated fraction after silica gel column chromatography (PE/EtOAc 85:15 to 70:30). The diastereomeric ratio (56:44) was determined by ^1H NMR on the crude mixture.

trans-3i (major isomer) White solid, m.p. = 130 - 132 $^\circ\text{C}$. $R_f = 0.45$ (PE/EtOAc = 2:1). $[\alpha]_D^{20} = -56.7$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IA column (*n*-heptane: *i*-PrOH = 85:15, 220nm, 1 mL/min), $t_R = 21.6$ min, $t_R = 24.6$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.64 – 7.57 (m, 2H), 7.52 – 7.45 (m, 1H), 7.39 – 7.30 (m, 2H), 7.01 (d, $J = 8.8$ Hz, 2H), 6.61 (d, $J = 8.8$ Hz, 2H), 4.07 (d, $J = 14.7$ Hz, 1H), 3.84 – 3.73 (m, 2H), 3.71 (s, 3H), 2.98 (d, $J = 14.7$ Hz, 1H), 2.01 – 1.92 (m, 2H), 1.63 – 1.54 (m, 1H), 0.92 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 169.4, 158.8, 140.0, 133.3, 130.7, 129.0, 128.4, 128.0, 113.6, 66.6, 60.7, 55.2, 29.6, 28.2, 17.1, 14.1.

cis-3i (minor isomer) White solid, m.p. = 93 - 95 $^\circ\text{C}$. $R_f = 0.31$ (PE/EtOAc = 2:1). $[\alpha]_D^{20} = -85.2$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IA column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_R = 20.2$ min, $t_R = 22.3$ min.

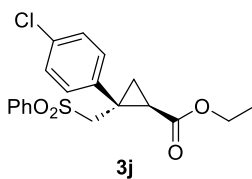
Experimental Part

¹H NMR (300.1 MHz, CDCl₃) δ 7.75 – 7.66 (m, 2H), 7.57 – 7.48 (m, 1H), 7.45 – 7.36 (m, 2H), 7.25 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H), 4.28 – 4.20 (m, 2H), 3.86 (s, 2H), 3.76 (s, 3H), 2.12 (dd, J = 8.3, 6.4 Hz, 1H), 1.54 – 1.46 (m, 2H), 1.34 (t, J = 7.1 Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.3, 158.9, 140.8, 133.2, 132.8, 130.4, 129.0, 127.9, 113.9, 61.9, 59.6, 55.3, 29.7, 26.2, 20.2, 14.4.

HRMS (AP⁺) calcd for C₂₀H₂₃O₅S ([M+H]⁺) 375.1266, found: 375.1273 (Δ 1.9 ppm).

IR (Neat) 3015, 2927, 2851, 1713, 1517, 1310, 1184, 1029, 740, 529 cm⁻¹.



3j
ethyl-2-(4-chlorophenyl)-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

3j. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 21.1 mg, *cis* 31.0 mg, 70% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). The diastereomeric ratio (40:60) was determined by ¹H NMR on the crude mixture.

***trans*-3j** (minor isomer) White solid, m.p. = 133 - 135 °C. R_f = 0.52 (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -60.3$ (c = 1.0, CHCl₃).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), t_R = 14.7 min, t_R = 27.5 min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.62 – 7.50 (m, 3H), 7.40 – 7.35 (m, 2H), 7.12 – 7.00 (m, 4H), 4.05 (d, J = 14.7 Hz, 1H), 3.81 (q, J = 7.1 Hz, 2H), 2.99 (d, J = 14.7 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.64 (dd, J = 7.7, 5.7 Hz, 1H), 0.94 (t, J = 7.1 Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 169.2, 139.8, 135.2, 133.6, 133.5, 131.1, 129.2, 128.4, 123.0, 66.3, 60.9, 29.7, 28.2, 17.2, 14.1.

***cis*-3j (major isomer)** White solid, m.p. = 68 - 70 °C. R_f = 0.33 (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -20.2$ (c = 1.0, CHCl₃).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 11.6 min, t_R = 15.0 min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.75 – 7.67 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H),

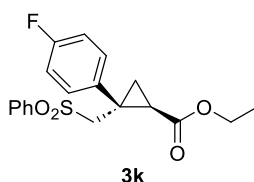
Experimental Part

7.29 (d, $J = 8.7$ Hz, 2H), 7.20 (d, $J = 8.7$ Hz, 2H), 4.33 – 4.16 (m, 2H), 3.87 (s, 2H), 2.14 (dd, $J = 8.6, 6.3$ Hz, 1H), 1.58 – 1.46 (m, 2H), 1.35 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.0, 140.6, 139.3, 133.6, 133.4, 130.8, 129.2, 128.8, 127.9, 61.5, 58.9, 29.7, 26.1, 20.1, 14.4.

HRMS (AP^+) calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{SCl}$ ($[\text{M}+\text{H}]^+$) 379.0771, found: 379.0746 (Δ -1.8 ppm).

IR (Neat) 2922, 1723, 1448, 1300, 1169, 1138, 824, 739, 523 cm^{-1} .



ethyl-2-(4-fluorophenyl)-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

3k. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 12.6 mg, *cis* 13.0 mg, 36% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). The diastereomeric ratio (49:51) was determined by ^1H NMR on the crude mixture.

***trans*-3k** (minor isomer) White solid, m.p. = 142 - 142 °C. $R_f = 0.52$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -68.6$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel ID column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), $t_R = 25.7$ min, $t_R = 33.6$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.61 (d, $J = 7.7$ Hz, 2H), 7.55 – 7.50 (m, 1H), 7.40 – 7.35 (m, 2H), 7.09 (dd, $J = 8.5, 5.4$ Hz, 2H), 6.79 (t, $J = 8.6$ Hz, 2H), 4.06 (d, $J = 14.7$ Hz, 1H), 3.80 (q, $J = 7.1$ Hz, 2H), 3.00 (d, $J = 14.7$ Hz, 1H), 2.05 – 1.92 (m, 2H), 1.64 (dd, $J = 7.5, 5.5$ Hz, 1H), 0.93 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 169.2, 162.0 (d, $J = 246.8$ Hz), 139.9, 133.6, 132.4 (d, $J = 3.3$ Hz), 131.4 (d, $J = 8.3$ Hz), 129.1, 128.0, 115.1 (d, $J = 21.6$ Hz), 66.5, 60.8, 29.5, 28.3, 17.2, 14.1.

^{19}F NMR (282.4 MHz, CDCl_3) δ -114.9 – -115.0 (m, 1F).

***cis*-3k** (major isomer) White solid, m.p. = 77 - 79 °C. $R_f = 0.35$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -140.0$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel

Experimental Part

IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_R = 11.5$ min, $t_R = 14.4$ min.

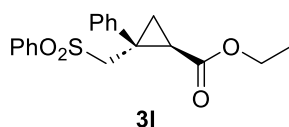
^1H NMR (300.1 MHz, CDCl_3) δ 7.76 – 7.67 (m, 2H), 7.59 – 7.51 (m, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.29 (m, 2H), 6.92 (t, $J = 8.7$ Hz, 2H), 4.25 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 2H), 2.14 (dd, $J = 8.5, 6.3$ Hz, 1H), 1.58 – 1.46 (m, 2H), 1.35 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.1, 162.1 (d, $J = 246.9$ Hz), 140.7, 136.7 (d, $J = 3.3$ Hz), 133.4, 131.2 (d, $J = 8.3$ Hz), 129.1, 127.9, 115.5 (d, $J = 21.6$ Hz), 61.5, 59.1, 29.6, 26.2, 20.2, 14.4.

^{19}F NMR (282.4 MHz, CDCl_3) δ -114.7 – -114.8 (m, 1F).

HRMS (AP⁺) calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{FS}$ ($[\text{M}+\text{H}]^+$) 363.1066, found: 363.1057 ($\Delta 2.5$ ppm).

IR (Neat) 3052, 2923, 1723, 1514, 1171, 1137, 1079, 832, 724, 528 cm^{-1} .



31
ethyl-2-phenyl-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

31. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 38.6 mg, *cis* 28.2 mg, 97% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). The diastereomeric ratio (58:42) was determined by ^1H NMR on the crude mixture.

***trans*-31** (major isomer) White solid, m.p. = 134 - 136 °C. $R_f = 0.53$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -74.3$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 85:15, 220 nm, 1 mL/min), $t_R = 17.2$ min, $t_R = 23.4$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.64 – 7.56 (m, 2H), 7.51 – 7.43 (m, 1H), 7.35 – 7.30 (m, 2H), 7.09 (s, 5H), 4.11 (d, $J = 14.7$ Hz, 1H), 3.86 – 3.64 (m, 2H), 3.02 (d, $J = 14.7$ Hz, 1H), 2.05 – 1.96 (m, 2H), 1.63 (dd, $J = 10.9, 8.5$ Hz, 1H), 0.86 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 169.3, 139.8, 136.5, 133.4, 129.7, 129.0, 128.1, 128.0, 127.5, 66.4, 60.6, 30.2, 28.3, 16.8, 13.9.

***cis*-31** (minor isomer) Colorless oil. $R_f = 0.36$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -80.5$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_R = 13.9$ min, $t_R = 16.0$ min.

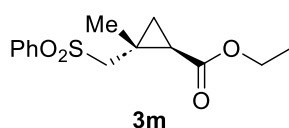
Experimental Part

¹H NMR (300.1 MHz, CDCl₃) δ 7.74 – 7.66 (m, 2H), 7.53 – 7.49 (m, 1H), 7.44 – 7.32 (m, 4H), 7.26 – 7.15 (m, 3H), 4.26 – 4.21 (m, 2H), 3.91 (s, 2H), 2.16 (dd, $J = 7.8, 7.0$ Hz, 1H), 1.55 (d, $J = 7.0$ Hz, 2H), 1.34 (t, $J = 7.2$ Hz, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 172.2, 140.7, 133.3, 129.3, 129.0, 128.6, 127.9, 127.7, 61.4, 59.1, 30.3, 26.1, 20.0, 14.4.

HRMS (AP⁺) calcd for C₁₉H₂₁O₄S ([M+H]⁺) 345.1161, found: 345.1150 (Δ -3.2 ppm).

IR (Neat) 2924, 1722, 1448, 1270, 1172, 1136, 1081, 742, 528 cm⁻¹.



ethyl-2-methyl-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate

3m. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 26.8 mg, *cis* 27.3 mg, 96% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 85:15 to 70:30). The diastereomeric ratio (50:50) was determined by ¹H NMR on the crude mixture.

***trans*-3m,** Colorless oil. $R_f = 0.38$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -75.3$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IA column (*n*-heptane: *i*-PrOH = 85:15, 220 nm, 1 mL/min), $t_R = 13.0$ min, $t_R = 13.9$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.98 – 7.87 (m, 2H), 7.71 – 7.63 (m, 1H), 7.62 – 7.52 (m, 2H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.15 (d, $J = 14.5$ Hz, 1H), 3.07 (d, $J = 14.5$ Hz, 1H), 1.56 (dd, $J = 8.5, 6.1$ Hz, 1H), 1.32 (s, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.10 (t, $J = 5.7$ Hz, 1H), 0.88 (dd, $J = 8.5, 5.3$ Hz, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 171.0, 140.0, 134.0, 129.5, 128.4, 66.3, 60.8, 25.8, 21.1, 20.0, 16.6, 14.5.

***cis*-3m,** Colorless oil. $R_f = 0.27$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -12.0$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 10.7$ min, $t_R = 12.4$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.93 – 7.85 (m, 2H), 7.66 – 7.59 (m, 1H), 7.58 – 7.49 (m, 2H), 4.19 – 4.08 (m, 2H), 3.54 (d, $J = 14.2$ Hz, 1H), 3.49 (d, $J = 14.2$ Hz, 1H), 1.69 (dd, $J = 8.2, 5.9$ Hz,

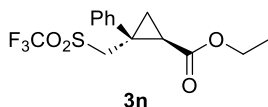
Experimental Part

1H), 1.43 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.00 (t, $J = 5.4$ Hz, 1H), 0.93 (dd, $J = 8.2, 5.0$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.6, 140.7, 133.7, 129.4, 128.1, 61.1, 58.3, 26.1, 24.4, 21.8, 21.5, 14.4.

HRMS (AP^+) calcd for $\text{C}_{14}\text{H}_{19}\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 283.1004, found: 283.1000 (Δ -1.4 ppm).

IR (Neat) 2982, 2924, 1708, 1384, 1305, 1180, 1147, 1084, 739, 522 cm^{-1} .



ethyl-2-phenyl-2-(((trifluoromethyl)sulfonyl)methyl)cyclopropane-1-carboxylate

3n. These cyclopropanes were obtained using the general procedure with 5 mol% of Ru(II)-Pheox I, (*trans* 11.8 mg, *cis* 8.7 mg, 31% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). The diastereomeric ratio (52:48) was determined by ^{19}F NMR on the crude mixture.

trans-**3n** (major isomer) Colorless oil. $R_f = 0.50$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -32.8$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 10.2$ min, $t_R = 11.2$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.41 – 7.27 (m, 5H), 4.06 (d, $J = 14.1$ Hz, 1H), 3.92 – 3.75 (m, 2H), 3.14 (d, $J = 14.1$ Hz, 1H), 2.19 – 2.11 (m, 2H), 1.71 (dd, $J = 10.9, 8.6$ Hz, 1H), 0.95 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.8, 136.2, 129.8, 128.7, 128.5, 119.2 (t, $J = 328.0$ Hz), 61.1, 60.8, 60.8, 28.2, 17.4, 14.0.

^{19}F NMR (282.4 MHz, CDCl_3) δ -79.6 (s, 3F).

cis-**3n** (minor isomer) Colorless oil. $R_f = 0.29$ (PE/EtOAc = 3:1). $[\alpha]_D^{20} = -67.0$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 6.4$ min, $t_R = 7.5$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.48 – 7.42 (m, 2H), 7.40 – 7.29 (m, 3H), 4.25 (q, $J = 7.2$ Hz, 2H), 4.13 (d, $J = 14.0$ Hz, 1H), 4.04 (d, $J = 14.0$ Hz, 1H), 2.31 (dd, $J = 8.5, 6.3$ Hz, 1H), 1.73 – 1.62 (m, 2H), 1.35 (t, $J = 7.1$ Hz, 3H).

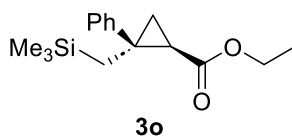
^{13}C NMR (75.5 MHz, CDCl_3) δ 172.0, 134.0, 129.4, 129.0, 128.5, 119.2 (q, $J = 328.0$ Hz), 61.7, 53.9, 28.6, 25.7, 20.7, 14.3.

Experimental Part

^{19}F NMR (282.4 MHz, CDCl_3) δ -80.0 (s, 3F).

HRMS (AP^+) calcd for $\text{C}_{14}\text{H}_{16}\text{O}_4\text{F}_3\text{S}$ ($[\text{M}+\text{H}]^+$) 337.0721, found: 337.0724 (Δ 0.9 ppm).

IR (Neat) 2989, 2922, 2851, 1721, 1355, 1183, 1116, 1019, 700, 530 cm^{-1} .



ethyl-2-phenyl-2-((trimethylsilyl)methyl)cyclopropane-1-carboxylate

3o. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 24.0 mg, *cis* 23.1 mg, 86% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/Et₂O 99:1 to 90:10). The diastereomeric ratio (51:49) was determined by ^1H NMR on the crude mixture. Colorless oil.

trans-**3o** (major isomer) $R_f = 0.64$ (PE/Et₂O = 10:1). $[\alpha]^{20}_D = -39.6$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-heptane: (25% EtOH + 75% MTBE) = 99.5:0.5, 220 nm, 0.75 mL/min), $t_R = 8.6$ min, $t_R = 12.3$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.26 – 7.10 (m, 5H), 3.85 – 3.67 (m, 2H), 1.91 – 1.78 (m, 2H), 1.68 (d, $J = 14.5$ Hz, 1H), 1.11 (dd, $J = 6.6, 4.3$ Hz, 1H), 0.88 (t, $J = 7.1$ Hz, 3H), 0.49 (d, $J = 14.5$ Hz, 1H), -0.27 (s, 9H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 171.2, 141.2, 129.4, 128.1, 126.8, 60.1, 34.2, 31.6, 30.7, 19.8, 14.1, -0.9.

cis-**3o** (minor isomer) $R_f = 0.40$ (PE/Et₂O = 10:1). $[\alpha]^{20}_D = -26.8$ ($c = 1.0$, CHCl_3).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by inverse phase HPLC with a Chiralcel IA3 column (H_2O : MeCN = 50:50, 254 nm, 1 mL/min), $t_R = 27.6$ min, $t_R = 29.4$ min.

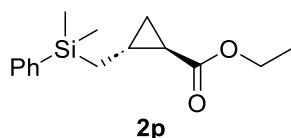
^1H NMR (300.1 MHz, CDCl_3) δ 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 2H), 7.19 – 7.12 (m, 1H), 4.22 – 4.09 (m, 2H), 1.79 (dd, $J = 8.3, 6.1$ Hz, 1H), 1.51 (dd, $J = 8.4, 4.8$ Hz, 1H), 1.32 – 1.24 (m, 4H), 1.22 (s, 2H), -0.29 (s, 9H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 172.6, 145.5, 128.5, 128.5, 126.8, 60.6, 33.8, 28.3, 21.4, 20.4, 14.6, -0.9.

HRMS (AP^+) calcd for $\text{C}_{16}\text{H}_{25}\text{O}_2\text{Si}$ ($[\text{M}+\text{H}]^+$) 277.1624, found: 277.1617 (Δ -2.5 ppm).

Experimental Part

IR (Neat) 2953, 2899, 1728, 1378, 1247, 1159, 1081, 856, 834, 698 cm^{-1} .



ethyl-2-((dimethyl(phenyl)silyl)methyl)cyclopropane-1-carboxylate

3p. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (*trans* 37.1 mg, *cis* 8.6 mg, 88% overall yield) were obtained as separated fractions after silica gel column chromatography (PE/Et₂O 99:1 to 90:10). The diastereomeric ratio (81:19) was determined by ¹H NMR on the crude mixture.

***trans*-3p** (major isomer) Colorless oil. $R_f = 0.72$ (PE/Et₂O = 10:1). $[\alpha]_D^{20} = -63.2$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), $t_R = 5.8$ min, $t_R = 7.1$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.57 – 7.48 (m, 2H), 7.40 – 7.31 (m, 3H), 4.21 – 3.99 (m, 2H), 1.68 – 1.60 (m, 1H), 1.28 – 1.19 (m, 4H), 1.07 – 0.96 (m, 3H), 0.84 (dt, $J = 7.2, 5.1$ Hz, 1H), 0.31 (d, $J = 1.5$ Hz, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 173.1, 139.1, 133.8, 129.0, 127.9, 60.3, 19.1, 17.9, 15.0, 14.5, 13.3, -2.8, -2.9.

***cis*-3p** (minor isomer) Colorless oil. $R_f = 0.66$ (PE/Et₂O = 10:1). $[\alpha]_D^{20} = -17.8$ ($c = 1.0$, CHCl₃).

Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with a Chiralcel OJ-H column (*n*-heptane: (25% EtOH + 75% MTBE) = 95:5, 220 nm, 1 mL/min), $t_R = 7.8$ min, $t_R = 9.7$ min.

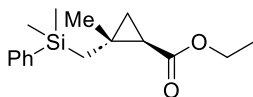
¹H NMR (300.1 MHz, CDCl₃) δ 7.55 – 7.47 (m, 2H), 7.40 – 7.31 (m, 3H), 4.10 (q, $J = 7.2$ Hz, 2H), 1.32 – 1.22 (m, 5H), 1.21 – 1.14 (m, 1H), 0.99 (dd, $J = 14.8, 5.8$ Hz, 1H), 0.73 – 0.58 (m, 2H), 0.34 (s, 3H), 0.33 (s, 3H).

¹³C NMR (75.5 MHz, CDCl₃) δ 174.6, 138.8, 133.7, 129.2, 127.9, 60.4, 22.3, 20.4, 19.0, 17.5, 14.5, -2.8, -2.9.

HRMS (AP⁺) calcd for C₁₅H₂₃O₂Si ([M+H]⁺) 263.1467, found: 263.1471 ($\Delta 1.5$ ppm).

IR (Neat) 3070, 2956, 1721, 1380, 1248, 1159, 1112, 833, 698 cm^{-1} .

Experimental Part



3q

ethyl-2-((dimethyl(phenyl)silyl)methyl)-2-methylcyclopropane-1-carboxylate

3q. These cyclopropanes were obtained using the general procedure with 2 mol% of Ru(II)-Pheox I, (48.4 mg, 92% yield) were obtained as an inseparable mixture of diastereoisomers after silica gel column chromatography (PE/Et₂O 99:1 to 90:10). R_f = 0.73 (PE/Et₂O = 10:1). The diastereomeric ratio (50:50) was determined by ¹H NMR on the crude mixture. Colorless oil.

trans-3q

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-heptane: (25% EtOH + 75% MTBE) = 99.5:0.5, 220 nm, 0.75 mL/min), t_R = 8.9 min, t_R = 11.5 min

cis-3q

Enantiomeric Excess: 86%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: (25% EtOH + 75% MTBE) = 99.5:0.5, 220 nm, 1 mL/min), t_R = 8.8 min, t_R = 9.7 min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.59 – 7.47 (m, 2H), 7.41 – 7.29 (m, 3H), 4.21 – 4.01 (m, 2H), 1.46 (dt, *J* = 8.1, 5.8 Hz, 1H), 1.26 (td, *J* = 7.1, 1.7 Hz, 3H), 1.19 – 0.92 (m, 6H), 0.83 (ddd, *J* = 12.7, 8.1, 4.5 Hz, 1H), 0.38 (s, 3H), 0.34 (d, *J* = 1.1 Hz, 3H).

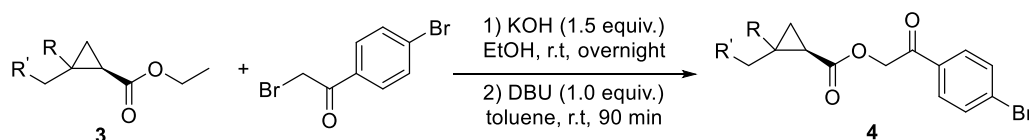
¹³C NMR (75.5 MHz, CDCl₃) δ 173.0, 172.8, 139.9, 139.6, 133.7, 133.6, 129.0, 128.9, 127.9, 127.8, 60.3, 60.2, 29.4, 28.2, 27.8, 27.5, 25.5, 24.9, 23.1, 23.0, 19.2, 19.1, 14.5, -1.6, -1.6, -1.7.

HRMS (AP⁺) calcd for C₁₆H₂₅O₂Si ([M+H]⁺) 277.1624, found: 277.1628 (Δ1.4 ppm).

IR (Neat) 3070, 2956, 1720, 1380, 1162, 1111, 832, 724, 699 cm⁻¹.

4. General procedures of the post-functionalization reactions

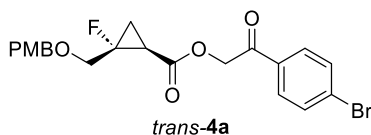
4.1. General procedure for the synthesis of 2-(4-bromophenyl)-2-oxoethyl cyclopropylcarboxylates 4.



Experimental Part

In a 25 mL flask charged with a magnetic stir bar, ethyl carboxylate cyclopropane **3** (0.5 mmol, 1.0 equiv.) was charged, followed by 5 mL EtOH. Then, 1 N potassium hydroxide in ethanol (0.75 mmol, 1.5 equiv.) was added in one portion at room temperature. This mixture was stirred at this temperature for overnight, and monitored by TLC. Once the reaction complete, solvent was evaporated under vacuum, and the residue was acidified with 4 N HCl until pH = 1. The mixture was extracted with dichloromethane (3×5 mL), combined the organic phases, washed with saturated brine (10 mL), dried over Na₂SO₄ and filtered. The filtrate was evaporated under vacuum to yield white solid crude product, this crude was used to next step directly.

In a flame dried flask, was added the crude from previous step and 2-bromo-1-(4-bromophenyl)ethan-1-one (0.5 mmol, 1.0 equiv.) followed by toluene (8 mL). The mixture was stirred at room temperature and DBU (0.5 mmol, 1.0 equiv.) was added and stirred at this temperature for another 90 min until TLC displayed the completion. 5 mL water was added and washed with saturated NaHCO₃ (10 mL) and 1 N HCl (10 mL), dried over Na₂SO₄, evaporated under reduced pressure and purified by silica gel chromatography to yield **4**.



2-(4-bromophenyl)-2-oxoethyl (1*S*,2*R*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropane-1-carboxylate

trans-**4a**. This product was obtained using the general procedure from *trans*-**3a**, 164.1 mg (73% yield) were obtained after silica gel column chromatography (PE/EtOAc 90:10 to 80:20). $R_f = 0.58$ (PE/EtOAc = 3:1). Colorless oil.

Enantiomeric Excess: 92%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 70:30, 254 nm, 1 mL/min), $t_R = 10.9$ min, $t_R = 12.3$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.62 (d, $J = 8.7$ Hz, 2H), 7.50 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 5.17 (d, $J = 16.4$ Hz, 1H), 5.03 (d, $J = 16.4$ Hz, 1H), 4.45 (d, $J = 11.6$ Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 3.87 (ddd, $J = 41.0, 24.9, 12.2$ Hz, 2H), 3.65 (s, 3H), 2.34 (ddd, $J = 18.1, 10.1, 7.7$ Hz, 1H), 1.65 – 1.50 (m, 1H), 1.40 (dt, $J = 12.1, 7.3$ Hz, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 190.9, 169.6 (d, $J = 1.9$ Hz), 159.2, 132.8, 132.2, 130.0, 129.5, 129.3, 129.1, 113.7, 82.3 (d, $J = 229.1$ Hz), 72.9, 68.2 (d, $J = 19.7$ Hz), 66.2, 55.2, 23.9 (d, $J = 14.3$

Experimental Part

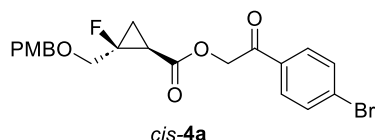
Hz), 17.9 (d, $J = 9.8$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -173.1 – -173.4 (m, 1 F).

HRMS (ES^+) calcd for $\text{C}_{21}\text{H}_{20}\text{O}_5\text{FBrNa}$ ($[\text{M}+\text{Na}]^+$) 473.0376, found: 473.0376 ($\Delta 0$ ppm).

IR (Neat) 2927, 1732, 1701, 1585, 1514, 1246, 1161, 1070, 814, 546 cm^{-1} .

$[\alpha]^{20}_{\text{D}} = -39.7$ ($c = 1.0$, CHCl_3).



2-(4-bromophenyl)-2-oxoethyl (1S,2S)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropane-1-carboxylate

cis-4a. This product was obtained using the general procedure from *cis*-3a, 149.3 mg (66% yield) were obtained after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). $R_f = 0.33$ (PE/EtOAc = 3:1). White solid, m.p. = 103 - 105 °C.

Enantiomeric Excess: 83%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 85:15, 254 nm, 1 mL/min), $t_R = 21.1$ min, $t_R = 25.8$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.70 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.6$ Hz, 2H), 6.81 (d, $J = 8.6$ Hz, 2H), 5.33 (d, $J = 16.4$ Hz, 1H), 5.19 (d, $J = 16.4$ Hz, 1H), 4.50 (s, 2H), 3.77 – 3.61 (m, 5H), 2.11 – 1.99 (m, 1H), 1.90 (dt, $J = 19.9, 7.1$ Hz, 1H), 1.27 (ddd, $J = 10.8, 9.4, 7.0$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 191.3, 167.9 (d, $J = 2.2$ Hz), 159.5, 133.0, 132.3, 129.7, 129.6, 129.4, 129.3, 114.0, 81.0 (d, $J = 233.7$ Hz), 73.0, 70.7 (d, $J = 24.3$ Hz), 66.4, 55.4, 23.5 (d, $J = 10.4$ Hz), 16.4 (d, $J = 11.5$ Hz).

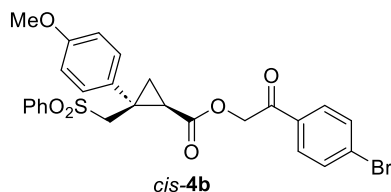
^{19}F NMR (282.4 MHz, CDCl_3) δ -195.5 – -195.8 (m, 1 F).

HRMS (ES^+) calcd for $\text{C}_{21}\text{H}_{20}\text{O}_5\text{FBrNa}$ ($[\text{M}+\text{Na}]^+$) 473.0376, found: 473.0376 ($\Delta 0$ ppm).

IR (Neat) 2926, 1731, 1701, 1585, 1247, 1139, 1070, 814, 546 cm^{-1} .

$[\alpha]^{20}_{\text{D}} = -42.4$ ($c = 1.0$, CHCl_3).

Experimental Part



2-(4-bromophenyl)-2-oxoethyl (1*R*,2*S*)-2-(4-methoxyphenyl)-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate *cis*-**4b**. This product was obtained using the general procedure from *cis*-**3i** (0.07 mmol, 26.4 mg), 21mg (55% yield) were obtained after silica gel column chromatography (PE/EtOAc 90:10 to 75:25). $R_f = 0.33$ (PE/EtOAc = 3:1). White solid, m.p. = 60 - 62 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), $t_R = 57.0$ min, $t_R = 65.9$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.81 (d, $J = 8.7$ Hz, 2H), 7.70 – 7.62 (m, 4H), 7.55 – 7.47 (m, 1H), 7.43 – 7.34 (m, 2H), 7.26 (d, $J = 8.8$ Hz, 2H), 6.74 (d, $J = 8.8$ Hz, 2H), 5.33 (d, $J = 16.4$ Hz, 1H), 5.19 (d, $J = 16.4$ Hz, 1H), 3.90 (d, $J = 14.6$ Hz, 1H), 3.84 (d, $J = 14.6$ Hz, 1H), 3.76 (s, 3H), 2.26 (t, $J = 7.4$ Hz, 1H), 1.65 (d, $J = 7.4$ Hz, 2H).

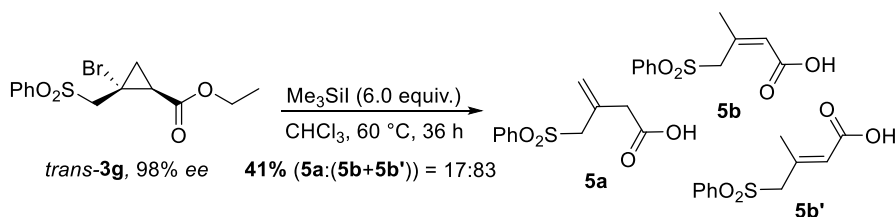
^{13}C NMR (75.5 MHz, CDCl_3) δ 191.5, 171.6, 159.0, 140.7, 133.2, 133.0, 132.5, 132.4, 130.4, 129.5, 129.4, 129.0, 127.9, 114.0, 66.7, 59.4, 55.4, 30.5, 26.4, 20.4.

HRMS (ES^+) calcd for $\text{C}_{26}\text{H}_{24}\text{O}_6\text{SBr}$ ($[\text{M}+\text{H}]^+$) 543.0477, found: 543.0459 (Δ -3.3 ppm).

IR (Neat) 2927, 2853, 1729, 1692, 1585, 1396, 1249, 1164, 1070, 815 cm^{-1} .

$[\alpha]_D^{20} = -88.7$ ($c = 1.0$, CHCl_3).

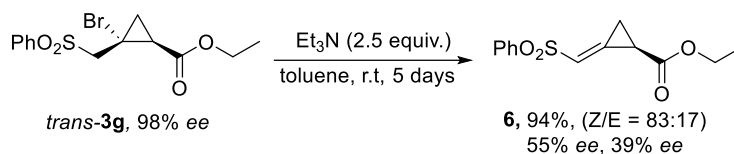
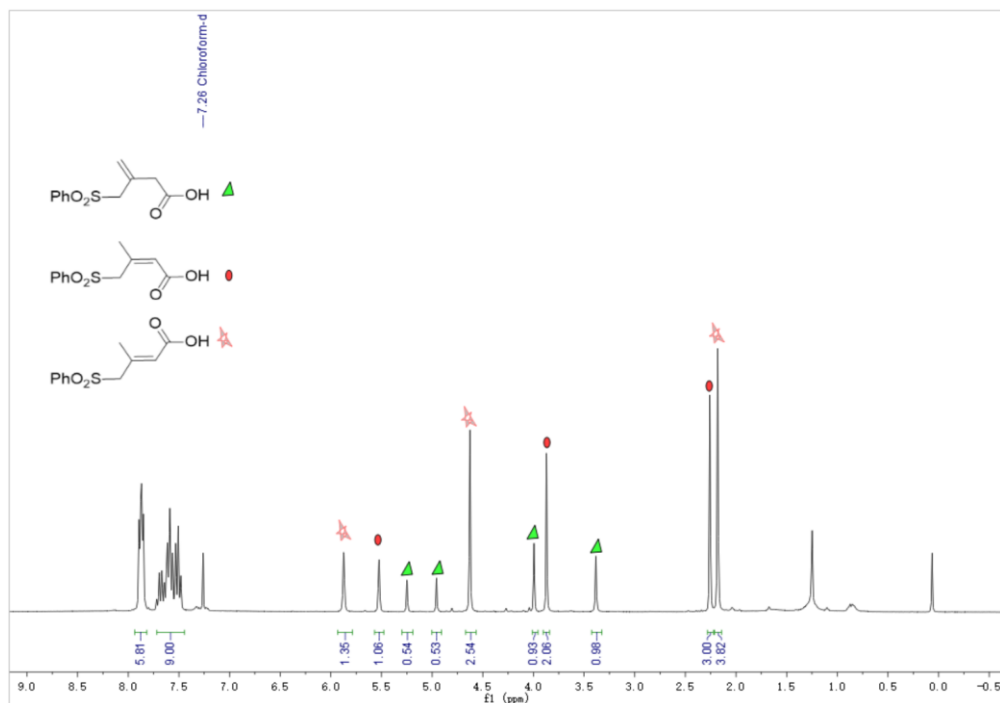
4.2. Post-functionalization reactions of *trans*-**3g**



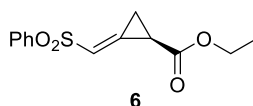
Under an argon protection, a flame dried 10 mL round bottom flask, which was equipped with a magnetic stir bar and charged with *trans*-**3g** (69.2 mg, 0.2 mmol, 1.0 equiv.). The flask was purged with argon for three times, and then anhydrous chloroform (2 mL) was added, followed by TMSI (171 μL , 1.2 mmol, 6.0 equiv.). This solution was heated to 60 °C for 72 h. When the reaction was complete, water (2 mL) was slowly added to the reaction mixture, extracted with DCM (3 \times 5 mL),

Experimental Part

the organic phases were combined and dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by silica-gel chromatography (MeOH/DCM 1:20) to afford inseparable mixture products **5a**, **5b**, **5b'** in 41% overall yields.



In a flame dried 10 mL reaction tube, *trans*-**3g** (69.2 mg, 0.2 mmol, 1.0 equiv.) was added followed by triethylamine (70 μL , 0.5 mmol, 2.5 equiv.) and 2 mL toluene. This reaction was stirred for 5 days and monitored by TLC until the completion. The mixture was evaporated under reduced pressure to remove solvent and excess triethylamine. The crude was purified by silica-gel chromatography (petroleum ether/EtOAc 8:92) to afford product **6** (50 mg, 94%, Z/E 83:17) as a colorless oil.



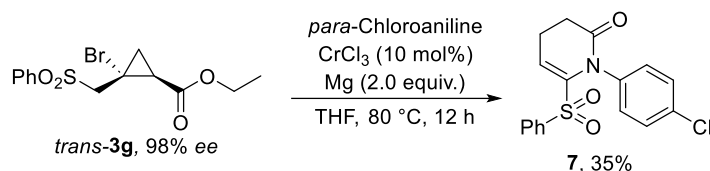
ethyl (*R*)-2-((phenylsulfonyl)methylene)cyclopropane-1-carboxylate

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 7.92 – 7.81 (m, 2H), 7.65 – 7.46 (m, 3H), 6.79 (d, $J = 1.5$ Hz, 1H, *E*), 6.72 (d, $J = 1.9$ Hz, 1H, *Z*), 4.29 – 4.04 (m, 2H), 2.73 – 2.65 (m, 1H, *Z*), 2.44 (dd, $J = 9.7, 6.7$, 1H, *E*), 2.13 (dd, $J = 6.7, 2.5$ Hz, 1H, *E*), 2.06 – 1.76 (m, 2H), 1.33 – 1.18 (m, 3H).

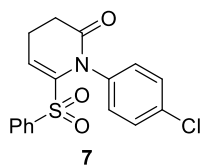
Experimental Part

Enantiomeric Excess: 55% (*Z*), 39% (*E*). The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 75:25, 220 nm, 1 mL/min), $t_{RZ} = 56.1$ min, $t_{RE} = 73.2$ min; $t_{RE} = 60.3$ min, $t_{RE} = 67.8$ min.

HRMS (AP⁺) calcd for C₁₃H₁₅O₄S ([M+H]⁺) 267.0691, found: 267.0681 (Δ -3.7 ppm).



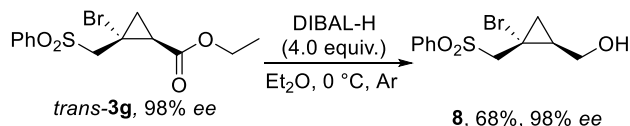
Under an argon protection, in a flame dried 10 mL reaction tube, *trans*-**3g** (138.4 mg, 0.4 mmol, 2.0 equiv.), *para*-chloroaniline (25.4 mg, 0.2 mmol, 1.0 equiv.), magnesium turning (9.6 mg, 0.4 mmol, 2.0 equiv.) and CrCl₃ (1.6 mg, 0.02 mmol, 0.1 equiv.) were added in order. This tube was sealed and stirred at 80 °C for 12 hours. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. The crude was purified by silica-gel chromatography (petroleum ether/EtOAc 10:90) to afford product **7** (24.2 mg, 35%) as a white solid.



7
1-(4-chlorophenyl)-6-(phenylsulfonyl)-3,4-dihydropyridin-2(1H)-one

¹H NMR (300.1 MHz, CDCl₃) δ 7.84 (d, $J = 7.4$ Hz, 2H), 7.63 – 7.42 (m, 6H), 7.08 (d, $J = 8.6$ Hz, 2H), 5.43 (d, $J = 1.7$ Hz, 1H), 3.46 – 3.35 (m, 2H), 2.77 – 2.67 (m, 2H).

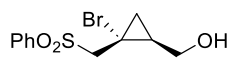
¹³C NMR (75.5 MHz, CDCl₃) δ 175.5, 158.1, 142.9, 135.7, 133.2, 131.9, 130.5, 129.4, 129.0, 126.8, 103.6, 28.0, 23.5.



Under an argon protection, in a flame dried 10 mL reaction tube, *trans*-**3g** (69.2 mg, 0.2 mmol, 1.0 equiv.) was added followed by 1 mL diethyl ether. This solution was placed in water-ice bath and DIBAL-H 1 N in THF (0.8 mL, 0.8 mmol, 4.0 equiv.) was added dropwise in 30 min. This reaction was stirred for additional 2 h and monitored by TLC. Until the completion, this reaction was

Experimental Part

quenched by addition dropwise of water (0.2 mL) and 4 N HCl (1 mL), extracted with diethyl ether (3×5 mL). The combined organic phases were washed with 1 N HCl (5 mL), saturated aqueous NaHCO₃ (5 mL) and brine (5 mL). The organic phase was dried over Na₂SO₄, filtered and evaporated under reduced pressure. The crude mixture was purified by silica-gel chromatography (petroleum ether/EtOAc 70:30 to 50:50, R_f = 0.41 petroleum ether/EtOAc = 1:1) to afford product **8** (41.3 mg, 68%) as a colorless oil.



8
((1*S*,2*R*)-2-bromo-2-((phenylsulfonyl)methyl)cyclopropyl)methanol

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (*n*-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), t_R = 23.1 min, t_R = 27.9 min.

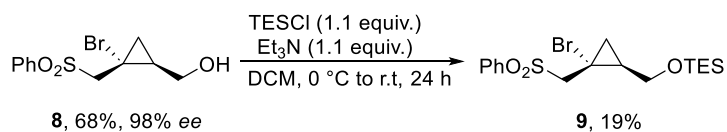
¹H NMR (300.1 MHz, CDCl₃) δ 8.04 – 7.91 (m, 2H), 7.72 – 7.64 (m, 1H), 7.62 – 7.54 (m, 2H), 3.99 (dd, *J* = 12.5, 4.0 Hz, 1H), 3.88 (d, *J* = 15.7 Hz, 1H), 3.65 (d, *J* = 15.7 Hz, 1H), 3.39 (dd, *J* = 12.5, 8.9 Hz, 1H), 3.16 (s, 1H), 2.02 – 1.90 (m, 1H), 1.34 (dd, *J* = 10.2, 6.8 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 139.6, 134.3, 129.4, 128.8, 63.2, 61.4, 31.1, 25.4, 19.9.

HRMS (AP⁺) calcd for C₁₁H₁₄O₃SBr ([M+H]⁺) 304.9847, found: 304.9840 (Δ-0.7 ppm).

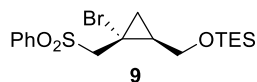
IR (Neat) 3341, 2929, 2864, 1524, 1393, 1140, 1071, 816, 747 cm⁻¹.

[α]_D²⁰ = -13.3 (c = 1.0, CHCl₃).



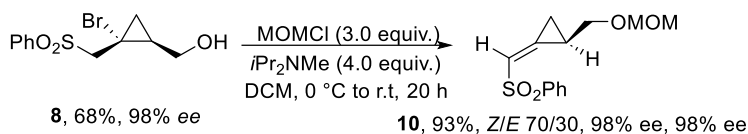
To a solution of **8** (40.0 mg, 0.132 mmol, 1.0 equiv.) in 2 mL dichloromethane was added triethylsilyl chloride (24.4 μL, 0.145 mmol, 1.1 equiv.) and triethylamine (22.0 μL, 0.145 mmol, 1.1 equiv.) at 0 °C. This mixture was allowed to recover to room temperature for stirring 24 h and monitored by TLC. This reaction was quenched by adding water (2 mL) and extracted with DCM (3×5 mL). The combined organic phase was washed with brine (10 mL) and dried over Na₂SO₄, filtered and evaporated under reduced pressure. The resulting crude was purified by silica gel chromatography (petroleum ether/EtOAc 80:20) to afford product **9** (10.3 mg, 19%) as a colorless oil.

Experimental Part

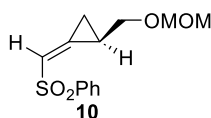


(((1*S*,2*R*)-2-bromo-2-((phenylsulfonyl)methyl)cyclopropyl)methoxy)triethylsilane

¹H NMR (300.1 MHz, CDCl₃) δ 7.99 (d, *J* = 7.0 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 3.98 (dd, *J* = 11.7, 3.7 Hz, 1H), 3.91 (d, *J* = 15.5 Hz, 1H), 3.68 (d, *J* = 15.5 Hz, 1H), 3.55 (dd, *J* = 11.7, 6.8 Hz, 1H), 1.77 – 1.66 (m, 1H), 1.27 (d, *J* = 8.6 Hz, 2H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 8.3 Hz, 6H).



To a solution of **8** (30.4 mg, 0.1 mmol, 1.0 equiv.) in 2 mL dichloromethane was added ethyl diisopropylamine (66 μL, 0.4 mmol, 4.0 equiv.) and MOMCl (22.8 μL, 0.3 mmol, 3.0 equiv.) at 0 °C. This mixture was allowed to recover to room temperature for stirring 20 h and monitored by TLC. 1 N HCl (2 mL) was added in the mixture, and EtOAc was added to dilute this reaction, then washed with 1 N HCl (2×2 mL), saturated NaHCO₃ aqueous (3 mL) and brine (3 mL). The organic phase was separated and dried over Na₂SO₄, filtered and evaporated under reduced pressure. The resulting crude was purified by silica gel chromatography (petroleum ether/EtOAc 80:20 to 65:35, *R_f* = 0.29, petroleum ether/EtOAc = 2:1). to afford product **10** (20.4 mg, 93%, *Z/E* 70:30) as a colorless oil.



(*R*)-(((2-((methoxymethoxy)methyl)cyclopropylidene)methyl)sulfonyl)benzene

Enantiomeric Excess: 98% (*E* isomer), 98% (*Z* isomer). The enantiomeric excesses were determined by HPLC with a Chiralcel AD-H column (*n*-heptane: *i*-PrOH = 90:10, 254 nm, 1 mL/min), *t_R* = 16.3 min, *t_R* = 17.2 min (*Z* isomer). *t_R* = 19.4 min, *t_R* = 22.8 min (*E* isomer)

¹H NMR (300.1 MHz, CDCl₃) δ 7.92 – 7.86 (m, 2H), 7.64 – 7.58 (m, 1H), 7.55 – 7.49 (m, 2H), 6.82 (dd, *J* = 3.6, 2.1 Hz, 0.7H, *Z*), 6.72 (d, *J* = 1.7 Hz, 0.3H, *E*), 4.67 – 4.62 (m, 0.6H, *E*), 4.60 – 4.54 (m, 1.4H, *Z*), 4.16 (dd, *J* = 10.7, 4.1 Hz, 0.3H, *E*), 3.46 (ddd, *J* = 30.1, 10.7, 7.0 Hz, 1.4H, *Z*), 3.36 (s, 0.9H, *E*), 3.31 (s, 2.1H, *Z*), 3.22 (dd, *J* = 10.6, 8.6 Hz, 0.3H, *E*), 2.28 – 2.16 (m, 0.3H, *E*), 2.04 – 1.93 (m, 0.7H, *Z*), 1.74 (td, *J* = 11.0, 2.1 Hz, 0.7H, *Z*), 1.56 (t, *J* = 10.5 Hz, 0.3H, *E*), 1.48 –

Experimental Part

1.41 (m, 0.7H, *Z*), 1.39 – 1.32 (m, 0.3H, *E*).

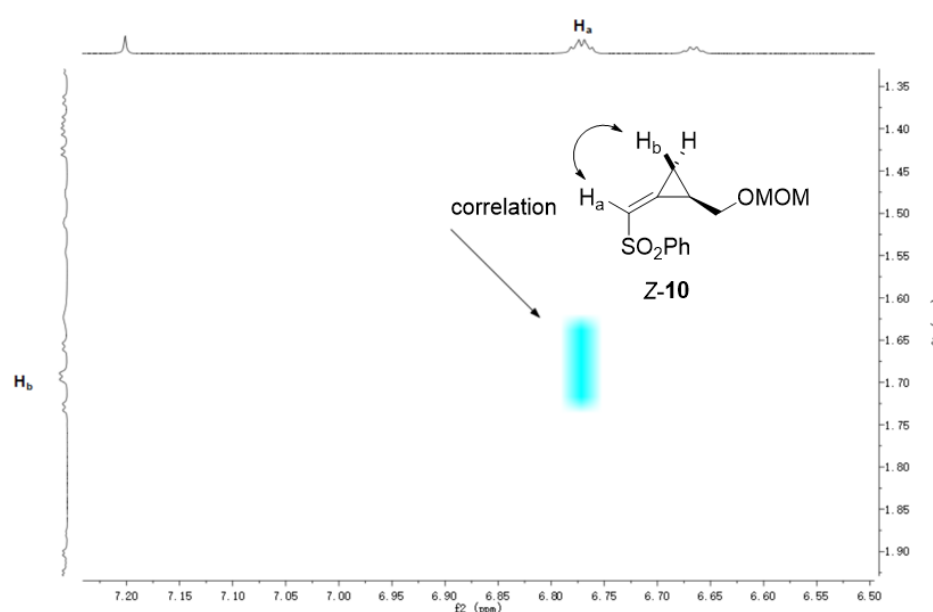
^{13}C NMR (75.5 MHz, CDCl_3) δ 143.7 (*Z*), 143.4 (*E*), 141.1 (*Z*), 140.7 (*E*), 133.8 (*E*), 133.5 (*Z*), 129.5 (*E*), 129.4 (*Z*), 127.8 (*Z*), 127.6 (*E*), 122.1 (*E*), 121.9 (*Z*), 95.1 (*E*), 95.0 (*Z*), 68.5 (*Z*), 68.0 (*E*), 64.5 (*E*), 63.6 (*Z*), 17.8 (*Z*), 15.3 (*E*), 10.2 (*E*), 9.9 (*Z*).

HRMS (AP^+) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 291.0667, found: 291.0675 ($\Delta 2.7$ ppm).

IR (Neat) 2926, 2852, 1700, 1585, 1394, 1162, 1139, 1067, 737, 535 cm^{-1} .

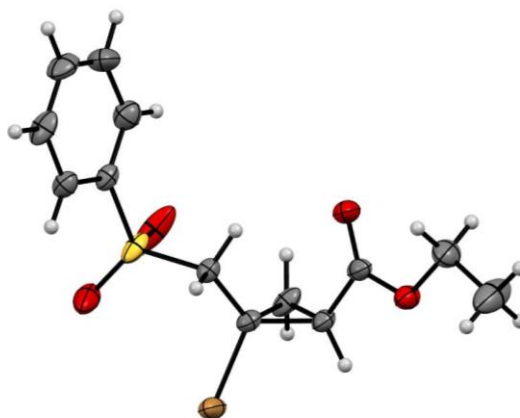
$[\alpha]_{\text{D}}^{20} = -5.5$ ($c = 1.0$, CHCl_3).

10 2D-Noesy NMR (CDCl_3)[⊖]



5. Crystallographic data for compounds *trans*-3g, *cis*-3g and *trans*-3i

Compound *trans*-3g

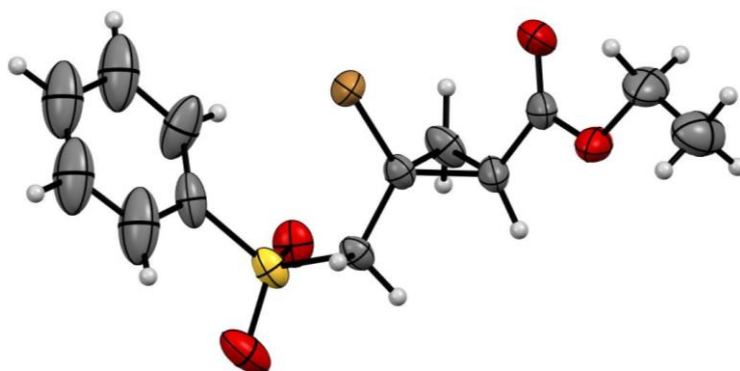


Displacement ellipsoids drawn at the 50% probability level

Experimental Part

Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of Et₂O and Petroleum Ether solution. X-ray diffraction experiments for monocrystal of *trans*-**3g** were performed at 150 K with graphite-monochromatized Mo K_α radiation ($\lambda = 0.71073 \text{ \AA}$) on a Bruker D8 QUEST diffractometer. Formula C₁₃H₁₅BrO₄S, formula weight 347.22. Crystal system orthorhombic, space group $P 2_1 2_1 2_1$, $a = 5.2424(3) \text{ \AA}$, $b = 9.1355(6) \text{ \AA}$, $c = 30.233(2) \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, $V = 1447.92(16) \text{ \AA}^3$, $Z = 4$, calculated density = 1.593 g/cm³, $m = 2.989 \text{ mm}^{-1}$, $R_{\text{int}} = 0.056$, $R[F^2 > 2s(F^2)] = 0.038$, $wR(F^2) = 0.072$. Independent reflections = 3175. GOF=1.089, 173 parameters, final difference map within 0.583 and -0.721 e \AA^{-3} . The structure was solved using direct methods and refined by full-matrix least-squares analysis on F^2 . Selected bond lengths (\AA) and angles (deg): C1-Br1 1.926(4), C1-C3 1.484(6), C1-C2 1.516(5), C2-C3 1.510(6), S1-O3 1.431(4), S1-O4 1.432(4), C3-C1-C2 60.4(3). Program(s) used to solve structure: SHELXT2014/5 (Sheldrick 2015). Program(s) used to refine structure: SHELXL-2019/1 (Sheldrick, 2019). Software used to prepare material for publication: SHELXTL. CCDC 2261664 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Compound *cis*-**3g**

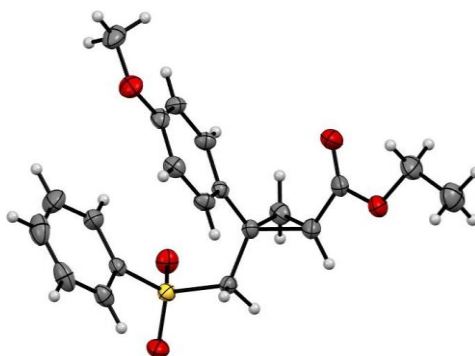


Displacement ellipsoids drawn at the 50% probability level

Experimental Part

Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of Et₂O and Petroleum Ether solution. X-ray diffraction experiments for monocrystal of *cis*-**3g** were performed at 150 K with graphite-monochromatized Mo K_α radiation ($\lambda = 0.71073 \text{ \AA}$) on a Bruker D8 QUEST diffractometer. Formula C₁₃H₁₅BrO₄S, formula weight 347.22. Crystal system monoclinic, space group *P* 2₁/*c*, $a = 5.3680(5) \text{ \AA}$, $b = 9.9781(8) \text{ \AA}$, $c = 13.7010(14) \text{ \AA}$, $\beta = 93.878(4)^\circ$, $V = 732.18(12) \text{ \AA}^3$, $Z = 2$, calculated density = 1.575 g/cm³, $m = 2.956 \text{ mm}^{-1}$, $R_{\text{int}} = 0.059$, $R[F^2 > 2s(F^2)] = 0.050$, $wR(F^2) = 0.139$. Independent reflections = 5506. GOF=1.060, 527 parameters, final difference map within 0.861 and -0.887 e \AA^{-3} . The structure was solved using direct methods and refined by full-matrix least-squares analysis on F^2 . Selected bond lengths (\AA) and angles (deg): C1-Br1 1.931(4), C1-C3 1.523(6), C1-C2 1.493(6), C2-C3 1.499(8), S1-O3 1.438(4), S1-O4 1.437(4), C3-C1-C2 59.6(3). Program(s) used to solve structure: SHELXT2014/5 (Sheldrick 2015). Program(s) used to refine structure: SHELXL-2019/1 (Sheldrick, 2019). Software used to prepare material for publication: SHELXTL. CCDC 2261665 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Compound *trans*-**3i**



Displacement ellipsoids drawn at the 50% probability level

Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of CHCl₃ and Hexane solution. X-ray diffraction experiments for monocrystal of *trans*-**3i** were

Experimental Part

performed at 150 K with graphite-monochromatized Mo K_α radiation ($\lambda = 0.71073 \text{ \AA}$) on a Bruker D8 QUEST diffractometer. Formula C₂₀H₂₂O₅S, formula weight 374.43. Crystal system monoclinic, space group $P 2_1$, $a = 10.9751 (16) \text{ \AA}$, $b = 5.7774(10) \text{ \AA}$, $c = 15.697(3) \text{ \AA}$, $\beta = 109.482(5)^\circ$, $V = 938.3(3) \text{ \AA}^3$, $Z = 2$, calculated density = 1.325 g/cm³, $m = 0.200 \text{ mm}^{-1}$, $R_{\text{int}} = 0.056$, $R[F^2 > 2s(F^2)] = 0.037$, $wR(F^2) = 0.088$. Independent reflections = 4803. GOF=1.055, 237 parameters, final difference map within 0.243 and -0.217 e \AA^{-3} . The structure was solved using direct methods and refined by full-matrix least-squares analysis on F^2 . Selected bond lengths (\AA) and angles (deg): C2-C1 1.545(3), C2-C3 1.507(4), C3-C1 1.495(3), S1-O3 1.4402(17), S1-O2 1.4419(18), C3-C1-C2 59.40(16). Program(s) used to solve structure: SHELXT2014/5 (Sheldrick 2015). Program(s) used to refine structure: SHELXL-2019/1 (Sheldrick, 2019). Software used to prepare material for publication: SHELXTL. CCDC 2261663 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

6. General Computational Details

The computational protocol reported by Mendoza, Himo, and co-workers was used.²⁷¹ The geometry optimizations were performed using the Gaussian 16 software package²⁷² with the B3LYP density functional,²⁷³ in combination with the 6-31G(d,p) basis set²⁷⁴ for all atoms except

²⁷¹ F. Planas, M. Costantini, M. Montesinos-Magraner, F. Himo, A. Mendoza, *ACS Catal.* **2021**, *11*, 10950–10963.

²⁷² Gaussian 16, Revision C.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

²⁷³ A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648.

²⁷⁴ a) J. Hehre, W.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, *28*, 213.

Experimental Part

ruthenium, for which LANL2DZ basis set and related pseudopotential were applied.²⁷⁵ The Grimme dispersion correction using the original D3 damping function (D3(BJ)) was applied during the geometry optimizations.²⁷⁶ The structures were optimized in the gas phase. Harmonic vibrational frequencies were computed for all optimized structures to verify that they were either minima or transition states, possessing zero or one imaginary frequency, respectively. The free energies were calculated from the unscaled harmonic vibrational frequencies. The final Gibbs energies were computed using the compound model described below:

$$G_{\text{Final}} = E_{\text{TZ}} + (E_{\text{PCM}} - E_{\text{GP}}) + G_{\text{corr}} + 1.89 \text{ kcal/mol}$$

E_{GP} : Electronic energy computed with the B3LYP-D3(BJ) functional and the 6-31G(d,p) basis set for all atoms except ruthenium, for which LANL2DZ and corresponding ECP were used.

E_{PCM} : Single-point electronic energy computed at the same theory model as E_{GP} , including PCM implicit solvation model²⁷⁷ for dichloromethane.

E_{TZ} : Single-point electronic energy computed with the B3LYP-D3(BJ) functional and triple-zeta basis sets: the 6-311+G(2d,2p) basis set for all atoms except ruthenium, for which LANL2TZ and corresponding ECP were used.²⁷⁸

G_{corr} : Thermal correction to Gibbs free energy calculated at the same level of theory as the geometry optimization, and using the unscaled harmonic vibrational frequencies, as implemented in Gaussian 16.

The free energies were corrected to a 1M standard state at 298.15K using a **+1.89 kcal/mol**

²⁷⁵ a) W. R. Wadt, P. J. Hay, *J. Chem. Phys.* **1985**, *82*, 284–298. b) C. E. Check, T. O. Faust, J. M. Bailey, B. J. Wright, T. M. Gilbert, L. S. Sunderlin, *J. Phys. Chem. A* **2001**, *105*, 8111.

²⁷⁶ S. Grimme, S. Ehrlich, L. Goerigk, *J. Comp. Chem.* **2011**, *32*, 1456.

²⁷⁷ G. Scalmani, M. J. Frisch, *J. Chem. Phys.* **2010**, *132*, 114110.

²⁷⁸ L. E. Roy, J. Hay, R. L. Martin, *J. Chem. Theory Comput.* **2008**, *4*, 1029.

Experimental Part

correction. It was added to the energies of all species except the dinitrogen (N₂) molecule.

The structures of the optimized geometries are provided as a zip file (Optimized_Structures.zip)

Table S1. Computed energetic values for propene.

Filename	E _{GP}	E _{PCM}	E _{TZ}	i _{Freq} (cm ⁻¹)	G _{corr}	G _{final}	ΔG _{rel} ^a
Catalyst_I	-1333.77725	-1333.82995	-1334.14484	0	0.35269	-1333.84184	
MDA_MethylDiazoAcetate	-376.63572	-376.64118	-376.76405	0	0.04499	-376.72151	
N2_Dinitrogen	-109.52147	-109.52184	-109.56372	0	-0.01285	-109.57693	
Propene_Sub_H-CH3	-117.92205	-117.92300	-117.95940	0	0.05485	-117.90550	
2FluoroPropene_Sub_F-CH3	-217.15764	-217.15942	-217.23576	0	0.04576	-217.19178	
2ChloroPropene_Sub_Cl-CH3	-577.52010	-577.52219	-577.59104	0	0.04340	-577.54973	
2BromoPropene_Sub_Br-CH3	-2688.73109	-2688.73317	-2691.50559	0	0.04174	-2691.46592	
Styrene_Sub_H-Ph	-309.68170	-309.68433	-309.77086	0	0.10201	-309.66846	
Alkene_1d_Sub_Cl-CH2Cl	-1037.10777	-1037.11206	-1037.21316	0	0.03223	-1037.18221	
ACN_Acetonitrile	-132.76040	-132.76709	-132.80497	0	0.02143	-132.78722	
Apsyn_Int1	-1468.13957	-1468.19185	-1468.55045	0	0.37137	-1468.22835	0.0(-18.3)
Apsyn_TS1_H-CH3	-1453.28656	-1453.34137	-1453.68811	1(-190.3)	0.41299	-1453.32993	10.5
Apsyn_Int2_H-CH3	-1453.29246	-1453.34743	-1453.69284	0	0.41415	-1453.33366	8.1
Apsyn_TS2_H-CH3	-1453.26851	-1453.32330	-1453.66930	1(-164.5)	0.41529	-1453.30880	23.7
Apsyn_TS-OS_H-CH3	-1586.06865	-1586.12029	-1586.50996	1(-312.3)	0.45284	-1586.10876	15.7

^a The relative Gibbs energies (ΔG_{rel}) are reported in kcal/mol. The value in parentheses is relative to the reference compounds. All other values are relative to the reported **Int1**.

Experimental Part

Table S2. Computed energetic values for the 2-halopropene series.

Filename	E _{GP} (Ha)	E _{PCM} (Ha)	E _{TZ} (Ha)	i _{Freq} (cm ⁻¹)	G _{corr} (Ha)	G _{final} (Ha)	ΔG _{rel} ^a
Apsyn_Int1	-1468.13957	-1468.19185	-1468.55045	0	0.37137	-1468.22835	0.0(-18.3)
Apsyn_TS1_F-CH3	-1552.52033	-1552.57513	-1552.95964	1(-161.0)	0.40411	-1552.61033	14.2
Apsyn_Int2_F-CH3	-1552.53205	-1552.58706	-1552.97045	0	0.40545	-1552.62001	8.1
Apsyn_TS2_F-CH3	-1552.50858	-1552.56355	-1552.94823	1(-158.8)	0.40754	-1552.59567	23.4
Apsyn_Int3_F-CH3	-1552.51912	-1552.57306	-1552.95987	0	0.40696	-1552.60685	16.3
Apsyn_TS3_F-CH3	-1552.51886	-1552.57276	-1552.95841	1(-93.4)	0.40796	-1552.60435	17.9
Apsyn_TS-OS_F-CH3	-1685.30852	-1685.35994	-1685.78872	1(-274.2)	0.44306	-1685.39709	14.5
Apsyn_TS1_Cl-CH3	-1912.87920	-1912.93378	-1913.31486	1(-127.5)	0.40287	-1912.96657	15.2
Apsyn_Int2_Cl-CH3	-1912.88826	-1912.94298	-1913.32276	0	0.40412	-1912.97336	11.0
Apsyn_TS2_Cl-CH3	-1912.86936	-1912.92434	-1913.30461	1(-139.2)	0.40599	-1912.95361	23.4
Apsyn_Int3_Cl-CH3	-1912.88195	-1912.93579	-1913.31809	0	0.40639	-1912.96554	15.9
Apsyn_TS3_Cl-CH3	-1912.88140	-1912.93490	-1913.31647	1(-106.2)	0.40657	-1912.96340	17.2
Apsyn_TS-OS_Cl-CH3	-2045.66907	-2045.72052	-2046.14488	1(-403.6)	0.44213	-2045.75420	15.0
Apsyn_TS1_Br-CH3	-4024.09247	-4024.14693	-4027.22985	1(-114.6)	0.40154	-4026.88278	15.2
Apsyn_Int2_Br-CH3	-4024.10121	-4024.15575	-4027.23726	0	0.40279	-4026.88901	11.3
Apsyn_TS2_Br-CH3	-4024.08300	-4024.13769	-4027.21979	1(-135.7)	0.40479	-4026.86969	23.4
Apsyn_Int3_Br-CH3	-4024.09576	-4024.14944	-4027.23351	0	0.40508	-4026.88212	15.6
Apsyn_TS3_Br-CH3	-4024.09518	-4024.14853	-4027.23182	1(-107.4)	0.40543	-4026.87973	17.1
Apsyn_TS-OS_Br-CH3	-4156.88198	-4156.93331	-4160.05976	1(-408.2)	0.44095	-4159.67014	15.1

^a The relative Gibbs energies (ΔG_{rel}) are reported in kcal/mol. The value in parentheses is relative to the reference compounds. All other values are relative to the reported **Int1**.

Experimental Part

Table S3. Computed energetic values for styrene.

Filename	E _{GP} (Ha)	E _{PCM} (Ha)	E _{TZ} (Ha)	i _{Freq} (cm ⁻¹)	G _{corr} (Ha)	G _{final} (Ha)	ΔG _{rel} ^a
Apsyn_Int1	-1468.13957	-1468.19185	-1468.55045	0	0.37137	-1468.22835	0.0(-18.3)
Apsyn_TS1_H-Ph	-1645.05437	-1645.10942	-1645.50613	1(-147.8)	0.46461	-1645.09356	10.1
Apsyn_Int2_H-Ph	-1645.06054	-1645.11585	-1645.51124	0	0.46596	-1645.09758	7.5
Apsyn_TS2_H-Ph	-1645.04059	-1645.09539	-1645.49197	1(-135.3)	0.46540	-1645.07835	19.6
Apsyn_TS-OS_H-Ph	-1777.84198	-1777.89200	-1778.33309	1(-296.7)	0.50347	-1777.87664	12.7

^a The relative Gibbs energies (ΔG_{rel}) are reported in kcal/mol. The value in parentheses is relative to the reference compounds. All other values are relative to the reported **Int1**.

Table S4. Computed energetic values for Alkene 1d.

Filename	E _{GP} (Ha)	E _{PCM} (Ha)	E _{TZ} (Ha)	i _{Freq} (cm ⁻¹)	G _{corr} (Ha)	G _{final} (Ha)	ΔG _{rel} ^a
Apsyn_Int1	-1468.13957	-1468.19185	-1468.55045	0	0.37137	-1468.22835	0.0(-18.3)
Apsyn_TS1_CI-CH2Cl	-2372.46696	-2372.52497	-2372.93751	1(-91.9)	0.39174	-2372.60078	14.2
Apsyn_Int2_CI-CH2Cl	-2372.47611	-2372.53376	-2372.94537	0	0.39316	-2372.60685	10.3
Apsyn_TS2_CI-CH2Cl	-2372.45951	-2372.51855	-2372.92942	1(-140.6)	0.39489	-2372.59056	20.6
Apsyn_Int3_CI-CH2Cl	-2372.47318	-2372.53130	-2372.94403	0	0.39518	-2372.60396	12.2
Apsyn_TS3_CI-CH2Cl	-2372.47238	-2372.52978	-2372.94212	1(-105.2)	0.39575	-2372.60077	14.2
Apsyn_TS-OS_CI-CH2Cl	-2505.25625	-2505.30858	-2505.76679	1(-421.2)	0.43191	-2505.38420	16.5
Apanti_Int1	-1468.14427	-1468.19798	-1468.55536	0	0.37194	-1468.23413	0.0(-21.9)
Apanti_TS1_CI-CH2Cl	-2372.46938	-2372.52486	-2372.93888	1(-123.5)	0.39319	-2372.59815	19.4
Apanti_Int2_CI-CH2Cl	-2372.48146	-2372.53599	-2372.94943	0	0.39495	-2372.60599	14.5
Apanti_Int3_CI-CH2Cl	-2372.47158	-2372.52863	-2372.94162	0	0.39833	-2372.59733	19.9

Experimental Part

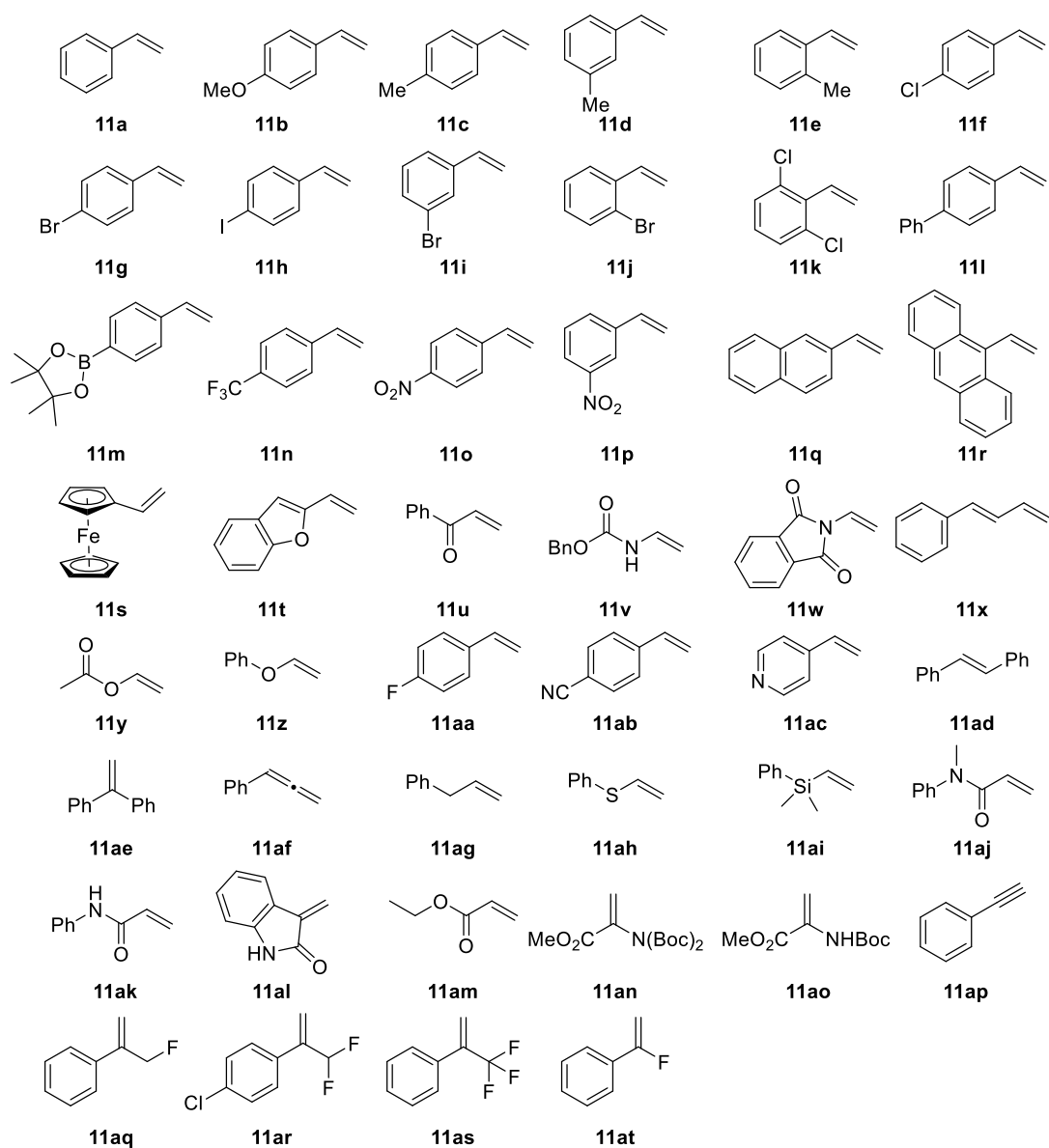
Apanti_TS3_CI-CH2Cl	-2372.47057	-2372.52705	-2372.93949	1(-106.5)	0.39790	-2372.59506	21.4
Apanti_TS-OS_CI-CH2Cl	-2505.25436	-2505.30670	-2505.76555	1(-410.2)	0.42931	-2505.38557	19.3
Eqtrans_Int1	-1468.13806	-1468.19214	-1468.55079	0	0.37460	-1468.22726	0.0(-17.6)
Eqtrans_TS1_CI-CH2Cl	-2372.46329	-2372.52207	-2372.93530	1(-111.2)	0.39281	-2372.59826	15.1
Eqtrans_Int2_CI-CH2Cl	-2372.47439	-2372.53201	-2372.94494	0	0.39384	-2372.60572	10.4
Eqtrans_Int3_CI-CH2Cl	-2372.47350	-2372.53020	-2372.94393	0	0.39879	-2372.59883	14.7
Eqtrans_TS3_CI-CH2Cl	-2372.47257	-2372.52864	-2372.94182	1(-109.0)	0.39897	-2372.59591	16.5
Eqtrans_TS-OS_CI-CH2Cl	-2505.24693	-2505.30234	-2505.75979	1(-407.6)	0.43074	-2505.38145	17.6

^a The relative Gibbs energies (ΔG_{rel}) are reported in kcal/mol. The values in parentheses are relative to the reference compounds (Table S1). All other values are relative to the reported **Int1**.

Chapter III – Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl α,α -difluoromethyl cyclopropanes

1. General procedures for the preparation of starting materials.

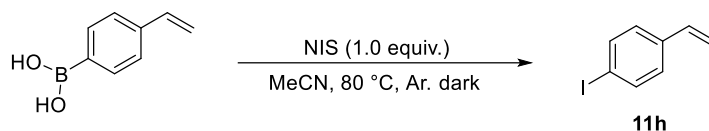
1.1. Synthesis of alkenes 11.



The alkenes starting material: **11a-11l, 11n, 11o, 11q, 11r, 11w, 11y-11ae, 11ag-11ai, 11am and 1ap** were commercially available.

Experimental Part

The alkenes starting material: **11h**,²⁷⁹ **11m**, **11p**²⁸⁰ and **11s**²⁸¹, **11t** and **11x**²⁸², **11u**,²⁸³ **1v**²⁸⁴, **11af**,²⁸⁵ **11aj**,²⁸³ **11ak**,²⁸⁶ **11al**,²⁸⁷ **11ao**,²⁸⁸ **11an**,²⁸⁹ **11aq-11as**,^{171d} and **11at**²⁹⁰ were synthesized according to reported literatures.



To a solution of 4-vinylphenylboronic acid (3 mmol, 444 mg, 1.0 equiv.) in dry acetonitrile (15 mL), N-iodosuccinimide (3.0 mmol, 675 mg, 1.0 equiv.) was added and the mixture was stirred at 80 °C protected from air and light until completion of the reaction was confirmed by TLC (silica gel, Pentane/ Ethyl acetate = 5:1). After the reaction was completed, the reaction mixture was extracted with pentane (3 x 20 mL). The collected hexane extracts were washed with distilled water, saturated aqueous solution of Na₂S₂O₃ (20 mL), saturated aqueous solution of NaHCO₃ (20 mL) and finally dried over MgSO₄. Filtration and evaporation of the solvent in vacuo gave final product **11m** as a light-yellow solid (391 mg, 57 %). The NMR spectra is consistent with reported literature.

²⁷⁹ H. Cao, H. Jiang, H. Feng, J. M. C. Kwan, X. Liu, J. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 16360–16367.

²⁸⁰ C.-P. Zhang, Z.-L. Wang, Q.-Y. Chen, C.-T. Zhang, Y.-C. Gu, J.-C. Xiao, *Chem. Commun.* **2011**, *47*, 6632–6634.

²⁸¹ X.-B. Yan, L. Li, W.-Q. Wu, L. Xu, K. Li, Y.-C. Liu, H. Shi, *Nat. Commun.* **2021**, *12*, 5881.

²⁸² N. Yasukawa, H. Yokoyama, M. Masuda, Y. Monguchi, H. Sajiki, Y. Sawama, *Green Chem.* **2018**, *20*, 1213–1217.

²⁸³ S. Chanthamath, S. Takaki, K. Shibatomi, S. Iwasa, *Angew. Chem. Int. Ed.* **2013**, *52*, 5818–5821.

²⁸⁴ S. Chanthamath, D. T. Nguyen, K. Shibatomi, S. Iwasa, *Org. Lett.* **2013**, *15*, 772–775.

²⁸⁵ X. Tao, C. G. Daniliuc, D. Dittrich, G. Kehr, G. Erker, *Angew. Chem. Int. Ed.* **2018**, *57*, 13922–13926.

²⁸⁶ V. R. Nascimento, M. L. S. Suenaga, L. H. Andrade, *Org. Biomol. Chem.* **2020**, *18*, 5458–5465.

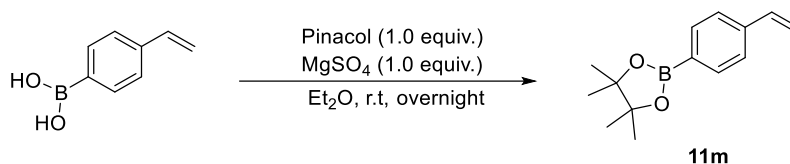
²⁸⁷ T. Watanabe, M. Arisawa, K. Narusuye, M. S. Alam, K. Yamamoto, M. Mitomi, Y. Ozoe, A. Nishida, *Biorg. Med. Chem.* **2009**, *17*, 94–110.

²⁸⁸ P. M. T. Ferreira, H. L. S. Maia, L. S. Monteiro and J. Sacramento, *J. Chem. Soc., Perkin Trans. 1*, **1999**, 3697–3703.

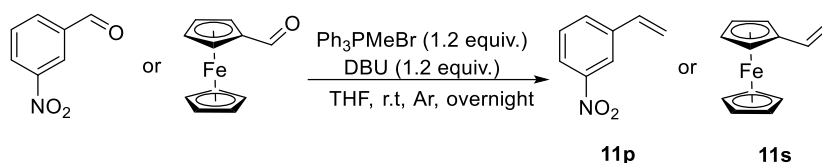
²⁸⁹ Natália O. Silva, Ana S. Abreu, Paula M. T. Ferreira, Luís S. Monteiro, M.-João R. P. Queiroz, *Eur. J. Org. Chem.* **2002**, *2002*, 2524–2528.

²⁹⁰ G. Zhang, J. D. McCorvy, S. Shen, J. Cheng, B. L. Roth, A. P. Kozikowski, *Eur. J. Med. Chem.* **2019**, *182*, 111626.

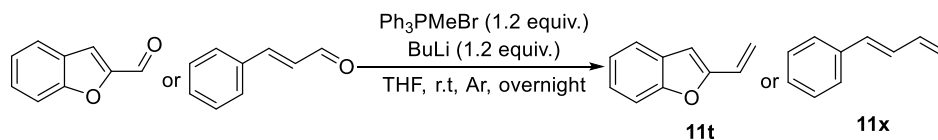
Experimental Part



(4-vinylphenyl)boronic acid (2.96 g, 20 mmol, 1.0 equiv.) was added to a solution of 2,3-dimethylbutane-2,3-diol (2.72 g, 20 mmol, 1.0 equiv.) and anhydrous MgSO_4 (2.4 g, 20 mmol, 1.0 equiv.) in Et_2O (0.2 M) at room temperature and then stirred overnight. Next, the reaction mixture was filtered, and concentrated on a rotary evaporator. The residue was purified by flash column chromatography on silica gel (hexane/ ethyl acetate 20:1) to give the product **11m** as a white solid (4.04 g, 88 %). The NMR spectra is consistent with reported literature.



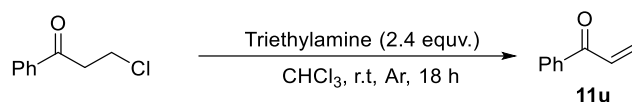
Aldehyde (5.0 mmol, 1.0 equiv.) was dissolved in dry THF (30 mL). Methyltriphenylphosphonium bromide (2.14 g, 6.0 mmol, 1.2 equiv.) and DBU (912 mg, 6.0 mmol, 1.2 equiv.) were added. The reaction mixture was then stirred at room temperature overnight. After diluted by ethyl ether (30 mL), the reaction mixture was washed with water (3×30 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent: petroleum ether/ethyl acetate 12:1), providing alkene **11p** as yellow liquid (548 mg, 74%) or **11s** as a brown solid (1.02 g, 96%). The NMR spectra is consistent with reported literature.



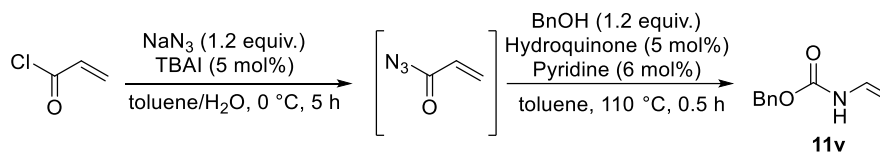
To a suspension of methyltriphenylphosphonium bromide (1.79 g, 5.0 mmol, 1.0 equiv.) in THF (25 mL) was added *n*-BuLi (2.5 M in *n*-hexane, 2.0 mL, 3.6 mmol, 1.0 equiv.) at 0 °C under argon. After stirring for 15min, an aldehyde derivative (5.0 mmol, 1.0 equiv.) was added. The reaction mixture was warmed to room temperature and the progress of the reaction was monitored by TLC. After the reaction was completed, the reaction mixture was quenched with sat. NH_4Cl aq. (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO_4 , and

Experimental Part

concentrated in vacuo. The residue was purified by silica-gel column chromatography to give corresponding product **11t** (309 mg, 43%, colorless oil) or **11x** (620 mg, 95%, colorless oil). The NMR spectra is consistent with reported literature.

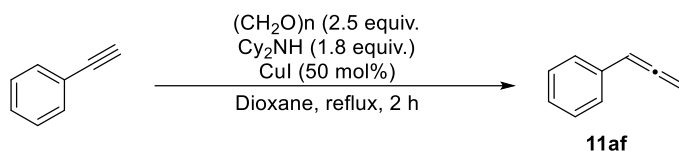


To a stirred solution of 3-chloropropiophenone (3.4 g, 20.0 mmol, 1.0 equiv.) in chloroform (60 mL) was added dropwise triethyl amine (6.4 mL, 48 mmol, 2.4 equiv.) for 5 min under atmosphere of argon. The reaction mixture was stirred during 18 h followed by washing with 1 N HCl aq. (2×20 mL), distilled water (2×40 mL), saturated NaHCO₃ aq. (2 x 30 mL), and brine (30 mL). The organic layer was dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/petroleum ether 5:95) to give corresponding product **11u** as colorless oil (2.4 g, 91%). The NMR spectra is consistent with reported literature.

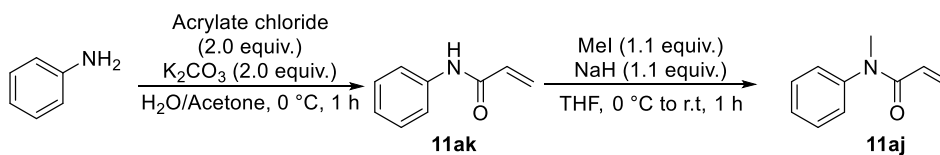


The mixture of acryloyl chloride (450 mg, 5.0 mmol, 1.0 equiv.) and tert-butyl ammonium iodide (TBAI) (92.5 mg, 0.025 mmol, 5 mol%) in toluene (2.5 mL), was added dropwise to cooled (0 °C) solution of sodium azide (390 mg, 6.0 mmol, 1.2 equiv.) in 5 mL of water. After finishing dropwise, the mixture was stirred at 0 °C for 5 h. The organic layer was separated and washed with 10.0 mL of toluene. The organic solution was dried over Na₂SO₄ before use in the subsequent step. The toluene solution of acryloyl azide was added dropwise to a stirred and heated to 100 °C mixture of hydroquinone (27.5 mg, 0.025 5 mol%), pyridine (24.5 μL, 0.3 mmol, 6 mol%), and benzyl alcohol (625 μL, 6.0 mmol, 1.2 equiv.). The mixture was stirred for 0.5 hour at 110 °C after completion of addition, and then the toluene was removed by rotary evaporation. The residue was isolated by silica gel column chromatography (EtOAc/petroleum ether 25:75) to give a colorless solid product **11v** (584 mg, 66%). The NMR spectra is consistent with reported literature.

Experimental Part



$(\text{CH}_2\text{O})_n$ (0.85 mL, 25 mmol, 2.5 equiv.), CuI (0.95 g, 5 mmol, 50 mol%), dioxane (50 mL), phenylacetylene (1.02 g, 10 mmol, 1.0 equiv.) and Cy_2NH (3.3 g, 18 mmol, 1.8 equiv.) were mixed sequentially into an oven-dried reaction tube equipped with a reflux condenser under an Argon atmosphere. The resulting mixture was stirred under reflux. After ca. 2h the reaction was complete as monitored by TLC, the reaction mixture was cooled down to room temperature. Water (50 mL) and ether (100 mL) were added to the resulting reaction mixture. The aqueous solution was separated and extracted with ether (3×50 mL). The organic layer was then washed with brine and dried over anhydrous Na_2SO_4 . Evaporation and column chromatography on silica gel (eluent: pentane) gave the corresponding phenylallene **11af** (647 mg, 56%) as pale-yellow liquid. The NMR spectra is consistent with reported literature.



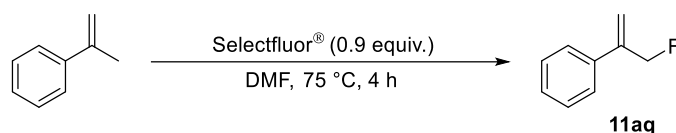
To a stirred suspension of potassium carbonate (1.38 g, 10.0 mmol, 2.0 equiv.) in distilled water (2.5 mL) and acetone (10 mL) was added acryloyl chloride (0.91 g, 10.0 mmol, 2.0 equiv.) at 0 °C under atmosphere of argon. Aniline (455 μL , 50.0 mmol, 1.0 equiv.) was then added dropwise to the mixture, and stirred for 1 h at 0 °C. After filtration, the mixture was concentrated under reduced pressure and extracted three times with dichloromethane (3×10 mL). The organic layer was dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/pentane 50:50) to give corresponding product **11ak** (623 mg, 85%) as white solid. The NMR spectra is consistent with reported literature.

A two-neck round-bottom flask (10 mL) containing a magnetic stirrer bar was charged with acrylamide **11ak** (294 mg, 2.0 mmol, 1.0 equiv.) and anhydrous THF (20 mL) under nitrogen atmosphere. Sodium hydride 60% (88 mg, 2.2 mmol, 1.1 equiv.) was added in portions with stirring at 0 °C. The mixture was stirred for an additional 15 min. Then, iodomethane (137 μL , 2.2 mmol, 1.1 equiv.) was added dropwise at 0 °C, and the mixture was stirred at room temperature for 1 h.

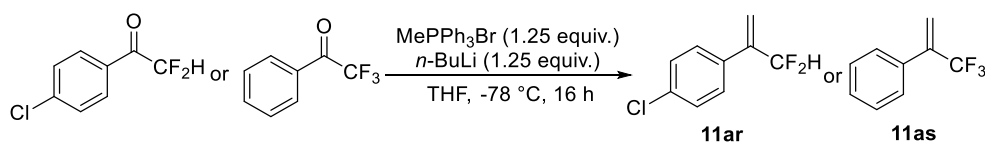
Experimental Part

gave a residue that was partitioned between 200 mL of diethyl ether and 100 mL of KHSO_4 (1 M). The organic phase was thoroughly washed with 50 mL KHSO_4 (1 M), 50 mL NaHCO_3 (1 M) and saturated brine (3×50 mL), and dried over MgSO_4 . Removal of the solvent afforded pure **11an** as white solid. The NMR spectra is consistent with reported literature.

Compound **11an** was dissolved in dichloromethane (0.1 M) and 2% of TFA was added slowly with vigorous stirring. The reaction was monitored by TLC and when no starting material was detected (ca. 1 hour) an additional 50 mL of dichloromethane was added. The organic phase was then washed with NaHCO_3 (1 M) and brine (3×30 mL each). After drying over MgSO_4 the extract was taken to dryness at reduced pressure to afford crude product. Crystallization of the latter from diethyl ether/*n*-hexane gave the pure **11ao** as a white solid. The NMR spectra is consistent with reported literature.



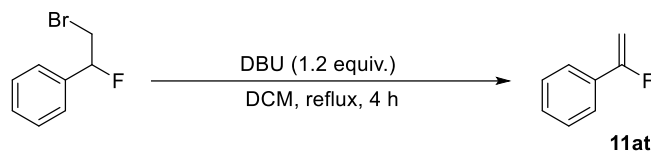
Selectfluor[®] (3.2 g, 9 mmol, 0.9 equiv.) was dissolved in DMF (10 mL) and α -methyl styrene (1.2 g, 10 mmol, 1 equiv.) was added at room temperature under argon atmosphere. The solution was heated at 75 °C for 4 hours. After water (150 mL) was added and the mixture was cooled down to room temperature. The aqueous layer was extracted with pentane (3×80 mL), dried over Na_2SO_4 , concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford the α -(fluoromethyl)styrene **11aq** (789 mg, 58%) as colorless oil. The NMR spectra is consistent with reported literature.



$n\text{-BuLi}$ 2.5 M in hexanes (12 mmol, 1.2 equiv.) was added slowly to a solution of methyltriphenylphosphonium bromide (13 mmol, 1.25 equiv.) in distilled THF (30 mL) at 0 °C under argon atmosphere. The mixture was stirred for 20 min and cooled at -78 °C. Then a solution of difluoro or trifluoro ketone (10 mmol, 1.0 equiv.) in distilled THF (10 mL) was slowly added. The mixture was stirred for 1 h at -78 °C and allowed then to warm to room temperature. After 15

Experimental Part

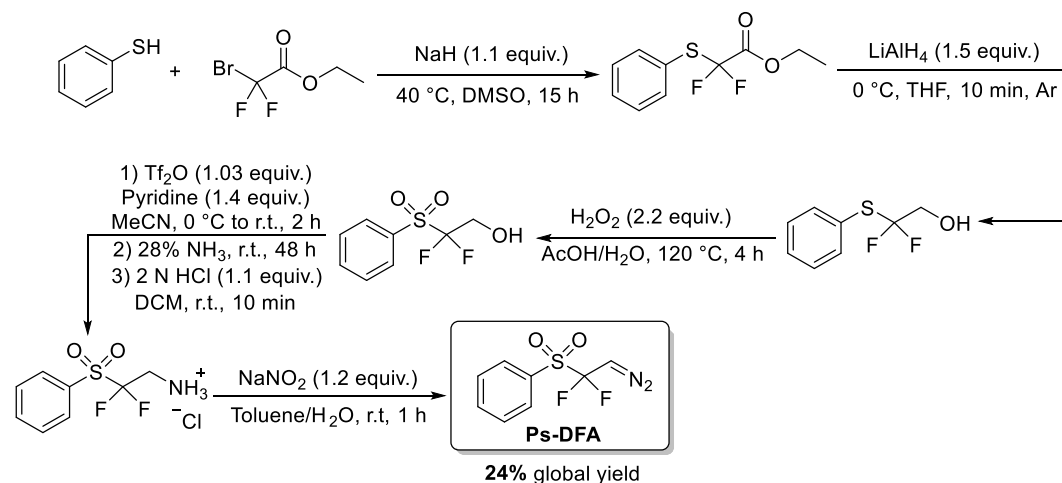
h, the reaction was quenched with NH_4Cl (20 mL), extracted with Et_2O ($3 \times 50\text{mL}$), dried over Na_2SO_4 , filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (pentane) to afford the desired styrene **11ar** (1.18 g, 63%) as colorless oil or **11as** (0.98 g, 57%) as colorless oil. The NMR spectra is consistent with reported literature.



To a solution of the bromofluoride (10 mmol, 1.0 equiv.) in CH_2Cl_2 (1.0 mol/L) Add DBU (12 mmol, 1.2 equiv.) at room temperature. The reaction mixture was heated to reflux for 4 h then cooled to room temperature and partition between water and Et_2O . The organic layer was separated and aqueous layer was extracted with Et_2O ($3 \times 10\text{mL}$), combined the organic phases and washed t with 1N HCl (20 mL) and brine (20 mL), dry over Na_2SO_4 , and concentrate. The residue was purified by flash chromatography on silica gel (pentane) to afford the desired styrene **11at** (708 mg, 58%) as colorless oil. The NMR spectra is consistent with reported literature.

1.2. Synthesis of difluoroalkyl diazo compounds

Synthesis of Ps-DFA was according to reported literatures.^{291,199}



Step 1: In an oven-dried 250 mL one-necked round-bottom flask, a solution of thiophenol (5.50 mL, 50.0 mmol, 1.0 equiv.) in DMSO (50 mL) was prepared. Then, the suspension was heated at 40°C

²⁹¹ J. Zhang, J. Wu, L. Shen, G. Jin, S. Cao, *Adv. Synth. Catal.* **2011**, 353, 580–584.

Experimental Part

and stirred for 1 h under an Ar atmosphere. Then, ethyl bromodifluoroacetate (7.10 mL, 55.0 mmol, 1.10 equiv.) was added to the suspension and was stirred in the same conditions for 15h. After this time, the reaction mixture was allowed to reach room temperature, quenched with aqueous 1 M HCl (25 mL), and extracted with Et₂O (4×50 mL). Organic layers were combined and washed successively with H₂O (3×50 mL) and brine (50 mL), dried over MgSO₄, filtered, and evaporated under reduced pressure, affording a yellow crude liquid. Ethyl 2,2-difluoro-2-(phenylthio)acetate was obtained as a pale-yellow liquid after purification by flash column chromatography (Pentane/EtOAc, 100:0 to 98:2).

Step 2: To a solution of Ethyl 2,2-difluoro-2-(phenylthio)acetate (8.72 g, 37.6 mmol, 1.0 equiv.) in THF (50 mL) was added LiAlH₄ (2.14 g, 56.4mmol, 1.5 equiv.) in portion at 0 °C. The resulting suspension was stirred at this temperature for 10 min and carefully quenched with H₂O (20 mL). Then, the reaction mixture was extracted with Et₂O (3×50 mL). The organic layers were recombined, washed with brine (50mL), and dried over MgSO₄. Finally, the solvent was removed under reduced pressure affording 2,2-difluoro-2-(phenylthio)ethan-1-ol as a pale-yellow liquid, this product was used in the next step without further purification.

Step 3: To a solution of 2,2-difluoro-2-(phenylthio)ethan-1-ol (6.2 g, 32.6 mmol, 1.0 equiv.) in a 1:1 mixture of AcOH/ H₂O (56 mL) was added dropwise 7.8 mL aq. 30% H₂O₂. The reaction mixture was heated at 120 °C and stirred under an Ar atmosphere for 4 h. Then, the reaction mixture was allowed to reach room temperature, quenched with saturated NaHCO₃ (30 mL), and extracted with EtOAc (3×40 mL). The organic extracts were recombined, washed with brine (60 mL), dried over MgSO₄ and filtered, the solvent was removed under reduced pressure, affording 2,2-difluoro-2-(phenylsulfonyl)ethan-1-ol as a yellowish solid, which was used in the next step without further purification.

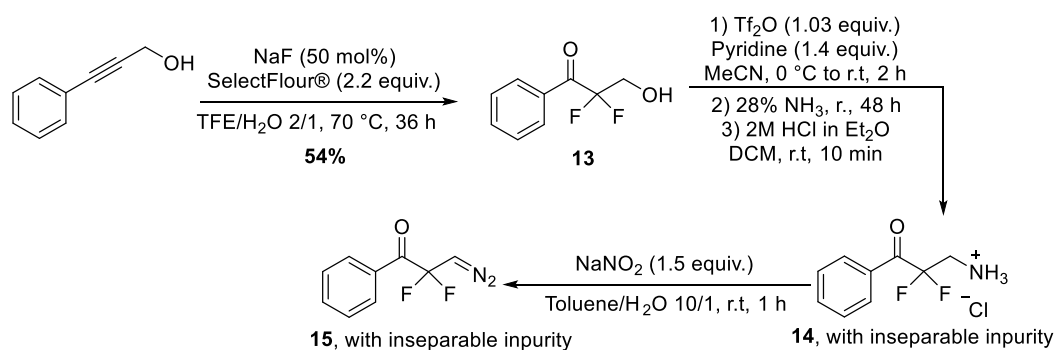
Step 4: Pyridine (3.3 mL, 41.1mmol, 1.4 equiv.) was added to a solution of 2,2-difluoro-2-(phenylsulfonyl)ethan-1-ol (6.53 mg, 29.4 mmol, 1.0 equiv.) in anhydrous MeCN (50 mL), and the reaction mixture was cooled to 0 °C. Subsequently, Tf₂O (6.4 g, 30.5 mmol, 1.03 equiv.) was added dropwise, and the reaction mixture was stirred at 0 °C for 30 min under an Ar atmosphere. Then, the solution was allowed to reach room temperature and stirred for 2 h, and then 20 mL NH₃•H₂O (28%~30%) was added. The reaction mixture was stirred for 48 h at room temperature, then quenched with H₂O (50 mL), and extracted with DCM (3×50mL). The organic layers were

Experimental Part

recombined, washed with brine (60 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure, affording a brown residue, which was dissolved in DCM (10 mL). Then, a solution of HCl (2 N) in Et₂O (16 mL, 1.1 equiv.) was added, and the resulting solution was stirred for 10 min. The red solid was filtered out and washed with Et₂O (3×15 mL), affording 2,2-difluoro-2-(phenylsulfonyl)ethan-1-aminium chloride as a brown solid.

Step 5: To a solution of 2,2-difluoro-2-(phenylsulfonyl)ethan-1-aminium chloride (3.0 g, 11.7 mmol, 1.0 equiv.) in a mixture of toluene (20 mL) and H₂O (2 mL) was added NaNO₂ (969 mg, 14.0 mmol, 1.2 equiv.). The resulting yellow solution was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc (3×20 mL), the organic layer was washed with brine (20 mL) and dried over MgSO₄, and the solvent was removed under reduced pressure, affording a yellow residue. Ps-DFA was obtained as a yellow oil (24% global yield) after purification by flash column chromatography (Pentane/ EtOAc, 100:0 to 80:20). The Ps-DFA compound was store at 0 °C with argon only for one week synthesis. The NMR spectra is consistent with reported literature.

Synthesis of **13** was according to reported literature.²⁹² Synthesis of **14** and **15** were following the procedures of Ps-DFA.

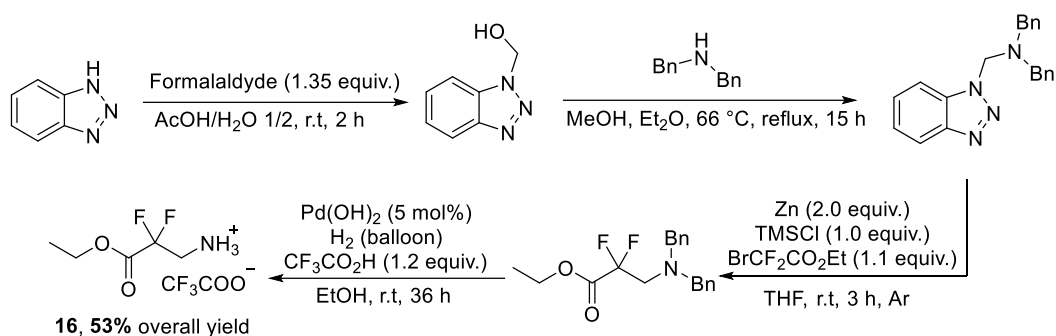


A solution of alkyne (1.32 g, 10 mmol, 1.0 equiv.), Selectfluor® (22 mmol, 2.2 equiv.), NaF (5.0 mmol, 0.5 equiv.), in CF₃CH₂OH/H₂O (2:1, 30 mL) were stirred at 70 °C for 36 h. After completion of the reaction, the solvent was removed under reduced pressure by rotary evaporation. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to obtain product **13** (1 g, 54%) as light-yellow oil. The NMR spectra is consistent with reported literature.

²⁹² C. Lin, Z. Lin, Z. Ye, L. Chen, Y. Li, C. Shen, M. Zhang, *Tetrahedron Lett.* **2022**, 154197.

Experimental Part

Synthesis of **16** was following the reported procedures.^{293,294}



Step 1: A mixture of benzotriazole (12 g, 100 mmol, 1.0 equiv.) and 37% formalin (10 mL) in 10 mL acetic acid and 10 mL water was allowed to stand at room temperature for 2 h. The product which had precipitated was dried and recrystallized from hot (not boiling) water to give 14.9 g of (1H-benzo[d][1,2,3]triazol-1-yl)methanol.

Step 2: To a solution of (1H-benzo[d][1,2,3]triazol-1-yl)methanol (14.9 g, 100 mmol, 1.1 equiv.) in MeOH (72 mL) and Et₂O (36 mL) was added dibenzyl amine (17.9 g, 90.9 mmol, 1.0 equiv.). The reaction was heated to reflux for overnight. Then, water (100 mL) was added to quench the reaction. The product precipitated and filtered out, washed with MeOH to afford *N*-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-*N*-benzyl-1-phenylmethanamine as white solid.

Step 3: To a suspension of zinc dust (3.22 g, 49.2 mmol, 2.0 equiv.) in dry THF (96 mL), stirred under argon atmosphere, was added chlorotrimethylsilane (3.14 mL, 24.6 mmol, 1.0 equiv.) followed, 10 min later, by ethyl bromodifluoroacetate (3.48 mL, 27.1 mmol, 1.1 equiv.). After 10 min, *N*-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)-*N*-benzyl-1-phenylmethanamine (8.08 g, 24.6 mmol, 1.0 equiv.) in THF (27.3 mL) was added dropwise. After 3 h at r.t, the mixture was poured on aque. 5% NaHCO₃ (100 mL) and filtered on Celite®. The layers were separated and the aqueous phase was extracted with EtOAc (3×50 mL). The organic layers were combined and washed with 1N HCl (80 mL), then dried over MgSO₄. After evaporation of the solvent, the residue was diluted in ether, the solid formed was removed by filtration and ether was evaporated. Distillation of the oil (pressure 3×10⁻³ mBar, temperature=115–120°C) give ethyl 3-(dibenzylamino)-2,2-

²⁹³ A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, L. Urogdi, *J. Chem. Soc., Perkin Trans. 1* **1989**, 225–233.

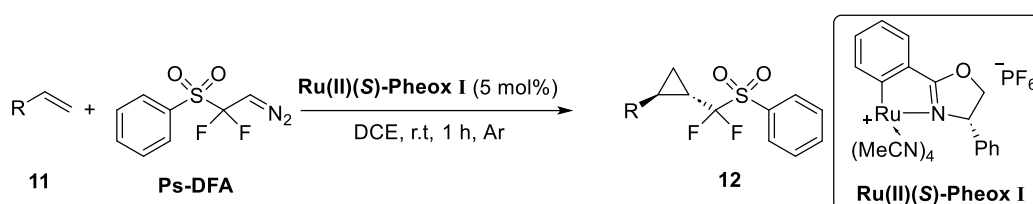
²⁹⁴ A. Cheguillaume, S. Lacroix, J. Marchand–Brynaert, *Tetrahedron Lett.* **2003**, 44, 2375–2377.

Experimental Part

difluoropropanoate.

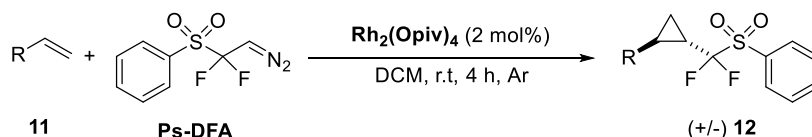
Step 4: To a solution of ethyl 3-(dibenzylamino)-2,2-difluoropropanoate (7.07 g, 21.23 mmol, 1.0 equiv.) in EtOH (28.3 mL) and trifluoroacetic acid (1.93 mL) was added Pd(OH)₂ (20 wt.% on carbon) (738 mg, 4.25 mmol, 5 mol%). After 36 h of stirring under H₂ atmosphere, the solution was filtered on Celite® and the solvent was evaporated to afford **16** (3.95 g, 53% overall yield) as a colorless oil. The NMR spectra is consistent with reported literature.

2. General procedure for producing enantiopure phenylsulfonyl difluoromethyl cyclopropanes **12**.



An oven-dried 10 mL reaction tube contained a stir bar, catalyst Ru(II)-Pheox I (0.005 mmol, 0.05 equiv.) which was stored in a glovebox was introduced to the reaction tube in this glovebox, followed by alkene substrates **11** (0.5 mmol, 5.0 equiv.) under argon atmosphere. Fresh distilled DCE 0.5 mL was added via a syringe. Diazo compound Ps-DFA (23.2 mg, 0.1 mmol, 1.0 equiv.) was dissolved in 1.0 mL fresh distilled DCE and added to the former solution with 1.0 mL/h rate by use of microinjection pump. When the addition finished, the completion of reaction was detected by TLC. The NMR yield and diastereomeric ratio were detected with ¹H NMR at the end of this reaction. The reaction mixture was evaporated under reduce pressure and purified by silica gel chromatography leading to the corresponding enantiopure cyclopropanes **12**.

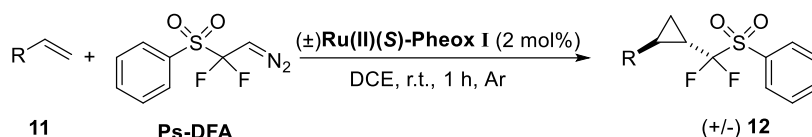
General procedures of produce racemic phenylsulfonyl difluoromethyl cyclopropanes



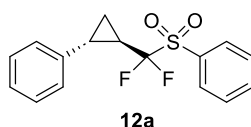
To an oven-dried 10 mL reaction tube contained a stir bar, Rh₂(Opiv)₄ (0.002 mmol, 0.02 equiv.) was introduced, followed by the alkene substrate **1** (0.2 mmol, 2.0 equiv.) under argon atmosphere. Freshly distilled DCM (0.5 mL) was added via a syringe. Diazo compound Ps-DFA (23.2 mg, 0.1

Experimental Part

mmol, 1.0 equiv.) was dissolved in 1.0 mL fresh distilled DCM and added to the former solution (0.25 mL/h) using a syringe pump at room temperature. After the addition of diazo compound finished, this solution was stirred at room temperature for another 1 h. The solution was then evaporated under reduce pressure and purified by silica gel chromatography leading to the corresponding racemic cyclopropanes **12a**, **12c**, **12d**, **12e**, **12f**, **12g**, **12h**, **12j**, **12k**, **12n**, **12o**, **12at**.



To an oven-dried 10 mL reaction tube contained a stir bar, (±)Ru(II)-Pheox I (0.002 mmol, 0.02 equiv.) was introduced, followed by the alkene substrate **1** (0.2 mmol, 2.0 equiv.) under argon atmosphere. Freshly distilled DCE (0.5 mL) was added via a syringe, and this solution was placed at 0 °C for 15 min. Diazo compound **Ps-DFA** (23.2 mg, 0.1 mmol, 1.0 equiv.) was dissolved in 1.0 mL fresh distilled DCE and added to the former solution (1.0 mL/h) using a syringe pump. After the addition of diazo compound finished, the solution was then evaporated under reduce pressure and purified by silica gel chromatography leading to the corresponding racemic cyclopropanes **12b**, **12i**, **12l**, **12m**, **12p**, **12q**, **12r**, **12s**, **12t**, **12u**, **12v**, **12w**, **12x**, **12y**, **12z**.



12a
(difluoro((1*R*,2*R*)-2-phenylcyclopropyl)methyl)sulfonylbenzene

12a. This cyclopropane was obtained using the general procedure, (22.6 mg, 74%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). $R_f = 0.43$ (Pentane/ Et₂O = 5:1). White solid. M.p. 74-76 °C. $[\alpha]_D^{20} = -116.5$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 96:4. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 8.2$ min, $t_R = 8.9$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.98 (d, $J = 7.8$ Hz, 2H), 7.80 – 7.72 (m, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.34 – 7.21 (m, 3H), 7.21 – 7.11 (m, 2H), 2.42 (ddd, $J = 9.6, 6.3, 5.0$ Hz, 1H), 2.06 – 1.88 (m, 1H), 1.47 – 1.39 (m, 1H), 1.37 – 1.27 (m, 1H).

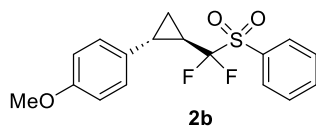
Experimental Part

^{13}C NMR (75.5 MHz, CDCl_3) δ 138.8, 135.4, 133.2, 130.8, 129.4, 128.7, 127.0, 126.9, 122.9 (t, $J = 283.9$ Hz), 20.0 (t, $J = 3.5$ Hz), 19.6 (t, $J = 23.9$ Hz), 10.9 (t, $J = 3.4$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -106.3 (d, $J = 13.4$ Hz).

HRMS (EI^+) calcd for $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 308.06826, found: 308.06748 (Δ -2.50 ppm).

IR (neat) 2963, 2926, 2856, 1336, 1163, 1073, 1005, 996, 711, 685, 598 cm^{-1} .



1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-methoxybenzene

12b. This cyclopropane was obtained using the general procedure, (25.4 mg, 75%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 95:5 to 90:10). $R_f = 0.25$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). White solid. M.p. 94-96 $^\circ\text{C}$. $[\alpha]_D^{20} = -106.2$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 94:6. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 19.2$ min, $t_R = 21.7$ min.

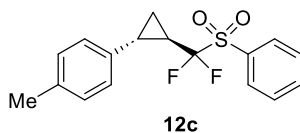
^1H NMR (300.1 MHz, CDCl_3) δ 7.99 (d, $J = 7.4$ Hz, 2H), 7.75 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.10 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 3.79 (s, 3H), 2.43 – 2.33 (m, 1H), 1.97 – 1.79 (m, 1H), 1.42 – 1.34 (m, 1H), 1.29 – 1.21 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 158.7, 135.3, 133.3, 130.8, 130.8, 129.4, 128.1, 123.0 (t, $J = 283.8$ Hz), 114.1, 55.5, 19.5 (dd, $J = 4.9, 2.2$ Hz), 19.3 (t, $J = 23.9$ Hz), 10.5 (dd, $J = 4.6, 2.0$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.6 (dd, $J = 228.5, 13.2$ Hz), -106.7 (dd, $J = 228.5, 13.7$ Hz).

HRMS (EI^+) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{O}_3\text{S}$ ($[\text{M}]^+$) 338.07882, found: 338.07954 (Δ 2.13 ppm).

IR (neat) 2966, 2925, 2861, 1516, 1330, 1249, 1107, 1029, 719, 588 cm^{-1} .



1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-methylbenzene

12c. This cyclopropane was obtained using the general procedure, (22.1 mg, 69%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.35$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). White solid. M.p. 77-79 $^\circ\text{C}$. $[\alpha]_D^{20} = -109.3$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel

Experimental Part

IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 7.6$ min, $t_R = 8.2$ min.

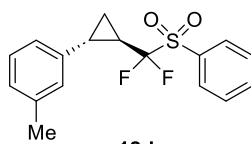
^1H NMR (300.1 MHz, CDCl_3) δ 7.99 (d, $J = 7.6$ Hz, 2H), 7.75 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.8$ Hz, 2H), 7.12 (d, $J = 8.1$ Hz, 2H), 7.05 (d, $J = 8.2$ Hz, 2H), 2.43 – 2.31 (m, 4H), 2.02 – 1.85 (m, 1H), 1.44 – 1.36 (m, 1H), 1.33 – 1.23 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 136.6, 135.7, 135.3, 133.3, 130.8, 129.4, 129.4, 126.8, 121.1 (t, $J = 283.8$ Hz), 21.2, 19.8 (dd, $J = 6.5, 3.2$ Hz), 19.5 (t, $J = 23.9$ Hz), 10.8 (t, $J = 3.5$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.8 (dd, $J = 228.4, 13.1$ Hz), -106.63 (dd, $J = 228.5, 13.3$ Hz).

HRMS (EI⁺) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 322.08391, found: 322.08262 (Δ -4.00 ppm).

IR (neat) 2963, 2925, 2860, 1336, 1161, 1074, 998, 811, 682, 597 cm^{-1} .



12d
1-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-3-methylbenzene

12d. This cyclopropane was obtained using the general procedure, (19.8 mg, 61%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.37$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Colorless oil. $[\alpha]^{20}_D = -97.3$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 7.4$ min, $t_R = 7.9$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.99 (d, $J = 7.4$ Hz, 2H), 7.75 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.19 (t, $J = 7.9$ Hz, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 7.1$ Hz, 2H), 2.43 – 2.31 (m, 4H), 2.06 – 1.88 (m, 1H), 1.45 – 1.37 (m, 1H), 1.35 – 1.26 (m, 1H).

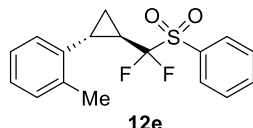
^{13}C NMR (75.5 MHz, CDCl_3) δ 138.7, 138.4, 135.3, 133.3, 130.8, 129.4, 128.6, 127.8, 127.6, 123.8, 122.9 (t, $J = 283.8$ Hz), 21.5, 19.9 (dd, $J = 4.7, 2.1$ Hz), 19.6 (t, $J = 23.9$ Hz), 11.0 (dd, $J = 4.8, 2.0$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.6 (dd, $J = 228.7, 13.1$ Hz), -106.8 (dd, $J = 228.7, 13.7$ Hz).

HRMS (EI⁺) calcd for $\text{C}_{17}\text{H}_{16}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 322.08391, found: 322.08380 (Δ -0.34 ppm).

IR (neat) 2964, 2924, 2861, 1336, 1167, 1085, 1009, 721, 685, 594 cm^{-1} .

Experimental Part



1-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-2-methylbenzene

12e. This cyclopropane was obtained using the general procedure, (22.6 mg, 70%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). R_f = 0.38 (Pentane/ Et₂O = 5:1). Colorless oil. $[\alpha]^{20}_D = -80.0$ (c = 1.0, CHCl₃).

Enantiomeric Ratio: 97:3. The enantiomeric ratio was determined by HPLC with a Chiralcel IE column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 15.7 min, t_R = 17.1 min.

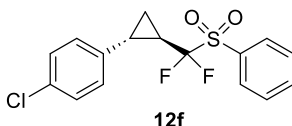
¹H NMR (300.1 MHz, CDCl₃) δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.21 – 7.12 (m, 3H), 7.11 – 7.04 (m, 1H), 2.49 – 2.36 (m, 4H), 2.08 – 1.91 (m, 1H), 1.47 – 1.39 (m, 1H), 1.32 – 1.23 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 138.0, 136.6, 135.4, 133.2, 130.8, 130.1, 129.4, 127.2, 126.2, 126.1, 123.2 (t, *J* = 283.8 Hz), 19.6, 18.4 (dd, *J* = 25.6, 22.5 Hz), 18.0 (dd, *J* = 5.3, 1.2 Hz), 10.4 (dd, *J* = 5.3, 1.4 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -102.1 (dd, *J* = 228.2, 10.1 Hz), -108.7 (dd, *J* = 228.2, 16.8 Hz).

HRMS (EI⁺) calcd for C₁₇H₁₆F₂O₂S ([M]⁺) 322.08391, found: 322.08557 (Δ5.17 ppm).

IR (neat) 2960, 2925, 2861, 1336, 1163, 1084, 1007, 717, 685, 583 cm⁻¹.



1-chloro-4-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzene

12f. This cyclopropane was obtained using the general procedure, (22.4 mg, 65%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). R_f = 0.36 (Pentane/ Et₂O = 5:1). Light yellow solid. M.p. 76-78 °C. $[\alpha]^{20}_D = -118.4$ (c = 1.0, CHCl₃).

Enantiomeric Ratio: 96:4. The enantiomeric ratio was determined by HPLC with a Chiralcel IE column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 20.1 min, t_R = 24.9 min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.98 (d, *J* = 7.7 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 2.47 – 2.36 (m, 1H), 2.02 – 1.84 (m, 1H), 1.48 – 1.40 (m, 1H), 1.33 – 1.24 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 137.3, 135.4, 133.1, 132.8, 130.8, 129.5, 128.8, 128.4, 122.7 (t, *J*

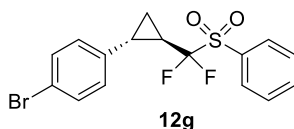
Experimental Part

= 284.1 Hz), 19.6 (dd, $J = 5.2, 2.0$ Hz), 19.6 (t, $J = 23.9$ Hz), 10.6 (dd, $J = 5.0, 1.5$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.4 (dd, $J = 228.8, 12.3$ Hz), -107.4 (dd, $J = 228.8, 14.1$ Hz).

HRMS (EI^+) calcd for $\text{C}_{16}\text{H}_{13}\text{ClF}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 342.02928, found: 342.02989 ($\Delta 1.77$ ppm).

IR (neat) 2963, 2922, 2852, 1338, 1162, 1074, 1007, 822, 685, 589 cm^{-1} .



1-bromo-4-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzene

12g. This cyclopropane was obtained using the general procedure, (24.8 mg, 64%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.36$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Light yellow solid. M.p. 85-86 °C. $[\alpha]_D^{20} = -113.7$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 97:3. The enantiomeric ratio was determined by HPLC with a Chiralcel IE column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 23.5$ min, $t_R = 29.3$ min.

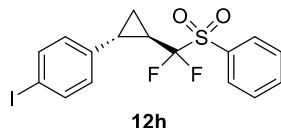
^1H NMR (300.1 MHz, CDCl_3) δ 7.98 (d, $J = 7.7$ Hz, 2H), 7.75 (d, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 7.05 (d, $J = 8.3$ Hz, 2H), 2.44 – 2.34 (m, 1H), 2.02 – 1.84 (m, 1H), 1.48 – 1.40 (m, 1H), 1.33 – 1.23 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 137.9, 135.4, 133.1, 131.8, 130.8, 129.5, 128.7, 122.7 (t, $J = 284.1$ Hz), 120.8, 19.7 (dd, $J = 5.7, 2.0$ Hz), 19.6 (t, $J = 23.9$ Hz), 10.6 (dd, $J = 5.1, 1.5$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.4 (dd, $J = 228.8, 12.4$ Hz), -107.4 (dd, $J = 228.8, 14.1$ Hz).

HRMS (EI^+) calcd for $\text{C}_{16}\text{H}_{13}\text{BrF}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 385.97877, found: 385.98026 ($\Delta 3.86$ ppm).

IR (neat) 2960, 2924, 2852, 1337, 1162, 1073, 1007, 818, 685, 587 cm^{-1} .



1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-iodobenzene

12h. This cyclopropane was obtained using the general procedure, (33.6 mg, 78%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.36$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Light yellow solid. M.p. 83-85 °C. $[\alpha]_D^{20} = -106.1$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 8.2$ min, $t_R = 9.2$ min.

Experimental Part

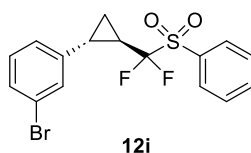
^1H NMR (300.1 MHz, CDCl_3) δ 7.98 (d, $J = 7.8$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.66 – 7.56 (m, 4H), 6.92 (d, $J = 8.2$ Hz, 2H), 2.43 – 2.32 (m, 1H), 2.02 – 1.84 (m, 1H), 1.48 – 1.40 (m, 1H), 1.31 – 1.24 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 138.6, 137.7, 135.4, 133.0, 130.8, 129.5, 129.0, 122.7 (t, $J = 284.1$ Hz), 92.1, 19.7 (dd, $J = 5.4, 1.8$ Hz), 19.6 (t, $J = 23.9$ Hz), 10.6 (d, $J = 5.0$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.5 (dd, $J = 228.8, 12.5$ Hz), -107.3 (dd, $J = 228.8, 14.0$ Hz).

HRMS (EI⁺) calcd for $\text{C}_{16}\text{H}_{13}\text{IF}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 433.96490, found: 433.96541 ($\Delta 1.18$ ppm).

IR (neat) 2962, 2924, 2855, 1336, 1161, 1074, 1004, 815, 684, 608, 583 cm^{-1} .



1-bromo-3-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzene

12i. This cyclopropane was obtained using the general procedure, (22.1 mg, 57%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.35$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Light yellow solid. M.p. 83-85 °C. $[\alpha]_D^{20} = -59.4$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 7.5$ min, $t_R = 8.0$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 8.01 (d, $J = 7.3$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.65 – 7.53 (m, 3H), 7.31 – 7.23 (m, 1H), 7.17 – 7.07 (m, 2H), 2.67 – 2.57 (m, 1H), 2.18 – 1.99 (m, 1H), 1.57 – 1.49 (m, 1H), 1.27 – 1.23 (m, 1H).

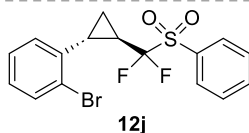
^{13}C NMR (75.5 MHz, CDCl_3) δ 138.0, 135.4, 133.1, 132.9, 130.8, 129.5, 128.7, 127.9, 127.8, 126.0, 122.9 (t, $J = 284.6$ Hz), 20.7 (dd, $J = 5.7, 1.2$ Hz), 18.8 (dd, $J = 25.3, 23.1$ Hz), 11.4 (dd, $J = 5.2, 1.2$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -102.8 (dd, $J = 228.4, 10.8$ Hz), -108.6 (dd, $J = 228.4, 15.8$ Hz).

HRMS (EI⁺) calcd for $\text{C}_{16}\text{H}_{13}\text{BrF}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 385.97877, found: 385.98030 ($\Delta 3.97$ ppm).

IR (neat) 2960, 2923, 2853, 1333, 1159, 1071, 1006, 751, 682, 590 cm^{-1} .

Experimental Part



1-bromo-2-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzene

12j. This cyclopropane was obtained using the general procedure, (28.2 mg, 73%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). $R_f = 0.34$ (Pentane/ Et₂O = 5:1). Yellow oil. $[\alpha]_D^{20} = -87.1$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 7.8$ min, $t_R = 8.5$ min.

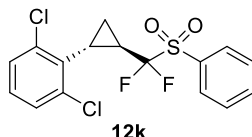
¹H NMR (300.1 MHz, CDCl₃) δ 7.98 (d, $J = 7.4$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.27 (t, $J = 1.8$ Hz, 1H), 7.17 (t, $J = 7.7$ Hz, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 2.43 – 2.32 (m, 1H), 2.06 – 1.87 (m, 1H), 1.49 – 1.41 (m, 1H), 1.35 – 1.27 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 141.2, 135.5, 133.0, 130.8, 130.3, 130.2, 130.0, 129.5, 125.6, 122.8 (t, $J = 284.6$ Hz), 19.8 (t, $J = 24.0$ Hz), 19.7 (dd, $J = 5.2, 2.1$ Hz), 10.8 (dd, $J = 4.8, 1.8$ Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -105.9 (dd, $J = 229.2, 12.7$ Hz), -107.2 (dd, $J = 229.2, 13.7$ Hz).

HRMS (EI⁺) calcd for C₁₆H₁₃BrF₂O₂S ([M]⁺) 385.97877, found: 385.98022 ($\Delta 3.75$ ppm).

IR (neat) 2960, 2925, 2854, 1336, 1162, 1071, 1008, 779, 684, 594 cm⁻¹.



1,3-dichloro-2-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzene

12k. This cyclopropane was obtained using the general procedure, (6.2 mg, 17%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). $R_f = 0.42$ (Pentane/ Et₂O = 5:1). White solid. M.p. 79-81 °C. $[\alpha]_D^{20} = -57.4$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 83:17. The enantiomeric ratio was determined by HPLC with a Chiralcel ID column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 15.2$ min, $t_R = 19.7$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.03 (d, $J = 7.8$ Hz, 2H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.63 (t, $J = 7.7$ Hz, 2H), 7.29 (d, $J = 8.2$ Hz, 2H), 7.14 (dd, $J = 8.3, 7.7$ Hz, 1H), 2.40 – 2.19 (m, 2H), 1.72 – 1.62 (m, 1H), 1.42 – 1.33 (m, 1H).

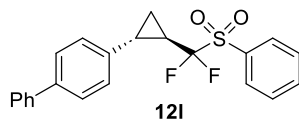
¹³C NMR (75.5 MHz, CDCl₃) δ 137.4, 135.4, 133.7, 133.3, 130.9, 129.4, 129.1, 128.8, 123.2 (t, $J = 284.1$ Hz), 19.8 (dd, $J = 26.0, 20.2$ Hz), 16.5 (d, $J = 5.8$ Hz), 13.8 (dd, $J = 5.3, 1.8$ Hz).

Experimental Part

^{19}F NMR (282.4 MHz, CDCl_3) δ -98.3 (dd, $J = 228.7, 2.7$ Hz), -114.7 (dd, $J = 228.7, 22.2$ Hz).

HRMS (EI^+) calcd for $\text{C}_{16}\text{H}_{12}\text{Cl}_2\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 375.99031, found: 375.99184 ($\Delta 1.53$ ppm).

IR (neat) 2961, 2924, 2854, 1427, 1333, 1069, 991, 740, 615, 580 cm^{-1} .



12l
4-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-1,1'-biphenyl

12l. This cyclopropane was obtained using the general procedure, (24.7 mg, 64%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.35$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). White solid. M.p. 158-160 $^\circ\text{C}$. $[\alpha]_D^{20} = -124.0$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 10.3$ min, $t_R = 11.5$ min.

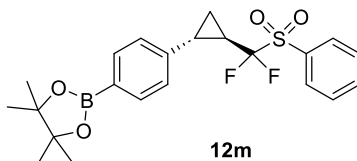
^1H NMR (300.1 MHz, CDCl_3) δ 8.01 (d, $J = 7.6$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.65 – 7.52 (m, 6H), 7.45 (t, $J = 7.4$ Hz, 2H), 7.36 (t, $J = 7.3$ Hz, 1H), 7.25 (d, $J = 8.3$ Hz, 2H), 2.54 – 2.43 (m, 1H), 2.11 – 1.94 (m, 1H), 1.52 – 1.44 (m, 1H), 1.40 – 1.34 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 140.8, 140.0, 137.9, 135.4, 133.2, 130.8, 129.5, 128.9, 127.4, 127.3, 127.1, 122.9 (t, $J = 284.0$ Hz), 19.8 (t, $J = 3.6$ Hz), 19.7 (t, $J = 23.9$ Hz), 11.0 (t, $J = 3.4$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.8 (dd, $J = 226.4, 11.0$ Hz), -106.68 (dd, $J = 226.4, 11.1$ Hz).

HRMS (EI^+) calcd for $\text{C}_{22}\text{H}_{18}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 384.09956, found: 384.10118 ($\Delta 4.22$ ppm).

IR (neat) 2958, 2924, 2853, 1337, 1161, 1075, 996, 829, 682, 600 cm^{-1} .



12m
2-(4-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

12m. This cyclopropane was obtained using the general procedure, (32.6 mg, 75%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 90:10 to 83:17). $R_f = 0.49$ (Pentane/ $\text{Et}_2\text{O} = 3:1$). White solid. M.p. 120-122 $^\circ\text{C}$. $[\alpha]_D^{20} = -78.5$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 93:7. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), $t_R = 7.1$ min, $t_R = 9.5$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.97 (d, $J = 7.4$ Hz, 2H), 7.78 – 7.70 (m, 3H), 7.59 (t, $J = 7.7$ Hz,

Experimental Part

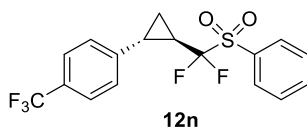
2H), 7.13 (d, $J = 8.0$ Hz, 2H), 2.43 – 2.33 (m, 1H), 2.07 – 1.90 (m, 1H), 1.48 – 1.40 (m, 1H), 1.38 – 1.32 (m, 13H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 142.1, 135.4, 135.2, 133.2, 130.8, 129.5, 126.1, 122.5 (t, $J = 283.8$ Hz), 83.9, 25.0, 20.2 (dd, $J = 4.6, 2.2$ Hz), 20.0 (t, $J = 23.9$ Hz), 11.3 (dd, $J = 4.6, 2.1$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -106.0 (dd, $J = 229.3, 13.0$ Hz), -107.1 (dd, $J = 229.3, 13.5$ Hz).

HRMS (AP^+) calcd for $\text{C}_{22}\text{H}_{26}\text{O}_4\text{F}_2\text{S}^{10}\text{B}$ ($[\text{M}+\text{H}]^+$) 434.1649, found: 434.1658 ($\Delta 2.1$ ppm).

IR (neat) 2975, 2924, 2852, 1359, 1344, 1165, 1081, 1011, 725, 689, 592 cm^{-1} .



12n
1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-(trifluoromethyl)benzene

12n. This cyclopropane was obtained using the general procedure, (13.2 mg, 35%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.37$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Colorless oil. $[\alpha]_D^{20} = -100.1$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel ID column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 13.4$ min, $t_R = 15.2$ min.

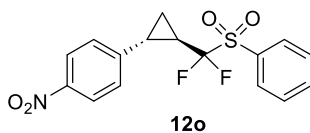
^1H NMR (300.1 MHz, CDCl_3) δ 7.99 (d, $J = 7.8$ Hz, 2H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.66 – 7.54 (m, 4H), 7.29 (d, $J = 8.1$ Hz, 2H), 2.55 – 2.44 (m, 1H), 2.09 – 1.92 (m, 1H), 1.55 – 1.47 (m, 1H), 1.41 – 1.32 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 143.0, 135.5, 133.0, 130.8, 129.5, 129.4 (q, $J = 32.5$ Hz), 127.3, 125.7 (q, $J = 3.8$ Hz), 124.3 (q, $J = 271.9$ Hz), 122.6 (t, $J = 283.1$ Hz), 20.0 (t, $J = 23.9$ Hz), 19.9 (dd, $J = 5.1, 1.6$ Hz), 10.9 (dd, $J = 5.1, 1.3$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -63.0 (s, CF_3), -105.5 (dd, $J = 229.0, 12.2$ Hz), -107.6 (dd, $J = 229.0, 14.0$ Hz).

HRMS (EI^+) calcd for $\text{C}_{17}\text{H}_{13}\text{F}_4\text{O}_2\text{S}$ ($[\text{M}]^+$) 357.05724, found: 357.05751 ($\Delta 0.76$ ppm).

IR (neat) 2966, 2927, 2858, 1323, 1162, 1119, 1067, 830, 685, 588 cm^{-1} .



12o
1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-nitrobenzene

Experimental Part

2o. This cyclopropane was obtained using the general procedure, (9.2 mg, 26%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 90:10 to 75:25). R_f = 0.43 (Pentane/ Et₂O = 3:1). Colorless oil. $[\alpha]^{20}_D = -102.3$ (c = 1.0, CHCl₃).

Enantiomeric Ratio: 96:4. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), t_R = 18.7 min, t_R = 21.8 min.

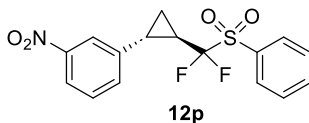
¹H NMR (300.1 MHz, CDCl₃) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 2.61 – 2.48 (m, 1H), 2.15 – 1.98 (m, 1H), 1.63 – 1.52 (m, 1H), 1.47 – 1.36 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 147.1, 146.6, 135.6, 132.8, 130.8, 129.5, 127.7, 124.0, 122.3 (t, *J* = 284.7 Hz), 20.5 (t, *J* = 24.3 Hz), 20.0 (dd, *J* = 5.7, 1.8 Hz), 11.2 (dd, *J* = 5.2, 1.3 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -105.3 (dd, *J* = 229.4, 11.9 Hz), -108.1 (dd, *J* = 229.1, 14.3 Hz).

HRMS (EI⁺) calcd for C₁₆H₁₃F₂NO₄S ([M]⁺) 353.05333, found: 353.05347 (Δ0.39 ppm).

IR (neat) 2965, 2924, 2854, 1520, 1336, 1161, 1088, 1008, 685, 593.



1-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-3-nitrobenzene

12p. This cyclopropane was obtained using the general procedure, (13.5 mg, 38%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 90:10 to 75:25). R_f = 0.42 (Pentane/ Et₂O = 3:1). Yellow solid. M.p. 83-85 °C. $[\alpha]^{20}_D = -75.9$ (c = 1.0, CHCl₃).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 13.6 min, t_R = 14.4 min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.11 (d, *J* = 8.0 Hz, 1H), 7.99 (m, 3H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.50 (t, *J* = 7.9 Hz, 1H), 2.60 – 2.49 (m, 1H), 2.14 – 1.96 (m, 1H), 1.58 – 1.51 (m, 1H), 1.46 – 1.37 (m, 1H).

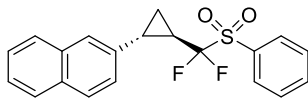
¹³C NMR (75.5 MHz, CDCl₃) δ 148.6, 141.0, 135.6, 133.4, 132.8, 130.8, 129.8, 129.6, 122.4 (t, *J* = 283.1 Hz), 122.2, 121.8, 20.1 (t, *J* = 23.9 Hz), 19.8 (dd, *J* = 5.8, 1.8 Hz), 10.7 (dd, *J* = 5.2, 1.3 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -105.1 (dd, *J* = 229.4, 11.5 Hz), -108.1 (dd, *J* = 229.3, 14.5 Hz).

HRMS (EI⁺) calcd for C₁₆H₁₃F₂NO₄S ([M]⁺) 353.05333, found: 353.05425 (Δ2.6 ppm).

Experimental Part

IR (neat) 2960, 2922, 2852, 1533, 1332, 1161, 1009, 732, 683, 609 cm^{-1} .



12q

2-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)naphthalene

12q. This cyclopropane was obtained using the general procedure, (29.7 mg, 83%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 90:10). $R_f = 0.41$ (Pentane/ Et₂O = 5:1). White solid. M.p. 112-114 °C. $[\alpha]_D^{20} = -123.3$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 9.4$ min, $t_R = 10.6$ min.

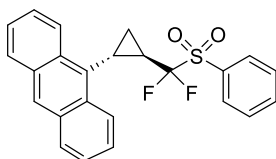
¹H NMR (300.1 MHz, CDCl₃) δ 8.01 (d, $J = 7.7$ Hz, 2H), 7.86 – 7.71 (m, 4H), 7.63 – 7.55 (m, 3H), 7.52 – 7.42 (m, 2H), 7.29 (dd, $J = 8.5, 1.8$ Hz, 1H), 2.64 – 2.53 (m, 1H), 2.17 – 1.99 (m, 1H), 1.56 – 1.41 (m, 2H).

¹³C NMR (75.5 MHz, CDCl₃) δ 136.2, 135.4, 133.4, 133.2, 132.6 130.8, 129.4, 128.5, 127.8, 127.6, 126.5, 125.8, 125.4, 125.1, 122.9 (t, $J = 283.8$ Hz), 20.3 (dd, $J = 4.4, 2.6$ Hz), 19.7 (t, $J = 23.9$ Hz), 10.9 (dd, $J = 4.2, 2.6$ Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -105.8 (dd, $J = 228.9, 13.3$ Hz), -106.7 (dd, $J = 228.9, 13.5$ Hz).

HRMS (EI⁺) calcd for C₂₀H₁₆F₂O₂S ([M]⁺) 358.08391, found: 358.08413 ($\Delta 0.64$ ppm).

IR (neat) 2961, 2923, 2853, 1336, 1162, 1074, 996, 824, 682, 596 cm^{-1} .



12r

9-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)anthracene

12r. This cyclopropane was obtained using the general procedure, (26.5 mg, 65%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 90:10). $R_f = 0.43$ (Pentane/ Et₂O = 5:1). Brown solid. M.p. 88-90 °C. $[\alpha]_D^{20} = -43.1$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 95.5:4.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), $t_R = 8.6$ min, $t_R = 11.0$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.57 (d, $J = 9.0$ Hz, 2H), 8.41 (s, 1H), 8.10 (d, $J = 7.5$ Hz, 2H),

Experimental Part

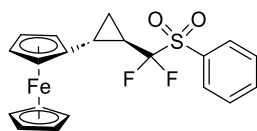
8.00 (d, $J = 7.9$ Hz, 2H), 7.80 (d, $J = 14.9$ Hz, 1H), 7.66 (t, $J = 7.7$ Hz, 2H), 7.51 (dddd, $J = 9.4, 7.7, 6.5, 1.2$ Hz, 4H), 3.14 – 3.01 (m, 1H), 2.30 – 2.12 (m, 1H), 1.99 – 1.91 (m, 1H), 1.42 – 1.31 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 135.5, 133.3, 131.5, 131.3, 130.9, 129.7, 129.5, 129.2, 127.9, 126.1, 125.1, 124.9, 124.9, 123.8 (t, $J = 283.8$ Hz), 19.9 (dd, $J = 26.5, 19.4$ Hz), 14.6 (d, $J = 4.8$ Hz), 14.4 (d, $J = 3.7$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -97.2 (dd, $J = 229.1, 2.5$ Hz), -114.1 (dd, $J = 229.1, 23.4$ Hz).

HRMS (EI^+) calcd for $\text{C}_{24}\text{H}_{18}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 408.09956, found: 408.09822 (Δ -1.34 ppm).

IR (neat) 2958, 2923, 2853, 1338, 1165, 1057, 1008, 736, 684, 589 cm^{-1} .



12t

(1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropylferrocene

12t. This cyclopropane was obtained using the general procedure, (25.8 mg, 62%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 85:15). $R_f = 0.40$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Brown solid. M.p. 111-113 $^\circ\text{C}$. $[\alpha]_D^{20} = -27.4$ ($c = 1.0, \text{CHCl}_3$).

Enantiomeric Ratio: 98:2. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 18.4$ min, $t_R = 19.6$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 8.01 (d, $J = 7.7$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 2H), 4.17 (s, 5H), 4.12 – 4.05 (m, 4H), 2.17 – 2.06 (m, 1H), 1.96 – 1.78 (m, 1H), 1.35 – 1.27 (dt, $J = 10.7, 5.4$ Hz, 1H), 1.14 – 1.03 (m, 1H).

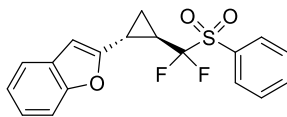
^{13}C NMR (75.5 MHz, CDCl_3) δ 135.3, 133.3, 130.8, 129.4, 123.0 (t, $J = 283.5$ Hz), 87.4, 68.8, 67.6, 67.6, 67.0, 66.9, 19.5 (dd, $J = 25.1, 22.7$ Hz), 15.3 (dd, $J = 5.2, 1.5$ Hz), 12.3 (dd, $J = 5.4, 1.3$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -103.5 (dd, $J = 227.9, 11.3$ Hz), -107.8 (dd, $J = 227.9, 16.0$ Hz).

HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{F}_2\text{S}^{56}\text{Fe}$ ($[\text{M}]^+$) 416.0345, found: 416.0354 (Δ 2.2 ppm).

IR (neat) 2962, 2922, 2853, 1336, 1162, 1073, 1010, 819, 685, 685 cm^{-1} .

Experimental Part



12u

2-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)benzofuran

12u. This cyclopropane was obtained using the general procedure, (32.1 mg, 92%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). $R_f = 0.33$ (Pentane/ Et₂O = 5:1). Light yellow solid. M.p. 77-79 °C. $[\alpha]_D^{20} = -146.9$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 10.8$ min, $t_R = 11.7$ min.

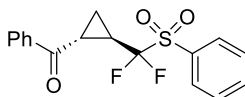
¹H NMR (300.1 MHz, CDCl₃) δ 8.00 (d, $J = 7.7$ Hz, 2H), 7.75 (t, $J = 7.5$ Hz, 1H), 7.59 (t, $J = 7.7$ Hz, 2H), 7.52 – 7.45 (m, 1H), 7.41 – 7.35 (m, 1H), 7.27 – 7.16 (m, 2H), 6.52 (s, 1H), 2.56 – 2.46 (m, 1H), 2.41 – 2.25 (m, 1H), 1.60 – 1.43 (m, 2H).

¹³C NMR (75.5 MHz, CDCl₃) δ 154.9, 154.5, 135.5, 133.0, 130.8, 129.5, 128.7, 123.9, 123.0, 122.4 (t, $J = 283.5$ Hz), 120.5, 111.0, 103.2, 18.5 (t, $J = 24.3$ Hz), 14.0 (dd, $J = 5.9, 2.0$ Hz), 10.1 (dd, $J = 5.4, 1.7$ Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -106.2 (dd, $J = 230.2, 12.5$ Hz), -108.2 (dd, $J = 230.1, 14.0$ Hz).

HRMS (AP⁺) calcd for C₁₈H₁₅O₃F₂S ([M+H]⁺) 349.0710, found: 349.0700 (Δ -2.9 ppm).

IR (neat) 2953, 29243 2855, 1335, 1166, 1077, 1012, 789, 754, 595 cm⁻¹.



12u

((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)(phenyl)methanone

12u. This cyclopropane was obtained using the general procedure, (19.2 mg, 57%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 80:20). $R_f = 0.28$ (Pentane/ Et₂O = 5:1). White solid. M.p. 77-79 °C. $[\alpha]_D^{20} = -70.0$ ($c = 1.0$, CHCl₃).

Enantiomeric Ratio: 98:2. The enantiomeric ratio was determined by HPLC with a Chiralcel IA column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), $t_R = 9.0$ min, $t_R = 9.4$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.09 – 7.95 (m, 4H), 7.74 (t, $J = 7.5$ Hz, 1H), 7.66 – 7.56 (m, 3H), 7.50 (t, $J = 7.5$ Hz, 2H), 3.15 – 3.03 (m, 1H), 2.54 – 2.34 (m, 1H), 1.67 – 1.60 (m, 1H), 1.50 – 1.42 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 196.5, 137.0, 135.6, 133.7, 132.9, 130.9, 129.5, 128.9, 128.5, 122.1

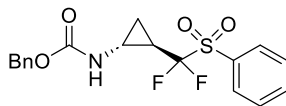
Experimental Part

(t, $J = 284.3$ Hz), 21.2 (dd, $J = 25.3, 23.6$ Hz), 20.2 (d, $J = 3.3$ Hz), 12.4 (dd, $J = 5.3, 1.7$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.8 (dd, $J = 231.8, 12.6$ Hz), -107.3 (dd, $J = 231.8, 13.6$ Hz).

HRMS (AP^+) calcd for $\text{C}_{17}\text{H}_{15}\text{O}_3\text{F}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 337.0710, found: 337.0710 ($\Delta 0$ ppm).

IR (neat) 2953, 2922, 2853, 1674, 1337, 1168, 1095, 1009, 733, 596 cm^{-1} .



benzyl ((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)carbamate

12v. These cyclopropanes were obtained using the general procedure, (*trans*, 19.0 mg, *cis*, 13.0 mg, 84% global yield) were obtained as separated fractions after silica gel column chromatography (Pentane/ EtOAc 90:10 to 75:25).

Trans-**12v**, $R_f = 0.44$ (Pentane/ EtOAc = 3:1). Colorless oil. $[\alpha]_D^{20} = -46.8$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 98.5:1.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 80:20, 220 nm, 1 mL/min), $t_R = 17.1$ min, $t_R = 21.3$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.98 (d, $J = 7.6$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 2H), 7.35 (s, 5H), 5.16 (s, 1H), 5.11 (s, 2H), 3.11 – 2.99 (m, 1H), 1.99 – 1.81 (m, 1H), 1.38 – 1.21 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 156.5, 136.2, 135.5, 132.8, 130.8, 129.5, 128.7, 128.4, 128.3, 122.2 (t, $J = 284.2$ Hz), 67.2, 26.9 (dd, $J = 7.1, 2.1$ Hz), 18.4 (dd, $J = 26.1, 3.9$ Hz), 11.3.

^{19}F NMR (282.4 MHz, CDCl_3) δ -104.4 (d, $J = 231.1$ Hz), -106.9 (d, $J = 229.6$ Hz).

Cis-**12v**, $R_f = 0.37$ (Pentane/ EtOAc = 3:1). White solid. $[\alpha]_D^{20} = -7.2$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 67:33. The enantiomeric ratio was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_R = 15.9$ min, $t_R = 18.4$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.99 (d, $J = 7.7$ Hz, 2H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 2H), 7.35 (s, 5H), 5.64 (s, 1H), 5.17 – 5.06 (m, 2H), 3.14 – 3.02 (m, 1H), 1.98 – 1.77 (m, 1H), 1.54 – 1.39 (m, 1H), 1.38 – 1.29 (m, 1H).

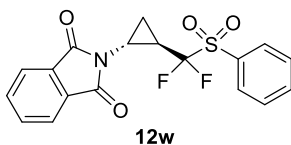
^{13}C NMR (75.5 MHz, CDCl_3) δ 156.8, 136.4, 135.7, 132.2, 131.0, 129.5, 128.7, 128.7, 128.3, 123.0 (t, $J = 284.2$ Hz), 67.1, 27.8, 15.7 (dd, $J = 25.0, 20.4$ Hz), 11.0.

^{19}F NMR (282.4 MHz, CDCl_3) δ -94.6 (d, $J = 232.4$ Hz), -104.5 (dd, $J = 232.5, 18.6$ Hz).

HRMS (AP^+) calcd for $\text{C}_{18}\text{H}_{18}\text{NO}_4\text{F}_2\text{S}$ ($[\text{M}+\text{H}]^+$) 382.0925, found: 382.0916 ($\Delta -2.4$ ppm).

Experimental Part

IR (neat) 3314, 2960, 2924, 2854, 1699, 1521, 1335, 1164, 1009, 737, 682, 590 cm⁻¹.



12w
2-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)isoindoline-1,3-dione

12w. This cyclopropane was obtained using the general procedure, (9.1 mg, 24%) was obtained as separated fractions after silica gel column chromatography (Pentane/ EtOAc 90:10 to 80:20). R_f = 0.48 (Pentane/ EtOAc = 3:1). White solid. M.p. 138-140 °C. [α]²⁰_D = -58.8 (c = 0.5, CHCl₃).

Enantiomeric Ratio: 98:2. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 70:30, 220 nm, 1 mL/min), t_R = 22.9 min, t_R = 31.0 min.

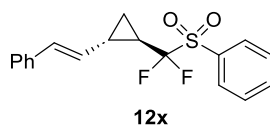
¹H NMR (300.1 MHz, CDCl₃) δ 8.02 (d, *J* = 7.8 Hz, 2H), 7.89 – 7.81 (m, 2H), 7.80 – 7.71 (m, 3H), 7.62 (t, *J* = 7.7 Hz, 2H), 3.45 – 3.33 (m, 1H), 2.75 – 2.56 (m, 1H), 1.87 – 1.75 (m, 1H), 1.52 (dd, *J* = 14.0, 7.0 Hz, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 167.9, 135.5, 134.5, 132.9, 131.6, 130.9, 129.5, 123.6, 122.1 (t, *J* = 284.6 Hz), 25.2 (dd, *J* = 7.5, 2.3 Hz), 16.0 (dd, *J* = 25.1, 23.2 Hz), 8.9 (dd, *J* = 5.3, 1.5 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -103.7 (dd, *J* = 231.7, 10.4 Hz), -109.4 (dd, *J* = 231.7, 16.4 Hz).

HRMS (AP⁺) calcd for C₁₈H₁₄NO₄F₂S ([M+H]⁺) 378.0612, found: 378.0617 (Δ 1.3 ppm).

IR (neat) 2961, 2922, 2853, 1716, 1338, 1163, 1088, 1006, 713, 686, 590 cm⁻¹.



12x
((difluoro((1R,2S)-2-((E)-styryl)cyclopropyl)methyl)sulfonyl)benzene

12x. This cyclopropane was obtained using the general procedure, (28.5 mg, 85%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et₂O 98:2 to 85:15). R_f = 0.44 (Pentane/ Et₂O = 5:1). White solid. M.p. 70-72 °C. [α]²⁰_D = -100.1 (c = 1.0, CHCl₃).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 15.7 min, t_R = 17.4 min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.00 (d, *J* = 7.7 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 2H), 7.34 – 7.19 (m, 5H), 6.50 (d, *J* = 15.8 Hz, 1H), 5.78 (dd, *J* = 15.8, 8.2 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.91 – 1.74 (m, 1H), 1.35 – 1.28 (m, 1H), 1.16 – 1.04 (m, 1H).

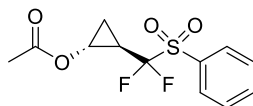
Experimental Part

^{13}C NMR (75.5 MHz, CDCl_3) δ 136.8, 135.3, 133.3, 131.3, 130.8, 129.4, 128.7, 128.5, 127.6, 126.1, 122.9 (t, $J = 284.1$ Hz), 19.0 (dd, $J = 5.1, 1.8$ Hz), 18.4 (t, $J = 24.0$ Hz), 10.4 (dd, $J = 5.0, 1.7$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -105.7 (dd, $J = 229.2, 13.0$ Hz), -107.2 (dd, $J = 229.2, 13.9$ Hz).

HRMS (EI^+) calcd for $\text{C}_{18}\text{H}_{16}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 334.08391, found: 334.08462 ($\Delta 2.15$ ppm).

IR (neat) 2961, 2923, 2853, 1336, 1166, 1116, 994, 714, 606, 593 cm^{-1} .



12y

(1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl acetate

12y. This cyclopropane was obtained using the general procedure, (13.1 mg, 45%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 80:20). $R_f = 0.40$ (Pentane/ $\text{Et}_2\text{O} = 3:1$). White solid. M.p. 46-48 $^\circ\text{C}$. $[\alpha]_D^{20} = -26.4$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_R = 13.4$ min, $t_R = 15.7$ min.

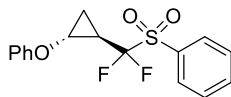
^1H NMR (300.1 MHz, CDCl_3) δ 7.98 (d, $J = 7.8$ Hz, 2H), 7.77 (t, $J = 7.5$ Hz, 1H), 7.62 (t, $J = 7.7$ Hz, 2H), 4.46 – 4.33 (m, 1H), 2.16 – 1.99 (m, 4H), 1.37 – 1.28 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 170.8, 135.6, 132.8, 130.9, 129.5, 121.8 (t, $J = 284.2$ Hz), 49.5 (dd, $J = 7.5, 2.2$ Hz), 20.8, 16.5 (dd, $J = 25.0, 24.1$ Hz), 10.1 (dd, $J = 5.1, 1.8$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -103.6 (dd, $J = 232.8, 12.1$ Hz), -107.5 (dd, $J = 232.7, 15.3$ Hz).

HRMS (AP^+) calcd for $\text{C}_{12}\text{H}_{13}\text{F}_2\text{O}_4\text{S}$ ($[\text{M}+\text{H}]^+$) 291.05026, found: 291.05179 ($\Delta 5.26$ ppm).

IR (neat) 2962, 2925, 2854, 1751, 1335, 1219, 1161, 992, 713, 684, 592 cm^{-1} .



12z

((difluoro((1*R*,2*R*)-2-phenoxy)cyclopropyl)methyl)sulfonyl)benzene

12z. This cyclopropane was obtained using the general procedure, (30.4 mg, 94%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et_2O 98:2 to 80:20). $R_f = 0.52$ (Pentane/ $\text{Et}_2\text{O} = 5:1$). Colorless oil. $[\alpha]_D^{20} = -28.3$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_R = 10.6$ min, $t_R = 11.4$ min.

Experimental Part

¹H NMR (300.1 MHz, CDCl₃) δ 8.02 (d, *J* = 7.6 Hz, 2H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 2H), 7.31 (dd, *J* = 8.8, 7.3 Hz, 2H), 7.10 – 6.98 (m, 3H), 4.05 (ddd, *J* = 8.1, 3.9, 2.3 Hz, 1H), 2.17 – 1.98 (m, 1H), 1.52 – 1.33 (m, 2H).

¹³C NMR (75.5 MHz, CDCl₃) δ 157.8, 135.6, 132.9, 130.9, 129.7, 129.5, 122.1 (t, *J* = 283.3 Hz), 122.1, 115.1, 52.0 (dd, *J* = 6.8, 1.8 Hz), 17.9 (dd, *J* = 25.8, 22.6 Hz), 11.1 (dd, *J* = 5.1, 1.7 Hz).

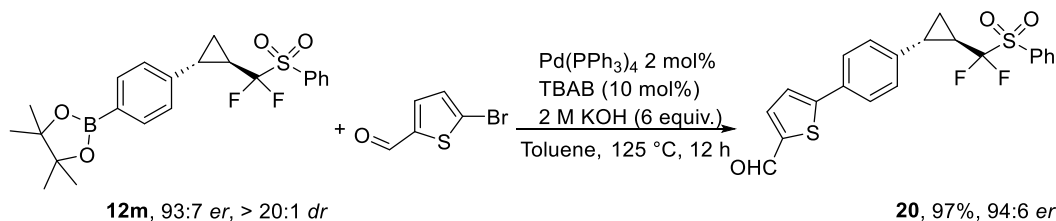
¹⁹F NMR (282.4 MHz, CDCl₃) δ -101.4 (dd, *J* = 232.5, 10.4 Hz), -107.6 (dd, *J* = 232.5, 17.5 Hz).

HRMS (EI⁺) calcd for C₁₆H₁₄F₂O₃S ([M]⁺) 324.06317, found: 324.06392 (Δ2.3 ppm).

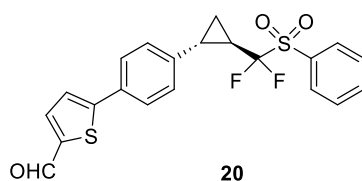
IR (neat) 2960, 2922, 2854, 1449, 1338, 1244, 1166, 1008, 753, 684, 592 cm⁻¹.

3. General procedures of the post-functionalization reactions

3.1. Synthesis of compound **20**



To a 10 mL tube with a stirring bar was charged Pd(Ph₃)₄ (2.3 mg, 0.002 mol, 0.02 equiv.), pinacol ester substrate **12m** (43.3 mg, 0.1 mol, 1.0 equiv.), thiophen bromide (28.7 mg, 0.15 mol, 1.5 equiv.), TBAB (3.2 mg, 0.01 mol, 0.1 equiv.) and aqueous 2 M KOH (0.3 mL) were added in order, following by 1 mL toluene. This tube was sealed and heated to 125 °C for stirring 12 h. The reaction was cooled to room temperature and extracted with EtOAc (3×5 mL) washed with water (10 mL) and then dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography to give a product **20** as a white solid (40.6 mg, 97%). M.p. 108-110 °C. [α]_D²⁰ = -130.9 (c = 1.0, CHCl₃).



5-(4-((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)phenyl)thiophene-2-carbaldehyde

¹H NMR (300.1 MHz, CDCl₃) δ 9.88 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.80 – 7.71 (m, 2H), 7.65 – 7.56 (m, 4H), 7.38 (d, *J* = 3.9 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 2.51 – 2.41 (m, 1H), 2.09 – 1.92 (m, 1H), 1.55 – 1.43 (m, 1H), 1.41 – 1.29 (m, 1H).

Experimental Part

^{13}C NMR (75.5 MHz, CDCl_3) δ 182.9, 153.9, 142.5, 140.5, 137.6, 135.5, 133.0, 131.8, 130.8, 129.5, 127.5, 126.7, 124.2, 122.7 (t, $J = 284.0$ Hz), 19.9 (dd, $J = 5.5, 1.7$ Hz), 19.9 (t, $J = 24.0$ Hz), 10.9 (dd, $J = 4.9, 1.3$ Hz).

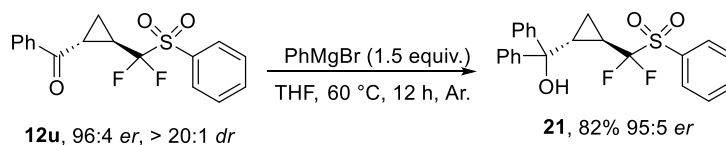
^{19}F NMR (282.4 MHz, CDCl_3) δ -105.5 (dd, $J = 228.8, 12.5$ Hz), -107.3 (dd, $J = 228.8, 13.9$ Hz).

Enantiomeric Ratio: 94:6. The enantiomeric ratio was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), $t_{\text{R}} = 27.5$ min, $t_{\text{R}} = 29.8$ min.

HRMS (EI⁺) calcd for $\text{C}_{18}\text{H}_{16}\text{F}_2\text{O}_2\text{S}$ ($[\text{M}]^+$) 418.05094, found: 418.05120 ($\Delta 0.62$ ppm).

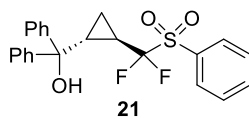
IR (neat) 2962, 2922, 2853, 1668, 1450, 1334, 1164, 1009, 807, 683, 589 cm^{-1} .

3.2. Synthesis of compound 21



To a solution of ketone substrate **12u** (33.6 mg, 0.1 mmol, 1.0 equiv.) in 1.0 mL THF was added phenyl magnesium bromide (1 mol/L in THF, 1.5 mL, 0.15 mmol, 1.5 equiv.), the mixture was stirred at 60 °C for 12 hours. The reaction was cooled to room temperature and quenched by saturated NH_4Cl solution, washed by water and then dried over MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (Et_2O /pentane, 10:90 to 25:75) to give product **21** as a white solid (34.0 mg, 82%). M.p. 94-96 °C.

$[\alpha]_{\text{D}}^{20} = -54.2$ ($c = 1.0, \text{CHCl}_3$)



21
((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)diphenylmethanol

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), $t_{\text{R}} = 21.9$ min, $t_{\text{R}} = 31.1$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.97 (d, $J = 7.5$ Hz, 2H), 7.74 (t, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 7.49 (d, $J = 6.8$ Hz, 2H), 7.41 – 7.22 (m, 8H), 2.59 (s, 1H), 2.20 (dt, $J = 9.3, 5.9$ Hz, 1H), 1.97 – 1.79 (m, 1H), 1.23 – 1.06 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 146.5, 145.2, 135.4, 133.0, 130.8, 129.4, 128.4, 128.3, 127.6, 127.0, 126.7, 123.4 (t, $J = 283.8$ Hz), 76.3, 25.9 (d, $J = 4.1$ Hz), 13.4 (t, $J = 24.0$ Hz), 7.2 (d, $J = 3.8$ Hz).

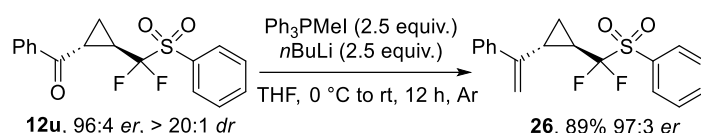
Experimental Part

^{19}F NMR (282.4 MHz, CDCl_3) δ -103.3 (dd, $J = 227.5, 11.8$ Hz), -106.44 (dd, $J = 227.5, 15.8$ Hz).

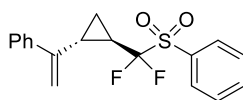
HRMS (Ei^+) calcd for $\text{C}_{23}\text{H}_{20}\text{F}_2\text{O}_3\text{S}$ ($[\text{M}]^+$) 414.11012, found: 414.11034 ($\Delta 0.53$ ppm).

IR (neat) 3524, 2960, 2923, 2853, 1447, 1330, 1163, 1010, 1006, 752, 683, 586 cm^{-1} .

3.3. Synthesis of compound 26



To an oven dried Schlenk flask was charged with methyltriphenylphosphonium iodide (110.0 mg, 0.25 mmol, 2.5 equiv.) followed by anhydrous THF (1.0 mL) and placed at 0 °C under argon atmosphere. *n*BuLi (2.5 M in hexane, 0.1 mL, 0.25 mmol, 2.5 equiv.) was added dropwise and stirred the mixture for 30 min. **12u** in THF (0.5 mL) was added to the suspension and kept stirring at 0 °C for another 30 min, the warmed to room temperature for overnight. This reaction was quenched by the addition of sat. NH_4Cl solution and extracted with Et_2O (3 \times 5 mL), combined organic layers washed with brine (10 mL) and dried over MgSO_4 . The solution was filtered and removed the solvent under vacuo evaporated. The residue was purified through a silica-gel flash column chromatography (Et_2O /pentane, 2:98 to 10:90), affording product **26** as a white solid (29.6 mg, 89%). M.p. 56-58 °C. $[\alpha]_D^{20} = -69.5$ ($c = 1.0, \text{CHCl}_3$).



26
(difluoro((1*R*,2*R*)-2-(1-phenylvinyl)cyclopropyl)methyl)sulfonylbenzene

Enantiomeric Ratio: 97:3. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), $t_R = 11.5$ min, $t_R = 12.6$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 8.01 (d, $J = 7.7$ Hz, 2H), 7.76 (t, $J = 7.5$ Hz, 1H), 7.61 (t, $J = 7.7$ Hz, 2H), 7.52 (d, $J = 6.5$ Hz, 2H), 7.40 – 7.27 (m, 3H), 5.43 (s, 1H), 5.11 (s, 1H), 2.27 – 2.17 (m, 1H), 2.04 – 1.87 (m, 1H), 1.39 – 1.30 (m, 1H), 1.21 – 1.12 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 145.3, 140.1, 135.4, 133.2, 130.8, 129.4, 128.5, 128.1, 126.2, 123.1 (t, $J = 283.8$ Hz), 112.3, 19.7 (dd, $J = 5.2, 1.1$ Hz), 18.0 (dd, $J = 25.2, 22.6$ Hz), 10.4 (dd, $J = 5.3, 1.4$ Hz).

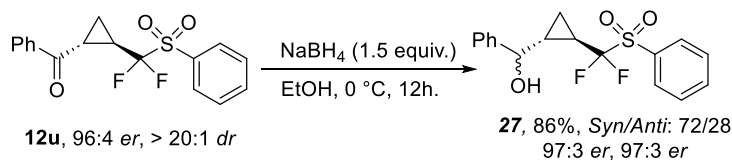
^{19}F NMR (282.4 MHz, CDCl_3) δ -102.7 (dd, $J = 228.6, 10.4$ Hz), -108.4 (dd, $J = 228.6, 16.5$ Hz).

Experimental Part

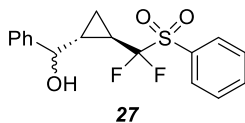
HRMS (EI⁺) calcd for C₁₈H₁₆F₂O₂S ([M]⁺) 334.08391, found: 334.08482 (Δ 2.73 ppm).

IR (neat) 2961, 2926, 2855, 1337, 1165, 1074, 1006, 704, 684, 594 cm⁻¹.

Synthesis of compound 27



To a solution of **12u** (67.2 mg, 0.2 mmol, 1.0 equiv.) in EtOH (2 mL) in a 10 mL tube at 0 °C was added NaBH₄ (11.4 mg, 0.3 mmol) in small amounts. After being stirred at this temperature for 12 h, the reaction mixture was quenched by addition of H₂O and acidified with 1 M aq. HCl, and extracted with DCM (2×10 mL). The combined organic layer was washed with brine (10 mL), and then dried over anhydrous MgSO₄, filtered and evaporated under vacuum. The residue was purified by silica-gel flash column chromatography (Et₂O/pentane, 10:90 to 25:75) to give alcohol product **27** as a colorless oil (58.4 mg, 86%, *syn/anti* 72/28).



((1*R*,2*R*)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)(phenyl)methanol

Enantiomeric Ratio: 97:3, 97:3. The enantiomeric ratio was determined by HPLC with a Chiralcel IE column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), minor: *t*_R = 41.5 min, *t*_R = 46.6 min, major: *t*_R = 55.1 min, *t*_R = 65.9 min.

¹H NMR (300.1 MHz, CDCl₃) δ 8.05 – 7.93 (m, 2H), 7.80 – 7.70 (m, 1H), 7.67 – 7.56 (m, 2H), 7.45 – 7.27 (m, 5H), 4.76 (s, 0.27H), 4.31 (d, *J* = 5.2 Hz, 0.73H), 2.76 (d, *J* = 3.1 Hz, 0.73H), 2.48 (d, *J* = 4.0 Hz, 0.27H), 1.99 – 1.68 (m, 2H), 1.14 – 0.96 (m, 2H).

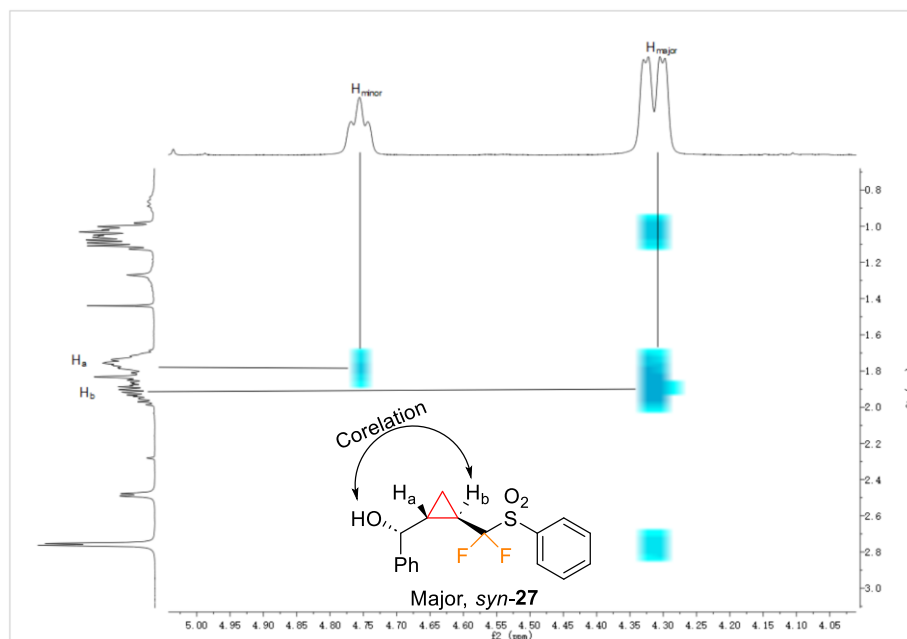
¹³C NMR (75.5 MHz, CDCl₃) δ 142.4 (*syn*), 142.3 (*anti*), 135.5 (*syn*), 135.3 (*anti*), 133.0 (*anti*), 132.7 (*syn*), 130.8 (*syn*), 130.7 (*anti*), 129.4 (*syn*), 129.4 (*anti*), 128.6 (*syn*), 128.6 (*anti*), 128.1 (*syn*), 128.1 (*anti*), 126.3 (*anti*), 126.1 (*syn*), 123.3 (*anti*, *t*, *J* = 283.9 Hz), 123.1 (*syn*, *t*, *J* = 283.9 Hz), 75.3 (*syn*), 72.2 (*anti*), 23.9 (*syn*, *d*, *J* = 3.7 Hz), 22.6 (*anti*, *d*, *J* = 3.9 Hz), 15.2 (*syn*, *t*, *J* = 23.9 Hz), 13.2 (*anti*, *t*, *J* = 23.9 Hz), 6.8 (*syn*, *dd*, *J* = 4.6, 1.0 Hz), 5.8 (*anti*, *dd*, *J* = 4.9, 1.3 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -103.7 (*syn*, *dd*, *J* = 227.2, 11.3 Hz), -104.4 (*anti*, *dd*, *J* = 227.5, 12.6 Hz), -106.7 (*anti*, *dd*, *J* = 227.7, 14.8 Hz), -107.5 (*syn*, *dd*, *J* = 227.2, 15.8 Hz).

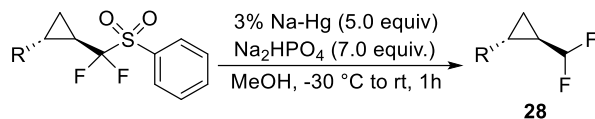
Experimental Part

HRMS (EI⁺) calcd for C₁₇H₁₆F₂O₃S ([M]⁺) 338.07882, found: 338.07996 (Δ 3.37 ppm).

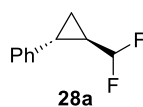
IR (neat) 3542, 3064, 2888, 1449, 1333, 1164, 1056, 1008, 731, 684, 594 cm⁻¹.



3.4. Synthesis of compound 28



To a solution of phenyl sulfonyl compound (1.0 equiv.) in MeOH (1 mL) in a 10 mL tube was added Na₂HPO₄ (7.0 equiv.), This tube was placed at -30 °C was added homemade 3% sodium amalgam (5.0 equiv.) in one portion. After being stirred at this temperature for 5 min, the reaction was warmed to room temperature for one hour. This suspension was quenched by addition of H₂O and stirred another one hour, and extracted with Et₂O (2×10 mL). The combined organic layer was washed with brine (10 mL), and then dried over anhydrous MgSO₄, filtered and evaporated carefully under vacuum to afford difluoromethyl cyclopropane **28a** or **28c**. Difluoromethyl cyclopropane **28b** was purified by silica-gel flash column chromatography.



28a
((1R,2R)-2-(difluoromethyl)cyclopropyl)benzene

28. This cyclopropane was obtained using the general procedure original from **12a** (48 mg, 0.156

Experimental Part

mmol, 1.0 equiv.), (23 mg, 88%) were obtained without purification. Colorless liquid. $[\alpha]_D^{20} = -12.3$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 94:6. The enantiomeric ratio was determined by inverse phase HPLC with a Chiralcel OJ-3R column (H_2O : $\text{MeCN} = 50:50$ (0.1% formic acid), 220 nm, 0.8 mL/min), $t_R = 10.5$ min, $t_R = 11.3$ min.

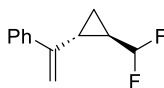
^1H NMR (300.1 MHz, CDCl_3) δ 7.29 (t, $J = 7.2$ Hz, 2H), 7.20 (t, $J = 7.3$ Hz, 1H), 7.11 (d, $J = 6.9$ Hz, 2H), 5.76 (td, $J = 57.5, 4.1$ Hz, 1H), 2.24 – 2.14 (m, 1H), 1.70 – 1.59 (m, 1H), 1.27 – 1.20 (m, 1H), 1.14 – 1.04 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 140.4, 128.6, 126.5, 126.5, 116.6 (t, $J = 238.4$ Hz), 24.1 (t, $J = 26.7$ Hz), 18.93 (t, $J = 4.6$ Hz), 10.6 (t, $J = 4.6$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -115.5 (ddd, $J = 280.6, 56.1, 10.6$ Hz), -116.7 (ddd, $J = 280.6, 57.2, 10.8$ Hz).

HRMS (EI^+) calcd for $\text{C}_{10}\text{H}_{10}\text{F}_2$ ($[\text{M}]^+$) 168.07506, found: 168.07619 ($\Delta 6.74$ ppm).

IR (neat) 2962, 2927, 2856, 1377, 1102, 1030, 751, 697 cm^{-1} .



28b
(1-((1R,2R)-2-(difluoromethyl)cyclopropyl)vinyl)benzene

28b. This cyclopropane was obtained using the general procedure original from **26** (28 mg, 0.084 mmol, 1.0 equiv.), (12.1 mg, 74%) was obtained as separated fractions after silica gel column chromatography (Pentane). $R_f = 0.62$ (Pentane/ $\text{Et}_2\text{O} = 20:1$). Colorless oil. $[\alpha]_D^{20} = -7.2$ ($c = 1.0$, CHCl_3).

Enantiomeric Ratio: 97:3. The enantiomeric ratio was determined by HPLC with a Chiralcel OJ column (n -heptane: i -PrOH = 99:1, 220 nm, 1 mL/min), $t_R = 7.4$ min, $t_R = 8.8$ min.

^1H NMR (300.1 MHz, CDCl_3) δ 7.56 (d, $J = 6.7$ Hz, 2H), 7.40 – 7.27 (m, 3H), 5.74 (td, $J = 57.4, 4.3$ Hz, 1H), 5.39 (s, 1H), 5.01 (s, 1H), 2.03 – 1.93 (m, 1H), 1.58 – 1.44 (m, 1H), 1.15 – 1.06 (m, 1H), 1.06 – 0.96 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 146.3, 140.6, 128.5, 128.0, 126.2, 117.0 (t, $J = 238.2$ Hz), 111.3, 22.6 (t, $J = 26.7$ Hz), 19.1 (t, $J = 4.6$ Hz), 8.8 (t, $J = 4.4$ Hz).

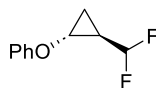
^{19}F NMR (282.4 MHz, CDCl_3) δ -114.6 (ddd, $J = 281.0, 57.5, 10.6$ Hz), -115.9 (ddd, $J = 281.0,$

Experimental Part

58.3, 11.9 Hz).

HRMS (EI⁺) calcd for C₁₂H₁₂F₂ ([M]⁺) 194.09071, found: 194.09082 (Δ 0.58 ppm).

IR (neat) 2960, 2925, 2853, 1488, 1235, 1143, 1036, 1001, 753, 695 cm⁻¹.



28c
((1R,2R)-2-(difluoromethyl)cyclopropoxy)benzene

28c. This cyclopropane was obtained using the general procedure original from **12z** (57.3 mg, 0.177 mmol, 1.0 equiv.), (27.2 mg, 88%) were obtained without purification. Colorless oil. $[\alpha]_D^{20} = -10.2$ (c = 1.0, CHCl₃).

Enantiomeric Ratio: 95:5. The enantiomeric ratio was determined by HPLC with a Chiralcel OJ column (*n*-heptane: *i*-PrOH = 99:1 220 nm, 1 mL/min), $t_R = 9.3$ min, $t_R = 11.1$ min.

¹H NMR (300.1 MHz, CDCl₃) δ 7.32 (dd, $J = 8.8, 7.3$ Hz, 2H), 7.08 – 6.98 (m, 3H), 5.90 (td, $J = 57.5, 3.4$ Hz, 1H), 3.91 (ddd, $J = 6.3, 3.9, 2.6$ Hz, 1H), 2.18 (s, 1H), 1.74 – 1.58 (m, 1H), 1.25 – 1.15 (m, 2H).

¹³C NMR (75.5 MHz, CDCl₃) δ 158.2, 129.7, 121.7, 114.9, 114.9 (t, $J = 238.6$ Hz), 51.7 (t, $J = 6.2$ Hz), 21.7 (t, $J = 26.0$ Hz), 9.5 (t, $J = 4.3$ Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -117.2 (dd, $J = 12.4, 5.6$ Hz), -117.4 (dd, $J = 12.4, 5.7$ Hz).

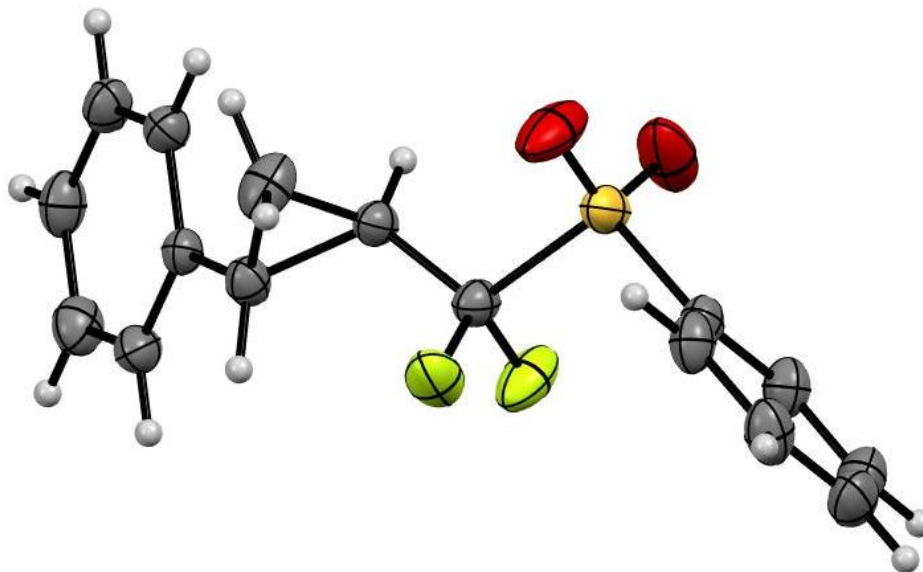
HRMS (EI⁺) calcd for C₁₀H₁₀F₂O ([M]⁺) 184.06997, found: 184.07090 (Δ 5.06 ppm).

IR (neat) 2960, 2926, 2855, 1495, 1239, 1143, 1036, 999, 752, 690 cm⁻¹.

4. Crystallographic data for compound

((difluoro((1R,2R)-2-phenylcyclopropyl)methyl)sulfonyl)benzene (**12a**)

Experimental Part



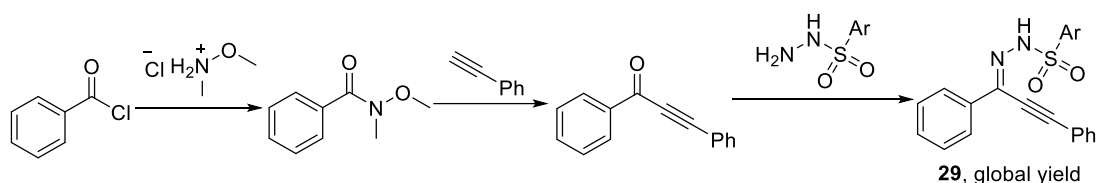
Displacement ellipsoids drawn at the 50% probability level

Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of CHCl_3 and heptane solution. X-ray diffraction experiments for monocystal of **((difluoro((1R,2R)-2-phenylcyclopropyl)methyl)sulfonyl)benzene** were performed at 150 K with graphite-monochromatized Mo K radiation ($\lambda = 0.71073 \text{ \AA}$) on a Bruker D8 QUEST diffractometer. Formula $\text{C}_{16}\text{H}_{14}\text{F}_2\text{O}_2\text{S}$, formula weight 308.33. Crystal system orthorhombic, space group $P 2_12_12_1$, $a = 7.3658(7) \text{ \AA}$, $b = 11.9868(12) \text{ \AA}$, $c = 16.4735(18) \text{ \AA}$, $\alpha = \beta = \gamma = 90^\circ$, $V = 1454.5(3) \text{ \AA}^3$, $Z = 4$, calculated density = 1.408 g/cm^3 , $\mu = 0.246 \text{ mm}^{-1}$, $R_{\text{int}} = 0.0833$, $R[F^2 - 2(F^2)] = 0.036$, $wR(F^2) = 0.096$. Independent reflections = 8993. GOF=1.053, 190 parameters, final difference map within 0.479 and -0.332 e\AA^{-3} . The structure was solved using direct methods and refined by full-matrix least-squares analysis on F^2 . Selected bond lengths (\AA) and angles (deg) : F2-C4 1.3530(15), F1-C4 1.3552(13), S1-C4 1.8471(11), C1-C2 1.4949(16), C1-C3 1.5202(15), C3-C2 1.5041(16), C1-C2-C3 60.92(7), C2-C3-C1 59.24(8), C2-C1-C3 59.84(8). Program(s) used to solve structure: SHELXT2014/5 (Sheldrick 2015). Program(s) used to refine structure: SHELXL-2019/1 (Sheldrick, 2019). Software used to prepare material for publication: SHELXTL. CCDC 2270075 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

Chapter IV – Rh(II)-Catalyzed *N*-sulfonylhydrazones decomposition for the synthesis of enantiopure alkynylcyclopropanes

1. The general procedures for the synthesis of starting materials

1.1. Synthesis of phenyl alkynyl hydrazones.



Step 1: To a solution of *N*-methoxy-*N*-methylamine hydrochloride (4.0 g, 40 mmol, 1.0 equiv.) in CH_2Cl_2 (80 mL) were sequentially added triethylamine (11.2 mL, 80 mmol, 2.0 equiv.) and benzoyl chloride (4.6 mL, 40 mmol, 1.0 equiv.) at 0 °C. The resulting mixture was warmed to room temperature and stirred for 16 h. The reaction was quenched with sat. aq. NaHCO_3 (50 mL), and the product was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (Petroleum ether/AcOEt = 2:1) to Weinreb's amide²⁹⁵ as a colorless oil.

Step 2: A flame-dried round bottom flask was charged with a stir bar and sealed with septa. Tetrahydrofuran (50 mL) and phenyl acetylene (4.0 g, 39 mmol, 1.0 equiv.) were added through a syringe. The solution was allowed to cool to -40 °C upon which *n*-BuLi (17.1 mL, 42.9 mmol, 2.5 M in hexanes) was added dropwise by syringe over 5 minutes. The mixture was allowed to stir at -40 °C for 10 min, the solution was allowed to warm to -15 °C. After 15 min the mixture was allowed to cool to -78 °C and a solution of Weinreb's amide (6.44 g, 39 mmol in 5 mL of dry THF) was added through a syringe. The mixture was allowed to stir at -78 °C for 10 min, and the solution was allowed to warm to room temperature for 30 min. The reaction was quenched through addition of a saturated aqueous solution of NaHCO_3 (40 mL). The mixture was diluted with EtOAc (40 mL) and extracted with EtOAc (2×40 mL), The combined organic layers were washed with a saturated brine (2×50 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography (Petroleum ether/AcOEt = 2:1) to afford 1,3-diphenyl-2-propyn-1-one²⁹⁶ as a light-yellow oil.

Step 3: Method A. A solution of 1,3-diphenyl-2-propyn-1-one (412 mg, 2 mmol, 1.0 equiv.) in absolute ethanol (2 mL) was added dropwise over 5 min to a slurry of aryl sulfonylhydrazide (2 mmol, 1.0 equiv.) in absolute ethanol (3 mL) with 0.2 mL concentrated sulfuric acid (cat.) at 0 °C. After stirring at 0 °C for an additional 15 min, the ice bath was removed, and the pale-yellow slurry was stirred at room temperature. After 15 min, the product began to precipitate from solution as a white solid. After stirring for three hours at room temperature, the white slurry was cooled to 0 °C and

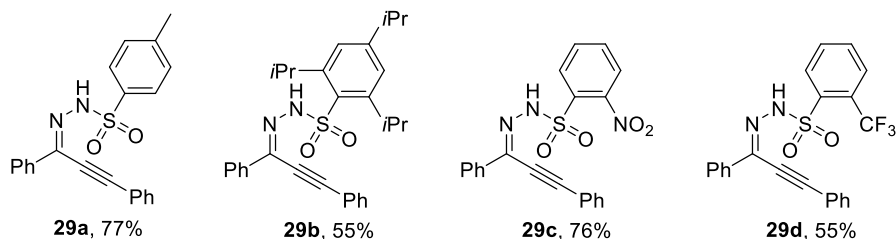
²⁹⁵ A. Kondoh, N. Tasato, T. Aoki, M. Terada, *Org. Lett.* **2020**, 22, 5170–5175.

²⁹⁶ D. K. Friel, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2008**, 130, 9942–9951.

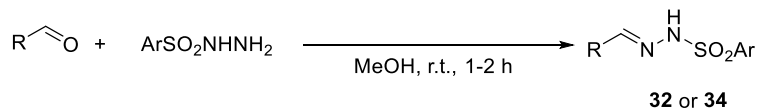
Experimental Part

stirred for 10 min. The white solid was isolated by suction filtration and washed with cold water. The crude product was dissolved in CH₂Cl₂ (10 mL), and the CH₂Cl₂ solution was washed with 5% NaHCO₃ (3×10 mL), saturated NaCl (aqueous) (2×10 mL), and water (2×10 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and the solvent was removed in vacuo to afford the crude product as a pale yellow solid. The crude product was recrystallized from absolute ethanol to afford the tosylhydrazone **29a** (740 mg, 77% overall yield), trisylhydrazone **29b** (650 mg, 55% overall yield) and **29d** (553 mg, 55% overall yield) as white crystals. The NMR data is correspondence to literature.²⁹⁷

Step 3: Method B. To a rapidly stirred suspension of NsNHNH₂ (2.0 mmol, 1.0 equiv) and La(OTf)₃ (2.0 mol %) in methanol (2.0 mL), alkynals or alkynones (2.2 mmol, 1.1 equiv) was added and stired at room temperature for 1~3 h (monitored by TLC) and the crude products are obtained as solid precipitates. The precipitations were filtered, washed by petroleum ether/diethyl ether then was dried in vacuo to afford alkynyl-*N*-nosylhydrazones **29c** (632 mg, 76% overall yield) as white solids. The NMR data is correspondence to reported literature.²⁹⁸



1.2. Synthesis of *N*-sulfonylhydrazones **32** and **34**.



To a stirred solution of ArSO₂NHNH₂ (2.0 mmol, 1.0 equiv.) in methanol (2 mL) were added carbonyl compounds (2.2 mmol, 1.1 equiv.) and the mixture was stirred for 1-2 h at room temperature. The mixture was filtered and the resulting solid was washed with ice cold diethyl ether and dried under reduced pressure to give pure *N*-Sulfonylhydrazones **32**, or **34** as white solids. The NMR data is correspondence to reported literature, **32a-c**, **32e**,²⁹⁹ **32d**³⁰⁰ or **34**²³¹.

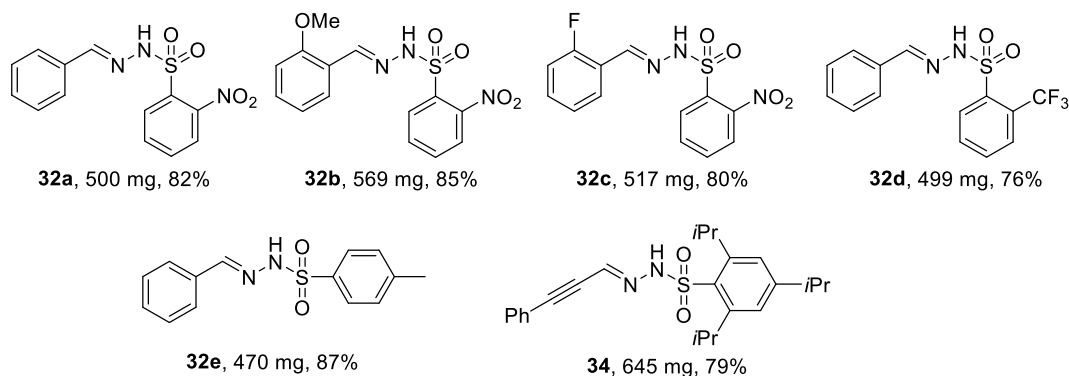
²⁹⁷ J. T. DePinto, W. A. DeProphetis, J. L. Menke, R. J. McMahon, *J. Am. Chem. Soc.* **2007**, *129*, 2308–2315.

²⁹⁸ Y. Yang, Z. Liu, A. Porta, G. Zanoni, X. Bi, *Chem. Eur. J.* **2017**, *23*, 9009–9013.

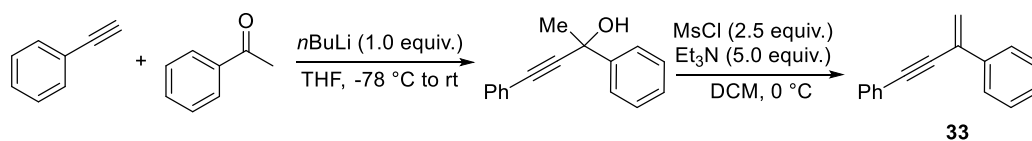
²⁹⁹ E. M. Allouche, A. Al-Saleh, A. B. Charette, *Chem. Commun.* **2018**, *54*, 13256–13259.

³⁰⁰ Z. Liu, K. R. Babu, F. Wang, Y. Yang, X. Bi, *Org. Chem. Front.* **2019**, *6*, 121–124.

Experimental Part



Synthesis of 1,3-enyne **33**.



Step 1: To a 100 mL round bottomed flask was charged with compound phenyl acetylene (2.04 g, 20 mmol, 1.0 equiv.) and 40 mL of anhydrous THF. The solution was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-BuLi (2.5 M in THF, 8 mL, 20 mmol, 1.0 equiv.) was added. The resulting solution was stirred for 20 minutes at room temperature and then cooled to $-78\text{ }^{\circ}\text{C}$ again. Acetophenone (2.4 g, 20 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was then allowed to warm to room temperature and was monitored by TLC for completion. On completion the reaction was quenched with saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with ethyl acetate ($3\times 20\text{ mL}$) and the combined organic layers were washed with brine (30 mL), dried over MgSO_4 and filtered. Then the organic layer was concentrated under reduced pressure to afford the crude 2,4-diphenylbut-3-yn-2-ol,³⁰¹ which was used directly in the next step without further purification.

Step 2: The resulting crude 2,4-diphenylbut-3-yn-2-ol was dissolved in dry CH_2Cl_2 (40 mL), and the mixture was cooled to $0\text{ }^{\circ}\text{C}$ with a cooling bath. To this solution was added triethylamine (10.1 g, 100 mmol, 5 equiv.) and methylsulfonyl chloride (5.73 g, 50 mmol, 2.5 equiv.) sequentially. After 30 min the reaction was monitored by TLC for completion. Once completion the reaction was quenched with saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with ethyl acetate ($3\times 20\text{ mL}$) and the combined organic layers were washed with brine (30 mL), dried over MgSO_4 , filtered, and concentrated under reduced pressure (control temperature below $30\text{ }^{\circ}\text{C}$). The crude material was purified by flash chromatography (pure petroleum ether) to yield the 1,3-enyne **33** (2.56 g, 63%) as a light-yellow oil. The NMR data is correspondence to reported literature.³⁰²

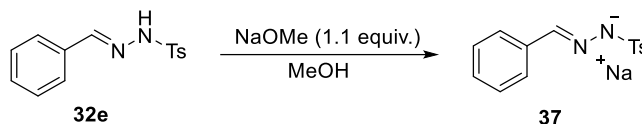
Synthesis of tosylhydrazone sodium salt **37**.³⁰³

³⁰¹ S. Sadhukhan, B. Baire, *J. Org. Chem.* **2022**, *87*, 5530–5542.

³⁰² L. Wang, R. Ma, J. Sun, G. Zheng, Q. Zhang, *Chem. Sci.* **2022**, *13*, 3169–3175.

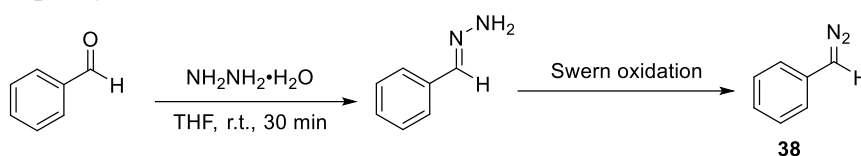
³⁰³ V. K. Aggarwal, E. Alonso, I. Bae, G. Hynd, K. M. Lydon, M. J. Palmer, M. Patel, M. Porcelloni, J. Richardson, R. A. Stenson, J. R. Studley, J.–L. Vasse, C. L. Winn, *J. Am. Chem. Soc.* **2003**, *125*, 10926–10940.

Experimental Part



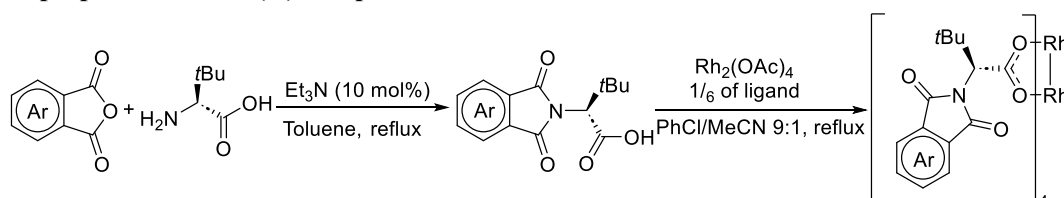
A 1 M sodium methoxide solution was prepared by adding sodium (115.2 mg, 5 mmol, 1.0 equiv.) to anhydrous methanol (5 mL) with external cooling. Once all of the metal had dissolved, the tosylhydrazone **32e** (1.37 g, 5 mmol, 1.0 equiv.) was added, and the mixture was stirred until the solid had dissolved. After stirring for an additional 15 minutes, the methanol was removed under reduced pressure at room temperature, yielding the hydrazone salt **37** in quantitative yield. The solid hydrazone salt was then ground using a pestle and mortar to obtain a free-flowing powder. All salts were stored at -20°C , and direct exposure to light was avoided.

Synthesis of phenyldiazomethane **38**.³⁰⁴



In a round-bottomed flask containing 12 mL of N_2H_4 (1 M in THF, 12 mmol), a solution of aldehyde (1 M in THF, 10 mmol) was slowly added. The mixture was stirred for 30 min at room temperature. The mixture was evaporated under reduced pressure to affording the desired hydrazone (>95% yield). All hydrazones were used without further purification for the generation of diazo compounds. Under a nitrogen atmosphere oxalyl chloride (0.225 mL, 1.05 equiv.) was added dropwise to a stirred solution of Et_2O (21 mL) containing DMSO (0.195 mL, 1.1 equiv.) at -55°C . After gas evolution ceased (~ 20 min), the reaction was cooled down to -78°C . Behind a blast shield, a mixture of Et_3N (0.732 mL, 2.1 equiv.) and hydrazone (300 mg, 2.50 mmol, 1.0 equiv.) in THF (6 mL) was added drop wise over a period of 5-7 min to the activated DMSO solution. An immediate color change and concomitant formation of a white precipitate were observed. The reaction mixture was maintained at -78°C for ~ 1 h and allowed to gradually warm up to 0°C followed by the addition of and ice-cold half saturated NH_4Cl solution (20ml) was added. The reaction mixture was extracted with cold Et_2O (dry ice was added to reach -30°C , 2×50 mL), and the combined organic layers were dried over magnesium sulfate, filtered and concentrated at 15°C under reduced pressure. The phenyldiazomethane was immediately dissolved in solvent and used for the cyclopropanations. The concentration was determined by titration of a 10 mL aliquot with 0.10 M benzylic acid in CH_2Cl_2 .

The preparation of Rh(II)-complexes.²³²



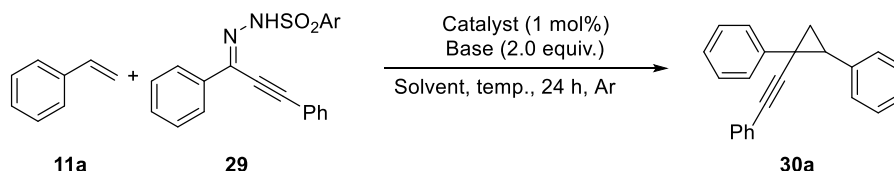
A 50 mL round-bottom flask was equipped with a stirring bar and charged with (*S*)-tert-leucine (10.0 mmol, 1.0 equiv.), phthalic anhydride (10.0 mmol, 1.0 equiv.) and toluene (25 mL). Triethylamine

³⁰⁴ N. Fei, B. Sauter, D. Gillingham, *Chem. Commun.* **2016**, 52, 7501–7504.

Experimental Part

(101 mg, 1.0 mmol) was added and the mixture was heated to reflux, while the solvent was distilled off at a rate such that ca. 2 mL of the solvent was removed per 10 min. After heating the mixture for 1 h, 5% hydrochloric acid (15 mL) was added and resulting solution was extracted with EtOAc (40 mL). The organic layer was washed with brine (15 mL) and dried over anhydrous Na₂SO₄. Filtration and concentration in vacuo provided a white solid (5.88 g). Recrystallization was performed by dissolving the solid in hot ethyl acetate (8 mL) and then adding hexane (24 mL). Colorless plates formed at room temperature after standing overnight, and were collected by suction, washed with 5 mL of hexane-EtOAc (3:1) and dried in vacuo to give corresponding *N*-phthaloyl-(*S*)-tert-leucine. A 100 mL round-bottom flask was equipped with a stirring bar and charged with Rh₂(OAc)₄ (506 mg, 1.0 mmol, 1.0 equiv.), *N*-phthaloyl-(*S*)-tert-leucine (6.0 mmol, 6.0 equiv.) and 40 mL of chlorobenzene-acetonitrile (9:1). The mixture was heated to reflux, while the solvent was distilled off at a rate such that ca. 5 mL of solvent was removed per hour. After 3 h, the remaining solvent was removed in vacuo, the residue was dissolved in benzene (60 mL). The resulting solution was washed with saturated aqueous NaHCO₃ (2×15 mL) and brine (15 mL), and dried over anhydrous Na₂SO₄. Filtration and evaporation in vacuo furnished a green solid (2.91 g), which was purified by column chromatography on silica gel (90 g, 50:50:1 hexane/dichloromethane/acetonitrile) to provide a green solid. Recrystallization was performed by dissolving the solid in hot benzene (6 mL) and then adding acetonitrile (6 mL). Green plates formed at room temperature after standing overnight, and were collected by suction, washed with 3 mL of acetonitrile-benzene (1:1) and dried in vacuo to yield toluene adduct of dirhodium(II)tetrakis[*N*-phthaloyl-(*S*)-tert-leucinate]: Rh₂(S-TBPTTL)₄ (177 mg, 23% overall yield), Rh₂(S-CF₃PTTL)₄ (280 mg, 23% overall yield), Rh₂(S-TBPTPG)₄ (300 mg, 58% overall yield). The NMR data is correspondence to reported literature.

2. Typical procedures for the synthesis of alkynyl cyclopropanes.

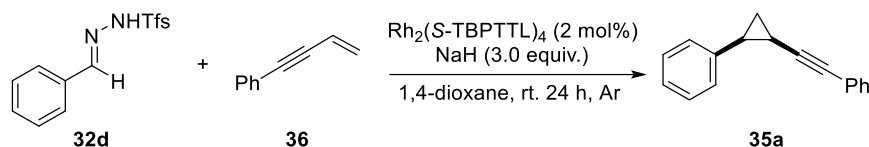


To an oven-dried 10 mL reaction tube was added sulfonylhydrazone **29** (0.2 mmol, 2.0 equiv.) and base (0.2 mmol, 2.0 equiv.) followed by 1 mL solvent. This reaction was protected under argon atmosphere and stirred at room temperature for 1 h. Then alkene **11a** (0.1 mmol, 1.0 equiv.) and 1 mol% catalyst was added in this order, additional 0.5 mL solvent was added. This suspension was stirred at room temperature for 24 h and monitored by TLC. Upon completion, the reaction was filtered through a celite and evaporated under reduce pressure. The residue was analyzed by NMR and purified by flash chromatography (petroleum ether/Et₂O) to yield corresponding alkynyl cyclopropane **30a**.

The racemic alkynylcyclopropane was prepared with Rh₂(Opiv)₄.

¹H NMR (300.1 MHz, CDCl₃) δ 7.57 – 7.50 (m, 2H), 7.47 – 7.35 (m, 3H), 7.33 – 7.27 (m, 2H), 7.26 – 7.20 (m, 2H), 7.17 – 7.06 (m, 3H), 6.96 – 6.91 (m, 1H), 3.02 (dd, *J* = 9.0, 7.3 Hz, 0.4H, *trans*), 2.72 (t, *J* = 8.2 Hz, 0.6H, *cis*), 2.12 – 1.90 (m, 2H).

Experimental Part

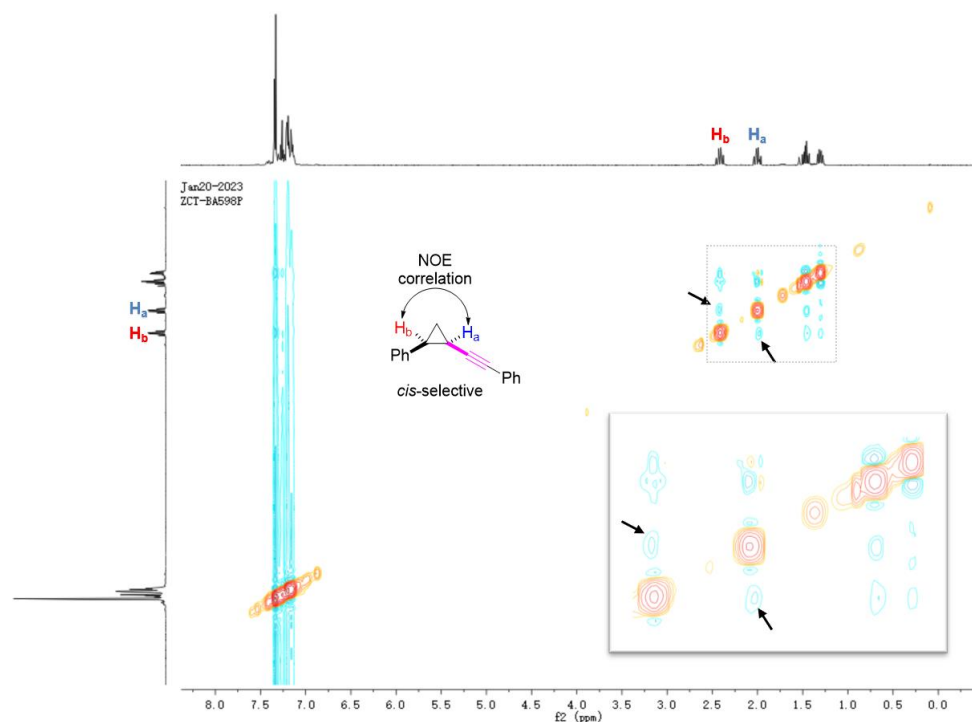


To an oven-dried 10 mL reaction tube was added sulfonylhydrazone **32d** (0.2 mmol, 2.0 equiv.) and base (0.3 mmol, 3.0 equiv.) followed by 1 mL solvent. This reaction was protected under argon atmosphere and stirred at room temperature for 1 h. Then alkene **36** (0.1 mmol, 1.0 equiv.) and 1 mol% catalyst were added in this order, additional 0.5 mL solvent was added. This suspension was stirred at room temperature for 24 h and monitored by TLC. Upon completion, the reaction was filtered through a celite and evaporated under reduce pressure. The residue was analyzed by NMR and purified by flash chromatography (petroleum ether/ Et_2O) to yield corresponding alkynyl cyclopropane **35a**.

The racemic alkynylcyclopropane was prepared with $\text{Rh}_2(\text{Opiv})_4$.

^1H NMR (300.1 MHz, CDCl_3) δ 7.28 – 7.25 (m, 3H), 7.23 – 7.17 (m, 2H), 7.16 – 7.11 (m, 3H), 7.10 – 7.04 (m, 2H), 2.35 (td, $J = 8.4, 6.8$ Hz, 1H), 1.93 (td, $J = 8.5, 5.8$ Hz, 1H), 1.40 (td, $J = 8.6, 5.0$ Hz, 1H), 1.28 – 1.19 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 138.1, 131.5, 128.5, 128.2, 127.9, 127.5, 126.4, 123.9, 89.9, 80.3, 24.1, 15.2, 10.4.

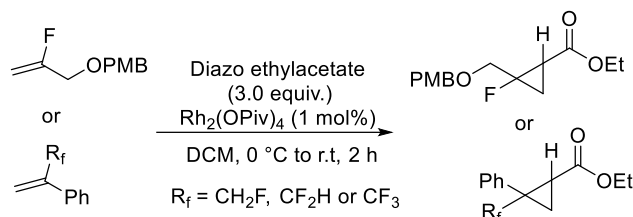


Chapter V – Access to 1,2,3-polysubstituted fluorinated cyclopropanes by Pd(II)-catalyzed C–H bond activation

1. General procedures for the preparation of the starting materials.

1.1. Procedure for the preparation of fluorinated cyclopropanes 37 and 41.

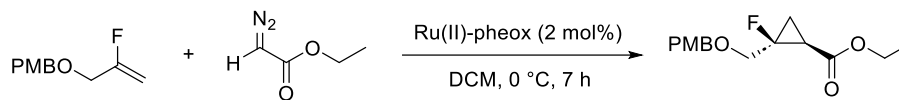
Synthesis of the ethyl carboxylate cyclopropane.



Racemic process: Under the argon atmosphere, to a flame dried 100 mL round bottom flask, $\text{Rh}_2(\text{OPiv})_4$ (61 mg, 0.1 mmol, 1 mol%) was added, then the fluorinated olefin (10 mmol, 1.0 equiv.) and 20 mL DCM were added to the flask. After cooling the solution to 0 °C, a solution of diazo ethyl acetate (3.42 g, 30 mmol, 3.0 equiv.) in 20 mL DCM was added dropwise by syringe pump (addition rate: 30 mL/h). When the diazo was added completely, the mixture was allowed to stir at room temperature until completion was indicated by ^{19}F NMR analysis. The solution was concentrated by vacuum rotary evaporator and the crude product was purified by silica column chromatography to afford the corresponding ethyl carboxylate cyclopropane.

(**Note:** Only the two diastereoisomers of ethyl carboxylate cyclopropane precursors for **41** couldn't be separated)

Synthesis of enantiomeric pure ethyl carboxylate cyclopropanes precursor for 37.

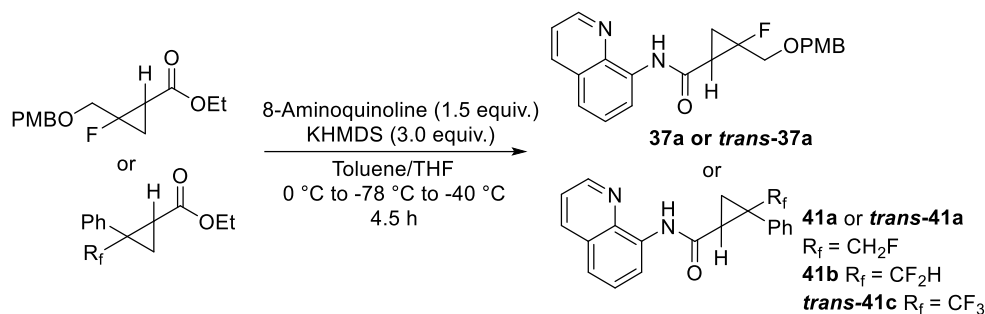


Under the argon atmosphere, to a flame dried 50 mL round bottom flask, Ru(II)-pheox (home-made) (25.6 mg, 0.04 mmol, 2 mol%) was added in glovebox, then the fluorinated olefin (392 mg, 2 mmol, 1.0 equiv.) and 5 mL distilled DCM were added. After cooling the solution to 0 °C, a solution of diazo ethyl acetate (1.14 g, 10 mmol, 5 equiv.) in 10 mL distilled DCM was added dropwise by syringe pump (addition rate: 1.5 mL/h). When the diazo was added completely, the mixture was allowed to stir at this temperature until completion was indicated by ^{19}F NMR analysis. The solution was concentrated by vacuum rotary evaporator and the crude product was purified by silica column chromatography to afford the corresponding ethyl carboxylate cyclopropane as a colorless oil in 82% yield (*cis:trans* 44:56).

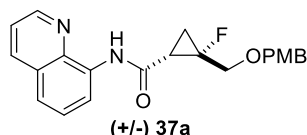
The enantiomeric pure ethyl carboxylate cyclopropane precursors for **41a**, **41b** and **41c** were prepared according to the reported literature.^{171d}

Experimental Part

Synthesis of starting materials **37a**, *trans*-**37a**, **41a**, *trans*-**41a**, **41b**, *trans*-**41c**.



A flame dried 100 mL three-necked round bottom flask, which was equipped with a magnetic stir bar and charged with 8-aminoquinoline (1.08 g, 7.5 mmol, 1.5 equiv.). The flask was purged with argon for three times, and then anhydrous THF (1 mL) was added via a syringe. The suspension was cooled to 0 °C. The KHMDS (0.7 mol/L in toluene, 10.7 mL, 7.5 mmol, 1.5 equiv.) was added slowly and stirred for 1 hour at 0 °C. The reaction mixture was cooled down to -78 °C, then a solution of ethyl carboxylate cyclopropane (5 mmol, 1.0 equiv.) in anhydrous THF (5 mL) was added to the mixture. After stirring at -40 °C for 4.5 hours, water and HCl (1 N) were added to the reaction mixture. The mixture was extracted with ethyl acetate three times, the organic phase was washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered via a funnel and concentrated by vacuum rotary evaporator. The crude product was purified by silica gel column chromatograph to afford the racemic products **37a**, *trans*-**37a**, **41a**, *trans*-**41a**, **41b** and *trans*-**41c**. This method was also adapted to prepare enantiomeric pure products (*1S*, *2S*)-**37a**, (*1S*, *2R*)-**37a**, (*1S*, *2R*)-**41a**, (*1S*, *2R*)-**41b** and *trans*-**41c** (Note: the diastereoisomers of **41c** could be separated by silica-gel chromatography)



(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 67%. $R_f = 0.24$. (petroleum ether / ethyl acetate, 75/25). Yellow foam.

¹H NMR (300.1 MHz, CDCl₃) δ 10.06 (s, 1H), 8.79 (dd, $J = 2.1, 1.7$ Hz, 1H), 8.77 (d, $J = 1.7, 0.8$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.58 – 7.47 (m, 2H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.32 (d, $J = 8.7$ Hz, 2H), 6.89 (d, $J = 8.7$ Hz, 2H), 4.62 (dd, $J = 18.0, 11.6$ Hz, 2H), 3.91 (dd, $J = 17.3, 11.7$ Hz, 1H), 3.83 – 3.68 (m, 4H), 2.21 – 2.03 (m, 2H), 1.33 (ddd, $J = 15.8, 9.8, 7.3$ Hz, 1H).

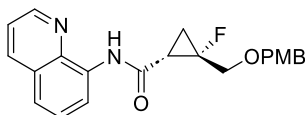
¹³C NMR (75.5 MHz, CDCl₃) δ 165.3, 159.5, 148.2, 138.4, 136.5, 134.6, 129.8, 129.6, 128.0, 127.5, 121.7, 121.6, 116.8, 114.0, 81.2 (d, $J = 231.1$ Hz), 73.1, 71.3 (d, $J = 24.3$ Hz), 55.4, 27.0 (d, $J = 11.1$ Hz), 15.3 (d, $J = 11.6$ Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -195.4 – -195.6 (m, 1F).

IR (neat) 3344, 3010, 2834, 1686, 1608, 1524, 1485, 1245, 1089, 790 cm⁻¹.

HRMS (ES⁺) calcd for C₂₂H₂₁FN₂O₃ m/z 381.1614 ([M+H]⁺) found 381.1611 (Δ -0.8 ppm).

Experimental Part

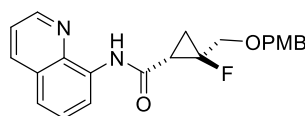


(1S,2S)-**37a**

(1S,2S)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 65%. $R_f = 0.24$ (petroleum ether / ethyl acetate, 75/25). Yellow foam.

Enantiomeric Excess: 83%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (n-heptane: *i*-PrOH = 70:30, 254 nm, 1 mL/min), $t_R = 10.5$ min, $t_R = 19.6$ min. $[\alpha]_D^{20} = +57.3$ ($c = 1$).



(+/-) *trans*-**37a**

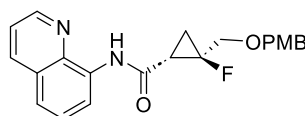
(*trans*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 35%. $R_f = 0.35$ (petroleum ether / ethyl acetate, 75/25). Yellow foam.

^1H NMR (300.1 MHz, CDCl_3) δ 10.16 (s, 1H), 8.80 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.71 (dd, $J = 6.2, 2.8$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.58 – 7.42 (m, 3H), 7.14 – 7.06 (m, 2H), 6.64 – 6.57 (m, 2H), 4.47 (dd, $J = 26.3, 11.5$ Hz, 2H), 4.16 (dd, $J = 18.9, 11.7$ Hz, 1H), 3.89 (dd, $J = 30.5, 11.9$ Hz, 1H), 3.70 (s, 3H), 2.56 – 2.39 (m, 1H), 1.72 – 1.53 (m, 2H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.0, 159.1, 148.3, 138.3, 136.4, 134.6, 130.1, 129.3, 128.0, 127.4, 121.8, 121.7, 116.5, 113.6, 82.2 (d, $J = 227.6$ Hz), 73.0, 68.3 (d, $J = 19.5$ Hz), 55.2, 27.3 (d, $J = 11.9$ Hz), 16.5 (d, $J = 9.6$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -173.3 - -173.6 (m, 1F).



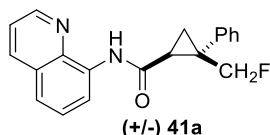
(1S, 2R)-**37a**

(1S,2R)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 35%. $R_f = 0.35$ (petroleum ether / ethyl acetate, 75/25). Yellow foam.

Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (n-heptane: *i*-PrOH = 70:30, 254 nm, 1 mL/min), $t_R = 8.1$ min, $t_R = 9.5$ min. $[\alpha]_D^{20} = +42.6$ ($c = 1$).

Experimental Part



(cis)-2-(fluoromethyl)-*N*-(naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 92/8). Yield: 82%. $R_f = 0.61$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 100 – 102 °C.

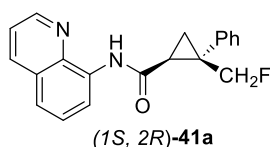
^1H NMR (300.1 MHz, CDCl_3) δ 10.10 (s, 1H), 8.86 – 8.58 (m, 2H), 8.06 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.51 – 7.15 (m, 8H), 4.88 (td, $J = 47.2, 10.2$ Hz, 2H), 2.32 – 2.13 (m, 1H), 1.89 – 1.71 (m, 1H), 1.53 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 168.4, 148.3, 141.7, 138.4, 136.5, 134.7, 128.8, 128.6, 128.1, 127.5, 127.5, 121.8, 121.7, 116.6, 85.1 (d, $J = 169.1$ Hz), 35.3 (d, $J = 22.6$ Hz), 30.0 (d, $J = 4.8$ Hz), 18.1 (d, $J = 7.4$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -214.5 (td, $J = 47.7, 5.6$ Hz, 1F).

IR (neat) 3344, 1681, 1578, 1522, 1484, 1424, 1164, 826, 791, 695 cm^{-1} .

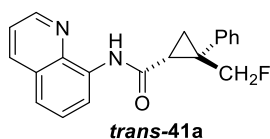
HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{17}\text{FN}_2\text{O}$ m/z 321.1403 ($[\text{M}+\text{H}]^+$) found 321.1402 (Δ -0.3 ppm)



(1S,2R)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 92/8). Yield: 79%. $R_f = 0.61$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 100 – 102 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (n-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), $t_R = 8.3$ min, $t_R = 9.7$ min. $[\alpha]_D^{20} = +23.6$ ($c = 0.5$, CHCl_3).



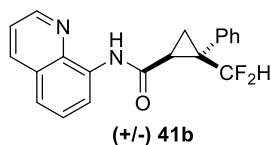
(trans)-2-(fluoromethyl)-*N*-(naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 92/8). Yield: 81%. $R_f = 0.48$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 105 – 107 °C.

^1H NMR (300.1 MHz, CDCl_3) δ 10.04 (s, 1H), 8.85 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.54 (dd, $J = 7.0, 2.0$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.50 – 7.37 (m, 5H), 7.32 – 7.23 (m, 3H), 4.62 (dd, $J = 41.8, 6.5$ Hz, 1H), 4.45 (dd, $J = 41.5, 6.5$ Hz, 1H), 2.44 (dd, $J = 8.2, 5.6$ Hz, 1H), 2.05 (dd, $J = 9.4, 5.1$ Hz, 1H), 1.52 (dd, $J = 8.2, 4.9$ Hz, 1H).

^{19}F NMR (282.4 MHz, CDCl_3) δ -215.0 (td, $J = 48.1, 4.0$ Hz, 1F).

Experimental Part



(*cis*)-2-(difluoromethyl)-*N*-(naphthalen-1-yl)-2-phenylcyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 74%. $R_f = 0.44$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 134 – 136 °C.

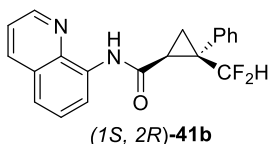
^1H NMR (300.1 MHz, CDCl_3) δ 10.26 (s, 1H), 8.84 (d, $J = 2.7$ Hz, 1H), 8.77 (dd, $J = 5.6, 3.1$ Hz, 1H), 8.19 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.60 – 7.46 (m, 5H), 7.39 (d, $J = 6.9$ Hz, 3H), 6.36 (t, $J = 55.5$ Hz, 1H), 2.41 – 2.26 (m, 1H), 2.03 (t, $J = 5.4$ Hz, 1H), 1.69 (dd, $J = 13.4, 6.9$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.9, 148.4, 138.3, 136.5, 135.9, 134.3, 131.1, 128.4, 128.3, 128.0, 127.4, 122.0, 121.8, 116.7, 115.5 (dd, $J = 239.0, 236.9$ Hz), 36.9 (dd, $J = 29.0, 26.2$ Hz), 28.7 (d, $J = 5.1$ Hz), 16.8 (d, $J = 7.4$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -112.9 (d, $J = 286.0$ Hz, 1F), -119.3 (d, $J = 286.0$ Hz, 1F).

IR (neat) 3332, 3059, 2931, 1679, 1522, 1484, 1166, 1028, 792, 697 cm^{-1} .

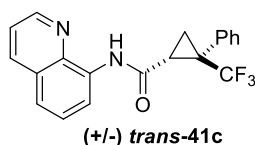
HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{16}\text{F}_2\text{N}_2\text{O}$ m/z 339.1309 ($[\text{M}+\text{H}]^+$) found 339.1302 (Δ -2.1 ppm).



(1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 70%. $R_f = 0.44$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 134 – 136 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (n-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), $t_R = 5.5$ min, $t_R = 6.7$ min. $[\alpha]_D^{20} = +65.8$ ($c = 0.5$, CHCl_3).



(*trans*)-*N*-(naphthalen-1-yl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxamide

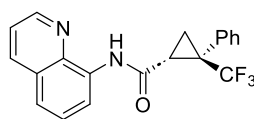
Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 65%. $R_f = 0.56$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 138 – 140 °C.

^1H NMR (300.1 MHz, CDCl_3) δ 10.15 (s, 1H), 8.88 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.48 (dd, $J = 7.5, 1.3$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.54 – 7.38 (m, 5H), 7.33 – 7.24 (m, 3H), 2.70 (dd, $J = 8.7, 6.1$ Hz, 1H), 2.16 – 2.01 (m, 1H), 1.83 (dd, $J = 8.8, 5.4$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 165.3, 148.3, 138.2, 136.4, 134.2, 131.3, 131.2, 128.8, 128.4, 127.9, 127.4, 125.3 (q, $J = 274.8$ Hz), 121.7, 121.7, 116.6, 36.1 (q, $J = 66.2, 33.1$ Hz), 26.2 (d, $J = 1.9$ Hz), 14.2 (d, $J = 2.4$ Hz).

Experimental Part

^{19}F NMR (282.4 MHz, CDCl_3) δ -70.5 (s, 3F).

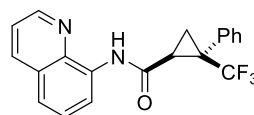


ent-trans-41c

ent-trans-2-phenyl-*N*-(quinolin-8-yl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 67%. R_f = 0.56 (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 138 – 140 °C.

Enantiomeric Excess: 83%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), t_R = 5.2 min, t_R = 7.1 min. $[\alpha]_D^{20}$ = +33.5 (c = 1).



(+/-) 41c

cis-*N*-(naphthalen-1-yl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 86/14). Yield: 50% over two steps. R_f = 0.45 (petroleum ether / ethyl acetate, 83/17). Yellow foam.

^1H NMR (300.1 MHz, CDCl_3) δ 10.27 (s, 1H), 8.87 (dd, J = 4.2, 1.6 Hz, 1H), 8.80 (dd, J = 6.4, 2.6 Hz, 1H), 8.18 (dd, J = 8.3, 1.6 Hz, 1H), 7.66 – 7.59 (m, 2H), 7.59 – 7.51 (m, 2H), 7.51 – 7.39 (m, 4H), 2.57 (t, J = 8.1 Hz, 1H), 2.22 (dd, J = 7.1, 5.9 Hz, 1H), 1.70 – 1.62 (m, 1H).

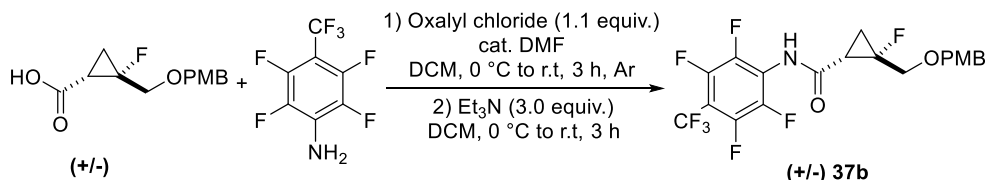
^{13}C NMR (75.5 MHz, CDCl_3) δ 164.9, 148.5, 138.4, 136.5, 135.9, 134.3, 130.9, 129.0, 128.8, 128.1, 127.5, 125.5 (q, J = 275.5 Hz), 122.0, 121.8, 116.7, 35.9 (q, J = 33.6 Hz), 30.6, 14.1 (q, J = 2.4 Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -65.7 (s, 3F).

IR (neat) 3350, 1699, 1584, 1527, 1486, 1300, 1151, 1138, 827, 667 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{20}\text{H}_{15}\text{F}_3\text{N}_2\text{O}$ m/z 357.1203 $[\text{M}+\text{H}]^+$, found 357.1209 (Δ 1.7 ppm)

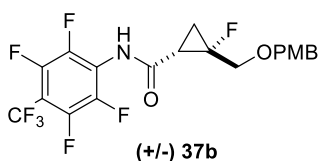
Synthesis of 37b.



Under argon and at 0 °C, oxalyl chloride (170 mg, 1.34 mmol, 1.1 equiv.) was added dropwise to a stirring solution of cyclopropane carboxyl acid (310 mg, 1.22 mmol, 1.0 equiv.) and a drop of DMF in DCM (2.5 mL). The reaction was allowed to warm up to room temperature for 3 h. The solution was cooled to 0 °C and a solution of aniline and Et_3N in DCM (2.5 mL) was added dropwise. This reaction was stirred at room temperature for 16 h, then quenched with NaHCO_3 (5 mL), extracted with DCM (3×10 mL). The organic layer was dried over MgSO_4 and concentrated in vacuo. The product mixture was purified by silica gel chromatography (Pentane/ EtOAc 80/20) to give the

Experimental Part

amide (+/-) **37b** (117 mg, 20% yield) as a yellowish foam.



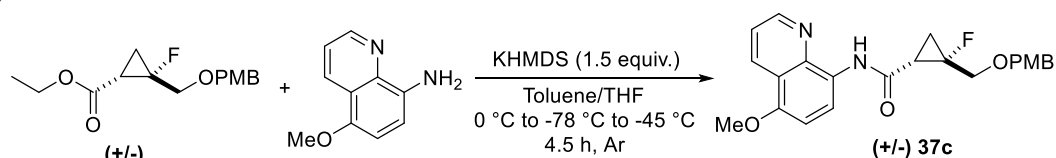
(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)cyclopropane-1-carboxamide

¹H NMR (300.1 MHz, CDCl₃) δ 7.47 (s, 1H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.57 (dd, *J* = 18.0, 11.5 Hz, 2H), 3.95 (dd, *J* = 15.1, 12.0 Hz, 1H), 3.81 (s, 3H), 3.72 – 3.53 (dd, *J* = 22.1, 11.6 Hz, 1H), 2.11 – 1.89 (m, 2H), 1.42 – 1.28 (m, 1H).

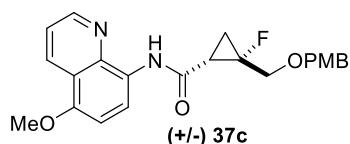
¹³C NMR (75.5 MHz, CDCl₃) δ 165.3, 159.7, 129.7, 129.4, 114.1, 81.4 (d, *J* = 230.5 Hz), 73.4, 70.9 (d, *J* = 24.3 Hz), 55.4, 25.3 (d, *J* = 10.9 Hz), 16.1 (d, *J* = 11.5 Hz). The carbons of fluorinated benzene were not detected.

¹⁹F NMR (282.4 MHz, CDCl₃) δ -56.6 (t, *J* = 21.7 Hz, CF_{3Ar}), -141.1 – -141.5 (m, F_{Ar}), -143.15 – -143.58 (m, F_{Ar}), -194.73 (s, F_{alkyl}).

Synthesis of 37c.



A flame dried 20 mL three-necked round bottom flask, which was equipped with a magnetic stir bar and charged with 5-methoxy-8-aminoquinoline (522 mg, 3.0 mmol, 1.5 equiv.). The flask was purged with argon for three times, and then anhydrous THF (1 mL) was added via a syringe. The suspension was cooled to 0 °C. The KHMDS (0.7 mol/L in toluene, 4.3 mL, 3 mmol, 1.5 equiv.) was added slowly and stirred for 1 hour under 0 °C. The reaction mixture was cooled down to -78 °C, then a solution of ethyl carboxylate cyclopropane (282 mg, 2 mmol, 1.0 equiv.) in anhydrous THF (2 mL) was added to the mixture. After stirring at -40 °C for 4.5 hours, water and HCl (1 N) were added to the reaction mixture. The mixture was extracted with ethyl acetate three times, the organic phase was washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered via a funnel and concentrated by vacuum rotary evaporator. The crude product was purified by silica gel column chromatograph to afford the racemic products (+/-) **37c** (550 mg, 67% yield) as a brown foam.



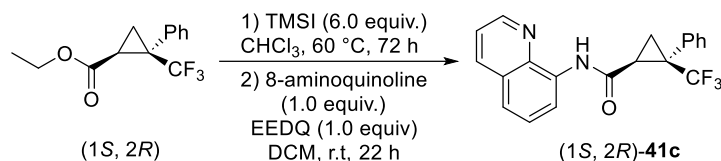
(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(5-methoxyquinolin-8-yl)cyclopropane-1-carboxamide

¹H NMR (300.1 MHz, CDCl₃) δ 9.82 (s, 1H), 8.80 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.70 (d, *J* = 8.6 Hz, 1H), 8.57 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.43 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 1H), 4.62 (dd, *J* = 18.0, 11.6 Hz, 2H), 3.98 (s, 3H), 3.95 – 3.68 (m, 5H), 2.19 – 2.03 (m, 2H), 1.33 – 1.24 (m, 1H).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -196.03 – -196.32 (m, 1F).

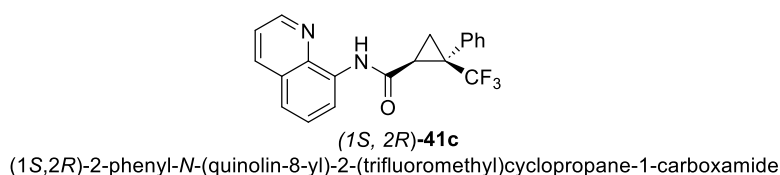
Experimental Part

Synthesis of the starting material (1*S*, 2*R*)-41c.



Step 1: A flame dried 25 mL three-necked round bottom flask, which was equipped with a magnetic stir bar and charged with ethyl carboxylate cyclopropane (258 mg, 1.0 mmol, 1.0 equiv.). The flask was purged with argon for three times, and then anhydrous chloroform (10 mL) was added, followed by TMSI (1.2 g, 6.0 mmol, 6.0 equiv.). This solution was heated to 60 °C for 72 h and monitored by ¹⁹F NMR analysis. When the reaction was complete, water was added to the reaction mixture, extracted with DCM three times, the organic phases were combined and dried over anhydrous MgSO₄, filtered and concentrated by vacuum rotary evaporator. The crude product was used to next step without purification.

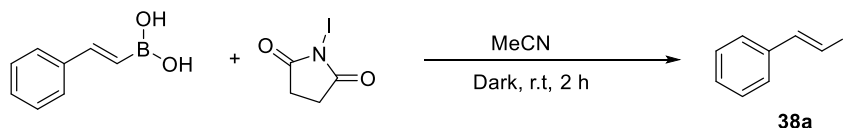
Step 2: A flame dried 25 mL three-necked round bottom flask, which was equipped with a magnetic stir bar and charged with the crude product of previous step, 8-aminoquinoline (158 mg, 1.1 mmol, 1.1 equiv.) and EEDQ (247 mg, 1.0 mmol, 1.0 equiv.). The flask was purged with argon for three times, and then anhydrous DCM (5 mL) was added via a syringe. This mixture was stirring at ambient for 22 h and monitored by ¹⁹F NMR analysis. The solvent was removed by vacuum rotary evaporator. The residue was purified by silica gel column chromatography to afford the products (1*S*, 2*R*)-41c.



Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 86/14). Yield: 48% over two steps. *R*_f = 0.45 (petroleum ether / ethyl acetate, 83/17). Yellow foam. The NMR spectra is consistent with *trans*-41c.

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane: *i*-PrOH = 70:30, 254 nm, 1 mL/min), *t*_R = 5.9 min, *t*_R = 7.0 min. [α]_D²⁰ = +25.7 (*c* = 1).

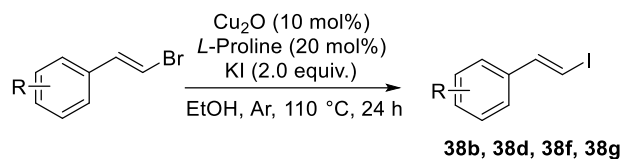
1.2. Preparation of electrophiles 38.



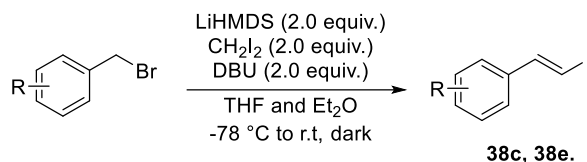
To a solution of boronated styrene (1.48 g, 10 mmol, 1.0 equiv.) in MeCN protect from light was added *N*-Iodosuccinimide (2.7 g, 12 mmol, 1.2 equiv.). After stirring at room temperature for 2 hours, the solution was extracted with pentane (3×50 mL), combined the organic layer and washed with aqueous Na₂S₂O₅ (2×40 mL), water (2×40 mL) and dried over MgSO₄. The solution was evaporated under reduced pressure and purified by flash silica gel column chromatograph, pentane as the elute to afford pure product 38a in 74% yield. The NMR data is consistent with reported

Experimental Part

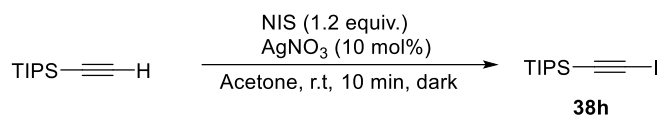
literature³⁰⁵.



A Schlenk tube was charged with Cu₂O (14.3 mg, 0.1 mmol, 0.1 equiv.), *L*-proline (23.0 mg, 0.2 mmol, 0.2 equiv.), vinyl bromide (1.0 mmol, 1.0 equiv.), KI (332 mg, 2.0 mmol, 2.0 equiv.), and anhydrous EtOH (3.0 mL) under an argon atmosphere. The Schlenk tube was sealed with a Teflon valve, and then the reaction mixture was stirred at 110 °C for 24 h. After the reaction was completed, the solvent was removed under reduced pressure. The residue obtained was purified by chromatography (silica gel, PE–EtOAc, 50:1) to produce the corresponding vinyl iodide **38b**, **38d**, **38f**, **38g**. The NMR data is consistent with reported literature³⁰⁶.



A solution of CH₂I₂ (644 μL, 8.0 mmol, 2.0 equiv.) in THF (1.9 mL) was added dropwise to a solution of LiHMDS (1.34 g, 8.0 mmol, 2.0 equiv.) in THF (8 mL) and ether (8 mL) at –78 °C (dry ice/acetone bath) in the dark. After 20 min, a solution of the benzyl bromide substrate (4.0 mmol, 1.0 equiv.) in THF (3 mL) was added dropwise. The reaction mixture was stirred at –78 °C allowing warm to room temperature slowly over 16 h. After this time DBU (1.19 mL, 8.0 mmol, 2.0 equiv.) was added dropwise and the solution stirred for 1 h before ether (50 mL) was added. The mixture was filtered through a plug of celite/silica (approximately 3 cm celite over 3 cm silica) and the solvent removed under reduced pressure. The residue was purified by flash chromatography to provide the vinyl iodide **38c**, **38e**. Where necessary, residual CH₂I₂ following flash chromatography was removed under high vacuum. The NMR data is consistent with reported literature³⁰⁷.



To a stirred solution of ethynyltriisopropylsilane (8.4 mL, 683 mg, 3.74 mmol, 1.0 equiv.) in anhydrous acetone (10.5 mL), protected from light with aluminum foil, were added sequentially NIS (1.01 g, 4.49 mmol, 1.2 equiv.) and silver nitrate (63.3 mg, 0.37 mmol, 0.1 equiv.). After stirring at 25 °C for 10 minutes the volatiles from the reaction mixture were removed under reduced pressure and the residue was filtered through a plug of silica (hexanes) to afford alkynyl iodide **38h** as a colorless liquid (1.06 g, 91 % yield). The NMR data is consistent with reported literature.³⁰⁸

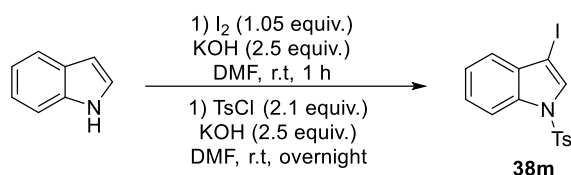
³⁰⁵ N. A. Petasis, I. A. Zavialov, *Tetrahedron Lett.* **1996**, *37*, 567–570.

³⁰⁶ X. Feng, H. Zhang, W. Lu, Y. Yamamoto, A. I. Almansour, N. Arumugam, R. S. Kumar, M. Bao, *Synthesis* **2017**, *49*, 2727–2732.

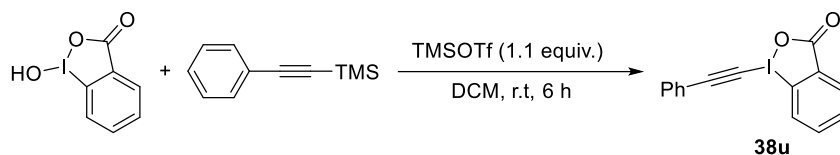
³⁰⁷ J. A. Bull, J. J. Mousseau, A. B. Charette, *Org. Lett.* **2008**, *10*, 5485–5488.

³⁰⁸ K. C. Nicolaou, G. Bellavance, M. Buchman, K. K. Pulukuri, *J. Am. Chem. Soc.* **2017**, *139*, 15636–15639.

Experimental Part



To a solution of the corresponding indole (1.67 g, 14.3 mmol, 1.0 equiv.) in DMF (22 mL) was added freshly KOH (2.0 g, 35.7 mmol, 2.5 equiv.) powder. The mixture was stirred for 30 min at room temperature. A solution of iodine (3.8, 15.0 mmol, 1.05 equiv.) in DMF (22 mL) was added dropwise and the reaction was stirred for 1 hour. KOH (2.0 g 35.7 mmol, 2.5 equiv.) powder was added followed by TsCl (5.73 g, 30.0 mmol, 2.1 equiv.). The reaction was stirred overnight and was then poured into water (200 mL). The product was filtered off, washed with water, a small amount of isopropanol and finally with petrol ether and dried in air to yield the corresponding 3-iodoindoles **38m** (5.2 g, 92% yield). The NMR data is consistent with reported literature.²⁵¹



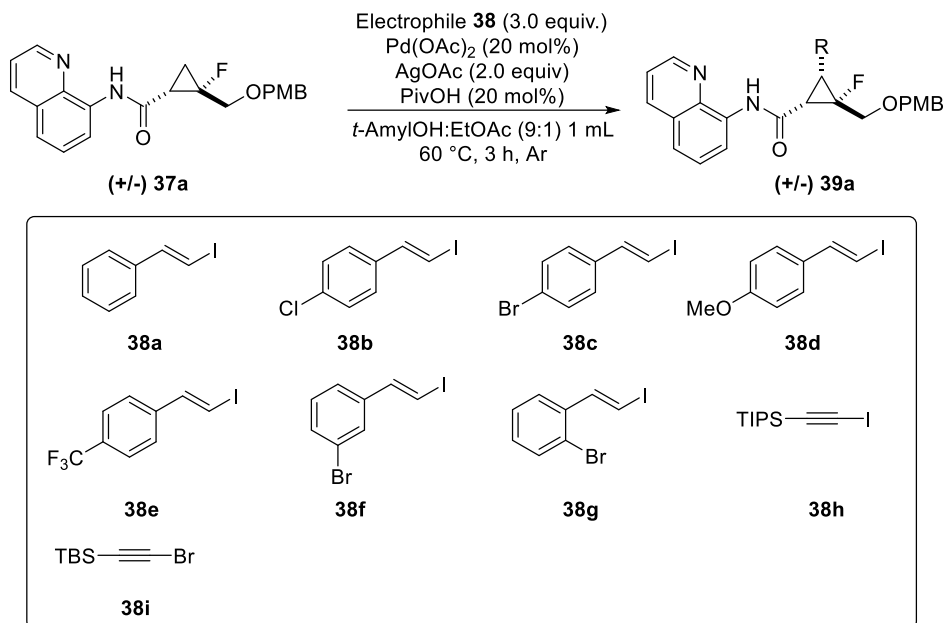
Trimethylsilyl triflate (0.397 mL, 2.2 mmol, 1.1 equiv.) was added to a suspension of 2-iodosylbenzoic acid (528 mg, 2.0 mmol, 1.0 equiv.) in CH₂Cl₂ (5.3 mL) at room temperature. The resulting yellow mixture was stirred for 1 hour, followed by the addition of trimethyl(phenylethynyl)silane (0.428 mL, 2.0 mmol, 1.0 equiv.). After stirring for 6 hours at room temperature, saturated NaHCO₃ (5.3 mL) was added and the mixture was stirred vigorously for 30 min. After filtration, the filtrate was washed with saturated NaHCO₃, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH as eluent) to afford **38u** (534 mg, 77% yield) as a white solid. The NMR data is consistent with reported literature.³⁰⁹

2. General procedure of the Pd(II)-catalyzed functionalization of monofluorinated cyclopropanes.

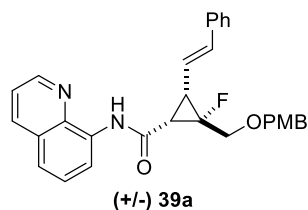
2.1. General procedure of the synthesis of 39.

³⁰⁹ D. Shimbo, A. Shibata, M. Yudasaka, T. Maruyama, N. Tada, B. Uno, A. Itoh, *Org. Lett.* **2019**, *21*, 9769–9773.

Experimental Part



An oven-dried tube was loaded with Pd(OAc)₂ (9.0 mg, 0.04 mmol, 20 mol%), monofluorinated cyclopropane (+/-) **37a** (76.0 mg, 0.2 mmol, 1.0 equiv.), AgOAc (62.4 mg, 0.4 mmol, 2.0 equiv.), pivalic acid (4.1 mg, 0.04 mmol, 0.2 equiv.) and Electrophile **38a** to **38i** (0.6 mmol, 3.0 equiv.) were added. Ether acetate (0.1 mL) and 2-methyl-2-butanol (0.9 mL) were added as solvent. The tube was sealed with a rubber septum and charged with argon via balloon. The suspension was stirred at 60 °C for 3 h. Then, the reaction was filtrated through a celite-gel and solvent was removed under vacuum. The residue was directly purified by silica gel column chromatography to give the desired product (+/-) **39a** to (+/-) **39i**.



(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)-3-((E)-styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 74% (71.4 mg). R_f = 0.24 (petroleum ether / ethyl acetate, 75/25). Yellowish foam.

¹H NMR (300.1 MHz, CDCl₃) δ 10.09 (s, 1H), 8.74 (dd, *J* = 7.0, 2.0 Hz, 1H), 8.55 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.04 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.49 – 7.38 (m, 2H), 7.35 – 7.27 (m, 4H), 7.26 – 7.05 (m, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.73 – 6.57 (m, 2H), 4.58 (dd, *J* = 18.0, 11.6 Hz, 2H), 3.83 (ddd, *J* = 22.0, 18.8, 11.7 Hz, 2H), 3.73 (s, 3H), 2.45 – 2.24 (m, 2H).

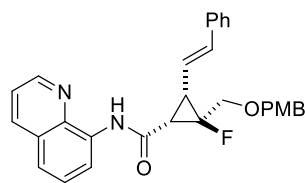
¹³C NMR (75.5 MHz, CDCl₃) δ 164.5, 159.5, 148.3, 138.4, 137.1, 136.3, 134.5, 134.0, 129.7, 129.6, 128.5, 127.9, 127.4, 126.4, 121.7, 121.6, 120.4, 120.3, 116.9, 114.0, 82.8 (d, *J* = 229.7 Hz), 73.0, 71.2 (d, *J* = 24.8 Hz), 55.3, 31.1 (d, *J* = 9.9 Hz), 30.1 (d, *J* = 9.2 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -201.05 – -204.82 (m, 1F).

IR (neat) 3338, 2925, 2840, 1681, 1521, 1484, 1302, 1244, 824, 748 cm⁻¹.

HRMS (ES⁺) calcd for C₃₀H₂₇FN₂O₃ *m/z* 483.2084 ([M+H]⁺) found 483.2096 (Δ2.5 ppm).

Experimental Part



trans-39a

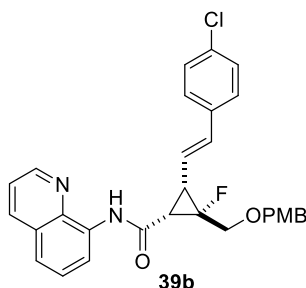
(*trans*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3-((*E*)-styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 62% (60.1 mg). $R_f = 0.33$ (petroleum ether / ethyl acetate, 75/25). Yellowish foam.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.11 (s, 1H), 8.75 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.70 (dd, $J = 6.1, 2.9$ Hz, 1H), 8.14 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.56 – 7.48 (m, 2H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 6.76 – 6.67 (m, 3H), 6.53 (ddd, $J = 15.9, 9.2, 1.4$ Hz, 1H), 4.71 – 4.20 (m, 4H), 3.72 (s, 3H), 2.92 – 2.65 (m, 2H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 165.7, 159.2, 148.3, 138.3, 137.0, 136.4, 134.4, 134.1, 130.2, 129.4, 128.6, 128.0, 127.6, 127.3, 126.4, 121.8, 121.8, 121.0, 116.7, 113.8, 85.0 (d, $J = 232.0$ Hz), 73.1, 66.1 (d, $J = 18.8$ Hz), 55.3, 34.6 (d, $J = 12.4$ Hz), 33.7 (d, $J = 11.8$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -164.9 – -165.3 (m, 1F).



39b

(*cis*)-3-((*E*)-4-chlorostyryl)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 61% (63.2 mg). $R_f = 0.28$ (petroleum ether / ethyl acetate, 75/25). Yellow solid. Mp: 138 – 140 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.13 (s, 1H), 8.78 (dd, $J = 6.6, 2.4$ Hz, 1H), 8.65 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.13 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.55 – 7.47 (m, 2H), 7.41 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.36 – 7.25 (m, 4H), 7.20 (d, $J = 8.6$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.69 – 6.65 (m, 2H), 4.64 (dd, $J = 18.0, 12.0$ Hz, 2H), 3.89 (dd, $J = 18.6, 8.1$ Hz, 2H), 3.80 (s, 3H), 2.47 – 2.32 (m, 2H).

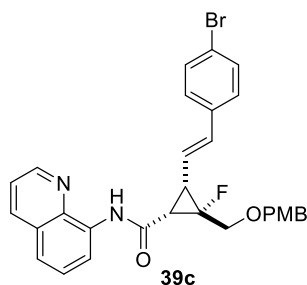
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.3, 159.5, 148.3, 138.4, 136.3, 135.6, 134.4, 132.9, 132.7, 129.6, 128.6, 127.9, 127.5, 127.4, 121.7, 121.6, 121.4, 121.2, 116.9, 113.9, 82.8 (d, $J = 230.0$ Hz), 73.1, 71.1 (d, $J = 24.9$ Hz), 55.3, 31.1 (d, $J = 9.9$ Hz), 30.0 (d, $J = 9.2$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -203.1 – -203.4 (m, 1F).

IR (neat) 3672, 3369, 2988, 2901, 1684, 1522, 1485, 1249, 1066, 789 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{30}\text{H}_{26}\text{ClFN}_2\text{O}_3$ m/z 517.1694 ($[\text{M}+\text{H}]^+$) found 517.1716 ($\Delta 4.3$ ppm).

Experimental Part



(*cis*)-3-((*E*)-4-bromostyryl)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 74% (82.6 mg). $R_f = 0.28$ (petroleum ether / ethyl acetate, 75/25). Yellow solid. Mp: 143 – 145 °C.

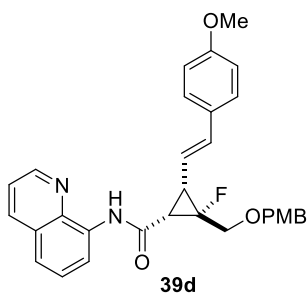
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.12 (s, 1H), 8.78 (dd, $J = 6.7, 2.3$ Hz, 1H), 8.65 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.55 – 7.46 (m, 2H), 7.41 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.38 – 7.29 (m, 4H), 7.22 (d, $J = 8.5$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.77 – 6.59 (m, 2H), 4.64 (dd, $J = 18.0, 12.0$ Hz, 2H), 3.89 (dd, $J = 18.6, 8.1$ Hz, 2H), 3.79 (s, 3H), 2.47 – 2.32 (m, 2H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.3, 159.5, 148.3, 138.4, 136.3, 136.1, 134.4, 132.8, 131.5, 129.6, 127.9, 127.9, 127.4, 121.8, 121.6, 121.5, 121.4, 121.1, 116.9, 114.0, 82.8 (d, $J = 230.1$ Hz), 73.1, 71.1 (d, $J = 25.0$ Hz), 55.3, 31.1 (d, $J = 9.8$ Hz), 30.0 (d, $J = 9.2$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -203.1 – -203.3 (m, 1F).

IR (neat) 3363, 2992, 2834, 1684, 1521, 1484, 1248, 1132, 970, 789 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{30}\text{H}_{26}\text{BrFN}_2\text{O}_3$ m/z 561.1189 ($[\text{M}+\text{H}]^+$) found 561.1190 ($\Delta 0.2$ ppm).



(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-((*E*)-4-methoxystyryl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 84% (86.0 mg). $R_f = 0.25$. (petroleum ether / ethyl acetate, 75/25) Yellow solid. Mp: 85 – 87 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.15 (s, 1H), 8.80 (dd, $J = 6.9, 2.0$ Hz, 1H), 8.64 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.55 – 7.45 (m, 2H), 7.39 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.36 – 7.26 (m, 4H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.77 (d, $J = 8.7$ Hz, 2H), 6.69 (d, $J = 16.0$ Hz, 1H), 6.53 (dd, $J = 16.0, 8.4$ Hz, 1H), 4.64 (dd, $J = 18.3, 11.6$ Hz, 2H), 3.89 (dd, $J = 18.9, 8.2$ Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 2.47 – 2.29 (m, 2H).

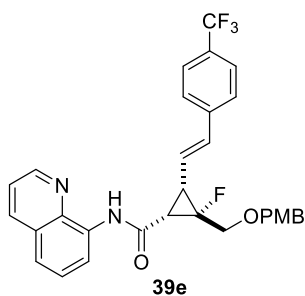
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.7, 159.5, 159.1, 148.3, 138.4, 136.3, 134.5, 133.7, 130.1, 129.7, 129.6, 127.9, 127.5, 127.4, 121.6, 121.6, 117.9, 117.8, 116.9, 113.9, 113.8, 82.7 (d, $J = 229.4$ Hz), 73.0, 71.2 (d, $J = 25.1$ Hz), 55.3 (d, $J = 1.7$ Hz), 31.1 (d, $J = 10.0$ Hz), 30.2 (d, $J = 9.3$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -203.3 – -203.5 (m, 1F).

IR (neat) 3344, 2924, 2840, 1681, 1510, 1484, 1241, 1029, 823, 790 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{31}\text{H}_{29}\text{FN}_2\text{O}_4$ m/z 513.2178 ($[\text{M}+\text{H}]^+$) found 513.2189 ($\Delta 2.1$ ppm).

Experimental Part



39e
(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3-((*E*)-4-(trifluoromethyl)styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 66% (72.7 mg). $R_f = 0.27$ (petroleum ether / ethyl acetate, 75/25). Yellow solid. Mp: 82 – 84 °C.

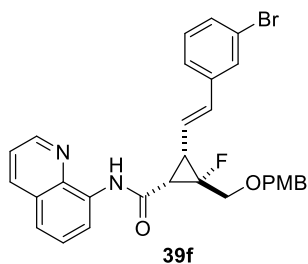
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.13 (d, $J = 2.0$ Hz, 1H), 8.78 (dd, $J = 6.5, 2.4$ Hz, 1H), 8.65 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.13 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.55 – 7.39 (m, 7H), 7.34 (d, $J = 8.6$ Hz, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.84 (dd, $J = 16.2, 6.2$ Hz, 1H), 6.73 (d, $J = 16.0$ Hz, 1H), 4.65 (dd, $J = 17.9, 12.0$ Hz, 2H), 3.91 (ddd, $J = 18.9, 18.6, 11.6$ Hz, 2H), 3.80 (s, 3H), 2.49 – 2.37 (m, 2H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.2, 159.5, 148.3, 140.6, 138.4, 136.4, 134.4, 132.5, 129.6, 129.0 (q, $J = 33.4$ Hz), 128.0, 127.4, 126.5, 125.4 (q, $J = 3.8$ Hz), 124.5 (q, $J = 273.1$ Hz), 123.8, 123.7, 121.8, 121.7, 116.9, 114.0, 82.9 (d, $J = 230.5$ Hz), 73.2, 71.0 (d, $J = 25.0$ Hz), 55.3, 31.3 (d, $J = 9.9$ Hz), 30.0 (d, $J = 9.1$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -62.9 (s, 3F), -203.0 – -203.3 (m, 1F).

IR (neat) 3320, 2841, 1686, 1529, 1485, 1324, 1106, 1066, 829, 793 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{31}\text{H}_{26}\text{F}_4\text{N}_2\text{O}_3$ m/z 551.1958 ($[\text{M}+\text{H}]^+$) found 551.1948 (Δ -1.8 ppm).



39f
(*cis*)-3-((*E*)-3-bromostyryl)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 58% (65.1 mg). $R_f = 0.28$ (petroleum ether / ethyl acetate, 75/25). Yellow solid. Mp: 124 – 126 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.11 (d, $J = 2.3$ Hz, 1H), 8.78 (dd, $J = 6.6, 2.4$ Hz, 1H), 8.68 (dd, $J = 4.2, 1.4$ Hz, 1H), 8.13 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.54 – 7.46 (m, 3H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.36 – 7.27 (m, 3H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.00 – 6.86 (m, 3H), 6.79 – 6.55 (m, 2H), 4.64 (dd, $J = 18.0, 11.6$ Hz, 2H), 3.89 (dd, $J = 18.6, 7.2$ Hz, 2H), 3.80 (s, 3H), 2.46 – 2.31 (m, 2H).

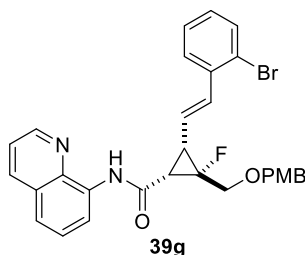
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.3, 159.5, 148.4, 139.3, 138.4, 136.3, 136.2, 135.1, 134.4, 132.5, 130.1, 129.6, 129.1, 127.9, 127.4, 125.6, 122.2, 121.8, 121.7, 116.9, 114.0, 94.6, 82.8 (d, $J = 230.4$ Hz), 73.1, 71.0 (d, $J = 25.0$ Hz), 55.3, 31.2 (d, $J = 10.1$ Hz), 30.0 (d, $J = 9.1$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -202.9 – -203.2 (m, 1F).

Experimental Part

IR (neat) 3344, 1682, 1613, 1523, 1486, 1245, 1127, 960, 790, 648 cm^{-1} .

HRMS (ES⁺) calcd for $\text{C}_{30}\text{H}_{26}\text{BrFN}_2\text{O}_3$ m/z 561.1189 ($[\text{M}+\text{H}]^+$) found 561.1170 (Δ -3.4 ppm).



39g
(cis)-3-((*E*)-2-bromostyryl)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide
Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 45% (50.6 mg). R_f = 0.24 (petroleum ether / ethyl acetate, 75/25). Yellow solid. Mp: 43 – 45 °C.

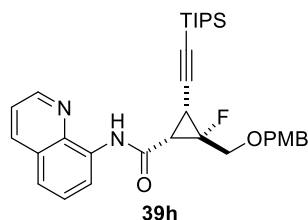
¹H NMR (300.1 MHz, CDCl₃) δ 10.13 (d, J = 1.7 Hz, 1H), 8.78 (dd, J = 6.6, 2.4 Hz, 1H), 8.68 (dd, J = 4.2, 1.7 Hz, 1H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.58 – 7.47 (m, 4H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.18 – 7.00 (m, 3H), 6.91 (d, J = 8.7 Hz, 2H), 6.70 (ddd, J = 15.9, 9.2, 1.1 Hz, 1H), 4.65 (dd, J = 18.0, 11.6 Hz, 2H), 4.93 (ddd, J = 30.0, 18.0, 11.8 Hz, 2H), 3.80 (s, 3H), 2.56 – 2.45 (m, 1H), 2.40 (dd, J = 10.6, 7.7 Hz, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 164.5, 159.5, 148.3, 138.4, 136.8, 136.3, 134.4, 132.7, 132.3, 129.6, 128.6, 127.9, 127.4, 127.4, 127.3, 123.7, 123.6, 123.1, 121.7, 121.6, 116.8, 114.0, 82.8 (d, J = 230.6 Hz), 73.1, 71.0 (d, J = 24.6 Hz), 55.3, 31.3 (d, J = 9.9 Hz), 30.2 (d, J = 8.9 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -203.1 – -203.5 (m, 1F).

IR (neat) 3343, 2924, 2846, 1683, 1541, 1244, 1086, 1009, 824, 791 cm^{-1} .

HRMS (ES⁺) calcd for $\text{C}_{30}\text{H}_{26}\text{BrFN}_2\text{O}_3$ m/z 561.1189 ($[\text{M}+\text{H}]^+$) found 561.1189 (Δ 0 ppm).



39h
(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3-((triisopropylsilyl)ethynyl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 62% (69.6 mg). R_f = 0.27 (petroleum ether / ethyl acetate, 75/25). Pale-yellow oil.

¹H NMR (300.1 MHz, CDCl₃) δ 10.31 (d, J = 10.2 Hz, 1H), 8.84 – 8.76 (m, 2H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.60 (dd, J = 18.0, 12.0 Hz, 2H), 3.95 – 3.77 (m, 5H), 2.35 (s, 1H), 2.33 (s, 1H), 0.76 – 0.64 (m, 21H).

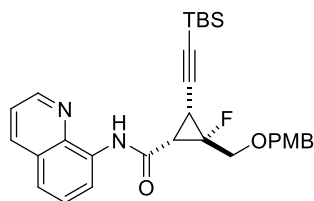
¹³C NMR (75.5 MHz, CDCl₃) δ 164.1, 159.6, 148.4, 138.9, 136.1, 134.8, 129.6, 129.5, 127.9, 127.3, 121.7, 121.5, 117.4, 114.1, 97.8 (d, J = 6.0 Hz), 86.0, 81.2 (d, J = 231.3 Hz), 73.2, 69.8 (d, J = 26.2 Hz), 55.4, 30.9 (d, J = 9.3 Hz), 18.3, 17.8 (d, J = 10.4 Hz), 11.1.

¹⁹F NMR (282.4 MHz, CDCl₃) δ -199.2 – -199.4 (m, 1F).

IR (neat) 3344, 2944, 2864, 2167, 1671, 1527, 1328, 1246, 1031, 824, 662 cm^{-1} .

Experimental Part

HRMS (ES⁺) calcd for C₃₃H₄₁FN₂O₃Si m/z 561.2937 ([M+H]⁺) found 561.2946 (Δ1.6 ppm).



39i

(*cis*)-3-((*tert*-butyldimethylsilyl)ethynyl)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 60% (62.6 mg). *R*_f = 0.28. (petroleum ether / ethyl acetate, 75/25) Pale-yellow oil.

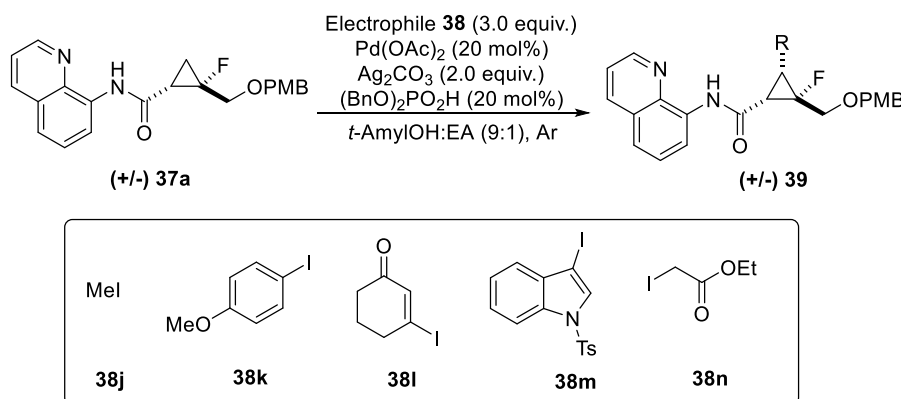
¹H NMR (300.1 MHz, CDCl₃) δ 10.23 (d, *J* = 9.4 Hz, 1H), 8.77 – 8.69 (m, 2H), 8.05 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.33 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 – 7.17 (m, 2H), 6.80 (d, *J* = 8.7 Hz, 2H), 4.51 (dd, *J* = 18.0, 12.0 Hz, 2H), 3.84 – 3.67 (m, 5H), 2.32 – 2.18 (m, 2H), 0.50 (s, 9H), -0.39 (d, *J* = 14.2 Hz, 6H).

¹³C NMR (75.5 MHz, CDCl₃) δ 164.0, 159.6, 148.5, 138.9, 136.1, 134.7, 129.6, 129.4, 127.9, 127.3, 121.8, 121.5, 117.2, 114.0, 96.9 (d, *J* = 6.0 Hz), 88.3, 81.1 (d, *J* = 231.5 Hz), 73.1, 69.7 (d, *J* = 26.2 Hz), 55.4, 30.9 (d, *J* = 9.4 Hz), 25.7, 17.6 (d, *J* = 10.2 Hz), 16.2, -5.1 (d, *J* = 5.4 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -195.4 – -202.9 (m, 1F).

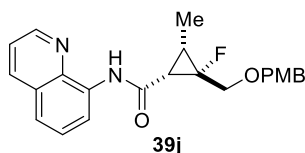
IR (neat) 3340, 2938, 2862, 1671, 1527, 1325, 1243, 1051, 844, 799, 669 cm⁻¹

HRMS (ES⁺): calcd for C₃₀H₃₅FN₂O₃Si m/z 519.2487 [M+H]⁺, found 519.2479 (Δ1.5 ppm)



An oven-dried tube was loaded with Pd(OAc)₂ (9.0 mg, 0.04 mmol, 20 mol%), monofluorinated cyclopropane (+/-) **37a** (76.0 mg, 0.2 mmol, 1.0 equiv.), Ag₂CO₃ (110.0 mg, 0.4 mmol, 2.0 equiv.), dibenzyl phosphate (11.1 mg, 0.04 mmol, 20 mol%) and electrophile **38** (0.6 mmol, 3.0 equiv.) were added. Ether acetate (0.1 mL) and 2-methyl-2-butanol (0.9 mL) were added as solvent. The tube was sealed with a rubber septum and charged with argon via balloon. The suspension was stirred at 110 °C or 130 °C and the reaction progress was detected by ¹⁹F NMR. Then, the reaction was filtrated through a celite-gel and solvent was removed under vacuum. The residue was directly purified by silica gel column chromatography to give the desired product (+/-) **39i** to (+/-) **39m**.

Experimental Part



(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-methyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

110 °C for 15 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 56% (44.3 mg). R_f = 0.28 (petroleum ether / ethyl acetate, 80/20). Yellow oil.

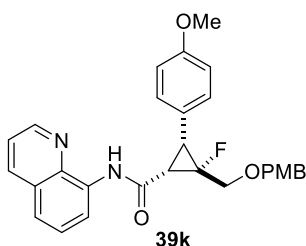
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.14 (d, J = 5.8 Hz, 1H), 8.84 – 8.74 (m, 2H), 8.14 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.63 (dd, J = 18.0, 12.0 Hz, 2H), 3.92 – 3.70 (m, 5H), 2.03 (dd, J = 11.0, 6.5 Hz, 1H), 1.65 – 1.50 (m, 1H), 1.42 (dd, J = 6.5, 1.3 Hz, 3H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 165.7, 159.4, 148.3, 138.5, 136.2, 134.6, 129.8, 129.5, 129.4, 127.9, 127.3, 121.6, 116.8, 113.9, 82.6 (d, J = 227.3 Hz), 72.9, 72.1 (d, J = 24.2 Hz), 55.3, 28.4 (d, J = 9.4 Hz), 20.9 (d, J = 10.7 Hz), 6.8 (d, J = 8.1 Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -207.4 - -207.6 (m, 1F).

IR (neat) 3350, 2931, 2859, 1686, 1541, 1484, 1244, 1115, 824, 791 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{23}\text{H}_{23}\text{FN}_2\text{O}_3$ m/z 395.1800 ($[\text{M}+\text{H}]^+$) found 395.1788 (Δ -3.0 ppm).



(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-(4-methoxyphenyl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

110 °C for 15 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 54% (52.4 mg). R_f = 0.24 (petroleum ether / ethyl acetate, 75/25). Yellow oil.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 9.70 (d, J = 6.8 Hz, 1H), 8.70 (dd, J = 7.2, 1.8 Hz, 1H), 8.56 (dd, J = 4.2, 1.7 Hz, 1H), 8.03 (dd, J = 8.3, 1.7 Hz, 1H), 7.49 – 7.38 (m, 3H), 7.37 – 7.29 (m, 4H), 6.91 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 4.68 (s, 2H), 3.95 (ddd, J = 32.7, 19.8, 11.7 Hz, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.79 (dd, J = 11.5, 6.4 Hz, 1H), 2.43 (dd, J = 11.5, 7.0 Hz, 1H).

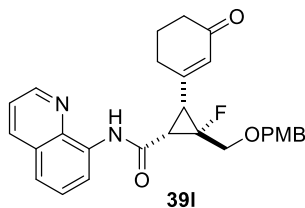
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 165.4, 159.5, 158.9, 147.9, 138.5, 135.9, 134.5, 131.8, 129.7, 129.5, 127.7, 127.2, 123.0, 121.4, 121.3, 116.7, 114.0, 113.9, 82.5 (d, J = 227.8 Hz), 73.0, 71.9 (d, J = 24.8 Hz), 55.3, 55.1, 30.9 (d, J = 9.3 Hz), 29.2 (d, J = 9.4 Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -201.2 - -201.4 (m, 1F).

IR (neat) 3332, 2917, 2849, 1662, 1513, 1485, 1244, 1030, 824, 790 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{29}\text{H}_{27}\text{FN}_2\text{O}_4$ m/z 487.2051 ($[\text{M}+\text{H}]^+$) found 487.2048 (Δ -0.6 ppm).

Experimental Part



39i
(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-(3-oxocyclohex-1-en-1-yl)-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

110 °C for 12 h, Toluene (1 mL) instead of *t*-AmylOH:EA as solvent. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: DCM / ethyl acetate, from 100/0 to 98/2). Yield: 39% (37.0 mg). $R_f = 0.57$ (DCM / ethyl acetate, 91/9). Brown oil.

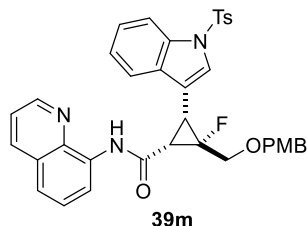
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 9.95 (d, $J = 5.4$ Hz, 1H), 8.74 (dd, $J = 5.6, 3.4$ Hz, 1H), 8.69 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.56 – 7.39 (m, 3H), 7.30 (d, $J = 8.7$ Hz, 2H), 6.90 (d, $J = 8.7$ Hz, 2H), 6.38 (s, 1H), 4.61 (s, 2H), 4.00 – 3.71 (m, 5H), 2.58 – 2.19 (m, 5H), 2.18 – 1.74 (m, 3H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 199.2, 164.4, 159.5, 154.6, 148.5, 138.4, 136.2, 134.3, 130.8, 129.5, 129.4, 127.9, 127.3, 125.5, 121.7, 116.8, 114.0, 85.1 (d, $J = 140.5$ Hz), 73.2, 70.8 (d, $J = 25.9$ Hz), 55.3, 37.3 (d, $J = 7.2$ Hz), 30.9 (d, $J = 10.0$ Hz), 30.6, 29.7, 22.4.

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) major: δ -201.8 – -202.0 (m, 1F).

IR (neat) 3332, 2926, 2859, 1663, 1524, 1486, 1324, 1244, 1984, 825 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{28}\text{H}_{27}\text{FN}_2\text{O}_4$ m/z 475.2022 ($[\text{M}+\text{H}]^+$) found 475.2032 ($\Delta 2.1$ ppm).



39m
(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3-(1-tosyl-1*H*-indol-3-yl)cyclopropane-1-carboxamide

130 °C for 20 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 91/9 to 50/50). Yield: 16% (20.4 mg). $R_f = 0.26$ (petroleum ether / ethyl acetate, 50/50). Brown oil.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 9.90 (d, $J = 7.6$ Hz, 1H), 8.66 (dd, $J = 5.6, 3.4$ Hz, 1H), 8.58 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.06 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.86 – 7.79 (m, 2H), 7.66 (dd, $J = 6.6, 1.7$ Hz, 1H), 7.49 – 7.42 (m, 2H), 7.41 – 7.32 (m, 5H), 7.26 – 7.16 (m, 2H), 6.91 (d, $J = 8.7$ Hz, 2H), 6.64 (d, $J = 8.0$ Hz, 2H), 4.69 (s, 2H), 4.12 (dd, $J = 17.1, 11.6$ Hz, 1H), 3.92 (dd, $J = 21.1, 11.6$ Hz, 1H), 3.80 (s, 3H), 2.71 (ddd, $J = 11.3, 6.9, 1.3$ Hz, 1H), 2.56 (dd, $J = 11.3, 7.2$ Hz, 1H), 2.09 (s, 3H).

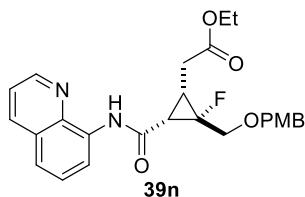
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.7, 159.6, 148.3, 144.4, 138.5, 135.9, 135.1, 134.6, 134.4, 131.7, 129.6, 129.5, 127.8, 127.3, 126.6, 125.8, 125.7, 124.9, 123.4, 121.7, 121.7, 119.8, 116.9, 114.1, 113.3, 112.5, 82.5 (d, $J = 227.6$ Hz), 73.3, 71.4 (d, $J = 25.2$ Hz), 55.4, 30.7 (d, $J = 9.3$ Hz), 21.5, 21.3 (d, $J = 9.9$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -201.3 – -201.5 (m, 1F).

IR (neat) 3338, 2918, 1667, 1522, 1485, 1169, 1087, 824, 747, 666 cm^{-1} .

HRMS (ES^+) calcd for $\text{C}_{37}\text{H}_{32}\text{FN}_3\text{O}_5\text{S}$ m/z 650.2125 ($[\text{M}+\text{H}]^+$) found 650.2130 ($\Delta 0.8$ ppm).

Experimental Part



ethyl 2-((*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-(quinolin-8-ylcarbamoyl)cyclopropyl)acetate

130 °C for 20 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: petroleum ether / ethyl acetate, from 95/5 to 75/25). Yield: 20% (18.2 mg). $R_f = 0.24$ (petroleum ether / ethyl acetate, 75/25). Brown oil.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.09 (d, $J = 5.4$ Hz, 1H), 8.89 – 8.64 (m, 2H), 8.13 (d, $J = 8.2$ Hz, 1H), 7.52 – 7.48 (m, 1H), 7.46 – 7.40 (m, 1H), 7.35 – 7.28 (m, 3H), 6.92 – 6.84 (m, 2H), 5.11 (dd, $J = 8.0, 1.7$ Hz, 1H), 4.71 – 4.55 (m, 2H), 4.23 – 4.07 (m, 2H), 4.02 – 3.92 (m, 1H), 3.78 (s, 3H), 3.13 (ddd, $J = 17.9, 6.8, 1.2$ Hz, 1H), 2.97 (dd, $J = 18.0, 8.0$ Hz, 1H), 2.22 – 2.13 (m, 1H), 1.92 – 1.77 (m, 1H), 1.23 – 1.17 (m, 3H).

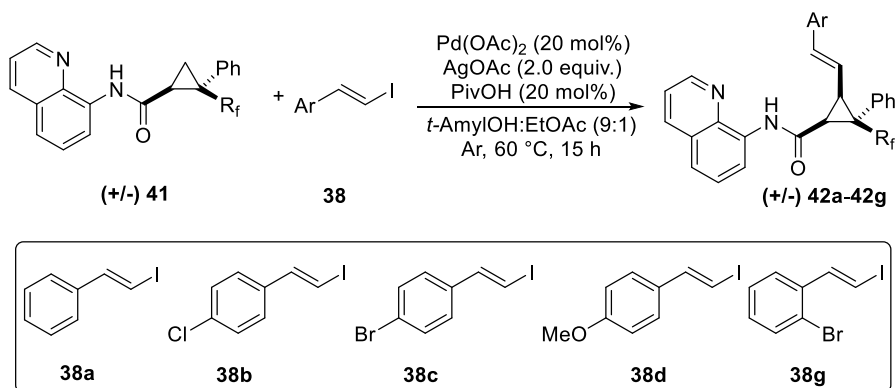
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 172.5, 165.5, 159.5, 148.3, 138.3, 136.5, 134.5, 129.6, 129.6, 128.7, 128.1, 127.5, 121.7, 116.9, 114.0, 81.7 (d, $J = 230.2$ Hz), 73.1, 71.6 (d, $J = 24.6$ Hz), 60.8, 55.4, 29.8, 27.0 (d, $J = 7.7$ Hz), 21.9 (d, $J = 9.6$ Hz), 14.3.

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) major: δ -205.9 – -206.6 (m, 1F).

IR (neat) 3344, 2934, 1730, 1687, 1523, 1486, 1246, 1030, 825, 791 cm^{-1} .

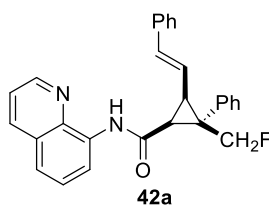
HRMS (ES^+) calcd for $\text{C}_{26}\text{H}_{27}\text{FN}_2\text{O}_5$ m/z 467.1971 ($[\text{M}+\text{H}]^+$) found 467.1989 ($\Delta 3.9$ ppm).

2.2. General procedure for the synthesis cyclopropanes **42**.



An oven-dried tube was loaded with $\text{Pd}(\text{OAc})_2$ (9.0 mg, 0.04 mmol, 20 mol%), monofluorinated cyclopropane (+/-) **41** (0.2 mmol, 1.0 equiv.), AgOAc (62.4 mg, 0.4 mmol, 2.0 equiv.), pivalic acid (4.1 mg, 0.04 mmol, 20 mol%) and electrophiles **38** (0.6 mmol, 3.0 equiv.) were added. Ether acetate (0.1 mL) and 2-methyl-2-butanol (0.9 mL) were added as solvent. The tube was sealed with a rubber septum and charged with argon via balloon. The suspension was stirred at 60 °C for 3 hours. Then, the reaction was filtrated through a celite-gel and solvent was removed under vacuum. The residue was directly purified by silica gel column chromatography to give the desired product (+/-) **42a** (+/-) **42g**.

Experimental Part



(*cis*)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 88/12). Yield: 80% (67.7 mg). $R_f = 0.37$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 95 – 97 °C.

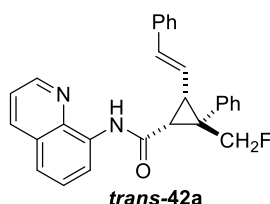
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.19 (s, 1H), 8.82 (dd, $J = 7.2, 1.8$ Hz, 1H), 8.75 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.60 – 7.50 (m, 4H), 7.48 – 7.39 (m, 5H), 7.37 – 7.30 (m, 3H), 7.27 – 7.20 (m, 1H), 6.95 (dd, $J = 15.8, 9.3$ Hz, 1H), 6.81 (d, $J = 15.8$ Hz, 1H), 5.35 (ddd, $J = 47.5, 10.0, 5.5$ Hz, 2H), 2.78 (td, $J = 9.1, 2.6$ Hz, 1H), 2.63 (dd, $J = 8.9, 2.4$ Hz, 1H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 167.6, 148.3, 142.7, 138.3, 137.2, 136.5, 134.5, 133.8, 129.0, 128.8, 128.6, 128.0, 127.6, 127.5, 127.5, 126.4, 122.8, 121.8, 116.7, 82.6 (d, $J = 167.9$ Hz), 39.6 (d, $J = 22.9$ Hz), 35.5 (d, $J = 5.3$ Hz), 34.8 (d, $J = 5.3$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -220.51 (t, $J = 47.5$ Hz, 1F).

IR (neat) 3341, 2924, 1677, 1520, 1484, 1321, 1165, 989, 790, 693 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{28}\text{H}_{23}\text{FN}_2\text{O}$ m/z 423.1873 ($[\text{M}+\text{H}]^+$) found 423.1875 ($\Delta 0.5$ ppm).



(*trans*)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)cyclopropane-1-carboxamide

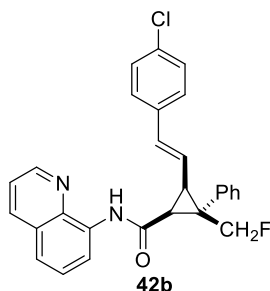
Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 88/12). Yield: 72% (65.6 mg). $R_f = 0.35$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 98 – 100 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.19 (s, 1H), 8.86 – 8.71 (m, 2H), 8.17 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.60 – 7.49 (m, 4H), 7.48 – 7.33 (m, 6H), 7.28 (d, $J = 7.0$ Hz, 2H), 6.92 (dd, $J = 15.8, 9.4$ Hz, 1H), 6.74 (d, $J = 15.8$ Hz, 1H), 5.33 (d, $J = 47.5$ Hz, 2H), 2.75 (td, $J = 9.1, 2.5$ Hz, 1H), 2.63 (dd, $J = 8.8, 2.5$ Hz, 1H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 167.5, 148.3, 142.6, 138.4, 136.5, 135.8, 134.5, 133.0, 132.5, 129.0, 128.8, 128.8, 128.1, 127.7, 127.6, 127.5, 123.7, 121.8, 121.8, 116.7, 82.5 (d, $J = 168.0$ Hz), 39.6 (d, $J = 22.9$ Hz), 35.4 (d, $J = 5.1$ Hz), 34.9 (d, $J = 5.4$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -220.59 (t, $J = 47.5$ Hz, 1F).

Experimental Part



(*cis*)-3-((*E*)-4-chlorostyryl)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 88/12). Yield: 62% (56.7 mg). $R_f = 0.37$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 73 – 75 °C.

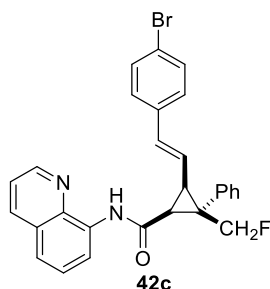
^1H NMR (300.1 MHz, CDCl_3) δ 10.19 (s, 1H), 8.80 (dd, $J = 6.9, 2.0$ Hz, 1H), 8.76 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.17 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.60 – 7.49 (m, 4H), 7.48 – 7.33 (m, 6H), 7.31 – 7.25 (m, 2H), 6.92 (dd, $J = 15.8, 9.4$ Hz, 1H), 6.74 (d, $J = 15.8$ Hz, 1H), 5.33 (d, $J = 47.5$ Hz, 2H), 2.75 (td, $J = 9.1, 2.5$ Hz, 1H), 2.63 (dd, $J = 8.8, 2.5$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.5, 148.3, 142.6, 138.4, 136.5, 135.8, 134.5, 133.0, 132.5, 129.0, 128.8, 128.8, 128.1, 127.7, 127.6, 127.5, 123.7, 121.8, 121.8, 116.7, 82.5 (d, $J = 168.0$ Hz), 39.6 (d, $J = 22.9$ Hz), 35.4 (d, $J = 5.1$ Hz), 34.9 (d, $J = 5.4$ Hz, 1F).

^{19}F NMR (282.4 MHz, CDCl_3) δ -220.59 (t, $J = 47.5$ Hz).

IR (neat) 3338, 2922, 2852, 1678, 1522, 1486, 1321, 1164, 1002, 790, 697 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{28}\text{H}_{22}\text{ClFN}_2\text{O}$ m/z 457.1477 ($[\text{M}+\text{H}]^+$) found 457.1480 ($\Delta 0.7$ ppm).



(*cis*)-3-((*E*)-4-bromostyryl)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 88/12). Yield: 70% (70.4 mg). $R_f = 0.37$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 87 – 89 °C.

^1H NMR (300.1 MHz, CDCl_3) δ 10.19 (s, 1H), 8.88 – 8.69 (m, 2H), 8.16 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.59 – 7.49 (m, 4H), 7.47 – 7.38 (m, 5H), 7.37 – 7.27 (m, 3H), 6.93 (dd, $J = 15.8, 9.5$ Hz, 1H), 6.72 (d, $J = 15.8$ Hz, 1H), 5.32 (d, $J = 47.6$ Hz, 2H), 2.74 (td, $J = 9.2, 2.4$ Hz, 1H), 2.63 (dd, $J = 8.8, 2.5$ Hz, 1H).

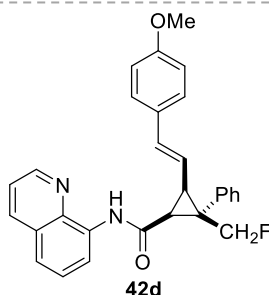
^{13}C NMR (75.5 MHz, CDCl_3) δ 167.5, 148.3, 142.6, 138.3, 136.5, 136.2, 134.5, 132.5, 131.7, 129.0, 128.8, 128.1, 127.9, 127.7, 127.4, 123.9, 121.8, 121.8, 121.2, 116.7, 82.5 (d, $J = 168.0$ Hz), 39.6 (d, $J = 22.9$ Hz), 35.4 (d, $J = 5.1$ Hz), 34.9 (d, $J = 5.4$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -220.52 (t, $J = 47.5$ Hz, 1F).

IR (neat) 3338, 2922, 2852, 1677, 1522, 1484, 1324, 1165, 991, 790, 699 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{28}\text{H}_{22}\text{BrFN}_2\text{O}$ m/z 503.0896 ($[\text{M}+\text{H}]^+$) found 503.0887 ($\Delta 1.8$ ppm).

Experimental Part



(*cis*)-2-(fluoromethyl)-3-((*E*)-4-methoxystyryl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 85/15). Yield: 66%. $R_f = 0.32$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 93 – 95 °C.

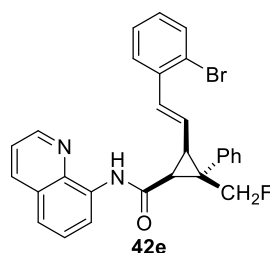
^1H NMR (300.1 MHz, CDCl_3) δ 10.17 (s, 1H), 8.81 (d, $J = 7.2, 1.8$ Hz, 1H), 8.75 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.59 – 7.49 (m, 4H), 7.47 – 7.31 (m, 6H), 6.85 (d, $J = 8.8$ Hz, 2H), 6.79 – 6.73 (m, 2H), 5.33 (ddd, $J = 47.5, 18.0, 9.9$ Hz, 2H), 3.81 (s, 3H), 2.75 (m, 1H), 2.60 (dd, $J = 8.9, 2.3$ Hz, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 167.7, 159.2, 148.3, 142.9, 138.4, 136.5, 134.6, 133.3, 130.2, 129.0, 128.8, 128.1, 127.6, 127.6, 127.5, 121.7, 121.7, 120.4, 116.7, 114.1, 82.6 (d, $J = 167.7$ Hz), 55.4, 39.4 (d, $J = 22.8$ Hz), 35.6 (d, $J = 5.3$ Hz), 34.8 (d, $J = 5.3$ Hz, 1F).

^{19}F NMR (282.4 MHz, CDCl_3) δ -220.5 (t, $J = 47.6$ Hz).

IR (neat) 3344, 2954, 2843, 1678, 1522, 1484, 1166, 989, 790, 700 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{29}\text{H}_{25}\text{FN}_2\text{O}_2$ m/z 453.1978 ($[\text{M}+\text{H}]^+$) found 453.1984 (Δ 1.3 ppm).



(*cis*)-3-((*E*)-2-bromostyryl)-2-(fluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 85/15). Yield: 63% (63.4 mg). $R_f = 0.35$. (petroleum ether / ethyl acetate, 83/17): Yellow solid. Mp: 90 – 92 °C.

^1H NMR (300.1 MHz, CDCl_3) δ 10.20 (s, 1H), 8.92 – 8.68 (m, 2H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.65 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.58 – 7.50 (m, 5H), 7.46 – 7.32 (m, 5H), 7.16 (d, $J = 15.7$ Hz, 1H), 7.11 – 7.03 (m, 1H), 6.93 (dd, $J = 15.7, 9.6$ Hz, 1H), 5.36 (d, $J = 47.5$ Hz, 2H), 2.84 (td, $J = 9.2, 2.4$ Hz, 1H), 2.66 (dd, $J = 8.8, 2.4$ Hz, 1H).

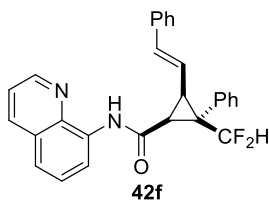
^{13}C NMR (75.5 MHz, CDCl_3) δ 167.5, 148.3, 142.6, 138.3, 136.9, 136.5, 134.5, 132.9, 132.2, 129.0, 128.8, 128.8, 128.5, 128.0, 127.7, 127.6, 127.4, 126.0, 123.2, 121.8, 121.8, 116.7, 82.5 (d, $J = 168.0$ Hz), 39.8 (d, $J = 22.9$ Hz), 35.5 (d, $J = 5.2$ Hz), 35.1 (d, $J = 5.3$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -220.5 (t, $J = 47.5$ Hz, 1F).

IR (neat) 3343, 2921, 2859, 1677, 1522, 1485, 1165, 992, 790, 699 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{28}\text{H}_{22}\text{BrFN}_2\text{O}$ m/z 503.0896 ($[\text{M}+\text{H}]^+$) found 503.0845 (Δ -10.1 ppm).

Experimental Part



(*cis*)-2-(difluoromethyl)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)cyclopropane-1-carboxamide

90 °C, 6 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 68% (60.1 mg). $R_f = 0.51$ (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 73 – 75 °C.

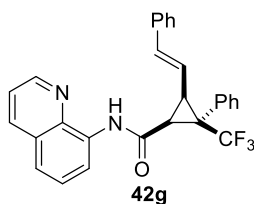
$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.25 (s, 1H), 8.88 – 8.69 (m, 2H), 8.17 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.61 – 7.52 (m, 4H), 7.48 – 7.37 (m, 6H), 7.34 (dd, $J = 8.0, 6.5$ Hz, 2H), 7.29 – 7.12 (m, 2H), 6.96 – 6.81 (m, 2H), 2.88 – 2.74 (m, 1H), 2.67 (d, $J = 9.0$ Hz, 1H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 167.1, 148.3, 138.3, 137.1, 136.9, 136.6, 134.9, 134.3, 131.2, 128.7, 128.5, 128.4, 128.1, 127.8, 127.5, 126.5, 122.0, 121.8, 121.0, 116.8, 111.8 (dd, $J = 473.5, 236.3$ Hz), 41.0 (dd, $J = 29.6, 25.1$ Hz), 34.9 (d, $J = 2.3$ Hz), 34.4 (d, $J = 3.4$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -118.6 (dd, $J = 55.1, 9.7$ Hz, 2F).

IR (neat) 3343, 2923, 2853, 1677, 1522, 1484, 1323, 1165, 988, 799, 693 cm^{-1} .

HRMS (ES⁺): calcd for $\text{C}_{28}\text{H}_{22}\text{F}_2\text{N}_2\text{O}$ m/z 441.1778 ($[\text{M}+\text{H}]^+$) found 441.1789 ($\Delta 2.5$ ppm).



(*cis*)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

60 °C, 20 h and without AgOAc. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 18% (16.5 mg). $R_f = 0.45$ (petroleum ether / ethyl acetate, 83/17). Yellow oil.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.27 (s, 1H), 8.87 (dd, $J = 7.0, 1.8$ Hz, 1H), 8.18 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.11 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.69 (d, $J = 6.3$ Hz, 2H), 7.61 – 7.52 (m, 2H), 7.50 – 7.41 (m, 5H), 7.35 – 7.27 (m, 4H), 7.04 (d, $J = 15.6$ Hz, 1H), 6.73 (dd, $J = 15.6, 10.1$ Hz, 1H), 2.92 (d, $J = 9.6$ Hz, 1H), 2.74 (dd, $J = 11.0, 9.8$ Hz, 1H).

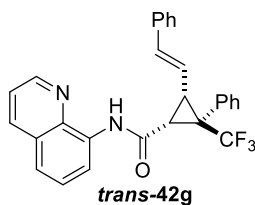
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.2, 148.6, 138.6, 137.2, 137.0, 136.5, 136.3, 134.3, 130.9, 129.0, 128.8, 128.6, 128.0, 127.9, 127.5, 126.8, 125.5 (q, $J = 278.1$ Hz), 122.1, 121.7, 121.2, 116.9, 38.9 (q, $J = 32.1$ Hz), 35.2, 32.4.

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -60.8 (s, 3F).

IR (neat) 3338, 2925, 2847, 1686, 1523, 1485, 1324, 1147, 966, 694 cm^{-1} .

HRMS (ES⁺): calcd for $\text{C}_{28}\text{H}_{21}\text{F}_3\text{N}_2\text{O}$ m/z 459.1684 ($[\text{M}+\text{H}]^+$) found 459.1685 ($\Delta 0.2$ ppm).

Experimental Part



(trans)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

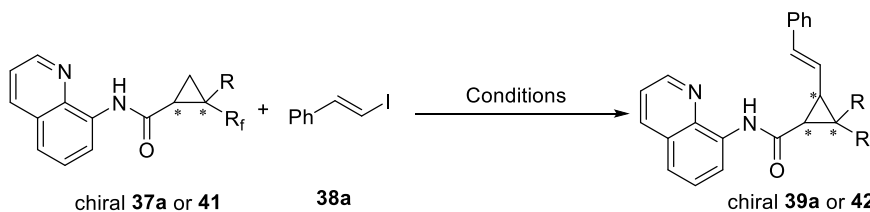
60 °C, 20 h. Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 75% (68.8 mg). R_f = 0.50 (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 66 – 68 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 10.21 (s, 1H), 8.76 (dd, J = 4.2, 1.6 Hz, 1H), 8.66 (dd, J = 6.9, 2.1 Hz, 1H), 8.16 (dd, J = 8.3, 1.6 Hz, 1H), 7.52 – 7.43 (m, 5H), 7.42 – 7.33 (m, 5H), 7.33 – 7.26 (m, 2H), 7.25 – 7.18 (m, 1H), 6.82 (d, J = 16.0 Hz, 1H), 6.58 (dd, J = 16.0, 9.5 Hz, 1H), 2.99 (dd, J = 10.8, 9.5 Hz, 1H), 2.90 (d, J = 9.4 Hz, 1H).

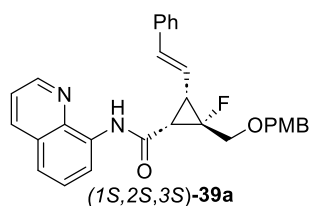
$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 164.9, 148.4, 138.3, 137.1, 136.5, 134.3, 133.7, 132.9, 129.0, 128.6, 128.4, 128.2, 128.0, 128.0, 127.6, 127.4, 126.6, 125.3 (q, J = 275.1 Hz), 123.0, 121.9, 121.8, 39.7 (q, J = 32.5 Hz), 30.6 (d, J = 2.4 Hz), 30.4 (d, J = 2.1 Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -71.6 (s, 3F).

2.3. Enantiopure compounds characterization.



The functionalization procedures of chiral fluorinated cyclopropanes are consistent with their racemates preparation process.

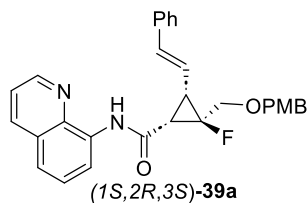


(1*S*,2*S*,3*S*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-*N*-(quinolin-8-yl)-3-((*E*)-styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 69%. (66.7 mg). R_f = 0.24 (petroleum ether / ethyl acetate, 75/25). Yellowish foam. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **39a**.

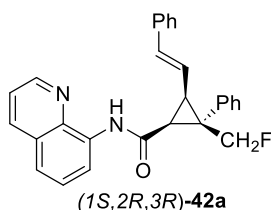
Enantiomeric Excess: 83%. The enantiomeric excess was determined by HPLC with a Chiralcel ID column (n-heptane: *i*-PrOH = 60:40, 254 nm, 1 mL/min), t_R = 23.3 min, t_R = 36.2 min. $[\alpha]_D^{20}$ = +18.4 (c = 1).

Experimental Part



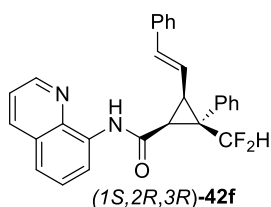
(1S,2R,3S)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)-3-((E)-styryl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 95/5 to 75/25). Yield: 60% (57.8 mg). $R_f = 0.33$ (petroleum ether / ethyl acetate, 75/25). Yellowish foam. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **trans-39a**. **Enantiomeric Excess:** 90%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (n-heptane: *i*-PrOH = 70:30, 254 nm, 1 mL/min), $t_R = 8.1$ min, $t_R = 9.5$ min. $[\alpha]_D^{20} = +24.3$ ($c = 1$).



(1S,2R,3R)-2-(fluoromethyl)-2-phenyl-N-(quinolin-8-yl)-3-((E)-styryl)cyclopropane-1-carboxamide

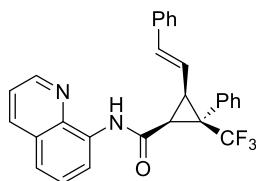
Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 88/12). Yield: 82% (68.4 mg). $R_f = 0.37$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **42a**. **Enantiomeric Excess:** 95%. The enantiomeric excess was determined by HPLC with a Chiralcel IE column (n-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), $t_R = 7.5$ min, $t_R = 9.4$ min. $[\alpha]_D^{20} = +11.8$ ($c = 0.5$, CHCl_3).



(1S,2R,3R)-2-(difluoromethyl)-2-phenyl-N-(quinolin-8-yl)-3-((E)-styryl)cyclopropane-1-carboxamide

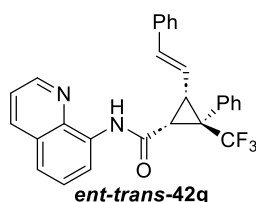
Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: n-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 73% (60.2 mg). $R_f = 0.51$ (petroleum ether / ethyl acetate, 83/17). White solid. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **42f**. **Enantiomeric Excess:** 97%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (n-heptane: *i*-PrOH = 90:10, 254 nm, 1 mL/min), $t_R = 7.5$ min, $t_R = 9.4$ min. $[\alpha]_D^{20} = +10.1$ ($c = 0.5$, CHCl_3).

Experimental Part



(1*S*,2*R*,3*R*)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 18% (16.7 mg). $R_f = 0.45$ (petroleum ether / ethyl acetate, 83/17). Yellow oil. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **42g**. **Enantiomeric Excess:** 96%. The enantiomeric excess was determined by HPLC with a Chiralcel AD column (*n*-heptane: *i*-PrOH = 80:20, 254 nm, 1 mL/min), $t_R = 9.5$ min, $t_R = 13.9$ min. $[\alpha]_D^{20} = +25.3$ ($c = 1$).

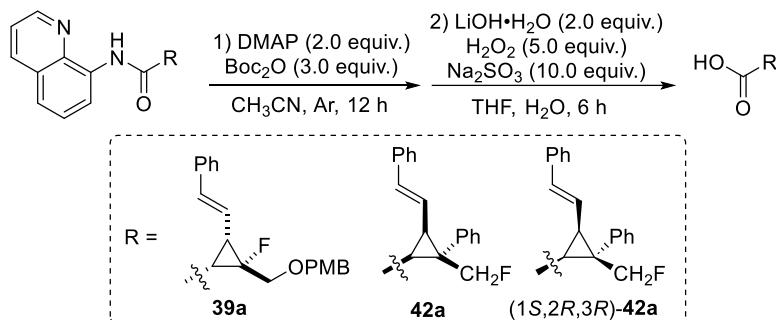


(1*R*,2*R*,3*S*)-2-phenyl-*N*-(quinolin-8-yl)-3-((*E*)-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

Purification by silica gel column chromatography (height 20 cm, width 1.5 cm, eluent: *n*-pentane / ethyl acetate, from 99/1 to 90/10). Yield: 75% (68.6 mg). $R_f = 0.50$ (petroleum ether / ethyl acetate, 83/17). Yellow solid. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with *trans*-**42g**. **Enantiomeric Excess:** 87%. The enantiomeric excess was determined by HPLC with a Chiralcel IB column (*n*-heptane: *i*-PrOH = 90:10, 254 nm, 1 mL/min), $t_R = 5.9$ min, $t_R = 7.9$ min. $[\alpha]_D^{20} = +24.5$ ($c = 1$).

3. General procedures for the post-functionalization reactions

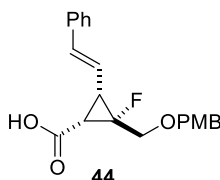
3.1. Synthesis of cyclopropyl carboxylic acids **44**, **47** and (1*S*, 2*R*, 3*R*)-**47a**.



To a solution of **39a**, **42a** or (1*S*, 2*R*, 3*R*)-**42a** (0.18 mmol, 1.0 equiv.) in CH_3CN (1 mL) were added DMAP (39 mg, 0.36 mmol, 2.0 equiv.) and Boc_2O (118 mg, 0.54 mmol, 3.0 equiv.) at room temperature, and the mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was partitioned between EtOAc (5 mL) and aqueous HCl (1 M, 5 mL). The organic layer was washed with saturated aqueous NaHCO_3 (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 , and evaporated to give a crude product as a yellow solid. To a solution of the crude product

Experimental Part

in THF (1.2 mL), and H₂O (0.38 mL) was added LiOH.H₂O (12.6 mg, 0.3 mmol). Then, the mixture was cooled to 0 °C. H₂O₂ (30% aq. 84 μL, 0.75 mmol) was added to the mixture. After stirring for 6 h at room temperature, Na₂SO₃ (185 mg, 1.5 mmol) was added. The reaction mixture was diluted with EtOAc and acidified with 0.5 M aq. HCl. The mixture was extracted with EtOAc. The organic layer was dried over anhydrous Na₂SO₄, filtered, and concentrated with the acid of a rotary evaporator. The residue was purified by silica gel column chromatography to provide carboxylic acids **44**, **47** and (1*S*, 2*R*, 3*R*)-**47a**.



(*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-((*E*)-styryl)cyclopropane-1-carboxylic acid

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, with 0.1% formic acid, from 80/20 to 65/35). Yield: 65% (40.4 mg). *R*_f = 0.42 (petroleum ether / ethyl acetate, 50/50, 1% formic acid). White solid. Mp: 131 – 133 °C.

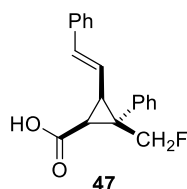
¹H NMR (300.1 MHz, CDCl₃) δ 7.43 (d, *J* = 7.0 Hz, 2H), 7.39 – 7.23 (m, 5H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 3.8 Hz, 2H), 4.61 (s, 2H), 3.91 – 3.74 (m, 5H), 2.50 – 2.36 (m, 1H), 2.28 – 2.12 (m, 1H).

¹³C NMR (75.5 MHz, CDCl₃) δ 159.6, 137.1, 134.1, 129.6, 129.5, 128.7, 127.6, 126.4, 120.0, 119.9, 114.1, 82.8 (d, *J* = 234.7 Hz), 73.1, 70.8, 70.5, 55.4, 31.5 (d, *J* = 9.0 Hz).

¹⁹F NMR (282.4 MHz, CDCl₃) δ -202.7 – -206.4 (m, 1F).

IR (neat) 3065, 2919, 2840, 1734, 1610, 1512, 1248, 1171, 755, 699 cm⁻¹.

HRMS (ES⁻): calcd for C₂₁H₂₁FO₄ *m/z* 355.1346 ([M-H]⁻) found 355.1349 (Δ0.8 ppm).



(*cis*)-2-(fluoromethyl)-2-phenyl-3-((*E*)-styryl)cyclopropane-1-carboxylic acid

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, with 0.1% formic acid, from 80/20 to 65/35). Yield: 65% (40.4 mg). *R*_f = 0.47 (petroleum ether / ethyl acetate, 50/50, 1% formic acid): 0.47. White solid. Mp: 158 – 160 °C.

¹H NMR (300.1 MHz, CDCl₃) δ 7.37 – 7.27 (m, 6H), 7.26 – 7.21 (m, 3H), 7.15 (dd, *J* = 8.4, 6.2 Hz, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.55 (dd, *J* = 15.8, 9.5 Hz, 1H), 5.07 (dd, *J* = 55.8, 9.4 Hz, 1H), 4.99 (dd, *J* = 56.3, 9.8 Hz, 1H), 2.62 (td, *J* = 9.2, 3.0 Hz, 1H), 2.42 (dd, *J* = 8.8, 1.9 Hz, 1H).

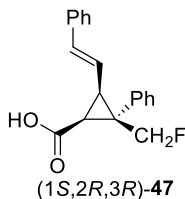
¹³C NMR (75.5 MHz, CDCl₃) δ 142.0, 136.9, 134.5, 129.1, 128.8, 128.8, 127.9, 127.8, 126.4, 121.6, 82.3 (d, *J* = 168.8 Hz), 40.8, 40.5, 36.2 (d, *J* = 5.7 Hz). One carbon wasn't detected.

¹⁹F NMR (282.4 MHz, CDCl₃) δ -221.5 (t, *J* = 47.2 Hz, 1F).

IR (neat) 3367, 3026, 2895, 1954, 1599, 1494, 982, 956, 750, 693 cm⁻¹.

HRMS (ES⁻): calcd for C₁₉H₁₇FO₂ *m/z* 295.1134 ([M-H]⁻) found 295.1120 (Δ-4.7 ppm).

Experimental Part

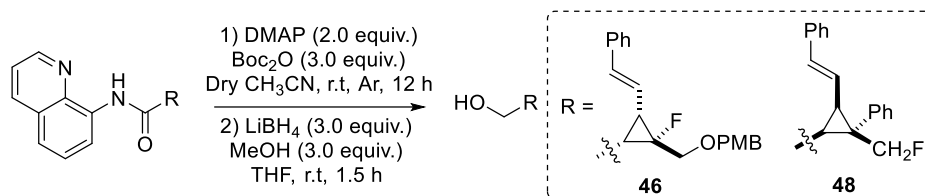


(1*S*,2*R*,3*R*)-2-(fluoromethyl)-2-phenyl-3-((*E*)-styryl)cyclopropane-1-carboxylic acid

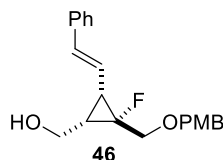
Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: *n*-pentane / ethyl acetate, with 0.1% formic acid, from 80/20 to 65/35). Yield: 72% (44.8 mg). $R_f = 0.47$ (petroleum ether / ethyl acetate, 50/50, 1% formic acid): 0.47. White solid. The characterization (^1H , ^{13}C , ^{19}F NMR and HRMS) is consistent with **47**.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with a Chiralcel IC column (*n*-heptane with 1% formic acid: *i*-PrOH = 90:10, 254 nm, 1 mL/min), $t_R = 4.1$ min, $t_R = 4.6$ min. $[\alpha]^{20\text{D}} = +32.6$ ($c = 0.5$, CHCl_3).

3.2. Synthesis of cyclopropyl primary alcohol **46** and **48**.



To a solution of **39a** or **42a** (0.22 mmol, 1.0 equiv.) in CH_3CN (1 mL) were added DMAP (53.7 mg, 0.44 mmol, 2.0 equiv.) and Boc_2O (144 mg, 0.66 mmol, 3.0 equiv.) at room temperature, and the mixture was stirred at room temperature for 12 h. The solvent was evaporated, and the residue was partitioned between EtOAc (5 mL) and aqueous HCl (1 M, 5 mL). The organic layer was washed with saturated aqueous NaHCO_3 (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 , and evaporated to give a crude product as a yellow solid. To a solution of the crude product in THF (2 mL) were added MeOH (23 μL , 0.57 mmol) and LiBH_4 (12.5 mg, 0.57 mmol) at 0 $^\circ\text{C}$, and the mixture was stirred at room temperature for 1.5 h. To the reaction mixture were added Et_2O (5 mL), saturated aqueous NH_4Cl (5 mL) and water (5 mL) at 0 $^\circ\text{C}$. The resulting mixture was extracted with Et_2O , and the organic layer was washed with brine, dried over anhydrous Na_2SO_4 , and evaporated. The residue was purified by silica gel column chromatography to give correspondent alcohol products **46** and **48**.



((*cis*)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-((*E*)-styryl)cyclopropyl)methanol

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: *n*-pentane / ethyl acetate, from 90/10 to 75/25). Yield: 74% (56.4 mg). $R_f = 0.61$ (petroleum ether / ethyl acetate, 50/50). Colorless oil.

^1H NMR (300.1 MHz, CDCl_3) δ 7.36 – 7.24 (m, 6H), 7.24 – 7.16 (m, 1H), 6.88 (d, $J = 8.2$ Hz 2H), 6.60 (d, $J = 15.9$ Hz, 1H), 6.09 (dd, $J = 15.9, 9.3$ Hz, 1H), 4.55 (s, 2H), 3.90 – 3.54 (m, 7H), 2.59

Experimental Part

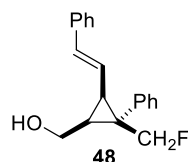
(s, 1H), 1.98 – 1.83 (m, 1H), 1.61 – 1.44 (m, 1H).

^{13}C NMR (75.5 MHz, CDCl_3) δ 159.4, 137.1, 133.3, 129.7, 129.5, 128.6, 127.3, 126.0, 121.3 (d, $J = 8.8$ Hz), 113.9, 82.9 (d, $J = 225.1$ Hz), 72.8, 72.5 (d, $J = 22.2$ Hz), 57.0 (d, $J = 9.1$ Hz), 55.3, 28.3 (d, $J = 10.3$ Hz), 27.1 (d, $J = 9.7$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -206.5 – -209.6 (m, 1F).

IR (neat) 3329, 2917, 2850, 1611, 1512, 1245, 1073, 1028, 817, 751, 693 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{21}\text{H}_{23}\text{FO}_3$ m/z 360.1975 ($[\text{M}+\text{H}_2\text{O}]^+$) found 360.1974 ($\Delta 0.8$ ppm).



(*cis*)-2-(fluoromethyl)-2-phenyl-3-((*E*)-styryl)cyclopropylmethanol

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: n-pentane / ethyl acetate, from 90/10 to 75/25). Yield: 69% (38.8 mg). $R_f = 0.2$. (petroleum ether / ethyl acetate, 80/20). Colorless oil.

^1H NMR (300.1 MHz, CDCl_3) δ 7.45 – 7.37 (m, 3H), 7.37 – 7.29 (m, 6H), 7.28 – 7.21 (m, 1H), 6.71 (d, $J = 15.6$ Hz, 1H), 6.17 (dd, $J = 15.6, 9.2$ Hz, 1H), 4.96 (dd, $J = 25.7, 10.4$ Hz, 1H), 4.80 (dd, $J = 24.8, 10.4$ Hz, 1H), 4.15 – 3.95 (m, 2H), 2.34 (td, $J = 9.2, 4.1$ Hz, 1H), 2.12 – 1.88 (m, 2H).

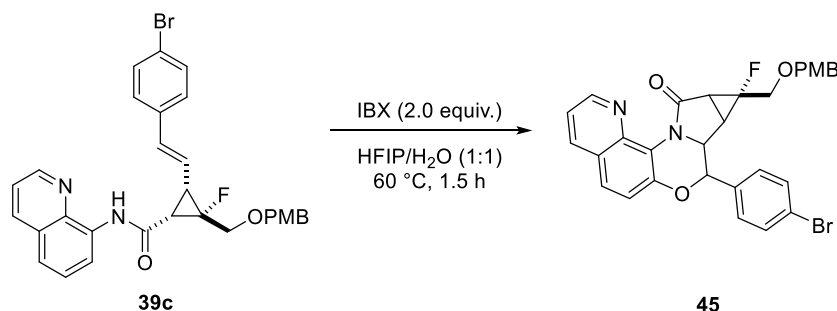
^{13}C NMR (75.5 MHz, CDCl_3) δ 143.7, 137.0, 134.1, 128.9, 128.8, 128.7, 127.6, 127.2, 126.1, 123.0, 85.5 (d, $J = 167.5$ Hz), 59.6, 35.9 (d, $J = 22.4$ Hz), 32.7 (d, $J = 3.8$ Hz), 32.3 (d, $J = 7.3$ Hz).

^{19}F NMR (282.4 MHz, CDCl_3) δ -215.1 (t, $J = 48.4$ Hz, 1F).

IR (neat) 3028, 2918, 2851, 1687, 1440, 1227, 994, 921, 709, 699 cm^{-1} .

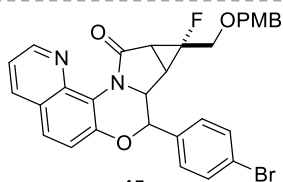
HRMS (ES^-): calcd for $\text{C}_{19}\text{H}_{19}\text{FO}$ m/z 281.1347 ($[\text{M}-\text{H}]^-$) found 281.1346 ($\Delta -0.4$ ppm).

3.3. Synthesis of cyclopropyl pyrrolyl oxazinone 45.



To an oven dried 10 mL tube with a stir bar, was charged with **39c** (112 mg, 0.2 mmol, 1.0 equiv.) and IBX (cas: 1717-82-6) (112 mg, 0.4 mmol, 2.0 equiv.), followed by HFIP (0.65 mL) and H_2O (0.65 mL). This mixture was sealed and stirred at 60 °C for 1.5 h. Then an aqueous saturated solution of NaHCO_3 and DCM were added, the two phases were separated, extracted inorganic phase 3 times with DCM. The organic phases were combined, dried over anhydrous Na_2SO_4 , and evaporated. The residue was purified by silica gel column chromatography to give correspondent cyclopropyl pyrrolyl oxazinone product **10**.

Experimental Part



8-(4-bromophenyl)-9-fluoro-9-(((4-methoxybenzyl)oxy)methyl)-8a,8b,9,9a-tetrahydrocyclopropa[3',4']pyrrolo[1',2':4,5][1,4]oxazino[2,3-*h*]quinolin-10(8*H*)-one

Purification by silica gel column chromatography (height 20 cm, width 3.0 cm, eluent: DCM / MeOH, from 100/0 to 99.5/0.5). Yield: 47% (54 mg). R_f (DCM / MeOH, 20/1): 0.71. White solid. Mp: 57 – 59 °C.

$^1\text{H NMR}$ (300.1 MHz, CDCl_3) δ 8.95 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.05 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.65 – 7.58 (m, 3H), 7.37 – 7.27 (m, 3H), 7.23 (d, $J = 8.9$ Hz, 1H), 7.15 (d, $J = 8.7$ Hz, 2H), 6.85 (d, $J = 8.7$ Hz, 2H), 4.98 (d, $J = 9.4$ Hz, 1H), 4.48 (s, 2H), 3.92 – 3.79 (m, 5H), 3.66 (dd, $J = 17.6, 11.3$ Hz, 1H), 2.45 (d, $J = 7.0$ Hz, 1H), 1.99 (dd, $J = 7.1, 2.4$ Hz, 1H).

$^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ 166.0, 159.5, 150.2, 148.1, 142.4, 135.8, 134.3, 132.4, 129.7, 129.6, 129.2, 126.6, 124.4, 124.0, 119.8, 118.2, 117.0, 114.0, 81.5 (d, $J = 55.2$ Hz), 73.0, 69.1, 68.8, 55.4, 54.7 (d, $J = 3.2$ Hz), 29.9 (d, $J = 13.8$ Hz), 23.5 (d, $J = 12.6$ Hz).

$^{19}\text{F NMR}$ (282.4 MHz, CDCl_3) δ -202.7 (t, $J = 15.3$ Hz, 1F).

IR (neat) 3344, 2923, 1613, 1714, 1513, 1484, 1248, 1009, 824, 793, 700 cm^{-1} .

HRMS (ES^+): calcd for $\text{C}_{30}\text{H}_{24}\text{FN}_2\text{O}_4$ m/z 575.0970 ($[\text{M}+\text{H}]^+$) found 575.0977 ($\Delta 1.2$ ppm).

Reference

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Curriculum Vitae

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Education

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Professional Experiences

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Conferences

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Publications

Ph.D:

1) C. Zhao, T. Besset, C. Legault, P. Jubault, Experimental and Computational Studies for the

Synthesis of Functionalized Cyclopropanes from α -Substituted Allylic Derivatives with Ethyl Diazoacetate. **2023**, *Chem. Eur. J.* e202303070.

Master:

2) J. Yan, Z. Song, C. **Zhao**, K. Shi, L. Yang, G. Zhong, Highly Chemoselective and Enantioselective Synthesis of 3,4-2*H*-Pyridin-2-ones by an NHC-Catalyzed [3+3] Cyclization. *Org. Lett.* **2020**, *22*, 3329–3334.

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Transition metal-catalyzed diazo compounds decomposition for the catalytic enantioselective synthesis of new cyclopropanic scaffolds

Abstract

Cyclopropane, a significant organic motif featuring the smallest carbocycle and the highest ring strain, exhibits distinctive properties in comparison to other cycloalkanes. This scaffold is prevalent in natural products and finds extensive applications in medicinal research programs aiming at enhancing the pharmaceutical features of drug candidates. With the continuous advancement of organic and pharmaceutical chemistry, there is a growing interest for versatile molecules incorporating cyclopropane skeleton, particularly those with optical activity or fluorine atom.

The first part (chapter II) of this Ph.D. thesis focuses on the use of chiral Ru(II)-Pheox complexes in [2+1] asymmetric cycloaddition, yielding highly functionalized cis and trans cyclopropanes with moderate to high yields (32-97%) and exceptional enantiomeric excess (86-99%). DFT calculations suggest an outer-sphere mechanism.

Chapter III introduces a groundbreaking protocol using Ru(II)-Pheox for catalytic synthesis, achieving versatile opportunities for stereocontrolled α,α -difluoroalkyl cyclopropane frameworks with high yields (17-94%) and outstanding diastereo- and enantioselectivity.

In chapter IV, we presents optimization studies for enantiomerically pure alkynylcyclopropanes, addressing challenges in enantioselectivity despite successful outcomes in yields and diastereoselectivity with Rh(II)-complexes.

Chapter V outlines an efficient methodology for accessing 1,2,3-polysubstituted fluorinated cyclopropanes, using Pd(II)-catalyzed C–C bond formation through C–H bond activation. The method proves tolerant to various electrophiles, offering a practical route for both racemic and enantiomeric fluorinated cyclopropane scaffolds.

Keywords: transition metal-catalysis, diazo compound, enantioselective, cyclopropane

Décomposition catalysée par des métaux de transition de composés diazo pour la synthèse énantiosélective catalytique de nouveaux cadres cyclopropaniques

Résumé

Le cyclopropane, un motif structural important présentant le carbocycle le plus petit et le plus contraint parmi les molécules organiques, possède des propriétés distinctives par rapport aux autres cycloalcanes. Ce motif est répandu dans les produits naturels et trouve des applications variées en chimie médicinale pour l'amélioration des caractéristiques pharmaceutiques des candidats médicaments. Avec l'avancement continu de la chimie organique et pharmaceutique, un intérêt croissant s'est manifesté pour les molécules polyvalentes incorporant le motif cyclopropane, en particulier celles présentant une activité optique ou un atome de fluor.

La première partie (chapitre II) de cette thèse de doctorat se concentre sur l'utilisation de complexes chiraux Ru(II)-Pheox dans une cycloaddition asymétrique [2+1], produisant des cyclopropanes *cis* et *trans* hautement fonctionnalisés avec des rendements modérés à élevés (32-97%) et une excellente pureté énantiomérique (86-99%). Les calculs de DFT suggèrent un mécanisme de sphère externe.

Le chapitre III introduit un protocole novateur utilisant Ru(II)-Pheox comme catalyseur pour la synthèse stéréosélective de divers cyclopropanes α,α -difluoroalkyl avec des rendements élevés (17-94%) et d'excellentes diastéréo- et énantiosélectivités.

Dans le chapitre IV, des études d'optimisation sont présentées pour la synthèse d'alkynylcyclopropanes énantiomériquement purs, abordant les défis de l'énantiosélectivité malgré des résultats prometteurs en termes de rendements et de diastéréosélectivité avec des complexes de Rh(II). Le chapitre V expose une méthodologie efficace pour l'accès à des cyclopropanes fluorés 1,2,3-polysubstitués, utilisant une formation de liaison C-C catalysée par Pd(II) par activation de liaisons C-H. La méthode se révèle tolérante à divers électrophiles, offrant une voie de synthèse pratique pour la préparation de motifs cyclopropanes fluorés tant racémiques qu'énantiopurs.

Mots-clés: catalyse par les métaux de transition, composé diazo, énantiosélectivité, cyclopropane