

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

Chengtao Zhao

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Chengtao Zhao. Transition metal-catalyzed diazo compounds decomposition for the catalytic enantioselective synthesis of new cyclopropanic scaffolds. Organic chemistry. Normandie Université, 2024. English. NNT: 2024NORMIR02. tel-04615718

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# **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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## Acknowledgements

First and foremost, I extend my gratitude to Pr. Julien Pytkowicz (Université de Cergy-Pontoise), Dr. Benoît Crousse (Université de Paris-Saclay), and Dr. Armen Panossian (Université de Strasbourg) for graciously agreeing to evaluate my thesis.

I am deeply thankful to my supervisors, Prof. Philippe Jubault and Dr. Tatiana Besset, for providing me with the opportunity to conduct my thesis work in the fluorine chemistry group. Their guidance, unwavering encouragement, and the considerable academic freedom they granted me are sincerely appreciated. This thesis owes much to their illuminating instruction and advice.

Special appreciation goes to Prof. Claude Legault for our collaborative work on DFT calculations, and my thanks to Prof. Rudi Fasan for providing several enantiomeric fluorinated cyclopropanes.

I express my sincere gratitude to Elisabeth Roger for her contributions to the lab, facilitating our chemistry endeavors (especially in IR analysis). Laetitia Bailly and Emilie Petit's invaluable assistance with chromatography techniques, Dr. Morgane Sanselme's dedicated efforts in X-ray analysis of my compounds, Dr. Albert Marcual for HRMS analyses, and Prof. Hassan Oulyadi and Dr. Lina Truong for their support in acquiring NMR analyses—all have played pivotal roles in shaping this thesis.

I extend my heartfelt thanks to all members of the "Fluorinated Biomolecules Synthesis" group for their generous suggestions and assistance, both in chemistry and daily life.

My appreciation also goes to my family members and friends, who have provided me with impartial love and support.

Finally, I am grateful to the China Scholarship Council (CSC) for their financial support.

## **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  $\alpha$ , $\alpha$ -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  $\alpha$ , $\alpha$ -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, -

CH<sub>2</sub>F, -CF<sub>2</sub>H, and -CF<sub>3</sub> 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  $\alpha$ , $\alpha$ -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  $\alpha$ , $\alpha$ -difluoroalkyl stéréocontrôlés.

Dans le chapitre IV, cette thèse présente ensuite des études d'optimisation pour la synthèse d'alkynylcyclopropanes énantiomériquement pures. 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, -CH<sub>2</sub>F, -CF<sub>2</sub>H et -CF<sub>3</sub>. 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**

 $\mathbf{A}$ 

Ac acetyl

AIBN azobisisobutyronitrile

В

Bn benzyl

Boc tert-butyloxycarbonyl

bpy bipyridine

Bz benzoyl

 $\mathbf{C}$ 

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 dichloromathane

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

*dr* diastereomeric ratio

E

EDG electron-donating group

ee enantiomeric excess

EEDQ N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

equiv. equivalent

er enantiomeric ratio

Et ethyl

EWG electron-withdrawing group

Н

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

mCPBA 3-chloroperoxybenzoic acid

Me methyl

MeCN acetonitrile

MOMCl chloromethyl methyl ether

m.p. melting point

Ms mesyl

N

NBS N-bromosuccinimide

nBu nbutyl

NCS N-chlorosuccinimide

NIS *N*-iodosuccinimide

NMP N-methyl-2-pyrrolidone

NMR nuclear magnetic resonance

NS 2-nitrophenyl sulfonyl

Nu nucleophile

P

PCC pyridinium chlorochromate

PE petroleum ether

Ph phenyl

PMB para-methoxybenzyl

PMP para-methoxyphenyl

 $\mathbf{R}$ 

r.t. room temperature

T

T temperature

t time

*t*-AmylOH 2-methylbutan-2-ol

TBAB *tetra-n*butylammonium bromide

TBAF tetra-nbutylammonium fluoride

TBDPS *tert*-butyldiphenylsilyl

TBME *tert*-butyl methyl ether

TBS *tert*-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

*t*Bu *tert*-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.<sup>1</sup> 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).<sup>2</sup> These bond angles deviate considerably from the ideal tetrahedral bond angles of 109.5° that are commonly found in sp<sup>3</sup> hybridized carbon atoms.<sup>3</sup> 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.<sup>4</sup>

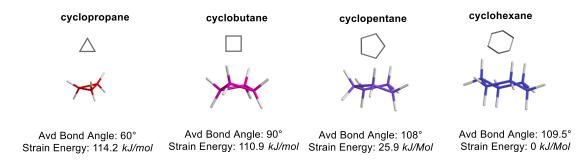


Figure 1. The properties of cycloalkanes.

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

<sup>&</sup>lt;sup>1</sup> 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.

<sup>&</sup>lt;sup>2</sup> K. B. Wiberg, Angew. Chem. Int. Ed. Engl. 1986, 25, 312–322.

<sup>&</sup>lt;sup>3</sup> A. de Meijere, Angew. Chem. Int. Ed. Engl. 1979, 18, 809–826.

<sup>&</sup>lt;sup>4</sup> 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.

<sup>&</sup>lt;sup>5</sup> 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.

<sup>&</sup>lt;sup>6</sup> H. Staudinger, L. Ruzicka, *Helv. Chim. Acta. 1924*, 7, 177–235.

### Chapter I – Introduction

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.<sup>7</sup> On the other hand, the three member carbon rings were explored to divert preclinical and clinical drug molecules.<sup>8</sup> 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).<sup>9</sup>

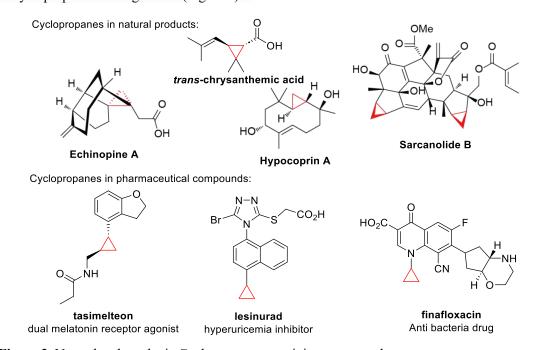


Figure 2. Natural and synthetic Cyclopropane-containing compounds.

<sup>&</sup>lt;sup>7</sup> Y.-Y. Fan, X.-H. Gao, J.-M. Yue, Sci. Chin. Chem. **2016**, *59*, 1126–1141.

<sup>&</sup>lt;sup>8</sup> 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.

<sup>&</sup>lt;sup>9</sup> 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. This low-boiling-point cycloalkane was employed as an anesthetic for a period of time. In 1884, 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, cyclopropanol 12, hexafluorocyclopropane 13, and *gem*-dichlorocyclopropane 14. 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. Building upon previous researches, organic chemists have to date successfully pioneered more than ten methods for generating cyclopropane derivatives (Scheme 1). Among these, we will focus on transition metal-catalyzed diazo compound decomposition in the context of cyclopropanation in my forthcoming studies.

<sup>&</sup>lt;sup>10</sup> A. Freund and U. Trimethylen, J. Prakt. Chem. **1882**, 26, 367–377.

<sup>&</sup>lt;sup>11</sup> W. H. Perkin, Ber. Dtsch. Chem. Ges. **1884**, 17, 54–59.

<sup>&</sup>lt;sup>12</sup> J. K. Magrane, D. L. Cottle, J. Am. Chem. Soc. **1942**, 64, 484–487.

<sup>&</sup>lt;sup>13</sup> Atkinson, B. J. Chem. Soc. 1952, 2684–2694.

<sup>&</sup>lt;sup>14</sup> Doering, W. E.; Hoffmann, A. K. J. Am. Chem. Soc. **1954**, 76, 6162–6165.

<sup>&</sup>lt;sup>15</sup> H. E. Simmons, R. D. Smith, J. Am. Chem. Soc. **1956**, 80, 5323–5324.

<sup>&</sup>lt;sup>16</sup> 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. Mühling, *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. <sup>17</sup> 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). <sup>18</sup>

<sup>&</sup>lt;sup>17</sup> R. Maty'a's, J. 'Sele'sovsk'y, T. Musil, *J. Hazard. Mater.*, **2012**, *213*, 236–241.

<sup>&</sup>lt;sup>18</sup> 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.

### Chapter I – Introduction

Diazo stability

$$N_{2} \leftarrow N_{2} \leftarrow N_{$$

**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 century<sup>19</sup>, coinciding with the emergence of asymmetric cyclopropanation reactions.<sup>20</sup> The mechanism investigation was primitively studied by Yates<sup>21</sup> 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.<sup>22</sup> To address the mechanism for above

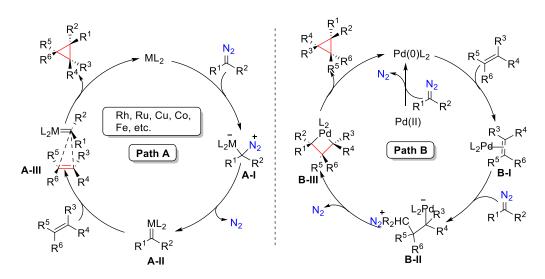
<sup>&</sup>lt;sup>19</sup> a) A. Loose, *Journ. f. prakt.* **1909**, *79*, 507–510. b) F. Kaplan, G. K. Meloy, *J. Am. Chem. Soc.* **1966**, *88*, 950–956.

<sup>&</sup>lt;sup>20</sup> 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.

<sup>&</sup>lt;sup>21</sup> P. Yates, J. Am. Chem. Soc. **1952**, 74, 5376–5381.

<sup>&</sup>lt;sup>22</sup> 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 Difunctionnalization 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.<sup>23</sup> 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.<sup>24</sup> 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-II**, 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.<sup>25</sup> In general, biosynthetic enzymes for cyclopropane rings fall into two classes of mechanism: carbocationic intermediates and carbanionic intermediates.<sup>26</sup>



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

<sup>&</sup>lt;sup>23</sup> 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.

<sup>&</sup>lt;sup>24</sup> a) Y. V. Tomilov, V. A. Dokichev, U. M. Dzhemilev, O. M. Nefedov, *Russ. Chem. Rev.* **1993**, *62*, 799–838. b) C. Rodriguez–Garcia, 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.

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

<sup>&</sup>lt;sup>26</sup> 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 safety introduced [2+1] cycloaddition reaction catalyzed by transition metal in 1992.<sup>27</sup> That because diazomethane is known as toxic and explosive<sup>28</sup> gas (b.p. -23 °C) since it was first synthesized from *N*-methyl-*N*-nitrosocarbamate by Pechmann.<sup>29</sup> Subsequently, the most commonly used sources for *in situ* generation of diazomethane were developed, for example, *N*-methyl-*N*-nitrosourea (MNU),<sup>30</sup> *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald), <sup>31</sup> *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (MNNG)<sup>32</sup> and temozolomide (TMZ) (Figure 3).<sup>33</sup> The use of diazomethane and its precursors in the context of cyclopropanation reactions involving batch and flow conditions were commendably summarized in two dedicated reviews<sup>34</sup> and several separated chapters of review publications.<sup>35</sup> Therefore, this topic will be continually stated only regarding different transition metals.

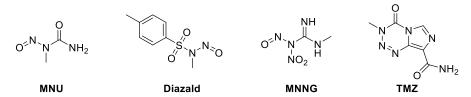


Figure 3. Most commonly diazomethane sources.

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

<sup>&</sup>lt;sup>27</sup> O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, V. A. Dokitchev, *Mendeleev Commun.* **1992**, *2*, 13–15.

<sup>&</sup>lt;sup>28</sup> 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**.

<sup>&</sup>lt;sup>29</sup> H. V. Pechmann, Ber. Dtsch. Chem. Ges. **1894**, 27, 1888–1891.

<sup>&</sup>lt;sup>30</sup> H. Lehmann, Green Chem. **2017**, 19, 1449–1453.

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

<sup>&</sup>lt;sup>32</sup> J. A. Montgomery, Nitrosoureas: current status and new developments **1981**, 3–8.

<sup>&</sup>lt;sup>33</sup> R. L. Svec, P. J. Hergenrother, *Angew. Chem. Ent. Ed.* **2019**, *132*, 1873–1878.

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.

<sup>&</sup>lt;sup>35</sup> 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.

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.<sup>36</sup> 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)<sub>2</sub>. Exactly as a previously prepared and separable [Pd(0)<sub>2</sub>(DVTMS)<sub>3</sub>] complex was employed in the cyclopropanation of vinylsilane substrates at -35 °C within one hour, yielding satisfactory results (Scheme 4).<sup>37</sup> Although Palladium complexes are excellent catalysts in CH<sub>2</sub>N<sub>2</sub>-cyclopropanation with alkenes, but are rarely used for stereoconvergent cyclopropanic derivatives. The strategy is effective with sterically demanding groups<sup>38</sup> but less so with linear alkenes,<sup>39</sup> while Pd-catalyzed diazo compound decomposition for asymmetric cyclopropanation relies heavily on a chiral auxiliary.<sup>40</sup>

Scheme 4. [Pd(0)<sub>2</sub>(DVTMS)<sub>3</sub>] 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

<sup>&</sup>lt;sup>36</sup> Y. V. Tomilov, V. G. Bordakov, I. E. Dolgii, O. M. Nefedov, *Russ. Chem. Bull.* **1984**, *33*, 533–538.

<sup>&</sup>lt;sup>37</sup> G. Berthon–Gelloz, M. Marchant, B. F. Straub, I. E. Marko, *Chem. Eur. J.* **2009**, *15*, 2923–2931.

<sup>&</sup>lt;sup>38</sup> a) K. Shimamoto, M. Ishida, H. Shinozaki, Y. Ohfune, *The Journal of Organic Chemistry* **1991**, *56*, 4167–4176. b) K. Shimamoto, Y. Ohfune, *Tetrahedron Lett.* **1989**, *30*, 3802–3804.

<sup>&</sup>lt;sup>39</sup> A. Davletbakova, I. Maidanova, N. Baibulatova, V. Dokichev, Y. V. Tomilov, M. Yunusov, O. Nefedov, *Russ. J. Org. Chem.* **2001**, *37*, 608–611.

<sup>&</sup>lt;sup>40</sup> a) J. Pietruszka, A. Witt, *J. Chem. Soc., Perkin Trans. 1* **2000**, 4293–4300. b) A. Alami, M. Calmes, J. Daunis, F. Escale, 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.<sup>41</sup> 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. <sup>42</sup> 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).

$$\frac{\text{CH}_2\text{N}_2}{\text{CuOTf+PhMe (5 mol\%)}} \\ \text{R} \qquad \qquad \frac{\text{CH}_2\text{N}_2}{\text{CuOTf+PhMe (5 mol\%)}} \\ \text{R} \qquad \qquad \text{yield/(\%)} \qquad \qquad \frac{\text{Ph}}{\text{Ph-BOX}}$$

R	yield/(%)	ee/(%)
OMe	81	50
Me	79	60
Н	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 (FeTPPCI) complex was first proposed as an efficient catalyst for diazomethane cyclopropanation.<sup>31a</sup> 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, FeTPPCI 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: Rh<sub>2</sub>(esp)<sub>2</sub> (52%), Co(II)-salen (23%), Rh<sub>2</sub>(Oct)<sub>4</sub> (45%), Pd(OAc)<sub>2</sub> (9%) CuOTf (0%), and Rh<sub>2</sub>(OAc)<sub>4</sub> (0%) (Scheme 5).

<sup>&</sup>lt;sup>41</sup> O. Nefedov, A. Ioffe, L. Menchikov, *Moscow: Khimiya* 1990, 177–183.

<sup>&</sup>lt;sup>42</sup> 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.<sup>43</sup> 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

<sup>&</sup>lt;sup>43</sup> 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.

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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).<sup>45</sup>

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).<sup>46</sup>

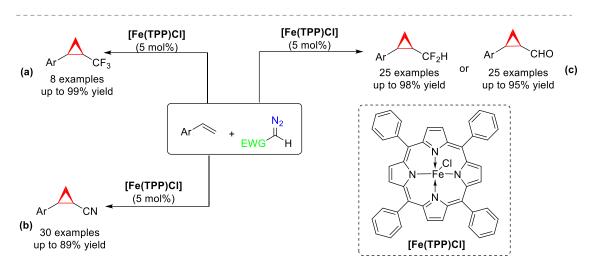
Recently, Bi and co-workers explored a difluoro-reagent (difluoroacetaldehyde *N*-Triftosylhydrazone) which is a difluoro-diazomethane precursor. Cyclopropanation reactions were carried out in the presence of [Fe(TPP)Cl] and have proved that this difluoro reagent was well tolerated for a large scope 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).<sup>47</sup>

<sup>&</sup>lt;sup>44</sup> 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.

<sup>&</sup>lt;sup>45</sup> B. Morandi, E. M. Carreira, Angew. Chem. Int. Ed. **2010**, 49, 938–941.

<sup>&</sup>lt;sup>46</sup> K. J. Hock, R. Spitzner, R. M. Koenigs, *Green Chem.* **2017**, *19*, 2118–2122.

<sup>&</sup>lt;sup>47</sup> 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 synthetized using diazo derivatives bearing one or two electron-withdrawing groups since the seminal work of Nozaki in 1966.<sup>48</sup> 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 diasteroisomeric 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).<sup>49</sup>

Furthermore, Bosyen 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).<sup>50</sup>

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"

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<sup>&</sup>lt;sup>48</sup> H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, Tetrahedron Lett. 1966, 7, 5239–5244.

<sup>&</sup>lt;sup>49</sup> H. Fritschi, U. Leutenegger, A. Pfaltz, Angew. Chem. Int. Ed. Engl. 1986, 25, 1005–1006.

<sup>&</sup>lt;sup>50</sup> T. Minuth, M. M. K. Boysen, *Beilstein J. Org. Chem.* **2010**, *6*, 23–29.

#### Chapter I – Introduction

(all substituents oriented in the same direction) Rh<sub>2</sub>(II)-(MEPY)<sub>4</sub> chiral catalyst in 1990.<sup>51</sup> 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).

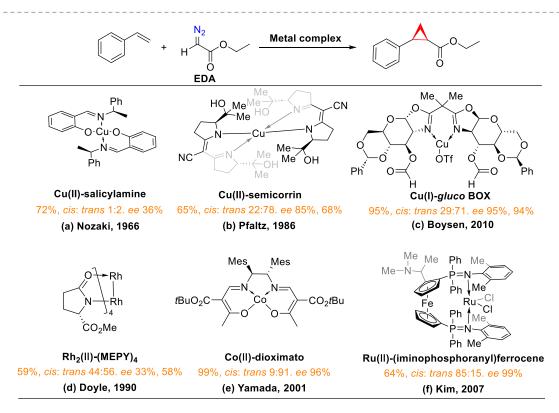
Few years later, an outstanding protocol was reported to produce both high diastereo- and enantiopure cyclopropanes from styrene and EDA. <sup>52</sup> The enantioselectivity of the cyclopronanation process using Co(II)-dioximato complexes was significantly influenced by the steric requirements of the 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.<sup>53</sup> 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).

<sup>&</sup>lt;sup>51</sup> 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.

<sup>&</sup>lt;sup>52</sup> T. Ikeno, M. Sato, H. Sekino, A. Nishizuka, T. Yamada, Bull. Chem. Soc. Jpn. 2001, 74, 2139–2150.

<sup>&</sup>lt;sup>53</sup> 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.

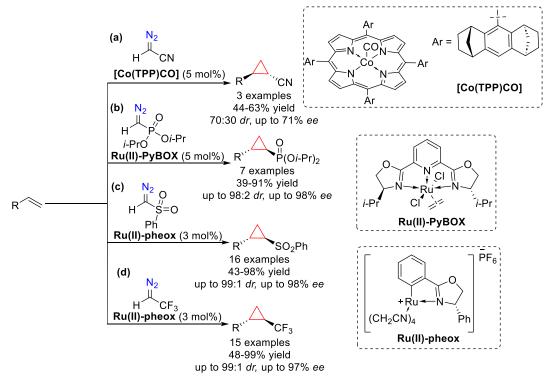
Generally, diazo derivatives bearing one carbonyl group, such as ketone, amide, and ester, exhibit important discrepancies in terms of reactivity and stereoselectivities. Therefore, we will not delve further into extensively documented massive cases in my discussion. Besides, there are three different 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  $D_4$ -symmetric [Co(TPP)CO] catalyst.<sup>54</sup> Unfortunately, the [Co(TPP)CO] complex led to poor diasteroselectivity (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.<sup>55</sup> 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

<sup>&</sup>lt;sup>54</sup> Y. Ferrand, P. Le Maux, G. Simonneaux, *Tetrahedron: Asymmetry* **2005**, *16*, 3829–3836.

<sup>&</sup>lt;sup>55</sup> A. L. Chandgude, R. Fasan, *Angew. Chem. Int. Ed.* **2018**, *57*, 15852–15856.

generate enantioenriched cyclopropanes using chiral catalyst Ru(II)-PyBOX.<sup>56</sup> 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.<sup>57</sup> 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.<sup>58</sup> 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*).



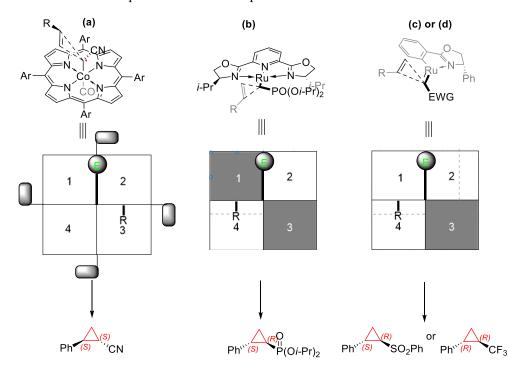
**Scheme 8**. Asymmetric cyclopropanation reactions with cyano, phosphonyl and sulfonyl diazomethane.

<sup>&</sup>lt;sup>56</sup> A. B. Charette, J.–E. Bouchard, Can. J. Chem. **2005**, 83, 533–542.

<sup>&</sup>lt;sup>57</sup> M. Kotozaki, S. Chanthamath, I. Fujisawa, K. Shibatomi, S. Iwasa, Chem. Commun. 2017, 53, 12193–12196.

<sup>&</sup>lt;sup>58</sup> M. Kotozaki, S. Chanthamath, T. Fujii, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2018**, *54*, 5110–5113.

According to metal complex symmetry theory,<sup>59</sup> 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*<sub>4</sub>-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. 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

<sup>&</sup>lt;sup>59</sup> A. Roy, S. Goswami, A. Sarkar, Synth. Commun. 2018, 48, 2003–2036.

<sup>&</sup>lt;sup>60</sup> 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.

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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.<sup>61</sup>

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.<sup>62</sup> This process involved the use of a  $\alpha$ -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  $\alpha$ -diazomalonate <sup>63</sup> had previously led to low enantioselectivities in cyclopropanation reactions. Additionally, a chiral catalyst Rh<sub>2</sub>(S-NTTL)<sub>4</sub> 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.<sup>64</sup>

**Scheme 10**. Rh<sub>2</sub>(S-NTTL)<sub>4</sub> catalyzed  $\alpha$ -diazodicarboxy derivative cyclopropanation.

Furthermore, Charette *et al.* exploited a couple of dirhodium complex catalysis strategies of diacceptor diazoalkanes asymmetric cyclopropanation (Scheme 11). They used the "all-up" structured Rh<sub>2</sub>(S-NTTL)<sub>4</sub> and Rh<sub>2</sub>(S-TCPTTL)<sub>4</sub> catalysts separately to decompose diazoalkanes, both of which

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

<sup>&</sup>lt;sup>61</sup> Y. Deng, H. Qiu, H. D Srinivas, M. P Doyle, Curr. Org. Chem. **2016**, 20, 61–81.

<sup>&</sup>lt;sup>62</sup> D. Marcoux, A. B. Charette, Angew. Chem. Int. Ed. 2008, 120, 10309–10312.

<sup>63</sup> Doyle, M.P.; Hu, W. ARKIVOC, 2003, 7, 15-22.

demonstrated superior stereocontrol abilities. To enhance selectivity, they unprecedently introduced an achiral hydrogen-bond donor, trifluoromethyl sulfonylamide, as an additive, exploiting the strong *trans*-directing ability of the amide substrates (Scheme 11a).<sup>65</sup> Unlikely, for the Rh<sub>2</sub>(S-TCTTL)<sub>4</sub> 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).<sup>66</sup>

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

Following the aforementioned developments, two  $\alpha$ -cyano diazo derivatives were used to access cyclopropane and methylenecyclopropane scaffolds by Charette and coworkers. The use of Rh<sub>2</sub>(S-IBAZ)<sub>4</sub> 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

<sup>65</sup> D. Marcoux, S. Azzi, A. B. Charette, J. Am. Chem. Soc. 2009, 131, 6970-6972.

<sup>66</sup> 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 reactionusing di-acceptor diazo compounds (Scheme 12a).<sup>67</sup> A groundbreaking study is reported by our group, focusing on the Rh<sub>2</sub>(S-IBAZ)<sub>4</sub>-catalyzed asymmetric cyclopropanation of donor-acceptor diazo compounds with  $\alpha$ -halogenated allylic substrates. <sup>68</sup> The method produced enantiomeric pure halogenated cyclopropanes in moderated to excellent yields and high ee, but in most cases with moderate diastereoselectivities (Scheme 12b).

(a) 
$$\frac{N_2}{NC - P(Oi-Pr)_2}$$
  $\frac{18 \text{ examples}}{81-99\% \text{ yield}}$   $\frac{199\% \text{ yield}}{99\% \text{ eve}}$   $\frac{N_2}{NC - P(Oi-Pr)_2}$   $\frac{N_2}{NC - P(Oi-Pr)_2}$   $\frac{N_2}{NC - P(Oi-Pr)_2}$   $\frac{11 \text{ examples}}{99\% \text{ yield}}$   $\frac{N_2}{NC - P(Oi-Pr)_2}$   $\frac{N_2}{N$ 

**Scheme 12**. Rh<sub>2</sub>(S-IBAZ)<sub>4</sub>-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.<sup>69</sup> 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 Rh<sub>2</sub>(S-BTPCP)<sub>4</sub>.<sup>70</sup>

<sup>67</sup> V. N. Lindsay, D. Fiset, P. J. Gritsch, S. Azzi, A. B. Charette, J. Am. Chem. Soc. 2013, 135, 1463-1470.

<sup>&</sup>lt;sup>68</sup> A. Pons, P. Ivashkin, T. Poisson, A. B. Charette, X. Pannecoucke, P. Jubault, *Chem. Eur. J.* **2016**, *22*, 6239–6242.

<sup>&</sup>lt;sup>69</sup> P. Müller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755–4763.

<sup>&</sup>lt;sup>70</sup> L. Chen, T. Minh Thi Le, J. P. Bouillon, T. Poisson, P. Jubault, *Chem. Eur. J.* **2022**, *28*, e202201254.

Scheme 13. Rh<sub>2</sub>(S-DOSP)<sub>4</sub> 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).<sup>71</sup>

**Scheme 14**. [Co(Por)]-mediated diaccepter diazoalkanes cyclopropanations undergo metalloradical pathway.

For instance, in recent work, Zhang and co-workers introduced a homolog of  $\alpha$ -diazomanolate as a carbene precursor mediated by chiral [Co(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

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<sup>&</sup>lt;sup>71</sup> 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. Snabilié, E. J. Meeus, R. F. Epping, Z. He, M. Zhou, B. de Bruin, *Chem. Eur. J.* **2023**, e202300336.

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.<sup>72</sup>

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.<sup>73</sup> Compared to more classical alkenes generally used in cyclopropanation process, they employed internal alkenes such as, indene, dihydronaphthalene and Z- $\beta$ -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.<sup>74</sup>

<sup>&</sup>lt;sup>72</sup> J. Wang, J. Xie, W.-C. C. Lee, D.-S. Wang, X. P. Zhang, *Chem Catal.* **2022**, *2*, 330–344.

<sup>&</sup>lt;sup>73</sup> C. Deng, H.-K. Liu, Z.-B. Zheng, L. Wang, X. Yu, W. Zhang, Y. Tang, Org. Lett. 2017, 19, 5717–5719.

<sup>&</sup>lt;sup>74</sup> 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).<sup>75</sup>

(a) 
$$N_2$$
  $Cu(CH_3CN)_4PF_6$   $CO_2Me$   $CO_2Me$ 

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.<sup>76</sup>

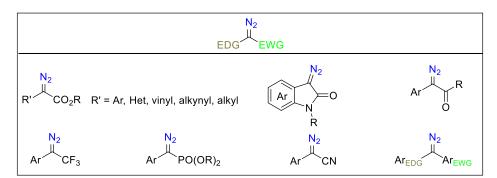


Figure 5. Donor-acceptor diazo compounds.

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

<sup>&</sup>lt;sup>75</sup> L. T. L. Chi, S. Chanthamath, K. Shibatomi, S. Iwasa, in *AIP Conference Proceedings, Vol. 1954*, AIP Publishing, **2018**.

<sup>&</sup>lt;sup>76</sup> 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 synthetized 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.<sup>77</sup> Based on this report, subsequently, miscellaneous metal complexes, such as Fe,<sup>78</sup> Ru,<sup>79</sup> Au,<sup>80</sup> Pd<sup>81</sup> and others,<sup>82</sup> have been proposed as carbene transfer agents for this [2+1] cycloaddition reaction (Scheme 17).

$$R^{1}$$
  $R^{2}$  +  $Ar$   $CO_{2}Me$   $R^{1}$   $R^{2}$   $R^$ 

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  $Rh_2(S-PTTL)_4^{83}$  and  $Rh_2(S-PTTL)_3 \cdot TPA_4^{84}$  as carbene transfers from  $\alpha$ -alkyldiazoesters. Even though the  $Rh_2(S-PTTL)_4$  have shown great capabilities within a series of  $\alpha$ -alkyldiazoesters and styrenes, the modified  $Rh_2(S-PTTL)_3 \cdot TPA$  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).

<sup>&</sup>lt;sup>77</sup> K. Paulini, H.-U. Reissig, *J. Prakt. Chem.* **1995**, *337*, 55–59.

<sup>&</sup>lt;sup>78</sup> 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.

<sup>&</sup>lt;sup>79</sup> C. del Pozo, A. Corma, M. Iglesias, F. Sánchez, *Green Chem.* **2011**, *13*, 2471–2481.

<sup>&</sup>lt;sup>80</sup> 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.

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

<sup>&</sup>lt;sup>82</sup> a) C. Tubaro, A. Biffis, R. Gava, E. Scattolin, 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.

<sup>83</sup> A. DeAngelis, O. Dmitrenko, G. P. Yap, J. M. Fox, J. Am. Chem. Soc. 2009, 131, 7230-7231.

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

**Scheme 18**. Asymmetric cyclopropanation of  $\alpha$ -alkyldiazoesters mediated by dirhodium complexes.

Indeed, asymmetric cyclopropanation reaction using rhodium catalysts, have been efficiently developed from donor-acceptor diazo compounds such as phenyldiazoacetates, <sup>85</sup> heteroaryldiazoacetates, <sup>86</sup> vinyldiazoacetates, <sup>87</sup> and alkynyl diazoacetates <sup>88</sup>. 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 Rh<sub>2</sub>(S-DOSP)<sub>4</sub> 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). <sup>87a</sup> Several years later, this approach was extended for the synthesis of optically pure diaryl cyclopropanes which are key intermediates of Tamoxifen derivatives (Scheme 19b). <sup>87b</sup>

In order to achieve highly enantioselective cyclopropanes with electronic deficient olefins, Davies and co-workers introduced Rh<sub>2</sub>(S-TCPTAD)<sub>4</sub> to decompose aryldiazoacetates and vinyldiazoacetates to generate reactive Rh-carbenes species (Scheme 19c). The outcome of reaction

<sup>a) H. M. L. Davies, P. R. Bruzinski, M. J. Fall,</sup> *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.
H. M. L. Davies, R. J. Townsend, *J. Org. Chem.* 2001, *66*, 6595–6603.

<sup>&</sup>lt;sup>87</sup> 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.

<sup>88</sup> 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.<sup>89</sup>

In 2014, Ball and co-workers studied an axial-binding component in ligand design to control Rh (II) diazo chemistry (Scheme 19d). This unprecedent 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.<sup>90</sup>

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 Rh<sub>2</sub>(*R-p-*Ph-TPCP)<sub>4</sub> 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, Rh<sub>2</sub>(*S-*TPPTTL)<sub>4</sub> was preferred.<sup>91</sup>

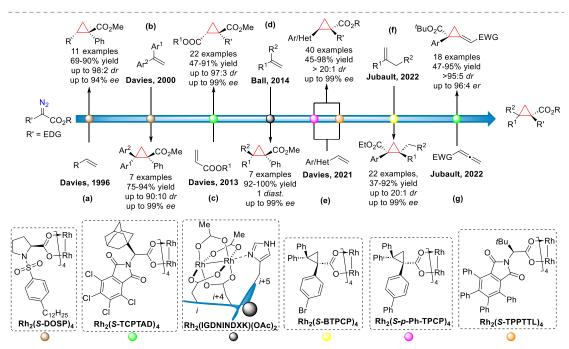
More recently, our group has depicted a Rh-catalyzed enantioselective cyclopropanation protocol with allylic substrates involving donor-acceptor diazo compound. The Rh<sub>2</sub>(S-BTPCP)<sub>4</sub> complex was selected to furnish a board range of cyclopropanes in moderate to excellent yields, high diastereo- and enantioselectivity (Scheme 19f). Additionally, the exploration of asymmetric cyclopropanation between arylallenes and donor-acceptor diazo compounds under the catalysis of Rh<sub>2</sub>(S-TCPTAD)<sub>4</sub> was reported by our group. 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 methylidene cyclopropane architectures.

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

<sup>&</sup>lt;sup>90</sup> R. Sambasivan, W. Zheng, S. J. Burya, B. V. Popp, C. Turro, C. Clementi, Z. T. Ball, *Chem. Sci.* **2014**, *5*, 1401–1407.

<sup>&</sup>lt;sup>91</sup> 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**.

<sup>&</sup>lt;sup>92</sup> Y. Hasegawa, T. Cantin, J. Decaens, S. Couve-Bonnaire, A. B. Charette, T. Poisson, P. Jubault, *Chem. Eur. J.* **2022**, 28, e202201438.



**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  $Rh_2(S-BTPCP)_4$  catalyst (Scheme 20a). Subsequently, our focus shifted to the asymmetric cyclopropanation of  $\alpha$ -trifluoromethyl styrenes.  $^{94}$  Introducing the  $Rh_2(S-BTPCP)_4$  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  $Rh_2(S-TCPTTL)_4$  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

<sup>&</sup>lt;sup>93</sup> M. Bos, W. S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* 2017, 129, 13504–13508.

<sup>&</sup>lt;sup>94</sup> W. S. Huang, C. Schlinquer, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2018**, *24*, 10339–10343.

<sup>&</sup>lt;sup>95</sup> 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.

(a) Jubault, 2017

Ar<sup>1</sup> CF<sub>2</sub>H + 
$$\frac{N_2}{Ar^2}$$
 CO<sub>2</sub>Et  $\frac{Rh_2(S\text{-BTPCP})_4 (1 \text{ mol}\%)}{21 \text{ examples, } 27\text{-93\% yield}}{22 \text{ examples, } 27\text{-93\% yield}}$ 

(b) Jubault, 2018

Ar<sup>2</sup> CO<sub>2</sub>Et  $\frac{Rh_2(S\text{-BTPCP})_4 (1 \text{ mol}\%)}{Ar^2}$  EtO<sub>2</sub>C, CF<sub>3</sub> Rh<sub>2</sub>(S-BTPCP)<sub>4</sub> (1 mol%) EtO<sub>2</sub>C, CF<sub>3</sub> Rh<sub>2</sub>(S-BTPCP)<sub>4</sub>

22 examples, 50-86% yield > 20:1 dr, up to 99% ee

(c) Jubault, 2019

(c) Jubault, 2019

Rh<sub>2</sub>(S-TCPTTL)<sub>4</sub> (2 mol%)  $\frac{Rh_2(S\text{-TCPTTL})_4}{Rh_2(S\text{-TCPTTL})_4}$  (2 mol%)  $\frac{Rh_2(S\text{-TCPTTL})_4}{Rh_2(S\text{-TCPTTL})_4}$  Rh<sub>2</sub>(S-TPPTTL)<sub>4</sub>

**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). <sup>96</sup> Simultaneously, the reaction rates are significantly faster, and the substrate scope is considerably broader compared to previous generation of chiral BiRh(S-PTTL)4 <sup>97</sup> catalysts. This BiRh(S-PT(TIPS)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.

<sup>&</sup>lt;sup>96</sup> S. Singha, M. Buchsteiner, G. Bistoni, R. Goddard, A. Fürstner, J. Am. Chem. Soc. 2021, 143, 5666–5673.

<sup>97</sup> 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)<sub>4</sub> 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<sub>EWD</sub>-aryl<sub>EDG</sub>, 101 trifluoromethyl, 102 and carbonyl 103 have also been explored. A dirhodium paddlewheel complex with adamantly glycine derivatives, Rh<sub>2</sub>(S-PTAD)<sub>4</sub>, was designed 99 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 Rh<sub>2</sub>(S-PTAD)<sub>4</sub> remains the

<sup>98</sup> X. Zhang, Y. Ning, C. Tian, G. Zanoni, X. Bi, iScience 2023, 26.

<sup>99</sup> R. P. Reddy, G. H. Lee, H. M. L. Davies, Org. Lett. 2006, 8, 3437–3440.

<sup>&</sup>lt;sup>100</sup> J. R. Denton, K. Cheng, H. M. Davies, *Chem. Commun.* **2008**, 1238–1240.

<sup>&</sup>lt;sup>101</sup> M. Lee, Z. Ren, D. G. Musaev, H. M. L. Davies, ACS Catal. **2020**, 10, 6240–6247.

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.

<sup>&</sup>lt;sup>103</sup> J. R. Denton, H. M. L. Davies, Org. Lett. **2009**, 11, 787–790.

<sup>&</sup>lt;sup>104</sup> 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 enantioselectivies.

**Scheme 22**. Asymmetric cyclopropanation of Rh<sub>2</sub>(S-PTAD)<sub>4</sub> catalyzed versatile donor-acceptor diazo compounds.

The oxindole scaffold is widely present in natural products and drugs, <sup>105</sup> 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 HgOTf<sub>2</sub> coordinated to (*R*)-difluorphos (Scheme 23a). <sup>106</sup> 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). <sup>107</sup> The spiroketal bisphosphine ligand-

<sup>&</sup>lt;sup>105</sup> 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.

<sup>&</sup>lt;sup>106</sup> Z.-Y. Cao, F. Zhou, Y.-H. Yu, J. Zhou, Org. Lett. **2013**, 15, 42-45.

<sup>&</sup>lt;sup>107</sup> 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.<sup>108</sup>

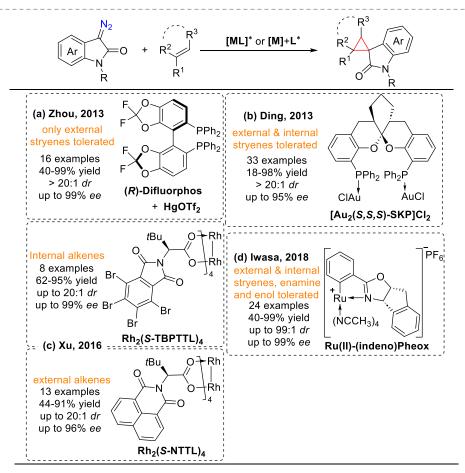
Furthermore, conventional dirhodium complexes were also employed to decompose diazo-oxindoles for construction of enantiomeric pure spirocyclopropanes as reported by Xu *et al.* (Scheme 23c). <sup>109</sup> In their procedures, two different Rh catalysts were used depending on the structure of the alkene partner. In other words, Rh<sub>2</sub>(S-TBPTTL)<sub>4</sub>-engaged carbenoid generated cyclopropanes from internal alkenes, while Rh<sub>2</sub>(S-NTTL)<sub>4</sub>-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). <sup>110</sup> 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.

<sup>&</sup>lt;sup>108</sup> Z.-Y. Cao, W. Wang, K. Liao, X. Wang, J. Zhou, J. Ma, Org. Chem. Front. **2018**, *5*, 2960–2968.

<sup>&</sup>lt;sup>109</sup> Y. Chi, L. Qiu, X. Xu, Org. Biomol. Chem. **2016**, 14, 10357–10361.

<sup>&</sup>lt;sup>110</sup> 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 diazo-oxindoles.

#### 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.<sup>111</sup> Generally, three methods are commonly applied to *in situ* generate mono-donor and di-donor diazoalkanes: oxidation of hydrazones, <sup>112</sup> conversion of sulfonylhydrazone sodium salts with a phase transfer catalyst, <sup>113</sup> and dissociation of

<sup>&</sup>lt;sup>111</sup> E. M. Allouche, A. B. Charette, Synthesis **2019**, *51*, 3947–3963.

<sup>&</sup>lt;sup>112</sup> H. Liu, Y. Wei, C. Cai, New J. Chem. **2016**, 40, 674–678.

<sup>&</sup>lt;sup>113</sup> V. Aggarwal, H. Smith, R. H. Jones, *Chem. Commun.* **1997**, 1785–1786.

sulfonylhydrazones under alkaline conditions (Figure 6).<sup>114</sup>

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

In 2011, a  $D_2$ -symmetric Rh<sub>2</sub>(R-(perfluoro)DOSP)<sub>4</sub> was reported to decompose aryldiazomethane and provided cis-selective cyclopropanes in the presence of styrenes (Scheme 24a).<sup>115</sup> Although dirhodium catalysts offered a board range of scope and slight improvement in the conversion rate of diazo compounds compared to Rh<sub>2</sub>(OAc)<sub>4</sub>,<sup>116</sup> the yields remained lower than 60% in most cases. Furthermore, various metals<sup>104,117</sup> 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. <sup>118</sup> 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 Fe(TPP)Cl predominantly afforded the corresponding products in *cis* isomers.

Moreover, the *meso*-tetraphenylporphyrin (TPP) ligand was proposed in combination with Cobalt, generating Co(TPP) complex, which catalyzed the cyclopropanarion of  $\alpha$ -pyryldiazomethane with alkenes in good to excellent yields.<sup>119</sup>

<sup>&</sup>lt;sup>114</sup> W.-H. Cheung, S.-L. Zheng, W.-Y. Yu, G.-C. Zhou, C.-M. Che, *Org. Lett.* **2003**, *5*, 2535–2538.

<sup>&</sup>lt;sup>115</sup> M. Verdecchia, C. Tubaro, A. Biffis, *Tetrahedron Lett.* **2011**, *52*, 1136–1139.

<sup>&</sup>lt;sup>116</sup> V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785–2788.

<sup>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.</sup> 

<sup>&</sup>lt;sup>118</sup> 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.

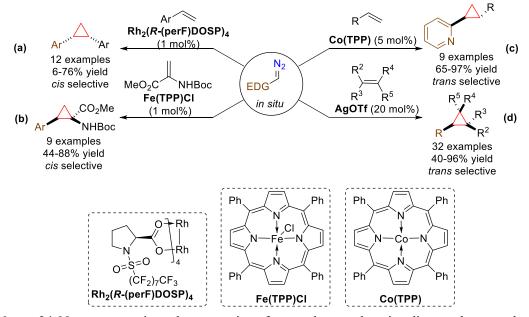
<sup>&</sup>lt;sup>119</sup> S. Roy, S. K. Das, B. Chattopadhyay, Angew. Chem. Int. Ed. 2018, 130, 2260–2265.

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  $\alpha$ -aryl- $\alpha$ -alkyldiazomethane.<sup>121</sup> In the study, they used Pd(OAc)<sub>2</sub> 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.<sup>122</sup>

More recently, Cai *et al.* described a Nickel-mediated non-asymmetric cyclopropanation methodology involving either  $\alpha$ -aryl- $\alpha$ -alkyldiaozomethane or  $\alpha$ -diaryldiaozomethane. <sup>123</sup> This

<sup>&</sup>lt;sup>120</sup> Z. Liu, X. Zhang, G. Zanoni, X. Bi, Org. Lett. 2017, 19, 6646–6649.

<sup>&</sup>lt;sup>121</sup> P. Chen, C. Zhu, R. Zhu, Z. Lin, W. Wu, H. Jiang, Org. Biomol. Chem. 2017, 15, 1228–1235.

<sup>122</sup> H. Jiang, W. Fu, H. Chen, Chem. Eur. J. 2012, 18, 11884-11888.

<sup>&</sup>lt;sup>123</sup> 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. Aggarwal<sup>124</sup> and Charette<sup>125</sup> 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  $\alpha$ -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  $\alpha$ -aryldiazomethanes led to excellent enantioselectivities (Scheme 26a).<sup>126</sup>

Furthermore, the asymmetric cyclopropanation strategy mentioned above has proven to be an effective process for synthesizing enantiomer-enriched cyclopropyl amino acid homologs. 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

<sup>&</sup>lt;sup>124</sup> V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem. Int. Ed.* **2001**, *40*, 1433–1436.

<sup>&</sup>lt;sup>125</sup> S. R. Goudreau, A. B. Charette, J. Am. Chem. Soc. **2009**, 131, 15633–15635.

<sup>&</sup>lt;sup>126</sup> Y. Wang, X. Wen, X. Cui, L. Wojtas, X. P. Zhang, J. Am. Chem. Soc. 2017, 139, 1049–1052.

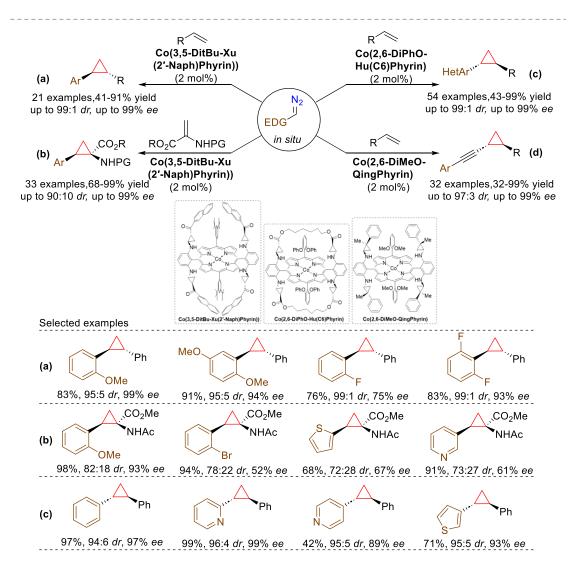
<sup>&</sup>lt;sup>127</sup> W.-C. C. Lee, D.-S. Wang, C. Zhang, J. Xie, B. Li, X. P. Zhang, *Chem* **2021**, 7, 1588–1601.

<sup>&</sup>lt;sup>128</sup> 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  $\alpha$ -alkynyldiazomethanes for the direct cyclopropanation of alkenes through Co(III)-based metalloradical catalysis. 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).

<sup>&</sup>lt;sup>129</sup> 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. <sup>130</sup> 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).

<sup>&</sup>lt;sup>130</sup> 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. 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 compounds or natural products 133

<sup>&</sup>lt;sup>131</sup> 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.

<sup>&</sup>lt;sup>132</sup> 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.

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. Recently, the palladium catalyzed C–H bond functionalization of cyclopropanes appeared as an efficient method. In order to promote such transformations, different types of directing groups 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.<sup>137</sup> An oxazoline auxiliary was used for the iodination of secondary C(sp<sup>3</sup>)–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. <sup>138</sup> 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

<sup>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. Maugel, 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.</sup> 

<sup>&</sup>lt;sup>135</sup> 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.

<sup>&</sup>lt;sup>136</sup> 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.

<sup>&</sup>lt;sup>137</sup> R. Giri, X. Chen, J.-Q. Yu, Angew. Chem. Int. Ed. **2005**, 44, 2112-2115.

<sup>&</sup>lt;sup>138</sup> D. Wang, M. Wasa, R. Giri, J.-Q. Yu, J. Am. Chem. Soc. **2008**, 130, 7190-7191.

well as  $\beta$ -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.<sup>139</sup> 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 Pd[MeCN]<sub>2</sub>BF<sub>4</sub>. In this case, a cyclized pyridinium salt was obtained in moderate yield and diastereoisomeric ratio (Scheme 30b).<sup>140</sup>

**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). 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, tetrafluoro-4-(trifluoromethyl)phenyl amide amide and *ortho-*

<sup>&</sup>lt;sup>139</sup> A. Kubota, M. S. Sanford, Synthesis **2011**, 2579–2589.

<sup>&</sup>lt;sup>140</sup> K. J. Stowers, K. C. Fortner, M. S. Sanford, J. Am. Chem. Soc. **2011**, 133, 6541–6544.

<sup>&</sup>lt;sup>141</sup> M. Wasa, K. M. Engle, J.-Q. Yu, J. Am. Chem. Soc. **2010**, 132, 3680–3681.

<sup>&</sup>lt;sup>142</sup> M. Wasa, K. M. Engle, D.-W. Lin, E.-J. Yoo, J.-Q. Yu, J. Am. Chem. Soc. 2011, 133, 19598-19601.

<sup>&</sup>lt;sup>143</sup> 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.

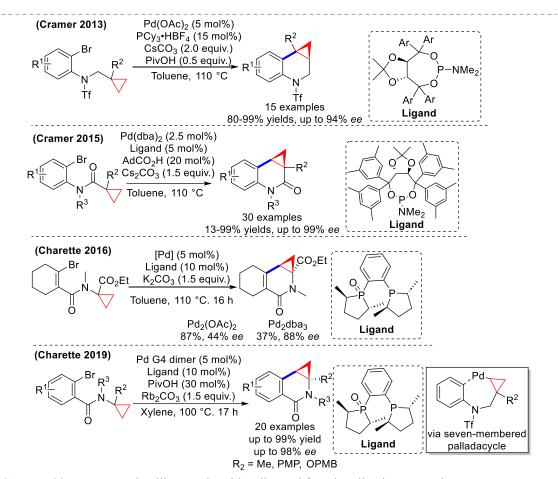
It is interesting to note that in the presence of a chiral ligand in the cyclopropanation process, chiral cyclopropanes are obtained. For example, cyclopropanes C–H bond activation followed by an intramolecular cyclization reaction was mainly investigated by the groups of Cramer, <sup>145</sup> and Charette. <sup>146</sup> *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.

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.

<sup>&</sup>lt;sup>145</sup> 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.

<sup>&</sup>lt;sup>146</sup> 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.

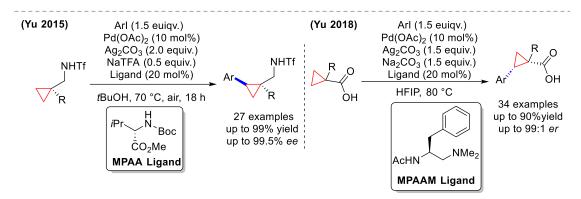


**Scheme 32**. *N*-protected anilines and amides directed functionalization on cyclopropanes.

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.<sup>147</sup> 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.<sup>148</sup> The presence of monoprotected aminoethyl amine chiral ligand based on an ethylenediamine backbone (MPAAM) led to enantiomerically pure carboxylic acids (Scheme 33).

<sup>&</sup>lt;sup>147</sup> K.-S. Chan, H.-Y. Fu, J.-Q. Yu, J. Am. Chem. Soc. 2015, 137, 2042–2046.

<sup>&</sup>lt;sup>148</sup> 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. Since 2005, Daugulis reported the arylation of unactivated C(sp³)–H bonds by using the amide derived from aminoquinoline and picolinamide as bidentate directing groups, with Pd(OAc)<sub>2</sub> as the catalyst. There are a number of transformations of C–H bonds which have been developed by using of bidentate directing groups. Since 2005,

In 2013, Charette and co-workers reported the first palladium catalyzed cyclopropane C–H bond functionalization with the picolinamide directing group. <sup>152</sup> 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-

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.

<sup>&</sup>lt;sup>150</sup> O. Daugulis, V. G. Zaitsev, Angew. Chem. Int. Ed. 2005, 44, 4046–4048.

<sup>&</sup>lt;sup>151</sup> O. Daugulis, J. Roane, L. D. Tran, Acc. Chem. Res. 2015, 48, 1053–1064.

<sup>&</sup>lt;sup>152</sup> D. S. Roman, A. B. Charette, *Org. Lett.* **2013**, *15*, 4394–4397.

workers in 2014. <sup>153</sup> 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 efficiently. 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.<sup>154</sup> Depending on the number of equivalents of iodoarenes, mono- or di-substituted products were obtained using 10 mol% Pd(OAc)<sub>2</sub> 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.<sup>155</sup>

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.<sup>156</sup> In this work, they disclosed a site-selective functionalization of C(sp<sup>3</sup>)–H bonds in cyclopropyl peptides at the *N*-terminal part. Di-,

<sup>&</sup>lt;sup>153</sup> Q. Zhang, X.-S. Yin, S. Zhao, S.-L. Fang, B.-F. Shi, Chem. Commun. 2014, 50, 8353-8355.

<sup>&</sup>lt;sup>154</sup> R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238–3241.

<sup>&</sup>lt;sup>155</sup> M. Corbet, F. De Campo, Angew. Chem. Int. Ed. 2013, 52, 9896–9898.

<sup>&</sup>lt;sup>156</sup> 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

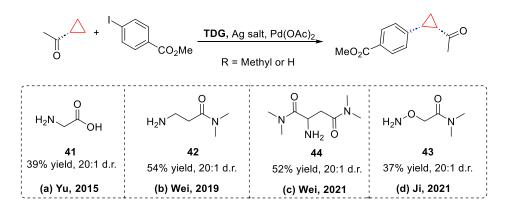
The pre-installed directing groups used in C–H bond activation needs several steps for the introduction and its removal. In comparison to above referred mono- or bidentate directing groups, the transient directing group (TDG) has some disparities for synthetic applications. In a general concept, <sup>157</sup> 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).

<sup>&</sup>lt;sup>157</sup> 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.

FG<sup>1</sup> FG Organic TDG catalyst MG formation . bond activation TM TDG TDG [TM]  $FG^2$ TDG reagent III TM]-FG<sup>2</sup>

**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 coworkers in 2015.<sup>158</sup> 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 Wei<sup>159</sup> and Ji<sup>160</sup> (Scheme 39).



Scheme 39. Transient directing groups involved functionalization on cyclopropanes.

<sup>&</sup>lt;sup>158</sup> F.-L. Zhang, K. Hong, T.-J. Li, H. Park, J.-Q. Yu, Science **2016**, 351, 252–256.

<sup>&</sup>lt;sup>159</sup> 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.

<sup>&</sup>lt;sup>160</sup> Y. Wang, G. Wu, X. Xu, B. Pang, S. Liao, Y. Ji, J. Org. Chem. 2021, 86, 7296–7303.

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### 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, albert the use of nonnoble 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

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.

# $Chapter\ I-Introduction$

Chapter II – Experimental and computational studies for the catalytic enantioselective synthesis of functionalized cyclopropanes from  $\alpha$ -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  $\alpha$ -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  $\alpha$ -cyano- $\alpha$ -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  $\alpha$  position of alkene (Scheme 2. 1).

**Scheme 2. 1.** Rh<sub>2</sub>((S)-IBAZ)<sub>4</sub>-catalyzed  $\alpha$ -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.<sup>70</sup> The combination of

<sup>&</sup>lt;sup>161</sup> A. Pons, P. Ivashkin, T. Poisson, A. B. Charette, X. Pannecoucke, P. Jubault, *Chem. Eur. J.* **2016**, 22, 6239–6242.

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

Rh<sub>2</sub>((S)-BTPCP)<sub>4</sub> and  $\alpha$ -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 nothing 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.** Rh<sub>2</sub>((S)-BTPCP)<sub>4</sub> and  $\alpha$ -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),<sup>162</sup> 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. <sup>163</sup> The allylic and cyclic alkene substrates have been beardly 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).  $^{164}$ 

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.

<sup>&</sup>lt;sup>163</sup> M. Montesinos-Magraner, M. Costantini, R. Ramírez-Contreras, M. E. Muratore, M. J. Johansson, A. Mendoza, Angew. Chem. Int. Ed. 2019, 58, 5930–5935.

<sup>&</sup>lt;sup>164</sup> N. Otog, H. Inoue, D. T. T. Trinh, Z. Batgerel, N. M. Langendorf, I. Fujisawa, S. Iwasa, *ChemCatChem* 2021, 13, 328–337.

(a, Nishiyama 1995) Ме Ru(II)-PheBox DCM, 0 °C Ĥ ΌH<sub>2</sub> CO 99% ee Ru(II)-PheBox (b, Mendoza 2019) DCM, 0 °C PF<sub>6</sub> 14 examples 55:45 to >20:1 dr 90 to 99% ee ŧŘπ (c, Iwasa 2021) (H<sub>3</sub>CNC)<sub>4</sub> SiH<sub>2</sub>R₃ Acetone, 0 °C Ru(II)-Pheox 17 examples 56:44 to 97:3 *dr* 92 to 99% ee

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, <sup>165</sup> Cu, <sup>166</sup> Fe, <sup>167</sup> Co <sup>168</sup> and Rh. <sup>169</sup> 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]

<sup>a) I. J. Munslow, K. M. Gillespie, R. J. Deeth, P. Scott,</sup> *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.

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.

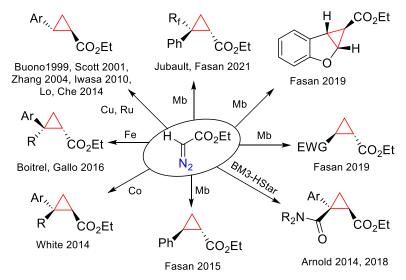
<sup>&</sup>lt;sup>167</sup> D. M. Carminati, D. Intrieri, A. Caselli, S. Le Gac, B. Boitrel, L. Toma, L. Legnani, E. Gallo, *Chem. Eur. J.* 2016, 22, 13599–13612.

<sup>&</sup>lt;sup>168</sup> 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.

<sup>&</sup>lt;sup>169</sup> 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.

diazoacetate

cycloaddition reactions have been reported by Arnold<sup>170</sup> and Fasan<sup>171</sup> 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<sup>70,161</sup> and other chemists<sup>163,164</sup> 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  $\alpha$ -halogeno or  $\alpha$ -electron-withdrawing group (EWG)

<sup>a) P. S. Coelho, E. M. Brustad, A. Kannan, F. H. Arnold,</sup> *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. Brandenberg, K. Chen, F. H. Arnold, *ACS Central Science* 2018, 4, 37377. d) O. F. Brandenberg, C. K. Prier, K. Chen, A. M. Knight, Z. Wu, F. H. Arnold, *ACS Catal.* 2018, 8, 2629–2634.

<sup>171</sup> 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.

allylic substrates remain a synthetic challenge.

2) Although Ru(II)-Pheox has proved to be an excellent carbene transfer catalyst for monoacceptor 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  $\alpha$ -fluoro-allylic substrate 1a and the commercially available diazo reagent EDA (2a) in the presence of a metal catalyst (Table 2. 1). When Rh<sub>2</sub>(OPiv)<sub>4</sub> 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 <sup>19</sup>F NMR when Cu(MeCN)<sub>4</sub>PF<sub>6</sub> was used. Rhodium catalysts were tested for this reaction as well, such as Rh<sub>2</sub>((S)-BTPCP)<sub>4</sub> (entry 8) and Rh<sub>2</sub>((S)-TCPTTL)<sub>4</sub> (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

pursue the optimization of the cyclopropanation process (Table 2. 2). Note that as fluorinated alkene

1a is quite expensive<sup>172</sup>, an excess of EDA was used.

entry	antolysis	trai	ns	cis	
	catalysis	conv. (%) <sup>b</sup>	ee <sup>c</sup>	conv. (%) <sup>b</sup>	ee <sup>c</sup>
1	Rh <sub>2</sub> (OPiv) <sub>4</sub>	47	0	39	0
2	Ru(II)(S)-Pheox I	14	92	18	94
3	Ru(II)(S)-Pheox II	6	96	7	94
4 <sup>d</sup>	CuI/ BOX	n.r	-	n.r	-
5 <sup>d</sup>	CuOAc/BOX	n.r	-	n.r	-
6 <sup>d</sup>	Cu(MeCN) <sub>4</sub> PF <sub>6</sub> /BOX	trace	-	trace	-
$7^{d}$	Cu(OTf)(PhH)/BOX	n.r	-	n.r	-
8	$Rh_2((S)-BTPCP)_4$	43	6	33	6
9	$Rh_2((S)\text{-TCPTTL})_4$	27	16	43	10

**Table 2. 1.** Optimization of metal catalysts. <sup>a</sup> 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. <sup>b</sup> Conversion was determined on the crude mixture by <sup>19</sup>F NMR. <sup>c</sup> Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> 5 mol% Cu catalyst and 10 mol% Box ligand were employed. n.r = no reaction.

-

<sup>&</sup>lt;sup>172</sup> 165.4€/1g, Sigma–Aldrich. Dec. 31, 2023.

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 <sup>1</sup>H-<sup>19</sup>F HOSEY NMR (see Experimental Part).

entry	equiv. EDA	T/ (°C)	t/ (h)	trans		cis	
				conv. (%) <sup>b</sup>	ee <sup>c</sup>	conv. (%) <sup>b</sup>	ee <sup>c</sup>
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 <sup>d</sup>	5	0	6.7	46(43)	92	53(51)	86

**Table 2. 2.** Parameters optimization. <sup>a</sup> 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. <sup>b</sup> conversion was determined on the crude mixture by <sup>19</sup>F NMR. <sup>c</sup> Enantiomeric excess (*trans/cis*) determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> 2 mol% of Ru(II)(S)-Pheox I was used.

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

diastereoselectivity (44:55), we aimed to improve the diastereoselectivity of this reaction by introducing several other mono-acceptor diazoalkanes (Scheme 2. 6). Unfortunately, when estertype 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. <sup>a</sup> 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. <sup>b</sup> Conversion and diastereoisomer ratio were determined on the crude mixture by <sup>19</sup>F NMR. n.r = no reaction

To check if a modification of the diastereoisomeric ratio occurs during the cyclopropanation reaction, the diastereomeric ratio of **3a** was monitored every two hours by <sup>19</sup>F 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.

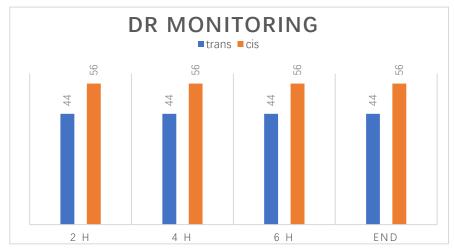


Chart 2. 1. Diastereomeric ratio monitoring. dr was analyzed by crude  $^{19}$ F NMR,  $C_6D_6$  was used as solvent.

## 2.4. Scope of $\alpha$ -substituted allylic derivatives

With the optimal reaction conditions in hand (Table 2. 2, entry 8), we systematically examined a series of  $\alpha$ -halogenated allylic derivatives for the scope of the reaction (Scheme 2. 7). Initially, an array of  $\alpha$ -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  $\alpha$ -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 isolated product yields from 51% to 82%. Additionally,  $\alpha$ -chloro and  $\alpha$ -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  $\alpha$ -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. <sup>a</sup> conversion was determined on the crude mixture by <sup>1</sup>H NMR. <sup>b</sup> isolated yield. <sup>c</sup> 5 mol% of Ru(II)(S)-Pheox I was used. <sup>d</sup> 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  $\alpha$ -arylated allylic sulfones,  $\alpha$ -methyl allylic sulfones,  $\alpha$ -substituted allylic trifluoromethyl sulfones, and allylic silanes (Scheme 2. 8). Firstly,  $\alpha$ -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

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  $\alpha$ -position was replaced by a methyl group leading to the cyclopropane 3m in excellent yield and ee. For less activated allyl derivatives such as  $\alpha$ -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  $\alpha$ -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. <sup>a</sup> Conversion was determined on the crude mixture by <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> 5 mol% of Ru(II)(*S*)-Pheox I was used. <sup>d</sup> 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,  $\alpha$ -fluorinated allylic chloride substrate

Ir 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  $\alpha$ -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  $\alpha$ -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,  $\alpha$ -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  $\alpha$ -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. <sup>a</sup> Conversion was determined on the crude mixture by <sup>1</sup>H NMR. <sup>b</sup> Isolated yield. <sup>c</sup> 5 mol% of Ru(II)(S)-Pheox I was used. Enantiomeric excess (*trans/cis*) determined

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). They have investigated the cyclopropanation reaction of N-hydroxy phthalimide diazoacetate (NHPI-DA) with propene and styrene, using Ru(II)(S)-Pheox  $\mathbf{L}^{173}$  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  $\mathbf{1a-1h}$  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 ( $\mathbf{X} = \mathbf{F}$ , Cl, Br,  $\mathbf{Y} = \mathbf{CH_3}$ ) 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  $\mathbf{Eq_{cis}}$ , which was found to be disfavored kinetically. Nonetheless, it also suggests that the most probable pathway occurs through isomer  $\mathbf{Ap_{syn}}$ . To simplify analysis, we have thus focused solely on the pathways involving this isomer, which is simply denoted  $\mathbf{Int1}$  (Scheme 2. 10b).

65

<sup>&</sup>lt;sup>173</sup> F. Planas, M. Costantini, M. Montesinos-Magraner, F. Himo, A. Mendoza ACS Catal. 2021, 11, 10950-10963.

a) 
$$[Ru] \cdot (ACN)_4 \qquad MDA \qquad [Ru] \cdot (ACN)_3 \qquad X \qquad Y \qquad Sub \qquad ACN \qquad Sub \qquad ACN \qquad Sub \qquad ACN \qquad Int1 \qquad Sub \qquad ACN \qquad Int1 \qquad Sub \qquad ACN \qquad Int2_{X-Y} \qquad TS-OS_{X-Y} \qquad TS$$

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

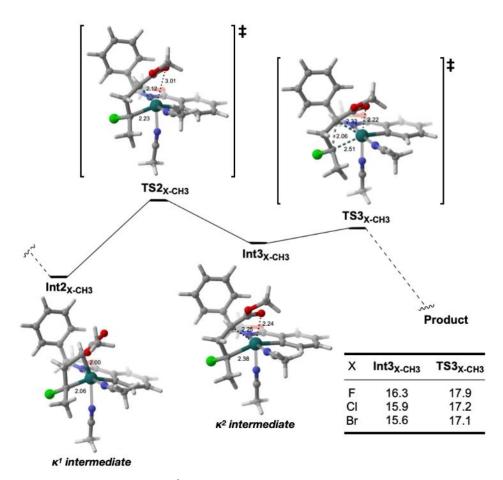
We investigated both inner-sphere and outer-sphere mechanisms for the three 2-haloalkene substrates, as well as propene as a reference point with respect to classical substrates and the study of Mendoza, Himo and co-workers. The results are summarized in Table 2. 3. The barriers found for MDA and propene 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**<sub>X-CH3</sub> barriers computed for the 2-halopropene series are very similar to the one found for propene, with the exception for **TS1**<sub>X-CH3</sub>, 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.

$$(ACN)_3 \qquad Ph \qquad + X \qquad CH_3 \qquad + [Ru] \cdot (ACN)_n$$
Int1

			araze	acciate		
Entry	X	TS1 <sub>X-CH3</sub>	Int2 <sub>X-CH3</sub>	TS2 <sub>X-CH3</sub>	TS-OS <sub>(X-CH3)</sub>	$\Delta\Delta G^{\ddagger_{(OS\text{-}IS)}}$
1	Н	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
	1 2 3	1 H 2 F 3 Cl	1 H 10.5 2 F 14.2 3 Cl 15.2	Entry         X         TS1x-CH3         Int2x-CH3           1         H         10.5         8.1           2         F         14.2         8.1           3         Cl         15.2         11.0	1     H     10.5     8.1     23.7       2     F     14.2     8.1     23.4       3     Cl     15.2     11.0     23.4	Entry         X         TS1 <sub>X-CH3</sub> Int2 <sub>X-CH3</sub> TS2 <sub>X-CH3</sub> TS-OS <sub>(X-CH3)</sub> 1         H         10.5         8.1         23.7         15.7           2         F         14.2         8.1         23.4         14.5           3         Cl         15.2         11.0         23.4         15.0

**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  $\kappa^1$  to  $\kappa^2$  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  $\kappa^2$  intermediate (**Int3**<sub>X-CH3</sub>) 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).

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**<sub>H-CH3</sub> to ensure that this isomerization process had not been missed for classical substrates such as propene. The IRC path of **TS2**<sub>H-CH3</sub> is illustrated in Figure 2. 2 (blue line). In this case, no intermediate could be found, and **TS2**<sub>H-CH3</sub> truly connects **Int2**<sub>H-CH3</sub> to the final cyclopropane product, but interestingly does proceed through a two-steps/no-intermediate process. 174

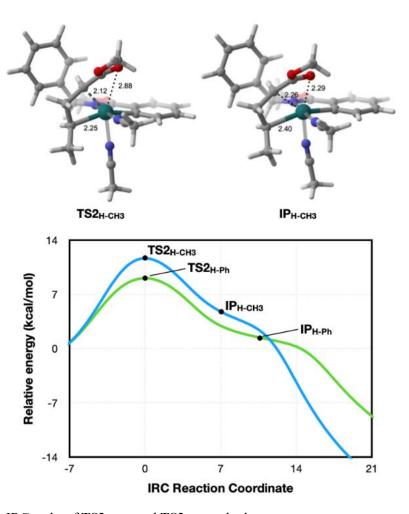
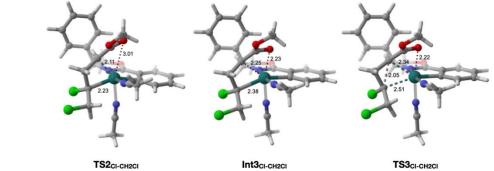


Figure 2. 2. IRC paths of  $TS2_{\text{H-CH3}}$  and  $TS2_{\text{H-Ph}}$  and relevant structures.

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

<sup>&</sup>lt;sup>174</sup> 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.

of  $Int3_{CI-CH3}$  (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  $\sigma^*_{C-X}$  orbital.



Y	TS1 <sub>Cl-Y</sub>	Int2 <sub>Cl-Y</sub>	TS2 <sub>Cl-Y</sub>	Int3 <sub>Cl-Y</sub>	TS3 <sub>Cl-Y</sub>	TS-OS <sub>(Cl-Y)</sub>	$\Delta \Delta G^{\ddagger_{(OS\text{-}IS)}}$
Н	15.2	11.0	23.4	15.9	17.2	15.0	-8.4
CH <sub>2</sub> 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  $Int3_{CI-CH2CI}$ . With this substrate we computed  $Int3_{CI-CH2CI}$  and  $TS3_{CI-CH2CI}$  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).

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  $d_{Ru} \rightarrow \sigma^*_{C-Cl}$  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  $\sigma^*_{C-X}$  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  $\kappa^1$  to  $\kappa^2$  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.

$$\begin{array}{c} \text{MeO} \\ \text{H} \\ \text{Int2}_{\text{X-Y}} \\ \text{16 e} \\ \end{array} \begin{array}{c} \text{MeO} \\ \text{H} \\ \text{Int2}_{\text{X-Y}} \\ \text{Int3}_{\text{X-Y}} (\text{IP}_{\text{X-Y}}) \\ \text{Int3}_$$

**Scheme 2. 11**. Mechanistic rationale for the requirement of the  $\kappa^2$  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.

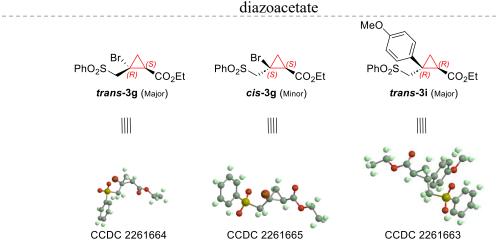


Figure 2. 3. X-ray diffraction analysis of cyclopropanes trans-3g, cis-3g, and trans-3i.

#### 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<sub>syn</sub> and Int1-Ap<sub>anti</sub>). Further more, the Int1-Ap<sub>syn</sub> 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<sub>anti</sub> 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.

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

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). 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),<sup>175</sup> 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,<sup>176</sup> 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),<sup>177</sup> 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).<sup>178</sup> However, the six-membered lactam **7** was achieved with decent yield instead of expected cyclopropyl amide product. Finally, under reductive conditions, <sup>179</sup>

<sup>&</sup>lt;sup>175</sup> P. Müller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755–4763.

<sup>&</sup>lt;sup>176</sup> G. A. Olah, S. C. Narang, *Tetrahedron* **1982**, *38*, 2225–2277.

<sup>&</sup>lt;sup>177</sup> L. Volta, C. J. Stirling, *Phosphorus, Sulfur, and Silicon* **2009**, *184*, 1508–1522.

<sup>&</sup>lt;sup>178</sup> C. Chen, L. Ling, M. Luo, X. Zeng, Bull. Chem. Soc. Jpn. **2021**, 94, 762–766.

<sup>&</sup>lt;sup>179</sup> S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055–2068.

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, <sup>180</sup> nonetheless it resulted in low yield (19%) (Scheme 2. 15d1). Another reaction was performed using MOMCl (chloromethoxymethane) and a base iPr<sub>2</sub>NMe (Scheme 2. 15d2). <sup>181</sup> 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.

<sup>&</sup>lt;sup>180</sup> 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.

<sup>&</sup>lt;sup>181</sup> T. Minami, K. Fukuda, N. Hoshiya, H. Fukuda, M. Watanabe, S. Shuto, *Org. Lett.* **2019**, *21*, 656–659.

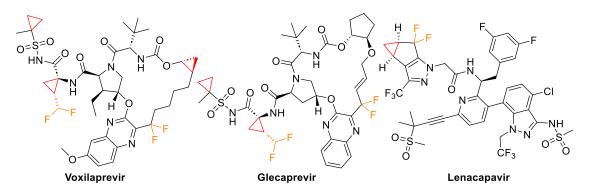
#### 2.7. Conclusion

In summary, we have successfully developed a catalytic enantioselective synthesis of highly functionalized cyclopropanes using  $\alpha$ -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 enantiomerically convergent phenylsulfonyl  $\alpha$ , $\alpha$ -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. 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. 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, as well as ketone or ester fragment. In addition, the  $\alpha$ ,  $\alpha$ -difluoromethylcyclopropane motif is present in several bioactive organic structures (Figure 3. 1), for example Voxilaprevir and Glecaprevir for the treatment of chronic hepatitis C, and also the recently developed HIV-1 capsid inhibitor Lenacapavir.



**Figure 3. 1.** Bioactive compounds containing  $\alpha$ ,  $\alpha$ -diffuoromethyl cyclopropane motif.

<sup>a) D. O'Hagan,</sup> *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.

<sup>&</sup>lt;sup>183</sup> 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.

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Because of the advantages mentioned above, the synthesis of  $\alpha$ , $\alpha$ -difluoromethylcyclopropane building blocks has become a hot research topic in the scientific community. Pioneering works regarding non-asymmetric approaches for example ring contraction (Scheme 3. 1a) leaves deoxofluorination (Scheme 3. 1b), ring contraction fluorination (Scheme 3. 1c), leaves deoxofluorination (Scheme 3. 1d), leaves nucleophilic [2+1] ring addition (Scheme 3. 1e), leaves metallocarbene [2+1] ring addition (Scheme 3. 1f) leaves and free carbene [2+1] ring addition leaves reactions were conducted by chemists in the previous several decades.

**Scheme 3. 1.** Non-asymmetric approaches regarding synthesis of  $\alpha$ ,  $\alpha$ -diffuoroalkylcyclopropanes.

<sup>a) J. Decaens, S. Couve–Bonnaire, A. B. Charette, T. Poisson, P. Jubault,</sup> *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.

<sup>&</sup>lt;sup>189</sup> 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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<sup>&</sup>lt;sup>191</sup> K. Livingstone, K. Siebold, S. Meyer, V. Martín–Heras, C. G. Daniliuc, R. Gilmour, *ACS Catal.* **2022**, *12*, 14507–14516.

<sup>&</sup>lt;sup>192</sup> 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.

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<sup>&</sup>lt;sup>194</sup> 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.

<sup>&</sup>lt;sup>195</sup> C.-F. Gao, Y.-J. Chen, J. Nie, F.-G. Zhang, C. W. Cheung, J.-A. Ma, Chem. Commun. 2023, 59, 11664–11667.

Asymmetric synthesis of  $\alpha$ , $\alpha$ -difluorocyclopropane scaffolds remained undiscovered until the first catalytic methodology was reported by our group in 2017.<sup>196</sup> Under the catalysis of the dirhodium paddlewheel complex Rh<sub>2</sub>((S)-BTPCP)<sub>4</sub>, a large number of  $\alpha$ -difluoromethyl styrenes were converted into the corresponding  $\alpha$ , $\alpha$ -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.** Rh<sub>2</sub>((S)-BTPCP)<sub>4</sub> catalyzed the asymmetric synthesis of  $\alpha,\alpha$ -difluoromethyl-cyclopropanes.

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

81

<sup>&</sup>lt;sup>196</sup> M. Bos, W. S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *129*, 13504–13508.

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# Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl $\alpha,\alpha$ difluoromethyl cyclopropanes

**Scheme 3. 3.** Nickel-catalyzed the asymmetric synthesis of  $\alpha, \alpha$ -difluoromethylcyclopropanes.

Subsequently, our group in collaboration with Prof. R. Fasan's group disclosed an enzyme-mediated cyclopropanation strategy for the synthesis of  $\alpha$ , $\alpha$ -difluoromethylcyclopropanes. This innovative approach utilized engineered myoglobin catalysts, enabling the incorporation of  $\alpha$ -difluoromethyl styrenes and ethyl diazoacetate to yield a diverse array of CHF<sub>2</sub>-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  $\alpha$ , $\alpha$ -difluoromethylcyclopropanes.

Very recently, the  $\alpha$ , $\alpha$ -diffuoro- $\beta$ -carbonyl ketone N-triftosylhydrazones reagents acting as diazo precursors, have been exploited by Bi an co-workers to access  $\alpha$ , $\alpha$ -diffuoromethylcyclopropane building blocks with  $\alpha$ , $\alpha$ -disubstituted alkenes. In the presence of the chiral catalyst Rh<sub>2</sub>((S)-PTAD)<sub>4</sub>, this methodology delivered a series of 1,1,2,2-tetra-functionalized cyclopropanes bearing diffuoroalkyl groups, in high yields (50-97% yield), high enantioselectivities (up to 99%), and demonstrated a broad substrate scope (Scheme 3. 5).

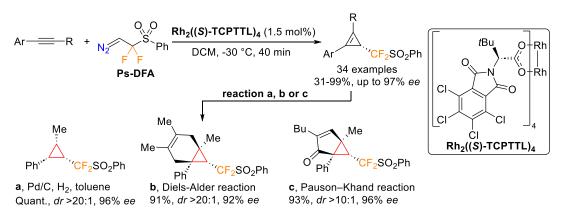
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<sup>&</sup>lt;sup>198</sup> X. Zhang, Y. Ning, C. Tian, G. Zanoni, X. Bi, iScience **2023**, 26. 105896.

$$\begin{array}{c} R^{1} \\ Ar^{1} \\ \end{array} \begin{array}{c} Rh_{2}((S)\text{-PTAD})_{4} \ (0.5 \ \text{mol}\%) \\ DIPEA \ (2.0 \ \text{equiv.}) \\ \hline TFT, \ r.t., \ 12 \ h \\ \end{array} \begin{array}{c} R^{1} \\ Ar^{2} \\ \end{array} \begin{array}{c} CF_{2}R^{2} \\ 42 \ \text{examples} \\ 50 \ \text{to } 97\% \ \text{yield} \\ \text{up to } 99\% \ \text{ee} \\ \end{array} \begin{array}{c} Rh_{2}((S)\text{-PTAD})_{4} \\ \end{array}$$

**Scheme 3. 5**. Rh<sub>2</sub>((S)-PTAD)<sub>4</sub> the asymmetric synthesis of  $\alpha$ , $\alpha$ -difluoroalkylcyclopropanes.

It should be mentioned that Ma *et al.* depicted a newly designed difluoro diazo compound, phenylsulfonyl difluorodiazomethane (Ps-DFA), in 2018.<sup>199</sup> Subsequently, this Ps-DFA reagent was found to be a crucial component in catalytic asymmetric synthesis of difluoromethylcyclopropenes 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).<sup>200</sup>



**Scheme 3. 6.** Synthesis of enantiopure  $\alpha, \alpha$ -difluoroalkyl cyclopropenes 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

<sup>&</sup>lt;sup>199</sup> J.-L. Zeng, Z. Chen, F.-G. Zhang, J.-A. Ma, Org. Lett. **2018**, 20, 4562–4565.

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# Ru(II)-Pheox-catalyzed synthesis of enantiomerically convergent phenylsulfonyl $\alpha,\alpha$ 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 work<sup>200</sup> on asymmetric cyclopropenation, we recognized that the Ps-DFA reagent could serve as an excellent metallocarbene precursor for generating difluoromethyl substituted (with a SO<sub>2</sub>Ph 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.

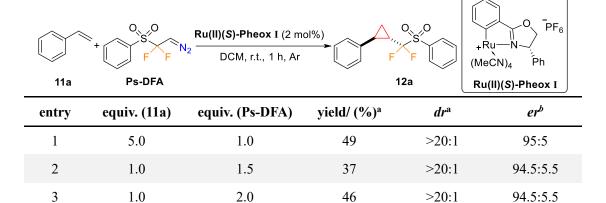
## 3.3. Optimization of the reaction conditions

When we proposed our project, we prepared the Ps-DFA reagent according to Ma's procedure<sup>199</sup> (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 $\alpha,\alpha$ 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 difluoroSO<sub>2</sub>Ph 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 <sup>1</sup>H-<sup>19</sup>F 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.



**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. <sup>a</sup> Yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromomethane as internal standard. <sup>b</sup>*er* was determined by HPLC chromatography using a chiral IC column.

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 difluoroSO<sub>2</sub>Ph cyclopropane 12a in a decent yield (37%) and good enantiomeric ratio (93:7), while Et<sub>2</sub>O 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 <sup>1</sup>H 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 PhCF<sub>3</sub>, CHCl<sub>3</sub> 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).

**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. <sup>a</sup> Yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromomethane as internal standard. <sup>b</sup> *er* was determined by HPLC chromatography using a chiral IC column.

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  $(Rh_2((S)-phTPCP)_4)$  and  $Rh_2((S)-TCPTTL)_4$ ) 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.

**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 <sup>1</sup>H NMR, dibromomethane as internal standard. *er* was determined by HPLC chromatography using a chiral IC column.

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% <sup>1</sup>H 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/(%) <sup>a</sup>	dr <sup>a</sup>	er <sup>b</sup>
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

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. <sup>a</sup> Yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromomethane as internal standard. <sup>b</sup> *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 difluoroSO<sub>2</sub>Ph 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 121 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  $(CF_3 \text{ and } NO_2)$  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-

**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. <sup>a</sup> NMR yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromethane as internal standard. <sup>b</sup> 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

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. <sup>a</sup> NMR yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromethane as internal standard. <sup>b</sup> 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

outcomes, with only 9% or 13% observed for 4-F styrene (11aa) and 10% for  $\alpha$ -diphenyl alkene (11ae), respectively. Furthermore, allene (11af), benzyl alkene (11ag), vinyl sulfide (11ah), and vinyl silane (11ai) substrates were reluctant. Additionally, substrates bearing in  $\alpha$  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 cyclopropenation 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. <sup>a</sup> NMR yield was determined on the crude product by <sup>1</sup>H NMR, dibromethane as internal standard. n.r. = no reaction.

The development of this asymmetric cyclopropanation strategy was then examined using fluorinated alkenes (Scheme 3. 12). The  $\alpha$ -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 <sup>1</sup>H NMR. However, both decomposed during the purification process (silicagel column chromatography).  $\alpha$ -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

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. <sup>a</sup> NMR yield and *dr* (*trans/cis*) were determined on the crude product by <sup>1</sup>H NMR, dibromethane as internal standard. <sup>b</sup> 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).

OH NaF (50 mol%) SelectFlour® (2.2 equiv.) TFE/H<sub>2</sub>O 
$$2/l_1$$
,  $70$  °C,m  $36$  h  $13$   $1$  Tf<sub>2</sub>O (1.03 equiv.) Pyridine (1.4 equiv.) MeCN,  $0$  °C to r.t.,  $2$  h  $2$ )  $28\%$  NH<sub>3</sub>, r.t.,  $48$  h  $3$ )  $2M$  HCl in Et<sub>2</sub>O DCM, r.t.,  $10$  min  $15$ , with inseparable inpurity  $14$ , with inseparable inpurity

**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

underwent a nucleophilic addition with BrCF<sub>2</sub>CO<sub>2</sub>Et, along with the cleavage of benzisotriazole. Subsequently, reductive conditions in the presence of Pd(OH)<sub>2</sub>, H<sub>2</sub>, and CF<sub>3</sub>CO<sub>2</sub>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<sub>2</sub>O) 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

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-Ap<sub>syn</sub> and Int1-Ap<sub>anti</sub>) are formed through ligand dissociation of Ru(II)-Pheox I in the presence of the Ps-DFA reagent. Furthermore, the Int1-Ap<sub>syn</sub> 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-Ap<sub>anti</sub> 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 though the inner-spere 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

#### 3.6.2. Post-functionalization reactions

Thanks to the developed approach, the products can be converted into high value added diversely functionalized cyclopropenes 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 LiHMDS<sup>201</sup> 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 (nBuLi), 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	nBuLi	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 anion<sup>202</sup> or a carbon radical.<sup>203</sup> 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<sup>202b</sup>

<sup>&</sup>lt;sup>201</sup> Z. He, M. Hu, T. Luo, L. Li, J. Hu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11545–11547.

<sup>&</sup>lt;sup>202</sup> 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.

<sup>&</sup>lt;sup>203</sup> 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<sup>202a</sup> (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,<sup>204</sup> but still, no conversion was observed (entry 3). The radical acceptor (styrene) was tested with substrate **12a** under the conditions of Sm, CH<sub>2</sub>I<sub>2</sub>, and *i*PrOH,<sup>203</sup> however, the reaction remained unresponsive (entry 4).

entry	substrate	reagents	reagents condition	
1	12a TMSCl Mg (2.0 equiv.), DMF, r.t.		n.r.	
2	Tolyl disulfide (2.0 tBuOK (2.0 equiv.)  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 <sub>2</sub> I <sub>2</sub> (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-carbaldehyde<sup>205</sup> 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.

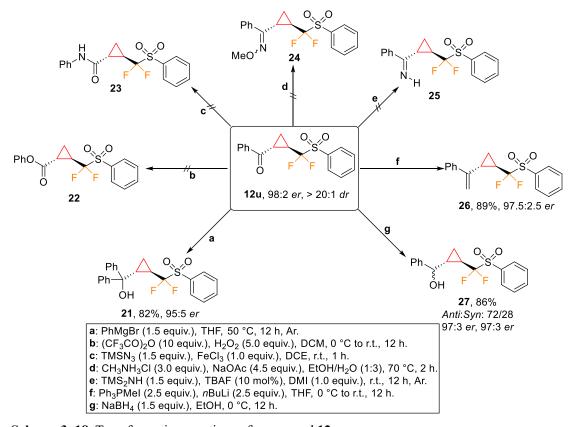
**Scheme 3. 17**. Suzuki-Miyaura reaction on cyclopropane 12m.

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

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

<sup>&</sup>lt;sup>204</sup> P. Xiao, C. Ni, W. Miao, M. Zhou, J. Hu, D. Chen, J. Hu, J. Org. Chem. **2019**, 84, 8345–8359.

(Scheme 3. 18). First, the addition of Grignard reagent PhMgBr<sup>206</sup> 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, <sup>207</sup> amide, <sup>208</sup> oxime, <sup>209</sup> imine <sup>210</sup> 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 Ph<sub>3</sub>P<sup>+</sup>MeI<sup>-</sup> 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 NaBH<sub>4</sub> in EtOH,<sup>211</sup> 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.

<sup>&</sup>lt;sup>206</sup> X. Y. Tang, M. Shi, Eur. J. Org. Chem. **2010**, 21, 4106–4110.

<sup>&</sup>lt;sup>207</sup> T. D. Avery, B. W. Greatrex, D. S. Pedersen, D. K. Taylor, E. R. Tiekink, J. Org. Chem. **2008**, 73, 2633–2640.

<sup>&</sup>lt;sup>208</sup> J. Yadav, B. S. Reddy, U. S. Reddy, K. Praneeth, *Tetrahedron Lett.* **2008**, 49, 4742–4745.

<sup>&</sup>lt;sup>209</sup> L. Da Ho, N. Otog, I. Fujisawa, S. Iwasa, *Org. Lett.* **2019**, *21*, 7470–7474.

<sup>&</sup>lt;sup>210</sup> Y. Kondo, Y. Hirazawa, T. Kadota, K. Yamada, K. Morisaki, H. Morimoto, T. Ohshima, *Org. Lett.* **2022**, *24*, 6594–6598.

<sup>&</sup>lt;sup>211</sup> X.-F. Tan, F.-G. Zhang, J.-A. Ma, Beilstein J. Org. Chem. **2020**, 16, 638-644.

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-disubtituted 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.<sup>212</sup> 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 HgCl<sub>2</sub><sup>213</sup> or the use of HOAc-NaOAc buffer,<sup>201</sup> failed. The following reductive conditions employing SmI<sub>2</sub> and MeOH in THF,<sup>214</sup> was also unsuccessful from **12a** (entry 4). To our delight, using 30.0 equiv. of magnesium and a catalytic amount of I<sub>2</sub> in MeOH<sup>215</sup> 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).

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.

<sup>&</sup>lt;sup>213</sup> J. Zhu, F. Wang, W. Huang, Y. Zhao, W. Ye, J. Hu, Synlett **2011**, 2011, 899–902.

<sup>&</sup>lt;sup>214</sup> 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.

<sup>&</sup>lt;sup>215</sup> 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.

<sup>&</sup>lt;sup>216</sup> C. Ni, L. Zhang, J. Hu, J. Org. Chem. 2008, 73, 5699–5713.

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entry	substrate	conditions	result
1	<b>12a</b> R = Ph	Mg (2.5 equiv.), HOAC/H <sub>2</sub> O (v/v 1:1), DMSO, r.t., 36 h	trace
2	<b>12a</b> R = Ph	Mg (2.0 equiv.), HgCl <sub>2</sub> (5 mol%), DMF, - 10 °C to r.t., 3 h	n.r.
3	<b>12a</b> R = Ph	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	trace
4	<b>12a</b> R = Ph	SmI <sub>2</sub> (3.0 equiv.), MeOH (2.0 equiv.), THF, r.t., 14 h, Ar	n.r.
5	<b>12a</b> R = Ph	Mg (30 equiv.), I <sub>2</sub> (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 <sub>2</sub> HPO <sub>4</sub> (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	$\mathbf{12u}$ $\mathbf{R} = \mathbf{benzoxyl}$	Mg (5.0 equiv.), HOAC/NaOAc, DMF, r.t., 36 h	n.r.
10	12u $R = benzoxyl$	3% Na-Hg (5.0 equiv.), Na <sub>2</sub> HPO <sub>4</sub> (7.0 equiv.), MeOH, -30 °C to r.t., 1 h	messy
11	12u $R = benzoxyl$	Mg (30 equiv.), I <sub>2</sub> (cat.), MeOH, r.t., 16 h	messy
12	$26$ $\mathbf{R} = \alpha \text{-styryl}$	3% Na-Hg (5.0 equiv.), Na <sub>2</sub> HPO <sub>4</sub> (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 <sub>2</sub> HPO <sub>4</sub> (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  $\alpha,\alpha$ -difluoroalkyl cyclopropanes using metallocarbene and alkenes [2+1] ring addition strategy. The metal complex Ru(II)(S)-Pheox I was introduced as efficient catalyst, which led to target  $\alpha,\alpha$ -difluoroalkyl cyclopropane products in a range of yield

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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  $\alpha$ , $\alpha$ -difluoroalkyl cyclopropane frameworks.

Chapter IV - Rh(II)-catalyzed N-sulfonylhydrazones decomposetion 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.<sup>217</sup> 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.<sup>218</sup> 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.<sup>219</sup> Furthermore, the alkynylcyclopropane unit is widespread in natural products and medical compounds. For example, Phorbasides A and its congeneric derivatives<sup>220</sup> exhibit significant cytotoxicity against the HCT 116 (human colon cancer) cell line, Cipralisant<sup>221</sup> was discovered as the lead H<sub>3</sub> receptor antagonist for treatment of cognitive deficiencies and other disorders of the central nervous system, and Efavirenz,<sup>222</sup>, 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.

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.
 a) T. T. Talele, *J. Med. Chem.* 2020, 63, 5625–5663. b) B. M. Trost, C.–J. Li, *Modern alkyne chemistry: catalytic and atom–economic transformations*, John Wiley & Sons, 2015.

<sup>a) R. K. Kumar, X. Bi,</sup> *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.

 <sup>&</sup>lt;sup>220</sup> 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.

<sup>&</sup>lt;sup>221</sup> J. Witkin, D. Nelson, *Pharmacol. Ther.* **2004**, *103*, 1–20.

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

Despite several reported works in recent years that provide efficient access to alkynylcyclopropanes *via* either diastereo-<sup>223</sup> or enantio-selective<sup>197</sup> 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 Rh<sub>2</sub>((*S*)-DOSP)<sub>4</sub> complex.<sup>224</sup> 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**.  $Rh_2((S)$ -DOSP)<sub>4</sub>-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.*, -CF<sub>3</sub>, -CF<sub>2</sub>H or -CO<sub>2</sub>Et) diazo reagents and substituted phenyl enynes, diastereoselectivity was achieved using Fe[TPP]Cl,<sup>225,194c</sup> while Ir-salen<sup>226</sup> and Cocomplexes <sup>227</sup> were employed for enantioselective approaches. Until 2021, Echavarren *et al.* described a unprecedent two-step alkynylcarbene transfer reaction.<sup>228</sup> This method facilitated the construction of alkynylcyclopropanes from alkenes and terminal alkynes from readily available 7-alkynyl cycloheptatriene. Utilizing Rh<sub>2</sub>(TFA)<sub>4</sub> catalyst enabled the efficient synthesis of diverse *cis*-

<sup>&</sup>lt;sup>223</sup> 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.

<sup>&</sup>lt;sup>224</sup> H. M. Davies, T. A. Boebel, *Tetrahedron Lett.* **2000**, *41*, 8189–8192.

<sup>&</sup>lt;sup>225</sup> 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.

<sup>&</sup>lt;sup>226</sup> H. Suematsu, S. Kanchiku, T. Uchida, T. Katsuki, *J. Am. Chem. Soc.* **2008**, *130*, 10327–10337.

<sup>&</sup>lt;sup>227</sup> X. Wang, J. Ke, Y. Zhu, A. Deb, Y. Xu, X. P. Zhang, J. Am. Chem. Soc. **2021**, 143, 11121–11129.

<sup>&</sup>lt;sup>228</sup> M. Mato, M. Montesinos–Magraner, A. R. Sugranyes, A. M. Echavarren, *J. Am. Chem. Soc.* **2021**, *143*, 10760–10769.

alkynylcyclopropanes, featuring substituents such as  $C(sp^3)$ -,  $C(sp^2)$ -, C(sp)-, H-, Si-, or Gesubstituents in the alkyne part (Scheme 4. 2).

$$R + R^{1}$$

$$R^{3}$$

$$R^{4}$$

$$R^{3}$$

$$R^{4}$$

$$R^{3}$$

$$R^{4}$$

$$R^{2}$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{2}$$

$$R^{2}$$

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$$R^{2}$$

$$R^{3}$$

$$R^{2}$$

$$R^{3}$$

$$R^{2}$$

$$R^{3}$$

$$R^{4}$$

$$R^{4}$$

$$R^{4}$$

$$R^{3}$$

$$R^{4}$$

**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.<sup>229</sup> They harnessed this approach for the synthesis of multi-substituted alkynylcyclopropanes. The method employed a silver-based complex (TP<sup>Br3</sup>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, <sup>224</sup> Gurubrahamam *et al.* described an alternative very efficient catalysts: Cu(I)-complexes. <sup>230</sup> This unprecedented [Cu(MeCN)4]PF<sub>6</sub> 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).

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

<sup>&</sup>lt;sup>229</sup> Y. Ning, M. Huo, L. Wu, X. Bi, Chem. Commun. 2022, 58, 3485–3488.

**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.<sup>231</sup> 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  $\alpha$ -alkynyldiazomethanes, 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

<sup>&</sup>lt;sup>231</sup> J. Ke, W.-C. C. Lee, X. Wang, Y. Wang, X. Wen, X. P. Zhang, J. Am. Chem. Soc. **2022**, 144, 2368–2378.

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

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).

$$R^{1}$$
 +  $R^{1}$   $R^{2}$  Chiral Rh-complex  $R^{2}$ 

**Scheme 4. 6**. Enantioselective access to alkynylcyclopropanes.

# 4.3. Optimization of the reaction conditions with phenyl alkynyl sulfonylhydrozones

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.

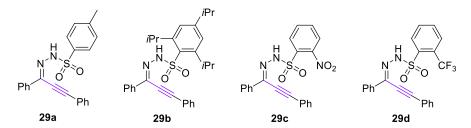


Figure 4. 2. Phenyl alkynyl hydrazone compounds.

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

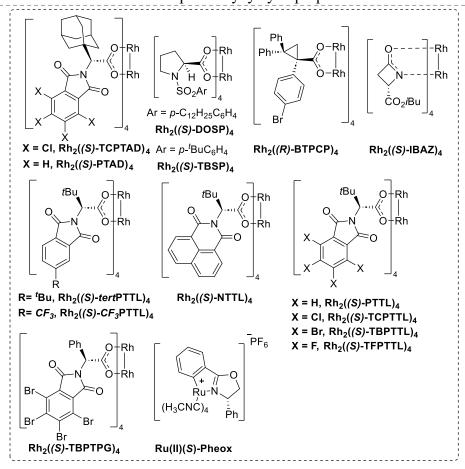


Figure 4. 3. Chiral catalysts used during this study

At first, reactions using styrene **11a** and different phenyl alkynylhydrazones **29** in the presence of Rh<sub>2</sub>((S)-PTAD)<sub>4</sub> 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 Rh<sub>2</sub>((S)-DOSP)<sub>4</sub> 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 Rh<sub>2</sub>((S)-DOSP)<sub>4</sub> 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

excess of product **30a**. Initially, the use of  $Rh_2(S)$ -TCPTTL)<sub>4</sub> 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  $Rh_2(S)$ -TCPTTL)<sub>4</sub> 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	<b>2</b> 9	cat. (1 mol%)	base	temp./(°C)	yield <sup>a</sup>	dr <sup>b</sup>	eec
1	29a	$Rh_2((S)-PTAD)_4$	DIPEA	r.t	n.r	-	-
2	29b	$Rh_2((S)-PTAD)_4$	DIPEA	r.t	n.r	-	-
3	29c	$Rh_2((S)-PTAD)_4$	DIPEA	r.t	n.r	-	-
4	29d	$Rh_2((S)-PTAD)_4$	DIPEA	r.t	n.r	-	-
5	29a	$Rh_2((S)-PTAD)_4$	DIPEA	40	n.r	-	-
6	29b	$Rh_2((S)-PTAD)_4$	DIPEA	40	n.r	-	-
7	29c	$Rh_2((S)-PTAD)_4$	DIPEA	40	n.r	-	-
8	29d	$Rh_2((S)-PTAD)_4$	DIPEA	40	n.r	-	-
9	29d	$Rh_2((S)-DOSP)_4$	$Cs_2CO_3$	40	26%	33:67	0%
10	29d	$Rh_2((S)-DOSP)_4$	K <sub>2</sub> CO <sub>3</sub>	40	11%	33:67	0%
11	29d	$Rh_2((S)-DOSP)_4$	<sup>t</sup> BuOK	40	27%	35:65	0%
12	29d	$Rh_2((S)-DOSP)_4$	KHMDS	40	17%	35:65	0%
13	29d	$Rh_2((S)-DOSP)_4$	NaH	40	72% (65)	33:67	0%

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		1		11			
14	29d	$Rh_2((S)-DOSP)_4$	KH	40	55%	33:67	0%
15	29d	$Rh_2((S)-DOSP)_4$	NaOAc	40	n.r	-	-
16	29d	$Rh_2((S)-DOSP)_4$	Na <sub>2</sub> CO <sub>3</sub>	40	n.r	-	-
17	29d	$Rh_2((S)-DOSP)_4$	NaTFA	40	n.r	-	-
18	29d	$Rh_2((S)-DOSP)_4$	CsOAc	40	trace	-	-
19	29d	$Rh_2((S)-DOSP)_4$	DBU	40	n.r	-	-
20	29d	$Rh_2((S)-DOSP)_4$	КОН	40	trace	-	-
21	29d	$Rh_2((S)\text{-TCPTTL})_4$	NaH	40	96%	27:73	33%
22	29d	$Rh_2((S)\text{-TCPTAD})_4$	NaH	40	96%	30:70	13%
23	29d	$Rh_2((R)-BTPCP)_4$	NaH	40	96%	35:65	-19%
24	29d	$Rh_2((R)-PTAD)_4$	NaH	40	95%	30:70	-4%
25	29d	$Rh_2((S)-IBAZ)_4$	NaH	40	96%	35:65	0%
26	29d	$Rh_2((S)-NTTL)_4$	NaH	40	70%	27:73	3%
27	29d	Rh <sub>2</sub> ((S)-TFPTTL) <sub>4</sub>	NaH	40	51%	26:74	30%
28	29d	$Rh_2((S)$ -tert $TPTTL)_4$	NaH	40	78%	26:74	3%
29	29d	Ru(II)(S)-Pheox I	NaH	40	12%	42:58	-
30	29d	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	NaH	0	38%	22:78	49%
31	29d	$Rh_2((S)\text{-TCPTTL})_4$	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. <sup>a</sup> NMR yield, 1,3,5-trimethoxyl benzene as internal standard. <sup>b</sup> dr (trans/cis) ratio was determined by <sup>1</sup>H NMR on the crude mixture. <sup>c</sup> 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 Rh<sub>2</sub>((S)-TCPTTL)<sub>4</sub> was introduced to decompose the diazo reagent derived from **29d** in the presence of NaH. However, fluorinated styrenes, including -CF<sub>3</sub>, -CF<sub>2</sub>H, -CH<sub>2</sub>F and -F, afforded the corresponding product **31a** to **31d** with

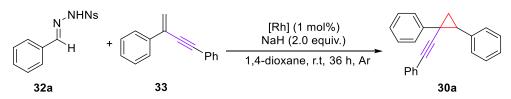
low to moderate yields (8-41%) and dr (around 50:50). Consequently, the enantiomeric excess values were not determined. Additionally, the -CF<sub>3</sub> alkynylcyclopropane **31a** was obtained under the catalysis of Rh<sub>2</sub>((S)-DOSP)<sub>4</sub> at 40 °C. Although both yield (47%) and dr (24:76) were improved, enantioselectivity was not observed.

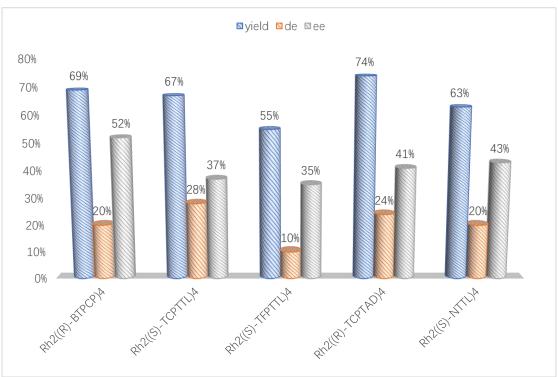
**31a**, 8%, 50:50 *dr*, n.d. ee **31b**, 41%, 56:44 *dr*, n.d. ee **31c**, 29%, 50:50 *dr*, n.d. ee **31d**, 40%, 45:55 *dr*, n.d. ee <sup>a</sup>47%, 24:76 *dr*, 0% ee

**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-trimethoxyl benzene as the internal standard, dr ratio was determined by <sup>1</sup>H NMR on the crude mixture, ee (major isomer) was determined with chiral HPLC analysis. TFT = trifluoromethyl benzene.  ${}^{a}Rh_{2}((S)-DOSP)_{4}$  (1 mol%) was employed at 40 °C.

# 4.4. Optimization of the reaction conditions with phenyl sulfonylhydrozones

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 Rh<sub>2</sub>((R)-BTPCP)<sub>4</sub> 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 synthetized using Rh<sub>2</sub>((S)-TCPTTL)<sub>4</sub> and Rh<sub>2</sub>((S)-TFPTTL)<sub>4</sub> in 67% and 55%, respectively, but with low *de* (28%, 10%, respectively) and enantioselectivity (37%, 35% *ee*, respectively). Similarly, when Rh<sub>2</sub>((R)-TCPTAD)<sub>4</sub> and Rh<sub>2</sub>((S)-NTTL)<sub>4</sub> were employed, the reactions afforded alkynylcyclopropane **30a** in good yields (74%, 63%) but modest stereocontrol (around 40% *ee*).





**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 <sup>1</sup>H NMR on the crude mixture, 1,3,5-trimethoxyl 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 work<sup>227</sup>, the product 35a was determined to have a cis relative configuration which reinforce the importance of our approach.

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

Upon the preliminary outset in hand, various solvents were screened. THF, Et<sub>2</sub>O, toluene, PhCF<sub>3</sub>, and CH<sub>3</sub>CN 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 Rh<sub>2</sub>((R)-BTPCP)<sub>4</sub> and Rh<sub>2</sub>((R)-phTPCP)<sub>4</sub> 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 Rh<sub>2</sub>((R)-PTAD)<sub>4</sub>, Rh<sub>2</sub>((S)-TCPTAD)<sub>4</sub>, and Rh<sub>2</sub>((S)-NTTL)<sub>4</sub>, but lower yields and stereoselectivity were obtained (Table 4. 2, entries 13-15). Moreover, Rh<sub>2</sub>((S)-IBAZ)<sub>4</sub>, generated from  $\beta$ -lactam, exhibited inactivity (Table 4. 2, entries 16), while Rh<sub>2</sub>((S)-DOSP)<sub>4</sub> and Rh<sub>2</sub>((S)-TBSP)<sub>4</sub> derived from proline showed undesired cyclopropanation results (Table 4. 2, entries 17-18). Other catalysts based on PTTL skeleton, such as Rh<sub>2</sub>((S)-tertPTTL)<sub>4</sub>, Rh<sub>2</sub>((S)-TFPTTL)<sub>4</sub>, and Rh<sub>2</sub>((S)-PTTL)<sub>4</sub>, 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

 $\label{eq:chapter_IV-Rh(II)-catalyzed} \ \textit{N-} sulfonylhydrazones \ decomposition \ for \ the \ synthesis \\ of \ enantiopure \ alkynylcyclopropanes$ 

enantioselectivity (Table 4. 2, entry 24).

entry	catalyst	solvent	yield <sup>a</sup>	dr <sup>b</sup>	ee <sup>c</sup>
1	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	THF	20	88:12	9
2	$Rh_2((S)\text{-TCPTTL})_4$	Et <sub>2</sub> O	21	88:12	38
3	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	Toluene	18	90:10	43
4	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	PhCF <sub>3</sub>	13	90:10	31
5	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	CH <sub>3</sub> CN	15	85:15	34
6	$Rh_2((S)\text{-TCPTTL})_4$	МеОН	n.r.	-	-
7	$Rh_2((S)\text{-TCPTTL})_4$	DCE	trace	-	-
8	$Rh_2((S)\text{-TCPTTL})_4$	Hexane	trace	-	-
9	$Rh_2((S)\text{-TCPTTL})_4$	DCM	45	89:11	40
10	$Rh_2((S)\text{-TCPTTL})_4$	1,4-dioxane	81	89:11	43
11	$Rh_2((R)-BTPCP)_4$	1,4-dioxane	96	88:12	-18
12	$Rh_2((R)-phTPCP)_4$	1,4-dioxane	84	88:12	-23
13	$Rh_2((R)-PTAD)_4$	1,4-dioxane	59	80:20	-36
14	$Rh_2((S)\text{-TCPTAD})_4$	1,4-dioxane	67	76:24	42
15	$Rh_2((S)-NTTL)_4$	1,4-dioxane	62	82:18	24
16	$Rh_2((S)-IBAZ)_4$	1,4-dioxane	n.r.	-	-
17	$Rh_2((S)-DOSP)_4$	1,4-dioxane	13	-	-
18	$Rh_2((S)-TBSP)_4$	1,4-dioxane	59	34:66	4
19	$Rh_2((S)-tertPTTL)_4$	1,4-dioxane	37	80:20	29
20	$Rh_2((S)\text{-TFPTTL})_4$	1,4-dioxane	35	50:50	30
21	$Rh_2((S)-PTTL)_4$	1,4-dioxane	44	90:10	35
22 <sup>d</sup>	$Rh_2((S)\text{-TCPTTL})_4$	1,4-dioxane	48	62:38	35
23 <sup>e</sup>	$Rh_2((S)\text{-TCPTTL})_4$	DCM	7	-	-
24 <sup>f</sup>	Rh <sub>2</sub> ((S)-TCPTTL) <sub>4</sub>	1,4-dioxane	50	92:8	40

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

mmol, 2.0 equiv.) and **36** (0.1 mmol, 1.0 equiv.) were employed with 2 mL solvent. <sup>a</sup> NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. <sup>b</sup> *dr* (cis/trans) ratio was determined by <sup>1</sup>H NMR on the crude mixture. <sup>c</sup> *ee* (*cis*) was determined using chiral HPLC analysis. <sup>d</sup> 40 °C. <sup>e</sup> 0 °C. <sup>f</sup> 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 Rh<sub>2</sub>((S)-TCPTTL)<sub>4</sub>. 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.

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% Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub> were tested individually with substrates **32d** and **36**. To our delight, the utilization of 2 mol% Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub> offered alkylcyclopropane **35a** in 77% yield with 91:9 *dr* and 68% *ee* (Table 4. 3, entry 1), while 1 mol% Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub> provided a lower yield (41%), diastereo- (98:2 *dr*), and enantio-selectivity (51% *ee*) (Table 4. 3, entry 2). Rh<sub>2</sub>((S)-CF<sub>3</sub>PTTL)<sub>4</sub> and Rh<sub>2</sub>((S)-TBPTPG)<sub>4</sub> 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 K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, and Li<sub>2</sub>CO<sub>3</sub> were tested (Table 4. 3, entries 5-7), only the reaction with K<sub>2</sub>CO<sub>3</sub> 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 K<sub>3</sub>PO<sub>4</sub>, were also tested but did not lead to any improvement in the cyclopropanation process (Table 4. 3, entries 12-14).

entry	catalyst	base	yield <sup>a</sup>	$dr^{\mathrm{b}}$	ee <sup>c</sup>
1 <sup>d</sup>	$Rh_2((S)\text{-TBPTTL})_4$	Cs <sub>2</sub> CO <sub>3</sub>	41	92:8	51
2	$Rh_2((S)$ -TBPTTL) <sub>4</sub>	$Cs_2CO_3$	77	91:9	68
3	$Rh_2((S)-CF_3PTTL)_4$	$Cs_2CO_3$	61	84:16	61
4	$Rh_2((S)$ -TBPTPG) <sub>4</sub>	$Cs_2CO_3$	70	82:18	60
5	$Rh_2((S)-TBPTTL)_4$	$K_2CO_3$	58	91:9	50
6	$Rh_2((S)-TBPTTL)_4$	Na <sub>2</sub> CO <sub>3</sub>	trace	-	-
7	$Rh_2((S)-TBPTTL)_4$	Li <sub>2</sub> CO <sub>3</sub>	n.r.	-	-
8	$Rh_2((S)$ -TBPTTL) <sub>4</sub>	CsF	66	91:9	53
9	$Rh_2((S)$ -TBPTTL) <sub>4</sub>	CsOPiv	75	91:9	57
10	$Rh_2((S)-TBPTTL)_4$	CsOAc	78	91:9	61
11	$Rh_2((S)$ -TBPTTL) <sub>4</sub>	CsOH	6	-	-
12	$Rh_2((S)-TBPTTL)_4$	LiOMe	32	91:9	50
13	Rh <sub>2</sub> (S-TBPTTL) <sub>4</sub>	LiHMDS	49	91:9	52
14	Rh <sub>2</sub> (S-TBPTTL) <sub>4</sub>	$K_3PO_4$	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. <sup>a</sup> NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. <sup>b</sup> *dr* (*cis/trans*) ratio was determined by <sup>1</sup>H NMR on the crude mixture. <sup>c</sup> *ee* (*cis*) was determined using chiral HPLC

analysis. d 1 mol% catalyst.

It is noteworthy that the HRMS analysis attested to the excellence purity of the optimal catalyst, Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub>, presenting an elegant form with a toluene adduct. This catalyst, employed by Hashimoto in enantioselective cyclopropenation reactions,<sup>232</sup> was replicated using our home-made Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub> 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 Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub> complex (Figure 4. 4).

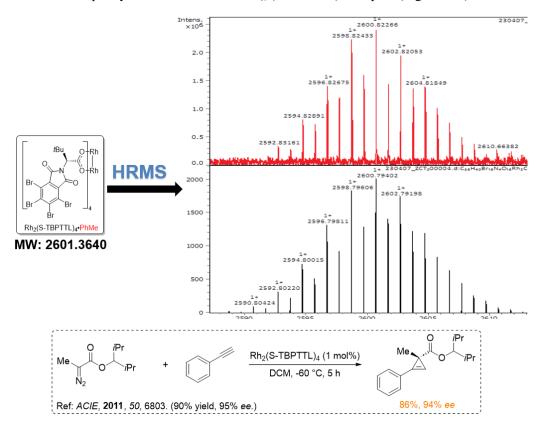


Figure 4. 4. Control experiments using Rh<sub>2</sub>((S)-TBPTTL)<sub>4</sub>.

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 SnCl<sub>2</sub>, ZnCl<sub>2</sub>, and AlCl<sub>3</sub> (entries 1-3). These reactions generated **35a** in yields ranging

<sup>&</sup>lt;sup>232</sup> T. Goto, K. Takeda, N. Shimada, H. Nambu, M. Anada, M. Shiro, K. Ando, S. Hashimoto, *Angew. Chem. Int. Ed.* **2011**, *50*, 6803–6808.

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

from 71% to 76%, with a mild decrease in stereoselectivity. Similarly, cyclopropanation reactions were conducted with Lewis acid additives Sc(OTf)<sub>3</sub> and BBr<sub>3</sub>, 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<sub>2</sub>, TfsNH<sub>2</sub>, and MeSO<sub>2</sub>NH<sub>2</sub> 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 (%) <sup>a</sup>	$dr^b$	ee (%)°
1	SnCl <sub>2</sub> (20 mol%)	76	89:11	60
2	$ZnCl_2$ (20 mol%)	71	90:10	62
3	AlCl <sub>3</sub> (20 mol%)	75	89:11	56
4	Sc(OTf) <sub>3</sub> (20 mol%)	78	89:11	59
5	BBr <sub>3</sub> (20 mol%)	73	89:11	57
6	TfNH <sub>2</sub> (10 mol%)	66	92:8	58
7	TfsNH <sub>2</sub> (10 mol%)	69	88:12	56
8	MeSO <sub>2</sub> NH <sub>2</sub> (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. <sup>a</sup> NMR yield, 1,3,5-trimethoxyl benzene as the internal standard. <sup>b</sup> *dr* (*cis/trans*) ratio was determined by <sup>1</sup>H NMR on the crude mixture. <sup>c</sup> *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.

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, fludrocortisone<sup>233</sup>, 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.<sup>234</sup> In the last few years, the FDA has approved 71 novel inventions for market release, spanning the period from 2015 to 2022.<sup>235</sup> These fluoridated 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. <sup>236</sup> 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.<sup>237</sup> For instance, the introduction of a fluorine atom improved the potency of the EC<sub>50</sub> of the NTR1 allosteric modulator (Figure 5. 1, top, left) and the K<sub>i</sub> 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).

<sup>&</sup>lt;sup>233</sup> R. M. Hussain, S. J. McIntosh, J. Lawson, R. A. Kenny, *Heart* **1996**, *76*, 507–509.

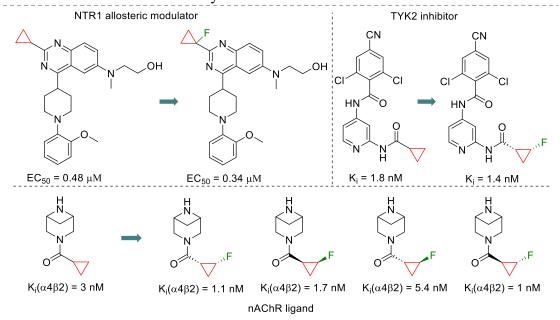
<sup>&</sup>lt;sup>234</sup> a) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633–10640. b) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai, N. Shibata, *Iscience* **2020**, *23*. 101467. c) V. P. Reddy, *Organofluorine compounds in biology and medicine*, Newnes, **2015**.

<sup>&</sup>lt;sup>235</sup> N. Sheikhi, M. Bahraminejad, M. Saeedi, S. S. Mirfazli, Eur. J. Med. Chem. 2023, 115758.

<sup>&</sup>lt;sup>236</sup> T. T. Talele, J. Med. Chem. **2016**, 59, 8712–8756.

<sup>&</sup>lt;sup>237</sup> O. O. Grygorenko, K. P. Melnykov, S. Holovach, O. Demchuk, *ChemMedChem* **2022**, *17*, e202200365.

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



**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<sup>166a,238</sup> and enantiomeric<sup>239</sup> 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<sup>2</sup>)-H or C(sp<sup>3</sup>)-H bonds.<sup>240</sup> 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.<sup>241</sup> This directing group has been already successfully used

<sup>&</sup>lt;sup>238</sup> 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.

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.

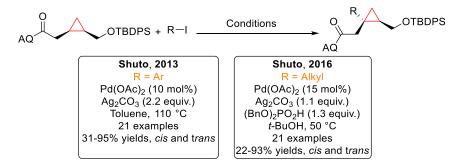
<sup>&</sup>lt;sup>240</sup> a) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J. Q. Yu, *Chem. Rev.* 2017, *117*, 8754–8786. b) N. Dastbaravardeh,
M. Christakakou, M. Haider, M. Schnürch, *Synthesis* 2014, *46*, 1421–1439. c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010, *110*, 1147–1169. d) X. Chen, K. M.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

<sup>&</sup>lt;sup>241</sup> 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.

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.<sup>242</sup> 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 arylation  $^{243}$  and alkylation  $^{244}$  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  $\beta$ -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 anylation and alkylation to access quaternary carbon center on cyclopropanes.

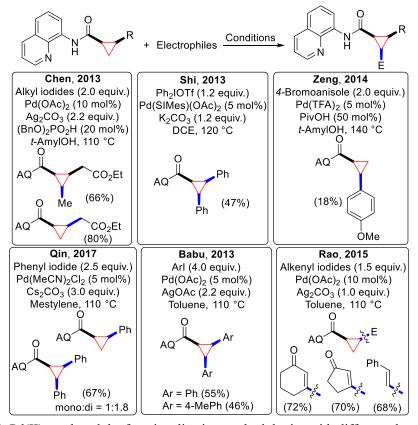
In subsequent years, Pd-catalyzed C-H functionalization of cyclopropanes has featured in various

<sup>&</sup>lt;sup>242</sup> R. Parella, B. Gopalakrishnan, S. A. Babu, *Org. Lett.* **2013**, *15*, 3238–3241.

<sup>&</sup>lt;sup>243</sup> N. Hoshiya, T. Kobayashi, M. Arisawa, S. Shuto, Org. Lett. **2013**, 15, 6202–6205.

<sup>&</sup>lt;sup>244</sup> N. Hoshiya, K. Takenaka, S. Shuto, J. I. Uenishi, *Org. Lett.* **2016**, *18*, 48–51.

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.<sup>245</sup> Similarly, Shi, Zeng, and Qin have explored the arylation of cyclopropanes using different electrophiles. When Ph<sub>2</sub>IOTf was employed, the cyclopropane substrate exclusively afforded the difunctionalization adduct in 47% yield. <sup>246</sup> Conversely, the introduction of 4-bromoanisole resulted in the mono-arylation exclusively, albeit with a low yield (18%).<sup>247</sup> The excess of phenyl iodide produced a mixture of mono- and di-arylated products, as indicated in Babu's work.<sup>242</sup> 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.<sup>248</sup>



**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

<sup>&</sup>lt;sup>245</sup> S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, J. Am. Chem. Soc. **2013**, 135, 12135–12141.

<sup>&</sup>lt;sup>246</sup> F. Pan, P.-X. Shen, L.-S. Zhang, X. Wang, Z.-J. Shi, Org. Lett. **2013**, 15, 4758-4761.

<sup>&</sup>lt;sup>247</sup> Y. Wei, H. Tang, X. Cong, B. Rao, C. Wu, X. Zeng, Org. Lett. **2014**, 16, 2248–2251.

<sup>&</sup>lt;sup>248</sup> G. Shan, G. Huang, Y. Rao, Org. Biomol. Chem. 2015, 13, 697–701.

directed aliphatic C(sp³)–H dienylation employing allenyl acetates as coupling partners.<sup>249</sup> 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, <sup>4a,250</sup> 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). <sup>181</sup> 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. <sup>251</sup> Notably, both studies used enantiomerically pure cyclopropanes as substrates and achieved their targeted products without epimerization (Scheme 5. 5, bottom).

<sup>&</sup>lt;sup>249</sup> R. K. Shukla, A. M. Nair, C. M. Volla, *Chem. Sci.* **2023**, *14*, 955–962.

<sup>&</sup>lt;sup>250</sup> a) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151–1196. b) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969–2984.

<sup>&</sup>lt;sup>251</sup> M. Häfner, Y. M. Sokolenko, P. Gamerdinger, E. Stempel, T. Gaich, *Org. Lett.* **2019**, *21*, 7370–7374.

**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

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. <sup>252</sup> Subsequently, upon reacting with ethyl diazoacetate under the catalysis of Rh<sub>2</sub>(OPiv)<sub>4</sub>, <sup>253</sup> the fluorinated cyclopropyl ester was produced in an 83% yield with a 55:45 *dr*. Following this, in the presence of 8-aminoquinoline, <sup>181</sup> 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, <sup>181</sup> a coupling reaction was set out under the conditions of 20% Pd(OAc)<sub>2</sub>, 2.0 equiv. AgOAc, and 20 mol% (BnO)<sub>2</sub>PO<sub>2</sub>H 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)<sub>2</sub>POH, and the product was obtained in a high yield (74%) (entry 6). By switching the additive to PivOH, the product **39a** 

<sup>&</sup>lt;sup>252</sup> A. Pons, H. Beucher, P. Ivashkin, G. Lemonnier, T. Poisson, A. B. Charette, P. Jubault, X. Pannecoucke, *Org. Lett.* **2015**, *17*, 1790–1793.

<sup>&</sup>lt;sup>253</sup> C. Zhao, T. Besset, C. Legault, P. Jubault, *Chem. Eur. J.*, **2023**, e202303070.

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 t-39a in a 74% isolated yield (entry 9).

entry	solvent	additive	T/ (°C)	t/ (h)	yield/ (%) <sup>a</sup>
1	t-AmylOH	(BnO) <sub>2</sub> PO <sub>2</sub> H	90	1	32
2	t-AmylOH	$(BnO)_2PO_2H$	60	1	32
3	t-AmylOH	-	90	1	39
4	t-AmylOH	-	60	1	38
5	t-AmylOH	-	r.t	18	-
6	t-AmylOH	(BnO) <sub>2</sub> POH	60	3	74
7	t-AmylOH	PivOH	60	3	77
8	t-AmylOH/DCE (1:1)	PivOH	60	3	n.r.
9	t-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)<sub>2</sub> (20 mol%), AgOAc (2.0 equiv.) and solvent (1 mL) were employed. Argon. <sup>a</sup> 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  $\beta$ -iodostyrene **38a** was well-tolerated, giving a 74% yield of product **39a**. The use of the same reaction conditions to *trans*-**37a** 

also well proceeded, giving product trans-39a in a 62% yield. Afterwards, a series of parasubstituted  $\beta$ -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  $\beta$ -iodostyrene with a strong electron-withdrawing group (CF<sub>3</sub>) 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  $\beta$ -iodostyrenes
arising from para to otho, the yield was reduced in a small range.

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

**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  $\beta$ -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<sub>2</sub>CO<sub>3</sub>) and additive ((BnO)<sub>2</sub>PO<sub>2</sub>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<sub>2</sub>CO<sub>3</sub> and 20 mol% (BnO)<sub>2</sub>PO<sub>2</sub>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<sub>2</sub>CO<sub>3</sub> and (BnO)<sub>2</sub>PO<sub>2</sub>H. It should be mentioned that a moderated *dr* (3:1) of **39n** was observed in the <sup>19</sup>F NMR spectra.

**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. <sup>a</sup> 110 °C. <sup>b</sup> 130 °C. <sup>c</sup> Ag<sub>2</sub>CO<sub>3</sub> (2.0 equiv.) as oxidant, (BnO)<sub>2</sub>PO<sub>2</sub>H (20 mol%) as additive. <sup>d</sup> Toluene as solvent. dr was determined by <sup>19</sup>F 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 B<sub>2</sub>Pin<sub>2</sub> (380), 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 (-SCF<sub>3</sub>) or 38ab (-SCN), and NCS (38ac) were tested. Unfortunately, none of them provided a positive result.

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  $^{19}$ F NMR. n.r = no reaction.

In order to obtain the fluorinated cyclopropanes **39** with our desired functional groups (*i.e.*, -Bpin, -SiMe<sub>3</sub>, -SCF<sub>3</sub>), 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.<sup>254</sup> 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;<sup>255</sup> similarly, the reaction failed (Scheme 5. 11b). Finally, our group has reported two elegant methodologies for the functionalization of C(sp<sup>2</sup>)—H and C(sp<sup>3</sup>)—H by introducing SCF<sub>3</sub> reagents **38aa**<sup>256</sup> and **38ae**<sup>257</sup> independently. It is unpleasant that when we tried the functional

<sup>&</sup>lt;sup>254</sup> 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.

<sup>&</sup>lt;sup>255</sup> J.-L. Pan, Q.-Z. Li, T.-Y. Zhang, S.-H. Hou, J.-C. Kang, S.-Y. Zhang, Chem. Commun. 2016, 52, 13151-13154.

<sup>&</sup>lt;sup>256</sup> Q. Zhao, T. Poisson, X. Pannecoucke, J.-P. Bouillon, T. Besset, Org. Lett. 2017, 19, 5106-5109.

<sup>&</sup>lt;sup>257</sup> H.-Y. Xiong, T. Besset, D. Cahard, X. Pannecoucke, J. Org. Chem. **2015**, 80, 4204–4212.

reagents individually in the presence of Pd(CH<sub>3</sub>CN)<sub>2</sub>Cl<sub>2</sub> or PdCl<sub>2</sub>, 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).

Scheme 5. 12. Side reactions with several electrophiles. a130 °C, 15 h. b110 °C, 12 h.

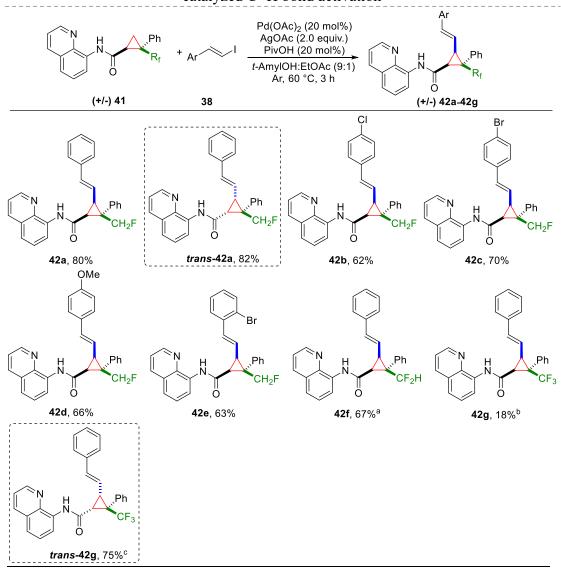
Scheme 5. 13. Coupling reaction with fluorocyclopropane 37c. a 130 °C, 15 h. b 110 °C, 12 h.

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.*, -CH<sub>2</sub>F, -CHF<sub>2</sub>, -CF<sub>3</sub>). Similar to the synthesis of compound 37a, fluoromethyl cyclopropyl amide 41 was synthesized through a cyclopropanation reaction with its  $\alpha$ -fluoromethyl styrene precursor (Scheme 5. 14). The use of ethyl diazoacetate and Rh<sub>2</sub>(OPiv)<sub>4</sub>, 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

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  $\beta$ -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  $\beta$ -iodostyrene 38a and monofluoromethyl cyclopropanes 41a and trans-41a. Para-substituted  $\beta$ -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  $\beta$ -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  $\beta$ -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(sp<sup>3</sup>)-H activation approach.



**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. <sup>a</sup> 90 °C, 6 h. <sup>b</sup> Without PivOH, 48 h. <sup>c</sup> 20 h.

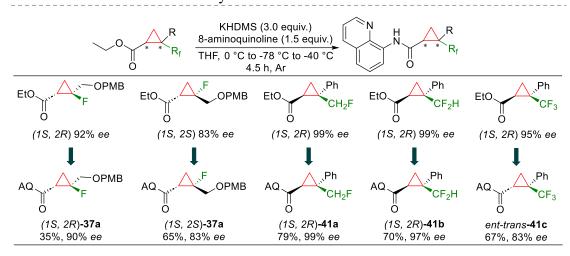
In light of the low yield obtained for the trifluoromethyl cyclopropane product 42g, the conditions were optimized to enhance the reactivity of 41g in the presence of electrophile 38a (Table 5. 2). Initially, when standard conditions were used with an extended reaction time (20 h) (entry 1), the reaction showed only an 18% conversion of 42g as observed by <sup>19</sup>F 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)<sub>2</sub>PO<sub>2</sub>H with a 60-hour reaction time slightly promoted the coupling process (entry 4),

resulting in a 23% conversion of 42g.

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

**Table 5. 2**. Optimization of coupling reaction between **41g** and **38a**. Conversion was determined by <sup>19</sup>F 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 group<sup>253</sup> and in collaboration with Fasan's group<sup>171d</sup>. 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.



**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 Me<sub>3</sub>SnOH (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: CDCl<sub>3</sub> and CHCl<sub>3</sub> 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, CHCl<sub>3</sub> was selected for further optimization. The reaction conducted in distilled CHCl<sub>3</sub> 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. (%)	dr
1	KOH (2.0 equiv.), EtOH, r.t, 2 h	72 (58)	19:81
2	Me <sub>3</sub> 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 <sub>2</sub> O <sub>2</sub> (3.0 equiv.), THF/H <sub>2</sub> O (3:1), r.t	n.r	-
6	LiOH (2.0 equiv.), H <sub>2</sub> O <sub>2</sub> (3.0 equiv.), THF/H <sub>2</sub> O (3:1), 40 °C	n.r	-
7	TMSI (3.0 equiv.), CDCl <sub>3</sub> , 50 °C, 24 h	61 (37)	39:61
8	TMSI (3.0 equiv.), CHCl <sub>3</sub> , 50 °C, 24 h	41	39:61
9	TMSI (3.0 equiv.), MeCN, 50 °C, 24 h	messy	-
10 <sup>a</sup>	TMSI (3.0 equiv.), CHCl <sub>3</sub> , 50 °C, 24 h, Ar	48	39:61
11ª	TMSI (6.0 equiv.), CHCl <sub>3</sub> , 50 °C, 24 h, Ar	69	39:61
12ª	TMSI (6.0 equiv.), CHCl <sub>3</sub> , 50 °C, 36 h, Ar	84(65)	39:61

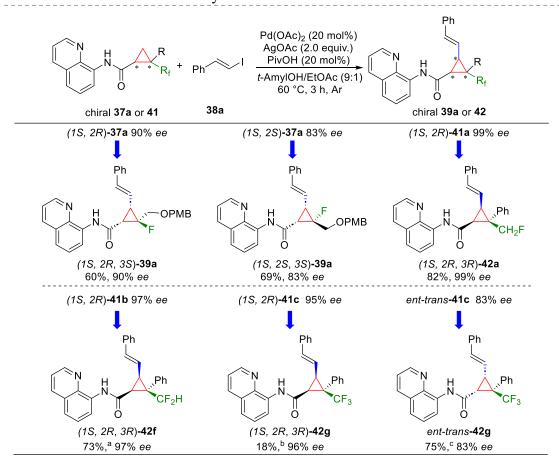
**Table 5. 3.** Optimization of the hydrolysis from trifluoromethyl cyclopropyl ester to carboxylic acid **43**. Isolated yield was presented in parenthesis. Conversion and dr were determined by <sup>19</sup>F NMR. n.r = no reaction. <sup>a</sup> Fresh distilled.

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).

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**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.



**Scheme 5. 18**. The formation of enantiopure 1,2,3-polysubstituted fluorinated cyclypropanes. 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. <sup>a</sup> 90 °C, 6 h. <sup>b</sup> without PivOH, 48 h. <sup>c</sup> 20 h.

#### 5.5. Propose plausible mechanism

Based on the previous advances in Pd(II)-catalyzed C(sp³) activation, <sup>258,247</sup> we propose a plausible Pd(II)/Pd(IV)-mechanism for this project (Scheme 5. 19). Initially, bidentate coordination of the catalyst Pd(OAc)<sub>2</sub> 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<sup>IV</sup> species **III**. After reductive elimination and reprotonation the expected product **39a** will be obtained and regenerate the catalyst.

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% HBr<sup>259</sup> solution in H<sub>2</sub>O 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,<sup>242</sup> 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);<sup>260</sup> surprisingly, the isolated product was determined to be the polycyclic compound 45 instead of our

<sup>&</sup>lt;sup>259</sup> Q. Zhu, D. Ji, T. Liang, X. Wang, Y. Xu, Org. Lett. 2015, 17, 3798–3801.

<sup>&</sup>lt;sup>260</sup> L. Ruyet, M. I. Lapuh, V. S. Koshti, T. Földesi, P. Jubault, T. Poisson, Z. Novák, T. Besset, *Chem. Commun.* **2021**, 57, 6241–6244.

desired primary amide (Scheme 5. 20c).

Scheme 5. 20. Testes 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<sub>2</sub>O,<sup>243</sup> compound **39a** could be transformed into a tertiary amide, followed by treatment with LiOOH (*in situ* generated);<sup>243</sup> the desired carboxylic acid product **44** was produced in a 65% yield (Scheme 5. 21a). On the other hand, under reductive reaction conditions (LiBH<sub>4</sub> with MeOH),<sup>181</sup> 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).

**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<sub>3</sub> and NaIO<sub>4</sub> (Scheme 5. 22).<sup>225a</sup> This consequence has proven the substrate **46** lack of reactivity to RuCl<sub>3</sub>/NaIO<sub>4</sub> 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, -CH<sub>2</sub>F, -CF<sub>2</sub>H, and -CF<sub>3</sub> 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  $\alpha,\alpha$ -difluoroalkyl cyclopropanes.

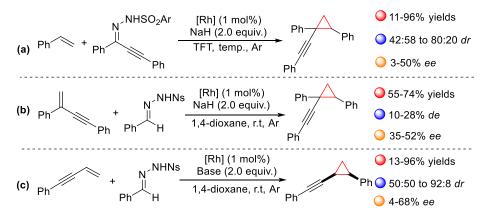
We initially reported the catalytic asymmetric synthesis of highly functionalized cyclopropanes from 2-substituted allylic derivatives (Scheme 6. 1). Using ethyl diazoacetate, the reaction, catalyzed by a chiral ruthenium complex (Ru(II)-Pheox), furnished the corresponding easily separable *cis* and *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  $\alpha$ , $\alpha$ -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  $\alpha$ , $\alpha$ -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  $\alpha$ , $\alpha$ -difluoroalkyl cyclopropane frameworks.

**Scheme 6. 2.** Ru(II)-Pheox-catalyzed synthesis of enantiomeric convergent phenylsulfonyl  $\alpha,\alpha$ -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-aminioquinoline 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, -CH<sub>2</sub>F, -CF<sub>2</sub>H, and -CF<sub>3</sub> 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  $C(sp^3)-C(sp)$ ,  $C(sp^3)-C(sp^2)$  and  $C(sp^3)-C(sp^3)$  bond. This method is particularly valuable for constructing diverse fluorinated cyclopropanes, given their synthetic significance and potential medicinal applications.

$$\begin{array}{c} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_6 \\ R_7 \\ R_7 \\ R_7 \\ R_8 \\ R_9 \\$$

**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.

# Chapter VI – Conclusion and perspectives

**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 KMnO<sub>4</sub> solution, p-anisaldehyde or a phosphomolybdic acid solution. Silica gel column chromatography was performed using 0.040-0.063 nm silica gel. <sup>1</sup>H NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer at 300.1 MHz, <sup>13</sup>C NMR spectra at 75.5 MHz and <sup>19</sup>F NMR spectra at 282.4 MHz. HOESY or NOESY were recorded on a Bruker DXP 300 MHz spectrometer. Chemical shifts ( $\delta$ ) are quoted in parts per million (ppm) relative to residual solvent peak for CDCl<sub>3</sub> ( $\delta_H = 7.26$  ppm,  $\delta_C = 77.00$  ppm) and relative to external CFCl<sub>3</sub> ( $\delta_F = 0$  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 (n) of recorded IR-signals are quoted in cm<sup>-1</sup>. Melting points were recorded on a Heizbank system Kofler WME and were uncorrected. Enantiomeric excesses (ee) or Enantiomeric ratio (er) were determined by highperformance liquid chromatography (HPLC) and gas chromatography (GC).

**Materials:** Dichloromethane (DCM), Dichloroethane (DCE), diethyl ether (Et<sub>2</sub>O) Ethyl acetate (EtOAc), 2-methyl-2-butanol (*tert*-AmylOH) tetrahydrofuran (THF) and toluene were distilled over CaH<sub>2</sub> 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  $\alpha$ -

#### 1. General procedures for the preparation of starting materials.

substituted allylic derivatives with ethyl diazoacetate

#### 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, <sup>161</sup> 1i, 1j, 1k, 1l, 1m, 1n, 1o, 1y were synthesized according to reported literature, <sup>70</sup> 1h, 1w, 1x was synthesized according to reported literature, <sup>95</sup> 1p, 1q was synthesized according to

#### **Experimental Part**

reported literature, <sup>261</sup> **1u**, **1v** was synthesized according to reported literature, <sup>262</sup> **1ae** was synthesized according to reported literature, <sup>252</sup> the characterization data is consistent with reported literatures. **1d**, **1e**, **1r**, **1ad** ware 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 Et<sub>2</sub>O (3×15 mL), and combined organic layers were washed with brine (20 mL), dried over MgSO<sub>4</sub> 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 PhMe<sub>2</sub>SiLi in THF<sup>263</sup> (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 NH<sub>4</sub>Cl (5 mL) and extracted with Et<sub>2</sub>O (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, 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.

<sup>&</sup>lt;sup>261</sup> C. Chen, T. R. Dugan, W. W. Brennessel, D. J. Weix, P. L. Holland, J. Am. Chem. Soc. 2014, 136, 945–955.

<sup>&</sup>lt;sup>262</sup> S. S. Salim, R. K. Bellingham, V. Satcharoen, R. C. D. Brown, Org. Lett. 2003, 5, 3403–3406.

<sup>&</sup>lt;sup>263</sup> I. Fleming, R. S. Roberts, S. C. Smith, J. Chem. Soc., Perkin Trans. 1 1998, 1209–1214.

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<sub>4</sub>Cl (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<sub>4</sub>, 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.

OH 
$$K_2CO_3$$
 (1.1 equiv.)  
 $K_2CO_3$  (1.1 equiv.)  
 $OBn$   $1h$ ,  $X = Br$   $1w$ ,  $X = F$   $1x$ ,  $X = Cl$ 

K<sub>2</sub>CO<sub>3</sub> (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<sub>3</sub> (10 mL) and brine (10 mL), dried over MgSO<sub>4</sub>, 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**.

$$\begin{array}{c} \text{1) } \text{Ar}^1 \text{Br, Mg, } \text{I}_2 \\ \text{OH} \\ \hline \text{2) } \text{Cul r.t, to reflux 24 h} \\ \text{Ar}^1 \\ \hline \text{2) } \text{Cul r.t, to reflux 24 h} \\ \text{Ar}^2 \\ \hline \end{array} \begin{array}{c} \text{Ph}_3 \text{P } \text{(1.2 equiv.)} \\ \text{OH} \\ \hline \text{CBr}_4 \text{ (1.2 equiv.)} \\ \text{DCM, 0 °C, 3 h} \\ \hline \text{DCM, 0 °C, 3 h} \\ \hline \text{DMF, r.t, overnight} \\ \hline \text{DMF, r.t, overnight} \\ \hline \text{NBS (1.05 equiv.)} \\ \hline \text{The } \text{O °C to r.t. 15 h} \\ \hline \end{array} \\ \text{Ar}^2 \\ \hline \end{array} \begin{array}{c} \text{Ph}_3 \text{P } \text{C1.2 equiv.)} \\ \hline \text{DMF, r.t, overnight} \\ \hline \text{NBS (1.05 equiv.)} \\ \hline \text{TSOH (10 mol\%)} \\ \hline \text{THe } \text{O °C, 4 h} \\ \hline \end{array}$$

Synthesis of allylic bromide bearing Ar¹: 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<sub>4</sub>Cl was added dropwise carefully. The organic phase was separated and the aqueous phase was extracted with Et<sub>2</sub>O

three times. The combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub> 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 CH<sub>2</sub>Cl<sub>2</sub> (0.4 M), PPh<sub>3</sub> (1.2 equiv.) was added at 0 °C, and the mixture was stirred for 10 min. CBr<sub>4</sub> (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 Ar<sup>2</sup>: 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 Na<sub>2</sub>SO<sub>4</sub>, 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 Na<sub>2</sub>SO<sub>4</sub>, 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 Na<sub>2</sub>SO<sub>4</sub>, 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.

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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 Na<sub>2</sub>SO<sub>4</sub>, 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 NaSO<sub>2</sub>CF<sub>3</sub> (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)<sub>2</sub> (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.), Et<sub>3</sub>N (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 Et<sub>2</sub>O (3×20mL). The organic layers were combined and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was purified by silica-gel flash column

chromatography (petroleum ether) to provide 1.44 g (76% yield) of desired product 10 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 °C. The resulting mixture was stirred at 0 °C for 15 min and then stirred at room temperature for 1 h. The reaction was then quenched with saturated NH<sub>4</sub>Cl (15 mL) and extracted with Et<sub>2</sub>O (3×10 mL). The organic layers were washed with brine (20 mL), dried over MgSO<sub>4</sub>, 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.

F CI 
$$K_2\text{CO}_3$$
 (2.0 equiv.)

DMF, r.t, 5 days

NBoc<sub>2</sub>

NBoc<sub>2</sub>

NBoc<sub>2</sub>

3-Chloro-2-fluoroprop-1-ene (174  $\mu$ L, 2 mmol,1.0 equiv.) was added to a stirred solution of NHBoc<sub>2</sub> (521 mg, 2.4 mmol, 1.2 equiv.) and K<sub>2</sub>CO<sub>3</sub> (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<sub>4</sub>Cl 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<sub>4</sub>, 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-fluoroprop1-ene (174 μL, 2 mmol, 1 equiv.) in DMF (4 mL) at room temperature. The resulting

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<sub>2</sub>CO<sub>3</sub> (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 °C and stirred for 20 hours. The reaction was monitored by <sup>19</sup>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<sub>4</sub>. 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 °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<sub>4</sub>. The solid was filtered off and the organic solvent was evaporated under reduced pressure. The crude was purified by silica-gel flash column

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-1ene (174  $\mu$ L, 2 mmol, 1 equiv.) and triethylphosphite (420  $\mu$ 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,<sup>264</sup> 2d,<sup>265</sup> 2e,<sup>266</sup> 2f,<sup>267</sup> 2g<sup>268</sup> 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)

<sup>&</sup>lt;sup>264</sup> J. V. Jun, R. T. Raines, Org. Lett., **2021**, 23, 3110–3114.

<sup>&</sup>lt;sup>265</sup> S. Chanthamath, S. Takaki, K. Shibatomi, S. Iwasa *Angew. Chem. Int. Ed.*, **2013**, *52*, 5818–5821.

<sup>&</sup>lt;sup>266</sup> G.Pisella, A. Gagnebin, J. Waser, Org. Lett., **2020**, 22, 3884–3889.

<sup>&</sup>lt;sup>267</sup> S. Chanthamath, S. Ozaki, K. Shibatomi, S. Iwasa, Org. Lett. **2014**, 16, 3012–3015.

<sup>&</sup>lt;sup>268</sup> X. Zhao, J.-Y. Shou, J. J. Newton, F.-L. Qing, *Org. Lett.* **2022**, *24*, 8412–8416.

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 NaHCO<sub>3</sub> (3×200 mL), followed by brine (20 mL). The organic layer was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, 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.

The resulting bromoacetate and *N,N'*-ditosylhydrazine <sup>269</sup> (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 NaHCO<sub>3</sub> aq. and extracted with Et<sub>2</sub>O (3×20 mL), the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated under reduced pressure. The crude was purified by silica-gel flash column chromatography (EtOAc/*n*Hexane 1:4) to give methyl (diazoacetoxy)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  $\mu$ L, 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 (3x30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by silica-gel flash column chromatography (Et<sub>2</sub>O/pentane 2:98) to afford desired product **2e** (1.25 g, 87%) as a yellow solid.

<sup>&</sup>lt;sup>269</sup> T. Toma, J. Shimokawa, T. Fukuyama, Org. Lett. **2007**, *9*, 3195–3197.

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 Na<sub>2</sub>CO<sub>3</sub> (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 CH<sub>3</sub>CN (10 mL) was added dropwise to a stirred solution 1-(phenylsulfonyl)-2- propanone (0.99 g, 5 mmol, 1.0 equiv.) in anhydrous CH<sub>3</sub>CN (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 Al<sub>2</sub>O<sub>3</sub> (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.

## 2. General procedure for the preparation Ru(II)-Pheox I (Iwasa's procedure)<sup>270</sup>

To a mixture of (*S*)-(+)-2-phenylglycinol (1.51g, 11.0 mmol) and triethylamine (5.6 mL, 40.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20.0 mL), a solution of benzoyl chloride (1.4 g, 10.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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 CHCl<sub>3</sub> (20.0 mL) was treated with SOCl<sub>2</sub> (3.8 mL, 50.0 mmol) at 0 °C. After stirring for 24 h at room temperature, the solvent and excess SOCl<sub>2</sub> was removed under reduced pressure. A saturated. NaHCO<sub>3</sub> aqueous solution (50.0 mL) was added to the residue with stirring for 5 min. The organic product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×30 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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 CH<sub>2</sub>Cl<sub>2</sub> (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), [RuCl<sub>2</sub>(benzene)]<sub>2</sub> (75.0 mg, 0.15 mmol), KPF<sub>6</sub> (220.9 mg, 1.2 mmol), and NaOH (aqua.) (0.3 mL, 0.30 mmol, ca. 1.0 M) in CH<sub>3</sub>CN (5.0 mL, degassed) was stirred for 48 h at 80 °C. The reaction mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×20 mL) and was dried over Na<sub>2</sub>SO<sub>4</sub>. After concentration, the residue was purified by silica-gel flash column chromatography (CH<sub>3</sub>CN/CH<sub>2</sub>Cl<sub>2</sub> 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.

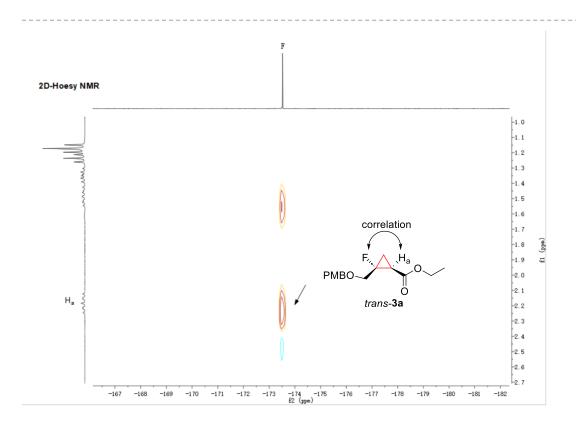
<sup>&</sup>lt;sup>270</sup> A.-M. Abu-Elfotoh, K. Phomkeona, K. Shibatomi S. Iwasa *Angew. Chem. Int. Ed.*, **2010**, 49, 8439–8443.

# 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 immerged 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 <sup>1</sup>H 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.







The corresponding racemic cyclopropanes were prepared using Rh<sub>2</sub>(Opiv)<sub>4</sub> or Rh<sub>2</sub>(esp)<sub>2</sub> catalysts among the following procedure: To an oven-dried 10 mL reaction tube contained a stir bar, Rh<sub>2</sub>(Opiv)<sub>4</sub> (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 Rh<sub>2</sub>(esp)<sub>2</sub>.

**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 <sup>19</sup>F NMR on the crude mixture.

trans-3a

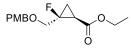
ethyl (1S,2R)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)cyclopropane-1-carboxylate

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

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  7.24 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 4.52 (d, J = 11.8Hz, 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -196.4 - -196.6 (m, 1 F).



cis-3a

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

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

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -178.4 --178.8 (m, 1 F).

**HRMS** (AP<sup>+</sup>) calcd for  $C_{15}H_{19}O_4F$  ([M+H]<sup>+</sup>) 282.1267, found: 282.1260 ( $\Delta$ -0.6 ppm).

IR (Neat) 2292, 2853, 1732, 1612, 1513, 1247, 1173, 1092, 1032, 819 cm<sup>-1</sup>.

**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/Et<sub>2</sub>O 95:5 to 85:15). The diastereomeric ratio (68:32) was determined by <sup>19</sup>F NMR on the crude mixture.

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

*trans*-3b (major isomer) Colorless oil.  $R_f = 0.60$  (PE/Et<sub>2</sub>O = 5:1). [ $\alpha$ ]<sup>20</sup>D = -14.5 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -156.5 - -156.8 (m, 1 F).

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

*cis*-3b (minor isomer) Colorless oil.  $R_f = 0.48$  (PE/Et<sub>2</sub>O = 5:1).  $[\alpha]^{20}D = -31.4$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -178.9 - -179.2 (m, 1 F).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{15}H_{22}O_2FSi$  ([M+H]<sup>+</sup>) 281.1373, found: 281.1371 ( $\Delta$ -0.7 ppm). **IR (Neat)** 3070, 2958, 1723, 1379, 1247, 1160, 1113, 891, 727, 697 cm<sup>-1</sup>.

**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 <sup>19</sup>F NMR of the crude mixture.

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

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

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -171.2 - -171.5 (m, 1 F).

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

cis-3c (minor isomer) Colorless oil.  $R_f = 0.24$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -8.0$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  167.2 (d, J = 2.4 Hz), 139.2, 134.3, 129.4, 128.7, 75.9 (d, J = 232.4

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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -189.2 - -189.5 (m, 1 F).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{13}H_{16}O_4FS$  ([M+H]<sup>+</sup>) 287.0753, found: 287.0742 ( $\Delta$ -3.8 ppm).

IR (Neat) 2983, 2931, 1727, 1447, 1380, 1153, 1084, 989, 749, 530 cm<sup>-1</sup>.

**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/Et<sub>2</sub>O 95:5 to 85:15). The diastereomeric ratio (83:17) was determined by <sup>1</sup>H NMR on the crude mixture.

Only the major diastereoisomer was fully characterized.

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ethyl (1S,2R)-2-chloro-2-(chloromethyl)cyclopropane-1-carboxylate

*trans*-3d (major isomer) Colorless oil.  $R_f = 0.60$  (PE/Et<sub>2</sub>O = 5:1). [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -165.1 (c = 1.0, CHCl<sub>3</sub>). **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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  169.9, 61.8, 48.8, 48.6, 30.0, 24.6, 14.3.

**HRMS (EI**<sup>+</sup>) calcd for  $C_7H_{10}Cl_2O_2$  ([M+H]<sup>+</sup>) 196.0058, found: 196.00578 ( $\Delta 0$  ppm).

IR (Neat) 2983, 1723, 1380, 1440, 1229, 1179, 1032, 728, 600 cm<sup>-1</sup>.

**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/Et<sub>2</sub>O 95:5 to 85:15). The diastereomeric ratio (85:15) was determined by <sup>1</sup>H NMR on the crude mixture.

Only the major diastereoisomer was fully characterized.

ethyl (1S,2R)-2-bromo-2-(bromomethyl)cyclopropane-1-carboxylate

trans-3e (major isomer) Colorless oil.  $R_f = 0.60$  (PE/Et<sub>2</sub>O = 5:1).  $[\alpha]^{20}_D = -153.0$  (c = 1.0, CHCl<sub>3</sub>). **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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  169.5, 61.8, 39.1, 37.4, 31.6, 26.6, 14.3.

**HRMS** (EI<sup>+</sup>) calcd for  $C_5H_6Br_2O_2$  ([(M-ethyl)+H]<sup>+</sup>) 255.8735, found: 255.8740 ( $\Delta 2.24$  ppm). **IR** (Neat) 2981, 1720, 1379, 1232, 1161, 1026, 857, 649 cm<sup>-1</sup>.

**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 <sup>1</sup>H NMR on the crude mixture.

 $ethyl\ (1S,2R)-2-chloro-2-((phenylsulfonyl)methyl)cyclopropane-1-carboxylate$ 

*trans*-3f (major isomer) White solid, m.p. = 62 - 64 °C.  $R_f = 0.57$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -61.8$  (c = 1.0, CHCl<sub>3</sub>).

**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,  $t_R$  = 19.7min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.3 140.2, 134.0, 129.4, 128.6, 61.9, 59.3, 40.4, 29.1, 23.4, 14.3.

ethyl (1S,2S)-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<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  167.6, 139.1, 134.4, 129.4, 129.1, 66.1, 61.7, 39.5, 28.1, 21.0, 14.5. HRMS (AP<sup>+</sup>) calcd for C<sub>13</sub>H<sub>16</sub>O<sub>4</sub>SCl ([M+H]<sup>+</sup>) 305.0428, found: 305.0425 (Δ-1.0 ppm). IR (Neat) 2288, 2922, 2852, 1719, 1318, 1182, 1148, 1083, 731, 519 cm<sup>-1</sup>.

**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 <sup>1</sup>H NMR on the crude mixture.

ethyl (1S,2R)-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). [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -77.8 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 170.4, 140.1, 134.0, 129.4, 128.6, 61.9, 60.2, 29.5, 26.2, 24.3, 14.3.

ethyl (1S,2S)-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).  $[\alpha]^{20}_D = -14.3$  (c = 1.0, CHCl<sub>3</sub>).

**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,  $t_R$  = 20.4min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  168.0, 139.1, 134.5, 129.5, 129.2, 67.2, 61.8, 27.9, 26.5, 21.7, 14.5. HRMS (AP<sup>+</sup>) calcd for C<sub>13</sub>H<sub>16</sub>O<sub>4</sub>SBr ([M+H]<sup>+</sup>) 348.9923, found: 348.9937 (Δ1.4 ppm).

IR (Neat) 2921, 2851, 1719, 1382, 1181, 1146, 1083, 746, 514 cm<sup>-1</sup>.

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 diastereosiomers 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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 =

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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{14}H_{16}O_4Br$  ([M+H]<sup>+</sup>) 327.0232, found: 327.0228 ( $\Delta$ -1.2 ppm). **IR (Neat)** 2982, 1723, 1376, 1266, 1180, 1118, 1030, 747, 696 cm<sup>-1</sup>.

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 <sup>1</sup>H NMR on the crude mixture.

*trans*-3i (major isomer) White solid, m.p. = 130 - 132 °C.  $R_f = 0.45$  (PE/EtOAc = 2:1).  $[\alpha]^{20}_D = -56.7$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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 °C.  $R_f = 0.31$  (PE/EtOAc = 2:1).  $[\alpha]^{20}_D = -85.2$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{20}H_{23}O_5S$  ([M+H]<sup>+</sup>) 375.1266, found: 375.1273 ( $\Delta$ 1.9 ppm).

IR (Neat) 3015, 2927, 2851, 1713, 1517, 1310, 1184, 1029, 740, 529 cm<sup>-1</sup>.

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 <sup>1</sup>H NMR on the crude mixture.

*trans*-3j (minor isomer) White solid, m.p. = 133 - 135 °C.  $R_f = 0.52$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -60.3$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).  $[\alpha]^{20}_D = -20.2$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 – 7.67 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H),

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 = 8.7 Hz, 2H), 4.34 (dd, J = 8.7 Hz, 2H), 4.35 (dd, J

8.6, 6.3 Hz, 1H), 1.58 - 1.46 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>) calcd for  $C_{19}H_{20}O_4SC1$  ([M+H]<sup>+</sup>) 379.0771, found: 379.0746 ( $\Delta$ -1.8 ppm).

IR (Neat) 2922, 1723, 1448, 1300, 1169, 1138, 824, 739, 523 cm<sup>-1</sup>.

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 <sup>1</sup>H NMR on the crude mixture.

*trans*-3k (minor isomer) White solid, m.p. = 142 - 142 °C.  $R_f = 0.52$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -68.6$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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. <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -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).  $[\alpha]^{20}_D = -140.0$  (c = 1.0, CHCl<sub>3</sub>).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with a Chiralcel

IB column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min),  $t_R$  = 11.5 min,  $t_R$  = 14.4 min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  δ -114.7 – -114.8 (m, 1F).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{19}H_{20}O_4FS$  ([M+H]<sup>+</sup>) 363.1066, found: 363.1057 ( $\Delta 2.5$  ppm).

IR (Neat) 3052, 2923, 1723, 1514, 1171, 1137, 1079, 832, 724, 528 cm<sup>-1</sup>.

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 <sup>1</sup>H NMR on the crude mixture.

*trans-3*I (major isomer) White solid, m.p. = 134 - 136 °C.  $R_f = 0.53$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -74.3$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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-3l (minor isomer) Colorless oil.  $R_f = 0.36$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -80.5$  (c = 1.0, CHCl<sub>3</sub>). 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. <sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{19}H_{21}O_4S$  ([M+H]<sup>+</sup>) 345.1161, found: 345.1150 ( $\Delta$ -3.2 ppm). **IR (Neat)** 2924, 1722, 1448, 1270, 1172, 1136, 1081, 742, 528 cm<sup>-1</sup>.

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 <sup>1</sup>H NMR on the crude mixture.

*trans*-3m, Colorless oil.  $R_f = 0.38$  (PE/EtOAc = 3:1).  $[\alpha]^{20}D = -75.3$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).  $[\alpha]^{20}D = -12.0$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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,

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). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  172.6, 140.7, 133.7, 129.4, 128.1, 61.1, 58.3, 26.1, 24.4, 21.8, 21.5,

**HRMS (AP**<sup>+</sup>) calcd for  $C_{14}H_{19}O_4S$  ([M+H]<sup>+</sup>) 283.1004, found: 283.1000 ( $\Delta$ -1.4 ppm). **IR (Neat)** 2982, 2924, 1708, 1384, 1305, 1180, 1147, 1084, 739, 522 cm<sup>-1</sup>.

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 <sup>19</sup>F NMR on the crude mixture.

*trans*-3n (major isomer) Colorless oil.  $R_f = 0.50$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -32.8$  (c = 1.0, CHCl<sub>3</sub>). **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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -79.6 (s, 3F).

14.4.

*cis-3n* (minor isomer) Colorless oil.  $R_f = 0.29$  (PE/EtOAc = 3:1).  $[\alpha]^{20}_D = -67.0$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -80.0 (s, 3F).

**HRMS (AP+)** calcd for  $C_{14}H_{16}O_4F_3S$  ([M+H]+) 337.0721, found: 337.0724 ( $\Delta 0.9$  ppm).

IR (Neat) 2989, 2922, 2851, 1721, 1355, 1183, 1116, 1019, 700, 530 cm<sup>-1</sup>.

ethyl-2-phenyl-2-((trimethylsilyl)methyl)cyclopropane-1-carboxylate

**30**. 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/Et<sub>2</sub>O 99:1 to 90:10). The diastereomeric ratio (51:49) was determined by <sup>1</sup>H NMR on the crude mixture. Colorless oil.

*trans*-30 (major isomer)  $R_f = 0.64$  (PE/Et<sub>2</sub>O = 10:1).  $[\alpha]^{20}_D = -39.6$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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*-30 (minor isomer)  $R_f = 0.40$  (PE/Et<sub>2</sub>O = 10:1).  $[\alpha]^{20}D = -26.8$  (c = 1.0, CHCl<sub>3</sub>).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by inverse phase HPLC with a Chiralcel IA3 column (H<sub>2</sub>O: MeCN = 50:50, 254 nm, 1 mL/min),  $t_R$  = 27.6 min,  $t_R$  = 29.4 min. <sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{16}H_{25}O_2Si$  ([M+H]<sup>+</sup>) 277.1624, found: 277.1617 ( $\Delta$ -2.5 ppm).

IR (Neat) 2953, 2899, 1728, 1378, 1247, 1159, 1081, 856, 834, 698 cm<sup>-1</sup>.

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/Et<sub>2</sub>O 99:1 to 90:10). The diastereomeric ratio (81:19) was determined by <sup>1</sup>H NMR on the crude mixture.

*trans*-3p (major isomer) Colorless oil.  $R_f = 0.72$  (PE/Et<sub>2</sub>O = 10:1).  $[\alpha]^{20}_D = -63.2$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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/Et<sub>2</sub>O = 10:1).  $[\alpha]^{20}_D = -17.8$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{15}H_{23}O_2Si$  ([M+H]<sup>+</sup>) 263.1467, found: 263.1471 ( $\Delta$ 1.5 ppm). **IR (Neat)** 3070, 2956, 1721, 1380, 1248, 1159, 1112, 833, 698 cm<sup>-1</sup>.

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 diastereosiomers after silica gel column chromatography (PE/Et<sub>2</sub>O 99:1 to 90:10).  $R_f = 0.73$  (PE/Et<sub>2</sub>O = 10:1). The diastereomeric ratio (50:50) was determined by <sup>1</sup>H 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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**<sup>+</sup>) calcd for  $C_{16}H_{25}O_2Si$  ([M+H]<sup>+</sup>) 277.1624, found: 277.1628 ( $\Delta$ 1.4 ppm). **IR (Neat)** 3070, 2956, 1720, 1380, 1162, 1111, 832, 724, 699 cm<sup>-1</sup>.

#### 4. General procedures of the post-fucntionalization reactions

4.1. General procedure for the synthesis of 2-(4-bromophenyl)-2-oxoethyl cyclopropylcarboxylates 4.

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 Na<sub>2</sub>SO<sub>4</sub> 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 NaHCO<sub>3</sub> (10 mL) and 1 N HCl (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, evaporated under reduced pressure and purified by silica gel chromatography to yield 4.

 $2-(4-bromophenyl)-2-oxoethyl\ (1S,2R)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl) cyclopropane-1-carboxylate$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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

Hz), 17.9 (d, J = 9.8 Hz).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -173.1 – -173.4 (m, 1 F).

HRMS (ES<sup>+</sup>) calcd for C<sub>21</sub>H<sub>20</sub>O<sub>5</sub>FBrNa ([M+Na]<sup>+</sup>) 473.0376, found: 473.0376 (Δ0 ppm). IR (Neat) 2927, 1732, 1701, 1585, 1514, 1246, 1161, 1070, 814, 546 cm<sup>-1</sup>.  $|\alpha|^{20}$ <sub>D</sub> = -39.7 (c = 1.0, CHCl<sub>3</sub>).

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).  $R_{\rm f} = 0.33$ 

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -195.5 – -195.8 (m, 1 F).

**HRMS** (ES<sup>+</sup>) calcd for  $C_{21}H_{20}O_5FBrNa$  ([M+Na]<sup>+</sup>) 473.0376, found: 473.0376 ( $\Delta 0$  ppm).

IR (Neat) 2926, 1731, 1701, 1585, 1247, 1139, 1070, 814, 546 cm<sup>-1</sup>.

$$[\alpha]^{20}$$
<sub>D</sub> = -42.4 (c = 1.0, CHCl<sub>3</sub>).

2-(4-bromophenyl)-2-oxoethyl (1R,2S)-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,  $t_R$  = 65.9min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

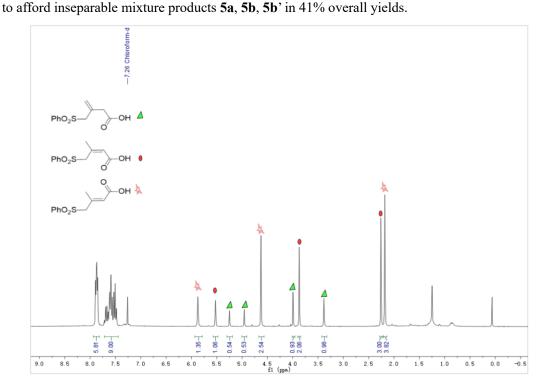
<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 191.5, 171.6, 159.0, 140.7, 133.2, 133.0, 132.5, 132.4, 130.4, 129.5, 129.4, 129.0, 127.9, 114.0, 66.7, 59.4, 55.4, 30.5, 26.4, 20.4.

HRMS (ES<sup>+</sup>) calcd for C<sub>26</sub>H<sub>24</sub>O<sub>6</sub>SBr ([M+H]<sup>+</sup>) 543.0477, found: 543.0459 (Δ-3.3 ppm). IR (Neat) 2927, 2853, 1729, 1692, 1585, 1396, 1249, 1164, 1070, 815 cm<sup>-1</sup>.  $|\alpha|^{20}$ <sub>D</sub> = -88.7 (c = 1.0, CHCl<sub>3</sub>).

#### 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 (3×5 mL),

the organic phases were combined and dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude was purified by silica-gel chromatography (MeOH/DCM 1:20)



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

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

**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,  $t_{RZ}$  = 73.2 min;  $t_{RE}$  = 60.3 min,  $t_{RE}$  = 67.8 min.

**HRMS** (AP<sup>+</sup>) calcd for  $C_{13}H_{15}O_4S$  ([M+H]<sup>+</sup>) 267.0691, found: 267.0681 ( $\Delta$ -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 CrCl<sub>3</sub> (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.

1-(4-chlorophenyl)-6-(phenylsulfonyl)-3,4-dihydropyridin-2(1*H*)-one

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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

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 NaHCO<sub>3</sub> (5 mL) and brine (5 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, 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.

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 139.6, 134.3, 129.4, 128.8, 63.2, 61.4, 31.1, 25.4, 19.9. HRMS (AP<sup>+</sup>) calcd for C<sub>11</sub>H<sub>14</sub>O<sub>3</sub>SBr ([M+H]<sup>+</sup>) 304.9847, found: 304.9840 (Δ-0.7 ppm). IR (Neat) 3341, 2929, 2864, 1524, 1393, 1140, 1071, 816, 747 cm<sup>-1</sup>.  $[\alpha]^{20}_{D} = -13.3$  (c = 1.0, CHCl<sub>3</sub>).

PhO<sub>2</sub>S OH 
$$\frac{\text{TESCI (1.1 equiv.)}}{\text{DCM, 0 °C to r.t, 24 h}}$$
 PhO<sub>2</sub>S Br. OTES **8**, 68%, 98% ee **9**, 19%

To a solution of **8** (40.0 mg, 0.132 mmol, 1.0 equiv.) in 2 mL dichloromethane was added triethylsilyl chloride (24.4  $\mu$ L, 0.145 mmol, 1.1 equiv.) and triethylamine (22.0  $\mu$ L, 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 Na<sub>2</sub>SO<sub>4</sub>, 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.

(((1S,2R)-2-bromo-2-((phenylsulfonyl)methyl)cyclopropyl)methoxy)triethylsilane

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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  $\mu$ L, 0.4 mmol, 4.0 equiv.) and MOMCl (22.8  $\mu$ L, 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 NaHCO<sub>3</sub> aqueous (3 mL) and brine (3 mL). The organic phase was separated and dried over Na<sub>2</sub>SO<sub>4</sub>, 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.

 $(R) \hbox{-} (((2 \hbox{-} ((methoxymethoxy)methyl) cyclopropylidene) methyl) sulfonyl) benzene$ 

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)

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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 –

1.41 (m, 0.7H, Z), 1.39 – 1.32 (m, 0.3H, E).

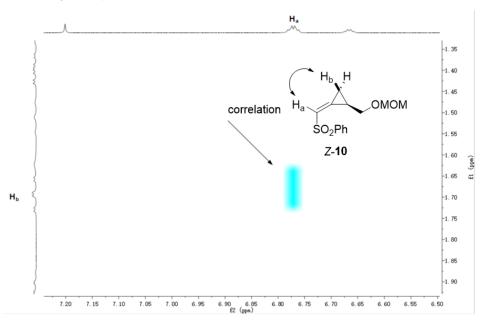
<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 143.7 (*Z*), 143.4 (*E*), 141.1 (*Z*), 140.7 (*E*), 133.8 (*E*), 133.5 (*Z*), 129.5 (*E*), 129.4 (*Z*), 127.8 (*Z*), 127.6 (*E*), 122.1 (*E*), 121.9 (*Z*), 95.1 (*E*), 95.0 (*Z*), 68.5 (*Z*), 68.0 (*E*), 64.5 (*E*), 63.6 (*Z*), 17.8 (*Z*), 15.3 (*E*), 10.2 (*E*), 9.9 (*Z*).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{13}H_{20}O_4S$  ([M+H]<sup>+</sup>) 291.0667, found: 291.0675 ( $\Delta 2.7$  ppm).

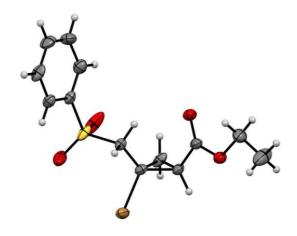
IR (Neat) 2926, 2852, 1700, 1585, 1394, 1162, 1139, 1067, 737, 535 cm<sup>-1</sup>.

$$[\alpha]^{20}$$
<sub>D</sub> = -5.5 (c = 1.0, CHCl<sub>3</sub>).

10 2D-Noesy NMR (CDCl<sub>3</sub>)←



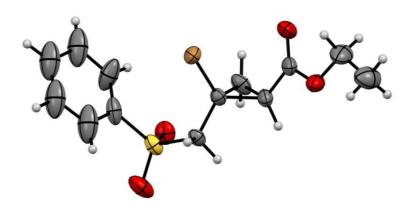
# 5. Crystallographic data for compounds *trans*-3g, *cis*-3g and *trans*-3i Compound *trans*-3g



Displacement ellipsoids drawn at the 50% probability level

Single crystals suitable for X–ray crystallographic analysis were obtained by slow evaporation of Et<sub>2</sub>O and Petroleum Ether solution. X–ray diffraction experiments for monocrystal of *trans-3g* were performed at 150 K with graphite–monochromatized Mo K<sub>a</sub> radiation (l = 0.71073 Å) on a Bruker D8 QUEST diffractometer. Formula  $C_{13}H_{15}BrO_4S$ , formula weight 347.22. Crystal system orthorhombic, space group  $P 2_12_12_1$ , a = 5.2424(3) Å, b = 9.1355(6) Å, c = 30.233(2) Å,  $a = b = \gamma = 90 ^{\circ}$ ,  $V = 1447.92(16) \text{ Å}^3$ , Z = 4, calculated density = 1.593 g/cm<sup>3</sup>,  $m = 2.989 \text{ mm}^{-1}$ ,  $R_{\text{int}} = 0.056$ ,  $R[F^2>2s(F^2)] = 0.038$ ,  $wR(F^2) = 0.072$ . Independent reflections = 3175. GOF=1.089, 173 parameters, final difference map within 0.583 and -0.721 eÅ<sup>-3</sup>. The structure was solved using direct methods and refined by full-matrix least-squares analysis on  $F^2$ . Selected bond lengths (Å) 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.

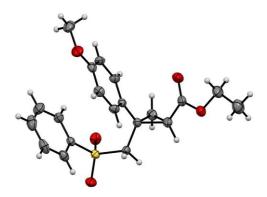
#### Compound cis-3g



Displacement ellipsoids drawn at the 50% probability level

Single crystals suitable for X–ray crystallographic analysis were obtained by slow evaporation of Et<sub>2</sub>O and Petroleum Ether solution. X–ray diffraction experiments for monocrystal of *cis-3g* were performed at 150 K with graphite–monochromatized Mo K<sub>a</sub> radiation (l = 0.71073 Å) on a Bruker D8 QUEST diffractometer. Formula  $C_{13}H_{15}BrO_4S$ , formula weight 347.22. Crystal system monoclinic, space group P  $2_1/c$ , a = 5.3680(5) Å, b = 9.9781(8) Å, c = 13.7010(14) Å, b = 93.878(4) °,  $V = 732.18(12) \text{ Å}^3$ , Z = 2, calculated density =  $1.575 \text{ g/cm}^3$ ,  $m = 2.956 \text{ mm}^{-1}$ ,  $R_{\text{int}} = 0.059$ ,  $R[F^2>2s(F^2)] = 0.050$ ,  $wR(F^2) = 0.139$ . Independent reflections = 5506. GOF=1.060, 527 parameters, final difference map within 0.861 and  $-0.887 \text{ eÅ}^{-3}$ . The structure was solved using direct methods and refined by full-matrix least-squares analysis on  $F^2$ . Selected bond lengths (Å) 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 CHCl<sub>3</sub> and Hexane solution. X-ray diffraction experiments for monocrystal of *trans*-3i were

performed at 150 K with graphite–monochromatized Mo K<sub>a</sub> radiation (I = 0.71073 Å) on a Bruker D8 QUEST diffractometer. Formula  $C_{20}H_{22}O_5S$ , formula weight 374.43. Crystal system monoclinic, space group  $P_{21}$ , a = 10.9751 (16) Å, b = 5.7774(10) Å, c = 15.697(3) Å, b = 109.482(5) °, V = 938.3(3) Å<sup>3</sup>, Z = 2, calculated density = 1.325 g/cm<sup>3</sup>, m = 0.200 mm<sup>-1</sup>,  $R_{int} = 0.056$ ,  $R[F^2>2s(F^2)] = 0.037$ , wR( $F^2$ ) = 0.088. Independent reflections = 4803. GOF=1.055, 237 parameters, final difference map within 0.243 and -0.217 eÅ<sup>-3</sup>. The structure was solved using direct methods and refined by full-matrix least-squares analysis on  $F^2$ . Selected bond lengths (Å) 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. <sup>271</sup> The geometry optimizations were performed using the Gaussian 16 software package<sup>272</sup> with the B3LYP density functional, <sup>273</sup> in combination with the 6-31G(d,p) basis set <sup>274</sup> for all atoms except

<sup>F. Planas, M. Costantini, M. Montesinos-Magraner, F. Himo, A. Mendoza, ACS Catal. 2021, 11, 10950-10963.
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.
A. D. Becke, J. Chem. Phys. 1993, 98, 5648.</sup> 

<sup>&</sup>lt;sup>274</sup> 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.

ruthenium, for which LANL2DZ basis set and related pseudopotential were applied. <sup>275</sup> The Grimme dispersion correction using the original D3 damping function (D3(BJ)) was applied during the geometry optimizations. <sup>276</sup> 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:

$$G_{Final} = E_{TZ} + (E_{PCM} - E_{GP}) + G_{corr} + 1.89 \text{ kcal/mol}$$

 $\mathbf{E}_{GP}$ : 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 model<sup>277</sup> 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

<sup>&</sup>lt;sup>275</sup> 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.

<sup>&</sup>lt;sup>276</sup> S. Grimme, S. Ehrlich, L. Goerigk, *J. Comp. Chem.* **2011**, *32*, 1456.

<sup>&</sup>lt;sup>277</sup> G. Scalmani, M. J. Frisch, J. Chem. Phys. **2010**, 132, 114110.

<sup>&</sup>lt;sup>278</sup> L. E. Roy, J. Hay, R. L. Martin, J. Chem. Theory Comput. **2008**, 4, 1029.

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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	$\mathbf{E}_{\mathbf{GP}}$	E <sub>PCM</sub>	$\mathbf{E}_{\mathbf{TZ}}$	i <sub>Freq</sub> (cm <sup>-1</sup> )	G <sub>corr</sub>	$G_{\text{final}}$	$\Delta G_{ m rel}{}^a$
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

<sup>&</sup>lt;sup>a</sup> The relative Gibbs energies ( $\Delta G_{rel}$ ) are reported in kcal/mol. The value in parentheses is relative to the reference compounds. All other values are relative to the reported Int1.

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Table S2. Computed energetic values for the 2-halopropene series.

Filename	E <sub>GP</sub> (Ha)	E <sub>PCM</sub> (Ha)	E <sub>TZ</sub> (Ha)	i <sub>Freq</sub> (cm <sup>-1</sup> )	G <sub>corr</sub> (Ha)	G <sub>final</sub> (Ha)	$\Delta { m G_{rel}}^a$
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

<sup>&</sup>lt;sup>a</sup> The relative Gibbs energies ( $\Delta G_{rel}$ ) are reported in kcal/mol. The value in parentheses is relative to the reference compounds. All other values are relative to the reported Int1.

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Table S3. Computed energetic values for styrene.

Filename	E <sub>GP</sub> (Ha)	E <sub>PCM</sub> (Ha)	E <sub>TZ</sub> (Ha)	i <sub>Freq</sub> (cm <sup>-1</sup> )	G <sub>corr</sub> (Ha)	G <sub>final</sub> (Ha)	$\Delta G_{\mathrm{rel}}{}^{a}$
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

<sup>&</sup>lt;sup>a</sup> The relative Gibbs energies ( $\Delta G_{rel}$ ) 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 <sub>GP</sub> (Ha)	E <sub>PCM</sub> (Ha)	E <sub>TZ</sub> (Ha)	i <sub>Freq</sub> (cm <sup>-1</sup> )	G <sub>corr</sub> (Ha)	G <sub>final</sub> (Ha)	$\Delta G_{rel}{}^a$
Apsyn_Int1	-1468.13957	-1468.19185	-1468.55045	0	0.37137	-1468.22835	0.0(-18.3)
Apsyn_TS1_Cl-CH2Cl	-2372.46696	-2372.52497	-2372.93751	1(-91.9)	0.39174	-2372.60078	14.2
Apsyn_Int2_Cl-CH2Cl	-2372.47611	-2372.53376	-2372.94537	0	0.39316	-2372.60685	10.3
Apsyn_TS2_Cl-CH2Cl	-2372.45951	-2372.51855	-2372.92942	1(-140.6)	0.39489	-2372.59056	20.6
Apsyn_Int3_Cl-CH2Cl	-2372.47318	-2372.53130	-2372.94403	0	0.39518	-2372.60396	12.2
Apsyn_TS3_Cl-CH2Cl	-2372.47238	-2372.52978	-2372.94212	1(-105.2)	0.39575	-2372.60077	14.2
Apsyn_TS-OS_Cl-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_Cl-CH2Cl	-2372.46938	-2372.52486	-2372.93888	1(-123.5)	0.39319	-2372.59815	19.4
Apanti_Int2_Cl-CH2Cl	-2372.48146	-2372.53599	-2372.94943	0	0.39495	-2372.60599	14.5
Apanti_Int3_Cl-CH2Cl	-2372.47158	-2372.52863	-2372.94162	0	0.39833	-2372.59733	19.9

Apanti_TS3_Cl-CH2Cl	-2372.47057	-2372.52705	-2372.93949	1(-106.5)	0.39790	-2372.59506	21.4
Apanti_TS-OS_Cl-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_Cl-CH2Cl	-2372.46329	-2372.52207	-2372.93530	1(-111.2)	0.39281	-2372.59826	15.1
Eqtrans_Int2_Cl-CH2Cl	-2372.47439	-2372.53201	-2372.94494	0	0.39384	-2372.60572	10.4
Eqtrans_Int3_Cl-CH2Cl	-2372.47350	-2372.53020	-2372.94393	0	0.39879	-2372.59883	14.7
Eqtrans_TS3_Cl-CH2Cl	-2372.47257	-2372.52864	-2372.94182	1(-109.0)	0.39897	-2372.59591	16.5
Eqtrans_TS-OS_Cl-CH2Cl	-2505.24693	-2505.30234	-2505.75979	1(-407.6)	0.43074	-2505.38145	17.6

<sup>&</sup>lt;sup>a</sup> The relative Gibbs energies ( $\Delta G_{rel}$ ) 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 $\alpha,\alpha$ -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.

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 Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL), saturated aqueous solution of NaHCO<sub>3</sub> (20 mL) and finally dried over MgSO<sub>4</sub>. 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.

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(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<sub>4</sub> (2.4 g, 20 mmol, 1.0 equiv.) in Et<sub>2</sub>O (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<sub>4</sub>Cl aq. (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, and

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 NaHCO<sub>3</sub> aq. (2 x 30 mL), and brine (30 mL). The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, 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.

$$\begin{array}{c} \text{NaN}_3 \text{ (1.2 equiv.)} \\ \text{TBAI (5 mol\%)} \\ \text{toluene/H}_2\text{O, 0 °C, 5 h} \end{array} \\ \begin{array}{c} \text{N}_3 \\ \text{O} \end{array} \\ \begin{array}{c} \text{BnOH (1.2 equiv.)} \\ \text{Hydroquinone (5 mol\%)} \\ \text{Pyridine (6 mol\%)} \\ \text{toluene, 110 °C, 0.5 h} \end{array} \\ \begin{array}{c} \text{BnO} \\ \text{N} \\ \text{H} \end{array}$$

The mixture of acryloyl chloride (450 mg, 5.0 mmol, 1.0 equiv.) and tert-butyl amonium 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  $Na_2SO_4$  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  $\mu$ L, 0.3 mmol, 6 mol%), and benzyl alcohol (625 uL, 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.

(CH<sub>2</sub>O)<sub>n</sub> (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<sub>2</sub>NH (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<sub>2</sub>SO<sub>4</sub>. 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.

Acrylate chloride (2.0 equiv.) H Mel (1.1 equiv.) NH2 
$$K_2CO_3$$
 (2.0 equiv.) H N NaH (1.1 equiv.) THF, 0 °C to r.t, 1 h O 11ak

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<sub>2</sub>SO<sub>4</sub>, 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  $\mu$ L, 2.2 mmol, 1.1 equiv.) was added dropwise at 0 °C, and the mixture was stirred at room temperature for 1 h.

Deionized water (2 mL) was slowly added to quench the reaction. THF was removed by reduced pressure. Ethyl acetate (5 mL) was added to the crude mixture and transferred to a separatory funnel. The organic phase was washed with HCl 2 M aqueous solution (3 mL), H<sub>2</sub>O (5 mL) and brine (5 mL). The organic phase was collected and dried over anhydrous MgSO<sub>4</sub> and the solvent was removed by reduced pressure. The crude material was purified by column chromatography on silica gel (1:1 hexane/ethyl acetate) to afford **11aj** (240 mg, 75%) as colorless oil. The NMR spectra is consistent with reported literature.

$$\begin{array}{c} O \\ \hline \\ N \\ H \\ \end{array} \begin{array}{c} O \\ \hline \\ TMSCH_2CI \ (2.0 \ equiv.) \\ \hline \\ THF, \ -78 \ ^{\circ}C \ to \ r.t, \ 3 \ h \\ \end{array} \begin{array}{c} HO \\ \hline \\ N \\ H \\ \end{array} \begin{array}{c} TMS \\ \hline \\ DCM, \ -78 \ ^{\circ}C, \ 12 \ h \\ \end{array} \begin{array}{c} O \\ \hline \\ N \\ H \\ \end{array} \begin{array}{c} O \\ \hline \\ 11al \\ \end{array}$$

To a solution of isatin (740 mg, 5 mmol, 1.0 equiv.) in THF (20 mL) was added a solution of TMSCH<sub>2</sub>MgCl in diethyl ether (1.0 M, 10 mL, 10 mmol, 2.0 equiv.) at -78 °C and the mixture was stirred for 15 min at -78 °C then for 3 h at room temperature. The reaction was quenched by the addition of MeOH. After removal of the solvent, the residue was subjected to column chromatography (PE/AcOEt 50:50) to give 3-hydroxy-3-trimethylsilylmethyloxindole (530 mg, 45%) as a yellow solid.

To a solution of 3-hydroxy-3-trimethylsilylmethyloxindole (530 mg, 2.26 mmol, 1.0 equiv.) in DCM (50 mL) was added BF<sub>3</sub>OEt<sub>2</sub> (850 μL, 6.78 mmol, 3.0 equiv.) at -78 °C and the mixture was stirred for 12 h at -78 °C then for 1 h at 0 °C. The reaction was quenched by the addition of sat. aq. NaHCO<sub>3</sub> and the organic compounds were extracted with DCM (3×30 mL) and the combined organic layers were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent, **11al** (241 mg, 73%) was obtained as a yellow solid. The NMR spectra is consistent with reported literature.

To a solution of Boc-Ser-OMe in dry acetonitrile, of 0.1 eq. DMAP was added followed by 2.2 eq. of tert-butyl pyrocarbonate under rapid stirring at room temperature. The reaction was stirred for 12 h while monitored by TLC (diethyl ether:*n*-hexane, 50 50). Evaporation under reduced pressure

gave a residue that was partitioned between 200 mL of diethyl ether and 100 mL of KHSO<sub>4</sub> (1 M). The organic phase was thoroughly washed with 50 mL KHSO<sub>4</sub> (1 M), 50 mL NaHCO<sub>3</sub> (1 M) and saturated brine (3×50 mL), and dried over MgSO<sub>4</sub>. 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<sub>3</sub> (1 M) and brine (3×30 mL each). After drying over MgSO<sub>4</sub> 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  $\alpha$ -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<sub>2</sub>SO<sub>4</sub>, concentrated. The residue was purified by column chromatography on silica gel (pentane) to afford the  $\alpha$ -(fluoromethyl)styrene **11aq** (789 mg, 58%) as colorless oil. The NMR spectra is consistent with reported literature.

*n*-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

h, the reaction was quenched with NH<sub>4</sub>Cl (20 mL), extracted with Et<sub>2</sub>O (3×50mL), dried over Na<sub>2</sub>SO<sub>4</sub>, 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<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>O. The organic layer was separated and aqueous layer was extracted with Et<sub>2</sub>O (3×10mL), combined the organic phases and washed t with 1N HCl (20 mL) and brine (20 mL), dry over Na<sub>2</sub>SO<sub>4</sub>, 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. <sup>291,199</sup>

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

<sup>&</sup>lt;sup>291</sup> J. Zhang, J. Wu, L. Shen, G. Jin, S. Cao, Adv. Synth. Catal. **2011**, 353, 580–584.

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 Et<sub>2</sub>O (4×50 mL). Organic layers were combined and washed successively with H<sub>2</sub>O (3×50 mL) and brine (50 mL), dried over MgSO<sub>4</sub>, 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 LiAlH<sub>4</sub> (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 H<sub>2</sub>O (20 mL). Then, the reaction mixture was extracted with Et<sub>2</sub>O (3×50 mL). The organic layers were recombined, washed with brine (50mL), and dried over MgSO<sub>4</sub>. 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/ H<sub>2</sub>O (56 mL) was added dropwise 7.8 mL aq. 30% H<sub>2</sub>O<sub>2</sub>. 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 NaHCO<sub>3</sub> (30 mL), and extracted with EtOAc (3×40 mL). The organic extracts were recombined, washed with brine (60 mL), dried over MgSO<sub>4</sub> 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, Tf<sub>2</sub>O (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 NH<sub>3</sub>•H<sub>2</sub>O (28%~30%) was added. The reaction mixture was stirred for 48 h at room temperature, then quenched with H<sub>2</sub>O (50 mL), and extracted with DCM (3×50mL). The organic layers were

recombined, washed with brine (60 mL), dried over MgSO<sub>4</sub>, 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 Et<sub>2</sub>O (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 Et<sub>2</sub>O (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 H<sub>2</sub>O (2 mL) was added NaNO<sub>2</sub> (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 MgSO<sub>4</sub>, 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.<sup>292</sup> 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  $CF_3CH_2OH/H_2O$  (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.

<sup>&</sup>lt;sup>292</sup> C. Lin, Z. Lin, Z. Ye, L. Chen, Y. Li, C. Shen, M. Zhang, *Tetrahedron Lett.* **2022**, 154197.

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Synthesis of 16 was following the reported procedures. <sup>293,294</sup>

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  $Et_2O$  (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*-((1*H*-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% NaHCO<sub>3</sub> (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 MgSO<sub>4</sub>. 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<sup>-3</sup> mBar, temperature=115–120°C) give ethyl 3-(dibenzylamino)-2,2-

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<sup>&</sup>lt;sup>293</sup> A. R. Katritzky, K. Yannakopoulou, P. Lue, D. Rasala, L. Urogdi, J. Chem. Soc., Perkin Trans. 1 1989, 225–233.

<sup>&</sup>lt;sup>294</sup> A. Cheguillaume, S. Lacroix, J. Marchand-Brynaert, *Tetrahedron Lett.* **2003**, 44, 2375–2377.

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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)<sub>2</sub> (20 wt.% on carbon) (738 mg, 4.25 mmol, 5 mol%). After 36 h of stirring under H<sub>2</sub> 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 <sup>1</sup>H 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, Rh<sub>2</sub>(Opiv)<sub>4</sub> (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

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 temperture. 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, 12m, 12p, 12q, 12r, 12s, 12t, 12u, 12v, 12w, 12x, 12y, 12z.

 $((\mathsf{difluoro}((1R,\!2R)\!-\!2\!-\!\mathsf{phenylcyclopropyl})\mathsf{methyl}) \mathsf{sulfonyl}) \mathsf{benzene}$ 

12a. This cyclopropane was obtained using the general procedure, (22.6 mg, 74%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.43 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 74-76 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -116.5 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -106.3 (d, J = 13.4 Hz).

**HRMS** (EI<sup>+</sup>) calcd for  $C_{16}H_{14}F_{2}O_{2}S$  ([M]<sup>+</sup>) 308.06826, found: 308.06748 ( $\Delta$ -2.50 ppm).

IR (neat) 2963, 2926, 2856, 1336, 1163, 1073, 1005, 996, 711, 685, 598 cm<sup>-1</sup>.

1-((1R,2R)-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<sub>2</sub>O 95:5 to 90:15.  $R_f$ = 0.25 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 94-96 °C.  $|\alpha|^{20}_D$  = -106.2 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.6 (dd, J = 228.5, 13.2 Hz), -106.7 (dd, J = 228.5, 13.7 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>O<sub>3</sub>S ([M]<sup>+</sup>) 338.07882, found: 338.07954 (Δ2.13 ppm). IR (neat) 2966, 2925, 2861, 1516, 1330, 1249, 1107, 1029, 719, 588 cm<sup>-1</sup>.

1-((1R,2R)-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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.35 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 77-79 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -109.3 (c = 1.0, CHCl<sub>3</sub>).

Enantiomeric Ratio: 96.5:3.5. The enantiomeric ratio was determined by HPLC with a Chiralcel

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IC column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min),  $t_R$  = 7.6 min,  $t_R$  = 8.2 min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.8 (dd, J = 228.4, 13.1 Hz), -106.63 (dd, J = 228.5, 13.3 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 322.08391, found: 322.08262 (Δ-4.00 ppm). IR (neat) 2963, 2925, 2860, 1336, 1161, 1074, 998, 811, 682, 597 cm<sup>-1</sup>.

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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.37 (Pentane/ Et<sub>2</sub>O = 5:1). Colorless oil. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -97.3 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.6 (dd, J = 228.7, 13.1 Hz), -106.8 (dd, J = 228.7, 13.7 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 322.08391, found: 322.08380 (Δ-0.34 ppm). IR (neat) 2964, 2924, 2861, 1336, 1167, 1085, 1009, 721, 685, 594 cm<sup>-1</sup>. -----

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/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.38 (Pentane/ Et<sub>2</sub>O = 5:1). Colorless oil. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -80.0 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -102.1 (dd, J = 228.2, 10.1 Hz), -108.7 (dd, J = 228.2, 16.8 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>17</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 322.08391, found: 322.08557 (Δ5.17 ppm). IR (neat) 2960, 2925, 2861, 1336, 1163, 1084, 1007, 717, 685, 583 cm<sup>-1</sup>.

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/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.36 (Pentane/ Et<sub>2</sub>O = 5:1). Light yellow solid. M.p. 76-78 °C.  $[\alpha]^{20}_D$  = -118.4 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 137.3, 135.4, 133.1, 132.8, 130.8, 129.5, 128.8, 128.4, 122.7 (t, J

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= 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.4 (dd, J = 228.8, 12.3 Hz), -107.4 (dd, J = 228.8, 14.1 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>ClF<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 342.02928, found: 342.02989 (Δ1.77 ppm). IR (neat) 2963, 2922, 2852, 1338, 1162, 1074, 1007, 822, 685, 589 cm<sup>-1</sup>.

1-bromo-4-((1R,2R)-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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.36 (Pentane/ Et<sub>2</sub>O = 5:1). Ligh yellow solid. M.p. 85-86 °C.  $|\alpha|^{20}_D$  = -113.7 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.4 (dd, J = 228.8, 12.4 Hz), -107.4 (dd, J = 228.8, 14.1 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>BrF<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 385.97877, found: 385.98026 (Δ3.86 ppm). IR (neat) 2960, 2924, 2852, 1337, 1162, 1073, 1007, 818, 685, 587 cm<sup>-1</sup>.

1-((1R,2R)-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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.36 (Pentane/ Et<sub>2</sub>O = 5:1). Light yellow solid. M.p. 83-85 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -106.1 (c = 1.0, CHCl<sub>3</sub>).

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.5 (dd, J = 228.8, 12.5 Hz), -107.3 (dd, J = 228.8, 14.0 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>IF<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 433.96490, found: 433.96541 (Δ1.18 ppm). IR (neat) 2962, 2924, 2855, 1336, 1161, 1074, 1004, 815, 684, 608, 583 cm<sup>-1</sup>.

1-bromo-3-((1R,2R)-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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.35 (Pentane/ Et<sub>2</sub>O = 5:1). Light yellow solid. M.p. 83-85 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -59.4 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -102.8 (dd, J = 228.4, 10.8 Hz), -108.6 (dd, J = 228.4, 15.8 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>BrF<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 385.97877, found: 385.98030 (Δ3.97 ppm). IR (neat) 2960, 2923, 2853, 1333, 1159, 1071, 1006, 751, 682, 590 cm<sup>-1</sup>.

1-bromo-2-((1R,2R)-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/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f = 0.34$  (Pentane/ Et<sub>2</sub>O = 5:1). Yellow oil.  $|\alpha|^{20}D = -87.1$  (c = 1.0, CHCl<sub>3</sub>).

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.9 (dd, J = 229.2, 12.7 Hz), -107.2 (dd, J = 229.2, 13.7 Hz).

HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>BrF<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 385.97877, found: 385.98022 (Δ3.75 ppm).

IR (neat) 2960, 2925, 2854, 1336, 1162, 1071, 1008, 779, 684, 594 cm<sup>-1</sup>.

1,3-dichloro-2-((1R,2R)-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/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.42 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 79-81 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -57.4 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -98.3 (dd, J = 228.7, 2.7 Hz), -114.7 (dd, J = 228.7, 22.2 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 375.99031, found: 375.99184 (Δ1.53 ppm). IR (neat) 2961, 2924, 2854, 1427, 1333, 1069, 991, 740, 615, 580 cm<sup>-1</sup>.

4-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-1,1'-biphenyl

121. This cyclopropane was obtained using the general procedure, (24.7 mg, 64%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.35 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 158-160 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -124.0 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.8 (dd, J = 226.4, 11.0 Hz), -106.68 (dd, J = 226.4, 11.1 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>22</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 384.09956, found: 384.10118 ( $\Delta$ 4.22 ppm). IR (neat) 2958, 2924, 2853, 1337, 1161, 1075, 996, 829, 682, 600 cm<sup>-1</sup>.

2-(4-((1R,2R)-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<sub>2</sub>O 90:10 to 83:17).  $R_f$ = 0.49

(Pentane/ Et<sub>2</sub>O = 3:1). White solid. M.p. 120-122 °C.  $[\alpha]^{20}$ <sub>D</sub> = -78.5 (c = 1.0, CHCl<sub>3</sub>).

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  7.97 (d, J = 7.4 Hz, 2H), 7.78 – 7.70 (m, 3H), 7.59 (t, J = 7.7 Hz,

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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -106.0 (dd, J = 229.3, 13.0 Hz), -107.1 (dd, J = 229.3, 13.5 Hz). HRMS (AP<sup>+</sup>) calcd for C<sub>22</sub>H<sub>26</sub>O<sub>4</sub>F<sub>2</sub>S<sup>10</sup>B ([M+H]<sup>+</sup>) 434.1649, found: 434.1658 (Δ2.1 ppm).

IR (neat) 2975, 2924, 2852, 1359, 1344, 1165, 1081, 1011, 725, 689, 592 cm<sup>-1</sup>.

1-((1R,2R)-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<sub>2</sub>O 98:2 to 85:15).  $R_f = 0.37$ (Pentane/ Et<sub>2</sub>O = 5:1). Colorless oil.  $[\alpha]^{20}_D = -100.1$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -63.0 (s, CF<sub>3</sub>), -105.5 (dd, J = 229.0, 12.2 Hz), -107.6 (dd, J = 229.0, 14.0 Hz).

**HRMS (EI**<sup>+</sup>) calcd for  $C_{17}H_{13}F_4O_2S$  ([M]<sup>+</sup>) 357.05724, found: 357.05751 ( $\Delta 0.76$  ppm). **IR (neat)** 2966, 2927, 2858, 1323, 1162, 1119, 1067, 830, 685, 588 cm<sup>-1</sup>.

12

1-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)-4-nitrobenzene

**20**. This cyclopropane was obtained using the general procedure, (9.2 mg, 26%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 90:10 to 75:25).  $R_f$ = 0.43 (Pentane/ Et<sub>2</sub>O = 3:1). Colorless oil.  $|\alpha|^{20}D$  = -102.3 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -105.3 (dd, J = 229.4, 11.9 Hz), -108.1 (dd, J = 229.1, 14.3 Hz).

**HRMS (EI**<sup>+</sup>) calcd for  $C_{16}H_{13}F_2NO_4S$  ([M]<sup>+</sup>) 353.05333, found: 353.05347 ( $\Delta 0.39$  ppm).

IR (neat) 2965, 2924, 2854, 1520, 1336, 1161, 1088, 1008, 685, 593.

1-((1R,2R)-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/ Et<sub>2</sub>O 90:10 to 75:25).  $R_f$ = 0.42 (Pentane/ Et<sub>2</sub>O = 3:1). Yellow solid. M.p. 83-85 °C.  $|\alpha|^{20}_D$  = -75.9 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.1 (dd, J = 229.4, 11.5 Hz), -108.1 (dd, J = 229.3, 14.5 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>16</sub>H<sub>13</sub>F<sub>2</sub>NO<sub>4</sub>S ([M]<sup>+</sup>) 353.05333, found: 353.05425 (Δ2.6 ppm). IR (neat) 2960, 2922, 2852, 1533, 1332, 1161, 1009, 732, 683, 609 cm<sup>-1</sup>.

12q

2-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)naphthalene

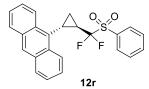
12q. This cyclopropane was obtained using the general procedure, (29.7 mg, 83%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 98:2 to 90:10).  $R_f$ = 0.41 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 112-114 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -123.3 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.8 (dd, J = 228.9, 13.3 Hz), -106.7 (dd, J = 228.9, 13.5 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>20</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 358.08391, found: 358.08413 ( $\Delta$ 0.64 ppm). IR (neat) 2961, 2923, 2853, 1336, 1162, 1074, 996, 824, 682, 596 cm<sup>-1</sup>.



9-((1R,2R)-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/ Et<sub>2</sub>O 98:2 to 90:10).  $R_f$ = 0.43 (Pentane/ Et<sub>2</sub>O = 5:1). Brown solid. M.p. 88-90 °C. [ $\alpha$ ]<sup>20</sup>D = -43.1 (c = 1.0, CHCl<sub>3</sub>).

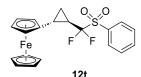
**Enantiomeric Ratio:** 95.5:4.5. The enantiomeric ratio was determined by HPLC with a Chiralcel IC column (n-heptane: i-PrOH = 95:5, 220 nm, 1 mL/min),  $t_R$  = 8.6 min,  $t_R$  = 11.0 min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  8.57 (d, J = 9.0 Hz, 2H), 8.41 (s, 1H), 8.10 (d, J = 7.5 Hz, 2H),

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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -97.2 (dd, J = 229.1, 2.5 Hz), -114.1 (dd, J = 229.1, 23.4 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>24</sub>H<sub>18</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 408.09956, found: 408.09822 (Δ-1.34 ppm). IR (neat) 2958, 2923, 2853, 1338, 1165, 1057, 1008, 736, 684, 589 cm<sup>-1</sup>.



(1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)ferrocene

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<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.40 (Pentane/ Et<sub>2</sub>O = 5:1). Brown solid. M.p. 111-113 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -27.4 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -103.5 (dd, J = 227.9, 11.3 Hz), -107.8 (dd, J = 227.9, 16.0 Hz). HRMS (ES<sup>+</sup>) calcd for C<sub>20</sub>H<sub>18</sub>O<sub>2</sub>F<sub>2</sub>S<sup>56</sup>Fe ([M]<sup>+</sup>) 416.0345, found: 416.0354 (Δ2.2 ppm). IR (neat) 2962, 2922, 2853, 1336, 1162, 1073, 1010, 819, 685, 685 cm<sup>-1</sup>.

 $2\hbox{-}((1R,2R)\hbox{-}2\hbox{-}(difluoro(phenylsulfonyl)methyl)cyclopropyl) benzofuran$ 

12u. This cyclopropane was obtained using the general procedure, (32.1 mg, 92%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 98:2 to 85:15). R<sub>f</sub>= 0.33 (Pentane/ Et<sub>2</sub>O = 5:1). Light yellow solid. M.p. 77-79 °C.  $[\alpha]^{20}_D$  = -146.9 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  8.00 (d, J = 7.7 Hz, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.7Hz, 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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 = 5.9, 2.0 Hz)5.4, 1.7 Hz).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -106.2 (dd, J = 230.2, 12.5 Hz), -108.2 (dd, J = 230.1, 14.0 Hz). **HRMS** (AP<sup>+</sup>) calcd for  $C_{18}H_{15}O_3F_2S$  ([M+H]<sup>+</sup>) 349.0710, found: 349.0700 ( $\Delta$ -2.9 ppm). IR (neat) 2953, 29243 2855, 1335, 1166, 1077, 1012, 789, 754, 595 cm<sup>-1</sup>.

((1R,2R)-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/ Et<sub>2</sub>O 98:2 to 80:20). R<sub>f</sub>= 0.28 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 77-79 °C.  $[\alpha]^{20}$ <sub>D</sub> = -70.0 (c = 1.0, CHCl<sub>3</sub>).

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) & 196.5, 137.0, 135.6, 133.7, 132.9, 130.9, 129.5, 128.9, 128.5, 122.1

(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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -105.8 (dd, J = 231.8, 12.6 Hz), -107.3 (dd, J = 231.8, 13.6 Hz).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{17}H_{15}O_3F_2S$  ([M+H]<sup>+</sup>) 337.0710, found: 337.0710 ( $\Delta 0$  ppm).

IR (neat) 2953, 2922, 2853, 1674, 1337, 1168, 1095, 1009, 733, 596 cm<sup>-1</sup>.

benzyl ((1R,2R)-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.  $[\alpha]^{20}_D = -46.8$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -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.  $[\alpha]^{20}D = -7.2$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -94.6 (d, J = 232.4 Hz), -104.5 (dd, J = 232.5, 18.6 Hz).

**HRMS (AP**<sup>+</sup>) calcd for  $C_{18}H_{18}NO_4F_2S$  ([M+H]<sup>+</sup>) 382.0925, found: 382.0916 ( $\Delta$ -2.4 ppm).

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IR (neat) 3314, 2960, 2924, 2854, 1699, 1521, 1335, 1164, 1009, 737, 682, 590 cm<sup>-1</sup>.

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.  $[\alpha]^{20}_D$  = -58.8 (c = 0.5, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -103.7 (dd, J = 231.7, 10.4 Hz), -109.4 (dd, J = 231.7, 16.4 Hz). HRMS (AP<sup>+</sup>) calcd for C<sub>18</sub>H<sub>14</sub>NO<sub>4</sub>F<sub>2</sub>S ([M+H]<sup>+</sup>) 378.0612, found: 378.0617 (Δ1.3 ppm).

IR (neat) 2961, 2922, 2853, 1716, 1338, 1163, 1088, 1006, 713, 686, 590 cm<sup>-1</sup>.

12x

 $((\mathsf{difluoro}((1R,2S)\text{-}2\text{-}((E)\text{-}\mathsf{styryl})\mathsf{cyclopropyl})\mathsf{methyl})\mathsf{sulfonyl})\mathsf{benzene}$ 

12x. This cyclopropane was obtained using the general procedure, (28.5 mg, 85%) was obtained as separated fractions after silica gel column chromatography (Pentane/ Et<sub>2</sub>O 98:2 to 85:15).  $R_f$ = 0.44 (Pentane/ Et<sub>2</sub>O = 5:1). White solid. M.p. 70-72 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -100.1 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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). <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -105.7 (dd, J = 229.2, 13.0 Hz), -107.2 (dd, J = 229.2, 13.9 Hz). HRMS (EI<sup>+</sup>) calcd for C<sub>18</sub>H<sub>16</sub>F<sub>2</sub>O<sub>2</sub>S ([M]<sup>+</sup>) 334.08391, found: 334.08462 (Δ2.15 ppm). IR (neat) 2961, 2923, 2853, 1336, 1166, 1116, 994, 714, 606, 593 cm<sup>-1</sup>.

(1R,2R)-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<sub>2</sub>O 98:2 to 80:20).  $R_f$ = 0.40 (Pentane/ Et<sub>2</sub>O = 3:1). White solid. M.p. 46-48 °C. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -26.4 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>**H NMR (300.1 MHz, CDCl<sub>3</sub>)**  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -103.6 (dd, J = 232.8, 12.1 Hz), -107.5 (dd, J = 232.7, 15.3 Hz). HRMS (AP<sup>+</sup>) calcd for C<sub>12</sub>H<sub>13</sub>F<sub>2</sub>O<sub>4</sub>S ([M+H]<sup>+</sup>) 291.05026, found: 291.05179 (Δ5.26 ppm). IR (neat) 2962, 2925, 2854, 1751, 1335, 1219, 1161, 992, 713, 684, 592 cm<sup>-1</sup>.

((difluoro((1R,2R)-2-phenoxycyclopropyl)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<sub>2</sub>O 98:2 to 80:20).  $R_f$ = 0.52 (Pentane/ Et<sub>2</sub>O =5:1). Colorless oil. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -28.3 (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -101.4 (dd, J = 232.5, 10.4 Hz), -107.6 (dd, J = 232.5, 17.5 Hz).

**HRMS** (EI<sup>+</sup>) calcd for  $C_{16}H_{14}F_2O_3S$  ([M]<sup>+</sup>) 324.06317, found: 324.06392 ( $\Delta 2.3$  ppm).

IR (neat) 2960, 2922, 2854, 1449, 1338, 1244, 1166, 1008, 753, 684, 592 cm<sup>-1</sup>.

#### 3. General procedures of the post-fucntionalization reactions

#### 3.1. Synthesis of compound 20

To a 10 mL tube with a stirring bar was charged Pd(Ph<sub>3</sub>)<sub>4</sub> (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 MgSO<sub>4</sub>. 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.  $[\alpha]^{20}_D = -130.9$  (c = 1.0, CHCl<sub>3</sub>).

5-(4-((1R,2R)-2-(difluoro(phenylsulfonyl)methyl)cyclopropyl)phenyl)thiophene-2-carbaldehyde

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -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),  $t_R$  = 27.5 min,  $t_R$  = 29.8 min.

**HRMS** (EI<sup>+</sup>) calcd for  $C_{18}H_{16}F_2O_2S$  ([M]<sup>+</sup>) 418.05094, found: 418.05120 ( $\Delta 0.62$  ppm).

IR (neat) 2962, 2922, 2853, 1668, 1450, 1334, 1164, 1009, 807, 683, 589 cm<sup>-1</sup>.

#### 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<sub>4</sub>Cl solution, washed by water and then dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure and the residue was purified by a flash column chromatography (Et<sub>2</sub>O/pentane, 10:90 to 25:75) to give product **21** as a white solid (34.0 mg, 82%). M.p. 94-96 °C.  $|\alpha|^{20}$ <sub>D</sub> = -54.2 (c = 1.0, CHCl<sub>3</sub>)

((1R,2R)-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),  $t_R$  = 21.9 min,  $t_R$  = 31.1 min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -103.3 (dd, J = 227.5, 11.8 Hz), -106.44 (dd, J = 227.5, 15.8 Hz). HRMS (Ei<sup>+</sup>) calcd for C<sub>23</sub>H<sub>20</sub>F<sub>2</sub>O<sub>3</sub>S ([M]<sup>+</sup>) 414.11012, found: 414.11034 ( $\Delta$ 0.53 ppm). IR (neat) 3524, 2960, 2923, 2853, 1447, 1330, 1163, 1010, 1006, 752, 683, 586 cm<sup>-1</sup>.

## 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. nBuLi (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<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O (3×5 mL), combined organic layers washed with brine (10 mL) and dried over MgSO<sub>4</sub>. The solution was filtered and removed the solvent under vacuo evaporated. The residue was purified through a silica-gel flash column chromatography (Et<sub>2</sub>O/pentane, 2:98 to 10:90), affording product **26** as a white solid (29.6 mg, 89%). M.p. 56-58 °C.  $|\alpha|^{20}$ <sub>D</sub> = -69.5 (c = 1.0, CHCl<sub>3</sub>).

 $((\mathsf{difluoro}((1R,2R)\text{-}2\text{-}(1\text{-}\mathsf{phenylvinyl})\mathsf{cyclopropyl})\mathsf{methyl})\mathsf{sulfonyl})\mathsf{benzene}$ 

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -102.7 (dd, J = 228.6, 10.4 Hz), -108.4 (dd, J = 228.6, 16.5 Hz).

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**HRMS** (EI<sup>+</sup>) calcd for  $C_{18}H_{16}F_2O_2S$  ([M]<sup>+</sup>) 334.08391, found: 334.08482 ( $\Delta 2.73$  ppm).

IR (neat) 2961, 2926, 2855, 1337, 1165, 1074, 1006, 704, 684, 594 cm<sup>-1</sup>.

#### 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 NaBH<sub>4</sub> (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 H<sub>2</sub>O 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 MgSO<sub>4</sub>, filtered and evaporated under vacuum. The residue was purified by silica-gel flash column chromatography (Et<sub>2</sub>O/pentane, 10:90 to 25:75) to give alcohol product **27** as a colorless oil (58.4 mg, 86%, *syn/ anti* 72/28).

 $((1R,\!2R)\!-\!2\!-\!(difluoro(phenylsulfonyl)methyl)cyclopropyl)(phenyl)methanol$ 

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

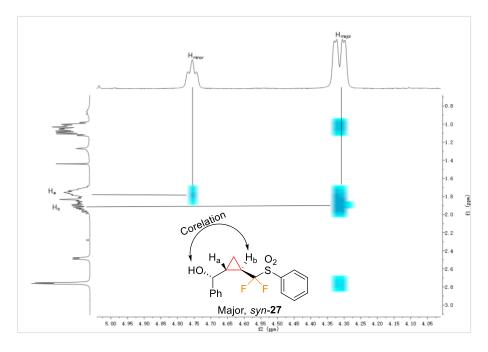
<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  142.4 (*syn*), 142.3 (*anti*), 135.5 (*syn*), 135.3 (*anti*), 133.0 (*anti*), 132.7 (*syn*), 130.8 (*syn*), 130.7 (*anti*), 129.4 (*syn*), 129.4 (*anti*), 128.6 (*syn*), 128.6 (*anti*), 128.1 (*syn*), 128.1 (*anti*), 126.3 (*anti*), 126.1 (*syn*), 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).

<sup>19</sup>**F NMR (282.4 MHz, CDCl<sub>3</sub>)** 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).

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**HRMS** (EI<sup>+</sup>) calcd for  $C_{17}H_{16}F_2O_3S$  ([M]<sup>+</sup>) 338.07882, found: 338.07996 ( $\Delta 3.37$  ppm).

IR (neat) 3542, 3064, 2888, 1449, 1333, 1164, 1056, 1008, 731, 684, 594 cm<sup>-1</sup>.



#### 3.4. Synthesis of compound 28

To a solution of phenyl sulfonyl compoumd (1.0 equiv.) in MeOH (1 mL) in a 10 mL tube was added Na<sub>2</sub>HPO<sub>4</sub> (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 H<sub>2</sub>O and stirred another one hour, and extracted with Et<sub>2</sub>O (2×10 mL). The combined organic layer was washed with brine (10 mL), and then dried over anhydrous MgSO<sub>4</sub>, filtered and evaporated carefully under vacuum to afford difluoromethyl cyclopropane **28a** or **28c**. Difluoromethyl cyclopropane **28b** was purified by silica-gel flash column chromatography.

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. [ $\alpha$ ]<sup>20</sup><sub>D</sub> = -12.3 (c = 1.0, CHCl<sub>3</sub>).

Enantiomeric Ratio: 94:6. The enantiomeric ratio was determined by inverse phase HPLC with a Chiralcel OJ-3R column (H<sub>2</sub>O: MeCN = 50:50 (0.1% formic acid), 220 nm, 0.8 mL/min),  $t_R = 10.5$  min,  $t_R = 11.3$  min.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -115.5 (ddd, J = 280.6, 56.1, 10.6 Hz), -116.7 (ddd, J = 280.6, 57.2, 10.8 Hz).

**HRMS** (EI<sup>+</sup>) calcd for  $C_{10}H_{10}F_2$  ([M]<sup>+</sup>) 168.07506, found: 168.07619 ( $\Delta$ 6.74 ppm).

IR (neat) 2962, 2927, 2856, 1377, 1102, 1030, 751, 697 cm<sup>-1</sup>.

(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/  $Et_2O = 20:1$ ). Colorless oil.  $[\alpha]^{20}_D = -7.2$  (c = 1.0, CHCl<sub>3</sub>).

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -114.6 (ddd, J = 281.0, 57.5, 10.6 Hz), -115.9 (ddd, J = 281.0,

## **Experimental Part**

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58.3, 11.9 Hz).

**HRMS** (EI<sup>+</sup>) calcd for  $C_{12}H_{12}F_2$  ([M]<sup>+</sup>) 194.09071, found: 194.09082 ( $\Delta 0.58$  ppm).

IR (neat) 2960, 2925, 2853, 1488, 1235, 1143, 1036, 1001, 753, 695 cm<sup>-1</sup>.

((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.  $[\alpha]^{20}_D = -10.2$  (c = 1.0, CHCl<sub>3</sub>).

**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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

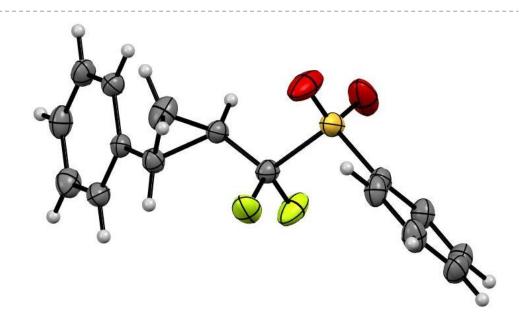
<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -117.2 (dd, J = 12.4, 5.6 Hz), -117.4 (dd, J = 12.4, 5.7 Hz).

**HRMS** (EI<sup>+</sup>) calcd for  $C_{10}H_{10}F_2O$  ([M]<sup>+</sup>) 184.06997, found: 184.07090 ( $\Delta 5.06$  ppm).

IR (neat) 2960, 2926, 2855, 1495, 1239, 1143, 1036, 999, 752, 690 cm<sup>-1</sup>.

## 4. Crystallographic data for compound

((difluoro((1R,2R)-2-phenylcyclopropyl)methyl)sulfonyl)benzene (12a)



Displacement ellipsoids drawn at the 50% probability level

Single crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of CHCl<sub>3</sub> and heptane solution. X-ray diffraction experiments for monocrystal of ((difluoro((1R,2R)-2-phenylcyclopropyl)methyl)sulfonyl)benzene were performed at 150 K with graphitemonochromatized Mo K radiation ( = 0.71073 Å) on a Bruker D8 QUEST diffractometer. Formula C<sub>16</sub>H<sub>14</sub>F<sub>2</sub>O<sub>2</sub>S, formula weight 308.33. Crystal system orthorhombic, space group P 2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>,  $a = 7.3658(7) \text{ Å}, b = 11.9868(12) \text{ Å}, c = 16.4735(18) \text{ Å}, \alpha = -2.5658(7) \text{ Å}, c = 16.4735(18) \text{ Å}, \alpha = -2.5658(7) \text{ Å}, c = 16.4735(18) \text{ Å}, \alpha = -2.5658(12) \text{ Å}, c = 16.4735(18) \text{ Å}, \alpha = -2.5658(12) \text{ Å}, c = 16.4735(18) \text{ Å}, \alpha = -2.5658(12) \text{ Å}, \alpha = -2.5688(12) \text{ Å}, \alpha$ calculated density = 1.408 g/cm<sup>3</sup>, = 0.246 mm<sup>-1</sup>,  $R_{int} = 0.0833$ ,  $R[F^2 \ 2 \ (F^2)] = 0.036$ ,  $wR(F^2)$ = 0.096. Indepedent reflections = 8993. GOF=1.053, 190 parameters, final difference map within 0.479 and -0.332 eÅ-3. The structure was solved using direct methods and refined by full-matrix least-squares analysis on F<sup>2</sup>. Selected bond lengths (Å) 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 hydrozones.

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<sub>3</sub> (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<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by silica gel column chromatography (Petroleum ether/AcOEt = 2:1) to Weinreb's amide <sup>295</sup> 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<sub>3</sub> (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 MgSO4, 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-one<sup>296</sup> 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 sulfonhydrazide (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

<sup>&</sup>lt;sup>295</sup> A. Kondoh, N. Tasato, T. Aoki, M. Terada, *Org. Lett.* **2020**, 22, 5170–5175.

<sup>&</sup>lt;sup>296</sup> 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 CH<sub>2</sub>Cl<sub>2</sub> (10 mL), and the CH<sub>2</sub>Cl<sub>2</sub> solution was washed with 5% NaHCO<sub>3</sub> (3×10 mL), saturated NaCl (aqueous) (2×10 mL), and water (2×10 mL). The organic layer was dried over anhydrous MgSO<sub>4</sub>, 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 tolsylhydrazone **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.<sup>297</sup>

<u>Step 3:</u> **Method B.** To a rapidly stirred suspension of NsNHNH<sub>2</sub> (2.0 mmol, 1.0 equiv) and La(OTf)<sub>3</sub> (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  $1\sim3$  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.<sup>298</sup>

#### 1.2. Synthesis of *N*-sulfonylhydrazones 32 and 34.

$$R \longrightarrow 0 + ArSO_2NHNH_2 \longrightarrow R \longrightarrow R \longrightarrow N^H SO_2Ar$$

MeOH, r.t., 1-2 h

32 or 34

To a stirred solution of ArSO<sub>2</sub>NHNH<sub>2</sub> (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,<sup>299</sup> 32d<sup>300</sup> or 34<sup>231</sup>.

<sup>&</sup>lt;sup>297</sup> J. T. DePinto, W. A. DeProphetis, J. L. Menke, R. J. McMahon, J. Am. Chem. Soc. 2007, 129, 2308–2315.

<sup>&</sup>lt;sup>298</sup> Y. Yang, Z. Liu, A. Porta, G. Zanoni, X. Bi, Chem. Eur. J. **2017**, 23, 9009–9013.

<sup>&</sup>lt;sup>299</sup> E. M. Allouche, A. Al-Saleh, A. B. Charette, *Chem. Commun.* **2018**, *54*, 13256–13259.

<sup>300</sup> Z. Liu, K. R. Babu, F. Wang, Y. Yang, X. Bi, Org. Chem. Front. 2019, 6, 121-124.

## 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 °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 °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<sub>4</sub>Cl (40 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with brine (30 mL), dried over MgSO<sub>4</sub> and filtered. Then the organic layer was concentrated under reduced pressure to afford the crude 2,4-diphenylbut-3-yn-2-ol,<sup>301</sup> 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<sub>2</sub>Cl<sub>2</sub> (40 mL), and the mixture was cooled to 0 °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<sub>4</sub>Cl (40 mL). The aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic layers were washed with brine (30 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure (control temperature below 30 °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.<sup>302</sup>

#### Synthesis of tosylhydrazone sodium salt 37.303

<sup>&</sup>lt;sup>301</sup> S. Sadhukhan, B. Baire, J. Org. Chem. **2022**, 87, 5530–5542.

<sup>&</sup>lt;sup>302</sup> L. Wang, R. Ma, J. Sun, G. Zheng, Q. Zhang, Chem. Sci. **2022**, 13, 3169–3175.

<sup>&</sup>lt;sup>303</sup> 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.

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<sub>2</sub>H<sub>4</sub> (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<sub>2</sub>O (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<sub>3</sub>N (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<sub>4</sub>Cl solution (20ml) was added. The reaction mixture was extracted with cold Et<sub>2</sub>O (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<sub>2</sub>Cl<sub>2</sub>.

# The preparation of Rh(II)-complexes.<sup>232</sup>

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

<sup>&</sup>lt;sup>304</sup> N. Fei, B. Sauter, D. Gillingham, *Chem. Commun.* **2016**, *52*, 7501–7504.

(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 Na<sub>2</sub>SO<sub>4</sub>. 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 Rh<sub>2</sub>(OAc)<sub>4</sub> (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 NaHCO<sub>3</sub> (2×15 mL) and brine (15 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. 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]: Rh<sub>2</sub>(S-TBPTTL)<sub>4</sub> (177 mg, 23% overall yield), Rh<sub>2</sub>(S-CF<sub>3</sub>PTTL)<sub>4</sub> (280 mg, 23% overall yield), Rh<sub>2</sub>(S-CF<sub>3</sub>PTTL TBPTPG)<sub>4</sub> (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 sulfonhydrazone **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 celit and evaporated under reduce pressure. The residue was analyzed by NMR and purified by flash chromatography (petroleum ether/Et<sub>2</sub>O) to yield corresponding alkynyl cyclopropane **30a**.

The racemic alkynylcyclopropane was prepared with Rh<sub>2</sub>(Opiv)<sub>4</sub>.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

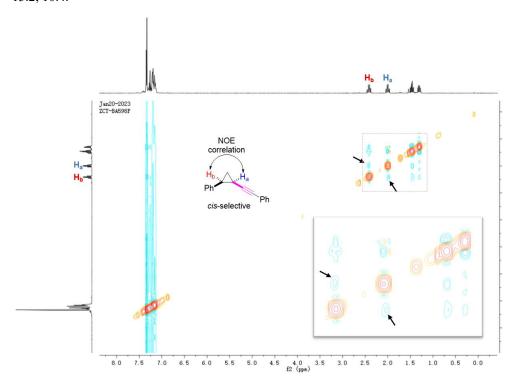
## **Experimental Part**

To an oven-dried 10 mL reaction tube was added sulfonhydrazone **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 celit and evaporated under reduce pressure. The residue was analyzed by NMR and purified by flash chromatography (petroleum ether/Et<sub>2</sub>O) to yield corresponding alkynyl cyclopropane **35a**.

The racemic alkynylcyclopropane was prepared with Rh<sub>2</sub>(Opiv)<sub>4</sub>.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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, Rh<sub>2</sub>(OPiv)<sub>4</sub> (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 <sup>19</sup>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 diasteroisomers 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 <sup>19</sup>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

Synthesis of starting materials 37a, trans-37a, 41a, trans-41a, 41b, trans-41c.

PMBO F

OEt

R-Aminoquinoline (1.5 equiv.)

KHMDS (3.0 equiv.)

Toluene/THF

$$0 \, ^{\circ}$$
C to -78  $^{\circ}$ C to -40  $^{\circ}$ C

 $4.5 \, h$ 
 $R_{f} = CH_{2}F$ 

41b  $R_{f} = CF_{2}H$ 

trans-41c  $R_{f} = CF_{3}H$ 

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 NaHCO<sub>3</sub> and brine, dried over anhydrous MgSO<sub>4</sub>, 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)-41a, (1S, 2R)-41b and *trans*-41c (Note: the diasteroisomers of 41c could be separated by silica-gel chromatography)

 $(\emph{cis}) - 2 - fluoro - 2 - (((4-methoxybenzyl)oxy)methyl) - \textit{N} - (quinolin - 8 - yl)cyclopropane - 1 - carboxamide - ((4-methoxybenzyl)oxy)methyl) - ((4-methoxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl)oxybenzyl$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -195.4 – -195.6 (m, 1F).

IR (neat) 3344, 3010, 2834, 1686, 1608, 1524, 1485, 1245, 1089, 790 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{22}H_{21}FN_2O_3$  m/z 381.1614 ([M+H]<sup>+</sup>) found 381.1611 ( $\Delta$ -0.8 ppm).

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(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.  $[\alpha]^{20}_D = +57.3$  (c = 1).

(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%.  $R_{\rm f}$  = 0.35 (petroleum ether / ethyl acetate, 75/25). Yellow foam.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -173.3 - -173.6 (m, 1F).

(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%.  $R_{\rm f} = 0.35$  (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.  $[\alpha]^{20}_D = +42.6$  (c = 1).

 $(\emph{cis}) \hbox{-} 2 \hbox{-} (fluoromethyl) \hbox{-} \emph{N-} (naphthalen-1-yl) \hbox{-} 2 \hbox{-} phenylcyclopropane-1-carboxamide}$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -214.5 (td, J = 47.7, 5.6 Hz, 1F).

IR (neat) 3344, 1681, 1578, 1522, 1484, 1424, 1164, 826, 791, 695 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{20}H_{17}FN_2O$  m/z 321.1403 ([M+H]<sup>+</sup>) found 321.1402 ( $\Delta$ -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<sub>f</sub> = 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.  $[\alpha]^{20}$ <sub>D</sub> = +23.6 (c = 0.5, CHCl<sub>3</sub>).

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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 (dd)Hz, 1H), 1.52 (dd, J = 8.2, 4.9 Hz, 1H).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -215.0 (td, J = 48.1, 4.0 Hz, 1F).

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{20}H_{16}F_2N_2O$  m/z 339.1309 ([M+H]<sup>+</sup>) found 339.1302 ( $\Delta$ -2.1 ppm).

(1S, 2R)-41b

(1S,2R)-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.  $[\alpha]^{20}_D = +65.8$  (c = 0.5, CHCl<sub>3</sub>).

(+/-) trans-41c

(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%.  $R_{\rm f}$  = 0.56 (petroleum ether / ethyl acetate, 83/17). White solid. Mp: 138 – 140 °C.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -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%.  $R_{\rm f}$  = 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.  $[\alpha]^{20}D = +33.5$  (c = 1).

 $(\emph{cis}) - \emph{N} - (naphthalen-1-yl) - 2 - phenyl-2 - (trifluoromethyl) cyclopropane-1 - carboxamide$ 

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.  $R_{\rm f}$  = 0.45 (petroleum ether / ethyl acetate, 83/17). Yellow foam.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -65.7 (s, 3F).

IR (neat) 3350, 1699, 1584, 1527, 1486, 1300, 1151, 1138, 827, 667 cm<sup>-1</sup>.

**HRMS (ES**<sup>+</sup>) calcd for  $C_{20}H_{15}F_3N_2O$  m/z 357.1203 [M+H]<sup>+</sup>, found 357.1209 ( $\Delta$ 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<sub>3</sub>N in DCM (2.5 mL) was added dropwise. This reaction was stirred at room temperature for 16 h, then quenched with NaHCO<sub>3</sub> (5 mL), extracted with DCM (3×10 mL). The organic layer was dried over MgSO<sub>4</sub> and concentrated in vacuo. The product mixture was purified by silica gel chromatography (Pentane/ EtOAc 80/20) to give the

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

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -56.6 (t, J = 21.7 Hz, CF<sub>3Ar</sub>), -141.1 – -141.5 (m, F<sub>Ar</sub>), -143.15 – -143.58 (m, F<sub>Ar</sub>), -194.73 (s, F<sub>alkyl</sub>).

#### 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-methoxyl-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 NaHCO<sub>3</sub> and brine, dried over anhydrous MgSO<sub>4</sub>, 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

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ -196.03 – -196.32 (m, 1F).

## Synthesis of the starting material (1S, 2R)-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 <sup>19</sup>F 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 MgSO<sub>4</sub>, 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 <sup>19</sup>F NMR analysis. The solvent was removed by vacuum rotary evaporator. The residue was purified by silica gel column chromatograph to afford the products (1*S*, 2*R*)-41c.

(1S,2R)-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 86/14). Yield: 48% over two steps.  $R_{\rm f} = 0.45$  (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.  $[\alpha]^{20}D = +25.7$  (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 Na<sub>2</sub>S<sub>2</sub>O<sub>5</sub> (2×40 mL), water (2×40 mL) and dried over MgSO<sub>4</sub>. 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

literature<sup>305</sup>.

38b, 38d, 38f, 38g

A Schlenk tube was charged with Cu<sub>2</sub>O (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 literature<sup>306</sup>.

$$R \stackrel{\text{II}}{=} Br \qquad \begin{array}{c} \text{LiHMDS (2.0 equiv.)} \\ \text{CH}_2\text{I}_2 \text{ (2.0 equiv.)} \\ \text{DBU (2.0 equiv.)} \\ \hline \\ \text{THF and Et}_2\text{O} \\ \text{-78 °C to r.t, dark} \end{array} \qquad R \stackrel{\text{II}}{=} \\ \hline \\ 38c, 38e. \\ \end{array}$$

A solution of  $CH_2I_2$  (644  $\mu$ L, 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  $CH_2I_2$  following flash chromatography was removed under high vacuum. The NMR data is consistent with reported literature<sup>307</sup>.

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.<sup>308</sup>

<sup>&</sup>lt;sup>305</sup> N. A. Petasis, I. A. Zavialov, *Tetrahedron Lett.* **1996**, *37*, 567–570.

<sup>&</sup>lt;sup>306</sup> X. Feng, H. Zhang, W. Lu, Y. Yamamoto, A. I. Almansour, N. Arumugam, R. S. Kumar, M. Bao, *Synthesis* **2017**, *49*, 2727–2732.

<sup>&</sup>lt;sup>307</sup> J. A. Bull, J. J. Mousseau, A. B. Charette, *Org. Lett.* **2008**, *10*, 5485–5488.

<sup>308</sup> K. C. Nicolaou, G. Bellavance, M. Buchman, K. K. Pulukuri, J. Am. Chem. Soc. 2017, 139, 15636–15639.

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.<sup>251</sup>

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 CH<sub>2</sub>Cl<sub>2</sub> (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 NaHCO<sub>3</sub> (5.3 mL) was added and the mixture was stirred vigorously for 30 min. After filtration, the filtrate was washed with saturated NaHCO<sub>3</sub>, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/MeOH as eluent) to afford **38u** (534 mg, 77% yield) as a white solid. The NMR data is consistent with reported literature.<sup>309</sup>

- 2. General procedure of the Pd(II)-catalyzed functionalization of monofluorinated cyclopropanes.
- 2.1. General procedure of the synthesis of 39.

<sup>309</sup> D. Shimbo, A. Shibata, M. Yudasaka, T. Maruyama, N. Tada, B. Uno, A. Itoh, *Org. Lett.* **2019**, *21*, 9769–9773.

An oven-dried tube was loaded with Pd(OAc)<sub>2</sub> (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**.

 $(\textit{cis}) - 2 - \text{fluoro} - 2 - (((4 - \text{methoxybenzyl}) \text{oxy}) \text{methyl}) - N - (\text{quinolin-8-yl}) - 3 - ((\textit{E}) - \text{styryl}) \text{cyclopropane-1-carboxamide}) - N - (\text{quinolin-8-yl}) - N - (\text{qu$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -201.05 – -204.82 (m, 1F).

IR (neat) 3338, 2925, 2840, 1681, 1521, 1484, 1302, 1244, 824, 748 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{30}H_{27}FN_2O_3$  m/z 483.2084 ([M+H]<sup>+</sup>) found 483.2096 ( $\Delta 2.5$  ppm).

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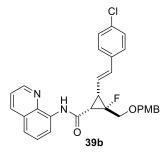
 $(\textit{trans}) - 2 - \text{fluoro-} 2 - (((4-\text{methoxybenzyI}) \text{oxy}) \text{methyI}) - N - (\text{quinolin-}8 - \text{yI}) - 3 - ((E) - \text{styryI}) \text{cyclopropane-} 1 - \text{carboxamide}) - N - (\text{yulinolin-}8 - \text{yI}) - N - (\text{yulinolin-}8 - \text{yulinolin-}8 - \text{$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -164.9 – -165.3 (m, 1F).



(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -203.1 – -203.4 (m, 1F).

IR (neat) 3672, 3369, 2988, 2901, 1684, 1522, 1485, 1249, 1066, 789 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{30}H_{26}ClFN_2O_3$  m/z 517.1694 ([M+H]<sup>+</sup>) found 517.1716 ( $\Delta 4.3$  ppm).

Br N N N O PMB

(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.

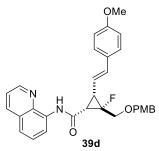
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.12 (s, 1H), 8.78 (dd, J = 6.7, 2.3 Hz, 1H), 8.65 (dd, J = 4.2, 1.7 Hz, 1H), 8.12 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.22 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.77 – 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) δ 164.3, 159.5, 148.3, 138.4, 136.3, 136.1, 134.4, 132.8, 131.5, 129.6, 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -203.1 – -203.3 (m, 1F).

IR (neat) 3363, 2992, 2834, 1684, 1521, 1484, 1248, 1132, 970, 789 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{30}H_{26}BrFN_2O_3$  m/z 561.1189 ([M+H]<sup>+</sup>) 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) δ-203.3 – -203.5 (m, 1F).

IR (neat) 3344, 2924, 2840, 1681, 1510, 1484, 1241, 1029, 823, 790 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{31}H_{29}FN_2O_4$  m/z 513.2178 ([M+H]<sup>+</sup>) found 513.2189 ( $\Delta 2.1$  ppm).

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -62.9 (s, 3F), -203.0 – -203.3 (m, 1F).

IR (neat) 3320, 2841, 1686, 1529, 1485, 1324, 1106, 1066, 829, 793 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{31}H_{26}F_4N_2O_3$  m/z 551.1958 ([M+H]<sup>+</sup>) found 551.1948 ( $\Delta$ -1.8 ppm).

 $(\textit{cis}) - 3 - ((\textit{E}) - 3 - \text{bromostyryI}) - 2 - \text{fluoro-} 2 - (((4 - \text{methoxybenzyI}) \text{oxy}) \text{methyI}) - \textit{N} - (\text{quinolin-} 8 - \text{yI}) \text{cyclopropane-} 1 - \text{carboxamide}) - (((4 - \text{methoxybenzyI}) \text{oxy}) - ((4 - \text{methoxybenzyI}) \text{oxy}) - ((4 - \text{methoxybenzyI}) \text{oxy}) - ((4 - \text{methoxybenzyI}) - ((4 - \text{methoxybenzyI}) \text{oxy}) - ((4 - \text{methoxybenzyI}) - (4 - \text{methoxybenzyI}) - ((4 - \text{methoxybenzyI}) - (4 - \text{methoxybenzyI}) - ((4 - \text{methoxybenzyI}) - (4 - \text{methoxybenzyI$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -202.9 – -203.2 (m, 1F).

TD ( ) 2244 1602 1612 1602 1406 1245 1125 262 602 612 1

IR (neat) 3344, 1682, 1613, 1523, 1486, 1245, 1127, 960, 790, 648 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{30}H_{26}BrFN_2O_3$  m/z 561.1189 ([M+H]+) found 561.1170 ( $\Delta$ -3.4 ppm).

(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.

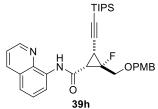
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) δ 10.13 (d, J = 1.7 Hz, 1H), 8.78 (dd, J = 6.6, 2.4 Hz, 1H), 8.68 (dd, J = 4.2, 1.7 Hz, 1H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.58 – 7.47 (m, 4H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.18 – 7.00 (m, 3H), 6.91 (d, J = 8.7 Hz, 2H), 6.70 (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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -203.1 – -203.5 (m, 1F).

IR (neat) 3343, 2924, 2846, 1683, 1541, 1244, 1086, 1009, 824, 791 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{30}H_{26}BrFN_2O_3$  m/z 561.1189 ([M+H]<sup>+</sup>) found 561.1189 ( $\Delta 0$  ppm).



(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -199.2 – -199.4 (m, 1F).

IR (neat) 3344, 2944, 2864, 2167, 1671, 1527, 1328, 1246, 1031, 824, 662 cm<sup>-1</sup>.

HRMS (ES<sup>+</sup>) calcd for C<sub>33</sub>H<sub>41</sub>FN<sub>2</sub>O<sub>3</sub>Si m/z 561.2937 ([M+H]<sup>+</sup>) found 561.2946 (Δ1.6 ppm).

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -195.4 – -202.9 (m, 1F).

IR (neat) 3340, 2938, 2862, 1671, 1527, 1325, 1243, 1051, 844, 799, 669 cm<sup>-1</sup>

**HRMS** (ES<sup>+</sup>): calcd for  $C_{30}H_{35}FN_2O_3Si \text{ m/z } 519.2487 \text{ [M+H]}^+$ , found 519.2479 ( $\Delta 1.5 \text{ ppm}$ )

An oven-dried tube was loaded with Pd(OAc)<sub>2</sub> (9.0 mg, 0.04 mmol, 20 mol%), monofluorinated cyclopropane (+/-) **37a** (76.0 mg, 0.2 mmol, 1.0 equiv.), Ag<sub>2</sub>CO<sub>3</sub> (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 <sup>19</sup>F 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**.

(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide

<u>110 °C for 15 h.</u> 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.

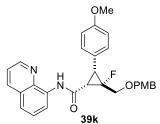
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.14 (d, J = 5.8 Hz, 1H), 8.84 – 8.74 (m, 2H), 8.14 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.43 (dd, J = 8.3, 4.2 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.63 (dd, J = 18.0, 12.0 Hz, 2H), 3.92 – 3.70 (m, 5H), 2.03 (dd, J = 11.0, 6.5 Hz, 1H), 1.65 – 1.50 (m, 1H), 1.42 (dd, J = 6.5, 1.3 Hz, 3H).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -207.4 - -207.6 (m, 1F).

IR (neat) 3350, 2931, 2859, 1686, 1541, 1484, 1244, 1115, 824, 791 cm<sup>-1</sup>.

**HRMS (ES**<sup>+</sup>) calcd for  $C_{23}H_{23}FN_2O_3$  m/z 395.1800 ([M+H]<sup>+</sup>) found 395.1788 ( $\Delta$ -3.0 ppm).



(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-(4-methoxyphenyl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide

 $\underline{110~^{\circ}\mathrm{C}~\text{for}~15~\text{h}}$ . 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -201.2 – -201.4 (m, 1F).

IR (neat) 3332, 2917, 2849, 1662, 1513, 1485, 1244, 1030, 824, 790 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{29}H_{27}FN_2O_4$  m/z 487.2051 ([M+H]<sup>+</sup>) found 487.2048 ( $\Delta$ -0.6 ppm).

(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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) major:  $\delta$  -201.8 – -202.0 (m, 1F).

IR (neat) 3332, 2926, 2859, 1663, 1524, 1486, 1324, 1244, 1984, 825 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{28}H_{27}FN_2O_4$  m/z 475.2022 ([M+H]<sup>+</sup>) found 475.2032 ( $\Delta 2.1$  ppm).

(cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide

<u>130 °C for 20 h.</u> 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -201.3 – -201.5 (m, 1F).

IR (neat) 3338, 2918, 1667, 1522, 1485, 1169, 1087, 824, 747, 666 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{37}H_{32}FN_3O_5S$  m/z 650.2125 ([M+H]<sup>+</sup>) found 650.2130 ( $\Delta$ 0.8 ppm).

ethyl 2-((cis)-2-fluoro-2-(((4-methoxybenzyl)oxy)methyl)-3-(quinolin-8-ylcarbamoyl)cyclopropyl)acetate

<u>130 °C for 20 h.</u> 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) major:  $\delta$  -205.9 – -206.6 (m, 1F).

IR (neat) 3344, 2934, 1730, 1687, 1523, 1486, 1246, 1030, 825, 791 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>) calcd for  $C_{26}H_{27}FN_2O_5$  m/z 467.1971 ([M+H]<sup>+</sup>) found 467.1989 ( $\Delta 3.9$  ppm).

# 2.2. General procedure for the synthesis cyclopropanes 42.

An oven-dried tube was loaded with Pd(OAc)<sub>2</sub> (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** to (+/-) **42g**.

 $(\textit{cis}) - 2 - (\text{fluoromethyl}) - 2 - \text{phenyl-} \textit{N} - (\text{quinolin-8-yl}) - 3 - ((\textit{E}) - \text{styryl}) \\ \text{cyclopropane-1-carboxamide}$ 

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.

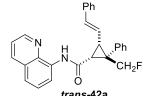
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.19 (s, 1H), 8.82 (dd, J = 7.2, 1.8 Hz, 1H), 8.75 (dd, J = 4.2, 1.7 Hz, 1H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.60 – 7.50 (m, 4H), 7.48 – 7.39 (m, 5H), 7.37 – 7.30 (m, 3H), 7.27 – 7.20 (m, 1H), 6.95 (dd, J = 15.8, 9.3 Hz, 1H), 6.81 (d, J = 15.8 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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, 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.51 (t, J = 47.5 Hz, 1F).

IR (neat) 3341, 2924, 1677, 1520, 1484, 1321, 1165, 989, 790, 693 cm<sup>-1</sup>.

**HRMS (ES**<sup>+</sup>): calcd for  $C_{28}H_{23}FN_2O$  m/z 423.1873 ([M+H]<sup>+</sup>) 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.59 (t, J = 47.5 Hz, 1F).

(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.

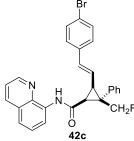
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.19 (s, 1H), 8.80 (dd, J = 6.9, 2.0 Hz, 1H), 8.76 (dd, J = 4.2, 1.7 Hz, 1H), 8.17 (dd, J = 8.3, 1.7 Hz, 1H), 7.60 – 7.49 (m, 4H), 7.48 – 7.33 (m, 6H), 7.31 – 7.25 (m, 2H), 6.92 (dd, J = 15.8, 9.4 Hz, 1H), 6.74 (d, J = 15.8 Hz, 1H), 5.33 (d, 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.59 (t, J = 47.5 Hz).

IR (neat) 3338, 2922, 2852, 1678, 1522, 1486, 1321, 1164, 1002, 790, 697 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{28}H_{22}C1FN_2O$  m/z 457.1477 ([M+H]<sup>+</sup>) found 457.1480 ( $\Delta 0.7$  ppm).



(cis)-3-((E)-4-Brorostyryl)-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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.52 (t, J = 47.5 Hz, 1F).

IR (neat) 3338, 2922, 2852, 1677, 1522, 1484, 1324, 1165, 991, 790, 699 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{28}H_{22}BrFN_2O$  m/z 503.0896 ([M+H]<sup>+</sup>) found 503.0887 ( $\Delta$ -1.8 ppm).

(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%.  $R_{\rm f}$  = 0.32 (petroleum ether / ethyl acetate, 83/17). Yellow solid. Mp: 93 – 95 °C.

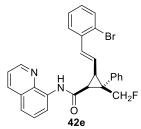
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.17 (s, 1H), 8.81 (d, J = 7.2, 1.8 Hz, 1H), 8.75 (dd, J = 4.2, 1.7 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.59 – 7.49 (m, 4H), 7.47 – 7.31 (m, 6H), 6.85 (d, J = 8.8 Hz, 2H), 6.79 – 6.73 (m, 2H), 5.33 (ddd, J = 47.5, 18.0, 9.9 Hz, 2H), 3.81 (s, 3H), 2.75 (m, 1H), 2.60 (dd, J = 8.9, 2.3 Hz, 1H).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.5 (t, J = 47.6 Hz).

IR (neat) 3344, 2954, 2843, 1678, 1522, 1484, 1166, 989, 790, 700 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{29}H_{25}FN_2O_2$  m/z 453.1978 ([M+H]<sup>+</sup>) found 453.1984 ( $\Delta$ 1.3 ppm).



 $(\textit{cis}) - 3 - ((\textit{E}) - 2 - \text{bromostyryI}) - 2 - (\text{fluoromethyI}) - 2 - \text{phenyI} - \textit{N} - (\text{quinolin-8-yI}) \\ \text{cyclopropane-1-carboxamide}$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -220.5 (t, J = 47.5 Hz, 1F).

IR (neat) 3343, 2921, 2859, 1677, 1522, 1485, 1165, 992, 790, 699 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{28}H_{22}BrFN_2O$  m/z 503.0896 ([M+H]<sup>+</sup>) found 503.0845 ( $\Delta$ -10.1 ppm).

(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.

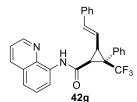
<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  10.25 (s, 1H), 8.88 – 8.69 (m, 2H), 8.17 (dd, J = 8.3, 1.6 Hz, 1H), 7.61 – 7.52 (m, 4H), 7.48 – 7.37 (m, 6H), 7.34 (dd, J = 8.0, 6.5 Hz, 2H), 7.29 – 7.12 (m, 2H), 6.96 – 6.81 (m, 2H), 2.88 – 2.74 (m, 1H), 2.67 (d, J = 9.0 Hz, 1H).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>) 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<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{28}H_{22}F_2N_2O$  m/z 441.1778 ([M+H]<sup>+</sup>) found 441.1789 ( $\Delta 2.5$  ppm).



 $(\textit{cis}) - 2 - \texttt{phenyl-} \textit{N-} (\texttt{quinolin-8-yl}) - 3 - ((\textit{E}) - \texttt{styryl}) - 2 - (\texttt{trifluoromethyl}) \\ \texttt{cyclopropane-1-carboxamide}$ 

<u>60 °C, 20 h and without AgOAc.</u> 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -60.8 (s, 3F).

IR (neat) 3338, 2925, 2847, 1686, 1523, 1485, 1324, 1147, 966, 694 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{28}H_{21}F_3N_2O$  m/z 459.1684 ([M+H]<sup>+</sup>) found 459.1685 ( $\Delta 0.2$  ppm).

(trans)-2-phenyl-N-(quinolin-8-yl)-3-((E)-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide

<u>60 °C, 20 h.</u> 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>) 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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -71.6 (s, 3F).

### 2.3. Enantiopure compounds characterization.

The functionalization procedures of chiral fluorinated cyclopropanes are consistent with their racemates preparation process.

(1S,2S,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: 69%. (66.7 mg).  $R_f = 0.24$  (petroleum ether / ethyl acetate, 75/25). Yellowish foam. The characterization ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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.  $[\alpha]^{20}D = +18.4$  (c = 1).

 $(1S,2R,3S)-2-{\rm fluoro}-2-(((4-{\rm methoxybenzyl}){\rm cxy}){\rm methyl})-N-({\rm quinolin}-8-{\rm yl})-3-((E)-{\rm styryl}){\rm cyclopropane}-1-{\rm carboxamide}-1-{\rm c$ 

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 ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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.  $|\alpha|^{20}D = +24.3$  (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 ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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.  $[\alpha]^{20}_{D} = +11.8$  (c = 0.5, CHCl<sub>3</sub>).

(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 ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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.  $[\alpha]^{20}D = +10.1$  (c = 0.5, CHCl<sub>3</sub>).

\_\_\_\_\_

 $(1S,2R,3R)\textbf{-42g} \\ (1S,2R,3R)\textbf{-2-phenyl-}N\textbf{-(quinolin-8-yl)-3-((\it{E})-styryl)-2-(trifluoromethyl)cyclopropane-1-carboxamide}$ 

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 ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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. [ $\alpha$ ]<sup>20</sup> $_D$  = +25.3 (c = 1).

(1R,2R,3S)-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 ( ${}^{1}H$ ,  ${}^{13}C$ ,  ${}^{19}F$  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.  $|\alpha|^{20}D = +24.5$  (c = 1).

## 3. General procedures for the post-functionalization reactions

### 3.1. Synthesis of cyclopropyl carboxylic acids 44, 47 and (1S, 2R, 3R)-47a.

To a solution of **39a**, **42a** or (1*S*, 2*R*, 3*R*)-**42a** (0.18 mmol, 1.0 equiv.) in CH<sub>3</sub>CN (1 mL) were added DMAP (39 mg, 0.36 mmol, 2.0 equiv.) and Boc<sub>2</sub>O (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<sub>3</sub> (5 mL) and brine (5 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated to give a crude product as a yellow solid. To a solution of the crude product

in THF (1.2 mL), and  $H_2O$  (0.38 mL) was added LiOH. $H_2O$  (12.6 mg, 0.3 mmol). Then, the mixture was cooled to 0 °C.  $H_2O_2$  (30% aq. 84  $\mu$ L, 0.75 mmol) was added to the mixture. After stirring for 6 h at room temperature,  $Na_2SO_3$  (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  $Na_2SO_4$ , 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) + ((4 - methoxybenzyl) + ((

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -202.7 – -206.4 (m, 1F).

IR (neat) 3065, 2919, 2840, 1734, 1610, 1512, 1248, 1171, 755, 699 cm<sup>-1</sup>.

**HRMS (ES-)**: calcd for  $C_{21}H_{21}FO_4$  m/z 355.1346 ([M-H]-) found 355.1349 ( $\Delta 0.8$  ppm).



 $(\textit{cis}) \hbox{-2-(fluoromethyl)-2-phenyl-3-(} (\textit{E}) \hbox{-styryl}) \hbox{cyclopropane-1-carboxylic acid}$ 

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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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.

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -221.5 (t, J = 47.2 Hz, 1F).

IR (neat) 3367, 3026, 2895, 1954, 1599, 1494, 982, 956, 750, 693 cm<sup>-1</sup>.

**HRMS** (ES<sup>-</sup>): calcd for  $C_{19}H_{17}FO_2$  m/z 295.1134 ([M-H]<sup>-</sup>) found 295.1120 ( $\Delta$ -4.7 ppm).

(1S,2R,3R)-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 ( $^{1}$ H,  $^{13}$ 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.  $[\alpha]^{20}D$  = +32.6 (c =0.5, CHCl<sub>3</sub>).

#### 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<sub>3</sub>CN (1 mL) were added DMAP (53.7 mg, 0.44 mmol, 2.0 equiv.) and Boc<sub>2</sub>O (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<sub>3</sub> (5 mL) and brine (5 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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<sub>4</sub> (12.5 mg, 0.57 mmol) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. To the reaction mixture were added Et<sub>2</sub>O (5 mL), saturated aqueous NH<sub>4</sub>Cl (5 mL) and water (5 mL) at 0 °C. The resulting mixture was extracted with Et<sub>2</sub>O, and the organic layer was washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, 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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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

(s, 1H), 1.98 – 1.83 (m, 1H), 1.61 – 1.44 (m, 1H).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -206.5 – -209.6 (m, 1F).

IR (neat) 3329, 2917, 2850, 1611, 1512, 1245, 1073, 1028, 817, 751, 693 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{21}H_{23}FO_3$  m/z 360.1975 ([M+H<sub>2</sub>O]<sup>+</sup>) found 360.1974 ( $\Delta$ 0.8 ppm).

(cis)-2-(fluoromethyl)-2-phenyl-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: 69% (38.8 mg).  $R_f = 0.2$ . (petroleum ether / ethyl acetate, 80/20). Colorless oil.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -215.1 (t, J = 48.4 Hz, 1F).

IR (neat) 3028, 2918, 2851, 1687, 1440, 1227, 994, 921, 709, 699 cm<sup>-1</sup>.

**HRMS (ES**-): calcd for  $C_{19}H_{19}FO$  m/z 281.1347 ([M-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<sub>2</sub>O (0.65 mL). This mixture was sealed and stirred at 60 °C for 1.5 h. Then an aqueous saturated solution of NaHCO<sub>3</sub> 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<sub>2</sub>SO<sub>4</sub>, and evaporated. The residue was purified by silica gel column chromatography to give correspondent cyclopropyl pyrrolyl oxazinone product **10**.

45 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(8H)-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.

<sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>) 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).

<sup>13</sup>C NMR (75.5 MHz, CDCl<sub>3</sub>)  $\delta$  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).

<sup>19</sup>F NMR (282.4 MHz, CDCl<sub>3</sub>)  $\delta$  -202.7 (t, J = 15.3 Hz, 1F).

IR (neat) 3344, 2923, 1613, 1714, 1513, 1484, 1248, 1009, 824, 793, 700 cm<sup>-1</sup>.

**HRMS** (ES<sup>+</sup>): calcd for  $C_{30}H_{24}FN_2O_4$  m/z 575.0970 ([M+H]<sup>+</sup>) found 575.0977 ( $\Delta$ 1.2 ppm).

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# **Curriculum Vitae**

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### **Education**

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### **Professional Experiences**

**2020.10**—**present:** Study on transition metal-catalyzed diazo compounds decomposition for the catalytic enantioslective synthesis of new cyclopropanic scaffolds in Group "Synthesis of Fluorinated Biomolecules" in COBRA institute, under supervision of Prof. Philippe JUBAULT and Dr. Tatiana BESSET INSA Rouen Normandie, France.

**2017.09–2020.07:** Study on NHC (nitrogen heterocyclic carbene) catalyzed  $\beta$ -halomethyl cinnamal aldehydes asymmetric cycloaddition reactions in "College of Materials and Chemical Engineering", under supervision of Prof. Guofu ZHONG and Associate Prof. Limin YANG. Hangzhou, China.

### **Conferences**

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#### **Publications**

Ph.D:

1) C. Zhao, T. Besset, C. Legault, P. Jubault, Experimental and Computational Studies for the

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#### Master:

- 2) J. Yan, Z. Song, C. **Zhao**, K. Shi, L. Yang, G. Zhong, Highly Chemoselective and Enantioselective Synthesis of 3,4-2*H*-Pyrindin-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

catalytic enantioselective synthesis for the 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  $\alpha,\alpha$ -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 contraintet 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 énantiosélèctivités.

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