Catalytic asymmetric cyclopropanation and oxidation of tri-, di- and monofluoromethyl styrenes

Weisheng Huang

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Normandie Université

THESE

Pour obtenir le diplôme de doctorat

Spécialité Chimie Organique

Préparée au sein de l'Institut National des Sciences Appliquées de Rouen

Catalytic Asymmetric Cyclopropanation and Oxidation of Tri-, Di- and Monofluoromethyl Styrenes

Présentée et soutenue par

Weisheng HUANG

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Abbreviations and Acronyms

B	BHT	2.6-di-*tert*-butyl-4-methylphenyl
	BINOL	1,1-bi-2-naphthol
	Boc	*tert*-butyloxycarbonyl
	Bn	benzyl
	Bz	benzoyl
C	Cbz	benzoxycarbonyl
	Cy	cyclohexanyl
D	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCE	1,2-dichloroethane
	DCM	dichloromathane
	DFT	density functional theory
	DIBAL-H	diisobutylaluminium hydride
	dr	diastereomeric ratio
E	ee	enantiomeric excess
	er	enantiomeric ratio
	Et	ethyl
	EWG	electron-withdrawing group
	eq *or* equiv	equivalent
F	FG	functional group
H	HRMS	high resolution mass spectroscopy
	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
K	KHMDS	potassium bis(trimethylsilyl)amide
M	*m*-CPBA	3-chloroperoxybenzoic acid
	Me	methyl
	Mes	2,4,6-trimethylphenyl
	Ms	mesyl
	MTBE	*tert*-butyl methyl ether
N	NBS	*N*-bromosuccinimide

	NMI	*N*-methylimidazole
	NMR	nuclear magnetic resonance
	Ns	nosyl
P	PE	petroleum ether
	PMP	*para*-methoxyphenyl
S	Su	succinimidyl
	S_N2	synchronous nucleophilic substitution
	TBS	*tert*-butyldimethylsilyl
	t-Bu	*tert*-butyl
	TEMPO	2,2,6,6-Tetramethylpiperidinooxy
	Tf	trifluoromethanesulfonyl
	THF	tetrahydrofuran
	Ts	tosyl
	t_R	retention time

Abstract

This thesis presents the enantioselective synthesis of functionalized trifluoromethyl, difluoromethyl and monohalomethyl cyclopropanes based on the cyclopropanation reaction of alkenes bearing various fluorinated groups. In addition, the synthesis of enantioenriched fluorinated tertiary alcohols resulting from the dihydroxylation of fluorinated olefins is discussed. This thesis is divided into three chapters.

In the first chapter, we reported the first example of catalytic asymmetric synthesis of difluoromethyl cyclopropanes, which is achieved by using Rh_2((*S*)-BTPCP)$_4$ as a catalyst to perform the cyclopropanation reaction of α,α-difluoromethyl olefins with donor-acceptor diazo compounds and di-acceptor diazo compounds. This methodology allows the access to a broad range of cyclopropanes in high yields with excellent diastereo- and enantioselectivities (up to >20:1 and up to 99% ee).

In the second chapter, a practical and efficient asymmetric synthesis of trifluoromethyl cyclopropane derivatives was described and a series of functionalized cyclopropanes were obtained in excellent diastereoselectivities with excellent enantioselectivities (up to >20:1 and 99% ee). These investigations also extended to the synthesis of highly enantioselective monohalomethyl cyclopropanes.

In the third chapter, the initial propose aimed at exploring the asymmetric epoxidation of α,α-difluoromethyl styrenes. The reaction was performed in the presence of a metal-catalyst or an organic catalyst, unfortunately, none of the result was positive. Therefore, we turned our attention to the asymmetric synthesis of α,α-difluoromethylated tertiary alcohols. To this propose, the use of commercially available reagents AD-mix-α and AD-mix-β as the best catalysts, allowed the reaction with α,α-difluoromethyl styrenes to construct the corresponding α,α-difluoromethylated tertiary alcohols in good to high yields with excellent enantioselectivities (up to 99% ee). In addition, this transformation could be applied to a broad range of substrates, including variety of α,α-difluoromethyl styrenes, α-monofluoromethyl styrenes, β-difluoromethyl styrene and β-trifluoromethyl styrene.

Résumé

Ce manuscrit décrit la synthèse énantiosélective de cyclopropanes trifluorométhylés, difluorométhylés et mono-halométhylés hautement fonctionnalisés. Cette synthèse repose sur la cyclopropanation d'alcènes. De plus, la synthèse d'alcools tertiaires difluorométhylés à partir des oléfines fluorées correspondantes suivant un processus de dihydroxylation asymétrique est décrite. Ce manuscrit se découpe en 3 chapitres.

Le premier chapitre décrit la première synthèse catalytique asymétrique de cyclopropanes difluorométhylés en utilisant le Rh_2((*S*)-BTPCP)$_4$ comme catalyseur pour la réaction de cyclopropanation d'oléfines α,α-difluoromethylées avec des composés diazoïques di-accepteurs. Un large éventail de cyclopropanes a été obtenu avec de très bon rendements et d'excellentes diastéréosélectivités et énantiosélectivités (>20:1 et jusqu'à 99% ee).

Le second chapitre illustre la synthèse de cyclopropanes trifluorométhylés suivant une stratégie similaire. Ces derniers ont été obtenus avec des très bons rendements et d'excellentes diastéréosélectivités et énantiosélectivités (>20:1 et jusqu'à 99% ee). Ces travaux ont également permis une extension aux dérivés mono-halométhylés.

Dans un troisième chapitre, l'époxydation asymétrique de styrenes α,α-difluoromethylés a été étudiée. Malheureusement, tous les essais métallo- ou organocatalysés se sont avérés infructueux. Par la suite la réaction de dihydroxylation asymétrique de ces styrenes α,α-difluorométhylés a été développée pour conduire aux alcools tertiaires difluorométhylés énantioenrichis. L'utilisation d'AD-mix-α et AD-mix-β comme catalyseurs a permis d'obtenir les produits désirés avec de très bons rendements et d'excellentes énantiosélectivités. De plus, cette réaction a été étendue aux styrenes α,α-difluorométhylés, α-monofluorométhylés, β-difluoromethylé et β-trifluorométhylé.

Introduction

Introduction

A. Fluorinated cyclopropane

1.1 The fluorine atom

With the atomic number 9th in the periodic table of elements – fluorine, ranks as the 24th most abundant element in the universe and the 13th most common element in the earth's crust by weight percent (0.054%).[1] From a chemical point of view, the fluorine atom is the most electronegative element, and reacts with almost all other elements. Moreover, with the strongest bonds in organic compounds (except for Si-F bond, 582 KJ/mol) as well as a low HOMO energy of C-F bond (**Table 1**).[2]

X	Van der Waals radii (Å)	Electronegativity (Pauling's scale)	C-X Bond length (Å)	C-X bond strength (KJ/mol)
F	**1.47**	**4.0**	**1.35**	**105.4**
O	1.52	3.5	1.43	84.0
N	1.55	3.0	1.47	69.7
C	1.70	2.5	1.54	83.1
H	1.20	2.1	1.09	98.8

Table 1. Characteristics of different atoms.

Fluorine is mainly found in mineral forms, of which fluorite, fluorapatite and cryolite are the three richest fluorine sources in the earth's crust. However, less than 30 natural fluorine-containing molecules were found so far, probably due to the low water solubility of inorganic fluoride salts. Moreover, only one fluorinases enzyme was found so far that catalyze the C-F bond formation, whereas thousands of organohalogenated compounds of biogenic origin have been identified.[3]

Since Henri Moissan succeeded in isolating the fluorine gas in 1886,[4] researches in fluorine have been of tremendous expansion and man-made organofluorine compounds played an important role in various applications, such as materials, agrochemicals, fine chemicals and particularly in pharmaceuticals.[2, 5] Recently, It was

[1] A. G. W. Cameron, *Space Sci. Rev*. **1973**, *15*, 121-146.
[2] D. O'Hagan, *Chem. Soc. Rev*. **2008**, *37*, 308-319.
[3] a) N. Budisa, V. Kubyshkin, D. S. Makuch, *Life*. **2014**, *4*, 374-385. b) D. O'Hagan, C. Schaffrath, S. L. Cobb, J. T. G. Hamilton, C. D. Murphy, *Nature* **2002**, *416*, 279-280. c) Y. Zhu, J. L. Han, J. D. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, F. D. Toste, *Chem. Rev*. **2018**, *118*, 3887-3964.
[4] a) H. Moissan, C. R. *Acad. Sci.* **1886**, *103*, 202-205. b) H. Moissan, C. R. *Acad. Sci*. **1886**, *103*, 256-258.
[5] a) W. K. Hagmann, *J. Med. Chem*. **2008**, *51*, 4359-4369. b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev*. **2008**, *37*, 320-330. c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev*. **2014**, *114*, 2432-2506. d) O'

found that 18% of the top 200 pharmaceutical products by retail sales in 2018 contained at least a fluorine atom (**Figure 1**).[6]

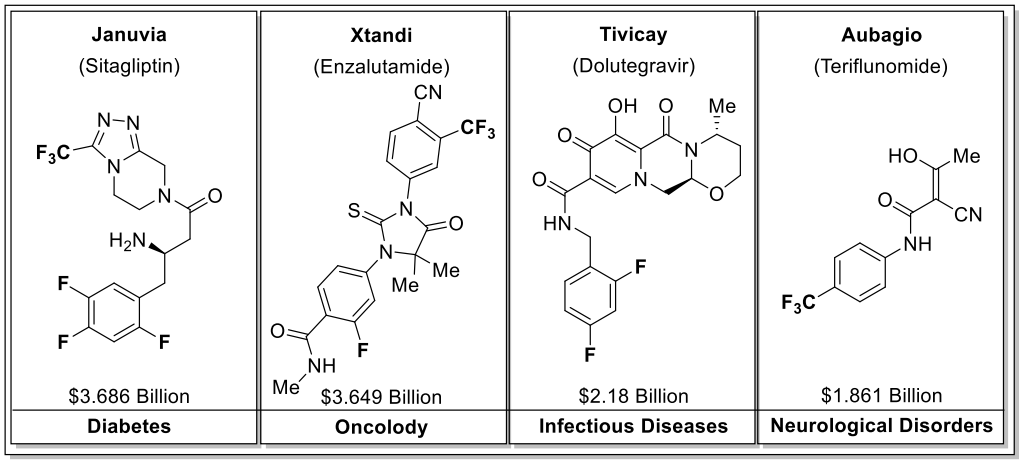
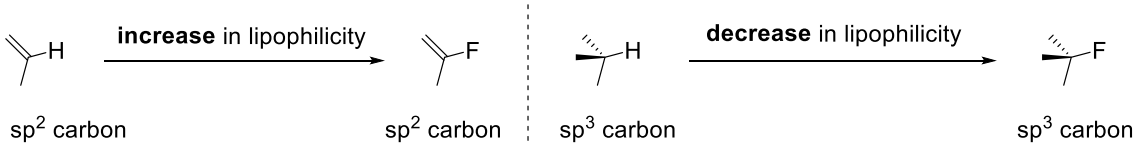


Figure 1. Selected examples of fluorinated molecules in top 200 pharmaceutical products by retail sales in 2018

Indeed, as the most electronegative element of the periodic table, the acidity of the neighboring functional groups can be affected by the presence of fluorinated moieties. Also, fluorinated moieties can significantly impact the physical and biological properties of molecules, such as the dipole moment, the acidity, the lipophilicity, the bioavailability and the metabolic stability of the molecules. For instance, regarding the lipophilicity, the fluorinated group attached to a sp^2 carbon increases the lipophilicity of the molecule. Conversely, the lipophilicity decreases when the fluorinated group is connected to a sp^3 carbon (**Scheme 1**).[2,7]



Scheme 1. Fluorine impact the lipophilicity on different hybridization carbons.

Moreover, as the fluorine nuclei has a high NMR sensitivity, it is an ideal marker for biological or chemistry studies.[8] Hence, tremendous methodologies have been developed for the introduction of fluorinated groups into the molecules over past

Hagan, H. Deng, *Chem. Rev*. **2015**, *115*, 634-649. e) V. Gouverneur, K. Seppelt, *Chem. Rev*. **2015**, *115*, 563-565.

[6] Produced by the Njarðarson Group at the University of Arizona.

[7] E. A. Ilardi, E. Vitaku, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 2832–2842.

[8] H. Chen, S. Viel, F. Ziarelli, L. Peng, *Chem. Soc. Rev*. **2013**, *42*, 7971-7982.

decades. (such as $-SF_5$, $-CF_3$, $-SCF_3$, $-CF_2R$, $-CH_2F$, -F, *etc.*).[9] However, one may agree that fluorine chemistry hasn't been fully explored. Therefore, researches in this field are still of great potential and attractive to the community.

1.2 The cyclopropane

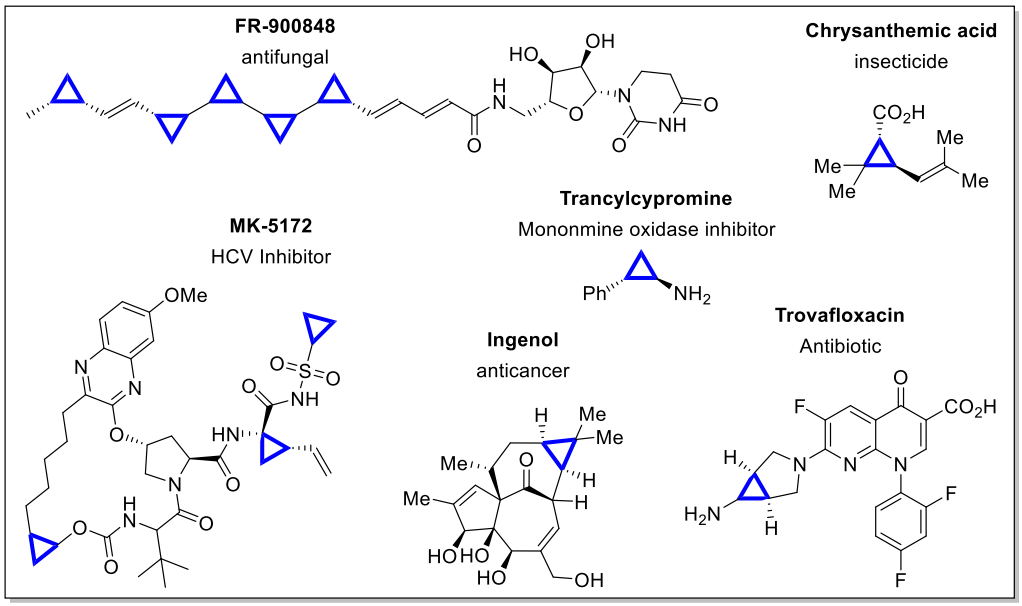


Figure 2. Examples of natural compounds or bioactive molecules containing the cyclopropyl ring.

Cyclopropane is the smallest and the most constrained cycloalkane, with a ring strain of approximately 27.5 kcal/mol. This three-membered ring is found as a basic structural motif in a wide range of natural products.[10] Moreover, synthetic cyclopropanes have attracted lots of attention from the organic chemists' community. Indeed, these three-membered carbocycles, as a part of larger molecular structures, possess a wide spectrum of biological properties ranging from enzyme inhibitions to insecticidal, herbicidal, antimicrobial, antifungal, antibiotic, antibacterial, anticancer and antiviral activities (**Figure 2**).[11] From a medicinal chemistry perspective, the cyclopropyl ring found application as a bioisostere for the lipophilic alkyl chains.[12] Additionally, the

[9] a) K. L. Kirk, Org. *Process Res. Dev*. **2008**, *12*, 305-321. b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature,* **2011**, *473*, 470-477. c) H. Chachignon, D. Cahard, *Chin. J. Chem*. **2016**, *34*, 445-454. d) S. B. Vallejo, S. Bonesi, A. Postigo, *Org. Biomol. Chem*. **2016**, *14*, 7150-7182.

[10] a) A. de Meijere, S. I. Kozhushkov, *Chem. Rev*. **2000**, *100*, 93–142. b) R. Faust, *Angew. Chem. Int. Ed.* **2001**, *40*, 2251-2253.

[11] a) W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589-8627. b) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev*. **2009**, *38*, 3051-3060. c) H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev*. **2009**, *38*, 3061-3071. d) D. Zhang, H. Song, Y. Qin, *Acc. Chem. Res*. **2011**, *44*, 447-457. e) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969-2984.

[12] S. Harper, J. A. McCauley, M. T. Rudd, M. Ferrara, M. DiFilippo, B. Crescenzi, U. Koch, A. Petrocchi, M. K. Holloway, J. W. Butcher, *et al. ACS Med. Chem. Lett.* **2012**, *3*, 332-336.

cyclopropyl ring is also able to adopt unique conformations leading to interesting spatial orientations of the substituents installed on the cyclopropyl subunit.[13] These specific features make the cyclopropyl ring a valuable synthetic building block in the course of the discovery of bioactive molecules.

1.3 Cyclopropane bearing fluorinated groups (-CF_3 and -CF_2H)

A fluorinated cyclopropyl moiety is the combination of a fluorine atom or a fluorinated group with a cyclopropane. As mentioned above, the introduction of a fluorinated group can impact the physicochemical and bioactivity properties of the molecule, as a consequence, the fluorinated cyclopropyl moiety has recently brought lots of interests due to their potential for discovering new bioactive compounds. In addition, the lack of rapid access to this type of scaffolds strengthen this interest. Hence, several methodologies have been developed for the preparation of fluorinated cyclopropanes. In this thesis, the accesses to trifluoromethylated and difluoromethylated ones will be mainly discussed.

1.3.1 The trifluoromethylated cyclopropane

The *tert*-butyl group is a common substituent encountered in medicinal chemistry. The introduction of a *tert*-butyl group into bioactive compounds often induces an increase of the lipophilicity, however with a decrease of the metabolic stability, leading to a lower oral bioavailability and shorter half-life times.[14] To overcome this challenge, polar substituents have been often used to increase the metabolic stability. The trifluoromethyl cyclopropyl group could be considered as a bioisostere of the *tert*-butyl group in the drug discovery process.

Hatsis and coworkers demonstrated an approach of replacing all full sp^3 C-Hs from the *tert*-butyl group with several substituents. The replacement from a *tert*-butyl group in compound **A** by a trifluoromethyl cyclopropyl group in compound **F** increased the in vitro clearance ($t_{1/2}$) in human liver microsomes (HLM) from 51 to 150 minutes (**Figure 3**).[15] This study confirmed that the replacement of the *tert*-butyl group by the cyclopropyl-CF_3 group provides a slightly higher stability in comparison with the *tert*-butyl group as shown in **Figure 3**.

[13] V. Summa, S. W. Ludmerer, J. A. McCauley, C. Fandozzi, C. Burlein, G. Claudio, P. J. Coleman, J. M. DiMuzio, M. Ferrara, M. Di Filippo, *Antimicrob. Agents Chemother* **2012**, *56*, 4161-4167.
[14] Y. Y. Lau, G. Krishna, N. P. Yumibe, D. E. Grotz, E. Sapidou, L. Norton, I. Chu, C. Chen, A. D. Soares, C. C. Lin, *Pharm. Res*. **2002**, *19*, 1606-1610.
[15] D. Barnes-Seeman, M. Jain, L. Bell, S. Ferreira, S. Cohen, X. Chen, J. Amin, B. Snodgrass, P. Hatsis, *ACS Med. Chem. Lett*. **2013**, *4*, 514-516.

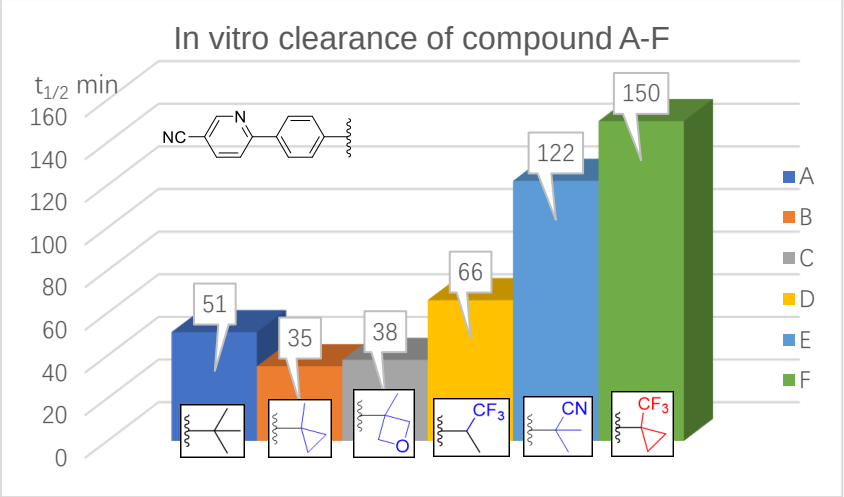
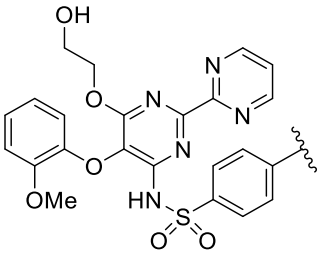
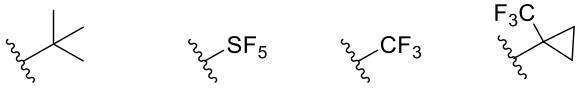


Figure 3. In vitro clearance of series of *tert*-butyl replacements in human liver microsomes.

Carreira and coworkers described the evaluation of drug bosentan's analogs and measured their bioactivities by replacing the *tert*-butyl group with several isosteres (selected physicochemical data are shown in **Figure 4**).[16] The lipophilicity decreased in the following order: *tert*-butyl > CF_3 cyclopropyl > -SF_5 > -CF_3. Besides, the p*K*a values reflect the electronic properties, which increase in the order: -SF_5 < -CF_3 < cyclopropyl-CF_3 < *tert*-butyl.





bosentan **a**	**b**	**c**	**d**
log *D* : 0.99 ± 0.04	0.37 ± 0.06	0.14 ± 0.04	0.81 ± 0.03
p*K*a : 4.6 ± 0.4	3.9 ± 0.4	4.1 ± 0.4	4.6 ± 0.02

Figure 4. Selected physicochemical data of bosentan analogs.

In fact, the trifluoromethyl cyclopropyl motif has found several applications in the elaboration bioactive compounds (**Figure 5**), such as antibiotic (**A**), drug candidate for the treatment of autoimmune diseases (**B**), chronic neurodegenerative disorders (**C**), epilepsy (**D**) and in analgesic (**E**).[17] With the increasing number of bioactive compounds bearing a trifluoromethyl cyclopropyl moiety incorporated on their structure,

[16] M. V. Westphal, B. T. Wolfstadter, J. Plancher, J. Gatfield, E. M. Carreira, *ChemMedChem*. **2015**, *10*, 461-469.

[17] a) B. T. Lapointe, P. H. Fuller, H. Gunaydin, K. Liu, N. Sciammetta, B. W. Trotter, H. Zhang, K. J. Barr, J. K. F. Maclean, D. F. Molinari, V. Simov, U.S. Patent Application 2018/016239, **2018**. b) J. Wityak, K. F. McGee. M. P. Conlon. R. H. Song. E. Freeman, P. Michels, M. Beconi, I. M. Sanjuan, J. Bard, C. Dominguez, *J. Med. Chem.* **2015**, *58*, 2967-2987. c) O. Bezencon, B. Heidmann, R. Siegrist, S. Stamm, S. Richard, D. Pozzi, O. Corminboeuf, C. Roch, M. Kessler, E. A. Ertel, I. Reymond, T. Pfeifer, R. de Kanter, M. T. Schafroth, L. G. Moccia, J. Mawet, R. Moon, M. Rey, B. Capeleto, E. Fournier, *J. Med. Chem*. **2017**, *60*, 9769-9789.

more and more reports dealing with the efficient preparation of trifluoromethyl cyclopropanes were recently published.

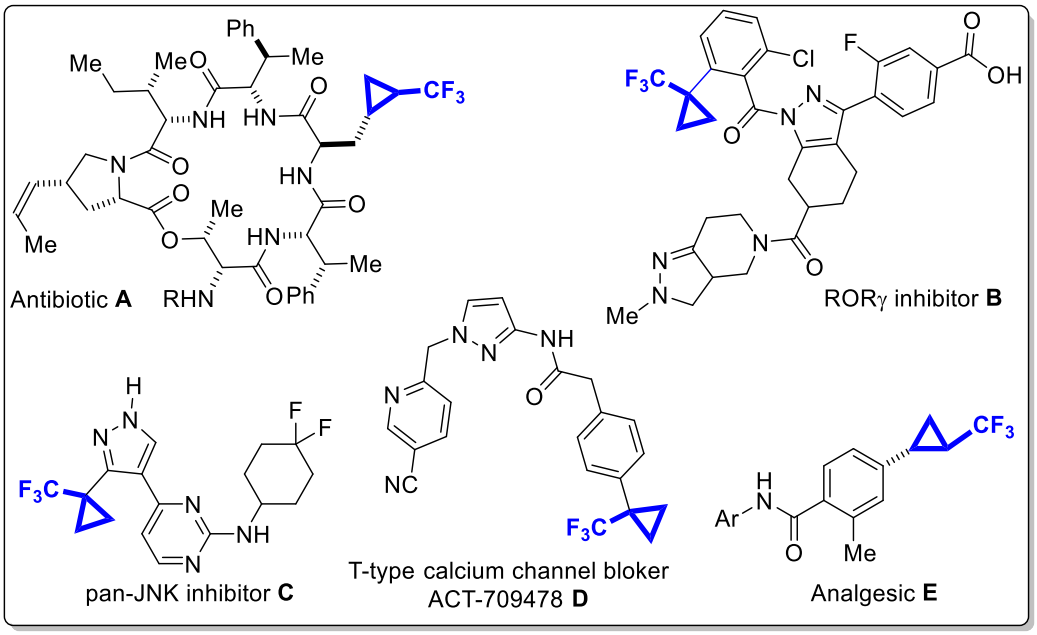


Figure 5. Bioactive molecules bearing the trifluoromethyl cyclopropyl motif.

1.3.2 The difluoromethyl group

The replacement of one fluorine atom of a trifluoromethyl group by a hydrogen atom leads a substituent named difluoromethyl group. The construction or the introduction of this motif is quite a new research area, which is underexplored. Therefore, it has attracted lots of interests. Indeed, the difluoromethyl group is described as an alcohol or thiol bioisostere, that can act as a hydrogen bond donor. In addition, it possesses lower lipophilicity and an increased polarity compared to that of the trifluoromethyl group. Thus, this motif is a good candidate nowadays in bioactive molecules discovery programs.

Lippard and coworkers demonstrated the hydrogen bond donor ability of the difluoromethyl group and confirmed the bioisosterism of the difluoromethyl group with hydroxyl group, which was determined by structural, spectroscopic and computational comparisons between *ortho*-nitrophenol and *ortho*-nitro-α,α-difluoromethyltoluene (**Figure 6**).[18]

[18] C. D. Seeeler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang, S. J. Lippard, *J. Am. Chem. Soc.* **2017**, 139, 9325-9332.

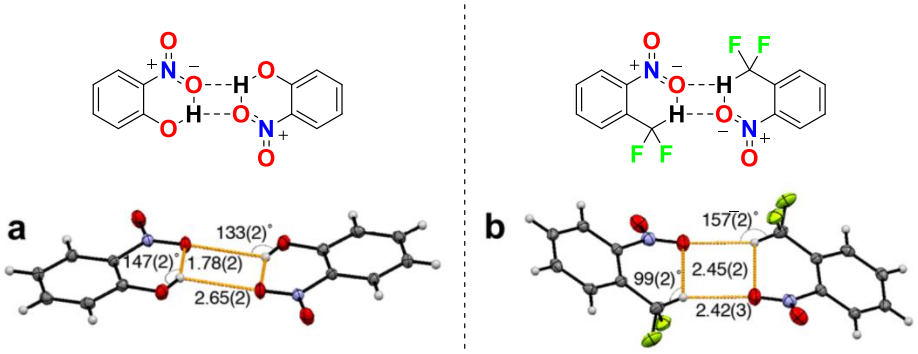
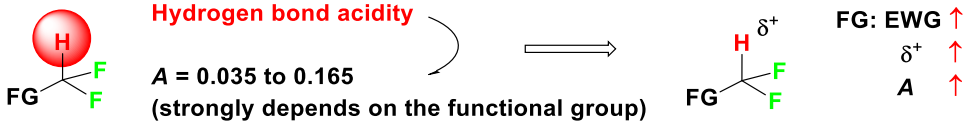


Figure 6. Crystal structures of -OH and -CF_2H depicting 50% probability thermal ellipsoids (**a**, **b**).[18]

Recently, Saphier and coworkers reported that the difluoromethyl group acts as a hydrogen bond donor. This phenomenon strongly depends on the attached functional group (*A* = 0.035 to 0.165) (**Figure 7**)[19]. The solute hydrogen bond acidity, *A,* was identified and could be determined by using ^{1}H NMR in different deuterated solvents using the following equation *A* = 0.0065 + 0.133 Δδ (Δδ = δ (DMSO) - δ ($CDCl_3$).[20] The authors also concluded that difluoromethyl substituted compounds are less lipophilic than the corresponding methyl (-CH_3) substituted compounds. In contrast, difluoromethylated compounds have a similar lipophilicity versus their corresponding thiol (-SH) substituted compounds and are more lipophilic than the corresponding hydroxyl (-OH) substituted compounds.



$Ar(Ak)SO_2CF_2H$ > $Ar(Ak)SOCF_2H$ > $ArOCF_2H$ > $ArSCF_2H$ > $AkSCF_2H$ > $AkOCF_2H$ > $ArCF_2H$ > $AkCF_2H$

Figure 7. Influence of the functional group on the *A* values of the difluoromethyl moiety.

One additional report by Budisa and coworkers investigated the lipophilicity and the hydrolytic stability of *N*-acetylproline derivatives bearing a varying number of fluorine atoms (**Table 2**).[21] The conclusion of this study is that the log*P* decreased in the following order: -CF_3 > -CF_2H ≈ -CH_3 > -CH_2F > H.

[19] Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, *J. Med. Chem.* **2019**, *62*, 5628-5637.
[20] a) M. H. Abraham, R. J. Abraham, J. Byrne, L. Griffiths, *J. Org. Chem.* **2006**, **71**, 3389-3394. b) M. H. Abraham, R. J. Abraham, W. E. Acree, A. E. Aliev, A. J. Leo, W. L. Whaley, *J. Org. Chem.* **2014**, *79*, 11075-11083.
[21] V. Kubyshkin, N. Budisa, *Beilstein J. Org. Chem.* **2017,** *13,* 2442-2457.

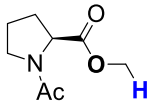
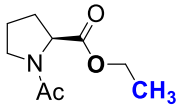
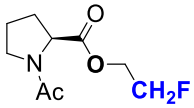
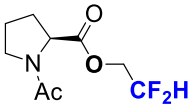
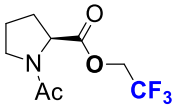
					
log*P*	-0.44 ± 0.05	0 ± 0.03	-0.43 ± 0.07 (octan-1-ol/ water)	0.02 ± 0.06	0.55 ± 0.07
$t_{1/2}$/min	224 ± 20	603 ± 58	80 ± 20 (pH 11.0)	19.7 ± 2.5	6.4 ± 1.7

Table 2. Properties of *N*-acetylproline derivatives.

Though the study of difluoromethyl cyclopropanes is scarcely reported, a few bioactive compounds containing a difluoromethyl cyclopropyl motif have been reported, such as Voxilaprevir, a molecule used for the treatment of hepatitis C virus infections, or with insecticide properties,[22] or RORγ modulator[23] (**Figure 8**).[24]

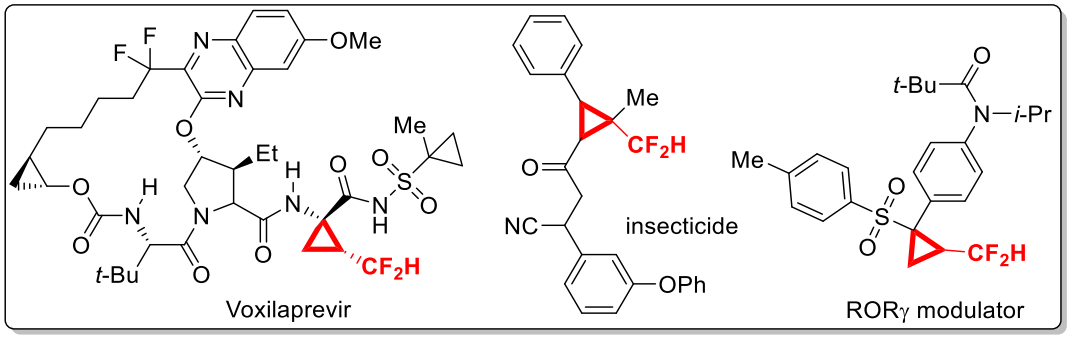


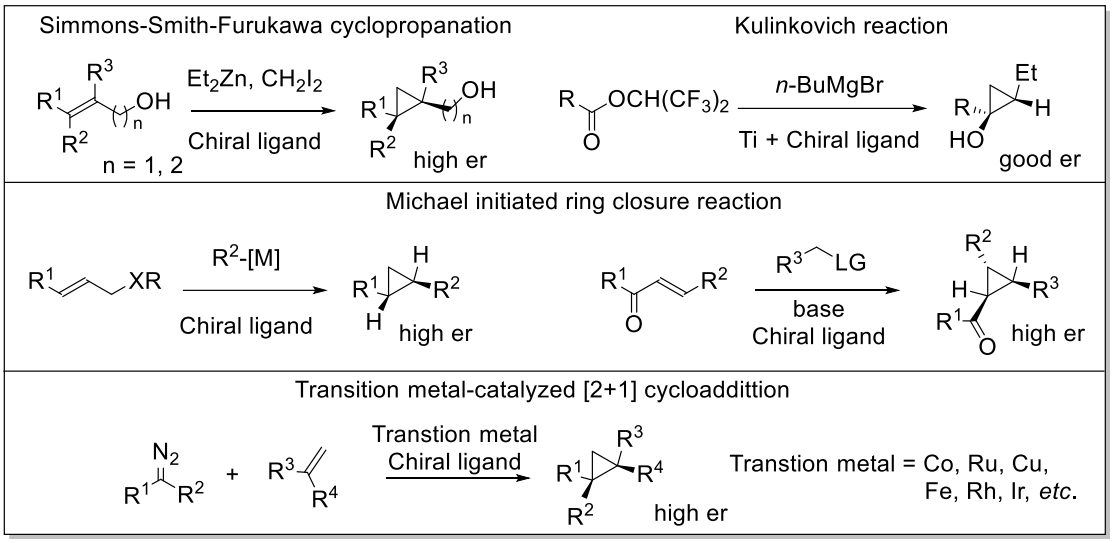
Figure 8. Applications of difluoromethyl cyclopropanes in medicinal and agrochemical research.

1.4 Asymmetric cyclopropanation reaction

Up to date, the preparation of cyclopropyl ring bearing various substituents as a research subject has been well studied over the years.[25] The most classical strategies for the asymmetric synthesis of cyclopropane derivatives could be divided into the following categories: (1) the Simmons-Smith-Furukawa cyclopropanation, (2) the Michael Initiated Ring Closure reaction also called the sequence Michael addition 1,3-elimination, such as Corey-Chaykovsky cyclopropanation, (3) the Kulinkovich reaction

[22] T. Mori, K. Ujihara, O. Matsumoto, K. Yanagi and N. Matsuo, *J. Fluorine. Chem*. **2007**, *128*, 1174-1181.
[23] R. H. Hutchings, J. H. Jones, J. Chao, I. J. Enyedy and D. Marcotte, WO 2014028669, Biogen Idec Ma, **2014**.
[24] M. Rodriguez-Torres, S. Glass, J. Hill, B. Freilich, D. Hassman, A. M. Di Bisceglie, J. G. Taylor, B. J. Kirby, H. Dvory-Sobol, J. C. Yang, D. An, L. M. Stamm, D. M. Brainard, S. Kim, D. Krefetz, W. Smith, T. Marbury and E. Lawitz, *J. Viral Hepatitis* **2016**, *23*, 614-622.
[25] a) H. Lebel, J. F. Marcoux, C. Molinaro, Charette, A. B. *Chem. Rev*. **2003**, 103, 977-1050. C. Ebner, E. M. Carreira, *Chem. Rev*. **2017**, *117*, 11651-11679. b) L. Y. Dian, I. Marek, *Chem. Rev*. **2018**, *118*, 8415-8434.

and (4) the metal-catalyzed decomposition of diazo derivatives (**Scheme 2**).



Scheme 2. Main strategies for the asymmetric synthesis of cyclopropane derivatives.

The enantioselective Simmons-Smith-Furukawa cyclopropanation reaction is a well-developed reaction and was mostly reported by Charette and coworkers. This approach using organozinc reagent with a Lewis base provides a broad range scope of cyclopropylmethanols with high enantioselectivities.[26,27]

The Kulinkovich reaction is a widely used method for the preparation of cyclopropanols, the reaction relies on the addition of a Grignard reagent to an ester in the presence of a chiral titanium species leading to the cyclopropanols in good enantioselectivities.[28]

Michael Initiate Ring Closure (MIRC) reaction is also a powerful method and has been widely used for the preparation of cyclopropanes. The Corey−Chaykovsky cyclopropanation reaction is one typical MIRC reaction involves the addition of a sulfur ylide to an enone, generating a transient enolate, which undergoes a subsequent intramolecular cyclization to give the cyclopropane motif.[29] The second representative approach: the asymmetric cyclopropanation of electron poor alkenes, such as enals, enones, α, β-unsaturated esters, amides and nitriles in the presence of a chiral organic

[26] a) A. B. Charette, B. Cote, J. F. Marcoux, *J. Am. Chem. Soc.* **1991**, *113*, 8166. b) A. B. Charette, J. F. Marcoux. *Tetrahedron Lett.* **1993**, *34*, 7157. c) A. B. Charette, N. Turcotte, J.-F Marcoux, *Tetrahedron Lett.* **1994**, *35*, 513. d) A. B. Charette, H. Juteau, *J. Am. Chem. Soc*. **1994**, *116*, 2651-2652. e) A. B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc*. **1998**, *120*, 11943-11952.

[27] a) A. B. Charette, C. Brochu, *J. Am. Chem. Soc.* **1995,** *117,* 11367. b) A. B. Charette, C. Molinaro, C. Brochu, *J. Am. Chem. Soc.* **2001,** *123,* 12168-12175.

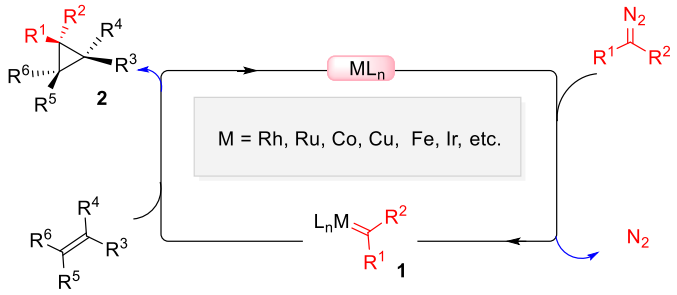
[28] a) Y. A. Konik, D. G. Kananovich, O. G. Kulinkovich, *Tetrahedron* **2013**, *69*, 6673-6678. b) O. G. Kulinkovich, D. G. Kananovich, M. Lopp, V. Snieckus, *Adv. Synth. Catal*. **2014**, *356*, 3615-3626.

[29] a) B. H. Zhu, R. Zhou, J. C. Zheng, X. M. Deng, X. L. Sun, Q. Shen, Y. Tang, *J. Org. Chem.* **2010**, *75*, 3454-3457. b) H. Y. Wang, F. Yang, X. L. Li, X. M. Yan, Z. Z. Huang, *Chem. Eur. J*. **2009**, *15*, 3784-3789. c) N. Kanomata, R. Sakaguchi, K. Sekine, S. Yamashita, H. Tanaka, *Adv. Synth. Catal*. **2010**, *352*, 296-2978.

catalyst, after the 1,3-elimination to form cyclopropane derivatives with excellent enantiomeric ratios.[30,31,32]

In this chapter, we will focus our attention on metal-catalyzed asymmetric cyclopropanation with diazo derivatives as it is the main purpose of this thesis.

1.4.1 Transition metal catalyzed cyclopropanation



Scheme 3. Catalytic cycle for the metal-catalyzed cyclopropanation reactions.

The cyclopropanation of olefins using a transient carbene species formed with a transition metal and a diazo compound is a well-studied subject and a widely used tool nowadays for the enantioselective synthesis of cyclopropanes. Reports about this transformation could occur either through an inter- or intramolecular process. It is generally accepted that the mechanism of the transition metal catalyzed cyclopropanation reaction proceeds via the generation of a metal-carbene complex **1** along with the extrusion of nitrogen gas. The cyclopropane ring **2** is then formed by the association of the metal-carbene **1** and the olefin through a [2+1] cycloaddition reaction (see **Scheme 3**).[25]

A wide range of transition metal catalysts in association with a large number of chiral ligands have been reported to catalyze the decomposition of diazo compounds for the enantioselective synthesis of cyclopropanes. Therefore, in this section, relevant examples of various transition metal asymmetric catalyzed cyclopropanation reaction

[30] a) J. vesely, G. Zhao, A. Bartoszewicz, A. Córdova, *Tetrahedron Lett.* **2008**, *49*, 4209-4212. b) I. Ibrahem, G.L. Zhao, R. Rios, J. Vesely, H. Sundén, P. Dziedzic, A. Córdova, *Chem. Eur. J.* **2008**, *14*, 7867-7879. c) X. Companyó, A. N. Alba, F. Cárdenas, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2009**, 3075-3080. d) W. Li, X. Li, T. Ye, W. Wu, X. Liang, J. Ye, *Tetrahedron Lett.* **2011**, 52, 2715–2718. e) M. Rueping, H. Sunden, L. Hubener, E. Sugiono, *Chem. Commun.* **2012**, *48*, 2201-2203.

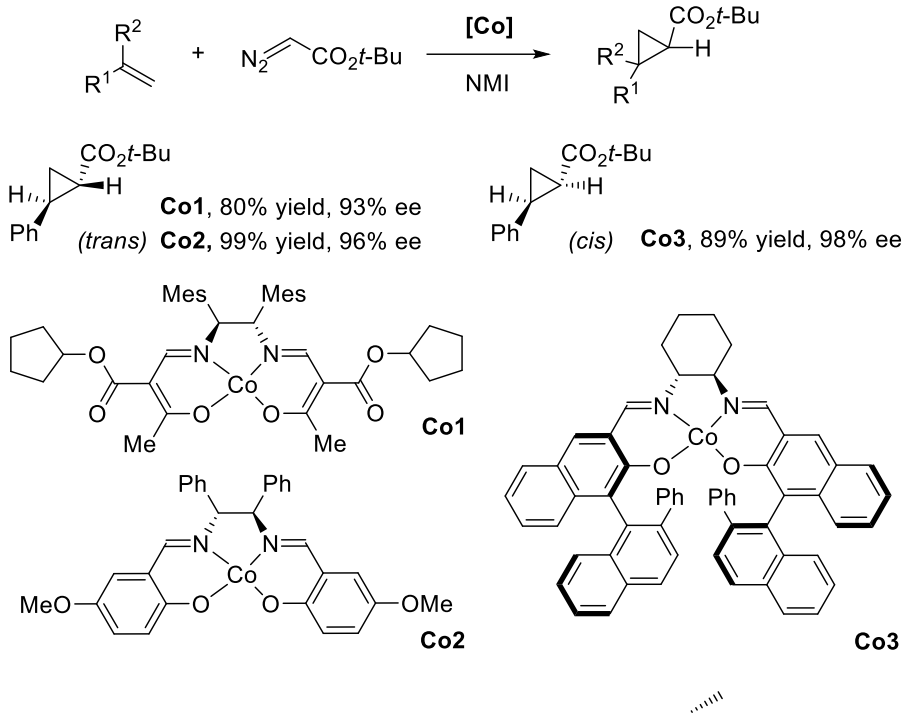
[31] a) U. Uxue, J. L. Vicario, D. Badía, L. Carrillo, E. Reyes, A. Pesquera, *Synthesis* **2010**, *4*, 701-713. b) A. Russo, S. Meninno, C. Tedesco, A. Lattanzi, *Eur. J. Org. Chem.* **2011**, 5096-5103. c) A. Russo, A. Lattanzi, *Tetrahedron: Asymmetry* **2010**, *21*, 1155-1157. d) A. Russo, A. Lattanzi, *Tetrahedron: Asymmetry* **2010**, *21*, 1155-1157. e) V. Wascholowski, H. M. Hansen, D. A. Longbottom, S. V Ley, *Synthesis* **2008**, 1269-1275.

[32] a) L. Dong, Q. Du, C. Lou, J. Zhang, R. Lu, M. Yan, *Synlett* **2010**, 266-270.b) J. Lv, J. Zhang, Z. Lin, Y. Wang, *Chem. Eur. J.* **2009**, *15*, 972-979. c) X. Dou, Y. Lu, *Chem. Eur. J.* **2012**, *18*, 8315-8319. d) U. Das, Y. Tsai, W. Lin, *Org. Biomol. Chem.* **2013**, *11*, 44-47.

will be highlighted.

Cobalt

Earlier studies in asymmetric cobalt catalyzed cyclopropanation reactions were quite limited because of modest diastereo- and enantioselectivities.[33] Yamada and coworkers reported the enantioselective cyclopropanation of styrenes and diazoacetates in the presence of a cobalt complex **Co1** with 2 equivalents of NMI (*N*-methyl-imidazole). The use of **Co1**, which derived from optically pure 1,2-(2,4,6-trimethylphenyl)-1,2-ethylenediamine (**Scheme 4**) in the cyclopropanation of styrene with *tert*-butyl diazoacetate proceeded very well, providing preferentially the *trans*-cyclopropane in excellent yield and ee (enantiomeric excess).[34]

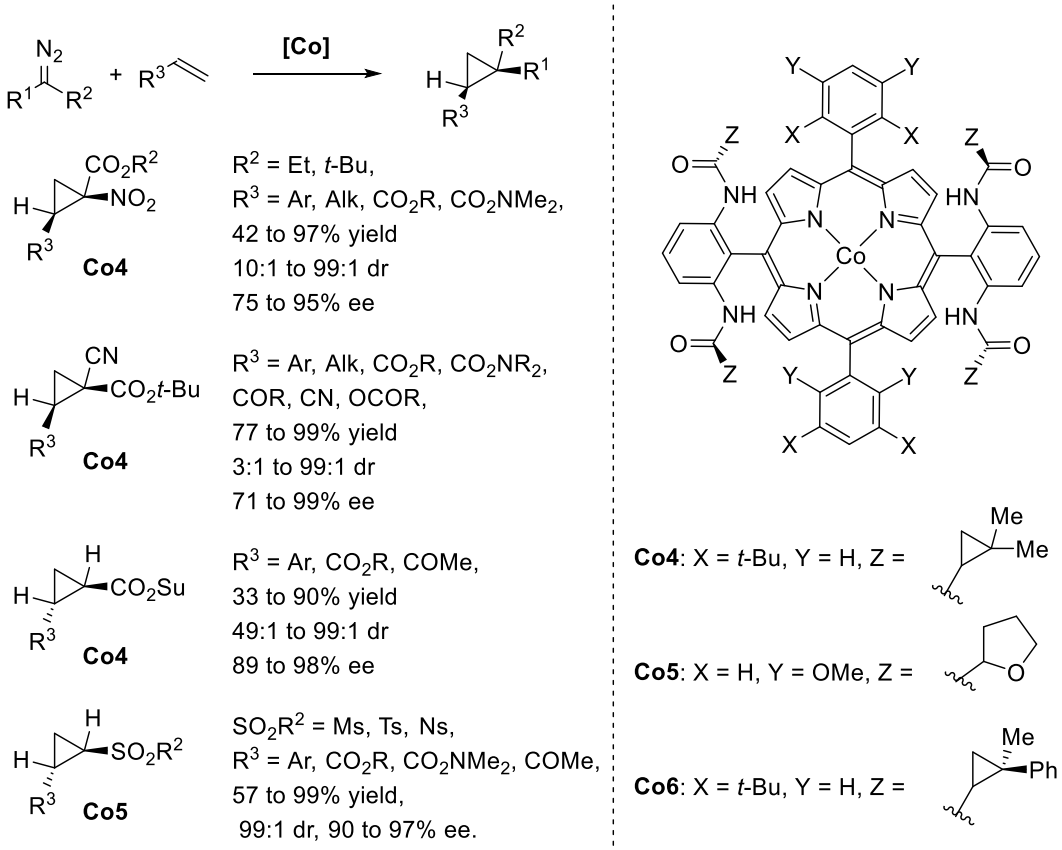


Scheme 4. Co-salen catalyzed asymmetric synthesis of *trans*- and *cis*-selective cyclopropanes.

Later, Katsuki and coworkers described two chiral cobalt (II) salens **Co2** and **Co3**, which were applied to the cyclopropanation of styrene with *tert*-butyl diazoacetate (**Scheme 4**). Both *trans*- and *cis*-selective asymmetric cyclopropanation reactions were achieved, independently. The catalyst **Co2**, directed related to the structure of the catalyst **Co1**, which was obtained from optically pure 1,2-diphenyl-1,2-

[33] a) Y. Tatsuno, A. Konishi, A. Nakamura, S. Otsuka, *J. Chem. Soc., Chem. Commun.* **1974**, 588. b) G. Jommi, R. Pagliarin, G. Rizzi, M. Sisti, *Synlett* **1993**, 833.
[34] T. Ikeno, M. Sato, T. Yamada, *Chem. Lett.* **1999**, *28*, 1345-1346.

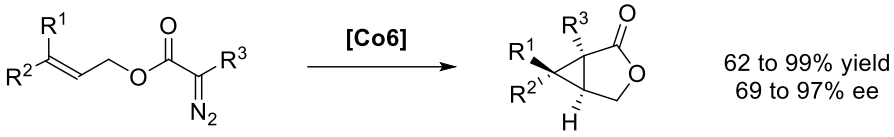
ethylenediamine, providing the *trans*-cyclopropane as Yamada's work. The use of the catalyst **Co3** gave *cis*-selective cyclopropanes in very good yields and excellent enantioselectives. In their report, the cyclopropanation of α-methyl styrene, a 1,1-disubstituted olefin, was also investigated in the presence of the catalyst **Co3**. The desired cyclopropane was obtained with a 4:1 ratio diastereoselectivity, both *cis*- and *trans*-cyclopropanes were observed with excellent enantiomeric excesses (99%).[35]



Scheme 5. Chiral cobalt porphyrin complexes catalyzed intermolecular cyclopropanation reactions.

Zhang and coworkers reported several successful synthetic applications of chiral cobalt porphyrins in the asymmetric cyclopropanation reactions. In the presence of the catalyst **Co4** or **Co5**, the intermolecular cyclopropanation of alkenes with α-nitro diazoacetates,[36] *tert*-butyl α-cyano diazoacetate,[37] succinimidyl diazoacetate[38] and α-diazosulfones[39] all proceeded very well, leading to the corresponding cyclopropanes with very good diastereo- and enantioselectivities **(Scheme 5**).

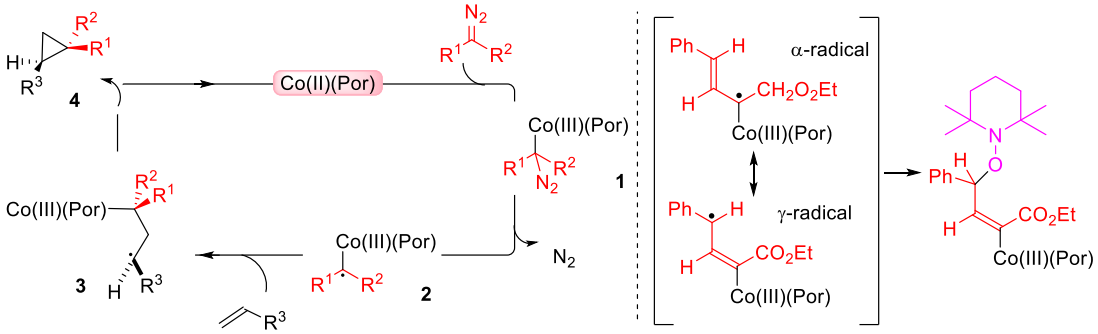
[35] T. Niimi, T.Uchida, R. Irie, T. Katsuki, *Tetrahedron Lett.* **2000**, *41*, 3647-3651.
[36] S. Zhu, J. A. Perman, X. P. Zhang, *Angew. Chem. Int. Ed.* **2008**, *47*, 8460-8463.
[37] S. Zhu, X. Xu, J. A. Perman, X. P. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12796-12799.
[38] J. V. Ruppel, T. J. Gauthier, N. L. Snyder, J. A. Perman, X. P. Zhang, *Org. Lett.* **2009**, *11*, 2273-2276.
[39] S. Zhu, J. V. Ruppel, H. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042-5043.



R^1 = H, Me, Et
R^2 = H, Ar, PhCH=CH
R^3 = H, Me, CN, NO_2, CO_2R, COR.

Scheme 6. Chiral cobalt porphyrin complexes catalyzed intramolecular cyclopropanation reactions.

Resulting from a slight modification in the structure of the **Co4**, cobalt complex **Co6** (**Scheme 5**) was found to be efficient in the intramolecular cyclopropanation reaction (**Scheme 6**), [40] Following this approach, a one-step synthesis of bicyclic compounds derived from linear unsaturated diazo precursors were obtained in good to excellent yields and enantioselectivities.



Scheme 7. Proposed mechanism for cobalt porphyrin catalyzed cyclopropanation and cobalt (III) carbene radical trapped by TEMPO.

DFT calculations suggested that the mechanism of this cobalt porphyrin catalyzed cyclopropanation reaction goes through a stepwise radical process. Zhang and coworkers reported that in the absence of alkene, the reaction of cobalt (II) porphyrin complex with ethyl styryldiazoacetate was found to generate the corresponding cobalt (III) vinylcarbene radical, and its γ-radical allylic resonance form was trapped by TEMPO via C-O bond formation to give a mononuclear cobalt (III) complex, which confirmed the existence of cobalt carbene radicals (**Scheme 7**).[41]

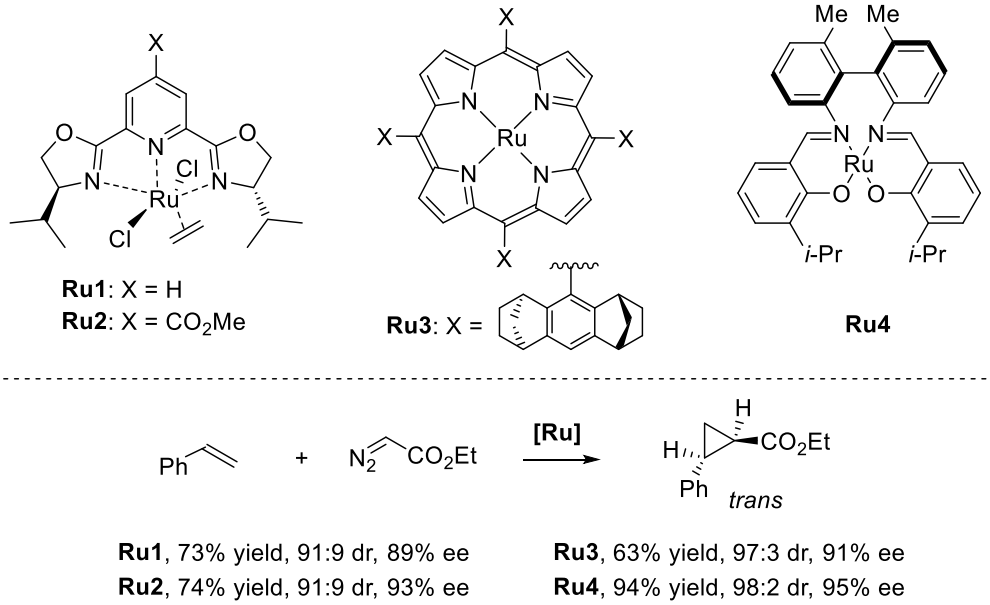
Ruthenium

Chiral ruthenium complexes are also known as efficient catalysts for the asymmetric

[40] X. Xu, H. Lu, J. V. Ruppel, X. Cui, S. Lopez de Mesa, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 15292-15295.
[41] a) W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2010**, *132*, 10891-10902. b) H. Lu, W. I. Dzik, X. Xu, L. Wojtas, B. de Bruin, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 8518-8521.

cyclopropanation reaction. In general, three main categories of chiral ligands have been successfully used in association with ruthenium for the asymmetric cyclopropanation reactions: (1) ligands including chiral oxazoline moiety,[42] (2) chiral ruthenium-porphyrin complex,[44] and (3) chiral ruthenium Schiff base.[45]

Nishiyama and coworkers developed a chiral ruthenium-pybox catalyst **Ru1 (Scheme 8**),[42] to perform the cyclopropanation of styrene with ethyl diazoacetate, providing the *trans*-cyclopropane in 73% yield with excellent diastereo- and enantioselectivity. The introduction of an ester substituent on the ligand (**Ru2**), allows the formation of the product with a higher enantioselectivity (93 vs 89% ee).[43]

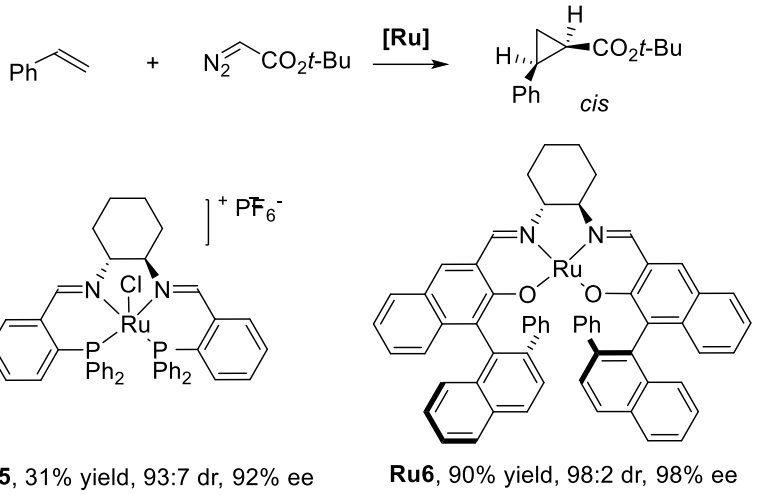


Scheme 8. Chiral ruthenium complexes catalyzed cyclopropanation of styrene with ethyl diazoacetate.

Similar to cobalt catalysts (**Co3** and **Co4**), ruthenium complexes based on a porphyrin core (**Ru3**) or a salen one (**Ru4**) (**Scheme 8**),[44] have shown their efficiency in the asymmetric cyclopropanation reaction. It's interesting to note that the ruthenium complexes **Ru1-4** allowed the formation of *trans*-cyclopropanes with very good enantioselectivities. Complementary, the use of ruthenium complex **Ru5** (**Scheme 9**), synthesized from optically pure *trans*-cyclohexanediamine, led the corresponding *cis*-cyclopropane as the major product.[45] A modification of the structure of the salen ligand, using a BINOL derivative (**Ru6)**, gave the *cis*-cyclopropane with better yield and

[42] H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223-2224.
[43] S. B. Park, K. Murata, H. Matsumoto, H. Nishiyama, *Tetrahedron: Asymmetry* **1995**, *6*, 2487-2494.
[44] a) W. C. Lo, C. M. Che, K. F. Cheng, T. C. W. Mak, *Chem. Commun.* **1997**, 1205–1206. b) I. J. Munslow, K. M. Gillespie, R. J. Deeth, P. Scott, *Chem. Commun.* **2001**, 1638–1639.
[45] S. Bachmann, M. Furler, A. Mezzetti, *Organometallics* **2001**, *20*, 2102–2108

enantioselectivity (**Scheme 9**).[46]

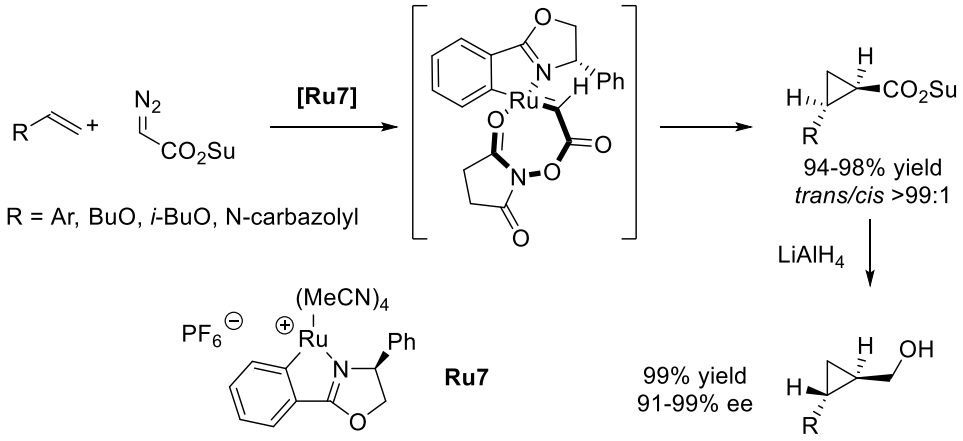


Ru5, 31% yield, 93:7 dr, 92% ee

Ru6, 90% yield, 98:2 dr, 98% ee

Scheme 9. Chiral ruthenium complex catalyzed *cis*-selective cyclopropanation reaction.

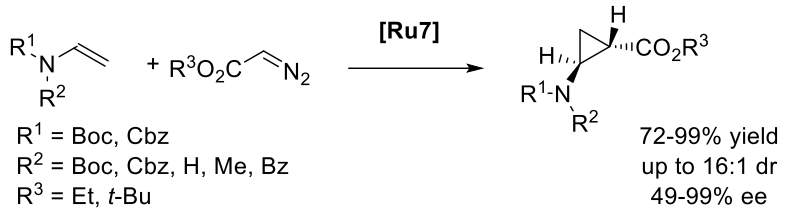
Iwasa and coworkers described a ruthenium-phenyloxazolidinyl complex **Ru7** (**Scheme 10**), which catalyzed the asymmetric cyclopropanation of monosubstituted alkenes with succinimidyl diazoacetate. The reaction was completed within minutes under mild conditions, provided the *trans*-cyclopropanes in excellent yields with very high diastereoselectivities, and excellent enantioselectivities were measured on the reduced cyclopropylmethanol adducts.[47] The formation of the *trans*-cyclopropane as a major isomer was explained because the reaction went through a seven-membered ring, which generated by the coordination between the ruthenium metal center and the succinimidyl carbonyl group. This steric hindrance determined the preferred direction for the terminal alkene attack to the ruthenium carbene.



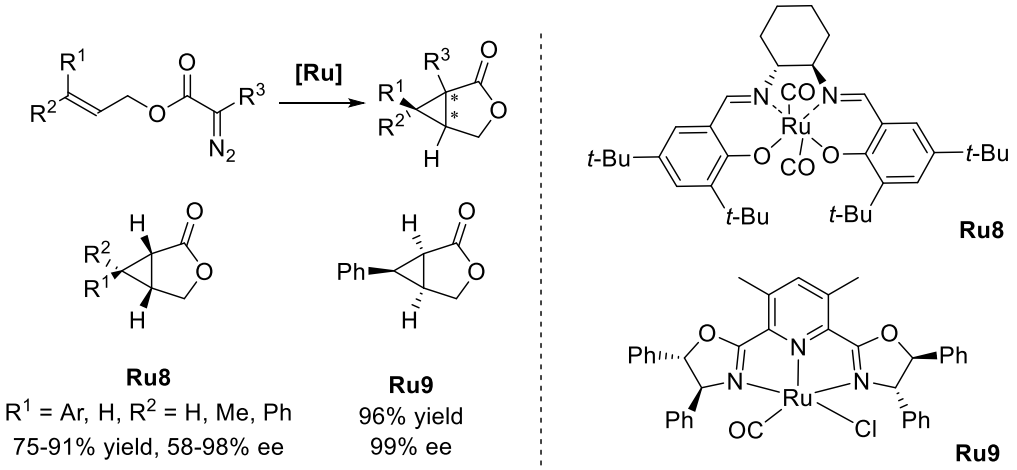
[46] T. Uchida, T. Katsuki, *Synthesis* **2006**, *10*, 1715–1723.
[47] S. Chanthamath, K. Phomkeona, K. Shibatomi, S. Iwasa, *Chem. Commun.* **2012**, *48*, 7750-7752.

Scheme 10. Ruthenium-pheox **Ru7** catalyzed cyclopropanation of terminal alkenes.

Later, the same group reported this complex **Ru7** could be used efficiently for the asymmetric cyclopropanation of vinyl carbamates with diazoesters (**Scheme 11**).[48]



Scheme 11. Catalytic asymmetric cyclopropanation of vinyl carbamates with **Ru7**.



Scheme 12. Asymmetric synthesis of 3-oxabicyclo[3.1.0]hexane-2-one derivatives.

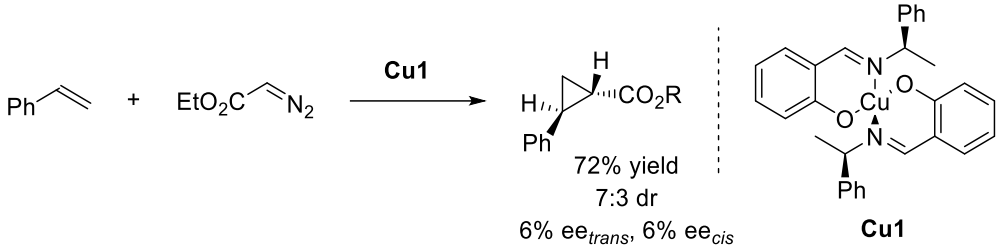
In addition, chiral ruthenium complexes were successfully applied to the intramolecular cyclopropanation reaction. For instance, the asymmetric synthesis of bicyclic compounds using 1 mol% of ruthenium-salen **Ru8** or ruthenium-phebox **Ru9**, led to the expected cyclopropane in high yields with excellent enantiomeric excesses (**Scheme 12**).[49] It's interesting to note that salen type ruthenium complex **Ru8** allowed the formation of *exo*-cyclopropanes, whereas the ruthenium-phebox **Ru9** provided *endo*-cyclopropanes as the major product.

Copper

In the past decades, plethora of chiral ligands have been designed and investigated in the copper catalyzed inter- or intramolecular cyclopropanation reaction. The structure of the chiral ligands includes salicylaldimines, bis(oxazolines), bipyridines, semicorrins, bisazaferrocenes, for instance. Hence, only the most efficient examples and relevant

[48] S. Chanthamath, D. T. Nguyen, K. Shibatomi, S. Iwasa, *Org. Lett.* **2013**, *15*, 772-775.
[49] a) J. I. Ito, S. Ujiie, H. Nishiyama, *Chem. Eur. J*. **2010**, *16*, 4986-4990. b) Z. J. Xu, R. Fang, C. Y. Zhao, J. S. Huang, G. Y. Li, N. Y Zhu, C. M. Che, *J. Am. Chem. Soc.* **2009**, *131*, 4405-4417.

examples will be discussed for the intermolecular cyclopropanation reaction in this section.



Scheme 13. Nozaki's copper catalyzed cyclopropanation reaction.

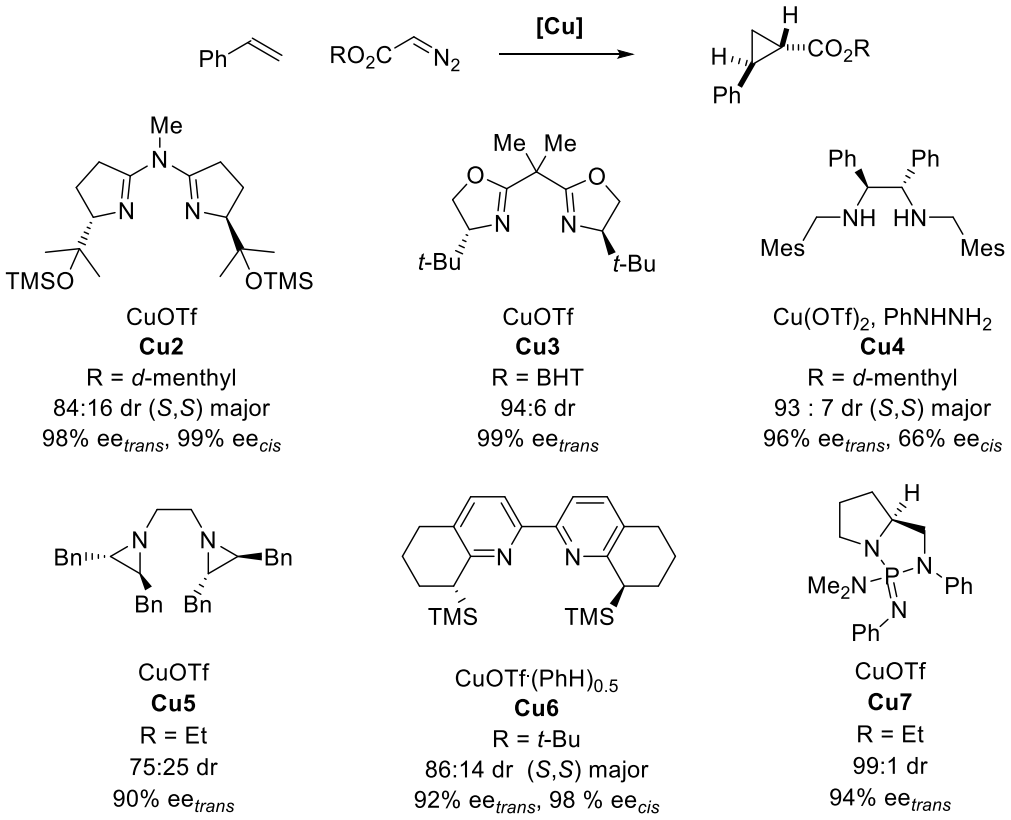
Nozaki reported the first asymmetric copper catalyzed cyclopropanation reaction in 1966, although the enantiomeric excess was modest (6% ee, **Scheme 13**). After this seminal report, significant efforts have been devoted to the design of efficient ligands for the asymmetric cyclopropanation reaction. For example, Pfaltz and coworkers designed and synthesized catalyst **Cu2** (**Scheme 14**), which proved to be an efficient catalyst for the enantioselective cyclopropanation of styrene and diazoacetates.[50]

Indeed, chiral bisoxazolines have played an important role for the metal catalyzed asymmetric reactions, including the asymmetric cyclopropanation reaction. Evans and coworkers described the use of the copper complex **Cu3** in the cyclopropanation reaction of diazoacetates with monosubstituted or 1,1-disubstituted alkenes. In general, the corresponding cyclopropanes were obtained in high yields and enantioselectivities.[51]

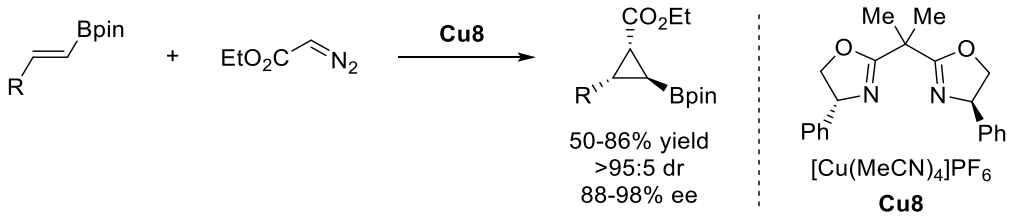
Copper complexes including diamines ligands such as **Cu4**,[52] **Cu5**,[53] or bipyridine (**Cu6**), were tested and were proved to be efficient in asymmetric copper catalyzed cyclopropanation reactions.

In the presence of iminodiazaphospholidine ligand (**Cu7**), the cyclopropanation of alkenes with non-bulky diazoesters proceed in high yields with excellent diastereo- and enantioselectivities.[54]

[50] U. Leutenegger, G. Umbricht, C. Fahrni, P. von Matt, A. Pfaltz, *Tetrahedron* **1992**, *48*, 2143-2156.
[51] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726-728.
[52] S. Kanemasa, S. Hamura, E. Harada, H. Yamamoto, *Tetrahedron Lett.* **1994**, *35*, 7985-7988.
[53] D. Tanner, F. Johansson, A. Harden, P. G Andersson, *Tetrahedron* **1998**, *54*, 15731-15738.
[54] J. M. Brunel, O. Legrand, S. Reymond, G. Buono, *J. Am. Chem. Soc.* **1999**, *121*, 5807-5808.



Scheme 14. Examples of chiral ligands used for the asymmetric copper catalyzed cyclopropanation reaction.



Scheme 15. Asymmetric copper catalyzed cyclopropanation of 1-alkenylboronates.

Recently, Pérez and coworkers reported a highly enantio- and diastereoselective synthesis of 1-boryl-2,3-disubstituted cyclopropanes by using catalytic amount of **Cu8** as the catalyst (**Scheme 15**).[55]

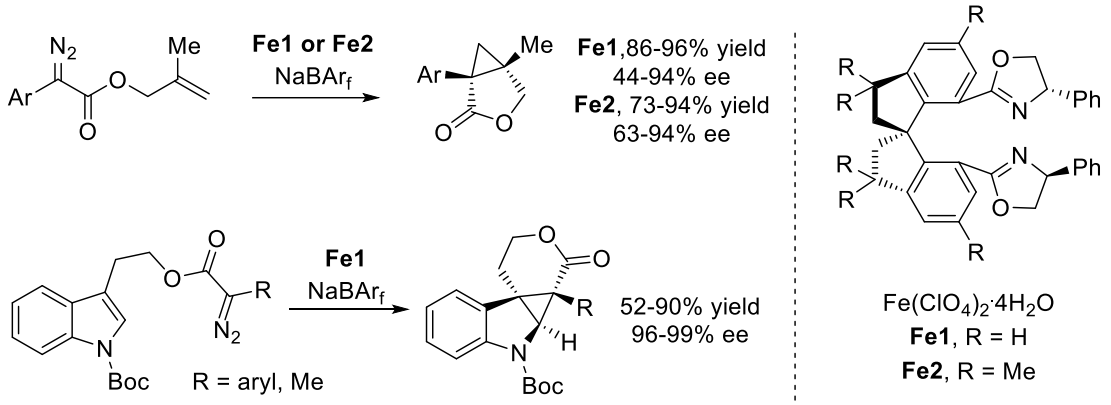
Iron

There are only a few reports dealing with the iron catalyzed asymmetric cyclopropanation reaction. First, Zhou and coworkers described an iron complex using chiral spiro-bisoxazoline as the ligand **Fe1**, and employed it as a catalyst in highly enantioselective intramolecular cyclopropanation of linear unsaturated diazo

[55] J. Carreras, A. Caballero, P. J. Pérez, *Angew. Chem. Int. Ed*. **2018**, *57*, 2334-2338.

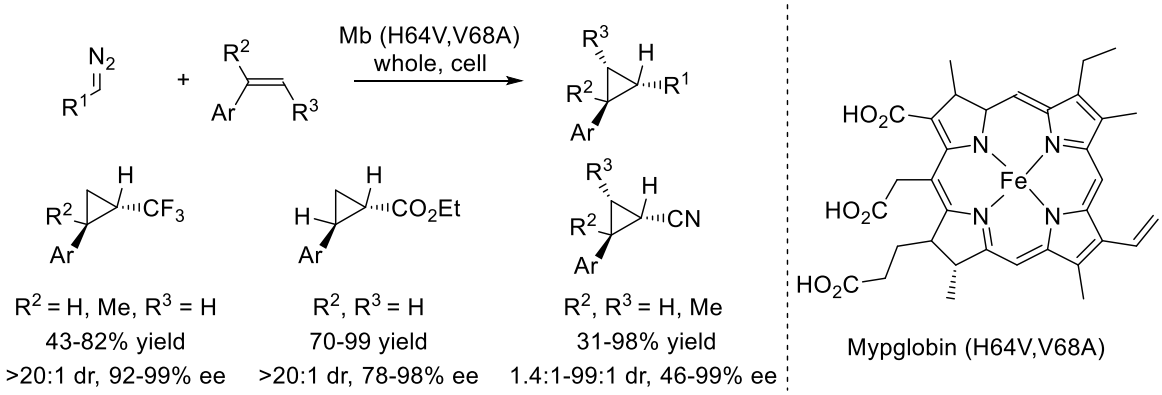
precursors or diazo derivatives bearing an indole residue (**Scheme 16**).[56]

Lin and coworkers reported a similar reaction for the preparation of [3.1.0]bicyclolactones using $FeCl_2 \cdot 4xH_2O$ and modified chiral spiro-bisoxazoline ligand as the catalyst, providing [3.1.0]bicyclolactones with high enantiomeric excesses.[57]



Scheme 16. Iron catalyzed asymmetric intramolecular cyclopropanation reactions.

Another strategy to access enantiomerically pure cyclopropanes was reported by Fasan and coworkers. This very specific and particular reaction was performed in the presence of engineered myoglobin catalysts expressed in bacterial cells. The iron porphyrin complex in the myoglobin is the active site, where the cyclopropanation occurs. This approach was successfully applied to the preparation of a variety of *trans*-cyclopropanes bearing trifluoromethyl,[134] ester[58] or cyano functions[59] in good to excellent yields with excellent diastereoselectivities and enantiomeric excesses in most cases (**Scheme 17**).



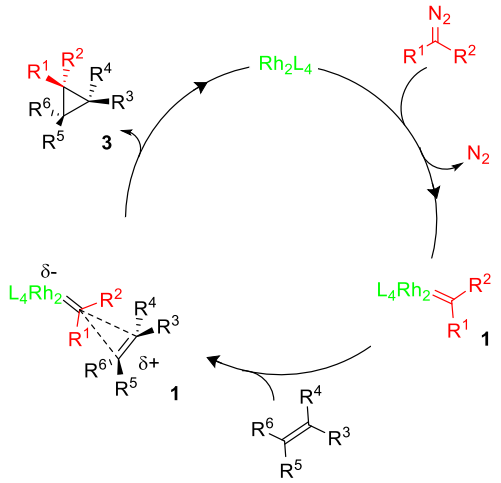
Scheme 17. Myoglobin catalyzed asymmetric intermolecular cyclopropanation

[56] a) J. Shen, S. Zhu, Y. Cai, H. Xu, X. Xie, Q. Zhou, *Angew. Chem. Int. Ed*. **2014**, *53*, 13188-13191. b) H. Xu, Y. Li, Y. Cai, G. Wang, S. Zhu, Q, Zhou, *J. Am. Chem. Soc*. **2017**, *139*, 7697-7700.
[57] H. Gu, S. Huang, X. Lin, *Org. Biomol. Chem*. **2019**, *17*, 1154-1162.
[58] G. Sreenilayam, E. J. Moore, V. Steck, R. Fasan, *ACS Catal.* **2017**, *7*, 7629-7633.
[59] A. L. Chandgude, R. Fasan, *Angew. Chem. Int. Ed.* **2018**, *57*, 15852-15856.

reactions.

Rhodium

The reaction of dirhodium (II) carbenoid species, formed from the reaction of a diazo compound with a dirhodium (II) catalyst, followed an addition of an alkene with this carbenoid species is one of the most efficient and commonly used method to construct the cyclopropyl motif.



Scheme 18. The proposed mechanism for rhodium catalyzed cyclopropanation reaction.

The general accepted mechanism for this reaction starts with the generation of the dirhodium (II) carbene intermediate (**Scheme 18**). The interesting point is that the carbene binding only occurs at one of the two rhodium active sites, which was proved by computational and kinetic studies.[60]

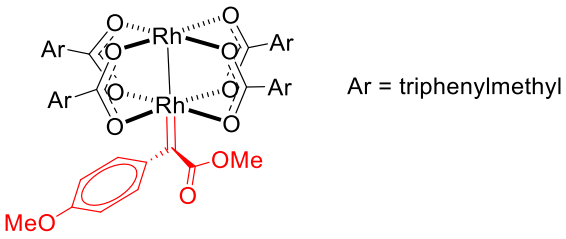


Figure 9. Metastable dirhodium (II) carbene complex.

The formation of a dirhodium (II) carbene intermediate in dirhodium (II) catalyzed diazo decompositions remained elusive until Davies, Berry and coworkers reported a metastable dirhodium (II) carbenoid intermediate (**Figure 9**). This species was stable

[60] a) M. C. Pirrung, A. T. Morehead, *J. Am. Chem. Soc*. **1996**, *118*, 8162-. b) E. Nakamura, N. Yoshikai, M. Yamanaka, *J. Am. Chem. Soc*. **2002**, *124*, 7181-7192. c) M. C. Pirrung, H. Liu, A. T. Morehead, *J. Am. Chem. Soc*. **2002**, *124*, 1014-1023.

at 0 ºC for hours (≈20 h) in chloroform, which allowed the authors to characterize the Rh=C bond vibrational and NMR spectroscopy, extended X-ray absorption, fine structure analysis, and quantum chemical calculations.[61]

Structurally, dirhodium (II) complexes are characterized by a bimetallic Rh-Rh single bond, bridging four μ^2-carboxylate, carboxamidate, phosphonate or other ligands (**Figure 10**).

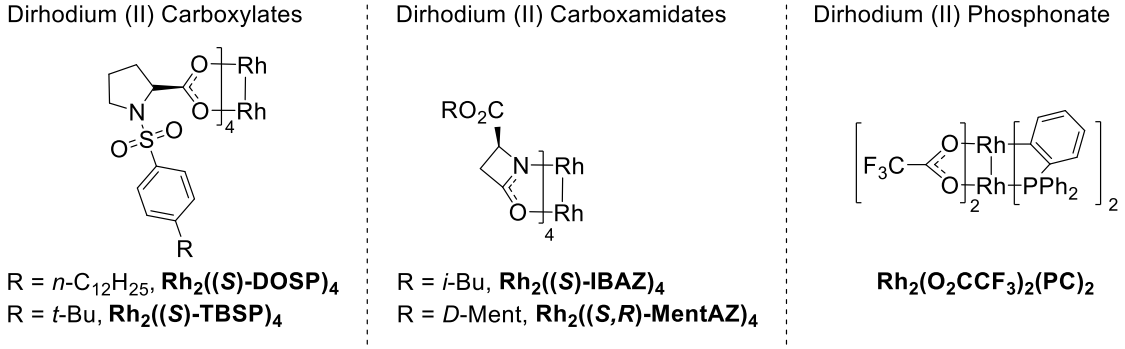


Figure 10. Examples of different classes of chiral dirhodium catalysts.

Dirhodium (II) carboxylates

Hansen and Davies reviewed that the conformation of chiral dirhodium (II) paddlewheel complexes is generally believed to be a critical factor in their chemistry. Considering that the four ligands can adapt an “up” or “down” conformation, by the distinct ligand orientations, there are four possible conformation models (**Figure 11**) : (1) the D_2 symmetric “up-down-up-down” conformation as suggested by Davies for the catalyst Rh_2((*S*)-DOSP)$_4$ or Rh_2((*R*)-BTPCP)$_4$ (**A**),[62] (2) the C_2 symmetric “up-up-down-down” arrangement for the catalyst Rh_2((*S*)-PTPA)$_4$ (**B**) described by Hashimoto,[63] (3) the Fox’s Rh_2((*S*)-PTTL)$_4$ model, which exists in an “all-up” distorted C_4 conformation (**C**), [64] and lastly, (4) the C_1 symmetric “up-up-up-down” arrangement.[62]

[61] K. P. Kornecki, J. F. Briones, V. Boyarskikh, F. Fullilove, J. Autschbach, K. E. Schrote, K. M. Lancaster, H. M. L. Davies, J. F. Berry, *Science* **2013**, *342*, 351-354.
[62] H. M. L. Davies, P. R. Bruzinski, D. H. Lake, N. Kong, M. J. Fall. *J. Am. Chem. Soc*. **1996**, *118*, 6897-6907.
[63] A. DeAngelis, O. Dmitrenko, G. P. Yap, J. M. Fox, *J. Am. Chem. Soc*. **2009**, *131*, 7230-7231.
[64] V. N. G. Lindsay, C. Nicolas, A. B. Charette, *J. Am. Chem. Soc*. **2011**, *133*, 8972-8981.

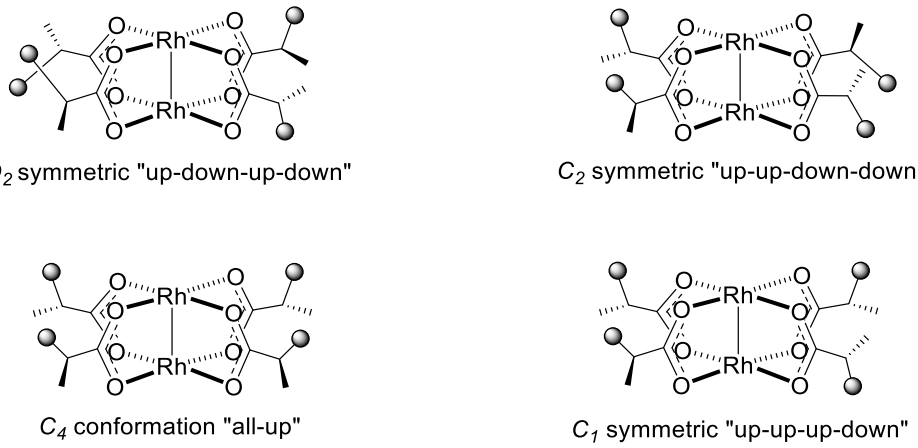


Figure 11. Four possible conformation models for different ligand arrangements.

In general, there are three main different ligands for chiral dirhodium (II) carboxylates (**Figure 12**). First, Mckervey explored the *N*-protected proline derivatives as carboxylate ligands.[65] However, this type catalysts weren't well noticed until Davies and coworkers found their applications. Then, Hashimoto, Ikegami and coworkers developed a series of dirhodium (II) carboxylates derived from *N*-phthalimido protected chiral amino acid. Lastly, dirhodium (II) catalysts derived from substituted cyclopropyl carboxylates explored by Davies and coworkers.

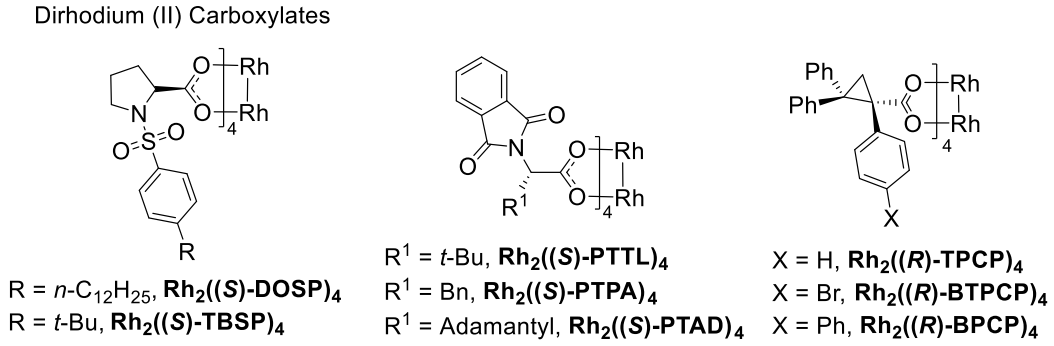


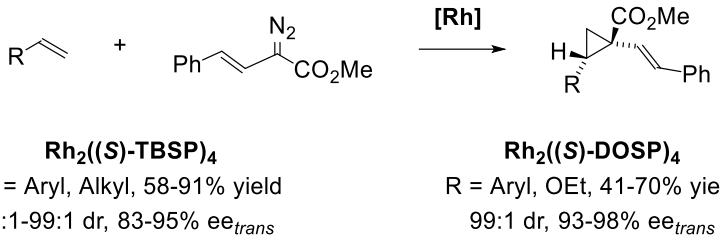
Figure 12. Typical dirhodium (II) carboxylates

Dirhodium (II) catalysts derived from proline.

Davies and coworkers reported the cyclopropanation of alkenes with vinyl diazoacetates in the presence of Rh_2((*S*)-TBSP)$_4$ or Rh_2((*S*)-DOSP)$_4$,[66] and the *trans*-cyclopropanes were obtained with high diastereoselectivities and enantioselectivities (**Scheme 19**). It's interesting to mention that no evidence of the formation of the

[65] M. Kennedy, M. A. McKervey, A. R. Maguire, G. H. P. Roos, J. *Chem. Soc., Chem. Commun*. **1990**, 361-362.
[66] a) H. M. L. Davies, D. K. Hutcheson, *Tetrahedron Lett.* **1993**, *34*, 7243–7246, b) H. M. L. Davies, P. R. Bruzinski, M. J. Fall, *Tetrahedron Lett.* **1996**, *37*, 4133–4136.

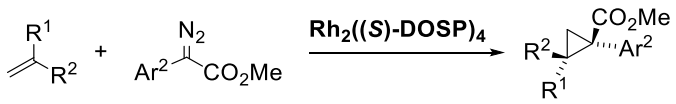
cyclized product (3*H*-pyrazole) resulting from an uncatalyzed [3+2] cycloaddition reaction was observed in this cyclopropanation reaction. Note that the long aliphatic chain variant: Rh_2((*S*)-DOSP)$_4$ was an exceptional chiral rhodium catalyst in this cyclopropanation transformation and led to the formation of the *trans*-cyclopropane products with 93-98% ees.



Scheme 19. Rhodium catalyzed cyclopropanation of α-vinyl diazoacetates.

The same authors reported that the reaction of methyl α-aryl diazoacetates with alkenes in the presence of Rh_2((*S*)-DOSP)$_4$ afforded the corresponding cyclopropanes in high diastereo- and enantioselectivities (**Table 3) (**entry 1).[66]

Note that under similar reaction conditions, 1,1-diarylethylenes were converted into the corresponding cyclopropanes with good to high diastereo- and enantioselectivities (entry 2).[67]



Entry	R^1	R^2	Yield, %	de, %	ee_{cis}, %
1[66]	Aryl, Alkyl, Alkoxy	H	63-90	74-96	64-88
2[67]	Aryl	Aryl	75-94	55-80	92-99
3[68]	Aryl	N_3	76-99	90-99	73-95

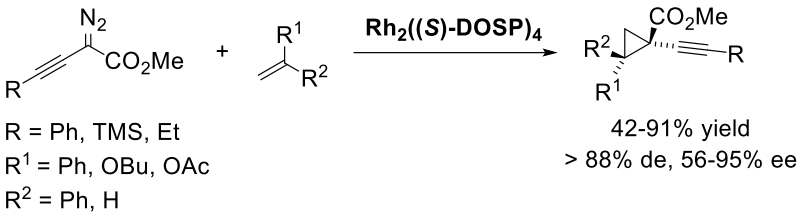
Table 3. Rh_2((*S*)-DOSP)$_4$ catalyzed asymmetric cyclopropanation reactions with α-aryl diazoacetates.

In 2003, Li and coworkers reported the use of Rh_2((*S*)-DOSP)$_4$ as the catalyst, for the catalyzed cyclopropanation of α-azidostyryl derivatives and the *cis*-azido cyclopropyl esters were synthesized with high diastereo- and enantioselectivities (entry 3).[68]

In 2002, Davies and Boebel reported the synthesis of cyclopropanes using Rh_2((*S*)-DOSP)$_4$ to catalyze the decomposition of α-alkynyl diazoacetates (**Scheme 20**).[69] This

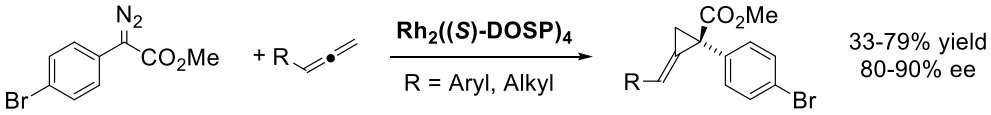
[67] H. M. L. Davies, T. Nagashima, J. L. Klino III, *Org. Lett*. **2000**, *2*, 823-826.
[68] P. Gu, Y. Su, X. Wu, J. Sun, W. Liu, P. Xue, R. Li, *Org. Lett*. **2012**, *14*, 2246-2249.
[69] H. M. L. Davies, T. A. Boebel, *Tetrahedron Lett*. **2000**, *41*, 8189-8192.

reaction led to the corresponding alkynyl cyclopropanes with good to excellent enantiomeric excess.

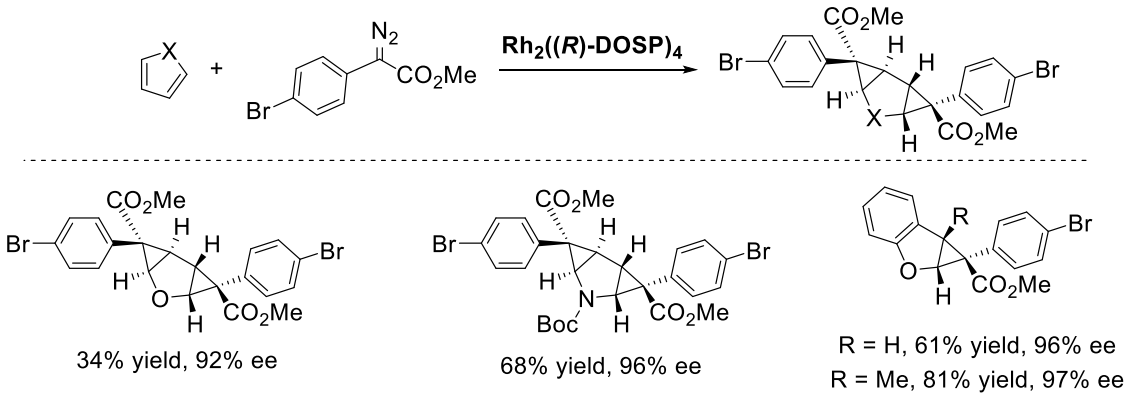


Scheme 20. $Rh_2((S)\text{-DOSP})_4$ catalyzed cyclopropanation of α-alkynyl diazoacetates.

Gregg and coworkers reported the asymmetric cyclopropanation of allenes with α-phenyl diazoacetate in the presence of $Rh_2((S)\text{-DOSP})_4$, resulting in the formation of the alkylidene cyclopropane derivatives in 80 to 90% ee (**Scheme 21**).[70]



Scheme 21. Cyclopropanation of allenes.



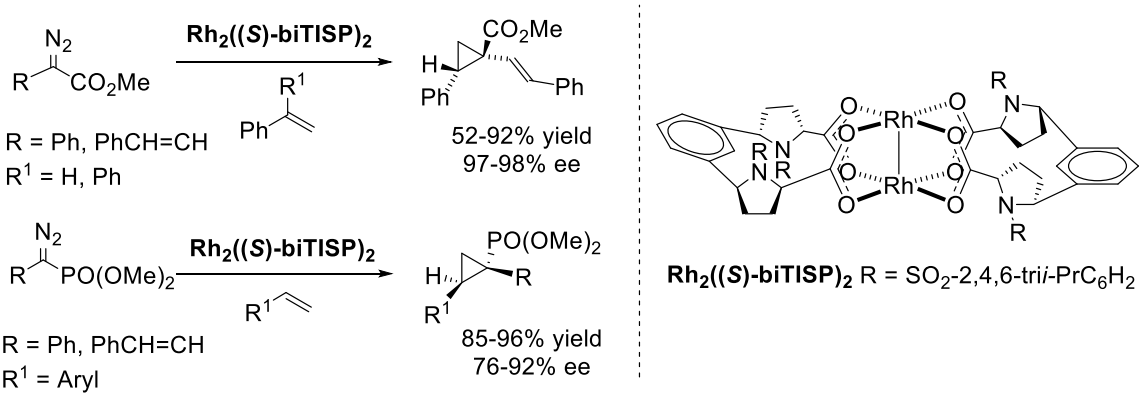
Scheme 22. $Rh_2((R)\text{-DOSP})_4$ catalyzed cyclopropanation of aryl diazoacetate with pyrroles or furans.

The enantiomer of $Rh_2((S)\text{-DOSP})_4$, namely $Rh_2((R)\text{-DOSP})_4$ can be used as the catalyst for the cyclopropanation of pyrroles or furans, leading to the formation of highly enantioselective mono- or bis-cyclopropylated heterocycles (**Scheme 22**).[71]

Indeed, $Rh_2((S)\text{-DOSP})_4$ is an excellent catalyst for asymmetric cyclopropanation reaction. However, this high level of asymmetric induction is limited to reaction involving donor-acceptor diazo compounds.[72]

[70] T. M. Gregg, M. K. Farrugia, J. R. Frost, *Org. Lett*. **2009**, *19*, 4434-4436.
[71] S. J. Hedley, D. L. Ventura, P. M. Dominiak, C. L. Nygren, H. M. L. Davies, *J. Org. Chem*. **2006**, *71*, 5349-5356.
[72] H. M. L. Davies, *Eur. J. Org. Chem*. **1999**, 2459-2469.

Davies and Panaro reported the synthesis of the D_2 symmetric dirhodium prolinate complex Rh_2((*S*)-biTISP)$_2$. This catalyst was efficient for the asymmetric cyclopropanation involving vinylcarbenoid and phenyl carbenoid (**Scheme 23**).[73] Later in 2004, Davies and Lee reported the Rh_2((*S*)-biTISP)$_2$ catalyzed reaction of dimethyl α-aryl diazomethylphosphonates with styrene derivatives in high yields with high diastereo- and enantioselectivities (>98% de, 76-92% ee) (**Scheme 23**).[74]



Scheme 23. Rh_2((*S*)-biTISP)$_2$ catalyzed cyclopropanation.

Dirhodium (II) catalysts derived from *N*-protected amino acids.

Structurally, dirhodium (II) carboxylate derived from chiral *N*-protected amino acid have a bimetallic Rh-Rh single bond, bridge with four μ^2-*N*-protected amino acid ligands, and these type of rhodium (II) catalysts were mainly developed by Hashimoto, Ikegami and coworkers.[75] The α-position of the amino acid is usually the modification site. Thus, a series of dirhodium (II) carboxylate complexes were derived from this structure (**Figure 13**).

[73] H. M. L. Davies, S. A. Panaro, *Tetrahedron Lett*. **1999**, *40*, 5287-5290.
[74] H. M. L. Davies, G. H. Lee, *Org. Lett*. **2004**, *13*, 2117-2120.
[75] a) T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajimaa, S. Hashimoto. *Chem. Commun*. **2001**, 1604-1605. b) S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc*. **1999**, *121*, 1417-1418. c) M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett*. **2002**, *43*, 9561-9564. d) S. Hashimoto, N. Watanabe, S. Ikegami, *Tetrahedron Lett*. **1990**, *31*, 5173-5174. e) K. Minami, H. Saito, H. Tsutsui, H. Nambu, M. Anada, S. Hashimoto, *Adv. Synth. Catal*. **2005**, *347*, 1483-1487.

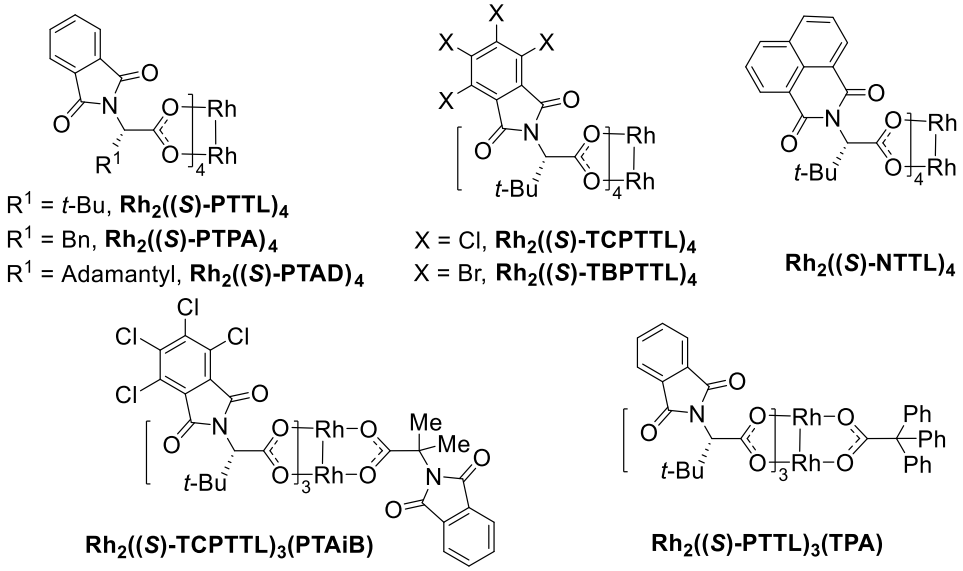
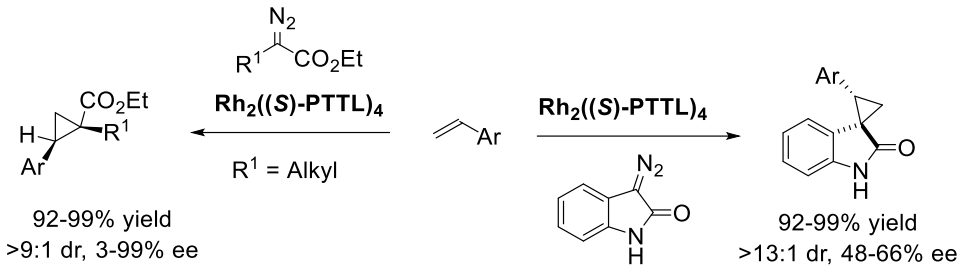


Figure 13. Dirhodium (II) carboxylates derived from chiral *N*-protected amino acids.

Fox and coworkers reported a Rh_2((*S*)-PTTL)$_4$ catalyst with a chiral crown conformation as determined by X-ray analysis. This conformation is also called “all-up” *C*$_4$ conformation. They applied the Rh_2((*S*)-PTTL)$_4$ catalyst in the asymmetric cyclopropanation of styrene with α-alkyl diazoacetates, providing the corresponding cyclopropanes in high yields with good diastereoselectivities, while the enantioselectivity depends on the substituent R^1 at the α position of the diazo compound. For instance, a bulky group at the α position led to higher enantioselectivity: Me (3% ee), Et (79% ee), *i*-Bu (99% ee) (**Scheme 24**).[63]

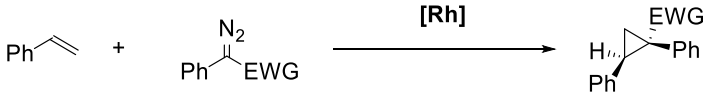


Scheme 24. Rh_2((*S*)-PTTL)$_4$ catalyzed cyclopropanation of alkyl diazoacetates and diazooxindole.

Arai and Awata reported the catalytic asymmetric cyclopropanation of styrene with diazooxindole in the presence of Rh_2((*S*)-PTTL)$_4$. The corresponding spiro-cyclopropyl oxindole derivatives were isolated in good yields with moderate to good enantioselectivities and diastereoselectivities (**Scheme 24**).[76]

[76] A. Awata, T. Arai, *Synlett* **2013**, *24*, 29-32.

Rh_2((*S*)-PTAD)$_4$ is another variant of the Hashimoto's phthalimido catalyst Rh_2((*S*)-TPTTL)$_4$, which was developed by Davies and coworkers.[77] It is usually an effective backup chiral rhodium catalyst when Rh_2((*S*)-DOSP)$_4$ fails to provide high asymmetric induction. Indeed, the Rh_2((*S*)-DOSP)$_4$ catalyzed cyclopropanation of styrene, with donor-acceptor diazo compounds with an acceptor group (EWG) such as nitrile, phosphonate or trifluoromethyl group, proved to be less effective (**Table 4**).[78] When the same cyclopropanation reactions were carried out with Rh_2((*S*)-PTAD)$_4$ as the catalyst, the corresponding products were obtained with exceptional diastereo- and enantioselectivities. [79] In addition, this high diastereo- and enantioselective cyclopropanation catalyzed by Rh_2((*S*)-PTAD)$_4$ were extended to a broad range of alkenes.



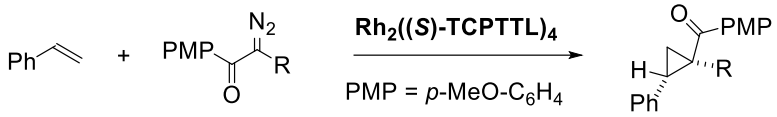
EWG	Rh_2((*S*)-DOSP)$_4$	Rh_2((*S*)-PTAD)$_4$
$PO(OMe)_2$	94% de, 34 % ee	94% de, 99 % ee
CF_3	94% de, 40 % ee	94% de, 98 % ee
CN	82% de, 17 % ee	94% de, 90% ee

Table 4. Rhodium catalyzed asymmetric cyclopropanation reactions.

In 2009, Charette and coworkers reported the asymmetric cyclopropanation of alkenes with α-nitro diazoacetophenones using Rh_2((*S*)-TCPTTL)$_4$ as the catalyst (**Table 5**), (entry 1). The corresponding products were obtained in very high ee. What's more, these cyclopropyl product were used as precursors for the synthesis of optically pure *cis*-cyclopropane α-amino acids.[80]

Later in 2011, Charette and coworkers extended this methodology to other di-acceptor diazo compounds (-CN, -CO_2Me) bearing an α-PMP-ketone group. The use of Rh_2((*S*)-TCPTTL)$_4$ as the catalyst allowed the formation of the corresponding cyclopropanes with high enantioselectivities (**Table 5**).[81]

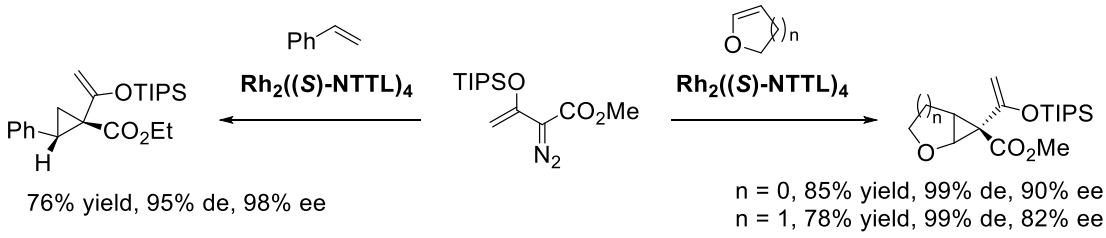
[77] R. P. Reddy, G. H. Lee, H. M. L. Davies, *Org. Lett*. **2006**, *16*, 3437-3440.
[78] H. M. L. Davies, A. M. Walji, In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; p 301.
[79] a) J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett*. **2007**, *9*, 2625-2628. b) J. R. Denton, K. Cheng, H. M. L. Davies, *Chem. Commun*. **2008**, 1238-1240.
[80] V. N. G. Lindsay, W. Lin, A. B. Charette, *J. Am. Chem. Soc*. **2009**, *131*, 16383-16385.
[81] V. N. G. Lindsay, C. Nicolas, A. B. Charette, *J. Am. Chem. Soc*. **2011**, *133*, 8972-8981.



Entry	R	Yield, %	dr	ee, %
1	NO_2	81	98:2	93
2	CN	98	95:5	84
3	CO_2Me	60	99:1	88

Table 5. Rh_2((*S*)-TCPTTL)$_4$ catalyzed decompose several diazo compounds.

Müller and coworkers described the synthesis of rhodium catalyst Rh_2((*S*)-NTTL)$_4$ using *N*-1,8-naphthaloyl-*L*-amino acid.[82] They found that Rh_2((*S*)-NTTL)$_4$ was efficient for the preparation of enantioenriched cyclopropanes from the decomposition of methyl α-silanyloxyvinyl diazoacetate (**Scheme 25**).[83] In addition, the reaction was extended to dihydrofuran and dihydropyran, respectively, providing the bicyclic products in good yields with high enantioselectivities (**Scheme 25**).[84]



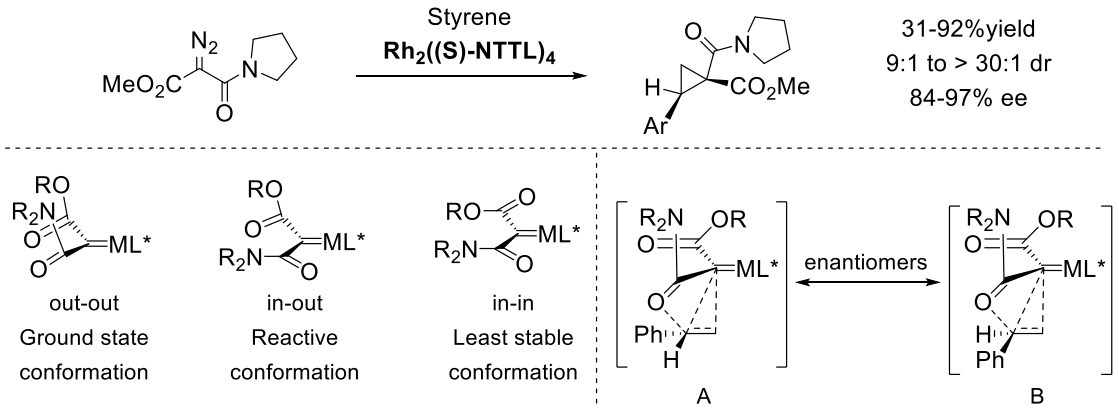
Scheme 25. Rh_2((*S*)-NTTL)$_4$ catalyzed cyclopropanation of methyl α-silanyloxyvinyl diazoacetate.

Charette and Marcoux reported a highly diastereo- and enantioselective synthesis of 1,1-dicarboxylic cyclopropane derivatives using Rh_2((*S*)-NTTL)$_4$ as the catalyst to decompose α-amide diazoacetate (**Scheme 26**).[85] In this report, the concept of the *trans*-directing ability of amide groups in rhodium (II) catalyzed cyclopropanation reactions was first introduced.

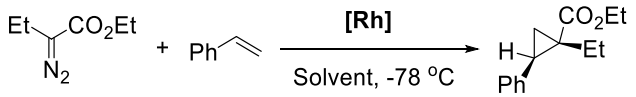
The authors hypothesized that the in-out conformation is the preferred conformation in the transition state, as the out-out conformation is unlikely positive for steric reasons. On the contrary, the in-in conformation should be higher in energy owing to the conjugation of the two electron-withdrawing groups, resulting in a very unstable

[82] P. Müller, Y. Allenbach, E. Robert, *Tetrahedron: Asymmetry* **2003**, *14*, 779-785.
[83] P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, H. D. Flack, *Org. Lett*. **2004**, *6*, 1725-1728.
[84] a) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri, S. Grass, *Synlett* **2005**, 1397-1400. b) P. Müller, Y. Allenbach, S. Chappellet, A. Ghanem, *Synthesis* **2006**, 1689-1696.
[85] D. Marcoux, A. B. Charette, *Angew. Chem. Int. Ed*. **2008**, *47*, 10155-10158.

conformation. The in-out conformation will be the preferred one in the transition state, as it provides increased electrophilicity of the metal carbene. In addition, the authors proposed to use an α-diazodicarboxy derivative bearing two carboxy groups with different *trans*-directing abilities, in combination with a chiral catalyst that would be effective at blocking one of the two prochiral faces to discriminate between A and B, led to high diastereoselectivity and enantioselectivity. By applying this concept, in the presence of Rh_2((*S*)-NTTL)$_4$, cyclopropane derivatives were obtained with high diastereo- and enantioselectivities (**Scheme 26**).[85]



Scheme 26. Rh_2((*S*)-NTTL)$_4$ catalyzed cyclopropanation of styrene with α-amide diazoacetate.



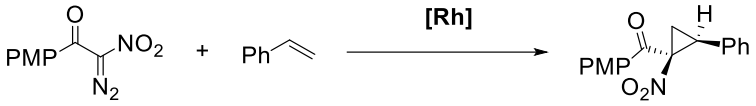
Entry	[Rh]	Solvent	Yield, %	dr	ee, %
1	Rh_2((*S*)-PTTL)$_4$	*n*-hexane	95	98:2	79
2	Rh_2((*S*)-NTTL)$_4$	toluene	61	75:25	45
3	Rh_2((*S*)-TBPTTL)$_4$	*n*-hexane	23	84:16	16
4	Rh_2((*S*)-PTTL)$_3$(TPA)	*n*-hexane	91	96:4	88

Table 6. Rh_2((*S*)-PTTL)$_3$(TPA) catalyzed cyclopropanation of ethyl α-diazobutanoate.

In 2012, Fox reported the synthesis of chiral dirhodium (II) complex with mixed ligands Rh_2((*S*)-PTTL)$_3$(TPA) (**Figure 13**). In this dirhodium (II) complex, all the ligands display on one face in the structure, the "all-up" C_4 conformation. From a screening of the catalysts for the enantioselective cyclopropanation of styrene with ethyl α-diazobutanoate, Rh_2((*S*)-PTTL)$_3$(TPA) afforded the best enantioselectivity (88% ee). This catalyst provides a scope of cyclopropanes with yields and enantioselectivities

that are comparable or superior to Rh_2((*S*)-PTTL)$_4$ (**Table 6**).[86]

Charette and Lindsay reported a comprehensive study for the synthesis of chiral heteroleptic rhodium (II) carboxylate catalysts. The replacement of one of the TCPTTL ligand of the Rh_2((*S*)-TCPTTL)$_4$ with an achiral PTAiB ligand, providing a novel catalyst Rh_2((*S*)-TCPTTL)$_3$(PTAiB) (**Figure 13**) in a "up-up-up-down" C_1 symmetric conformation, which was ascertained with the X-ray crystal structure. The use of this catalyst gave better asymmetric induction in the cyclopropanation of alkenes with α-nitro diazoacetophenones (**Table 7**).[87]



Entry	[Rh]	Yield, %	dr	ee, %
1	Rh_2((*S*)-TCPTTL)$_4$	81	98:2	93
2	Rh_2((*S*)-TCPTTL)$_3$(PTAiB)	84	92:8	96

Table 7. Rh_2((*S*)-TCPTTL)$_3$(PTAiB) catalyzed cyclopropanation of styrene with α-nitro diazoacetophenone.

Dirhodium (II) catalysts derived from substituted cyclopropyl carboxylates

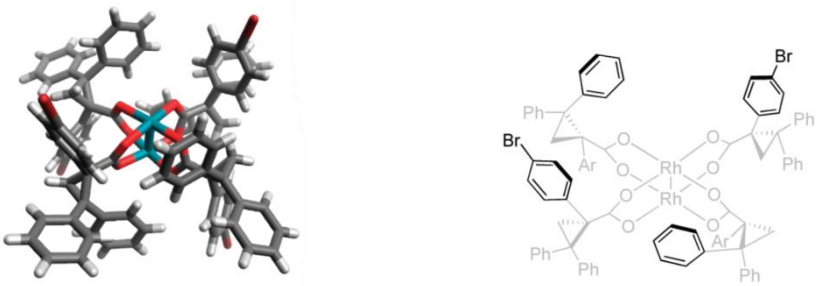


Figure 14. X-ray crystal structure of Rh_2((*R*)-BTPCP)$_4$ (axial ligands omitted for clarity).[88]

In 2011, Davies and coworkers reported the synthesis of the dirhodium (II) catalyst Rh_2((*R*)-BTPCP)$_4$ using chiral cyclopropane carboxylic acids as ligands. The structure of this complex, determined by X-ray crystallographic analysis, shown that the ligands are organized in a "up-down-up-down" D_2 symmetric arrangement, forming an identical rectangular orthogonal binding cavity with a size of approximately 8.5 ×10.5 Å, which

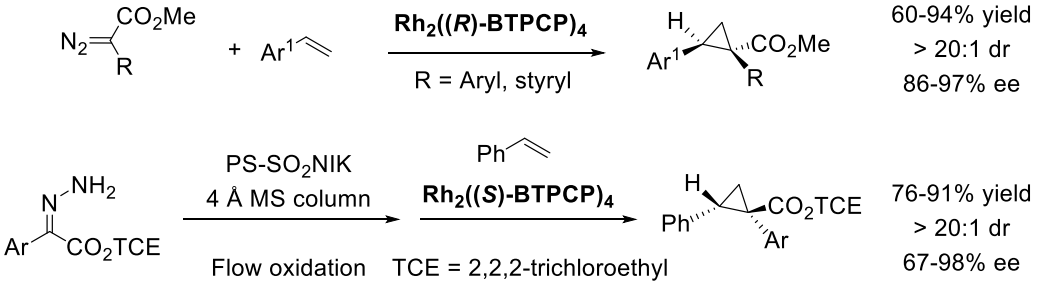
[86] D. T. Boruta, O. Dmitrenko, G. P. A. Yap, J. M. Fox, *Chem. Sci*. **2012**, *3*, 1589-1593.
[87] V. N. G. Lindsay, A. B. Charette, *ACS Catal*. **2012**, *2*, 1221-1225.

is significantly smaller than the cavity of Rh_2((*S*)-PTTL)$_4$ (12.8 x 14.1 Å) (**Figure 14**).[88]

As a new class of chiral dirhodium (II) carboxylates, Rh_2((*R*)-BTPCP)$_4$ and its variants (**Figure 12**) have shown to be exceptional catalysts in several enantioselective transformations involving metal-carbene. Including inter- or intramolecular cyclopropanation, C-H functionalization, and B-H bond insertion reaction, for instance.[89]

Davies and coworkers reported the asymmetric cyclopropanation of styrene using either α-vinyldiazoacetate or α-diazophenylacetates, allowing the products were formed in excellent yields with very high enantioselectivities as well as diastereoselectivites in the presence of Rh_2((*R*)-BTPCP)$_4$ (**Scheme 27**).[88]

Later on, the same research group developed a tandem reaction system for the preparation of α-aryl diazoacetate in continuous flow. The use of solid supported *N*-iodo-*p*-toluenesulfonamide potassium salt (PS-SO_2NIK) as an oxidant, followed by passing through a molecular sieves/sodium thiosulfate cartridge, provided the diazo compound was directly used in the cyclopropanation reaction without any purification. In the presence of Rh_2((*S*)-BTPCP)$_4$ the cyclopropanes were obtained in high yields with very good enantioselectivities as a single diastereoisomer (**Scheme 27**).[90]



Scheme 27. Rh_2((*R or S*)-BTPCP)$_4$ catalyzed asymmetric cyclopropanation.

The authors suggested a stereochemical model that explains the selectivity obtained with the catalyst Rh_2((*R*)-BTPCP)$_4$. The ester group of the carbene aligns perpendicular to the rhodium carbene plane, which blocks its side from nucleophilic reagent to attack. When the substrate approaches over the donor group, the aryl ring of the ligand blocks the *Re*-face, while the *Si*-face is open. This model matches with the absolute configuration of the products, therefore can allow prediction of the

[88] C. M. Qin, V. Boyarskikh, J. H. Hansen, K. I. Hardcastle, D. G. Musaev, H. M. L. Davies, *J. Am. Chem. Soc*. **2011**, *133*, 19198-19204.
[89] a) J. M. Yang, Z. Q. Li, Q. He, S. F. Zhu, Q. L. Zhou, *J. Am. Chem. Soc.* **2017**, *139*, 3784-3789. b) P. E. Guzmán, Y. J. Lian, H. M. L. Davies, *Angew. Chem. Int. Ed.* **2014**, *53*, 13083-13087.
[90] D. Rackl, C. J Yoo, C. W. Jones, M. L. Davies, *Org. Lett.* **2017**, *19*, 3055-3058.

stereochemical outcome of the reaction (**Figure 15**).

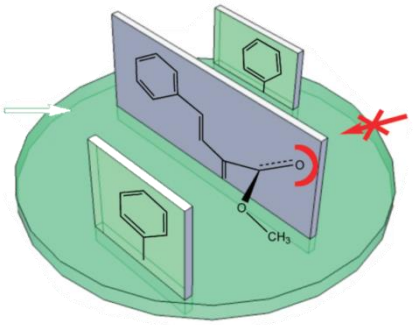
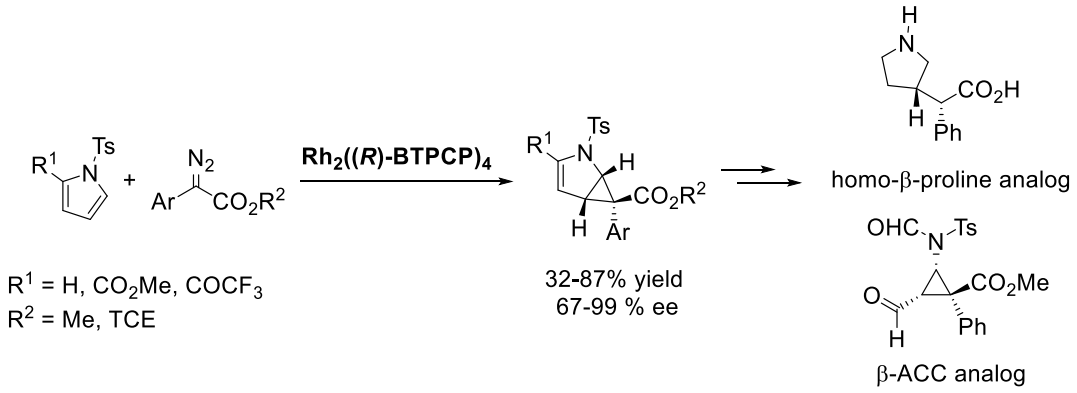


Figure 15. Predictive stereochemical model for $Rh_2((R)\text{-BTPCP})_4$ catalyzed transformation.[88]

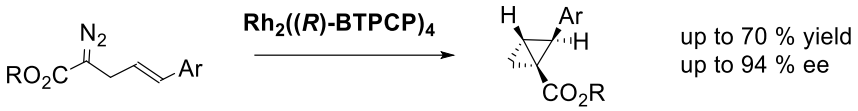
More recently, the same group reported $Rh_2((R)\text{-BTPCP})_4$ catalyzed asymmetric monocyclopropanation of *N*-tosylpyrrole, providing the corresponding dearomatized products with high level of enantioselectivities (up to >99% ee) (**Scheme 28**).[91] The monocyclopropanated product can be converted into a homo-β-proline analog and a β-aminocarboxylic acid (β-ACC) analog.



Scheme 28. $Rh_2((R)\text{-BTPCP})_4$ catalyzed asymmetric monocyclopropanation of pyrroles.

Davies and Qin reported the use of $Rh_2((R)\text{-BTPCP})_4$ as an effective catalyst for the asymmetric synthesis of 2-arylbiccyclo[1.1.0]butane carboxylates. The decomposition of α-allyldiazoesters followed by an intramolecular cyclopropanation reaction with a very low catalyst loading (0.01 mol %) led to the corresponding 2-arylbiccyclo[1.1.0]butane carboxylates as a single distereoisomer in good yields with excellent enantiomeric excesses (**Scheme 29**).[92]

[91] J. Fu, N. Wurzer, V. Lehner, O. Reiser, H. M. L. Davies, *Org. Lett*. **2019**, *21*, 6102-6106.
[92] C. M. Qin, H. M. L. Davies, *Org. Lett*. **2013**, *15*, 310-313.



Scheme 29. $Rh_2((R)\text{-BTPCP})_4$ catalyzed asymmetric intramolecular cyclopropanation.

Dirhodium (II) carboxamidates

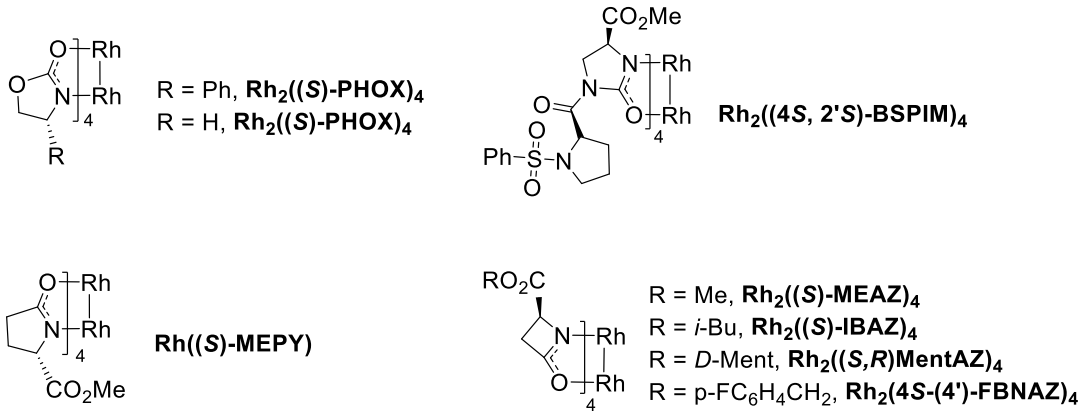


Figure 16. Typical dirhodium (II) carboxamidates.

Doyle and coworkers first reported the preparation of chiral dirhodium (II) carboxamidates in early 1990.[93] The modification of the bridging chiral carboxamidate ligands in the catalyst structure normally can be divided into four classes, oxazolidinates,[94] imidazolidinates,[95] pyrrolidinates,[96] and azetidinates (**Figure 16**).[97] Due to the electron-rich property of dirhodium (II) carboxamidates, compared to dirhodium (II) carboxylates, the Rh-carbene is therefore less reactive. However, dirhodium (II) carboxamidates are efficient in the decomposition of diazo compounds, and are widely used for the intra- or intermolecular cyclopropanation reactions, intramolecular C-H insertion reactions,[98] and often provide high asymmetric induction.

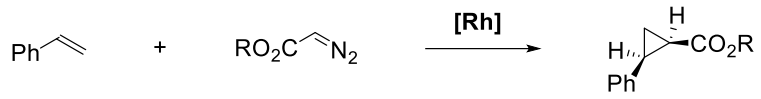
Doyle and coworkers reported the synthesis and X-ray structure of a rhodium complex bearing oxazolidinone ligands: $Rh_2((S)\text{-PHOX})_4$. In the presence of this catalyst, the cyclopropanation of styrene with diazoacetate resulted preferentially in formation of

[93] 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.
[94] M. P. Doyle, A. B. Dyatkin, M. N. Protopopova, C. I. Yang, C. S. Miertschin, W. R. Winchester, S. H. Simonsen, V. Lynch, R. Ghosh, *Recl. Trav. Chim. Pays-Bas*. **1995**, *114*, 163-170.
[95] M. P. Doyle, Q. L. Zhou, C. E. Raab, G. H. P. Roos, S. H. Simonsen, V. Lynch, *Inorg. Chem*. **1996**, *35*, 6064-6073.
[96] M. P. Doyle, W. R. Winchester, J. A. A. Hoorn, V. Lynch, S. H. Simonsen, R. J. Ghosh, *J. Am. Chem. Soc*. **1993**, *115*, 9968-9978.
[97] M. P. Doyle, S. B. Davies, W. Hu, *Org. Lett*. **2000**, *2*, 1145-1147.
[98] M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev*. **2010**, *110*, 704-724.

cis-cyclopropane in moderate yield and enantioselectivity (**Scheme 30**).[99]

Three years later, the same authors described a rhodium complex bearing β-lactam ligands: Rh_2((*S*)-IBAZ)$_4$, which was applied to the cyclopropanation reaction of styrene, providing a 1:1.5 (*trans*/*cis*) mixture, 95% ee for *cis*-cyclopropane, and 77% ee for *trans*-cyclopropane (**Scheme 30**).[100]

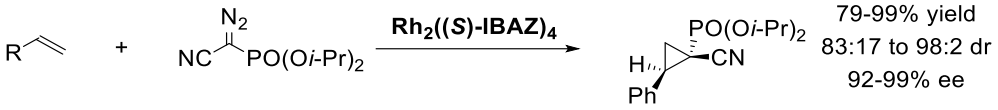
Later on, Doyle and coworkers reported the modification of the catalyst by changing the ester in the structure of the lactam ligand from *tert*-butyl group to *l*-menthyl group, namely Rh_2((*S, R*)-MentAZ)$_4$. The use of this catalyst, gave the cyclopropanes with a slight better diastereoselectivity (1:2.8) in favor of the *cis* isomer (**Scheme 30**).[101]



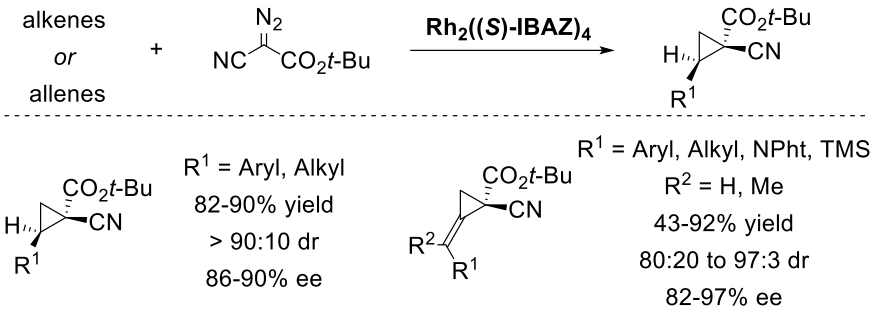
Rh_2((*S*)-PHOX)$_4$	**Rh_2((*S*)-IBAZ)$_4$**	**Rh_2((*S, R*)-MentAZ)$_4$**
R = Et, 41%	R = (*c*-Hex)$_2$CH, 74%	R = *t*-Bu, 47%
trans:*cis* = 1:2	*trans*:*cis* = 1:1.5	*trans*:*cis* = 1:2.8
24% ee$_{trans}$	77% ee$_{trans:}$	71% ee$_{trans}$
57% ee$_{cis}$	95% ee$_{cis}$	94% ee$_{cis}$

Scheme 30. Rhodium-catalyzed asymmetric cyclopropanation of styrene with diazoacetates.

In 2013, Charette and coworkers reported the use of Rh_2((*S*)-IBAZ)$_4$ as a catalyst in the asymmetric cyclopropanation of alkenes and allenes with di-acceptor diazo compounds bearing a nitrile group.[102] In this report, the phosphonate moiety was employed as an efficient *trans*-directing group, providing the cyclopropane derivatives with very high diastereo- and enantioselectivities. This highly stereoselective methodology also can be applied to cyclopropanation of alkenes, allenes with *tert*-butyl α-cyanoacetate, the corresponding cyclopropanes were obtained in very good diastereo- and enantioselectivities (**Scheme 31**). It's worth to mention that, the scope can be extended to alkynes to afford cyclopropenes with high enantiomeric excesses.

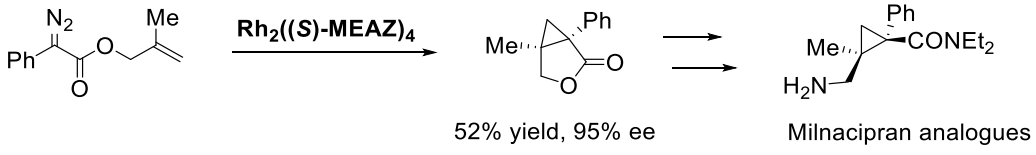


[99] M. P. Doyle, W. R. Winchester, M. N. Protopopova, P. Müller, G. Bernardinelli, D. Ene, S. Motallebi, *Helv. Chim. Acta.* **1993**, *76*, 2227-2235.
[100] M. P. Doyle, Q. L. Zhou, S. H. Simonsen, V. Lynch, *Synlett* **1996**, 697-698.
[101] W. Hu, D. J. Timmons, M. P. Doyle, *Org. Lett.* **2002**, *4*, 901-904.
[102] V. N. G. Lindsay, D. Fiset, P. J. Gritsch, S. Azzi, A. B. Charette, *J. Am, Chem. Soc.* **2013**, *135*, 1463-1470.



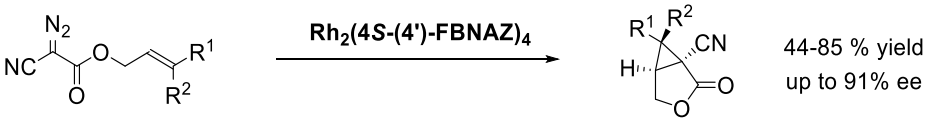
Scheme 31. $Rh_2((S)\text{-IBAZ})_4$ catalyzed cyclopropanation of alkenes and allenes.

In 2001, Doyle and Hu reported the use of an azetidinate based dirhodium (II) catalyst: $Rh_2((S)\text{-MEAZ})_4$ in an intramolecular cyclopropanation reaction. The enantioenriched lactone was obtained with high ee, and it is a key intermediate for the synthesis of Milnacipran and analogues (**Scheme 32**).[103]



Scheme 32. $Rh_2((S)\text{-MEAZ})_4$ catalyzed synthesis of Milnacipran analogues.

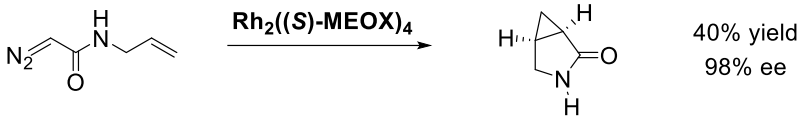
Later, Charette and Lin described a variant of $Rh_2((S)\text{-IBAZ})_4$, namely $Rh_2(4S\text{-}(4')\text{-FBNAZ})_4$, and its use in the asymmetric intramolecular cyclopropanation of substituted allyl α-cyano diazoacetate derivatives. Alkenes bearing an electron-deficient substituent including carbonyl and halogens were converted into the corresponding cyclopropanes with enantioselectivities up to 91% ee (**Scheme 33**).[104] However, alkenes bearing electron-donating groups such as alkyl substituents were obtained with moderate enantioselectivities.



Scheme 33. Intramolecular cyclopropanation of allyl α-cyano diazoacetates.

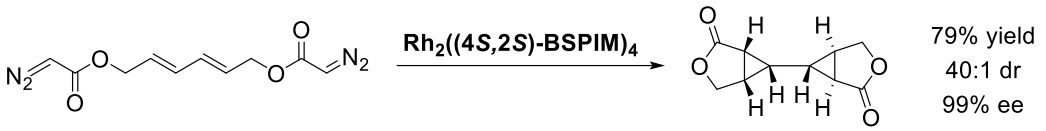
Doyle and coworkers reported that the $Rh_2((S)\text{-MEOX})_4$ was an efficient catalyst in the intramolecular cyclopropanation of *N*-allyl diazoacetamide. The formation of cyclopropyl lactam was achieved with highly enantioselectivity (**Scheme 34**).[105]

[103] M. P. Doyle, W. Hu, *Adv. Synth. Catal*. **2001**, *343*, 299-302.
[104] W. Lin, A. B. Charette, *Adv. Synth. Catal*. **2005**, *347*, 1547-1552.
[105] M. P. Doyle, R. E. Austin, A. S. Bailey, M. P. Dwyer, A. B. Dyatkin, A. V. Kalinin, M. M. Y. Kwan, S. Liras, C. J. Oalmann, *J. Am. Chem. Soc*. **1995**, *117*, 5763-5775.



Scheme 34. Rh_2((*S*)-MEOX)$_4$ catalyzed decompose *N*-allyl diazoacetamide.

Furthermore, Doyle and coworkers also reported a sequence of two successive intramolecular cyclopropanation reactions by using bis-diazoacetate in the presence of Rh_2((4*S*, 2*S*)-BSPIM)$_4$ (**Scheme 35**).[106]

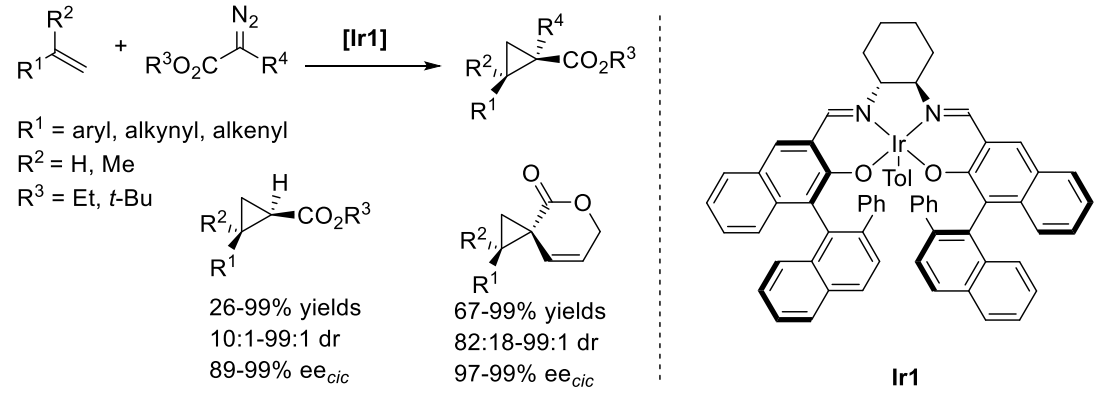


Scheme 35. Double intramolecular cyclopropanation in the presence of Rh_2((4*S*, 2'*S*)-BSPIM)$_4$.

Other metals

In addition to cobalt, ruthenium, copper, iron and rhodium, there are some reports describing the cyclopropanation reaction using other transition metals.

Katsuki and coworkers reported the use of the chiral aryl iridium salen complex **Ir1** as the catalyst (**Scheme 36**), providing a high enantio- and *cis*-selective cyclopropanation method from conjugated or non-conjugated olefins with diazoacetates or vinyl diazolactone.[107]

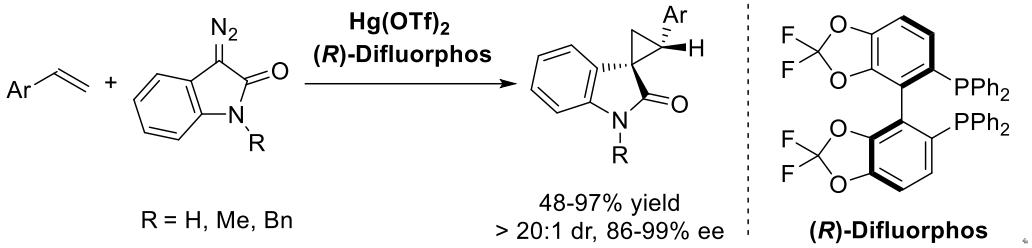


Scheme 36. Iridium salen catalyzed cyclopropanation reaction.

Zhou and coworkers discovered the first example of mercury-catalyzed highly diastereo- and enantioselective cyclopropanation of diazooxindoles with styrenes

[106] M. P. Doyle, Y. Wang, P. Ghorbani, E. Bappert, *Org. Lett*. **2005**, *7*, 5035-5038.
[107] a) H. Suematsu, S. Kanchiku, T. Uchida, T. Katsuki, *J. Am. Chem. Soc.* **2008**, *130*, 10327-10337. b) M. Ichinose, H. Suematsu, T. Katsuki, *Angew. Chem. Int. Ed.* **2009**, *48*, 3121-3123.

(**Scheme 37**).[108] In this report, the authors observed that the cyclopropanation only proceeded in the presence of the chiral diphosphine ligand (*R*)-Difluorphos with $Hg(OTf)_2$. The authors suggested that the chiral diphosphine ligand modulates the reactivity of Hg (II) catalyst and accelerates the reaction.



Scheme 37. Enantioselective mercury-catalyzed cyclopropanation reaction.

B. Objectives

As illustrated in this chapter, the use of cyclopropane ring as a motif in the structure of bioactive molecules often with pleasant outcomes. In addition, the modification by combining with the specific properties of the fluorine atom, results in the fluorinated cyclopropane derivatives more potential in finding bioactive compounds.

Hence, the synthesis of fluorinated cyclopropanes fascinated scientists from a broad range of backgrounds, especially studies on their asymmetric synthesis. The introduction of a trifluoromethyl group into cyclopropanes has been well studied,[109] however, most of the reported strategies to prepare trifluoromethyl cyclopropanes are racemic approaches. Only few examples (5 reports prior our study) described the enantioselective synthesis of trifluoromethyl cyclopropanes achieved by a [2+1] cycloaddition of an alkene with a transition metal-carbene (Fe, Co, Rh and Ru). On the other hand, the synthesis of difluoromethyl cyclopropanes is scarcely reported. Although the first access was described in 1980, the asymmetric synthesis of this motif remains an elusive goal prior our investigations.

Therefore, it is important to provide new strategies to access enantioenriched trifluoromethylated and difluoromethylated substituted cyclopropanes. Hence, the synthesis and a fortiori the enantioselective synthesis of diverse these fluorinated cyclopropanes remains a challenge.

On the basis of these fundamental insights and previous findings of our research group, the core of the current project is the development of a new methodology for highly

[108] Z. Y. Cao, F. Zhou, Y. H. Yu, J. Zhou, *Org. Lett.* **2013**, *15*, 42-45.
[109] M. Bos, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J*. **2017**, *23*, 4950-4961.

diastereo- and enantioselective cyclopropanation of α,α,α-trifluoromethyl or α,α-difluoromethyl styrenes in the presence of a dirhodium (II) catalyst. As the reactivity and the enantioselectivity of the cyclopropanation reaction are sensitive to the substitution on the diazocompound, it is important to discover a suitable dirhodium catalyst for cyclopropanation reaction that be able to react efficiently with di-acceptor and donor-acceptor diazo compounds.

Chapter I

Catalytic Asymmetric Synthesis of Difluoromethyl Cyclopropanes

Chapter I Catalytic Asymmetric Synthesis of Difluoromethyl Cyclopropanes

1.1 Introduction

Nowadays, the introduction of a fluorine atom or fluorinated groups on a molecule is quite an important strategy in all aspects of the chemical industry, including pharmaceuticals, agrochemicals, materials and fine chemicals. As the properties of the fluorine atom have a significantly impact on the physicochemical properties of molecules and a fortiori on their bioactivity. Hence, the development of different methods to introduce a fluorine atom or fluorinated groups has attracted the attention of organic chemists. As part of this field, the difluoromethyl moiety (-CF_2H) is considered as an excellent bioisostere of an alcohol or a thiol. Moreover, this moiety can act as a hydrogen bond donor.[18,19]Besides, cyclopropane ring is an amazing building block, and widely spread in natural, synthetic bioactive compounds and in materials science. Especially, the introduction of cyclopropane core can tremendous modify the biological properties of the target molecule.[12]

By combining the features of the difluoromethyl group and cyclopropanes, difluoromethyl cyclopropyl motifs have recently brought lots of interests due to their potential for discovering new bioactive compounds. In fact, there are a few applications of difluoromethyl cyclopropanes in medicinal and agrochemical research (see **Figure 8**, page 8).

1.2 State of the art

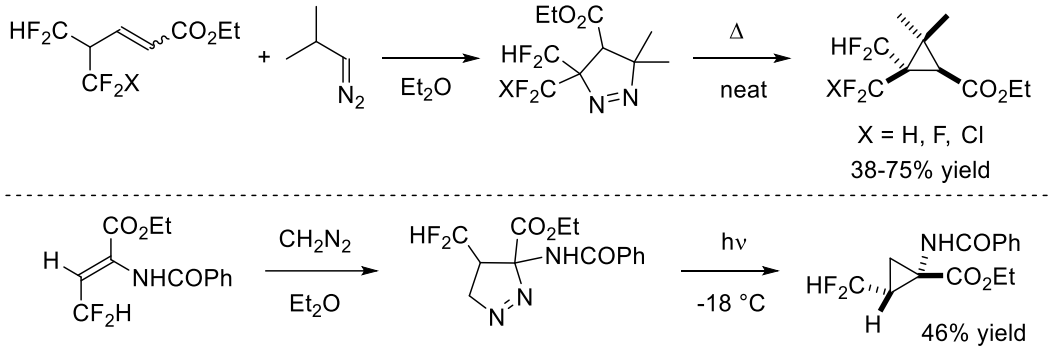
Surprisingly, despite their potential in discovering new bioactive compounds, the study on difluoromethyl cyclopropane derivatives is quite an underexplored research area. Compared to the advances reported for the synthesis trifluoromethyl cyclopropanes, only five publications described the synthesis of difluoromethyl cyclopropanes prior our contribution. Moreover, none of these publications described an asymmetric approach to access chiral difluoromethyl cyclopropanes.

The first example for the synthesis of difluoromethyl cyclopropanes was described by Huff and coworkers in 1980 (**Scheme 38**).[110] The [3+2] cycloaddition strategy was applied to the reaction of difluoromethyl acrylates with 1-diazo-2-methylpropane led to

[110] R. K. Huff, E. G. Savins, *J. Chem. Soc. Chem. Commun.* **1980**, 742–743.

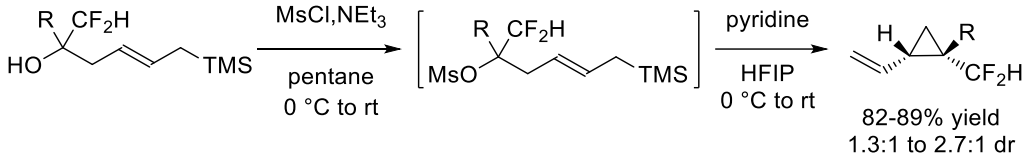
the corresponding pyrazolines. Subsequent thermal ring contraction of these pyrazolines gave birth to the corresponding cyclopropanes in moderate yields.

About thirty years later, Hao and Wan reported the synthesis of difluoromethyl cyclopropyl amino ester (**Scheme 38**).[111] The authors used a similar [3+2] cycloaddition reaction of diazomethane on a CF_2H-containing alkene to access the pyrazoline. This five-membered ring was decomposed by photolysis at low temperature, leading to the expected difluoromethyl cyclopropane amino ester in 46% yield as a single diastereoisomer.



Scheme 38. [3+2] cycloaddition / ring contraction sequence for the synthesis of difluoromethyl cyclopropanes.

In 2015, Leadbeater and coworkers investigated the formation of difluoromethyl cyclopropanes from homoallylic alcohols by means of ring closure, involving a 1,3-γ-silyl-elimination (**Scheme 39**).[112] In this paper, the initial work focused on the investigation of trifluoromethyl group, and an extension to the difluoromethyl group. The corresponding cyclopropanes were obtained in high yields with better diastereoselectivities than those obtained products with trifluoromethyl group.

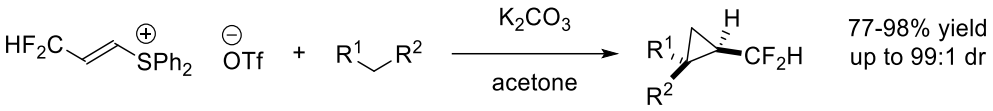


Scheme 39. Cyclopropanation of homoallylic alcohols by 1,3-γ-silyl-elimination.

In 2015, Ishikawa and Hanamoto described the preparation and application of β-difluoromethyl vinylsulfonium salt (**Scheme 40**).[113] This approach is similar to the methodology developed by Lu and Hanamoto.[121,122] The addition of a wide range of

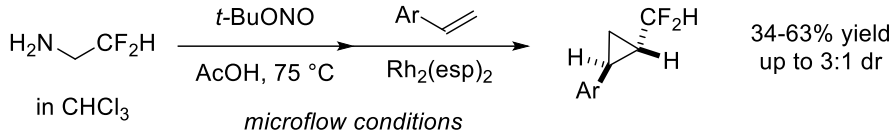
[111] W. Wan, Y. Gao, H. Jiang, J. Hao, *J. Fluorine Chem*. **2008**, *129*, 510–514.
[112] C. B. Kelly, M. A. Mercadante, E. R. Carnaghan, M. J. Doherty, D. C. Fager, J. J. Hauck, A. E. MacInnis, L. J. Tilley, N. E. Leadbeater, *Eur. J. Org. Chem*. **2015**, 4071-4076.
[113] T. Ishikawa, N. Kasai, Y. Yamada, T. Hanamoto, *Tetrahedron* **2015**, *71*, 1254–1260.

active methylene compounds onto β-difluoromethyl vinylsulfonium salt provided the corresponding cyclopropanes in high to excellent yields with moderate to excellent diastereoselectivities.



Scheme 40. Cyclopropanation with β-difluoromethyl vinyl sulfonium salt.

Finally, Koenigs and Hock reported the synthesis of difluoromethyl cyclopropanes from 2,2-difluoromethyl diazomethane in the presence of a rhodium (II) catalyst (**Scheme 41**).[114] Note that this approach was performed under microflow conditions using 2,2-difluoroethane-1-amine as precursor of the diazo derivative. This one-pot synthesis of the difluoromethyl cyclopropanes was achieved in moderate to good yields and moderate diastereoselectivities.



Scheme 41. Koenigs and Hock's cyclopropanation reaction in flow.

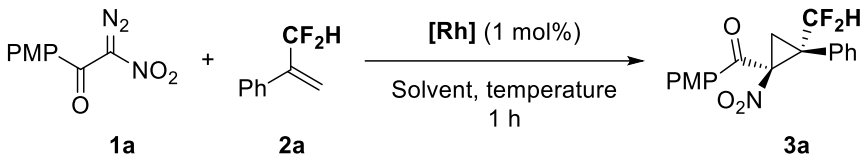
1.3 Objectives and challenges

As illustrated in the state of the art, the current protocols for the preparation of difluoromethyl cyclopropanes are extremely insufficient to offer a broad range of substrates, therefore it is important to develop new methodologies for this propose. Herein, we intend to explore a new strategy: the catalytic asymmetric cyclopropanation reaction using α,α-difluoromethyl styrene in the presence of a metal catalyst.

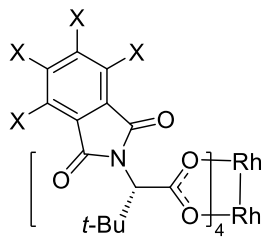
One of the challenges of this project is that the introduction of an acceptor group (difluoromethyl function) to an alkene might impact the nucleophilicity of the alkene, leading to lower reactivity in the cyclopropanation process. On the other hand, it is also important to find a suitable chiral metal catalyst that allows the reaction of the metal-carbene species with this electro-deficient alkene along with a high control of both diastereo- and enantioselectivity.

[114] K. J. Hock, L. Mertens, R. M. Koenigs, *Chem. Commun*. **2016**, *52,* 13783-13786.

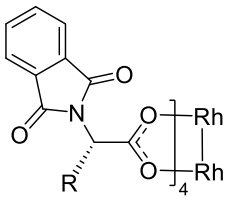
1.4 Optimization study



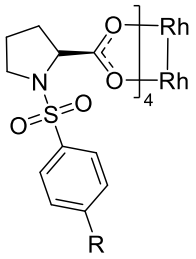
Entry	[Rh]	Solvent	T(°C)	Yield [%][b]	dr[c]	Ee [%][d]
1	Rh_2((*S*)-TCPTTL)$_4$	DCM	0-25	52	9:1	86
2	Rh_2((*S*)-TFPTTL)$_4$	DCM	0-25	40	2:1	78
3	Rh_2((*S*)-PTAD)$_4$	DCM	0-25	6	1.2:1	20
4	Rh_2((*S*)-DOSP)$_4$	DCM	0-25	8	9:1	60
5	Rh_2((*S*)-BTPCP)$_4$	DCM	0-25	30	5.6:1	97
6	**Rh_2((S)-BTPCP)$_4$**	**DCM**	**-50**	**93**	**11.5:1**	**99**
7	Rh_2((*S*)-BTPCP)$_4$	Toluene	-50	62	5.3:1	98
8	Rh_2((*S*)-BTPCP)$_4$	DCE	-50	88	9:1	97
9	Rh_2((*S*)-BTPCP)$_4$	MTBE	-50	13	ND	ND
10	Rh_2((*S*)-BTPCP)$_4$	THF	-50	NR	-	-
11	Rh_2((*S*)-BTPCP)$_4$	CH_3CN	-50	NR	-	-



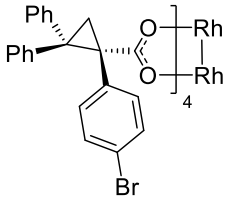
X = Cl, **Rh_2((*S*)-TCPTTL)$_4$**
X = F, **Rh_2((*S*)-TFPTTL)$_4$**



R = Adamantyl
Rh_2((*S*)-PTAD)$_4$



R = *n*-$C_{12}H_{25}$
Rh_2((*S*)-DOSP)$_4$



Rh_2((*R*)-BTPCP)$_4$

Table 8. Optimization study in the presence of a chiral Rh-catalyst. [a] Conditions: **2a** (0.25 mmol, 1 eq), **1a** (0.375 mmol, 1.5 eq), [Rh] (1 mol%), [diazo] = 0.7 M. [b] Isolated yield. [c] Determined by ^{19}F NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. PMP = *para*-methoxyphenyl. ND = not determined. NR = no reaction.

At the outset of the project, we investigated the reaction between α,α-difluoromethyl styrene **1a** and α-nitro diazoketone **2a**, a di-acceptor type diazo compound in the presence of a chiral rhodium catalyst (**Table 8**). First, Rh_2((*S*)-TCPTTL)$_4$ was tested in DCM and the desired cyclopropane **3a** was obtained in 52% yield with 9:1

diastereomeric ratio, the major diastereoisomer was isolated with 86% enantiomeric excess (entry 1). The use of the fluorinated analogue, namely Rh_2((*S*)-TFPTTL)$_4$ did not provide any improvement, while the reactions were carried out in the presence of Rh_2((*S*)-PTAD)$_4$ and Rh_2((*S*)-DOSP)$_4$ led to poor conversion (entries 2-4). Pleasingly, the use of Rh_2((*S*)-BTPCP)$_4$ provided the cyclopropane **3a** with very high enantiomeric excess (97%), but a moderate conversion and dr (entry 5).

Next, the reaction was carried out at lower temperature (-50 °C) in the presence of Rh_2((*S*)-BTPCP)$_4$, to our delight, the formation of the cyclopropane **3a** was obtained in 93% yield, 11.5:1 diastereoselectivity and 99% ee (entry 6).

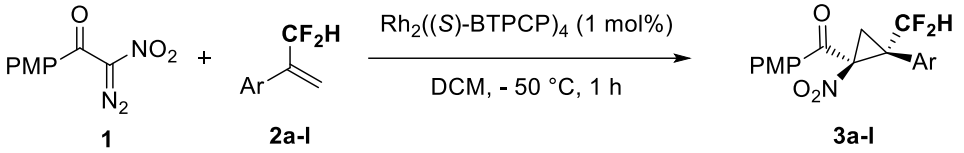
Then, the reaction was performed in different solvents, the use of toluene or DCE as the solvent did not improve the conversion and the diastereoselectivity (entries 7-8). The replacement of DCM by other solvents (MTBE, THF and CH_3CN) led to poor conversion (entries 9-11). So, we selected entry 6 as the best reaction conditions for this cyclopropanation transformation.

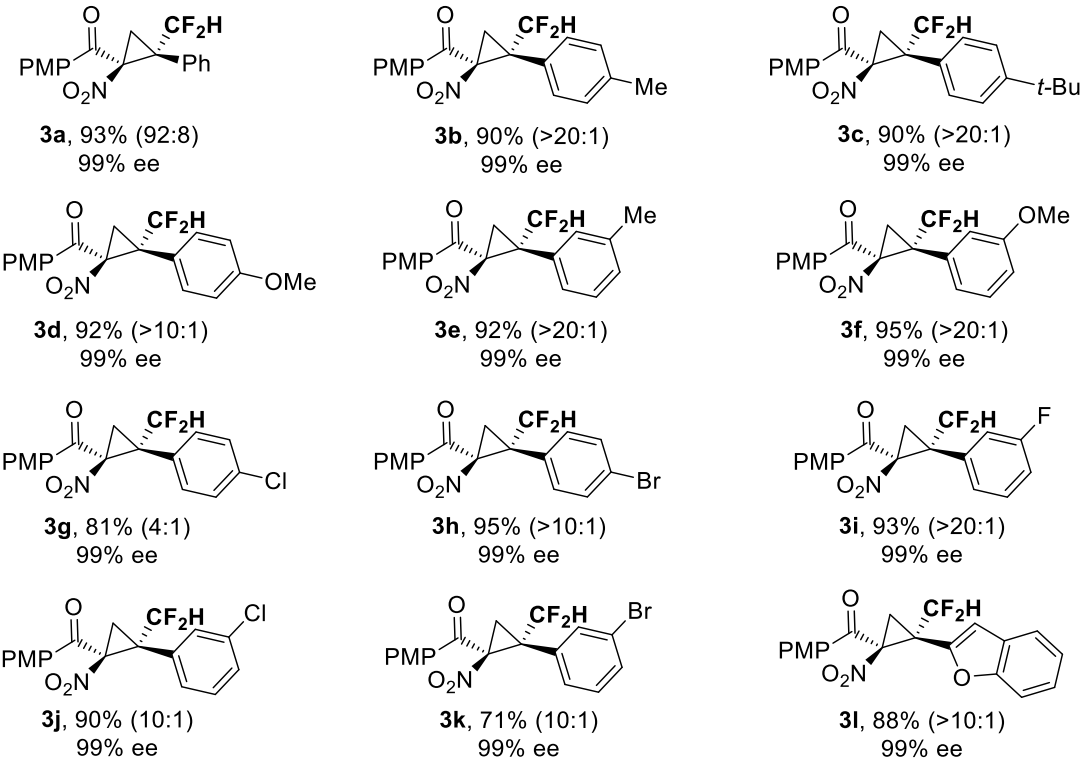
1.5 Scope study of α-nitro diazoketone with α,α-difluoromethyl olefins

With these optimized conditions in hand (**Table 8**, entry 6), we examined the scope of the reaction. First, a range of different substituted α,α-difluoromethyl styrenes was reacted with α-nitro diazoketone **1a**. Electron-donating substituents at the *para* position, such as methyl, *tert*-butyl and methoxy derivatives **2b-d** were well tolerated, providing the corresponding difluoromethyl cyclopropanes **3b-d** in excellent yields, good to excellent diastereoselectivities in favor of the *trans*-isomer and 99% ee in all cases.

Next, the *meta*-methyl and *meta*-methoxy aryl derivatives were converted into the desired products **3e** and **3f** in excellent yields with a complete diastereoselectivity and 99% ee. Pleasingly, a similar reactivity was observed for halo-substituted derivatives, whatever its position (*para* or *meta*), the corresponding cyclopropanes **3g-k** were obtained with excellent enantio- and diastereoselectivities, except for **3g**, which was isolated as a 4:1 of diastereoisomer.

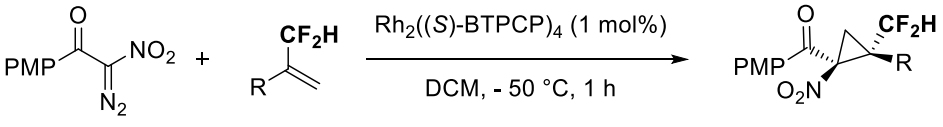
Then, the presence of a benzofuran ring was tested and the cyclopropane product **3l** was obtained in high yield and dr with excellent ee. Notice that, no side reaction was observed on the double bond of the benzofuran ring.

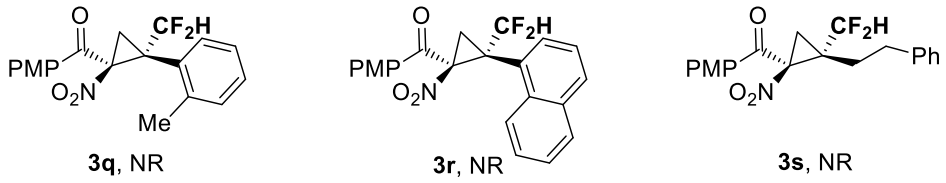




Scheme 42. Scope of the reaction between α-nitro diazoketone **1a** and α,α-difluoromethyl styrenes **2a-l**.

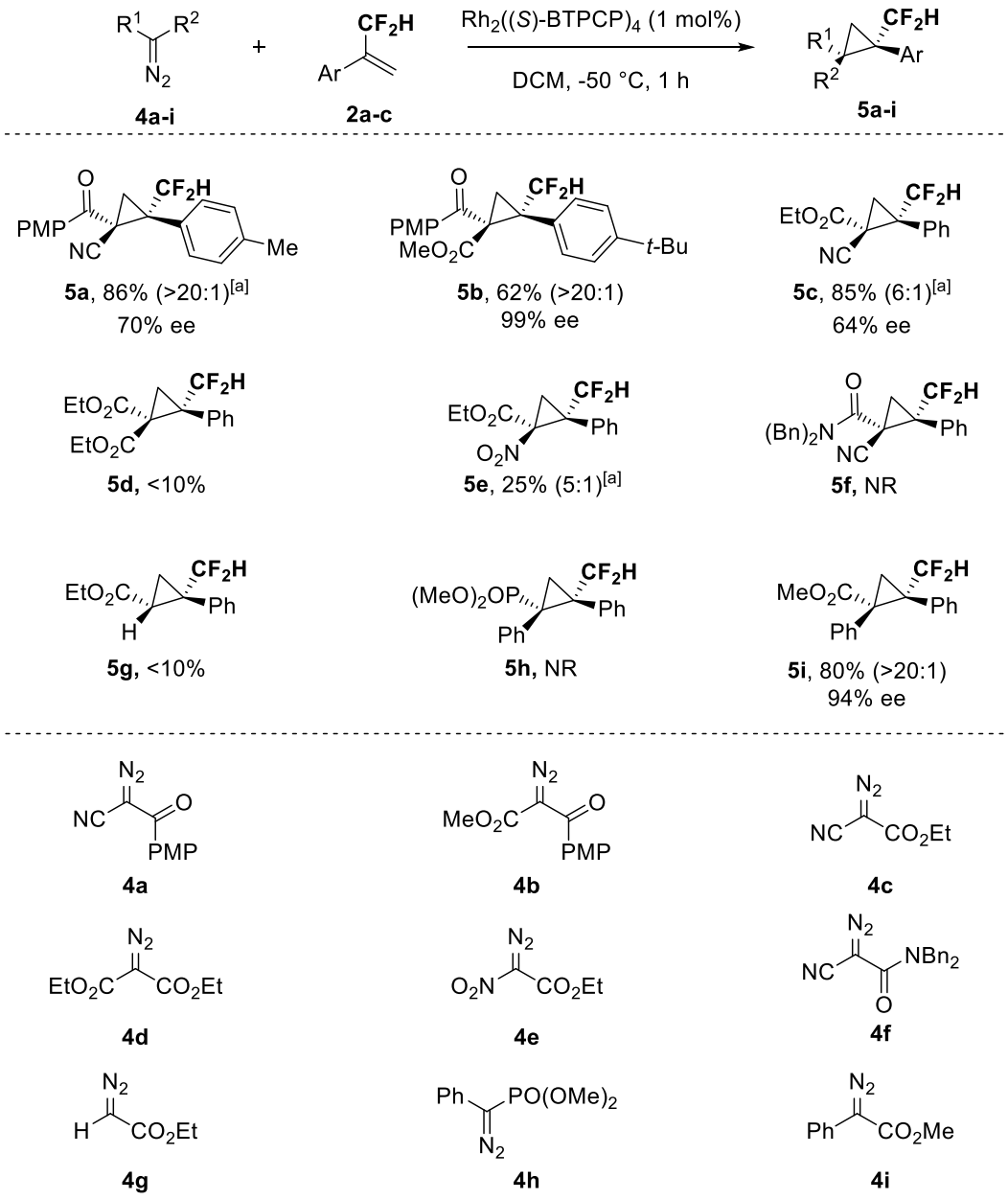
It is worth to mention that some limitations were observed during the scope evaluation (**Scheme 43**). The *ortho*-methyl and 1-naphthyl-substituted derivatives were inert in this Rh_2((*S*)-BTPCP)$_4$ catalyzed cyclopropanation process, probably because of the steric hindrance. The use of alkyl olefin also led to no conversion.





Scheme 43. Limitations of the scope study in the cyclopropanation of α-nitro diazoketone **1a** with olefins.

1.6 Screening of diazo compounds



Scheme 44. Screening of diazo compounds. [a] the reaction was carried out at -20 °C. NR = no reaction.

To further extend the application of this methodology, we investigated the cyclopropanation of α,α-difluoromethyl olefins with other diazo compounds (**Scheme 44**). First, two other diazo ketones **4a** (R^2 = CN) and **4b** (R^2 = CO_2Et) were tested. The reaction of **4a** was carried out at -20 °C, as no conversion was observed at -50 °C, and the desired cyclopropane **5a** was isolated in high yield with a high diastereoselectivity, albeit with a decrease of the enantiomeric excess (70%). While α-ester diazo ketone **4b** was converted into corresponding cyclopropane **5b** in good yield, very high

diastereo- and enantioselective.

The use of α-cyano diazoacetate **4c** at -20 °C provides **5c** in high yield as a 6:1 diastereoisomer with a 64% of enantiomeric excess.

The use of other diazo compounds, such as diazomalonate **4d**, α-nitro diazoacetate **4e**, α-cyano diazoacetamide **4f**, diazoacetate **4g** or diazophosphonate **4h** led to poor or no conversion.

Finally, a typical donor-acceptor type diazo derivative, α-phenyl diazoacetate **4i** was readily converted into corresponding cyclopropane **5i** in excellent yield with a complete diastereoselectivity and 94% ee.

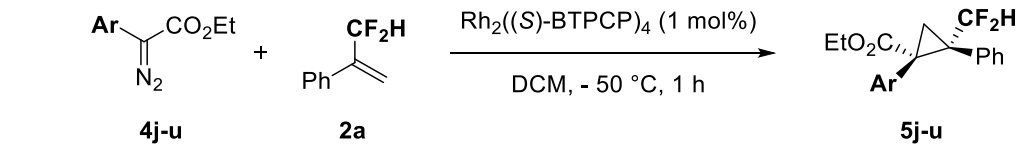
It is interesting to know that the rhodium-catalyzed decomposition of both di-acceptor and donor-acceptor diazo compounds in highly asymmetric cyclopropanation process is scarcely reported. To our delight, this methodology is able to handle both two type of diazo compounds.

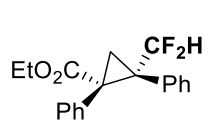
1.7 Scope of the reaction between α-aryl diazoacetates and α,α-difluoromethyl olefins

To demonstrate the versatility of this methodology, the reaction of **2a** with ethyl α-phenyl diazoacetate **4j** was performed under similar reaction conditions (**Scheme 45**). The desired cyclopropane **5j** was isolated in excellent yield as a single diastereoisomer with 96% ee.

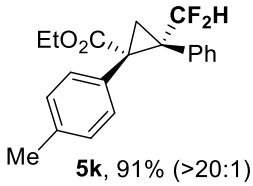
Next, various α-aryl diazoacetates were investigated. Methyl substituted aryl diazoacetates at *para*, *meta* and *ortho* position were tested, and the corresponding cyclopropanes **5k-m** were isolated in very high yields (91-92%) with complete diastereoselectivity and excellent enantiomeric excesses (91-97%). The presence of α-(*para*-methoxy) phenyl diazoacetate gave the cyclopropane product **5n** in lower yield (40%), while the dr and ee remained excellent.

Then, halo-substituted aryl diazoacetates **4o-r** were tested in this cyclopropanation process, the corresponding products **5o-r** were isolated in good to excellent yields with complete diastereoselectivity and high enantiomeric excesses, except for *para*-fluoro **5o** and 3,4-di-chloro-substituted **5q**, for which lower ees were observed when the reactions were performed at -50 °C. A decrease of reaction temperature to -78 °C gave **5o** with 90% ee at a cost of lower yield (50%), compared to the reaction carried out at -50 °C (90% yield, 87% ee). The reaction with **4q** was carried out at -60 °C, and gave the compound **5q** with 73% ee, since no conversion was observed at -78 °C.

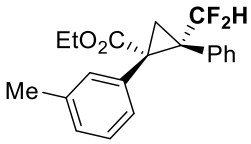




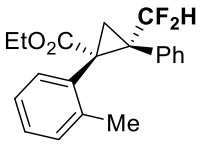
5j, 90% (>20:1)
96% ee



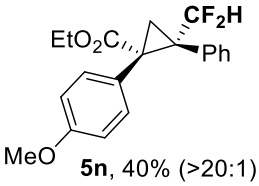
5k, 91% (>20:1)
91% ee



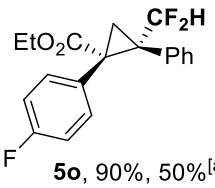
5l, 92% (>20:1)
97% ee



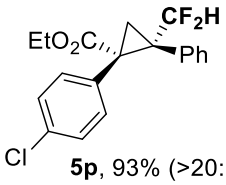
5m, 92% (>20:1)
91% ee



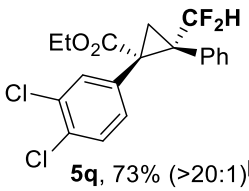
5n, 40% (>20:1)
90% ee



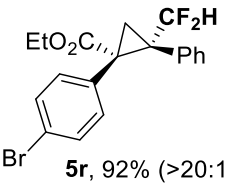
5o, 90%, 50%[a] (>20:1)
87%, 90%[a] ee



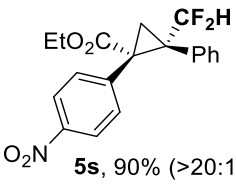
5p, 93% (>20:1)
94% ee



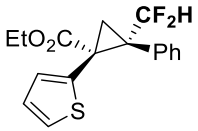
5q, 73% (>20:1)[b]
73% ee



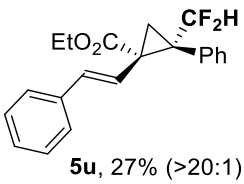
5r, 92% (>20:1)
91% ee



5s, 90% (>20:1)
66% ee



5t, 77% (>20:1)
97% ee



5u, 27% (>20:1)
97% ee

Scheme 45. Scope of the reaction between α-aryl diazoacetates **4j-u** with α,α-difluoromethyl styrene **2a**. [a] reaction was carried out at -78 °C. [b] reaction was carried out at -60 °C.

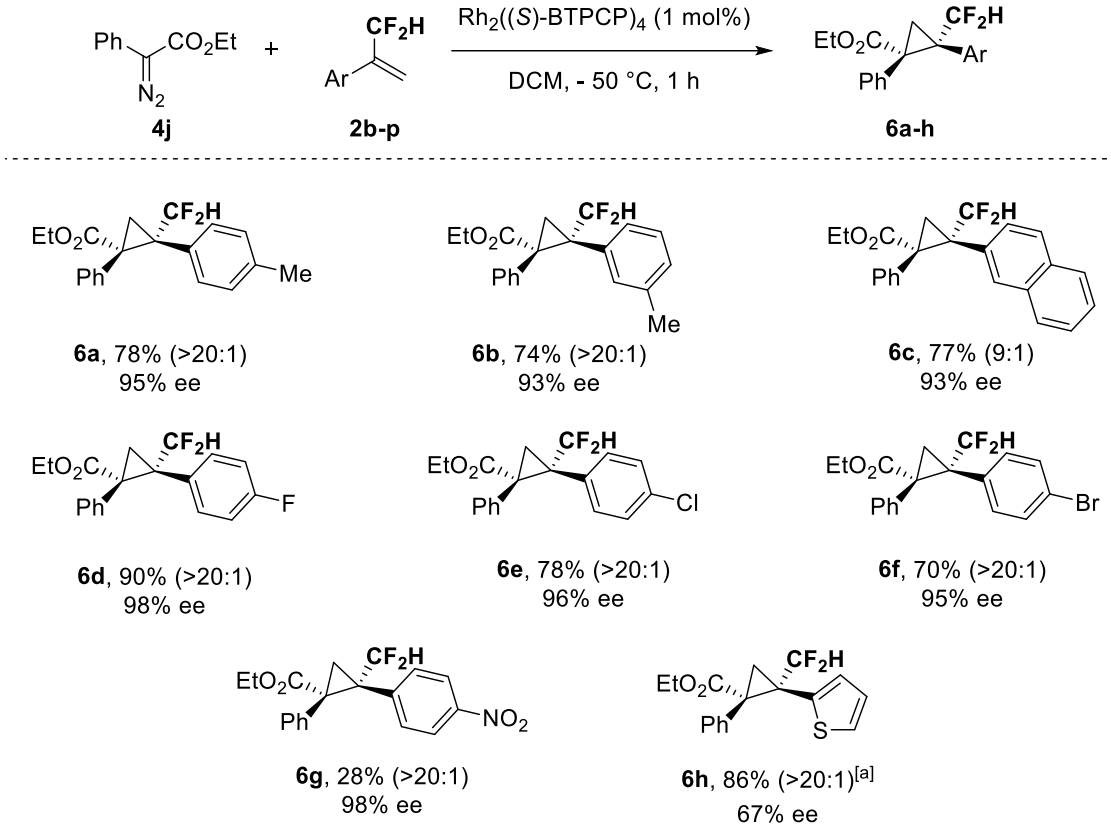
Aryl ring of diazo bearing a nitro group at the *para*-position **4s** was converted in to product **5s** in high yield as a single diastereoisomer, but with a moderate enantioselectivity (66% ee). The use of thienyl-substituted diazoacetates **4t** in this process, provided the cyclopropane **5t** in good yield with excellent diastereo- and enantioselectivity.

Finally, the α-styryl diazoacetate **4u** was tested and gave the desired cyclopropane **5u** with excellent diastereo- and enantioselectivity, albeit with a low yield.

To broaden the scope of this transformation. Various α,α-difluoromethyl olefins **2b-p** were tested in this cyclopropanation process with **4j** (**Scheme 46**). First, the α,α-difluoromethyl styryl derivatives **2b** and **2e** bearing a methyl group at *para* and *meta*

position were tested, providing the corresponding cyclopropanes **6a** and **6b** in good yields as a single diastereoisomer with excellent enantiomeric excesses (93% ee and 95% ee, respectively).

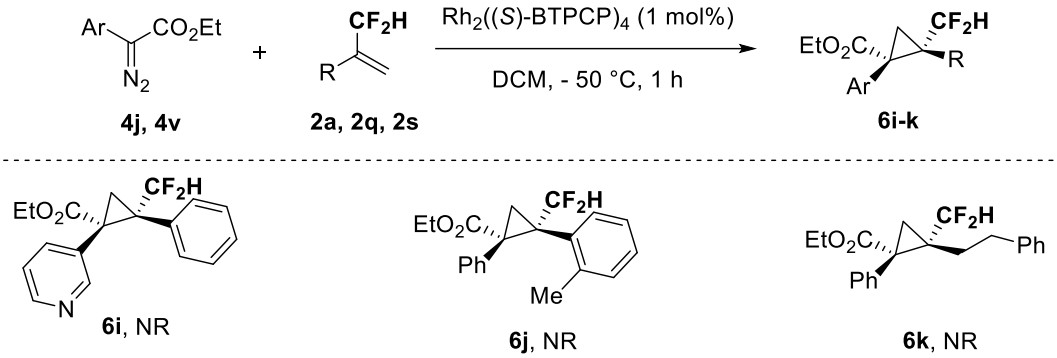
The 2-naphthyl-substituted olefin gave lower dr (9:1), while the enantiomeric excess of the major isomer remained excellent.



Scheme 46. Scope of the reaction between α-phenyl diazoacetate **4j** and α,α-difluoromethyl olefins **2**. [a] reaction was carried out at -60 °C.

Then, aryl of α,α-difluoromethyl styrene bearing a halogen or a nitro group reacted with **4j**, and converted into the corresponding cyclopropanes **6d-g** in good yields with complete diastereoselectivity and excellent enantioselectivities (95-98% ee). Cyclopropane **6g** was isolated in a low yield (28%) although the levels of diastereo- and enantioselectivity remained outstanding.

Finally, thienyl olefin was transformed into the desired cyclopropane **6h** in good yield with a complete diastereoselectivity, albeit with a moderate ee (67% ee).



Scheme 47. Limitations of the scope study in the cyclopropanation of α-aryl diazoacetates with olefins **2**.

In the scope investigation, some substrates were inert in this process (**Scheme 47**). The presence of α-pyridyl diazoacetate shut down the reaction, which was considered reasonable as pyridine can inhibit the catalyst. Indeed, pyridine is usually used to quench the reaction before the purification of the crude material. The use of *ortho*-methyl substituted olefin **2q** in this process led to no trace of desired cyclopropane was formed. Finally, alkyl substituted olefin **2s** was recovered after the reaction.

1.8 X-Ray Analysis and proposed mechanism

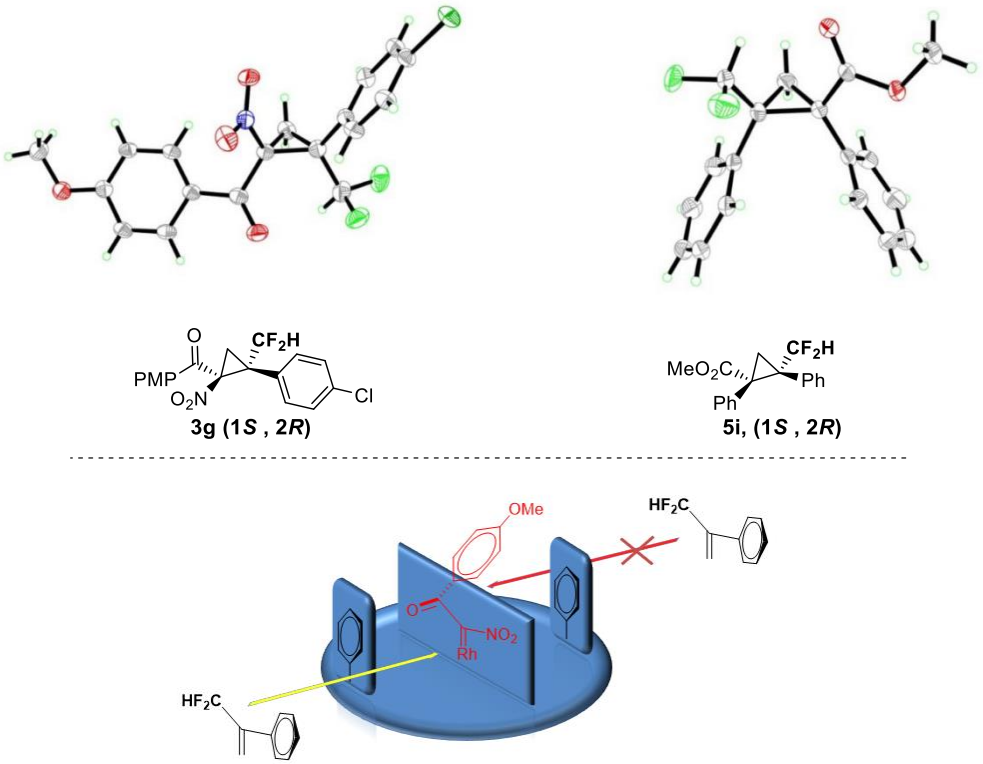


Figure 17. The absolute configuration of **3g** and **5i**, and the stereochemical model explains the selectivity.

Suitable crystals were obtained from **3g** (CCDC 1558858) and **5i** (CCDC 1558859), the X-Ray crystallographic analysis of the corresponding cyclopropanes confirmed the relative and absolute configuration of the compounds. The major diastereoisomer of cyclopropane **3g** is a *trans*-configuration, while **5i** was determined as a *cis*-cyclopropane from the X-ray analysis (**Figure 17**).

The mechanism for this rhodium-catalyzed transformation can be suggested on the basis of the absolute configuration that observed from the two cyclopropanes (**3g** and **5i**) and the stereochemical model depicted by Davies (**Figure 15**).[88] The generation of the rhodium carbene from diazo compound is generally accepted. Then a stereochemical model was proposed to explain the selectivity for Rh_2((*S*)-BTPCP)$_4$ catalyzed this transformation (**Figure 17**). In this model, the rhodium and bridging carboxyl acid ligands arrange as a chiral cavity, where the rhodium atom is in the center of this cavity. The ketone group aligns perpendicular to the carbene plane, and blocks attack on its side. When the olefin approaches over the nitro group, the back side of Rh-cabene is blocked by the aryl ring of the ligand and the PMP group, leaving the front side open for attack. This predictive model could explain the observation on experimental data, where α-nitro diazoketone provided selectively the *trans*-cyclopropanes.

Regarding the α-phenyl diazoacetates, the ester group aligns perpendicular to the carbene plane as a blocker. When the olefin approaches over the carbene, a favored aryl rings π-stacking interaction between the phenyl ring of the carbene and the phenyl ring of the α,α-difluoromethyl styrene might occur during the cyclopropanation event. This model explains the diastereoselectivity observed in all cases, as this reaction favors the *cis*-isomer over the *trans*-isomer with a very high diastereomeric ratio (> 20:1 dr).

1.9 Summary

In summary, we described in this chapter is that our contribution towards the first catalytic asymmetric synthesis of highly functionalized difluoromethyl cyclopropanes. This methodology, using Rh_2((*S*)-BTPCP)$_4$ as the catalyst, allowed the decomposition of both di-acceptor and donor-acceptor diazo compounds and provided the corresponding difluoromethyl cyclopropanes in good to high yields (up to 95%), with excellent diastereoselectivities (up to >20:1) and excellent enantioselectivities (up to 99%). Moreover, this work demonstrates that the rhodium-catalyzed asymmetric cyclopropanation of electron-deficient olefins is possible, even with di-acceptor diazo derivatives. The scope of the reaction is quite broad and offers a new access to

difluoromethylated cyclopropane derivatives.

Chapter II

Catalytic Asymmetric Synthesis of Trifluoromethyl Cyclopropanes

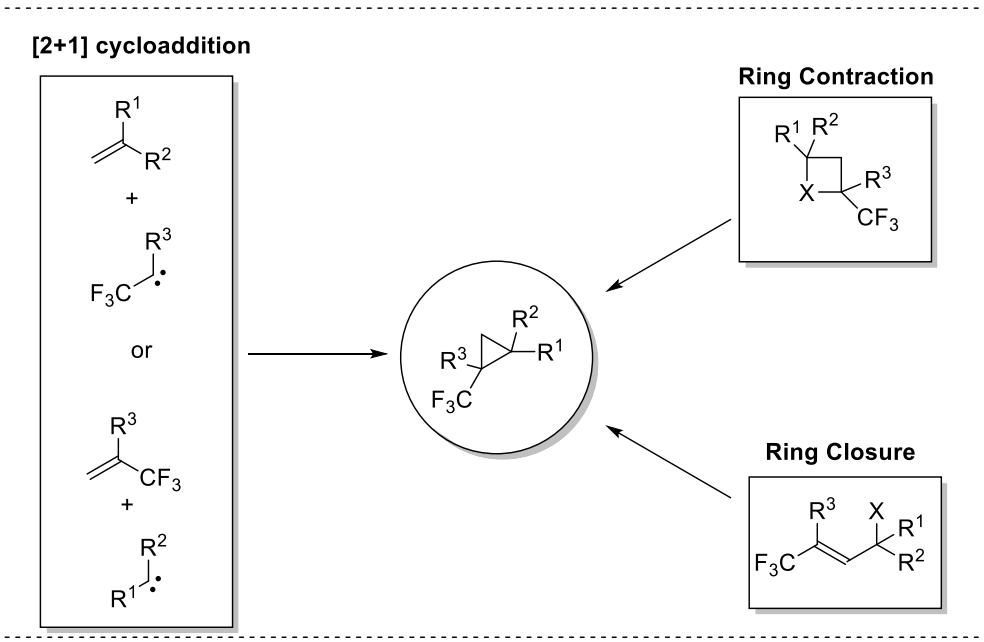
Chapter II Catalytic Asymmetric Synthesis of Trifluoromethyl Cyclopropanes

2.1 Introduction

The incorporation of cyclopropane ring into organic molecules has been widely studied, as this three-membered ring is known to be an important structure in many biologically active compounds. On the other hand, owing to the special properties of fluorine, the introduction of a fluorine atom or fluorinated group into organic molecules is also an important research area for medicinal chemistry community.

The combination of the fluorine atom and cyclopropane, fluorinated cyclopropyl motif plays an important role in all aspects of the chemical industry. As part of this field, the study of trifluoromethyl cyclopropane has attracted much attention of scientists in recent years. In medicinal chemistry, trifluoromethyl cyclopropane is recognized as a *tert*-butyl bioisostere, it is an important building block in the design of bioactive compounds. Selected applications of trifluoromethyl cyclopropane core were shown in **Figure 5** (see page 6).

2.2 State of the art



Scheme 48. Strategies for the preparation of trifluoromethyl cyclopropanes.

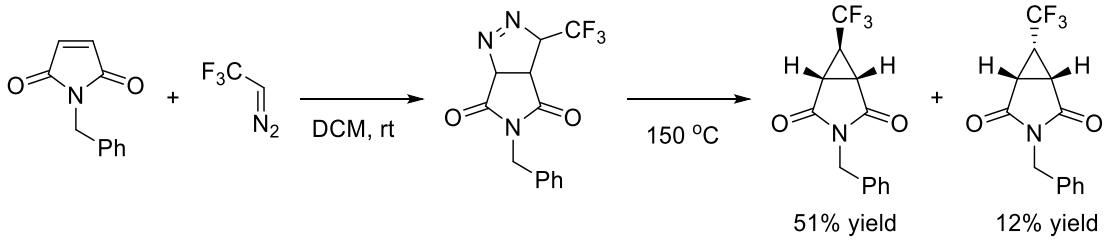
The strategies used for the preparation of trifluoromethyl cyclopropanes could be

divided into three main classes (**Scheme 48**): (1) the ring contraction of a trifluoromethyl cyclic precursor, (2) the ring closure cyclopropanation of an acyclic precursor bearing a trifluoromethyl group, and (3) the [2+1] cycloaddition of a carbene with an alkene. Note that the [2+1] cycloaddition reaction is one of the most developed strategy that has been applied to build up trifluoromethyl cyclopropanes.[109]

Ring contraction cyclopropanation

The ring contraction cyclopropanation relies on a non-catalyzed [3+2] cycloaddition followed by a ring contraction sequence, which gave birth to the cyclopropane.

In 2013, Mykhailiuk and coworkers reported the preparation of bicyclo[3.1.0]hexane compound as relies on the [3+2] cycloaddition/ring contraction sequence (**Scheme 49**).[115] The reaction firstly occurred through a cycloaddition of *N*-benzyl maleimide with 2,2,2-trifluoro-diazoethane providing the pyrazoline in quantitative yield. Then the thermal decomposition of the pyrazoline gave the corresponding cyclopropanes in moderate yields with good diastereoselectivity (4:1 dr).

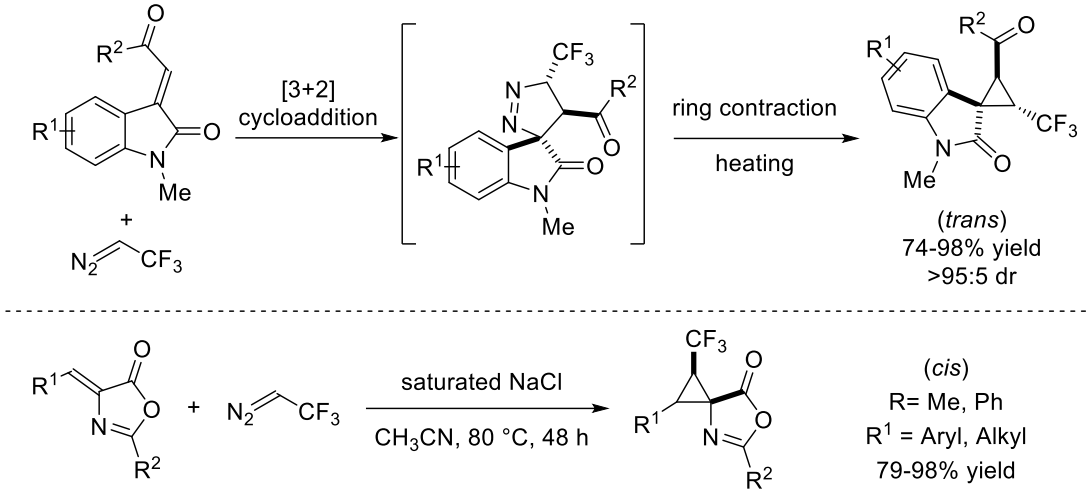


Scheme 49. Cycloaddition/ring contraction sequence.

Similarly, Xiao and Ma's groups independently described the synthesis of trifluoromethyl cyclopropanes. In Xiao's report, the cycloaddition of olefins, derived from isatin with the generated 2,2,2-trifluoro-diazoethane was achieved in high yields with a complete *trans* selectivity (**Scheme 50**).[116]

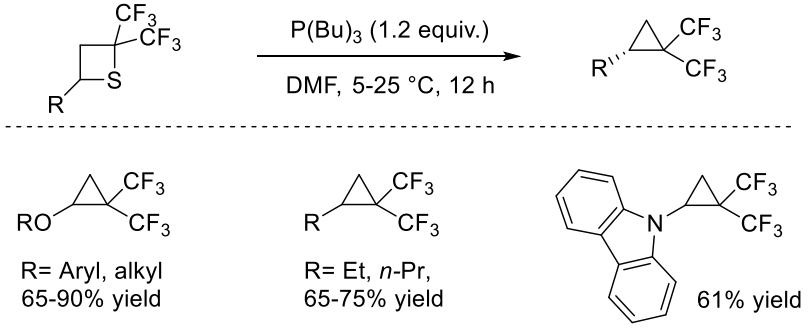
On the other hand, Ma and coworkers initially intended to explore a cyclopropanation reaction using transition metals, however, in the course of their investigations, they found that the reaction between 2,2,2-trifluoro-diazoethane and benzylidene azlactones proceeded very well using a small amount of brine, providing the *cis*-cyclopropanes in good to excellent yields (**Scheme 50**).[117]

[115] O. S. Artamonov, E. Y. Slobodyanyuk, O. V. Shishkin, I. V. Komarov, P. K. Mykhailiuk, *Synthesis* **2013**, *45*, 225-230.
[116] T. R. Li, S. W. Duan, W. Ding, Y. Y. Liu, J. R. Chen, L. Q. Lu, W. J. Xiao, *J. Org. Chem*. **2014**, *79*, 2296-2302.
[117] C. L. Zhu, L. J. Yang, S. Li, Y. Zheng, J. A. Ma, *Org. Lett*. **2015**, *17*, 3442-3445.



Scheme 50. Xiao and Ma's [3+2] cycloaddition / ring contraction reaction.

An alternative to the [3+2] cycloaddition/ring contraction reaction has been reported. Indeed, Marshall's group reported the transformation of 2,2-bis(trifluoromethyl) thietanes into cyclopropanes in good to excellent yields promoted by tributyl phosphine (**Scheme 51**).[118] This methodology was successfully applied to alkyl, alkoxy and carbazolyl substituted thietanes.



Scheme 51. Trifluoromethyl cyclopropanation of 2,2-bis(trifluoromethyl)thietanes.

Ring closure cyclopropanation

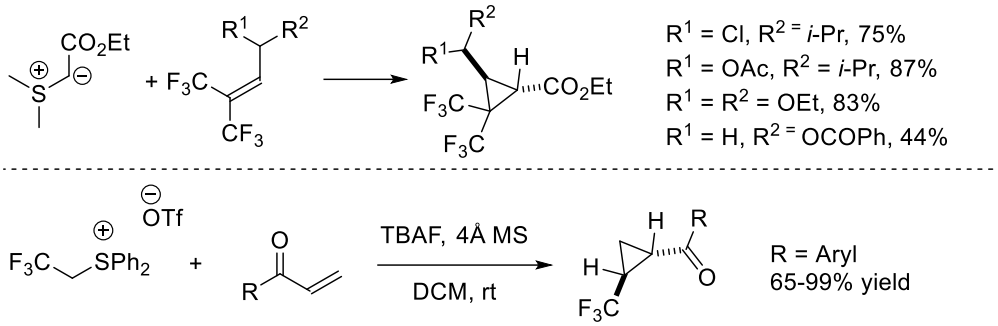
This approach is based on the generation of a carbanion, followed by an intramolecular nucleophilic substitution at the γ-position of an alkyl chain. Note that the Michael Initiated Ring Closure (MIRC) reaction and the Johnson-Corey-Chaykovsky reaction are the most used processes for this propose.

These reports have been both described by means of the Johnson-Corey-Chaykovsky reaction to access trifluoromethyl cyclopropanes, either with the trifluoromethyl group on a sulfur ylide or on an alkene. For example, the cyclopropanation of several

[118] V. A. Petrov, W. Marshall, *J. Fluorine Chem*. **2012**, 133, 61-66.

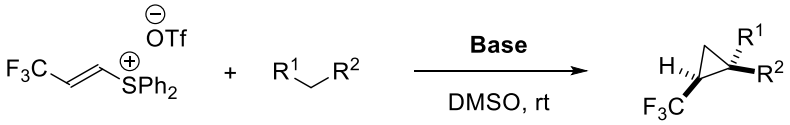
trifluoromethyl substituted alkenes with (ethoxycarbonylmethylene)dimethylsulfurane resulted in the formation of *trans*-substituted cyclopropanes (**Scheme 52**).[119]

Xiao and coworkers reported the synthesis of trifluoromethyl cyclopropanes using (2,2,2-trifluoroethyl)diphenyl sulfonium triflate. Vinyl aryl ketones were used in this sequence, in the presence of tetrabutylammonium fluoride (TBAF), leading to the corresponding cyclopropanes in good to excellent yields as a single *trans* isomer (**Scheme 52**).[120]



Scheme 52. Synthesis trifluoromethyl cyclopropanes by Johnson-Corey-Chaykovsky reaction.

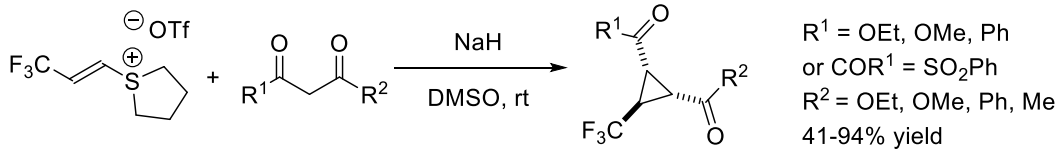
In 2011, Lu and coworkers reported the synthesis of trifluoromethyl cyclopropanes from the addition of activated methylene compounds on β-(trifluoromethyl)-vinyl sulfonium salts (**Scheme 53**).[121] In this paper, the use of DBU gave the disubstituted cyclopropanes in moderate to excellent yields and regioselectivities. Note that the change from DBU to NaH afforded the trisubstituted cyclopropanes in moderate to excellent yields with complete *trans*-stereocontrol. Hanamoto and coworkers described a similar process for the preparation of cyclopropanes using β-(trifluoromethyl)-vinyl sulfonium salt, which required the presence of K_2CO_3 and provided the corresponding cyclopropanes in good to high yields.[122]



Base = **DBU**, 15-95% yield
R^1 = CO_2Et, CO_2Bn, C=OPh, CN
R^2 = CO_2Et, CO_2Bn, Ts, CN

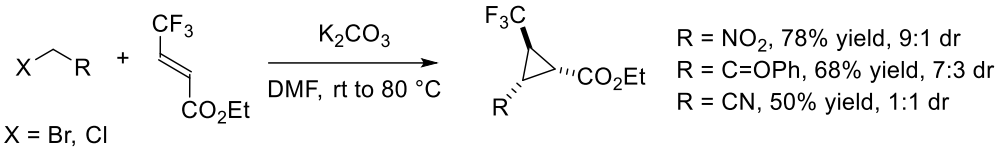
Base = **K_2CO_3**, 72-98% yield
R^1 = CO_2i-Pr, CN
R^2 = CO_2i-Pr, CN

[119] a) U. M. Nagele, M. Hanack, *Liebigs Ann. Chem*. **1989**, 847-852. b) R. Rothermel, M. Hanack, *Liebigs Ann. Chem*. **1991**, 1013-1020.
[120] Y. Duan, B. Zhou, J. H. Lin, J. C. Xiao, *Chem. Commun*. **2015**, *51*, 13127-13130.
[121] H. Lin, Q. Shen, L. Lu, *J. Org. Chem*. **2011**, *76*, 7359-7369.
[122] N. Kasai, R. Maeda, H. Furuno, T. Hanamoto, *Synthesis* **2012**, *44*, 3489-3495.



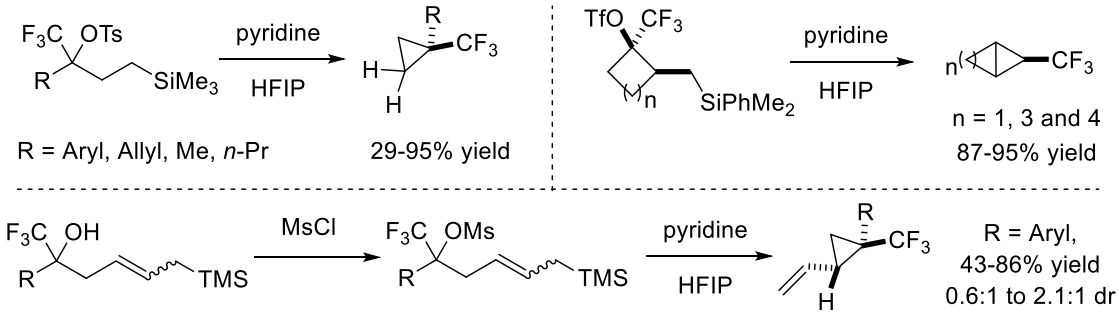
Scheme 53. Ring closure cyclopropanation from vinylsulfonium salts.

Crousse and coworkers described the synthesis of trifluoromethyl cyclopropanes (**Scheme 54**), using the Michael addition of a nucleophile (bearing nitro, ketone or nitrile as activating group) to ethyl 4,4,4-trifluorocrotonate, leading to the corresponding enolates followed by a spontaneous intramolecular nucleophilic substitution providing the expected trifluoromethyl cyclopropanes in moderate to good yields and diastereoselectivities.[123]



Scheme 54. Michael addition / ring closure cyclopropanation reaction.

Finally, Tilley and coworkers reported the synthesis of trifluoromethyl cyclopropanes by 1,3-γ-silyl-elimination (**Scheme 55**). The trifluoromethylated cyclopropanes were obtained in moderate to good yields.[124] In addition, the authors also extended the reaction to homoallylic alcohols by a two-step and one-pot protocol for the preparation of trifluoromethyl substituted vinylcyclopropanes.[125]

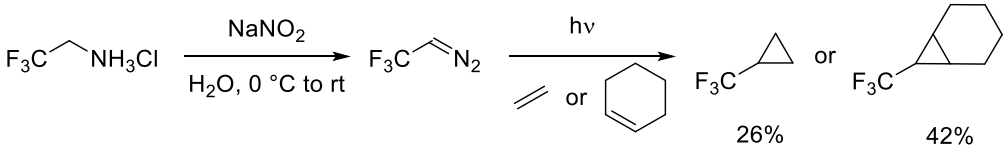


Scheme 55. cyclopropanation reaction by means of 1,3-γ-silyl-elimination.

123 M. Keita, R. De Bona, M. D. Santos, O. Lequin, S. Ongeri, T. Milcent, B. Crousse, *Tetrahedron* **2013**, *69*, 3308-3315.
124 A. Mercadante, C. B. Kelly, T. A. Hamlin, K. R. Delle Chiaie, M. D. Drago, K. K. Duffy, M. T. Dumas, D. C. Fager, B. L. C. Glod, K. E. Hansen, C. R. Hill, R. M. Leising, C. L. Lynes, A. E. MacInnis, M. R. McGohey, S. A. Murray, M. C. Piquette, S. L. Roy, R. M. Smith, K. R. Sullivan, B. H. Truong, K. M. Vailonis, V. Gorbatyuk, N. E. Leadbeater, L. J. Tilley, *Chem. Sci*. **2014**, *5*, 3983-3994.
125 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**, 4071-4076.

[2+1] Cycloaddition

In 1964, Fields and Haszeldine reported the first synthesis of trifluoromethyl cyclopropanes by using 2,2,2-trifluoro-diazoethane, which reacts with ethylene or cyclohexene. providing the corresponding cyclopropanes in 26% and 42% yield, respectively (**Scheme 56**).[126] In this report, 2,2,2-trifluoro-diazoethane was rapidly prepared by a diazotization reaction from the corresponding amine, followed the photolysis of the 2,2,2-trifluoro-diazoethane providing the trifluoroethyl carbene, finally, the addition of this trifluoroethyl carbene on alkenes, led to the formation of trifluoromethyl cyclopropanes.

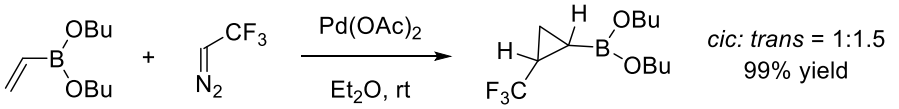


Scheme 56. [2+1] cycloaddition for the synthesis of trifluoromethyl cyclopropanes.

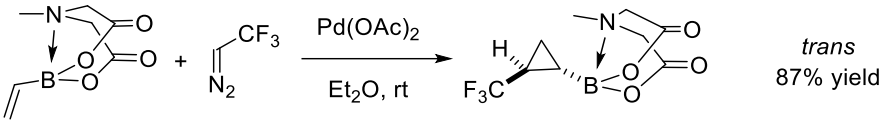
Inspired by this seminal report, the synthesis of trifluoromethyl cyclopropanes using a trifluoromethyl-substituted carbene was well explored, which was generated from a transition metal-catalyzed decomposition reaction. This [2+1] cycloaddition strategy has been largely developed using various transition metals such as iron, cobalt, copper, ruthenium, rhodium or palladium, for example.

In 2010, Duncton and coworkers reported the palladium catalyzed cyclopropanation of 2,2,2-trifluoro-diazoethane with dibutyl vinylborate, providing a mix of *trans* and *cis* cyclopropane in a ratio of 1.5:1 (**Scheme 57**).[127]

Three years later, Duncton and Singh described a similar reaction using vinyl boronic acid *N*-methyl iminodiacetic (MIDA) ester instead of dibutyl vinylborate allowing the efficient synthesis of the corresponding cyclopropanes in good yields as a *trans* diastereoisomer (**Scheme 57**).[128] The subsequent Suzuki cross-coupling of these cyclopropyl borates with aryl or heteroaryl bromide provided new building blocks for drug discovery or material sciences.

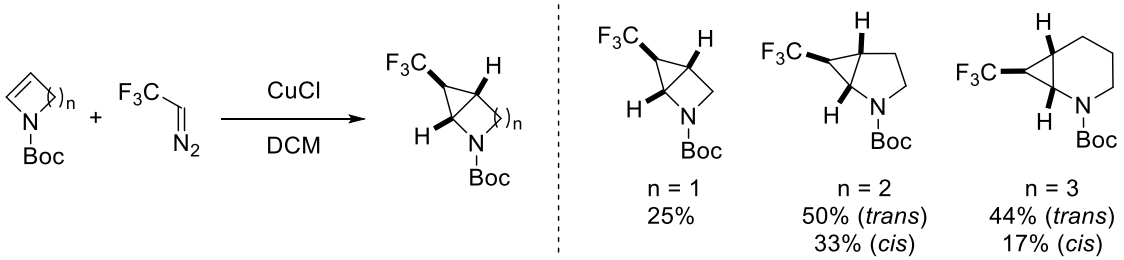


[126] R. Fields, R. N. Haszeldine, *J. Chem. Soc*. **1964**, 1881-1889
[127] M. A. J. Duncton, L. Ayala, C. Kauba, S. Janagania, W. T. Edwards, N. Orike, K. Ramamoorthy, J. Kincaid, M. G. Kelly, *Tetrahedron Lett*. **2010**, *51*, 1009-1011.
[128] M. A. J. Duncton, R. Singh, *Org. Lett*. **2013**, *15*, 4284-4287.



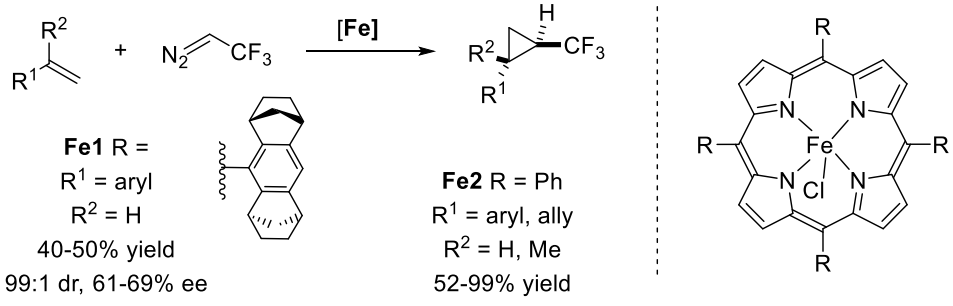
Scheme 57. Palladium-catalyzed cyclopropanation reaction.

Mykhailiuk and coworkers reported a copper-catalyzed cyclopropanation of unsaturated cyclic amines with 2,2,2-trifluoro-diazoethane for the design of trifluoromethylated bicyclic amines. In their report, 3-azabicyclo[2.1.0]pentane (n = 1) was obtained in low yield probably due to the steric strain of the product. When larger cyclic enamides (n = 2 or 3) were reacted with 2,2,2-trifluoro-diazoethane, the corresponding bicyclo compounds were obtained in moderate yields and diastereoselectivities (**Scheme 58**).[129]



Scheme 58. Copper-catalyzed cyclopropanation reaction of enamides.

In 2006, Simmoneaux and coworkers reported the first asymmetric cyclopropanation of styrene with 2,2,2-trifluoro-diazoethane. The use of Fe-metalloporphyrin catalyst **Fe1** in DCM led to the corresponding cyclopropanes in moderate yields with excellent dr and 61-69% ee values (**Scheme 59**).[130]



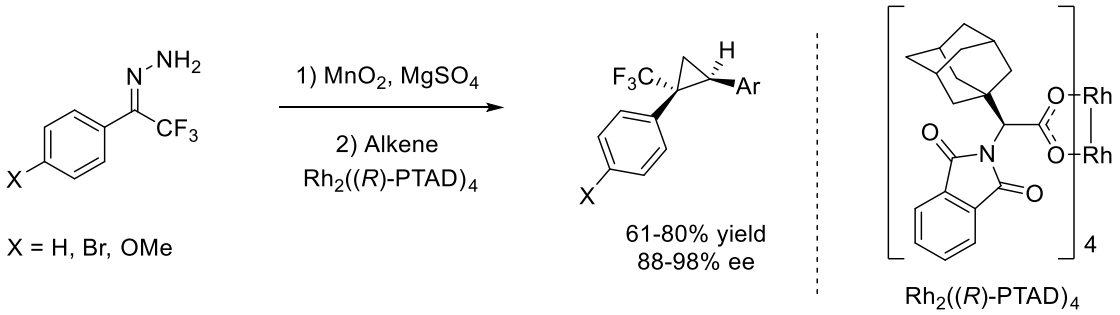
Scheme 59. Iron porphyrin catalyzed cyclopropanation.

Carreira and coworkers reported a tandem sequence (diazotization/carbene generation/cyclopropanation) for the preparation of racemic trifluoromethyl

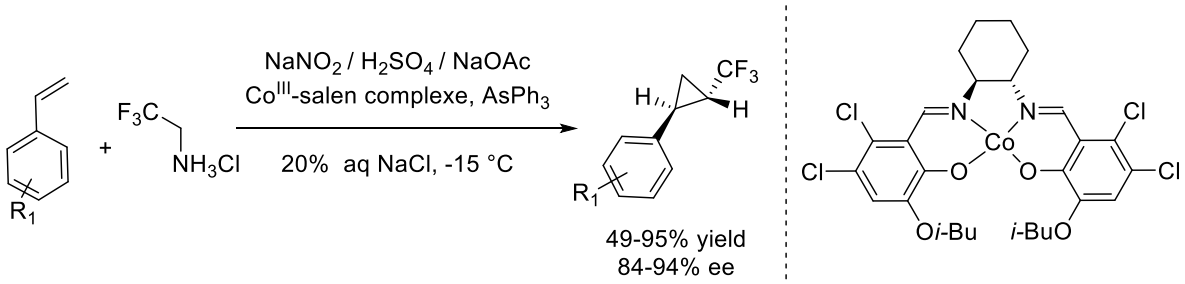
[129] O. S. Artamonov, E. Y. Slobodyanyuk, D. M. Volochnyuk, I. V. Komarov, A. A. Tolmachev, P. K. Mykhailiuk, *Eur. J. Org. Chem*. **2014**, 3592-3599.
[130] P. Le Maux, S. Juillard, G. Simonneaux, *Synthesis* **2006**, 1701-1704.

cyclopropanes from the corresponding amine. The reaction proceeded very well with various substituted styrenes, dienes, or enynes using catalyst **Fe 2** in aqueous solution, affording a large scope of trifluoromethyl cyclopropanes in good to excellent yields and diastereoselectivities (**Scheme 59**).[131]

Another approach to perform the asymmetric synthesis of trifluoromethyl cyclopropanes was described by Davies and coworkers in 2007 (**Scheme 60**). Note that this approach was also performed via diazotization/carbene generation/cyclopropanation sequence. The use of $Rh_2((R)\text{-PTAD})_4$ as the chiral catalyst provided the *trans*-selective products in good to high yields with high to excellent ee values.[132]



Scheme 60. Enantioselective rhodium-catalyzed cyclopropanation reaction.



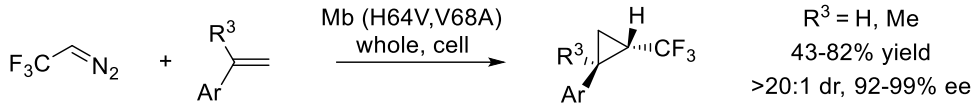
Scheme 61. Enantioselective cobalt salen catalyzed cyclopropanation reaction.

In 2011, Carreira and coworkers reported another efficient methodology for the catalytic enantioselective synthesis of chiral trifluoromethyl cyclopropanes (**Scheme 61**).[133] The use of Co(III) salen as the catalyst, under similar conditions as the ones used with **Fe2** (**Scheme 59**), allows the catalytic asymmetric cyclopropanation of a broad range of styrene derivatives, providing the corresponding cyclopropanes in good to excellent yields with excellent diastereoselectivities and ee values. This strategy was the most efficient catalytic enantioselective synthesis of chiral trifluoromethyl

131 B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed*. **2010**, *49*, 938-941.
132 J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett*. **2007**, *9*, 2625-2628.
133 B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed*. **2011**, *50*, 1101-1104.

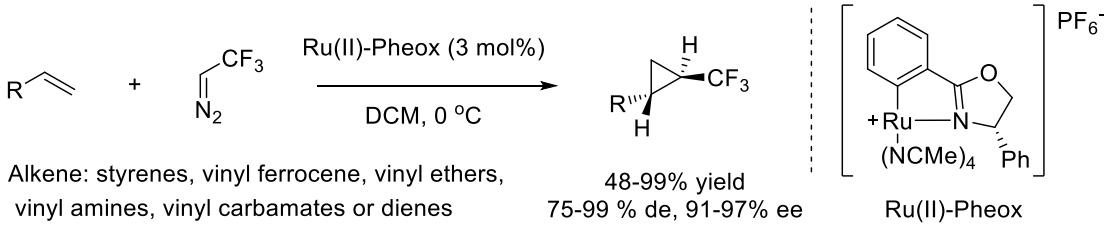
cyclopropanes at that time.

Recently, Fasan and coworkers reported an efficient biocatalytic approach for the synthesis of trifluoromethyl substituted cyclopropanes using myoglobin as the biocatalyst. This strategy was compatible with a broad range of styrenes and led to the corresponding cyclopropanes in moderate to high yields with excellent diastereoselectivity and ee values (**Scheme 62**).[134]



Scheme 62. Myoglobin catalyzed asymmetric cyclopropanation reactions.

Finally, Iwasa and coworkers described a Ru(II)–Pheox complex promoting the asymmetric synthesis of trifluoromethyl cyclopropanes.[135] Note that olefins such as vinyl ferrocene, vinyl ethers, vinyl amines, vinyl carbamates, and dienes were investigated and converted into the corresponding cyclopropanes in moderate to high yields with excellent diastereoselectivities (up to >99:1) and enantioselectivities (up to 97% ee) (**Scheme 63**).



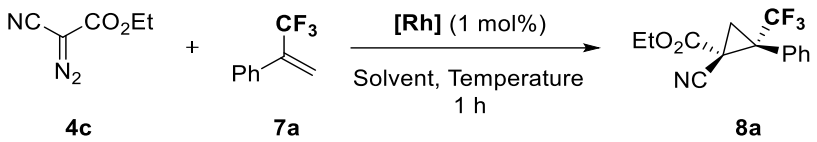
Scheme 63. Ruthenium-catalyzed cyclopropanation reaction.

2.3 Objectives

The studies of trifluoromethyl cyclopropane derivatives have been well explored. However, only few examples described the enantioselective synthesis of trifluoromethyl cyclopropane derivatives. Moreover, only -CF_3 diazo derivatives were used as a carbene precursor in previous reports, therefore it is important to provide new strategies to access enantioenriched trifluoromethyl cyclopropanes. Herein, on the basis of previous research of our group, the Rh-catalyzed asymmetric cyclopropanation of α,α,α-trifluoromethyl styrenes will be investigated.

[134] A. Tinoco, V. Steck, V. Tyagi, R. Fasan, *J. Am. Chem. Soc.* **2017**, *139*, 5293-5296
[135] M. Kotozaki, S. Chanthamath, T. Fujii, K. Shibatomi, S. Iwasa, *Chem. Commun*. **2018**, *54*, 5110-5113.

2.4 Optimization study



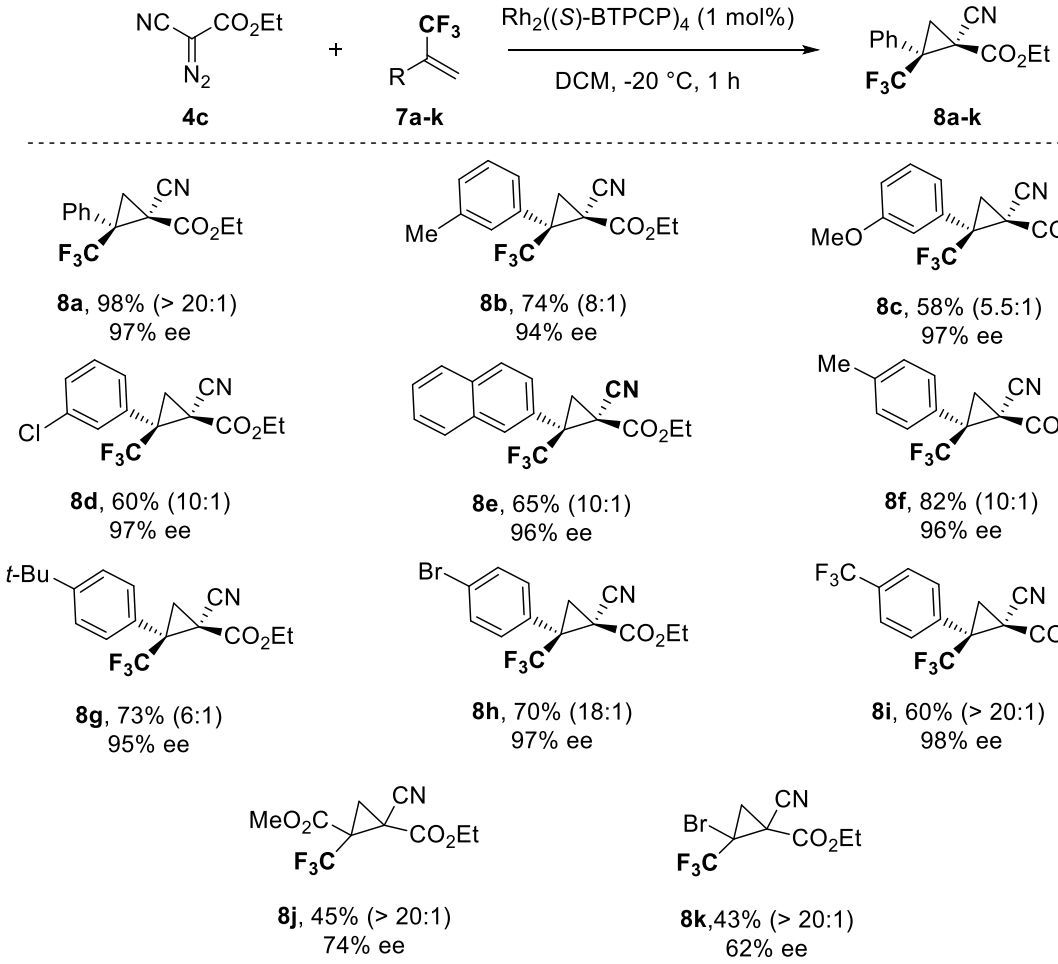
Entry	[Rh]	Solvent	T(°C)	Yield [%][b]	dr[c]	ee [%][d]
1	Rh_2((*S*)-TCPTTL)$_4$	EtOAc	0-25	22	2.8:1	ND
2	Rh_2((*S*)-TCPTTL)$_4$	*n*-hexane	0-25	13	4:1	ND
3	Rh_2((*S*)-TCPTTL)$_4$	DCE	0-25	65	3:1	50
4	Rh_2((*S*)-TCPTTL)$_4$	DCM	-20	68	4:1	70
5	**Rh_2((*S*)-BTPCP)$_4$**	**DCM**	**-20**	**98**	**>20:1**	**97**
6	Rh_2((*S*)-BTPCP)$_4$	DCM	-30	87	>20:1	96
7	Rh_2((*S*)-BTPCP)$_4$	DCM	-40	82	>20:1	96
8	Rh_2((*S*)-BTPCP)$_4$	THF	-40	0	-	-

Table 9. Optimization study. [a] Conditions: **7a** (0.25 mmol, 1 eq), **4c** (0.375 mmol, 1.5 eq), [Rh] (1% mol), [diazo] = 1 M. [b] Isolated yield. [c] Determined by ^{19}F NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. ND = not determined.

At the outset of this project, α,α,α-trifluoromethyl styrene **7a** used in the reaction with a di-acceptor type diazo compound, ethyl α-cyano diazoacetate **8a**, in the presence of two different chiral rhodium catalysts, namely Rh_2((*S*)-TCPTTL)$_4$ and Rh_2((*S*)-BTPCP)$_4$ (**Table 9**).

First, Rh_2((*S*)-TCPTTL)$_4$ was tested in different solvents and the reaction was carried out at 0 °C for 1 h, then warm up to room temperature (25 °C). The desired trifluoromethyl cyclopropane **8a** was generally obtained in low conversion in EtOAc and hexane, while the use of DCE as the solvent provided **8a** in 65% yield with 3:1 dr and 50% ee (**Table 9**, entries 1-3). A slight better yield, dr and ee were observed when the reaction was carried out in DCM at -20 °C (entry 4). Pleasingly, the cyclopropanation of **4c** with **7a** proceeded very well in the presence of Rh_2((*S*)-BTPCP)$_4$ in DCM at -20 °C, and **8a** was isolated in good yield with excellent dr (> 20:1) and 97% ee (entry 5). When the reaction temperature was lowered to -30 or -40 °C, the compound **8a** was isolated as a single diastereoisomer with 96% ee, but with a slight decrease of the yield (entry 6 and 7). Finally, we observed the reaction was inhibited when THF was employed as the solvent (entry 8).

2. 5 Scope study of α-cyano diazoacetate with α,α,α-trifluoromethyl olefins



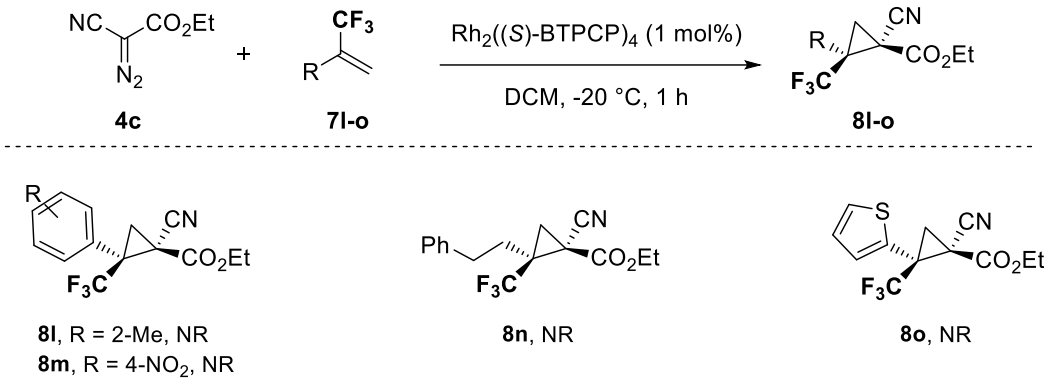
Scheme 64. Scope of the reaction between ethyl α-cyano diazoacetate **4c** and α,α,α-trifluoromethyl alkenes **7a-k**.

With these data in hand, we selected the conditions from entry 5 as the optimal ones and examined the scope of the reaction (**Scheme 64**). First, the reaction was carried out with a range of different substituted α,α,α-trifluoromethyl styrenes. Different electron-donating substituents (**7b**, **7c**) and halogen substituent (**7d**) at *meta* position were well tolerated, providing the corresponding trifluoromethyl cyclopropanes (**8b-d**) in moderate to good yields (58-74%), good diastereoselectivities (8:1-10:1) and high enantioselectivities (94-97%). The 2-naphthyl substituted olefin **7e** was reacted to give **8e** in 65% yield with 10:1 dr and 96% ee.

Next, α-styryl derivative bearing an electron-donating or an electron-withdrawing group at the *para* position were tested. Pleasingly, the *para*-methyl, *para*-*tert*-butyl, *para*-bromo, and *para*-trifluoromethylated derivatives **7f-i** were converted into the

corresponding cyclopropanes **8f-i** in good yield (60-82%) with high levels of diastereoselectivity (6:1 to >20:1), and excellent enantiomeric excesses in all cases (95-98%).

Then, the attention was turned to the use of electron deficient olefins, such as methyl 2-(trifluoromethyl) acrylate **7j** and 2-bromo-3,3,3-trifluoropropene (BTP) **7k**, in combination with ethyl α-cyano diazoacetate **4c**. Notice that the Rh-catalyzed asymmetric cyclopropanation of these two olefins remains elusive to date. In both cases, the electron-deficient olefins **7j** and **7k** were converted into the corresponding cyclopropanes **8j** and **8k** in moderate yields with excellent diastereoselectivities, although the enantiomeric excesses were modest (74% and 62%, respectively) (**Scheme 64**).



Scheme 65. Limitations of the reaction.

Although the reaction had an interesting scope, some limitations remained. When *para*-nitro or *ortho*-methyl olefin derivatives were submitted to this catalytic system, no conversion of these two olefins was observed. The same outcome was observed when alkyl derivative and thiophenyl derivative were tested in our Rh-catalyzed cyclopropanation process (**Scheme 65**).

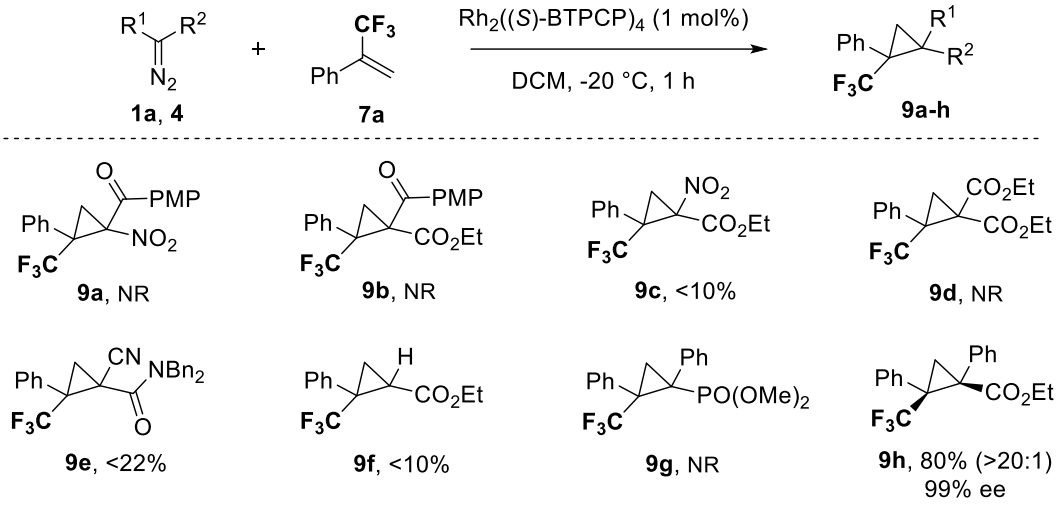
2.6 Screening of diazo compounds

To further extend the application of this methodology, various substituted diazo compounds (di-acceptor and donor-acceptor) were tested in the cyclopropanation of α,α,α-trifluoromethyl styrene **7a** under similar reaction conditions (**Scheme 66**). Surprisingly, the use of α-diazoketones **1a** and **4b** in this cyclopropanation process gave no conversion into the desired cyclopropane, which is in contrast with the excellent results obtained with the α-difluoromethyl styrene **2a**.

Next, the use of other diazo compounds (α-nitro diazoacetate **4e**, diazomalonate **4d**, diazoacetate **4g** and diazophosphonate **4h**) in the presence of Rh_2((*S*)-BTPCP)$_4$, led

to low or no conversion.

Finally, α-phenyl diazoacetate **4j** was tested. To our delight, the reaction proceeded smoothly, providing the desired cyclopropane **9g** in 80% isolated yield as a single diastereoisomer with an excellent enantioselectivity (99% ee).



Scheme 66. Screening of diazo compounds in the presence of Rh_2((*S*)-BTPCP)$_4$.

2.7 Scope study between α-aryl diazoacetates with α,α,α-trifluoromethyl olefins

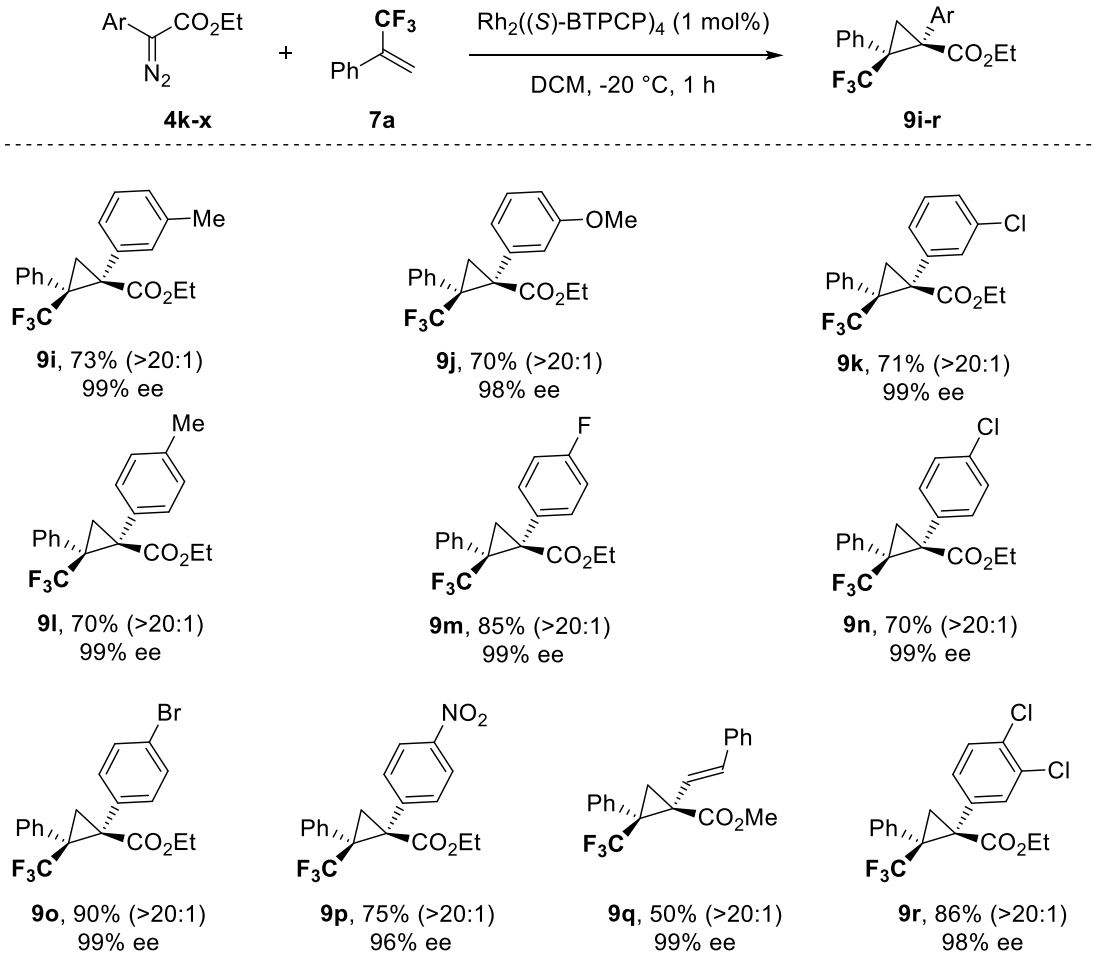
Various α-aryl diazoacetates were tested with α,α,α-trifluoromethyl styrene **7a** under similar reaction conditions to demonstrate the broad scope of this process (**Scheme 67**).

First, *meta*-methyl, *meta*-methoxy and *meta*-chloro substituted α-aryl diazoacetates were submitted to this cyclopropanation process, giving the desired trifluoromethylated products **9i-k** in good isolated yields with a complete diastereoselectivity (> 20:1) and excellent enantiomeric excess (98-99%).

Next, α-(*para*-substituted)aryl diazoacetates, bearing a methyl and a halogen atom were tested, the corresponding cyclopropanes **9l-o** were isolated in good to excellent yield as a single diastereoisomer with an almost perfect control of the enantioselectivity (99% ee in all cases). The *para*-nitroaryl cyclopropane **9p** was obtained in 75% yield from the reaction between **4s** and **7a** without the observation of the other diastereoisomer and with 96% ee in a 0.25 mmol scale reaction. Note that the preparation of **9p** has been scaled up to a 10 mmol scale, providing **9p** in a higher yield (95%) without the erosion of diastereo- and enantioselectivity.

Then, the reaction was carried out with α-styryl diazoacetate, and the vinyl

cyclopropane **9q** was isolated as a single diastereoisomer and excellent ee (99%), albeit in a moderate isolated yield (50%). Finally, ethyl α-(3,4-dichlorophenyl) diazoacetate was used as a substrate, providing compound **9r** in very good yield, dr and ee value.



Scheme 67. The scope of the reaction between α-aryl diazoacetates **4k-x** and α,α,α-trifluoromethyl styrene **7a**.

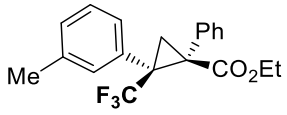
The investigations were pursued by modifying the aryl group in the structure of α,α,α-trifluoromethyl styrene (**Scheme 68**).

First, the *meta*-substituted styrene derivatives were tested in this cyclopropanation process, *meta*-methyl, *meta*-chloro and *meta*-methoxy aryl cyclopropanes **10a-c** were isolated with a complete diastereoselectivity and excellent ee values and moderate to good yields, except in the case of **10c**, which was obtained in poor yield (11%). The presence of 2-naphthyl olefin afforded the cyclopropane **10d** in very good yield with excellent diastereo- and enantioselectivity.

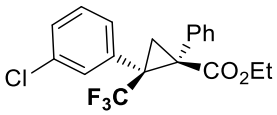
Next, *para*-methyl, *para*-*tert*-butyl and *para*-bromo alkenes were reacted smoothly to give trifluoromethyl cyclopropane derivatives **10e-g** as a single diastereoisomer with

almost perfect control of enantioselectivity (96-99%).

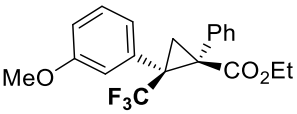
The presence of thienyl olefin with ethyl α-phenyl diazoacetate gave the desired cyclopropane **10h** in 60% yield with excellent diastereo- and enantioselectivity. Moreover, the reaction of *para*-trifluoromethylaryl olefin was carried out, associated with α-(*para*-bromo)phenyl diazoacetate **4r**, providing functionalized cyclopropane **10i** in 63% yield with excellent dr and ee. The *meta*-chloroaryl olefin reacted with diazoacetate **4r** and was converted into the corresponding cyclopropane **10j** in 66% yield with excellent dr and ee again.



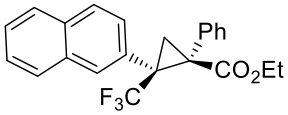
10a, 78% (>20:1)
98% ee



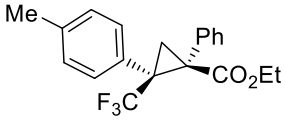
10b, 56% (>20:1)
97% ee



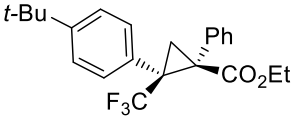
10c, 11% (>20:1)
95% ee



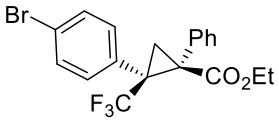
10d, 83% (>20:1)
99% ee



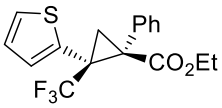
10e, 70% (>20:1)
96% ee



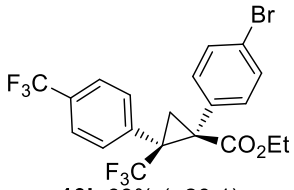
10f, 83% (>20:1)
98% ee



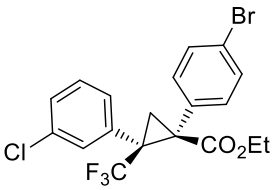
10g, 82% (>20:1)
99% ee



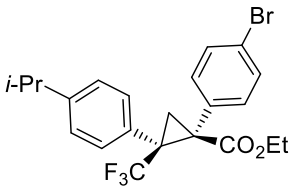
10h, 60% (>20:1)
95% ee



10i, 63% (>20:1)
99% ee



10j, 66% (>20:1)
92% ee



10k, 75% (>20:1)
98% ee

Scheme 68. The scope of the reaction between α-aryl diazoacetates and α,α,α-trifluoromethyl styrenes **7**.

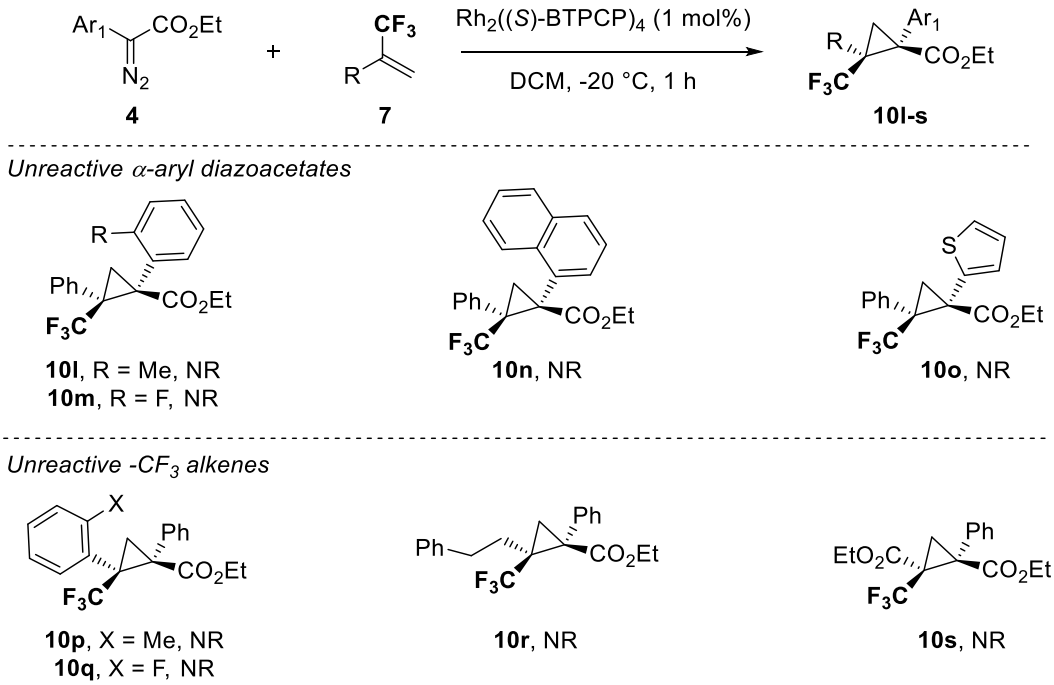
Finally, an *iso*-propyl group at the *para* position of the aromatic ring was tested in this cyclopropanation process, for which a competitive C-H insertion reaction might

occur.[136] To our delight, only the formation of cyclopropane was observed in this methodology and the expected cyclopropane **10k** was isolated in 75% yield as a single diastereoisomer with an excellent enantiomeric excess (98%).

It's worth to mention that some limitations were observed in the scope study of the reaction (**Scheme 69**). When the substituents are present at the *ortho* position of the α-aryl diazoacetates (*ortho*-methyl and *ortho*-choloro) or on the aromatic ring of the α,α,α-trifluoromethyl styrene derivatives (*ortho*-methyl and *ortho*-fluoro), no conversion to the desired products was observed. Probably this catalytic system is highly sensitive to the steric effect hindrance.

Moreover, the use of α-(1-naphthyl) and α-thienyl diazoacetates with α,α,α-trifluoromethyl styrene, gave no trace of the desired cyclopropanes. Alkyl substituted olefin proved to be inert in this cyclopropanation process as well.

Finally, α,α,α-trifluoromethyl acylate was tested. Surprisingly, no reaction was observed with this donor-acceptor type diazo compound, while a moderate yield was obtained with α-cyano diazoacetate (see **8j** in **Scheme 64**).

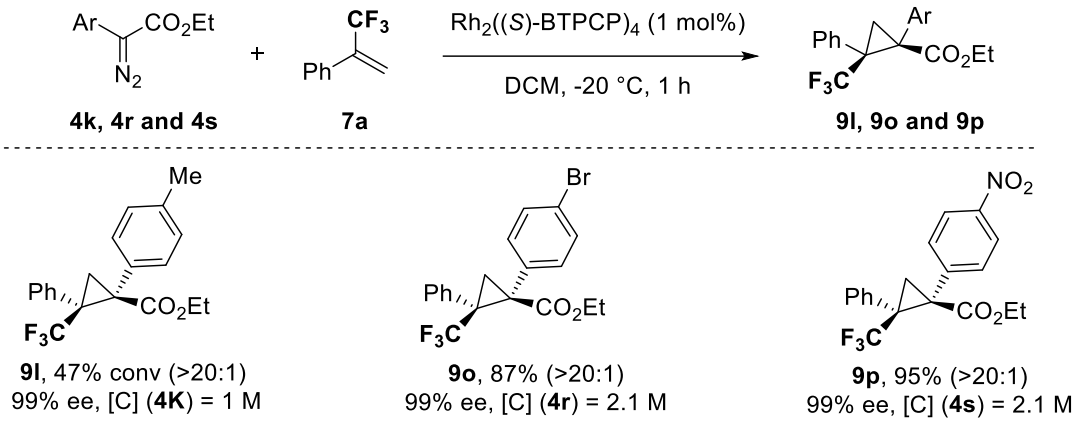


Scheme 69. Limitation of the scope study.

To demonstrate the efficiency of this cyclopropanation reaction, the scale was increased from 0.25 to 10 mmol scale (**Scheme 70**). During our first attempt, a similar concentration of the diazo compound was used (1.0 M in DCM). Unfortunately, only a

[136] C. Tortoreto, D. Rackl, H. M. L. Davies, *Org. Lett*. **2017**, *19*, 770-773.

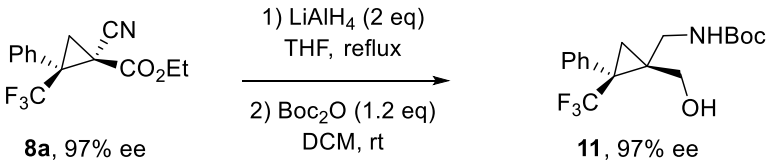
moderate conversion (47 %) into **9l** was determined by ^{19}F NMR. To overcome this problem, the reaction was performed by using more concentrated solution of the diazo (2.1 M in DCM). Pleasingly, under these conditions, the α,α,α-trifluoromethyl styrene **7a** was readily converted into **9o** with diastereo- and enantioselectivity as excellent as the 0.25 mmol scale. Using a similar reaction scale, *para*-nitroaryl cyclopropane **9p** was obtained in better yield (95% vs 75%).



Scheme 70. Scale up of the reaction.

2.8 Post-functionalization

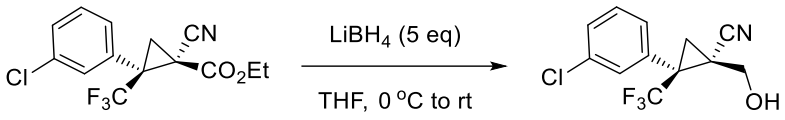
To showcase the versatility of these highly functionalized cyclopropanes, compound **8a** was used to perform further transformations. First, the reduction of both nitrile and ethyl ester group of **8a** was performed.[64] After Boc-protection of the amine function to avoid a tedious purification, the corresponding primary alcohol **11** was obtained in 49% yield over two steps reaction, and the ee value remained high (**Scheme 71**).



Scheme 71. Reduction of nitrile and ethyl ester group of **8a**.

Then, the reduction of **8d** in the presence of $LiBH_4$ was carried out,[137] providing the alcohol **12** in 80% yield with 98% ee (**Scheme 72**).

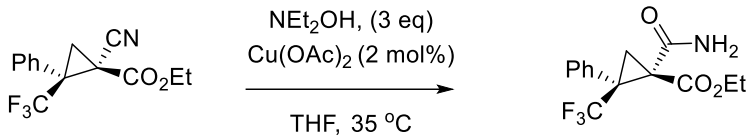
[137] Y. Rew, D. L. McMinn, Z. L. Wang, X, He, R. W. Hungate, J. C.Jaen, A. Sudom, D. Sun, H. Tu, S. Ursu, E. Villemure, N. P. C. Walker, X. Yan, Q. Ye, J. P. Powers, *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1797-1801.



8d, 97% ee **12**, 98% ee

Scheme 72. Preparation of alcohol 12.

Next, using NEt_2OH and $Cu(OAc)_2$,[138] the nitrile function of **8a** was readily hydrolyzed into the amido cyclopropane **13** in excellent yield without the erosion of the optical purity (**Scheme 73**).

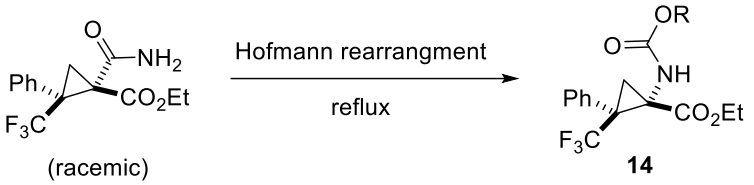


8a, 98% (> 20:1)
97% ee

13, 98% (> 20:1)
97% ee

Scheme 73. Synthesis of amido cyclopropane **13**.

Finally, we aimed at preforming a Hofmann rearrangement on the amido cyclopropane **13** to the corresponding chiral amino acid derivative **14**. Unfortunately, the reaction performed on the racemic amido cyclopropane **13** in the presence of NBS and DBU system or $Pb(OAc)_4$,[139] no trace of desired product was observed and only starting material **13** was recovered (**Table 10**).



(racemic) **14**

Entry	R	Reagent	Solvent	Conversion
1	Me	NBS (2 eq), DBU (2 eq)	MeOH	NR
2	*t*-Bu	$Pb(OAc)_4$ (2 eq)	*t*-BuOH	NR

Table 10. The Hofmann rearrangement of racemic amido cyclopropane **13**. NR = no reaction.

2.9 X-ray analysis and proposed mechanism

Single crystals were obtained from **8h** (CCDC 1841121) and **9o** (CCDC 1841122), The X-Ray crystallographic analysis confirmed the relative and absolute configuration of

[138] P. Marce, J. Lynch, A. J. Blacker, J. M. J. Williams, *Chem. Commun*. **2016**, *52*, 1436-1438.
[139] a) W. K. Jeffrey, X. Huang, *Org. Synth.* **2002**, *78*, 234, b) H. E. Baumgarten, H. L. Smith, A. Staklis, *J. Org. Chem*. **1975**, *40*, 3554-3561.

the compounds (**Figure 18**).

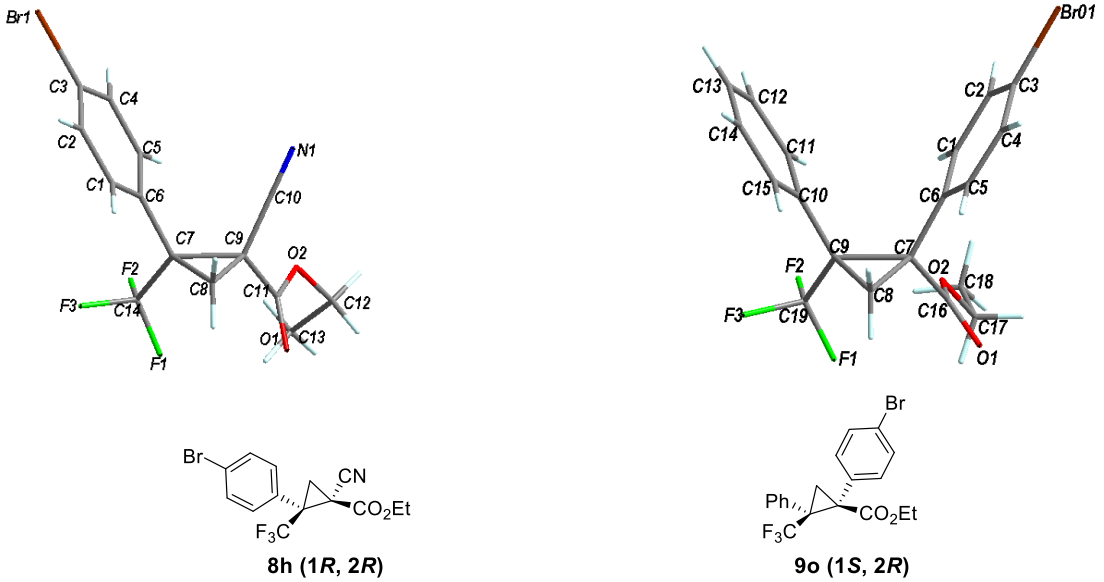


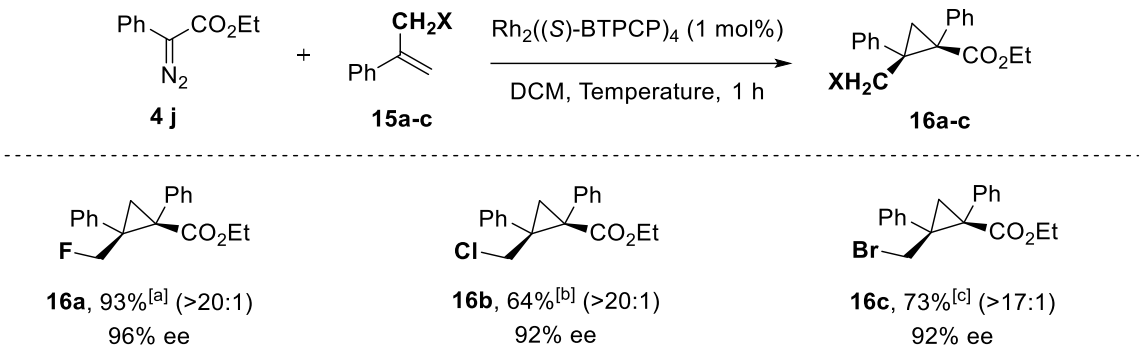
Figure 18. X-Ray analysis of **8h** and **9o** and the stereochemical model explains the selectivity.

The stereochemical outcome of the reaction, which led to the *cis*-trifluoromethyl cyclopropane, is in agreement with the stereochemical model that explains the selectivity depicted for the cyclopropanation of α,α-difluoromethyl styrene (see page 51).

2.10 Extension to α-monohalomethyl styrenes

Inspired by our previous work demonstrating the efficiency of this catalytic system, we wondered if α-monohalomethyl styrenes could also be efficiently converted into the corresponding optically pure mono-halomethyl (F, Cl, Br) cyclopropanes.

First, the reaction between **4j** and α-monofluoromethyl styrene **15a** was examined at -20 °C. Pleasingly, the excepted monofluoromethyl cyclopropane **16a** was isolated in very good yield (90%) with excellent dr (>20:1), and an enantiomeric excess of 84%. A decrease of the reaction temperature to -50 °C gave **16a** in 93% yield with excellent dr and excellent ee (96% ee). Similarly, the monochloro and monobromomethyl cyclopropanes (**16b** and **16c**) were obtained in good yields with excellent diastereoselectivities and enantiomeric excesses (92% ee) under a slight modification of the reaction conditions. Indeed, the reaction of α-monochloromethyl styrene **15b** with α-phehyl diazoacetate **4j** was carried out at -20 °C, while α-monobromomethyl styrene **15c** was performed at -30 °C since no conversion of **15b** and **15c** was observed at -50 °C (**Scheme 74**).



Scheme 74. Scope study between **4j** and monohalomethyl styrenes. [a] Reaction was carried out at -50 °C. [b] Reaction was carried out at -20 °C. [c] Reaction was carried out at -30 °C.

The extension scope and post-functionalization of this transformation was carried out by Mrs. Claire Schlinquer and Ling Chen within the course of their PhD work.[140]

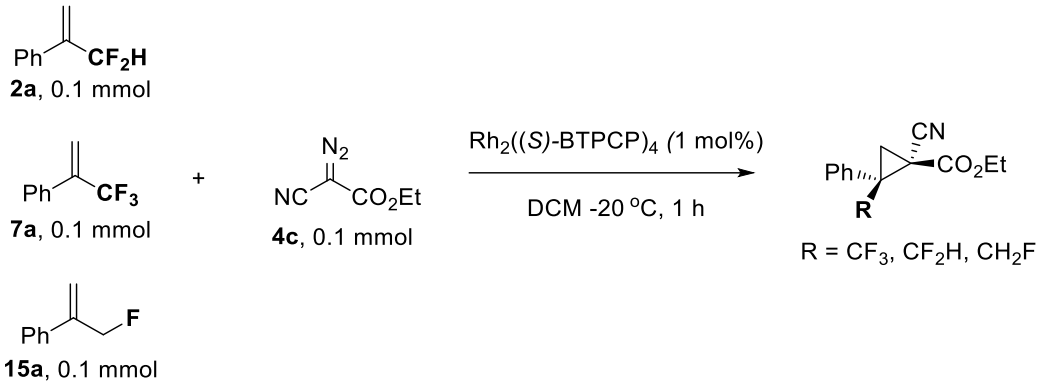
2. 11 Reactivity study towards different fluorinated styrenes

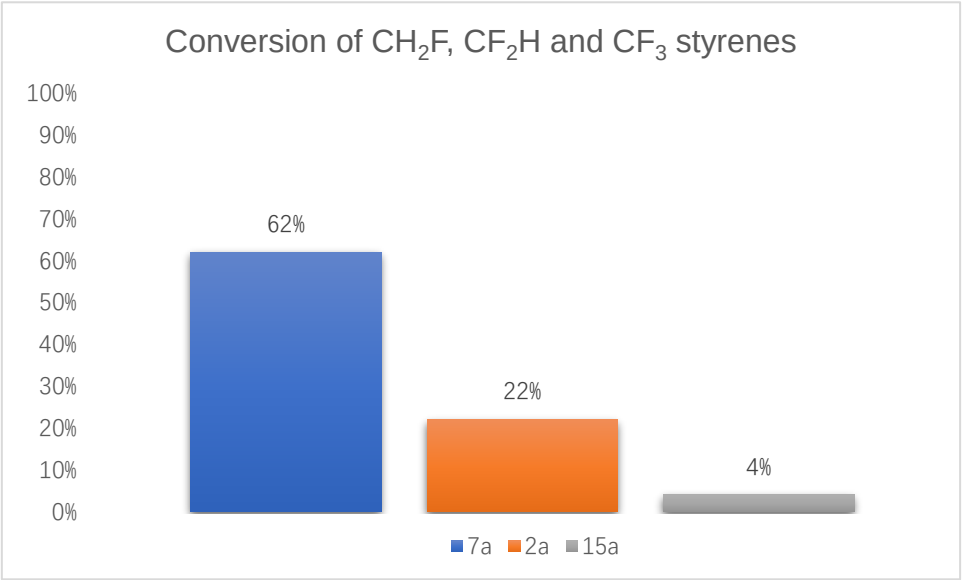
In the chapter I and II of this thesis, we have developed a highly efficiency cyclopropanation of α,α,α-trifluoromethyl, α,α-difluoromethyl and α-monofluoromethyl styrenes using Rh_2((*S*)-BTPCP)$_4$ as the catalyst. Herein, an investigation was carried out to evaluate the compared reactivity of these fluorinated styrenes in the Rh_2((*S*)-BTPCP)$_4$ catalyzed cyclopropanation reaction.

To this aim, a solution of α-cyano diazoacetate **4c** (0.1 mmol) in DCM was injected to a mixture fluorinated styrenes (**7a**, **4a** and **15a**, 0.1 mmol each) at -20 °C in the presence of Rh_2((S)-BTPCP)$_4$, leading a competition between three olefins.

By analyzing ^{19}F NMR spectrum of the crude reaction mixture, the conversion of each fluorinated styrene was measured and was observed in a decreasing trend from -CH_2F, -CF_2H then -CF_3 (62%, 22% and 4%, respectively) (**Scheme 75**). The outcome of this examination is in agreement with the theory that, in the rhodium-catalyzed cyclopropanation process, the rhodium carbene is an electrophilic species, as a consequence the stronger the nucleophilicity of the olefin is, the better reactivity will be.

[140] C. Schlinquer, W. S. Huang, L. Chen, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Org. Biomol. Chem*. **2019**, *17*, 472-476.



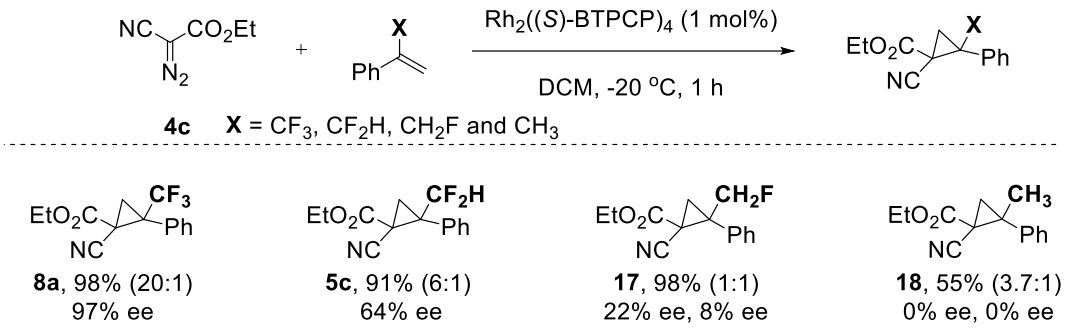


Scheme 75. The reactivity of CH_2F, CF_2H and CF_3 styrenes.

2.12 Stereoselectivity study towards different fluorinated styrenes

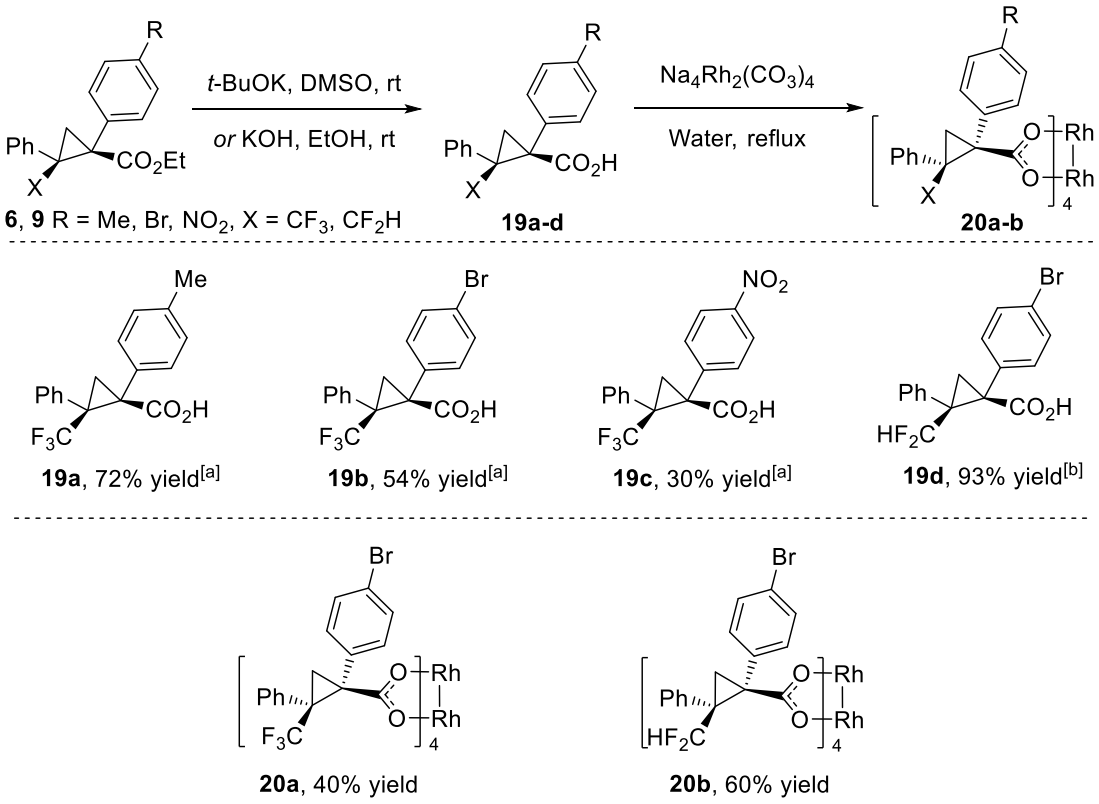
The interests were targeted probing the stereoselectivity study towards fluorinated styrenes and methyl styrene.

In this investigation, α-cyano-diazoacetate **4c** was used to react with α,α,α-trifluoromethyl, α,α-difluoromethyl, α-monofluoromethyl styrenes (**7a**, **2a** and **15a)** and α-methyl styrene, respectively. The outcome of these four experiments provided the enantiomeric excess in an increasing trend from methyl < α-monofluoromethyl < α,α-difluoromethyl < α,α,α-trifluoromethyl styrene (**Scheme 76**). Probably because of the nucleophilicity and steric effect of the α position on the styrene. Currently, DFT calculation to explain the phenomenon of selectivity on this cyclopropanation process is ongoing.



Scheme 76. The stereoselectivity of different styrenes.

2.13 Towards the development of rhodium catalysts with a cyclopropane core



Scheme 77. The synthesis of new rhodium catalysts. [a] the reaction was carried out using *t*-BuOK. [b] the reaction was carried out using NaOH.

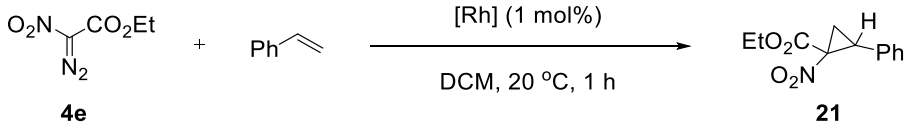
We have achieved the access to highly functionalized optically pure cyclopropanes bearing a CF_3 and CF_2H function. Refer to the cyclopropane structure of Rh_2((*S*)-BTPCP)$_4$, we wonder if we could develop new chiral catalysts using our chiral trifluoromethyl and difluoromethyl cyclopropanes, which might lead to more electrophilic rhodium carbenes because the introduction of CF_3 or CF_2H group, enhanced their reactivity towards alkene derivatives. Here in, cyclopropanes having a

CF_3 or CF_2H group, **6f, 9l, 9o** and **9p** were selected as precursors of chiral ligands for the design of new rhodium catalysts.

After saponification using *t*-BuOK as the base, the tri- and difluoromethyl cyclopropyl carboxylic acids **19a-d** were obtained in moderated to good yields. Note that the KOH/EtOH system is also efficient in this transformation.

Then these carboxylic acids refluxed with $Na_4Rh_2(CO_3)_4$ in water for three days. Surprisingly, the *para*-methyl (**9l**) and the *para*-nitro (**9p**) cyclopropyl carboxylic acids did not convert into the corresponding rhodium complexes, on the contrary the *para*-bromo ones converted into **20a** and **20b** in moderate yields (40% and 60%) as deep green solids (**Scheme 77**).

With these new catalysts in hand, we compared their catalytic activity and efficiency with Rh_2((*S*)-BTPCP)$_4$. First, we tested these catalysts in the cyclopropanation of styrene with α-nitro diazoacetate (**Table 11**). The use of Rh_2((*S*)-BTPCP)$_4$ provided the cyclopropane **21** in 62% isolated yield with moderate diastereo- and enantioselectivity (2.6:1, 57%). While, in the presence of rhodium catalysts **20a** and **20b**, the cyclopropane **21** was obtained with a slight better of diastereoselectivity, though moderate yield and enantiomeric excess (52% and 16%) were observed.

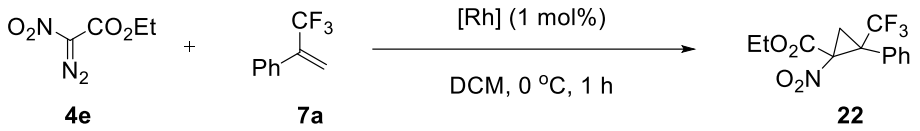


4e **21**

Entry	Olefin/diazo	[Rh]	Yield [%][b]	dr[c]	ee [%][d]
1	2:1	Rh_2((*S*)-BTPCP)$_4$	62	2.6:1	57
2	5:1	**20a**	51	3.7:1	52
3	2:1	**20b**	39	2.8:1	16

Table 11. The cyclopropanation of styrene with α-nitro diazoacetate in the presence of different rhodium catalysts. [a] Conditions: styrene (0.5 mmol, 2 eq or 2.5 mmol, 5 eq), **4e** (0.25 mmol, 1 eq), [Rh] (1% mol), [diazo] = 1 M. [b] Isolated yield. [c] Determined by ^{1}H NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase.

Next, the alkene was changed from styrene to α,α,α-trifluoromethyl styrene **7a** (**Table 12**). In the three following experiments, only rhodium catalyst **20a** gave the cyclopropane **22** in 26% yield with a 2:1 mixture of diastereoisomer and 70% ee. The use of Rh_2((*S*)-BTPCP)$_4$ and **20b** led to poor or no conversion in this transformation.

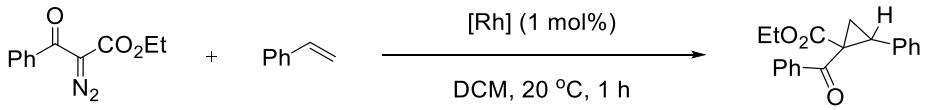


4e **7a** **22**

Entry	Olefin/diazo	[Rh]	Yield [%][b]	dr[c]	ee [%][d]
1	1:1.5	Rh_2((*S*)-BTPCP)$_4$	7[e]	1.5:1	ND
2	1:1.5	**20a**	26	2:1	70
3	1:1.5	**20b**	NR	-	-

Table 12. The cyclopropanation of α,α,α-trifluoromethyl styrene **7a** with α-nitro diazoacetate **4e** in the presence of different rhodium catalysts. [a] Conditions: **7a** (0.25 mmol, 1 eq), **4e** (0.375 mmol, 1.5 eq), [Rh] (1% mol), [diazo] = 1 M. [b] Isolated yield. [c] Determined by ^{19}F NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. NR = not reaction. ND = not determined.

We further tested the reaction between styrene and α-ketone diazoacetate **4z** in the presence of these three catalysts (**Table 13**). The cyclopropane **23** was obtained in a similar yield and diastereoselectivity in all cases. Whereas a decrease of the enantiomeric excess was observed in the following order: Rh_2((*S*)-BTPCP)$_4$ (94% ee) > **20a** (88% ee) > **20b** (76% ee).



4z **23**

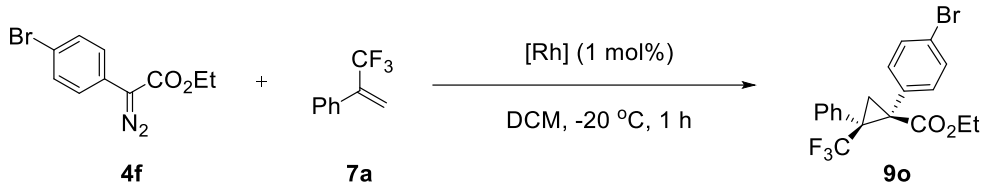
Entry	Olefin/diazo	[Rh]	Yield [%][b]	dr[c]	ee [%][d]
1	4:1	Rh_2((*S*)-BTPCP)$_4$	37	> 10:1	94
2	4:1	**20a**	33	> 10:1	88
3	4:1	**20b**	36	> 10:1	76

Table 13. The cyclopropanation of styrene with α-nitro diazoacetate in the presence of different rhodium catalysts. [a] Conditions: styrene (1.0 mmol, 4 eq), **4e** (0.25 mmol, 1.5 eq), [Rh] (1% mol), [diazo] = 1 M. [b] Isolated yield. [c] Determined by ^{1}H NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase.

Lastly, the model reaction of **4f** and **7a**[141] was used to compare Rh_2((*S*)-BTPCP)$_4$ and **20a**. As shown in **Table 14**, the desired cyclopropane was isolated in a similar yield as

[141] The model reaction was normally used in our group to evaluate the quality of Rh_2((*S*)-BTPCP)$_4$.

a single diastereoisomer in both cases, whereas, rhodium catalyst **20a** provided lower enantioselectivity (62%).



4f **7a** **9o**

Entry	Olefin/diazo	[Rh]	Yield [%][b]	dr[c]	ee [%][d]
1	1:1.5	Rh_2((*S*)-BTPCP)$_4$	90	> 20:1	99
2	1:1.5	**20a**	90	> 20:1	62

Table 14. The cyclopropanation of styrene with α-nitro diazoacetate in the presence of different rhodium catalysts. [a] Conditions: **7a** (0.25 mmol, 1 eq), **4f** (0.375 mmol, 1.5 eq), [Rh] (1% mol), [diazo] = 1 M. [b] Isolated yield. [c] Determined by ^{1}H NMR on the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase.

2.14 Summary

In summary, we developed an efficient catalytic enantioselective method to access chiral functionalized trifluoromethyl cyclopropanes from electron-deficient olefin α,α,α-trifluoromethyl styrenes. Moreover, this method provides an efficient and practical strategy for the preparation of highly diastereo- and enantioselective trifluoromethyl cyclopropane derivatives with broad range of scope.

Then, the synthetic utility of these highly functionalized chiral cyclopropanes was showcased through various post-functionalization without the erosion of the optical purity.

Thirdly, this methodology was extended to the synthesis of monohalomethyl cyclopropanes in good yields with excellent diastereo- and enantioselectivities.

Moreover, we investigated the reactivity and stereoselectivity towards three fluorinated styrenes, which allowed us to further study the mechanism of this cyclopropanation process.

Finally, the attempts to explore the access to new rhodium catalysts were performed. Even these new catalysts demonstrated moderate efficiency in asymmetric cyclopropanation process, we believe they would be interesting catalysts in the other transformations in the future.

Chapter III

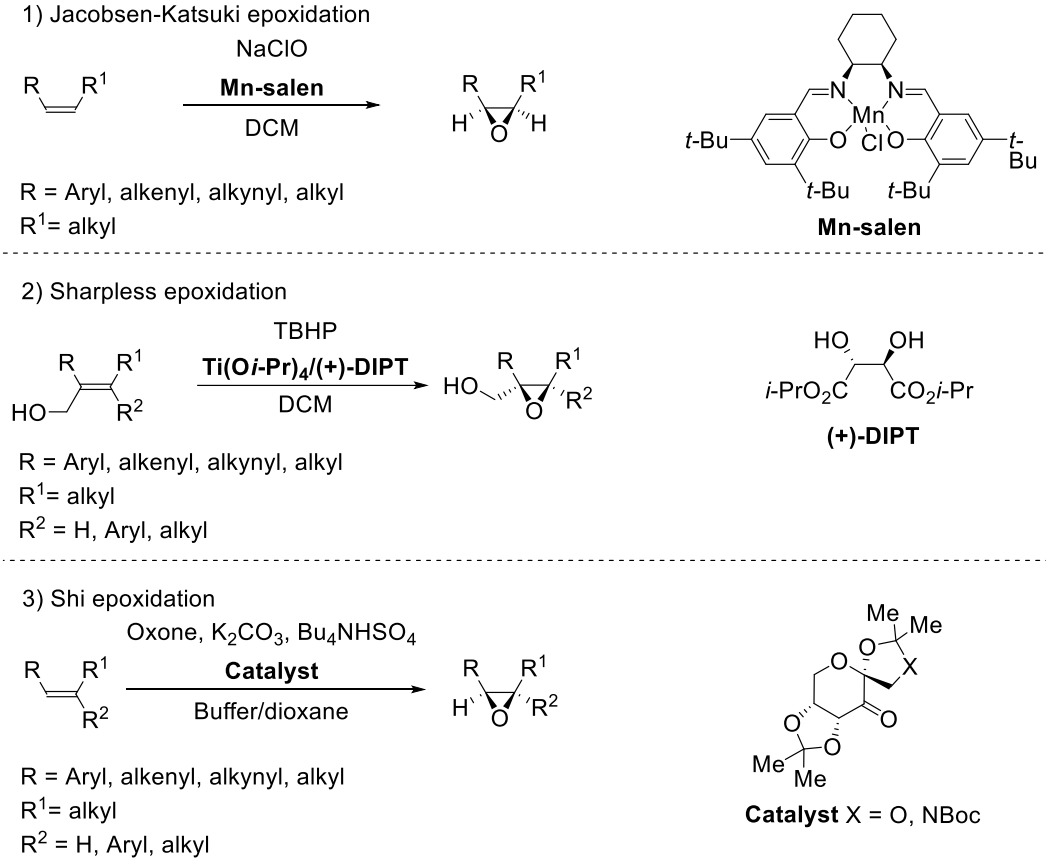
Asymmetric Oxidation of α,α-Difluoromethyl Styrenes

Chapter III Catalytic Asymmetric Oxidation of α,α-Difluoromethyl styrenes

3.1 Initial interests of the project

Initially, we aimed at exploring the catalytic asymmetric epoxidation reaction of those electron-deficient olefins what we used for the preparation of optically pure tri-, di- and monofluoromethyl cyclopropanes.

3.1.1 Brief introduction and background



Scheme 78. Main strategies for the asymmetric epoxidation of alkenes.

Epoxides, namely oxiranes are three-membered ring cyclic ether structures with a similar ring strain to the cyclopropane, of approximately 27.3 kcal/mol. As a result, epoxides are highly reactive. The typical transformation of epoxides is their reaction with nucleophiles, which proceeds through a S_N2 mechanism. Therefore, epoxide motif

is a versatile intermediate to access a wide range of chemical functionality.[142]

In general, there are three representative strategies for the asymmetric epoxidation of alkenes (**Scheme 78**). (1) The Jacobsen-Katsuki epoxidation, which relies on the use of a chiral Mn-salen catalyst and a stoichiometric oxidant such as bleach, allows the formation of optically pure epoxides from various *cis*-substituted alkenes.[143] Notice that the use of Cr-salen can also afford enantiopure epoxides.[142] (2) The Sharpless epoxidation, using Ti(O*i*-Pr)$_4$ coordinated with a chiral tartrate derivative in the presence of TBHP, allows the enantioselective synthesis of epoxides from primary and secondary allylic alcohols.[144] Finally, (3) the Shi epoxidation is a broad-spectrum strategy that allows the conversion of various alkenes into the chiral epoxides using Oxone® as the oxidant (potassium peroxymonosulfate) in the presence of a fructose derivative as the catalyst.[145]

3.2 Optimization

3.2.1 Transition metal catalyzed asymmetric epoxidation

At the outset of this study, we investigated the reaction of α,α-difluoromethyl styrene in the presence of a Mn-salen catalyst (Mn-salen **A** or **B**) with different oxidants (**Table 15**). The use of *m*-CPBA with salen **1**, provided the desire epoxide **24** in 50% yield with no enantioselectivity (entry 1).

Then, several solvents were tested in this transformation, unfortunately, modest isolated yields (51% and 60%) and no improvement of enantioselectivity was observed in DCM or EtOAc as the solvent. The use of THF as the solvent suppressed the reaction (entries 2-4).

Next, the change of the oxidant from *m*-CPBA to H_2O_2 or AcOOH gave poor conversion (< 10%) into the desired product **24** (entries 5 and 6). When *t*-BuOOH and bleach (NaClO) were used as the oxidant, only starting material was recovered from the reaction mixture (entries 7 and 8).

Finally, when salen **B** was used as the catalyst with 20 mol% of pyridine-*N*-oxide as an additive, the α,α-difluoromethyl styrene **2a** was not convert into the expected product.

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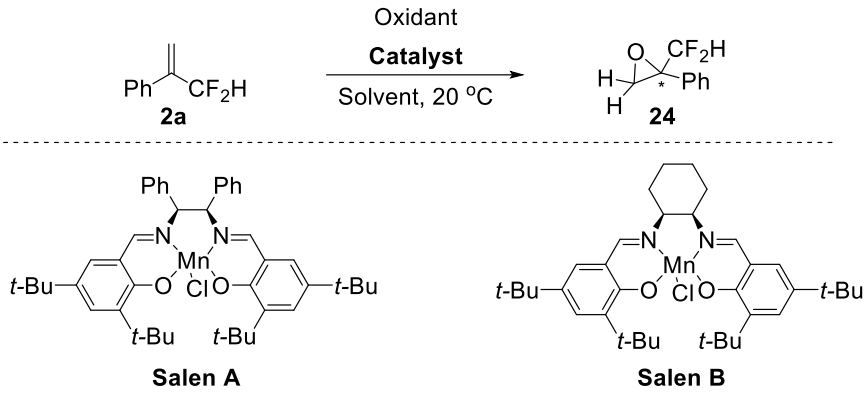
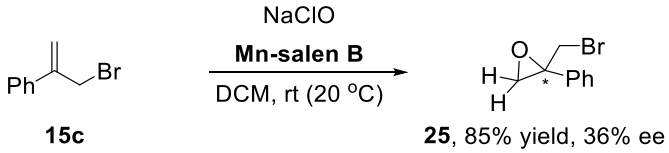
142 E. M. McGarrigle, D. Gilheany, *Chem. Rev.* **2005**, *105*, 1563-1602.
143 a) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Am. Chem. Soc.* **1991**, *113*, 7063-7064. b) B. D. Brandes, E. N. Jacobsen, *J. Org. Chem*. **1994**, *59*, 4378-4380.
144 J. G. Hill, K. B. Sharpless, C. M. Exon, R. Regenye, *Org. Synth*. **1985**, *63*, 66-78.
145 a) Z. X. Wang, Y. Tu, M. Frohn, J. R. Zhang, Y. Shi, *J. Am. Chem. Soc*. **1997**, *119*, 11224-11235. b) H. Tian, X. She, L. Shu, H. Yu, Y. Shi, *J. Am. Chem. Soc*. **2000**, *122*, 11551-11552. c) B. Wang, O. A. Wong, M. X. Zhao, Y. Shi, *J. Org. Chem*. **2008**, *73*, 9539-9543.



Entry	Oxidant	Catalyst	Solvent	Yield[%][c]	ee[%][d]
1[a]	*m*-CPBA	Salen A	CH_3CN	50	0
2[a]	*m*-CPBA	Salen A	DCM	51	0
3[a]	*m*-CPBA	Salen A	EtOAc	60	0
4[a]	*m*-CPBA	Salen A	THF	NR	-
5[b]	H_2O_2	Salen A	DCM	<10	ND
6[b]	AcOOH	Salen A	DCM	<10	ND
7[b]	*t*-BuOOH	Salen A	DCM	NR	-
8[b]	NaClO	Salen A	DCM	NR	-
9[e]	NaClO	Salen B	DCM	NR	-

Table 15. Optimization using Mn-salen as the catalyst. [a] Conditions: **2a** (0.25 mmol, 1 eq), Oxidant (0.375 mmol, 1.5 eq), catalyst (10 mol%), solvent/$NaHCO_3$(saturated in water). [b] Conditions: **2a** (0.25 mmol, 1 eq), Oxidant (0.375 mmol, 1.5 eq), catalyst (10% mol), DCM 1mL. [c] Isolated yield. [d] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. [e] Pyridine-*N*-oxide (0.2 eq) was added. ND = not determined. NR = no reaction.



Scheme 79. Mn-salen B catalyzed epoxidation of α-monobromomethyl styrene **15c**.

A further test was carried out with α-monobromomethyl styrene **15c** (**Scheme 79**). The use of Mn-salen **B** with NaClO in the process, provided the desired product **25** in 85% yield with modest enantioselectivity (36%).

Since no interesting result was obtained with Mn-salen catalysts, we concluded that this might not be a suitable strategy for the asymmetric synthesis of epoxide from α,α-difluoromethyl styrene and α-monobromomethyl styrene.

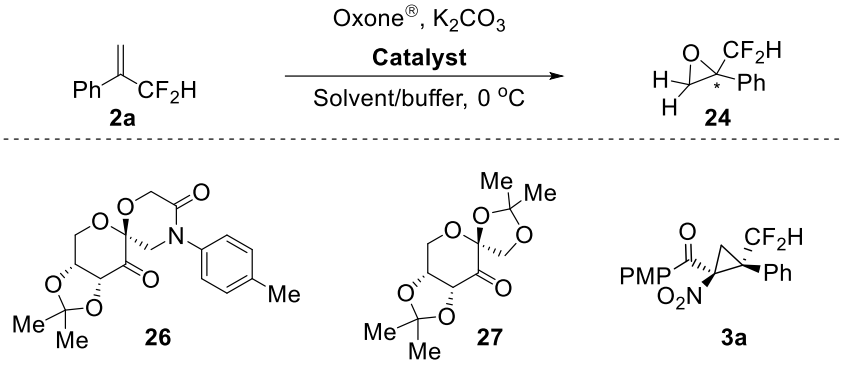
3.2.2 Asymmetric epoxidation using organic catalyst

Then, we explored the epoxidation of α,α-difluoromethyl styrene by means of organic catalysts (**Table 16**). First, **26** and **27** were tested as the catalyst in this transformation, note that they were developed by Shi and coworkers.[145] The use of catalyst **26** with Oxone® in 1,4-dioxane gave the desired epoxide **24** in 17% yield with 25% ee. while the use of catalyst **27** led to not conversion (entries 1 and 2).

Next compound **3a**, a cyclopropyl ketone derivative was synthesized using the method developed in the first chapter was tested in this transformation. However, **3a** was inefficient as a catalyst in this epoxidation reaction (entry 3).

Then, the reaction was performed at room temperature (24 °C) in the presence of **26**, the epoxide **24** was obtained in a similar yield and ee (entry 4).

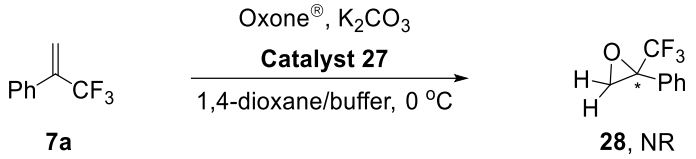
Finally, we tested the effect of solvent using compound **26** as the catalyst. The use of DMM as the solvent shut down the reaction (entry 5), while CH_3CN provided compound **24** in 23% yield with 26% ee (entry 6).



Entry	Catalyst	Solvent	Yield[%][b]	ee[%][c]
1	**26**	1,4-dioxane	17	25
2	**27**	1,4-dioxane	NR	-
3	**3a**	1,4-dioxane	NR	-
4[d]	**26**	1,4-dioxane	20	20
5	**26**	DMM	NR	-
6	**26**	CH_3CN	23	26

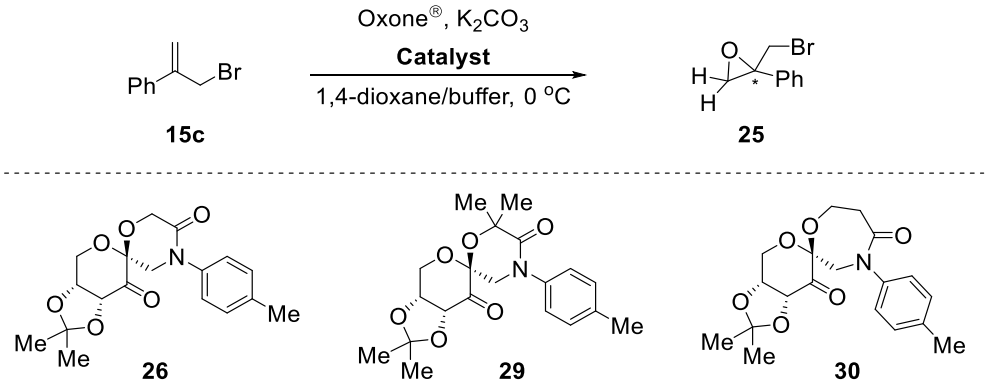
Table 16. Optimization using organic catalyst. [a] Conditions: **2a** (0.25 mmol, 1 eq), Oxone (0.4 mmol, 1.6 eq), K_2CO_3 (6.7 eq) in buffer 1.6 mL, buffer (0.1 M K_2CO_3 - AcOH in $4x10^{-4}$ M EDTA), catalyst (30 mol%), solvent 1.6 mL. [b] Isolated yield. [c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. [d] the reaction was carried out at room temperature (24 °C). NR = no reaction.

From these experimental data, we learned that α,α-difluoromethyl styrene is not a good substrate for the catalytic asymmetric epoxidation reaction. Hence, we changed the olefin from α,α-difluoromethyl styrene **2a** to α,α,α-trifluoromethyl styrene **7a** to perform the epoxidation under similar reaction conditions (**Table 16**, entry 1). Disappointingly, we observed no conversion of **7a** into desired product and **7a** was recovered from the reaction mixture (**Scheme 80**).



Scheme 80. Epoxidation of α,α,α-trifluoromethyl styrene **7a**.

Next, α-monobromomethyl styrene **15c** was used as the starting material (**Table 17**). First, in the presence of catalyst **26**, olefin **15c** was rapidly converted into the desired epoxide **25** in 92% yield with 45% enantioselectivity.



Entry	Catalyst	Solvent	Yield[%][b]	ee[%][c]
1	**26**	1,4-dioxane	92	45
2	**29**	1,4-dioxane	85	-18
3	**30**	1,4-dioxane	<10	ND

Table 17. Epoxidation of **15c** using different organic catalysts. [a] Conditions: **15c** (0.25 mmol, 1 eq), Oxone (0.4 mmol, 1.6 eq), K_2CO_3 (6.7 eq) in buffer 1.6 mL, buffer (0.1 M K_2CO_3 - AcOH in $4x10^{-4}$ M EDTA), catalyst (30 mol%), solvent 1.6 mL. [b] Isolated yield. [c] Enantiomeric excess of the major diastereoisomer determined by HPLC on a chiral stationary phase. ND = no determined.

With this promising result, we further investigated the epoxidation of **15c** by using modified catalysts based on the structure of **26**. The introduction of di-methyl group to the structure, catalyst **29** provided the expected product in 85% yield with an inversed

enantioselectivity (18% ee). Compound **30**, bearing a seven-membered ring in the structure gave poor conversion into the desired product **26**.

3.2.3 Brief summary

In summary, it remains a challenge to carry out the catalytic asymmetric epoxidation of α,α-difluoromethyl styrene. The exploration of this reaction using Mn-catalyst or organic catalyst led to the desired product with moderate conversion and a poor control of the enantioselectivity.

3.3 Towards the preparation of α,α-difluoromethyl alcohols

Organofluorine compounds have drawn a lot of attention in the field of drug discovery process, crop science or material science.[3,5] Among various fluoroalkyl derivatives, difluoromethylated analogues of biologically active compounds are new competitive candidates and difluoromethylated molecules are becoming desirable targets to develop new pharmaceuticals. Indeed, the difluoromethyl group is recognized as an alcohol or thiol bioisostere and this motif can carry out hydrogen bonding interactions.[18] Despite such high interest of this motif, the stereospecific construction of a chiral center bearing a -CF_2H group has been underexplored, in contrast to the formation of -F or -CF_3 containing stereogenic centers.[146] Therefore, It is important to provide new strategies to access optically pure difluoromethylated derivatives.

As α,α-difluoromethyl styrene is an unsuitable substrate for the asymmetric epoxidation reaction using Mn-catalysts and organic catalysts, we turned our attention to the enantioselective synthesis of α,α-difluoromethyl alcohols. In this purpose, we believed that the catalytic asymmetric dihydroxylation of α,α-difluoromethyl styrene was a straightforward strategy.

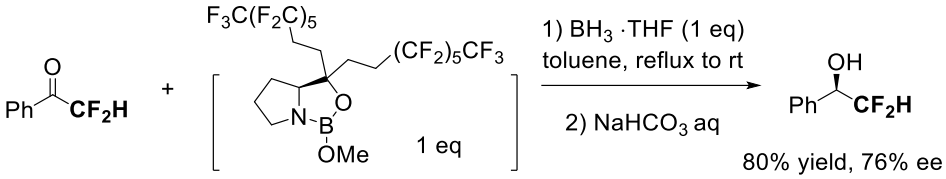
3.4 State of the art

Regarding the catalytic asymmetric formation of α,α-difluoromethyl alcohols, only a handful of straightforward methods was reported prior our study, and mainly were performed with a ketone or aldehyde derivatives.

[146] a) J. A. Ma, D. Cahard, *Chem. Rev*. **2004**, *104*, 6119-6146. b) J. Nie, H. C. Guo, D. Cahard, J. A. Ma, *Chem. Rev*. **2011**, *111*, 455-529. c) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev*. **2010**, *39*, 558-568. d) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev*. **2015**, *115*, 826-870.

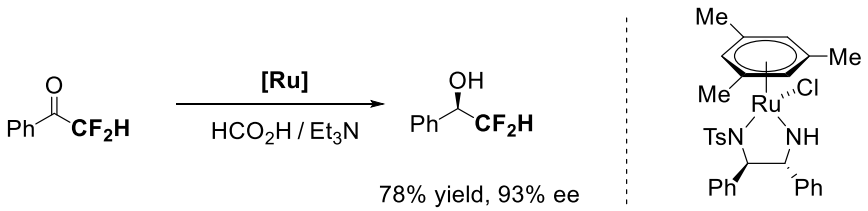
3.4.1 Asymmetric synthesis of secondary α,α-difluoromethyl alcohols

In 2007, Matsui and coworkers reported a proline derivative as a starting chiral substrate, the catalytic asymmetric borane reduction of various ketones to afford enantiopure alcohols (**Scheme 81**). Among the substrates scope, the α,α-difluoromethyl acetophenone was converted into the corresponding secondary alcohol with modest enantioselectivity (76% ee).[147]



Scheme 81. Asymmetric borane reduction of α,α-difluoromethyl acetophenone.

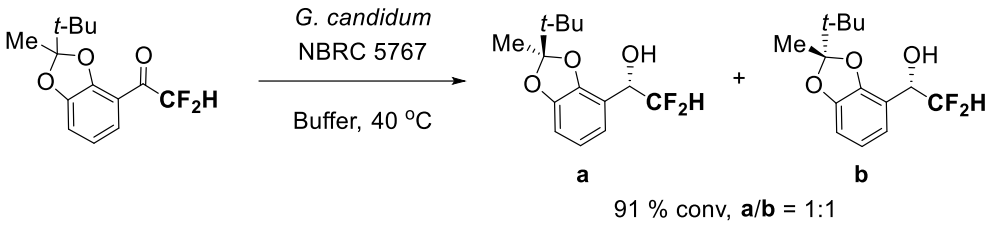
Hoff and coworkers described the use of the typical ruthenium-arene-diamine transfer hydrogenation catalyst for the preparation of chiral alcohols from fluorinated acetophenones. [148] In the presence of a chiral ruthenium catalyst, the α,α-difluoromethyl acetophenone was converted into the corresponding alcohol in good yield (78%) with 93% ee (**Scheme 82**).



Scheme 82. Asymmetric reduction of α,α-difluoromethyl acetophenone using ruthenium catalyst.

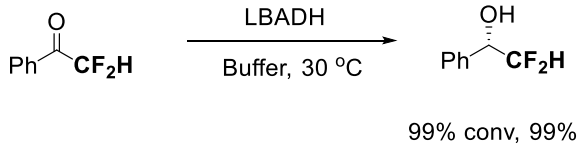
Later, Sugai and coworkers reported the reduction of acetophenones using microorganisms. *Geotrichum candidum* NBRC 5767 was found to be a good biocatalyst, which provided (1'*S*)-alcohols (**a** and **b**) from the α,α-difluoromethyl acetophenone derivative in a highly facially selective manner (**Scheme 83**).[149] Note that, in this transformation, if the aromatic ring of the α,α-difluoromethyl acetophenone without a bulky group on *ortho* position, the enantioselectivity would be lost in its corresponding alcohol.

147 S. Goushi, K. Funabiki, M. Ohta, K. Hatano, M. Matsui, *Tetrahedron* **2007**, *63*, 4061-4066.
148 S. V. Slungård, T. A. Krakeli, T. H. K. Thvedt, E. Fuglseth, E. Sundby, B. H. Hoff, *Tetrahedron* **2011**, *67*, 5642-5650
149 C. Abe, T. Sugawara, T. Machida,T. Higashi, K. Hanaya, M. Shoji, C. Cao, T. Yamamoto, T. Matsuda, T. Sugai, *J. Molecular catalysis B: Enzymatic* **2012**, *82*, 86-91.



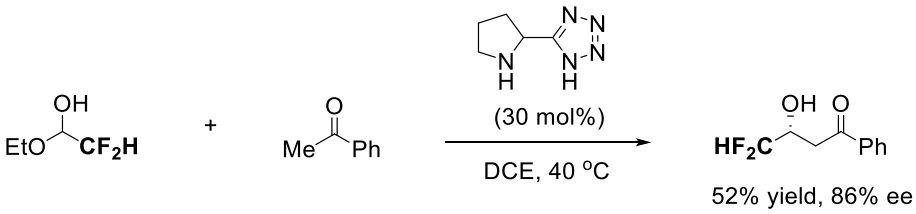
Scheme 83. *G. candidum* catalyzed reduction of α,α-difluoromethyl acetophenone derivative.

In 2013, Gotor and coworkers reported the biocatalytic reduction of trifluoromethyl, difluoromethyl and monohalomethyl acetophenones to synthesize the enantiopure fluorohydrins.[150] In the presence of LBADH, provided the α,α-difluoromethylated alcohol in very high yield with an excellent enantioselectivity (**Scheme 84**).



Scheme 84. LBADH catalyzed reduction of α,α-difluoromethyl acetophenone.

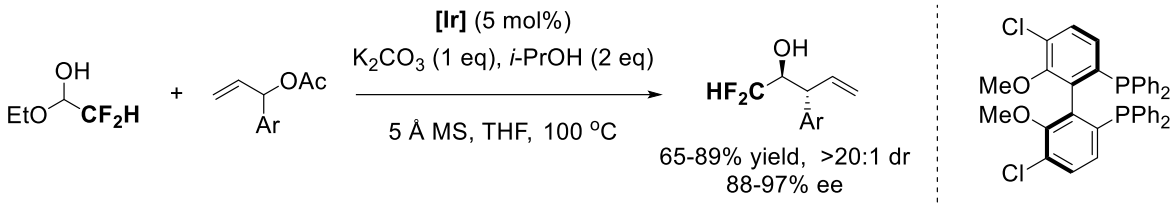
Direct Aldol reaction of a difluoroacetaldehyde ethyl hemiacetal with a ketones is another strategy to construct α,α-difluoromethylated alcohols. The use of proline derivative as the catalyst provided the corresponding product in 52% yield with 86% ee (**Scheme 85**).[151]



Scheme 85. Catalyzed asymmetric direct Aldol reactions of difluoroacetaldehyde ethyl hemiacetal with acetophenone.

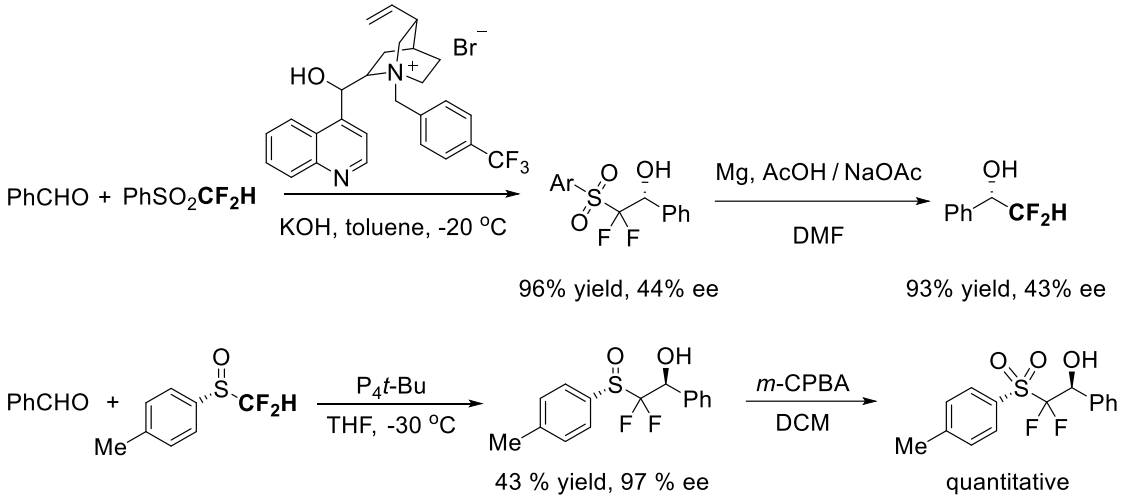
In 2018, Krische and coworkers reported an enantioselective iridium-catalyzed *anti*-(α-aryl)allylation of difluoroacetaldehyde ethyl hemiacetal.[152] α,α-Difluoromethylated β-aryl alcohols were formed in good yields with a complete *anti*-diastereoselectivity and excellent enantioselectivities (**Scheme 86**).

[150] a) W. Borzęcka, I. Lavandera, V. Gotor, *J. Org. Chem*. **2013**, *78*, 7312-7317. b) T. Matsuda, T. Harada, *J. Org. Chem*. **2000**, *65*, 157-163.
[151] a) K. Funabiki, Y. Itoh, Y. Kubota, M. Matsui, *J. Org. Chem*. **2011**, *76*, 3545–3550. b) K. Funabiki, Y. Furuno, Y. Yano, Y. Sakaida, Y. Kubota, M. Matsui, *Chem. Asian J*. **2015**, *10*, 2701-2707.
[152] J. M. Cabrera, J. Tauber, W. Zhang, M. Xiang, M. J. Krische, *J. Am. Chem. Soc.* **2018***, 140,* 9392-9395.



Scheme 86. Iridium catalyzed *anti*-(α-aryl)allylation of difluoroacetaldehyde ethyl hemiacetal.

Alternatively, Hu and coworkers reported the diastereoselective addition of difluoromethyl nucleophiles to access the α,α-difluoromethylated alcohol.[153] Later, Leroux and coworkers reported the use of sulfoxides as traceless chiral auxiliaries to access enantiopure α,α-difluoromethylated alcohols in the presence of Schwesinger's superbase (P_4t-Bu) (**Scheme 87**).[154]

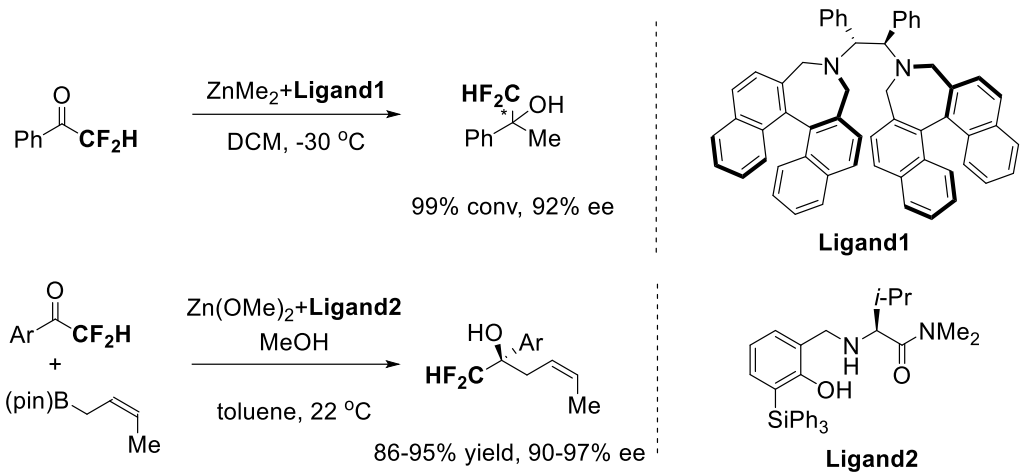


Scheme 87. Diastereoselective addition of difluoromethyl nucleophiles.

3.4.2 Asymmetric synthesis of tertiary α,α-difluoromethyl alcohols

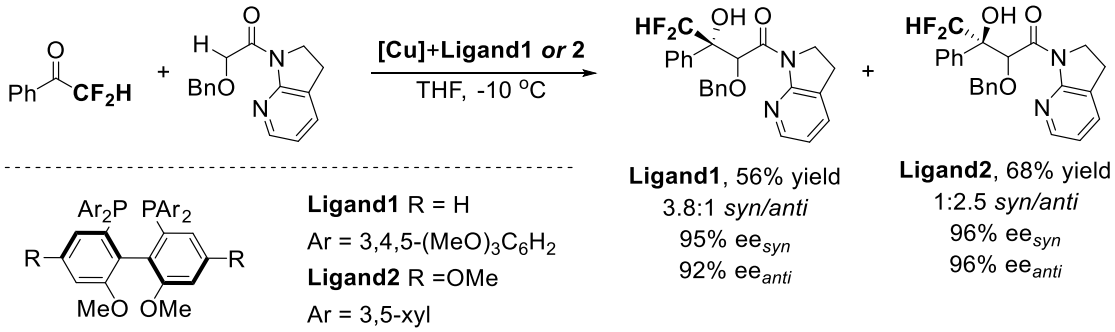
On the other hand, α,α-difluoromethyl tertiary alcohols can be obtained from the catalytic asymmetric alkylation and allylation of the corresponding difluoromethylated ketones with organic zinc reagents.[155] Although restricted to few examples, the additions to α,α-difluoromethylated acetophenones providing the α,α-difluoromethyl tertiary alcohols in high yields with excellent enantioselectivities (**Scheme 88**).

[153] C. Ni, F. Wang, J. B. Hu, *Beilstein J. Org. Chem*. **2008**, 21.
[154] a) C. Batisse, A. Panossian, G. Hanquet, F. R. Leroux, *Chem. Commun*. **2018**, *54*, 10423-10426. b) 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.
[155] a) T. Neves-Garcia, A. Vèlez, J. M. Martinez-Ilarduya, P. Espinet, *Chem. Commun*. **2018**, *54*, 11809-11812. b) F. W. van der Mei, C. Qin, R. J. Morrison, A. H. Hoveyda, *J. Am. Chem. Soc*. **2017**, *139*, 9053-9065.



Scheme 88. Catalytic asymmetric alkylation and allylation of difluoromethylated acetophenones.

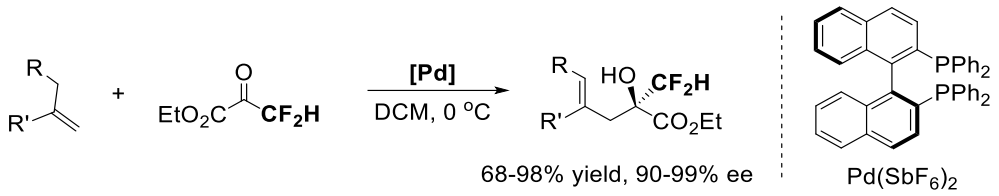
More recently, Shibasaki and coworkers reported a direct catalytic asymmetric Aldol reaction of α-alkoxyamides with α-fluorinated ketones. This transformation was extended to α,α-difluoromethylated acetophenone, both *syn*- and *anti*-aldol adduct were obtained with high enantioselectivity by judicious choice of chiral ligands (**Scheme 89**).[156]



Scheme 89. Direct catalytic asymmetric Aldol reaction of α-benzyloxyamide with difluoromethylated acetophenone.

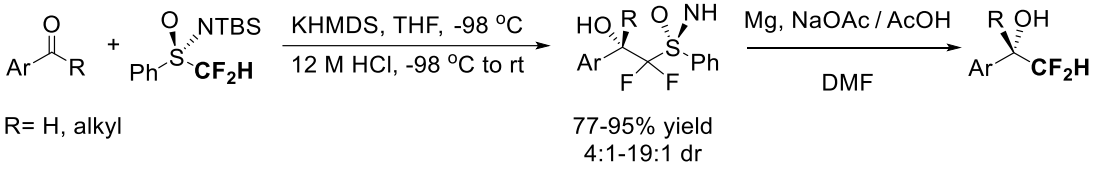
A palladium-catalyzed asymmetric Ene reaction of alkene with ethyl difluoropyruvate was reported by Mikami and coworkers. This method affords various α,α-difluoromethyl tertiary alcohols in high yields with excellent enantioselectivities (**Scheme 90**).[157]

[156] R. Pluta, N. Kumagai, M Shibasaki, *Angew. Chem. Int. Ed.* **2019**, *58*, 2459-2463.
[157] K. Aikawa, S. Yoshida, D. Kondo, Y. Asai, K. Mikami, *Org. Lett.* **2015**, *17*, 5108-5111.



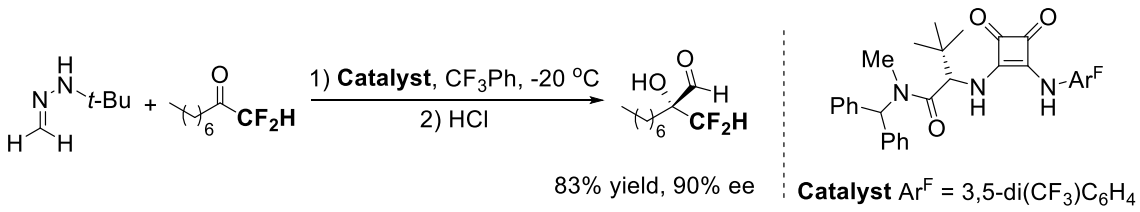
Scheme 90. Catalytic asymmetric Ene reaction with difluoropyruvate.

Hu and coworkers reported a diastereoselective addition of the difluoromethyl sulfoximine to ketones or aldehydes in the presence of KHMDS, followed the desulfoximination, allowing the formation of the enantiomerically enriched α,α-difluoromethyl tertiary alcohols (**Scheme 91**).[158]



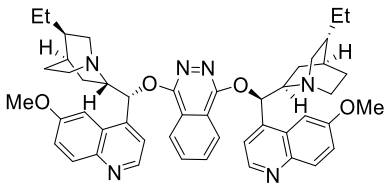
Scheme 91. Synthesis of chiral difluoromethyl alcohols.

Finally, Lassaletta and coworkers reported an addition of formaldehyde *tert*-butyl hydrazine to difluoromethyl ketone to provide the corresponding α,α-difluoromethyl product in good yield and ee value (**Scheme 92**).[159]

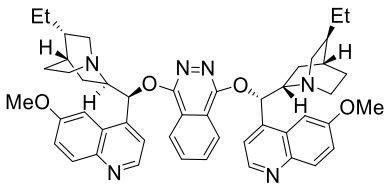


Scheme 92. Synthesis of α,α-difluoromethylated azoxy alcohol.

3.4.3 Asymmetric dihydroxylation reaction using AD-mix-α or AD-mix-β



$(DHQ)_2PHAL$
ligand of AD-mix-α



$(DHQD)_2PHAL$
ligand of AD-mix-β

[158] X. Shen, W. Zhang, C. Ni, Y. Gu, J. B. Hu, *J. Am. Chem. Soc*. **2012**, *134*, 16999-17002.
[159] E. Matador, M. de Gracia Retamosa, A. Jiménez-Sánchez, D. Monge, R. Fernández, J. M. Lassaletta, *Eur. J. Org. Chem*. **2019**, 130–138.

Figure 19. Ligands of AD-mix-α and AD-mix-β.

AD-mix-α and AD-mix-β are ideal catalysts for the asymmetric dihydroxylation reaction. It is worth to mention that these exceptional catalysts were developed by Sharpless and coworkers. AD-mix-α is known as a mixture of $(DHQ)_2PHAL$, potassium osmate dihydrate ($K_2OsO_4 \cdot 2H_2O$), potassium carbonate (K_2CO_3), and potassium ferricyanide ($K_3Fe(CN)_6$), whereas AD-mix-β contains a similar mixture with the chiral ligand $(DHQD)_2PHAL$ (**Figure 19**), and these catalysts are capable to react with various olefins, including trisubstituted olefins, 1,1-disubstituted, 1,2-disubstituted olefins and terminal olefins, providing the corresponding diols in high yields and ee values.[160]

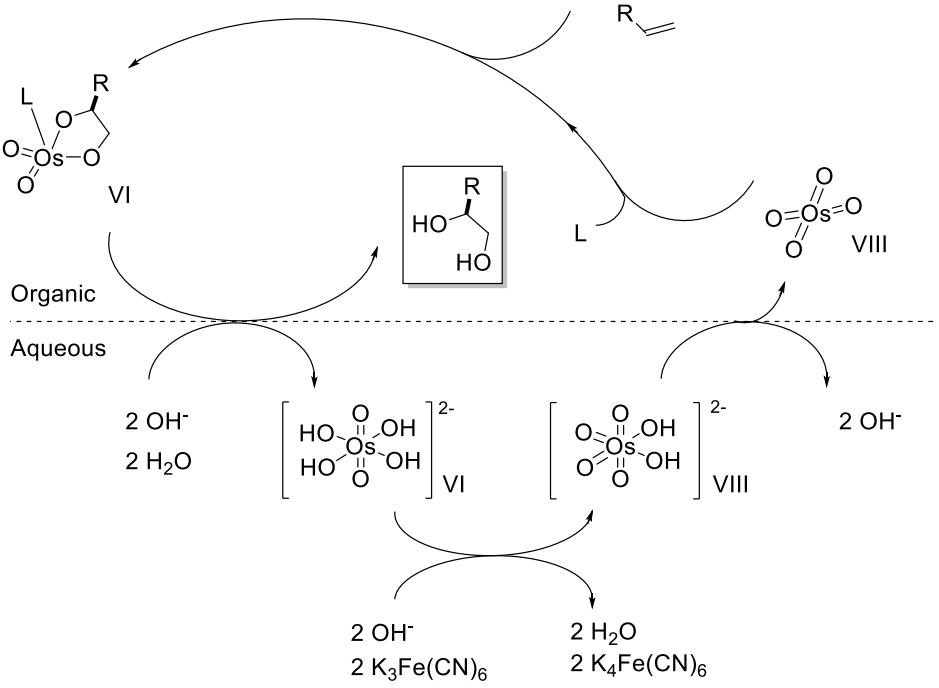


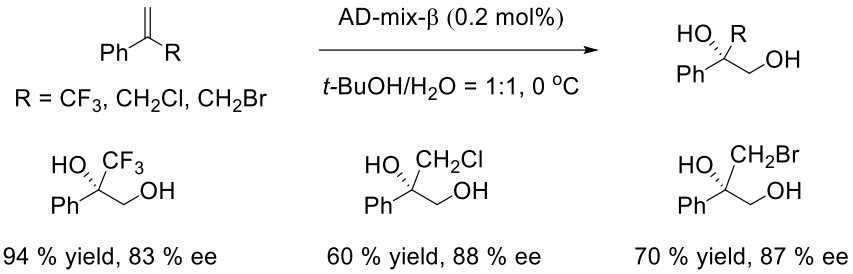
Figure 20. Mechanism for asymmetric dihydroxylation of alkene.

The mechanism of the osmium-catalyzed dihydroxylation with $K_3Fe(CN)_3$ as the re-oxidant was proposed.[161] First, the addition of alkene to a chiral osmium complex, resulting an Os (VI) glycolate intermediate. Followed the hydrolysis of this species with a base to afford the diol product and Os $(VI)^{2-}$. In the presence of $K_3Fe(CN)_3$, allowing Os $(VIII)^{2-}$ was regenerated from Os $(VI)^{2-}$ to proceed the reaction (**Figure 20**). A called second catalytic cycle was proposed to explain lower enantioselectivity. Another alkene was added to the five-membered ring Os (VI) glycolate prior to hydrolysis, leading to a spiro Os (VIII) species. Lower enantioselectivity resulted from lacking a

[160] K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K, Morikawa, Z. M. Wang, D. Q. Xu, X. L. Zhang. *J. Org. Chem*. **1992**, *57*, 2768-2771.
[161] M. H. Junttila, O. E. O. Hormi, *J. Org. Chem.* **2004**, *69*, 4816-4820.

chiral environment of the second alkene.

Few examples described the dihydroxylation of α,α,α-trifluoromethyl and α-monohalomethyl styrenes using AD-mix-β in *t*-BuOH and water mixture. The α,α,α-trifluoromethylated diols was isolated in 94% yield with 83% ee, while the α-monochloro and α-monobromo ones were obtained in good yields with 88% and 87% ee, respectively (**Scheme 93**).[162] Surprisingly, no example of α,α difluoromethyl diol was reported prior our study.



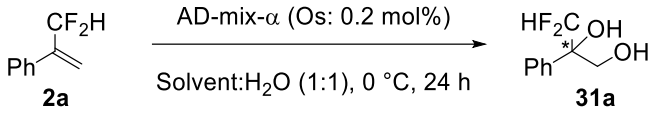
Scheme 93. Dihydroxylation of α,α,α-trifluoromethyl and α-monohalomethyl styrenes.

3.5 Optimization study

At the beginning of the investigation, the reaction of α,α-difluoromethyl styrene **2a** with AD-mix-α (Os: 0.2 mol%) was tested. The reaction was performed in a mixture of organic solvent with water (1:1) at 0 °C for 24 hours (**Table 18**).

First, EtOH and *i*-PrOH were tested as a co-solvent, and provided the desired α,α-difluoromethylated diols **31a** in moderate yields (24% and 30%) with modest enantiomeric excesses (52% and 26%) (entries 1 and 2). Then *t*-BuOH and *tert*-amyl alcohol were used in this transformation. Pleasingly, the use of *t*-BuOH gave the diols **31a** in better yield (51%) with 90% ee (entry 3). Note that, the increase of the reaction time from 24 h to 72 h allowing **31a** was isolated in 93% yield with 90% ee (entry 6). The presence of *tert*-amyl alcohol afforded the diols **31a** in a similar yield as EtOH and *i*-PrOH, with 87% ee (entry 4). Surprisingly, ethylene glycol proved to be inefficient in this reaction (entry 5). An additional survey of solvent (1,4-dioxane and acetone) did not provide the diols **31a** in better yield and enantioselectivity (entries 7 and 8). Finally, the replacement from AD-mix-α to AD-mix-β in the presence of *t*-BuOH and water, allowed the conformation of **31a** in 88% yield with 95% ee (entry 9).

[162] a) Y. L. Bennani, K. P. M. Vanhessche, K. B. Sharpless, *Tetrahedron: Asymmetry* **1994**, *5*, 1473-1476. b) Z. M. Wang, K. B. Sharpless, *Synlett* **1993**, 603-604.



Entry	Solvent	Yield (%)[b]	ee[c]
1	EtOH	24	54
2	*i*-PrOH	30	26
3	*t*-BuOH	51	90
4	*tert*-amyl alcohol	31	87
5	Ethylene glycol	NR	-
6[d]	***t*-BuOH**	**93**	**90**
7[d]	1,4-dioxane	77	88
8[d]	Acetone	75	82
9[d],[e]	***t*-BuOH**	**88**	**95**

Table 18. Optimization study of the asymmetric dihydroxylation of **2a**. [a] Reaction conditions: **2a** (0.25 mmol), AD-mix-α (Os: 0.2 mol%), Solvent: H_2O (1:1, 2.5 mL), 0 °C, 24 h. [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d] 72 h instead of 24 h. [e] AD-mix-β was used instead of AD-mix-α, NR = no reaction.

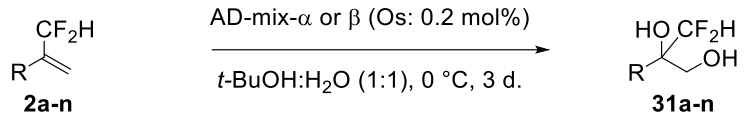
3.6 Scope study

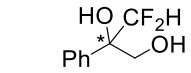
With these optimized conditions in hand, we tested the scope of this transformation using various α,α-difluoromethyl olefins with the two catalysts (AD-mix-α and AD-mix-β) (**Scheme 94**).

First, α,α-difluoromethyl styrenes bearing a *para*-methyl, *meta*-methyl and *ortho*-methyl on the aromatic ring were tested with the two catalysts. Both *para*- and *meta*-methyl substituted diols **31b** and **31c** were isolated in good yields (82-90%) with excellent enantioselectivities (95-98%), while the *ortho*-methyl substituted diols **31d** were obtained in poor yields (13% and 14%) with moderate enantioselectivities (67% and 77% ee) in the presence of the two catalysts. To our delight, the use of 2,4-dimethyl olefin provided the desired diols **31e** in better yields and enantiomeric excesses. *Para*- and *ortho*- methoxy substituted were tolerated, and **31f** were isolated in moderate yields with excellent enantiomeric excesses, while **31g** were obtained in similar yields with moderate enantioselectivities.

Then, 1-naphthyl and 2-naphthyl substituted olefins were tested in this process, the presence of 2-naphthyl substituted olefin afforded **31h** in very good yields with

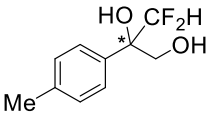
excellent enantioselectivities, while, 1-naphthyl substituted product **31i** were isolated in moderate yields, but with very good enantiomeric excesses.





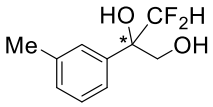
31a

90%, 90% ee (α)
88%, 95% ee er (β)
98%, 94% ee (β)[a]



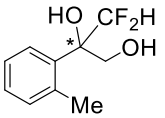
31b

88%, 95% ee (α)
82%, 98% ee (β)



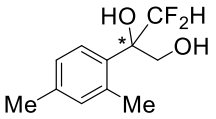
31c

90%, 95% ee (α)
87%, 96% ee (β)



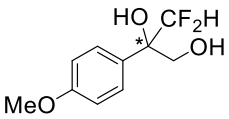
31d

13%, 67% ee (α)
14%, 77% ee (β)



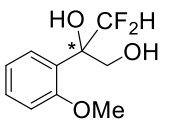
31e

40%, 82% ee (α)
43%, 87% ee (β)



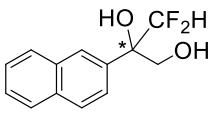
31f

64%, 96% ee (α)
63%, 98% ee (β)



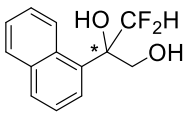
31g

61%, 81% ee (α)
61%, 88% ee (β)



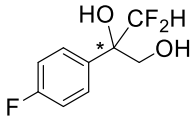
31h

83%, 98% ee (α)
92%, 99% ee (β)



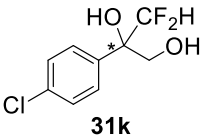
31i

40%, 89% ee (α)
56%, 94% ee (β)



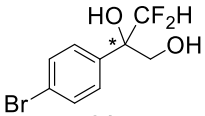
31j

89%, 95% ee (α)
80%, 96% ee (β)



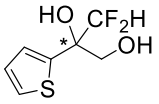
31k

78%, 94% ee (α)
77%, 97% ee (β)



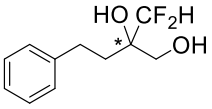
31

83%, 95% ee (α)
81%, 97% ee (β)



31m

76%, 89% ee (α)
56%, 93% ee (β)



31n

76%, 78% ee (α)
56%, 87% ee (β)

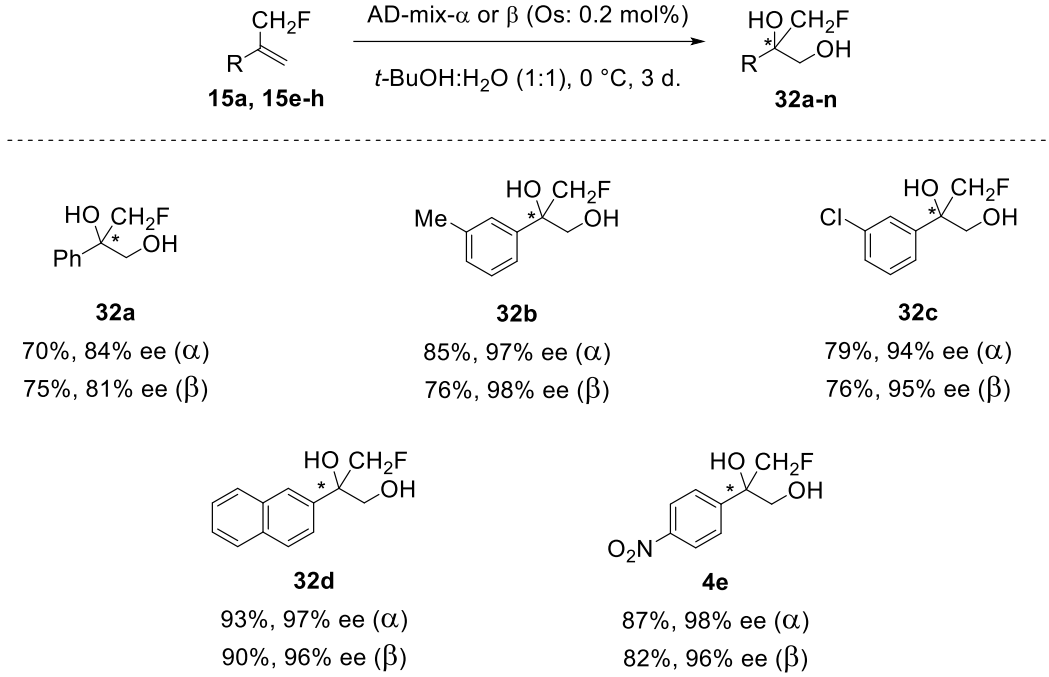
Scheme 94. Scope reaction for α,α-difluoromethyl styrenes. [a] 4 mmol scale reaction.

Next, olefins having a halogen substituent on the aromatic ring were submitted to this dihydroxylation process. the *para*-fluoro, *para*-chloro and *para*-bromo substituted α,α-difluoromethyl tertiary alcohols **31j**, **31k**, and **31l** were isolated in excellent yields with excellent ee values. The thienyl diols **31m** was isolated in good yield and enantioselectivity in the presence of AD-mix-α, while the use of AD-mix-β gave **31m** with an erosion of the yield and the ee. Pleasingly, the aliphatic derivative was tolerated and the corresponding α,α-difluoromethyl tertiary alcohols **31n** were isolated in decent yields with moderate to good ee.

The methodology was extended to the α-mono-fluoromethyl styrenes under standard conditions (**Scheme 95**).

First, α-monofluoromethyl styrene was readily converted into the corresponding diols **32a** in good yields with modest ee in the presence of AD-mix-α (84% ee) and AD-mix-β (81% ee). Pleasingly, the aromatic ring bearing a *meta*-methyl, *meta*-chloro substituents provided **32b** and **32c** in good yields with excellent enantioselectivities (94%-98% ee).

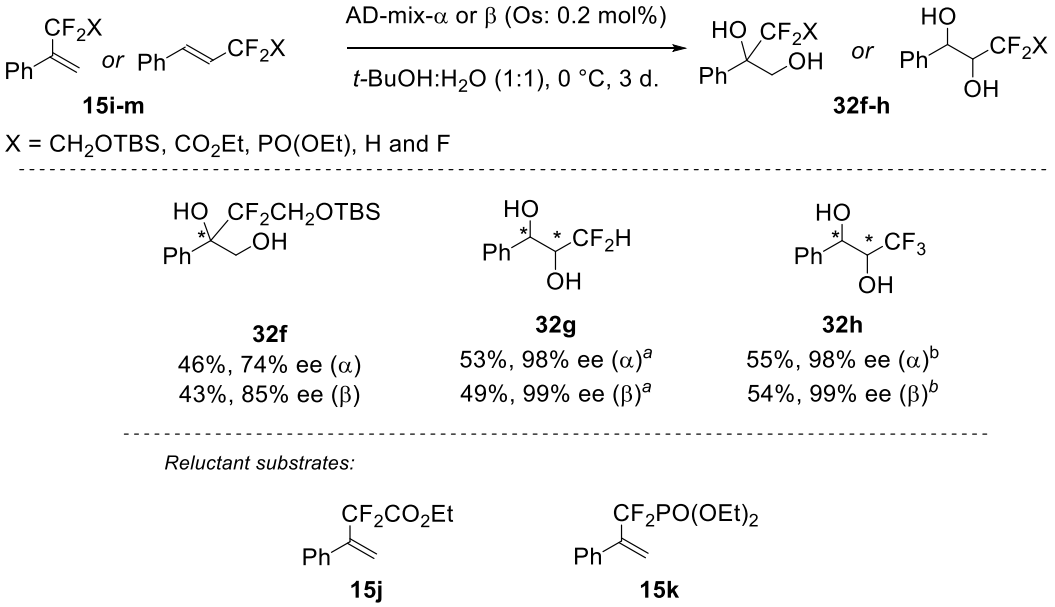
Similarly, the presence of 2-naphthyl and *para*-nitro substituent on the olefin were also tolerated, and the corresponding diols **32d** and **32e** were obtained in excellent yields with excellent enantioselectivities (96%-97% ee).



Scheme 95. Scope reaction for α-monofluoromethyl styrenes.

Other styrene derivatives, where the substituent replaces the H atom on the difluoromethyl group by other functions (such as $-CF_2CO_2Et$, $-CF_2PO(OEt)_2$ and $-CF_2OTBS$) were tested under similar reaction conditions (**Scheme 96**). Unfortunately, the $-CF_2CO_2Et$, $-CF_2PO(OEt)_2$ derivatives **15j** and **15k** were inert in this transformation, whereas, the $-CF_2OTBS$ substituent gave the desired product **32f** in moderate yields and ee.

Finally, we showed that α,β-disubstituted styryl derivatives were reactive under our conditions. β-(Difluoromethyl) and β-(trifluoromethyl) styrenes were tolerated with both AD-mix-α and AD-mix-β. Pleasingly, in both cases a very high enantioselectivity was observed with this catalytic system, and **32g** and **32h** were isolated in moderate yields.

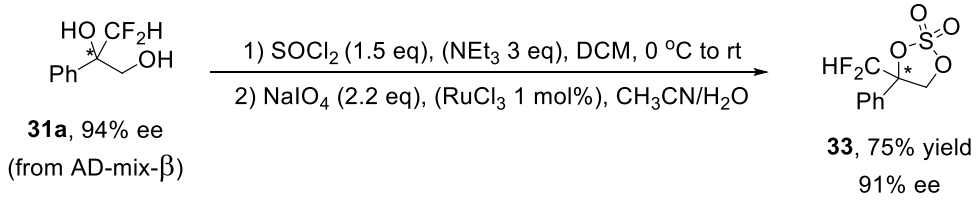


Scheme 96. Scope reaction for other styrenes. [a] reaction time 6 days. [b] reaction was carried out at 20 ºC.

3.7 Post-functionalization

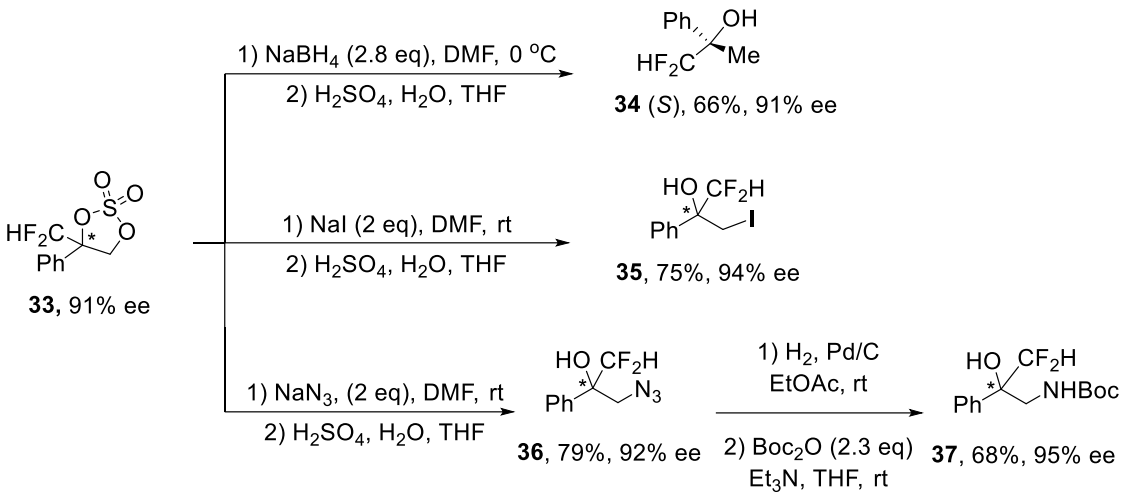
To demonstrate the synthetic utility of this transformation, the scale of the reaction with **2a** was increased to 4 mmol in the presence of AD-mix-β and **31a** was isolated in an excellent yield (98%) and a similar enantioselectivity (94% ee). Then we used **31a** to investigate the versatility and the synthetic utility of these chiral α,α-difluoromethyl tertiary alcohols.

The chiral alcohol **31a** was transformed into a cyclic sulfate **33** in 75% yield with a similar enantiomeric excess over two steps (**Scheme 97**). Indeed, cyclic sulfates proved to be a versatile chemical platform.[163]



Scheme 97. The preparation of cyclic sulfate **33**.

[163] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev*. **1994**, *94*, 2483-2547.



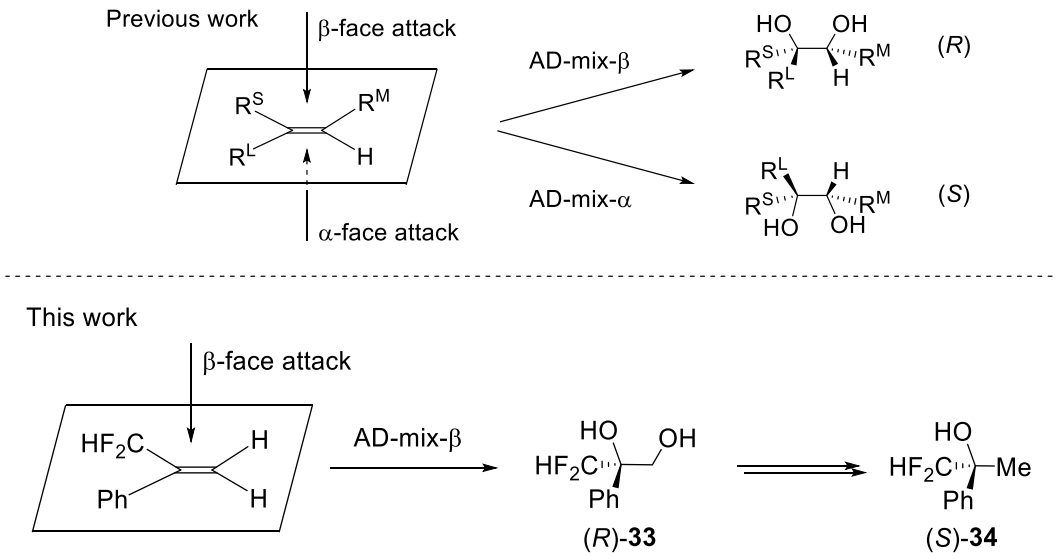
Scheme 98. Transformations of 36.

Then, this versatile intermediate **33** was converted into different substituted alcohols (Scheme 98). Firstly, compound **33** was reduced by $NaBH_4$, provided the corresponding alcohol **34** in 66 %yield with very high ee. Note that the absolute configuration of **34** was determined as *S*, by comparison with the literature data.[159]

The introduction of iodine after treating **33** with NaI, led to the corresponding product **35**, which was isolated in 75% yield without the erosion of enantioselectivity.

Finally, the reaction of the cyclic sulfate **33** with NaN_3 provided the azide **36** in 79%yield with similar ee. A subsequent reduction of **36** using Pd/C and a *N*-protection gave **37** in 68% yield over two steps with 95% ee.

3.8 Stereochemical model



Scheme 99. Confirmation of absolute configuration. [a] S, M and L denotes small,

medium and large.

The enantiofacial selectivity in the AD reaction has been rationalized in the literature (**Scheme 99**).[163] An alkene will be attacked from in flavor of its β-face (top face) in the presence of AD-mix-β, while from its α-face (bottom face) in the case of AD-mix-α. As conformed with literature, compound **34** was determined as a *S* configuration. Hence, the α,α-difluoromethyl alcohol **33** can be defined as a *R* configuration, which is in agreement with the proposed mechanism.[163]

3.9 Summary

In summary, we developed an efficient and practical methodology to access highly optical pure tertiary α,α-difluoromethyl alcohols with good yields and very high enantioselectivities. This transformation was applied to a broad range of substrates, involving variety of α,α-difluoromethyl styrenes, α-monofluoromethyl styrenes, β-difluoromethyl styrene and β-trifluoromethyl styrene, the use of whatever AD-mix-α or AD-mix-β as the catalyst provided the desired diols in very similar results.

Then the scale of the reaction could be increased to 4 mmol. In addition, various of synthetically useful transformations were carried out to demonstrate the synthetic utility of the reaction.

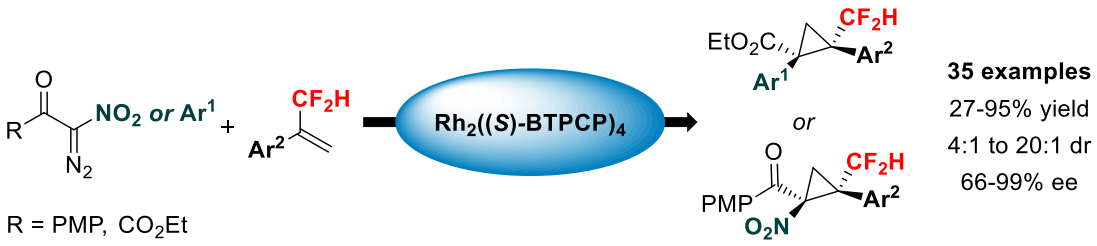
Conclusion and Perspectives

Conclusion and Perspectives

Conclusion

Our research group is highly interested in the preparation of fluorinated cyclopropane derivatives, and a lot of efforts have been made in recent years. This Ph.D. thesis is part of it and contributed to the development of new protocols to access enantiopure fluorinated cyclopropanes (focused on tri-, di- and monofluoromethyl derivatives), by means of Rh-catalyzed asymmetric cyclopropanation of fluorinated olefins with diazo compounds.

First, we reported the first example of the enantioselective synthesis of difluoromethyl cyclopropanes (**Scheme 100**). This unique methodology, using Rh_2((*S*)-BTPCP)$_4$ as the catalyst, on the one hand, was used with di-acceptor type diazo compounds (diazoketones) and donor-acceptor type diazo compounds (α-phenyl diazoacetates). On the other hand, the use of electron-deficient olefin (α-difluoromethyl styrenes) proved to be possible in the Rh-catalyzed asymmetric cyclopropanation reaction and provided the corresponding cyclopropanes in good to excellent yields with excellent diastereo- and enantioselectivities.[164]

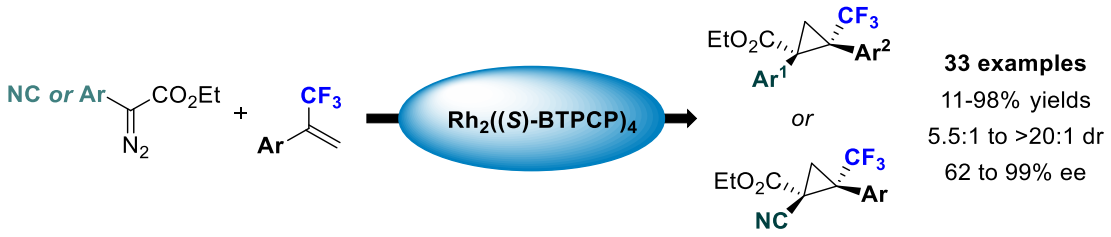


Scheme 100. Catalytic asymmetric cyclopropanation of α,α-difluoromethyl styrenes.

Inspired by the high performance of Rh_2((*S*)-BTPCP)$_4$ in catalytic asymmetric synthesis of difluoromethyl cyclopropanes. We then, move our attention to the more electro-deficient olefins (α-trifluoromethyl styrenes). To our delight, we developed a practical and efficient asymmetric synthesis of optically pure trifluoromethyl cyclopropane derivatives.[165] Moreover, the investigation was also extended to the synthesis of highly enantioselective monohalomethyl cyclopropanes.[140] This methodology represents the first catalytic asymmetric synthesis of highly functionalized trifluoromethyl

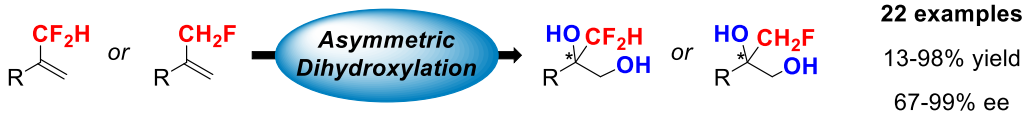
[164] M. Bos, W.-S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Angew. Chem. Int. Ed.* **2017**, *56*, 13319-13323.
[165] W. S. Huang, C. Schlinquer, T. Poisson, X. Pannecoucke, A. B. Charette, P. Jubault, *Chem. Eur. J.* **2018**, *24*, 10339-10343.

cyclopropanes and it is a complementary method to the ones already reported in the literature.



Scheme 101. Catalytic asymmetric cyclopropanation of α-trifluoromethyl styrenes.

Finally, we took the advantage of these olefins used for the preparation of enantiopure fluorinated cyclopropanes to develop a catalytic asymmetric oxidation process. Despite our efforts, we have not been able to carry out the catalytic asymmetric epoxidation reaction using Mn-catalysts or organic catalysts. However, we successfully used these olefins in a catalytic asymmetric dihydroxylation reaction and these substrates were straightforwardly converted into highly enantiopure α,α-difluoromethyl tertiary alcohols in the presence of AD-mix-α and AD-mix-β.[166]



Scheme 102. Catalytic Asymmetric dihydroxylation of α-difluoromethyl styrenes.

Perspective

During the study of the Rh_2((*S*)-BTPCP)$_4$ catalyzed cyclopropanation, we have obtained series of optically pure tri-, di and monofluoromethyl cyclopropanes and their derivatives after further functional group manipulations.

From the view of bioactive molecule discovery, these structures combine the features of fluorinated group and cyclopropane core. It is a great potential to explore their application in fields of drug discovery, crop science or material science, for instance.

From a chemical point of view, it is interesting to develop their application in chemical transformation. For example, we used these fluorinated cyclopropanes derivatives as ligands with rhodium to obtain new rhodium catalysts. Despite the first set of developed catalysts was inefficient in catalytic asymmetric cyclopropanation. Therefore, it is worthy to explore further their application in other transformations.

[166] W. S. Huang, M.-L. Delcourt, X. Pannecoucke, A. B. Charette, T. Poisson, P. Jubault, *Org. Lett.* **2019**, 21, 7509-7513.

In recent years, chemistry in continuous flow has been attracting a lot of interests. First, if we could prepare the diazo compounds as well as the cyclopropanation in a continuous flow set-up, we would avoid security problems in the preparation and purification of diazo compounds. In addition, the scale-up of reaction would be easier with a continuous flow process.

Besides, the use of analytic instruments applied on a continuous flow set-up is a straightforward way to determine the conversion of the reaction or to study the mechanism of the reaction. With online IR technology, we could be able to further study this rhodium-catalyzed cyclopropanation reaction.

Experimental Part

Experimental Part

General information

All reactions were carried out using oven dried glassware and magnetic stirring under an atmosphere of argon unless otherwise stated. Thin-layer chromatography (TLC) analyses were done using aluminum sheets coated with silica gel 60 F254. Flash column chromatography was carried out using silica gel 60 Å (0.04−0.06 mm). NMR spectra were recorded on a Bruker DXP 300, ^{1}H NMR spectra at 300.1 MHz, ^{13}C NMR spectra at 75.5 MHz, ^{19}F NMR spectra at 282.4 MHz (or 400 MHz (BBFO + Z-GRD Probe, ^{1}H: 400 100 MHz, ^{13}C: 100 MHz, 500 MHz (BBFO + Z-GRD Probe, ^{1}H: 500, ^{13}C: 126 MHz). Chemical shifts (δ) are quoted in parts per million (ppm) relative to residual solvent peak for $CDCl_3$ (δ_H = 7.26 ppm; δ_C = 77.4 ppm, or relative to external $CFCl_3$ δ_F = 0 ppm). Data are reported as follows: chemical shifts (δ), multiplicity: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublets, t = triplet, tt = triplet of triplets, q = quartet, m = multiplet, coupling constant = *J* (expressed in hertz). High-resolution mass spectra (HRMS) were recorded on Waters LCT Premier. IR spectra were recorded on a PerkinElmer Spectrum 100. Optical rotations were recorded on a PerkinElmer Polarimeter 341 at 20 °C. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) with a chiral column. Crystallographic data were collected using a Bruker D8 VENTURE diffractometer configured with a METALJET liquid-metal source and a PHOTON 100 CMOS-based.

THF, toluene and Et_2O were distilled from sodium-benzophenone. DCM and NEt_3 were distilled from calcium hydride. CH_3CN was obtained from solvent purifier MBRAUN MB SPS-800. Unless otherwise mentioned, all other solvents and chemicals were commercially available and used as received. Ethyl diazoacetate **4g**, ethyl 2-(trifluoromethyl)acrylate **7j**, 2-bromo-3,3,3-trifluoropropene **7k**, styrene, α-methyl styrene were commercially available and used as received.

Rh_2((*S*)-DOSP)$_4$[66] and Rh_2((*S*)-BTPCP)$_4$,[88] were prepared according to literature procedures.

Chapter I Asymmetric synthesis of difluoromethyl cyclopropanes

Synthesis of diazo compounds

General procedure A Synthesis of diazo compounds

A 0.56 M TfN_3 solution in hexane (1.5 equiv.) was added dropwise to a solution of

cyanoacetate (or α-nitroketone, α-esterketone, α-cyanoketone[167]) (1 equiv., 10 mmo) in MeCN (15 mL) at 0 °C. Pyridine (2 equiv., 20 mmol, 1.6 mL) was then added over a period of 10 min at 0 °C, and the mixture was allowed to warm up to room temperature overnight. The solvent was removed under reduced pressure (without heating) and the residue was directly purified by column chromatography.[81,168]

All the spectra data of diazo compounds (2-diazo-1-(4-methoxyphenyl)-2-nitro-ethanone **1a,** α-diazo-4-methoxy-β-oxobenzenepropanenitrile **4a,** methyl 2-diazo-3-(4-methoxyphenyl)-3-oxopropanoate **4b**),[81] ethyl α-cyano diazoacetate **4c**,[169] ethyl α-nitro diazoacetate **4e**[170] and 2-cyano-2-diazo-*N*,*N*-bis(phenylmethyl)acetamide **4f**[171] were in agreement with the literature.

General procedure B Synthesis of diazo compounds

The corresponding arylacetate (diethyl malonate) (1.5 g, 10 mmol, 1 equiv.) and tosyl azide (2.36 g, 12 mmol, 1.2 equiv.) were dissolved in dry CH_3CN (40 mL). DBU (1.8 g, 12 mmol, 1.2 equiv.) was added dropwise at 0 °C. The reaction mixture was allowed warm to room temperature overnight. At this point, approximately 20 mL of CH_3CN were evaporated under vacuum and 50 mL of Et_2O were added. The solution was filtered and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (PE: Et_2O = 70:1 to 30:1) to provide the corresponding α-aryl diazoacetates.[172]

All the spectra data of diazo compounds **4d**,[173] **4i-4y**[174] were in agreement with the literature.

4h was prepared according to the literature.[175]

Synthesis of difluoromethyl olefins

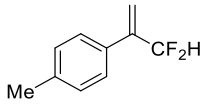
General procedure C Synthesis of difluoromethyl olefins

A flame dried 100mL round-bottom flask equipped with a magnetic stirring bar was charged with methyl triphenylphosphonium bromide (12.5 mmol, 1.25 equiv.). Dry Et_2O (37 mL) was added and the resulting suspension was cooled to 0 °C. *n*-BuLi (12 mmol, 1.2 equiv.) was added dropwise and the orange solution was stirred for 15-30 min at 0 °C. The reaction mixture was cooled to -78 °C then a solution of corresponding difluoromethyl ketone (were prepared

167 J. Zhou, X. Zhu, M. Huang, Y. Wan, *Eur. J. Org. Chem*. **2017**, *16*, 2317-2321.
168 S. Fritschi, A. Vasella, *Helv. Chim. Acta*. **1991**, *74*, 2024–2034.
169 R. P. Wurz, W. Lin, A. B. Charette, *Tetrahedron Lett.* **2003**, *44*, 8845-8848.
170 A. B. Charette, R. P. Wurz, T. Ollevier, *Helv. Chim. Acta.* **2002**, *85*, 4468-4484.
171 S. Y. Mo, J. X. Xu, *ChemCatChem*. **2014**, *6*, 1679-1683.
172 H. Saito, D. Morita, T. Uchiyama, M. Miyake, S. Miyairi, *Tetrahedron Lett.* **2012**, *53*, 6662-6664.
173 N. G. Koduri, H. Scott, B. Hileman, J. D. Cox, M. Coffin, L. Glicksberg, S. R. Hussaini, *Org. Lett*. **2012**, *14*, 440-443.
174 a) C. Peng, J. Cheng, J. Wang, *J. Am. Chem. Soc*. **2007**, *129*, 8708-8709. b) M. Hu, C. Ni, J. B. Hu, *J. Am. Chem. Soc*. **2012**, *134*, 15257-15260. c) F. Ye, S. Qu, L. Zhou, C. Peng, C. Wang, J. Cheng, M. L. Hossain, Y. Wang, J. B. Wang, *J. Am. Chem. Soc*. **2015**, *137*, 4435-4444.
175 Y. Zhou, Y. Zhang, J. B. Wang, *Org. Biomol. Chem.* **2016**, *14*, 10444-10453.

according to literature procedures)[176] (10 mmol, 1.0 equiv.) in Et_2O (5 mL) was added dropwise over 30 min. The cooling bath was removed and the reaction was allowed warm to room temperature. The reaction was stirred at room temperature for 12h. At this point, the reaction was quenched with NH_4Cl aq (sat.), Et_2O was added and the organic layers were separated. The organic layer was dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography over silica gel (pentane) to give the corresponding olefins.

α,α-difluoromethyl styrene **2a**[177] and 2-(1-(difluoromethyl)ethenyl)naphthalene **2m**[178] are in accordance with the literature characterization data.



α,α-difluoromethyl-*p*-methyl styrene **2b** (467 mg, 43%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

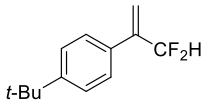
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.47 (t, *J* = 55.3 Hz, 1H), 5.79 (t, *J* = 1.9 Hz, 1H), 5.70 (t, *J* = 2.3 Hz, 1H), 2.46 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.9 (t, *J* = 20.0 Hz), 138.7, 131.9, 129.4, 126.9, 118.1 (t, *J* = 9.5 Hz), 115.7 (t, *J* = 239.4 Hz), 21.2.

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.1 (d, *J* = 55.1 Hz).

IR (film): 2970, 1613, 1391, 1358, 1192, 1125, 1095, 1067, 1020, 929, 822, 763, 735, 692, 640, 533, 471, 451 cm^{-1}.

HRMS (APPI): calcd for $C_{10}H_{10}F_2$ ([M^+]) 168.0745, found 168.0753.



α,α-difluoromethyl-*p*-*tert*-butyl styrene **2c** (634 mg, 51%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 – 7.28 (m, 4H), 6.43 (t, *J* = 55.4 Hz, 1H), 5.76 (t, *J* = 1.6 Hz, 1H), 5.66 (t, *J* = 2.1 Hz, 1H), 1.38 (s, 9H).

^{13}C NMR (126 MHz, CDCl3): δ 151.8, 141.7 (t, *J* = 19.9 Hz), 131.8, 126.6, 125.6, 118.1 (t, *J* =

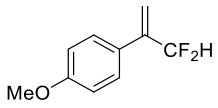
[176] a) C. B. Kelly, M. A. Mercadante, E. R. Carnaghan, M. J. Doherty, D. C. Fager, J. J. Hauck, A. E. MacInnis, L. J. Tilley, N. E. Leadbeater, *Eur. J. Org. Chem.* **2015**, 4071–4076. b) D. J. Leng, C. M. Black, G. Pattison, *Org. Biomol. Chem*. **2016**, *14*, 1531-1535. c) G. K. S. Prakash, J. B. Hu, G. A. Olah, *J. Fluorine Chem*. **2001**, *112*, 357-362.
[177] T. Ichitsuka, T. Fujita, J. Ichikawa, *ACS Catal*. **2015**, *5*, 5947-5950.
[178] T. Miura, Y. Ito, M. Murakami, *Chem. Lett.* **2008**, *37*, 1006-1007.

9.5 Hz), 115.6 (t, *J* = 239.5 Hz), 34.6, 31.3.

^{19}F NMR (471 MHz, CDCl3): δ -113.2 (d, *J* = 56.2 Hz).

IR (film): 2906, 1517, 1463, 1393, 1364, 1270, 1138, 1105, 1067, 1025, 928, 838, 805, 683, 645, 553 cm^{-1}.

HRMS (APPI): calcd for $C_{13}H_{16}F_2$ ([M$^+$]) 210.1215, found 210.1225.



α,α-difluoromethyl-*p*-methoxy styrene **2d** (363 mg, 33%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

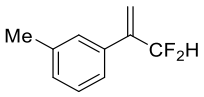
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.44 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.37 (td, *J* = 55.4, 0.6 Hz, 1H), 5.66 (t, *J* = 1.9 Hz, 1H), 5.57 (t, *J* = 2.3 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (126 MHz, CDCl$_3$): δ 160.1, 141.3 (t, *J* = 20.0 Hz), 128.3, 127.2, 117.3 (t, *J* = 9.6 Hz), 115.8 (t, *J* = 239.3 Hz), 114.1, 55.4.

^{19}F NMR (471 MHz, CDCl$_3$): δ -113.1 (d, *J* = 55.4 Hz).

IR (film): 2965, 1608, 1514, 1463, 1287, 1249, 1183, 1128, 1095, 1021, 908, 834, 807, 730, 647, 541, 428 cm^{-1}.

HRMS (APPI): calcd for $C_{10}H_{11}F_2O$ ([M+H]$^+$) 185.0772, found 185.0757.



α,α-difluoromethyl-*m*-methyl styrene **2e** (504 mg, 30%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

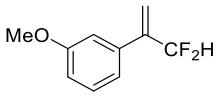
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.39 – 7.16 (m, 4H), 6.43 (t, *J* = 55.3 Hz, 1H), 5.75 (s, 1H), 5.69 (s, 1H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 142.1 (t, *J* = 20.0 Hz), 138.2, 134.7, 129.4, 128.5, 127.6, 124.0, 118.7 (t, *J* = 9.5 Hz), 115.4 (t, *J* = 239.5 Hz), 21.5.

^{19}F NMR (282 MHz, CDCl$_3$): δ -113.2 (d, *J* = 1.7 Hz).

IR (film): 2958, 1606, 1585, 1491, 1392, 1357, 1125, 1099, 1023, 932, 792, 722, 695, 666, 524, 494 cm^{-1}.

HRMS (APPI): calcd for $C_{10}H_{10}F_2$ ([M]$^+$) 168.0751, found: 168.0738.



α,α-difluoromethyl-*m*-methoxy styrene **2f** (1.3 g, 73%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

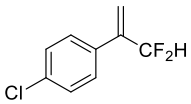
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 – 7.25 (m, 1H), 7.09 (ddd, *J* = 7.7, 1.7, 0.8 Hz, 1H), 7.05 (t, *J* = 2.2 Hz, 1H), 6.93 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 6.40 (td, *J* = 55.3, 0.6 Hz, 1H), 5.75 (t, *J* = 1.8 Hz, 1H), 5.69 (td, *J* = 2.3, 0.6 Hz, 1H), 3.84 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8, 142.0 (t, *J* = 20.0 Hz), 136.2, 129.7, 119.5, 119.2 (t, *J* = 9.4 Hz), 115.4 (t, *J* = 239.6 Hz), 114.1, 112.9, 55.3.

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.2 (d, *J* = 55.2 Hz).

IR (film): 2967 1600, 1578, 1491, 1464, 1229, 1182, 1119, 1097, 1019, 935, 863, 784, 694, 514, 481 cm^{-1}.

HRMS (APPI): calcd for $C_{10}H_9F_2O$ ($[M-H]^-$) 183.0627, found: 183.0628.



α,α-difluoromethyl-*p*-chloro styrene **2g** (1.1 g, 61%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

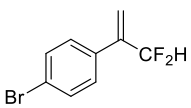
^{1}H NMR (500 MHz, $CDCl_3$): 7.43 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.37 (td, *J* = 55.1, 0.6 Hz, 1H), 5.73 (t, *J* = 2.0 Hz, 1H), 5.68 (td, *J* = 2.2, 0.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.1 (t, *J* = 20.4 Hz), 134.8, 133.1, 128.9, 128.5, 119.7 (t, *J* = 9.5 Hz), 115.6 (t, *J* = 239.6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.0 (d, *J* = 55.0 Hz).

IR (film): 2971, 1593, 1558, 1478, 1391, 1356, 1316, 1132, 1099, 1022, 937, 885, 833, 787, 695, 457, 491 cm^{-1}.

HRMS (APPI): calcd for $C_9H_7ClF_2$ ($[M]^+$) 188.0199, found: 188.0184.



α,α-difluoromethyl-*p*-bromo styrene **2h** (1.2 g, 71%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 – 7.46 (m, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 6.37 (td, *J*

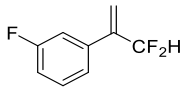
= 55.1, 0.6 Hz, 1H), 5.74 (t, *J* = 2.0 Hz, 1H), 5.68 (td, *J* = 2.3, 0.7 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.1 (t, *J* = 20.4 Hz), 133.6, 131.8, 128.7, 123.0, 119.8 (t, *J* = 9.5 Hz), 115.5 (t, *J* = 239.6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -112.9 (d, *J* = 55.2 Hz).

IR (film): 2923, 1590, 1490, 1387, 1123, 1022, 1008, 933, 930, 755, 565, 519, 465 cm^{-1}.

HRMS (APPI): calcd for $C_9H_7BrF_2$ ($[M]^+$) 231.9694, found: 231.9696.



α,α-difluoromethyl-*m*-fluoro styrene **2i** (516 mg, 29%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

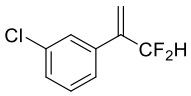
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (td, *J* = 8.0, 5.9 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.21 (dt, *J* = 10.2, 2.2 Hz, 1H), 7.07 (tdd, *J* = 8.3, 2.6, 1.1 Hz, 1H), 6.38 (td, *J* = 55.1, 0.7 Hz, 1H), 5.76 (t, *J* = 1.9 Hz, 1H), 5.71 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.8 (d, *J* = 246.1 Hz), 141.0 (td, *J* = 20.3, 2.3 Hz), 136.7 (d, *J* = 7.9 Hz), 130.1 (d, *J* = 8.3 Hz), 122.7 (d, *J* = 3.0 Hz), 120.0 (t, *J* = 9.4 Hz), 115.5 (d, *J* = 21.1 Hz), 115.3 (t, *J* = 239.6 Hz), 114.1 (d, *J* = 22.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -112.59 – -112.8 (m, 1F), -113.2 (d, J = 54.9 Hz, 2F).

IR (film): 2967, 1614, 1582, 1490, 1209, 1167, 1116, 1097, 1024, 939, 876, 788, 728, 704, 666, 522 cm^{-1}.

HRMS (APPI): calcd for $C_9H_7F_3$ ($[M]^+$) 172.0494, found: 172.0496.



α,α-difluoromethyl-*m*-chloro styrene **2j** (620 mg, 33%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.42 – 7.28 (m, 3H), 6.38 (t, *J* = 55.1 Hz, 1H), 5.76 (t, *J* = 1.9 Hz, 1H), 5.72 (t, *J* = 2.3 Hz, 1H).

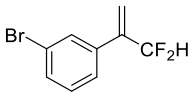
^{13}C NMR (126 MHz, $CDCl_3$): δ 141.1 (t, *J* = 20.5 Hz), 136.5, 134.7, 129.9, 128.8, 127.3, 125.3, 120.3 (t, *J* = 9.4 Hz), 115.4 (t, *J* = 239.6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.0 (dd, *J* = 55.0, 3.6 Hz).

IR (film): 2966, 1596, 1565, 1480, 1391, 1357, 1136, 1102, 1032, 938, 789, 730, 673, 549,

496, 420 cm^{-1}.

HRMS (APPI): calcd for $C_9H_7ClF_2$ ($[M]^+$) 188.0199, found: 188.0207.



α,α-difluoromethyl-*m*-bromo styrene **2k** (982 mg, 45%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.7 (pentane).

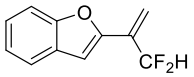
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (t, *J* = 1.9 Hz, 1H), 7.50 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 6.37 (t, *J* = 55.1 Hz, 1H), 5.74 (t, *J* = 1.9 Hz, 1H), 5.71 (t, *J* = 2.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 141.0 (t, *J* = 20.4 Hz), 136.8, 131.8, 130.2, 130.2, 125.8, 122.8, 120.4 (t, *J* = 9.4 Hz), 115.3 (t, *J* = 239.7 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -113.0 (d, *J* = 55.0 Hz).

IR (film): 2971, 1593, 1558, 1478, 1391, 1356, 1332, 1099, 1022, 937, 787, 695, 547, 491, 425 cm^{-1}.

HRMS (APPI): calcd for $C_9H_7BrF_2$ ($[M]^+$) 231.9694, found: 231.9674.



2-(1-(difluoromethyl)ethenyl)benzofuran **2l** (445 mg, 36%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

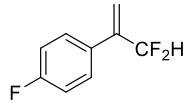
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.48 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 6.89 (q, *J* = 1.4 Hz, 1H), 6.44 (td, *J* = 54.9, 0.7 Hz, 1H), 6.18 (t, *J* = 2.0 Hz, 1H), 5.75 (t, *J* = 2.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 154.7, 150.0, 132.5 (t, *J* = 21.6 Hz), 128.6, 125.5, 123.3, 121.7, 117.5 (t, *J* = 8.6 Hz), 114.2 (t, *J* = 239.9 Hz), 111.2, 105.5 (d, *J* = 1.6 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -115.3 (d, *J* = 54.8 Hz).

IR (film): 2958, 1731, 1452, 1257, 1223, 1120, 1033, 886, 852, 808, 740, 678, 537, 429 cm^{-1}.

HRMS (APPI): calcd for $C_{11}H_8F_2O$ ($[M]^+$) 194.0538, found: 194.0545.



α,α-difluoromethyl-*p*-fluoro styrene **2n** (848 mg, 30%) was obtained as a colorless liquid after

silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

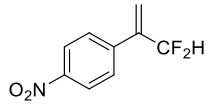
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.17 – 7.02 (m, 2H), 6.38 (t, *J* = 55.2 Hz, 1H), 5.71 (t, *J* = 1.9 Hz, 1H), 5.67 (t, *J* = 2.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (d, *J* = 248.2 Hz), 141.1 (t, *J* = 20.3 Hz), 130.7 (d, *J* = 3.4 Hz), 128.9 (d, *J* = 8.2 Hz), 119.2 (dd, *J* = 10.2, 8.9 Hz), 115.6 (t, *J* = 239.4 Hz), 115.5 (d, *J* = 21.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -113.0 (s, 2F), -113.1 (s, 1F).

IR (film): 1606, 1511, 1357, 1234, 1164, 1125, 1094, 1023, 934, 837, 741, 530, 449 cm^{-1}.

HRMS (CI+): calcd for $C_9H_8F_3$ ($[M+H]^+$) 173.0578, found: 173.0583.



α,α-difluoromethyl-*p*-nitro styrene **2o** (200 mg, 30%) was obtained as a yellow solid after silica gel column chromatography (pentane as eluent). Rf = 0.5 (pentane). Mp: 57 °C.

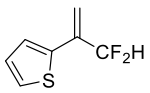
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 6.35 (t, *J* = 54.9 Hz, 1H), 5.82 (t, *J* = 2.0 Hz, 1H), 5.78 (t, *J* = 2.2 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 140.8, 140.5, 128.0, 123.8, 122.5 (t, *J* = 9.4 Hz), 115.2 (t, *J* = 239.9 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -112.8 (dt, *J* = 2.1, 15 Hz).

IR (film): 1632, 1417, 1398, 1344, 1236, 1107, 1022, 917, 854, 751, 635, 698, 491, 539, 491 cm^{-1}.

HRMS (EI): calcd for $C_9H_7F_2NO_2$ ($[M]^+$) 199.0445, found: 199.0451.



2-(3,3-difluoroprop-1-en-2-yl)thiophene **2p** (120 mg, 30%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

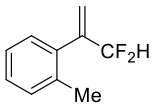
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 – 7.19 (m, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.28 (t, *J* = 55.2 Hz, 1H), 5.68 (s, 1H), 5.47 (s, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.0, 135.8 (t, *J* = 21.1 Hz), 127.8, 125.9, 125.7, 116.6 (t, *J* = 9.2 Hz), 114.7 (t, *J* = 240.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -114.4.

IR (film): 1632, 1397, 1344, 1235, 1107, 1023, 917, 853, 751, 635, 698, 538 cm^{-1}.

HRMS (EI): calcd for $C_7H_6F_2S$ ([M]$^+$): 160.0158, found: 160.0164.



α,α-difluoromethyl-*o*-methyl styrene **2q** (840 mg, 50%) was obtained as a colorless liquid after silica gel column chromatography (pentane as eluent). Rf = 0.6 (pentane).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.26 (m, 3H), 7.22 (d, *J* = 4.2 Hz, 1H), 6.43 (t, *J* = 55.3 Hz, 1H), 5.75 (s, 1H), 5.69 (s, 1H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.1 (t, *J* = 20.0 Hz), 138.2, 134.7, 129.4, 128.5, 127.6, 124.0, 118.7 (t, *J* = 9.5 Hz), 115.5 (t, *J* = 239.5 Hz), 21.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ -113.17 (d, *J* = 1.7 Hz).

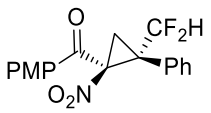
HRMS (CI+): calcd for $C_{10}H_{11}F_2$ ([M]$^+$): 169.0829, found: 169.0823. (-2.96 ppm)

Synthesis of difluoromethylated Cyclopropanes

General procedure D Enantioselective synthesis of difluoromethylated cyclopropanes

An oven-dried 2 mL reaction vial equipped with a magnetic stirring bar was charged with Rh_2((*S*)-BTPCP)$_4$ (4.4 mg, 1 mol%), filled with argon and sealed. DCM (0.150 mL) was added followed by the olefin (0.25 mmol, 1 equiv.) and the reaction was cooled to -50 °C. A solution of α-nitro diazoketone (66.4 mg, 0.3 mmol, 1.2 equiv.) in DCM (0.3 ml) was added over 30 min. The reaction was stirred at -50 °C until full completion of the reaction (monitored by ^{19}F NMR). At this point, pyridine (20 µL) was added to quench the reaction and the mixture was allowed warm to room temperature. The crude material was directly purified by flash chromatography on silica gel (from 100% hexanes to PE: EtOAc = 4:1) affording the desired difluoromethylated cyclopropane.

Note that all racemic difluoromethyl cyclopropanes were obtained using general procedure D with $Rh_2(OPiv)_4$ as a catalyst.



((1*S*,2*R*)-2-(difluoromethyl)-1-nitro-2-phenylcyclopropyl)(4-methoxyphenyl)methanone **3a** (76.5 mg, 92%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (92:8) was determined by ^{19}F NMR of the crude mixture. Rf = 0.28 (PE: EtOAc = 70:30). Mp: 127-129 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 80:20, 220 nm, 1 mL/min), t_R = 8.4 min, t_R = 8.9 min.

$[\alpha]^{20}_D$ = -212 (*c* = 1, $CHCl_3$).

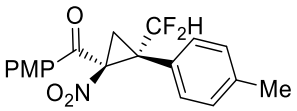
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.56 – 7.36 (m, 5H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.21 (t, *J* = 55.6 Hz, 1H), 3.88 (s, 3H), 3.09 (dt, *J* = 7.5, 1.8 Hz, 1H), 2.37 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 165.0, 131.6, 130.1 (d, *J* = 2.4 Hz), 129.8, 129.6, 129.1, 127.2, 114.6, 113.6 (t, *J* = 244.6 Hz), 75.23 (t, *J* = 2.8 Hz), 55.8, 42.7 (dd, *J* = 28.6, 25.5 Hz), 20.5 (dd, *J* = 5.3, 3.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -114.6 (ddd, *J* = 279.5, 55.4, 1.8 Hz, 1F), -117.2 (ddd, *J* = 279.5, 55.7, 1.5 Hz, 1F).

IR (film): 2938, 1680, 1599, 1548, 1512, 1425, 1339, 1266, 1164, 1119, 1053, 1031, 844, 721, 700 cm^{-1}.

HRMS (ESI): calcd for $C_{18}H_{16}F_2NO_4$ ($[M+H]^+$) 348.1042, found 348.1037.



((1*S*,2*R*)-2-(difluoromethyl)-2-(*p*-tolyl)-1-nitrocyclopropyl)(4-methoxyphenyl)methanone **3b** (81.4 mg, 90%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.28 (PE: EtOAc = 70:30). Mp: 124-126 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 90:10, 220 nm, 1 mL/min), t_R = 6.5 min, t_R = 7.0 min.

$[\alpha]^{20}_D$ = -177 (*c* = 1, $CHCl_3$).

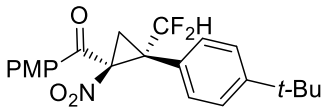
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 8.5, 0.8 Hz, 2H), 7.03 – 6.94 (m, 2H), 6.19 (t, *J* = 55.7 Hz, 1H), 3.89 (s, 3H), 3.06 (dt, *J* = 7.4, 1.7 Hz, 1H), 2.38 – 2.32 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 184.0, 165.0, 139.6, 131.7, 129.9, 129.7, 127.3, 127.0 (d, *J* = 2.6 Hz), 114.6, 113.7 (t, *J* = 244.5 Hz), 75.4 (d, *J* = 3.3 Hz), 55.8, 42.5 (dd, *J* = 28.6, 25.4 Hz), 21.4, 20.5, 20.5 (dd, *J* = 5.5, 3.2 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -114.6 (ddd, *J* = 279.5, 55.4, 1.8 Hz, 1F), -117.2 (ddd, *J* = 279.5, 55.7, 1.5 Hz, 1F).

IR (film): 2938, 1680, 1599, 1547, 1515, 1338, 1251, 1163, 1118, 1026, 907, 880, 842, 806, 778, 733, 554 cm^{-1}.

HRMS (ESI): calcd for $C_{19}H_{18}F_2NO_4$ ($[M+H]^+$) 362.1198, found 362.1214.



((1*S*,2*R*)-2-(difluoromethyl)-2-(4-*tert*-butylphenyl)-1-nitrocyclopropyl)(4-methoxyphenyl) methanone **3c** (90.8 mg, 90%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.27 (PE: EtOAc = 70:30). Mp: 157-158 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 90:10, 220 nm, 1 mL/min), t_R = 3.4 min, t_R = 3.9 min.

$[\alpha]^{20}_D$ = -182 (*c* = 1, $CHCl_3$).

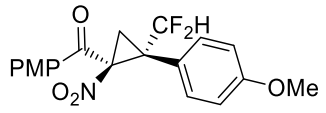
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 – 7.97 (m, 2H), 7.42 – 7.38 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.01 – 6.96 (m, 2H), 6.18 (t, *J* = 55.7 Hz, 1H), 3.89 (s, 3H), 3.06 (d, *J* = 7.4 Hz, 1H), 2.35 (d, *J* = 7.4 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 183.9, 164.8, 152.4, 131.6, 129.3, 127.2, 126.7 (d, *J* = 2.5 Hz), 126.0,
114.5, 113.6 (t, *J* = 244.5 Hz), 75.2, 55.7, 42.3 (dd, *J* = 28.6, 25.1 Hz), 34.7, 31.2, 20.3 (m).

^{19}F NMR (471 MHz, $CDCl_3$): δ -114.8 (dd, *J* = 278.8, 55.3 Hz, 1F), -117.2 (dd, *J* = 278.7, 56.3 Hz, 1F).

IR (film): 2966, 1678, 1598, 1548, 1511, 1338, 1256, 1217, 1120, 1052, 1032, 842, 751, 594, 532 cm^{-1}.

HRMS (ESI): calcd for $C_{22}H_{23}F_2NO_4Na$ ($[M+Na]^+$) 426.1487, found 426.1487.



((1*S*,2*R*)-2-(difluoromethyl)-2-(4-methoxyphenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3d** (86.8 mg, 92%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.28 (PE: EtOAc = 70:30). Mp: 127-128 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 90:10, 220 nm, 1 mL/min), t_R = 4.7 min, t_R = 6.7 min.

$[\alpha]^{20}_D$ = -190 (*c* = 1, $CHCl_3$).

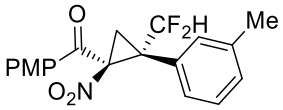
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.15 (t, *J* = 55.7 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.05 (dt, *J* = 7.5, 1.8 Hz, 1H), 2.32 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 184.1, 165.0, 160.5, 131.6, 131.1, 127.3, 121.8 (d, *J* = 2.6 Hz), 116.1, 114.6, 113.7 (d, *J* = 244.5 Hz), 75.5 (t, *J* = 2.8 Hz), 55.8, 55.4, 42.0 (dd, *J* = 28.5, 25.8 Hz), 20.5 (m).

^{19}F NMR (471 MHz, $CDCl_3$): δ -114.7 (dd, *J* = 278.8, 55.4 Hz, 1F), -117.0 (dd, *J* = 279.0, 55.8 Hz, 1F).

IR (film): 2967, 2937, 1680, 1599, 1548, 1515, 1463, 1339, 1252, 1164, 1118, 1052, 1033, 880 cm^{-1}.

HRMS (ESI): calcd for $C_{19}H_{17}F_2NO_5Na$ ([M+Na]$^+$) 400.0963, found 400.0967.



((1*S*,2*R*)-2-(difluoromethyl)-2-(3-methylphenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3e** (83.3 mg, 92%) was obtained as a pale-yellow sticky oil after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.28 (PE: EtOAc = 70:30).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 90:10, 220 nm, 1 mL/min), t_R = 5.5 min, t_R = 6.4 min.

$[\alpha]^{20}_D$ = -183 (*c* = 1, $CHCl_3$).

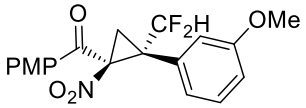
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.0 Hz, 2H), 7.52 – 7.11 (m, 4H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.21 (t, *J* = 55.7 Hz, 1H), 3.89 (s, 3H), 3.07 (dd, *J* = 7.4, 1.8 Hz, 1H), 2.58 – 2.19 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 184.0, 165.0, 138.9, 131.7, 130.43, 130.39, 130.0 (d, *J* = 2.5 Hz), 129.0, 127.2, 126.9, 114.6, 113.6 (t, *J* = 244.6 Hz), 75.2, 55.8, 42.7 (dd, *J* = 28.8, 24.9 Hz), 21.5, 20.4 (dd, *J* = 5.9, 2.9 Hz).

^{19}F NMR (471 MHz, $CDCl_3$): δ -114.9 (dd, *J* = 279.1, 55.9 Hz, 1F), -117.3 (dd, *J* = 278.7, 55.8 Hz, 1F).

IR (film): 2967, 1681, 1599, 1574, 1548, 1512, 1424, 1340, 1263, 1159, 1119, 845, 598 cm^{-1}.

HRMS (ESI): calcd for $C_{19}H_{18}F_2NO_4$ ([M+H]$^+$) 362.1198, found 362.1213.



((1*S*,2*R*)-2-(difluoromethyl)-2-(3-methoxyphenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3f** (89.6 mg, 95%) was obtained as a pale-yellow sticky oil after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.27 (PE: EtOAc = 70:30).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-RH column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 5.8 min, t_R = 6.9 min.

[α]$^{20}_D$ = -160 (*c* = 1, $CHCl_3$).

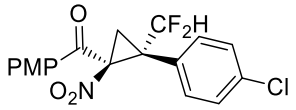
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.9 Hz, 2H), 7.31 (ddd, *J* = 8.1, 7.6, 0.5 Hz, 1H), 7.09 – 6.85 (m, 5H), 6.21 (t, *J* = 55.7 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.07 (dt, *J* = 7.5, 1.7 Hz, 1H), 2.35 (d, *J* = 7.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.2, 165.3, 160.2, 131.9, 131.8 (d, *J* = 2.4 Hz), 130.4, 127.4, 122.3, 115.9, 115.3, 114.9, 113.8 (t, *J* = 244.8 Hz), 75.5, 56.1, 55.7, 42.9 (dd, *J* = 28.8, 25.2 Hz), 20.8 (dd, *J* = 5.6, 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.9 (dd, *J* = 279.4, 55.5 Hz), -117.3 (dd, *J* = 279.3, 55.6 Hz).

IR (film): 2938, 1678, 1597, 1547, 1338, 1255, 1228, 1174, 1160, 1117, 1073, 982, 908, 843, 810, 771, 732, 647 cm^{-1}.

HRMS (ESI): calcd $C_{19}H_{17}F_2NO_5H$ ([M+H]$^+$) 378.1148, found 378.1088.



((1*S*,2*R*)-2-(difluoromethyl)-2-(4-chlorophenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3g.** (77.4 mg, 81%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (4:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.25 (PE: EtOAc = 70:30). Mp: 147-148 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/CH_3CN = 90:10, 294 nm, 1 mL/min), t_R = 3.7 min, t_R = 4.3 min.

[α]$^{20}_D$ = -184 (*c* = 1, $CHCl_3$).

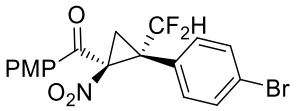
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.47 – 7.35 (m, 4H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.15 (t, *J* = 55.4 Hz, 1H), 3.89 (s, 3H), 3.06 (dt, *J* = 7.6, 1.8 Hz, 1H), 2.35 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.7, 165.1, 135.9, 131.6, 131.3, 129.5, 128.6 (d, *J* = 2.4 Hz), 127.1, 114.7, 113.44 (d, *J* = 243.4 Hz), 75.3, 55.9, 41.9 (dd, *J* = 28.5, 26.2 Hz), 20.7 (dd, *J* = 5.1, 3.2 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.3 (dd, *J* = 280.1, 55.1 Hz), -117.0 (dd, *J* = 280.2, 55.5 Hz).

IR (film): 2845, 1674, 1599, 1575, 1512, 1337, 1294, 1253, 1115, 1094, 1045, 1020, 881, 845, 597, 522 cm^{-1}.

HRMS (ESI): calcd $C_{18}H_{14}ClF_2NO_4H$ ($[M+H]^+$) 382.0652, found 382.0701.



((1*S*,2*R*)-2-(difluoromethyl)-2-(4-bromophenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3h** (101 mg, 95%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.29 (PE: EtOAc = 70:30). Mp: 156-157 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with a OJ-H column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 6.2 min, t_R = 7.2 min.

$[\alpha]^{20}_D$ = -179 (*c* = 1, $CHCl_3$).

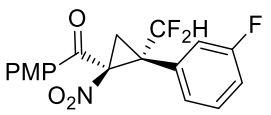
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 – 7.81 (m, 2H), 7.81 – 7.46 (m, 2H), 7.46 – 7.28 (m, 2H), 7.11 – 6.74 (m, 2H), 6.15 (t, *J* = 55.4 Hz, 1H), 3.88 (s, 3H), 3.05 (dt, *J* = 7.6, 1.7 Hz, 1H), 2.35 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.7, 165.1, 132.4, 131.6, 131.5, 129.1 (d, *J* = 2.3 Hz), 127.0, 124.1, 114.7, 113.4 (t, *J* = 244.8 Hz), 75.2 (t, *J* = 2.7 Hz), 55.8, 42.0 (dd, *J* = 28.5, 26.1 Hz), 20.6 (t, *J* = 4.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.3 (dd, *J* = 280.5, 55.6 Hz), -117.0 (dd, *J* = 280.4, 55.9 Hz).

IR (film): 2843, 1678, 1573, 1547, 1425, 1256, 1163, 1118, 1073, 982, 907, 844, 807, 778, 737 cm^{-1}.

HRMS (ESI): calcd $C_{18}H_{14}BrF_2NO_4Na$ ($[M+Na]^+$) 447.9966, found 447.9968.



((1*S*,2*R*)-2-(difluoromethyl)-2-(3-fluorophenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3i** (84.9 mg, 93%) was obtained as a pale-yellow sticky oil after silica gel column

chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.32 (PE: EtOAc = 70:30).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 5.2 min, t_R = 5.9 min.

$[\alpha]^{20}_D$ = -168 (*c* = 1, $CHCl_3$).

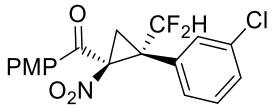
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.37 (td, *J* = 8.0, 5.8 Hz, 1H), 7.22 (ddt, *J* = 7.7, 1.6, 0.8 Hz, 1H), 7.19 – 7.05 (m, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.18 (t, *J* = 55.4 Hz, 1H), 3.89 (s, 3H), 3.07 (dt, *J* = 7.5, 1.8 Hz, 1H), 2.37 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.6, 165.1, 162.8 (d, J = 248.0 Hz), 132.3 (dd, *J* = 7.9, 2.4 Hz), 131.6, 130.8 (d, *J* = 8.5 Hz), 127.0, 125.6 (d, *J* = 3.1 Hz), 117.3 (d, *J* = 22.5 Hz), 116.8 (d, J = 20.9 Hz), 114.7, 113.4 (t, *J* = 245.0 Hz), 75.2 (t, *J* = 2.6 Hz), 55.8, 42.1 (ddd, J = 27.8, 25.9, 1.4 Hz), 20.6 (dd, *J* = 5.4, 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -111.6 (q, *J* = 8.2 Hz, 1F), -114.5 (dd, *J* = 280.2, 55.2 Hz, 1F), -117.1 (dd, *J* = 280.1, 55.4 Hz, 1F).

IR (film): 2846, 1679, 1597, 1545, 1491, 1445, 1424, 1338, 1255, 983, 845, 811, 794, 774, 735, 696, 647 cm-1.

HRMS (ESI): calcd $C_{18}H_{14}F_3NO_4H$ ($[M+H]^+$) 366.0948, found 366.0888.



((1*S*,2*R*)-2-(difluoromethyl)-2-(3-chlorophenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3j** (85.9 mg, 90%) was obtained as a pale-yellow sticky oil after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.30 (PE: EtOAc = 70:30).

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 5.5 min, t_R = 6.4 min.

$[\alpha]^{20}_D$ = -157 (*c* = 1, $CHCl_3$).

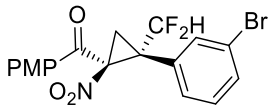
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.9 Hz, 2H), 7.43 (s, 1H), 7.41 – 7.28 (m, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.17 (t, *J* = 55.4 Hz, 1H), 3.89 (s, 3H), 3.07 (dt, *J* = 7.6, 1.8 Hz, 1H), 2.37 (d, *J* = 7.5 Hz, 1H).

^{13}C NMR (104 MHz, $CDCl_3$): δ 183.5, 165.0, 134.9, 131.9 (d, *J* = 2.4 Hz), 131.5, 130.2, 130.1, 129.8, 127.9, 126.9, 114.6, 113.3 (dd, *J* = 245.5, 244.4 Hz), 75.0 (t, *J* = 2.7 Hz), 55.7, 41.9 (dd, J = 28.6, 25.9 Hz), 20.5 (dd, *J* = 5.4, 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.4 (dd, *J* = 280.6, 55.5 Hz), -117.0 (dd, *J* = 280.5, 55.6 Hz).

IR (film): 2842, 1678, 1596, 1573, 1338, 1252, 1163, 1119, 1076, 1051, 1025, 843, 767, 733, 696, 597cm-1.

HRMS (ESI): calcd $C_{18}H_{14}ClF_2NO_4Na$ ([M+Na]$^+$) 404.0472, found 404.0513.



((1*S*,2*R*)-2-(difluoromethyl)-2-(3-bromophenyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3k** (75.7 mg, 71%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.30 (PE: EtOAc = 70:30). Mp: 118-119 ºC.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 3.6 min, t_R = 4.2 min.

$[\alpha]^{20}_D$ = -145 (*c* = 1, $CHCl_3$).

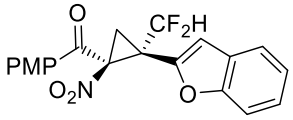
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, *J* = 8.9 Hz, 2H), 7.62 (bs, 1H), 7.57 (dt, *J* = 7.9, 1.5 Hz, 1H), 7.44 – 7.34 (m, 1H), 7.34 – 7.22 (m, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.19 (t, *J* = 55.4 Hz, 1H), 3.92 (s, 3H), 3.10 (dt, *J* = 7.7, 1.7 Hz, 1H), 2.40 (dd, *J* = 7.6, 1.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.6, 165.1, 133.1, 132.9, 132.2 (d, *J* = 2.3 Hz), 131.6, 130.6, 128.4, 127.0, 123.0, 114.7, 113.4 (t, *J* = 244.7 Hz), 75.1 (t, *J* = 2.9 Hz), 55.8, 42.0 (dd, *J* = 28.7, 26.0 Hz), 20.6 (dd, *J* = 5.3, 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.4 (dd, *J* = 279.9, 55.3 Hz), -117.0 (dd, *J* = 281.0, 55.5 Hz).

IR (film): 2923, 1674, 1599, 1575, 1555, 1337, 1294, 1079, 987, 847, 692, 650, 625, 597, 522 cm^{-1}.

HRMS (ESI): calcd $C_{18}H_{15}BrF_2NO_4$ ([M+H]$^+$) 426.0147, found 426.0197.



((1*S*,2*R*)-2-(difluoromethyl)-2-(2-benzofuranyl)-1-nitrocyclopropyl) (4-methoxyphenyl) methanone **3l** (85.2 mg, 88%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (>10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.25 (PE: EtOAc = 70:30). Mp: 172-173 ºC.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/CH_3CN = 90:10, 254 nm, 1 mL/min), t_R = 6.7 min, t_R = 8.7 min.

[α]$^{20}_{D}$ = -178 (*c* = 1, $CHCl_3$).

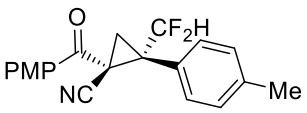
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 9.0 Hz, 2H), 7.60 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.52 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.35 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.26 (td, *J* = 7.6, 1.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 0.9 Hz, 1H), 6.17 (t, *J* = 55.4 Hz, 1H), 3.91 (s, 3H), 3.13 (dt, *J* = 7.7, 1.6 Hz, 1H), 2.53 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 183.2, 165.3, 155.6, 146.5 (d, *J* = 3.4 Hz), 132.2, 128.0, 127.7, 125.8, 123.7, 121.9, 114.9, 112.7 (t, *J* = 246.0 Hz), 111.9, 109.9, 74.7, 56.1, 37.7 (dd, *J* = 28.9, 27.0 Hz), 19.9 (t, *J* = 3.8 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.9 (dd, *J* = 283.4, 55.6 Hz), -118.9 (dd, *J* = 283.6, 55.1 Hz).

IR (film): 2845, 1674, 1599, 1549, 1337, 1253, 1187, 1117, 1094, 1079, 1047, 1020, 986, 909, 843, 751, 615 cm^{-1}.

HRMS (ESI): calcd $C_{18}H_{14}BrF_2NO_4H$ ($[M+H]^+$) 388.0991, found 388.0961.



(1*R*, 2*R*)-2-(difluoromethyl)-1-(4-methoxybenzoyl)-2-(4-methylphenyl)cyclopropane-1-carbonitrile **5a** (73.0 mg, 86%) was obtained according to General procedure D at -20 °C as a colorless sticky oil after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.35 (PE: EtOAc = 80:20).

Enantiomeric Excess: 70%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/H_2O = 90:10, 220 nm, 0.4 mL/min), t_R = 11.2 min, t_R = 12.5 min.

[α]$^{20}_{D}$ = -165 (*c* = 1, $CHCl_3$).

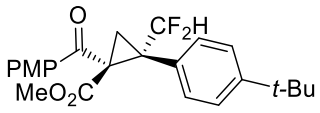
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.9 Hz, 2H), 7.55 – 7.47 (m, 2H), 7.38 – 7.29 (m, 2H), 7.06 (d, *J* = 9.0 Hz, 2H), 5.52 (dd, *J* = 55.8, 54.2 Hz, 1H), 3.92 (s, 3H), 2.78 (dd, *J* = 6.0, 1.1 Hz, 1H), 2.42 (s, 3H), 2.18 (t, *J* = 6.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 186.6, 164.8, 139.9, 132.0, 130.6, 129.9, 127.8, 127.7, 117.9, 114.2, δ
114.0 (t, J = 242.2 Hz), 55.7, 44.3 (dd, J = 31.0, 24.9 Hz), 29.4 (d, J = 6.4 Hz), 21.9 (d, *J* = 7.1 Hz), 21.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -112.2 (ddd, *J* = 291.7, 55.9, 6.2 Hz), -118.4 (dd, *J* = 291.6, 54.0 Hz).

IR (film): 2924, 2240, 1671, 1597, 1524, 1166, 1133, 1052, 844 cm^{-1}.

HRMS (ESI): calcd for $C_{20}H_{18}F_2NO_2$ ([M+H]$^+$) 342.1306, found 342.1300.



Methyl (1*R*, 2*R*)-2-(difluoromethyl)-2-(4-*tert*-butylphenyl)-1-(4-methoxybenzoyl)cyclopropane-1-carboxylate **5b** (61.0 mg, 62%) was obtained according to General procedure D as a white solid after silica gel column chromatography (PE: EtOAc = 80:20). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.35 (PE: EtOAc = 80:20). Mp: 95-97 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OJ-H column (MeOH/H_2O = 90:10, 220 nm, 0.4 mL/min), t_R = 14.6 min, t_R = 15.9 min.

[α]$^{20}_D$ = -137 (*c* = 1, $CHCl_3$).

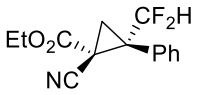
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.61 – 7.18 (m, 4H), 6.96 (d, *J* = 8.9 Hz, 2H), 5.98 (t, *J* = 55.8 Hz, 1H), 3.87 (s, 3H), 3.34 (s, 3H), 2.49 (dt, *J* = 4.3, 1.6 Hz, 1H), 2.04 (d, *J* = 5.6 Hz, 1H), 1.31 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 190.4, 167.8, 164.1, 151.4, 131.5, 130.2, 129.5, 129.0, 125.4, 115.1 (t, *J* = 242.6 Hz), 114.1, 55.6, 52.9, 42.9, 40.7 (m), 34.7, 31.4, 19.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ -113.24 – -113.60 (m, 1F), -113.98 (dd, *J* = 55.0, 1.8 Hz, 1F).

IR (film): 2960, 1737, 1675, 1598, 1511, 1257, 1176, 1123, 1030, 843, 733, 598 cm^{-1}.

HRMS (ESI): calcd for $C_{24}H_{27}F_2O_4$ ([M+H]$^+$) 417.1877, found 417.1900.



Ethyl (1*R*, 2*R*)-2-(difluoromethyl)-2-phenylcyclopropane-1-cynao-1-carboxylate **5c** (60.3 mg, 91%) was obtained as a white solid after silica gel column chromatography (PE: EtOAc = 70:30). The diastereomeric ratio (6:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.30 (PE: EtOAc = 70:30). Mp: 50-51 °C.

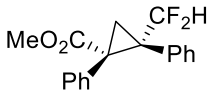
Enantiomeric Excess: 64%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 210 nm, 1 mL/min), t_R = 7.4 min, t_R = 8.4 min.

[α]$^{20}_D$ = +10.7 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 5H), 6.05 (t, *J* = 55.2 Hz, 1H), 4.49 – 4.27 (m, 2H), 2.44 (d, *J* = 6.0 Hz, 1H), 2.24 (t, *J* = 6.3 Hz, 1H), 1.40 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 131.1, 130.1, 129.8, 128.8, 114.9 (dd, *J* = 188.4, 54.6 Hz), 110.4, 64.0, 43.7 (dd, *J* = 32.4, 25.4 Hz), 25.0 (dd, *J* = 6.0, 1.7 Hz), 24.8 (d, *J* = 7.4 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -113.99 (ddd, *J* = 294.3, 55.4, 6.6 Hz, 1F), -117.65 – -119.20 (m, 1F).



Methyl (1*S*,2*R*)-1,2-diphenyl-2-(difluoromethyl)cyclopropane-1-carboxylate **5i** (60 mg, 80%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.25 (PE: Et_2O = 90:10). Mp: 68-69 °C.

Enantiomeric Excess: 94%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:2, 230 nm, 1 mL/min), t_R = 5.2 min, t_R = 6.3 min.

$[\alpha]^{20}_D$ = -8 (*c* = 1, $CHCl_3$).

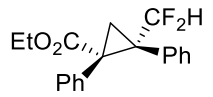
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.22 (m, 4H), 7.15 – 7.05 (m, 6H), 6.19 (t, *J* = 56.0 Hz, 1H), 3.74 (s, 3H), 2.34 (d, *J* = 6.2 Hz, 1H), 2.25 (t, *J* = 5.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 134.2, 132.2 (d, *J* = 2.0 Hz), 131.2, 131.0, 128.1, 128.1, 127.9, 127.7, 116.6 (dd, *J* = 241.9, 240.8 Hz), 53.4, 40.8 (t, *J* = 2.2 Hz), 40.0, 19.2 (d, *J* = 6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.3 (ddd, *J* = 284.2, 56.4, 5.6 Hz, 1F), -117.40 (dd, *J* = 284.5, 55.7 Hz,1F).

IR (Neat): 1709, 1497, 1435, 1253, 1207, 1180, 1013, 716, 694 cm^{-1}.

HRMS (EI): calcd for $C_{18}H_{16}F_2O_2$ ($[M]^+$) 302.1118, found 302.1117.(-0.2 ppm).



Ethyl (1*S*,2*R*)-1,2-diphenyl-2-(difluoromethyl)cyclopropane-1-carboxylate **5j** (71 mg, 90%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.25 (PE: Et_2O = 90:10). Mp: 65-66 °C.

Enantiomeric Excess: 94%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/ (MTBE/EtOH 75:25): 95: 5), 254 nm, 1 mL/min), t_R = 4.8 min, t_R = 5.7

min.

$[\alpha]^{20}_D$ = -3.9 (*c* = 1, $CHCl_3$).

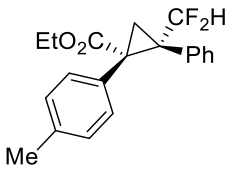
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 8.0, 1.7 Hz, 4H), 7.06 – 6.96 (m, 6H), 6.09 (t, *J* = 55.5 Hz, 1H), 4.23 – 4.01 (m, 2H), 2.25 (d, *J* = 6.2 Hz, 1H), 2.15 (t, *J* = 5.9 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 134.0, 132.0, 130.8, 130.8, 127.8, 127.8, 127.5, 127.3, 116.6 (dd, *J* = 242.2, 240.7 Hz), 62.0, 40.6 (dd, *J* = 26.4, 24.6 Hz), 40.6, 18.5 (d, *J* = 6.6 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.1 (ddd, *J* = 283.8, 56.4, 5.5 Hz, 1F), -117.2 (dd, *J* = 283.8, 55.7 Hz, 1F).

IR (Neat): 2964, 1715, 1497, 1449, 1400, 1252, 1201, 1136, 1094, 1036, 1022, 1013, 711, 695, 553 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{18}F_2O_2$ ($[M]^+$) 316.1275, found: 316.1276. (+0.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-methylphenyl)cyclopropane-1-carboxylate **5k** (75 mg, 91%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 49-51 °C.

Enantiomeric Excess: 91%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/ (MTBE/EtOH 75:25): 95: 5), 230 nm, 1 mL/min), t_R = 5.4 min, t_R = 6.1 min.

$[\alpha]^{20}_D$ = -9 (*c* = 1, $CHCl_3$).

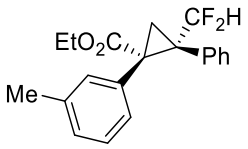
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 7.7 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 5H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.13 (t, *J* = 56.1 Hz, 1H), 4.31 – 4.08 (m, 2H), 2.30 (d, *J* = 6.1 Hz, 1H), 2.18 (d, *J* = 7.6 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 137.0, 132.1, 130.9, 130.9, 130.7, 128.3, 127.8, 127.7, 116.6 (dd, *J* = 242.0, 240.8 Hz), 61.9, 40.5 (t, *J* = 25.5 Hz), 39.7, 21.0, 18.5 (d, *J* = 7.1 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.2 (ddd, *J* = 283.6, 56.5, 5.4 Hz, 1F), -117.2 (dd, *J* = 283.5, 55.7 Hz, 1F).

IR (Neat): 2993, 1705, 1516, 1253, 1200, 1137, 1085, 1062, 796, 719, 700, 655, 552 cm^{-1}.

HRMS (EI): calcd for $C_{20}H_{20}F_2O_2$ ($[M]^+$) 330.1431, found: 330.1421. (-3.1 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(3-methylphenyl)cyclopropane-1-carboxylate **5l** (78 mg, 92%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 64-66 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:5, 220 nm, 1 mL/min), t_R = 4.6 min, t_R = 4.9 min.

$[\alpha]^{20}_D$ = -5.9 (*c* = 1, $CHCl_3$).

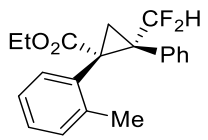
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.18 – 7.07 (m, 5H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 7.4 Hz, 1H), 6.19 (t, *J* = 56.1 Hz, 1H), 4.33 – 4.11 (m, 2H), 2.33 (d, *J* = 6.1 Hz, 1H), 2.24 (d, *J* = 5.7 Hz, 1H), 2.20 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 137.0, 134.0, 132.1, 132.1, 131.6, 130.8 (d, *J* = 1.0 Hz), 128.1, 128.0, 127.8, 127.4, 116.7 (dd, *J* = 242.1, 240.7 Hz), 62.0, 40.4 (dd, *J* = 26.2, 24.5 Hz), 40.0 (dd, *J* = 3.3, 2.1 Hz), 21.3, 18.5 (dd, *J* = 6.5, 1.2 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.1 (ddd, *J* = 283.5, 56.5, 5.4 Hz, 1F), -117.1 (dd, *J* = 283.4, 55.7 Hz, 1F).

IR (Neat): 2985, 1714, 1608, 1450, 1289, 1258, 1223., 1179, 1137, 1091, 1062, 1037, 909, 859, 784, 731, 718, 697, 616, 552, 419 cm^{-1}.

HRMS (ES): calcd for $C_{20}H_{21}F_2O_2$ ($[M+H]^+$) 331.1510, found: 331.1503. (2.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(2-methylphenyl)cyclopropane-1-carboxylate **5m** (78 mg, 92%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 66-67 °C.

Enantiomeric Excess: 91%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/ (MTBE/EtOH 75:25): 98: 2), 230 nm, 1 mL/min), t_R = 5.2 min, t_R = 6.7

min.

$[\alpha]^{20}_D$ = -4.8 (*c* = 1, $CHCl_3$).

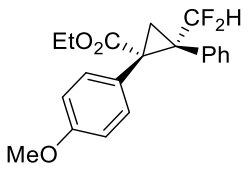
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 – 7.21 (m, 2H), 7.13 – 7.08 (m, 3H), 7.01 – 6.85 (m, 4H), 6.54 (t, *J* = 55.6 Hz, 1H), 4.31 – 4.03 (m, 2H), 2.37 – 2.32 (m, 2H), 2.29 (s, 3H,)1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 139.1, 132.9, 131.7, 130.7, 130.2, 129.6 (d, *J* = 2.2 Hz), 127.6, 127.5, 127.4, 125.0, 117.4 (dd, *J* = 242.3, 239.9 Hz), 62.0, 40.7 (dd, *J* = 27.5, 24.4 Hz), 39.5 (dd, *J* = 3.6, 1.5 Hz), 22.2 (d, *J* = 8.0 Hz), 20.0, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -104.2 – -112.6 (m, 1F), -116.5 (dd, *J* = 285.2, 55.4 Hz, 1F).

IR (Neat): 1706, 1393, 1253, 1201, 1085, 825, 718, 702, 475 cm^{-1}.

HRMS (ES): calcd for $C_{20}H_{20}F_2O_2$ ($[M]^+$) 330.1431, found: 330.1439. (2.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-methoxyphenyl)cyclopropane-1-carboxylate **5n** (39 mg, 45%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.17 (PE: Et_2O = 90:10). Mp: 87-89 ºC.

Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 6.6 min, t_R = 7.2 min.

$[\alpha]^{20}_D$ = -7.6 (*c* = 1, $CHCl_3$).

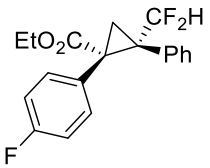
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.9 Hz, 2H), 7.20 – 7.13 (m, 5H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.15 (t, *J* = 56.1 Hz, 1H), 4.31 – 4.13 (m, 2H), 3.70 (s, 3H), 2.33 (d, *J* = 6.1 Hz, 1H), 2.19 (t, *J* = 5.9 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 158.6, 132.1 (d, *J* = 2.1 Hz), 132.0, 130.8, 127.8, 127.7, 126.1, 116.7 (dd, *J* = 242.0, 240.6 Hz), 112.9, 61.9, 55.0, 40.6 (dd, *J* = 26.1, 24.6 Hz), 39.3, 18.6 (d, *J* = 6.7 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.1 (ddd, *J* = 283.7, 56.5, 5.6 Hz, 1F), -117.1 (dd, *J* = 283.7, 55.6 Hz, 1F).

IR (Neat): 2929, 1711, 1612, 1582, 1516, 1461, 1449, 1389, 1366, 1327, 1245, 1202, 1186, 1136, 1115, 1085, 1033, 983, 861, 837, 794, 719, 699. 633, 577, 552, 540, 473, 405 cm^{-1}.

HRMS (EI): calcd for $C_{20}H_{20}F_2O_3$ ([M]$^+$) 346.1381, found: 346.1372. (-2.4 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-fluorophenyl)cyclopropane-1-carboxylate **5o** (50 mg, 50%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10). Mp: 95-96 °C.

Enantiomeric Excess: 90%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane/ (MTBE/EtOH 75:25): 98:2, 230 nm, 1 mL/min), t_R = 5.9 min, t_R = 6.3 min.

$[\alpha]^{20}_D$ = -7 (*c* = 1, $CHCl_3$).

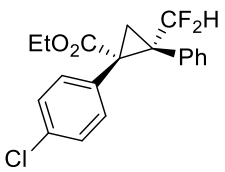
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 – 7.12 (m, 7H), 6.76 (t, *J* = 8.7 Hz, 2H), 6.15 (t, *J* = 56.0 Hz, 1H), 4.31 – 4.09 (m, 2H), 2.35 (d, *J* = 6.2 Hz, 1H), 2.19 (t, *J* = 6.0 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 163.4, 160.2, 132.6 (d, *J* = 8.3 Hz), 131.8, 130.6 (d, *J* = 1.2 Hz), 129.9 (d, *J* = 3.3 Hz), 128.0, 127.9, 116.5 (dd, *J* = 242.1, 240.8 Hz), 114.5 (d, *J* = 21.5 Hz), 40.7 (dd, *J* = 26.6, 24.5 Hz), 39.2, 18.9 (d, *J* = 7.8 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 284.6, 56.4, 5.8 Hz, 1F), -114.6 (tt, *J* = 8.6, 5.4 Hz, 1F), -117.1 (dd, *J* = 284.6, 55.6 Hz, 1F).

IR (Neat): 1715, 1606, 1513, 1444, 1256, 1226, 1201, 1089, 1059, 1034, 839, 801, 840, 733, 699, 544, 488 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{17}F_3O_2$ ([M]$^+$) 334.1181, found: 334.1176. (-1.5 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-chlorophenyl)cyclopropane-1-carboxylate **5p** (81 mg, 93%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 60-61 °C.

Enantiomeric Excess: 94%. The enantiomeric excess was determined by HPLC with an IA-

H column (*n*-heptane/ (MTBE/EtOH 75:25): 98:2, 230 nm, 1 mL/min), t_R = 5.6 min, t_R = 6.7 min.

$[\alpha]^{20}_D$ = -6 (*c* = 1, $CHCl_3$).

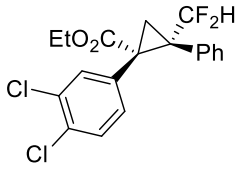
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.12 (m, 4H), 7.09 – 7.02 (m, 5H), 6.08 (t, *J* = 56.0 Hz, 1H), 4.23 – 4.01 (m, 2H), 2.27 (d, *J* = 6.2 Hz, 1H), 2.10 (t, *J* = 6.0 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 133.3, 132.6, 131.6 (d, *J* = 2.1 Hz), 130.7, 130.6, 130.6, 128.1, 121.6, 116.4 (dd, *J* = 242.2, 240.9 Hz), 62.2, 40.7 (dd, *J* = 26.9, 24.5 Hz), 39.4 (dd, *J* = 3.4, 2.1 Hz), 18.8 (d, *J* = 5.9 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.1 (ddd, *J* = 284.8, 56.3, 5.7 Hz, 1F), -117.2 (dd, *J* = 284.8, 55.6 Hz, 1F).

IR (Neat): 2925, 1710, 1495, 1255, 1085, 1060, 1023, 1015, 834, 719, 643, 609 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{17}ClF_2O_2$ ($[M]^+$) 350.0885, found: 350.0887. (+0.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(3,4-dichlorophenyl)cyclopropane-1-carboxylate **5q** (68 mg, 71%) was obtained according to general procedure D at -60 °C as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.26 (PE: Et_2O = 90:10).

Enantiomeric Excess: 73%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/ (MTBE/EtOH 75:25): 98:2, 230 nm, 1 mL/min), t_R = 8.1 min, t_R = 10.1 min.

$[\alpha]^{20}_D$ = 8 (*c* = 1, $CHCl_3$).

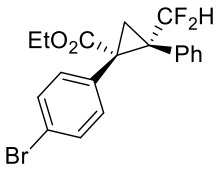
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 1.9 Hz, 1H), 7.16 – 6.97 (m, 7H), 6.08 (t, *J* = 55.9 Hz, 1H), 4.22 – 4.01 (m, 2H), 2.29 (d, *J* = 6.3 Hz, 1H), 2.09 (t, *J* = 6.1 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 134.7, 133.0, 131.6, 131.6, 131.4 (d, *J* = 2.0 Hz), 130.63, 130.61, 129.5, 128.35, 128.27, 116.4 (dd, *J* = 242.3, 241.1 Hz), 62.5, 41.1 (dd, *J* = 27.3, 24.5 Hz), 39.0 (dd, *J* = 3.5, 2.1 Hz), 19.1 (d, *J* = 6.5 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 285.6, 56.3, 5.8 Hz, 1F), -117.2 (dd, *J* = 285.6, 55.5 Hz, 1F).

IR (Neat): 2983, 1719, 1476, 1252, 1202, 1134, 1093, 1031, 719, 698, 517 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{16}C_{l2}F_2O_2$ ([M]$^+$) 384.0495, found: 384.0482. (-3.5 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-bromophenyl)cyclopropane-1-carboxylate **5r** (91 mg, 92%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.13 (PE: Et_2O = 90:10). Mp: 81-82 °C.

Enantiomeric Excess: 91%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/ (MTBE/EtOH 75:25): 98:2, 230 nm, 1 mL/min), t_R = 7.2 min, t_R = 9.4 min.

[α]$^{20}_D$ = -35 (*c* = 1, $CHCl_3$).

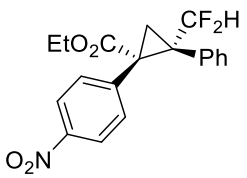
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 – 7.13 (m, 9H), 6.19 (t, *J* = 56.0 Hz, 1H), 4.34 – 4.12 (m, 2H), 2.38 (d, *J* = 6.2 Hz, 1H), 2.21 (t, *J* = 6.0 Hz, 1H), 1.28 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ δ 170.2, 133.3, 132.7, 132.3, 131.7, 131.6, 130.6 (d, *J* = 1.2 Hz), 128.0, 127.8, 116.45 (dd, *J* = 242.2, 240.9 Hz), 62.2, 40.8 (dd, *J* = 26.9, 24.5 Hz), 39.3 (d, *J* = 3.5 Hz), 18.8 (d, *J* = 7.7 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.1 (ddd, *J* = 284.8, 56.3, 5.6 Hz, 1F), -117.2 (dd, *J* = 284.8, 55.6 Hz, 1F).

IR (Neat): 2990, 1715, 1593, 1491, 1389, 1271, 1253, 1200, 1137, 1078, 1059, 1034, 1010, 833, 749, 699, 623, 502 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{17}BrF_2O_2$ ([M]$^+$) 394.0380, found: 394.0366. (-3.4 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(4-nitrophenyl)cyclopropane-1-carboxylate **5s** (70 mg, 77%) was obtained as a pale yellow solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.12 (PE: Et_2O = 90:10). Mp: 55-56 °C.

Enantiomeric Excess: 66%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), t_R = 9.4 min, t_R = 12.1 min.

$[\alpha]^{20}_D$ = 7.2 (*c* = 1, $CHCl_3$).

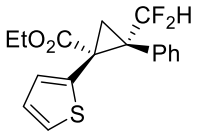
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 – 7.92 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.24 – 7.22 (m, 2H), 7.17 – 7.11 (m, 3H), 6.23 (t, *J* = 55.8 Hz, 1H), 4.30 – 4.15 (m, 2H), 2.46 (d, *J* = 6.4 Hz, 1H), 2.32 (t, *J* = 6.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 146.9, 141.7, 132.0, 131.1 (d, *J* = 2.0 Hz), 130.4 (d, *J* = 1.2 Hz), 128.3, 128.2, 122.7, 116.2 (dd, *J* = 242.3, 241.2 Hz), 62.5, 41.3 (dd, *J* = 27.8, 24.5 Hz), 39.4 (dd, *J* = 3.5, 2.1 Hz), 19.4 (d, *J* = 6.8 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 286.1, 56.2, 5.8 Hz, 1F), -117.2 (dd, *J* = 286.2, 55.5 Hz, 1F).

IR (Neat): 2925, 1719, 1604, 1521, 1499, 1449, 1368, 1346, 1296, 1257, 1201,1138, 1090, 1060, 1016, 908, 855, 908, 731, 698, 509 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{17}BrF_2O_4$ ($[M]^+$) 361.1126, found: 361.1114. (-3.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(2-thienyl)cyclopropane-1-carboxylate **5t** (62 mg, 77%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane/ (MTBE/EtOH 75:25): 98:2, 254 nm, 1 mL/min), t_R = 7.2 min, t_R = 8.3 min.

$[\alpha]^{20}_D$ = -7.8 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.16 – 7.14 (m, 3H), 7.01 – 6.94 (m, 2H), 6.92 (m, 1H), 6.04 (t, *J* = 56.1 Hz, 1H), 4.31 – 4.13 (m, 2H), 2.36 (d, *J* = 6.1 Hz, 1H), 2.13 (t, *J* = 5.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

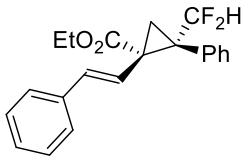
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 135.0, 132.0 (d, *J* = 2.0 Hz), 131.1, 129.5, 127.9, 127.8, 124.5, 124.3, 116.2 (dd, *J* = 241.9, 240.9 Hz), 62.1, 41.3 (dd, *J* = 26.1, 25.0 Hz), 35.5, 19.6 (d, *J* = 5.2 Hz), 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ -112.1 (ddd, *J* = 284.6, 56.4, 5.3 Hz, 1F), -117.1 (dd, *J* = 284.6,

55.7 Hz, 1F).

IR (Neat): 2919, 2127, 1717, 1369, 1262, 1217, 1183, 1136, 1091, 1037, 717, 633, 553 cm^{-1}.

HRMS (EI): calcd for $C_{17}H_{16}F_2O_2S$ ([M]$^+$) 322.0839, found: 322.0828. (-1.1 ppm).



Methyl (1*S*,2*R*)-2-(difluoromethyl)-2-phenyl-1-(2-phenylethenyl)cyclopropane-1-carboxylate **5u** (64 mg, 27%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 88-89 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 95:5, 254 nm, 1 mL/min), t_R = 5.2 min, t_R = 5.5 min.

$[\alpha]^{20}_D$ = -5.7 (*c* = 1, $CHCl_3$).

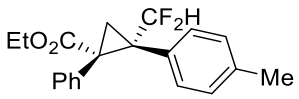
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 – 7.15 (m, 5H), 7.13 – 7.06 (m, 3H), 6.96 (dd, *J* = 7.7, 1.6 Hz, 2H), 6.06 (s, 2H), 5.88 (t, *J* = 55.8 Hz, 1H), 3.73 (s, 3H), 2.19 (d, *J* = 6.0 Hz, 1H), 1.84 (t, *J* = 6.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 136.6, 132.2, 131.8 (d, *J* = 1.7 Hz), 131.7, 128.4, 128.3, 128.2, 127.7, 126.2, 124.7, 116.0 (dd, *J* = 240.9, 239.8 Hz), 53.0, 41.5 (dd, *J* = 27.0, 25.1 Hz), 35.6 (dd, *J* = 4.1, 1.6 Hz), 19.9, 19.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ -112.8 (ddd, *J* = 286.8, 56.3, 6.0 Hz, 1F), -117.3 (dd, *J* = 287.0, 55.4 Hz, 1F).

IR (Neat): 3001, 1732, 1712, 1517, 1448, 1432, 1329, 1241, 1205, 1187, 1155, 1129, 1087, 1025, 838, 740, 700, 689, 554, 541, 519, 429 cm^{-1}.

HRMS (EI): calcd for $C_{20}H_{18}F_2O_2$ ([M]$^+$) 328.1275, found: 328.1262. (-1.3 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(4-methylphenyl)cyclopropane-1-carboxylate **6a** (64 mg, 78%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 75-76 °C.

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with an IC-

H column (*n*-heptane: *i*-PrOH = 95:5, 254 nm, 1 mL/min), t_R = 4.3 min, t_R = 4.9 min.

[α]$^{20}_D$ = +24 (*c* = 1, $CHCl_3$).

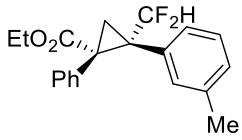
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.16 (m, 2H), 7.05 – 6.96 (m, 5H), 6.84 (d, *J* = 7.8 Hz, 2H), 6.05 (t, *J* = 56.1 Hz, 1H), 4.22 – 3.99 (m, 2H), 2.22 (d, *J* = 6.0 Hz, 1H), 2.11 – 2.09 (m, 4H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 137.4, 134.2, 130.9, 130.6, 128.9 (d, *J* = 2.1 Hz), 128.6, 127.6, 127.3, 116.6 (dd, *J* = 241.8, 240.6 Hz), 62.0, 40.3 (dd, *J* = 28.0, 26.3 Hz), 40.0 (d, *J* = 3.4 Hz), 21.1, 18.6 (d, *J* = 5.5 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.2 (ddd, *J* = 283.5, 56.5, 4.3 Hz, 1F), -117.2 (dd, *J* = 283.5, 55.8 Hz, 1F).

IR (Neat): 2975, 1711, 1447, 1366, 1321, 1290, 1257, 1203, 1086, 1059, 1022, 930, 864, 825, 788, 753, 702, 668, 640, 545, 423 cm^{-1}.

HRMS (CI): calcd for $C_{20}H_{20}F_2O_2$ ($[M]^+$) 330.1431, found: 330.1430. (-0.3 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(3-methylphenyl)cyclopropane-1-carboxylate **6b** (64 mg, 74%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10).

Enantiomeric Excess: 93%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 99.5:0.5, 220 nm, 1 mL/min), t_R = 10.1 min, t_R = 11.1 min.

[α]$^{20}_D$ = 13 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19 – 7.15 (m, 2H), 7.03 – 6.89 (m, 6H), 6.80 (d, *J* = 7.0 Hz, 1H), 6.07 (t, *J* = 56.1 Hz, 1H), 4.22 – 4.00 (m, 2H), 2.23 (d, *J* = 6.1 Hz, 1H), 2.14 – 2.11 (m, 4H), 1.17 (t, *J* = 7.1 Hz, 3H).

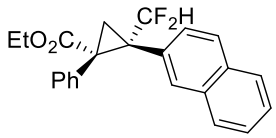
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 137.3, 134.1, 131.9 (d, *J* = 2.2 Hz), 131.6 (d, *J* = 0.8 Hz), 130.9, 128.5, 127.9 (d, *J* = 0.9 Hz), 127.7, 127.5, 127.3, 116.6 (dd, *J* = 242.1, 240.7 Hz), 62.0, 40.5 (dd, *J* = 26.2, 24.6 Hz), 39.90 (dd, *J* = 3.3, 2.2 Hz), 21.30, 18.5 (dd, *J* = 6.6, 1.4 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ 111.2 (ddd, *J* = 283.3, 56.5, 5.3 Hz, 1F), -117.2 (dd, *J* = 283.3, 55.8 Hz, 1F).

IR (Neat): 2988, 1715, 1606, 1449, 1366, 1290, 1258, 1198, 1134, 1090, 1062, 1037, 1023,

860, 779, 738, 716, 698, 626, 510, 493, 444, 404. cm^{-1}.

HRMS (CI): calcd for $C_{20}H_{20}F_2O_2$ ([M]$^+$) 330.1431, found: 330.1441.(+2.9 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(2-naphthalenyl)cyclopropane-1-carboxylate **6c** (79 mg, 86%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.26 (PE: Et_2O = 90:10). Mp: 105-106 °C.

Enantiomeric Excess: 93%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), t_R = 8.1 min, t_R = 9.1 min.

$[\alpha]^{20}_D$ =-10 (*c* = 1, $CHCl_3$).

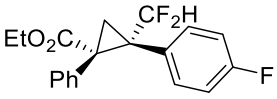
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 – 7.52 (m, 4H), 7.40 – 7.18 (m, 5H), 6.98 – 6.88 (m, 3H), 6.14 (t, *J* = 56.0 Hz, 1H), 4.27 – 4.04 (m, 2H), 2.34 (d, *J* = 5.8 Hz, 1H), 2.29 (t, *J* = 5.7 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 133.9, 132.8, 132.7, 130.8, 130.3, 129.7 (d, *J* = 2.1 Hz), 128.4 (d, *J* = 1.7 Hz), 127.9, 127.6, 127.5, 127.4, 127.3, 126.1, 125.9, 116.6 (dd, *J* = 242.2, 240.9 Hz), 62.1, 40.8 (dd, *J* = 26.3, 24.7 Hz), 40.2 (dd, *J* = 3.3, 1.9 Hz), 18.8 (d, *J* = 5.4 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 284.0, 56.4, 5.0 Hz, 1F), -117.0 (dd, *J* = 283.8, 55.7 Hz, 1F).

IR (Neat): 2923, 1715, 1606, 1449, 1366, 1290, 1258, 1198, 1134, 1090, 1062, 1037, 1023, 860, 779, 738, 716, 698, 626, 510, 493, 444, 404. cm^{-1}.

HRMS (CI): calcd for $C_{23}H_{20}F_2O_2$ ([M]$^+$) 366.1431, found: 366.1421.(-2.6 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(4-fluorophenyl)cyclopropane-1-carboxylate **6d** (60 mg, 80%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 98:2, 254 nm, 1 mL/min), t_R = 4.9 min, t_R = 5.3 min.

[α]$^{20}_{D}$ = -7 (*c* = 1, $CHCl_3$).

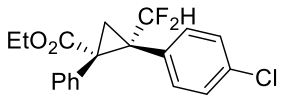
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.10 (m, 4H), 7.05 – 6.98 (m, 3H), 6.72 (t, *J* = 8.6 Hz, 2H), 6.05 (t, *J* = 55.9 Hz, 1H), 4.21 – 4.08 (m, 2H), 2.25 (d, *J* = 6.2 Hz, 1H), 2.11 (t, *J* = 6.0 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 162.2 (d, *J* = 247.1 Hz), 133.8, 132.6 (d, *J* = 1.2 Hz), 132.5 (d, *J* = 1.3 Hz), 130.8, 127.7, 127.5, 116.5(t, *J* = 241.2 Hz), 114.8 (d, *J* = 21.5 Hz), 62.1, 40.0 (dd, *J* = 26.7, 24.7 Hz), 39.93 (dd, *J* = 3.4, 1.5 Hz), 19.0 (d, *J* = 6.6 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.2 (ddd, *J* = 284.3, 56.3, 5.8 Hz, 1F), -114.0 (tt, *J* = 8.6, 5.3 Hz, 1F), -116.9 (dd, *J* = 284.3, 55.6 Hz, 1F).

IR (Neat): 2988, 1715, 1606, 1449, 1366, 1290, 1258, 1198, 1134, 1090, 1062, 1037, 1023, 860, 779, 738, 716, 698, 626, 510, 493, 444, 404 cm^{-1}.

HRMS (AP): calcd for $C_{19}H_{17}F_3O_2$ ($[M+H]^+$) 335.1259, found: 335.1259. (+1.8 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(4-chlorophenyl)cyclopropane-1-carboxylate **6e** (68 mg, 78%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10). Mp: 58-59 °C.

Enantiomeric Excess: 94%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), t_R = 5.8 min, t_R = 6.5 min.

[α]$^{20}_{D}$ = 8 (*c* = 1, $CHCl_3$).

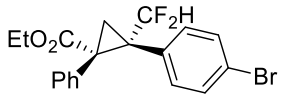
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16 – 7.00 (m, 9H), 6.05 (t, *J* = 55.8 Hz, 1H), 4.22 – 3.99 (m, 2H), 2.25 (d, *J* = 6.2 Hz, 1H), 2.10 (t, *J* = 6.1 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 133.8, 133.7, 132.2 (d, *J* = 1.2 Hz), 130.8, 130.6 (d, *J* = 1.9 Hz), 128.1, 127.8, 127.6, 116.4 (dd, *J* = 242.0, 240.8 Hz), 62.1, 40.0 (dd, *J* = 3.5, 1.7 Hz), 40.1 (dd, *J* = 26.7, 24.7 Hz), 18.9 (d, *J* = 6.2 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 284.6, 56.2, 5.8 Hz, 1F), -116.8 (dd, *J* = 284.6, 55.5 Hz, 1F).

IR (Neat): 298, 1715, 1600, 1496, 1392, 1273, 1254, 1200, 1110, 1138, 1090, 1059, 1035, 1015, 835, 758, 700, 627, 516, 404.8 cm-^{1}.

HRMS (CI): calcd for $C_{19}H_{17}ClF_2O_2$ ($[M]^+$) 351.0963, found: 351.0971. (+2.2 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(4-bromophenyl)cyclopropane-1-carboxylate **6f** (69 mg, 70%) was obtained as a colorless oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10).

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 99:1, 230 nm, 1 mL/min), t_R = 5.7 min, t_R = 6.5 min.

$[\alpha]^{20}_D$ = +5.3 (*c* = 1, $CHCl_3$).

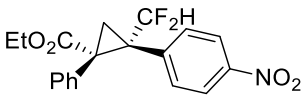
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 – 7.13 (m, 4H), 7.04 – 7.01 (m, 5H), 6.04 (t, *J* = 55.8 Hz, 1H), 4.23 – 4.00 (m, 2H), 2.25 (d, *J* = 6.2 Hz, 1H), 2.10 (t, *J* = 6.1 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 133.6, 132.5 (d, *J* = 1.2 Hz), 131.2 (d, *J* = 2.0 Hz), 131.0, 130.8, 127.8, 127.6, 122.1, 116.3 (dd, *J* = 242.1, 240.8 Hz), 62.1, 40.0 (dd, *J* = 3.5, 1.7 Hz), 40.1 (dd, *J* = 26.7, 24.7 Hz), 18.8 (d, *J* = 6.8 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -111.0 (ddd, *J* = 284.6, 56.2, 5.8 Hz, 1F), -116.9 (dd, *J* = 284.6, 55.5 Hz, 1F).

IR (Neat): 2988, 1715, 1593, 1491, 1389, 1272, 1253, 1200, 1137, 1110, 1090, 1078, 1059, 1034, 931, 833, 720, 749, 720, 699, 623, 561, 205 cm^{-1}.

HRMS (AP): calcd for $C_{19}H_{18}BrF_2O_2$ ($[M+H]^+$) 395.0458, found: 395.0460. (+ 0.5 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(4-nitrophenyl)cyclopropane-1-carboxylate **6g** (26 mg, 28%) was obtained as a yellow solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>12:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.12 (PE: Et_2O = 90:10). Mp: 47-48 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 95:5, 254 nm, 1 mL/min), t_R = 8.5 min, t_R = 9.0 min.

$[\alpha]^{20}_D$ = -4.3 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.9 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.15

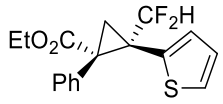
– 7.12 (m, 2H), 7.06 – 6.99 (m, 3H), 6.12 (t, *J* = 55.4 Hz, 1H), 4.26 – 4.03 (m, 2H), 2.35 (d, *J* = 6.4 Hz, 1H), 2.23 (t, *J* = 6.3 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 147.2, 139.7, 133.0, 131.8, 131.7, 130.6, 128.8, 127.9 (t, *J* = 2.7 Hz), 122.9, 116.2 (dd, *J* = 242.9, 241.1 Hz), 62.4, 40.3 (dd, *J* = 27.0, 24.7 Hz), 19.2 (d, *J* = 6.7 Hz), 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ -110.3 (ddd, *J* = 286.3, 55.8, 6.1 Hz, 1F), -116.4 (dd, *J* = 286.5, 55.1 Hz, 1F).

IR (Neat): 2930, 1715, 1593, 1491, 1389, 1272, 1253, 1200, 1137, 1110, 1090, 1078, 1059, 1034, 931, 833, 720, 749, 720, 699, 623, 561, 205 cm^{-1}.

HRMS (EI): calcd for $C_{19}H_{17}F_2NO_4$ ($[M]^+$) 361.1126, found: 361.1114. (-2.8 ppm).



Ethyl (1*S*,2*R*)-2-(difluoromethyl)-1-phenyl-2-(2-thienyl)cyclopropane-1-carboxylate **6h** (69 mg, 86%) was obtained as a colorless oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.12 (PE: Et_2O = 90:10).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 99:1, 220 nm, 1 mL/min), t_R = 6.4 min, t_R = 8.6 min.

$[\alpha]^{20}_D$ = +8.9 (*c* = 1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.05 – 7.03 (m, 3H), 6.96 (dd, *J* = 5.1, 1.0 Hz, 1H), 6.79 (d, *J* = 3.6 Hz, 1H), 6.68 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.07 (t, *J* = 55.7 Hz, 1H), 4.20 – 3.99 (m, 2H), 2.39 (d, *J* = 6.3 Hz, 1H), 2.13 (t, *J* = 6.1 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 135.0, 133.9, 131.2, 128.7 (d, *J* = 1.1 Hz), 127.6, 127.5, 126.6, 125.7, 115.9 (t, *J* = 241.3 Hz), 62.2, 41.4 (d, *J* = 2.1 Hz), 36.2 (dd, *J* = 26.7, 25.9 Hz), 21.3 (d, *J* = 6.7 Hz), 13.9.

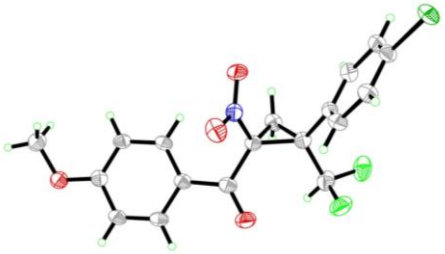
^{19}F NMR (282 MHz, $CDCl_3$): δ -112.0 (ddd, *J* = 284.4, 56.0, 5.9 Hz, 1F), -117.8 (dd, *J* = 284.4, 55.4 Hz, 1F).

IR (Neat): 2988, 1713, 1600, 1450, 1360, 1302, 1260, 1222, 1196, 1089, 1037, 1022, 920, 853, 696, 545, 405 cm^{-1}.

HRMS (CI): calcd for $C_{17}H_{17}F_2O_2S$ ($[M]^+$) 323.0917, found: 323.0927. (+3.1 ppm)

X-ray analysis

Crystallographic data for 3g (CCDC 1558858)



Empirical formula	$C_{18}H_{14}ClF_2NO_4$
Formula weight	381.75
Temperature/K	150
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	7.3361(3)
b/Å	11.2680(4)
c/Å	20.2108(7)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1670.69(11)
Z	4
ρ_{calc}g/cm^3	1.518
μ/mm^{-1}	1.612
F(000)	784.0
Crystal size/mm^3	0.4 × 0.12 × 0.08
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	7.612 to 121.582
Index ranges	-9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -26 ≤ l ≤ 26

Reflections collected	24579
Independent reflections	3833 [R_{int} = 0.0366, R_{sigma} = 0.0235]
Data/restraints/parameters	3833/0/236
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0276, wR_2 = 0.0731
Final R indexes [all data]	R_1 = 0.0295, wR_2 = 0.0745
Largest diff. peak/hole / e $Å^{-3}$	0.26/-0.33
Flack parameter	0.055(5)

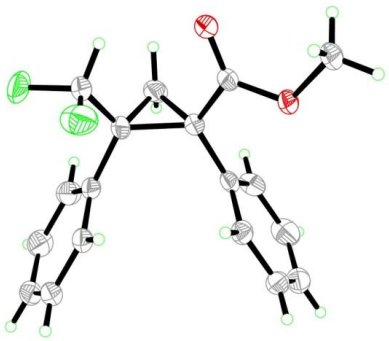
Table 19. Crystal data and structure refinement for **3g**.

Atom	*x*	*y*	*z*	U(eq)
Cl1	12074.0(7)	6614.5(4)	6938.9(2)	34.67(12)
F1	10606(2)	7048.2(12)	3769.9(7)	48.5(4)
F2	12124.0(19)	5393.7(13)	3782.8(6)	44.1(3)
O1	2885(2)	284.8(13)	2738.9(7)	35.2(3)
O2	9764(2)	3536.8(14)	3210.3(7)	38.1(3)
O3	6738(2)	4004.1(14)	5156.9(6)	37.1(3)
O4	8490(2)	2628.2(12)	4759.3(7)	39.4(4)
N1	7713(2)	3586.6(13)	4728.4(7)	28.2(3)
C1	1354(3)	58(2)	3157.7(11)	38.9(5)
C2	4108(3)	1114.0(16)	2948.0(9)	27.7(4)
C3	3782(3)	1907.6(17)	3466.7(8)	27.9(4)
C4	5138(3)	2703.8(16)	3641.1(8)	27.5(4)
C5	6810(3)	2719.1(16)	3315.9(8)	26.4(4)
C6	7081(3)	1943.0(16)	2780.0(8)	28.5(4)
C7	5749(3)	1150.0(17)	2600.4(9)	29.0(4)
C8	8336(3)	3494.5(17)	3510.4(8)	27.5(4)

C9	8060(3)	4289.7(16)	4113.9(8)	25.4(3)
C10	7140(3)	5474.9(16)	4074.4(9)	30.0(4)
C11	9140(3)	5424.3(17)	4243.5(9)	27.5(4)
C12	10406(3)	5843.4(19)	3704.5(10)	36.5(5)
C13	9811(3)	5695.0(15)	4930.7(8)	26.3(4)
C14	9053(3)	6619.5(17)	5296(1)	30.2(4)
C15	9740(3)	6890.8(16)	5919.2(10)	30.9(4)
C16	11192(3)	6248.2(16)	6165.5(9)	27.3(4)
C17	11959(3)	5323.9(16)	5810.2(9)	29.6(4)
C18	11254(3)	5045.4(16)	5192.2(9)	28.4(4)

Table 20. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **3g**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Crystallographic data for 5a (CCDC 1558859)



Empirical formula	$C_{18}H_{16}F_2NO_2$
Formula weight	302.31
Temperature/K	150
Crystal system	hexagonal
Space group	$P6_5$
a/Å	17.5697(4)
b/Å	17.5697(4)
c/Å	9.1671(2)

α/°	90
β/°	90
γ/°	120
Volume/Å^3	2450.71(12)
Z	6
ρ_{calc}g/cm^3	1.229
μ/mm^{-1}	0.508
F(000)	948.0
Crystal size/mm^3	0.16 × 0.02 × 0.02
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	5.052 to 121.228
Index ranges	-22 ≤ h ≤ 22, -22 ≤ k ≤ 22, -11 ≤ l ≤ 11
Reflections collected	48789
Independent reflections	3723 [R_{int} = 0.0429, R_{sigma} = 0.0212]
Data/restraints/parameters	3723/1/200
Goodness-of-fit on F^2	1.105
Final R indexes [I>=2σ (I)]	R_1 = 0.0349, wR_2 = 0.0807
Final R indexes [all data]	R_1 = 0.0424, wR_2 = 0.0842
Largest diff. peak/hole / e Å^{-3}	0.13/-0.22
Flack parameter	0.14(5)

Table 21. Crystal data and structure refinement for **5a**.

Atom	*x*	*y*	*z*	U(eq)
F1	6802.9(15)	2413(1)	2353.9(16)	62.3(6)
F2	5735.7(10)	1716.9(9)	3904.2(19)	49.0(4)
O1	6916.3(11)	2498.8(9)	6802.5(16)	31.4(4)
O2	6501(1)	1266.8(9)	8070.2(16)	25.6(3)

C1	6818.1(13)	1769.6(13)	6886(2)	22.5(4)
C2	7060.3(13)	1326.4(13)	5723(2)	22.9(4)
C3	6987.3(14)	1548.4(13)	4102(2)	25.9(4)
C4	7863.9(14)	1954.5(14)	4836(2)	30.2(5)
C5	6634.0(17)	2156.2(15)	3770(3)	33.7(5)
C6	6911.7(14)	426.1(13)	6080(2)	22.7(4)
C7	7603.0(15)	283.4(15)	6352(3)	32.2(5)
C8	7449.9(18)	-543.9(17)	6775(3)	41.1(6)
C9	6597.9(18)	-1231.7(15)	6911(3)	37.9(6)
C10	5901.9(16)	-1099.9(14)	6639(3)	31.2(5)
C11	6055.9(14)	-277.2(14)	6222(2)	25.7(4)
C12	6754.5(14)	842.4(13)	2966(2)	26.0(4)
C13	7387.2(16)	861.0(15)	2043(3)	34.5(5)
C14	7164.4(17)	245.3(16)	939(3)	38.3(6)
C15	6297.8(17)	-399.4(15)	734(3)	34.6(5)
C16	5657.4(16)	-432.0(15)	1652(3)	31.3(5)
C17	5879.8(14)	184.2(13)	2757(2)	27.1(4)
C18	6311.3(16)	1670.4(15)	9293(2)	31.2(5)

Table 22. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **5a**. U_{eq} is defined as 1/3 of the trace of the orthogonalised U_{IJ} tensor.

Chapter II Asymmetric synthesis of trifluoromethyl cyclopropanes

Synthesis of α,α,α-trifluoromethyl styrenes

General procedure E Synthesis of α,α,α-trifluoromethyl styrenes

An oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was charged with methyl triphenyl phosphonium bromide (12.5 mmol, 1.25 equiv.). Dry Et_2O (37 mL) was added and the resulting suspension was cooled to 0 °C. *n*-BuLi (12 mmol, 1.2 equiv.) was added dropwise and the orange solution was stirred for 15-30 min at 0 °C. The reaction mixture was cooled to -78 °C then a solution of corresponding α,α,α-trifluoromethyl ketone (were

prepared according to literature procedures)[179] (10 mmol, 1.0 equiv.) in Et_2O (5 mL) was added dropwise over 30 min. The reaction was allowed warm to room temperature. The reaction was stirred at room temperature for 12 h. At this point, the reaction was quenched with NH_4Cl aq. (sat.), Et_2O was added and the organic layers were separated. The organic layer was dried over anhydrous Na_2SO_4. The residue was purified by flash chromatography over silica gel (pentane) to give the corresponding olefins.

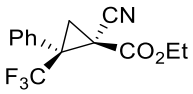
α,α,α-trifluoromethyl styrenes **7a-7i**, **7l, 7n-p** were prepared according to the literature procedures and were in agreement with the literature.[180] **7m** was prepared according to the literature procedures.[181]

Synthesis of trifluoromethyl cyclopropanes

General procedure F Synthesis of trifluoromethyl cyclopropanes

An oven-dried 2 mL reaction vial equipped with a magnetic stirring bar was charged with Rh_2((*S*)-BTPCP)$_4$ (4.4 mg, 1 mol%), filled with argon and sealed. DCM (0.15 mL) was added followed by the α,α,α-trifluoromethyl styrenes **7** (0.25 mmol, 1 equiv.) and the reaction was cooled to -20 °C. A solution of diazo compound (0.32 mmol, 1.3 equiv.) in DCM (0.2 mL) was added over 30 min. The reaction was stirred at -20 °C until completion of the reaction (monitored by ^{19}F NMR). At this point, pyridine (20 µL) was added to quench the reaction and the mixture was allowed to warm to room temperature. The crude material was directly purified by flash chromatography on silica gel (PE/Et_2O = 100:0 to 90:10) affording the corresponding trifluoromethyl cyclopropanes.

Note that all racemic cyclopropanes were obtained using general procedure G with $Rh_2(OPiv)_4$ as a catalyst.



Ethyl (1*R*, 2*R*) 1-cyano-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **8a** (69 mg, 98%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 54-55 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IC-

[179] T. Ichitsuka, T. Fujita, J. Ichikawa, *ACS Catal.* **2015**, *5*, 5947-5950.
[180] a) T. Fujita, M. Takazawa, K. Sugiyama, J. Ichikawa, *Org. Lett*. **2017**, *19*, 588-591. b) Y. Li, B. Zhao, K. Dai, D. H. Tu, B. Wang, Y. Wang, Z. Liu, Z. Liu, J. Lu, *Tetrahedron* **2016**, *72*, 5684-5690. c) A. Jiménez-Aquino, J. A. Vega, A. A. Trabanco, C. Valdés, *Adv. Synth. Catal*. **2014**, *356*, 1079-1084.
[181] H. Cheng, Y. Pei, F. Leng, J. Li, A. Liang, D. Zou, Y. Wu, Y. Wu, *Tetrahedron Lett*. **2013**, *54*, 4483-4486.

H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 5.4 min, t_R = 6.3 min.

$[\alpha]^{20}_D$ = +21.8 (*c* = 9.4, $CHCl_3$).

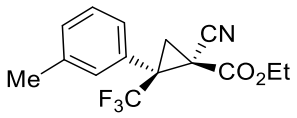
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 – 7.46 (m, 5H), 4.53 – 4.24 (m, 2H), 2.61 (d, *J* = 6.6 Hz, 1H), 2.16 (dd, *J* = 6.5, 1.4 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.0, 130.7, 130.4, 130.3, 129.1, 123.5 (q, *J* = 277.0 Hz), 115.4, 64.0, 42.6 (q, *J* = 35.0 Hz), 26.5 (q, *J* = 1.5 Hz), 21.1 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ -64.6 (S).

IR (Neat): 2972, 1751, 1469, 1353, 1258, 1176, 1159, 1093, 855, 693, 602, 565, 480 cm^{-1}.

HRMS (EI+): calcd for $C^{14}H^{12}F^3NO^2$ ($[M]^+$) 283.0820, found: 283.0815. (-1.8 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(3-methylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8b** (55 mg, 74%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (8:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 80-81 ºC.

Enantiomeric Excess: 94%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 6.2 min, t_R = 6.9 min.

$[\alpha]^{20}_D$ = +16.9 (*c* = 4.0, $CHCl_3$).

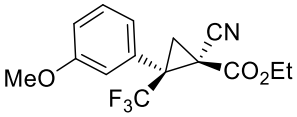
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 – 7.19 (m, 4H), 4.40 – 4.21 (m, 2H), 2.52 (d, *J* = 6.6 Hz, 1H), 2.33 (s, 3H), 2.08 (dd, *J* = 6.5, 1.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 138.9, 131.12, 131.07, 130.2, 129.0, 127.7, 123.6 (q, *J* = 276.9 Hz), 115.4, 63.9, 42.6 (q, *J* = 35.0 Hz), 26.5 (q, *J* = 1.6 Hz), 21.4, 21.1 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.5 (S).

IR (Neat): 2965, 1747, 1461, 1350, 1261, 1195, 1175, 1162, 1139, 1054, 1007, 856, 812, 799, 720, 702, 476, 442 cm^{-1}.

HRMS (AP+): calcd for $C_{15}H_{15}F_3NO_2$ ($[M+H]^+$) 298.1055, found: 298.1042. (-4.4 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(3-methoxyphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8c** (45 mg, 58%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (5:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 6.8 min, t_R = 7.4 min.

$[\alpha]^{20}_D$ = -15.2 (*c* = 2.5, $CHCl_3$).

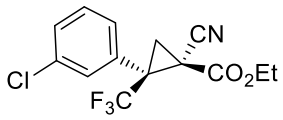
^{1}H NMR (300 MHz, $CDCl_3$) (Major) δ: 7.30 (t, *J* = 7.9 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.92 (dd, *J* = 10.9, 2.1 Hz, 2H), 4.39-4.20 (m, 2H), 3.77 (s, 3H), 2.51 (d, *J* = 6.6 Hz, 1H), 2.09 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) (Major) δ: 161.9, 159.8, 131.6, 130.2, 123.5 (q, *J* = 277.0 Hz), 122.8, 116.6, 115.4, 115.3, 63.9, 55.4, 42.5 (q, *J* = 35.0 Hz), 26.5 (q, *J* = 1.5 Hz), 21.2 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) (Major) δ: -64.4 (S).

IR (Neat): 2985, 1752, 1603, 1585, 1493, 1454, 1370, 1349, 1335, 1289, 1263, 1238, 1200, 1157, 1096, 1069, 1030, 857, 784, 720, 697, 560, 476, 460 cm^{-1}

HRMS (AP+): calcd for $C_{15}H_{15}F_3NO_3$ ($[M+H]^+$) 314.1004, found: 314.0999. (-1.6 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(3-chlorophenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8d** (48 mg, 60%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 64-65 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 5.6 min, t_R = 5.9 min.

$[\alpha]^{20}_D$ = +7.8 (*c* = 3, $CHCl_3$).

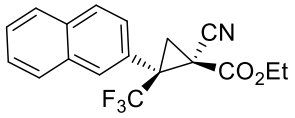
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.38 (m, 4H), 4.48 – 4.29 (m, 2H), 2.61 (d, *J* = 6.7 Hz, 1H), 2.15 (dd, *J* = 6.7, 1.6 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.6, 135.0, 132.2, 130.7, 130.6, 130.4, 129.0, 123.2 (q, *J* = 277.2 Hz), 115.0, 64.1, 41.9 (q, *J* = 35.3 Hz), 26.4 (m), 21.0 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.4 (S).

IR (Neat): 2992, 1755, 1370, 1349, 1301, 1256, 1207, 1163, 1038, 1002, 857, 788, 753, 705, 690, 443 cm^{-1}.

HRMS (AP+): calcd for $C_{14}H_{12}ClF_3NO_2$ ($[M+H]^+$) 318.0509, found: 318.0505. (-1.3 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(2-naphthalenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8e** (48 mg, 74%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.18 (PE: Et_2O = 90:10). Mp: 116-117 ºC.

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 6.8 min, t_R = 7.7 min.

$[\alpha]^{20}_D$ = -20.5 (*c* = 2.6, $CHCl_3$).

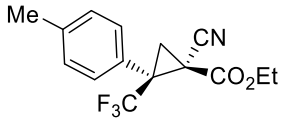
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 – 7.94 (m, 2H), 7.90 (dd, *J* = 9.3, 5.3 Hz, 2H), 7.63 – 7.55 (m, 3H), 4.51 – 4.32 (m, 2H), 2.70 (d, *J* = 6.6 Hz, 1H), 2.31 (dd, *J* = 6.5, 1.5 Hz, 1H), 1.41 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 133.8, 133.0, 130.8, 129.2, 128.3, 127.9, 127.7, 127.5, 126.92, 126.90, 123.6 (q, *J* = 277.1 Hz), 115.4, 64.0, 42.8 (q, *J* = 35.0 Hz), 26.6 (q, *J* = 1.4 Hz), 21.4 (dd, *J* = 2.3 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.2 (S).

IR (Neat): 2253, 1742, 1595, 1362, 1325, 1290, 1167, 1149, 1126, 1069, 1015, 863, 823, 750, 714, 483, 440 cm^{-1}.

HRMS (AP+): calcd for $C_{18}H_{15}F_3NO_2$ ($[M+H]^+$) 334.1055, found: 334.1048. (-2.1 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(4-methylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8f** (61 mg, 82%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 46-47 ºC.

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 6.3 min, t_R = 6.8 min.

$[\alpha]^{20}_D$ = +4.4 (*c* = 8.0, $CHCl_3$).

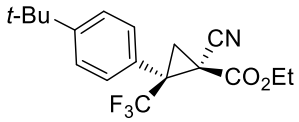
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.38 – 4.19 (m, 2H), 2.50 (d, *J* = 6.5 Hz, 1H), 2.30 (s, 3H), 2.05 (dd, *J* = 6.4, 1.2 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 140.4, 130.5, 129.8, 127.4, 123.6 (q, *J* = 276.9 Hz), 115.5, 63.9, 42.4 (q, *J* = 35.0 Hz), 26.6 (q, *J* = 1.5 Hz), 21.3, 21.2 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.6 (S).

IR (Neat): 2992, 2247, 1754, 1517, 1447, 1370, 1350, 1332, 1298, 1257, 1206, 1159, 1097, 1057, 1036, 1018, 1003, 859, 815, 727, 600, 563, 514, 472 cm^{-1}.

HRMS (AP+): calcd for $C_{15}H_{15}F_3NO_2$ ($[M+H]^+$) 298.1055, found: 298.1043. (-4.0 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(4-methylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8g** (62 mg, 73%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (6:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 87-88 ºC.

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.7 min, t_R = 5.2 min.

$[\alpha]^{20}_D$ = -1.6 (*c* = 4.6, $CHCl_3$).

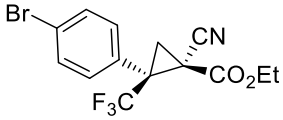
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 – 7.41 (m, 4H), 4.47 – 4.28 (m, 2H), 2.58 (d, *J* = 6.5 Hz, 1H), 2.13 (dd, *J* = 6.5, 1.6 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.33 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.1, 153.4, 130.3, 127.2, 126.0, 123.6 (q, *J* = 276.8 Hz), 115.4, 63.9, 42.2 (q, *J* = 35.0 Hz), 34.8, 31.2, 26.5 (q, *J* = 1.4 Hz), 21.1 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.8 (S).

IR (Neat): 2965, 1750, 1468, 1369, 1354, 1335, 1258, 1160, 1108, 1093, 995, 855, 829, 692, 601, 564, 480 cm^{-1}.

HRMS (AP+): calcd for $C_{18}H_{21}F_3NO_2$ ($[M+H]^+$) 340.1524, found: 340.1508. (-4.7 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(4-bromophenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8h** (63 mg, 70%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (18:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 60-61 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 7.6 min, t_R = 8.8 min.

$[\alpha]^{20}_D$ = +9.7 (*c* = 9.4, $CHCl_3$).

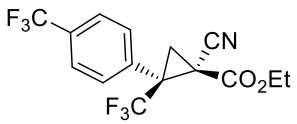
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 4.47 – 4.28 (m, 2H), 2.61 (d, *J* = 6.7 Hz, 1H), 2.12 (dd, *J* = 6.6, 1.5 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.6, 132.5, 132.3, 129.4, 125.0, 123.2 (q, *J* = 277.1 Hz),115.2, 64.1, 41.9 (q, *J* = 35.3 Hz), 26.4 (d, *J* = 1.5 Hz), 21.1 (q, *J* = 2.3 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -64.6 (S).

IR (Neat): 2985, 1755, 1602, 1493, 1370, 1350, 1332, 1257, 1207, 1165, 1073, 1011, 858, 821, 737, 565, 514 cm^{-1}.

HRMS (AP+): calcd for $C_{14}H_{12}BrF_3NO_2$ ($[M+H]^+$) 362.0003, found: 361.9986. (-4.7 ppm)



Ethyl (1*R*, 2*R*) 1-cyano-2-(4-trifluoromethylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **8a** (53 mg, 60%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (10:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10). Mp: 54-55 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 6.9 min, t_R = 8.3 min.

$[\alpha]^{20}_D$ = +18.3 (*c* = 4.8, $CHCl_3$).

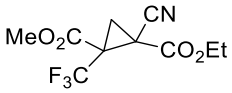
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 4.46 – 4.32 (m, 2H), 2.66 (d, *J* = 6.8 Hz, 1H), 2.17 (d, *J* = 5.2 Hz, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.4, 134.2, 132.5 (q, *J* = 33.0 Hz), 131.3, 126.2 (q, *J* = 3.7 Hz), 123.5 (q, *J* = 272.6 Hz), 123.2 (q, *J* = 277.2 Hz), 115.0, 64.2, 42.0 (q, *J* = 35.3 Hz), 26.3 (m), 21.0 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -63.0 (S), -64.4 (S).

IR (Neat): 2966, 1751, 1327, 1259, 1210, 1172, 1141, 1113, 1068, 1017, 862, 840, 749, 720, 678, 610, 565, 514, 480 cm^{-1}.

HRMS (AP+): calcd for $C_{15}H_{11}F_6NO_2$ ($[M]^+$) 351.0694, found: 351.0688. (-1.7 ppm)



1-Ethyl, 2-methyl 1-cyano-2-(trifluoromethyl)cyclopropane-1,2-dicarboxylate **8j** (30 mg, 45%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10).

Enantiomeric Excess: 74%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 7.2 min, t_R = 11.1 min.

$[\alpha]^{20}_D$ = -47.1 (*c* = 1.5, $CHCl_3$).

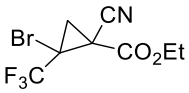
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.24-4.43 (m, 2H), 3.94 (s, 3H), 2.47 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.6, 160.5, 121.7 (q, *J* = 277.1 Hz), 113.9, 64.5, 54.4, 40.8 (q, *J* = 36.9 Hz), 25.7 (q, *J* = 1.5 Hz), 20.4 (q, *J* = 2.1 Hz), 13.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -61.7 (S).

IR (Neat): 3227, 2991, 2252, 1750, 1440, 1363, 1329, 1244, 1185, 1094, 1080, 1052, 1008, 962, 880, 858, 747, 561,479 cm^{-1}.

HRMS (AP+): calcd for $C_{10}H_{11}F_3NO_4$ ($[M+H]^+$) 266.0640, found: 266.0647. (+2.6 ppm)



Ethyl 1-cyano-2-bromo-2-(trifluoromethyl)cyclopropane-1-carboxylate **8k** (31 mg, 43%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.20 (PE: Et_2O = 90:10).

Enantiomeric Excess: 62%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.9 min, t_R = 5.2 min.

$[\alpha]^{20}_D$ = -31.4 (*c* = 2.3, $CHCl_3$).

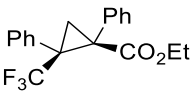
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.37-4.18 (m, 2H), 2.57 (d, *J* = 8.3 Hz, 1H), 2.06 (d, *J* = 1.0 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.9, 121.7 (q, *J* = 276.2 Hz), 114.6, 64.6, 33.7 (q, *J* = 41.7 Hz), 28.5 (q, *J* = 1.0 Hz), 25.0 (q, *J* = 1.7 Hz), 13.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.5 (S).

IR (Neat): 3106, 2925, 2260, 1747, 1371, 1354, 1280, 1236, 1196, 1175, 1060, 1036, 1003, 857, 776, 699, 655, 565, 540, 451 cm^{-1}.

HRMS (CI+): calcd for $C_8H_8BrF_3NO_2$ ($[M+H]^+$) 285.9690, found: 285.9702. (+4.0 ppm)



Ethyl (1*S*,2*R*)-1,2-diphenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9h** (67 mg, 73%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.25 (PE: Et_2O = 90:10). Mp: 84-85 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 98:2, 213 nm, 1 mL/min), t_R = 5.2 min, t_R = 6.7 min.

$[\alpha]^{20}_D$ = -80 (*c* = 5.3, $CHCl_3$).

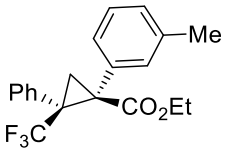
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 – 7.36 (m, 2H), 7.32 – 7.30 (m, 2H), 7.17 – 7.05 (m, 6H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.33 (d, *J* = 6.5 Hz, 1H), 2.19 (d, *J* = 6.6 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 133.2, 131.3, 131.2, 129.7, 128.3, 128.0, 127.9, 127.8, 125.5 (q, *J* = 275.7 Hz), 61.9, 41.0 (m), 39.4 (q, *J* = 32.3 Hz), 16.8 (q, *J* = 2.4 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2988, 1723, 1493, 1449, 1355, 1338, 1263, 1230, 1179, 1153, 1135, 1096, 1082, 1026, 895, 819, 639, 623, 610,512, 490, 447, 426 cm^{-1}.

HRMS (EI+): calcd for $C_{19}H_{17}F_3O_2$ ($[M]^+$) 334.1181, found: 334.1182. (0.3 ppm)



Ethyl (1*S*,2*R*)-1-(3-methylphenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9j** (64 mg, 73%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 91-92 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 4.2 min, t_R = 4.9 min.

$[\alpha]^{20}_D$ = -78 (*c* = 5.0, $CHCl_3$).

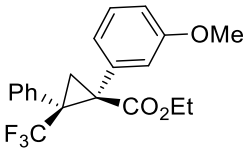
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (dd, *J* = 6.5, 2.5 Hz, 2H), 7.17 – 7.13 (m, 5H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.32 (d, *J* = 6.5 Hz, 1H), 2.20 (s, 3H), 2.17 (dd, *J* = 6.3, 1.7 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 137.6, 133.2, 131.4, 131.3, 130.4, 128.6, 128.3, 127.9(2), 126.9, 125.6 (q, *J* = 273.8 Hz), 61.9, 41.0 (m), 39.3 (q, *J* = 32.3 Hz), 21.3, 16.9 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 3101, 1724, 1603, 1450, 1371, 1355, 1336, 1268, 1237, 1197, 1151, 1131, 1081, 1049, 1026, 853, 783, 770, 724, 704, 695, 620, 495, 442 cm^{-1}.

HRMS (ES+): calcd for $C_{20}H_{20}F_3O_2$ ($[M+H]^+$) 349.1415, found: 349.1406. (-2.6 ppm)



Ethyl (1*S*,2*R*)-1-(3-methoxyphenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9j** (64 mg, 70%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.3 (PE: Et_2O = 8:1). Mp: 133-134 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 210 nm, 1 mL/min), t_R = 5.7 min, t_R = 7.0 min.

$[\alpha]^{20}_D$ = -107.8 (*c* = 1.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 6.4, 2.7 Hz, 2H), 7.16 - 7.13 (m, 3H), 7.05 - 6.99 (m, 1H), 6.93 - 6.91 (m, 2H), 6.64 - 6.60 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 2.30 (d, *J* = 6.6 Hz, 1H), 2.15 (dd, *J* = 7.1, 1.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

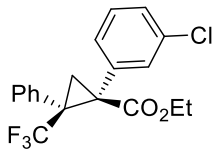
^{13}C NMR (75 MHz, CDCl3) δ: 169.1, 159.1, 134.7, 131.3, 131.2 (d, *J* = 0.7 Hz), 128.9, 128.3, 127.9, 125.4 (q, *J* = 275.7 Hz), 122.0, 115.6, 113.4, 61.9, 55.2, 41.0 (m), 39.4 (q, *J* = 32.3 Hz), 17.0 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 3108, 2940, 2837, 1604, 1581,1488, 1370, 1353, 1334, 1287, 1278, 1236, 1211,

1180, 1155, 1135, 1101,1101, 878, 859, 778, 769, 737, 510 cm^{-1}.

HRMS (AP+): calcd for $C_{20}H_{20}F_3O_3$ ($[M+H]^+$) 365.1365, found: 365.1378. (3.6 ppm)



Ethyl (1*S*,2*R*)-1-(3-chlorophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9k** (65 mg, 71%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 10:1). Mp: 74-75 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 4.8 min, t_R = 5.2 min.

$[\alpha]^{20}_D$ = -81 (*c* = 4.4, $CHCl_3$).

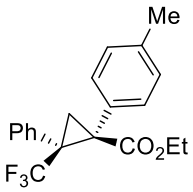
^{1}H NMR (300 MHz, CDCl3) δ: 7.28 (s, 1H), 7.22 – 7.15 (m, 3H), 7.11 – 7.07 (m, 3H), 7.00 – 6.92 (m, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.26 (d, *J* = 6.7 Hz, 1H), 2.07 (dd, *J* = 6.6, 1.0 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, CDCl3) δ: 168.6, 135.4, 133.8, 131.2, 130.8, 130.0, 129.2, 128.5, 128.11, 128.10, 128.0, 125.3 (q, *J* = 275.8 Hz), 62.2, 40.6 (m), 39.6 (q, *J* = 32.6 Hz), 16.9 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, CDCl3) δ: -65.5 (S).

IR (Neat): 2972, 1732, 1576, 1449, 1369, 1351, 1331, 1278, 1250, 1228, 1160, 1138, 1080, 1044, 860, 776, 765, 702, 682, 638, 590, 496, 445, 423 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}ClF_3O_2$ ($[M+H]^+$) 369.0869, found: 369.0865. (-1.1 ppm)



Ethyl (1*S*,2*R*)-1-(4-methylphenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9l** (61 mg, 70%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 89-90 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-

H column (*n*-heptane: *i*-PrOH = 98:2, 213 nm, 1 mL/min), t_R = 5.2 min, t_R = 6.7 min.

$[\alpha]^{20}_D$ = -77 (*c* = 4.5, $CHCl_3$).

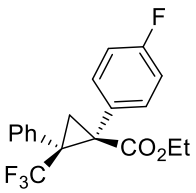
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (dd, *J* = 6.4, 2.7 Hz, 2H), 7.17 – 7.14 (m, 2H), m, 7.08 – 7.04 (3H), 6.83 (d, *J* = 7.9 Hz, 2H), 4.13 (dd, *J* = 7.1, 1.2 Hz, 2H), 2.21 (d, *J* = 6.5 Hz, 1H), 2.08 (s, 3H), 2.05 (dd, *J* = 6.5, 1.5 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 137.6, 131.4, 131.3, 130.2, 129.6, 128.8, 128.2, 127.9, 125.5 (q, *J* = 275.6 Hz), 61.8, 40.8 (m), 39.3 (q, *J* = 32.2 Hz), 21.0, 16.9 (q, *J* = 2.4 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ -66.0 (S).

IR (Neat): 3069, 2998, 1731, 1518, 1453, 1331, 1290, 1274, 1232, 1153, 1129, 1093, 1078, 1044, 1015, 820, 793, 741, 702, 676, 599, 513, 494, 414 cm^{-1}.

HRMS (ES+): calcd for $C_{20}H_{20}F_3O_2$ ($[M+H]^+$) 349.1415, found: 349.1417. (0.6 ppm)



Ethyl (1*S*,2*R*)-1-(4-fluorophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9m** (75 mg, 85%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.18 (PE: Et_2O = 90:10). Mp: 96-97 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.1 min, t_R = 5.2 min.

$[\alpha]^{20}_D$ = -72 (*c* = 4.9, $CHCl_3$).

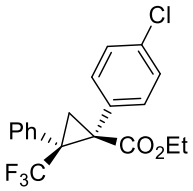
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 – 7.16 (m, 4H), 7.11 – 7.04 (m, 3H), 6.74 – 6.66 (m, 2H), 4.21 – 4.06 (m, 2H), 2.25 (d, *J* = 6.6 Hz, 1H), 2.05 (dd, *J* = 6.6, 1.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.0, 162.2 (d, *J* = 247.5 Hz), 131.6 (d, *J* = 8.3 Hz), 131.2, 131.1 (d, *J* = 0.5 Hz), 129.2 (d, *J* = 3.3 Hz), 128.4, 128.1, 125.4 (q, *J* = 275.7 Hz), 115.0 (d, *J* = 21.6 Hz), 62.0, 40.4 (m), 39.5 (q, *J* = 32.3 Hz), 17.0 (q, *J* = 2.6 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S), -113.9 (m).

IR (Neat): 3004, 2171, 1719, 1608, 1511, 1368, 1337, 1301, 1275, 1234, 1155, 1129, 1094, 1070, 1042, 1024, 865, 840, 803, 768, 746, 730, 706, 667, 637, 599, 522, 503, 428 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}F_4O_2$ ([M+H]$^+$) 353.1165, found: 353.1179. (-1.1 ppm)



Ethyl (1*S*,2*R*)-1-(4-chlorophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9n** (64 mg, 70%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.24 (PE: Et_2O = 90:10). Mp: 77-78 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.0 min, t_R = 5.2 min.

[α]$^{20}_D$ = -59 (*c* = 5.0, $CHCl_3$).

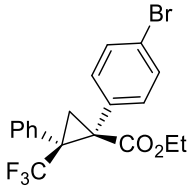
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 – 7.21 (m, 4H), 7.12 – 7.09 (m, 3H), 7.03 (d, *J* = 8.6 Hz, 2H), 4.25 – 4.10 (m, 2H), 2.29 (d, *J* = 6.6 Hz, 1H), 2.08 (d, *J* = 6.6 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 133.9, 131.9, 131.2, 131.1, 130.9, 128.5, 128.2, 128.2, 125.3 (q, *J* = 275.8 Hz), 62.1, 40.4 (m), 39.5 (q, *J* = 32.5 Hz), 16.9 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2996, 1729, 1495, 1450, 1351, 1332, 1292, 1231, 1139, 1092, 1041, 1011, 869, 842, 818, 772, 723, 702, 683, 636, 530, 496, 472, 403 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}ClF_3O_2$ ([M+H]$^+$) 369.0869, found: 369.0877. (2.2 ppm)



Ethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9o** (93 mg, 73%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.26 (PE: Et_2O = 90:10). Mp: 91-92 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.1 min, t_R = 5.3 min.

$[\alpha]^{20}_D$ = -82 (*c* = 4.5, $CHCl_3$).

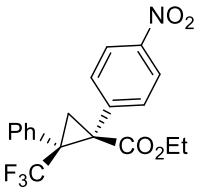
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.19 (dd, *J* = 6.3, 2.6 Hz, 2H), 7.16 - 7.15 (m, 4H), 7.07 – 7.05 (m, 3H), 4.18 – 4.05 (m, 2H), 2.25 (d, *J* = 6.6 Hz, 1H), 2.04 (dd, *J* = 6.6, 1.1 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.7, 132.6, 131.5, 131.23, 131.18, 130.9, 128.6, 128.2, 125.4 (q, *J* = 275.8 Hz), 122.2, 62.1, 40.6 (m), 39.6 (q, *J* = 32.5 Hz), 16.9 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 2998, 1728, 1488, 1369, 1350, 1331, 1290, 1276, 1233, 1150, 1135, 1096, 1075, 1042, 1026, 1008, 869, 839, 819, 767, 716, 678, 522, 492 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}BrF_3O_2$ ($[M+H]^+$) 413.0364, found: 413.0372. (-1.9 ppm)



Ethyl (1*S*,2*R*)-1-(4-nitrophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9p** (90 mg, 95%) was obtained as a pale yellow sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 8:1).

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 7.9 min, t_R = 8.8 min.

$[\alpha]^{20}_D$ = -79 (*c* = 2.4, $CHCl_3$).

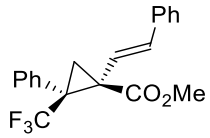
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 8.9 Hz, 2H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.19 (d, *J* = 3.4 Hz, 2H), 7.08 – 7.06 (m, 3H), 4.25 – 4.10 (m, 2H), 2.37 (d, *J* = 6.9 Hz, 1H), 2.18 (dd, *J* = 6.8, 0.8 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.0, 147.3, 140.7, 130.9, 130.7, 130.3, 128.8, 128.4, 125.1 (q, *J* = 276.0 Hz), 123.1, 62.5, 40.6 (m), 40.1 (q, *J* = 32.9 Hz), 17.1 (q, *J* = 2.5 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2984, 1732, 1702, 1604, 1521, 1451, 1369, 1346, 1298, 1263, 1228, 1158, 1140, 1093, 1043, 1015, 855, 763, 740, 636, 591, 528, 489 cm^{-1}.

HRMS (ES-): calcd for $C_{19}H_{16}ClF_3NO_4$ ($[M+Cl]^-$) 414.0720, found: 414.0718. (-0.5 ppm).



Methyl (1*S*,2*R*)-1-(2-phenylethenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9q** (43 mg, 50%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.17 (PE: Et_2O = 90:10). Mp: 64-65 ºC.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 213 nm, 1 mL/min), t_R = 4.3 min, t_R = 4.8 min.

$[\alpha]^{20}_D$ = -112 (*c* = 3.6, $CHCl_3$).

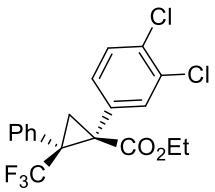
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 – 7.32 (m, 2H), 7.28 -7.22 (m, 3H), 7.13 - 7.07 (m, 3H), 6.96 (dd, *J* = 7.5, 1.8 Hz, 2H), 6.24 (d, *J* = 16.0 Hz, 1H), 5.63 (d, *J* = 16.0 Hz, 1H), 3.74 (s, 3H), 2.23 (d, *J* = 6.3 Hz, 1H), 1.67 (dd, *J* = 6.3, 1.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 136.2, 132.6, 131.8, 131.6 (d, *J* = 0.8 Hz), 128.9, 128.5, 128.4, 127.9, 126.3, 125.2, 125.1 (q, *J* = 273.8 Hz), 52.9, 39.7 (q, *J* = 32.7 Hz), 37.6 (m), 19.1 (q, *J* = 2.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.4 (S).

IR (Neat): 3140, 3017, 2956, 2093, 1733, 1449, 1436, 1338, 1262, 1242, 1199, 1173, 1132, 1151, 1071, 1049, 960, 750, 695, 638, 588, 507, 415 cm^{-1}.

HRMS (AP+): calcd for $C_{20}H_{18}F_3O_2$ ($[M+H]^+$) 347.1259, found: 347.1257. (-0.6 ppm)



Ethyl (1*S*,2*R*)-1-(3,4-dichlorophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **9r** (86 mg, 86%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 95-96 ºC.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 3.8 min, t_R = 4.4 min.

$[\alpha]^{20}_D$ = -76.3 (*c* = 7.3, $CHCl_3$).

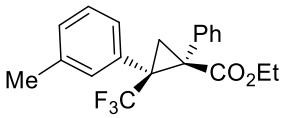
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 1.8 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.14 – 7.07 (m, 5H), 4.20 – 4.10 (m, 2H), 2.28 (d, *J* = 6.8 Hz, 1H), 2.04 (dd, *J* = 6.8, 1.3 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.3, 133.8, 132.2, 132.2, 131.8, 131.1, 130.6, 130.0, 129.2, 128.8, 128.3, 125.2 (q, *J* = 275.9 Hz), 62.31, 40.2 (m), 39.8 (q, *J* = 32.7 Hz), 17.0 (q, *J* = 2.4 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 3022, 1731, 1450, 1368, 1259, 1199, 1174, 1161, 1133, 1071, 1049, 1011, 959, 846, 829, 750, 725, 694, 702, 637, 507, 443, 415 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{16}Cl_2F_3O_2$ ($[M+H]^+$) 403.0479, found: 403.0482. (0.7 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(3-methylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10a** (68 mg, 73%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 75-76 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 4.2 min, t_R = 4.6 min.

$[\alpha]^{20}_D$ = -76 (*c* = 4.5, $CHCl_3$).

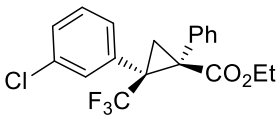
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 – 7.36 (m, 2H), 7.15 – 7.09 (m, 5H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.4 Hz, 1H), 4.23 (q, *J* = 6.9 Hz, 2H), 2.30 (d, *J* = 6.5 Hz, 1H), 2.20 (s, 3H), 2.16 (d, *J* = 6.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 137.4, 133.3, 132.1, 131.0, 129.7, 129.0, 128.4, 127.9, 127.8, 127.7, 125.5 (q, *J* = 275.6 Hz), 61.9, 40.9 (m), 39.3 (q, *J* = 32.3 Hz), 21.2, 16.8 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2985, 1722, 1447, 1330, 1271, 1243, 1206, 1053, 1139, 1151, 1094, 1053, 1021, 863, 785, 720, 700, 494, 446 cm^{-1}.

HRMS (ES+): calcd for $C_{20}H_{20}F_3O_2$ ($[M+H]^+$) 349.1415, found: 349.1423. (2.3 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(3-chlorophenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10b** (52 mg, 56%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10).

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 5.3 min, t_R = 6.3 min.

$[\alpha]^{20}_D$ = -53 (*c* = 2, $CHCl_3$).

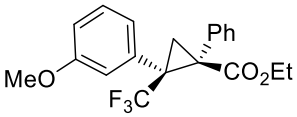
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 - 7.28 (m, 3H), 7.20 – 7.03 (m, 6H), 4.23 (q, *J* = 7.0 Hz, 2H), 2.33 (d, *J* = 6.7 Hz, 1H), 2.16 (dd, *J* = 6.5, 0.8 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 133.8, 133.3, 132.8, 131.4, 129.6, 129.5 (d, *J* = 86.6 Hz), 129.2, 128.6, 128.2, 128.1, 125.2 (q, *J* = 275.8 Hz), 62.0, 41.1 (m), 39.0 (q, *J* = 32.7 Hz), 16.8 (q, *J* = 2.4 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 2985, 1732, 1602, 1568, 1479, 1450, 1369, 1350, 1331, 1260, 1228, 1159, 1138, 1112, 1093, 1081, 1039, 859, 786, 761, 700, 513, 448, 425 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}ClF_3O_2$ ($[M+H]^+$) 369.0869, found: 369.0854. (-4.1 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(3-methoxyphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10c** (10 mg, 11%) was obtained as a colorless sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 8:1).

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 5.1 min, t_R = 5.8 min.

$[\alpha]^{20}_D$ = -51.3 (*c* = 2.1, $CHCl_3$).

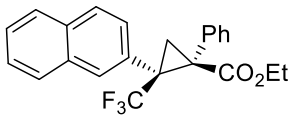
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.15 – 7.03 (m, 4H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 6.66 (dd, *J* = 8.2, 2.1 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 2.31 (d, *J* = 6.5 Hz, 1H), 2.17 (d, *J* = 6.2 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 158.9, 133.2, 132.6, 129.6, 128.9, 128.0, 127.9, 125.4 (q, *J* = 275.7 Hz), 123.7, 117.3, 113.7, 61.9, 55.2, 41.0 (m), 39.4 (q, *J* = 32.4 Hz), 16.9 (q, *J* = 2.4 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 2992, 1731, 1602, 1584, 1494, 1453, 1369, 1351, 1334, 1289, 1250, 1183, 1152. 1095, 1080, 1051, 1030, 860, 782, 734, 698, 495, 464 cm^{-1}.

HRMS (AP+): calcd for $C_{20}H_{20}F_3O_3$ ($[M+H]^+$) 365.1365, found: 365.1358. (-1.9 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(2-naphthalenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10d** (80 mg, 83%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.21 (PE: Et_2O = 90:10). Mp: 109-110 ºC.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.9 min, t_R = 5.7 min.

$[\alpha]^{20}_D$ = -87 (*c* = 3, $CHCl_3$).

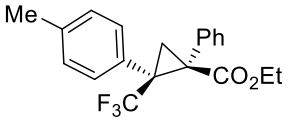
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 – 7.69 (m, 3H), 7.63 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.40 (m, 5H), 7.10 - 6.98 (m, 3H), 4.27 (q, *J* = 7.0 Hz, 2H), 2.43 (d, *J* = 6.5 Hz, 1H), 2.33 (d, *J* = 6.2 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2, 133.1, 132.8, 132.7, 131.1, 129.7, 128.9, 128.6, 128.1 (2), 127.9, 127.6, 127.5, 126.5, 126.1, 125.6 (q, *J* = 274.5 Hz), 62.0, 41.3 (m), 39.6 (q, *J* = 32.3 Hz), 17.1 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.2 (S).

IR (Neat): 3066, 2986, 1726, 1602, 1454, 1323, 1297, 1276, 1248, 1224, 1156, 1134, 1123, 1097, 1046, 1033, 1015, 957, 858, 735, 746, 699, 492 cm^{-1}.

HRMS (ES+): calcd for $C_{23}H_{23}NF_3O_2$ ($[M+NH_4]^+$) 402.1681, found: 402.1677. (-1.0 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(4-methylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10e** (61 mg, 70%) was obtained as a white solid after silica gel column chromatography (PE:

Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 97-98 °C.

Enantiomeric Excess: 96%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 4.3 min, t_R = 4.9 min.

$[\alpha]^{20}_D$ = -70 (*c* = 5.2, $CHCl_3$).

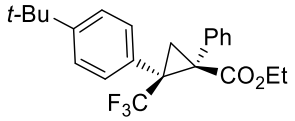
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 6.2 Hz, 2H), 7.23 - 7.11 (m, 5H), 6.97 (d, *J* = 7.8 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 2.34 (d, *J* = 6.4 Hz, 1H), 2.21 (s, 3H), 2.18 (d, *J* = 6.6 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 138.0, 133.4, 131.2, 129.8, 128.7, 128.1, 128.0, 127.8, 125.6 (q, *J* = 275.8 Hz), 61.9, 41.1, 39.1 (q, *J* = 32.3 Hz), 21.1, 16.9 (q, *J* = 2.6 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.6 (S).

IR (Neat): 3033, 2986, 1722, 1515, 1448, 1336, 1296, 1273, 1228, 1151, 1130, 1095, 1033, 1013, 865, 812, 736, 725, 698, 673, 624, 517, 488, 432 cm^{-1}.

HRMS (ES+): calcd for $C_{20}H_{20}F_3O_2$ ($[M+H]^+$) 349.1415, found: 349.1414. (-0.3 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(4-*tert*-butylphenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10f** (81 mg, 83%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.21 (PE: Et_2O = 10:1). Mp: 67-68 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 3.9 min, t_R = 4.5 min.

$[\alpha]^{20}_D$ = -62 (*c* = 6.3, $CHCl_3$).

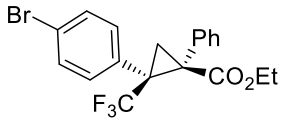
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.04 (m, 5H), 4.27 – 4.17 (m, 2H), 2.30 (d, *J* = 6.5 Hz, 1H), 2.15 (dd, *J* = 6.4, 0.7 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.19 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.3, 151.1, 133.4, 130.9, 129.7, 128.0, 127.9, 127.6, 125.6 (q, *J* = 275.6 Hz), 124.8, 61.8, 41.0 (m), 39.0 (q, *J* = 32.3 Hz), 34.4, 31.1, 16.9 (q, *J* = 2.6 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2966, 2865, 1729, 1468, 1353, 1336, 1263, 1230, 1174, 1155, 1112, 1082, 1019, 832, 744, 730, 697, 688, 594, 559, 494, 472 cm^{-1}.

HRMS (ES+): calcd for $C_{23}H_{26}F_3O_2$ ($[M+H]^+$) 391.1885, found: 391.1873. (-3.1 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(4-bromophenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10g** (85 mg, 82%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.2 (PE: Et_2O = 90:10). Mp: 80-81 ºC.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 5.6 min, t_R = 6.9 min.

$[\alpha]^{20}_D$ = -51.2 (*c* = 3.2, $CHCl_3$).

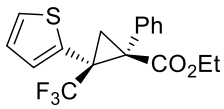
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 – 7.34 (m, 2H), 7.28 – 7.25 (m, 2H), 7.17 - 7.13 (m, 5H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.32 (d, *J* = 6.6 Hz, 1H), 2.13 (d, *J* = 6.6 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.9, 133.0, 132.8, 131.2, 130.4, 129.6, 128.2, 128.1, 125.2 (q, *J* = 275.7 Hz), 122.7, 62.0, 41.0 (m), 38.9 (q, *J* = 32.6 Hz), 16.9 (q, *J* = 2.5 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.6 (S).

IR (Neat): 2923, 1726, 1458, 1377, 1228, 1169, 1127, 1010, 721, 699, 511 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{17}BrF_3O_2$ ($[M+H]^+$) 413.0364, found: 413.0373. (2.2 ppm)



Ethyl (1*S*,2*R*)-1-phenyl-2-(2-thienyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10h** (51 mg, 60%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.23 (PE: Et_2O = 90:10). Mp: 72-73 ºC.

Enantiomeric Excess: 95%. The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.4 min, t_R = 5.1 min.

$[\alpha]^{20}_D$ = -16.6 (*c* = 2.2, $CHCl_3$).

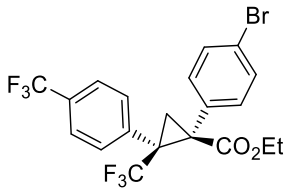
^{1}H NMR (300 MHz, $CDCl_3$) δ:7.40 (dd, *J* = 6.5, 2.8 Hz, 2H), 7.16 – 7.14 (m, 3H), 7.05 (d, *J* = 5.0 Hz, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 6.77 (dd, *J* = 4.8, 3.9 Hz, 1H), 4.27 – 4.10 (m, 2H), 2.42 (d, *J* = 6.6 Hz, 1H), 2.18 (d, *J* = 6.5 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.6, 134.2, 133.2, 130.2, 129.6, 128.1, 128.0, 126.7, 126.1, 125.0 (q, *J* = 275.6 Hz), 62.0, 42.8 (m), 34.6 (q, *J* = 34.0 Hz), 19.2 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.9 (S).

IR (Neat): 2986, 1732, 1690, 1450, 1368, 1349, 1314, 1269, 1213, 1149, 1135, 1093, 1077, 1018, 859, 734, 696, 613, 509 cm^{-1}.

HRMS (AP+): calcd for $C_{17}H_{16}SF_3O_2$ ($[M+H]^+$) 341.0823, found: 341.0834. (3.2 ppm)



Ethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-(4-trifluoromethylphenyl)-2-(trifluoromethyl)cyclopropane -1-carboxylate **10i** (76 mg, 63%) was obtained as a white solid after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.19 (PE: Et_2O = 90:10). Mp: 67-68 °C.

Enantiomeric Excess: 99%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 7.4 min, t_R = 8.1 min.

$[\alpha]^{20}_D$ = -67 (*c* = 3.0, $CHCl_3$).

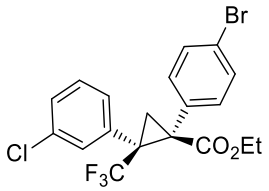
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38 – 7.32 (m, 4H), 7.22 – 7.14 (m, 4H), 4.19 - 4.12 (m, 2H), 2.32 (d, *J* = 6.8 Hz, 1H), 2.06 (d, *J* = 6.7 Hz, 1H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.2, 135.0, 131.8, 131.6, 131.5, 131.2, 130.7 (q, *J* = 32.7 Hz), 125.2 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 224.2 Hz), 123.7 (d, *J* = 272.4 Hz), 122.6, 62.3, 40.6 (m), 39.2 (q, *J* = 32.9 Hz), 16.9 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -62.8 (S), -65.4 (S).

IR (Neat): 2985, 1727, 1615, 1489, 1326, 1282, 1233, 1159, 1138, 1157, 1084, 1069, 1037, 1008, 869, 837, 815, 762, 716, 679, 607, 522, 500, 420, 410 cm^{-1}.

HRMS (AP+): calcd for $C_{22}H_{19}NBrF_6O_2$ ($[M+H+ACN]^+$) 522.0503, found: 522.0494. (-1.7 ppm)



Ethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-(3-chlorophenyl)-2-(trifluoromethyl)cyclopropane-1-carboxylate **10j** (74 mg, 66%) was obtained as a pale-yellow sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.22 (PE: Et_2O = 90:10).

Enantiomeric Excess: 92%. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.7 min, t_R = 5.2 min.

$[\alpha]^{20}_D$ = -64 (*c* = 2.5, $CHCl_3$).

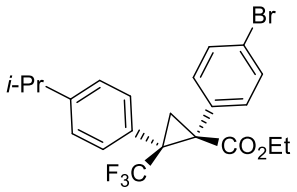
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 – 7.20 (m, 5H), 7.17 – 7.10 (m, 3H), 4.30 - 4.22 (m, 2H), 2.38 (d, *J* = 6.8 Hz, 1H), 2.14 (d, *J* = 6.1 Hz, 1H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.3, 134.0, 132.9, 132.0, 131.4, 131.3, 131.2 (2), 129.4, 128.9, 125.0 (q, *J* = 275.9 Hz), 122.5, 62.2, 40.6 (m), 39.1 (q, *J* = 32.8 Hz), 16.9 (q, *J* = 2.4 Hz), 13.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.4 (S).

IR (Neat): 2985, 1732, 1568, 1490, 1369, 1332, 1281, 1258, 1228, 1159, 1140, 1078, 1039, 1008, 860, 837, 785, 755, 719, 637, 458, 443, 427 cm^{-1}.

HRMS (AP+): calcd for $C_{19}H_{16}BrClF_3O_2$ ($[M+H]^+$) 446.9974, found: 446.9984. (+2.2 ppm)



Ethyl (1*S*,2*R*)-1-(4-bromophenyl)-2-(4-*iso*-propylphenyl)-2-(trifluoromethyl) cyclopropane -1-carboxylate **10k** (85 mg, 75%) was obtained as a pale-yellow sticky oil after silica gel column chromatography (PE: Et_2O = 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.233 (PE: Et_2O = 90:10).

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.4 min, t_R = 4.6 min.

$[\alpha]^{20}_D$ = -65 (*c* = 3.1, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.17 - 7.15 (m, 4H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 2H), 4.17 – 4.07 (m, 2H), 2.68 (m, 1H), 2.23 (d, *J* = 6.6 Hz, 1H), 2.00 (dd, *J* = 6.5, 1.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 149.1, 132.7, 131.5, 131.1, 131.0, 128.0, 126.2, 125.4 (q, *J* = 274.1 Hz), 122.0, 62.0 , 40.6 (d, *J* = 1.0 Hz), 39.2 (q, *J* = 32.4 Hz), 33.6, 23.7 (m), 17.0 (q, *J* = 2.4 Hz), 13.9.

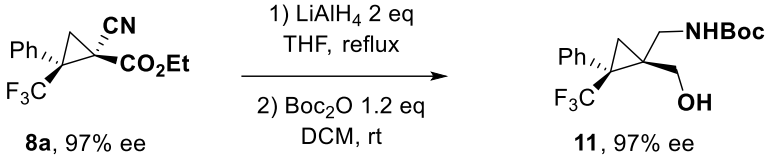
^{19}F NMR (282 MHz, $CDCl_3$) δ: -65.5 (S).

IR (Neat): 2962, 1733, 1594, 1490, 1368, 1350, 1333, 1258. 1228, 1128, 1139, 1077, 1037, 1010, 864, 829, 762, 758, 716, 597, 521, 502 cm^{-1}.

HRMS (AP+): calcd for $C_{22}H_{23}BrF_3O_2$ ($[M+H]^+$) 455.0834, found: 455.0822. (-2.6 ppm)

Preparation of 11

General procedure G Preparation of **11**



8a, 97% ee — **11**, 97% ee

A solution of **8a** (70.8 mg, 0.25mmol, 1.0 equiv., 96% ee) in dry THF (0.5 mL) was added to a oven-dried reaction tube equipped with condenser and a magnetic stirring bar. $LiAlH_4$ (0.5 mL, 1 M in THF) was added dropwise at room temperature and the reaction mixture was refluxed for 1 h. Then the reaction was cool down to 0 °C with an ice bath. Then, MeOH (0.5 mL) was slowly added to quench the reaction, water (50 mL) was added and the reaction mixture was extracted with EtOAc (3 x 30 mL), dried with Na_2SO_4 and concentrated under vacuum. The crude product was dissolved in DCM (0.5 mL), Boc_2O (81.8 mg, 0.38 mmol, 1.5 eq) was added and the reaction was stirred at room temperature overnight. Then, water (50 mL) was added to the mixture, extracted with EtOAc (3 x 30 mL), dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash chromatography (SiO_2, PE/EtOAc = 15:1 to 3:1) to provide *tert*-butyl ((1*R*,2*R*)-1-(hydroxymethyl)-2-phenyl-2-(trifluoromethyl) cyclopropyl)methyl carbamate **11** as a white solid in 49% yield (42.3 mg), Rf = 0.5 (PE/EtOAc = 2:1). Mp: 125-126 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 10.7 min, t_R = 14.7 min.

$[\alpha]^{20}_D$ = -54.1 (c = 5.9, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 - 7.41 (m, 1H), 7.35 – 7.29 (m, 3H), 7.21 - 7.19 (m, 1H), 4.61 (t, *J* = 5.7 Hz, 1H), 3.87 (t, *J* = 10.2 Hz, 2H), 3.76 (d, *J* = 6.3 Hz, 1H), 2.99 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.53 (dd, *J* = 15.0, 6.1 Hz, 1H), 1.51 (d, *J* = 6.1 Hz, 1H), 1.36 (s, 9H), 1.26 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.5, 133.7, 130.5, 129.1, 128.5, 126.2 (q, *J* = 275.8 Hz), 80.4, 60.4 (m), 42.8 (m), 37.5 (q, *J* = 32.4 Hz), 33.3, 28.3, 18.0 (q, *J* = 5.5 Hz).

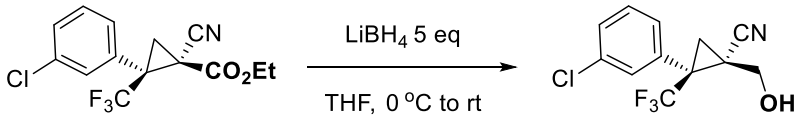
^{19}F NMR (282 MHz, $CDCl_3$) δ: -59.7 (S).

IR (Neat): 3397, 3274, 1682, 1543, 1367, 1282, 1267, 1176, 1146, 1132, 1039, 897, 764, 704, 664, 583 cm^{-1}.

HRMS **(ES-):** calcd for $C_{13}H_{10}NClF_3O_3$ ($[M+HCO_2]^-$) 320.0301, found: 320.0287. (-4.4 ppm)

Preparation of 12

General procedure H Preparation of **12**



8d, 97% ee **12**, 98% ee

To a solution of **8d** (70.8 mg, 0.25 mmol, 1.0 equiv., 97% ee) in dry THF (0.5 mL) at 0 °C was added $LiBH_4$ (27 mg, 5 equiv.) and the reaction mixture was slowly warmed up to room temperature and stirred overnight. Then the reaction mixture was quenched with MeOH (0.2 mL) at 0 °C, extracted with EtOAc (3 x 20 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (SiO_2, PE/EtOAc = 15:1 to 5:1) to provide (1*R*, 2*R*)-2-(3-chlorophenyl)-1-(hydroxymethyl)-2-(trifluoromethyl)cyclopropane-1-carbonitrile **12** as a white solid in 80% yield (55 mg), Rf = 0.3 (PE/EtOAc = 4:1). Mp: 121-122 °C.

Enantiomeric Excess: 98%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 9.1 min, t_R = 9.7 min.

$[\alpha]^{20}_D$ = +54 (c = 1.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.40 (m, 4H), 4.15 (dd, *J* = 12.3, 6.0 Hz, 1H), 4.01 (dd, *J* = 12.4, 5.3 Hz, 1H), 2.39 (s, 1H), 2.02 (dd, *J* = 6.6, 1.6 Hz, 1H), 1.97 (d, *J* = 6.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.8, 133.4, 130.9, 130.3, 130.2, 129.1, 124.3 (q, *J* = 276.3 Hz), 118.5, 61.5 (q, *J* = 3.3 Hz), 38.2 (q, *J* = 34.4 Hz), 26.2, 20.5 (q, *J* = 2.5 Hz).

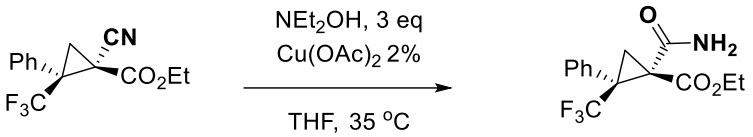
^{19}F NMR (282 MHz, $CDCl_3$) δ: -62.0 (S).

IR (Neat): 3495, 2250, 1269, 1150, 794, 782, 705, 769, 573, 464, 439 cm^{-1}.

HRMS (ES-): calcd for $C_{13}H_{10}NClF_3O_3$ ($[M+HCO_2]^-$) 320.0301, found: 320.0287. (-4.4 ppm)

Preparation of 13

General procedure I Preparation of **13**



8a, 98% (> 20:1)
97% ee

13, 98% (> 20:1)
97% ee

An oven-dried reaction tube equipped with a magnetic stirring bar was charged with $Cu(OAc)_2$ (0.9 mg, 2 mmol%) and **8a** (70.8 mg, 0.25 mmol, 1.0 equiv., 96% ee), NEt_2OH (66.8 mg, 075 mmol, 3.0 equiv.) in dry THF (0.25 mL) was added. The reaction mixture was stirred at 35 °C for 3 h. Then, the solvent was removed under vacuum and crude product was purified by flash chromatography (SiO_2, PE/EtOAc = 10:1 to 1:1) to provide the desired amide[138] ethyl (1*R*, 2*R*)-1-carbamoyl-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **13** as a white solid in 90% yield (67.7 mg), Rf = 0.4 (PE/EtOAc = 1:1), Mp: 142-143 °C.

Enantiomeric Excess: 97%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 10.9 min, t_R = 14.3 min.

$[\alpha]^{20}_D$ = -166.0 (c = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44 – 7.41 (m, 2H), 7.35 – 7.31 (m, 3H), 7.24 (s, 1H), 5.75 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.46 (dd, *J* = 6.0, 1.5 Hz, 1H), 2.20 (d, *J* = 6.1 Hz, 1H), 1.33 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.5, 164.3, 130.9, 130.5, 129.1, 128.4, 124.6 (q, *J* = 276.2 Hz), 62.8, 41.0 (q, *J* = 33.8 Hz), 39.8, 16.3 (q, *J* = 2.1 Hz), 13.7.

^{19}F NMR (282 MHz, $CDCl_3$) δ: -66.1 (S).

IR (Neat): 3427, 3240, 1714, 1693, 1371, 1319, 1276, 1161, 1055, 723, 703, 573, 429 cm^{-1}.

HRMS **(AP+):** calcd for $C_{14}H_{15}NF_3O_3$ ($[M+H]^+$) 302.1004, found: 302.1014. (3.3 ppm)

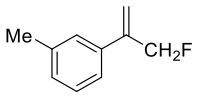
Synthesis of α-CH_2F-stryenes

general procedure J Synthesis of α-CH_2F-stryenes

To a solution of Selectfluor (3.2 g, 9 mmol, 0.9 equiv.) in dry DMF (30 mL), the corresponding α-methyl styrenes (10 mmol, 1.0 equiv.) was added dropwise at room temperature under

argon. Then the solution was stirred at 75 °C for 4 h. Water (150 mL) was added after the mixture was cooled down to room temperature and extracted with *n*-pentane (3 x 50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (*n*-pentane) to deliver the desired α-CH_2F-stryenes.[182]

α-Monofluoromethyl styrene **15a**,[182] α-monochloromethyl styrene **15b** [183] and α-monobromomethyl styrene **15c**[184] were prepared according to the literature and analytic data is the same as described in the literature.



1-(1-(Fluoromethyl)ethenyl)-3-methylbenzene **15e** was obtained as a colorless oil after silica gel column chromatography (pentane). Rf = 0.72 (PE).

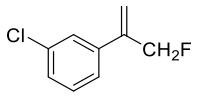
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 4H), 5.66 (s, 1H), 5.48 (d, *J* = 1.9 Hz, 1H), 5.30 (d, *J* = 47.2 Hz, 2H), 2.45 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3 (d, *J* = 14.6 Hz), 138.3, 137.4 (d, *J* = 2.1 Hz), 129.1, 128.6, 126.8, 123.2, 115.3 (d, *J* = 10.7 Hz), 84.6 (d, *J* = 169.1 Hz), 21.6.

^{19}F NMR (282 MHz, $CDCl_3$) δ -212.6 (td, *J* = 47.1, 2.9 Hz).

IR (Neat) 2924, 1134, 1030, 987, 949, 905, 882, 791, 726, 684, 644, 618, 512, 444 cm^{-1}.

HRMS (EI+) calcd for $C_{10}H_{11}F$ ($[M]^+$) 150.0845, found: 150.0857 (8.17 ppm)



1-(1-(Fluoromethyl)ethenyl)-3-chlorobenzene **15f** was obtained as a colorless oil after silica gel column chromatography (pentane). Rf = 0.70 (PE).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.35 – 7.29 (m, 3H), 5.63 (s, 1H), 5.47 (m, 1H), 5.20 (dd, *J* = 47.1, 0.9 Hz, 2H).

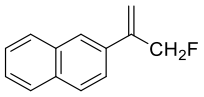
^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1 (d, *J* = 14.9 Hz), 139.3 (d, *J* = 1.9 Hz), 134.7, 130.0, 128.4, 126.4, 124.3, 117.0 (d, *J* = 10.4 Hz), 84.3 (d, *J* = 169.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -213.0 (td, *J* = 47.1, 3.3 Hz).

[182] H. Q. Luo, T. P. Loh, *Tetrahedron Letters,* **2009***, 50*, 1554–1556.
[183] M. Yamanaka, M. Arisawa, A. Nishida, M. Nakagawa, *Tetrahedron Letters*, **2002**, *43*, 2403–2406.
[184] X. Dong, Y. Han, F. C. Yan, Q. Liu, P. Wang, K. X. Chen, Y. Y. Li, Z. D. Zhao, Y. H. Dong, H. Liu, *Org. Lett*. **2016**, *18*, 3774-3777.

IR (Neat) 1595, 1563, 1478, 1417, 1129, 1097, 1082, 1030, 1061, 1009, 988, 946, 924, 882, 811, 788, 725, 689, 676, 614, 516, 447, 414, 388 cm^{-1}.

HRMS (EI+) calcd for C_9H_8FCl ($[M]^+$) 170.0299, found: 170.0289. (-5.89 ppm)



2-(1-(Fluoromethyl)ethenyl)naphthalene **15g** was obtained as a white solid after silica gel column chromatography (pentane). Rf = 0.57 (PE). Mp: 42-43 °C.

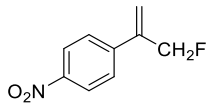
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 4H), 7.64 (d, *J* = 1.4 Hz, 1H), 7.51 – 7.48 (m, 2H), 5.78 (s, 1H), 5.54 (d, *J* = 2.1 Hz, 1H), 5.42 (d, *J* = 48.0 Hz, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8 (d, *J* = 14.6 Hz), 134.5 (d, *J* = 2.1 Hz), 133.3, 133.1, 128.3, 128.2, 127.6, 126.4, 126.3, 124.9, 123.9, 115.9 (d, *J* = 10.6 Hz), 84.5 (d, *J* = 169.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -212.4 (td, *J* = 47.2, 2.3 Hz).

IR (Neat) 1597, 1506, 1273, 1086, 1026, 986, 957, 916, 894, 857, 816, 716, 680, 559, 472 cm^{-1}.

HRMS (EI+) calcd for $C_{13}H_{11}F$ ($[M]^+$) 186.0845, found: 186.0853. (4.35 ppm)



1-(1-(Fluoromethyl)ethenyl)-4-nitrobenzene **15h** was obtained as a pale yellow solid after silica gel column chromatography (pentane/Et_2O: 100:1). Rf = 0.51 (PE). Mp: 44-45 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 5.71 (s, 1H), 5.56 (d, *J* = 3.4 Hz, 1H), 5.19 (d, *J* = 47.1 Hz, 2H).

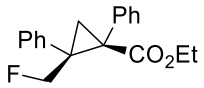
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 143.7, 141.4 (d, *J* = 15.1 Hz), 126.8, 123.9, 119.6 (d, *J* = 10.1 Hz), 83.9 (d, *J* = 169.6 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -212.1 (td, *J* = 47.0, 3.5 Hz).

IR (Neat) 1597, 1510, 1423, 1340, 1192, 1104, 1029, 1011, 984, 933, 855, 769, 752, 715, 681, 644, 530 cm^{-1}.

HRMS (EI+) calcd for $C_9H_8FNO_2$ ($[M]^+$) 181.0539, found: 181.0523. (-8.92 ppm)

General procedure K The preparation of monohalomethyl cyclopropanes is similar as the general procedure F using different α-monohalomethyl styrenes.



Ethyl (1*S*,2*R*)-2-(fluoromethyl)-1,2-diphenylcyclopropane-1-carboxylate **16a** (69.7 mg, 93%) was obtained as a colorless oil after silica gel column chromatography (PE/Et_2O 100:0 to 90:10). The diastereomeric ratio (>20:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.27 (PE/Et_2O = 10:1).

Enantiomeric Excess 96%. The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 5.3 min, t_R = 5.6 min.

$[\alpha]^{20}_D$ = +42.6 (c = 5.3, $CHCl_3$).

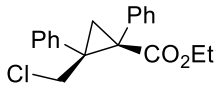
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 – 7.07 (m, 5H), 7.04 – 6.93 (m, 5H), 4.93 – 4.69 (m, 2H), 4.21 – 3.96 (m, 2H), 2.14 – 2.07 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 137.3, 135.3, 131.5, 128.9 (d, *J* = 1.5 Hz), 128.0, 127.4, 127.03, 127.02, 87.5 (d, *J* = 171.6 Hz), 61.8, 40.9 (d, *J* = 5.3 Hz), 38.8 (d, *J* = 21.1 Hz), 20.7 (d, *J* = 7.5 Hz), 14.1.

^{19}F NMR (282 MHz, $CDCl_3$) δ -210.0 (td, *J* = 47.9, 5.1 Hz).

IR (Neat) 2983, 1714, 1498, 1465, 1450, 1389, 1367, 1291, 1257, 1202, 1129, 1095, 1061, 1018, 989, 860, 785, 763, 742, 695, 648, 602, 556, 546, 507 cm^{-1}.

HRMS (AP+) calcd for $C_{19}H_{20}FO_2$ ($[M+H]^+$) 299.1447, found: 299.1440. (-2.3 ppm)



Ethyl (1*S*,2*R*)-2-(chloromethyl)-1,2-diphenylcyclopropane-1-carboxylate **16b** (50.2 mg, 64%) was obtained as a yellow solid after silica gel column chromatography (PE/Et_2O 100:0 to 90:10). The diastereomeric ratio (>20:1) was determined by ^{1}H NMR of the crude mixture. Rf = 0.28 (PE/Et_2O =10:1). Mp: 75-76 °C.

Enantiomeric Excess 92%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/*i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 5.2 min, t_R = 5.5 min.

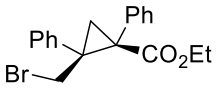
$[\alpha]^{20}_D$ = +33.9 (c = 3.8, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 4H), 7.15 – 7.01 (m, 6H), 4.34 (d, *J* = 11.3 Hz, 1H), 4.29 – 4.10 (m, 2H), 3.93 (d, *J* = 11.3 Hz, 1H), 2.24 (dd, *J* = 14.8, 6.0 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 137.1, 135.3, 131.2, 129.4, 127.9, 127.5, 127.2, 127.1, 61.9, 51.1, 43.5, 40.4, 23.0, 14.2.

IR (Neat) 1704, 1497, 1448, 1366, 1293, 1272, 1250, 1213, 1167, 1131, 1114, 1082, 1057, 1038, 1025, 1005, 928, 871, 781, 765, 751, 718, 556, 527, 495, 467, 427 cm^{-1}.

HRMS (AP+) calcd for $C_{19}H_{20}ClO_2$ ($[M+H]^+$) 315.1152, found: 315.1147. (-1.6 ppm)



Ethyl (1*S*,2*R*)-2-(bromomethyl)-1,2-diphenylcyclopropane-1-carboxylate **16c** (57.3 mg, 64%) was obtained as a white solid after silica gel column chromatography (PE/Et_2O 100:0 to 90:10). The diastereomeric ratio (17:1) was determined by ^1H NMR of the crude mixture. Rf = 0.30 (PE/Et_2O =10:1). Mp: 90-92 °C.

Enantiomeric Excess 90%. The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/*i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 5.3 min, t_R = 5.6 min.

$[\alpha]^{20}_D$ = +30.3 (c =4.9, $CHCl_3$).

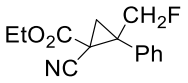
^1H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 4H), 7.15 – 7.00 (m, 6H), 4.32 – 4.11 (m, 3H), 3.83 (d, *J* = 10.3 Hz, 1H), 2.31 (dd, *J* = 6.0, 0.8 Hz, 1H), 2.18 (d, *J* = 6.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 137.2, 135.4, 131.1, 129.3, 127.9, 127.5, 127.2, 127.1, 61.9, 45.5, 40.5, 40.4, 23.8, 14.2.

IR (Neat) 1712, 1497, 1449, 1367, 1290, 1250, 1206, 1150, 1126, 1080, 1052, 1024, 1005, 994, 861, 800, 756, 695, 662, 638, 619, 569, 553, 512, 488 cm^{-1}.

HRMS (AP+) calcd for $C_{19}H_{20}BrO_2$ ($[M+H]^+$) 359.0647, found: 359.0654. (1.9 ppm)

General procedure L The preparation of cyclopropanes **17** and **18** is similar as the general procedure F using different styrenes.



Ethyl 1-cyano-2-(difluoromethyl)-2-phenylcyclopropane-1-carboxylate **17** (60.5 mg, 98%) was obtained as a white solid after silica gel column chromatography (PE/Et_2O 100:0 to 90:10). The diastereomeric ratio (1:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.30 (PE/Et_2O =10:1). Mp: 49-50 °C.

Enantiomeric Excess 64% (t_R = 8.4 min, t_R = 8.7 min), 22% (t_R = 9.1 min, t_R = 9.6 min). The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane/*i*-PrOH = 95:5, 220 nm, 1 mL/min).

$[\alpha]^{20}_D$ = +9.4 (c =3.5, $CHCl_3$).

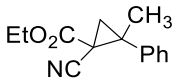
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 – 7.37 (m, 5H), 7.37 – 7.26 (m, 5H), 4.80 (ddd, *J* = 21.7, 10.9, 8.8 Hz, 2H), 4.64 (ddd, *J* = 21.8, 11.0, 8.6 Hz, 2H), 4.42 – 4.27 (m, 2H), 3.98 (qq, *J* = 10.8, 7.1 Hz, 2H), 2.46 (dd, *J* = 5.7, 4.5 Hz, 1H), 2.27 (dd, *J* = 5.7, 1.7 Hz, 1H), 2.18 (t, *J* = 5.9 Hz, 1H), 1.99 (dd, *J* = 5.8, 0.8 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). (mixture of two diastereoisomer)

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 164.0, 135.8, 134.0, 129.5, 129.4, 129.2, 129.0, 128.9, 128.8, 116.8, 116.6, 86.2 (d, *J* = 179.9 Hz), 84.1 (d, *J* = 174.4 Hz), 63.5, 63.0, 43.5 (d, *J* = 20.8 Hz), 42.8 (d, *J* = 21.8 Hz), 25.4 (d, *J* = 7.6 Hz), 25.3 (d, *J* = 6.1 Hz), 25.0 (d, *J* = 3.7 Hz), 23.3 (d, *J* = 6.4 Hz), 14.0, 13.9. (mixture of two diastereoisomer)

^{19}F NMR (282 MHz, $CDCl_3$) δ -215.81 (td, *J* = 46.9, 5.8 Hz), -216.38 (td, *J* = 47.2, 4.4 Hz) (two diastereoisomer)

IR (Neat) 2984, 2243, 1740, 1449, 1370, 1303. 1243, 1191, 1109,1012, 856, 767, 703. 553, 430 cm^{-1}.

HRMS (AP+) calcd for $C_{14}H_{15}NO_2F$ ($[M+H]^+$) 248.1087, found: 248.1080. (-2.8 ppm)



Ethyl 1-cyano-2-methyl-2-phenylcyclopropane-1-carboxylate **18** (60.5 mg, 98%) was obtained as a colorless sticky oil after silica gel column chromatography (PE/Et_2O 100:0 to 90:10). The diastereomeric ratio (3.6:1) was determined by ^{1}H NMR of the crude mixture. Rf = 0.33 (PE/Et_2O =10:1).

Enantiomeric Excess 0%, 0% The enantiomeric excess was determined by HPLC with an IE-H column (*n*-heptane/*i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 12.0 min, t_R = 13.2 min, t_R = 14.3 min (only observe three peaks on HPLC chromatogram, and the ratio of three peaks are the same in racemic and chiral reaction).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 5H), 3.96 – 3.76 (m, 2H), 2.38 (d, *J* = 5.4 Hz, 1H), 1.70 (s, 3H), 1.67 (d, *J* = 5.4 Hz, 1H), 0.95 (t, *J* = 7.1 Hz, 3H). (major)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 6.97 (m, 5H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.05 (q, *J* = 5.5 Hz, 2H), 1.52 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). (minor)

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 164.9, 140.1, 138.7, 129.0, 128.7, 128.4, 128.3, 128.0, 118.0, 117.7, 63.0, 62.5, 41.4, 40.8, 27.4, 27.3, 26.7, 26.3, 26.2, 20.9, 14.3, 13.9. (mixture of two diastereoisomer)

IR (Neat) 2982, 2934, 2240, 1733, 1260 cm^{-1}.

HRMS (AP-) calcd for $C_{14}H_{15}NO_2$ ($[M]^+$) 229.1103, found: 229.1108. (2.2 ppm)

Saponification of 6a, 6f, 6g and 9p

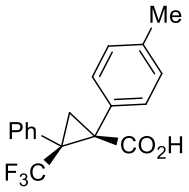
General procedure M Saponification of **6f**

KOH (2.5 g, 45 mmol, 5.0 equiv.) was added to a solution of cyclopropane ester **6f** (5 mmol, 1.0 equiv.) in EtOH (40 mL). The reaction mixture stirred at room temperature overnight. Water (250 mL) was added to the mixture at 0 °C, then neutralized with HCl (2 M) to pH = 1. Extracted with EtOAc (3 x 60 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (SiO_2, PE/EtOAc = 3:1 to 1:1 (1% AcOH)) to provide the corresponding carboxylic acid.

Saponification of 9l and 9o

General procedure N Saponification of **9l**, **9o** and **9p**

t-BuOK (2.0 g, 17.6 mmol, 2.2 equiv.) was added to a solution of cyclopropane (8 mmol, 1.0 equiv.) in dry DMSO (16 mL). The reaction mixture stirred at room temperature overnight. Water (250 mL) was added to the mixture at 0 °C, then neutralized with HCl (2 M) to pH = 3. Extracted with EtOAc (3 x 60 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (SiO_2, PE/EtOAc = 3:1 to 1:1 (1% AcOH)) to provide the corresponding carboxylic acid.



(1*S*,2*R*)-1-(4-methylphenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylic acid **19a** (1.8 g, 72%) was obtained as a white solid, Rf = 0.17 (1% AcOH of PE/EtOAc =1:1). Mp: 148-149 °C. **$[\alpha]^{20}_D$** = -2.2 (c =7.6, $CHCl_3$).

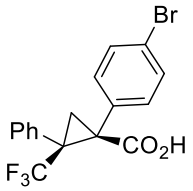
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.24 – 7.16 (m, 4H), 7.08 – 7.06 (m, 3H), 6.85 (d, *J* = 8.0 Hz, 2H), 2.26 (d, *J* = 6.5 Hz, 1H), 2.10-2.08 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 137.9, 131.3, 131.0, 129.8, 129.4, 128.9, 128.3, 128.0, 125.3 (d, *J* = 275.7 Hz), 40.4 (d, *J* = 0.9 Hz), 39.8 (d, *J* = 32.4 Hz), 21.0, 16.8 (dd, *J* = 4.6, 2.0 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.4.

IR (Neat) 3448, 25.5, 1683, 1336, 1250, 1180, 1164, 1139, 1020, 761, 730, 699, 680, 638, 500, 412 cm^{-1}.

HRMS (ES-) calcd for $C_{18}H_{14}F_3O_2$ ($[M-H]^-$) 319.0946, found: 319.0591. (1.6 ppm)



(1*S*,2*R*)-1-(4-bromophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylic acid **19b** (1.6 g, 54%) was obtained as a white solid, Rf = 0.17 (1% AcOH of PE/EtOAc =1:1). Mp: 159-160 °C. **$[\alpha]^{20}_D$** = -7.1 (c =10.1, $CHCl_3$).

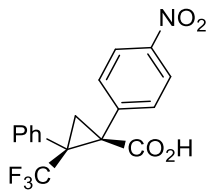
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.17 (m, 6H), 7.14 – 6.95 (m, 3H), 2.31 (d, *J* = 6.7 Hz, 1H), 2.08 (d, *J* = 6.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 131.7, 131.4, 131.1, 130.5, 130.0, 128.7, 128.2, 125.2 (q, *J* = 275.9 Hz), 122.6, 40.2, 40.0 (q, J = 33.0 Hz), 16.8.

^{19}F NMR (282 MHz, $CDCl_3$) δ -65.3.

IR (Neat) 3429, 2512, 1681, 1710, 1489, 1250, 1180, 1152, 1142, 1011, 757, 731, 700, 677, 635, 498 cm^{-1}.

HRMS (ES-) calcd for $C_{17}H_{11}BrF_3O_2$ ($[M-H]^-$) 382.9895, found: 382.9904. (2.3 ppm)



(1*S*,2*R*)-1-(4-nitrophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylic acid **19c** (0.8 g, 30%) was obtained as a yellow solid, Rf = 0.12 (1% AcOH of PE/EtOAc =1:1). Mp: 212-214 °C. **$[\alpha]^{20}_D$** = -3.5 (c =0.5, $CHCl_3$).

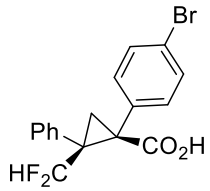
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 30.0 Hz, 5H), 2.50 (d, *J* = 5.2 Hz, 1H), 2.18 (d, *J* = 6.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 147.7, 140.6, 132.0, 131.3, 130.6, 129.2, 128.6, 124.3 (q, *J* = 276.5 Hz), 123.3, 41.6 (q, *J* = 32.7 Hz), 39.6, 19.0.

^{19}F NMR (282 MHz, $CDCl_3$) δ -63.9.

IR (Neat) 3429, 2160, 1708, 1520, 1348, 1258, 1170, 1149, 857, 766, 744, 698, 575, 502, 480, 411 cm^{-1}.

HRMS (ES-) calcd for $C_{18}H_{13}NF_3O_6$ ($[M+HCO_2H-H]^-$) 396.0695, found: 396.0689. (-1.5 ppm)



(1*S*,2*R*)-1-(4-bromophenyl)-2-phenyl-2-(difluoromethyl)cyclopropane-1-carboxylic acid **19d** (1.7 g, 93%) was obtained as a yellow solid, Rf = 0.17 (1% AcOH of PE/EtOAc =1:1). Mp: 158-160 °C. **$[\alpha]^{20}_D$** = -9.3 (c =1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.96 (s, 1H), 7.55 – 6.75 (m, 9H), 6.20 (t, *J* = 55.8 Hz, 1H), 2.31 (d, *J* = 6.2 Hz, 1H), 2.23 (t, *J* = 6.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ177.0, 132.8, 132.5, 131.1, 130.9, 130.6, 128.3, 128.1, 122.0, 116.1 (dd, *J* = 242.2, 240.6 Hz), 42.2 (dd, *J* = 28.0, 24.6 Hz), 38.7, 20.2 (d, *J* = 7.2 Hz).

^{19}F NMR (282 MHz, $CDCl_3$) δ -110.5 (dd, *J* = 287.3, 1.5 Hz), -116.4 (dd, *J* = 287.3, 2.6 Hz).

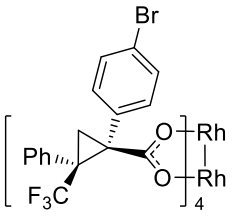
IR (Neat) 3003, 2870, 2532, 1693, 1489, 1393, 1265, 1211, 1091, 1039, 931, 750, 715, 697, 677, 551, 451 cm^{-1}.

HRMS (ES-) calcd for $C_{17}H_{12}BrF_2O_2$ ($[M-H]^-$) 364.9989, found: 364.9997. (2.2 ppm)

Synthesis of rhodium catalyst

General procedure O Synthesis of Rh catalyst

A solution of $Na_4Rh_2(CO_3)_4$ (250 mg, 0.5 mmol, 1.0 equiv.) and cyclopropyl carboxylic acid (4.0 mmol, 8.0 equiv.) in 25 mL distilled water was refluxed for 3 days under argon. Then the mixture was extracted with DCM (3 x 50 mL). Combined the organic layers and washed with saturated $NaHCO_3$ (3 x 10 mL), 10 % NaOH (3 x 10 mL), brine (3 x 10 mL), dried over Na_2SO_4 and concentrated. The crude material was purified by flash chromatography on silica gel (toluene/acetonitrile, 50:1) to provide rhodium catalyst.

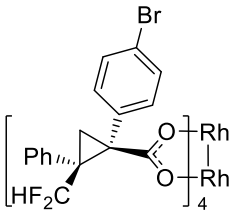


Dirhodium (II) tetrakis (1*S*,2*R*)-1-(4-bromophenyl)-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **20a** (352 mg, 40%) was obtained as a yellow solid, Rf = 0.17 (1% AcOH of PE/EtOAc =1:1). Mp: 233-234 °C.

$[\alpha]^{20}_D$ = -99.2 (c = 0.8, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 – 6.92 (m, 5H), 6.83 (dd, *J* = 27.5, 5.2 Hz, 4H), 2.33 (d, *J* = 6.3 Hz, 1H), 1.99 (d, *J* = 5.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 133.3, 132.0, 131.8, 130.4, 130.3, 128.1, 128.0, 124.9 (q, *J* = 277.0 Hz), 121.3, 41.5, (q, *J* = 33.1 Hz), 41.1, 18.3.
^{19}F NMR (282 MHz, $CDCl_3$) δ -60.6.



Dirhodium (II) tetrakis (1*S*,2*R*)-1-(4-bromophenyl)-2-phenyl-2-(difluoromethyl)cyclopropane-1-carboxylate **20b** (528 mg, 60%) was obtained as a yellow solid, Rf = 0.17 (PE/EtOAc =1:1). Mp: 231-233 °C.

$[\alpha]^{20}_D$ = -25.7 (c =1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 6.99 (m, 7H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.98 (t, *J* = 56.2 Hz, 1H).

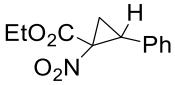
^{13}C NMR (75 MHz, $CDCl_3$) δ188.9, 133.8, 132.6, 131.7, 130.6, 130.4, 128.02, 127.97, 121.2, 116.2 (dd, *J* = 242.5, 240.7 Hz), 41.2 (t, *J* = 26.1 Hz), 40.5, 19.3.

^{19}F NMR (282 MHz, $CDCl_3$) δ -110.3 (dd, *J* = 283.9, 55.9 Hz), -116.4 (dd, *J* = 283.6, 56.1 Hz).

Cyclopropanation to construct 21, 23

General procedure P Cyclopropanation to construct **21, 23**

An oven-dried 2 mL reaction vial equipped with a magnetic stirring bar was charged with Rh-catalyst (4.4 mg, 1 mol%), filled with argon and sealed. DCM (0.150 mL) was added followed by the olefin (0.5 mmol, 2 equiv. or 2.5 mmol, 5 equiv.). A solution of diazo compound (0.25 mmol, 1.5 equiv.) in DCM (0.25 ml) was added over 30 min at room temperature. The reaction was stirred for further 60 min, pyridine (20 µL) was added to quench the reaction and the crude material was directly purified by flash chromatography on silica gel to afford the desired cyclopropanes.



Ethyl 1-nitro-2-phenylcyclopropane-1-carboxylate **21** was obtained as a colorless oil. The diastereomeric ratio was determined by ^{1}H NMR of the crude mixture. Rf = 0.33 (PE/Et_2O =

4:1). The enantiomeric excess was determined by HPLC with an IC-H column (*n*-heptane/*i*-PrOH = 80:20, 220 nm, 1 mL/min), t_R = 5.7 min, t_R = 6.1 min.

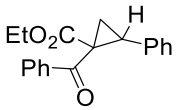
Rh_2((*S*)-BTPCP)$_4$: 62% yield, 2.6:1 dr, 57% ee

20a: 51% yield, 3.7:1 dr, 52% ee

20b: 39% yield, 2.8:1 dr, 16% ee

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, 3H), 7.17 – 7.06 (m, 2H), 4.00 – 3.82 (m, 2H), 3.80 – 3.55 (m, 1H), 2.37 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.12 (dd, *J* = 10.7, 6.6 Hz, 1H), 0.83 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 132.1, 128.5, 128.2, 71.7, 62.5, 34.0, 20.7, 13.5.



Ethyl 1-benzoyl-2-phenylcyclopropane-1-carboxylate **23** was obtained as a colorless oil. The diastereomeric ratio was determined by ^{1}H NMR of the crude mixture. Rf = 0.33 (PE/Et_2O =10:1). The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane/*i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 4.8 min, t_R = 5.8 min.

Rh_2((*S*)BTPCP)$_4$: 37% yield, 10:1 dr, 94% ee

20a: 33% yield, 10:1 dr, 88% ee

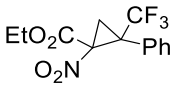
20b: 36% yield, 10:1 dr, 76% ee

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 – 7.74 (m, 2H), 7.63 – 7.32 (m, 3H), 7.29 – 7.08 (m, 5iiuH), 3.73 – 3.54 (m, 2H), 3.51 (t, *J* = 8.6 Hz, 1H), 2.37 (dd, *J* = 8.1, 4.8 Hz, 1H), 1.60 (dd, *J* = 9.1, 4.8 Hz, 1H), 0.58 (t, *J* = 7.1 Hz, 3H).

Cyclopropanation to construct 22

General procedure Q Cyclopropanation to construct **22**

An oven-dried 2 mL reaction vial equipped with a magnetic stirring bar was charged with Rh-catalyst (1 mol%), filled with argon and sealed. DCM (0.150 mL) was added followed by the olefin (0.25 mmol, 1 equiv.). A solution of diazo compound (0.375 mmol, 1.5 equiv.) in DCM (0.22 ml) was added over 30 min at 0 °C. The reaction was stirred for further 60 min at 0 °C, pyridine (20 µL) was added to quench the reaction and the crude material was directly purified by flash chromatography on silica gel to afford the desired cyclopropanes.



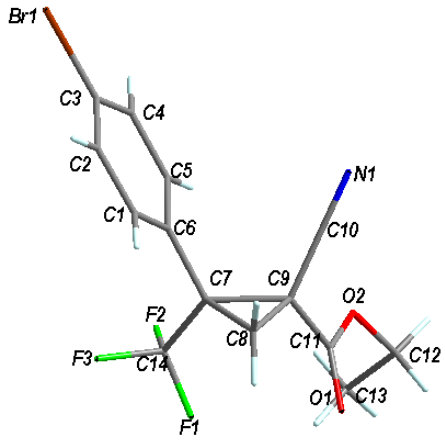
Ethyl 1-nitro-2-phenyl-2-(trifluoromethyl)cyclopropane-1-carboxylate **22** (20 mg, 26%) was obtained as colorless oil after silica gel column chromatography (PE/Et_2O 85:15). The diastereomeric ratio (2:1) was determined by ^{19}F NMR of the crude mixture. Rf = 0.15 (PE/Et_2O =10:1). The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane/*i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 6.2 min, t_R = 6.5 min.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.22 (m, 5H), 4.01 – 3.84 (m, 2H), 2.57 (d, *J* = 7.7 Hz, 1H), 2.46 (dd, *J* = 7.7, 1.4 Hz, 1H), 0.96 – 0.69 (m, 3H). (major)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 – 7.22 (m, 5H), 4.32 (dq, *J* = 21.4, 7.2 Hz, 2H), 3.87 (d, *J* = 18.2 Hz, 1H), 3.55 (d, *J* = 18.3 Hz, 1H), 1.35 – 1.23 (m, 3H). (minor)

X-ray analysis

Crystallographic data for 8h (CCDC 1841121)



Chemical Formula	$C_{14}H_{11}BrF_3NO_2$
Molecular Weight / *g.mol*$^{-1}$	362.1
Crystal System	Triclinic
Space Group	*P*1
Z , Z' (asymmetric units per unit cell)	1, 1
a / *Å*	6.050(4)
b / *Å*	7.181(5)
c / *Å*	9.232(6)
α / °	97.737(10)
β / °	90.909(11)
γ / °	108.243(11)

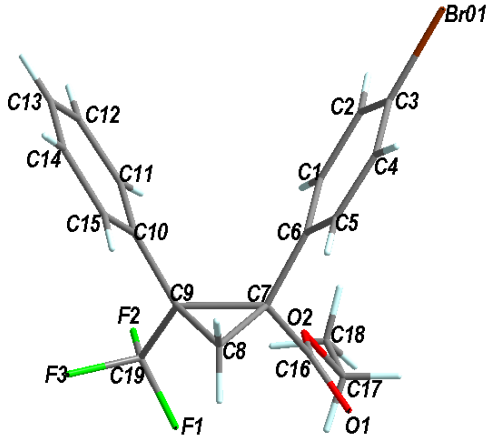
V / *Å*^{3}	376.7(4)
d_{calc} / *g.cm*$^{-3}$	1.596
F(000) / *e*$^-$	180
Absorption coefficient μ (MoKα_1) / *mm*$^{-1}$	2.763
Absolute structure parameter	0.02(1)

Table 23. Crystal data and structure refinement for **8h**.

Atom	*x*	*y*	*z*	U(eq)
C(1)	7612(11)	5695(9)	3159(7)	57(2)
C(2)	7379(11)	6796(9)	2083(7)	67(2)
C(3)	5671(12)	7723(8)	2185(6)	60(2)
C(4)	4251(13)	7561(8)	3318(7)	63(2)
C(5)	4508(10)	6490(8)	4391(7)	58(2)
C(6)	6229(10)	5561(8)	4321(6)	49(2)
C(7)	6534(9)	4430(9)	5511(6)	53(1)
C(8)	6893(11)	2449(9)	5147(7)	62(2)
C(9)	4555(9)	2480(8)	5653(6)	49(1)
C(10)	2651(13)	1946(10)	4566(9)	54(2)
C(11)	3857(12)	1861(10)	7095(7)	61(2)
C(12)	885(13)	1562(10)	8809(7)	77(2)
C(13)	1891(16)	3191(13)	10033(8)	105(3)
C(14)	7726(15)	5762(12)	6882(9)	72(2)
Br(1)	5332(1)	9240(1)	725(1)	93(1)
F(1)	8248(10)	4846(7)	7901(5)	130(2)
F(2)	6525(9)	6826(8)	7490(5)	118(2)
F(3)	9730(8)	7021(8)	6563(6)	123(2)
N(1)	1184(10)	1490(8)	3673(7)	72(2)
O(1)	4932(10)	1132(9)	7810(6)	107(2)
O(2)	1864(8)	2154(7)	7437(5)	66(1)

Table 24. Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Crystallographic data for 9o (CCDC 1841122)



Chemical Formula	$C_{19}H_{16}BrF_3O_2$
Molecular Weight / *g.mol*$^{-1}$	413.2
Crystal System	Monoclinic
Space Group	$P2_1$
Z , Z' (asymmetric units per unit cell)	2,1
a / *Å*	6.745(7)
b / *Å*	8.537(9)
c / *Å*	16.422(17)
α / °	90
β / °	101.342(16)
γ / °	90
V / *Å*^{3}	927.2(17)
d_{calc} / *g.cm*$^{-3}$	1.480
F(000) / *e*$^-$	416
Absorption coefficient μ (MoKα_1) / *mm*$^{-1}$	2.254
Absolute structure parameter	0.009(4)

Table 25. Crystal data and structure refinement for **9o**.

Atom	x	y	z	U(eq)
C(1)	1761(12)	2909(11)	3079(7)	59(3)
C(2)	759(12)	3203(12)	3725(6)	59(2)
C(3)	1804(14)	3099(15)	4524(8)	81(3)
C(4)	3784(17)	2681(18)	4651(8)	110(5)
C(5)	4793(16)	2343(15)	4055(9)	89(4)

C(6)	3800(12)	2456(10)	3241(7)	54(3)
C(7)	4918(12)	2196(11)	2558(7)	54(3)
C(8)	6640(12)	1043(11)	2639(7)	57(3)
C(9)	4651(13)	604(11)	2072(7)	61(3)
C(10)	3340(13)	-621(11)	2327(7)	59(3)
C(11)	1256(13)	-651(11)	1994(8)	66(3)
C(12)	44(13)	-1792(14)	2170(8)	78(3)
C(13)	832(18)	-2951(14)	2711(8)	82(4)
C(14)	2884(18)	-2991(12)	3076(8)	77(3)
C(15)	4131(13)	-1839(12)	2871(6)	64(3)
C(16)	5120(14)	3669(11)	2089(6)	59(2)
C(17)	3400(20)	5414(13)	1056(8)	87(4)
C(18)	1380(20)	5514(16)	514(8)	107(5)
C(19)	4722(16)	613(14)	1198(7)	67(3)
Br(01)	407(2)	3477(3)	5380(1)	124(1)
F(1)	6080(9)	1629(7)	990(4)	90(2)
F(2)	2986(10)	905(8)	706(4)	88(2)
F(3)	5324(10)	-825(7)	972(5)	95(2)
O(1)	6639(10)	4465(8)	2184(5)	83(2)
O(2)	3426(9)	4013(7)	1563(4)	63(2)

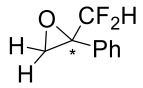
Table 26. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2$ x 10^3). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Chapter III Catalytic Asymmetric Oxidation of α,α-Difluoromethyl styrenes

Epoxidation using Mn-catalyst

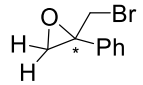
General procedure R Epoxidation using Mn-catalyst

Bleach (0.55 M, 1.5 equiv., buffered with Na_2HPO_4-NaOH, Ph = 11.3) was added to a solution of olefin (0.2 mmol, 1 equiv.) and Mn-salen (10% mol) in DCM (1 mL). The two-phase mixture was stirred at room temperature and the reaction progress was monitored by TLC or ^{19}F NMR. After 6 h, DCM (15 mL) was added to the mixture and the brown organic phase was separated, washed with water (2x30 mL), saturated NaCl solution, and then dried over $MgSO_4$. concentrated, the residue was purified by flash chromatography on silica gel to afford epoxide.



2-(difluoromethyl)-2-phenyloxirane **25** was obtained as colorless oil after silica gel column chromatography (PE/Et_2O 100 to 95:5). Rf = 0.45 (PE/Et_2O =10:1). The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane/*i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 6.2 min, t_R = 6.9 min.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.28 (m, 5H), 5.78 (t, *J* = 55.1 Hz, 1H), 3.26 (d, *J* = 5.0 Hz, 1H), 2.94 (ddd, *J* = 5.1, 3.2, 2.0 Hz, 1H).



2-(monobromomethyl)-2-phenyloxirane **26** Rf = 0.45 (PE/Et_2O =10:1). The conversion was determined by GC-MS. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane/*i*-PrOH = 98:2, 220 nm, 1 mL/min), t_R = 6.2 min, t_R = 6.9 min.

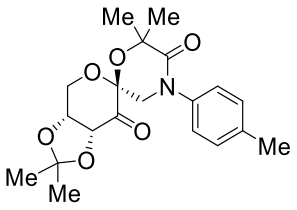
27: 92% yield, 45% ee.

29: 85% yield, 18% ee.

Synthesis of Shi catalysts

General procedure S Synthesis of Shi catalysts

Shi catalyst **26**[145] and **27**[185] were prepared according to the literature. The modified catalyst **29** was prepared according to the literature[185] using 2-bromoisobutyryl bromide (**30** was prepared from 3-chloropropionyl chloride).



(2*S*,3a'*R*,7a'*R*)-2',2',6,6-tetramethyl-4-(*p*-tolyl)dihydrospiro[morpholine-2,6'-[1,3]dioxolo[4,5-c]pyran]-5,7'(4'*H*)-dione **29** (0.5 g, 53% yield, 2.5 mmol scale) was obtained as a pale orange solid after silica gel chromatography (PE: Et_2O = 4:1 to 2:1). R_f (PE: EtOAc = 2:1): 0.21. Mp: 121 °C

$[\alpha]^{20}_D$ = -86.7 (c = 1.5, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.16 (m, 4H), 4.84 (d, *J* = 5.5 Hz, 1H), 4.59 (dd, *J* = 5.4,

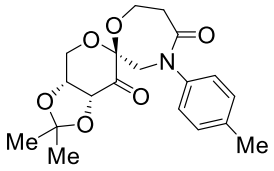
[185] B. Wang, O. A. Wong, W. X. Zhao, Y. Shi, *J. Org. Chem*. **2008**, *73*, 9539–9543.

1.4 Hz, 1H), 4.45 (dd, *J* = 13.5, 2.1 Hz, 1H), 4.37 (d, *J* = 13.9 Hz, 1H), 4.16 (d, *J* = 13.5 Hz, 1H), 3.76 (d, *J* = 13.9 Hz, 1H), 2.33 (s, 3H), 1.65 (s, 4H), 1.55 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 170.6, 139.0, 136.9, 129.7, 125.6, 110.6, 96.3, 78.4, 78.2, 75.5, 59.5, 51.8, 27.6, 27.2, 26.4, 26.1, 21.1.

IR (Neat) 2990, 1774, 1672, 1515, 1376, 1339, 1227, 1181, 1157, 1096, 1074, 985, 952, 891, 849, 817, 715, 512 cm^{-1}.

HRMS (ES+) calcd for $C_{20}H_{26}NO_6$ ($[M+H]^+$) 376.1760, found: 376.1750. (-2.7 ppm)



(3a*R*,6*R*,7a*R*)-2,2-dimethyl-4'-(*p*-tolyl)dihydrospiro[[1,3]dioxolo[4,5-c]pyran-6,2'-[1,4]oxazepane]-5',7(4*H*)-dione **30** (0.5 g, 59% yield, 2.5 mmol scale) was obtained as a pale yellow sticky oil after silica gel chromatography (PE: Et_2O = 4:1 to 2:1). R_f (PE: EtOAc = 2:1): 0.21. **$[\alpha]^{20}_D$** = -84.8 (c = 2.7, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 6.99 (m, 4H), 6.33 (d, *J* = 16.9 Hz, 1H), 6.13 (dd, *J* = 10.2, 3.2 Hz, 1H), 5.52 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.96 (d, *J* = 17.9 Hz, 1H), 4.86 (t, *J* = 6.4 Hz, 2H), 4.69 (d, *J* = 18.0 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 1H), 4.10 (d, *J* = 1.9 Hz, 2H), 2.34 (s, 3H), 1.27 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 166.0, 139.6, 137.9, 130.0, 127.7, 112.9, 105.5, 86.5, 80.2, 72.2, 60.4, 57.1, 54.8, 25.8, 24.2, 21.1.

IR (Neat) 3322, 2990, 1748, 1647, 1614, 1419, 1373, 1271, 1511, 1161, 1207, 1088, 1041, 857, 721 cm^{-1}.

HRMS (ES+) calcd for $C_{19}H_{24}NO_6$ ($[M+H]^+$) 362.1604, found: 362.1617. (3.6 ppm)

Epoxidation using organic catalyst

General procedure T Epoxidation using organic catalyst

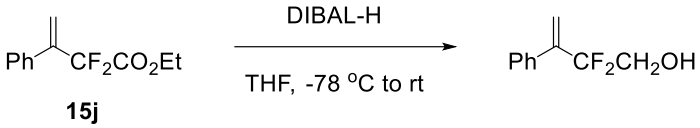
To a solution of olefin (0.20 mmol, 1.0 equiv.), tetrabutylammonium hydrogen sulfate (0.0038 g, 0.010 mmol), and ketone **3d** (0.0208 g, 0.06 mmol) in dioxane (3 mL) was added buffer (0.1 M K_2CO_3-AcOH in 4 × 10^{-4} M EDTA aq., pH = 9.3, 2 mL) with stirring. After the mixture was cooled to 0 °C (bath temperature), a solution of Oxone (0.20 M in 4 × 10^{-4} M EDTA aq., 1.6 mL) (0.197 g, 0.32 mmol) and a solution of K_2CO_3 (0.84 M in 4 × 10^{-4} M EDTA aq., 1.6 mL) (0.185 g, 1.344 mmol) were added separately and simultaneously via a syringe pump over a

period of 2 h. The reaction mixture was quenched with hexane, extracted with EtOAc, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel, hexane/Et_2O = 20:1) to give the epoxide.

Synthesis of olefins

General procedure U Synthesis of olefins

(Ethyl 2,2-difluoro-3-phenylbut-3-enoate **15j** and diethyl (1,1-difluoro-2-phenylallyl) phosphonate **15k**),[187] (3,3-difluoro-1-propenyl benzene **15l** and 3,3,3-trifluoro-1-propenyl benzene **15m**)[186] could be prepared according to the literature. The product is in accordance with the literature characterization data.



15j

To a flame-dried round-bottomed flask was added the ester derivative **15j**[187] (1.25 g, 5.5 mmol, 1 equiv.) and dry THF (50 mL). The solution was cooled to -78 °C in a dry ice/acetone bath and DIBAL-H (25% wt in toluene, 11.6 mL, 3 eq.) was added dropwise at -78 °C. The reaction was allowed warm to rt and stirred for further 4 h. EtOAc (150 mL) was then added, followed by HCl (1M). The resulting solution was stirred at room temperature for 30 min then diluted with H_2O, extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using Cy/EtOAc (90:10 to 80:10) as eluent to afford the desired alcohol (0.83 g, 4.50 mmol, 82 % yield) as a colorless oil. Rf (Cy: EtOAc = 80:20): 0.41.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7.35 (m, 5H), 5.84 (s, 1H), 5.60 (s, 1H), 3.82 (td, *J* = 13.3, 7.1 Hz, 2H), 1.96 (t, *J* = 7.1 Hz, 1H).

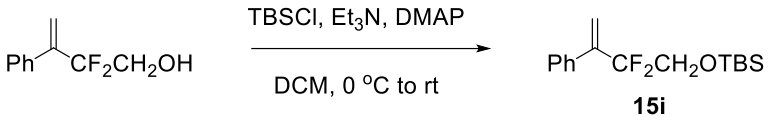
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.7 (t, *J* = 22.1 Hz), 136.5, 128.6, 128.2, 123.5, 120.3 (t, *J* = 8.6 Hz), 117.1, 64.2 (t, *J* = 31.1 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 107.19 (t, *J* = 13.3 Hz).

HRMS (CI+): calcd for $C_{10}H_{10}F_2O$ ($[M]^+$): 184.0700, found: 184.0693 (-3.8 ppm).

IR (Neat): 3358, 2936, 1706, 1495, 1445, 1242, 1189, 1044, 1029, 914, 831, 775, 763, 697, 626, 570, 521 cm-^{1}.

[186] X. L. Jiang, Z.-H Chen, X. H. Xu, F. L. Qing, *Org. chem. Front.* **2014**, *1*, 774-776.
[187] H. Y. Zhao, Z. Feng, Z. Luo, X. Zhang, *Angew. Chem. Int. Ed*, **2016**, *55*, 10401-10405.



15i

To an ice cold solution of alcohol derivative from last step (782 mg, 4.25 mmol, 1 equiv.) and DMAP (7.7 mg, 0.063 mmol, 1.5 mol %) in dry DCM (10 mL) was added dropwise a solution of TBSCl (719 mg, 4.77 mmol, 1.1 equiv.) in dry DCM (10 mL) followed by Et_3N (0.71 mL, 5.09 mmol, 1.2 equiv.). After stirring overnight at rt, the reaction solution was washed with brine (3 x 40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography using Cy/EtOAc (90:10 to 70:30) as eluent to afford *tert*-butyl((2,2-difluoro-3-phenylbut-3-en-1-yl)oxy)dimethylsilane **15i** (513 mg, 1.72 mmol, 40 % yield) as a colorless oil. Rf (Cy: EtOAc = 80:20): 0.91.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.32 (m, 5H), 5.79 (s, 1H), 5.53 (s, 1H), 3.80 (t, *J* = 12.0 Hz, 2H), 0.85 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.35 (t, *J* = 22.5 Hz), 137.2, 128.4, 128.3, 128.2, 123.7, 120.2, 119.9 (t, *J* = 9 Hz), 117.2, 64.5 (t, *J* = 33 Hz), 25.8, 18.4, 5.5.

^{19}F NMR (282 MHz, $CDCl_3$): δ – 105.81 (t, *J* = 14.1 Hz).

HRMS (CI+): calcd for $C_{16}H_{25}F_2OSi$ ($[M+H]^+$):299.1642, found: 299.1634 (-2.8 ppm).

IR (Neat): 2954, 2931, 2886, 2858, 1463, 1256, 1203, 1126, 1060, 935, 835, 774, 696 cm^{-1}.

Catalytic asymmetric synthesis of diols

General procedure V Catalytic asymmetric synthesis of diols

A solution of AD-mix-α (0.36 g, 0.2 mol % of [Os]) in a mixture of *t*-BuOH and water (2.5 mL, 1:1) was cooled to 0 °C and stirred for 5 min, Olefin (0.25 mmol) was added. The reaction mixture was stirred at 0 °C for 72 h then solid sodium metabisulfite (0.36 g) was added in 3 portions and stirred for 10 min (bubble generated and the color of reaction mixture change from orange to grey). Water (50 mL) was added and the mixture was extracted with Et_2O (3 x 18 mL). Combined the organic layers and dried over Na_2SO_4 then concentrated under vacuum. The residue was purified by flash chromatography on silica gel (PE: Et_2O= 95:5 to 45:55) to provide the corresponding diols.

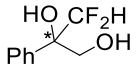
General procedure W the procedure is the same as general procedure V using AD-mix-β as the catalyst

Synthesis of racemic diols

General procedure X Synthesis of racemic diols

The racemic diols were prepared by using $KMnO_4$ (1.3 eq.) and $BnEt_3NCl$ (1.3 eq.) in

acetone[188].



3,3-difluoro-2-phenyl-1,2-propanediol **31a** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). R_f (PE: EtOAc = 2:1): 0.23.

AD-mix-α: 42.3 mg, 90 % yield, 90% ee, **$[\alpha]^{20}_D$** = +9.4 (c = 4.0, acetone).

AD-mix-β: 41.4 mg, 88 % yield, 95% ee, **$[\alpha]^{20}_D$** = –10.2 (c = 3.5, acetone).

Procedure for large scale reaction: 737 mg, 98% yield, 94% ee.

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 12.0 min, t_R = 13.5 min.

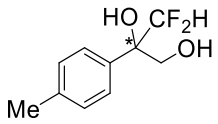
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.61 (d, *J* = 7.3 Hz, 2H), 7.40 – 7.29 (m, 3H), 6.15 (t, *J* = 56.0 Hz, 1H), 4.87 (s, 1H), 4.35 (t, *J* = 5.7 Hz, 1H), 4.10 – 4.04 (m, 1H), 3.83 – 3.77 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 139.3 (d, *J* = 2.5 Hz), 128.7, 128.5, 127.4 (dd, *J* = 1.8, 0.7 Hz), 122.0 – 110.7 (m), 76.8 (dd, *J* = 20.9, 20.3 Hz), 66.4 (dd, *J* = 4.0, 2.7 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.3 (dd, *J* = 281.1, 55.5 Hz), -134.9 (dd, *J* = 281.1, 56.5 Hz).

IR (Neat): 3378, 2976, 1065, 1497, 1450, 1132, 1055, 989, 903, 800, 761, 552, 471 cm^{-1}.

HRMS (ES-): calcd for $C_9H_9F_2O_2$ ($[M-H]^-$): 187.0571, found: 187.0569 (-1.1 ppm).



3,3-difluoro-2-(4-methylphenyl)-1,2-propanediol **31b** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). R_f (PE: EtOAc = 2:1): 0.24.

AD-mix-α: 44.4 mg, 88 % yield, 95% ee, **$[\alpha]^{20}_D$** = +7.3 (c = 3.0, acetone).

AD-mix-β: 41.4 mg, 82 % yield, 98% ee, **$[\alpha]^{20}_D$** = -9.0 (c = 4.0, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 11.5 min, t_R = 15.2 min.

^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.12 (dd, *J* = 56.4, 55.7 Hz, 1H), 4.81 (s, 1H), 4.32 (t, *J* = 5.7 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.80 – 3.74 (m, 1H), 2.31 (s, 3H).

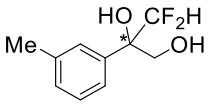
^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 138.0, 136.3 (d, *J* = 2.5 Hz), 129.4, 127.3 (dd, *J* = 1.7, 0.7 Hz), 117.6 (t, *J* = 246.5 Hz), 76.7 (dd, *J* = 21.1, 20.2 Hz), 66.4 (dd, *J* = 4.0, 2.7 Hz), 21.0.

^{19}F NMR (282 MHz, Acetone): δ -128.2 (ddd, *J* = 280.6, 55.7, 0.8 Hz), -134.9 (ddd, *J* = 280.8, 56.5, 2.9 Hz).

[188] Z. B. Luo, C. Zhao, J. Xie, H. F. Lu, *Synthesis* **2016**, *48*, 3696-3700.

HRMS (ES-): calcd for $C_{10}H_{11}F_2O_2$ ([M-H]$^-$): 201.0727, found: 201.0725 (-1.0 ppm).

IR (Neat): 3394, 2926, 1056, 815, 724, 654, 550 cm^{-1}.



3,3-difluoro-2-(3-methylphenyl)-1,2-propanediol **31c** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). R_f (PE: EtOAc = 2:1): 0.23.

AD-mix-α: 45.4 mg, 90 % yield, 95% ee, **[α]$^{20}_D$** = +10.8 (c = 4.2, acetone).

AD-mix-β: 43.9 mg, 87 % yield, 96% ee, **[α]$^{20}_D$** = -11.6 (c = 4.0, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 10.8 min, t_R = 12.7 min.

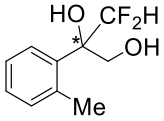
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.54 – 7.48 (m, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 6.23 (t, *J* = 57.0 Hz, 1H), 4.92 (s, 1H), 4.43 (t, *J* = 5.8 Hz, 1H), 4.19 – 4.13 (m, 1H), 3.92 – 3.85 (m, 1H), 2.44 (s, 3H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 139.3 (d, *J* = 2.5 Hz), 138.1, 129.2, 128.7, 128.0 (d, *J* = 0.9 Hz), 124.4 (d, *J* = 1.2 Hz), 117.6 (t, *J* = 246.6 Hz), 76.8 (dd, *J* = 20.7, 20.3 Hz), 66.4 (dd, *J* = 3.9, 2.8 Hz), 21.6.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.2 (dd, *J* = 280.8, 55.5 Hz), -134.8 (ddd, *J* = 280.7, 56.4, 2.8 Hz).

HRMS (ES-): calcd for $C_{10}H_{11}F_2O_2$ ([M-H]$^-$): 201.0727, found: 201.0730 (+1.5 ppm).

IR (Neat): 3390, 2965, 1609, 1380, 1057, 786, 705, 494 cm^{-1}.



3,3-difluoro-2-(2-methylphenyl)-1,2-propanediol **31d** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). R_f (PE: EtOAc = 2:1): 0.24.

AD-mix-α: 6.6 mg, 13 % yield, 67% ee, **[α]$^{20}_D$** = +2.8 (c = 0.5, acetone).

AD-mix-β: 7.1 mg, 14 % yield, 77% ee, **[α]$^{20}_D$** = -4.2 (c = 0.6, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 9.5 min, t_R = 11.0 min.

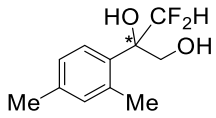
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.45 (d, *J* = 6.8 Hz, 1H), 7.18 – 7.13 (m, 3H), 6.24 (t, *J* = 55.7 Hz, 1H), 4.72 (bs, 1H), 4.39 (t, *J* = 5.7 Hz, 1H), 4.17 (ddd, J = 11.2, 5.7, 2.0, 1H), 3.97 – 3.91 (m, 1H), 2.57 (s, 3H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 138.7, 133.4, 128.7, 128.6, 128.5, 126.0, 117.7 (t, *J* = 246.0 Hz), 78.4 (t, *J* = 20.3 Hz), 65.2, 22.8.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ – 124.31 (dd, *J* = 278.8, 55.4 Hz), – 129.47 (ddd, *J* = 279.0, 55.7, 2.5 Hz).

HRMS (ES-): calcd for $C_{10}H_{11}F_2O_2$ ([M-H]$^-$): 201.0727, found: 201.0732 (+2.5 ppm).

IR (Neat): 3391, 2972, 1053, 758, 725, 659, 554 cm^{-1}.



3,3-difluoro-2-(2,4-dimethylphenyl)-1,2-propanediol **31e** was obtained as a white solid after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.22. Mp: 42-44 °C.

AD-mix-α: 23.2 mg, 43 % yield, 82% ee, **$[\alpha]^{20}_D$** = +4.3 (c = 1.9, acetone).

AD-mix-β: 21.6 mg, 40 % yield, 87% ee, **$[\alpha]^{20}_D$** = -5.9 (c = 1.2, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 95:5, 210 nm, 1 mL/min), t_R = 8.9 min, t_R = 11.7 min.

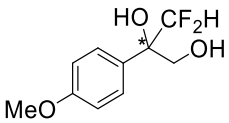
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.32 (d, *J* = 7.9 Hz, 1H), 6.97 – 6.95 (m, 2H), 6.20 (t, *J* = 55.8 Hz, 1H), 4.65 (s, 1H), 4.35 (t, *J* = 5.8 Hz, 1H), 4.18 – 4.11 (m, 1H), 3.93 – 3.92(m, 1H), 2.53 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 138.5, 137.9, 134.1, 134.0 (dd, *J* = 2.0, 0.5 Hz), 128.6 (dd, *J* = 2.3, 0.9 Hz), 126.7, 117.8 (dd, *J* = 247.4, 246.2 Hz), 78.2 (t, *J* = 20.3 Hz), 65.2 (dd, *J* = 4.0, 3.3 Hz), 22.7 (dd, *J* = 1.8, 1.3 Hz), 20.8.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.3 (dd, *J* = 278.9, 55.7 Hz), -133.6 (ddd, *J* = 279.0, 55.9, 2.6 Hz).

HRMS (ES-): calcd for $C_{11}H_{13}F_2O_2$ ([M-H]$^-$): 215.0884, found: 215.0885 (+0.5 ppm).

IR (Neat): 3442, 2953, 1379, 1160, 1067, 1049, 986, 899, 814, 706, 662, 587, 440 cm^{-1}.



3,3-difluoro-2-(4-methoxyphenyl)-1,2-propanediol **31f** was obtained as a white solid after silica gel chromatography (PE: Et_2O = 95:5 to 40:60). Rf (PE: EtOAc = 2:1): 0.20. Mp: 78-80 °C.

AD-mix-α: 34.9 mg, 64 % yield, 96% ee, **$[\alpha]^{20}_D$** = +15.3 (c = 2.1, acetone).

AD-mix-β: 34.4 mg, 63 % yield, 98% ee, **$[\alpha]^{20}_D$** = -14.7 (c = 3.3, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 80:20, 210 nm, 1 mL/min), t_R = 9.1 min, t_R = 13.5 min.

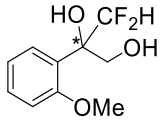
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.52 (d, *J* = 8.8 Hz, 2H), 6.94 – 6.90 (m, 2H), 6.10 (t, *J* = 60.0 Hz, 1H), 4.78 (s, 1H), 4.30 (t, *J* = 5.7 Hz, 1H), 4.07 – 4.01 (m, 1H), 3.79 – 3.75 (m, 4H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 160.3, 131.1 (d, *J* = 2.5 Hz), 128.6 (dd, *J* = 1.7, 0.6 Hz), 120.8 – 114.3 (m), 114.1, 76.5 (dd, *J* = 21.2, 20.2 Hz), 66.4 (dd, *J* = 4.0, 2.6 Hz), 55.5.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.2 (dd, *J* = 280.7, 55.5 Hz), -135.0 (ddd, *J* = 280.5, 56.7, 3.0 Hz).

HRMS (ES-): calcd for $C_{10}H_{11}F_2O_3$ ([M-H]$^-$): 217.0676, found: 217.0677 (0.5 ppm).

IR (Neat): 3405, 2954, 1612, 1514, 1300, 1249, 1180, 1055, 1031, 831, 654, 583 cm^{-1}.



3,3-difluoro-2-(2-methoxyphenyl)-1,2-propanediol **31g** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 40:60). Rf (PE: EtOAc = 2:1): 0.20.

AD-mix-α: 33.2 mg, 61 % yield, 81% ee, **$[\alpha]^{20}_D$** = +16.7 (c = 3.0, acetone).

AD-mix-β: 33.1 mg, 61 % yield, 88% ee, **$[\alpha]^{20}_D$** = -18.1 (c = 2.6, acetone).

The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 14.0 min, t_R = 15.3 min.

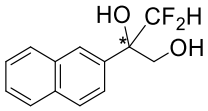
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.71 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.00 (dd, *J* = 14.0, 7.5 Hz, 2H), 6.44 (dd, *J* = 56.7, 55.1 Hz, 1H), 4.77 (d, *J* = 0.7 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.99 – 3.87 (m, 5H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 157.3, 130.1, 129.5 (d, *J* = 1.0 Hz), 127.6 (dd, *J* = 3.6, 1.5 Hz), 121.5, 116.5 (t, *J* = 245.0 Hz), 112.1, 85.8 – 72.3 (m), 64.9 (dd, *J* = 4.9, 1.9 Hz), 55.9.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -129.0 (ddd, *J* = 280.6, 55.0, 1.8 Hz), -131.5 (dd, *J* = 280.6, 56.8 Hz).

HRMS (ES-): calcd for $C_{10}H_{11}F_2O_3$ ([M-H]$^-$): 217.0676, found: 217.0676 (0 ppm).

IR (Neat): 3405, 2948, 1601, 1489, 1463, 1438, 1285, 1238, 1124, 1053, 1018, 811, 754, 658, 513 cm^{-1}.



3,3-difluoro-2-(2-naphthalenyl)-1,2-propanediol **31h** was obtained as a white solid after silica gel chromatography (PE: Et_2O = 95:5 to 45:55).

Rf (PE: EtOAc = 2:1): 0.16. Mp: 76-78 °C**.**

AD-mix-α: 49.4 mg, 83% yield, 98% ee, **$[\alpha]^{20}_D$** = +14.2 (c = 3.7, acetone).

AD-mix-β: 54.8 mg, 92 % yield, 99% ee, **$[\alpha]^{20}_D$** = -12.8 (c = 5.4, acetone).

The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 90:10, 220 nm, 1 mL/min), t_R = 18.4 min, t_R = 27.7 min.

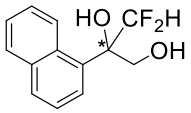
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.90 – 7.84 (m, 3H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 6.2, 3.2 Hz, 2H), 6.01 (t, *J* = 55.8 Hz, 1H), 4.30 (dd, *J* = 11.5, 6.2 Hz, 1H), 3.97 (dd, *J* = 7.8, 4.5 Hz, 1H), 3.40 (s, 1H), 1.88 (t, *J* = 6.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 133.3, 133.2, 128.5, 128.4, 127.7, 126.8, 126.6, 125.9, 123.4, 116.7 (t, *J* = 248.3 Hz), 76.2 (t, *J* = 21.0 Hz), 65.4 (t, *J* = 2.3 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ – 128.49 (dd, *J* = 282.4, 55.7 Hz), – 132.48 (dd, *J* = 283.7, 55.7 Hz).

HRMS (ES-): calcd for $C_{13}H_{11}F_2O_2$ ([M-H]$^-$): 237.0727, found: 237.0724 (-1.3 ppm).

IR (Neat): 3339, 2954, 1699, 1380, 1192, 1121, 1062, 1047, 1003, 908, 815, 744, 672, 576, 483 cm^{-1}.



3,3-difluoro-2-(1-naphthalenyl)-1,2-propanediol **31i** was obtained as a white solid after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.17. Mp: 80-82 °C.

AD-mix-α: 23.8 mg, 40 % yield, 89% ee, **[α]$^{20}_D$** = +18.6 (c = 2.0, acetone).

AD-mix-β: 33.3 mg, 56 % yield, 95% ee, **[α]$^{20}_D$** = -20.3 (c = 2.5, acetone).

The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 10.3 min, t_R = 11.7 min.

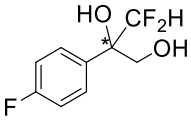
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 9.04 – 9.00 (m, 1H), 7.99 – 7.94 (m, 2H), 7.76 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 3H), 6.62 (t, *J* = 55.5 Hz, 1H), 5.23 (s, 1H), 4.53 (t, *J* = 5.8 Hz, 1H), 4.46 – 3.40 (m, 1H), 4.29 – 4.23 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 135.8, 134.9 (d, *J* = 1.6 Hz), 133.1, 130.2, 129.8, 128.20 – 128.17 (m), 126.9 (dd, *J* = 2.4, 0.9 Hz), 126.2, 126.1, 125.4, 117.6 (dd, *J* = 247.4, 246.1 Hz), 78.9 (t, *J* = 20.4 Hz), 65.3 (dd, *J* = 4.2, 3.5 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -129.5 (dd, *J* = 278.9, 55.6 Hz), -133.3 (ddd, *J* = 278.9, 55.4, 1.8 Hz).

HRMS (ES-): calcd for $C_{13}H_{11}F_2O_2$ ([M-H]$^-$): 237.0727, found: 237.0725 (-0.8 ppm).

IR (Neat): 3384, 3243, 1605, 1388, 1194, 1149, 1089, 1063, 1029, 905, 805, 777, 699, 665, 613, 530, 492 cm^{-1}.



3,3-difluoro-2-(4-fluorophenyl)-1,2-propanediol **31j** was obtained as a white solid after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.21. Mp: 40-42 °C.

AD-mix-α: 45.9 mg, 89 % yield, 95% ee, **[α]$^{20}_D$** = +8.0 (c = 2.0, acetone).

AD-mix-β: 41.2 mg, 80 % yield, 96% ee, **$[\alpha]^{20}_D$** = -8.3 (c = 3.5, acetone).

The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 97:3, 210 nm, 1 mL/min), t_R = 31.3 min, t_R = 33.4 min.

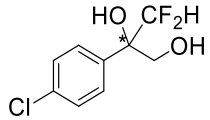
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.65 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.13 (t, *J* = 8.9 Hz, 2H), 6.14 (t, *J* = 57.0, 1H), 4.98 (s, 1H), 4.42 (t, *J* = 5.5 Hz, 1H), 4.04 – 4.02 (m, 1H), 3.84 – 3.78 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 163.3 (d, *J* = 244.1 Hz), 135.4 – 135.3 (m), 129.6 (ddd, *J* = 8.2, 1.9, 0.7 Hz), 117.3 (td, *J* = 246.6, 0.7 Hz), 115.4 (d, *J* = 21.3 Hz), 76.6 (dd, *J* = 21.2, 20.2 Hz), 66.3 – 66.2 (m).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -115.7 (tt, *J* = 8.9, 5.5 Hz), -128.4 (dd, *J* = 281.5, 55.4 Hz), -135.0 (ddd, *J* = 281.4, 56.4, 2.9 Hz).

HRMS (ES-): calcd for $C_9H_8F_3O_2$ ($[M-H]^-$): 205.0476, found: 205.0470 (-2.9 ppm).

IR (Neat): 3391, 2975, 1606, 1511, 1229, 1056, 835, 652, 578, 548 cm^{-1}.



3,3-difluoro-2-(4-chlorophenyl)-1,2-propanediol **31k** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.21.

AD-mix-α: 43.4 mg, 78 % yield, 94% ee, **$[\alpha]^{20}_D$** = +11.8 (c = 2.7, acetone).

AD-mix-β: 42.8 mg, 77 % yield, 97% ee, **$[\alpha]^{20}_D$** = -12.1 (c = 3.4, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 95:5, 220 nm, 1 mL/min), t_R = 23.1 min, t_R = 25.9 min.

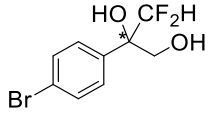
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.63 (d, *J* = 8.6 Hz, 2H), 7.43 – 7.38 (m, 2H), 6.16 (t, *J* = 57.0 Hz, 1H), 5.02 (s, 1H), 4.43 (t, *J* = 5.7 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.85 – 3.79 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 138.3 (d, *J* = 2.7 Hz), 134.1, 129.3 (dd, *J* = 1.8, 0.6 Hz), 128.8, 117.2 (dd, *J* = 246.8, 246.4 Hz), 76.7 (dd, *J* = 21.1, 20.1 Hz), 66.2 (dd, *J* = 3.9, 2.8 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.6 (ddd, *J* = 281.6, 55.4, 0.8 Hz), -134.9 (ddd, *J* = 281.7, 56.3, 2.8 Hz).

HRMS (ES-): calcd for $C_9H_8ClF_2O_2$ ($[M-H]^-$): 221.0181, found: 221.0185 (+1.8 ppm).

IR (Neat): 3384, 2960, 1597, 1491, 1355, 1013, 1061, 991, 824, 761, 650, 555, 459 cm^{-1}.



3,3-difluoro-2-(4-bromophenyl)-1,2-propanediol **31l** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.21.

AD-mix-α: 55.4 mg, 83 % yield, 95% ee, **$[\alpha]^{20}_D$** = +15.1 (c = 4.7, acetone).

AD-mix-β: 54.1 mg, 81 % yield, 97% ee, **[α]$^{20}_{D}$** = –16.7 (c = 3.1, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 11.6 min, t_R = 13.0 min.

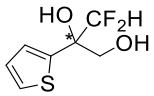
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.56 (s, 4H), 6.34 (dd, *J* = 56.1, 55.5 Hz, 1H), 5.03 (s, 1H), 4.44 (t, *J* = 5.6 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.85 – 3.80 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 138.8(d, *J* = 2.7 Hz), 131.8, 129.7 (dd, *J* = 1.8, 0.6 Hz), 122.4, 120.5 – 113.9 (m), 76.8 (dd, *J* = 21.1, 20.2 Hz), 66.2 (dd, *J* = 3.9, 2.8 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.6 (dd, *J* = 281.8, 55.3 Hz), -134.8 (ddd, *J* = 281.8, 56.3, 2.8 Hz).

HRMS (ES-): calcd for $C_9H_8BrF_2O_2$ ([M-H]$^-$): 266.9655, found: 266.9652 (-1.1 ppm).

IR (Neat): 3329, 2923, 1128, 1059, 988, 821, 751, 646, 553, 416 cm^{-1}.



3,3-difluoro-2-(2-thienyl)-1,2-propanediol **31m** was obtained as a pale-yellow oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.24.

AD-mix-α: 36.9 mg, 76% yield, 89% ee, **[α]$^{20}_{D}$** = +6.4 (c = 3.5, acetone).

AD-mix-β: 27.2 mg, 56 % yield, 93% ee, **[α]$^{20}_{D}$** = –7.9 (c = 2.1, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 14.0 min, t_R = 15.1 min.

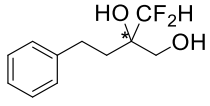
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.42 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.14 (d, *J* = 3.6 Hz, 1H), 7.03 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.13 (dd, *J* = 56.6, 55.6 Hz, 1H), 5.30 (s, 1H), 4.48 (t, *J* = 5.9 Hz, 1H), 4.02 – 3.95 (m, 1H), 3.86 – 3.80 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 143.0 (d, *J* = 2.7 Hz), 127.6, 126.2, 125.6 (dd, *J* = 1.8, 0.5 Hz), 116.6 (dd, *J* = 247.4, 246.0 Hz), 76.7 (dd, *J* = 22.3, 20.5 Hz), 66.9 (dd, *J* = 3.9, 2.4 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -128.7 – -129.9 (m), -135.4 (ddd, *J* = 280.1, 56.7, 3.1 Hz).

HRMS (ES-): calcd for $C_7H_7F_2O_2S$ ([M-H]$^-$): 193.0135, found: 193.0136 (0.5 ppm).

IR (Neat): 3371, 2973, 1697, 1347, 1241, 1127, 1059, 1043, 852, 701, 541 cm^{-1}.



2-(difluoromethyl)-4-phenylbutane-1,2-diol **31n** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.21.

AD-mix-α: 40.0 mg, 74 % yield, 78% ee, **[α]$^{20}_{D}$** = +5.6 (c = 3.5, acetone).

AD-mix-β: 37.8 mg, 70 % yield, 87% ee, **[α]$^{20}_{D}$** = –6.6 (c = 3.7, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH

= 90:10, 210 nm, 1 mL/min), t_R = 10.0 min, t_R = 10.8 min.

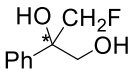
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.16 – 7.00 (m, 5H), 5.78 (t, *J* = 56.1 Hz, 1H), 4.22 (s, 1H), 4.05 (t, *J* = 5.6 Hz, 1H), 3.57 (d, *J* = 5.6 Hz, 2H), 2.73 – 2.56 (m, 2H), 1.85 – 1.69 (m, 2H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 143.5, 129.2, 129.1, 126.6, 118.2 (t, *J* = 245.3 Hz), 74.6 (dd, *J* = 20.1, 19.5 Hz), 63.9 (dd, *J* = 3.9, 3.2 Hz), 34.0 (dd, *J* = 3.0, 1.8 Hz), 29.4.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -133.5 (dd, *J* = 280.8, 55.8 Hz), -135.9 (dd, *J* = 280.8, 56.5 Hz).

HRMS (ES-): calcd for $C_{11}H_{13}F_2O_2$ ([M-H]$^-$): 215.0884, found: 215.0883 (-0.5 ppm).

IR (Neat): 3395, 2939, 1603, 1455, 1049, 745, 698, 494 cm^{-1}.



3-fluoro-2-phenylpropane-1,2-diol **32a** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc= 2:1): 0.20.

AD-mix-α: 29.7 mg, 70% yield, 84% ee, **$[\alpha]^{20}_D$** = +4.2 (c = 2.1, acetone).

AD-mix-β: 31.9 mg, 75 % yield, 81% ee, **$[\alpha]^{20}_D$** = –4.8 (c = 2.5, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 12.6 min, t_R = 14.1 min.

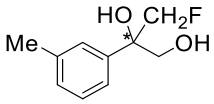
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.58 (d, *J* = 7.1 Hz, 2H), 7.37 – 7.26 (m, 3H), 4.68 (dd, *J* = 22.5, 9.2 Hz, 1H), 4.49 (dd, *J* = 22.6, 9.2 Hz, 1H), 4.42 (s, 1H), 4.11 (t, *J* = 5.8 Hz, 1H), 3. – 3.82 (m, 1H), 3.76 – 3.70 (m, 1H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 143.0 (d, *J* = 2.7 Hz), 128.7, 128.0, 126.8 (d, *J* = 1.4 Hz), 86.8 (d, *J* = 175.5 Hz), 76.1 (d, *J* = 17.7 Hz), 66.9 (d, *J* = 4.2 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -227.08 (t, *J* = 47.9 Hz).

HRMS (ES-): calcd for $C_9H_{11}FO_2$ ([M-H]$^-$): 169.0665, found: 169.0661 (-2.4 ppm).

IR (Neat): 3388, 2957, 1702, 1449, 1013, 761, 761,699, 647, 531 cm^{-1}.



3-fluoro-2-(3-methylphenyl)propane-1,2-diol **32b** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.21.

AD-mix-α: 39.1 mg, 85 % yield, 97% ee, **$[\alpha]^{20}_D$** = +6.1 (c =3.8, acetone).

AD-mix-β: 35.0 mg, 76 % yield, 98% ee, **$[\alpha]^{20}_D$** = –6.4 (c = 3.5, acetone).

The enantiomeric excess was determined by HPLC with an AS-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 10.8 min, t_R = 12.6 min.

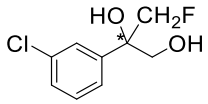
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 7.41 – 7.34 (m2H), 7.22 (t, *J* = 7.6 Hz, 1H), 6.09 (d, *J* = 7.5 Hz, 1H), 4.67 (dd, *J* = 20.8, 9.2 Hz, 1H), 4.51 (dd, *J* = 20.9, 9.2 Hz, 1H), 4.29 (s, 1H), 3.99 (t, *J* = 5.8 Hz, 1H), 3.88 – 3.81 (m, 1H), 3.76 – 3.69 (m, 1H), 2.33 (s, 3H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 142.9 (d, *J* = 2.7 Hz), 138.1, 128.68, 128.66, 127.4 (d, *J* = 1.3 Hz), 123.9 (d, *J* = 1.4 Hz), 86.9 (d, *J* = 175.5 Hz), 76.1 (d, *J* = 17.6 Hz), 66.9 (d, *J* = 4.2 Hz), 21.6.

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -227.02 (t, *J* = 47.8 Hz).

HRMS (ES-): calcd for $C_{10}H_{12}FO_2$ ([M-H]$^-$): 183.0821, found: 183.0820 (-0.5 ppm).

IR (Neat): 3378, 2954, 1608, 1457, 1239, 1151, 1012, 910, 785, 703, 650, 603, 448 cm^{-1}.



3-fluoro-2-(3-chlorophenyl)propane-1,2-diol **32c** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55).

Rf (PE: EtOAc = 2:1): 0.35.

AD-mix-α: 51.1 mg, 93 % yield, 94% ee, **$[\alpha]^{20}_D$** = +13.6 (c = 5.0, acetone).

AD-mix-β: 49.5 mg, 90 % yield, 95% ee, **$[\alpha]^{20}_D$** = –12.8 (c = 4.5, acetone).

The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 18.1 min, t_R = 24.5 min.

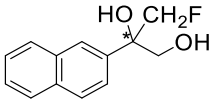
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.13 (s, 1H), 7.93 – 7.87 (m, 3H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.51 – 7.48 (m, 2H), 4.64 (q, *J* = 9.3 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.25 (t, *J* = 5.9 Hz, 1H), 4.02 – 3.86 (m, 2H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 140.5 (d, *J* = 2.7 Hz), 134.2, 133.7, 129.0, 128.4, 128.3, 126.8, 126.7, 126.0 (d, *J* = 1.2 Hz), 125.2 (d, *J* = 1.2 Hz), 87.0 (d, *J* = 175.5 Hz), 76.5 (d, *J* = 17.7 Hz), 67.0 (d, *J* = 4.3 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -227.18 (t, *J* = 47.7 Hz).

HRMS (ES-): calcd for $C_{13}H_{12}FO_2$ ([M-H]$^-$): 219.0821, found: 219.0821 (0.0 ppm).

IR (Neat): 3397, 2957, 1698, 1359, 1248, 1015, 818, 748, 662, 530, 476 cm^{-1}.



3-fluoro-2-(2-naphthalenyl)propane-1,2-diol **32d** was obtained as a colorless oil after silica gel chromatography (PE: Et_2O = 95:5 to 45:55). Rf (PE: EtOAc = 2:1): 0.35.

AD-mix-α: 51.1 mg, 93 % yield, 97% ee, **$[\alpha]^{20}_D$** = +13.6 (c = 5.0, acetone).

AD-mix-β: 49.5 mg, 90 % yield, 96% ee, **$[\alpha]^{20}_D$** = -12.8 (c = 4.5, acetone).

The enantiomeric excess was determined by HPLC with an OD-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 18.1 min, t_R = 24.5 min.

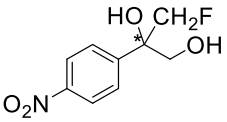
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.13 (s, 1H), 7.93 – 7.87 (m, 3H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.51 – 7.48 (m, 2H), 4.64 (q, *J* = 9.3 Hz, 1H), 4.73 – 4.63 (m, 2H), 4.25 (t, *J* = 5.9 Hz, 1H), 4.02 – 3.86 (m, 2H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 140.5 (d, *J* = 2.7 Hz), 134.2, 133.7, 129.0, 128.4, 128.3, 126.8, 126.7, 126.0 (d, *J* = 1.2 Hz), 125.2 (d, *J* = 1.2 Hz), 87.0 (d, *J* = 175.5 Hz), 76.5 (d, *J* = 17.7 Hz), 67.0 (d, *J* = 4.3 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -227.18 (t, *J* = 47.7 Hz).

HRMS (ES-): calcd for $C_{13}H_{12}FO_2$ ([M-H]$^-$): 219.0821, found: 219.0821 (0.0 ppm).

IR (Neat): 3397, 2957, 1698, 1359, 1248, 1015, 818, 748, 662, 530, 476 cm^{-1}.



3-fluoro-2-(4-nitrophenyl)propane-1,2-diol **32e** was obtained as a colorless solid after silica gel chromatography (PE: Et_2O= 95:5 to 45:55). Rf (PE: EtOAc= 2:1): 0.35. Mp: 79-81 °C.

AD-mix-α: 46.8 mg, 87 % yield, 98% ee, **$[\alpha]^{20}_D$** = +10.1 (c = 4.5, acetone).

AD-mix-β: 44.1 mg, 82 % yield, 96% ee, **$[\alpha]^{20}_D$** = -12 (c = 4.0, acetone).

The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 20.5 min, t_R = 22.1 min.

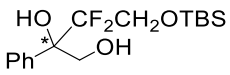
^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ 8.23 – 8.20 (m, 2H), 7.89 – 7.86 (m, 2H), 4.89 (s, 1H), 4.77 (dd, *J* = 28.4, 9.4 Hz, 1H), 4.62 (dd, *J* = 28.6, 9.4 Hz, 1H), 4.36 (t, *J* = 5.8 Hz, 1H), 3.89 – 3.78 (m, 2H).

^{13}C NMR (75 MHz, $(CD_3)_2CO$): δ 150.6 (d, *J* = 2.7 Hz), 148.2, 128.4 (d, *J* = 1.4 Hz), 123.7, 86.6 (d, *J* = 175.6 Hz), 76.6 (d, *J* = 17.8 Hz), 66.6 (d, *J* = 4.5 Hz).

^{19}F NMR (282 MHz, $(CD_3)_2CO$): δ -228.26 (t, *J* = 47.6 Hz).

HRMS (ES-): calcd for $C_9H_{10}FClNO_4$ ([M+Cl]$^-$): 250.0282., found: 250.0284 (0.8 ppm).

IR (Neat): 3410, 2924, 1605, 1517, 1349, 1202, 1111, 1034, 986, 856, 749, 701, 616, 560, 531 473 cm^{-1}.



4-((*tert*-butyldimethylsilyl)oxy)-3,3-difluoro-2-phenylbutane-1,2-diol **32f** was obtained as a colorless oil after silica gel chromatography (Cy: EtOAc = 80:20).

R_f (Cy: EtOAc = 80:10): 0.49.

AD-mix-α: 38 mg, 46 % yield, 74% ee, **$[\alpha]^{20}_D$** = +19.4 (c = 0.35, $CHCl_3$).

AD-mix-β: 35 mg, 43 % yield, 85% ee, **$[\alpha]^{20}_D$** = -19.2 (c = 0.26, $CHCl_3$).

The enantiomeric excess was determined by HPLC with Lux 5u Cellulose-2 column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 6.9 min, t_R = 8.2 min.

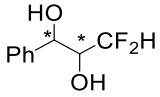
^{1}H NMR (300 MHz, Acetone): δ 7.61 – 7.58 (m, 2H), 7.39 – 7.27 (m, 3H), 4.81 (s, 1H), 4.24 (dd, *J* = 11.3, 5.5 Hz, 1H), 4.18 – 4.04 (m, 2H), 3.92 (dd, *J* = 11.2, 5.0 Hz, 1H), 3.82 – 3.68 (m, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (75 MHz, Acetone): δ 140.3, 128.7, 128.4, 127.6, 122.6 (t, *J* = 250.3 Hz), 78.3 (t, *J* = 20.4 Hz), 65.3 (t, *J* = 3.6 Hz), 63.3 (t, *J* = 26.6 Hz), 26.1, 18.9, – 5.4.

^{19}F NMR (282 MHz, Acetone): δ -115.84 (ddd, *J* = 252.1, 20.4, 9.9 Hz), -118.04 (ddd, *J* = 252.1, 19.5, 10.0 Hz).

HRMS (ES-): calcd for $C_{16}H_{25}O_3F_2Si$ ([M-H]$^-$): 331.1541, found: 331.1533 (2.3 ppm).

IR (Neat): 3417, 2953, 2887, 2858, 1450, 1256, 1099, 1072, 930, 834, 778, 759, 700, cm^{-1}.



3,3-difluoro-1-phenylpropane-1,2-diol **32g** was obtained as a colorless oil after silica gel chromatography (Cy: EtOAc = 70:30). Rf (Cy: EtOAc = 80:20): 0.24

Modified AD-mix-α: 6d at 0°C, 25.1 mg, 53 % yield, 98% ee, **[α]$^{20}_{D}$** = +65.5 (c = 0.22, MeOH).

Modified AD-mix-β: 6d at 0°C, 23.3 mg, 49 % yield, 99% ee, **[α]$^{20}_{D}$** = -58.5 (c = 0.2, MeOH).

The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 12.3 min, t_R = 16.6 min.

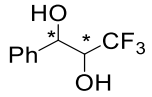
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.41 – 7.43 (m, 5H), 5.73 (td, *J* = 55.2, 4.0 Hz, 1H), 4.90 (bs, 1H), 3.91 – 3.84 (m, 1H), 2.64 – 2.59 (m, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 139.5, 128.9, 128.7, 126.5, 114.9 (t, *J* = 242.0 Hz), 74.9 (dd, *J* = 23.5, 21.4 Hz), 71.9 (t, *J* = 4.2 Hz).

^{19}F NMR (282 MHz, CDCl$_3$): δ -129.65 (ddd, *J* = 290.4, 54.9, 8.5 Hz), -132.60 (ddd, *J* = 290.5, 55.8, 13.5 Hz).

HRMS (ES-): calcd for $C_9H_{10}NO_5F_2$ ([M+NO_3]$^-$): 250.0527, found: 250.0536 (3.6 ppm)

IR (Neat): 3371, 2923, 1627, 1496, 1455, 1392, 1199, 1148, 1117, 1059, 1029, 1010, 890, 763, 723, 699, 559, 540 cm^{-1}.



3,3,3-trifluoro-1-phenylpropane-1,2-diol **32h** was obtained as a colorless solid after silica gel chromatography (Cy: EtOAc = 70:30). Rf (Cy: EtOAc = 80:10): 0.28.

Modified AD-mix-α: 3d at RT, 27.9 mg, 55 % yield, 98% ee, **[α]$^{20}_{D}$** = +55.4 (c = 0.28, MeOH).

Modified AD-mix-β: 3d at RT, 28.4 mg, 54 % yield, 99% ee, **[α]$^{20}_{D}$** = -47.4 (c = 0.22, MeOH).

The enantiomeric excess was determined by HPLC with a Chiralpak-IB column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 7.1 min, t_R = 8.2 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.37 – 7.34 (m, 5H), 4.97 (d, *J* = 2.6 Hz, 1H), 4.00 (m, 1H), 3.51

(d, *J* = 7.1 Hz, 1H), 2.84 (bs, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 128.9, 128.8, 126.4, 124.5 (q, *J* = 282.0 Hz), 73.7 (q, *J* = 29.4 Hz), 70.7 (d, *J* = 1.6 Hz).

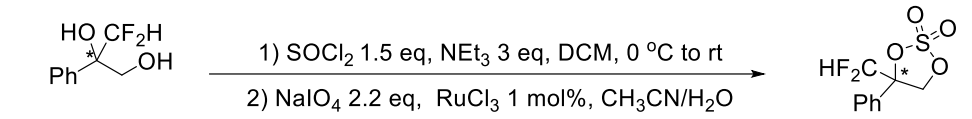
^{19}F NMR (282 MHz, $CDCl_3$): δ -77.26 (d, *J* = 7.1 Hz).

HRMS (ES-): calcd for $C_9H_9NO_5F_3$ ($[M+NO_3]^-$): 268.0432, found: 263.0433 (- 0.4 ppm)

IR (Neat): 3193, 2923, 2854, 1452, 1369, 1275, 1172, 1125, 1090, 1012, 864, 766, 736, 700, 618, 490 cm^{-1}.

Synthesis of 33

General procedure Y Synthesis of **33**



31a, 94% ee
(from AD-mix-β)

33, 75% yield
91% ee

In an oven-dried round-bottomed flask, $SOCl_2$ (0.16 mL, 2.19 mmol, 1.5 eq.) in dry DCM (5 mL) was added dropwise to a solution of **31a** (95% ee, 278 mg, 1.47 mmol, 1 equiv.) and Et_3N (0.4 mL, 2.96 mmol, 2 equiv.) in dry DCM (5 mL) at 0 °C. The mixture stirred at 0 °C for 1 h. The reaction was then diluted with DCM (20 mL), quenched by addition of HCl (1M, 20 mL), extracted with DCM, dried over MgSO4, filtrated and concentrated under reduced pressure. The obtained crude was directly diluted in MeCN (10 mL) and $RuCl_3.xH_2O$ (5.4 mg) was added. Then $NaIO_4$ (677.1 mg, 3.17 mmol, 2.2 eq) was added to the mixture. The resulting solution was stirred at rt for 1 h. Then CH_3CN was removed under reduced pressure and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic phases were then washed by a saturated aqueous solution of Na_2CO_3, H_2O and brine then dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography. (Cy/EtOAc = 80:20) to afford 4-(difluoromethyl)-4-phenyl-1,3,2-dioxathiolane 2,2-dioxide **33** (275 mg, 75 % yield, 91 % ee) as a colorless oil. Rf (Cy/EtOAc = 80:20): 0.52 The enantiomeric excess was determined by HPLC with an IA-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 8.7 min, t_R = 10.0 min.

$[\alpha]^{20}_D$ = +8.3 (c = 0.29, $CHCl_3$).

^{1}H NMR (300 MHz, Acetone): δ 7.57 – 7.54 (m, 5H), 6.58 (t, *J* = 53.5 Hz, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 5.15 (d, *J* = 10.1 Hz, 1H).

^{13}C NMR (75 MHz, Acetone): δ 133.1, 131.1, 130.0, 126.4, 114.1, (t, *J* = 248.2 Hz), 89.4 (t, *J* = 23.3 Hz), 73.8 (t, *J* = 2.6 Hz).

^{19}F NMR (282 MHz, Acetone): δ -130.6 (ddd, *J* = 285.8, 52.9, 1.6 Hz), -132.1 (dd, *J* = 285.7,

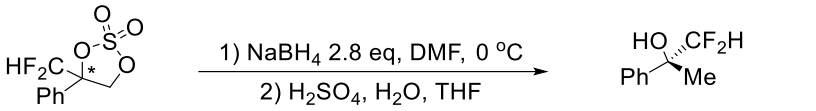
52.9 Hz).

HRMS (CI+): calcd for $C_9H_9F_2O_4S$ ([M+H]$^+$): 251.0190, found: 251.0198 (3.5 ppm)

IR (Neat): 2924, 1452, 1398, 1212, 1167, 1087, 1059, 979, 903, 812, 759, 697, 656, 559, 499, 467 cm^{-1}.

Synthesis of 34

General procedure Z Synthesis of **34**



33, 91% ee

34 (*S*), 66%, 91% ee

To a stirred solution of cyclic sulfate **33** (91% ee, 44.3 mg, 0.18 mmol, 1 equiv.) in dry DMF (2 mL) at 0 °C, was added $NaBH_4$ (18.9 mg, 0.50 mmol, 2.8 eq) under N_2 atm. After 1 hour of stirring, the solution was diluted in dry THF (4 mL). At 0 °C, conc. H_2SO_4 (35 µL) and H_2O (15 µL) were added slowly with stirring for another 1 hour and excess sodium bicarbonate (200 mg) was added with stirring further for 1 hour. After filtration through a celite pad washed with EtOAc, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAc = 100:0 to 70:30) to afford (*S*)-1,1-difluoro-2-phenylpropan-2-ol **34** (20 mg, 0.12 mmol, 66 % yield, 91 % ee) as a colorless oil. Rf (Cy: EtOAc = 80:20): 0.50

The enantiomeric excess was determined by HPLC with a Lux 5u Cellulose-2 column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 4.4 min, t_R = 4.6 min.

$[\alpha]^{20}_D$ = -10.8 (c = 0.32, $CHCl_3$).[159]

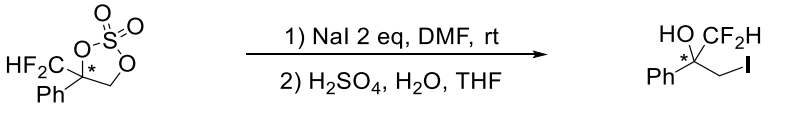
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.43 – 7.32 (m, 3H), 5.73 (t, *J* = 56.3 Hz, 1H), 2.27 (s, 1H), 1.67 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.4, 128.6, 128.3, 125.9, 117.0 (t, *J* = 247.7 Hz), 74.4 (t, *J* = 21.5), 22.5 (t, *J* = 2.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ -129.91 (dd, *J* = 275.8, 56.1 Hz), -131.2 (dd, *J* = 275.8, 56.6 Hz).

Synthesis of 35

General procedure AA Synthesis of **35**



33, 91% ee

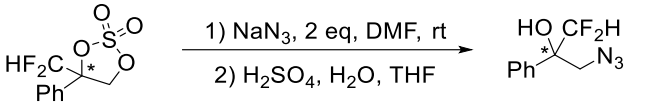
35, 75%, 94% ee

To a stirred solution of cyclic sulfate **33** (91 % ee, 50 mg, 0.20 mmol, 1 equiv.) in dry DMF (2 mL) at rt, was added NaI (66 mg, 0.44 mmol, 2.2 equiv.) under N_2 atm. After 1 hour of stirring, the solution was diluted in dry THF (10 mL). At 0 °C, conc. H_2SO_4 (35 µL) and H2O (15 µL) were added slowly with stirring for another 1 hour and excess $NaHCO_3$ (200 mg) was added with stirring further for 1 hour. After filtration through a celite pad washed with EtOAc, filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAc = 100:0 to 70:30) to 1,1-difluoro-3-iodo-2-phenylpropan-2-ol **35** (44 mg, 0.15 mmol, 75 % yield, 94 % ee) as a colorless oil. Rf (Cy: EtOAc = 80:20): 0.56.
The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 6.6 min, t_R = 7.6 min.
$[\alpha]^{20}_D$ = -4.9 (c = 0.29, $CHCl_3$).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 – 7.41 (m, 5H), 5.88 (t, *J* = 57.0 Hz, 1H), 3.76 (q, *J* = 9.0 Hz, 2H), 2.65 (s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 129.0, 128.8, 126.3, 114.9 (t, *J* = 249.6 Hz) 75.2 (t, *J* = 21.8 Hz), 66.0.
^{19}F NMR (282 MHz, $CDCl_3$): δ -127.84 (dd, *J* = 276.4, 53.6 Hz), -130.7 (dd, *J* = 279.2, 56.4 Hz).
HRMS (ES-): calcd for $C_9H_9NO_4F_2I$ ($[M+NO_3]^-$): 359.9544, found: 359.9541 (0.8 ppm)

IR (Neat): 3523, 2927, 2859, 1713, 1496, 1449, 1289, 1182, 1126, 1068, 1023, 944, 757, 699, 541 cm^{-1}.

Synthesis of 36

General procedure BB Synthesis of **36**



33, 91% ee — **36**, 79%, 92% ee

To a stirred solution of cyclic sulfate **33** (91% ee, 0.048 g, 0.19 mmol, 1 equiv.) in dry DMF (2 mL) at rt, was added NaN_3 (31 mg, 0.48 mmol, 2.5 equiv.) under N_2 atm. After 1 hour of stirring, the solution was diluted in dry THF (4 mL). At 0 °C, conc. H_2SO_4 (35 µL) and H_2O (15 µL) were added slowly with stirring for another 1 hour and excess $NaHCO_3$ (200 mg) was added with stirring further for 1 hour. After filtration through a celite pad washed with EtOAc, the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel chromatography (Cy/EtOAc = 100:0 to 70:30) to afford 3-azido-1,1-difluoro-2-phenylpropan-2-ol **36** (32 mg, 0.15 mmol, 79 % yield, 92 % ee) as a colorless oil. Rf (Cy: EtOAc = 80:20): 0.56.

The enantiomeric excess was determined by HPLC with an IB-H column (*n*-heptane: *i*-PrOH = 90:10, 210 nm, 1 mL/min), t_R = 7.2 min, t_R = 7.9 min.

$[\alpha]^{20}_D$ = +7.9 (c = 0.32, $CHCl_3$).

^{1}H NMR (300 MHz, Acetone): δ 6.74 – 6.71 (m, 2H), 6.55 – 6.44 (m, 3H), 5.24 (t, *J* = 55.6 Hz, 1H), 4.66 (s, 1H), 3.00 – 2.89 (m, 2H).

^{13}C NMR (75 MHz, Acetone): δ 138.6, 129.0 (2C), 127.3, 117.2 (t, *J* = 246,2 Hz), 77.5 (t, *J* = 20.9 Hz), 56.2.

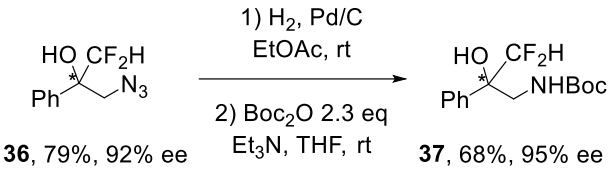
^{19}F NMR (282 MHz, Acetone): δ -128.54 (dd, *J* = 281.7, 55.2 Hz), -132.4 (dd, *J* = 281.7, 56.2 Hz).

HRMS (ES-): calcd for $C_9H_9N_4O_4F_2$ ($[M+NO_3]^-$): 275.0592, found: 275.0597 (1.8 ppm).

IR (Neat): 3447, 2980, 2103, 1497, 1450, 1283, 1241, 1135, 1062, 762, 699, 549 cm^{-1}.

Synthesis of 37

General procedure CC Synthesis of **37**



36, 79%, 92% ee — **37**, 68%, 95% ee

To a solution of compound **36** (92% ee, 45.4 g, 0.21 mmol, 1 equiv.) in EtOAc under Ar atmosphere, was added palladium on carbon (Pd/C) (4 mg). The resulting suspension was then stirred at rt for 16 h under a hydrogen atmosphere. The mixture was filtered through a short pad of Celite washed with EtOAc and the filtrate was concentrated under reduced pressure. The crude product (48.6 mg) was then diluted in dry THF (5 mL). To the stirred solution was then added $(Boc)_2O$ (105 mg, 0.48 mmol, 2.3 equiv.), and Et_3N (0. 1 mL, 0.72 mmol, 3.4 equiv.). The mixture was stirred at rt for 2 h. After concentration under reduced pressure, the residue was purified by silica gel column chromatography (Cy/EtOAc 90:10 to 80:20) to provide *tert*-butyl (3,3-difluoro-2-hydroxy-2-phenylpropyl)carbamate **37** (41.4 mg, 68 % yield over two steps, 95 % ee) as a white solid. Rf (Cy/EtOAc = 80:20): 0.38. Mp: 98–100 °C

The enantiomeric excess was determined by HPLC with a Lux 5u Cellulose-2 column (*n*-heptane: *i*-PrOH = 90:10, 254 nm, 1 mL/min), t_R = 5.2 min, t_R = 5.6 min.

$[\alpha]^{20}_D$ = -96.7 (*c* = 0.15, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 – 7.53 (m, 2H), 7.43 – 7.32 (m, 3H), 5.79 (t, *J* = 55.8 Hz, 1H), 4.81 (sl, 1H), 4.68 (sl, 1H), 3.83 (dd, *J* = 14.9, 6.6 Hz, 1H), 3.62 (dd, *J* = 14.9, 6.0 Hz, 1H), 1.40 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 137.7, 128.6, 128.4, 126.5, 116.7 (t, *J* = 248.6 Hz), 81.0, 45.9, 28.3.

^{19}F NMR (282 MHz, $CDCl_3$): δ -128.53 (dd, *J* = 279.0, 55.8 Hz), -132.0 (dd, *J* = 279.0, 52.5 Hz).

HRMS (ES-): calcd for $C_{14}H_{18}NO_3F_2$ ($[M-H]^-$): 286.1255, found: 286.1252 (0.9 ppm).

IR (neat): 3320, 2980, 2931, 1667, 1545, 1449, 1394, 1368, 1296, 1255, 1166, 1129, 1066, 1043, 895, 810, 788, 737, 701, 541 cm^{-1}.