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The *in situ* Generation of Diazo Compounds: Development of Novel Methods for Organic Synthesis

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Publications and Presentations

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Org. Lett. **2012**, *14*, ASAP.
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- [2] Stefan Künzi, **Bill Morandi**, Erick M. Carreira,
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“Rapid Preparation of Trifluoromethyl-Substituted Aziridines with *in Situ* Generated CF_3CHN_2 ”
- [3] **Bill Morandi**, Erick M. Carreira,
Science **2012**, *335*, 1471.
“Iron-Catalyzed Cyclopropanation in 6 M KOH with *in situ* Generation of Diazomethane”
- [4] **Bill Morandi**, Erick M. Carreira,
Org. Lett. **2011**, *13*, 5984.
“Expedient Preparation of Trifluoromethyl-Substituted Dehydrobenzofuranols”
- [5] **Bill Morandi**, Erick M. Carreira,
Angewandte Chemie International Edition **2011**, *50*, 9085.
“Synthesis of Trifluoroethyl-Substituted Ketones from Aldehydes and Cyclohexanones”
- [6] **Bill Morandi**, Jeremy Cheang, Erick M. Carreira,
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“Iron-Catalyzed Preparation of Trifluoromethyl Substituted Vinyl- and Alkynylcyclopropanes”
- [7] **Bill Morandi**, Brian Mariampillai, Erick M. Carreira,
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“Enantioselective Cobalt-Catalyzed Preparation of Trifluoromethyl-Substituted Cyclopropanes”
- [8] **Bill Morandi**, Erick M. Carreira,

- [8] **Bill Morandi**, Erick M. Carreira,
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“Rhodium-Catalyzed Cyclopropenation of Alkynes: Synthesis of Trifluoromethyl-Substituted Cyclopropenes”
- [9] **Bill Morandi**, Erick M. Carreira,
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“Iron-Catalyzed Cyclopropanation with Trifluoroethylamine Hydrochloride and Olefins in Aqueous Media: In Situ Generation of Trifluoromethyl Diazomethane”
- [10] **Bill Morandi**, Erick M. Carreira,
Synlett **2009**, 2076.
“Catalytic Decarbonylation of Epoxyaldehydes: Applications to the Preparation of Terminal Epoxides”

Presentations:

- 2011 Presentations to multiple visiting professors
 “*in situ Generated Trifluoromethyl Diazomethane: from Classical Organic Synthesis to Extreme Catalysis*”
- 07/14/2011 Poster presentation
 ESOC 2011 (Crete, Greece)
 “*Tandem Diazotization/Metal-Catalyzed Carbene Transfer with in situ Generated Trifluoromethyl Diazomethane in Aqueous Media*”
- 11/05/2010 Poster presentation
 SSCI Symposium (Zürich, Switzerland)
 “*Carbene-Chemistry under Aqueous Oxidative Conditions with in situ Generated Trifluoromethyl Diazomethane*”
- 10/07/2010 Invited talk
 Givaudan AG (Dübendorf, Switzerland)
 “*Carbene-Chemistry under Aqueous Oxidative Conditions with in situ Generated Trifluoromethyl Diazomethane*”
- 10/22/2009 Invited talk
 Johnson and Johnson (Cilag AG, Schaffhausen, Switzerland)
 “*The Triangle Revisited: New Perspectives in Cyclopropane and Cyclopropene Chemistry*”

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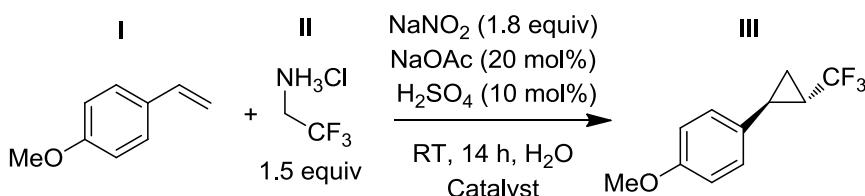
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Abstract

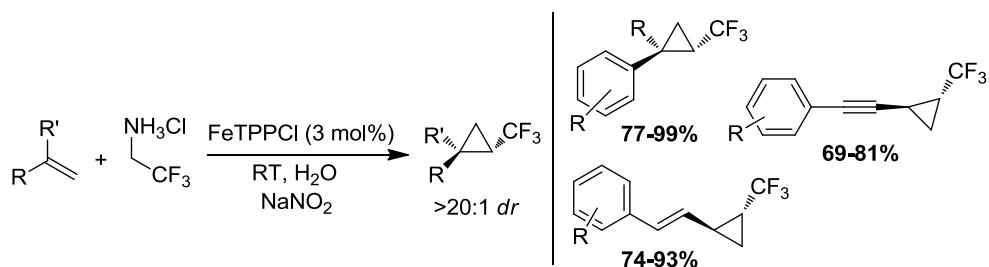
The development of safer methods for organic synthesis is one of the important goals of modern chemical research. In fact, many current synthetic methodologies use toxic and explosive reagents, including the particularly intriguing diazo compounds. Since their discovery over 125 years ago, and despite their toxicity and explosiveness, these reagents have proved to be valuable reactive intermediates in the preparation of many compounds of interest. The high versatility of these reagents combined with their dangerous handling make them perfect candidates for the development of novel strategies for their safer use in organic synthesis. Herein, we describe our approach towards that goal via the development of methods for organic synthesis, wherein diazo compounds are generated *in situ* avoiding the hazards of purification.

At the outset of our investigations, we decided to study the use of trifluoromethyl diazomethane in catalysis using an *in situ* generation strategy for the following reasons: (1) importance of fluorine chemistry in modern synthesis; (2) trifluoromethyl diazomethane is a toxic, explosive and gaseous reagent and (3) the reagent is easily prepared by simple diazotization of a commercially available starting material. We selected the cyclopropanation of *p*-methoxy styrene as our test reaction for catalyst screening. The goal was to identify active catalysts under the conditions necessary for the *in situ* generation of trifluoromethyl diazomethane (aqueous, acidic, oxidizing) (Scheme I).



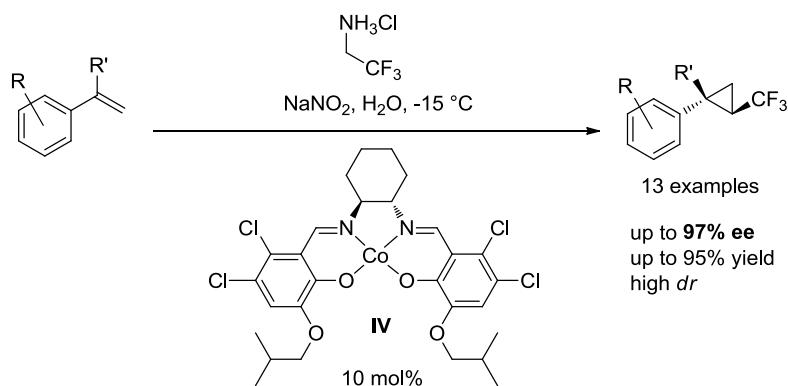
Scheme I: Initial Test Reaction.

A wide range of metal catalysts (Fe, Co, Ru, Rh) were active and afforded the product III under these unusual reaction conditions. These initial results led to the development of three new reaction methodologies for the preparation of trifluoromethylated building blocks. First, an iron-catalyzed preparation of trifluoromethyl-substituted cyclopropanes was developed (Scheme II).



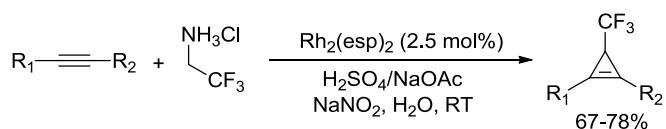
Scheme II: Iron-Catalyzed Cyclopropanation.

Shortly thereafter, we took advantage of the observation that Co-salens were competent catalysts under these conditions and after subsequent screening and optimization, we were able to develop a novel catalyst (**IV**) that catalyzes the enantioselective cyclopropanation reaction (Scheme III).



Scheme III: Asymmetric Cyclopropanation Using Catalyst IV.

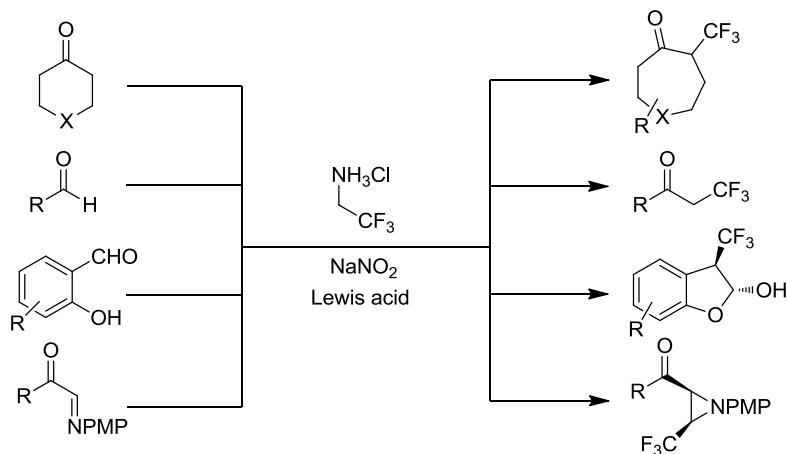
Finally, these reaction conditions proved compatible with a rhodium-catalyzed preparation of trifluoromethyl-substituted cyclopropenes (Scheme IV). These unprecedented compounds were then further studied (reduction, Diels-Alder, deprotonation/trapping, Heck).



Scheme IV: Rhodium-Catalyzed Cyclopropanation.

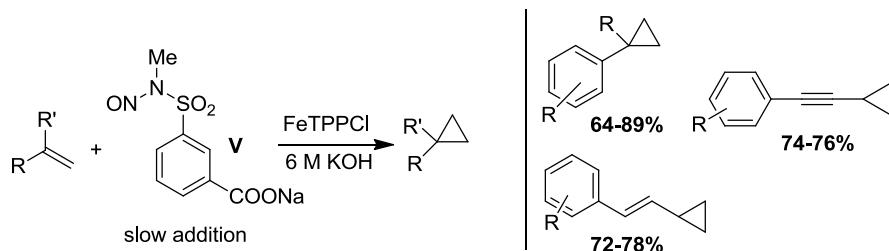
The use of *in situ* generated trifluoromethyl diazomethane was also studied in the context of Lewis acid-mediated transformations. Homologation of aldehydes, cyclic ketones, salicylaldehydes

and aziridination could successfully be developed using a two-step, one pot procedure, with *in situ* generation of the reagent followed by the reaction of interest (Scheme V).



Scheme V: Lewis Acid-Mediated Transformations.

Finally, a novel approach to the use of diazomethane in catalysis was discovered. Using a similar strategy as for the catalytic cyclopropanation with trifluoromethyl diazomethane, we developed a tandem base-mediated decomposition of nitrosamides/cyclopropanation reaction using FeTPP⁺Cl⁻ as the catalyst (Scheme VI). Phase separation was shown to be an important feature of the reaction. A particularly salient feature of this method is the identification of metal catalysts compatible with the extreme conditions necessary for diazomethane preparation from diazald (6 M KOH).



Scheme VI: Iron-Catalyzed Cyclopropanation Using Reagent V.

Résumé

Le développement de méthodes plus sûres est une tâche essentielle de la chimie moderne. En effet, une grande majorité des méthodes utilisées de nos jours emploient encore des réactifs toxiques ou explosifs. Les composés diazotés sont particulièrement dangereux du fait de leurs propriétés physiques. Ces réactifs sont néanmoins devenus très utiles depuis leur découverte il y a plus de 100 ans. Cette combinaison de dangerosité et de grande utilité en fait une classe de composés parfaite pour étudier le développement de stratégies de production *in situ*. Ce travail décrit nos études concernant le développement de ces stratégies.

Nous avons choisi le trifluorométhyle de diazométhane comme réactif pour nos expériences initiales pour les raisons suivantes: (1) importance de l'utilisation du fluor en chimie médicinale ; (2) ce réactif est toxique, explosif et gazeux à température ambiante ; (3) ce réactif est facilement préparé par une réaction de diazotation en utilisant un produit de départ simple. Une réaction de cyclopropanation fût choisie comme réaction pour tester notre concept. Notre objectif était l'identification de complexes capables de catalyser la cyclopropanation de I pour former III en utilisant les conditions nécessaires pour produire II *in situ* (Schéma I).



Schéma I: Réaction test.

Plusieurs métaux de transition furent actifs dans ces conditions (Fe, Rh, Ru, Co). Basé sur ces résultats initiaux, une cyclopropanation catalysée par un complexe de fer fût développée (Schéma II).

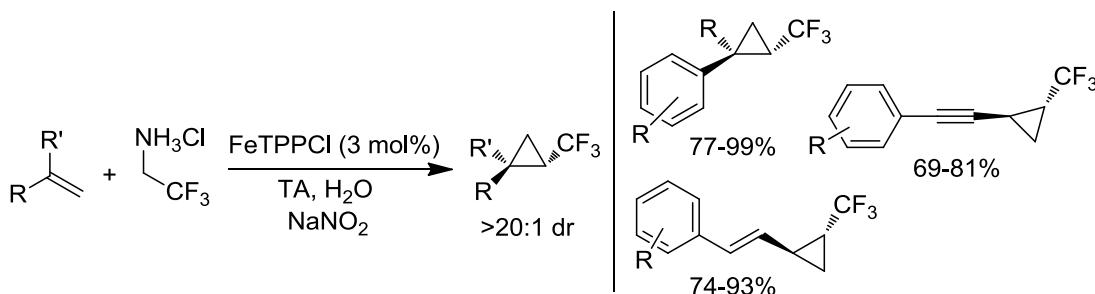


Schéma II: Cyclopropanation catalysée par un complexe de fer.

Ensuite, une version asymétrique de cette cyclopropanation fût découverte utilisant un complexe asymétrique de cobalt (Schéma III).

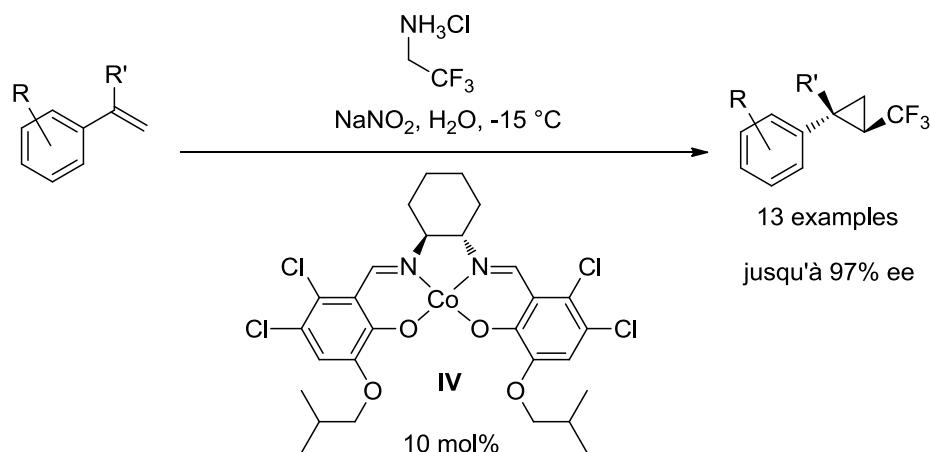


Schéma III: Cyclopropanation asymétrique utilisant un complexe de cobalt.

Finalement, une réaction de cyclopropagation fût développée utilisant un complexe de rhodium (Schéma IV). Les nouveaux produits obtenus fûrent ensuite testés dans d'autres réactions (réduction, Heck, Diels-Alder, déprotonation).

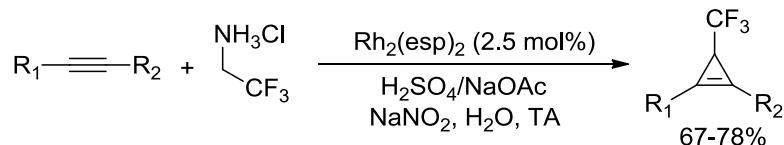


Schéma IV: Cyclopropagation catalysée par un complexe de rhodium.

L'utilisation du trifluorométhyle de diazométhane fût aussi étudiée dans le cadre des réactions d'homologations facilitées par des acides de Lewis. L'homologation d'aldéhydes, de cétones et une aziridination fûrent développées, permettant un accès rapide à de nouveaux produits fluorés (Schéma V).

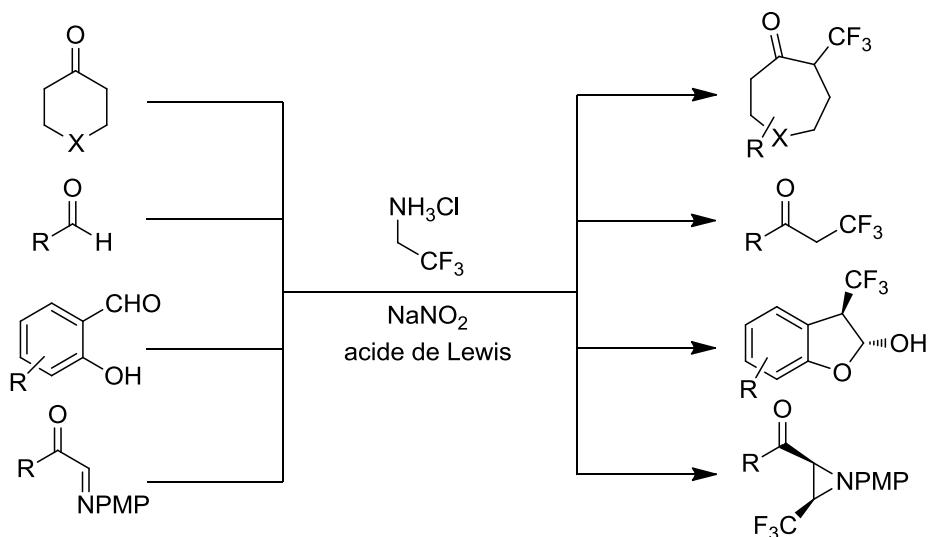


Schéma V: Réactions d'homologation.

Une nouvelle méthode pour l'utilisation de diazométhane fût ensuite étudiée, utilisant une stratégie similaire. Le réactif est formé *in situ* parallèlement à son utilisation catalysée par un métal de transition (Fe). Une séparation de phase fût observée et son importance pour la réaction déterminée. Il est important de mentionner que le complexe de fer est capable de catalyser la réaction sous des conditions extrêmes (6 M KOH, environnement oxidant, présence d'eau).

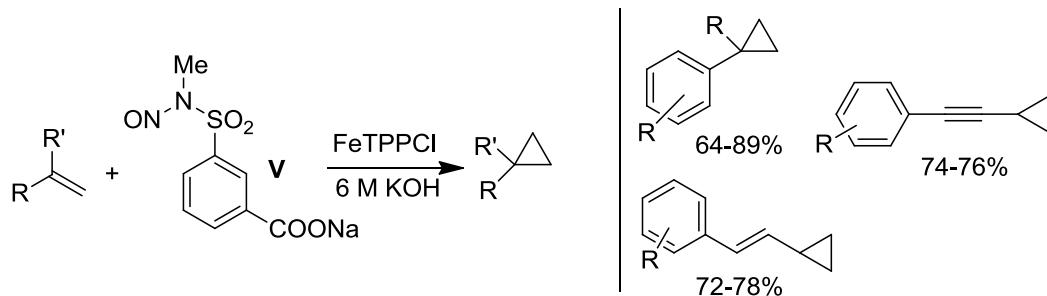


Schéma VI: Cyclopropanation utilisant un complexe de fer et du diazométhane.

List of Abbreviations

Ac	acetyl
Ar	aryl
BHT	butyl hydroxyl toluene
Bn	benzyl
br	broad
Bu	butyl
Cm	centimeter
c	<i>cyclo</i>
CAN	ceric ammonium nitrate
coe	cyclooctene
d	doublet
dba	dibenzylideneacetone
DBU	1,8-Diazabicycloundec-7-ene
DCM	dichloromethane
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DOSP	<i>N</i> -(<i>p</i> -dodecylphenylsulfonyl)prolinato
dr	diastereoisomeric ratio
EDG	electron-donating group
ee	enantiomeric excess
EWG	electron-withdrawing group
equiv	equivalent
Et	ethyl

esp	Espino
g	gram
HPLC	high-performance liquid chromatography
Hx	hexyl
Hz	Hertz
<i>i</i>	<i>iso</i>
IR	infrared
<i>J</i>	coupling constant
Ms	mesityl
<i>m</i>	<i>meta</i>
m	multiplet
M	molar
Me	methyl
MEAZ	methyl azetidinone
MEPY	methyl 2-pyrrolidine-5-carboxylate
MG	masking group
MOM	methoxymethyl
MS	mass spectroscopy
NBS	<i>N</i> -bromosuccinimide
NMI	<i>N</i> -methyl imidazole
NMR	nuclear magnetic resonance
NMU	<i>N</i> -methyl urea
NOE	nuclear Overhauser effect
<i>o</i>	<i>ortho</i>
<i>p</i>	<i>para</i>
p-ABSA	4-acetamidobenzenesulfonyl azide

P	porphyrin
pm	picometer
PMP	<i>para</i> -methoxyphenyl
Ph	phenyl
Piv	pivalate
Pr	propyl
PTC	phase-transfer catalyst
q	quartet
RT	room temperature
s	singlet
SFC	super-critical chromatography
Su	succinamidyl
<i>t</i>	<i>tert</i>
t	triplet
TBS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TPP	tetr phenylporphyrin
Ts	toluenesulfonyl
UV	ultraviolet

1. Introduction: Diazo Compounds

1.1. Properties and Chemistry

1.1.1. Properties¹

The first diazo compound, ethyl diazoacetate, was prepared by *Curtius* in 1883.² At first a matter of debate, it is nowadays well-established that diazo compounds are molecules that bear the general formula R₂N₂ and have a linear form of the N₂-unit (In contrast to diazirines, cyclic isomers) (Figure 1).

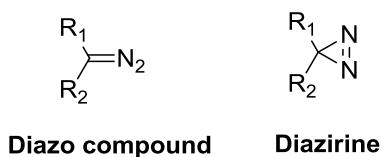
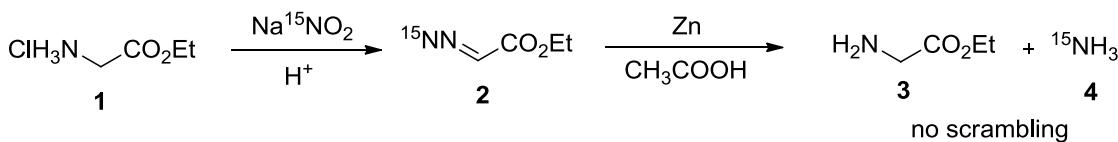


Figure 1: Structures of Diazo Compounds and Diazirines.

This structural puzzle (linear versus cyclic) was definitely solved by an elegant labeling experiment performed in 1957 (Scheme 1).³ In this experiment, ethyl glycinate (**1**) was diazotized using ¹⁵N-labeled sodium nitrite, and the corresponding labeled ethyl diazoacetate (**2**) was reductively cleaved to glycine (**3**) and ammonia (**4**). This resulted in clean formation of ¹⁵N-ammonia and unlabeled glycine. The cyclic structure could thus be excluded, since no scrambling of the label was observed.

Clusius and Lüthi (1957)



Scheme 1: Experimental Evidence for the Linear Structure of Ethyl Diazoacetate.

¹ For general reviews see: (a) H. Zollinger, *Diazo Chemistry I and II*, VCH Weinheim, **1994**. (b) M. Regitz, G. Maas, *Diazo Compounds—Properties and Synthesis*, Academic Press, Orlando, **1986**. (c) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**.

² T. Curtius, *Chem. Ber.* **1883**, *16*, 2230.

³ K. Clusius, U. Lüthi, *Helv. Chim. Acta* **1957**, *40*, 445.

Two main resonance structures are contributing to the overall structure and properties of simple diazoalkanes (Figure 2).

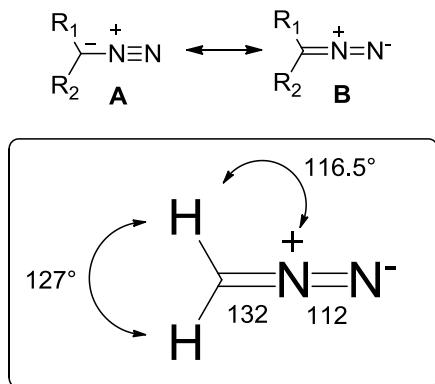


Figure 2: Two Main Resonance Structures of Diazo Compounds. Geometry of Diazomethane.

The length of the C-N bond in diazomethane is 132 pm whereas the N-N bond is 112 pm long.^{1b} It indicates that the actual structure of the diazo compound lies between the two resonance structures **A** and **B**, since the C-N bond is shorter than a regular C-N single bond (147 pm) and the N-N bond is longer than a N-N triple bond (109.8 pm). Due to the planarity of the structure and high delocalization of the charges, diazo compounds can be described as C(sp²)-N(sp)-N(sp) hybridized molecules. Substituted diazoalkanes having electron-withdrawing groups are thought to look more like resonance structure **A** (Figure 2), since the negative charge can be further delocalized into the additional group.

Diazo compounds also bear very characteristic spectral properties.^{1b} They are usually colored (yellow to red) and are thus absorbing light in the visible region of the spectrum. Two maximums are observable in the UV/VIS spectrum of diazo compounds. For diazomethane the first (weak one) is partially located in the visible region and has its maximum at 410 nm. The second, strong one has its maximum at 270 nm. The so-called “diazo band” is also very characteristic in the IR-spectrum, giving a strong signal between 1950 cm⁻¹ and 2300 cm⁻¹ depending on the substituents (2100 for diazomethane itself) and corresponds to the stretching of the N-N triple bond.

Due to their high nitrogen content and easy release of thermodynamically stable dinitrogen, diazo compounds are inherently reactive molecules.^{1b} First, they are thermally unstable and generate free carbenes upon heating. Stability towards heating is increased by mesomeric stabilizing substituents (such as esters) and decreased upon substitution with electron-donating (alkyl) substituents. Second, diazo compounds are acid-labile compounds due to the significant contribution

of resonance structure **A** (Figure 2) bearing a carbanion. Diazomethane is the most labile compound, and unstabilized diazoalkanes are generally much more acid-labile than electron-withdrawing-substituted ones (Figure 3).

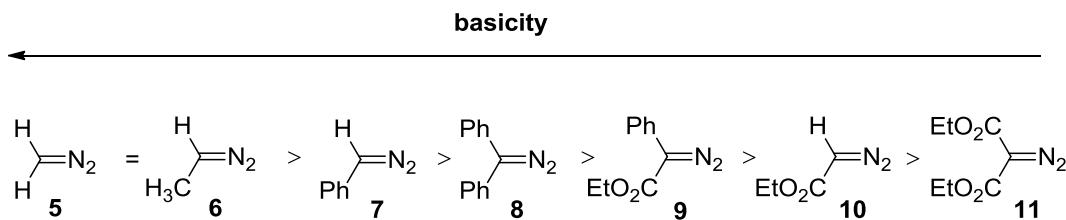


Figure 3: Relative Basicity of Selected Diazo Compounds.

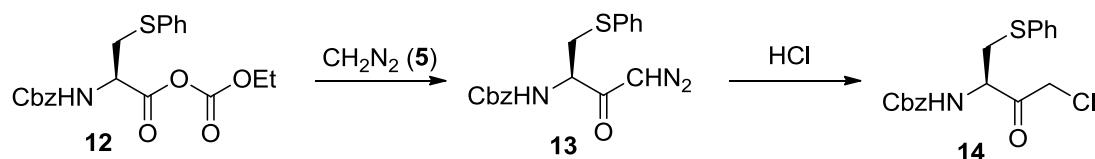
Finally, diazo compounds liberate the free carbene under photochemical activation.^{1b} Usually forming singlet carbenes, this process can be directed towards the formation of triplet carbene using a triplet sensitizer like benzophenone.

Due to their high reactivity and high nitrogen content, diazo compounds are explosive compounds. Detonation has been observed with several compounds of this class, and therefore they have been limited in use to small-scale laboratory work. The prototypical explosive compound is diazomethane (**5**) itself, and a wide range of factors have been reported to cause severe explosions. *De Boer* and *Backer* have reported that the compound had exploded during distillation, upon drying over sharp KOH pellets, and on exposure to light.⁴ However, the use of diazomethane (**5**) has been reported in a publication describing its large-scale use and generation (Scheme 2).⁵ This industrial setup used a continuous generation of diazomethane, ensuring that no more than 80 g of diazomethane is present in the system at any time.

⁴ T. J. de Boer, H. J. Backer, *Org. Syn.* **1963**, Coll. Vol. 4, 250.

⁵ L. D. Proctor, A. J. Warr, *Org. Proc. Res. Dev.* **2002**, 6, 884.

Phoenix chemicals (2002)



50-60 tons/year

continuous generation of CH_2N_2 , less than 80 g at any time

Scheme 2: Large Scale Production and Use of Diazomethane.

Another common diazo compound, ethyl diazoacetate (**2**), has been studied thermochemically by Monsanto and did not show any explosive properties under normal conditions.^{6,7} Thus, as described above, diazo compounds bearing electron-withdrawing substituents are expected to be safer to handle and more stable.

Another issue arising from the use of diazo compounds comes from their high toxicity. In fact, diazomethane was reported to be a very potent carcinogen and acute toxic compound.⁸ A fatal case of intoxication has even been reported in the medical literature.⁹ More recently, two chemists died from lung failure after inhalation of trimethylsilyl diazomethane.¹⁰ The toxicity of diazo compounds probably arises from their ease of protonation, forming highly electrophilic alkyl diazoniums that can decompose to free carbocations. These species can then alkylate nucleophilic biomolecules like DNA leading to irreversible damages. Great care is thus recommended in the use of these compounds.

1.1.2. Chemistry

Despite their high instability and toxicity mentioned above, diazo compounds have emerged as one the most versatile and useful class of reagents in organic synthesis.^{1c} Many factors are responsible for their large use: (1) they are inexpensively and easily accessible via several methods (see Section 1.2). (2) They are versatile precursors to carbenes, metal-carbenoids and carbocations.

⁶ J. D. Clark, A. S. Shah, J. C. Peterson, L. Patelis, R. J. A. Kersten, A. H. Heemskerk, *Therm. Acta* **2002**, 386, 73.

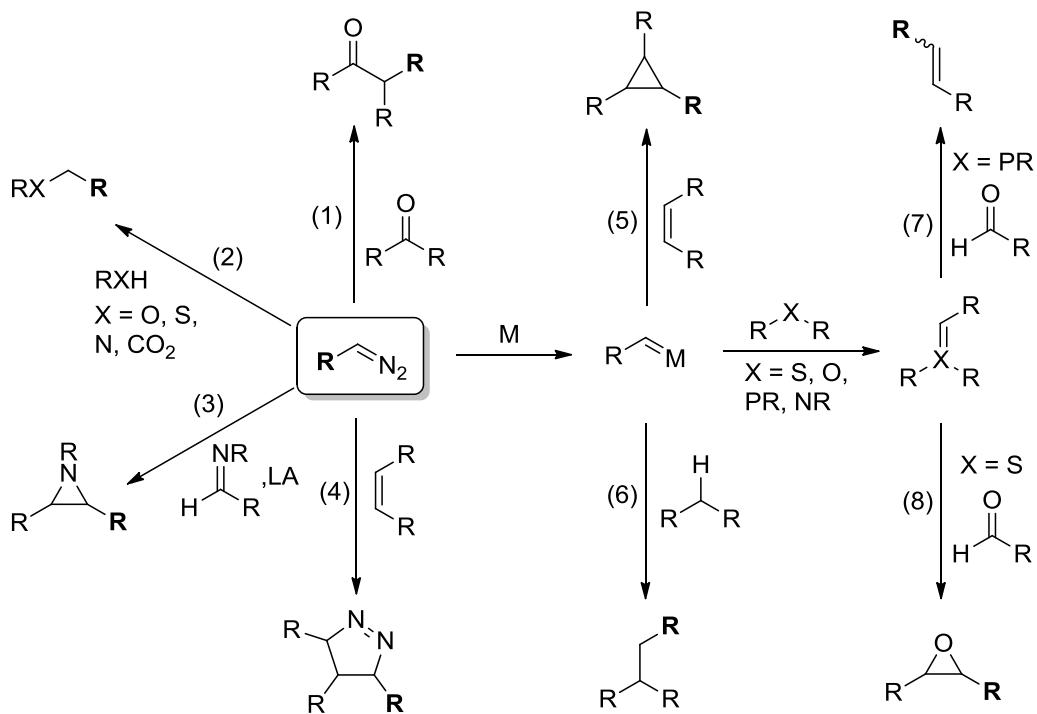
⁷ The compound is known to explode upon heating or treatment with strong acid. See: Ethyl Diazoacetate, in *Encyclopedia of Reagents for Organic Chemistry*, Wiley.

⁸ R. Schoental, *Nature* **1960**, 188, 420.

⁹ E. B. LeWINN, *Am. J. Med. Sci.* **1949**, 218, 556.

¹⁰ J. N. Kemsley, *Chem. Eng. News* **2011**, 89, 15.

(3) The sole by-product of their decomposition is N₂. Scheme 3 summarizes some of the most useful reactions of diazo compounds.



Scheme 3: Summary of Selected Transformations of Diazo Compounds.

It is clear from this scheme that diazo compounds are useful reagents for the preparation of a wide range of building blocks. The left side of the scheme describes the direct reaction between diazo compounds and organic substrates. A very useful transformation is the homologation of carbonyl compounds with or without the use of Lewis acid activators (1). This class of transformation will be discussed in Section 1.3. Probably one of the historically most useful reactions is the direct conversion of carboxylic acids into their corresponding methyl esters under neutral conditions using diazomethane (2).¹¹ This reaction can be extended to other H-X-R compounds (X being a heteroatom), sometimes requiring the use of a Lewis or protic acid as mediator. Another common reaction of diazo compounds is the aziridination of imines via the aza-Darzens route (3) (see Section 1.3). Diazo compounds are also often involved in dipolar cycloadditions due to their 1,3-dipole nature (4).^{1a} The middle part of the scheme summarizes the

¹¹ T. H. Black, *Aldrichim. Acta* **1983**, 16, 3.

use of metal-carbenoids in the direct transfer to an organic nucleophile.^{12,13} One of the most well-studied metal-catalyzed transformation of diazo compounds in this category is the cyclopropanation (5) (and to a lesser extent cyclopropenation) and those are further described in Section 1.3. Furthermore, C-H insertion using carbenoids has become a major area of research affording the direct functionalization of unreactive C-H bonds (6).^{14,15} The right part shows selected examples of ylide-mediated transformations. These compounds are accessible via metal-catalyzed carbene transfer from a diazo compound to a suitable heteroatom triggering further reactions like Wittig olefination (7)¹⁶ or additions to suitable electrophiles (8).¹⁷ Important reactions absent from this picture include: Wolff-rearrangement (*Arndt-Eistert* homologation),^{1c} cross-coupling reactions (vide infra), dipolar cycloadditions with oxonium/ammonium ylides issued from metal-carbene,¹⁸ and free carbene/carbocation reactions.^{1a,b}

1.1.3. Conclusion

Diazo compounds are highly reactive reagents commonly used in a wide range of transformations. Despite their untoward properties, they are used on a daily basis in academia in the preparation of complex molecules. The next Section (1.2) will provide an overview of the synthetic methods for the preparation of diazo compounds, immediately followed by a detailed discussion of the literature precedent for the reactions relevant to this dissertation (cyclopropanation, cyclopropenation, homologation and aziridination) in Section 1.3.

1.2. Preparative Methods

1.2.1. Diazotization

A common method for the preparation of diazo compounds is the diazotization of the corresponding aliphatic amine using a variety of nitrosating agents, the most common being sodium

¹² M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919.

¹³ M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911.

¹⁴ M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704.

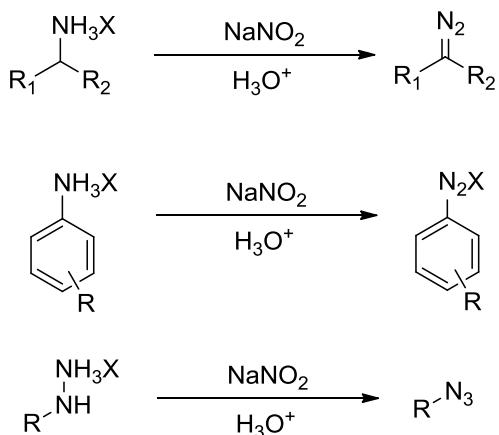
¹⁵ H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861.

¹⁶ X. L. Sun, J. C. Zheng, Y. Tang, *Pure Appl. Chem.* **2010**, *82*, 625.

¹⁷ J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, 1479.

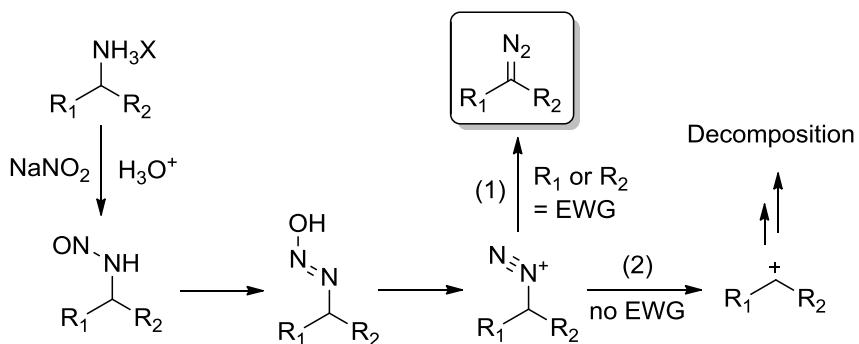
¹⁸ A. Padwa, *Helv. Chim. Acta* **2005**, *88*, 1357.

nitrite.^{1a} This method does not only apply to the synthesis of diazo compounds, but is also the standard preparative method for diazonium salts from anilines and is occasionally used for the synthesis of certain azides from the corresponding hydrazines (Scheme 4).^{1a}



Scheme 4: Diazotization of Amines, Anilines and Hydrazines.

The standard procedure usually prescribes the use of an amine salt dissolved in aqueous acidic media at lower temperature (usually 0 °C or lower) followed by portionwise addition of sodium nitrite.^{1a} The active reagent, nitrous acid (HNO_2), is formed *in situ* and performs the diazotization.^{1a} The mechanism of this reaction involves the formation of a transient *N*-nitroso intermediate that forms an aliphatic diazonium upon dehydration (Scheme 5). The so-formed aliphatic diazonium can then undergo two different pathways: (1) elimination of the acidic proton to form a diazo compound; (2) loss of dinitrogen to form a carbocation leading to several by-products.



Scheme 5: Mechanism of the Diazotization Reaction.

Path (1) is only preferred in the case of aliphatic diazoniums bearing acidifying substituents at the α -position.^{1a} This feature is the major limitation of this method of preparation. Selected examples of diazo compounds (**15**, **2**, **16**, and **17**) prepared by this method are presented in Figure 4.

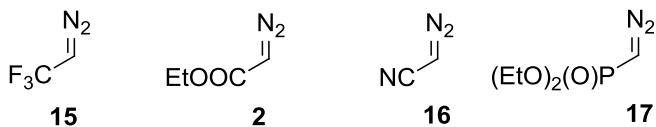
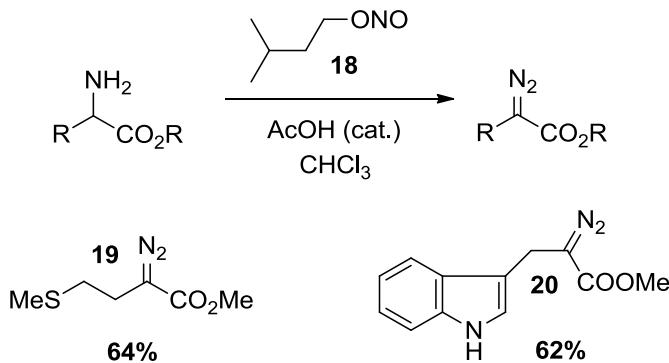


Figure 4: Selected Diazo Compounds of Interest Prepared by Diazotization.

An alternative to the aqueous diazotization is the use of alkyl nitrite reagents to perform the diazotization in organic media. For example, this strategy has been used in the direct preparation of substituted diazoesters (e.g. **19** and **20**) from amino acids, a reaction not possible with aqueous HNO_2 (Scheme 6).¹⁹



Scheme 6: Diazotization of Substituted Aminoesters Using Isoamyl Nitrite (18).

Hazardous, strongly reactive reagents like dinitrogen tetroxide and nitrosonium salt (NOCl or NOBF_4) have also been used for selected diazotizations but due to their untoward properties their use has been abandoned.^{1a}

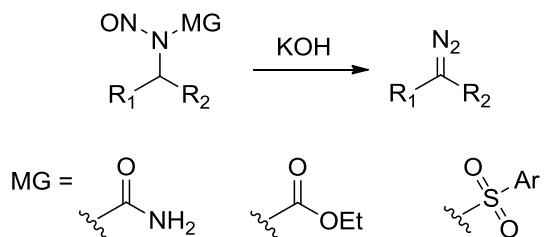
In conclusion, the direct diazotization of aliphatic amines is an important synthetic method for the preparation of diazo compounds. It is the method of choice in the case of easy to synthesize or commercially available amine precursors. Advantageous is the use of water as the solvent and inexpensive, atom-economical reagents (NaNO_2). However, the method is limited to activated amines bearing an extra acidifying group (COOEt , CF_3 , NO_2 , $\text{P}(\text{O})(\text{OEt})_2$) on the α -carbon, and thus

¹⁹ N. Takamura, T. Mizoguchi, K. Koga, S. Yamada, *Tetrahedron* **1975**, *31*, 227.

other methods (*Bamford-Stevens*, nitroso decomposition, hydrazone oxidation, *vide infra*) have to be used in the case of electron-rich (alkyl, phenyl) diazo compounds.

1.2.2. Base-mediated decomposition of nitrosamides

As mentioned previously, not all the diazo compounds are accessible by direct diazotization of the corresponding amine. Diazoalkanes not bearing any electron-withdrawing groups have thus to be accessed by other methods. The first of those is the base-mediated decomposition of nitrosamide derivatives. This method was first used by *von Franchimont* and *von Pechman* over 100 years ago, when they discovered that the treatment of nitrosomethylcarbamates with alkali evolved a yellow gas, diazomethane.²⁰ The general equation for this type of diazo preparation is disclosed in Scheme 7.



Scheme 7: Generic Description of the Base-Mediated Decomposition of Nitrosamides.

A wide range of different masking groups (MG in the scheme) were used, including ureas, carbamates and sulfonamides.^{1a} Carbamates were used in the early days of diazo chemistry, and were later replaced by urea-derived reagents. Unfortunately, these reagents were shown to be very potent carcinogenic substances, and their use is discouraged nowadays.²¹ Diazald, a commercially available compound, was later shown to be the reagent of choice for the preparation of diazomethane.²² Details about diazomethane preparation will be further discussed in Chapter 6. Higher diazoalkanes are preferentially prepared by other methods, including the *Bamford-Stevens* reaction and the direct oxidation of hydrazones (*vide infra*).

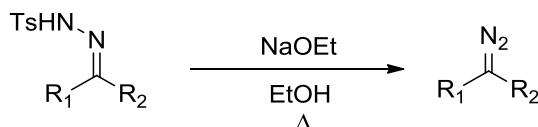
²⁰ H. von Pechman, *Chem. Ber.* **1894**, 27, 1888. H. von Pechman, *Chem. Ber.* **1895**, 28, 855.

²¹ U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *Reports on Carcinogen*, 12th edition, 316 (2011).

²² See Reference 4.

1.2.3. Bamford-Stevens Reaction^{1a}

The *Bamford-Stevens* reaction is a general method for the preparation of a wide range of diazo compounds from the corresponding ketone or aldehyde. The standard procedure involves condensation of the required ketone or aldehyde with tosylhydrazine.^{1a} The obtained tosylhydrazone is then deprotonated by a base (usually NaOEt in ethanol) and heated between 50-70 °C to undergo pyrolytic decomposition and form the diazo compound (Scheme 8).

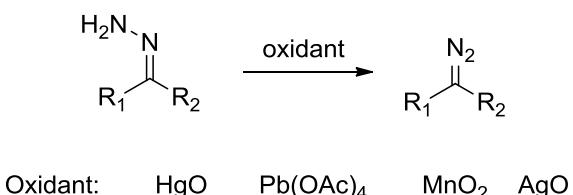


Scheme 8: *Bamford-Stevens* Reaction.

The method is particularly indicated for the preparation of semi-stabilized diazo compounds like aryl-substituted diazo compounds,^{1a} since they offer increased thermal stability compared to alkyl substituted diazoalkanes. The low thermal stability (formation of free carbenes) of aliphatic diazo compounds renders their preparation difficult using this methodology, and oxidation of hydrazones is preferred.

1.2.4. Oxidation of hydrazones

This method is related to the previously described *Bamford-Stevens* reaction; however this time an external oxidant is used to prepare the diazo compound. A positive feature of the oxidation method is that sensitive aliphatic diazo compounds can be prepared since no heating is required.^{1a} This method usually employs a hydrazone of the corresponding ketone that is treated with a stoichiometric oxidant in an apolar organic solvent (Scheme 9).^{1a}

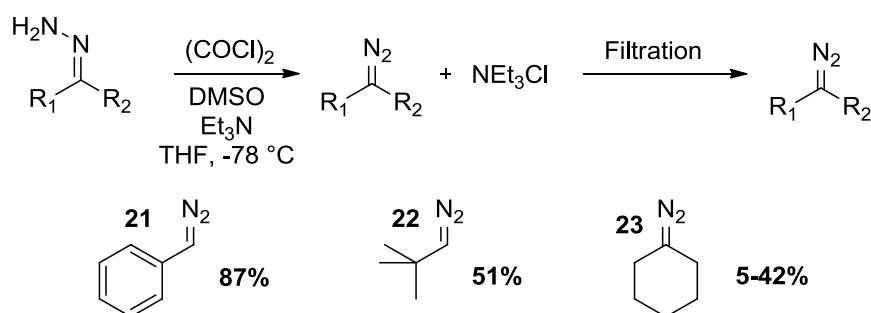


Scheme 9: Oxidation of Hydrazones Using Heavy Metals.

The first oxidant used was mercury oxide, and its use was reported by *Curtius* in 1889.²³ The use of two other oxidants, Pb(OAc)₄ and MnO₂ was developed later.^{1a} Lead tetraacetate produces acetic acid as a side-product, and is thus not suitable for acid-labile diazoalkanes. Activated manganese dioxide needs to be used in excess and is thus a less toxic, but non atom-economical solution.

Recent developments have been reported using organic oxidants to transform hydrazones into diazo compounds. *Javed* and *Brewer* described an elegant oxidation of hydrazones under *Swern* conditions (Scheme 10).²⁴

Javed and Brewer (2007)



Scheme 10: Oxidation of Hydrazones under Swern Conditions.

A wide range of different, sensitive diazoalkanes (e.g. **21**, **22** and **23**) could be obtained in good yields as solutions in THF. The only by-product was the insoluble triethylammonium chloride salt, that could easily be removed by simple filtration. The method was also suitable for the preparation of stabilized diazoketones.

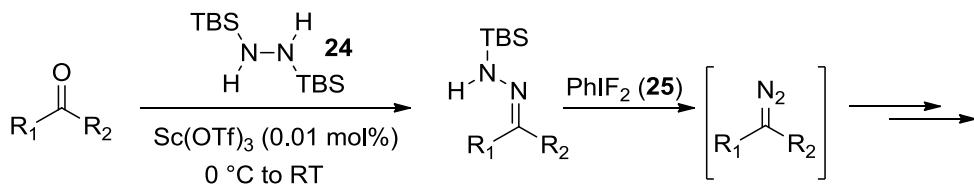
Furrow and *Myers* described a convenient protocol for *in situ* generation of diazoalkanes from a silylated hydrazone (**24**) derivative by using difluoriodobenzene (**25**) as the oxidant.²⁵

²³ T. Curtius, *Chem. Ber.* **1889**, 22, 2161.

²⁴ M. I. Javed, M. Brewer, *Org. Lett.* **2007**, 9, 1789.

²⁵ M. E. Furrow, A. G. Myers, *J. Am. Chem. Soc.* **2004**, 126, 12222.

Furrow and Myers (2004)



Scheme 11: Myers' Strategy for the Preparation of Diazoalkanes.

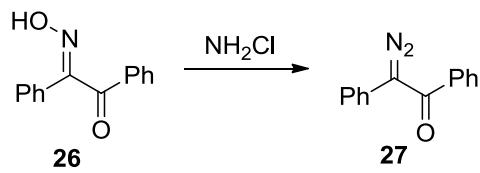
The prepared diazo compounds were directly used in esterification reactions of complex natural products. This synthetic method is limited by the availability and difficult handling of difluoroiodobenzene.

In conclusion, the oxidation of hydrazones represents one of the most commonly used routes for the preparation of labile diazoalkanes. Particularly interesting is the report by *Brewer* dealing with metal-free dehydrogenation of hydrazones.

1.2.5. Forster reaction

Related to the two previous methods, the *Forster* reaction is scarcely used for the preparation of diazoalkanes. This reaction involves the reaction of an oxime (e.g. **26**) with chloramine (generated from sodium hypochlorite and ammonia) to form diazoketone (e.g. **27**) and was first reported by *Forster* in 1915 (Scheme 12).²⁶

Forster (1915)

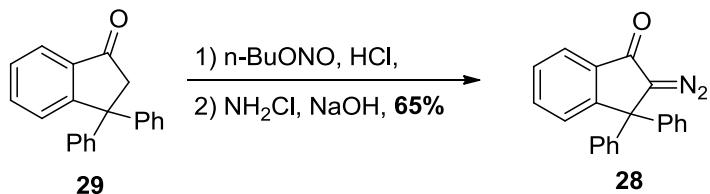


Scheme 12: Seminal Report by Forster.

²⁶ M. O. Forster, *J. Chem. Soc.* **1915**, 107, 260.

The strong oxidizing nature of chloramine has been a limitation to the larger development of this method. However, a modification using hydroxylamine *o*-sulfonic acid has been published later, in which the solid reagent is used as a convenient alternative to chloramine.²⁷ Although its use is not widespread, the *Forster* reaction proved useful in certain instances. For example, it was used in the preparation of a five-membered ring diazoketone (**28**) in two steps from the corresponding free ketone (**29**).²⁸

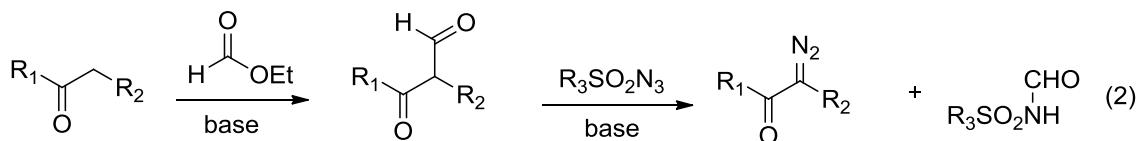
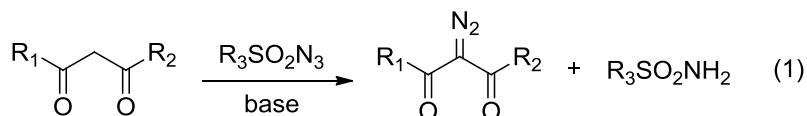
Cava et al (1958)



Scheme 13: A Sequential Oximation/*Forster* Reaction for the Preparation of Diazo **28**.

1.2.6. *Regitz* diazo transfer

The last classical method to be discussed is the *Regitz* diazo transfer from azides to activated C-H compounds.²⁹ This method has found widespread use in the preparation of diazoketones and diazoesters from carbonyl compounds. Reaction of an activated C-H compound is performed with a sulfonyl azide in the presence of base.²⁹



Scheme 14: *Regitz* Diazo Transfer: (1) Direct Diazo Transfer. (2) Deacylating Diazo Transfer.

²⁷ J. Meinwald, P. G. Gassman, E. G. Miller, *J. Am. Chem. Soc.* **1959**, *81*, 4751.

²⁸ M. P. Cava, R. L. Little, D. R. Napier, *J. Am. Chem. Soc.* **1958**, *80*, 2257.

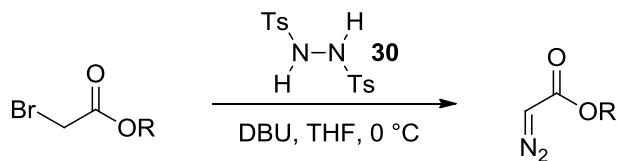
²⁹ L. Kürti, B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, **2005**, p.376-377.

Two cases are possible: (1) the compound is doubly activated by an electron-withdrawing group (e.g., diketones or ketoesters) (2) the compound has only one activating group and the starting material needs to be further activated by addition of a transient formyl or trifluoroacetyl group that will be lost during the diazo transfer. In both cases a very similar procedure is used. Classical diazo transfer reagents include: TfN₃, MsN₃, TsN₃ and the commercially available P-ABSA (4-acetamidobenzenesulfonyl azide). The method is widely applicable and was thus employed in a large number of total syntheses.²⁹

1.2.7. Miscellaneous

Some miscellaneous methods for the preparation of diazo compounds are worth mentioning here. The first one was recently published by *Fukuyama* and describes the preparation of a wide range of diazoacetates starting from bromoacetyl bromide (Scheme 15).³⁰

Fukuyama and co-workers (2007)



Scheme 15: *Fukuyama's Method for Diazoesters Preparation.*

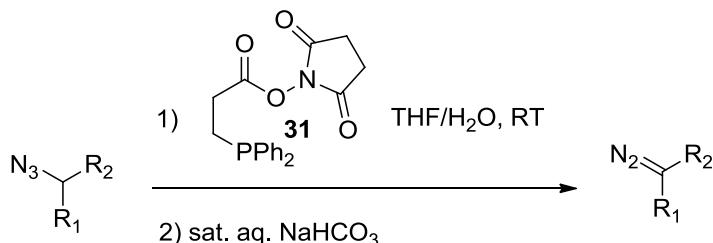
Treatment of bromoacetyl bromide with the desired alcohol afforded bromoacetate products. These products were then treated with reagent **30** and DBU in THF, and afforded the corresponding diazoacetates.

Another recently published procedure used a conceptually novel strategy to access diazo compounds from the corresponding azides (Scheme 16).³¹

³⁰ T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2007**, *9*, 3195.

³¹ E. L. Myers, R. T. Raines, *Angew. Chem. Int. Ed.* **2009**, *48*, 2359.

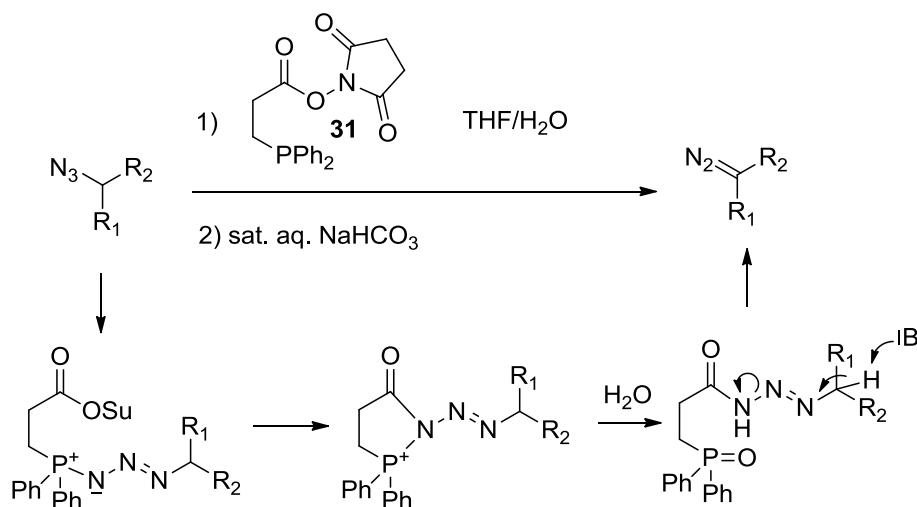
Myers and Raines (2009)



Scheme 16: Phosphine-Mediated Preparation of Diazo Compounds Using Azides.

In this report, *Myers and Raines* showed that a newly designed phosphine reagent (**31**) bearing an acylating reagent could be used in the direct transformation of azides into diazo compounds. The reaction is believed to occur via the formation of a transient phosphazide, which is subsequently trapped intramolecularly by the neighboring acylating group (Scheme 17). This intermediate then reacts with water to form the phosphine oxide and the corresponding acyltriazene that collapses to the diazo compound.

Myers and Raines (2009)



Scheme 17: Mechanism of the Phosphine-Mediated Diazo Preparation.

The two reactions discussed in this last section illustrate the fact that, even though diazo chemistry is a 125 years old field of research, groundbreaking developments in the preparation of diazo compounds are still possible. In fact many of the current state-of-the-art methods still use dangerous reagents, are limited in scope or use atom-inefficient reagents. As a result, much room is available for the development of new diazo syntheses.

1.3. Reactions of Diazo Compounds

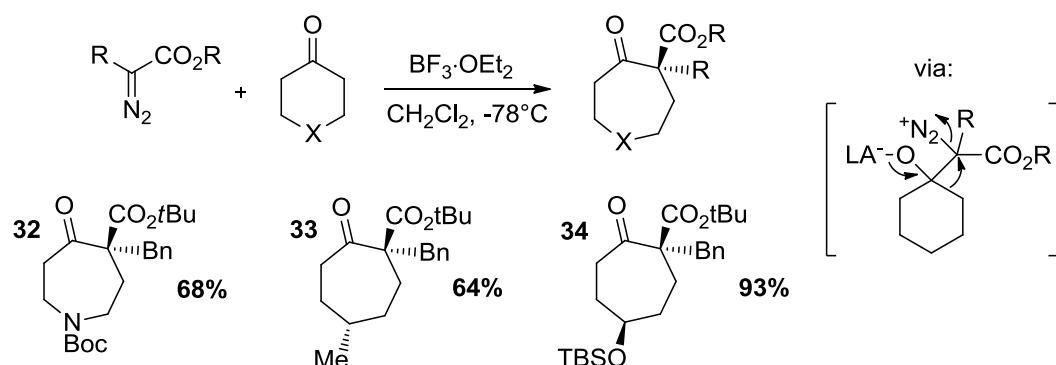
1.3.1. Introduction

A wide range of reactions using diazo compounds have been described in the literature (vide supra), attesting for their utility in organic synthesis. Since a complete description of the applications of diazo compounds goes beyond the scope of this work, only the chemistry relevant to our work, Lewis acid-catalyzed reactions and metal-catalyzed carbenoid (only cyclopropanation and cyclopropenation) reactions will be described extensively. Only the most relevant and recent examples from the literature will be presented.

1.3.2. Lewis acid-mediated transformations

Homologation of carbonyl compounds is a widespread synthetic method for the preparation of synthetically useful products.³² Upon activation with a suitable Lewis acid, carbonyl compounds react with diazo compounds to form alkoxide-diazonium intermediates that can further undergo migration or elimination reactions. *Maruoka* recently described the ring-expansion reaction of cyclic ketones to afford cycloheptanones bearing a quaternary center in good diastereoselectivity (Scheme 18).³³

Maruoka and co-workers (2009)



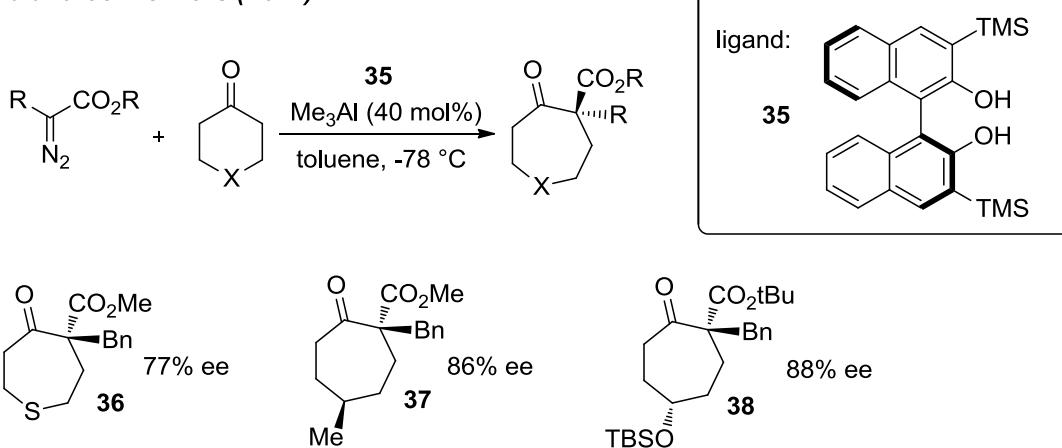
Scheme 18: *Maruoka's Diastereoselective Direct Tiffenau-Demjanov Strategy to Access Cycloheptanones.*

³² T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091.

³³ T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 6614.

A wide range of disubstituted diazo acetates could be used and afforded the products (e.g. **32**, **33** and **34**) in good yields. Maruoka and co-workers later reported an asymmetric version of this reaction using trimethyl aluminum and chiral ligand **35**.³⁴ The desired cycloheptanones bearing products (e.g. **36**, **37** and **38**) were obtained with high enantioselectivities. (Scheme 19).

Maruoka and co-workers (2011)



Scheme 19: Enantioselective Preparation of Cycloheptanones via Ring-Expansion.

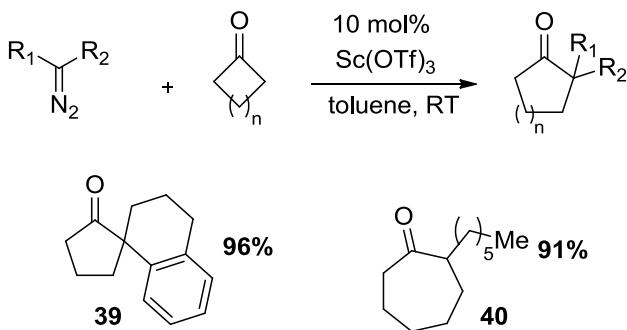
Aliphatic diazoalkane compounds are even better partners for the homologation of ketones since they are not stabilized by an electron-withdrawing group. They thus show increased nucleophilicity and milder Lewis acids can be used.³⁵ A recent example was disclosed by Moebius and Kingsbury (Scheme 20).³⁶ In this report they showed that Sc(OTf)₃ was an efficient catalyst for the direct *Tiffenau-Demjanov* ring-expansion of cyclic ketones. A wide range of products (e.g. **39** and **40**) could be prepared in good yields.

³⁴ T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834.

³⁵ Even protic solvents are strong enough to induce a reaction between non-stabilized diazoalkanes and aldehydes or ketones: see K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis* **1994**, 1283.

³⁶ D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878.

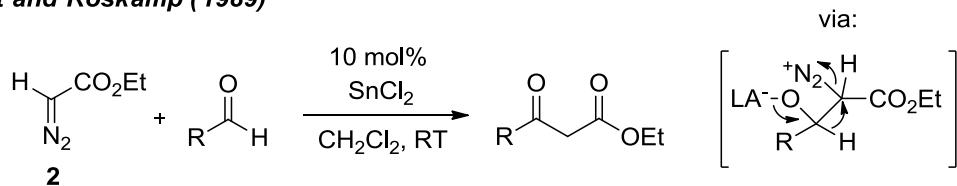
Moebius and Kingsbury (2009)



Scheme 20: Direct Tiffenau-Demjanov Reaction of Cyclic Ketones Using non-Stabilized Diazo Compounds.

The homologation of aldehydes with diazoacetates to form a variety of acetate products is also a common reaction. Roskamp reported in 1989 an efficient homologation of simple aldehydes to the corresponding keto-esters using ethyl diazoacetate (**2**) and SnCl_2 as the catalyst (Scheme 21).³⁷

Holmquist and Roskamp (1989)

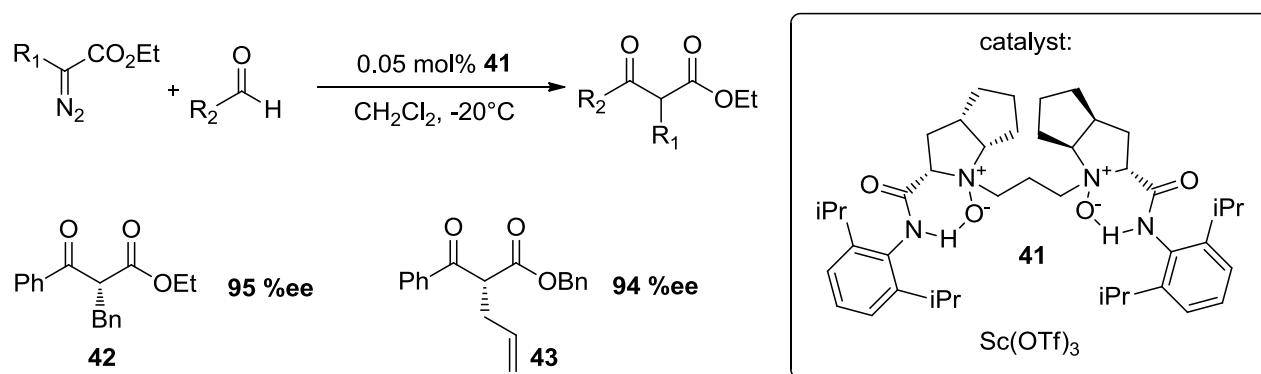


Scheme 21: Seminal Report by Roskamp on the Homologation of Aldehydes.

Recently, Feng and co-workers reported an asymmetric version of this reaction using alkyl-substituted diazoesters and a chiral scandium catalyst (**41**). They obtained a wide range of chiral ketoesters (e.g. **42** and **43**) in high enantiomeric purity.³⁸

³⁷ C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258.³⁸ W. Li, J. Wang, X. L. Hu, K. Shen, W. T. Wang, Y. Y. Chu, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 8532.

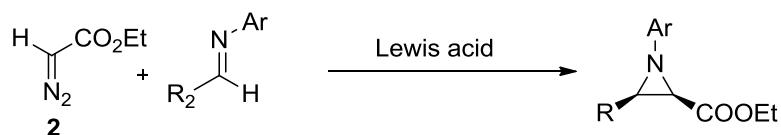
Feng and co-workers (2010)



Scheme 22: Asymmetric *Roskamp* Reaction.

Beyond carbonyl homologation reactions, many other transformations using Lewis acids and diazo compounds have been described. One further example is the preparation of aziridines via the *aza-Darzens* reaction. This field was pioneered by *Brookhart* and *Templeton* in 1996, when they published their seminal report on Lewis acid-catalyzed synthesis of aziridines (Scheme 23).³⁹

Brookhart and Templeton (1996)



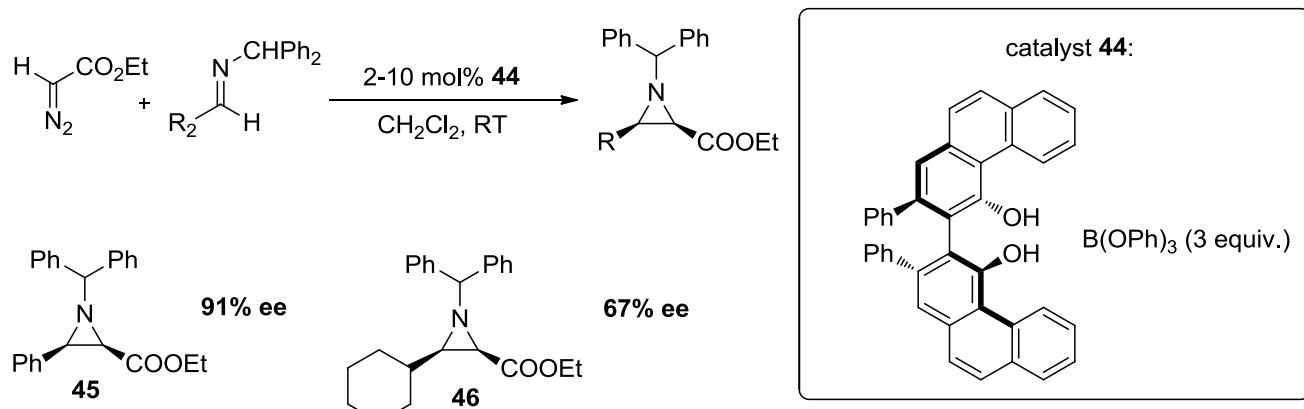
Scheme 23: Seminal Report by Brookhart on the Aziridination of Imines.

A recent extensive study was reported by *Wulff* and co-workers,⁴⁰ where they developed a chiral boron-based Lewis acid (**44**) competent for the catalytic enantioselective reaction between diazoacetates and imines to afford aziridine products (e.g. **45** and **46**) in high enantiopurity (Scheme 24).

³⁹ L. Casarrubios, J. A. Perez, M. Brookhart, J. L. Templeton, *J. Org. Chem.* **1996**, *61*, 8358.

⁴⁰ Z. J. Lu, Y. Zhang, W. D. Wulff, *J. Am. Chem. Soc.* **2007**, *129*, 7185.

Wulff and co-workers (2007)



Scheme 24: Wulff's Asymmetric Aziridination of Imines with Ethyl Diazoacetate.

1.3.3. Metal-catalyzed Cyclopropanation and Cyclopropenation

Cyclopropanation is one the most studied reaction of diazo compounds.^{41,42} This is not surprising, since cyclopropanes are highly versatile intermediates and are present in a wide range of natural products.⁴³ Part of the interest for cyclopropanes, as well as for cyclopropenes, is their interesting physical properties and bonding characteristics.⁴⁴ These compounds possess significant ring strain, as shown in the following figure.⁴⁵



Scheme 25: Ring Strains of All-Carbon Three-Membered Rings.

Cyclopropane preparation is mainly achieved, in a selective manner, by *Simmons-Smith* cyclopropanation⁴⁶ or by metal-catalyzed decomposition of diazo compounds. The cyclopropanation of alkenes using diazo compounds and a metal catalyst is thought to occur via two potential mechanistic pathways (Scheme 26).

⁴¹ H. Lebel, J. F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.

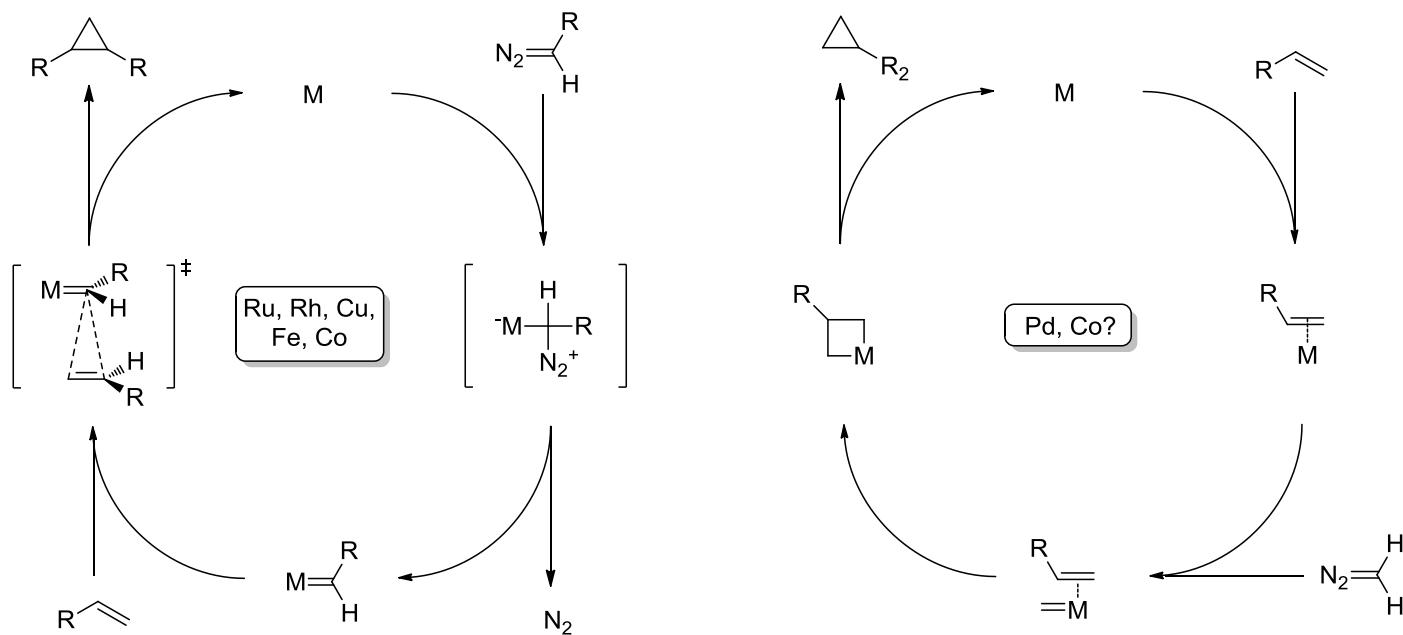
⁴² H. Pellissier, *Tetrahedron* **2008**, *64*, 7041.

⁴³ W. A. Donaldson, *Tetrahedron* **2001**, *57*, 8589.

⁴⁴ Z. Rapoport, *The Chemistry of the Cyclopoly Group*, John Wiley and Sons, **1987**.

⁴⁵ K. B. Wiberg, *Angew. Chem. Int. Ed.* **1986**, *25*, 312.

⁴⁶ See Reference 41



Scheme 26: Two Proposed Mechanisms for Olefin Cyclopropanation Using Diazo Compounds.

The left part of scheme illustrates the most common mechanism in cyclopropanation reactions with metal-carbenoids.⁴⁷ The nucleophilic diazo compound is thought to attack the coordinatively unsaturated metal-center, forming a metal-carbenoid after extrusion of N₂. This species then react in a concerted [2+1] addition with the alkene to give the product cyclopropane. The second mechanism is apparently limited to certain metals such as palladium. In that case, coordination of the alkene to the metal-centre is followed by formation of the metal-carbenoid by a similar mechanism as mentioned before. A formal [2+2] addition gives a metallocyclobutane intermediate that gives, after reductive elimination, the recovered metal center and the product cyclopropane.^{48,49}

Many metals have shown catalytic activity in cyclopropanation reactions with diazo compounds. Early work has shown specific trends among the different metals. *Anciaux*

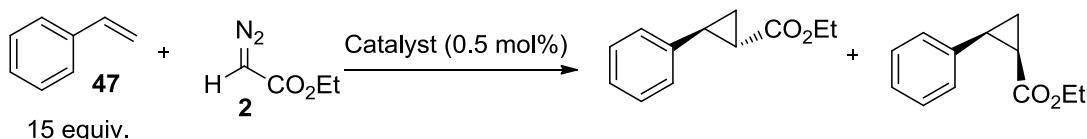
⁴⁷ For a mechanistic study with Rh, see: (a) M. P. Doyle, J. H. Griffin, V. Bagheri, R. L. Dorow, *Organometallics* **1984**, 3, 53. (b) M. P. Doyle, *Acc. Chem. Res.* **1986**, 19, 348. An isolated Fe-porphyrin carbene complex was shown to undergo a reaction with styrene: (c) Y. Li, J. S. Huang, Z. Y. Zhou, C. M. Che, X. Z. You, *J. Am. Chem. Soc.* **2002**, 124, 13185. For Ru (d) C. M. Che, J. S. Huang, F. W. Lee, Y. Li, T. S. Lai, H. L. Kwong, P. F. Teng, W. S. Lee, W. C. Lo, S. M. Peng, Z. Y. Zhou, *J. Am. Chem. Soc.* **2001**, 123, 4119. For Cu (e) X. L. Dai, T. H. Warren, *J. Am. Chem. Soc.* **2004**, 126, 10085.

⁴⁸ B. F. Straub, *J. Am. Chem. Soc.* **2002**, 124, 14195.

⁴⁹ G. Berthon-Gelloz, M. Marchant, B. F. Straub, I. E. Marko, *Chem. Eur. J.* **2009**, 15, 2923.

systematically compared the activity of different transition metal catalysts in the cyclopropanation of styrene with ethyl diazoacetate (Table 1).⁵⁰

Table 1: Comparison of Different Metal Catalysts in the Cyclopropanation of Styrene.

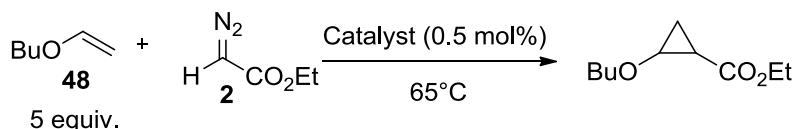


Catalyst	Yield	Trans/cis ratio
Pd(OAc) ₂	98%	2
Cu(acac) ₂	65%	2.1
Rh ₂ (OAc) ₄	92%	1.5
Rh ₂ (TFA) ₄	66%	0.9
Mo ₂ (OAc) ₄	5%	ND
Ru ₂ (OAc) ₄ Cl	38%	1.8

Palladium, rhodium and copper were shown to be good catalysts for this transformation. A ruthenium dimer afforded less product, and molybdenum showed very low reactivity. Study of the scope with the three different catalysts (Pd(OAc)₂, Cu(OTf)₂ and Rh₂(OAc)₄) determined that the rhodium catalyst was the most versatile, and allowed a wide range of aliphatic and disubstituted alkenes to give the product cyclopropane in good yield. A similar systematic comparison was later undertaken by Doyle using an electron-rich alkene (Table 2).⁵¹

⁵⁰ A. J. Anciaux, A. J. Hubert, A. F. Noels, N. Petiniot, P. Teyssie, *J. Org. Chem.* **1980**, *45*, 695.

⁵¹ W. H. Tamblyn, S. R. Hoffmann, M. P. Doyle, *J. Org. Chem.* **1981**, *216*, C64.

Table 2: Comparison of Different Catalysts in the Cyclopropanation of Butyl Vinyl Ether (48).

Catalyst	Yield
Pd(PPh ₃) ₄	31%
Cu(acac) ₂	71%
Rh ₂ (OAc) ₄	86% ^[a]
Rh ₆ (CO) ₁₆	86% ^[a]
Co ₂ (CO) ₈	18%
Fe ₃ (CO) ₁₂	18%
Ru ₃ (CO) ₁₂	65%
Mo(CO) ₆	38%

[a] Performed at room temperature.

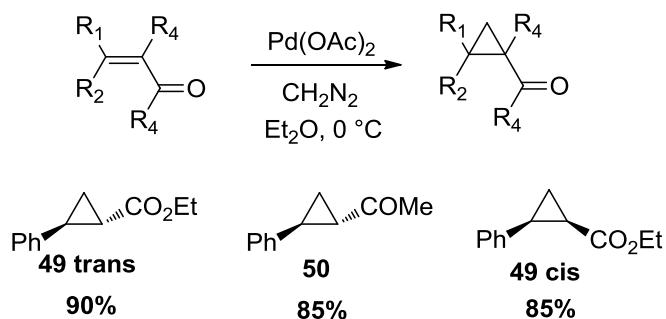
This study showed that rhodium and copper catalyst are superior for the cyclopropanation of electron-rich olefins. These results were later summarized by Maas.⁵² Rh₂(OAc)₄ is the catalyst of choice for conjugated, aliphatic and internal alkenes. Pd(OAc)₂ is an excellent catalyst for sterically unhindered alkenes (terminal) and electron-deficient alkenes.

In the following discussion, selected state-of-the-art catalytic systems (mostly asymmetric ones) will be discussed according to the metal used. The diastereoselectivity and enantioselectivity of the reaction between diazoacetates (particularly ethyl diazoacetate, a commercially available compound) and styrene has always been considered as a test reaction to compare the efficiency of different catalysts. Therefore, this reaction has also been selected in many cases in the next section as a tool to directly compare catalyst performance.

⁵² G. Maas, *Top. Curr. Chem.* **1987**, 137, 75.

Pd

Palladium was shown to be one of the best catalysts for the cyclopropanation of terminal and electron-deficient double bonds using diazomethane.⁵³ The method was shown to be efficient on a wide range of unsaturated carbonyl compounds (Scheme 27).



Scheme 27: Stereospecific Catalytic Cyclopropanation of Unsaturated Carbonyl Compounds.

This chemoselectivity is particularly attractive since most of the other catalytic systems described below are more efficient with electron-rich alkenes. This inherent complementarity of palladium-catalyzed cyclopropanation can be attributed to its different mechanism (*vide supra*). However, the larger use of palladium in cyclopropanation has been limited, principally because of the incapacity to induce asymmetry upon coordination of chiral enantiopure ligands. For instance, cyclopropanation using BOX-ligands was shown to be ineffective by Denmark and co-workers.⁵⁴

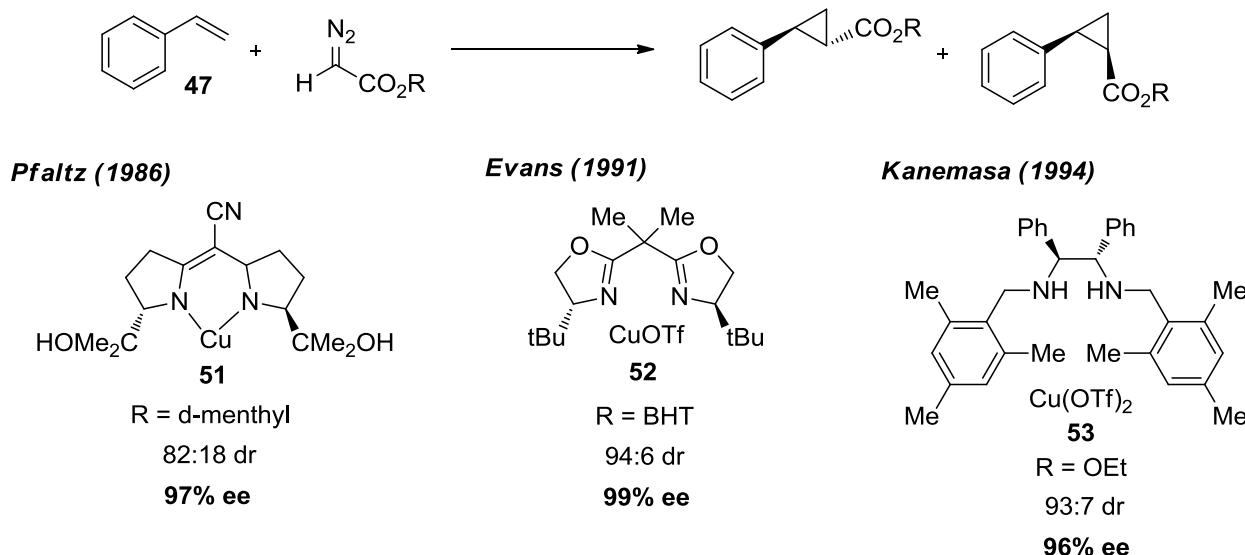
Cu

Copper complexes are among the most useful catalysts for both racemic and asymmetric cyclopropanations. The first asymmetric copper-catalyzed cyclopropanation was reported in 1966, when Nozaki and co-workers described the enantioselective cyclopropanation of styrene with ethyl diazoacetate in 6% ee.⁵⁵ This seminal report led to the development of a wide range of asymmetric copper catalysts. Scheme 28 highlights some of these complexes.

⁵³ E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley and Sons, **2002**, Chapter IV.9.

⁵⁴ S. E. Denmark, R. A. Stavenger, A. M. Faucher, J. P. Edwards, *J. Org. Chem.* **1997**, *62*, 3375.

⁵⁵ H. Nozaki, S. Moriuti, H. Takaya, R. Noyori, *Tetrahedron Lett.* **1966**, 5239.



Scheme 28: Selected State-of-the-Art Copper Catalysts.

One of the first examples of highly enantioselective cyclopropanation was described by *Pfaltz* in 1986. He used semi-corrin ligand **51** to obtain the product in 97% ee.⁵⁶ Later *Evans* et al introduced the use of BOX-ligands (e.g **52**) to perform the cyclopropanation of styrenes in 99% ee.⁵⁷ Another class of diamine ligands (e.g **53**), easily prepared from commercially available diphenyldiamines, was used by *Kanemasa* to obtain the product in 96% ee.⁵⁸ Intramolecular asymmetric cyclopropanations are generally less successful and their use has been supplanted by rhodium-catalysts.⁵⁹

Ru

Ru is a useful metal for carbene-transfer to double bonds. However, the Ru-carbenes have a high propensity to undergo metathesis reaction, and it is therefore necessary to use coordinatively saturated Ru-carbenes to selectively perform cyclopropanation.⁴² Nevertheless, a wide range of Ru-based catalysts have been developed and afforded results that could compete with their Rh and Cu-

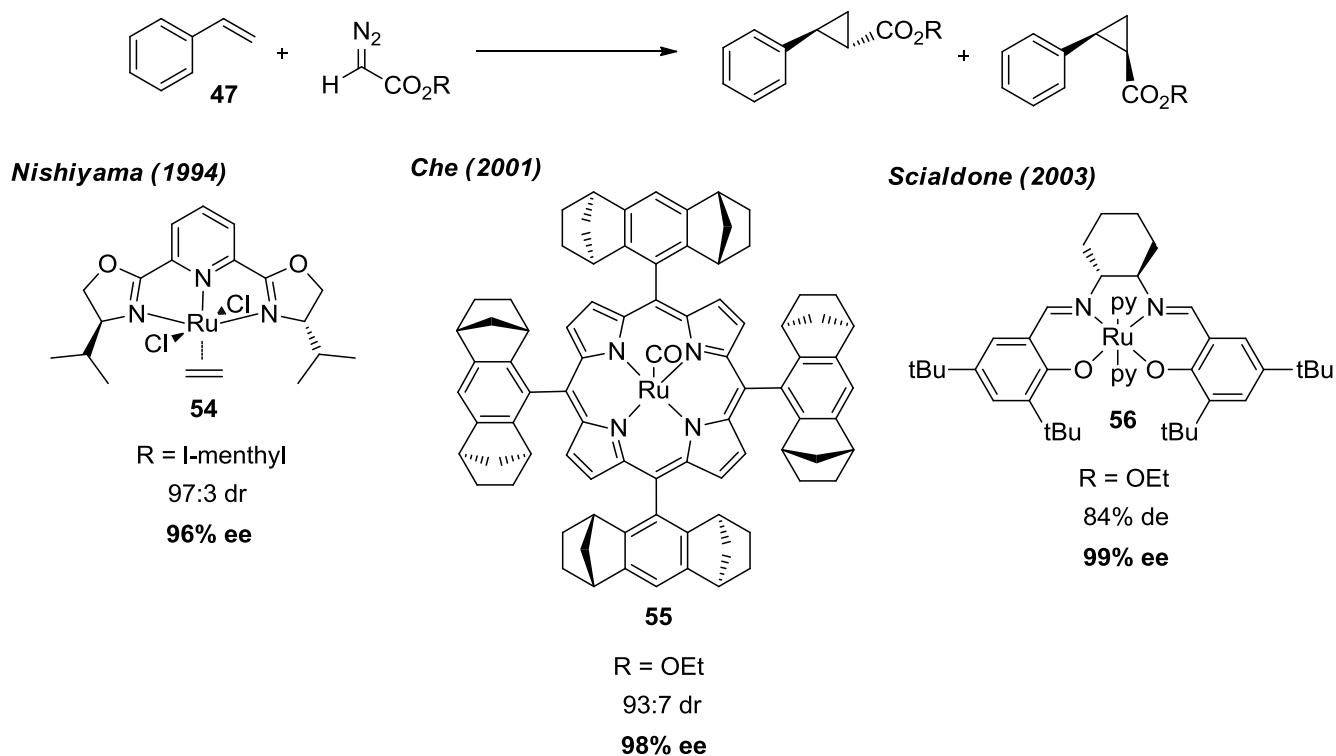
⁵⁶ H. Fritschi, U. Leutenegger, A. Pfaltz, *Angew. Chem. Int. Ed.* **1986**, *25*, 1005.

⁵⁷ D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726.

⁵⁸ S. Kanemasa, S. Hamura, E. Harada, H. Yamamoto, *Tetrahedron Lett.* **1994**, *35*, 7985.

⁵⁹ See Reference 41

counterparts. A selection of catalysts for the asymmetric cyclopropanation of styrene is presented in Scheme 29.



Scheme 29: Selected State-of-the-Art Ruthenium Catalysts.

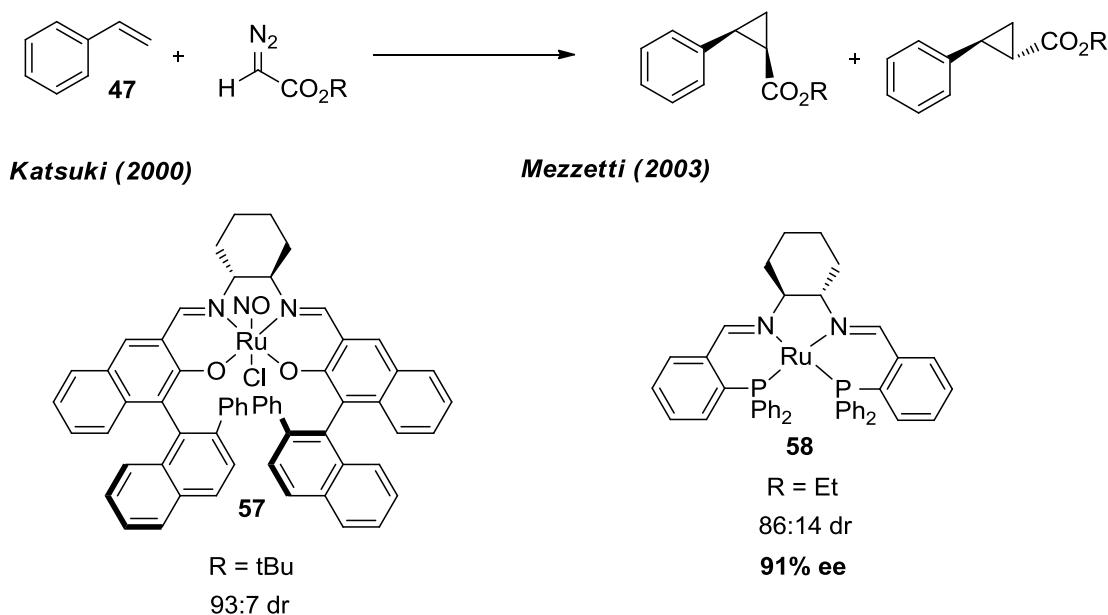
Nishiyama pioneered the field of ruthenium-catalyzed asymmetric cyclopropanation in 1994 by introducing pybox complex **54**.⁶⁰ 96% ee and high diastereoselectivity were obtained using this catalyst. *Che* et al showed later that a ruthenium complex (**55**) bearing *Halterman's* porphyrin⁶¹ as the ligand could give ee values as high as 98% ee.⁶² Recently *Scialdone* reported the use of a salen ligand (**56**) to afford the product in 99% ee.⁶³ Interestingly, several examples of *cis*-selective cyclopropanation using ruthenium catalysts have been reported, affording for the first time these products in good diastereoselectivities and high enantioselectivities (Scheme 30).

⁶⁰ H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park, K. Itoh, *J. Am. Chem. Soc.* **1994**, *116*, 2223.

⁶¹ R. L. Halterman, S. T. Jan, *J. Org. Chem.* **1991**, *56*, 5253.

⁶² C. M. Che, J. S. Huang, F. W. Lee, Y. Li, T. S. Lai, H. L. Kwong, P. F. Teng, W. S. Lee, W. C. Lo, S. M. Peng, Z. Y. Zhou, *J. Am. Chem. Soc.* **2001**, *123*, 4119.

⁶³ J. A. Miller, E. J. Hennessy, W. J. Marshall, M. A. Scialdone, S. T. Nguyen, *J. Org. Chem.* **2003**, *68*, 7884.



Scheme 30: *Cis*-Selective Ruthenium Catalysts.

Katsuki described the use of an elaborated salen ligand (complex **57**) that afforded the *cis*-cyclopropane in an unprecedented 93:7 dr and 97% ee.⁶⁴ *Mezzetti* and co-workers developed a PNNP salen ligand (complex **58**) that afforded the desired *cis*-cyclopropane in 91% ee and 86:14 dr.⁶⁵

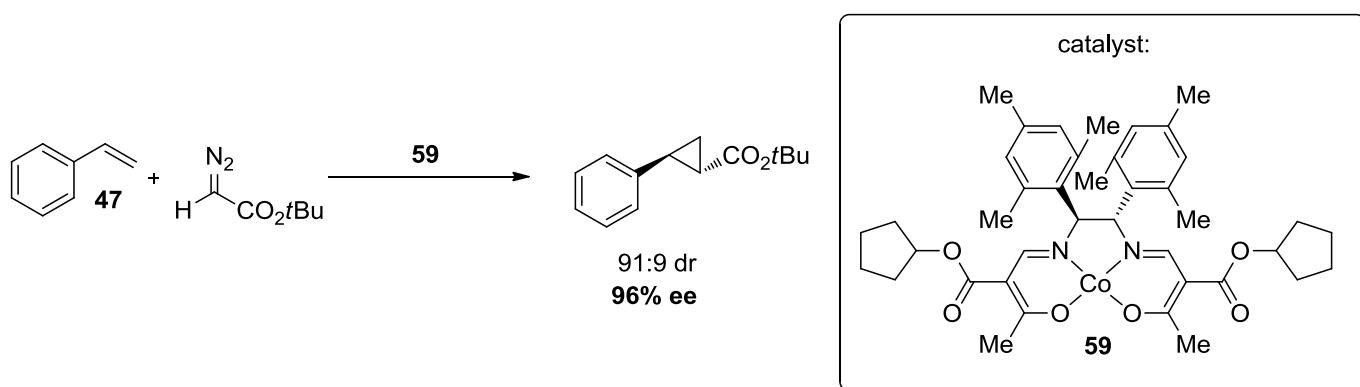
Co

An emerging area in asymmetric cyclopropanation is the use of inexpensive first-row, cobalt-based catalysts. Early examples include the development of chiral Co-salen complexes, and this precedent will be discussed in Chapter 3 in the context of the asymmetric trifluoromethyl cyclopropanation. Another interesting ligand scaffold similar to the salen scaffold was developed by *Yamada* and co-workers (Scheme 31).⁶⁶

⁶⁴ T. Uchida, R. Irie, T. Katsuki, *Synlett* **1999**, 1793.

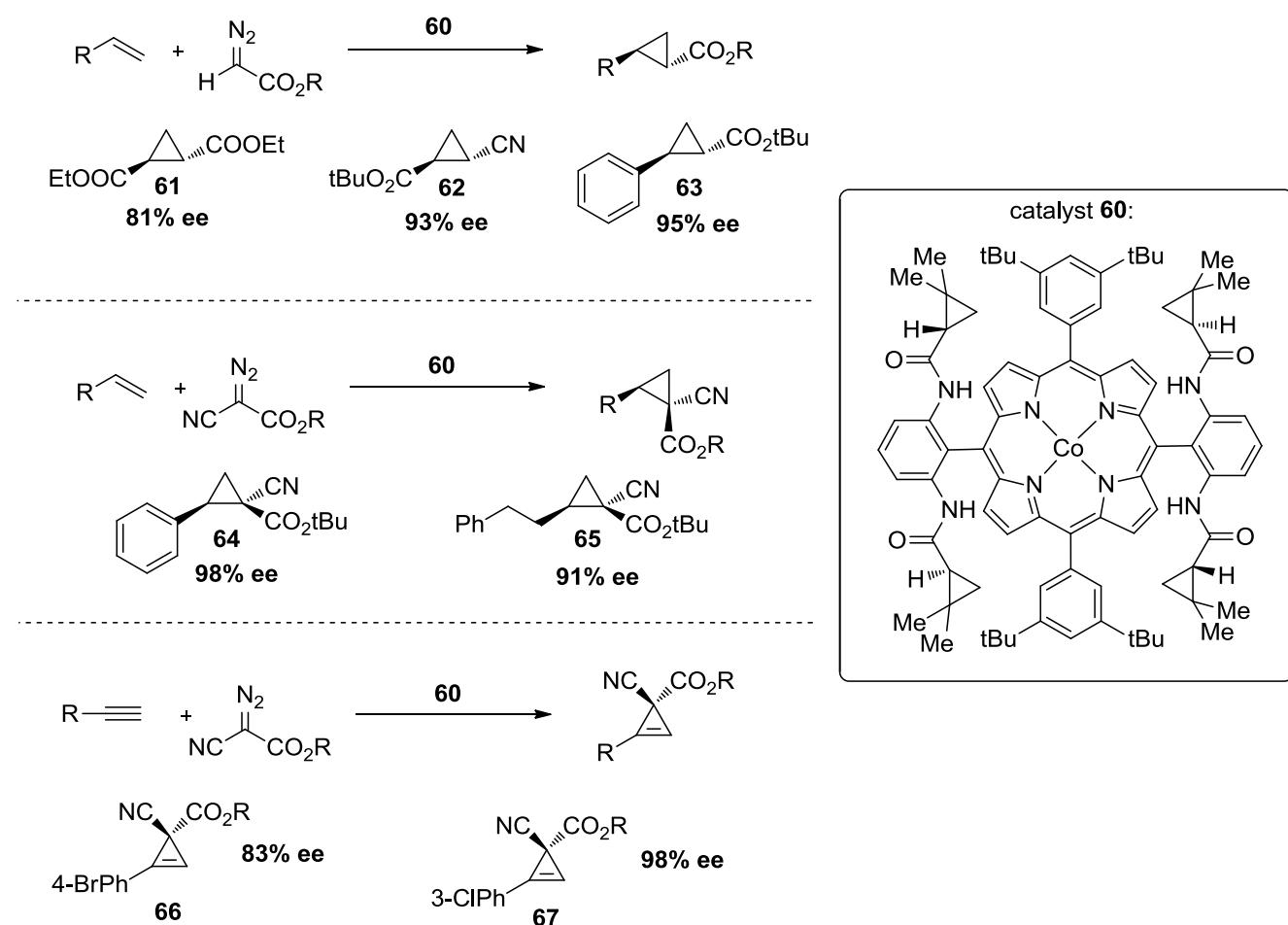
⁶⁵ C. Bonaccorsi, S. Bachmann, A. Mezzetti, *Tetrahedron:Asymmetry* **2003**, *14*, 845.

⁶⁶ T. Yamada, T. Ikeno, H. Sekino, M. Sato, *Chem. Lett.* **1999**, 719.



Scheme 31: Yamada's Asymmetric Cobalt Catalyst.

Important to emphasize herein are the impressive results obtained by *Zhang* and co-workers using chiral Co-porphyrins (Scheme 32).

Zhang and co-workers

Scheme 32: Zhang's Catalyst and Selected Catalyzed Reactions.

Zhang initially developed a new route to chiral porphyrin derivatives starting from a common bromoporphyrin starting material.⁶⁷ This strategy enabled them to prepare chiral catalyst **60** that was shown to be an excellent catalyst for the cyclopropanation of styrenes. Interestingly, this catalyst was one of the first to show high chemoselectivity and avoided the formation of the diazo compound-derived dimer, enabling the alkene to be used as the limiting reagent with a slight excess of the diazo compound (1.2 equiv). This feature is very important in the context of cyclopropanation of more valuable alkene substrates. The reaction was later shown to be extendable to electron-poor substrates (e.g. **61** and **62**),⁶⁸ a result that is remarkable, since until this point electron-deficient olefins were notably known as difficult substrates for transition-metal catalyzed cyclopropanations (apart from palladium catalysts). This feature is due to the electrophilicity of the putative metal-carbene intermediate that shows increased rate of reaction with more electron-rich double bonds.⁶⁹ The use of Zhang's catalyst was later shown to be effective for the cyclopropanation of alkenes and alkynes using ethyl cyanodiazoacetate in high enantioselectivity.^{70,71} Using a slightly different porphyrin catalyst, the method could be extended to the cyclopropanation of alkenes using diazo sulfones and to the intramolecular cyclopropanation of a variety of allyl diazoacetates.^{72,73} The unusual features of this class of catalysts (high chemoselectivity, reactivity with electron-deficient olefins) has raised questions about their mechanism. The reaction catalyzed by complex **68** was therefore studied by EPR spectroscopy and modeled using DFT calculations (Scheme 33). It is believed that the reaction occurs via a stepwise radical mechanism with involvement of a Co(III)-radical carbene intermediate, and that the porphyrin is non-innocent and participates in the process.^{74,75}

⁶⁷ Y. Chen, K. B. Fields, X. P. Zhang, *J. Am. Chem. Soc.* **2004**, *126*, 14718.

⁶⁸ Y. Chen, J. V. Ruppel, X. P. Zhang, *J. Am. Chem. Soc.* **2007**, *129*, 12074.

⁶⁹ For a recent example of a mechanistic study of a copper-catalyzed cyclopropanations, see: X. L. Dai, T. H. Warren, *J. Am. Chem. Soc.* **2004**, *126*, 10085.

⁷⁰ S. F. Zhu, X. Xu, J. A. Perman, X. P. Zhang, *J. Am. Chem. Soc.* **2010**, *132*, 12796.

⁷¹ X. Cui, X. Xu, H. J. Lu, S. F. Zhu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 3304.

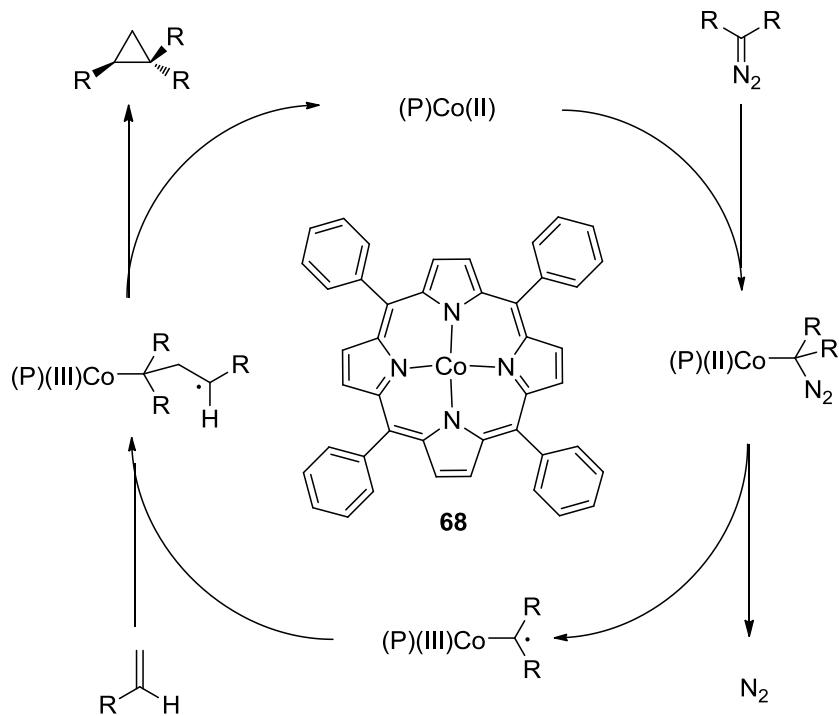
⁷² S. F. Zhu, J. V. Ruppel, H. J. Lu, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 5042.

⁷³ X. Xu, H. J. Lu, J. V. Ruppel, X. Cui, S. L. de Mesa, L. Wojtas, X. P. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 15292.

⁷⁴ W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.* **2010**, *132*, 10891.

⁷⁵ H. J. Lu, W. I. Dzik, X. Xu, L. Wojtas, B. de Bruin, X. P. Zhang, *J. Am. Chem. So.* **2011**, *133*, 8518.

Zhang and Bas de Bruin (2010/2011)



Scheme 33: Zhang's Metalloradical Mechanism.

Fe

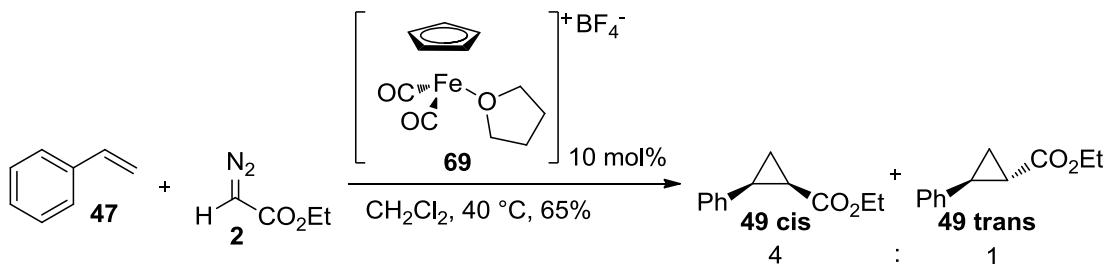
Iron-catalyzed cyclopropanation has seen much less development compared to other transition metals in the last years. This is in contrast with the large interest for this metal as a replacement for noble metal catalysts in other transformations.^{76,77} One of the first examples of an iron-catalyzed cyclopropanation was reported by Hossain and co-workers (Scheme 34). They reported that complex **69** was able to catalyze the cyclopropanation of styrene with ethyl diazoacetate in 65% yield and, interestingly, with 4:1 selectivity in favor of the *cis*-isomer.⁷⁸

⁷⁶ S. Enthaler, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2008**, *47*, 3317.

⁷⁷ Iron-Catalysis in Organic Synthesis: Reactions and Applications (Eds: B. Plikter), Wiley-VCH, **2008**

⁷⁸ W. J. Seitz, A. K. Saha, D. Casper, M. M. Hossain, *Tetrahedron Lett.* **1992**, *33*, 7755.

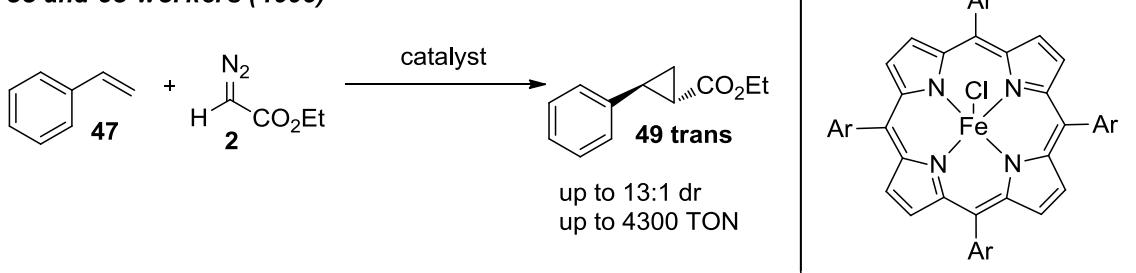
Hossain and co-workers (1992)



Scheme 34: Hossain's *cis*-Selective Cyclopropanation with an Iron Catalyst.

Woo and co-workers later reported a systematic study of cyclopropanation reactions catalyzed by iron-porphyrin complexes (Scheme 35).⁷⁹ A range of iron-porphyrin catalysts gave the product cyclopropanes in up to 13:1 diastereoselectivity and with TON as high as 4300. The catalyst showed high shape-selectivity and the electrophilic nature of the transition-state was determined by a Hammett study.

Woo and co-workers (1995)



Scheme 35: Woo's Iron Porphyrin Catalyst.

The same group reported that the active form of the catalyst is Fe(II), not Fe(III), but in the case of perfluoroarylporphyrin ligands ethyl diazoacetate was a competent reducing reagent to reduce the metal-center to Fe(II) *in situ*. In the case of less electron-deficient iron-porphyrrins, a higher temperature was required for the *in situ* reduction of the metal or an external source of electron (cobaltocene) had to be used.⁷⁹ The reaction showed much lower activity in the cyclopropanation of aliphatic alkenes and no reaction at all with *trans*-substituted double bonds. This was assigned to the high shape-selectivity of the catalyst due to a late, product-like transition

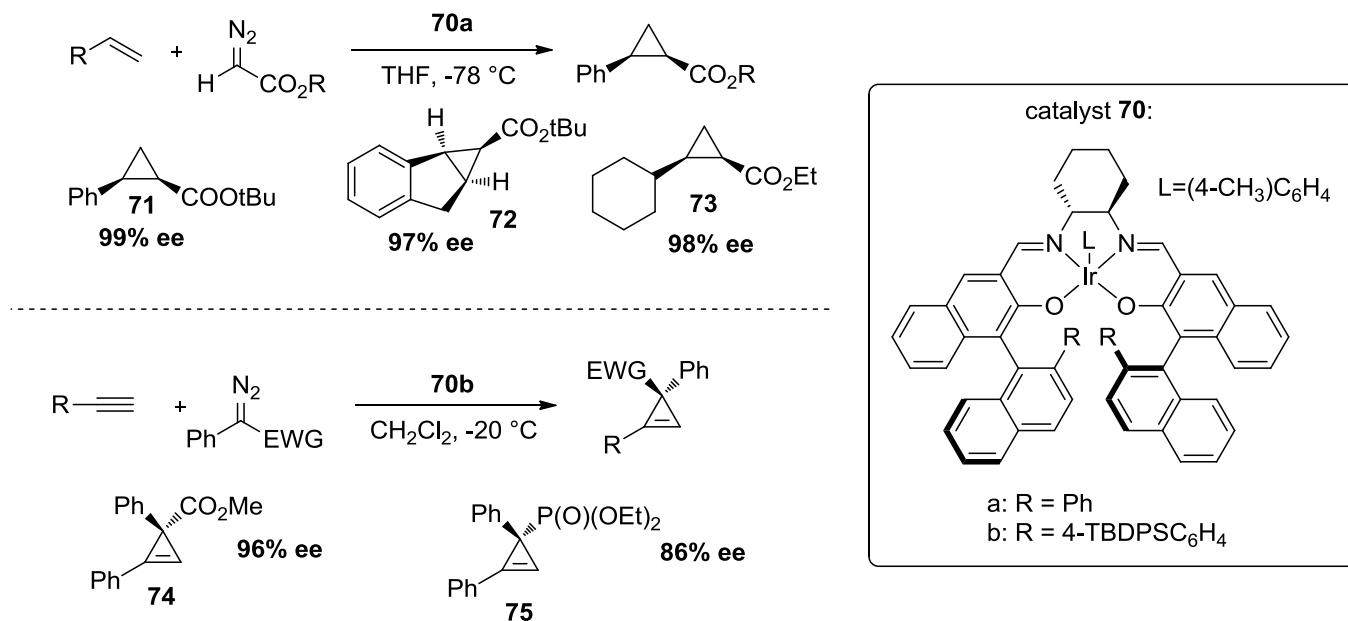
⁷⁹ J. R. Wolf, C. G. Hamaker, J. P. Djukic, T. Kodadek, L. K. Woo, *J. Am. Chem. Soc.* **1995**, *117*, 9194.

state.⁷⁹ Wong showed later that using a chiral porphyrin ligand (Haltermann's porphyrin) the cyclopropane product could be obtained in up to 96% ee.⁸⁰

Ir

In recent years, iridium has emerged as one of the newcomers in catalytic cyclopropanations due to the pioneering work of *Katsuki* and co-workers (scheme 36).⁸¹ In this seminal report, they developed the first iridium-catalyzed cyclopropanation reaction using catalyst **70**. Moreover, this reaction is highly stereoselective and affords the *cis*-product (e.g. **71**, **72** and **73**) in high diastereoselectivity. The scope of this reaction was later expanded to aliphatic and *cis*-1,2-disubstituted alkenes^{82,83,84} and cyclopropenation could also be performed with high levels of enantioinduction.⁸⁵

Katsuki and co-workers



Scheme 36: *Katsuki's Chiral Iridium Catalyst and Selected reactions.*

⁸⁰ T. S. Lai, F. Y. Chan, P. K. So, D. L. Ma, K. Y. Wong, C. M. Che, *Dalton Trans.* **2006**, 4845.

⁸¹ S. Kanchiku, H. Suematsu, K. Matsumoto, T. Uchida, T. Katsuki, *Angew. Chem. Int. Ed.* **2007**, 46, 3889.

⁸² H. Suematsu, S. Kanchiku, T. Uchida, T. Katsuki, *J. Am. Chem. Soc.* **2008**, 130, 10327.

⁸³ H. Suematsu, T. Katsuki, *J. Am. Chem. Soc.* **2009**, 131, 14218.

⁸⁴ M. Ichinose, H. Suematsu, T. Katsuki, *Angew. Chem. Int. Ed.* **2009**, 48, 3121.

⁸⁵ M. Uehara, H. Suematsu, Y. Yasutomi, T. Katsuki, *J. Am. Chem. Soc.* **2011**, 133, 170.

Rh

Rhodium catalysts, and particularly rhodium(II) dimers have emerged as the most versatile class of complexes for carbene-transfer reactions.⁸⁶ Besides cyclopropanation, they have shown unique utility in a wide range of reactions, including C-H insertions.⁸⁷ Their activities and selectivities can easily be tuned by the choice of the ligand (Figure 5).⁸⁸ Therefore, fluorinated, electron-deficient carboxylate ligands afford increased activity but lower selectivity compared to alkyl carboxylate ligands. On the other hand, amide and lactam-ligands have diminished reactivities but afford more selective process.

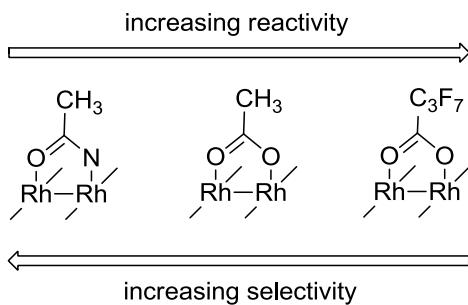


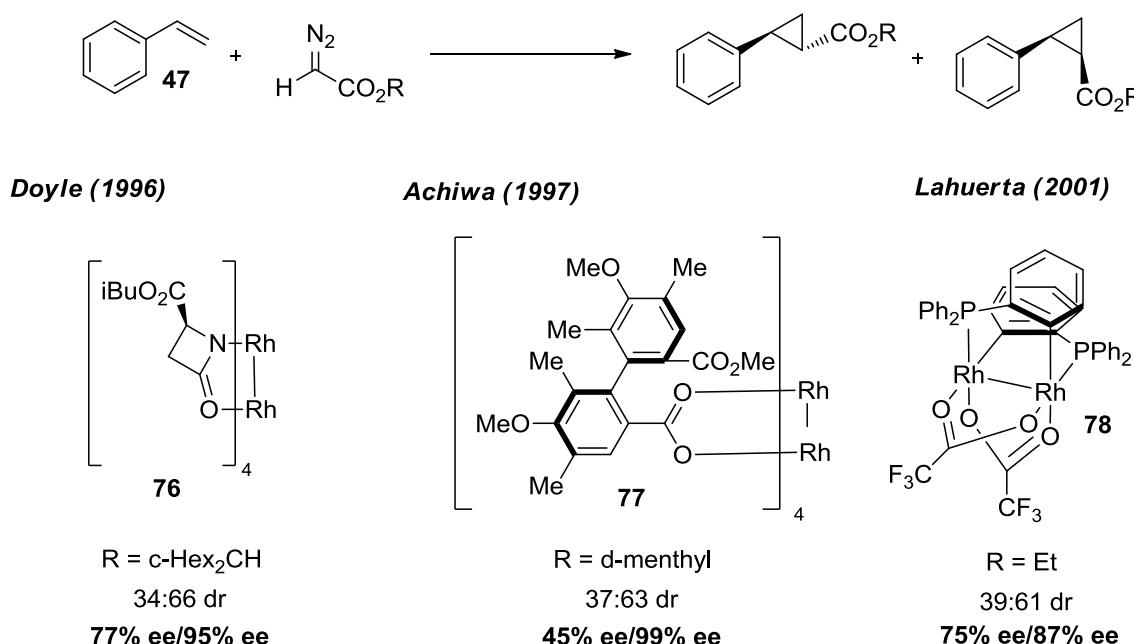
Figure 5: Relative Reactivity of Different Rhodium-Dimers.

In intermolecular cyclopropanation reactions, a wide range of rhodium dimers have shown high propensity for good enantiodiscrimination, however with low diastereoselectivity, a recurrent problem of rhodium catalysts. Scheme 37 shows selected state-of-the-art cyclopropanation catalysts and their performance in the cyclopropanation of styrene with diazoacetates.

⁸⁶ See Reference 1c

⁸⁷ See References 14 and 15

⁸⁸ M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911.



Scheme 37: Selected State-of-the-Art Dimeric Rhodium Catalysts.

Three different ligand-classes are represented in this scheme. Lactam-based ligands were developed by *Doyle* and the use of complex **76** gave a 95% ee for the *cis* isomer with a 2:1 diastereoselectivity.⁸⁹ Related are carboxylate ligands bearing different stereoinducing moieties, like complex **77** having a biaryl moiety. Using this complex, *Achiwa* and co-workers obtained 99% ee for the *cis*-cyclopropyl esters.⁹⁰ Finally, an interesting ligand-type was introduced later by *Lahuerta* and co-workers bearing a phosphorous-carbon moiety.⁹¹ This catalyst (**78**) is easily accessed via direct C-H activation of triphenylphosphine with rhodium, followed by resolution via transient ligand-exchange with a proline derivative.⁹² It gave the product in 87% ee enantioselectivity and represents a unique example of chiral-at-metal catalyst bearing achiral ligands.

Davies and co-workers introduced the use of donor/acceptor diazo compounds in rhodium-catalyzed carbene-transfer reactions.^{93,94} They showed that these diazo compounds exhibited high diastereoselectivity, in contrast to classical diazoacetates. Using simple chiral Rh-carboxylates complexes, they achieved excellent results in a wide range of reactions. These diazo compounds also

⁸⁹ M. P. Doyle, Q. L. Zhou, S. H. Simonsen, V. Lynch, *Synlett* **1996**, 697.

⁹⁰ H. Ishitani, K. Achiwa, *Synlett* **1997**, 781.

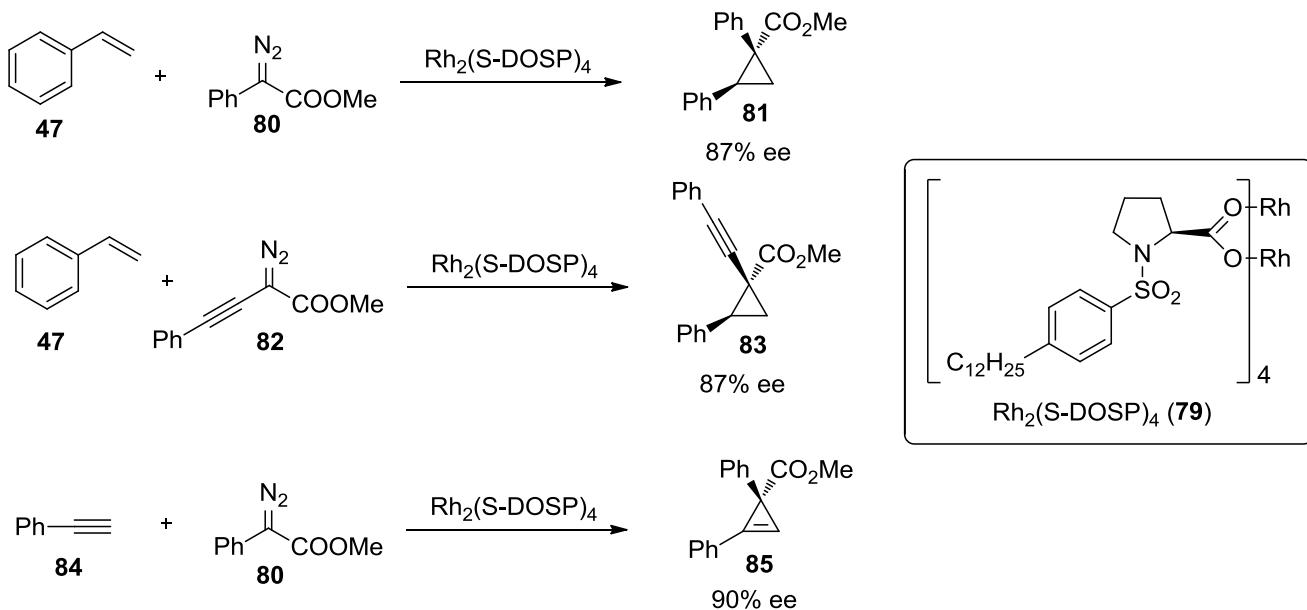
⁹¹ M. Barberis, P. Lahuerta, J. Perez-Prieto, M. Sanau, *Chem. Comm.* **2001**, 439.

⁹² D. F. Taber, S. C. Malcolm, K. Bieger, P. Lahuerta, M. Sanau, S. E. Stiriba, J. Perez-Prieto, M. A. Monge, *J. Am. Chem. Soc.* **1999**, 121, 860.

⁹³ H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, 38, 3061.

⁹⁴ H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, 40, 1857.

form carbenes with lower propensity for dimerization and higher stability. This allowed his group to report highly enantioselective C-H insertion reactions as well.⁹⁵ Scheme 38 shows selected examples of cyclopropanation and cyclopropenation using donor/acceptor diazo compounds and catalyst **79**.



Scheme 38: Selected Examples of Enantioselective Reactions 79 and EDG/EWG Diazo Compounds.

The first example shown took advantage of the excellent diastereoselectivity obtained with donor/acceptor diazo compounds (e.g. **80**).⁹⁶ In fact, it was shown in the same publication that the use of methyl diazoacetate gave the product in only 6% ee. This chemistry was later extended to the use of vinyl and alkynyl diazoacetates (e.g. **82**).⁹⁷ In the last example, the chemistry could be applied to the enantioselective cyclopropanation of alkynes.⁹⁸ The products (e.g. **85**) were obtained in high enantioselectivities and further studies were reported.^{99,100}

Doyle and co-workers developed the first highly enantioselective cyclopropenation of alkynes using $\text{Rh}_2(5\text{S-MEPY})$ (**86**) as the catalyst (Scheme 39).¹⁰¹ They obtained the corresponding products (e.g. **90**) in good yields and in up to 98% ee. *Corey* recently introduced a new catalyst (**87**) for

⁹⁵ See Reference 15

⁹⁶ H. M. L. Davies, P. R. Bruzinski, M. J. Fall, *Tetrahedron Lett.* **1996**, 37, 4133.

⁹⁷ H. M. L. Davies, T. A. Boebel, *Tetrahedron Lett.* **2000**, 41, 8189.

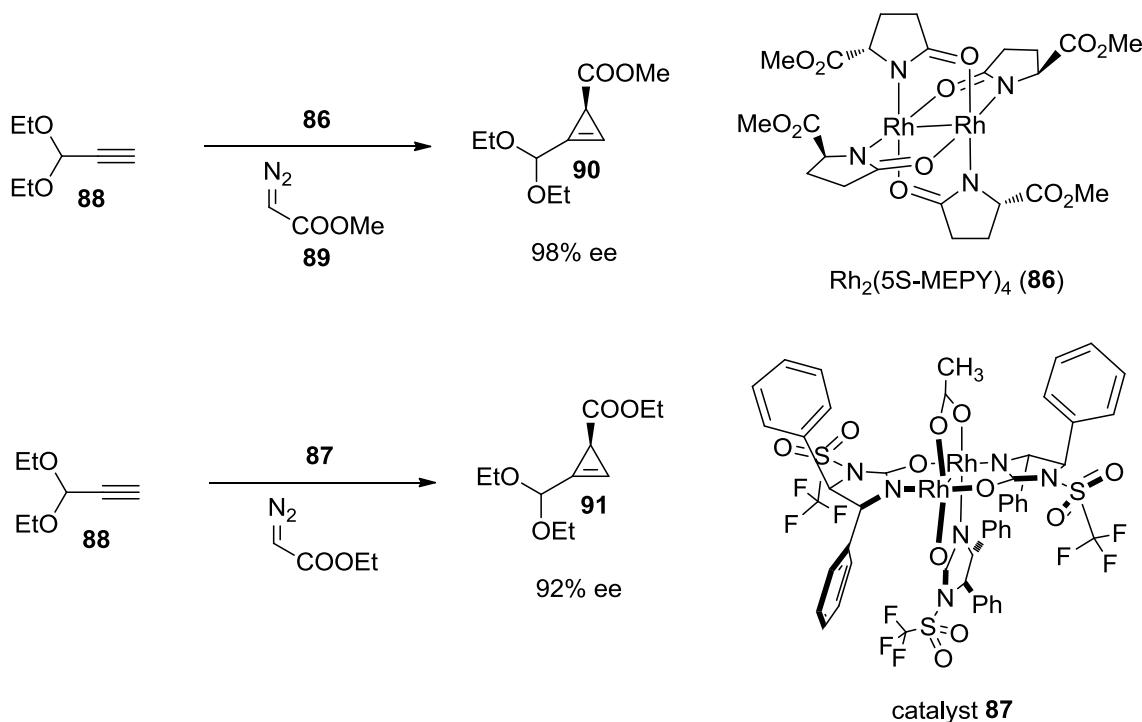
⁹⁸ H. M. L. Davies, G. H. Lee, *Org. Lett.* **2004**, 6, 1233.

⁹⁹ J. F. Briones, J. Hansen, K. I. Hardcastle, J. Autschbach, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, 132, 17211.

¹⁰⁰ J. F. Briones, H. M. L. Davies, *Tetrahedron* **2011**, 67, 4313.

¹⁰¹ M. N. Protopopova, M. P. Doyle, P. Muller, D. Ene, *J. Am. Chem. Soc.* **1992**, 114, 2755.

cyclopropanation and cyclopropenation based on the use of easily accessed chiral urea-based ligands (Scheme 39).^{102,103} He could reach high levels of enantioselectivities using this system.



Scheme 39: Literature Precedent For The Enantioselective Cyclopropanation with Rh-Catalysts.

In conclusion, a wide range of metal catalysts can catalyze cyclopropanation reactions in high enantioselectivities with electron-rich alkenes. Copper and cobalt are ideally suited for *trans* and enantioselective cyclopropanations. A particularly impressive cobalt catalyst is the porphyrin complex reported by *Zhang*, a catalyst not only working with electron-rich but also electron-deficient olefins. On the other hand, certain ruthenium and iridium catalysts offer a unique *cis*-selectivity, a complementary feature of standard catalysts. Rhodium complexes are highly active and enantiodiscriminating, but only poorly diastereoselective. Thus, they are ideally suited for cyclopropenation reactions, where only one stereocenter is formed. Finally, palladium and iron are widely used catalysts for racemic cyclopropanations, the first one with electron-deficient alkenes and the second one in the cyclopropanation of electron-rich alkenes.

¹⁰² Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawryluk, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 8916.

¹⁰³ Y. Lou, T. P. Remarchuk, E. J. Corey, *J. Am. Chem. Soc.* **2005**, *127*, 14223.

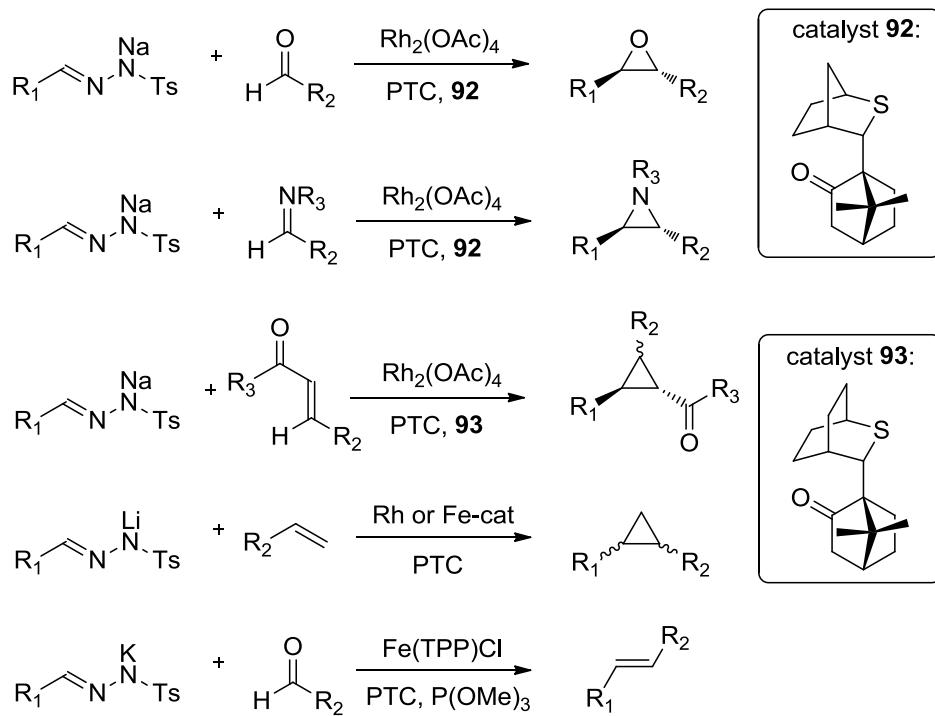
1.4. Previous Examples of *in situ* Generation

Due to their hazardous nature, it would be of high interest to devise protocols wherein diazo compounds could be generated *in situ* concomitantly to the catalytic process. Diazo compounds are extremely versatile reagents in organic synthesis as illustrated by the number of publications using them as reagents, and the few examples of *in situ* generation of these compounds will be presented.

1.4.1. *In situ* generation via the *Bamford-Stevens* reaction

Aggarwal and co-workers have extensively studied the *in situ* generation of diazo compounds via thermal decomposition of tosylhydrazone salts (*Bamford-Stevens* reaction).¹⁰⁴ They used this strategy in a wide range of transformations to efficiently avoid the hazard of isolating diazo compounds.

Aggarwal and co-workers



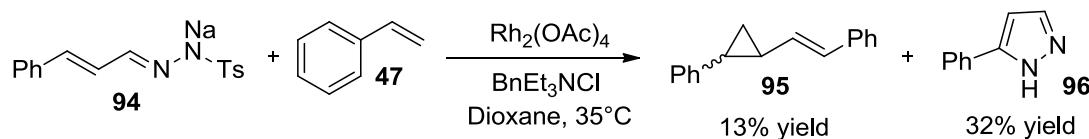
Scheme 40: Reactions Using Aggarwal's *in Situ* Generation of Diazo Compounds. PTC = Phase-Transfer Catalyst.

¹⁰⁴ J. R. Fulton, V. K. Aggarwal, J. de Vicente, *Eur. J. Org. Chem.* **2005**, 1479.

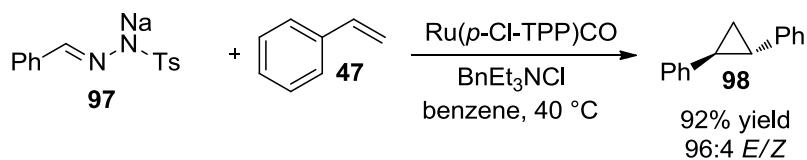
The group initially developed a user-friendly protocol for the *in situ* generation of diazo compounds in a tandem catalytic ylide formation/asymmetric epoxidation reaction.¹⁰⁵ The goal was to minimize the risks associated with the use of solutions of isolated diazo compounds. Using this strategy they could devise a protocol that allowed for the preparation of chiral, non-racemic epoxides in high enantioselectivity and good diastereoselectivity. The convenient protocol using newly designed chiral thioethers catalysts was then extended to the aziridination of imines and cyclopropanation of electron-deficient alkenes.¹⁰⁶ This strategy for *in situ* preparation of diazo compounds also proved compatible with transition metal-catalyzed carbene-transfer, leading to a novel cyclopropanation reaction¹⁰⁷ and to the development of a *trans*-selective Wittig reaction using catalytic amounts of Fe(TPP)Cl.¹⁰⁸ The latter reaction affords a new entry into the fine-tuning of phosphines for enhanced reactivity and selectivity in Wittig reactions.

The innovative strategy from the Aggarwal group stimulated further research in this area (Scheme 41). Notably, Doyle and co-workers developed a cyclopropanation reaction using vinyl diazo compound generated *in situ* from the corresponding tosylhydrazone.¹⁰⁹ Che and co-workers used the same strategy in a ruthenium-porphyrin catalyzed cyclopropanation reaction.¹¹⁰

Doyle and co-workers (2002)



Che and co-workers (2003)



Scheme 41: Doyle's and Che's Use of *in situ* Generation of Diazo Compounds.

¹⁰⁵ V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430.

¹⁰⁶ V. K. Aggarwal, E. Alonso, G. Y. Fang, M. Ferrara, G. Hynd, M. Porcelloni, *Angew. Chem. Int. Ed.* **2001**, *40*, 1433.

¹⁰⁷ V. K. Aggarwal, J. de Vicente, R. V. Bonnert, *Org. Lett.* **2001**, *3*, 2785.

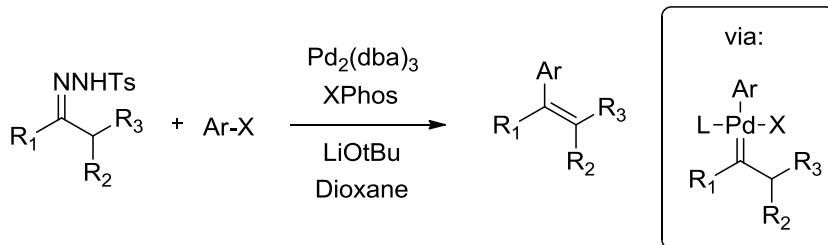
¹⁰⁸ V. K. Aggarwal, J. R. Fulton, C. G. Sheldon, J. de Vicente, *J. Am. Chem. Soc.* **2003**, *125*, 6034.

¹⁰⁹ M. P. Doyle, M. Yan, *J. Org. Chem.* **2002**, *67*, 602.

¹¹⁰ J. L. Zhang, P. W. H. Chan, C. M. Che, *Tetrahedron Lett.* **2003**, *44*, 8733.

A related approach involves the cross-coupling reaction of tosylhydrazones with electrophiles using palladium catalysts. This topic has recently been reviewed by *Barluenga*¹¹¹ and *Shao*¹¹². This field of research was pioneered by *Barluenga* and co-workers in 2007 when they reported the first palladium-catalyzed cross-coupling of tosylhydrazones with aryl halides to give alkene products (Scheme 42).¹¹³

Barluenga and co-workers (2007)



Scheme 42: Barluenga's Seminal Report on Pd-Catalyzed Cross-Coupling of Tosylhydrazones.

1.4.2. *In situ* generation via diazotization reaction

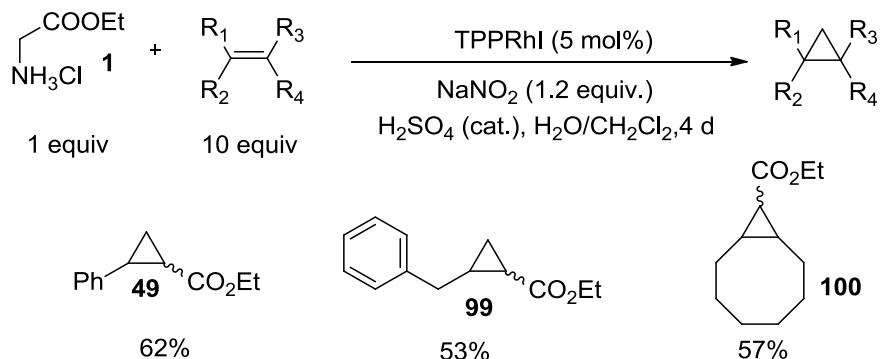
Concomitantly with the initial results from the *Aggarwal* lab, *Barrett* and co-workers reported the use of glycine ester hydrochloride as an ethyl diazoacetate precursor (Scheme 43).¹¹⁴ The active diazo was generated *in situ* under the conditions necessary for the diazotization reaction (NaNO_2 and acid). They claimed that the use of copper (I), copper (II), rhodium (II) and rhodium (III) was inefficient. Fortunately, the use of RhTPPI proved essential to the success of the reaction. The reaction proceeded in a water/dichloromethane mixture using glycine ester hydrochloride (1 equiv.), NaNO_2 (1.2 equiv.), sulfuric acid (5 mol%), and RhTPPI (0.5 mol%) at room temperature. Major drawbacks of this protocol were the large excess of alkene required (10 equiv.), the non-existent diastereoselectivity (1:1) and the long reaction time (4 days). The reaction did not afford the product when using substituted glycine derivatives (alanine, cysteine, serine, phenylalanine and phenylglycine). Monitoring of the reaction by IR-spectroscopy revealed that the maximum concentration of ethyl diazoacetate was reached after 2 h.

¹¹¹ J. Barluenga, C. Valdes, *Angew. Chem. Int. Ed.* **2011**, *50*, 7486.

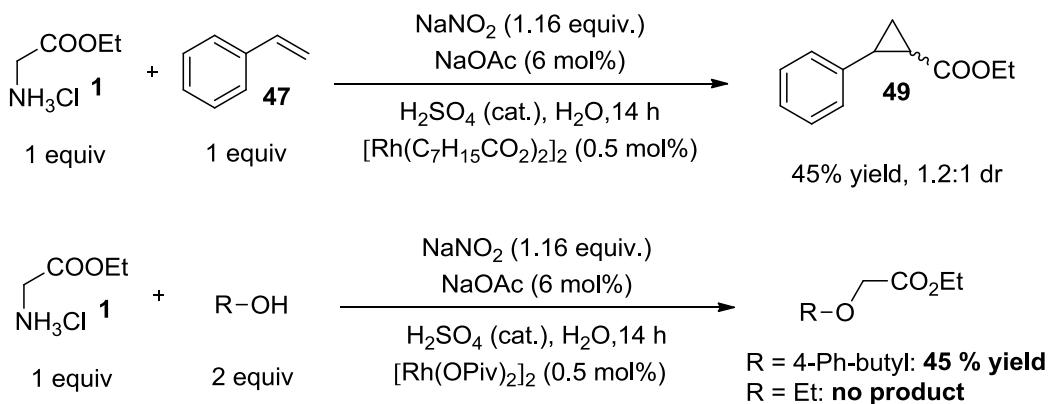
¹¹² Z. H. Shao, H. B. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560.

¹¹³ J. Barluenga, P. Moriel, C. Valdes, F. Aznar, *Angew. Chem. Int. Ed.* **2007**, *46*, 5587.

¹¹⁴ A. G. M. Barrett, D. C. Braddock, I. Lenoir, H. Tone, *J. Org. Chem.* **2001**, *66*, 8260.

Barrett and coworkers (2001)**Scheme 43: Barrett's Cyclopropanation Using *in situ* Generated Ethyl Diazoacetate.**

Shortly after, Charette systematically studied the activity of different cyclopropanation catalysts in water using ethyl diazoacetate (Scheme 44).¹¹⁵ In a single example, he described the use of glycine ethyl ester hydrochloride for the *in situ* generation of ethyl diazoacetate in an organic-solvent free system. Using an apolar, lipophilic rhodium complex (rhodium octanoate), they could obtain a 45% yield of phenyl cyclopropyl ethyl ester (**49**) in no diastereoselectivity (1.2:1) using the alkene as limiting reagent. To illustrate his rationale that the reaction occurs in the alkene micelles, he submitted the water-insoluble 4-Ph-1-butanol and obtained the product of O-H insertion in 45% yield, while performing the same reaction with ethanol led to no-product formation.

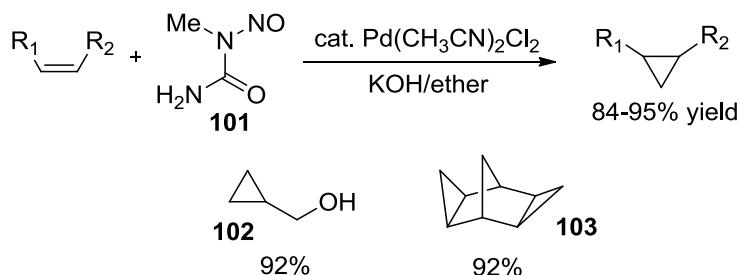
Charette and coworkers (2002)**Scheme 44: Charette's Cyclopropanation Using *in situ* Generated Ethyl Diazoacetate.**

¹¹⁵ R. P. Wurz, A. B. Charette, *Org. Lett.* **2002**, 4, 4531.

1.4.3. *In situ* generation via base-mediated decomposition of nitrosamides

A single example of *in situ* generation of diazomethane in a cyclopropanation reaction has been reported by Nefedov et al in 1992 (Scheme 45).¹¹⁶ They used the toxic and carcinogenic *N*-nitroso-*N*-methyl urea (**101**) as the diazomethane precursor. Their protocol involved slow addition of NMU (**101**) to a mixture of substrate and KOH in a biphasic water/organic solvent mixture. Using Pd(CH₃CN)₂Cl₂ as the active catalyst, they could cyclopropanate a wide range of terminal and strained olefins.

Nefedov et al (1992)



Scheme 45: Cyclopropanation of Olefins Using *in Situ* Generated Diazomethane.

1.5. Conclusion and Project Outline

This introductory chapter has described the many known applications of diazo compounds in organic synthesis. Since their discovery over 100 years ago, these reagents have been used in a wide range of processes, ranging from homologation reactions to metal-catalyzed C-H insertions and cyclopropanations. However, many of these chemically interesting reactions have not found widespread use in synthesis due to the hazard associated with the use of these toxic, sometimes highly explosive reagents. Chemists have thus tried to devise protocols where these reagents could be generated concomitantly to the reaction of interest. Promising results obtained by Aggarwal have shown that astute coupling of the *Bamford-Stevens* reaction with different metal-catalyzed carbene-transfer processes allowed to develop novel and safer reactions. This method is limited by the type

¹¹⁶ O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, V. A. Dokitchev, *Mendeleev Communications* **1992**, 13.

of diazo compounds accessible via this reaction. Thus, other potentially easily accessible diazo compounds such as monosubstituted ones bearing an electron-withdrawing groups (accessible by diazotization) or such as diazomethane (accessible by base-mediated decomposition of nitrosamides) are not suitable using this approach. There is a need to identify conditions wherein the preparation of these other diazo compounds and the reaction of interest can be performed in the same reaction flask as part of a continuous process. Interesting preliminary results have been obtained by *Charette, Barrett* and *Nefedov*, but they were limited in scope and utility of the diazo compound (*Charette* and *Barrett*) or used extremely dangerous reagents (NMU, *Nefedov*). These results anyway showed the potential to couple metal catalysis and diazo preparation via diazotization or base-mediated decomposition of nitrosamides. The goal of our work was to identify such reactions and catalysts, as well as expand their use to synthetically useful and safer transformations. Chapter Two describes the initial development of an *in situ* strategy to couple the preparation of trifluoromethyl diazomethane with an iron-catalyzed cyclopropanation and was extended to an asymmetric cobalt-catalyzed process in Chapter Three. Chapter Four deals with a rhodium-catalyzed cyclopropanation using trifluoromethyl diazomethane, whereas Chapter Five describes our further studies on the use of this reagent in homologation reactions. Finally, Chapter Six will introduce the concept of extreme catalysis illustrated by the development of an iron-catalyzed cyclopropanation with *in situ* generated diazomethane in aqueous 6 M KOH.

2. Iron-Catalyzed Cyclopropanations Using *in situ* Generated Diazo Compounds

2.1. Trifluoromethyl Diazomethane: An Underused Reagent in Fluorine Chemistry

2.1.1. Importance of fluorinated compounds in organic synthesis

Fluorine compounds and methods for their preparation have recently attracted a lot of attention due to their wide use in drug discovery. In fact, around 20% of the drugs currently on the market as well as 30% of the agrochemicals bear at least one fluorine atom in their chemical structure.^{117,118} This is largely due to the interesting properties that fluorine causes upon its introduction in a molecule. First, its electronegativity (it is the most electronegative element) can induce dramatic changes in acidity and basicity of neighboring functional groups. Second, the replacement of a hydrogen atom by a fluorine atom alters the polarity of drug targets (decreases the lipophilicity in the case of mono- and trifluoromethylation of alkanes; increases it in the case of aromatic fluorination and perfluorination).¹¹⁷ Also, fluorine can have a substantial effect on the conformation of molecules due to inherent stereoelectronic preferences like the gauche effect.¹¹⁷ Moreover, the C-F bond is metabolically stable, and its introduction allows an isosteric replacement of metabolically sensitive C-H bonds to increase the stability of the drug candidate. These tunable effects make the use of fluorine an essential part of drug design. Among the different fluorinated groups, the trifluoromethyl group, not naturally occurring, has attracted much interest in the synthetic community due to the many challenges associated with its introduction in molecules.

2.1.2. Trifluoromethyl diazomethane: Synthesis and Properties

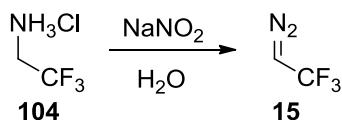
Although many nucleophilic, electrophilic and radical processes¹¹⁹ have recently been disclosed affording trifluoromethylated building blocks, the preparation of some structural units bearing this group still represents a challenge to the organic chemist. Unlike the many one-carbon-reagents used in trifluoromethylation, trifluoromethyl diazomethane represents a mechanistically complementary reagent for the preparation of fluorinated organic compounds. Indeed, the chemistry

¹¹⁷ S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320.

¹¹⁸ K. Muller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881.

¹¹⁹ J. A. Ma, D. Cahard, *J. Fluorine Chem.* **2007**, 128, 975.

of diazo compounds is well-established (*vide supra*) and applications of this reagent to numerous known or unknown processes with diazo compounds could provide a rapid access to new trifluoromethylated compounds. The most straightforward approach to the preparation of this reagent involves the diazotization of the commercially available trifluoroethylamine hydrochloride (**104**, 14 CHF/g, Sigma-Aldrich). This method prescribes the use of sodium nitrite with or without addition of acid in water (Scheme 46).¹²⁰



Scheme 46: Preparation of Trifluoromethyl Diazomethane.

This yellow gas, first reported in 1943 by Gilman and Jones, has a boiling point of 13 °C and is a suspected toxic compound. Moreover, its explosiveness is well-appreciated and exothermic decomposition of this reagent was reported to release 50-100% of the energy released by the same weight of TNT.¹²¹

2.1.3. Uses in organic synthesis

Although this reagent represents a useful trifluoroethyl carbene source, its use in the preparation of trifluoromethylated compounds has been very limited in the literature. The largest use of trifluoromethyl diazomethane prior to our work was in the field of cyclopropanation, and the corresponding literature precedent will be discussed below (2.2.1). Dipolar cycloaddition reactions to electron-deficient alkenes as well as to alkynes are examples of its use in other reactions, and these reactions allowed *Zhang* and *Atherton* to obtain trifluoromethylated heterocycles **106** and **107**, respectively (Scheme 47).^{122,123,124,125} Other transformations include C-H insertion of the trifluoroethyl carbene generated photochemically from trifluoromethyl diazomethane, as illustrated

¹²⁰ H. Gilman, R. G. Jones, *J. Am. Chem. Soc.* **1943**, *65*, 1458.

¹²¹ R. Fields, J. P. Tomlinson, *J. Fluorine Chem.* **1979**, *13*, 147.

¹²² X. Q. Zhang, X. J. Li, G. F. Allan, T. Sbriscia, O. Linton, S. G. Lundeen, Z. H. Sui, *J. Med. Chem.* **2007**, *50*, 3857.

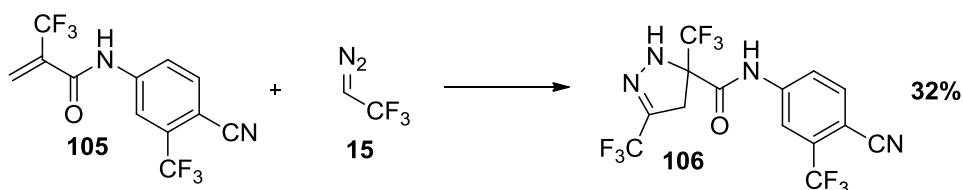
¹²³ J. Grobe, D. Levan, M. Hegemann, B. Krebs, M. Lage, *Chem. Ber.* **1992**, *125*, 411.

¹²⁴ R. Fields, J. P. Tomlinson, *J. Fluorine Chem.* **1979**, *14*, 19.

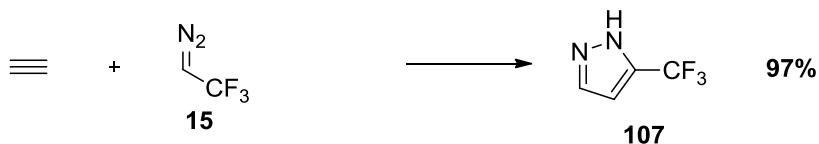
¹²⁵ J. H. Atherton, R. Fields, *J. Chem. Soc. C* **1968**, 1507.

by the preparation of **108** by Atherton.¹²⁶ Moreover, the reagent was used in the preparation of trifluoromethyl sulfonates.^{127,128} Finally, homologation of activated aldehydes with trifluoromethyl diazomethane was described and will be discussed in Chapter 5.

Zhang et al (2007)



Atherton and Fields (1968)



Atherton and Fields (1968)



Scheme 47: Selected Examples of Reactions Involving Trifluoromethyl Diazomethane.

2.1.4. Conclusion and outline

Trifluoromethyl diazomethane should be a versatile reagent for the introduction of the trifluoroethyl carbene unit in molecules. While it has the potential to be used broadly, this reagent was used scarcely in the literature prior to our work. The untoward nature of this reagent (gaseous, toxic, and explosive) limits its applicability in organic synthesis. The development on an *in situ* strategy for its use in cyclopropanation reaction will be presented in this Chapter.

¹²⁶ J. H. Atherton, R. Fields, *J. Chem. Soc. C* **1968**, 2276.

¹²⁷ N. A. Karst, T. F. Islam, F. Y. Avci, R. J. Linhardt, *Tetrahedron Lett.* **2004**, 45, 6433.

¹²⁸ C. O. Meese, *Synthesis* **1984**, 1041.

2.2. Iron-Catalyzed Cyclopropanation using Trifluoroethylamine Hydrochloride and Olefins in Aqueous Media: *In Situ* Generation of Trifluoromethyl Diazomethane

2.2.1. Background

Fluorine molecules have attracted much attention in the past few years which have led to the development of many new methodologies for its introduction. It is therefore striking that few methods for the preparation of trifluoromethyl-substituted cyclopropanes have been disclosed prior to our work.¹²⁹ Based on the widespread use of cyclopropane motifs in medicinal chemistry, it is expected that trifluoromethyl-substituted cyclopropanes would be a valuable addition to the building block library available to the synthetic chemist. Among the few known methods for the preparation of trifluoromethyl-substituted cyclopropanes, the use of the metal-catalyzed decomposition of fluorinated diazoalkanes has attracted much attention (Scheme 48). Davies and co-workers recently described the preparation of trisubstituted trifluoromethyl-substituted cyclopropanes in enantiomerically enriched form using a chiral rhodium catalyst (**109**).¹³⁰ Their protocol involved the preparation of aryl trifluoromethyl disubstituted diazomethanes that, combined with the use of 5 equiv. alkene and $\text{Rh}_2(\text{S-PTAD})_4$ as the catalyst, afforded the corresponding trifluoromethyl-substituted cyclopropanes in high enantioselectivities. Another strategy published by Simmoneaux and co-workers used trifluoromethyl diazomethane as a reagent for the preparation of trifluoromethyl-substituted cyclopropanes using an iron-porphyrin catalyst.¹³¹ Using a chiral version of this catalyst, they obtained enantioselectivities as high as 75% ee. The major drawback of this methodology was the isolation of untoward trifluoromethyl diazomethane by distillation prior to the catalytic step. Trifluoromethyl cyclopropanation using trifluoromethyl diazomethane was also reported by Komarov and co-workers.¹³² They could cyclopropanate styrene with $\text{Rh}_2(\text{OAc})_4$ and trifluoromethyl diazomethane which was generated in a reactor and bubbled through the reaction mixture using a 10-fold excess of the reagent. The corresponding product (**111**) was obtained in 82%

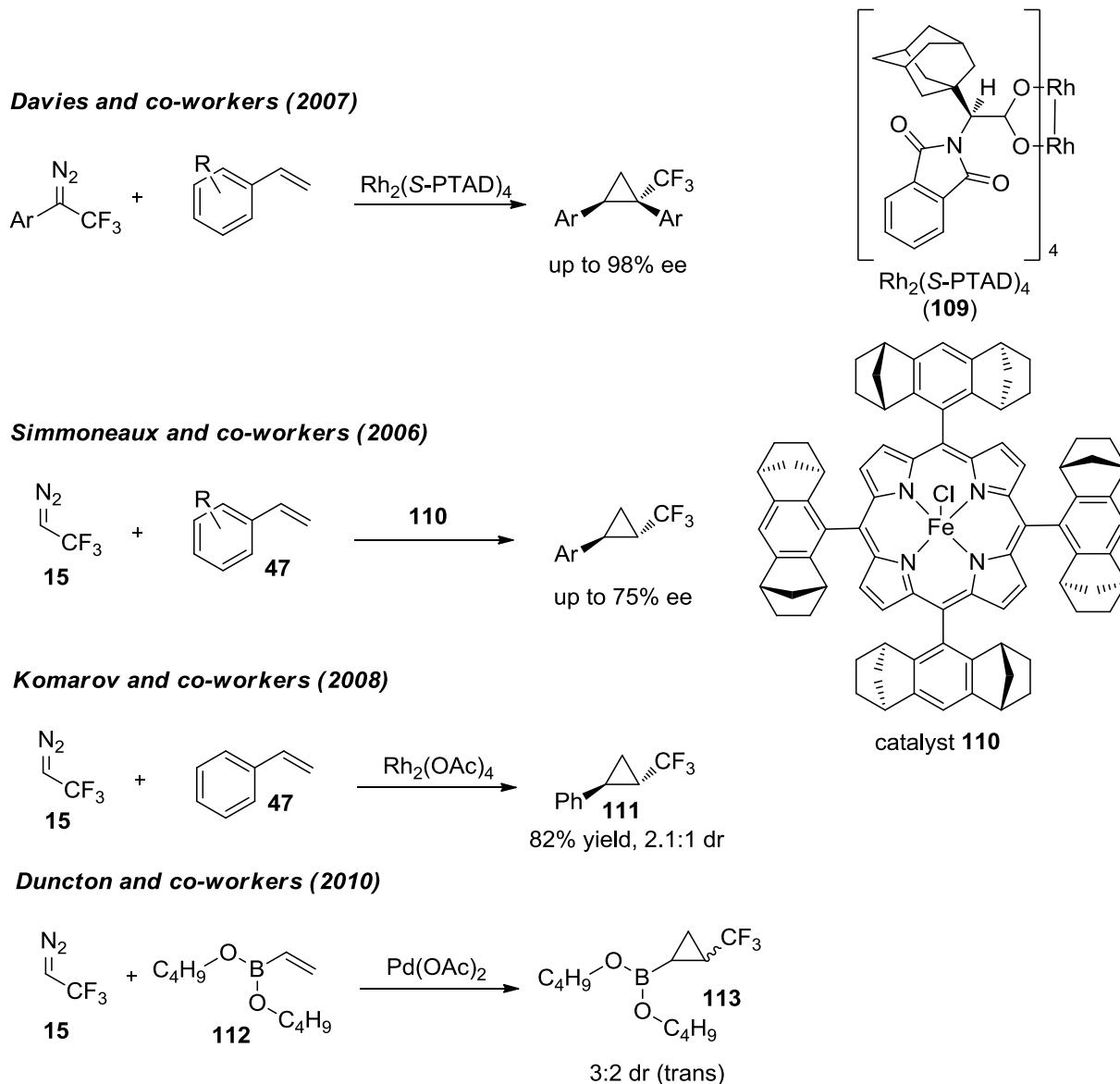
¹²⁹ O. O. Grygorenko, O. S. Artamonov, I. V. Komarov, P. K. Mykhailiuk, *Tetrahedron* **2011**, 67, 803.

¹³⁰ J. R. Denton, D. Sukumaran, H. M. L. Davies, *Org. Lett.* **2007**, 9, 2625.

¹³¹ P. Le Maux, S. Juillard, G. Simmoneaux, *Synthesis* **2006**, 1701.

¹³² P. K. Mykhailiuk, S. Afonin, A. S. Ulrich, I. V. Komarov, *Synthesis* **2008**, 1757.

yield with low diastereoselectivity (2.1:1) for the *trans*-isomer. More recently *Duncton* and co-workers showed that a vinyl boronic ester was a suitable substrate for palladium-catalyzed cyclopropanation with trifluoromethyl diazomethane.¹³³ They used the crude product in a cross-coupling reaction with an aryl bromide. It is also important to mention here the use of proline derivatives bearing trifluoromethyl-substituted cyclopropanes in the conformational analysis of proteins using solid-state ¹⁹F-NMR spectroscopy (Scheme 49) by *Komarov* and co-workers.¹³⁴

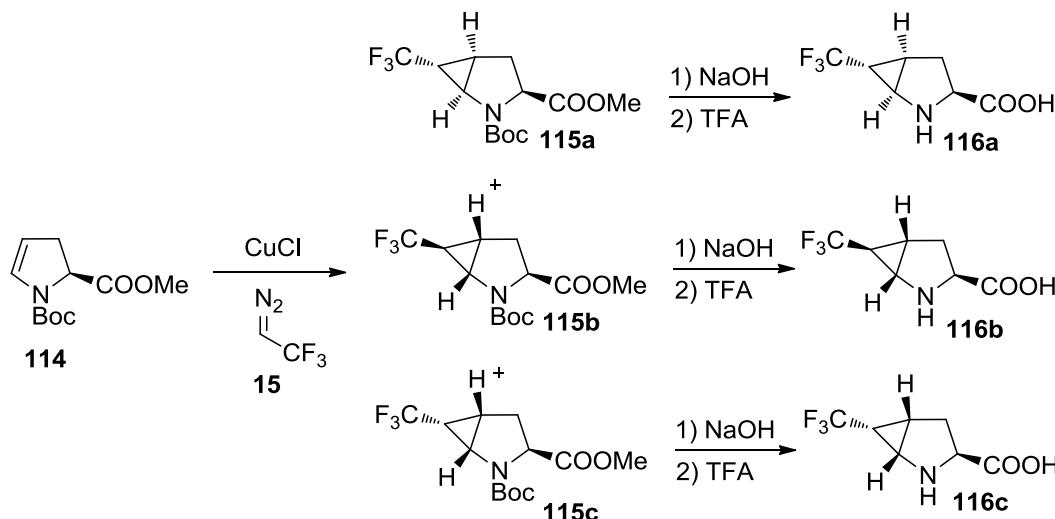


Scheme 48: Preparation of Trifluoromethylated Cyclopropanes Using Metal-Catalyzed Carbene-Transfer.

¹³³ M. A. J. Duncton, L. Ayala, C. Kaub, S. Janagani, W. T. Edwards, N. Orike, K. Ramamoorthy, J. Kincaid, M. G. Kelly, *Tetrahedron Letters* **2010**, *51*, 1009.

¹³⁴ P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich, I. V. Komarov, *Angew. Chem. Int. Ed.* **2008**, *47*, 5765.

Komarov and co-workers (2008)



Scheme 49: Preparation of Trifluoromethyl Proline Derivatives Bearing a Trifluoromethyl-Substituted Cyclopropane.

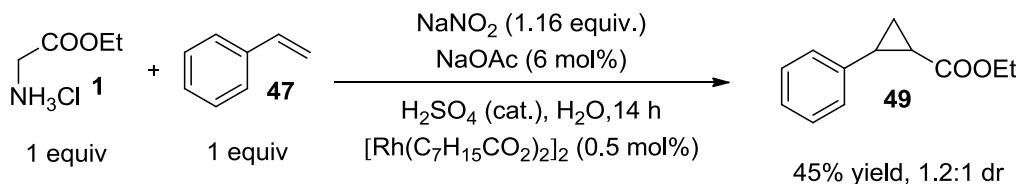
2.2.2. Initial experiments and catalyst screening

At the outset of our studies a report from *Charette* and co-workers attracted our attention (Scheme 50, see also Section 1.4).¹³⁵ They reported a single example of a styrene cyclopropanation using a lipophilic Rh-complex in aqueous media affording the corresponding cyclopropyl ester with glycine ethyl ester hydrochloride and sodium nitrite. The two latter reagents react together in water to form ethyl diazoacetate *in situ* which effects the cyclopropanation reaction. They hypothesized that the phase separation forced the reaction to occur in the styrene micelles, and thus allowed the metal-carbene transfer to selectively occur with the substrate over quenching of the metal-carbene with water. A similar report by *Barrett* and co-workers described the use of a rhodium-porphyrin complex for cyclopropanation of alkenes with glycine ethyl ester hydrochloride in a biphasic dichloromethane/water mixture.¹³⁶

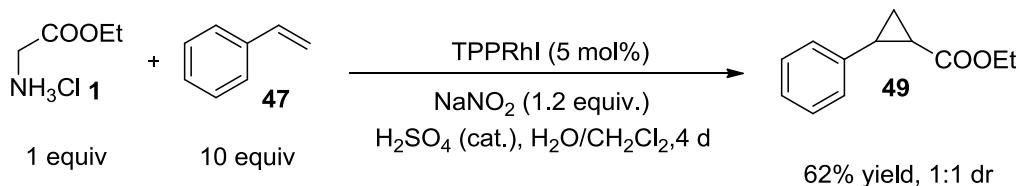
¹³⁵ R. P. Wurz, A. B. Charette, *Org. Lett.* **2002**, *4*, 4531.

¹³⁶ A. G. M. Barrett, D. C. Braddock, I. Lenoir, H. Tone, *J. Org. Chem.* **2001**, *66*, 8260.

Charette and coworkers (2002)



Barrett and coworkers (2001)



Scheme 50: Literature Precedent for Cyclopropanation Using *in situ* Generated Ethyl Diazoacetate.

In these two reports, the products were isolated with almost no diastereoselectivity, which limits their applicability. Nevertheless, we were intrigued by the concept of *in situ* generation of diazo compounds in aqueous media combined with metal-catalyzed carbene-transfer. Extensive literature search demonstrated that trifluoromethyl diazomethane could easily be prepared from the corresponding trifluoroethylamine hydrochloride by simple aqueous diazotization with sodium nitrite. As this reagent is volatile, dangerous and not commercially available (vide supra), we sought a new strategy for the preparation of trifluoromethyl-substituted cyclopropanes by combining the diazotization process in aqueous media with the actual metal-catalyzed cyclopropanation in a similar manner as Charette and Braddock. We reasoned that this would provide a user-friendly access to these poorly studied fluorinated building-blocks.

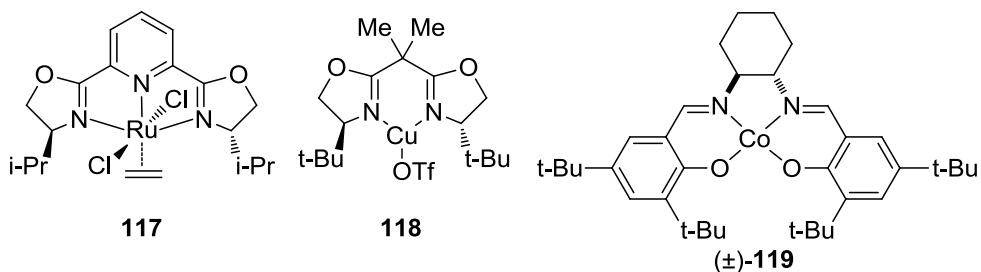
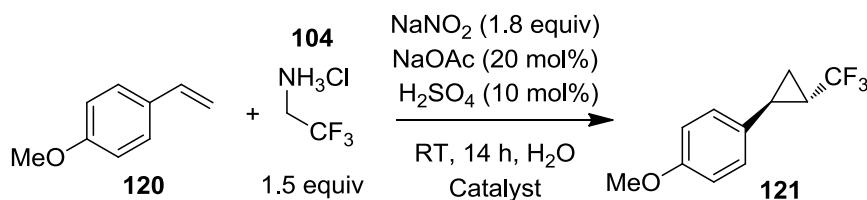


Figure 6: Structures of Some Cyclopropanation Catalysts Tested in Table 3.

A variety of transition-metals known for their activity in cyclopropanation reactions were screened to evaluate their catalytic efficiency under these unusual reaction conditions: *p*-methoxystyrene as test substrate (1.0 equiv.), trifluoroethylamine hydrochloride (1.5 equiv.), catalyst, acidic buffer (sulfuric acid/sodium acetate), water. To this mixture was added a NaNO₂ solution in water over 10 h. The product was then isolated by flash chromatography (Figure 6 and Table 3).

Table 3: Screening of Metal Catalysts for the Cyclopropanation Using *in situ* Generated CF₃CHN₂.^[a]



Entry	Catalyst	Loading	dr ^[b]	Yield ^[c]
1	Fe(TPP)Cl ^[d]	3 mol%	>95:5	89
2	Fe(TPP)Cl ^[d]	1 mol%	>95:5	70
3	Co(TPP) ^[d]	3 mol%	>95:5	50
4	Ru(TPP)CO	3 mol%	86:14	56
5	119^[e]	5 mol%	>95:5	51
6	117	5 mol%	-	NR
7	Rh ₂ (esp) ₂	1.5 mol%	1:1	74
8	118	5 mol%	-	NR

[a] General procedure (GP 2.1): alkene (0.22 mmol, 1 equiv), CF₃CH₂NH₃Cl (1.5 equiv), NaNO₂ (1.8 equiv.), H₂O, RT. [b] Determined by ¹H NMR spectroscopy. [c] Yield of isolated product. [d] DMAP (3 equiv. with respect to the catalyst) was used as an additive. [e] NMI (10 mol%) was used as an additive.

Surprisingly, a wide range of transition metal catalysts proved to be competent under these reaction conditions. Fe, Co- and Ru-porphyrins all afforded the product (**121**) with high *trans*-selectivity as well as moderate to high isolated yields (Table 3, Entries 1-4). A rhodium dimer, Rh₂(esp)₂ gave a good yield albeit without diastereoselectivity (Entry 7). This is a particularly interesting result in light of all the known transformations using rhodium catalysts and diazo compounds,¹³⁷ and we later took advantage of this result to develop a route to trifluoromethyl-substituted cyclopropenes derivatives (Chapter 4). The result obtained with the racemic Jacobsen

¹³⁷ See Reference 1c.

salen complex (**119**, Entry 5) was also very exciting, and led later to the development of the asymmetric cyclopropanation (Chapter 3). The product was obtained in moderate yield with this catalyst with almost perfect diastereoselectivity. An exciting feature of this screening phase was the discovery that FeTPP^{Cl}, a simple iron porphyrin catalyst commercially available, was not only effective for this transformation in water but was also the most effective catalyst under these extreme conditions (oxidizing, water, acid). This is particularly interesting due to the recent interest in this metal as an alternative to noble metal catalysts.¹³⁸

2.2.3. Scope of the transformation

Having a practical protocol in hand for the iron-catalyzed preparation of trifluoromethyl-substituted cyclopropanes using *in situ* generated trifluoromethyl diazomethane, we studied the scope of styrene derivatives that could be used under these conditions (Table 4). Many styrene derivatives afforded the corresponding products in high yield. Electron-donating (Table 4, Entry 5) as well as electron-withdrawing (Table 4, Entries 2, 4, 7) functionalities were tolerated. The reaction was also compatible with 1,1-disubstituted styrenes (Entry 6). The transformation could not be extended to aliphatic substrates or *cis*-substituted alkenes (Entries 8, 9).

¹³⁸ See Reference 76 and 77.

Table 4: Scope of the FeTPP₂Cl-Catalyzed Trifluoromethyl Cyclopropanation.^[a]

Entry	Alkene	Product	Yield ^[b]
1			86
2			85
3			99
4			77
5			89
6			86
7			95
8			10 ^[c]
9			NR

[a] General procedure (GP 2.2): alkene (0.22 mmol, 1 equiv), CF₃CH₂NH₃Cl (1.5 equiv), NaNO₂ (1.8 equiv.), Fe(TPP)Cl (3 mol%), DMAP (10 mol%), H₂O, RT. [b] Yield of isolated product. [c] Yield based on ¹H NMR spectroscopy.

Aliphatic substrates were shown by Woo and co-workers to be much less reactive in an iron porphyrin-catalyzed cyclopropanation using ethyl diazoacetate.¹³⁹ By studying the mechanism of this cyclopropanation reaction with Hammett and isotope effect studies, they concluded that the reaction proceeds via nucleophilic attack of the alkene onto the electrophilic metal-carbene, giving rise to the building of a partial positive charge on the higher substituted olefinic carbon in the transition state. These observations are extendable to our transformation, which probably proceeds via a similar mechanism. We therefore propose the following model for the transition state of our reaction in Figure 7.

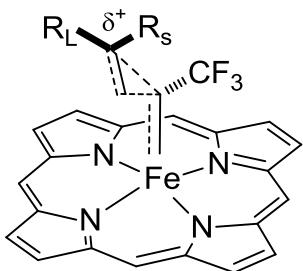


Figure 7: Working Model for the Transition State of the Trifluoromethyl Cyclopropanation.

Conjugated substrates (like styrenes) and electron-rich alkenes in general are thus better substrates because they are able to stabilize the partial positive charge formed in the transition-state, lowering its energy and therefore accelerating the reaction. This model explains the high diastereoselectivity obtained, since the shielding porphyrin ligand forces an eclipsed attack of the alkene onto the metal-carbene. This eclipsing interaction determines the diastereoselectivity of the process. Another limitation of our reaction and of FeTPP^{Cl}-catalyzed cyclopropanation in general is the non-existent reactivity with both 1,2-*cis* and *trans*-substituted alkenes. Steric congestion around the metal-carbene between one of the two alkene substituents and the porphyrin ligand excludes a productive interaction.

¹³⁹ See Reference 79.

2.2.4. Extension to diene and enyne substrates and reevaluation of the reaction conditions

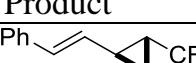
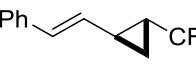
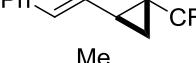
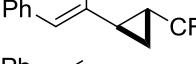
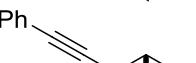
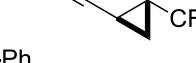
Having successfully established a protocol for the preparation of trifluoromethyl-substituted cyclopropane from styrenes using an iron catalyst, in collaboration with an exchange student (Jeremy Cheang),¹⁴⁰ we attempted to simplify our original reaction conditions for its extension to diene and enyne substrates. It was rapidly discovered that the reaction could, quite surprisingly, be performed in an open vial under air without degassed water. This was surprising as literature had proposed that Fe(II)TPP, a very oxygen sensitive complex, was the active catalyst in cyclopropanations using FeTPPCl.¹⁴¹ Also, the axial ligand, DMAP, from our initial protocol, proved not to be an essential additive for the reaction. Slow addition of sodium nitrite was also not necessary as long as the buffer was omitted and slightly more trifluoroethylamine hydrochloride and sodium nitrite were employed. The acidic buffer is thought to accelerate the diazotization reaction and is thus deleterious to the reaction when sodium nitrite is added in one portion. High concentrations of the diazo compound lead to its dimerization, a well-known side-reaction in metal-catalyzed transformations with diazo compounds.^{1c}

Having a simple procedure in hand, we then studied the scope of dienes and enynes that could be used under these reaction conditions (Table 5). Both electron-rich (Table 5, Entries 2, 6 ,7) and electron-poor (Entries 3 and 5) dienes as well as enynes (Entries 8-10) proved to be efficient substrates for this transformation. These products have not been synthesized before and represent some attractive alkene and alkyne functionalized trifluoromethyl-substituted cyclopropanes with potential for further elaboration. The reaction is *trans*-selective and highly regioselective for the reaction at the terminal olefin. The selectivity observed for the less electron-rich terminal alkene is likely due to the high shape-selectivity of the iron-porphyrin catalyst described above.

¹⁴⁰ The results presented in section 2.2.4 were performed by Jeremy Cheang (UWA, deceased) and Bill Morandi (B.M.). All the experiments were designed by B.M. and all the results interpreted by B.M.

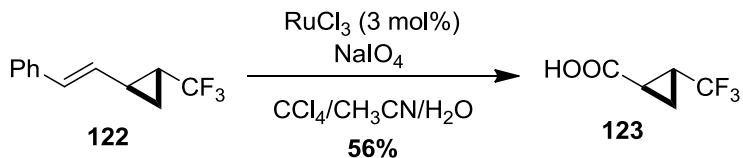
¹⁴¹ The Fe(III) center is reduced to Fe(II) *in situ* by the diazo compound. See reference 79.

Table 5: Scope of the Iron-Catalyzed Cyclopropanation with Dienes and Enynes.^[a]

Entry	Product	x/y	Yield ^[b]
1		2/2.4	74%
2 ^[c]		2/2.4	93%
3 ^[c]		2/2.4	60%
4		2/2.4	83% ^[d]
5 ^[c]		3/3.6	95%
6		2/2.4	52%
7		2/2.4	93%
8		3.5/4.2	76%
9		4/4.8	81%
10		4/4.8	69% ^[e]

[a] General procedure (GP 2.3): FeTPPCl (3 mol %), CF₃CH₂NH₃Cl (x equiv), NaNO₂ (y equiv), substrate, H₂O, RT. [b] Isolated yield. [c] Toluene was used as a cosolvent. [d] Isolated as a 12:1 mixture of E/Z isomers. [e] Isolated as an inseparable mixture containing additional starting material (9%).

To illustrate the utility of this method, we oxidatively cleaved product **122** to give *trans*-trifluoromethyl cyclopropane carboxylic acid (**123**) in 56% yield, a commonly used building block in the development of new insecticides and drug candidates (Scheme 51).¹⁴²

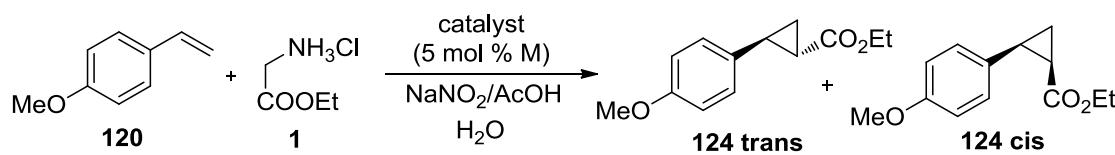
**Scheme 51: Oxidative Cleavage of Vinyl Cyclopropane **122** to Form Cyclopropane Carboxylic Acid **123**.**

¹⁴² (a) WO 2005/011655, 2005. (b) T. Mori, K. Ujihara, O. Matsumoto, K. Yanagi, N. Matsuo *J. Fluorine Chem.* **2007**, *128*, 1174.

2.2.5. Iron-catalyzed cyclopropanation with glycine ethyl ester hydrochloride in aqueous media

Having established the chemistry of trifluoromethyl diazomethane in an iron-catalyzed cyclopropanation we reevaluated the two reports by *Charette* and *Braddock* (*vide supra*). While they both showed the feasibility of the cyclopropanation of olefins with *in situ* generated ethyl diazoacetate from glycine ethyl ester hydrochloride, both of them experienced issues with the diastereoselectivity of the reaction. We therefore tried to improve their protocol for this transformation. We (in collaboration with Amund Dolva)¹⁴³ reasoned that using FeTPP⁻Cl or other transition metals, we could eventually solve the diastereoselectivity problem. We screened common transition metal catalysts known to mediate the cyclopropanation of alkenes with ethyl diazoacetate (Table 6).

Table 6: Screening of Metal-Catalysts for the Cyclopropanation Using *in situ* Generated Ethyl Diazoacetate.^[a]



Entry	Catalyst	Conversion ^[b]	dr ^[b]
1	Cu(OTf) ₂	44%	2:1
2	Pd(OAc) ₂	25%	1:1
3	Rh ₂ (OAc) ₄	10%	1:1.5
4	Rh ₂ (CH ₃ (CH ₂) ₅ COO ⁻) ₄	87%	1:1
5	Rh ₂ (esp) ₂	93%	1:1
6	CoTPP	27%	7:1
7	RuTPPCO	100%	8:1
8	FeTPP ⁻ Cl	100%	9:1

[a] General procedure (GP 2.4): Catalyst (5 mol % M), EtO₂CCH₂NH₃Cl (2 equiv), NaNO₂ (2.4 equiv), substrate, H₂O, 40 °C. [b] Determined by ¹H-NMR analysis of the crude reaction mixture.

The most common catalysts in cyclopropanation reactions, Cu(OTf)₂, Pd(OAc)₂ and Rh₂(OAc)₄, afforded the product in low to moderate conversions and poor diastereoselectivities (Table 6, Entries 1-3). Lipophilic Rh complexes afforded the product with good conversion albeit in almost no diastereoselectivity (Entries 4-5), in accordance with the results obtained by *Charette*. To our delight, both a Ru and an Fe-porphyrin gave the product with full conversions and good

¹⁴³ This work (section 2.2.5.) was performed by Amund Dolva (NTNU) and B.M. All the experiments were designed and analyzed by B.M.

diastereoselectivities (Entries 7-8). Being inexpensive and more easily available, the Fe-catalyst was chosen for further studies. Interestingly, the catalyst loading could be decreased to 1 mol% after further optimization. The scope of this reaction was then assessed (Table 7). A wide range of styrene derivatives gave the *trans*-product in good isolated yield. Both electron-rich (Table 7, Entries 1 and 3) and electron-deficient (Entries 9 and 10) were good substrates. Furthermore, *ortho*-substitution (Entries 2 and 6) was well-tolerated. The diastereoselectivity was good in all cases (6:1 to 10:1).

Table 7: Scope of the FeTPP^{Cl}-Catalyzed Cyclopropanation.^[a]

Entry	Product	Yield ^[b]	dr ^[c]
1		79%	8:1
2		70%	10:1
3		68%	8:1
4		74%	9:1
5		64%	8:1
6		62%	10:1
7 ^[d]		72%	7:1
8		71%	10:1
9 ^[d]		55% ^[e]	6:1
10 ^[f]		67%	7:1
11 ^[d]		39%	nd

[a] GP 2.5: FeTPP^{Cl} (1 mol%), EtO₂CCH₂NH₃Cl (2 equiv), NaNO₂ (2.4 equiv), substrate, H₂O, 40 °C. [b] Isolated yield of pure *trans*-product. [c] Determined by ¹H-NMR analysis of the crude reaction mixture. [d] FeTPP^{Cl} (1.5 mol%), EtO₂CCH₂NH₃Cl (3 equiv), NaNO₂ (3.6 equiv). [e] Isolated yield of 66% (83% purity). [f] FeTPP^{Cl} (1 mol%), EtO₂CCH₂NH₃Cl (4 equiv), NaNO₂ (4.8 equiv).

2.2.6. Conclusion and Outlook

We have described a convenient and general iron-catalyzed cyclopropanation reaction of activated olefins to prepare trifluoromethyl-substituted cyclopropanes using *in situ* generated trifluoromethyl diazomethane. The active reagent was generated from trifluoroethylamine hydrochloride and sodium nitrite in aqueous solution. The initial reaction conditions could further be simplified to afford a user-friendly protocol (no protective atmosphere, one-pot addition of all the reagents) and was extended to the regioselective and diastereoselective cyclopropanation of dienes and enynes. Interestingly, the method proved to be more general and could be extended to the formation of cyclopropyl esters using glycine ethyl ester hydrochloride and sodium nitrite. Beyond representing a practical synthetic methodology, these initial transformations illustrate the power of a new strategy for the safe handling of diazo compounds in catalysis. In fact, a wide range of metals have proven to be active under these harsh conditions, and open new research directions for catalytic carbene-transfer. The next two chapters will discuss two important new reactions (cobalt-salen catalyzed asymmetric preparation of trifluoromethyl-substituted cyclopropanes and rhodium-catalyzed trifluoromethyl cyclopropenation) that were developed based on the results obtained during the exploratory experiments described in this chapter.

3. Cobalt-Catalyzed Asymmetric Preparation of Trifluoromethyl-Substituted Cyclopropanes

3.1. Development of the Cobalt-Catalyzed Asymmetric Preparation of Trifluoromethyl-Substituted Cyclopropanes

3.1.1. Background

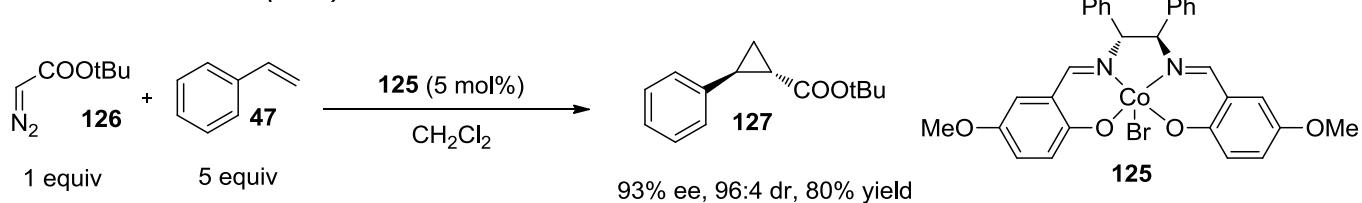
Building on the results we described in the preceding chapter, we became interested in developing an asymmetric reaction for the preparation of enantioenriched trifluoromethyl-substituted cyclopropanes under reaction conditions similar to the ones described for the iron-catalyzed cyclopropanation. Among the many catalysts that showed compatibility with the reaction conditions necessary for the *in situ* generation of trifluoromethyl diazomethane, the cobalt-salen **119** (Figure 6) attracted our interest. These salen-ligands have been extensively used in asymmetric synthesis due to their modular nature and ease of synthesis.¹⁴⁴ Interestingly, *Katsuki* described the use of cobalt-salen **125** as a highly enantiodiscriminating catalyst for the preparation of cyclopropyl esters (Scheme 52).¹⁴⁵ They obtained the product (**127**) of the reaction between *t*-butyl diazoacetate and styrene in 80% yield, 93% ee and 96:4 diastereomeric ratio favoring the *trans*-adduct. A wide range of Co-salens were probed and catalyst **125** proved to be optimal in terms of enantioselectivity. *Katsuki* rationalized this result by invoking a more product-like transition state due to stabilization of the putative metal-carbene intermediate by electron-donating substituent (MeO) on the salen scaffold. Later *Zingaro* and co-workers reported an asymmetric cobalt-catalyzed cyclopropanation with ethyl diazoacetate using a bimetallic Co-salen complex (**128**).¹⁴⁶ They obtained cyclopropane **49** in up to 94.3% ee using this catalyst. In their case, similar yields and enantioselectivities were obtained albeit the diastereoselectivity of the reaction was largely decreased to a 3:1 ratio favoring the *trans*-product.

¹⁴⁴ Selected reviews: (a) J. F. Larrow, E. N. Jacobsen *Top. Organomet. Chem.* **2004**, 6, 123. (b) T. Katsuki, *Synlett* **2003**, 281.

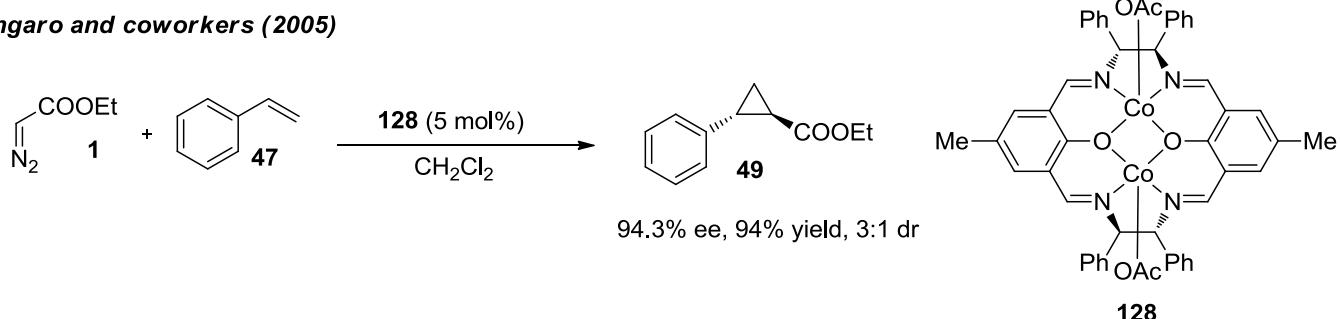
¹⁴⁵ (a) T. Fukuda, T. Katsuki, *Synlett* **1995**, 825. (b) T. Fukuda, T. Katsuki, *Tetrahedron* **1997**, 53, 7201.

¹⁴⁶ J. Gao, F. R. Woolley, R. A. Zingaro, *Org. Biomol. Chem.* **2005**, 3, 2126.

Katsuki and coworkers (1997)



Zingaro and coworkers (2005)

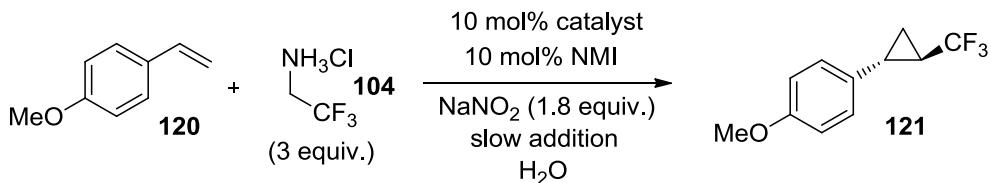


Scheme 52: Previously Reported Asymmetric Co-Salen-Catalyzed Cyclopropanation.

Based on this literature precedent, we reasoned that the screening of Co-salen complexes, easily accessible from commercially available salicylaldehydes, would represent a facile entry into the development of an enantioselective asymmetric preparation of trifluoromethyl-substituted cyclopropanes with *in situ* generated trifluoromethyl diazomethane.

3.1.2. Initial experiments and catalyst screening

Our investigation rested on the initial result obtained in the preceding Chapter using Co-salen catalyst **119** (Figure 6) in a racemic form. Performing the reaction with the enantiopure catalyst (*S,S*-**119**) afforded a promising 45% ee for the product as shown by SFC analysis (Scheme 53 and Figure 8).



Scheme 53: General Conditions for the Initial Screening of Catalysts.

When we replaced the catalyst for its oxidized version (*S,S*-**129**), no product was formed under the standard reaction conditions. This result was unexpected considering the results obtained by *Katsuki* and *Zangaro* (vide supra). Identical outcome was obtained using *Katsuki*'s complex (**125**). After these initial unsuccessful experiments, we synthesized and screened a large library of cobalt(II)-salen complexes. They are easily accessible from condensation of commercially available diamines and salicylaldehyde derivatives followed by complex formation in refluxing ethanol. The so-formed complexes were directly tested in the cyclopropanation reactions after filtration. Initially, various diamines were evaluated to determine the influence of the backbone on the conversion and enantioselectivity of the reaction (Figure 8).

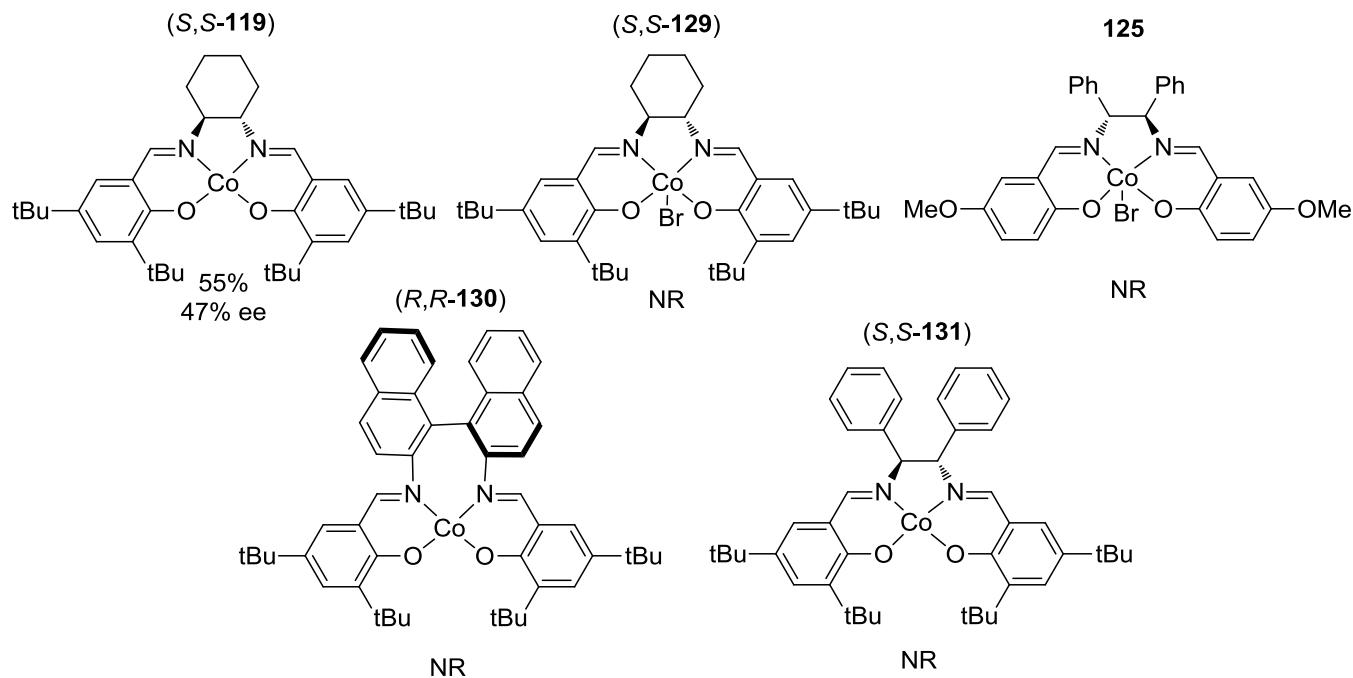
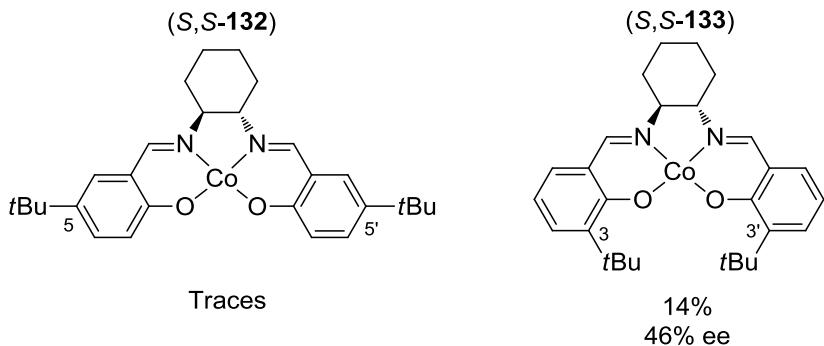
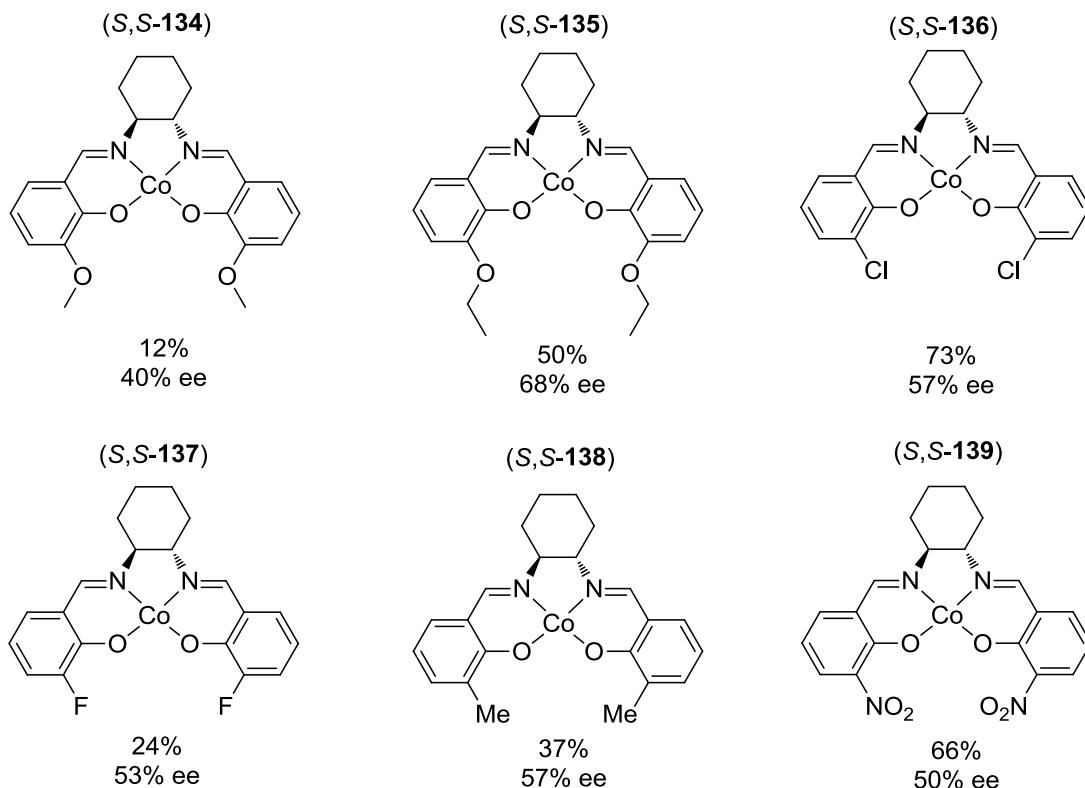


Figure 8: Results Using Salen Ligands Bearing Different Diamine Linkers.

Unfortunately, replacing the cyclohexyldiamine motif with two commercial enantiopure chiral diamines gave worse results (Figure 8). The binaphthyl diamine-based salen catalyst (*R,R*-**130**) gave no conversion to the product, whereas diphenyldiamines-based catalyst (*S,S*-**131**) resulted in a poor 19% conversion and 13% ee. These results indicated to us that the cyclohexyldiamine moiety held the most promise for further screening. We next investigated the influence of the sterically demanding t-butyl groups on the aromatic scaffold (Figure 9).

**Figure 9: Co-Salens Bearing two *t*-Butyl Groups.**

Interestingly, these results showed that the 3,3'-*t*-butyl groups are responsible for the enantiodiscrimination, as catalyst (S,S-133) gave similar ee as the bis-*t*-butyl analogue (46% ee vs 47% ee), albeit in a lower conversion, while catalyst (S,S-132) which bears the *t*-butyl groups in the 5,5'-position was found to be inactive (Figure 9). Following this result, we systematically evaluated catalysts bearing substituents at the 3,3'-positions to probe the steric and electronic effects on the enantioselectivity (Figure 10).

**Figure 10: Co-Salens Bearing Different *ortho*-Substituents.**

Enantioselectivities were all rather similar among the different groups tested; only the ethoxy substituted complex (*S,S*-**135**) gave a clearly superior enantioselectivity, 68% ee. The fact that this ligand gave a significantly better result led us to the preparation of additional ether-substituted salen complexes (Figure 11).

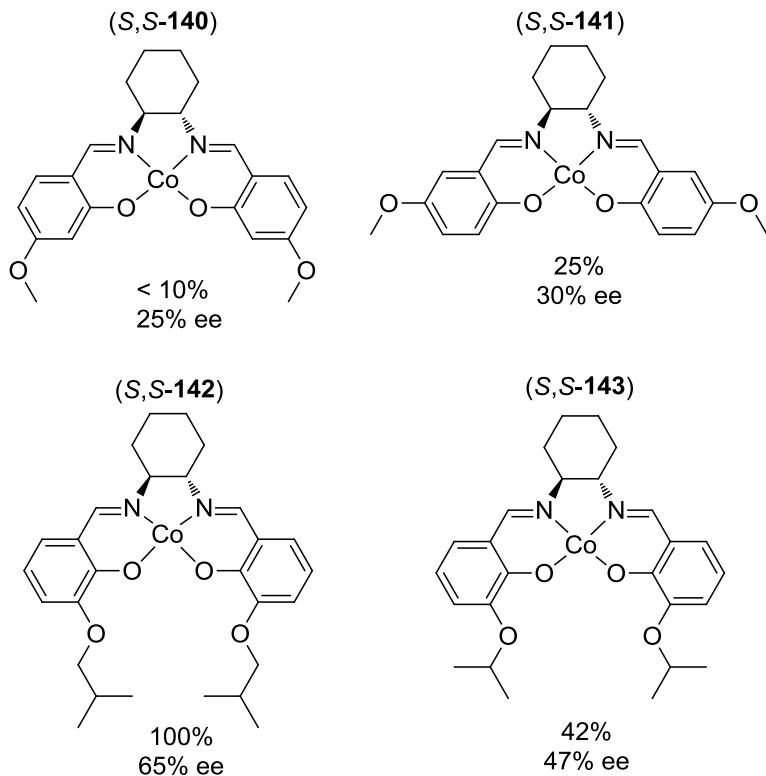


Figure 11: Co-Salens Bearing Different Alkyl Ether Substituents.

The results in Figure 11 confirmed that the preferred position for substitution is the 3,3'-position. Increasing the size of the alkyl rest on the ether group had a beneficial effect on the conversion (in the case of isobutyl, catalyst (*S,S*-**142**)) while giving the same enantioselectivity as with the ethoxy-substituted catalyst. A sterically more hindered ether group (catalyst (*S,S*-**143**), isopropyl) led to a decreased enantioselectivity, indicating that a fine steric balance is essential for good results in this reaction. At this stage, we decided to keep the isobutyl ether at the 3,3'-position for subsequent optimization studies. New catalysts based on this complex were prepared having different additional substituents on the aromatic scaffold (Figure 12).

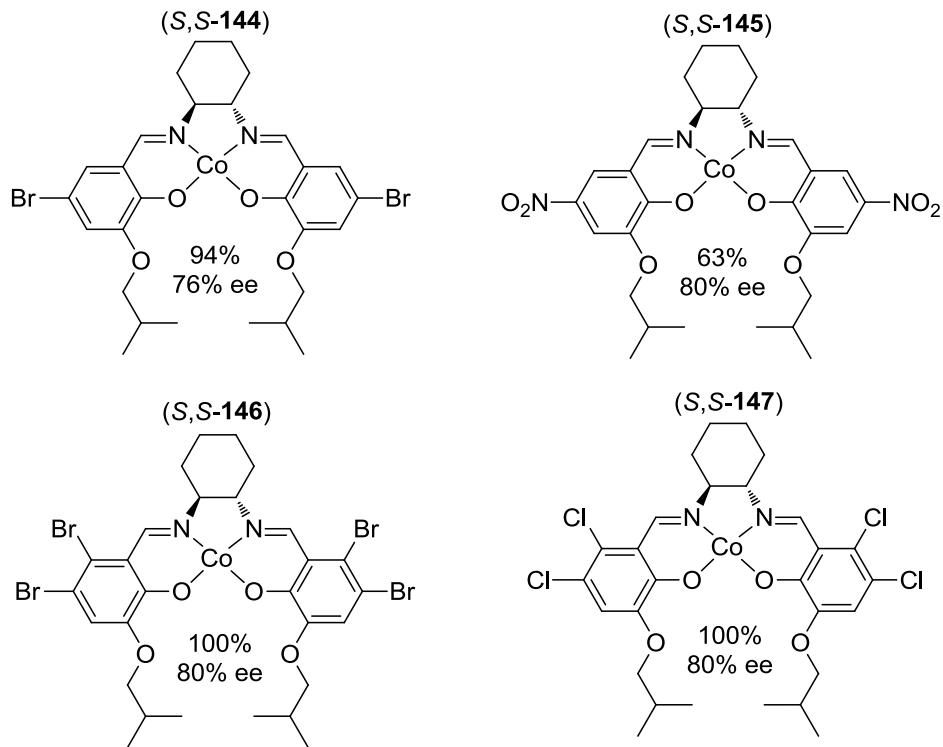
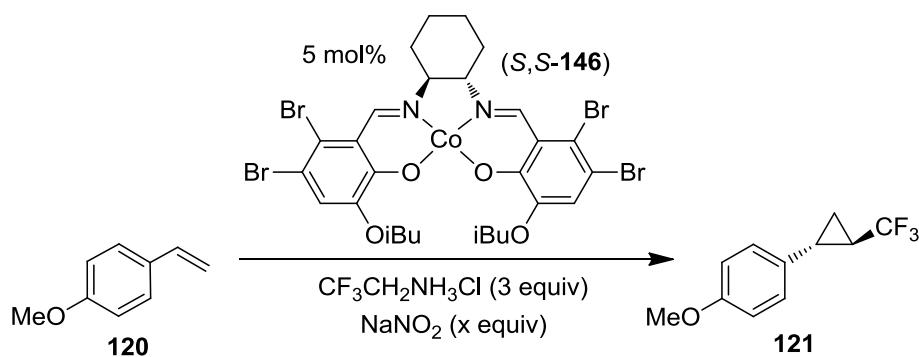


Figure 12: Co-Salens Bearing Additional Substituents on the Aromatic Ring.

Electron-withdrawing substituents on the aromatic ring greatly improved the enantioselectivity of the reaction, with three different catalysts affording 80% ee. Two of these catalysts, the dichloro- and dibromo-substituted catalysts (*S,S*-147) and (*S,S*-146), gave the product with full conversion. At this stage we decided to further optimize the reaction conditions in order to improve the enantioselectivity. We selected the dibromo catalyst (*S,S*-146) for further optimization (Table 8).

Table 8: Optimization of Reaction Conditions Using Catalyst 146.^[a]

Entry	Additive	x	Temp.	Conv. ^[b]	ee ^[b]
1	NMI (10 mol%)	1.8	RT	60%	80%
2	-	1.8	RT	33%	80%
3	NaCN (10 mol%)	1.8	RT	61%	80%
4	DMAP (10 mol%)	1.8	RT	61%	80%
5	CO	1.8	RT	28%	80%
6	AsPh ₃ (20 mol%)	1.8	RT	98%	80%
7	AsPh ₃ (20 mol%)	1.8	4 °C	18%	85%
8	AsPh ₃ (20 mol%)	3.6	4 °C	31%	85%

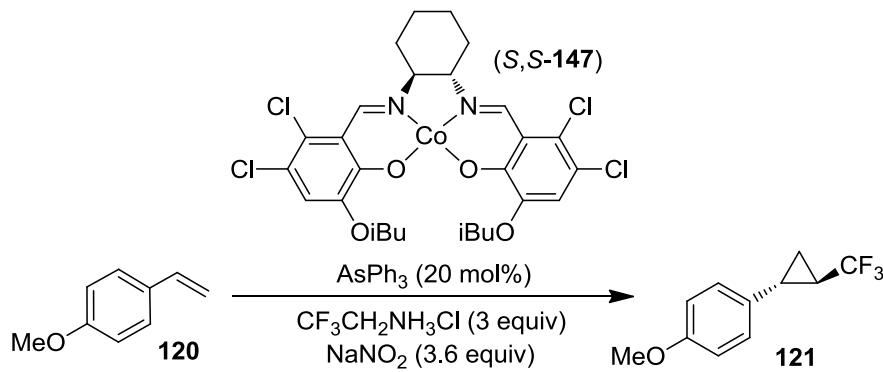
[a] General procedure (GP 3.2): Catalyst **146** (0.011 mmol, 5 mol%), additive, alkene (0.22 mmol, 1 equiv), CF₃CH₂NH₃Cl (0.66 mmol, 3 equiv), NaNO₂ (slow addition), water. [b] Determined by SFC analysis of the crude product.

First, different additives known to act as axial ligands were probed under the standard conditions using 5 mol% of the catalysts to observe their effect on conversions and enantioselectivities (Table 8). These axial ligands have been shown to influence the enantioselectivity in similar reactions by stabilizing the electrophilic metal-carbene intermediate.^[147] Carbon monoxide (Entry 5) had no effect on the reaction, giving almost exactly the same result as the control reaction without any additive (Entry 2). NaCN (Entry 3) and DMAP (Entry 4) had a positive influence on the reaction, giving increased conversions (similar result as the classical reaction with NMI, Entry 1). Adding AsPh₃ afforded complete conversion to the product (Entry 6). The difficult dissolution of the catalyst in *p*-methoxystyrene was apparently facilitated in the presence of triphenylarsine. Surprisingly, the enantioselectivities obtained using these additives were the same as the control reaction. Lowering the temperature had an effect on selectivity (85% ee), but the conversion dropped considerably (Entries 7 and 8). Due to the poor solubility of the catalyst at 4

^[147] For a discussion about *trans*-axial effects in cobalt-catalyzed cyclopropanations see: Y. Chen, X. P. Zhang, *Synthesis* **2006**, 1697.

$^{\circ}\text{C}$, we decided to re-evaluate the chloride catalyst (*S,S*-**147**) under these new found reaction conditions (Table 9). Under these conditions (4 $^{\circ}\text{C}$, Table 9, Entry 1), this catalyst retained its activity with a slight increased in enantioselectivity to 83% ee (Table 9, Entry 1). We therefore decided to continue the optimization of the reaction conditions with this catalyst instead.

Table 9: Optimization of Reaction Conditions Using Catalyst **147.**^[a]

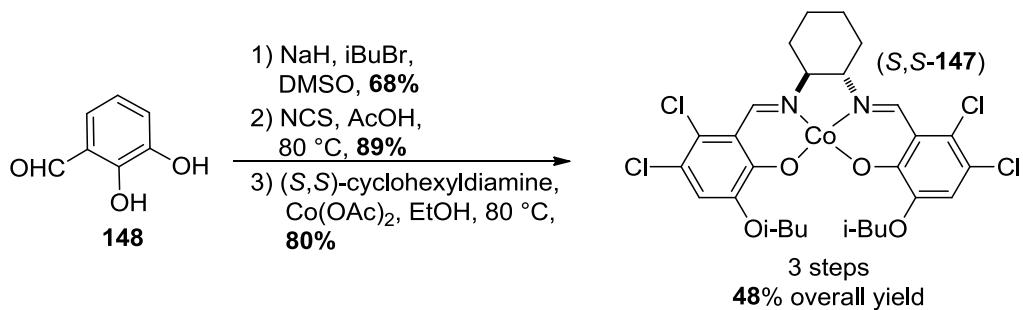


Entry	mol% x	Temp.	buffer ^[b]	SP ^[c]	Conv. ^[d]	ee ^[d]
1	5	4 $^{\circ}\text{C}$	No	Yes	100%	83%
2	5	0 $^{\circ}\text{C}$	No	Yes	100%	85%
3	5	-25 $^{\circ}\text{C}$ ^[e]	No	Yes	Traces	92%
4	5	-15 $^{\circ}\text{C}$ ^[e]	No	Yes	30%	90%
5	5	-15 $^{\circ}\text{C}$ ^[e]	No	No	52%	90%
6	5	-15 $^{\circ}\text{C}$ ^[e]	Yes	No	79%	90%
7	10	-15 $^{\circ}\text{C}$ ^[e]	Yes	No	100%	90%

[a] General procedure (GP 3.2): Catalyst **147**, AsPh₃ (0.044 mmol, 20 mol%), alkene (0.22 mmol, 1 equiv), CF₃CH₂NH₃Cl (0.66 mmol, 3 equiv), NaNO₂ (0.8 mmol, 3.6 equiv). [b] NaOAc (0.044 mmol, 20 mol%), H₂SO₄ (0.022 mmol, 10 mol%). [c] Yes: Syringe pump addition of NaNO₂ over 10 h. No: Direct addition of NaNO₂. [d] Determined by SFC analysis of the crude product. [e] 20% NaCl solution as solvent.

Lowering the temperature further increased the enantioselectivity, and 90% ee could be reached with 30% conversion at -15 $^{\circ}\text{C}$ (Entry 4). The one-time addition of the sodium nitrite instead of a slow addition with a syringe pump increased the conversion to 52% (Entry 5). This is probably due to the rate-limiting diazoformation at this low temperature. We then considered the addition of buffered sulfuric acid, reasoning that this would further accelerate the slow diazotization process. Indeed, the conversion could be further increased (79%, Entry 6). Finally, increasing the catalyst loading to 10 mol% afforded full conversion to the product in 90% ee (Entry 7).

Having successfully optimized the conditions, the synthesis of the best catalyst, (*S,S*-**147**), was optimized to enable its preparation on scale. The following scheme illustrates this synthesis.



Scheme 54: Synthesis of Catalyst (*S,S*-147**).**

Treatment of the bisphenol **148** with 2 equiv. of NaH gives rise to the dianion that was selectively alkylated at the least hindered, more nucleophilic phenolate site. Chlorination of the obtained product with NCS under forcing conditions (AcOH , 80°C) allowed a double chlorination to occur. This aldehyde was then condensed with cyclohexyldiamine in EtOH , followed by addition of $\text{Co}(\text{OAc})_2$ and refluxing overnight during which the product had slowly precipitated. Simple filtration afforded the catalyst in analytically pure form. A crystal suitable for X-Ray crystallography was obtained by slow evaporation of a $\text{CH}_2\text{Cl}_2/\text{MeOH}$ solution. The crystal structure of the solvate is shown below (Figure 13).

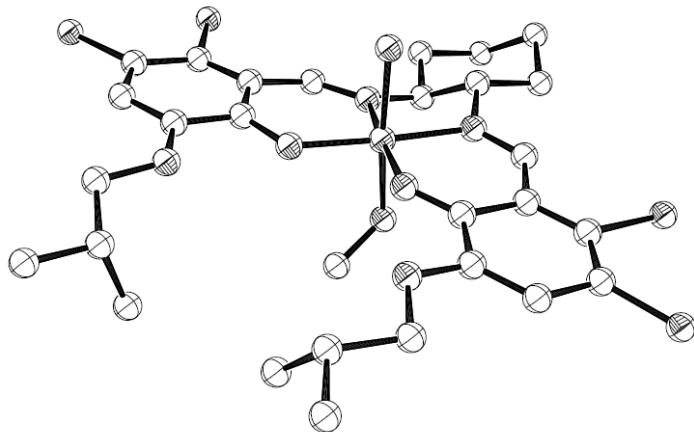


Figure 13: Crystal Structure of Solvated Catalyst (S,S-147).

3.1.3. Scope of the transformation

Having a well-defined complex and reaction conditions to catalyze the preparation of trifluoromethyl-substituted cyclopropanes in enantiomerically enriched form, we studied the scope of the reaction (Table 10). The transformation showed a broad substrate scope. Both electron-withdrawing (Entries 2, 4, 9 and 10) and electron-donating substituents (Entry 5) were tolerated. Not only *para*- (Entries 2, 3, 4, 5, 6 and 8), but also *meta*- (Entries 7, 9 and 10) as well as *ortho*-substitution (Entries 8 and 11) were all compatible with the reaction conditions. All the products were obtained in good yields and high enantioselectivities with almost perfect diastereoselectivity.

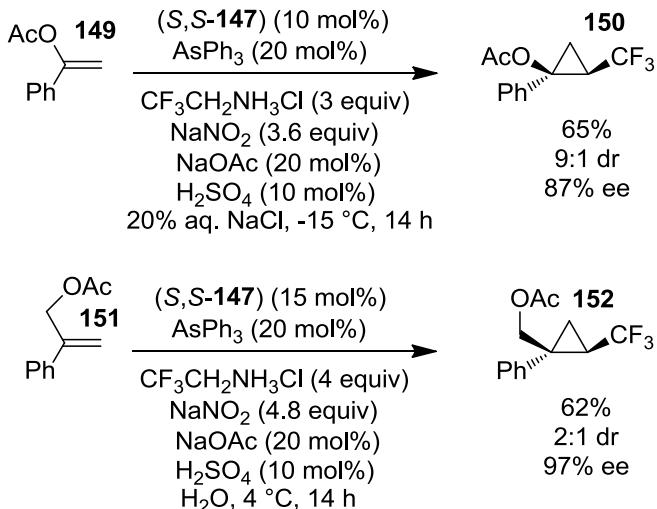
Table 10: Substrate Scope for the Asymmetric Cobalt-Catalyzed Trifluoromethyl Cyclopropanation.^[a]

$\text{Ar}=\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3 + \text{CF}_3\text{CH}_2\text{NH}_3\text{Cl} + \text{NaNO}_2 \xrightarrow[\text{20% aq. NaCl, } -15^\circ\text{C, } 14\text{ h}]{\text{(S,S-147) (10 mol%), AsPh}_3 (20 mol%), \text{NaOAc (20 mol%), H}_2\text{SO}_4 (10 mol%)} \text{Ar}\cdots\text{C}_3\text{F}_3$

Entry	Alkene	Product	Yield ^[b]	dr ^[c]	ee[%] ^[d]
1			81	56:1	91
2			82	66:1	86
3			91	38:1	91
4			73	22:1	84
5			95	35:1	90
6			84	37:1	87
7			91	57:1	94
8			93	63:1	88
9			49	11:1	86
10			78	27:1	90
11			77	180:1	92

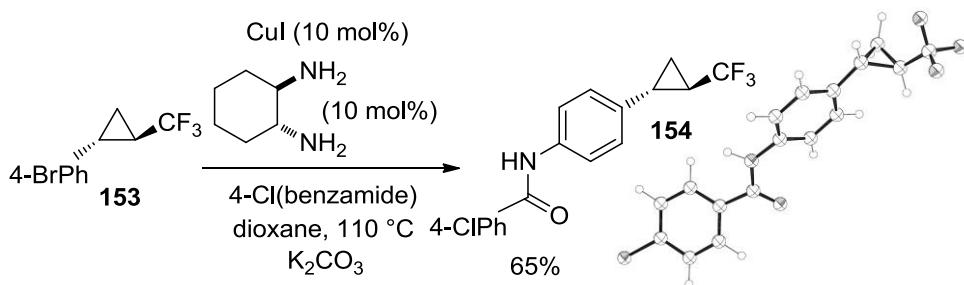
[a] General procedure (GP 3.3): Catalyst **147** (0.022 mmol, 10 mol%), AsPh₃ (0.044 mmol, 20 mol%), alkene (0.22 mmol, 1 equiv), CF₃CH₂NH₃Cl (0.66 mmol, 3 equiv), NaNO₂ (0.8 mmol, 3.6 equiv), NaOAc (0.044 mmol, 20 mol%), H₂SO₄ (0.022 mmol, 10 mol%), 1.8 mL 20% NaCl solution, -15°C, 14 h. [b] Isolated yield in %. [c] Determined by ¹⁹F NMR analysis of the crude mixture. [d] Determined by enantioselective HPLC or SFC of the pure product.

After having successfully applied the reaction to monosubstituted styrene derivatives, we investigated the reaction of two disubstituted styrene derivatives to expand the scope of possible substrates (Scheme 55).



Scheme 55: Use of Disubstituted Alkenes.

Product **150** was obtained in high enantioselectivity using the standard procedure. Additional trifluoroethylamine hydrochloride and sodium nitrite were required in the case of alkene **151** to ensure good conversion to the product **152**. In order to assign the absolute configuration of the products prepared via our method, a crystalline derivative was obtained via a copper-catalyzed cross-coupling of trifluoromethyl-substituted cyclopropane **153** with 4-chlorobenzamide to give amide **154**. Crystals suitable for X-ray crystallography were obtained by recrystallization from methanol and established the $(1R, 2R)$ -configuration (Scheme 56). The absolute configuration of the other products was assigned in analogy.



Scheme 56: Determination of Absolute Configuration.

At this stage Givaudan AG showed interest for product **121**, **150** and **152** as potential flavors or fragrances for perfumery. Thus, we prepared samples of these compounds in racemic form for GC-sniff analysis. The results that came back from their analysis were the following (Table 11).

Table 11: Results of the GC-Sniff Analysis Performed at Givaudan AG.

Compound	Odor evaluation
	Fruity, powdery, raspberry, green
	Powdery, dry, woody
	Powdery, clay, green, chemical solvent note

3.1.4. Rationale for the observed enantioinduction

As discussed previously, our reaction showed high sensitivity to subtle steric and electronic changes in the catalyst structure. Indeed, the screening showed that a fine steric balance was important at the 3,3'-position. This indicates a possible attack of the alkene from the front side, over these substituents. This would be in contrast to *Jacobsen's* model for enantioselective Mn-epoxidations, where the substrate attacks from the back side over the chiral diamine backbone.¹⁴⁸ Interestingly, *Corey* has proposed an alternative model for the enantioinduction in the Mn-catalyzed epoxidation. He proposed a bent structure of the Mn-salen in the transition state, leading to an attack of the alkene over the “down” side of the salen scaffold (Figure 14).¹⁴⁹

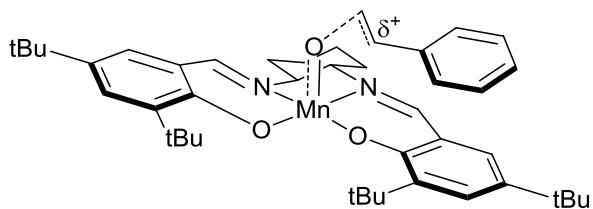


Figure 14: Corey's Model for the Facial Selectivity of the Mn-Catalyzed Epoxidation.

¹⁴⁸ E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, *J. Amer. Chem. Soc.* **1991**, *113*, 7063.

¹⁴⁹ L. Kurti, M. M. Blewett, E. J. Corey, *Org. Lett.* **2009**, *11*, 4592.

Based on *Corey's* model, that implies a bent structure of the salen-ligand in the transition state, we propose the following model for the enantioinduction of our reaction (Figure 15).

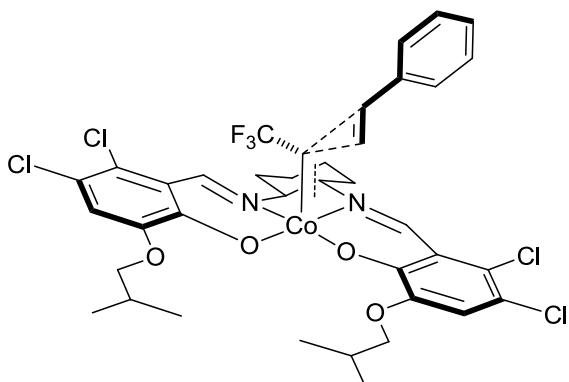


Figure 15: A Possible Model for the Facial Selection.

The trifluoromethyl moiety is located at the sterically more favorable position over the less hindered side of the cyclohexyl moiety. Bending of the structure (potentially favored by a steric interaction between the two bulky isobutyl groups), opens a space above the right side of the salen scaffold, allowing a front/right-side attack of the styrene onto the carbene. This model could account for the experimentally observed sensitivity to the steric bulk at the 3,3'-position. Moreover, it is corroborated by the experimentally observed stereoinduction. Finally, the crystal structure of our complex shows that the catalyst already adopts a slightly bent structure in the resting state.

3.1.5. Conclusion and Outlook

The transformation disclosed in this chapter possesses many interesting features: (1) preparation of trifluoromethyl-substituted cyclopropanes in high optical purity, (2) development of a new type of salen catalyst and (3) asymmetric catalysis under the conditions necessary for the preparation of the reactive intermediate. The reaction showed a broad substrate scope with both mono- and disubstituted styrene derivatives. We believe these results will stimulate further research in the development of catalysts for asymmetric carbene-transfer in aqueous media with *in situ* generated diazo compounds.

4. Rhodium-Catalyzed Cyclopropenation Using *In Situ* Generated Trifluoromethyl Diazomethane

4.1. Rhodium-Catalyzed Cyclopropenation of Alkynes Using Trifluoroethylamine Hydrochloride and Olefins in Aqueous Media

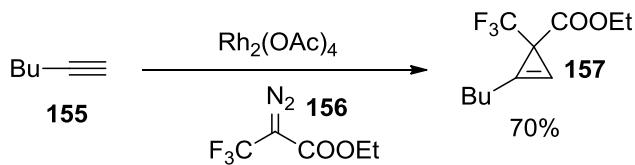
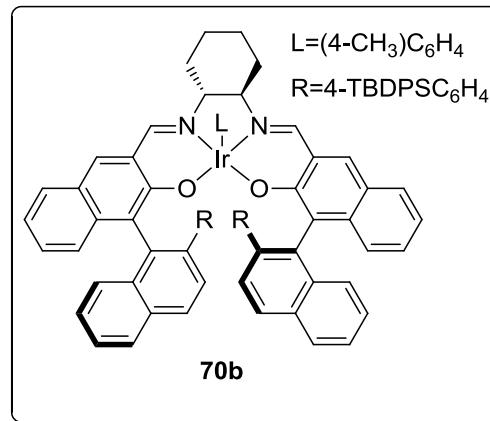
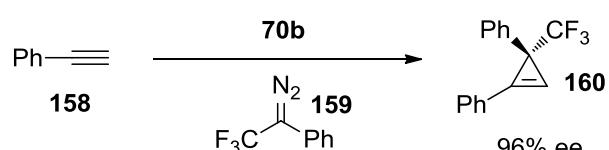
4.1.1. Background

In the previous two chapters we have discussed the development of an iron-catalyzed cyclopropanation as well as an asymmetric, cobalt-catalyzed cyclopropanation of olefins using trifluoroethylamine hydrochloride generated *in situ*. Due to our continuous interest in the preparation of new trifluoromethylated building blocks, we decided to take advantage of the many catalysts that showed compatibility with the media required for the *in situ* generation of trifluoromethyl diazomethane to develop new reactions. A particularly interesting result was the observation that rhodium dimers, and particularly $\text{Rh}_2(\text{esp})_2$, did afford good conversions to form trifluoromethyl-substituted cyclopropanes. We hypothesized that the use of this catalyst could probably be extended to the cyclopropenation of alkynes.

Few examples of the synthesis of trifluoromethyl-substituted cyclopropenes via metal-catalyzed decomposition of diazo compounds have been reported. One of the first example came from Müller et al,¹⁵⁰ where they used disubstituted diazo compound **156** to effect the cyclopropenation of pentyne (**155**) in 70% yield using $\text{Rh}_2(\text{OAc})_4$ (Scheme 57). Recently Katsuki reported the preparation of trisubstituted cyclopropenes bearing a trifluoromethyl group in high yields and with high enantioselectivities using disubstituted donor/acceptor diazocompound **159**.¹⁵¹

¹⁵⁰ P. Muller, S. Grass, S. P. Shahi, G. Bernardinelli, *Tetrahedron* **2004**, *60*, 4755.

¹⁵¹ M. Uehara, H. Suematsu, Y. Yasutomi, T. Katsuki, *J. Am. Chem. Soc.* **2011**, *133*, 170.

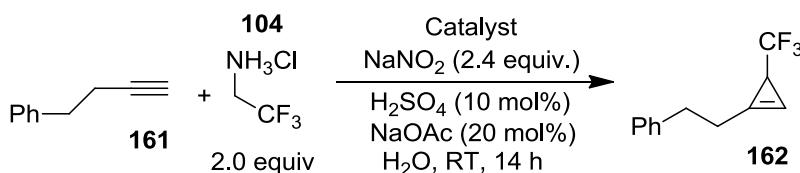
Müller (2004)**Katsuki (2011)**

Scheme 57: Preparation of Trifluoromethyl-Substituted Cyclopropenes.

Due to the absence of any known disubstituted trifluoromethyl-substituted cyclopropenes in the literature, we took the opportunity to extend the use of *in situ* generated trifluoromethyl diazomethane to the preparation of these new fluorinated compounds. This methodology could be a potentially versatile entry into the synthesis of new fluorinated compounds in drug discovery.

4.1.2. Initial experiments and catalyst screening

Drawing from the initial observation in Chapter 2 that $Rh_2(esp)_2$ was competent for the cyclopropanation of alkenes with *in situ* generated trifluoromethyl diazomethane, we tested a range of metal catalysts, including many different rhodium dimers, in the cyclopropanation of phenylbutyne (**161**) as a test substrate (Table 12).

Table 12: Catalyst Screening for the Cyclopropanation Reaction.^[a]

Entry	Catalyst	Loading	Conversion ^[b]
1	$\text{Fe}(\text{TPP})\text{Cl}^{[c]}$	3 mol%	NR
2	Co-salen ^[d]	5 mol%	NR
3	$\text{Rh}_2(\text{OAc})_4$	2.5 mol%	20%
4	$\text{Rh}_2(\text{TFA})_4$	2.5 mol%	32%
5	$\text{Rh}_2(\text{C}_7\text{H}_{15}\text{COO}^-)_4$	2.5 mol%	60%
6	$\text{Rh}_2(\text{esp})_2$	2.5 mol%	92%
7	$[\text{Rh}(\text{coe})\text{Cl}]_2$	2.5 mol%	15%

[a] General procedure (GP 4.1): alkyne (0.22 mmol, 1.0 equiv), $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (2.0 equiv), NaNO_2 (2.4 equiv), NaOAc (20 mol%), H_2SO_4 (10 mol%), H_2O (1.3 mL).

[b] Conversion determined by NMR spectroscopy. [c] 10 mol% DMAP. [d] 10 mol% *N*-methylimidazole. coe = cyclooctene. esp = espino.

Initially two non rhodium-based catalysts were tested under the following reaction conditions: phenylbutyne (1 equiv.), trifluoroethylamine hydrochloride (2.0 equiv.), sulfuric acid (10 mol%), sodium acetate (20 mol%) and water were mixed at RT. The sodium nitrite (2.4 equiv) was then added as an aqueous solution over 10 h. Unfortunately, reactions catalyzed by $\text{Fe}(\text{TPP})\text{Cl}$ and the cobalt-salen were ineffective and led to full recovery of starting material (Table 12, Entries 1 and 2). We then screened several Rh-catalysts as they were reported to be active in cyclopropanation with diazoacetates. $[\text{Rh}(\text{coe})\text{Cl}]_2$ gave the product in a meager 15% conversion (Entry 7). Hydrophilic Rh-dimers, such as $\text{Rh}_2(\text{OAc})_4$ and $\text{Rh}_2(\text{TFA})_4$, gave the product in low conversion, 20 and 32% respectively (Entries 3 and 4). We turned our attention to the use of more apolar Rh-catalysts, as they were shown by *Charette* to be more active in water compared to the more hydrophilic catalysts.¹⁵² Gratifyingly, the product was obtained with moderate conversions using $\text{Rh}_2(\text{Oct})_4$ and with almost full conversion when employing $\text{Rh}_2(\text{esp})_2$ as the catalyst (Entries 5 and 6). The conversion seems to correlate with the lipophilicity of the catalyst, showing the importance of having a phase separation in this reaction (*vide infra*). The tethered nature of the esp ligand makes the catalyst particularly robust towards catalyst decomposition under the harsh conditions required for trifluoromethyl diazomethane generation.

¹⁵² See Reference 115.

4.1.3. Scope of the transformation and preliminary transformations of the products

Having a practical protocol in hand for the preparation of trifluoromethyl substituted cyclopropenes, we studied the scope of the transformation (Table 13).

Table 13: Scope of the Rh-catalyzed cyclopropanation.^[a]

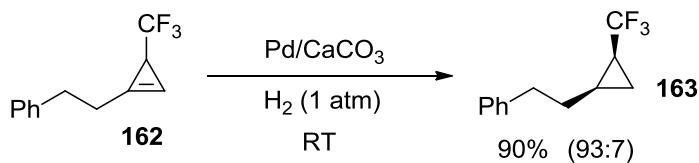
Entry	Alkyne	Product	Yield ^[b]
1			78%
2			71%
3			71%
4			70%
5			67%
6			69% ^[c]
7			73% ^[c]

[a] General procedure (GP 4.2): $\text{Rh}_2(\text{esp})_2$ (2.5 mol%), alkyne (0.22 mmol, 1 equiv), $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (2.0 equiv), NaNO_2 (2.4 equiv), NaOAc (20 mol%), H_2SO_4 (10 mol%), H_2O (1.3 mL). [b] Yield of isolated product. [c] 1:1 dr.

A wide range of alkyne substrates afforded the products under our reaction conditions. Interestingly, both aliphatic substrates as well as aromatics are compatible with the reaction conditions. Additionally, both mono- (terminal) and disubstituted alkynes were equally reactive. Importantly, all the products that we synthesized were unprecedented. We therefore studied the

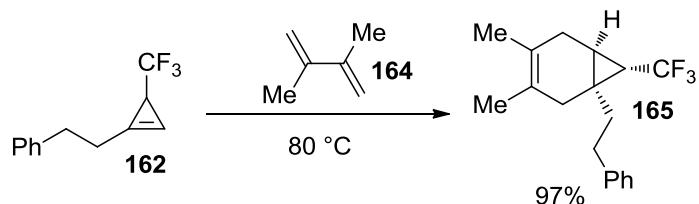
reactivity of product **162** in different transformations (Scheme 58-61). For that purpose larger amounts of **162** were required, and the reaction was scaled up 20 times, using 4.4 mmol of starting material. The amount of trifluoroethylamine hydrochloride could be reduced to 1.5 equiv. (1.8 equiv. NaNO₂) and the product was obtained in 75% isolated yield, illustrating the scalability of the process.

Having a larger amount of compound **162**, we tested its use in a range of reactions. Reduction of **162** gave the corresponding *cis*-substituted cyclopropane (**163**) in high yield and good diastereoselectivity using *Lindlar's* catalyst (Pd over CaCO₃) and 1 atm H₂ (Scheme 58).¹⁵³ Interestingly, the selectivity obtained via this cyclopropanation/reduction sequence is complementary to our previously described iron-catalyzed *trans*-selective cyclopropanation reaction.



Scheme 58: Diastereoselective Reduction Using *Lindlar's* Catalyst.

We then tested a *Diels-Alder* cycloaddition with dimethylbutadiene (**164**).¹⁵⁴ The corresponding bicyclic product **165** was isolated in 97% yield. The product was obtained as a single diastereoisomer, as the addition occurred *anti* to the trifluoromethyl group (Scheme 59).



Scheme 59: Diels-Alder Reaction Between Cyclopropene **162 and Dimethylbutadiene (**164**).**

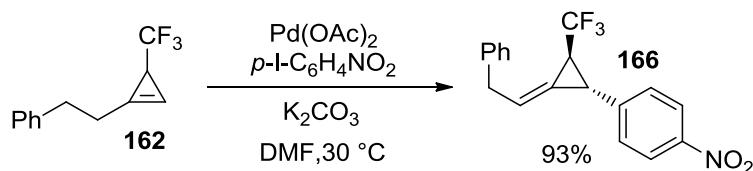
A *Heck* reaction with nitroiodobenzene and palladium acetate as the catalyst afforded the methylene cyclopropane **166** as a single diastereoisomer with high *E/Z* selectivity.¹⁵⁵ The β -hydride

¹⁵³ See Reference 102.

¹⁵⁴ See Reference 102.

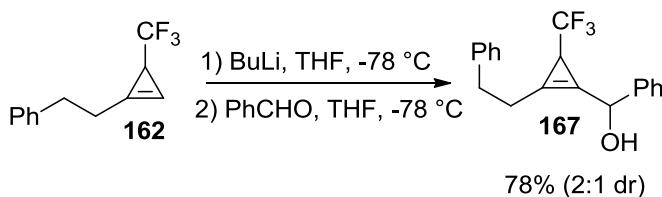
¹⁵⁵ S. Chuprakov, M. Rubin, V. Gevorgyan, *J. Am. Chem. Soc.* **2005**, *127*, 3714.

elimination occurred preferentially *exo* to the ring due to a strain-release by the formation of the methylenecyclopropane compared to a cyclopropene (Scheme 60).



Scheme 60: Diastereoselective Heck-Reaction of Cyclopropene **162 with Iodonitrobenzene.**

Finally, we performed a deprotonation/trapping reaction sequence. It has been reported in the literature that ester-substituted cyclopropenes undergoes ring-opening when treated with a strong base to give the corresponding alkynyl ester.¹⁵⁶ When we submitted the cyclopropene **162** to deprotonation with BuLi, a deep blue solution of the anion was formed, and, after a quench with water, the starting material was recovered, indicating that the cyclopropenyl anion was stable. Following this observation, we trapped the formed anion at -78°C with benzaldehyde as a prototypical electrophile to obtain the disubstituted cyclopropene **167** in 78% as a mixture of diastereoisomers (Scheme 61). This exciting result opens many possibilities for further functionalizations of the trifluoromethyl-substituted cyclopropenes.



Scheme 61: Deprotonation/Trapping with Benzaldehyde.

4.1.4. Preliminary Observations Consistent with a Biphasic Reaction Mixture

At the beginning of Chapter 2 it was mentioned that any catalytic carbene-transfer under the diazotization conditions necessary for the *in situ* preparation of trifluoromethyl diazomethane would have to overcome several challenges: be compatible with water (avoid OH insertion), be compatible

¹⁵⁶ L. A. Liao, N. Yan, J. M. Fox, *Org. Lett.* **2004**, 6, 4937.

with a strong oxidant (NaNO_2) and compatible with an acidic media (acetic acid). Surprisingly, a wide range of catalysts were competent under these reaction conditions. We believe that the biphasic nature of the reaction is a key feature that allows the diazotization and the metal-carbene transfer process to be compatible. In fact, the lipophilicity of the catalysts seems to be important to the process, as shown in this Chapter. $\text{Rh}_2(\text{OAc})_4$, for instance, was poorly active for the cyclopropanation and the cyclopropenation with CF_3CHN_2 , whereas $\text{Rh}_2(\text{CH}_3(\text{CH}_2)_6\text{COO}^-)_4$ proved to be competent. These two complexes differ mainly in their lipophilicity. Moreover, other metal catalysts mediating the cyclopropanation in Chapter Two also bear lipophilic ligand environment (porphyrin or salen), whereas $\text{Cu}(\text{OTf})_2$ or $\text{Pd}(\text{OAc})_2$, water-soluble catalysts, were poor catalysts.

Visual assessment of the reaction mixture in the rhodium-catalyzed cyclopropenation provides further informations, since the localization of the rhodium catalyst can be easily monitored due to its deep color (Figure 16 and 17).

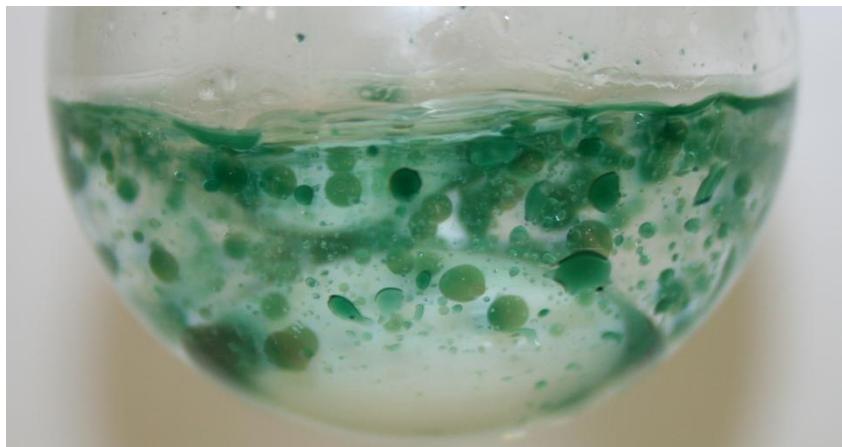


Figure 16: Picture of the Reaction before Addition of the Active Reagents ($\text{Rh}_2(\text{esp})_2$, NaOAc buffer, water, phenylbutyne).

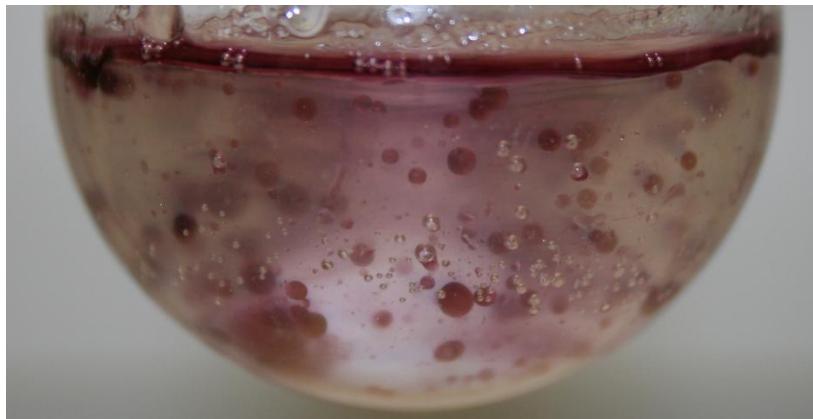
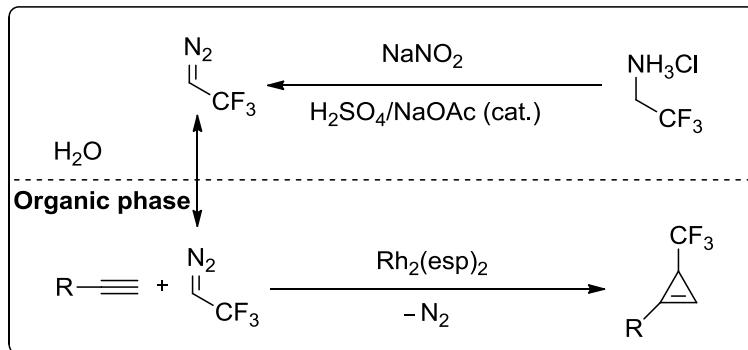


Figure 17: Picture of the Reaction after Addition of Trifluoroethylamine Hydrochloride and Sodium Nitrite.

The first picture (Figure 16) shows the reaction mixture before the addition of the active reagents and thus contains: alkyne substrate, $Rh_2(esp)_2$, buffer (H_2SO_4 , $NaOAc$). The green rhodium catalyst is exclusively dissolved in the alkyne drops and is absent from the aqueous phase. 5 minutes after the addition of trifluoroethylamine hydrochloride and sodium nitrite, a second picture (Figure 17) was taken. The Rh catalyst turned violet, and is still largely dissolved in the organic (substrate) phase. The diazo compound gives the yellowish color to the aqueous phase, before migrating to the alkyne drops and reacting with the Rh catalyst upon release of nitrogen gas (gas evolution can be seen in Figure 17). Based on these visual observations and the correlation between the lipophilicity and conversion mentioned above, we propose the following working model for the reaction mechanism (Scheme 62).



Scheme 62: Mechanistic Rationale for the Tandem Transformation.

All the water soluble reagents (trifluoroethylamine hydrochloride, sodium nitrite, sulfuric acid and sodium acetate) are dissolved in the aqueous phase and react to form diazo compound **15**. This compound shows higher lipophilicity and can therefore migrate to the lipophilic alkyne beads where it reacts with the catalyst to form a metallocarbene intermediate under extrusion of nitrogen. The metallocarbene can further react with the substrate locally present in excess. This rationale explains the selectivity of the carbene transfer to the substrate over water present in excess. It also provides a rationale why lipophilic catalysts perform better. Finally, it explains why the metal-carbene transfer is compatible with the diazotization reaction, since the two processes are physically separated and located in two different liquid phases minimizing their interactions.

4.1.5. Towards the preparation of chiral Rh₂(esp)₂¹⁵⁷

It would be highly desirable to develop a chiral version of the trifluoromethyl cyclopropenation. In preliminary experiments, poor results were obtained with standard catalysts (among them Rh₂(MEPY)₄ and *Corey's* catalyst (**87**), both giving <20% ee and low conversions), indicating that a completely new type of asymmetric Rh catalyst might be required. Rh₂(esp)₂ has clearly showed superior activity when compared to other catalysts for the racemic transformation, indicating that a tethering asymmetric ligand might be more suitable. While Rh₂(esp)₂ has demonstrated its superiority as a catalyst in C-H amination¹⁵⁸ reactions and certain cyclopropanation reactions¹⁵⁹, surprisingly, very few tethering, asymmetric ligands were reported in the literature.^{160,161} We thus recently engaged ourselves in the design and synthesis of new chiral chelating ligands for Rh-dimers. This work was done in collaboration with Michael Schafroth in the context of his master thesis at the ETH Zürich.¹⁶² Initially, we targeted two different ligand-types (Figure 18).

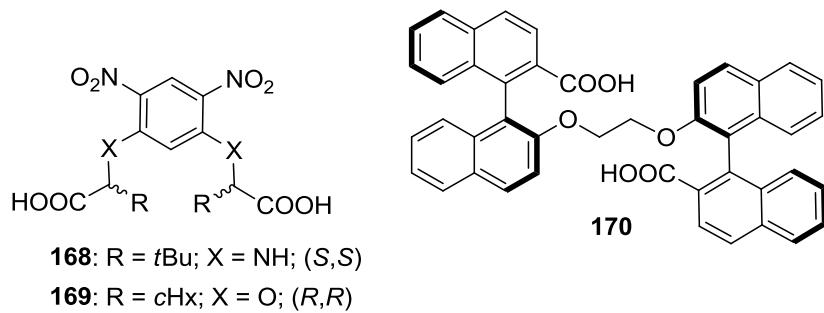


Figure 18: Newly Developed Chiral Dicarboxylic Acid Ligands for Rh Dimers.

The first class of ligands was designed based on a key nucleophilic aromatic substitution using commercially available amino or hydroxyacids. We selected one amino acid (*tert*-leucine, **172**) and one hydroxyacid (**175**) for the initial studies. The SN_{Ar} reaction using *tert*-leucine smoothly

¹⁵⁷ The experiments presented in this section (4.1.5) were performed by Michael Schafroth during his master thesis (2012). All the experiments were designed and analyzed by B. Morandi.

¹⁵⁸ C. G. Espino, K. W. Fiori, M. Kim, J. Du Bois, *J. Am. Chem. Soc.* **2004**, *126*, 15378.

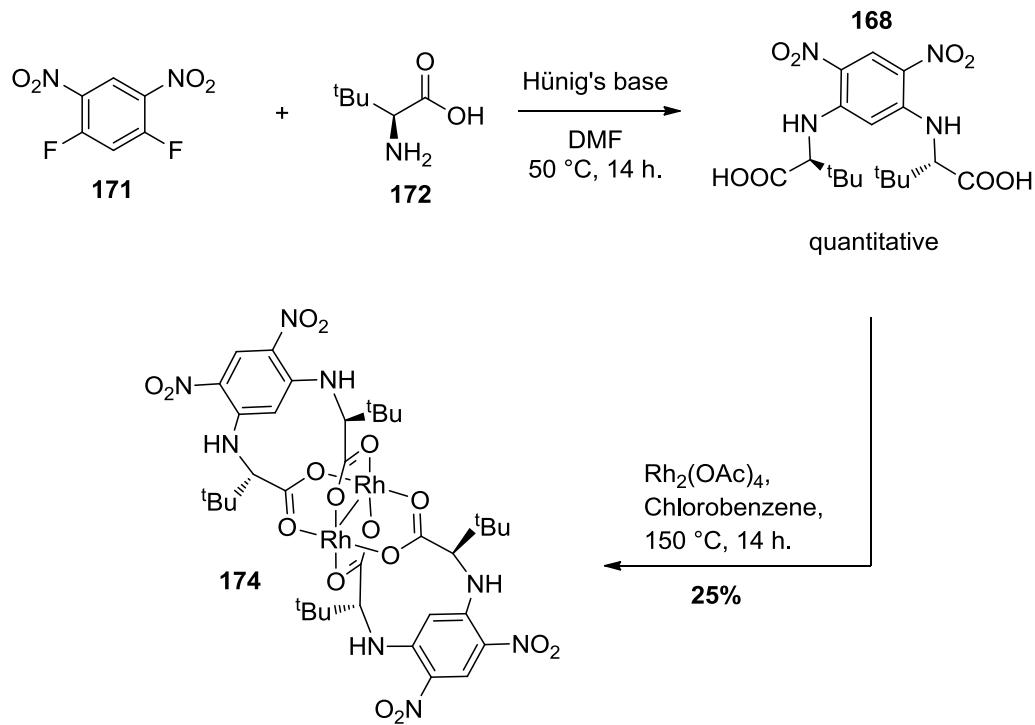
¹⁵⁹ F. Gonzalez-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin, M. Soumeillant, *Adv. Synth. Cat.* **2008**, *350*, 813.

¹⁶⁰ K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562.

¹⁶¹ H. M. L. Davies, S. A. Panaro, *Tetrahedron Lett.* **1999**, *40*, 5287.

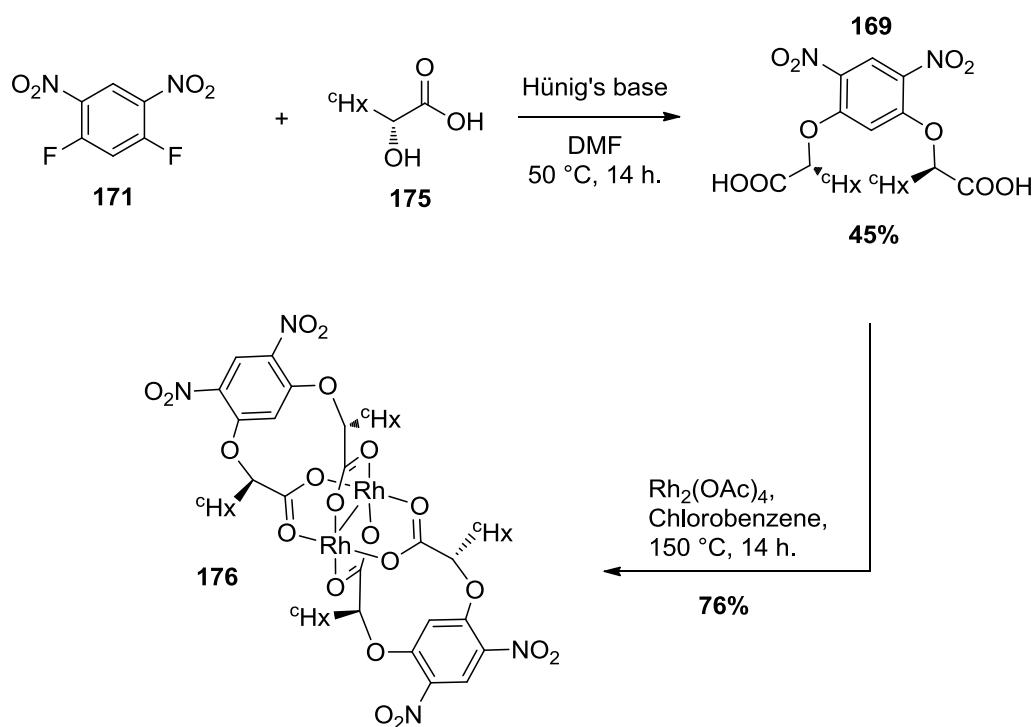
¹⁶² For further details and extended results, see: M. Schafroth, ETH Master Thesis **2012**.

gave the expected product in quantitative yield with no required purification. Refluxing this ligand with $Rh_2(OAc)_4$ in chlorobenzene overnight gave the expected complex ($Rh_2(^tL\text{-DINO})_2$, **174**) in 25% isolated yield after column chromatography (Scheme 63).



Scheme 63: Synthesis of DINO-complex **174**.

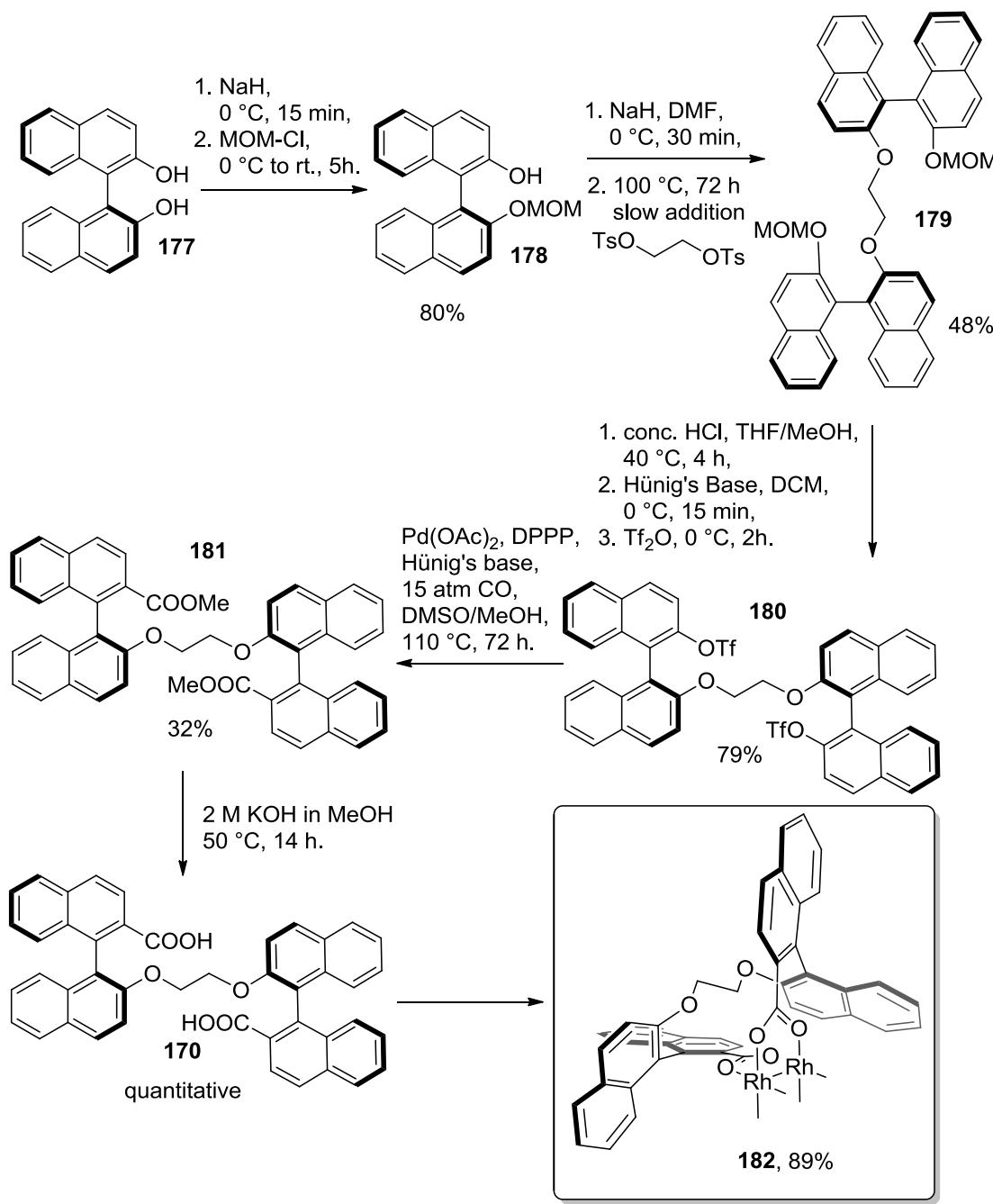
The nucleophilic aromatic substitution using the hydroxyacid **175** proceeded in a reduced 45% yield after purification by column chromatography. Refluxing this ligand with $Rh_2(OAc)_4$ overnight in chlorobenzene gave the expected complex ($Rh_2(^cH\text{-DINO})_2$, **176**) in 76% yield (Scheme 64).



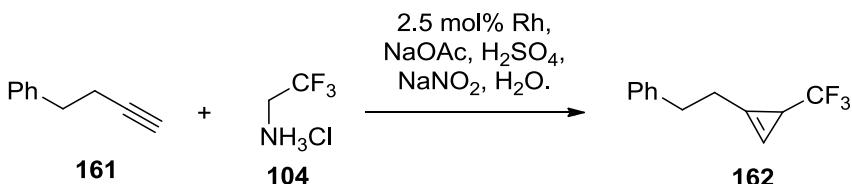
Scheme 64: Synthesis of DINO-complex **176**.

After the successful syntheses of two new complexes based on a one-step synthesis, we became interested in the preparation of synthetically more challenging ligand **170** based on the binaphthyl moiety. It was thought that the axial chiral information would be in close proximity to the metal center and therefore potentially highly enantiodiscriminating. After several unsuccessful attempts, we synthesized the desired ligand (**170**) in 8 linear steps (Scheme 12). Mono MOM-protection of (*S,S*)-BINOL (80% yield of **178**) was followed by an alkylation reaction giving the bisbinaphthyl compound **179** in 48% yield. Deprotection under acidic conditions followed by triflation using triflic anhydride gave the compound **180** in 79% yield. A palladium-catalyzed carbonylative coupling of the obtained bis-triflate **180** was performed under high pressure to afford the diester **181** in 32% isolated yield. High pressure of carbon monoxide was required for the full conversion to the bis-ester and minimization of the reduction by-products. Final saponification, followed by refluxing of the ligand with Rh₂(OAc)₄ in chlorobenzene afforded the complex (Rh₂(elba)₂, **182**) in an excellent 89% yield.

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**Scheme 65: Synthesis of Binaphthyl-Derived Catalyst 182.**

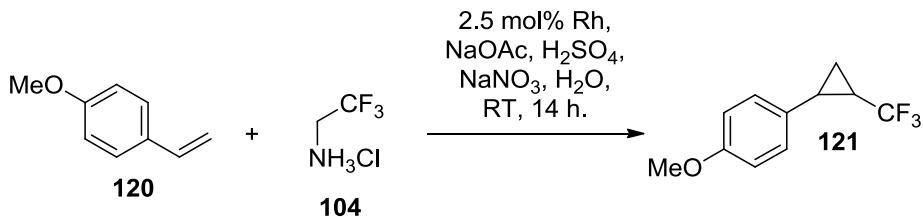
Finally, the enantiodifferentiating ability of these three new complexes was tested in known asymmetric carbene processes to evaluate their performance. The first reaction tested was the Rh-catalyzed cyclopropanation with *in situ* generated trifluoromethyl diazomethane (Table 14).

Table 14: Cyclopropanation Using Newly Developed Catalysts.^[a]

Entry	Catalyst	Conversion ^[b]	% ee ^[c]
1	Rh ₂ (^t L-DINO) ₂	5%	10
2	Rh ₂ (^c H-DINO) ₂	41%	Not Determined
3	Rh ₂ (elba) ₂	17%	15

[a] General Procedure GP 4.3. [b] Determined by analysis of the crude ¹H-NMR. [c] Determined by chiral SFC.

Unfortunately, poor enantioselection was obtained for this reaction with all the three complexes studied. They were further tested in the asymmetric trifluoromethyl cyclopropanation reported in the previous chapter (Table 15).

Table 15: Cyclopropanation Using Newly Developed Catalysts.^[a]

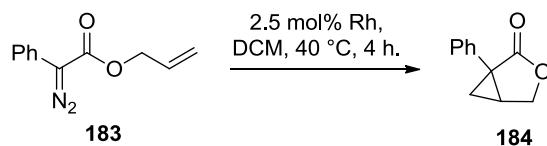
Entry	Catalyst	Conversion ^[b]	% ee ^[c]	dr ^[d]
1	Co-Salen 147	95% ^[e]	<i>trans</i> : 90	35:1
2	Rh ₂ (^t L-DINO) ₂	100%	<i>cis</i> : 0, <i>trans</i> : 7	1:1
3	Rh ₂ (^c H-DINO) ₂	100%	<i>cis</i> : 0, <i>trans</i> : 18	1:1
4	Rh ₂ (elba) ₂	100%	<i>cis</i> : 0, <i>trans</i> : 43	1:1

[a] General Procedure GP 4.4. [b] Determined by analysis of the crude ¹H-NMR. [c] Determined by chiral SFC. [d] Determined by analysis of the crude ¹⁹F-NMR. [e] Isolated Yield.

Relatively poor results were obtained with the two DINO-derived ligands, but a promising 43% ee was obtained with the binaphthyl-derived catalyst (Rh₂(elba)₂, **182**) for the *trans*-isomer. This result shows the enantiodiscriminating potential of this complex using the trifluoromethyl carbene moiety. Finally, the three catalysts were probed in a challenging intramolecular cyclopropanation reaction (Table 16). This reaction was reported to proceed in up to 68% ee using an optimized

Doyle-type ligand ($Rh_2(4S\text{-}MEAZ)_4$).¹⁶³ Gratifyingly, the reaction catalyzed by the binaphthyl-derived complex **182** gave the product in an unoptimized 76% ee. Performing the reaction at 10 °C afforded the product in 83% ee.

Table 16: Intramolecular Cyclopropanation Using Newly Developed Catalysts.^[a]



Entry	Catalyst	Conversion ^[b]	% ee ^[c]
1	$Rh_2(4S\text{-}MEAZ)_4$	95% ^[d]	68
2	$Rh_2(L\text{-}DINO)_2$	54%	20
3	$Rh_2(H\text{-}DINO)_2$	46%	0
4	$Rh_2(elba)_2$	70%	76

[a] General Procedure GP 4.5. [b] Determined by analysis of the crude 1H -NMR. [c] Determined by chiral SFC. [d] Isolated Yield.

Our initial attempts at synthesizing new bidentate carboxylate-based ligands showed encouraging results, particularly in the case of the binaphthyl-based ligand ($Rh_2(elba)_2$). This ligand outperformed the best previously known ligand for the intramolecular cyclopropanation of **183** and gave moderate enantioselectivity for the intermolecular trifluoromethyl cyclopropanation of *p*-methoxystyrene. Future structural modification of the binaphthyl moiety as well as the length and nature of the tether will be evaluated.

4.1.5. Conclusion and Outlook

The chemistry presented in this chapter represents a major advance in the preparation of functionalized trifluoromethylated compounds. The rhodium-catalyzed trifluoromethyl cyclopropanation allowed for the preparation of a new class of trifluoromethyl-substituted cyclopropenes, which showed high potential for further elaboration. A particularly interesting feature was the broad scope of both mono- and disubstituted alkynes as well as unactivated and activated substrates. This project also engaged us in the preparation of unprecedented new chiral tethering ligands for Rh-dimers mimicking the esp ligand popularized by DuBois. This has already

¹⁶³ M. P. Doyle, W. H. Hu, T. M. Weathers, *Chirality* **2003**, *15*, 369.

led to the preliminary identification of one new complex as a very efficient catalyst for an intramolecular cyclopropanation, reaching higher enantioselectivities than any ligand previously reported.

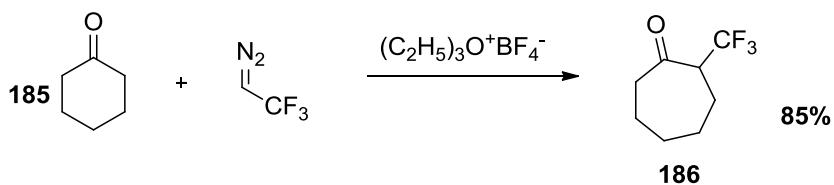
5. Lewis Acid-Mediated Reaction Using *In Situ* Generated Trifluoromethyl Diazomethane

5.1. Initial Experiments and Development of the ZrCl₄-Mediated Tiffenau-Demjanov Reaction of Cyclic Ketones and Roskamp Reaction of Aliphatic Aldehydes

5.1.1. Background

As previously discussed, trifluoromethyl diazomethane has been used in the homologation of aldehydes and ketones (Scheme 66). *Mock* and *Hartman* reported in 1977 the ring-expansion reaction of cyclohexanone (**185**) to give trifluoromethylcycloheptanone (**186**) in 85% yield.^{164,165} Superstoichiometric amounts of triethyloxonium tetrafluoroborate were used and they showed that the reaction was also effective with 2-methylcyclohexanone, albeit giving a mixture of regioisomers (3:1). Later, *Tordeux* and *Wakselman* described the antimony pentachloride-mediated homologation of pentanal (**187**) using trifluoromethyl diazomethane to give trifluoroethyl ketone **188** in 52% yield.^{166,167,168}

Mock and Hartman (1977)



Tordeux and Wakselman (1981)



Scheme 66: Literature Precedent for the Use of Trifluoromethyl Diazomethane in Carbonyl Homologations.

¹⁶⁴ W. L. Mock, M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 466.

¹⁶⁵ W. L. Mock, M. E. Hartman, *J. Org. Chem.* **1977**, *42*, 459.

¹⁶⁶ M. Tordeux, C. Wakselman, *J. Fluorine Chem.* **1981**, *17*, 299.

¹⁶⁷ C. Wakselman, M. Tordeux, *J. Fluorine Chem.* **1982**, *21*, 99.

¹⁶⁸ R. Fields, J. P. Tomlinson, *J. Fluorine. Chem.* **1979**, *14*, 19.

Trifluoromethyl-substituted ketones and aldehydes are normally prepared via a direct electrophilic trifluoromethylation of aldehydes and ketones.¹⁶⁹ We thus reasoned that an *in situ* generation strategy using trifluoromethyl diazomethane combined with the Lewis acid-mediated homologation reactions in the same pot could take advantage of this complementary synthetic route for the preparation of trifluoromethyl ketones.

5.1.2. Initial studies

At the outset of our reaction development, we selected the direct *Tiffenau-Demjanov* reaction of 4-phenylcyclohexanone (**189**) using trifluoromethyl diazomethane. The inexpensive and convenient aqueous diazotization of trifluoroethylamine hydrochloride with sodium nitrite in water was selected as the method of choice for the *in situ* preparation of the reagent. The combination of the aqueous diazotization with the Lewis acid-mediated homologation raises the question of compatibility of the Lewis acid in the presence of the water required in the first step. We reasoned that the use of water-tolerant Lewis acid catalysts (e.g. lanthanides) would be the best strategy to pursue. Indeed, seminal studies on Lewis acid-catalyzed reactions in water have been reported by *Kobayashi* and co-workers.^{170,171} Therefore, we started our investigations with water-compatible Lewis acids. Reactions performed in water with *in situ* generated trifluoromethyl diazomethane, 4-phenylcyclohexanone and $Sc(OTf)_3$, $Ln(OTf)_3$ or $Yb(OTf)_3$ afforded full recovery of starting material at room temperature. After these unsuccessful initial reactions, the use of strong Lewis-acids was probed (Table 17). Due to the well-known water sensitivity of strong Lewis acids, we designed reaction conditions to minimize the amount of water used in the diazotization step. We also reasoned that higher chances of success would be encountered if the two reactions would be performed sequentially, such that the Lewis acid-mediated reaction could be run at lower temperature. The hydrolysis of the Lewis acid could thus be slowed down enough to allow the desired reaction to occur. A particularly important feature was the choice of the drying reagent to remove as much water as possible from the reaction media after initial diazotization. A wide range of desiccants are offered, among them molecular sieves and $MgSO_4$. To quantitatively assess the

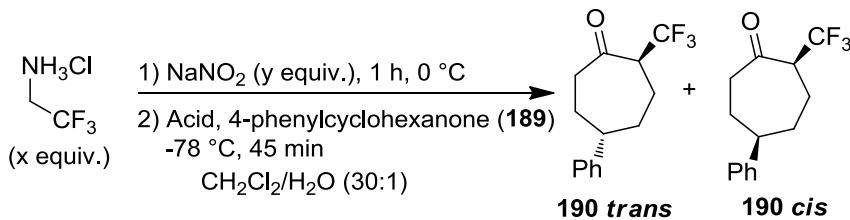
¹⁶⁹ T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470.

¹⁷⁰ S. Kobayashi, S. Nagayama, T. Busujima, *J. Am. Chem. Soc.* **1998**, *120*, 8287.

¹⁷¹ S. Kobayashi, *Pure and Appl. Chem.* **2007**, *79*, 235.

benefits of the added drying agent, we initially tested the reaction without additives (Table 17). The conditions probed were the following: $\text{F}_3\text{CCH}_2\text{NH}_2\cdot\text{HCl}$ and NaNO_2 were stirred for 1 hour at 0 °C in a $\text{CH}_2\text{Cl}_2/\text{water}$ (30:1) followed by cooling to -78 °C and addition of 4-phenylcyclohexanone and the Lewis acid after 10 minutes (Table 1).

Table 17: Screening of Lewis Acids for the Direct Tiffenau-Demjanov Reaction of 189.^[a]



Entry	Acid (equiv.)	x	y	Yield ^[b]	dr ^[c]
1	$\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.0)	4	4.6	46%	59:41
2	$\text{BF}_3\cdot\text{Et}_2\text{O}$ (0.3)	4	4.6	61%	61:39
3	AlCl_3 (1.0)	4	4.6	48%	19:81
4	TiCl_4 (1.0)	4	4.6	73%	93:7
5	ZrCl_4 (1.0)	4	4.6	70%	94:6
6	ZrCl_4 (1.3)	4	4.6	81%	92:8
7	HCl (1.0)	4	4.6	nr	-
8	$\text{HBF}_4\cdot\text{Et}_2\text{O}$ (1.0)	4	4.6	nr	-
9	ZrCl_4 (0.3)	4	4.6	28%	95:5
10	ZrCl_4 (1.3)	3	3.6	81%	93:7
11	ZrCl_4 (1.3)	2	2.4	83%	94:6
12	ZrCl_4 (1.3)	1.5	1.8	79%	94:6

[a]. General procedure (GP 5.1): $\text{F}_3\text{CCH}_2\text{NH}_2\cdot\text{HCl}$ and NaNO_2 were stirred for 1 h at 0 °C in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition of the Lewis acid and the substrate (0.22 mmol, 1 equiv) at -78 °C. [b] Yield based on $^1\text{H-NMR}$ analysis with an internal standard. [c] Determined by $^1\text{H-NMR}$ analysis of the crude reaction mixture.

Surprisingly, most of the Lewis Acids screened under these reaction conditions afforded the product (**190**), even if no drying agent was added to the reaction mixture. Mediation of the reaction by the Lewis acid appears to be faster than hydrolytic decomposition of the acid. Interestingly, control reactions using HCl and HBF_4 afforded none of the desired product (Entries 7 and 8), proving that the potentially released protic acids are not competent in mediating the reaction. Among the various Lewis acids probed, ZrCl_4 proved to be the best in terms of yields and diastereoselectivities (Entry 10). Importantly, reducing the amount of Lewis acid to catalytic

amounts drastically reduced the yield (Entry 9). Gratifyingly, the amount of trifluoroethylamine hydrochloride could be reduced to 2 equiv (Entry 11).

5.1.3. Scope of the transformation

Having developed a practical protocol for the homologation of cyclic ketones with trifluoromethyl diazomethane generated *in situ*, we studied the scope of the reaction. A wide range of cyclohexanone derivatives gave the product in good isolated yields and high diastereoselectivities. In the case of 2-substituted cyclohexanones, the products were obtained as single regioisomers with the lowest substituted carbon atom migrating selectively (Entries 6 and 7). The fact that pyranone (Entry 9) required 3 additions of $ZrCl_4$ for completion might be due to competing coordination of the ethereal group onto the Lewis acid. In this case, it is possible that the hydrolysis of the Lewis acid became a competitive reaction, requiring further additions of the activator. Other ring-sizes (Entry 10) and aliphatic ketones (Entry 11) proved unreactive under these reaction conditions and starting material was fully recovered in all cases.

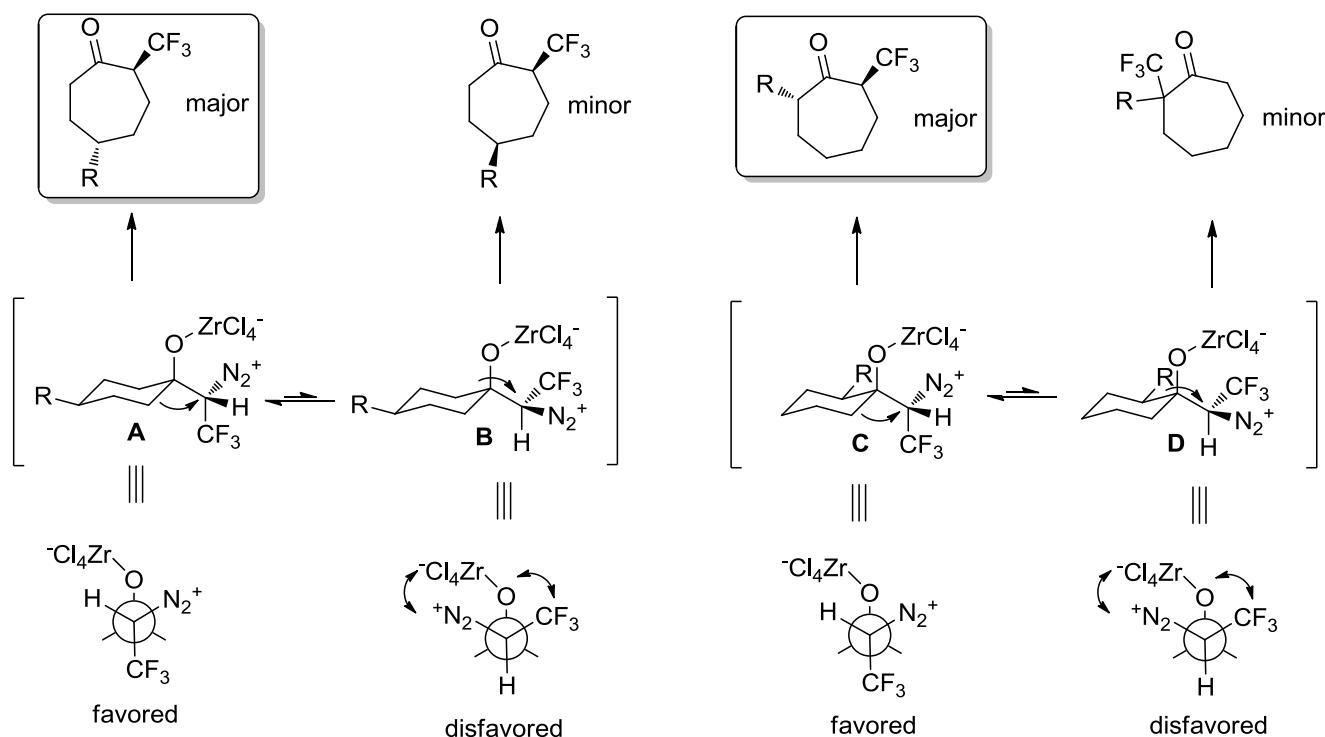
Table 18: Scope of the ZrCl₄-Mediated Homologation of Cyclic Ketones.^[a]

NH₃Cl 1) NaNO₂, 1 h, 0 °C
 CF₃ 2) ZrCl₄, cyclic ketone
 -78 °C, 45 min
 CH₂Cl₂/H₂O (30:1)

Entry	Ketone	Product	Yield ^[b]	dr ^[c]
1			80%	14:1
2			77%	14:1
3			70%	9:1
4			76%	10:1
5			71%	-
6			85%	>20:1
7			85%	>20:1
8			76%	11:1
9 ^[d]			65%	-
10			NR	-
11			NR	-

[a] Conditions (GP 5.2): F₃CCH₂NH₃Cl (2.0 equiv) and NaNO₂ (2.4 equiv) were stirred for 1 h at 0 °C in CH₂Cl₂/H₂O (30:1), followed by addition at -78 °C of ZrCl₄ (1.3 equiv.) and the substrate (0.22 mmol, 1 equiv). [b] Isolated yield. [c] determined by analysis of the crude ¹⁹F-NMR spectrum. [d] 3.9 equiv. of ZrCl₄ were used.

The diastereoselectivity of the reaction can be rationalized using the following model (Scheme 67). The thermodynamically more stable conformer with the R-substituent in equatorial position is attacked equatorially at the ketone to form a zwitterionic intermediate. Two rotameric conformations (A and B; C and D) that lies in equilibrium are set up for a productive antiperiplanar attack onto the nitrogen leaving group. Due to strong steric repulsion in rotameric structures B and D and unfavorable dipole alignments, the rotamers A and C are favored. The alkyl moiety located at the antiperiplanar position then migrates upon formation of a carbon-oxygen double bond to afford the observed *trans*-products. The product of Entry 8 afforded the *cis*-product because the axial cyclohexane conformer is preferred in the case of 4-OR-substituted cyclohexanones.¹⁷² The stereochemistry of products from Entries 1 and 6 (Table 18) was confirmed by X-ray crystallography.¹⁷³



Scheme 67: Mechanistic Rationale Explaining the Observed *trans*-Selectivity.

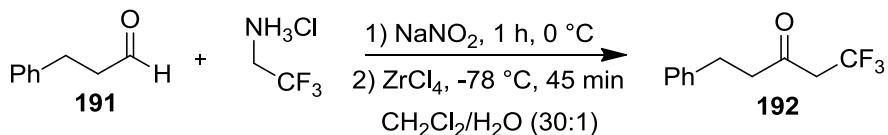
¹⁷² Y. Nagao, M. Goto, M. Ochiai, M. Shiro, *Chem. Lett.* **1990**, 1503.

¹⁷³ See Experimental Part

5.1.4. Extension of the Methodology to the Roskamp Homologation of Aldehydes

Having established the reactivity of *in situ* generated trifluoromethyl diazomethane in homologation reactions with cyclohexanones, we turned our attention to the homologation of phenylpropionaldehyde (**191**) using the same reaction conditions (Table 19).

Table 19: Screening of Lewis acids for the Roskamp Reaction with Trifluoromethyl Diazomethane.^[a]

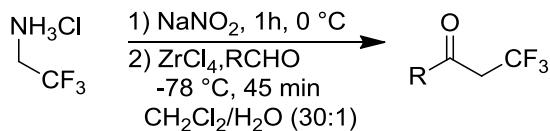


Entry	Lewis acid	Yield ^[b]
1	$\text{BF}_3\cdot\text{Et}_2\text{O}$	30 %
2	AlCl_3	32 %
3	SnCl_2	NR
4	ZrCl_4	71 %
5	$\text{ZrCl}_4^{\text{[c]}}$	29 %
6	HCl	NR

[a] General procedure (GP 5.1): $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (2.0 equiv) and NaNO_2 (2.4 equiv) were stirred 1 h at 0 °C in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition at -78 °C of the Lewis acid (1.3 equiv.) and the substrate (0.22 mmol, 1 equiv). [b] NMR yield. [c] Performed at 0 °C. NR = no reaction.

The reaction gave full conversion and afforded a 71% isolated yield of **192**. Screening of other Lewis acids did not improve the yield. We then studied the scope of the reaction (Table 20). Aliphatic aldehydes proved to be excellent substrates for this transformation, giving the expected trifluoroethylketone products in good yields. Aromatic substrates gave, surprisingly, the product of a double homologation. This result can be explained by the different migratory aptitudes between the different groups: phenyl > hydride > alkyl.¹⁷⁴

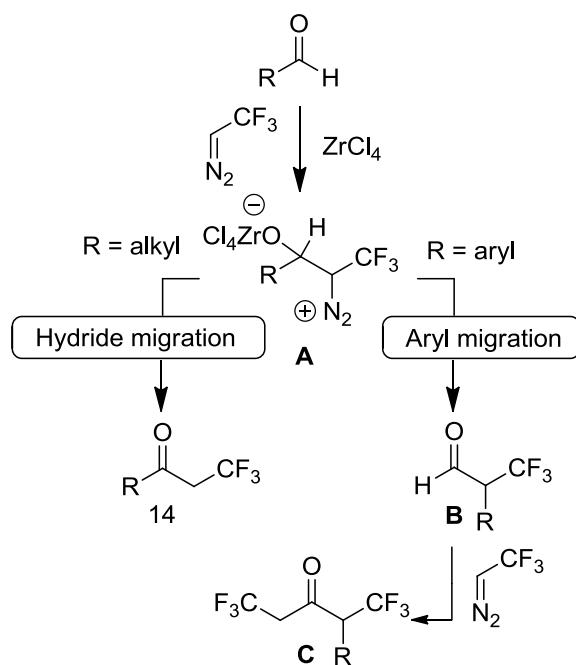
¹⁷⁴ M. B. Smith, J. March "March's advanced organic chemistry: reactions, mechanisms, and structure", 6th edition, Wiley-VCH 2007.

Table 20: Scope of Aldehydes in the Roskamp Reaction.^[a]

Entry	Aldehyde	Product	Yield ^[b]
1			67%
2			74%
3			65%
4			70%
5			70%
6			73 %
7			63%
8 ^[c]			47%
9 ^[c]			67%
10 ^[c]			76%
11 ^[c,d]			56% (1:1)

[a] Conditions (GP 5.2): $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (2.0 equiv) and NaNO_2 (2.4 equiv) were stirred 1 h at 0 °C in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition at -78 °C of ZrCl_4 (1.3 equiv.) and the substrate (0.22 mmol, 1 equiv). [b] Isolated yield. [c] Performed with ZrCl_4 (2.6 equiv.), $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (4.0 equiv) and NaNO_2 (4.8 equiv). [d] NMR-yield.

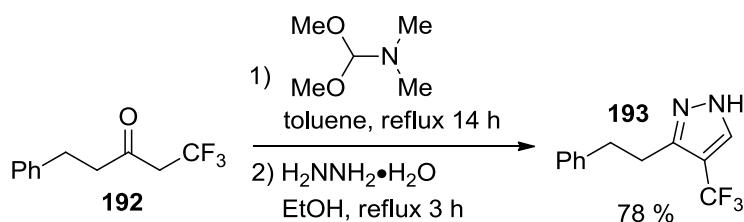
A mechanistic rationale for the reaction is proposed in the following Scheme.



Scheme 68: Mechanistic Rationale for the *Roskamp* Reaction.

Upon activation of the aldehyde substrate with the Lewis acid, a zwitterionic intermediate **A** is formed upon attack of the diazo compound. The group bearing the highest migratory aptitude (hydride in the aliphatic case, phenyl in the aromatic case) migrates preferentially concomitantly with N_2 -loss. In the case of aromatics, benzyl aldehydes (**B**) are initially formed, which undergo a second addition of trifluoromethyl diazomethane to give the product of bis-homologation **C** (Entry 11). This rationale is in accordance with the result obtained with the nitro-substituted aromatic, which gave a mixture of both products due to the lower migratory aptitude of the electron-deficient aromatic ring.

The trifluoroethylated products obtained with our methodology are useful synthetic building blocks. To showcase this utility, we made trifluoromethylated pyrazole **193** (78% yield) from ketone **192** using a sequence of condensation reactions (Scheme 69).



Scheme 69: Preparation of CF_3 -Substituted Pyrazole 193 from Ketone 192.

5.1.5. Conclusion

In this section the development of a one-pot, sequential diazotization/Lewis acid-mediated homologation reaction was described. Demonstration that a Lewis acid can be effective in the presence of water represents a key development in the use of *in situ* generated diazo compounds in homologation chemistry. Using this strategy, a direct *Tiffenau-Demjanov* and a *Roskamp* reaction could be developed that afford complementarity routes to the current state-of-the-art electrophilic trifluoromethylation for the preparation of α -trifluoromethyl-substituted carbonyl compounds. In addition, this chemistry holds great promise in the development of other processes involving Lewis acids and *in situ* generated trifluoromethyl diazomethane.

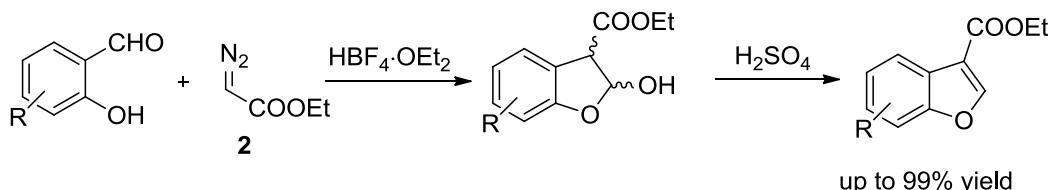
5.2. $BF_3 \bullet Et_2O$ -Mediated Homologation of Salicylaldehyde Derivatives Using *in situ* Generated Trifluoromethyl Diazomethane

5.2.1. Background

Benzofuran derivatives are important heterocyclic motifs in drug discovery, and many different synthetic routes have been reported. A particularly interesting preparative method is the direct homologation reaction of largely available salicylaldehydes with a diazo compound using a protic or Lewis acid. *Hossain* and co-workers reported a direct benzofuran synthesis using salicylaldehydes, ethyl diazoacetate and tetrafluoroboric acid, followed by a dehydration of the product using concentrated sulfuric acid (Scheme 70).¹⁷⁵

¹⁷⁵ M. E. Dudley, M. M. Morshed, M. M. Hossain, *Synthesis* **2006**, 1711.

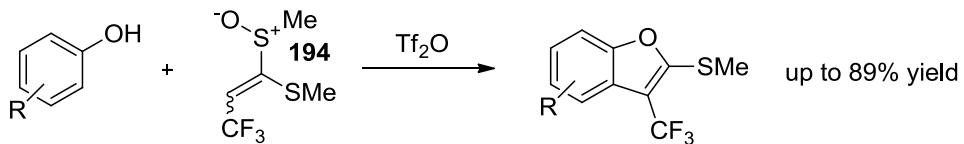
Hossain and co-workers (2006)



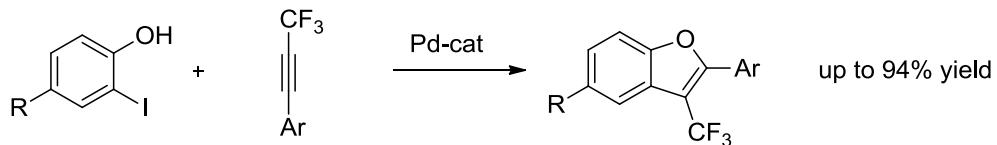
Scheme 70: Literature Precedent for the Preparation of Benzofurans with Diazo Compounds.

On the other hand, very few methods have been disclosed for the preparation of C3-trifluoromethyl-substituted benzofurans (Scheme 71), even though they are interesting starting materials in drug design. *Oshima* and co-workers recently reported the preparation of thioethers substituted trifluoromethylated benzofuran derivatives.¹⁷⁶ For that purpose they used trifluoromethylated sulfonium reagent **193** and triflic acid anhydride as an initiator. The reaction afforded the products in good yields using simple phenols as the starting materials. Another synthetic strategy was employed by *Konno* and co-workers, wherein they used a palladium-catalyzed annulation reaction between trifluoromethylated phenyacetylenes and iodophenols.¹⁷⁷

Oshima and co-workers (2010)



Konno and co-workers (2004)



Scheme 71: Literature Precedent for the Preparation of Trifluoromethyl-Substituted Benzofurans.

¹⁷⁶ T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2010**, *132*, 11838.

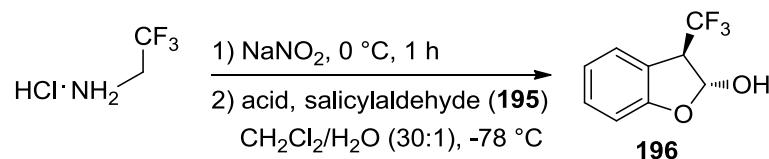
¹⁷⁷ T. Konno, J. Chae, T. Ishihara, H. Yamanaka, *Tetrahedron* **2004**, *60*, 11695.

Due to the scarcity of approaches for the preparation of trifluoromethyl-substituted benzofurans, we decided to study the application of *in situ* generated trifluoromethyl diazomethane to the homologation of salicylaldehydes in a similar manner as described by Hossain.

5.2.2. Screening and scope of the reaction

We started our investigations using the reaction conditions employed above for the homologation of aldehydes and cyclohexanones: $\text{F}_3\text{CCH}_2\text{NH}_2\cdot\text{HCl}$ (3 equiv.) and NaNO_2 (3.6 equiv.) were stirred at 0 °C for 1 h in a mixture of 30:1 $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, which was then cooled over 10 min to -78 °C; the test substrate (salicylaldehyde, **195**) and ZrCl_4 (1.8 equiv.) were then added and the reaction was stirred at -78 °C for 45 min. The desired trifluoromethyl-substituted dehydrobenzofuranol product was obtained in a promising 18% yield (Table 21, Entry 1). We then screened further different Lewis acids to optimize the reaction outcome.

Table 21: Screening of Lewis Acids for the Homologation of Salicylaldehydes with CF_3CHN_2 .^[a]



Entry	Acid	Equiv	Yield ^[b]
1	ZrCl_4	1.8	18%
2	AlCl_3	1.8	traces
3	TiCl_4	1.8	10%
4	SnCl_4	1.8	NR
5	SbCl_5	1.8	25%
6	$\text{BF}_3\cdot\text{OEt}_2$	1.8	74%
7	$\text{BF}_3\cdot\text{OEt}_2$	0.3	13%
8	$\text{HBF}_4\cdot\text{OEt}_2$	1.8	NR

[a] General procedure (GP 5.3): $\text{F}_3\text{CCH}_2\text{NH}_2\text{Cl}$ (3.0 equiv) and NaNO_2 (3.6 equiv) were stirred for 1 h at 0 °C in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition of the Lewis acid and salicylaldehyde (0.22 mmol, 1 equiv) at -78 °C. [b] Yield based on NMR analysis.

Table 22: Scope of Salicylaldehydes.^[a]

Entry	Substrate	Product	Yield ^[b]
1			74%
2			70%
3			68%
4			71%
5			67%
6			73%
7			54%
8			57%
9			72%
10			69%

[a] General procedure (GP 5.4): $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ (3.0 equiv) and NaNO_2 (3.6 equiv) are stirred for 1 h at 0 °C in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition of $\text{BF}_3\text{-OEt}_2$ (1.8 equiv) and substrate (0.22 mmol, 1 equiv) at -78 °C. [b] Isolated yield.

A wide range of strong Lewis acids afforded the product in low yields ($AlCl_3$, $TiCl_4$, $SnCl_4$, $SbCl_5$). Fortunately, the reaction mediated by $BF_3\cdot OEt_2$ gave the product **196** in 74% yield. As previously mentioned, the reduction to a catalytic amount of Lewis acid lowered the yield considerably (Entry 7). The control reaction with $HBF_4\cdot OEt_2$, possibly arising from the hydrolysis of BF_3 with water afforded no product (Entry 8). Having established a practical protocol for the reaction of salicylaldehyde with *in situ* generated trifluoromethyl diazomethane, we studied the scope of the reaction (Table 22). A wide range of salicylaldehydes bearing both withdrawing (Entry 8) and donating substituents (Entries 2 and 6) afforded the product selectively as a single diastereoisomeric hemiacetal. X-Ray quality crystals could be obtained for the ethoxy substituted product **197** and confirmed the expected *trans*-stereochemistry unambiguously (Figure 19).

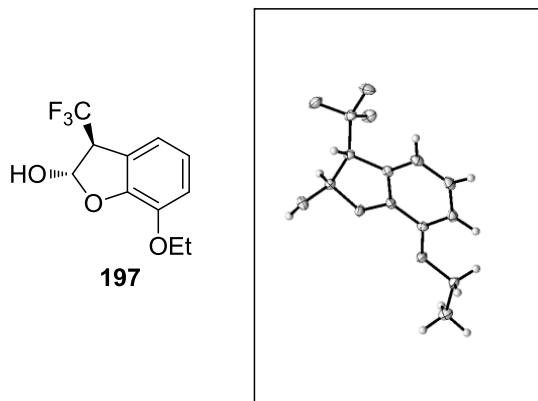
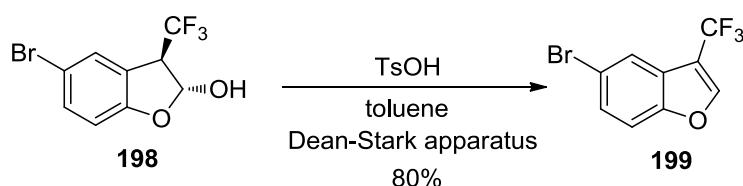


Figure 19: Crystal Structure of **197**.

To further illustrate the utility of our methodology, we probed the dehydration of the bromo-substituted product (Table 22, Entry 10). Using $TsOH$ as mediator and azeotropic removal of water, the desired trifluoromethyl-substituted benzofuran **199** could be obtained in 80% isolated yield.



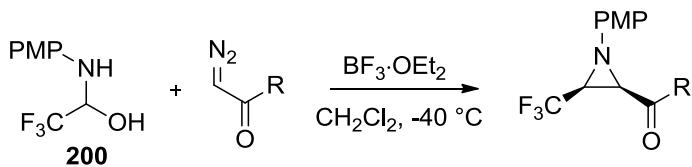
Scheme 72: Dehydration of Dehydrobenzofuranol **198** to Form Benzofuran **199**.

5.3. $\text{BF}_3\cdot\text{Et}_2\text{O}$ -Mediated Aziridination Using *in situ* Generated Trifluoromethyl Diazomethane¹⁷⁸

5.3.1. Background

Trifluoromethyl-substituted aziridines represent another class of potentially useful fluorinated heterocycles. In fact, they were used as intermediates in the preparation of trifluoromethylated amino acid derivatives as well as β -lactams.^{179,180} While the synthesis of some of these compounds were reported in the literature, their preparation usually suffer from a limited substrate scope or involve multistep synthesis.^{181,182,183,184} To the best of our knowledge, only one method reported by Akiyama allows for the preparation of a wide range of different trifluoromethylated aziridines (Scheme 73).¹⁸⁵

Akiyama et al (2003)



Scheme 73: Literature Precedent for the Preparation of CF_3 -Substituted Aziridines.

Unfortunately, their procedure requires the preparation of a different diazo compound for each desired aziridine product, limiting the practicality of the process. Extending our protocol using *in situ* generated trifluoromethyl diazomethane and a Lewis Acid in a one-pot diazotization/aza-Darzens reaction could afford a practical entry into this class of products using a single diazo compound (Scheme 74).

¹⁷⁸ The experiments presented in this section (5.3) were performed by Stefan Künzi during his semester work (2011). All the experiments were designed and analyzed by B. Morandi.

¹⁷⁹ P. Davoli, A. Forni, C. Franciosi, I. Moretti, F. Prati, *Tetrahedron: Asymmetry* **1999**, *10*, 2361.

¹⁸⁰ B. Crousse, S. Narizuka, D. Bonnet-Delpont, J. P. Begue, *Synlett* **2001**, 679.

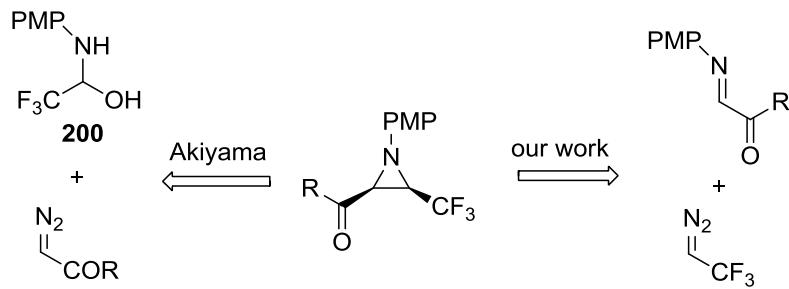
¹⁸¹ D. Colantoni, S. Fioravanti, L. Pellacani, P. A. Tardella, *Org. Lett.* **2004**, *6*, 197.

¹⁸² R. Maeda, K. Ooyama, R. Anno, M. Shiosaki, T. Azema, T. Hanamoto, *Org. Lett.* **2010**, *12*, 2548.

¹⁸³ O. G. Khomutov, V. I. Filyakova, K. I. Pashkevich, *Russ. Chem. Bull.* **1994**, *43*, 261.

¹⁸⁴ M. V. Spanedda, B. Crousse, S. Narizuka, D. Bonnet-Delpont, J. P. Begue, *Coll. Czech. Chem. Comm.* **2002**, *67*, 1359.

¹⁸⁵ T. Akiyama, S. Ogi, K. Fuchibe, *Tetrahedron Lett.* **2003**, *44*, 4011.

**Scheme 74: Retrosynthetic Analysis of CF_3 -Aziridines.**

5.3.2. Initial Studies and Scope of the aza-Darzens Reaction between glyoxal derivatives and trifluoromethyl diazomethane

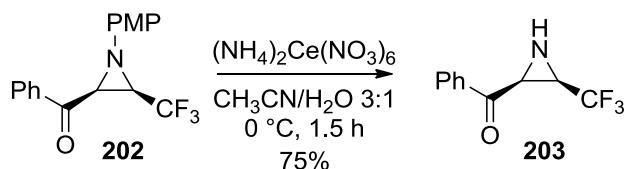
We initiated the project towards the development of an efficient aza-*Darzens* reaction between *in situ* generated trifluoromethyl diazomethane and imines using the reaction conditions described previously for the homologation of salicylaldehydes: $F_3CCH_2NH_2 \cdot HCl$ (3 equiv.) and $NaNO_2$ (3.6 equiv.) were stirred at 0 °C for 1 h in a mixture of 30:1 CH_2Cl_2/H_2O , which was then cooled over 10 min to -78 °C; the imine and $BF_3 \cdot OEt_2$ (1.8 equiv.) were then added and the reaction stirred at this temperature for further 2 h. A *p*-methoxyphenyl-protected benzaldimine substrate gave full recovery of starting material under these reaction conditions. We thus reasoned that a more strongly activated substrate (**201**) was required to undergo the reaction at this low temperature. Gratifyingly, the use of *p*-methoxyphenyl-protected phenylglyoxal imine **201** gave the desired product in 64% yield with an excellent diastereoselectivity of 17:1 in favor of the *cis* adduct after column chromatography (Table 23, Entry 1). Having a practical protocol for the preparation of aziridines, we explored the scope of the reaction (Table 23).

Table 23: Scope of the Aziridination Reaction.^[a]

Entry	Product	Yield ^[b]	<i>cis/trans</i> ^[c]
1		64%	17:1
2		78%	19:1
3		50%	12:1
4		60% ^[d]	11:1
5		61%	16:1
6		60%	16:1
7		47%	13:1
8		70%	15:1
9		73%	15:1

[a] General procedure (GP 5.6): 3 equiv $\text{F}_3\text{CCH}_2\text{NH}_3\text{Cl}$ and 3.6 equiv NaNO_2 were stirred at 0 °C for 1 h in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (30:1), followed by addition of imine (0.5 mmol, 1 equiv) and $\text{BF}_3\cdot\text{OEt}_2$ (1.8 equiv) at -78 °C.[b] Isolated yield of *cis* product.[c] Based on ^{19}F NMR spectroscopy. [d] 83% purity, total 72% yield.

Both the electron-withdrawing (Entries 2, 5 and 7) and electron-donating (Entry 3) substrates are well-tolerated. The reaction could also be performed with ethyl glyoxylate derived PMP-imine (Entry 4). The deprotection of one of the product (**202**) using CAN afforded the free aziridine (**203**) in 75% yield (Scheme 75). This underscores the utility of our method in the preparation of complex trifluoromethylated building blocks.



Scheme 75: Deprotection Using CAN.

5.3.3. Conclusion

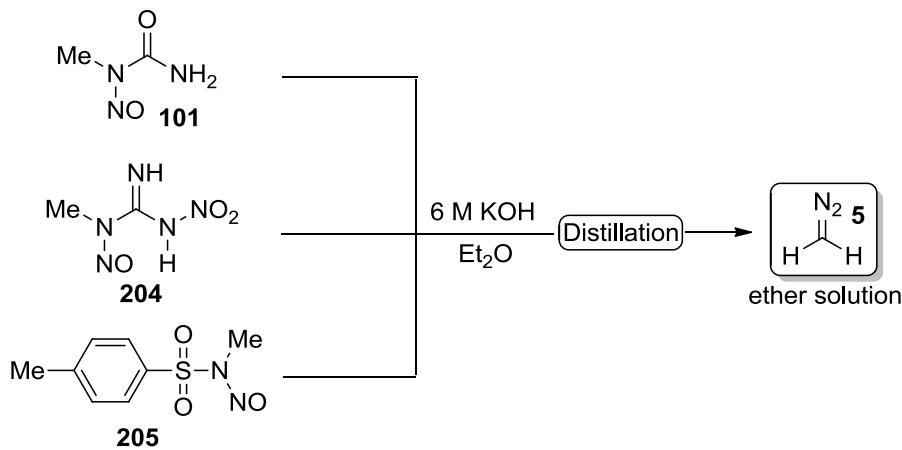
In this Chapter we have described four new reaction methodologies using *in situ* generated trifluoromethyl diazomethane under pseudo-anhydrous conditions. The observation that the use of strong Lewis acids is compatible with *in situ* generation of trifluoromethyl diazomethane opens many possibilities for the development of new processes due to the rich chemistry of diazoalkanes upon Lewis acid activation. We believe that this will lead to the development of many new reactions for the preparation of novel fluorinated products.

6. Iron-Catalyzed Cyclopropanation in 6 M KOH with *in situ* Generation of Diazomethane

6.1. Diazomethane: a Highly Versatile but Dangerous Reagent for Organic Synthesis

6.1.1. Synthesis and properties of diazomethane

In 1894, Von Pechman first reported the preparation of diazomethane, a yellow gas, by treating a nitrosamide compound with alkali.¹⁸⁶ Since then, diazomethane has become one of the most versatile C1-reagent in organic synthesis.¹⁸⁷ The most common methods for its preparation involve a base-mediated decomposition of a variety of nitrosamide reagents, typically performed in diethyl ether (Scheme 76). The diazomethane is then co-distilled with ether to afford a pure ethereal solution of diazomethane.



Scheme 76: Common Procedure for the Preparation of Diazomethane.

A historically important reagent for the synthesis of diazomethane is *N*-nitrosomethyl urea (**101**),¹⁸⁸ a reagent still occasionally used today albeit it is shock-sensitive and extremely toxic (carcinogenic).¹⁸⁹ A convenient feature of this reagent lies in its clean decomposition to diazomethane, such that distillation can be omitted for most purposes. Another rather well-developed diazomethane precursor is reagent **204**. It is commonly employed for the preparation of

¹⁸⁶ See Reference 20.

¹⁸⁷ T. H. Black, *Aldrichim. Acta* **1983**, *16*, 3.

¹⁸⁸ B. Eistert, *Angew. Chem.* **1941**, *54*, 99.

¹⁸⁹ U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, *Report on Carcinogens* (U.S. Department of Health and Human Services, Washington, DC, ed. 12, **2011**), p. 316.

less than 1 mmol of diazomethane. Unfortunately, it bears similar properties to reagent **101**, being very toxic and potentially explosive. The need for a safer precursor for diazomethane generation has led to the development of diazald **205**, a stable, low-toxicity compound (LD50 2.7g/Kg) that is commercially available.¹⁹⁰ The sole drawback of this reagent is the need to purify the obtained ethereal solution of diazomethane by distillation. This operation comes with risk as many explosions have been reported.¹⁹¹ To limit the risk of uncontrolled decomposition, a special, polished-glass kit has been developed for the preparation of diazomethane in up to 300 mmol scale (diazald kit).¹⁹² It is worth noting that while the ethereal solution of diazomethane is much more stable than the pure compound, several explosions have still been reported.¹⁹³ The ethereal solution is then generally used as such in the subsequent desired transformation.

6.2. Development of an Iron-Catalyzed Cyclopropanation of Olefins in 6 M KOH with *in situ* Generation of Diazomethane

6.2.1. Background

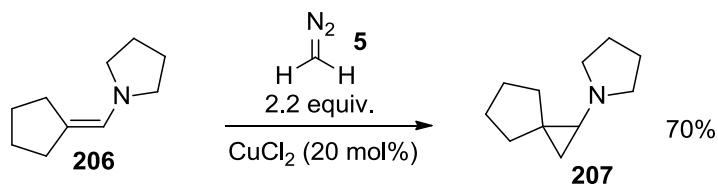
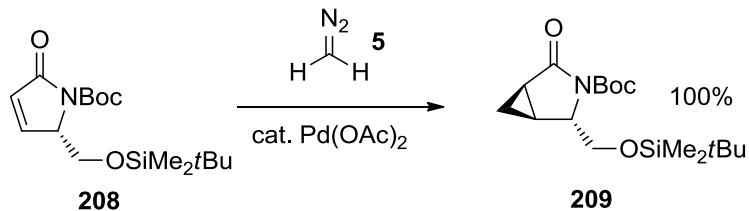
As previously discussed, diazomethane is an extremely versatile reagent in organic chemistry. For instance, it has been extensively used in cyclopropanation reactions. A wide array of different metals (e.g. Rh, Pd, Cu) have been used to catalyze this reaction. Two selected examples of cyclopropanation of olefins are presented in Scheme 77.

¹⁹⁰ Material Data Safety Sheet for *N*-methyl-*N*-nitroso-p-toluenesulfonamide (Sigma-Aldrich Chemical Company).

¹⁹¹ T. H. Black, Aldrichim. Acta. **1983**, *16*, 3.

¹⁹² Aldrich Technical Bulletin No. AL-180 (Aldrich Chemical Company)

¹⁹³ See Reference 4.

Muck and Wilson (1968)**Shimamoto and Ohfune (1989)**

Scheme 77: Examples of Copper- and Palladium-Catalyzed Cyclopropanation of Olefins.

In the first example, *Muck and Wilson* used CuCl_2 as a catalyst for the cyclopropanation of an enamine as the alkene partner.¹⁹⁴ The use of electron-rich alkenes favors a smooth reaction with the electrophilic copper-carbene intermediate formed during the reaction. Alternatively, palladium was shown to be a highly effective catalyst for the reaction between electron-deficient olefins and diazomethane (see also Section 1.3). This catalyst has also been found to be active for the cyclopropanation of terminal alkenes and strained cycloalkenes such as norbornene.¹⁹⁵ Rhodium catalysts were used in the cyclopropanation of aromatics (Büchner reaction) and C-H insertion reactions using diazomethane.¹⁹⁶

A particularly relevant example of cyclopropanation of alkenes using diazomethane was reported by *Nefedov* et al. In this report, they showed that the palladium-catalyzed cyclopropanation reaction of alkenes could be performed under the reaction conditions required for an *in situ* generation of diazomethane (KOH/ether mixture).¹⁹⁷ This method allowed for a safe handling of the toxic diazoalkane. Unfortunately, the reagent (**101**) was shown later to be highly carcinogenic and explosive (vide supra).

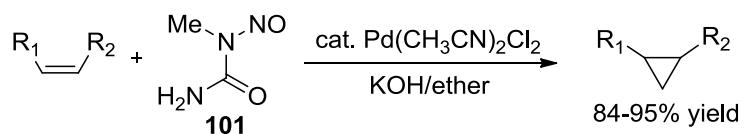
¹⁹⁴ D. L. Muck, E. R. Wilson, *J. Org. Chem.* **1968**, *33*, 419.

¹⁹⁵ K. Shimamoto, Y. Ohfune, *Tetrahedron Lett.* **1989**, *30*, 3803.

¹⁹⁶ Y. V. Tomilov, V. A. Dokichev, U. M. Dzhemilev, O. M. Nefedov, *Russ. Chem. Rev.* **1993**, *62*, 799.

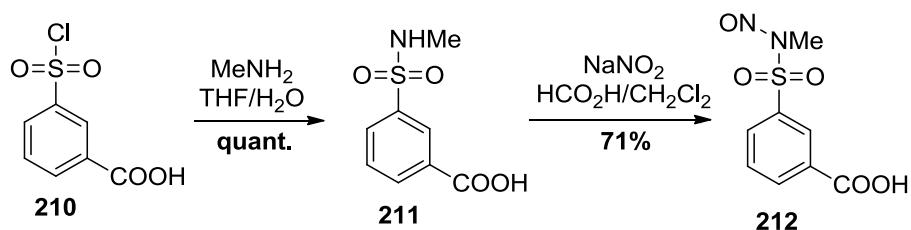
¹⁹⁷ O. M. Nefedov, Y. V. Tomilov, A. B. Kostitsyn, U. M. Dzhemilev, V. A. Dokichev, *Mendeleev Communications* **1992**, *13*.

Nefedov et al (1992)

Scheme 78: Pd-Catalyzed Cyclopropanation Using *in situ* Generated Diazomethane from NMU.

6.2.2. Initial experiments and screening of metal catalysts

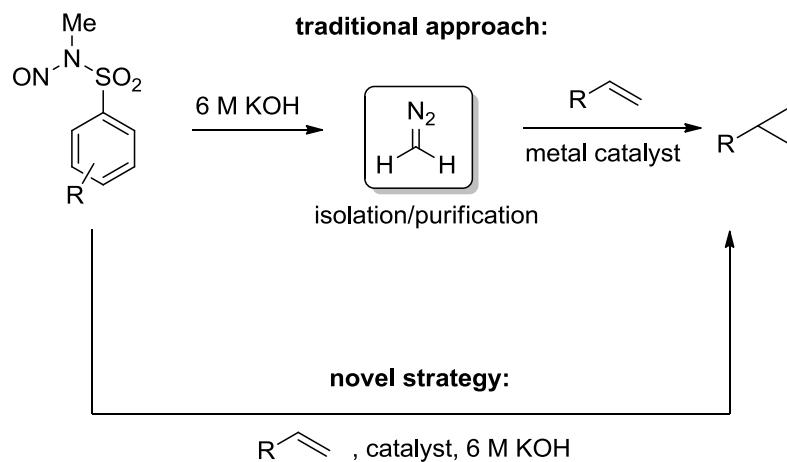
Inspired by our previous success in the development of a catalytic carbene-transfer reaction using *in situ* generated trifluoromethyl diazomethane, we sought to develop an alternative protocol for the use of diazomethane in catalytic reactions. Our strategy involves the development of a process, wherein diazomethane is generated *in situ* as a part of a continuous process and subsequently consumed by the metal catalyst. We reasoned that this strategy would avoid any buildup of the reagent and limit both human exposure and explosion risks. Unlike the work described by Nefedov, it was our goal at the outset to use a safer precursor that does not have the acute toxicity and explosiveness issues associated with NMU (**101**). While Diazald would seem to be a suitable reagent, it usually requires the use of an alcoholic co-solvent due to solubility issues. This co-solvent could interfere with the carbene-transfer step. A recently reported novel diazald analogue (**212**), which bears a carboxylic acid, has attracted our attention since this compound was reported to be water-soluble after deprotonation.¹⁹⁸ Unfortunately, this reagent could not be prepared in good purity following the literature procedure, and we thus improved its synthesis (Scheme 79).

Scheme 79: Improved Synthesis of Water-Soluble Diazomethane Precursor **212**.

¹⁹⁸ D. Moody, WO/2008/040947.

The nitrosation step was found to be particularly cumbersome. After extensive optimization, we achieved full conversion to the desired product using a mixture of formic acid and dichloromethane as the solvent. The so-obtained new synthetic route afforded the product from commercially available **210** in 71% overall yield without any purification by column chromatography. This improved synthesis should thus be amenable to a large scale preparation of this potentially very useful diazomethane precursor. The reagent was found to be stable as no decomposition was observed after being stored at 0 °C over several months. The corresponding carboxylate sodium salt (**213**) is water-soluble and stock solutions of it were easily prepared by addition of 1.1 equiv. of NaHCO₃ to a suspension of **212** in water. These stock solutions were then used within one week because slow denitrosation of the reagent in water was observed.¹⁹⁹

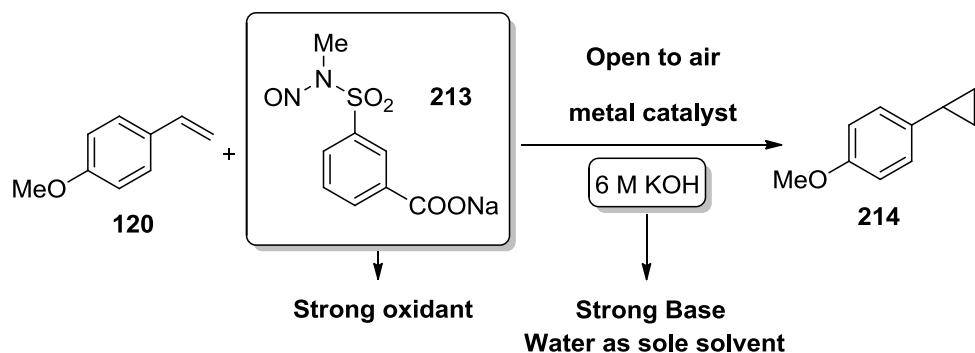
Having established an efficient protocol for the preparation of the water-soluble reagent **213**, we studied its use in the tandem base-mediated diazomethane generation/metal-catalyzed cyclopropanation of *p*-methoxystyrene (Scheme 80).



Scheme 80: Extreme Catalysis Concept Avoids the Isolation of Diazomethane.

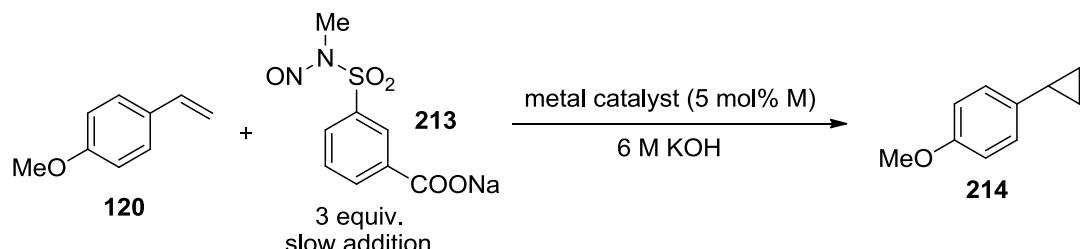
It is worth noting that any active catalyst under these conditions will need the following features (Scheme 81): (1) stability to strong base (6 M KOH). (2) Stability to strong oxidizing agents (diazald). (3) Selectivity of the carbene transfer to the olefin over C-H insertion with water present in excess.

¹⁹⁹ A ratio of 4:1 reagent/denitrosated reagent was obtained by ¹H-NMR analysis of a sample stored at 0 °C for 6 days, what represents a decay of 20% in 6 days.



Scheme 81: Boundary Conditions for a Tandem *in situ* Generation of Diazomethane/Metal-Catalyzed Cyclopropanation.

A wide range of metal catalysts were screened under the following conditions: catalyst (5 mol % M), *p*-MeO-styrene (1 equiv., limiting reagent) and 6 M KOH were vigorously stirred in an open vial, while an aqueous solution of reagent **213** (3 equiv.) was added slowly over 4 h to avoid any concentration buildup of diazomethane (Scheme 82). Furthermore, the reaction was performed without organic solvent and under air to simplify the experimental setup.



Metal Catalyst:

$\text{Cu}(\text{OTf})_2$	$\text{Pd}(\text{OAc})_2$	$\text{Rh}_2(\text{CH}_3\text{COO}^-)_4$	$\text{Rh}_2(\text{CH}_3(\text{CH}_2)_6\text{COO}^-)_4$
0%	9%	0%	45%
53%	23%	M = RuCO: 93%	M = Co: 33%
		M = FeCl: 100%	

Scheme 82: Screening of Metal Catalysts (GP 6.1).

$\text{Cu}(\text{OTf})_2$ and $\text{Pd}(\text{OAc})_2$ gave no product formation and 9% conversion to the expected product, respectively. A disappointing result was also obtained using rhodium acetate. Further screening of rhodium dimer complexes revealed that more apolar catalysts such as $\text{Rh}_2(\text{esp})_2$ and $\text{Rh}_2(\text{CH}_3(\text{CH}_2)_6\text{COO}^-)_4$ were compatible with the reaction conditions, giving the product in a moderate conversion (53% and 45% respectively). Co-salen (**119**) and Co-porphyrin complexes afforded the product in low conversion (23% and 33%), whereas the Ru and Fe-porphyrin proved to be excellent catalysts for this transformation. Using 0.1 mol% catalyst loading, FeTPP Cl afforded 60% conversion to the product, what represents a TON of 600.

6.2.3. Scope of the transformation and preliminary mechanistic studies

Under these optimized reaction conditions we studied the scope of the transformation (Table 24). A wide range of substituted styrenes bearing both electron-donating (Entries 1 and 2) and withdrawing (Entries 4 and 8) substituents were obtained in high yields. The chemistry could be extended to the regioselective cyclopropanation of dienes as well as to the preparation of alkynyl cyclopropanes (Entries 9-12).

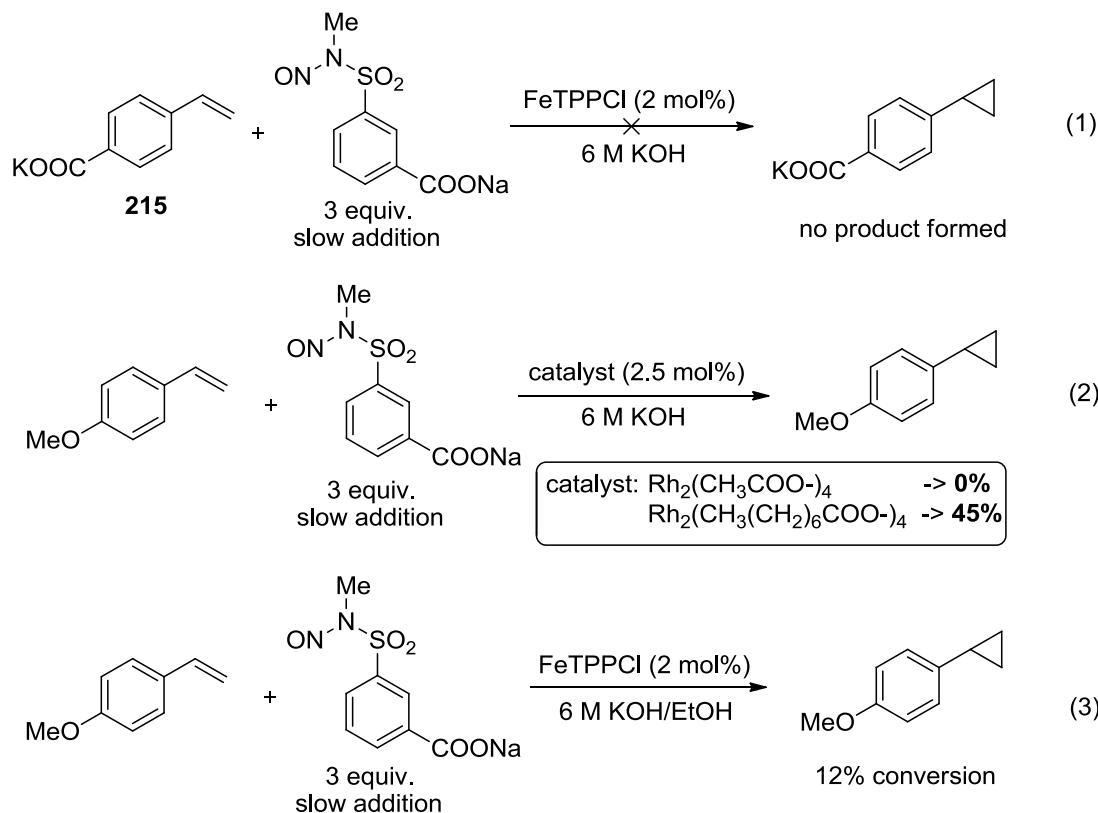
Table 24: Scope of the Iron-Catalyzed Cyclopropanation.^[a]

Entry	Conditions	Alkene	Product	Yield ^[b]
1	A			80
2	A			89
3	A			78
4	A			81
5	A			76
6	A			74
7	B			70
8	B			64
9	B			78
10	B			72
11	B			74
12	B			76

[a] Conditions (GP 6.2) A: FeTPPCl (2 mol%), **1** (3 equiv. added over 4 h).

Conditions B: FeTPPCl (3 mol%), **1** (5 equiv. added over 7 h). [b] Isolated yield of pure product.

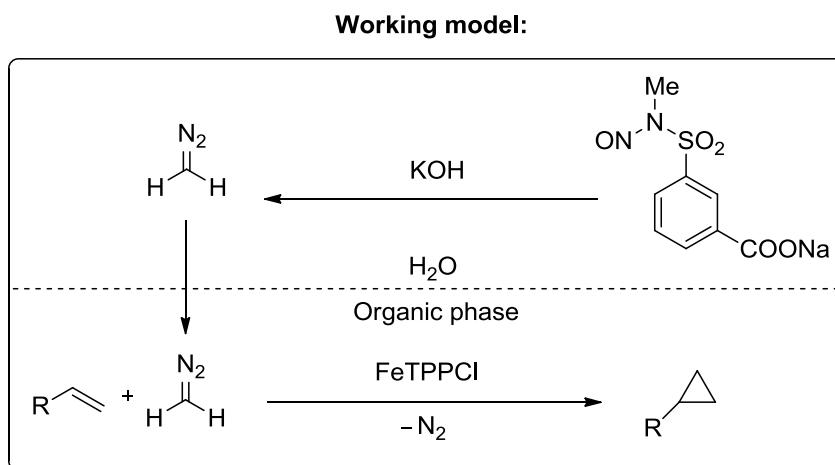
To further elucidate the reasons for the compatibility of the catalytic reaction with the *in situ* generation of diazomethane, we performed some key experiments to understand its mechanism (Scheme 83).



Scheme 83: Preliminary Mechanistic Investigations.

Since two distinct phases are observed during the reaction, we reasoned that this phase separation might be a key feature responsible for the success of the reaction. We therefore designed experiments aiming to evaluate the importance of this phase separation. In the first experiment (1), we employed a water-soluble substrate. This reaction led to full recovery of starting material, indicating the necessity to have a substrate that is immiscible with water such as to form an organic phase. A second experiment (2) performed was the comparison of the performances of two different rhodium dimers, with very similar reactivity but different polarity. We could therefore probe the localization of the catalyst, since a polar catalyst would be mostly dissolved in the aqueous phase, whereas a lipophilic complex like rhodium octanoate would be located in the organic phase. The result of this experiment clearly showed that the catalyst needs to be dissolved in the organic phase, avoiding the quenching of the putative metal-carbene intermediate by water. The last experiment (3)

performed used a mixture of 6 M KOH and ethanol as co-solvent. The reaction run under these conditions was homogenous, and led to a dramatic decrease in conversion. Formation of a homogenous reaction mixture shuts down the reaction, probably due to quenching of the metal-carbene by water and ethanol located in the same phase. Based on these observations, we propose the following working model for the reaction (Scheme 84).



Scheme 84: Working Model for the Mechanism.

The water-soluble nitrosamide and the base are located in the aqueous phase, where they react to form diazomethane. Diazomethane, a liposoluble compound, migrates into the organic phase where it reacts with the metal catalyst to form a metal-carbene intermediate. This intermediate then selectively reacts with the alkene locally present in excess in the organic phase to give the cyclopropane product. This rationale explains both the insensitivity of the metal-catalyzed process to the strong oxidizing and basic conditions, but also gives an explanation for the observed selective carbene-transfer to the olefin over O-H insertion with water present in excess in the reaction mixture.

6.2.3. Conclusion

In this chapter we have described the development of a novel strategy for the safe handling of diazomethane in a catalytic reaction. We have shown that several metals are tolerant of the strongly basic (6 M KOH) and oxidizing (diazald) media which allows a tandem organic solvent free process to take place under air. The simplicity of this protocol, combined with the wide accessibility of

diazoalkanes through a base-mediated decomposition of nitrosoamides, affords many possibilities for the discovery of new reactions involving diazoalkane-derived carbenes. This opens the door for discovery of new reactions with reactive intermediates generated *in situ* under aqueous basic conditions. Further, this concept of generating *in situ* a reactive intermediate under reaction conditions compatible with the subsequent transformation could open new avenues in the development of low-cost and safe catalytic reactions using inexpensive reagents.

7. Conclusion and Outlook

In this work, we have described the development of new transformations using *in situ* generated diazo compounds. An iron-catalyzed cyclopropanation using *in situ* generated trifluoromethyl diazomethane was described. This chemistry was later extended to the preparation of alkenyl- and alkynylcyclopropanes bearing a trifluoromethyl group. A similar transformation using glycine ethyl ester hydrochloride as an inexpensive ester-substituted carbene source was also implemented using the same iron catalyst. The observation that metal-catalyzed carbene-transfer can be performed under the demanding conditions (oxidizing, aqueous, acidic) for diazo preparation is expected to stimulate further research in the metal-catalyzed decomposition of diazo compounds under user-friendly conditions.

We then further described the development of the first asymmetric cyclopropanation reaction under the diazotization conditions necessary for the *in situ* generation of a diazo compound. A new type of Co-salen catalyst had to be designed in order to perform the cyclopropanation of styrenes using *in situ* generated trifluoromethyl diazomethane in aqueous media. A further expansion of the scope of this reaction to non-styrene derivatives can now be pursued, for instance, employing more active catalysts like Co-porphyrins.

We later disclosed a new cyclopropanation reaction leading to the synthesis of novel trifluoromethyl-substituted cyclopropenes. These compounds showed interesting preliminary results in their further functionalization, holding great promise for their use as valuable fluorinated building blocks for medicinal chemistry. We also attempted to develop chiral analogues of the tethering esp ligand, a ligand that showed improved reactivity in our studies as well as related reactions in the literature. A promising chiral scaffold could be identified that led to the highest enantioselectivity observed in an intramolecular cyclopropanation reaction. The identification of an efficient rhodium complex for the asymmetric transfer of the trifluoromethyl carbene group would be valuable due to the rich chemistry (C-H insertion, ylide chemistry) of this metal in carbene-transfer reaction and should prompt further studies in this direction.

We then studied the use of trifluoromethyl diazomethane in homologation and other Lewis acid-mediated reactions. Successful implementation of reaction condition allowing the diazotization and the reaction of interest to be performed sequentially in the same pot led to the preparation of novel trifluoromethylated seven-membered rings. Using the same conditions, the process could be extended to the direct homologation of aliphatic aldehydes to prepare trifluoromethylated ketones.

Finally, trifluoromethyl-substituted dehydrobenzofuranols and aziridines were prepared using a similar strategy. Several additional known reactions combine the use of diazo compounds and Lewis acids (e.g., homologation of acetals, asymmetric dipolar cycloadditions), and it is thus expected that our reaction conditions could be applied to novel processes leading to an expansion of the chemical space.

Finally, we described a conceptually new approach to the use of diazomethane in catalysis, wherein the conditions necessary for diazomethane preparation (strong base, oxidizing, water) define catalyst selection and reaction optimization. Following the same path as in our tandem diazotization/metal-catalyzed carbene transfer described previously, this reaction clearly shows that the use of biphasic systems allows very sensitive catalytic processes to be performed concomitantly with the generation of the reactive intermediate.

Many new useful reaction methodologies were described in this work. Trifluoromethyl diazomethane, a previously scarcely used reagent in synthesis, was used in a wide range of transformation using *in situ* generation strategies. This allowed a safe access to many unprecedented trifluoromethylated building blocks for drug discovery. Furthermore, we believe that this reagent has the potential to compete with many of the state-of-the-art trifluoromethylating reagents, since it allows in many cases a retrosynthetically complementary route to similar products but also an access to unique products difficult to obtain using other reagents. A very important feature of our work is the development of two complementary strategies for the use of this reagent generated *in situ*. The first one involves a tandem diazotization/metal-carbene transfer that occurs in water, whereas the second strategy allows the use of strong Lewis acids in an organic media. Potential reactions that could be developed in future work with this reagent, include, but are not restricted to: C-H insertion, which could give a general entry into aliphatic trifluoromethyl-substituted compounds; rhodium-catalyzed ylide formation followed by cycloadditions, forming valuable fluorinated heterocycles; cross-coupling of this reagent, giving versatile trifluoromethyl-substituted alkenes.

Furthermore, we believe that the results described herein are not limited to the preparation of fluorinated building blocks. As shown in the last chapter, the concept of *in situ* generation of diazo compounds in a biphasic water/substrate mixture can be used in combination with other reagents in catalysis. The phase separation protects the catalytic cycle and the catalyst from the strong reagents present in the aqueous phase. It is expected that this concept of extreme catalysis could be extended

to almost any catalytic systems, wherein an apolar reagent can be generated in an aqueous environment, providing that the metal catalyst remains in the organic phase during the entire catalytic cycle. Typical reagents include diazonium salts, obtainable by diazotization of anilines, as well as certain azides accessible from the corresponding hydrazone. Eventually, this strategy could lead to the use and discovery of reagents in catalysis that are too unstable to isolate and characterize, a concept that still remains unexplored.

Taken altogether, the strategies described in this work represent a conceptual advance in the field of catalysis. The results are expected to stimulate research for the development of powerful methodologies to prepare organic molecules using *in situ* generation strategies.

8. Experimental Part

General Methods

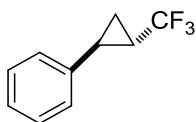
For flash chromatography technical grade solvents were used, which were distilled prior to use. Chromatographic purification was performed as flash chromatography using Brunschwig silica 32-63, 60Å, using pentane/diethylether as eluent with 0.3-0.5 bar pressure. TLC was performed on Merck silica gel 60 F254 TLC glass plates and visualized with UV light and potassium permanganate stain. ¹H-NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm as standard. The data is being reported as (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration). ¹³C-NMR spectra were recorded with ¹H-decoupling on a Bruker 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm as standard. ¹⁹F-NMR spectra were recorded on a VARIAN Mercury 300 MHz with CFCl₃ as an external standard. Infrared spectra were recorded neat on a Perkin-Elmer spectrum RX-I FT-IR spectrometer. The data is reported as absorption maxima (n, cm⁻¹). Mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETHZ on a Waters-Micromass-AutoSpec-Ultima spectrometer at 70 eV (EI), a VARIAN IonSpec-FT-ICR spectrometer (ESI) or on a VARIAN IonSPec-FT-ICR spectrometer (matrix-assisted laser desorption/ionization; MALDI; 3-Hydroxypicolinic acid (3-HPA) as matrix). Chemicals were purchased from commercial sources and used without further purification. Water was degassed by sparging Ar during 30 min.

8.1. Experimental Part to Chapter 2

General Procedure 2.1 (GP 2.1) for Cyclopropanation with Different Catalysts (Table 3): Catalyst, additives and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then trifluoroethylamine hydrochloride (45 mg, 0.33 mmol) and H₂SO₄ (1.2 μ L, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with Ar. *p*-methoxystyrene (29.5 μ L, 0.22 mmol) was subsequently added, and NaNO₂ (27 mg, dissolved in 0.5 mL of water) was added via syringe pump over 10 hr. After 4 hr, CH₂Cl₂ and water were added, and the water phase was extracted with CH₂Cl₂ (3 x), dried with MgSO₄ and evaporated under reduced pressure. After analysis of the crude NMR spectrum (to determine the diastereoselectivity), the crude mixture was chromatographed on silica gel (pentane/diethyl ether) to afford (\pm)-1-methoxy-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene. Nishiyama's catalyst was prepared according to a literature-procedure.²⁰⁰

General procedure 2.2 (GP 2.2) for Cyclopropanation with Fe(TPP)Cl and Trifluoroethylamine Hydrochloride (Table 4): Fe(TPP)Cl (4.6 mg, 0.0066 mmol), DMAP (2.6 mg, 0.022 mmol) and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then trifluoroethylamine hydrochloride (45 mg, 0.33 mmol) and H₂SO₄ (1.2 μ L, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with Ar. The alkene (0.22 mmol) was subsequently added, and NaNO₂ (27 mg, dissolved in 0.5 mL of water) was added via syringe pump over 10 hr. After 4 hr, CH₂Cl₂ and water were added, and the water phase was extracted with CH₂Cl₂ (3 x), dried with MgSO₄ and evaporated under reduced pressure. After analysis of the crude NMR spectrum (to determine the diastereoselectivity), the crude mixture was chromatographed on silica gel (pentane/diethyl ether) to afford product.

²⁰⁰ See Reference 60.

(\pm)-(*(trans*)-2-(trifluoromethyl)cyclopropyl)benzene (216, Table 4, Entry 1)

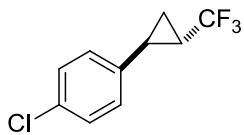
Was obtained as an oil (35.0 mg, 86 %) following **GP 2.2** with $\text{Fe}(\text{TPP})\text{Cl}$ and $\text{CF}_3\text{CH}_2\text{NH}_3\text{Cl}$.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.33\text{--}7.20$ (m, 3H), 7.15–7.10 (m, 2H), 2.38 (dt, $J = 9.6, 5.4$ Hz, 1H), 1.88–1.72 (m, 1H), 1.38 (dt, $J = 9.6, 5.7$ Hz, 1H), 1.22–1.12 (m, 1H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 138.0, 127.6, 125.8, 125.5, 123.2$ (q, $J = 270$ Hz), 22.07 (q, $J = 36$ Hz), 18.6 (q, $J = 3.2$ Hz), 9.8 (q, $J = 3.2$ Hz).

$^{19}\text{F-NMR}$ (282 MHz, CDCl_3): $\delta = -66.7$ (d, $J = 6.2$ Hz).

Spectral data are in accordance with the literature.²⁰¹

(\pm)-1-chloro-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene (217, Table 4, Entry 2)

Was obtained as an oil (41.0 mg, 85 %) following **GP 2.2** with $\text{Fe}(\text{TPP})\text{Cl}$ and $\text{CF}_3\text{CH}_2\text{NH}_3\text{Cl}$.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 2.37 (dt, $J = 9.6, 5.4$ Hz, 1H), 1.82–1.70 (m, 1H), 1.39 (dt, $J = 9.6, 5.7$ Hz, 1H), 1.18–1.10 (m, 1H).

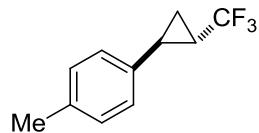
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 137.5, 132.6, 128.7, 127.4, 125.3$ (q, $J = 270$ Hz), 23.0 (q, $J = 37$ Hz), 19.0 (q, $J = 3$ Hz), 10.7 (q, $J = 3$ Hz).

$^{19}\text{F-NMR}$ (282 MHz, CDCl_3): $\delta = -66.8$ (d, $J = 7.3$ Hz).

HRMS (EI): calcd for $\text{C}_{10}\text{H}_8\text{ClF}_3^+$ (M^+) 220.0263, found 220.0262.

IR (neat): 2953, 2924, 2853, 1459, 1377, 814.

²⁰¹ See Reference 131.

(\pm)-1-methyl-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene (218, Table 4, Entry 3)

Was obtained as an oil (43.7 mg, 99 %) following **GP 2.2** with Fe(TPP)Cl and CF₃CH₂NH₃Cl.

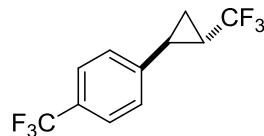
¹H-NMR (300 MHz, CDCl₃): δ = 7.12 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 2.38–2.28 (m, 4H), 1.82–1.70 (m, 1H), 1.35 (dt, *J* = 9.3, 5.4 Hz, 1H), 1.20–1.10 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 136.4, 136.0, 130.0, 126.4, 125.5 (q, *J* = 270 Hz), 22.8 (q, *J* = 37 Hz), 20.9, 19.2 (q, *J* = 3 Hz), 10.6 (q, *J* = 3 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.7 (d, *J* = 7.6 Hz).

HRMS (EI): calcd for C₁₁H₁₁F₃⁺ (M⁺) 200.0809, found 200.0808.

IR (neat): 2953, 2922, 2853, 1459, 1377, 1261, 1098, 1026, 804.

(\pm)-1-(trifluoromethyl)-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene (219, Table 4, Entry 4)

Was obtained as an oil (43.1 mg, 77 %) following **GP 2.2** with Fe(TPP)Cl and CF₃CH₂NH₃Cl.

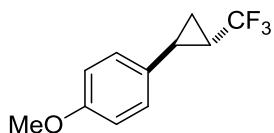
¹H-NMR (300 MHz, CDCl₃): δ = 7.55 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.41 (dt, *J* = 9.6, 5.4 Hz, 1H), 1.92–1.78 (m, 1H), 1.44 (dt, *J* = 9.9, 5.4 Hz, 1H), 1.26–1.18 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 143.1, 129.2 (q, *J* = 33 Hz), 126.8 (q, *J* = 270 Hz), 125.6, 125.5 (q, *J* = 270 Hz), 122.7, 23.5 (q, *J* = 37 Hz), 19.4, 11.1.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.5, -66.9 (d, *J* = 6.8 Hz).

HRMS (EI): calcd for C₁₁H₈F₆⁺ (M⁺) 254.0526, found 254.0525.

IR (neat): 2954, 2923, 2853, 1457, 1378, 720.

(\pm)-1-methoxy-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene (121, Table 4, Entry 5)

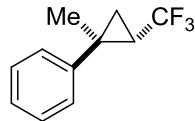
Was obtained as an oil (42.3 mg, 89 %) following **GP 2.2** with Fe(TPP)Cl and CF₃CH₂NH₃Cl.

¹H-NMR (300 MHz, CDCl₃): δ = 7.06 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 2.32 (dt, *J* = 9.3, 5.1 Hz, 1H), 1.80–1.65 (m, 1H), 1.33 (dt, *J* = 9.6, 5.4 Hz, 1H), 1.15–1.05 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 157.5, 135.2, 130.0, 126.3 (q, *J* = 270 Hz), 113.0, 54.3, 21.6 (q, *J* = 36 Hz), 17.9 (q, *J* = 2 Hz), 9.4 (q, *J* = 3 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.6 (d, *J* = 6.5 Hz).

Spectral data are in accordance with the literature.²⁰¹

(\pm)-((*trans*)-1-methyl-2-(trifluoromethyl)cyclopropyl)benzene (220, Table 4, Entry 6)

Was obtained as an oil (37.9 mg, 86 %) following **GP 2.2** with Fe(TPP)Cl and CF₃CH₂NH₃Cl.

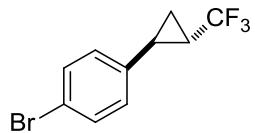
¹H-NMR (300 MHz, CDCl₃): δ = 7.33–7.20 (m, 5H), 1.82–1.70 (m, 1H), 1.53 (d, *J* = 0.4 Hz, 3H), 1.40–1.32 (m, 1H), 1.22 (t, *J* = 5.7 Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 145.5, 128.6, 127.5, 126.9, 126.7 (q, *J* = 270 Hz), 26.1 (q, *J* = 36 Hz), 26.2, 20.7 (q, *J* = 2 Hz), 16.5(q, *J* = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -59.8 (d, *J* = 8.5 Hz).

HRMS (EI): calcd for C₁₁H₁₁F₃⁺ (M⁺) 200.0809, found 200.0809.

IR (neat): 2954, 2924, 2850, 1458, 1377.

(\pm)-1-bromo-4-((*trans*)-2-(trifluoromethyl)cyclopropyl)benzene (221, Table 4, Entry 7)

Was obtained as an oil (55.0 mg, 95 %) following **GP 2.2** with Fe(TPP)Cl and CF₃CH₂NH₃Cl.

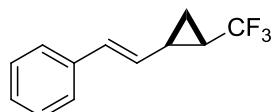
¹H-NMR (300 MHz, CDCl₃): δ = 7.42 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 2.32 (dt, *J* = 9.3, 5.4 Hz, 1H), 1.82–1.75 (m, 1H), 1.40 (dt, *J* = 9.3, 5.4 Hz, 1H), 1.20–1.10 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 138.0, 131.4, 127.0, 125.5 (q, *J* = 270 Hz), 120.5, 23.2 (q, *J* = 36 Hz), 19.0 (q, *J* = 2 Hz), 10.7 (q, *J* = 3 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.8 (d, *J* = 6.2 Hz).

Spectral data are in accordance with the literature.²⁰¹

General procedure 2.3 (GP 2.3) for Cyclopropanation with Fe(TPP)Cl and Trifluoroethylamine Hydrochloride (Table 5): Substrate, trifluoroethylamine hydrochloride, sodium nitrite and FeTPP₂Cl (3 mol %) were dissolved in water in an open vial. For solid substrates a minimum amount of toluene was used to dissolve them. The heterogeneous mixture was vigorously stirred at room temperature until TLC showed completion of the reaction. In some cases further trifluoroethylamine hydrochloride and sodium nitrite were added to ensure full conversion. The mixture was then quenched with sat. NH₄Cl, extracted with CH₂Cl₂, washed with water, dried over MgSO₄ and evaporated in vacuo. After analysis of the crude product by NMR, it was purified by flash chromatography on silica gel (hexane/ethyl acetate).

((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (122, Table 5, Entry 1)

Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), phenylbutadiene (130 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 75 min the mixture was quenched with saturated ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as a white solid (156 mg, 74 %).

¹H NMR (300 MHz, CDCl₃): δ 7.35–7.15 (m, 5H), 6.54 (d, *J* = 15.7 Hz, 1H), 5.76 (dd, *J* = 15.7, 8.3 Hz, 1H), 2.00 (dt, *J* = 8.3, 7.3 Hz, 1H), 1.75–1.58 (m, 1H), 1.25 (dt, *J* = 9.1, 5.5 Hz, 1H), 1.01–0.94 (m, 1H).

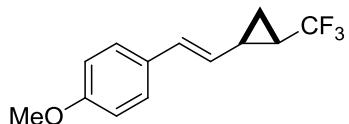
¹³C NMR (125 MHz, CDCl₃): δ 136.7, 130.8, 128.8, 128.6, 127.4, 125.9 (q, *J* = 272 Hz), 125.9, 21.7 (q, *J* = 36.8 Hz), 18.4 (q, *J* = 2.7 Hz), 9.9 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.4 (d, *J* = 6.7 Hz).

IR (Neat): 3024, 1418, 1266, 1130, 1105, 1076, 739, 697, 649 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₂H₁₁F₃ [M]⁺ 212.0808, found 212.0802.

1-methoxy-4-((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (222, Table 5, Entry 2)



Prepared according to **GP 2.3** with toluene (70 μL), *p*-methoxyphenylbutadiene (160 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), NaNO₂ (166 mg, 2.40 mmol) and water (8.1 mL). The mixture was stirred for 60 min before being quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (90:10 hexane/ethyl acetate) to give the product as an oil (224 mg, 93 %).

¹H NMR (300 MHz, CDCl₃): δ 7.24 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 15.7 Hz, 1H), 5.63 (dd, *J* = 15.7, 8.1 Hz, 1H), 3.81 (s, 3H), 2.05–1.89 (m, 1H), 1.72–1.57 (m, 1H), 1.31–1.15 (m, 1H), 1.01–0.87 (m, 1H).

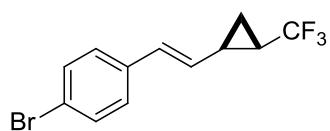
¹³C NMR (101 MHz, CDCl₃): δ 159.1, 130.2, 129.8, 127.1, 126.5, 126.0 (q, *J* = 272 Hz), 114.0, 55.3, 21.6 (q, *J* = 36.7 Hz), 18.4 (q, *J* = 2.7 Hz), 9.8 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.3 (d, *J* = 6.8 Hz).

IR (Neat): 2959, 2839, 1607, 1511, 1263, 1244, 1126, 1067, 1033, 959 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₃H₁₃F₃O [M]⁺ 242.0913, found 242.0913.

1-bromo-4-((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (223, Table 5, Entry 3)



Prepared according to **GP 2.3** with toluene (20 μL), *p*-bromophenylbutadiene (47 mg, 0.22 mmol), Fe(TPP)Cl (4.6 mg, 6.7 μmol), trifluoroethylamine hydrochloride (60 mg, 0.45 mmol), NaNO₂ (37 mg, 0.54 mmol) and water (1.8 mL). The mixture was stirred for 60 min before being quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as a colorless oil (39 mg, 60 %).

¹H NMR (300 MHz, CDCl₃): δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.48 (d, *J* = 15.7 Hz, 1H), 5.74 (dd, *J* = 15.7, 8.4 Hz, 1H), 2.00 (qd, *J* = 9.0, 5.2 Hz, 1H), 1.77–1.58 (m, 1H), 1.37–1.18 (m, 1H), 1.05–0.91 (m, 1H).

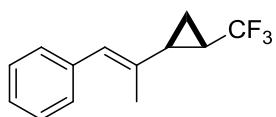
¹³C NMR (101 MHz, CDCl₃): δ 135.7, 131.7, 129.7, 129.6, 127.4, 125.9 (q, *J* = 272 Hz), 121.1, 21.7 (q, *J* = 36.9 Hz), 18.4 (q, *J* = 2.7 Hz), 9.9 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.4 (d, *J* = 6.7 Hz).

IR (Neat): 3028, 2926, 1488, 1421, 1265, 1129, 1071, 958, 802 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₂H₁₀BrF₃ [M]⁺ 289.9913, found 289.9914.

((E)-2-((1SR,2SR)-2-(trifluoromethyl)cyclopropyl)prop-1-en-1-yl)benzene (224, Table 5, Entry 4)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.4 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), the butadiene (144 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). The mixture was stirred for 60 min before being quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as a colorless oil (188 mg, 83 %, 12:1 mixture of isomers).

¹H NMR (300 MHz, CDCl₃): δ 7.38–7.28 (m, 2H), 7.25–7.17 (m, 3H), 6.37 (s, 1H), 2.04–1.95 (m, 1H), 1.82 (s, 3H), 1.77–1.58 (m, 1H), 1.21–1.04 (m, 2H).

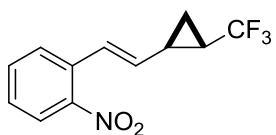
¹³C NMR (101 MHz, CDCl₃): δ 137.5, 134.9, 128.8, 128.2, 126.4, 126.2 (q, *J* = 272 Hz), 126.0, 23.8 (q, *J* = 2.5 Hz), 20.1 (q, *J* = 36.7 Hz), 16.1, 8.0 (q, *J* = 2.5 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.2 (d, *J* = 6.8 Hz).

IR (Neat): 3025, 1418, 1265, 1129, 1105, 1076, 739, 697, 649 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₃H₁₃F₃ [M]⁺ 226.0964, found 226.0964.

1-nitro-2-((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (225, Table 5, Entry 5)



Prepared according to **GP 2.3** with toluene (160 μL), *o*-nitrophenylbutadiene (175 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), NaNO₂ (166 mg, 2.40 mmol) and water (8.1 mL). After 75 min further trifluoroethylamine hydrochloride (136 mg, 1.00 mmol) and NaNO₂ (83 mg, 1.20 mmol) were added. The mixture was stirred for 30 min before being quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (75:25 hexane/ethyl acetate) to give the product as an oil (245 mg, 95 %).

¹H NMR (300 MHz, CDCl₃): δ 7.92 (d, *J* = 7.8 Hz, 1H), 7.59–7.46 (m, 2H), 7.43–7.31 (m, 1H), 7.04 (d, *J* = 15.6 Hz, 1H), 5.77 (dd, *J* = 15.6, 8.4 Hz, 1H), 2.14–2.03 (m, 1H), 1.79–1.65 (m, 1H), 1.38–1.21 (m, 1H), 1.07–0.99 (m, 1H).

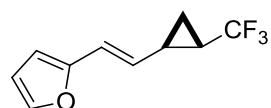
¹³C NMR (101 MHz, CDCl₃): δ 147.6, 134.3, 133.0, 132.3, 128.2, 128.0, 125.9, 125.7 (q, *J* = 272 Hz), 124.6, 22.1 (q, *J* = 37.1 Hz), 18.5 (q, *J* = 2.7 Hz), 10.2 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.5 (d, *J* = 6.6 Hz).

IR (Neat): 3067, 1521, 1344, 1265, 1128, 1067, 958, 738 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₂H₁₀F₃NO₂ [M]⁺ 257.0659, found 257.0656.

2-((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)furan (226, Table 5, Entry 6)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), the diene (120 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 60 min the mixture was quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as an oil (104 mg, 52 %).

¹H NMR (300 MHz, CDCl₃): δ 7.30 (s, 1H), 6.43–6.28 (m, 2H), 6.17 (d, *J* = 3.3 Hz, 1H), 5.71 (dd, *J* = 15.7, 8.6 Hz, 1H), 2.02–1.84 (m, 1H), 1.72–1.57 (m, 1H), 1.34–1.16 (m, 1H), 1.00–0.83 (m, 1H).

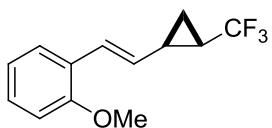
¹³C NMR (101 MHz, CDCl₃): δ 152.3, 141.7, 127.6, 125.9 (q, *J* = 272 Hz), 119.2, 111.3, 107.1, 21.8 (q, *J* = 36.8 Hz), 18.2 (q, *J* = 2.7 Hz), 10.0 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.4 (d, *J* = 6.7 Hz).

IR (Neat): 2927, 1418, 1266, 1129, 1066, 1013, 953, 924, 731 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₀H₉F₁₀O [M]⁺ 202.0600, found 202.0594.

1-methoxy-2-((E)-2-((1RS,2SR)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (227, Table 5, Entry 7)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), *o*-methoxyphenylbutadiene (160 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 75 min the mixture was quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as an oil (226 mg, 93 %).

¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, *J* = 7.6 Hz, 1H), 7.24–7.17 (m, 1H), 6.95–6.80 (m, 3H), 5.78 (dd, *J* = 15.9, 8.3 Hz, 1H), 3.85 (s, 3H), 2.08–1.97 (m, 1H), 1.73–1.57 (m, 1H), 1.27–1.18 (m, 1H), 1.03–0.91 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ 156.4, 129.5, 128.4, 126.5, 125.8, 126.0 (q, *J* = 272 Hz), 125.6, 120.7, 110.9, 55.4, 21.7 (q, *J* = 36.7 Hz), 18.9 (q, *J* = 2.7 Hz), 10.0 (q, *J* = 2.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -66.4 (d, *J* = 6.8 Hz).

IR (Neat): 2938, 2839, 1597, 1490, 1418, 1266, 1243, 1126, 1104, 961, 748 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₃H₁₃F₃O [M]⁺ 242.0913, found 242.0909.

((1SR,2SR)-2-(trifluoromethyl)cyclopropyl)ethynylbenzene (228, Table 5, Entry 8)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), the enyne (128 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 75 min, further trifluoroethylamine hydrochloride (136 mg, 1.00 mmol) and NaNO₂ (83 mg, 1.20 mmol) were added. After further 60 min, additional trifluoroethylamine hydrochloride (67 mg, 0.50 mmol) and NaNO₂ (41 mg, 0.60 mmol) were added. After a further 30 min the mixture was quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as an oil (160 mg, 76 %).

¹H NMR (300 MHz, CDCl₃): δ 7.43–7.33 (m, 2H), 7.33–7.26 (m, 3H), 2.07–1.86 (m, 2H), 1.37–1.15 (m, 2H).

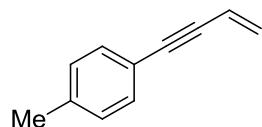
¹³C NMR (101 MHz, CDCl₃): δ 131.7, 128.3, 128.2, 125.2 (q, *J* = 272 Hz), 122.9, 88.2, 78.0, 22.8 (q, *J* = 37.1 Hz), 11.4 (q, *J* = 2.5 Hz), 5.1 (q, *J* = 3.6 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -67.1 (d, *J* = 6.1 Hz).

IR (Neat): 3025, 1738, 1492, 1418, 1265, 1137, 1113, 754, 689 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₂H₉F₃ [M]⁺ 210.0651, found 210.0649.

1-(but-3-en-1-yn-1-yl)-4-methylbenzene (229)



A solution of *p*-tolylacetylene (290 mg, 2.50 mmol) in diethylamine (1.25 mL) was degassed by purging with argon for 30min. 1.0 M Vinyl Bromide in THF solution (3.75 mL, 3.75 mmol) was added and the solution was cooled to 0 °C. Pd(PPh₃)₄ (46 mg, 0.040 mmol, 1.6 mol%) and CuI (48 mg, 0.25 mmol, 10 mol %) were added and the mixture was stirred at room temperature for 19 h. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL), washed with 1M HCl (2 x 20 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane) to give the product as oil (351 mg, 99 %).

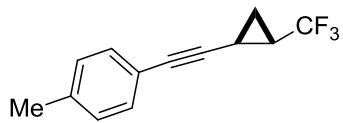
¹H NMR (300 MHz, CDCl₃): δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 6.02 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.71 (d, *J* = 17.5 Hz, 1H), 5.52 (d, *J* = 11.1 Hz, 1H), 2.35 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 138.4, 131.5, 129.1, 126.4, 120.1, 117.3, 90.2, 87.5, 21.5.

IR (Neat): 3008, 2920, 1602, 1508, 968, 916, 813 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₁H₉ [M – H]⁺ 141.0699, found 141.0699.

1-methyl-4-(((1SR,2SR)-2-(trifluoromethyl)cyclopropyl)ethynyl)benzene (230, Table 5, Entry 9)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), the enyne (142 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 60 min, 120 min and 150 min further trifluoroethylamine hydrochloride (136 mg, 1.00 mmol), (67 mg, 0.50 mmol), (67 mg, 0.50 mmol) and NaNO₂ (83 mg, 1.20 mmol), (41 mg, 0.60 mmol), (41 mg, 0.60 mmol) were added respectively. After a further 30 min the mixture was quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as an oil (181 mg, 81 %).

¹H NMR (300 MHz, CDCl₃): δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 2.34 (s, 3H), 2.04–1.85 (m, 2H), 1.37–1.11 (m, 2H).

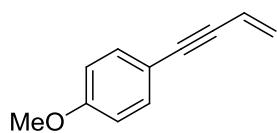
¹³C NMR (101 MHz, CDCl₃): δ 138.3, 131.6, 129.0, 125.2 (q, *J* = 272 Hz), 119.8, 87.4, 78.1, 22.8 (q, *J* = 37.0 Hz), 21.4, 11.4 (q, *J* = 2.4 Hz), 5.2 (q, *J* = 3.6 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -67.2 (d, *J* = 6.1 Hz).

IR (Neat): 2924, 1511, 1418, 1265, 1143, 815 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₃H₁₁F₃ [M]⁺ 224.0808, found 224.0805.

1-(but-3-en-1-yn-1-yl)-4-methoxybenzene (231)



A solution of *p*-methoxyphenylacetylene (330 mg, 2.50 mmol) in diethylamine (1.25 mL) was degassed by purging with argon for 30min. 1.0 M Vinyl Bromide in THF solution (3.75 mL, 3.75 mmol) was added and the solution was cooled to 0 °C. Pd(PPh₃)₄ (46 mg, 0.040 mmol, 1.6 mol%) and CuI (48 mg, 0.25 mmol, 10 mol%) were added and the mixture was stirred at room temperature

for 19 h. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 x 20 mL), washed with 1M HCl (2 x 20 mL), dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (90:10 hexane/ethyl acetate) to give the product as an oil (395 mg, 99 %).

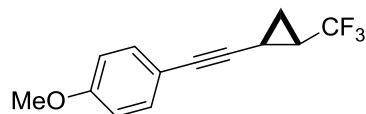
¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.01 (dd, *J* = 17.5, 11.1 Hz, 1H), 5.69 (d, *J* = 17.5 Hz, 1H), 5.49 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ 159.6, 133.0, 126.0, 117.4, 115.3, 114.0, 90.0, 86.9, 55.3.

IR (Neat): 3006, 2957, 2836, 1599, 1506, 1290, 1243, 1171, 1029, 828 cm⁻¹.

HRMS (EI): *m/z* calcd for C₁₁H₁₀O [M]⁺ 158.0727, found 158.0725.

1-methoxy-4-(((1S,R,2S,R)-2-(trifluoromethyl)cyclopropyl)ethynyl)benzene (232, Table 5, Entry 10)



Prepared according to **GP 2.3** with NaNO₂ (166 mg, 2.40 mmol), trifluoroethylamine hydrochloride (271 mg, 2.00 mmol), the enyne (158 mg, 1.00 mmol), Fe(TPP)Cl (20 mg, 0.030 mmol) and water (8.2 mL). After 75 min, 135 min and 165 min further trifluoroethylamine hydrochloride (136 mg, 1.00 mmol), (67 mg, 0.50 mmol), (67 mg, 0.50 mmol) and NaNO₂ (83 mg, 1.20 mmol), (41 mg, 0.60 mmol), (41 mg, 0.60 mmol) were added respectively. After a further 30 min the mixture was quenched with ammonium chloride. The residue was purified by flash chromatography on silica gel (hexane) to give the product as an oil (187 mg, 78 %).

¹H NMR (300 MHz, CDCl₃): δ 7.32 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 1.99–1.88 (m, 2H), 1.31–1.16 (m, 2H).

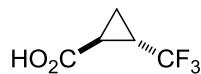
¹³C NMR (101 MHz, CDCl₃): δ 159.5, 133.1, 125.2 (q, *J* = 272 Hz), 114.9, 113.9, 86.7, 77.8, 55.3, 22.8 (q, *J* = 37.0 Hz), 11.4 (q, *J* = 2.4 Hz), 5.2 (q, *J* = 3.7 Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -67.2 (d, *J* = 5.9 Hz).

IR (Neat): 2936, 2839, 1606, 1509, 1265, 1245, 1171, 1137, 1113, 1028, 830 cm⁻¹.

HRMS (EI): m/z calcd for $C_{13}H_{11}F_3O$ [M]⁺ 240.0757, found 240.0753.

(1S_R,2S_R)-2-(trifluoromethyl)cyclopropanecarboxylic acid (123)²⁰²



((E)-2-((1R,2S)-2-(trifluoromethyl)cyclopropyl)vinyl)benzene (**122**, 499 mg, 2.35 mmol) was dissolved in a mixture of CCl_4 (4.7 mL), acetonitrile (4.7 mL) and water (7.0 mL) at room temperature. $NaIO_4$ (4.02g, 18.8 mmol) was added and after the suspension turned uniform, $RuCl_3 \cdot H_2O$ (16 mg, 0.071 mmol) was added. After 2 h, 2M HCl was added (30 mL) and the mixture was extracted with EtOAc (3 x 30 mL). The organic extract was filtered through celite, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by Kugelrohr distillation to give the product as an oil (203 mg, 56 %).

¹H NMR (300 MHz, CDCl₃): δ 10.87 (br s, 1H), 2.29–2.13 (m, 1H), 2.10–1.98 (m, 1H), 1.48–1.31 (m, 2H).

¹³C NMR (101 MHz, CDCl₃): δ 177.4, 124.6 (q, $J = 272$ Hz), 22.7 (q, $J = 38.3$ Hz), 16.6 (q, $J = 2.6$ Hz), 10.9 (q, $J = 2.6$ Hz).

¹⁹F NMR (282 MHz, CDCl₃): δ -67.2 (d, $J = 6.4$ Hz).

IR (Neat): 2885 (br), 1704, 1401, 1261, 1139, 1113, 1090, 934, 632 cm^{-1} .

HRMS (EI): m/z calcd for $C_5H_4F_3O_2$ [M – H]⁺ 153.0158, found 153.0161.

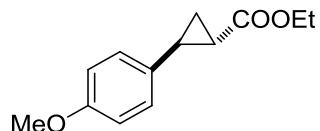
General procedure 2.4 (GP 2.4) for Cyclopropanation with Different Catalysts and Glycine Ethyl Ester Hydrochloride (Table 6): The catalyst was dissolved in *p*-methoxystyrene (29.5 μ L, 0.22 mmol) in an open vial under air. To this mixture was added glycine ethyl ester hydrochloride (61 mg, 0.44, 2.0 equiv.), water (1.0 mL) and acetic acid (2.0 mg, 0.033 mmol, 0.15 equiv.). To this vigorously stirred heterogeneous mixture was added $NaNO_2$ (36 mg, 0.53 mmol, 2.4 equiv.) in one

²⁰² This product has been previously reported: M. Ratier, M. Pereyre, A. G. Davies, R. Sutcliffe, *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907.

portion at 40 °C. After 14 h, the mixture was diluted with water, extracted with CH₂Cl₂ (3x), dried over MgSO₄ and evaporated in vacuo. The crude product was then analyzed by ¹H-NMR analysis to determine the conversion and the dr.

General procedure 2.5 (GP 2.5) for Cyclopropanation with Fe(TPP)Cl and Glycine Ethyl Ester Hydrochloride (Table 7): FeTPP¹Cl (7.0 mg, 0.01 mmol, 1 mol%) was dissolved in the substrate (1.0 mmol) in an open vial under air. In cases where solid substrates were used, a minimum amount of toluene was added. To this mixture was then added glycine ethyl ester hydrochloride (279 mg, 2.0 mmol, 2.0 equiv.), water (5.0 mL) and acetic acid (10.0 mg, 0.15 mmol, 0.15 equiv.). To this vigorously stirred heterogeneous mixture was added NaNO₂ (166 mg, 2.4 mmol, 2.4 equiv.) in one portion at 40 °C. After 14 h, the mixture was diluted with water, extracted with CH₂Cl₂ (3x), dried over MgSO₄ and evaporated in vacuo. The crude product was then analyzed by ¹H-NMR analysis to determine the conversion and the dr. It was further purified by flash chromatography to afford the pure *trans* product.

(1RS,2RS)-ethyl 2-(4-methoxyphenyl)cyclopropanecarboxylate (233, Table 7, Entry 1)



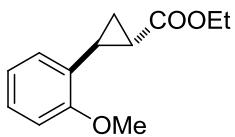
Was obtained as an oil (174 mg, 0.79 mmol, 79 %) following GP 2.5.

¹H-NMR (300 MHz, CDCl₃): δ = 7.06–7.00 (m, 2H), 6.84–6.80 (m, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.78 (s, 3H), 2.52–2.44 (m, 1H), 1.82 (ddd, *J* = 4.3, 5.3, 8.5 Hz, 1H), 1.59–1.51 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 1.26–1.21 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.5, 158.3, 132.0, 127.3, 113.9, 60.6, 55.3, 25.6, 23.9, 16.7, 14.3.

Spectral data are in accordance with the literature.²⁰³

²⁰³ L. Y. Huang, Y. Chen, G. Y. Gao, X. P. Zhang, *J. Org. Chem.* **2003**, 68, 8179.

(1RS,2RS)-ethyl 2-(2-methoxyphenyl)cyclopropanecarboxylate (234, Table 7, Entry 2)

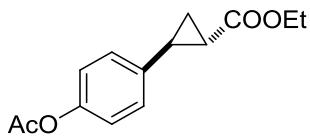
Was obtained as an oil (155 mg, 0.70 mmol, 70 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.18 (ddd, *J* = 8.1, 6.4, 2.8 Hz, 1H), 6.91–6.77 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 2.74 (ddd, *J* = 9.2, 6.8, 4.4 Hz, 1H), 1.85 (ddd, *J* = 8.3, 5.2, 4.4 Hz, 1H), 1.55 (ddd, *J* = 9.3, 5.2, 4.3 Hz, 1H), 1.32–1.27 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.9, 158.3, 128.4, 127.5, 125.9, 120.4, 110.4, 60.5, 55.5, 22.7, 21.2, 15.8, 14.3.

HRMS (EI): calcd for C₁₃H₁₆O₃⁺ (M⁺) 220.1094, found 220.1092.

IR (neat): 2980, 1719, 1497, 1246, 1178.

(1RS,2RS)-ethyl 2-(4-acetoxyphenyl)cyclopropanecarboxylate (235, Table 7, Entry 3)

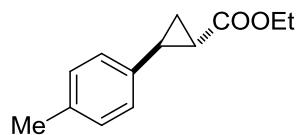
Was obtained as an oil (168 mg, 0.68 mmol, 68 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.11 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.51 (m, 1H), 2.29 (s, 3H), 1.87 (m, 1H), 1.59 (m, 1H), 1.25, (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.2, 169.6, 149.1, 137.7, 127.2, 121.5, 60.7, 25.6, 24.1, 21.1, 16.9, 14.2.

Spectral data are in accordance with the literature²⁰³

(1RS,2RS)-ethyl 2-(p-tolyl)cyclopropanecarboxylate (236, Table 7, Entry 4)



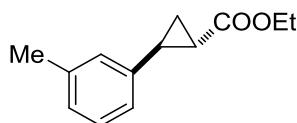
Was obtained as an oil (151 mg, 0.74 mmol, 74 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.11 (d, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 4.19 (q, *J* = 7.2 Hz, 2H), 2.51 (ddd, *J* = 9.3, 6.3, 4.2 Hz, 1H), 2.33 (s, 3H), 1.88 (ddd, *J* = 8.4, 5.1, 4.2 Hz, 1H), 1.59 (ddd, *J* = 9.0, 5.4, 4.5 Hz, 1H), 1.26-1.36 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.5, 137.0, 136.0, 129.1, 126.0, 60.6, 25.9, 24.0, 20.9, 16.9, 14.2.

Spectral data are in accordance with the literature.²⁰³

(1RS,2RS)-ethyl 2-(m-tolyl)cyclopropanecarboxylate (237, Table 7, Entry 5)



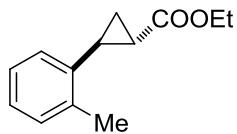
Was obtained as an oil (130 mg, 0.64 mmol, 64 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.23–6.92 (m, 4H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.52 (ddd, *J* = 9.3, 6.3, 4.2 Hz, 1H), 2.36 (s, 3H), 1.93 (ddd, *J* = 8.4, 5.1, 3.9 Hz, 1H), 1.62 (m, 1H), 1.28-1.39 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.4, 140.0, 138.0, 128.3, 127.2, 126.9, 123.1, 60.6, 26.1, 24.1, 21.3, 17.0, 14.2.

Spectral data are in accordance with the literature.²⁰³

(1RS,2RS)-ethyl 2-(o-tolyl)cyclopropanecarboxylate (238, Table 7, Entry 6)



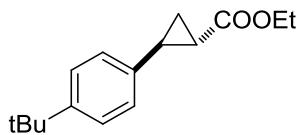
Was obtained as an oil (126 mg, 0.62 mmol, 62 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.22–7.00 (m, 4H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.54 (ddd, *J* = 9.0, 6.6, 4.2 Hz), 2.41 (s, 3H), 1.81 (m, 1H), 1.60 (m, 1H), 1.24–1.40 (m, 1H), 1.32 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.8, 137.9, 137.8, 129.8, 126.6, 125.8, 60.6, 24.6, 22.3, 19.5, 15.3, 14.3.

Spectral data are in accordance with the literature.²⁰³

(1RS,2RS)-ethyl 2-(4-(tert-butyl)phenyl)cyclopropanecarboxylate (239, Table 7, Entry 7)



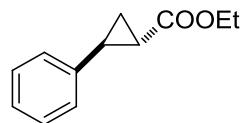
Was obtained as an oil (178 mg, 0.72 mmol, 72 %) following **GP 2.5** with glycine ethyl ester hydrochloride (3.0

¹H-NMR (300 MHz, CDCl₃): δ = 7.34 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 4.21 (q, *J* = 7.2 Hz, 2H), 2.54 (ddd, *J* = 9.0, 6.9, 4.5 Hz, 1H), 1.94 (ddd, *J* = 8.4, 5.1, 4.2 Hz, 1H), 1.63 (m, 1H), 1.34–1.38 (m, 1H), 1.35 (s, 9H), 1.32 (t, *J* = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.4, 149.3, 137.0, 125.7, 125.3, 60.5, 34.4, 31.3, 25.8, 24.1, 16.9, 14.2.

Spectral data are in accordance with the literature.²⁰³

(1RS,2RS)-ethyl 2-phenylcyclopropanecarboxylate (49 trans, Table 7, Entry 8)



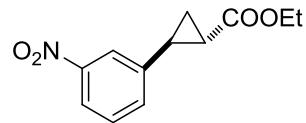
Was obtained as an oil (135 mg, 0.71 mmol, 71 %) following **GP 2.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.33–7.11 (m, 5H), 4.19 (q, J = 7.2 Hz, 2H), 2.52 (ddd, J = 9.6, 6.3, 4.5 Hz, 1H), 1.91 (m, 1H), 1.61 (m, 1H), 1.28–1.38 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.6, 140.4, 128.7, 126.7, 126.4, 60.9, 26.4, 24.4, 17.3, 14.5.

Spectral data are in accordance with the literature.²⁰³

(1RS,2RS)-ethyl 2-(3-nitrophenyl)cyclopropanecarboxylate (240, Table 7, Entry 9)



Was obtained as an oil (155 mg total, 83 % purity (17% diethyl maleate), 129 mg, 0.55 mmol, 55%) following **GP 2.5** with glycine ethyl ester hydrochloride (3.0 equiv.), NaNO₂ (3.6 equiv.) and FeTPPCl (1.5 mol%). The NaNO₂ was added as an aqueous solution over 10 h.

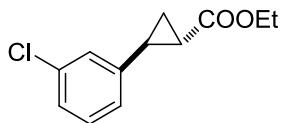
¹H-NMR (300 MHz, CDCl₃): 8.11–7.96 (m, 1H), 7.91 (dd, J = 1.4, 0.9 Hz, 1H), 7.43 (dt, J = 3.3, 0.9 Hz, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.60 (ddd, J = 9.6, 6.4, 4.2 Hz, 1H), 1.96 (dddd, J = 8.5, 5.2, 4.2, 0.9 Hz, 1H), 1.84–1.59 (m, 1H), 1.41–1.33 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 172.6, 148.5, 142.4, 132.7, 129.4, 121.5, 120.9, 61.02, 25.4, 24.5, 17.1, 14.2.

HRMS (EI): calcd for C₁₂H₁₃NO₄⁺ (M⁺) 235.0839, found 235.0843.

IR (neat): 2983, 1720, 1528, 1348, 1179.

(1RS,2RS)-ethyl 2-(3-chlorophenyl)cyclopropanecarboxylate (241, Table 7, Entry 10)



Was obtained as an oil (150 mg, 0.67 mmol, 67 %) following **GP 2.5** following the general procedure with glycine ethyl ester hydrochloride (4.0 equiv.), NaNO₂ (4.8 equiv.).

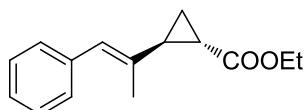
¹H-NMR (300 MHz, CDCl₃): δ = 7.24–7.11 (m, 2H), 7.06 (dd, *J* = 2.9, 0.8 Hz, 1H), 6.98 (dt, *J* = 6.8, 1.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.48 (ddd, *J* = 9.2, 6.5, 4.2 Hz, 1H), 1.90 (ddd, *J* = 8.5, 5.4, 4.2 Hz, 1H), 1.67–1.51 (m, 1H), 1.32–1.26 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 173.0, 142.3, 134.4, 129.7, 126.7, 126.4, 124.5, 60.9, 25.6, 24.2, 17.0, 14.3.

HRMS (EI): calcd for C₁₂H₁₃ClO₂⁺ (M⁺) 224.0599, found 224.0599.

IR (neat): 2981, 1720, 1325, 1178, 779.

(1RS,2RS)-ethyl 2-((E)-1-phenylprop-1-en-2-yl)cyclopropanecarboxylate (242, Table 7, Entry 11))



Was obtained as an oil (89 mg, 0.39 mmol, 39 %) following **GP 2.5** with glycine ethyl ester hydrochloride (3.0 equiv.), NaNO₂ (3.6 equiv.) and FeTPPCL (1.5 mol%). The NaNO₂ was added as an aqueous solution over 10 h.

¹H-NMR (300 MHz, CDCl₃): δ = 7.36–7.27 (m, 2H), 7.25–7.14 (m, 3H), 6.39 (s, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.43–1.99 (m, 1H), 1.81 (ddd, *J* = 8.5, 5.1, 4.4 Hz, 1H), 1.76 (d, *J* = 1.3 Hz, 1H), 1.37 (dd, *J* = 9.1, 4.5 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.25–1.17 (m, 1H).

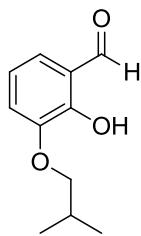
¹³C-NMR (100 MHz, CDCl₃): δ = 173.9, 137.8, 135.8, 128.8, 128.1, 126.2, 125.9, 60.6, 30.7, 20.4, 15.5, 14.3, 14.0.

HRMS (EI): calcd for C₁₅H₁₈O₂⁺ (M⁺) 230.1302, found 230.1299.

IR (neat): 2981, 1720, 1318, 1175, 697.

8.2. Experimental Part to Chapter 3

2-hydroxy-3-isobutoxybenzaldehyde (243)



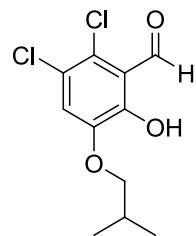
NaH (0.700 g, 29.2 mmol) was suspended in dry DMSO (25 mL). To this suspension a DMSO-solution of 2,3-dihydroxybenzaldehyde (**148**, 2.00 g, 14.5 mmol) was slowly added at RT. The resulting mixture was stirred for 3 h at room-temperature, and isobutyl bromide (1.98 g, 14.5 mmol) was added slowly. Stirring was continued for 24 h at RT. The reaction mixture was then quenched by slow addition of NH₄Cl and extracted with CH₂Cl₂ (3x). Drying over MgSO₄, followed by evaporation of the solvent and column chromatography (Hexane/ CH₂Cl₂ 1:1) afforded the pure product (1.90 g, 68 %) as a yellow oil.

¹H-NMR (300 MHz, CDCl₃): δ = 10.96 (s, 1H), 9.88 (s, 1H), 7.25–6.85 (m, 3H), 3.78 (d, *J* = 6.9 Hz, 2H), 2.25-2.20 (m, 1H), 1.03 (d, *J* = 4.5 Hz, 6H).

¹³C-NMR (100 MHz, CDCl₃): δ = 196.4, 152.7, 148.4, 124.3, 121.6, 119.8, 119.5, 75.3, 28.2, 19.2.

HRMS (EI): calcd for C₁₁H₁₄O₃⁺ (M)⁺ 194.0938, found 194.0937.

IR (neat): 3352, 1655, 1256, 631.

2,3-dichloro-6-hydroxy-5-isobutoxybenzaldehyde (244)

2-hydroxy-3-isobutoxybenzaldehyde (1.0 g, 5.2 mmol) was dissolved in acetic acid (20 mL) and NCS (1.4 g, 11 mmol) was added all at once. The reaction mixture was stirred overnight at 80 °C, then cooled to room temperature. Water and CH₂Cl₂ were then added, the phases were separated and the water phase was further extracted with CH₂Cl₂, dried over MgSO₄ and evaporated under vacuo. The crude product was purified by flash chromatography (CH₂Cl₂/hexane) to afford the pure product (1.2 g, 89 %) as a yellow solid.

¹H-NMR (300 MHz, CDCl₃): δ = 12.27 (s, 1H), 10.39 (s, 1H), 7.09 (s, 1H), 3.76 (d, *J* = 6.6 Hz, 2H), 2.25-2.20 (m, 1H), 1.03 (d, *J* = 4.5 Hz, 6H).

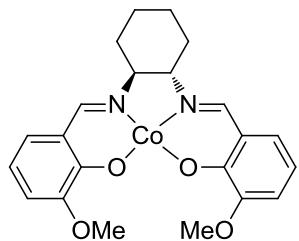
¹³C-NMR (100 MHz, CDCl₃): δ = 195.9, 153.8, 147.6, 125.4, 122.9, 120.0, 117.0, 76.1, 28.1, 19.1.

HRMS (EI): calcd for C₁₁H₁₂Cl₂O₃⁺ (M)⁺ 262.0158, found 262.0158.

IR (neat): 3262, 1626, 1296, 1173, 980, 631.

MP: 90 °C

General Procedure (GP 3.1) for the condensation/complex formation of cobalt-salen catalysts: The corresponding salicylaldehyde (2 equiv) and (*S,S*)-cyclohexyldiamine (1 equiv.) were dissolved in ethanol (0.1 M) and stirred for 8 h. The mixture was then degassed by purging with Argon for 15 min. Dry Co(OAc)₂ (1.1 equiv.) was added and the mixture was refluxed overnight, while precipitation of the product occurred. The product was filtered and washed with cold ethanol until the filtrate became colorless, and the collected solid was dried 12 h under vacuo affording the pure complex.

(S,S)-134

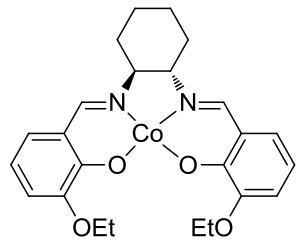
Prepared following **GP 3.1** from 2-hydroxy-3-methoxybenzaldehyde (152 mg, 1.00 mmol). Brown solid (150 mg, 68 %).

Elemental analysis: calcd for $C_{22}H_{24}CoN_2O_4$: C 60.14, H 5.51, N 6.38 Found: C 59.36, H 5.75, N 6.30.

HRMS (MALDI): calcd for $C_{22}H_{24}CoN_2O_4Na^+$ ($M+Na$)⁺ 462.0960, found 462.0968.

IR (neat): 2907, 2359, 1597, 1538, 1318, 982, 720.

MP: >300 °C

(S,S)-135

Prepared following **GP 3.1** from 2-hydroxy-3-ethoxybenzaldehyde (166 mg, 1.00 mmol). Brown solid (165 mg, 71 %).

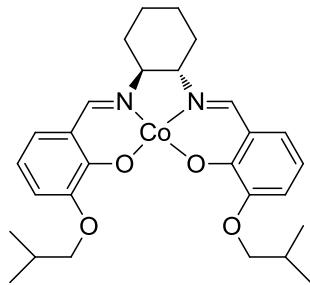
Elemental analysis: calcd for $C_{24}H_{28}CoN_2O_4$: C 61.67, H 6.04, N 5.99 Found: C 61.47, H 6.17, N 5.98.

HRMS (MALDI): calcd for $C_{24}H_{28}CoN_2O_4Na^+$ ($M+Na$)⁺ 490.1273, found 490.1273.

IR (neat): 2907, 2348, 1594, 1537, 1318, 1120, 982, 721.

MP: >300 °C

(S,S)-142



Prepared following **GP 3.1** from 2-hydroxy-3-isobutyloxybenzaldehyde (194 mg, 1.00 mmol). Brown solid (146 mg, 56 %).

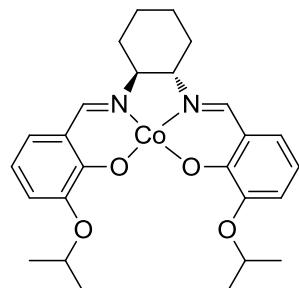
Elemental analysis: calcd for C₂₈H₃₆CoN₂O₄: C 64.24, H 6.93, N 5.35 Found: C 63.65, H 7.03, N 5.35.

HRMS (MALDI): calcd for C₂₈H₃₆CoN₂O₄Na⁺ (M+Na)⁺ 546.1899, found 546.1905.

IR (neat): 2907, 2284, 1601, 1316, 1153, 993, 721.

MP: >300 °C

(S,S)-143



a) NaH (0.700 g, 29.2 mmol) was suspended in dry DMSO (25 mL). To this suspension a DMSO-solution of 2,3-dihydroxybenzaldehyde (2.00 g, 14.5 mmol) was slowly added at RT. The resulting mixture was stirred for 3 h at room-temperature, and 2-bromopropane (1.78 g, 14.5 mmol) was added slowly. Stirring was continued for 24 h at RT. The reaction mixture was then quenched by

slow addition of NH₄Cl and extracted with CH₂Cl₂ (3x). Drying over MgSO₄, followed by evaporation of the solvent and column chromatography (Hexane/ CH₂Cl₂ 1:1) afforded the pure product (1.75 g, 69 %) as a yellow oil.

b) **143** was prepared from the previous material according to **GP 3.1** (180 mg, 1.00 mmol) as a brown solid (180 mg, 72 %).

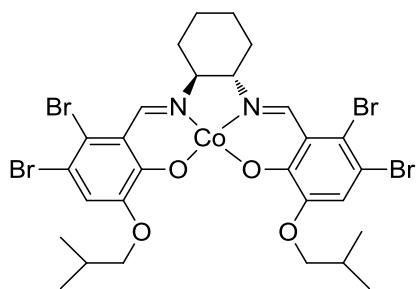
Elemental analysis: calcd for C₂₆H₃₂CoN₂O₄: C 63.03, H 6.51, N 5.65 Found: C 63.13, H 6.68, N 5.70.

HRMS (MALDI): calcd for C₂₆H₃₂CoN₂O₄⁺ (M)⁺ 495.1689, found 495.1683.

IR (neat): 2911, 2208 1609, 1154, 993, 825.

MP: >300 °C

(S,S)-146



2-hydroxy-3-isobutoxybenzaldehyde (250 mg, 1.3 mmol) was dissolved in acetic acid (5 mL) and Br₂ (200 µl, 3.9 mmol) was added all at once. The reaction mixture was stirred overnight at RT for 4 h. Water and ice were then added, and precipitation occurred. The solid was filtered and washed with water and hexanes to afford the product (283 mg, 0.8 mmol, 63%) as a yellow solid. Catalyst **146** was prepared from the previous material according to **GP 3.1** giving a brown solid (420 mg, 0.5 mmol, 63%).

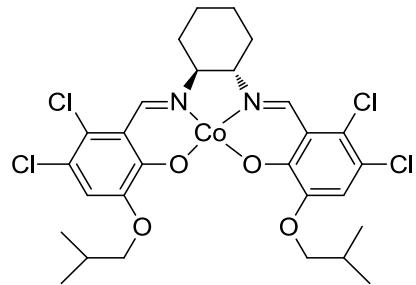
Elemental analysis: calcd for C₂₈H₃₂CoBr₄N₂O₄: C 40.08, H 3.84, N 3.34 Found: C 38.57, H 4.17, N 3.15.

HRMS (MALDI): calcd for C₂₈H₃₃CoN₂O₄Br₄⁺ (M+H)⁺ 835.8500, found 835.8502

IR (neat): 2910, 1610, 1319, 1145, 982, 819.

MP: >300 °C

(S,S)-147



Prepared following **GP 3.1** from 2,3-dichloro-6-hydroxy-5-isobutoxybenzaldehyde (753 mg, 2.86 mmol). Brown solid (757 mg, 80 %).

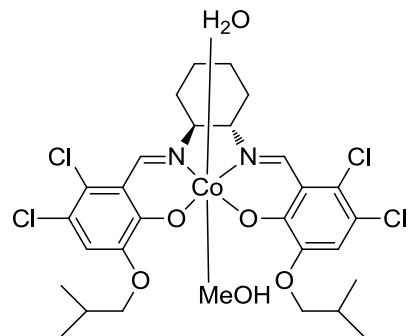
Elemental analysis: calcd for C₂₈H₃₂CoCl₄N₂O₄: C 64.24, H 6.93, N 5.35 Found: C 63.65, H 7.03, N 5.35.

HRMS (MALDI): calcd for C₂₈H₃₂CoN₂O₄Cl₄Na⁺ (M+Na)⁺ 682.0340, found 682.0340.

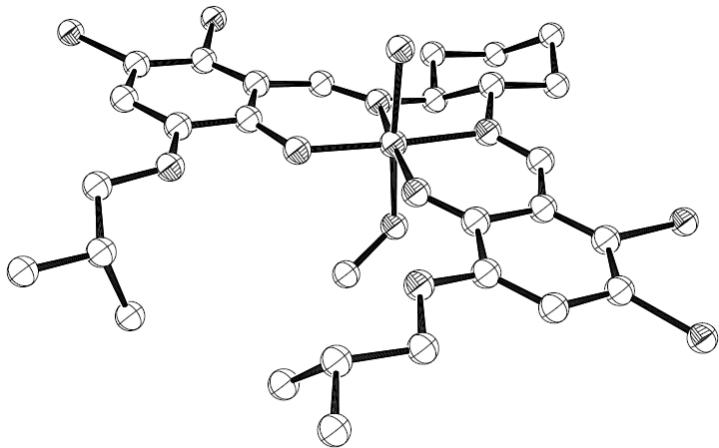
IR (neat): 2909, 2205, 1609, 1317, 1152, 995, 823.

MP: >300 °C

(S,S)-147 MeOH/H₂O solvate



Obtained by recrystallization of **147** from CH₂Cl₂/MeOH, affording a single amber crystal that was analyzed by X-ray crystallography. (**CCDC 783661**).

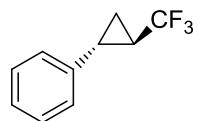


General procedure (GP 3.2) for cyclopropanation with different catalysts (Scheme 53, Figure 8-12, Table 8 and 9): Catalyst, additives and trifluoroethylamine hydrochloride (90 mg, 0.66 mmol) were dissolved in degassed water (1.8 mL). *p*-methoxystyrene (30 mg, 0.22 mmol, 1 equiv.) was then added and the reaction mixture was stirred for 5 minutes at the corresponding temperature. NaNO₂ was then added all at once and stirred 14 h or added via syringe pump addition over 14 h. The mixture was extracted with hexane (3 x), dried with MgSO₄ and directly submitted to SFC-analysis to determine the dr (not reported in the table, in all cases over 20:1), the ee and the conversion.

General procedure (GP 3.3) for asymmetric cyclopropanation with Catalyst 147: Catalyst 147 (14 mg, 22 µmol), AsPh₃ (13 mg, 44 µmol), NaOAc (3.6 mg, 44 µmol) and trifluoroethylamine hydrochloride (90 mg, 0.66 mmol) were dissolved in degassed, 20% NaCl solution (1.8 mL). Then H₂SO₄ (1.2 µL, 22 µmol) was added. The alkene (0.22 mmol) was subsequently added and the mixture stirred for 5 min at -15 °C, and NaNO₂ (54 mg, 0.70 mmol) was added all at once. After 14 hr, water was added and the aqueous phase was extracted with CH₂Cl₂ (3x), dried with MgSO₄ and evaporated under reduced pressure. After analysis of the crude NMR spectrum (to determine the diastereoselectivity by F¹⁹-NMR), the crude mixture was chromatographed on silica gel

(pentane/diethyl ether) to afford the pure product. The ee was then determined by SFC or HPLC analysis of the pure product.

(-)-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (216, Table 10, Entry 1)



Was obtained as an oil (33 mg, 81 %) following **GP 3.3**.

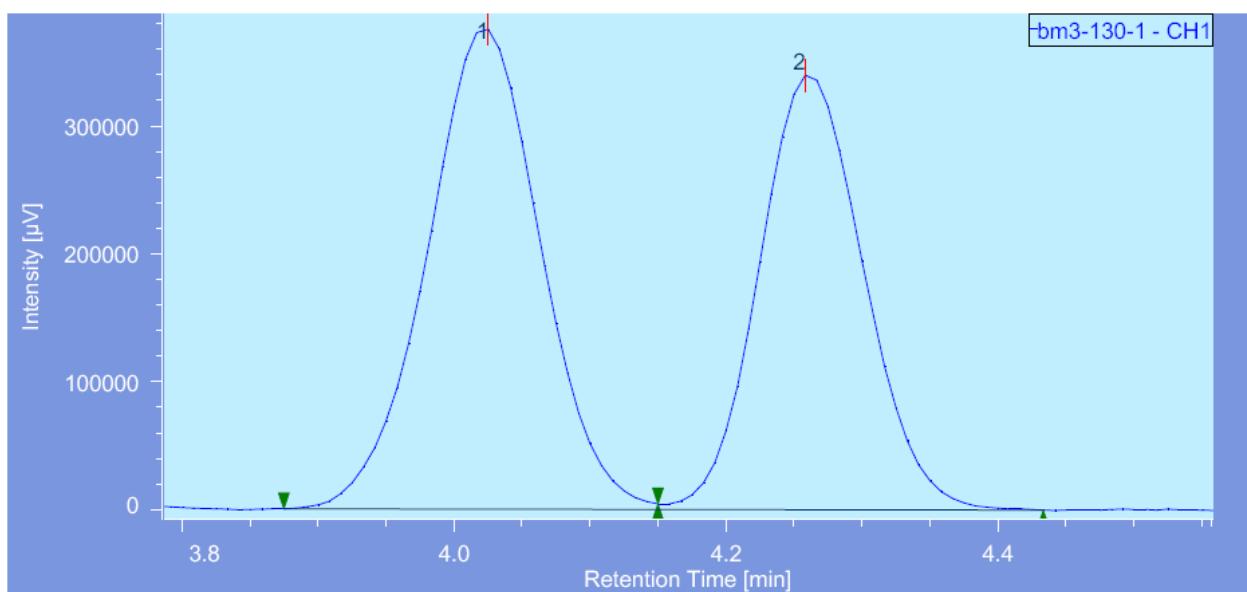
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.33\text{--}7.20$ (m, 3H), 7.15–7.10 (m, 2H), 2.38 (dt, $J = 9.6, 5.4$ Hz, 1H), 1.88–1.72 (m, 1H), 1.38 (dt, $J = 9.6, 5.7$ Hz, 1H), 1.22–1.12 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

a_D^{25} : -42 (c=1, CHCl_3).

SFC: 100 % CO_2 , 2 mL/min, OJ-H. **91 %ee.**

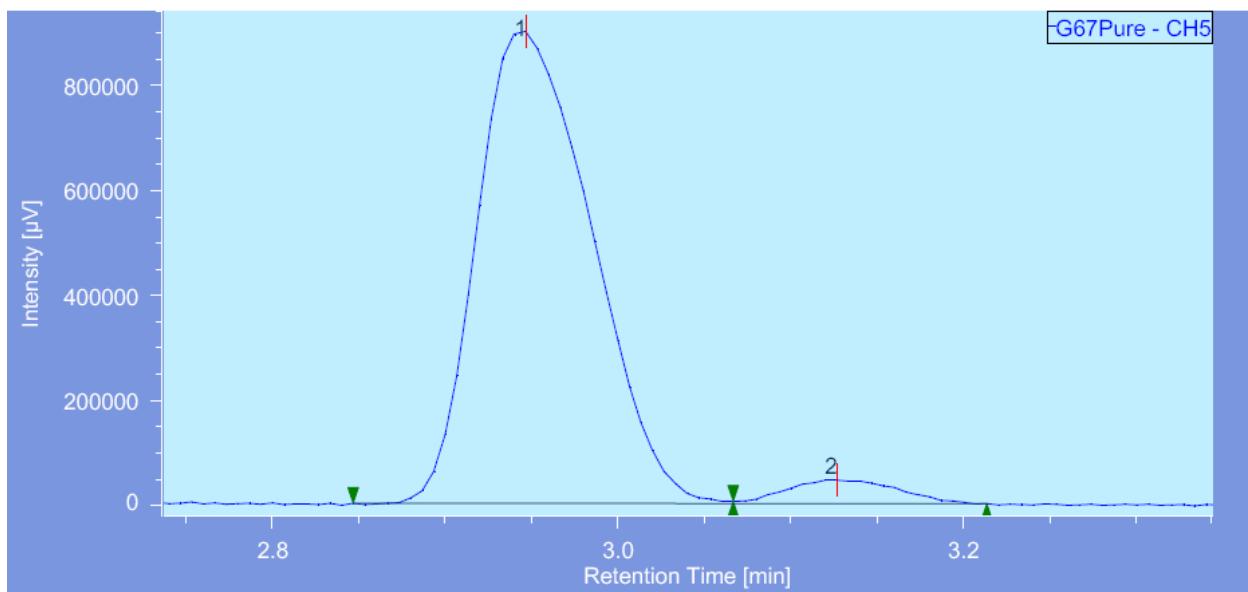
Racemic:



²⁰⁴ See Experimental Part, Part 2.

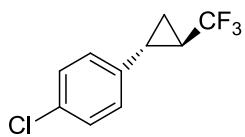
#	Peak Name	CH	tR [min]	Area [μ V·sec]	Height [μ V]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	4.025	2178493	374780	54.501	52.464	N/A	11286	1.593	0.970	
2	Unknown	1	4.258	1818649	339577	45.499	47.536	N/A	14378	N/A	1.121	

Enantioenriched:



#	Peak Name	CH	tR [min]	Area [μ V·sec]	Height [μ V]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	2.947	4139359	898360	95.397	95.294	N/A	8615	1.445	1.252	
2	Unknown	5	3.127	199733	44365	4.603	4.706	N/A	10364	N/A	N/A	

(-)-1-chloro-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (217, Table 10, Entry 2)



Was obtained as an oil (40 mg, 82 %) following **GP 3.3**.

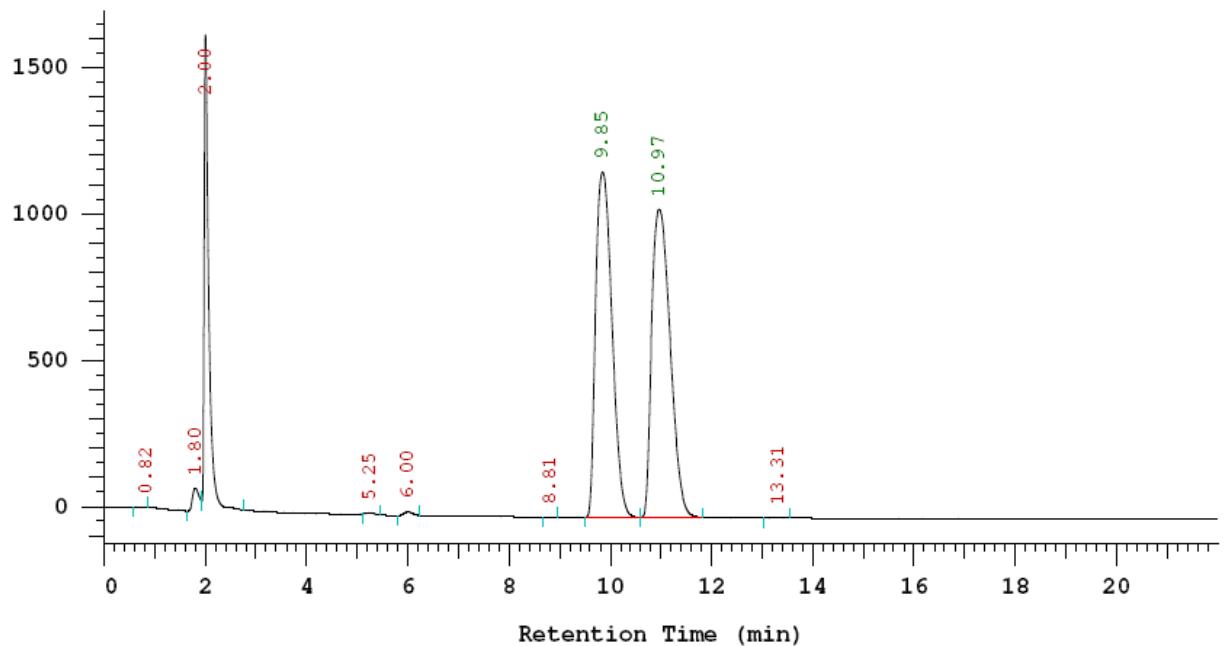
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.26$ (d, $J = 8.7$ Hz, 2H), 7.05 (d, $J = 8.7$ Hz, 2H), 2.37 (dt, $J = 9.6, 5.4$ Hz, 1H), 1.82–1.70 (m, 1H), 1.39 (dt, $J = 9.6, 5.7$ Hz, 1H), 1.18–1.10 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

$\alpha_D^{25} = -32$ ($c=1$, CHCl_3)

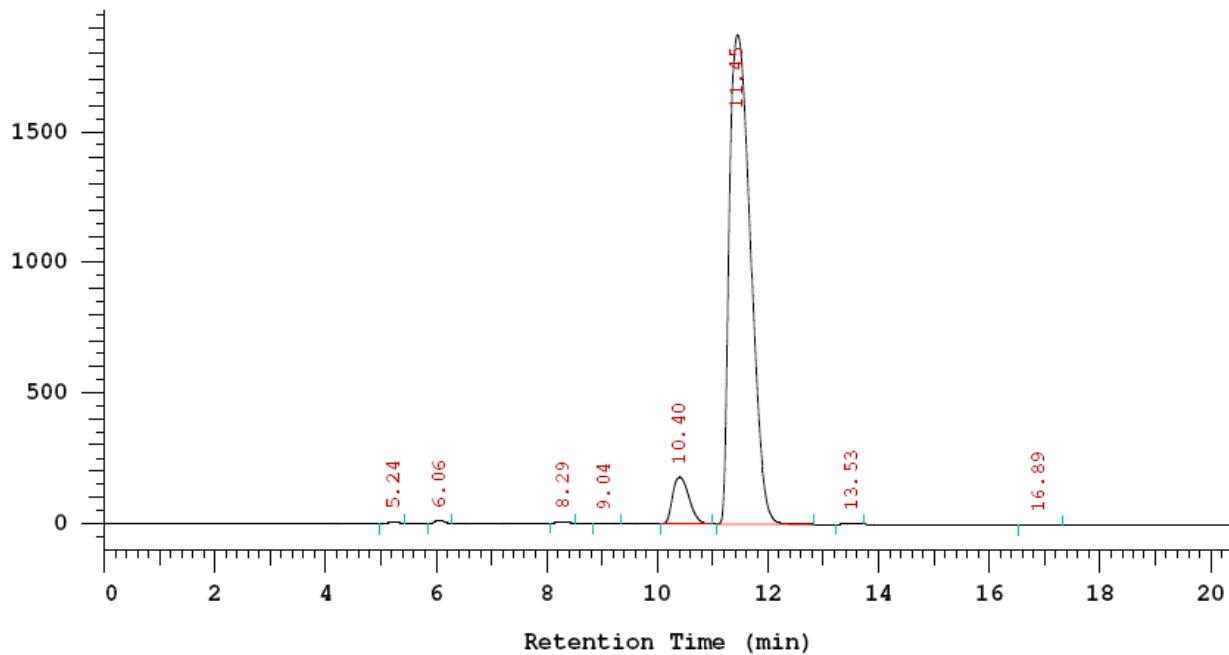
HPLC: 100 % hexane, 1 mL/min, OD-H long + OD-H short in sequence, 220 nm. **86 %ee.**

Racemic:



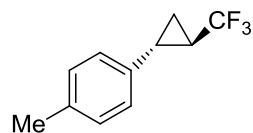
7	9.85	26224899	49.704
8	10.97	26537209	50.296

Enantioenriched:



5	10.40	3700107	6.940
6	11.45	49616297	93.060

(-)-1-methyl-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (218, Table 10, Entry 3)



Was obtained as an oil (40 mg, 91 %) following **GP 3.3**.

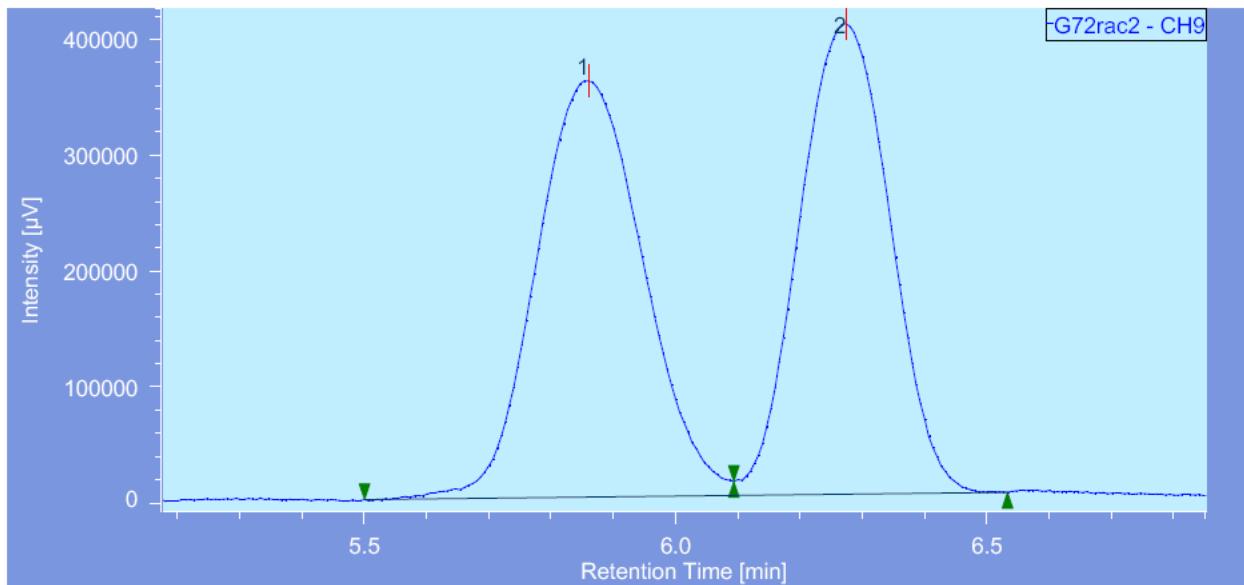
¹H-NMR (300 MHz, CDCl₃): δ = 7.12 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 8.1 Hz, 2H), 2.38–2.28 (m, 4H), 1.82–1.70 (m, 1H), 1.35 (dt, *J* = 9.3, 5.4 Hz, 1H), 1.20–1.10 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

α_D²⁵: -43 (c=1, CHCl₃)

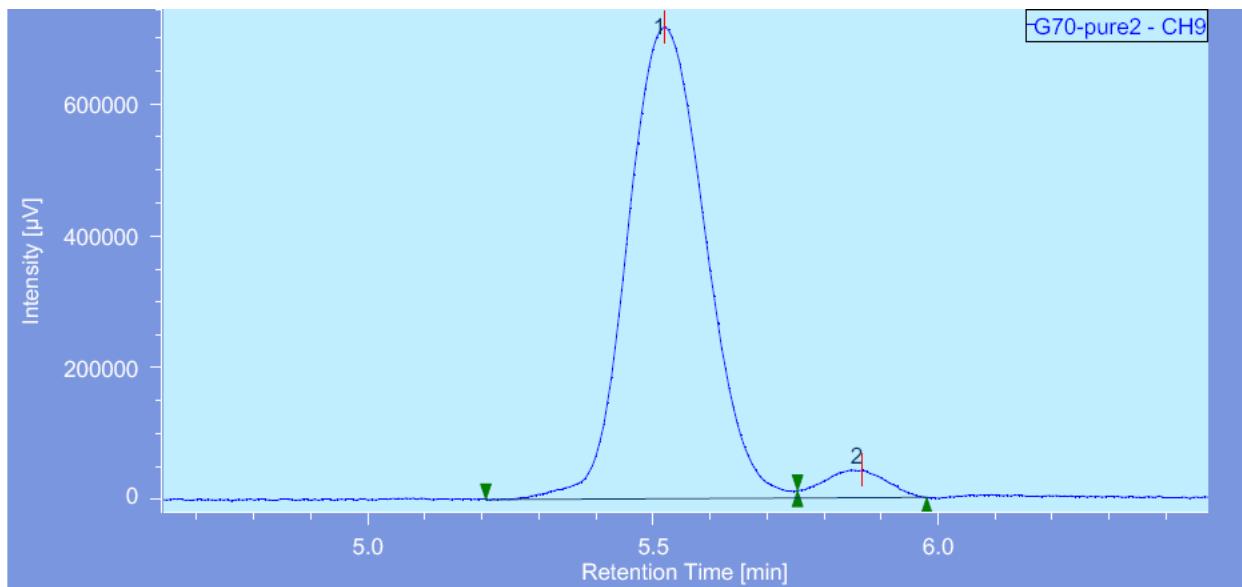
SFC: 100 % CO₂, 1 mL/min, OB-H. **91 %ee.**

Racemic:



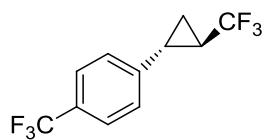
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
2	Unknown	9	5.860	4274122	358317	51.016	46.922	N/A	5367	1.390	1.097	
1	Unknown	9	6.273	4103832	405334	48.984	53.078	N/A	8238	N/A	1.011	

Enantioenriched:



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	5.520	6775134	714912	95.405	94.451	N/A	7658	1.473	1.109	
2	Unknown	9	5.867	326323	42000	4.595	5.549	N/A	11423	N/A	N/A	

(-) **1-(trifluoromethyl)-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (219, Table 10, Entry 4)**



Was obtained as an oil (41 mg, 73 %) following **GP 3.3**.

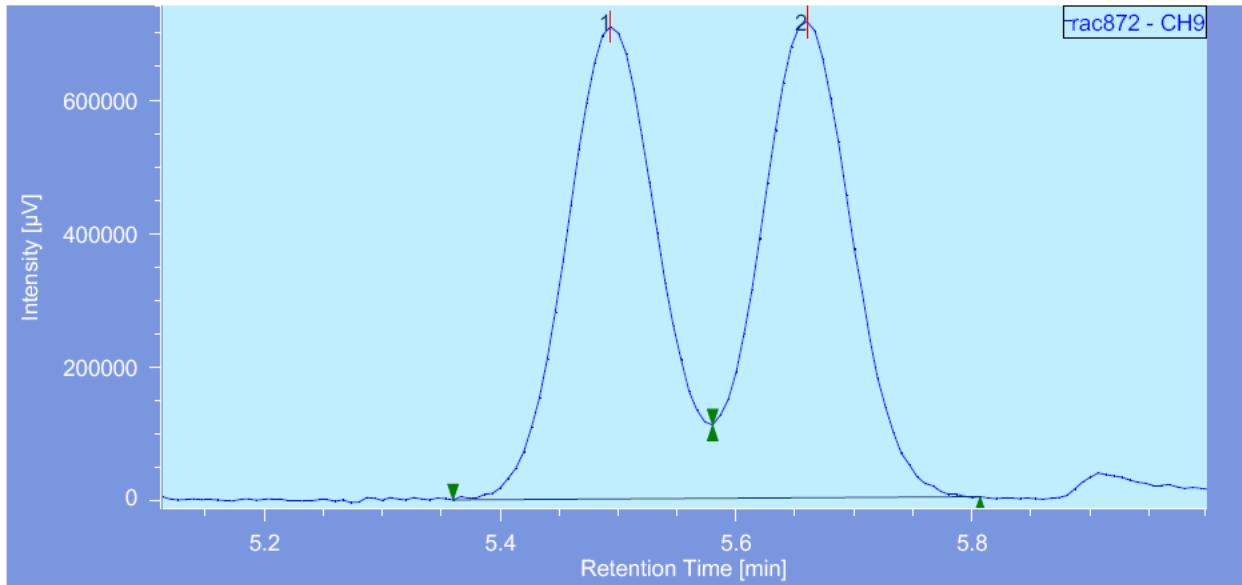
¹H-NMR (300 MHz, CDCl₃): δ = 7.55 (d, *J* = 8.1 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 2.41 (dt, *J* = 9.6, 5.4 Hz, 1H), 1.92–1.78 (m, 1H), 1.44 (dt, *J* = 9.9, 5.4 Hz, 1H), 1.26–1.18 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

a_D²⁵: -10 (c=0.75, CHCl₃)

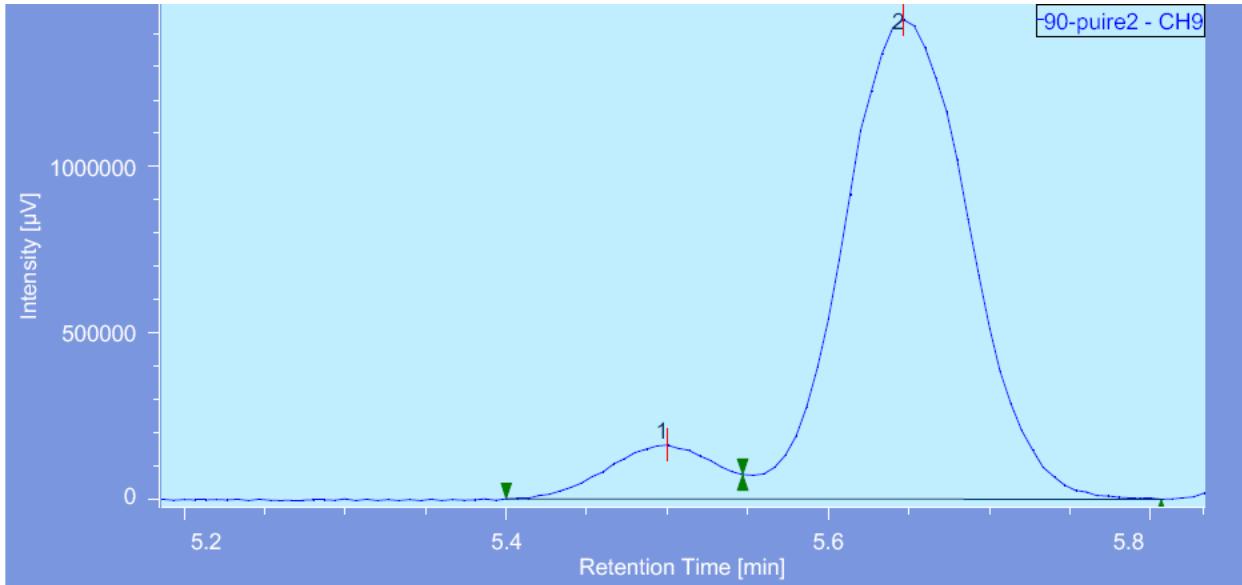
SFC: 100 % CO₂, 1 mL/min, OJ-H. **84 %ee.**

Racemic:

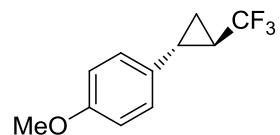


#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
2	Unknown	9	5.493	3819243	705872	49.737	49.797	N/A	23598	1.167	N/A	N/A
1	Unknown	9	5.660	3859567	711622	50.263	50.203	N/A	24901	N/A	N/A	N/A

Enantioenriched:



#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
2	Unknown	9	5.500	750976	162152	8.762	10.120	N/A	25399	1.043	N/A	N/A
1	Unknown	9	5.647	7819835	1440164	91.238	89.880	N/A	24594	N/A	N/A	N/A

(-) -1-methoxy-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (121, Table 10, Entry 5)

Was obtained as an oil (45 mg, 95 %) following **GP 3.3.**

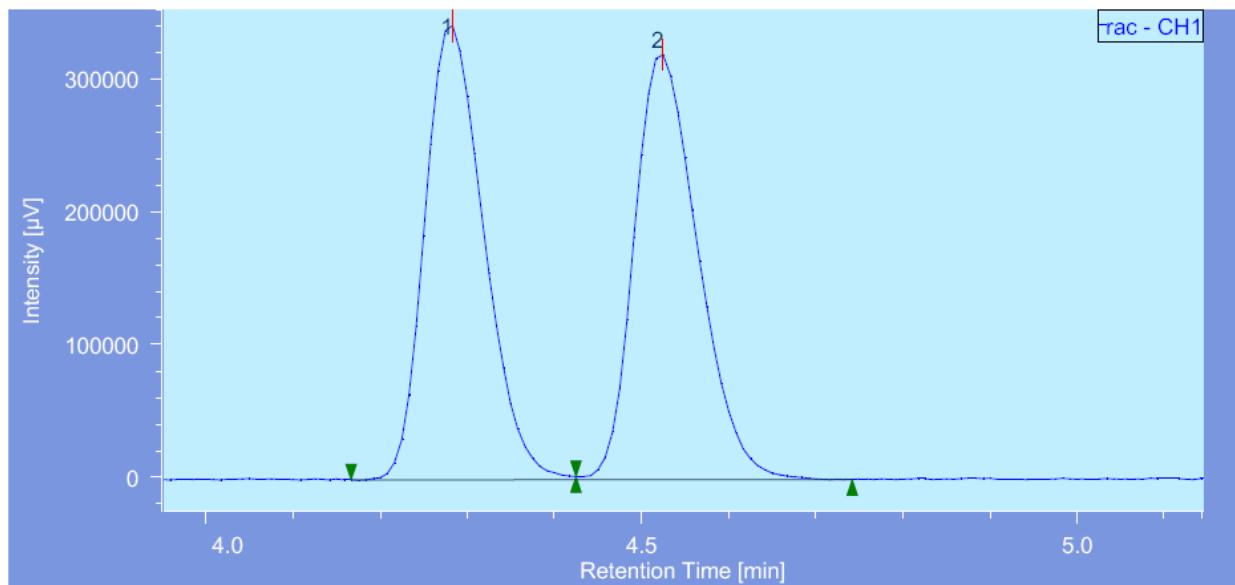
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.06$ (d, $J = 9.0$ Hz, 2H), 6.84 (d, $J = 9.0$ Hz, 2H), 3.79 (s, 3H), 2.32 (dt, $J = 9.3, 5.1$ Hz, 1H), 1.80–1.65 (m, 1H), 1.33 (dt, $J = 9.6, 5.4$ Hz, 1H), 1.15–1.05 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

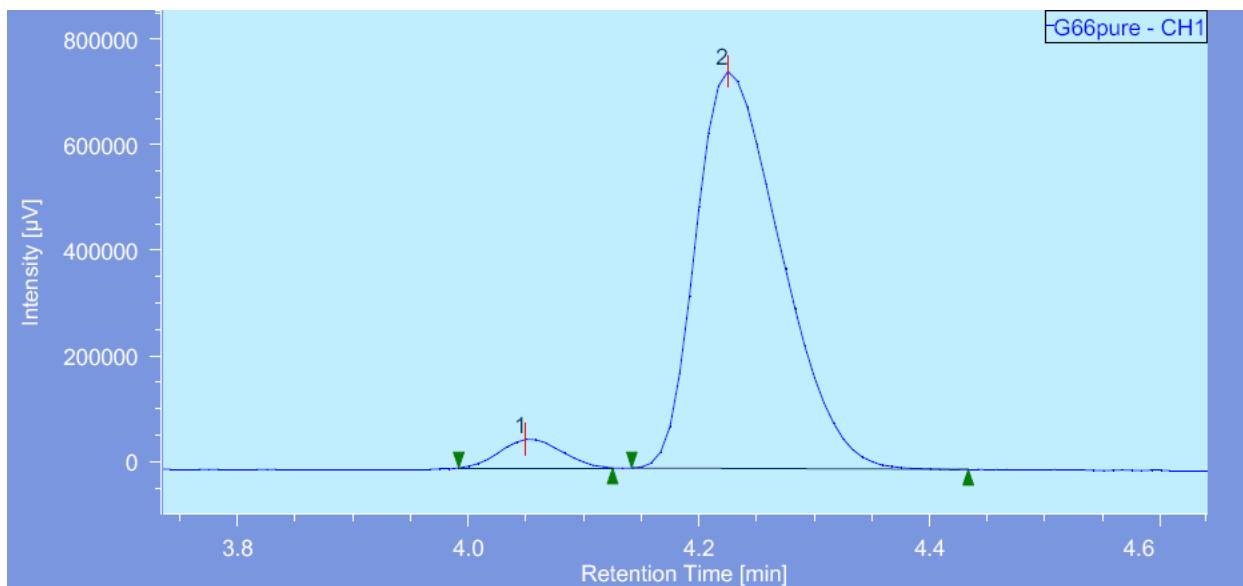
$\alpha_D^{25}:$ -35 (c=1, CHCl_3)

SFC: 100 % CO_2 , 2 mL/min, IB. **90 %ee.**

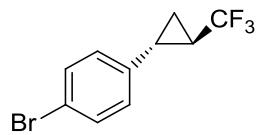
Racemic:



Enantioenriched:



(-)-1-bromo-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (221, Table 10, Entry 6)



Was obtained as an oil (49 mg, 84 %) following **GP 3.3**.

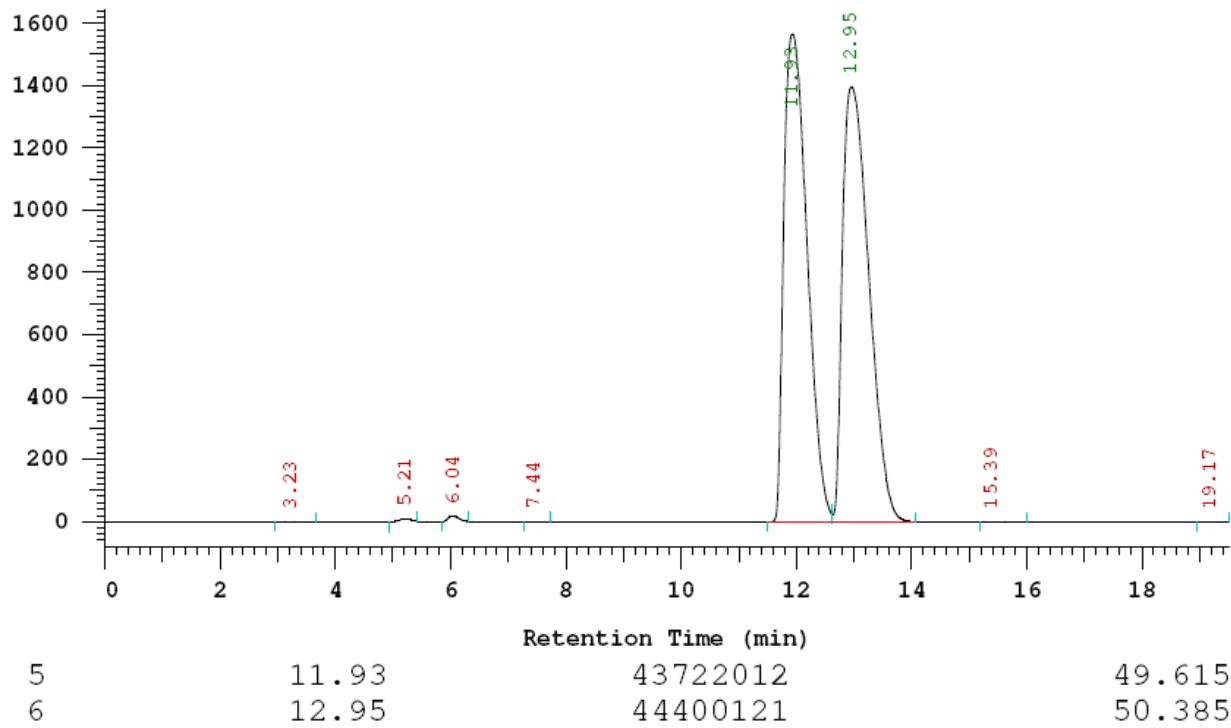
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.42$ (d, $J = 8.4$ Hz, 2H), 6.99 (d, $J = 8.4$ Hz, 2H), 2.32 (dt, $J = 9.3, 5.4$ Hz, 1H), 1.82–1.75 (m, 1H), 1.40 (dt, $J = 9.3, 5.4$ Hz, 1H), 1.20–1.10 (m, 1H).

Spectral data are in accordance with the literature.²⁰⁴

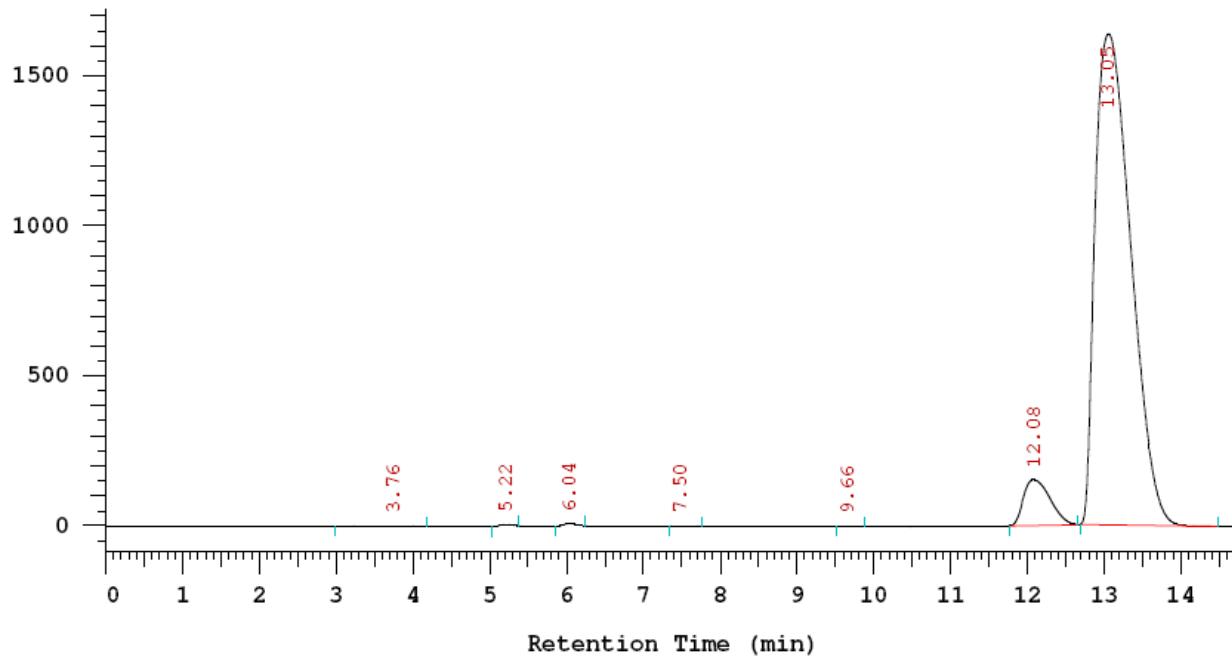
$\alpha_D^{25} = -28$ ($c=1$, CHCl_3)

HPLC: 100 % hexane, 1 mL/min, OD-H long and OD-H short in sequence, 220 nm. **87 %ee.**

Racemic:

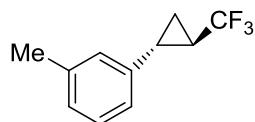


Enantioenriched:



6	12.08	3683714	6.534
7	13.05	52691177	93.466

(-)-1-methyl-3-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (245, Table 10, Entry 7)



Was obtained as an oil (40 mg, 91 %) following **GP 3.3**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.23–6.90 (m, 4H), 2.35–2.30 (m, 4H), 1.85–1.75 (m, 1H), 1.36 (dtd, *J* = 9.5, 5.6, 0.5 Hz, 1H), 1.20–1.13 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 140.0, 139.3, 128.5, 127.5, 127.3, 126.0 (q, *J* = 269 Hz), 123.4, 23.0 (q, *J* = 36 Hz), 21.4, 19.5 (q, *J* = 2 Hz), 10.8 (q, *J* = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.7 (d, *J* = 6.7 Hz).

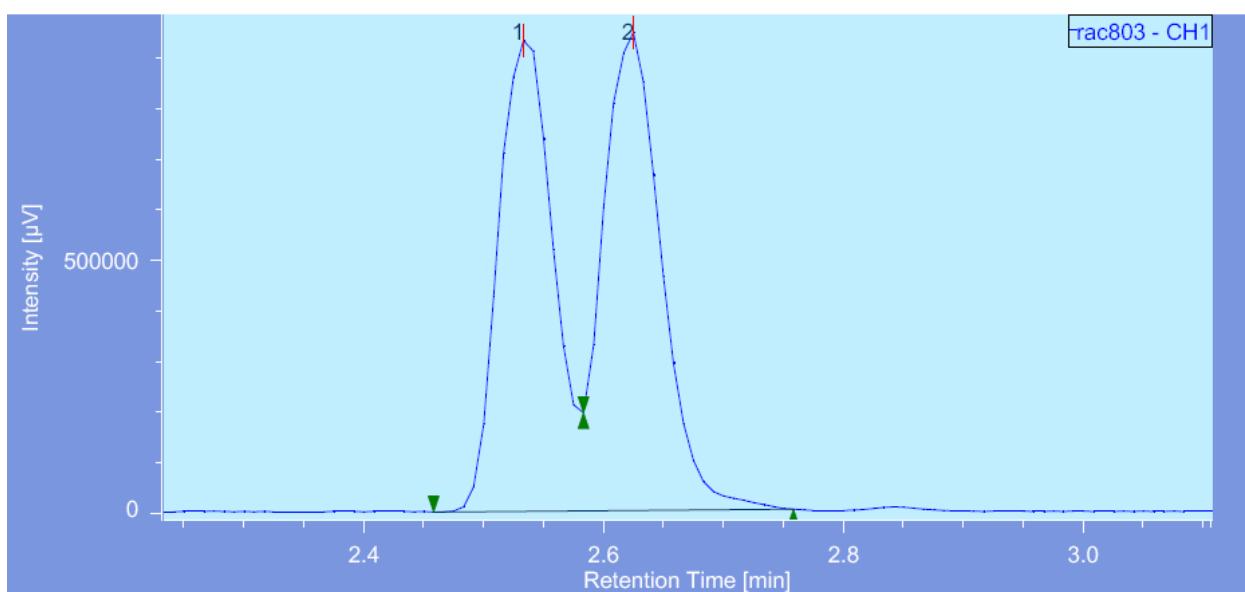
HRMS (EI): calcd for C₁₁H₁₁F₃⁺ (M)⁺ 200.0808, found 200.0811.

IR (neat): 3053, 1467, 1335, 1267, 1131, 697.

α_D²⁵: -28 (c=1, CHCl₃)

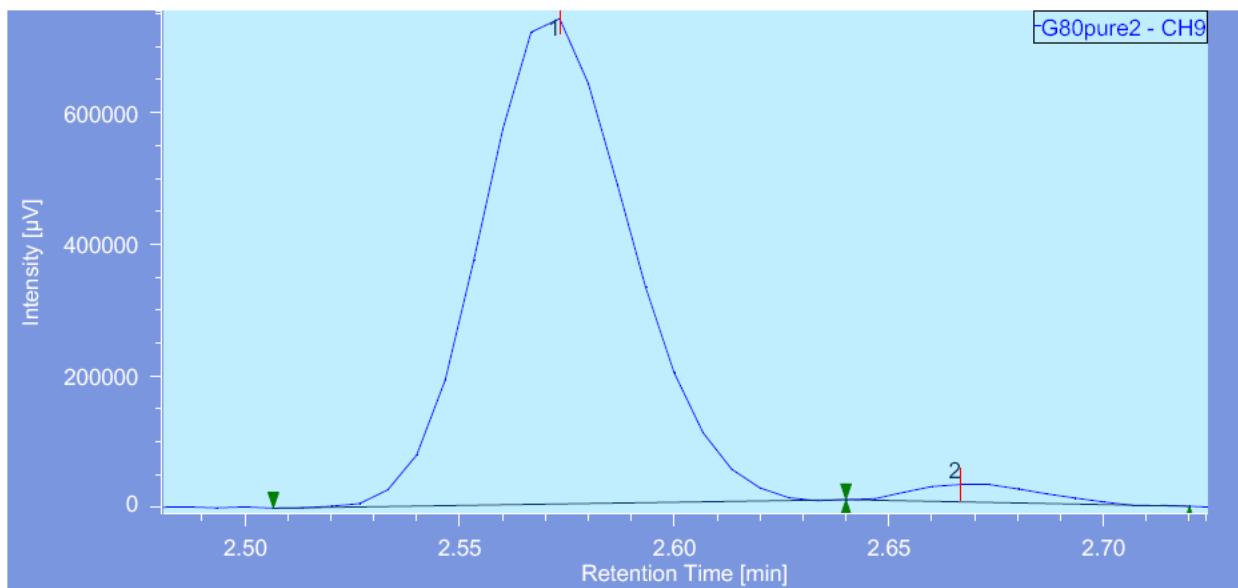
SFC: 100 % CO₂, 2 mL/min, IA. **94 %ee.**

Racemic:



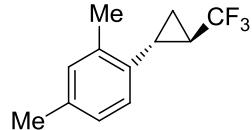
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
2	Unknown	1	2.533	2981003	931513	48.164	49.622	N/A	13603	1.034	N/A	
1	Unknown	1	2.625	3208334	945710	51.836	50.378	N/A	13319	N/A	N/A	

Enantioenriched:



#	Peak Name	CH	tR [min]	Area [$\mu\text{V}\cdot\text{sec}$]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	2.573	1808362	736632	96.994	96.563	N/A	24844	1.504	1.056	
2	Unknown	9	2.667	56036	26215	3.006	3.437	N/A	32412	N/A	1.312	

(-)2,4-dimethyl-1-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (246, Table 10, Entry 8)



Was obtained as an oil (44 mg, 93 %) following **GP 3.3**.

¹H-NMR (300 MHz, CDCl₃): $\delta = 7.03\text{--}6.88$ (m, 3H), 2.39 (s, 3H), 2.35–2.25 (m, 4H), 1.75–1.60 (m, 1H), 1.33 (dtd, $J = 9.5, 5.4, 0.5$ Hz, 1H), 1.20–1.12 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): $\delta = 137.9, 136.7, 133.7, 130.9, 126.5, 126.3$ (q, $J = 269$ Hz), 126.3, 21.8 (q, $J = 36$ Hz), 20.9, 19.3, 17.8 (q, $J = 2$ Hz), 9.1 (q, $J = 2$ Hz).

¹⁹F-NMR (282 MHz, CDCl₃): $\delta = -66.3$ (d, $J = 6.8$ Hz).

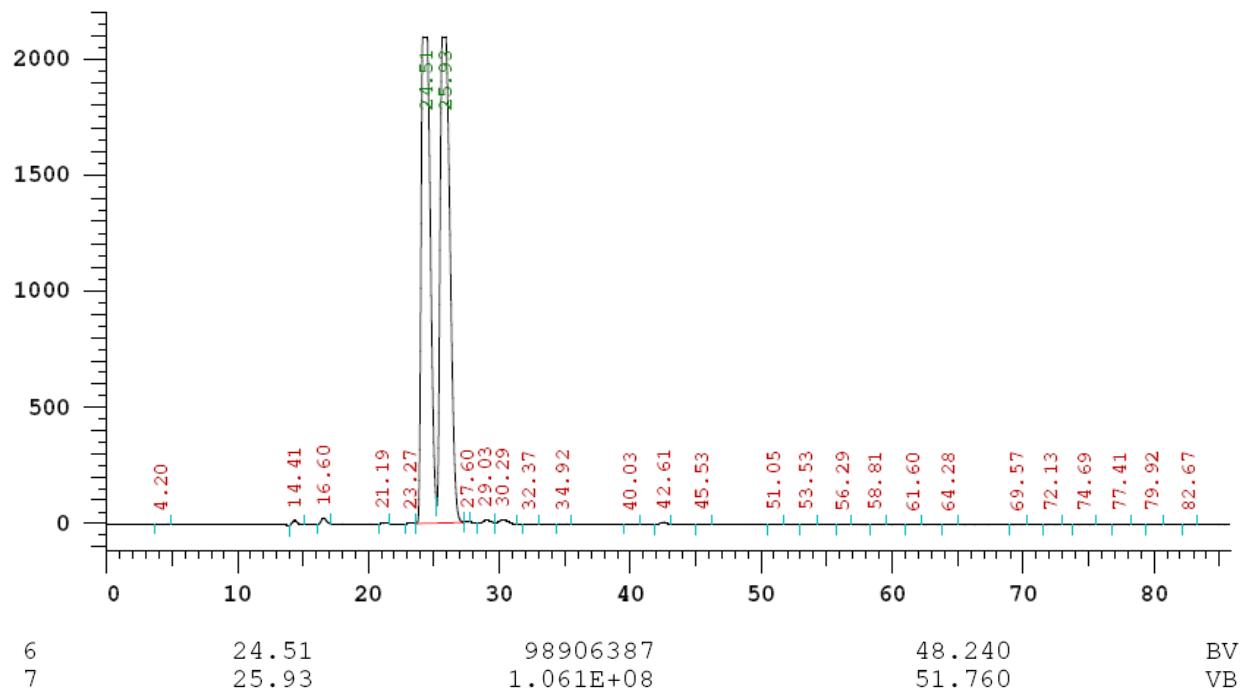
HRMS (EI): calcd for C₁₂H₁₃F₃⁺ (M)⁺ 214.0964, found 214.0967.

IR (neat): 3053, 2564, 1465, 1417, 1265, 1131, 815, 697.

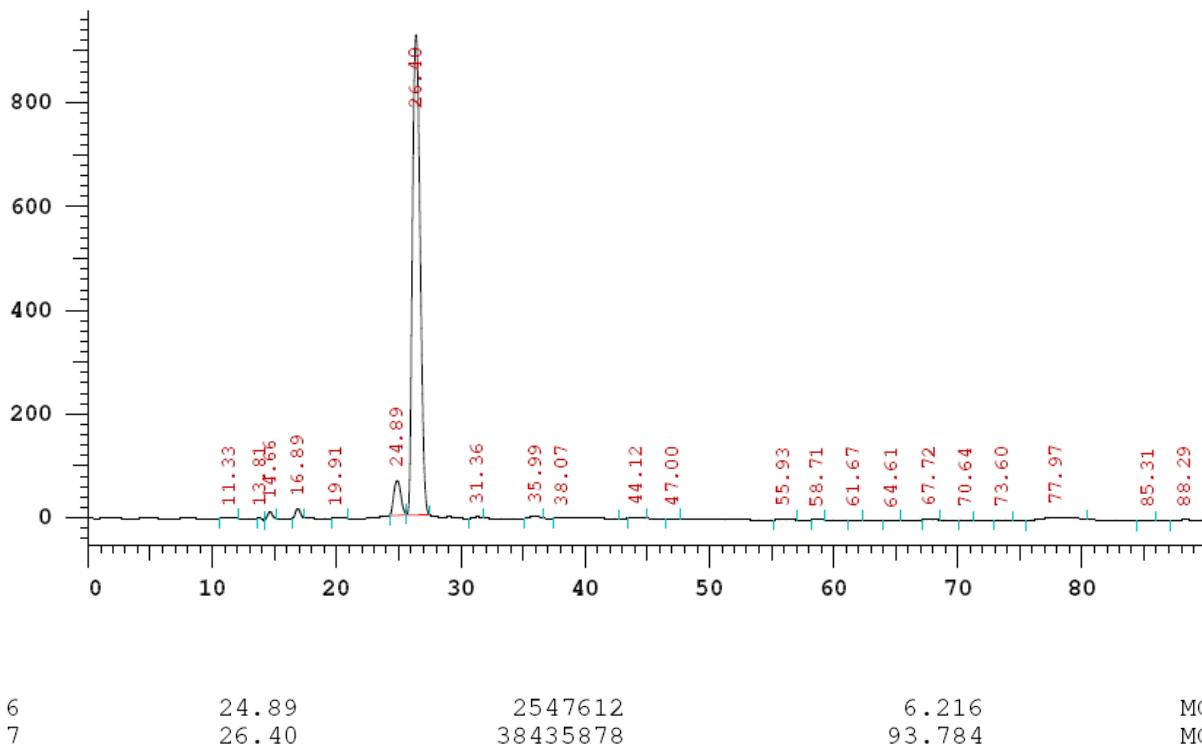
α_D^{25} : -13 (c=1, CHCl₃). **88 %ee.**

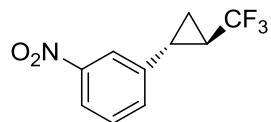
HPLC: 100 % hexane, 0.5 mL/min, OD-H long, OD-H short and another OD-H short in sequence, 220 nm.

Racemic:



Enantioenriched:



(-)-1-nitro-3-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (247, Table 10, Entry 9)

Was obtained as an oil (25 mg, 49 %) following **GP 3.3**.

¹H-NMR (300 MHz, CDCl₃): δ = 8.15–8.05 (m, 1H), 7.97–7.94 (m, 1H), 7.50–7.45 (m, 2H), 2.51–2.41 (m, 1H), 1.97–1.82 (m, 1H), 1.50 (dt, *J* = 9.5, 5.8 Hz, 1H), 1.32–1.23 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 148.5, 141.2, 133.0, 129.6, 125.4 (q, *J* = 269 Hz), 121.9, 121.3, 23.5 (q, *J* = 37 Hz), 19.3 (q, *J* = 2 Hz), 11.2 (q, *J* = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.9 (d, *J* = 6.4 Hz).

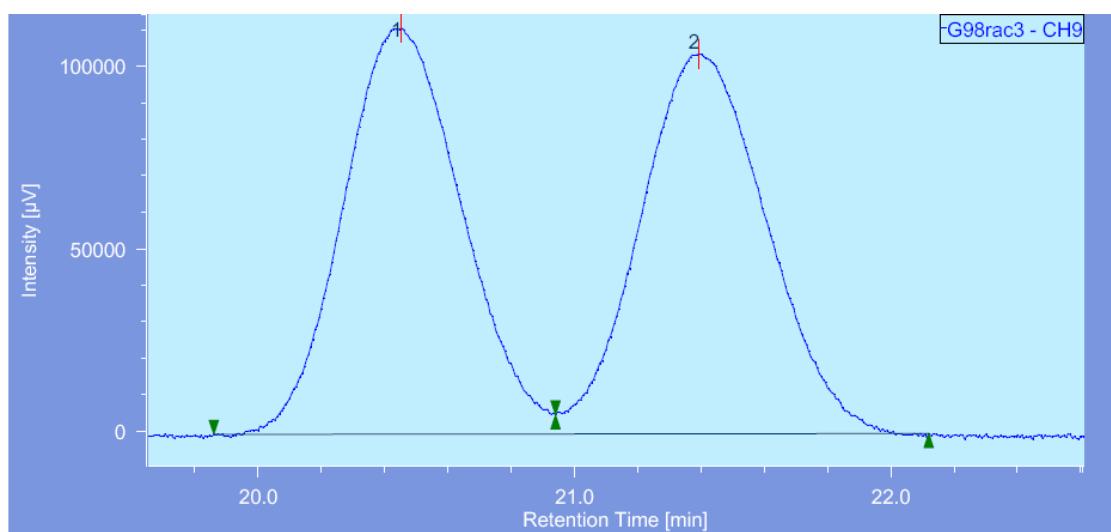
HRMS (EI): calcd for C₁₀H₈NO₂F₃⁺ (M)⁺ 231.0502, found 231.0505.

IR (neat): 3072, 1529, 1421, 1350, 1267, 1133, 735, 683.

a_D²⁵: -23 (c=0.9, CHCl₃)

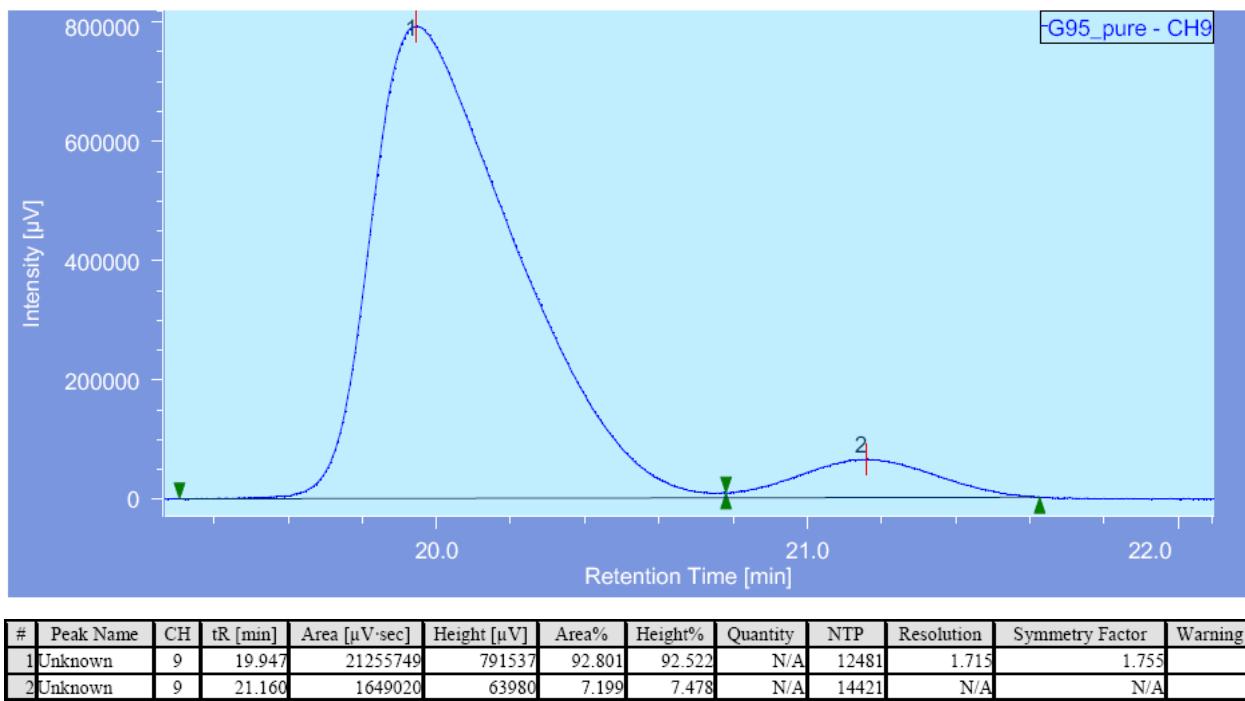
SFC: 100 % CO₂, 1 mL/min, OJ-H. **86 %ee**.

Racemic:

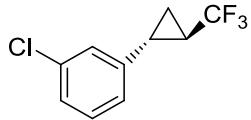


#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	20.453	2889131	111223	50.031	51.651	N/A	13821	1.308	1.123	
2	Unknown	9	21.393	2885604	104115	49.969	48.349	N/A	13181	N/A	N/A	

Enantioenriched :



(-)-1-chloro-3-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (248, Table 10, Entry 10)



Was obtained as an oil (38 mg, 78 %) following **GP 3.3**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.25–7.01 (m, 4H), 2.38–2.32 (m, 1H), 1.88–1.72 (m, 1H), 1.40 (dtd, J = 9.4, 5.7, 0.5 Hz, 1H), 1.22–1.14 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 141.1, 134.5, 129.8, 127.0, 126.7, 124.8, 123.0 (q, J = 270 Hz), 23.0 (q, J = 37 Hz), 19.3 (q, J = 2 Hz), 10.8 (q, J = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.7 (d, J = 6.6 Hz).

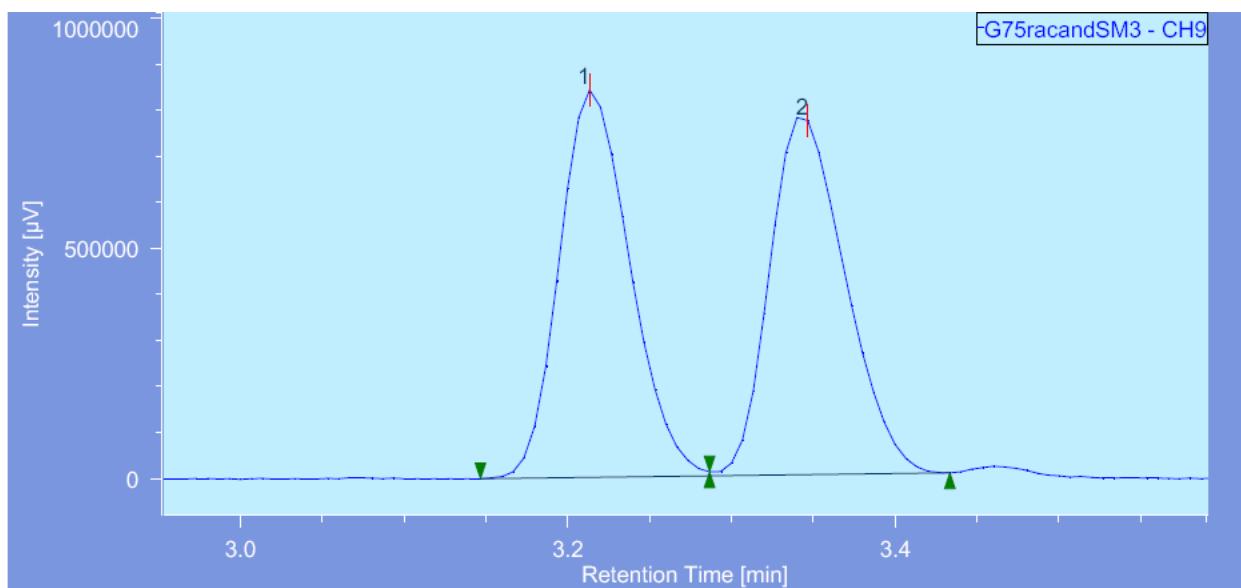
HRMS (EI): calcd for C₁₀H₈ClF₃⁺ (M)⁺ 220.0262, found 220.0262.

IR (neat): 3065, 1572, 1467, 1266, 1132, 999, 735.

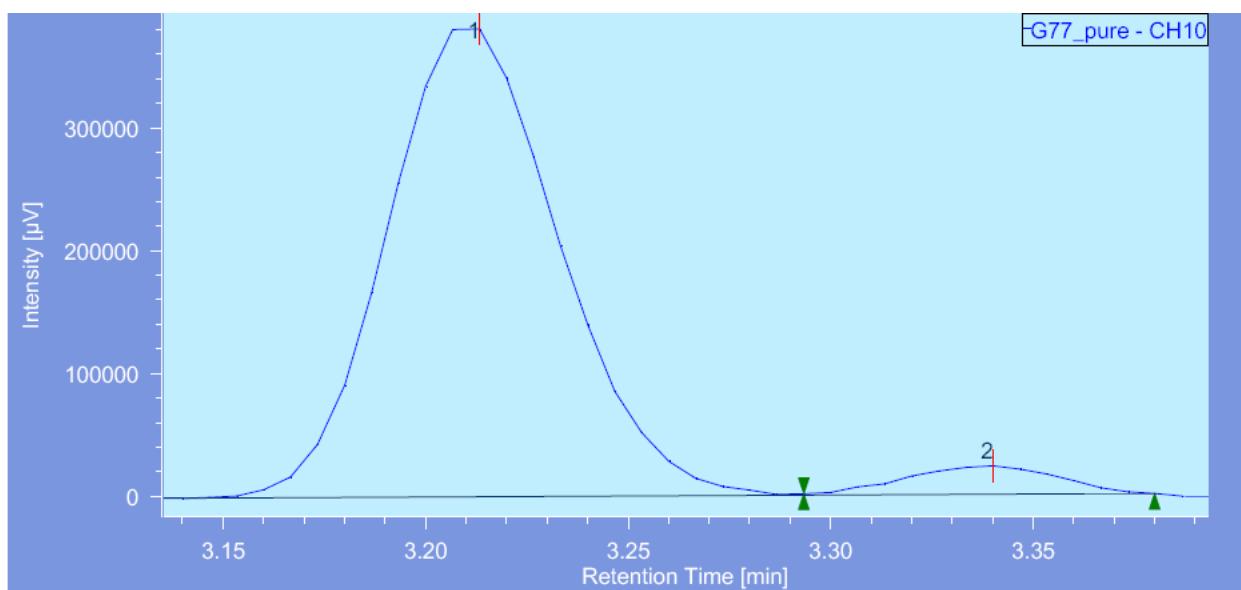
α_D^{25} : -12 (c=0.65, CHCl₃)

SFC: 100 % CO₂, 2 mL/min, IA. **90 %ee.**

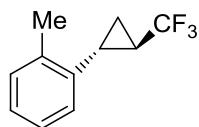
Racemic:



Enantioenriched:



(-)-1-methyl-2-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (249, Table 10, Entry 11)



Was obtained as an oil (34 mg, 77 %) following **GP 3.3**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.20–7.01 (m, 4H), 2.43 (s, 3H), 2.40–2.33 (m, 1H), 1.78–1.65 (m, 1H), 1.36 (dtd, *J* = 9.4, 5.4, 0.5 Hz, 1H), 1.25–1.15 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 138.1, 136.7, 130.0, 127.0, 126.2 (q, *J* = 270 Hz), 126.2, 126.0, 21.8 (q, *J* = 36 Hz), 19.4, 18.1 (q, *J* = 2 Hz), 9.1 (q, *J* = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.3 (d, *J* = 6.8 Hz).

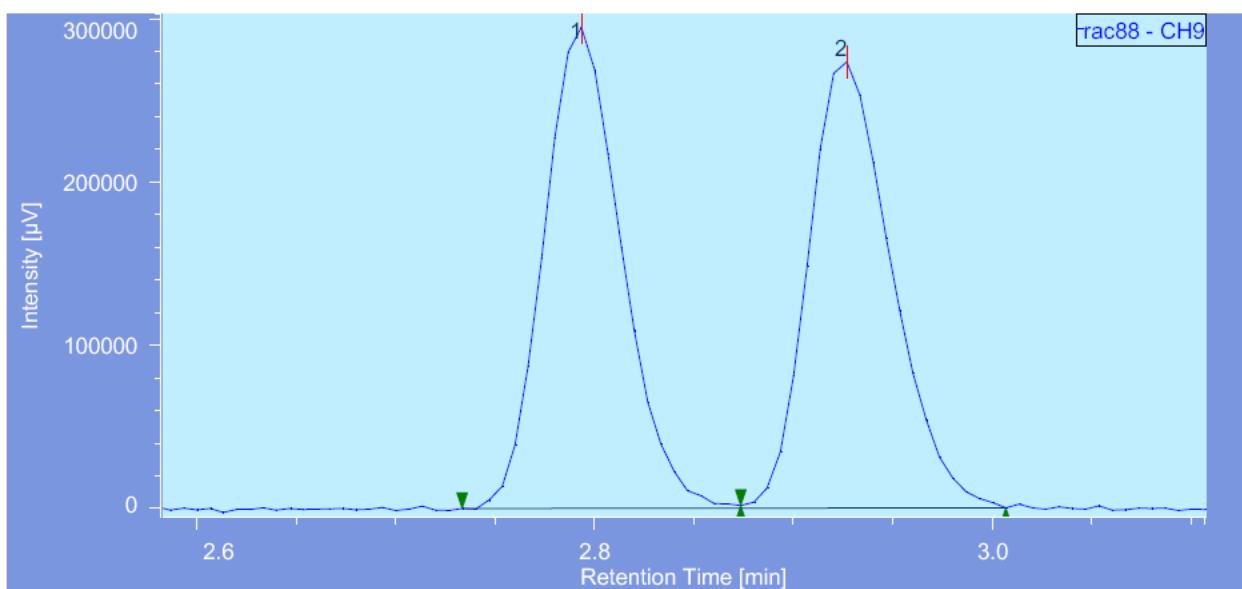
HRMS (EI): calcd for C₁₁H₁₁F₃⁺ (M)⁺ 200.0808, found 200.0806.

IR (neat): 3065, 1418, 1365, 1266, 1216, 1132, 995, 756.

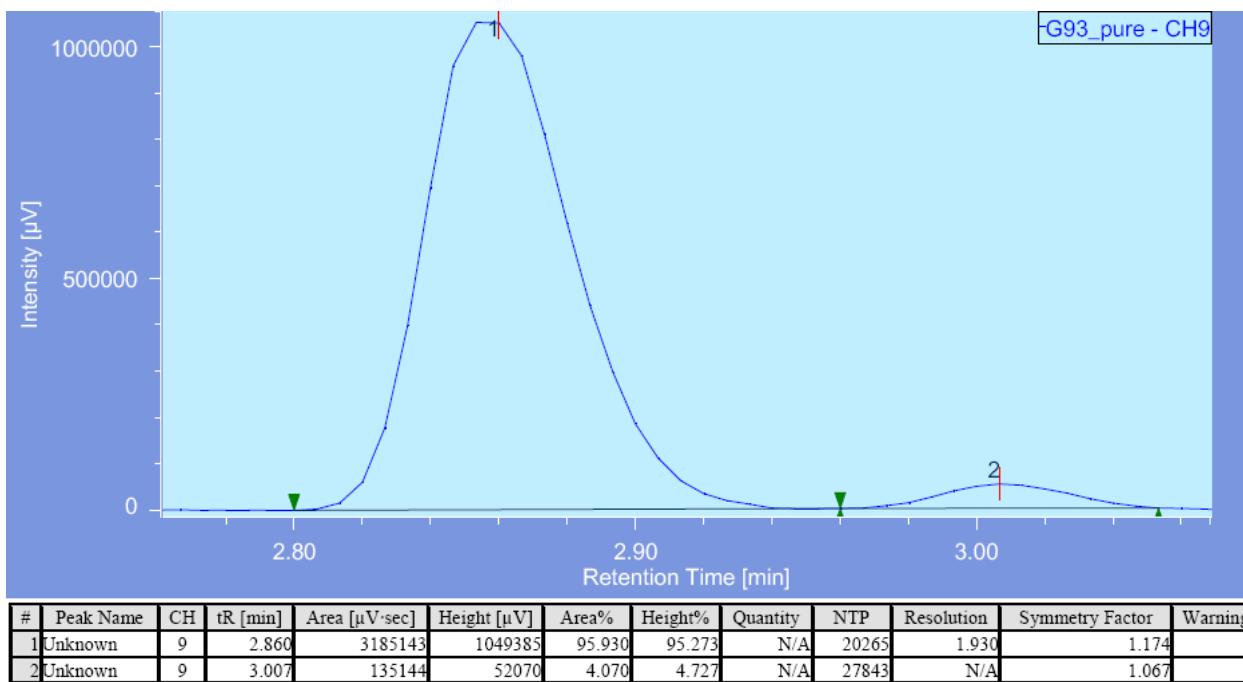
α_D²⁵: -19 (c=0.9, CHCl₃)

SFC: 100 % CO₂, 2 mL/min, IA. **92 %ee**.

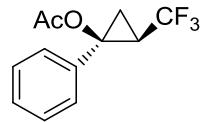
Racemic:



Enantioenriched:



(*)-(1S,2R)-1-phenyl-2-(trifluoromethyl)cyclopropyl acetate (150)*



Was obtained as an oil (35 mg, 65 %, pure major isomer) following **GP 3.3**. Crude Fluorine NMR showed a dr of 9:1. The minor isomer (cis) was not isolated.

¹H-NMR (300 MHz, CDCl₃): δ = 7.43–7.25 (m, 5H), 2.05 (s, 3H), 1.95–1.85 (m, 2H), 1.80–1.75 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 169.9, 137.5, 128.6, 128.5, 127.4, 126.2 (q, J = 272 Hz), 60.7 (q, J = 2 Hz), 26.1 (q, J = 36 Hz), 21.0, 16.2 (q, J = 2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -61.7.

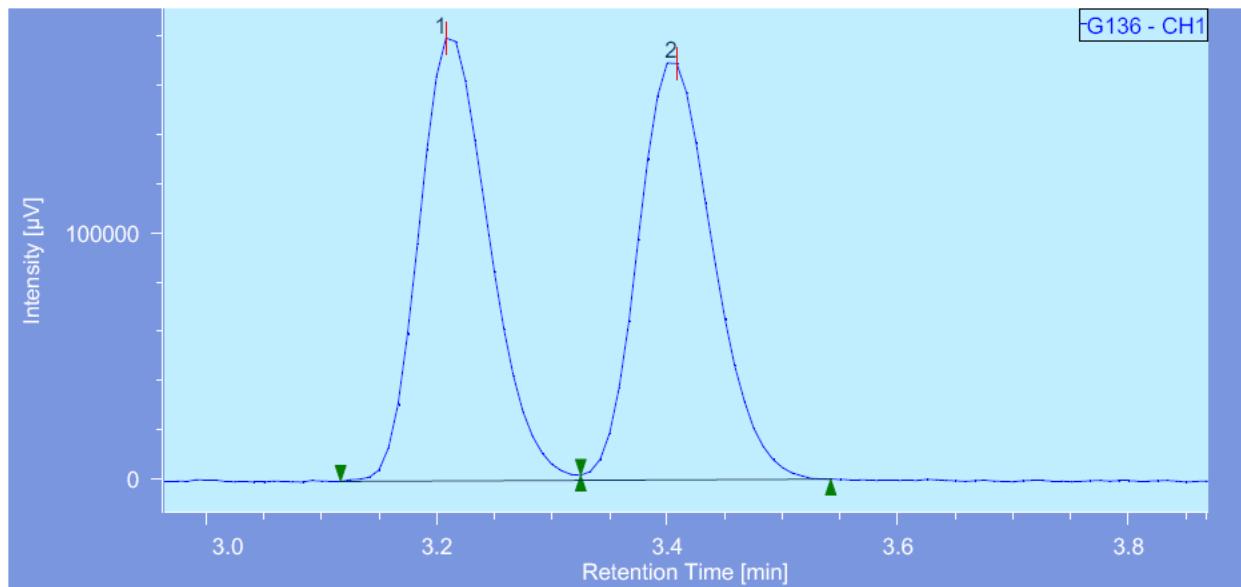
HRMS (EI): calcd for C₁₂H₁₁F₃O₂⁺ (M)⁺ 244.0706, found 244.0700.

IR (neat): 3062, 1759, 1408, 1370, 1269, 1208, 1126, 696.

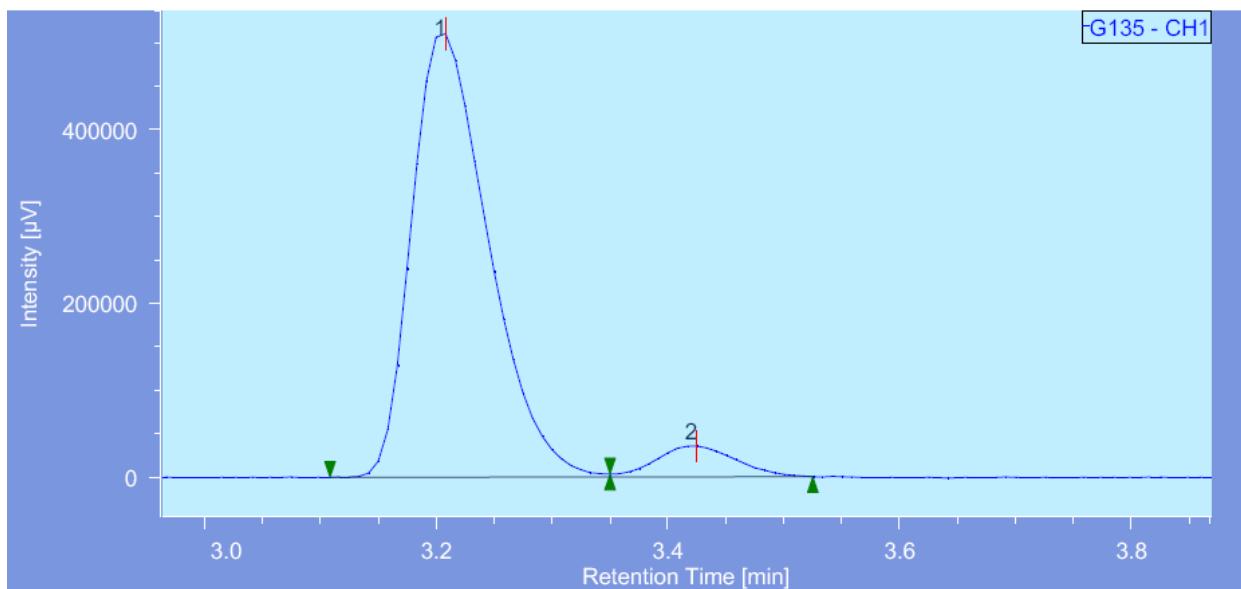
α_D^{25} : -5.6 (c=1, CHCl₃)

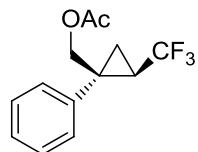
SFC: 100 % CO₂, 3 mL/min, OJ-H. **87 %ee.**

Racemic:



Enantioenriched:



(-)-(1*S*,2*R*)-1-phenyl-2-(trifluoromethyl)cyclopropylmethyl acetate (152)

Was obtained as an oil (35 mg, 62 %, pure major isomer) following **GP 3.3** with 15 mol% cat, 4 equiv. trifluoroethylamine hydrochloride and 4.8 equiv. NaNO₂ at 4 °C in distilled (degassed) water. Crude Fluorine NMR showed a dr of 2:1. The minor isomer (cis) was not isolated.

¹H-NMR (300 MHz, CDCl₃): δ = 7.35–7.26 (m, 5H), 4.47–4.25 (m, 2H), 2.02–1.85 (m, 4H), 1.47–1.44 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 170.7, 141.1, 129.1, 128.6, 127.6, 126.1 (q, *J* = 272 Hz), 66.9 (q, *J* = 2 Hz), 30.3, 25.7 (q, *J* = 37 Hz), 20.7, 14.8 (q, *J* = 2 Hz).

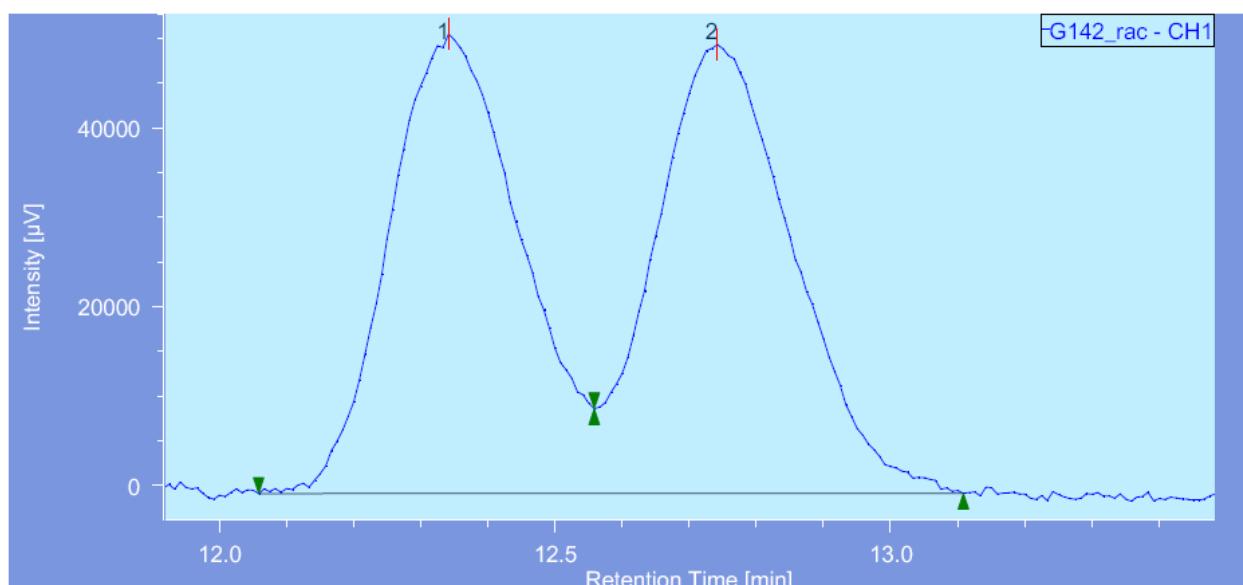
¹⁹F-NMR (282 MHz, CDCl₃): δ = -60.2 (d, *J* = 8.2 Hz).

HRMS (EI): calcd for C₁₃H₁₃F₃O₂⁺ (M)⁺ 258.0863, found 258.0862.

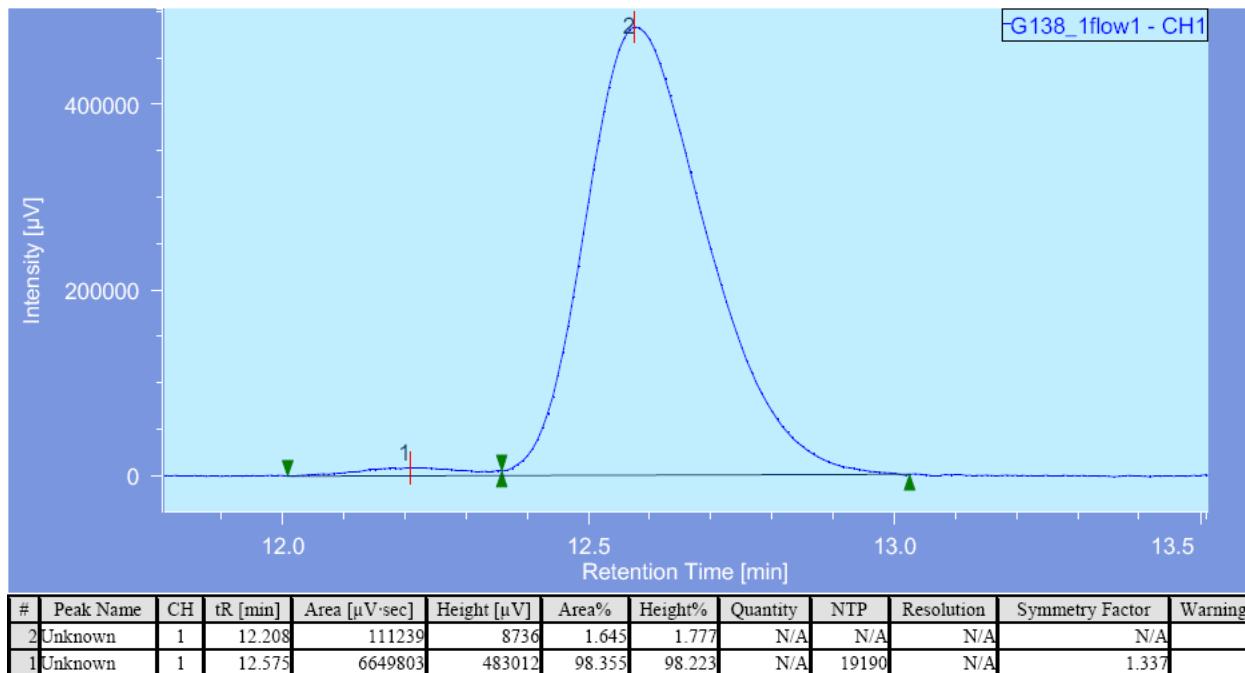
IR (neat): 2924, 1739, 1417, 1270, 1129, 699.

α_D^{25} : -17.3 (c=1, CHCl₃). **SFC:** 100 % CO₂, 1 mL/min, 2xOJ-H. **97 %ee.**

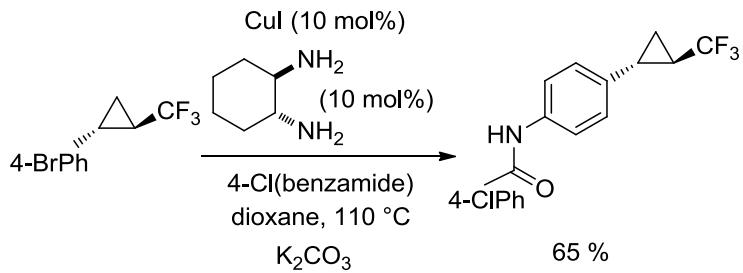
Racemic:



Enantioenriched:

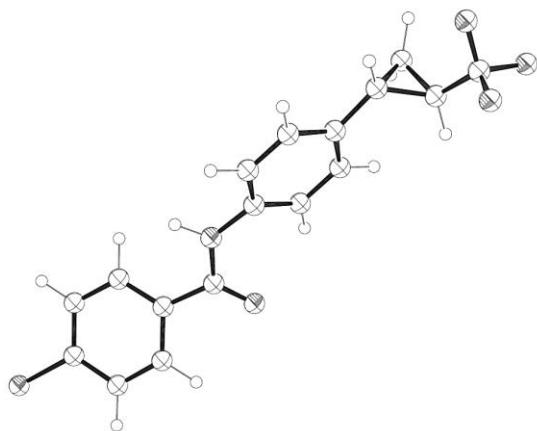


Determination of the absolute configuration



(-)1-bromo-4-(1*R*, 2*R*)-(2-(trifluoromethyl)cyclopropyl)benzene (**153**, 27 mg, 0.10 mmol, 87 % ee), CuI (2 mg, 0.01 mmol), rac-*trans*-diaminocyclohexyldiamine (1 mg, 0.01 mmol), 4-chlorobenzamide (20 mg, 0.13 mmol) and K₂CO₃ (28 mg, 0.20 mmol) were dissolved in dioxane (1 mL) in a resealable tube under argon. The mixture was heated at 110°C overnight, cooled and extracted with CH₂Cl₂. The crude product was purified by flash chromatography (CH₂Cl₂) to afford the pure product (**154**, 22 mg, 65 %). Suitable crystals were grown by recrystallization from hot methanol.

X-Ray analysis (CCDC 784005):

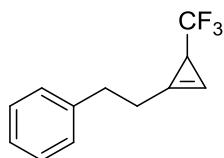


8.3. Experimental Part to Chapter 4

General procedure 4.1 (GP 4.1) for the screening of catalysts (Table 12): Catalyst and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then trifluoroethylamine hydrochloride (60 mg, 0.44 mmol) and H₂SO₄ (1.2 μL, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with Ar. The alkyne (0.22 mmol) was subsequently added, and NaNO₂ (36 mg, dissolved in 0.5 mL of water) was added via syringe pump over 10 hr. After 4 hr, CH₂Cl₂ and water were added, and the water phase was extracted with CH₂Cl₂ (3 x), dried with MgSO₄ and evaporated under reduced pressure. Analysis of the crude NMR spectrum was then performed to determine the conversion by integration.

General procedure 4.2 (GP 4.2) for cyclopropenation with Rh₂(esp)₂ and Trifluoroethylamine hydrochloride (Table 13): Rh₂(esp)₂ (4.2 mg, 0.0055 mmol), and NaOAc (3.6 mg, 0.044 mmol) were dissolved in degassed, distilled water (0.8 mL). Then trifluoroethylamine hydrochloride (60 mg, 0.44 mmol) and H₂SO₄ (1.2 μL, 0.022 mmol) were added, and the solution was degassed for one minute by sparging with Ar. The alkyne (0.22 mmol) was subsequently added, and NaNO₂ (36 mg, dissolved in 0.5 mL of water) was added via syringe pump over 10 hr. After 4 hr, CH₂Cl₂ and water were added, and the water phase was extracted with CH₂Cl₂ (3 x), dried with MgSO₄ and evaporated under reduced pressure. After analysis of the crude NMR spectrum, the crude mixture was chromatographed on silica gel (pentane/diethyl ether) to afford product.

(2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (162, Table 13, Entry 1)



Was obtained as an oil (36.4 mg, 78 %) following GP 4.2.

¹H-NMR (300 MHz, CDCl₃): δ = 7.35–7.17 (m, 5H), 6.41–6.39 (m, 1H), 2.97–2.78 (m, 4H), 1.98 (qd, *J* = 4.4, 1.5 Hz, 1H).

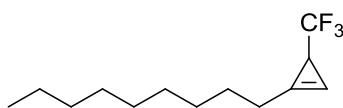
¹³C-NMR (100 MHz, CDCl₃): δ = 140.5, 128.5, 128.3, 126.3, 126.3 (q, *J* = 273 Hz), 116.2, 95.3 (q, *J* = 3 Hz), 32.8, 26.6, 19.2 (q, *J* = 39 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.9 (dd, *J* = 4.4, 1.9 Hz).

HRMS (EI): calcd for C₁₂H₁₀F₃⁺ [M-H]⁺ 211.0730, found 211.0732.

IR (neat): 3030, 2954, 1274, 1120, 698.

1-nonyl-3-(trifluoromethyl)cycloprop-1-ene (250, Table 13, Entry 2)



Was obtained as an oil (36.5 mg, 71 %) following **GP 4.2.**

¹H-NMR (300 MHz, CDCl₃): δ = 6.39–6.36 (m, 1H), 2.48 (t, *J* = 7.5 Hz, 2H), 1.96–1.94 (m, 1H), 1.65–1.55 (m, 2H), 1.40–1.20 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H).

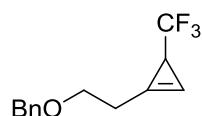
¹³C-NMR (100 MHz, CDCl₃): δ = 126.49 (q, *J* = 274.6 Hz), 117.0 (q, *J* = 2 Hz), 93.4 (q, *J* = 4 Hz), 31.9, 29.4, 29.2, 29.2, 29.1, 26.5, 24.9, 22.6, 19.0 (q, *J* = 39 Hz), 14.1.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.0 (dd, *J* = 4.4, 1.8 Hz).

HRMS (EI): calcd for C₁₀H₁₄F₃⁺ [M-C₃H₇]⁺ 191.1043, found 191.1042.

IR (neat): 2926, 2856, 1275, 1126.

((2-(3-(trifluoromethyl)cycloprop-1-enyl)ethoxy)methyl)benzene (251, Table 13, Entry 3)



Was obtained as an oil (38.0 mg, 71 %) following **GP 4.2.**

¹H-NMR (300 MHz, CDCl₃): δ = 7.40–7.20 (m, 5H), 6.52–6.48 (m, 1H), 4.54 (s, 2H), 3.72 (t, J = 6.3 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H), 2.01 (qd, J = 4.4, 1.5 Hz, 1H).

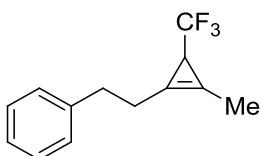
¹³C-NMR (100 MHz, CDCl₃): δ = 138.0, 128.4, 127.7, 127.7, 127.2 (q, J = 270 Hz), 114.4 (q, J = 2.8 Hz), 96.1 (q, J = 3.3 Hz), 73.1, 66.8, 25.9, 19.0 (q, J = 39.5 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.1 (dd, J = 4.4, 1.8 Hz).

HRMS (EI): calcd for C₁₃H₁₂OF₃⁺ [M-H]⁺ 241.0835, found 241.0836.

IR (neat): 2969, 2901, 1274, 1116, 829, 696.

(2-(2-methyl-3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (252, Table 13, Entry 4)



Was obtained as an oil (35.0 mg, 70 %) following **GP 4.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.40–7.18 (m, 5H), 2.93–2.63 (m, 4H), 1.96 (s, 3H), 1.85 (q, J = 4.6 Hz, 1H).

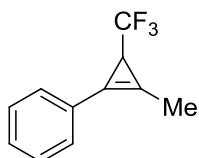
¹³C-NMR (100 MHz, CDCl₃): δ = 139.9, 127.4, 127.2, 126.2 (q, J = 270 Hz), 125.2, 105.2 (q, J = 2.8 Hz), 102.5 (q, J = 3.0 Hz), 32.0, 25.0, 20.4 (q, J = 38.2 Hz), 8.5.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -65.7 (d, J = 4.6 Hz).

HRMS (EI): calcd for C₁₃H₁₃F₃⁺ [M]⁺ 226.0969, found 226.0970.

IR (neat): 2937, 2854, 1269, 1114, 698.

(2-methyl-3-(trifluoromethyl)cycloprop-1-enyl)benzene (253, Table 13, Entry 5)



Was obtained as an oil (29.0 mg, 67 %) following **GP 4.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.55–7.33 (m, 5H), 2.34 (s, 3H), 2.27 (q, J = 4.5 Hz, 1H).

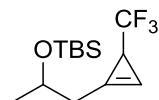
¹³C-NMR (100 MHz, CDCl₃): δ = 128.3, 127.9, 127.7, 126.0, 125.7 (q, J = 274 Hz), 104.6, 104.5, 20.5 (q, J = 38.7 Hz), 9.5.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -65.3 (d, J = 4.5 Hz).

HRMS (EI): calcd for C₁₁H₉F₃⁺ [M]⁺ 198.0651, found 198.0654.

IR (neat): 2929, 1270, 1127.

tert-butyldimethyl(1-(3-(trifluoromethyl)cycloprop-1-enyl)propan-2-yloxy)silane (254, Table 13, Entry 6)



Was obtained as an oil (42.5 mg, 69 %, 1:1 mixture of diastereoisomers) following **GP 4.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 6.48–6.46 (m, 1H), 4.17–4.04 (m, 1H), 2.75–2.50 (m, 2H), 2.00–1.94 (m, 1H), (1.22 (d, J = 1.6 Hz, first isomer), 1.20 (d, J = 1.6 Hz, second isomer), 3H together), 0.89–0.86 (m, 9H), 0.07–0.00 (m, 6H).

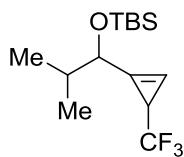
¹³C-NMR (100 MHz, CDCl₃): δ = 125.4 (q, J = 274.5 Hz), 125.4 (d, J = 274.7 Hz), 113.2, 95.1 (q, J = 3.3 Hz), 94.8 (q, J = 3.3 Hz), 65.4, 65.3, 34.3, 34.2, 24.7, 24.7, 22.5, 22.5, 18.0 (q, J = 39.1 Hz), 17.0, -5.5, -5.6, -5.9.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -66.9 (dd, J = 4.5, 1.9 Hz, first isomer), -67.0 (dd, J = 4.4, 1.9 Hz, second isomer).

HRMS (EI): calcd for C₉H₁₄F₃OSi⁺ [M-*t*Bu]⁺ 223.0762, found 223.0764.

IR (neat): 2956, 2931, 2858, 1276, 1125, 830.

tert-butyldimethyl(2-methyl-1-(3-(trifluoromethyl)cycloprop-1-enyl)propoxy)silane (255, Table 13, Entry 7)



Was obtained as an oil (47.0 mg, 73 %, 1:1 mixture of diastereoisomers) following **GP 4.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 6.48–6.46 (m, 1H), (4.49 (dd, *J* = 4.8, 1.6 Hz, first isomer), 4.43 (dd, *J* = 4.4, 0.9 Hz, second isomer), 1H together), 2.14–2.06 (m, 1H), 2.03–1.87 (m, 1H), 0.99–0.88 (m, 15H), 0.08–0.03 (m, 6H).

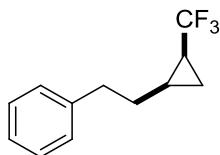
¹³C-NMR (100 MHz, CDCl₃): δ = 126.0 (q, *J* = 274.4 Hz), 118.6, 118.0, 97.0 (q, *J* = 3.1 Hz), 96.8 (d, *J* = 2.9 Hz), 72.8, 72.1, 33.5, 33.3, 26.0, 25.7, 18.5, 18.4, 18.2, 17.4, 17.0, –4.7, –5.1, –5.3.

¹⁹F-NMR (282 MHz, CDCl₃): δ = –66.7 (dd, *J* = 4.4, 1.7 Hz, first isomer), –67.0 (dd, *J* = 4.4, 1.7 Hz, second isomer).

HRMS (EI): calcd for C₁₀H₁₆F₃OSi⁺ [M-*t*Bu]⁺ 237.0917, found 237.0915.

IR (neat): 2959, 2932, 2859, 1279, 1134, 837.

2-(trifluoromethyl)cyclopropyl(ethyl)benzene (163)



5% Pd on CaCO₃ (3.5 mg, 0.0015 mmol, 1 mol%) was added to a solution of (2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (30 mg, 0.14 mmol) in ethyl acetate (0.5 mL) after being purged with hydrogen. The suspension was stirred vigorously under hydrogen atmosphere for 6 h when TLC indicated the complete consumption of the starting material. The reaction mixture was then filtered through a short plug of celite, and concentrated in vacuo. The residue was purified by column chromatography (pentane) to give the desired cyclopropane (27 mg, 90%, 93:7 dr) as colorless liquid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.35–7.15 (m, 5H), 2.80–2.72 (m, 2H), 1.96–1.82 (m, 1H), 1.80–1.64 (m, 1H), 1.50 (ddd, *J* = 17.2, 8.6, 5.7 Hz, 1H), 1.15–1.01 (m, 1H), 1.00–0.90 (m, 1H), 0.67 (dd, *J* = 11.9, 5.7 Hz, 1H).

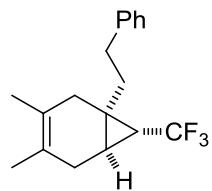
¹³C-NMR (100 MHz, CDCl₃): δ = 140.7, 127.6, 127.4, 126.0 (q, *J* = 271.7 Hz), 124.9, 34.7, 28.4, 16.9 (q, *J* = 35.9 Hz), 15.0, 7.4.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -59.4 (d, *J* = 8.4 Hz, major, cis), -64.0 (d, *J* = 6.3 Hz, minor, trans).

HRMS (EI): calcd for C₁₂H₁₃F₃⁺ [M⁺] 214.0964, found 214.0966.

IR (neat): 3028, 2930, 2869, 1415, 1274, 1120, 697.

(1RS,6RS,7RS)-3,4-dimethyl-1-phenethyl-7-(trifluoromethyl)bicyclo[4.1.0]hept-3-ene (165)



A solution of (2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (30 mg, 0.14 mmol) in 2,3-dimethylbutadiene (0.4 mL) was heated at 80 °C in a sealed tube for 24 h. After being cooled to room temperature, the mixture was concentrated and purified by column chromatography (pentane) to provide the desired product (40.6 mg, 97%) as colorless liquid.

¹H-NMR (300 MHz, CDCl₃): δ = 7.33–7.15 (m, 5H), 2.82–2.67 (m, 2H), 2.38–2.12 (m, 4H), 1.93–1.73 (m, 2H), 1.63–1.57 (m, 6H), 1.50–1.26 (m, 2H).

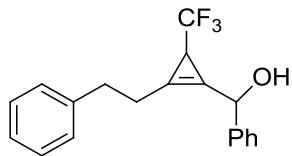
¹³C-NMR (100 MHz, CDCl₃): δ = 137.0, 123.0, 122.3 (q, *J* = 271.9 Hz), 121.0, 116.5, 116.4, 30.4, 30.2, 27.5, 24.9, 19.9, 19.8 (q, *J* = 35.1 Hz), 16.9 (q, *J* = 2.4 Hz), 13.9, 13.7.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -57.3 (d, *J* = 8.8 Hz)

HRMS (EI): calcd for C₁₈H₂₁F₃⁺ [M⁺] 204.1590, found 204.1593.

IR (neat): 3027, 2932, 2865, 1275, 1122, 698.

(2-phenethyl-3-(trifluoromethyl)cycloprop-1-enyl)(phenyl)methanol (167)



A solution of (2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (30 mg, 0.14 mmol) in THF (1 mL) was treated at -78°C with BuLi (142 μL , 0.17 mmol, 1.2 M in hexane). After being stirred for 15 min, benzaldehyde (29 μL , 0.28 mmol, 2 equiv.) was added to the deep blue solution at -78°C . After 15 min, the solution was slowly warmed up to room temperature and subsequently quenched with sat. NH_4Cl . Extraction with dichloromethane, followed by evaporation and column chromatography (pentane/ether 10:1) gave the pure product as colorless liquid (35 mg, 78 %, 2:1 mixture of diastereoisomers).

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.38\text{--}7.12$ (m, 10H), 5.57–5.50 (m, 1H), 2.89–2.75 (m, 4H), 2.13–1.99 (m, 2H).

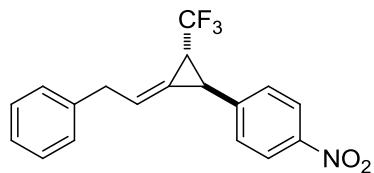
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 140.4, 140.3, 128.7, 128.6, 128.6, 128.3, 128.2, 128.2, 126.4, 126.3$ (q, $J = 274.5$ Hz), 109.4 (q, $J = 2.6$ Hz), 109.1 (q, $J = 2.4$ Hz), 109.0 (q, $J = 2.5$ Hz), 108.6 (q, $J = 2.4$ Hz), 69.6, 68.3, 32.8, 32.7, 25.8, 25.6, 22.8 (q, $J = 38.8$ Hz), 21.9 (q, $J = 38.8$ Hz).

$^{19}\text{F-NMR}$ (282 MHz, CDCl_3): $\delta = -65.4$ (d, $J = 4.4$ Hz, major), -65.5 (d, $J = 4.4$ Hz, minor).

HRMS (EI): calcd for $\text{C}_{19}\text{H}_{16}\text{OF}_3^+ [\text{M}-\text{H}]^+$ 317.1148, found 317.1146.

IR (neat): 3346, 3029, 2955, 2930, 2859, 1453, 698.

1-nitro-4-((1S_R,3R_S,Z)-2-(2-phenylethylidene)-3-(trifluoromethyl)cyclopropyl)benzene (166)



Palladium acetate (3.2 mg, 0.014 mmol, 10 mol%), *p*-iodonitrobenzene (38 mg, 0.15 mmol, 1.1 equiv.), (2-(3-(trifluoromethyl)cycloprop-1-enyl)ethyl)benzene (30 mg, 0.14 mmol) and anhydrous potassium carbonate (42 mg, 0.35 mmol) were dissolved in dimethylformamide (0.2 mL) and the

reaction mixture was stirred at 30 °C for 18 hrs. TLC analysis showed the completion of the reaction. The reaction mixture was filtered through a short column of silica gel (eluent ether), evaporated and purified by column chromatography to give the pure compound as a thick oil (44 mg, 93 %, 14:1 mixture of Z/E-isomers).

¹H-NMR (300 MHz, CDCl₃, major): δ = 8.14–8.09 (m, 2H), 7.30–7.00 (m, 8H), 6.55–6.48 (m, 1H), 3.56 (d, *J* = 6.6 Hz, 2H), 2.97 (br s, 1H), 2.31–2.20 (m, 1H).

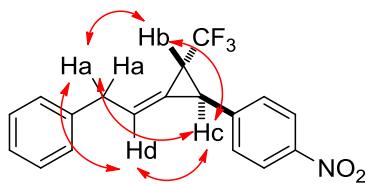
¹³C-NMR (100 MHz, CDCl₃): δ = 145.9, 144.6, 137.3, 127.6, 127.5, 126.2, 125.3, 123.6, 123.0 (q, *J* = 273.2 Hz), 122.8, 119.3 (q, *J* = 2.8 Hz), 36.8, 27.0 (q, *J* = 37.8 Hz), 22.6 (q, *J* = 3.4 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -65.2 (d, *J* = 6.2 Hz, minor), -66.2 (d, *J* = 6.1 Hz, major).

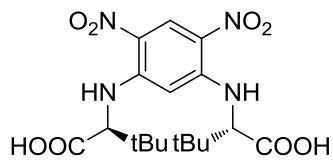
HRMS (EI): calcd for C₁₈H₁₄F₃NO₂⁺ [M]⁺ 333.0972, found 333.0969.

IR (neat): 3028, 1601, 1518, 1345, 1259, 1125, 698.

NOE: H_a-H_b, H_a-H_c, H_a-H_d, H_b-H_c, H_c-H_d; no NOE between H_b-H_d.



(2S,2'S)-2,2'-(4,6-dinitro-1,3-phenylene)bis(azanediyl)bis(3,3-dimethylbutanoic-acid) (168)



Hünig's base (1.54 mL, 8.82 mmol, 6.0 eq.) was added to a solution of 1,5-difluoro-2,4-dinitrobenzene (300 mg, 1.47 mmol, 1.0 eq.) and (*L*)-tert Leucine (386 mg, 2.94 mmol, 2.0 eq.) in DMF (15 mL) was added at RT. and the reaction mixture was stirred for 14 h at 60 °C. After the reaction mixture was allowed to cool to room temperature the reaction mixture was acidified by addition of 1 M HCl (pH adjusted to 2) and the precipitate was filtered. The residue was dissolved in DCM, washed with 5% aq. LiCl, dried over MgSO₄, filtered and concentrated under reduced pressure to give **168** in quantitative yield.

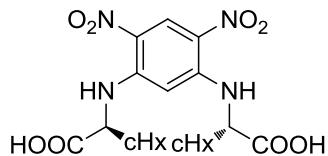
¹H NMR (400 MHz, CD₃CN): δ = 9.09 (s, 1H), 8.80 (d, *J* = 8.4 Hz, 2H), 5.84 (s, 1H), 4.12 (d, *J* = 8.5 Hz, 2H), 1.10 (s, 18H).

¹³C NMR (101 MHz, CD₃CN): δ = 172.7, 149.8, 130.6, 125.9, 93.0, 65.4, 35.9, 27.3.

IR (neat): 3357, 2964, 2922, 1712, 1620, 1574, 1546, 1477, 1413, 1373, 1318, 1259, 1211, 1104, 1068, 930, 832, 797, 744, 699.

HRMS (MALDI): calculated mass for C₁₈H₂₅N₄O₈⁻ [M-H⁺]: 425.1678, found: 425.1678.

(2S,2'S)-2,2'-(4,6-dinitro-1,3-phenylene)bis(azanediyl)bis(2-cyclo hexylacetic acid) (169)



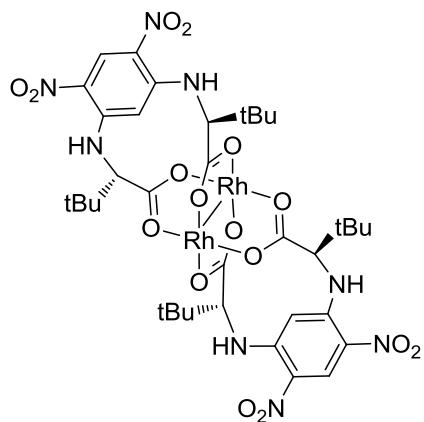
Hünig's base (0.75 mL, 4.31 mmol, 4.4 equiv.) was added to a solution of 1,5-difluoro-2,4-dinitrobenzene (0.20 g, 0.98 mmol, 1.0 equiv.) and (*R*)-2-cyclohexyl-2-hydroxyacetic acid (0.31 g, 1.96 mmol, 2.0 equiv.) in DMF (1 mL) was added at RT. and the reaction mixture was stirred for 100 h at 50 °C. After the reaction mixture was allowed to cool to room temperature the reaction mixture was acidified by addition of 1 M HCl (pH adjusted to 2). The reaction mixture was extracted with DCM, washed with 5% aq. LiCl, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (Hexanes/EtOAc 2:1 with 1.5% AcOH) afforded **169** (0.21 g, 45%) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ = 8.74 (s, 1H), 6.45 (s, 1H), 4.56 (d, *J* = 4.5 Hz, 2H), 1.77 (dd, *J* = 42.5, 9.4 Hz, 10H), 1.54 – 1.10 (m, 12H).

¹³C NMR (101 MHz, CDCl₃): δ = 178.2, 156.3, 132.2, 125.8, 101.6, 82.9, 40.7, 28.9, 27.2, 25.7.

IR (neat): 2928, 2855, 2282, 1720, 1613, 1590, 1524, 1450, 1346, 1301, 1204, 1097, 1069, 1022, 909, 832, 730, 707.

HRMS (MALDI): calculated mass for C₂₂H₂₈N₂NaO₁₀⁺ [M+Na⁺]: 503.1636, found: 503.1635.

Rh₂(^tL-dino)₄ (174)

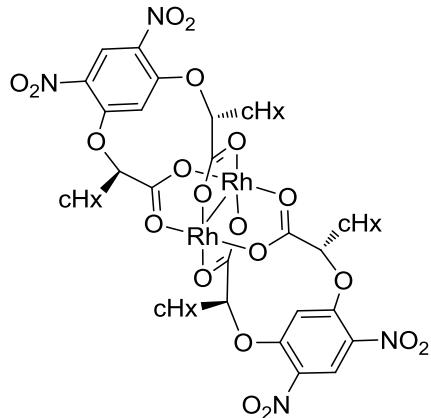
Rh₂(OAc)₄ (22.5 mg, 0.05 mmol, 1.0 equiv.) and **168** (43.5 mg, 0.10 mmol, 2.0 equiv.) were dissolved in chlorobenzene (1 mL) and the reaction mixture was stirred at 130 °C for 14 h. The reaction mixture was allowed to cool to room temperature and was purified directly by flash chromatography (Hexanes/EtOAc 4:1) to give **174** (13.5 mg, 25%) as a green solid.

¹H NMR (400 MHz, CD₃CN): δ = 9.10 (s, 1H), 8.67 (d, *J* = 5.8 Hz, 2H), 4.71 (s, 1H), 3.83 (d, *J* = 5.8 Hz, 2H), 1.05 (s, 18H).

¹³C NMR (101 MHz, CD₃CN): δ = 188.6, 146.9, 128.3, 124.5, 96.6, 66.1, 35.4, 27.0.

IR (neat): 3341, 2921, 2852, 2167, 1620, 1603, 1574, 1552, 1464, 1397, 1361, 1322, 1205, 1096, 1060, 924, 832, 821, 776, 745, 699, 663.

HRMS (MALDI): calculated mass for C₃₆H₄₈ClN₈O₁₆Rh₂⁻ [M+Cl⁻]: 1089.0992, found: 1089.0990.

Rh₂(^cH-dino)₄ (176)

$\text{Rh}_2(\text{OAc})_4$ (20.0 mg, 0.05 mmol, 1.0 equiv.) and **169** (43.5 mg, 0.10 mmol, 2.0 equiv.) were dissolved in chlorobenzene (1 mL) and the reaction mixture was stirred at 130 °C for 14 h. The reaction mixture was allowed to cool to room temperature and was purified directly by flash chromatography (Hexanes/EtOAc 3:1) to give **176** (39.8 mg, 76%) as a green solid.

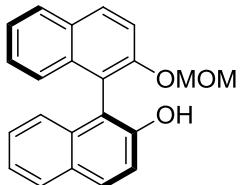
$^1\text{H NMR}$ (400 MHz, CD_3CN): $\delta = 8.61$ (s, 2H), 6.14 (s, 2H), 4.14 (d, $J = 6.8$ Hz, 4H), 1.86–1.61 (m, 20H), 1.45–0.90 (m, 24H);

$^{13}\text{C NMR}$ (101 MHz, CD_3CN): $\delta = 190.4, 154.9, 134.8, 124.8, 112.9, 86.6, 39.6, 28.3, 27.6, 25.8, 25.6, 25.3$.

IR (neat): 2927, 2854, 2162, 2050, 1680, 1588, 1529, 1485, 1449, 1405, 1342, 1301, 1270, 1187, 1135, 1062, 1003, 975, 914, 889, 832.

HRMS (ESI): calculated and found mass not consistent.

(S)-2'-(methoxymethoxy)-[1,1'-binaphthalen]-2-ol (**178**)

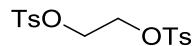


Hünig's base (3.84 mL, 22.0 mmol, 2.2 equiv.) was added at 0 °C to a solution of (S)-BINOL (2.86 g, 10.0 mmol, 1.0 equiv.) in DCM (25 mL) and was stirred for 2.5 h. MOM-Cl (1.14 mL, 13.5 mmol, 1.35 equiv.) was added drop wise at 0 °C and the reaction mixture was stirred for 15 min. The reaction mixture was quenched by addition of 0.5 M HCl (100 mL) and was extracted with DCM. The organic phase was dried over MgSO_4 , filtered and concentrated under reduced pressure. The product was purified by flash chromatography (SiO_2 ; pentanes/acetone 10:1) and was concentrated in vacuo to give **178** (2.17 g, 66%) as a white solid.

¹H NMR (300 MHz, CDCl₃): δ = 8.04 (d, *J* = 9.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 1H), 7.45–7.27 (m, 4H), 7.26–7.17 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 1H), 5.16–5.04 (q, 2H), 4.97 (s, 1H), 3.19 (s, 3H).

Spectral data were in accordance with literature.²⁰⁵

Ethane-1,2-diyI bis(4-methylbenzenesulfonate)

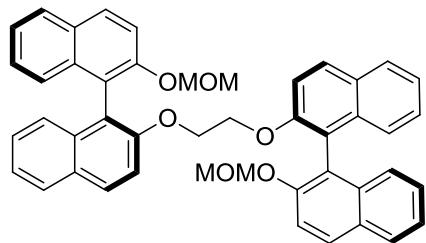


Ethane-1,2-diol (5 mL, 88 mmol, 1.0 equiv.) in THF (80 mL) was added to a solution of NaOH (20.5 g, 308 mmol, 3.5 equiv.) in water and the reaction mixture was stirred at room temperature for 1 h. Tosyl chloride (37.2 g, 193 mmol, 2.2 equiv.) in THF (80 mL) was added drop wisely at 0 °C and the reaction mixture was stirred for 6 h. The reaction mixture was poured in 1 M HCl (150 mL) and the precipitate was collected by filtration. The white solid was washed with cold water and aqueous NaHCO₃. Concentration in vacuo gave the product (25.7 g, 79%) as a white solid.

Spectral data were in accordance with literature.²⁰⁶

¹H NMR (300 MHz, CDCl₃): δ = 7.78–7.69 (m, 4H), 7.40–7.27 (m, 4H), 4.19 (s, 4H), 2.46 (s, 6H).

1,2-bis(((S)-2'-(methoxymethoxy)-[1,1'-binaphthalen]-2-yl)oxy) ethane (179)



²⁰⁵ T. Taniguchi, T. A. Fukuba, S. Nakatsuka, S. Hayase, M. Kawatsura, H. Uno, T. Itoh, *J. Org. Chem.* **2008**, *73*, 3875.

²⁰⁶ E. M. D. Keegstra, J. W. Zwikker, M. R. Roest, L. W. Jenneskens, *J. Org. Chem.* **1992**, *57*, 6678.

A solution of **178** (1.0 g, 3.03 mmol, 1.0 equiv.) in DMF (10 mL) was added at RT. to a solution of NaH (115 mg, 4.54 mmol, 1.5 equiv.) in DMF (5 mL) and was stirred for 1 h at the same temperature. A solution of ethylene glycol bistosylate (0.56 g, 1.51 mmol, 0.5 equiv.) in DMF (5 mL) was added at 110 °C during 24 h by means of a syringe pump. After addition the reaction mixture was stirred for further 60 h at the same temperature. The reaction mixture was allowed to cool to 0 °C and was quenched by addition of water (10 mL) and sat., aqueous NaCl (10 mL). The reaction mixture was extracted with DCM (2 x 25 mL) and the combined organic phases were washed with sat., aqueous NaCl, then with 5% aqueous LiCl, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by purified by flash chromatography (DCM/hexanes 3:1, then 5:1 then 100% DCM) and was concentrated in vacuo to give **179** (0.51 g, 48%; 68% based on recovered starting material) as a white solid.

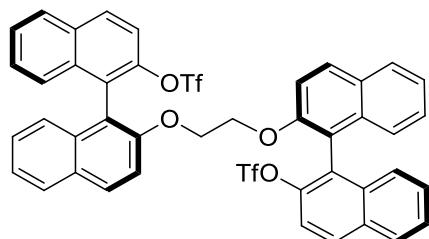
¹H NMR (400 MHz, CDCl₃): δ = 7.99 (d, *J* = 9.0 Hz, 2H), 7.91 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.44–7.30 (m, 4H), 7.26–7.17 (m, 4H), 7.16–7.05 (m, 4H), 6.99 (d, *J* = 9.0 Hz, 2H), 4.95 (dd, *J* = 42.5, 6.7 Hz, 2H), 4.00–3.86 (m, 4H), 3.09 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 154.3, 152.7, 134.0, 133.9, 129.9, 129.5, 129.4, 129.3, 127.9, 127.8, 126.2, 126.2, 125.5, 125.4, 124.0, 123.7, 121.3, 120.5, 117.4, 116.3, 95.2, 69.0, 55.8.

IR (neat): 3054, 2922, 2851, 2286, 2051, 1621, 1591, 1505, 1461, 1430, 1403, 1355, 1326, 1259, 1237, 1196, 1146, 1078, 1063, 1031, 1010, 919, 903, 864, 806, 746, 688, 619 .

HRMS (MALDI): calculated mass for C₄₆H₃₈NaO₆⁺ [M+Na⁺]: 709.2561, found: 709.2561.

(1S,1'S)-(ethane-1,2-diylbis(oxy))bis([1,1'-binaphthalene]-2',2-diyl)bis(trifluoromethanesulfonate) (180)



To a solution of **179** (430 mg, 0.626 mmol, 1.0 equiv.) in MeOH (10 mL) and THF (8 mL) was added conc. HCl (0.02 mL, 0.626 mmol, 1.0 equiv.) at room temperature and the reaction mixture was stirred for 5 h at 45 °C. After evaporation of solvent, the residue was dissolved in DCM and was washed with water. The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in DCM and cooled to 0 °C. After addition of Hünig's base (0.328 mL, 1.878 mmol, 3.0 equiv.) at 0°C the reaction mixture was stirred for 15 min at the same temperature, then triflic anhydride was added and the reaction mixture was stirred for 2 h. The reaction was quenched by addition of sat., aq. NaHCO₃ and extracted with DCM. The organic phase was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The product was purified by purified by flash chromatography Hexanes/EtOAc 9:1) and was concentrated in vacuo to give **180** (425 mg, 79%) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ = 8.07 (d, *J* = 9.1 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 9.1 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 7.52–7.42 (m, 2H), 7.39–7.31 (m, 2H), 7.26–7.14 (m, 6H), 7.07 (d, *J* = 9.1 Hz, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 4.28–4.07 (m, 4H).

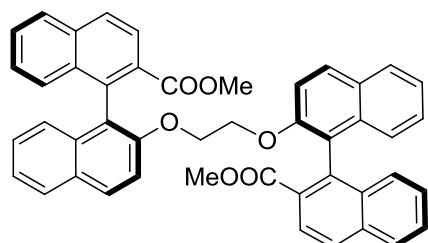
¹³C NMR (101 MHz, CDCl₃): δ = 154.3, 145.4, 133.6, 133.3, 132.5, 130.8, 130.2, 128.9, 128.1, 128.0, 127.3, 127.2, 126.9, 126.8, 126.7, 124.8, 123.7, 119.5, 115.4, 114.2, 67.9.

¹⁹F NMR (376 MHz, CDCl₃): δ = -74.9.

IR (neat): 2923, 2286, 1623, 1592, 1508, 1471, 1415, 1360, 1324, 1262, 1245, 1205, 1171, 1135, 1083, 1058, 1024, 937, 861, 832, 806, 773, 747, 705, 690, 674, 630, 619.

HRMS (MALDI): calculated mass for C₄₄H₂₈F₆NaO₈S₂⁺ [M+Na⁺]: 885.1022, found: 885.1026, C₄₄H₂₈F₆KO₈S₂⁺ [M + K⁺]: 901.0761, found: 901.0763.

(1S,1"S)-dimethyl 2',2'''-(ethane-1,2-diylbis(oxy))bis([1,1'-binaphthalene]-2-carboxyl-ate) (181)



MeOH (6.1 mL) and Hünig's base (0.73 mL, 4.17 mmol, 9.0 equiv.) were added at RT. to a solution of **76** (0.4 g, 0.46 mmol, 1.0 equiv.), Pd(OAc)₂ (62 mg, 0.28 mmol, 0.6 equiv.) and DPPP (126 mg, 0.31 mmol, 0.66 equiv.) in DMSO (18 mL). The reaction mixture was then transferred into an autoclave and the reaction mixture was stirred at 110 °C and under 15 bar CO pressure for 72 h.^[1] The reaction mixture was allowed to cool to RT. and was then diluted with water and extracted with DCM. The combined organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The product was purified by flash chromatography (Hexanes/EtOAc 5:1) and was concentrated in vacuo to give **181** (102 mg, 32%) as a white solid.

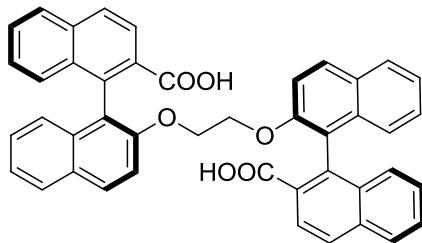
¹H NMR (400 MHz, CDCl₃): δ = 8.17 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.7 Hz, 2H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 9.0 Hz, 2H), 7.53 (ddd, *J* = 8.1, 4.9, 3.1 Hz, 2H), 7.39–7.15 (m, 8H), 6.96 (t, *J* = 8.3 Hz, 4H), 3.92 (s, 4H), 3.45 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ = 167.8, 153.4, 137.1, 135.1, 133.7, 133.0, 129.4, 129.1, 128.9, 127.9 (2 peaks), 127.7, 127.6, 126.6, 126.3, 126.1 (2 peaks), 124.9, 123.7, 122.8, 115.6, 68.8, 51.8.

IR (neat): 2948, 1724, 1621, 1593, 1507, 1460, 1432, 1360, 1330, 1274, 1238, 1149, 1125, 1081, 1057, 1022, 977, 941, 871.

HRMS (MALDI): calculated mass for C₄₆H₃₄NaO₆⁺ [M+Na⁺]: 705.2248, found: 705.2242.

(1S,1'S)-2',2'''-(ethane-1,2-diylbis(oxy))bis([1,1'-binaphthalene]-2-carboxylic acid)) (170)



181 (75 mg, 0.11 mmol, 1.0 equiv.) was dissolved in 2 M KOH (30 mL) and was stirred at 50 °C for 14 h. The reaction mixture was allowed to cool to RT. and was then acidified by addition of conc. HCl (pH was adjusted to 2) and extracted with DCM. The combined organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure to give **170** (70 mg, 97%) as a white solid.

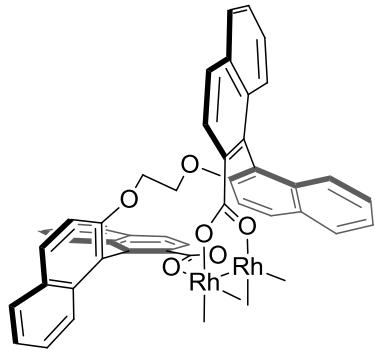
¹H NMR (400 MHz, CDCl₃): δ = 8.09 (d, *J* = 8.7 Hz, 2H), 8.03–7.95 (m, 4H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 9.0 Hz, 2H), 7.54 (ddd, *J* = 8.1, 6.6, 1.4 Hz, 2H), 7.38–7.30 (m, 2H), 7.25–7.15 (m, 6H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.03–3.91 (m, 4H);

¹³C NMR (101 MHz, CDCl₃): δ = 172.7, 153.2, 137.4, 135.5, 133.7, 132.9, 129.6, 129.2, 128.2, 128.0 (2 peaks), 127.9 (2 peaks), 127.8, 126.7, 126.4, 126.4, 125.3, 123.7, 122.1, 115.4, 68.8.

IR (neat): 2925, 2286, 1697, 1678, 1621, 1593, 1510, 1463, 1433, 1407, 1328, 1273, 1242, 1219, 1146, 1073, 1058, 1024, 980, 946, 871, 834, 801, 768, 744, 629 .

HRMS (MALDI): calculated mass for C₄₄H₃₀O₆⁺ [M⁺]: 654.2037, found: 654.2037.

Synthesis of Rh₂(elba)₂ (182)



Rh₂(OAc)₄ (20.3 mg, 0.046 mmol, 1.0 equiv.) and **170** (60.0 mg, 0.92 mmol, 2.0 equiv.) were dissolved in chlorobenzene (2 mL) and the reaction mixture was stirred at 130 °C for 14 h. The reaction mixture was allowed to cool to room temperature and was purified directly by flash chromatography (Hexanes/EtOAc 3:1) to give **182** (62.0 mg, 90%) as a green solid.

¹H NMR (400 MHz, CDCl₃): δ = 8.10–7.67 (m, 8H), 7.58–7.37 (m, 6H), 7.28–7.02 (m, 6H), 6.87 (d, *J* = 8.4 Hz, 4H), 3.61–3.38 (m, 4H).

¹³C NMR (101 MHz, CDCl₃): δ = 185.3, 153.6, 134.4, 133.8, 133.8, 132.7, 131.3, 131.2, 129.3, 128.9, 127.9, 127.8, 127.5, 126.8, 126.8, 126.2, 125.9, 124.5, 123.7, 117.5, 100.0, 69.6.

IR (neat): 3054, 2924, 2359, 1732, 1696, 1648, 1621, 1591, 1559, 1509, 1462, 1391, 1316, 1261, 1222, 1175, 1150, 1082, 1045, 979, 949, 870, 795, 767, 747, 701, 668, 611, 634 .

HRMS (MALDI): calculated mass for C₈₈H₅₆NaO₁₂Rh₂⁺ [M + Na⁺]: 1533.1774, found: 1533.1770 and calculated mass for C₈₈H₅₆KO₁₂Rh₂⁺ [M + K⁺]: 1549.1513, found: 1549.1513.

General procedure 4.3 (GP 4.3) for asymmetric cyclopropenation using different rhodium catalysts and Trifluoroethylamine hydrochloride (Table 14): The appropriate catalyst (1.9 µmol, 0.025 equiv.) was dissolved in but-3-yn-1-ylbenzene (10.8 µL, 10 mg, 0.08 mmol, 1.0 equiv.), then NaOAc (1.2 mg, 0.02 mmol, 0.2 equiv.), trifluoroethylamine hydrochloride (20 mg, 0.15 mmol, 2.0 equiv.), degassed water (0.3 mL) and H₂SO₄ (0.73 mg, 0.01 mmol, 0.1 equiv.) were added. A solution of NaNO₃ (13 mg, 0.15 mmol, 2.0 equiv.) in degassed water (0.5 mL) was added at RT by means of a syringe pump during 10 h. After additional 4 h., DCM and water were added, and the water phase was extracted with DCM, dried over MgSO₄ and evaporated under reduced pressure. The crude product was used to determine conversion by ¹H-NMR. The product was purified by Preparative TLC (pentane) and isolated by extraction with Hexanes. Enantiomeric excess was determined by SFC analysis (OB-H, 100% CO₂, 15 °C, 1.0 mL/min, 210 nm): t_R = 7.74 min and 9.24 min.

General procedure 4.4 (GP 4.4) for asymmetric cyclopropanation using different rhodium catalysts and Trifluoroethylamine hydrochloride (Table 15): The appropriate catalyst (1.9 µmol, 0.025 equiv.) was dissolved in *para*-methoxy styrene (10.0 µL, 10 mg, 0.08 mmol, 1.0 equiv.), then NaOAc (1.2 mg, 0.02 mmol, 0.2 equiv.), trifluoroethylamine hydrochloride (20 mg, 0.15 mmol, 2.0 equiv.), degassed water (0.3 mL) and H₂SO₄ (0.73 mg, 0.01 mmol, 0.1 equiv.) were added. A solution of NaNO₃ (13 mg, 0.15 mmol, 2.0 equiv.) in degassed water (0.5 mL) was added at RT. by means of a syringe pump during 10 h. After additional 4 h., DCM and water were added, and the water phase was extracted with DCM, dried over MgSO₄ and evaporated under reduced pressure. The crude product was used to determine conversion by ¹H-NMR and enantiomeric excess by SFC analysis (IB, 100% CO₂, 25 °C, 2.0 mL/min, 195 nm): t_R = 3.93 min and 4.14 min, 6.49 min and 7.01 min.

General procedure 4.5 (GP 4.5) for asymmetric intramolecular cyclopropanation using different rhodium catalysts (Table 16): A solution of allyl 2-diazo-2-phenylacetate (10 mg, 0.05 mmol, 1.0 eq.) in DCM (1 mL) was added at 40 °C, RT or 10 °C respectively, by means of a syringe pump during 2 h to a solution of the appropriate catalyst (1.2 µmol, 0.025 equiv.) in DCM (0.75 mL). After complete conversion of starting material (3 h, 5 h or 14 h respectively) the solvent was removed under reduced pressure. The crude product was used to determine conversion by ¹H-NMR.

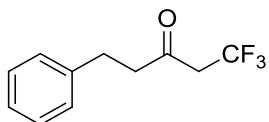
The product (**184**) was purified by Preparative TLC (Hexanes/EtOAc 5:1) and was isolated by extraction with Hexanes/ⁱPrOH 97.5/2.5. Enantiomeric excess was determined by SFC analysis (AS-H, 98:2 CO₂MeOH, 25 °C, 2.0 mL/min, 200 nm): t_R = 5.81 min and 6.62 min.

8.4. Experimental Part to Chapter 5

General procedure 5.1 (GP 5.1) for the screening of Lewis acids (Table 17 and 19): Trifluoroethylamine hydrochloride (2.0 equiv.) and NaNO₂ (2.4 equiv.) are dissolved in a CH₂Cl₂/H₂O mixture (3 mL/0.1 mL) and stirred for one hour in a sealed Schlenk (10 mL) in an ice bath under Ar atmosphere. The yellow mixture is then cooled to -78 °C in a dry-ice/acetone bath and stirred for 10 min, followed by the addition of the substrate (0.22 mmol) and the Lewis acid. After 45 min, the mixture is quenched by the addition of MeOH (3 mL) followed by sat. NaHCO₃, extracted with DCM (3x), dried over MgSO₄ and evaporated in vacuo. The crude product was then analyzed by NMR (yield was determined by ¹⁹F-NMR analysis with an internal standard).

General procedure 5.2 (GP 5.2) for the Ring Expansion and Roskamp Reaction (Table 18 and 20): Trifluoroethylamine hydrochloride (60 mg, 0.44 mmol, 2.0 equiv.) and NaNO₂ (36 mg, 0.52 mmol, 2.4 equiv.) are dissolved in a DCM/water mixture (3 mL/0.1 mL) and stirred for one hour in a sealed Schlenk (10 mL) in an ice bath under Ar atmosphere. The yellow mixture is then cooled to -78 °C in a dry-ice/acetone bath and stirred for 10 min, followed by the addition of the substrate (0.22 mmol) and ZrCl₄ (67 mg, 0.29 mmol, 1.3 equiv.). After 45 min, the mixture is quenched by the addition of MeOH (3 mL) followed by sat. NaHCO₃, extracted with DCM (3x), dried over MgSO₄ and evaporated in vacuo. After analysis of the crude NMR spectrum, the crude mixture was chromatographed on silica gel (pentane/diethyl ether) to afford the pure product.

1,1,1-trifluoro-5-phenylpentan-3-one (192, Table 20, Entry 1)



Was obtained as an oil (32 mg, 67 %) following the GP 5.2.

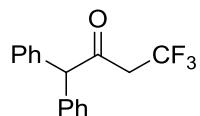
¹H-NMR (300 MHz, CDCl₃): δ = 7.33–7.15 (m, 5H), 3.19 (q, *J* = 10.4 Hz, 2H), 2.97–2.83 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 199.1 (q, *J* = 2.3 Hz), 140.1, 128.6, 128.3, 126.4, 123.6 (q, *J* = 277.0 Hz), 46.5 (q, *J* = 28.3 Hz), 45.0 (q, *J* = 1.9 Hz), 29.2.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.3 (t, *J* = 10.4 Hz).

Data were in accordance with literature.²⁰⁷

4,4,4-trifluoro-1,1-diphenylbutan-2-one (256, Table 20, Entry 2)



Was obtained as an oil (45 mg, 74 %) following **GP 5.2.**

¹H-NMR (300 MHz, CDCl₃): δ = 7.40–7.20 (m, 10H), 5.20 (s, 1H), 3.33 (q, *J* = 10.2 Hz, 2H).

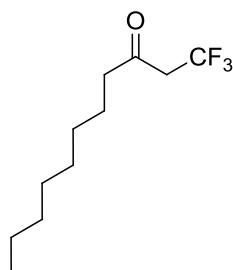
¹³C-NMR (100 MHz, CDCl₃): δ = 197.9 (q, *J* = 2.1 Hz), 136.7, 129.0 (2 C), 127.8, 123.6 (q, *J* = 277.2 Hz), 64.8 (q, *J* = 1.8 Hz), 45.8 (q, *J* = 28.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.3 (t, *J* = 10.1 Hz).

HRMS (EI): calcd for C₁₆H₁₃F₃O⁺ [M]⁺ 278.0913, found 278.0919.

IR (neat): 3030, 2930, 1729, 1495, 1364, 1258, 1151, 1099, 1045.

1,1,1-trifluoroundecan-3-one (257, Table 20, Entry 3)



Was obtained as an oil (32 mg, 65 %) following **GP 5.2.**

²⁰⁷ Y. Itoh, K. Mikami, *Tetrahedron* **2006**, 62, 7199.

¹H-NMR (300 MHz, CDCl₃): δ = 3.21 (q, *J* = 10.5 Hz, 2H), 2.52 (t, *J* = 7.3 Hz, 2H), 1.65–1.53 (m, 2H), 1.35–1.20 (m, 10H), 0.96–0.84 (m, 3H).

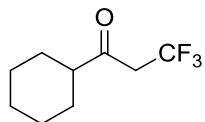
¹³C-NMR (100 MHz, CDCl₃): δ = 200.2 (q, *J* = 2.2 Hz), 123.7 (q, *J* = 277.0 Hz), 46.3 (q, *J* = 28.1 Hz), 43.5 (q, *J* = 1.9 Hz), 31.2, 29.3, 29.1, 28.9, 23.2, 22.6, 14.1.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.4 (t, *J* = 10.4 Hz).

HRMS (EI): calcd for C₁₁H₁₉F₃O⁺ [M]⁺ 224.1383, found 224.1389.

IR (neat): 2926, 2856, 1729, 1376, 1268, 1155, 1092.

1-cyclohexyl-3,3,3-trifluoropropan-1-one (258, Table 20, Entry 4)



Was obtained as an oil (30 mg, 70 %) following **GP 5.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 3.25 (q, *J* = 10.3 Hz, 2H), 2.45–2.35 (m, 1H), 1.95–1.65 (m, 5H), 1.43–1.15 (m, 5H).

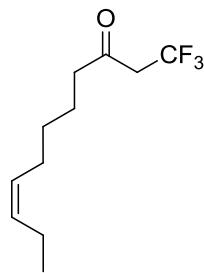
¹³C-NMR (100 MHz, CDCl₃): δ = 203.1 (q, *J* = 2.0 Hz), 123.8 (q, *J* = 277.0 Hz), 51.2 (q, *J* = 1.6 Hz), 43.8 (q, *J* = 27.9 Hz), 27.9, 25.6, 25.4.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.3 (t, *J* = 10.2 Hz).

Data were in accordance with the literature.²⁰⁸

(Z)-1,1,1-trifluoroundec-8-en-3-one (259, Table 20, Entry 5)

²⁰⁸ See Reference 166.



Was obtained as an oil (34 mg, 70 %) following **GP 5.2.**

¹H-NMR (300 MHz, CDCl₃): δ = 5.43–5.23 (m, 2H), 3.21 (q, *J* = 10.5 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.03 (p, *J* = 7.1 Hz, 4H), 1.68–1.55 (m, 2H), 1.40–1.30 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H).

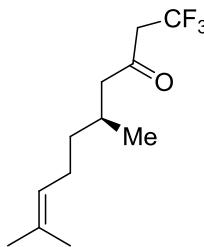
¹³C-NMR (100 MHz, CDCl₃): δ = 200.0 (q, *J* = 2.2 Hz), 132.3, 128.3, 123.6 (q, *J* = 276.9 Hz), 46.3 (q, *J* = 28.2 Hz), 43.4 (q, *J* = 1.9 Hz), 28.9, 26.7, 22.8, 20.5, 14.3.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.4 (t, *J* = 10.4 Hz).

HRMS (EI): calcd for C₁₁H₁₇F₃O⁺ [M]⁺ 222.1226, found 222.1231.

IR (neat): 2936, 1730, 1419, 1366, 1266, 1155.

(S)-1,1,1-trifluoro-5,9-dimethyldec-8-en-3-one (260, Table 20, Entry 6)



Was obtained as an oil (38 mg, 73 %) following **GP 5.2.**

¹H-NMR (300 MHz, CDCl₃): δ = 5.11–5.03 (m, 1H), 3.19 (q, *J* = 10.5 Hz, 2H), 2.42 (ddd, *J* = 24.8, 16.8, 6.8 Hz, 2H), 2.10–1.90 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.40–1.15 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 199.8 (q, *J* = 2.2 Hz), 131.8, 124.0, 123.6 (q, *J* = 277.0 Hz), 50.8 (q, *J* = 1.8 Hz), 46.6 (q, *J* = 28.0 Hz), 36.7, 28.5, 25.7, 25.4, 19.6, 17.6.

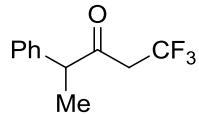
¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.4 (t, *J* = 10.4 Hz).

HRMS (EI): calcd for $C_{12}H_{19}F_3O^+ [M]^+$ 236.1383, found 236.1384.

IR (neat): 2964, 2918, 1729, 1375, 1267, 1147, 1039.

α_{25}^D : -6.48 (c = 1, CHCl₃)

1,1,1-trifluoro-4-phenylpentan-3-one (261, Table 20, Entry 7)



Was obtained as an oil (30 mg, 63 %) following **GP 5.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.40–7.15 (m, 5H), 3.79 (q, J = 6.9 Hz, 1H), 3.31–3.02 (m, 2H), 1.43 (d, J = 6.9 Hz, 3H).

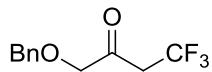
¹³C-NMR (100 MHz, CDCl₃): δ = 200.0 (q, J = 2.1 Hz), 138.9, 129.4, 127.9, 127.8, 123.6 (q, J = 277.0 Hz), 53.8 (q, J = 1.7 Hz), 44.0 (q, J = 28.2 Hz), 17.0.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.5 (t, J = 10.2 Hz).

HRMS (EI): calcd for $C_{11}H_{11}F_3O^+ [M]^+$ 216.0757, found 216.0757.

IR (neat): 2934, 1731, 1366, 1266, 1109, 1026.

1-(benzyloxy)-4,4,4-trifluorobutan-2-one (262, Table 20, Entry 8)



Was obtained as an oil (24 mg, 47 %) following **GP 5.2** using ZrCl₄ (2.6 equiv), NaNO₂ (4.8 equiv) and CF₃CH₂NH₃Cl (4.0 equiv).

¹H-NMR (300 MHz, CDCl₃): δ = 7.46–7.28 (m, 5H), 4.60 (s, 2H), 4.09 (s, 2H), 3.39 (q, J = 10.3 Hz, 2H).

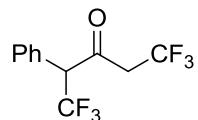
¹³C-NMR (100 MHz, CDCl₃): δ = 198.8 (q, J = 2.2 Hz), 136.5, 128.7, 128.4, 128.0, 123.7 (q, J = 276.8 Hz), 75.0 (q, J = 1.9 Hz), 73.7, 42.8 (q, J = 28.7 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.3 (t, J = 10.2 Hz).

HRMS (EI): calcd for C₁₁H₁₁F₃O₂⁺ [M]⁺ 232.0706, found 232.0713.

IR (neat): 3033, 2868, 1742, 1267, 1109.

1,1,1,5,5,5-hexafluoro-2-phenylpentan-3-one (263, Table 20, Entry 9)



Was obtained as an oil (40 mg, 67 %) following **GP 5.2** using ZrCl₄ (2.6 equiv.), CF₃CH₂NH₃Cl (4.0 equiv.) and NaNO₂ (4.8 equiv.) in CH₂Cl₂/H₂O (6 mL/0.2 mL).

¹H-NMR (300 MHz, CDCl₃): δ = 7.81–7.03 (m, 5H), 4.45 (q, J = 8.1 Hz, 1H), 3.43–2.78 (m, 2H).

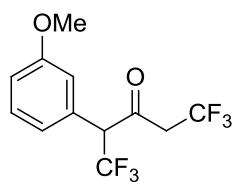
¹³C-NMR (100 MHz, CDCl₃): δ = 190.8, 130.0, 129.8, 129.7, 127.5, 123.6 (q, J = 280.3 Hz), 123.0 (q, J = 277.4 Hz), 61.5 (q, J = 27.5 Hz), 45.1 (q, J = 29.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.4 (t, J = 9.8 Hz), -66.7 (d, J = 8.1 Hz).

HRMS (EI): calcd for C₁₁H₈F₆O⁺ [M]⁺ 270.0474, found 270.0472.

IR (neat): 2987, 2901, 1742, 1373, 1255, 1104, 1045.

1,1,1,5,5,5-hexafluoro-2-(3-methoxyphenyl)pentan-3-one (264, Table 20, Entry 10)



Was obtained as an oil (25 mg, 76 %) following **GP 5.2** using ZrCl₄ (2.6 equiv.), CF₃CH₂NH₃Cl (4.0 equiv.) and NaNO₂ (4.8 equiv.) in CH₂Cl₂/H₂O (3 mL/0.1 mL) on a 0.11 mmol scale.

¹H-NMR (300 MHz, CDCl₃): δ = 7.36 (m, 1H), 6.93 (m, 3H), 4.41 (q, *J* = 8.1 Hz, 1H), 3.82 (s, 3H), 3.45–2.85 (m, 2H).

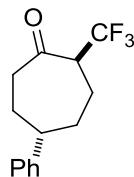
¹³C-NMR (100 MHz, CDCl₃): δ = 190.7, 160.4, 130.8, 128.7 (q, *J* = 1.7 Hz), 123.2 (q, *J* = 280.2 Hz), 123.0 (q, *J* = 277.3 Hz), 122.0, 115.5, 115.4, 61.4 (q, *J* = 29.2 Hz), 55.4, 45.1 (q, *J* = 29.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -62.4 (t, *J* = 9.9 Hz), -66.6 (d, *J* = 8.0 Hz).

HRMS (EI): calcd for C₁₂H₁₀F₆O₂⁺ [M]⁺ 300.0580, found 300.0580.

IR (neat): 2947, 2842, 1742, 1602, 1258, 1156.

(±)-(2S,5S)-5-phenyl-2-(trifluoromethyl)cycloheptanones (190 trans, Table 18, Entry 1)



Was obtained as an oil (45 mg, 80 %) following **GP 5.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 7.35–7.15 (m, 5H), 3.33 (dqd, *J* = 12.6, 8.8, 3.8 Hz, 1H), 2.90–2.75 (m, 1H), 2.75–2.60 (m, 2H), 2.38–2.25 (m, 1H), 2.25–2.05 (m, 2H), 1.98–1.78 (m, 2H), 1.73–1.58 (m, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 205.7, 146.5, 128.7, 126.6, 126.4, 124.8 (q, *J* = 280.2 Hz), 56.1 (q, *J* = 25.0 Hz), 47.9, 42.2 (q, *J* = 1.6 Hz), 35.5, 32.5, 24.6.

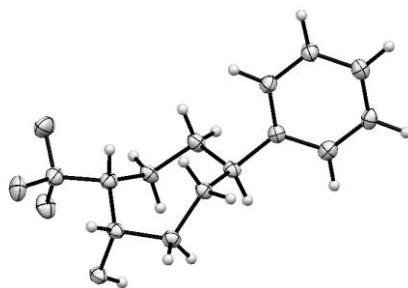
¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.5 (d, *J* = 8.7 Hz).

HRMS (EI): calcd for C₁₄H₁₅F₃O⁺ [M]⁺ 256.1070, found 256.1069.

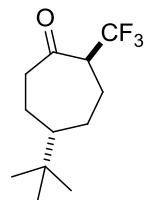
IR (neat): 2933, 2873, 1714, 1276, 1175, 1095, 759.

Relative stereochemistry was determined after the reduction with excess NaBH₄ in MeOH (15:1 dr in ¹⁹F-NMR). Crystals of this alcohol product were grown by slow evaporation from an EtOH solution.

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(\pm)-(2*S*,5*S*)-5-tert-butyl-2-(trifluoromethyl)cycloheptanones (265, Table 18, Entry 2)



Was obtained as an oil (40 mg, 77 %) following **GP 5.2**.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 3.24$ (dqd, $J = 12.3, 8.7, 3.6$ Hz, 1H), 2.65–2.50 (m, 2H), 2.30–2.00 (m, 3H), 1.73–1.58 (m, 1H), 1.42–1.28 (m, 1H), 1.18–1.00 (m, 2H), 0.88 (s, 9H).

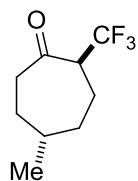
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 206.4, 124.8$ (q, $J = 280.0$ Hz), 55.6 (q, $J = 24.9$ Hz), 51.3, 42.4 (q, $J = 1.7$ Hz), 33.6, 28.8, 27.4, 26.1, 25.0 (q, $J = 2.3$ Hz).

$^{19}\text{F-NMR}$ (282 MHz, CDCl_3): $\delta = -68.7$ (d, $J = 8.6$ Hz).

HRMS (EI): calcd for $\text{C}_{12}\text{H}_{19}\text{F}_3\text{O}^+$ [M]⁺ 236.1383, found 236.1392.

IR (neat): 2960, 2871, 1718, 1278, 1172, 1098.

(\pm)-(2*S*,5*S*)-5-methyl-2-(trifluoromethyl)cycloheptanones (266, Table 18, Entry 3)



Was obtained as an oil (30 mg, 70 %) following **GP 5.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 3.20 (dqd, *J* = 12.6, 8.8, 3.8 Hz, 1H), 2.72–2.50 (m, 2H), 2.23–2.12 (m, 1H), 2.05–1.65 (m, 3H), 1.65–1.50 (m, 1H), 1.42–1.05 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H).

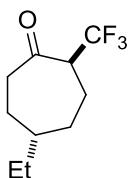
¹³C-NMR (100 MHz, CDCl₃): δ = 206.1, 124.8 (q, *J* = 280.1 Hz), 56.0 (q, *J* = 24.8 Hz), 42.0 (q, *J* = 1.7 Hz), 36.1, 36.0, 32.9, 24.2, 23.5.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.6 (d, *J* = 8.8 Hz).

HRMS (EI): calcd for C₉H₁₃F₃O⁺ [M]⁺ 194.0913, found 194.0908.

IR (neat): 2931, 2874, 1715, 1278, 1182, 1100.

(±)-(2S,5S)-5-ethyl-2-(trifluoromethyl)cycloheptanones (267, Table 18, Entry 4)



Was obtained as an oil (35 mg, 76 %) following **GP 5.2**.

¹H-NMR (300 MHz, CDCl₃): δ = 3.29–3.14 (m, 1H), 2.70–2.50 (m, 2H), 2.25–2.15 (m, 1H), 2.05–1.88 (m, 2H), 1.80–1.65 (m, 1H), 1.40–1.20 (m, 4H), 1.20–1.05 (m, 1H), 0.90 (t, *J* = 7.1 Hz, 3H).

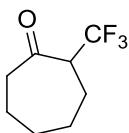
¹³C-NMR (100 MHz, CDCl₃): δ = 206.2, 124.8 (q, *J* = 280.1 Hz), 55.8 (q, *J* = 24.8 Hz), 42.6, 42.4 (q, *J* = 1.6 Hz), 33.5, 30.5, 30.2, 24.2, 11.4.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.4 (d, *J* = 8.7 Hz).

HRMS (EI): calcd for C₁₀H₁₅F₃O⁺ [M]⁺ 208.1070, found 208.1069.

IR (neat): 2935, 2861, 1717, 1277, 1181, 1088, 908.

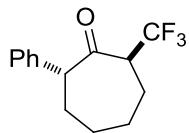
(±)-2-(trifluoromethyl)cycloheptanones (268, Table 18, Entry 5)



Was obtained as an oil (28 mg, 71 %) following **GP 5.2**.

Spectroscopic data were in accordance with the literature.²⁰⁷

(\pm)-(2R,7S)-2-phenyl-7-(trifluoromethyl)cycloheptanones (269, Table 18, Entry 6)



Was obtained as a white solid (48 mg, 85 %) following **GP 5.2**.

Obtained in 91 % yield (803 mg) on a 3.44 mmol scale with two additions of ZrCl₄ (total 2.6 equiv.).

¹H-NMR (300 MHz, CDCl₃): δ = 7.38–7.23 (m, 5H), 3.90 (dd, *J* = 12.1, 4.2 Hz, 1H), 3.47–3.31 (m, 1H), 2.30–2.00 (m, 4H), 2.00–1.71 (m, 2H), 1.55–1.40 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 205.4, 138.3, 128.7, 127.6, 127.4, 124.8 (q, *J* = 280.2 Hz), 58.0, 54.8 (q, *J* = 25.3 Hz), 31.6, 28.0, 27.6, 25.6 (q, *J* = 4.5 Hz.)

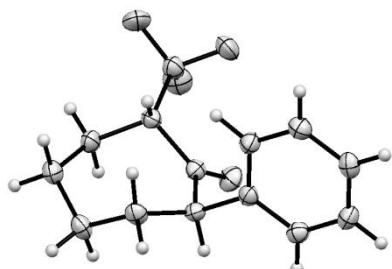
¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.1 (d, *J* = 8.4 Hz).

HRMS (EI): calcd for C₁₄H₁₅F₃O⁺ [M]⁺ 256.1070, found 256.1068.

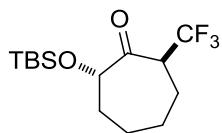
IR (neat): 2934, 2860, 1707, 1276, 1161, 1096, 919.

X-Ray crystals were grown by slow evaporation of a DCM solution

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(\pm)-(2S,7S)-2-(tert-butyldimethylsilyloxy)-7-(trifluoromethyl)cycloheptanones (270, Table 18, Entry 7)



Was obtained as an oil (58 mg, 85 %) following **GP 5.2.**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 4.28$ (ddd, $J = 6.6, 4.8, 1.7$ Hz, 1H), 3.44 (qd, $J = 9.4, 4.7$ Hz, 1H), 2.70–2.45 (m, 2H), 2.00–1.80 (m, 3H), 1.75–1.50 (m, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

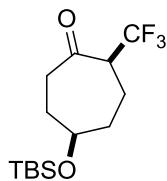
$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 204.2, 124.6$ (q, $J = 280.7$ Hz), 66.0 (q, $J = 2.4$ Hz), 63.8 (q, $J = 23.0$ Hz), 43.4 (q, $J = 1.4$ Hz), 34.6, 25.7, 24.4, 22.1, 17.9, -4.7, -5.3.

$^{19}\text{F-NMR}$ (282 MHz, CDCl_3): $\delta = -65.2$ (d, $J = 9.3$ Hz).

HRMS (EI): calcd for $\text{C}_{13}\text{H}_{22}\text{F}_3\text{O}_2\text{Si}^+ [\text{M}-\text{CH}_3]^+$ 295.1336, found 295.1342.

IR (neat): 2931, 2859, 1724, 1363, 1216, 1056, 834.

(\pm)-(2S,5R)-5-(tert-butyldimethylsilyloxy)-2-(trifluoromethyl)cycloheptanones (271, Table 18, Entry 8)



Was obtained as an oil (52 mg, 76 %) following **GP 5.2.**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 4.19$ (tt, $J = 5.3, 1.7$ Hz, 1H), 3.12 (dqd, $J = 12.4, 8.9, 3.7$ Hz, 1H), 2.98 (ddd, $J = 14.7, 12.7, 3.5$ Hz, 1H), 2.31 (ddd, $J = 14.7, 5.6, 3.2$ Hz, 1H), 2.19 (dtd, $J = 14.1, 11.9, 1.8$ Hz, 1H), 2.07–1.80 (m, 3H), 1.77–1.65 (m, 1H), 1.49 (ddt, $J = 14.2, 12.1, 2.0$ Hz, 1H), 0.89 (s, 9H), 0.05 (s, 6H).

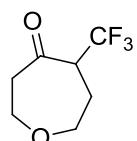
¹³C-NMR (100 MHz, CDCl₃): δ = 205.7, 124.9 (q, *J* = 280.2 Hz), 67.0, 55.8 (q, *J* = 24.7 Hz), 36.4 (q, *J* = 1.7 Hz), 35.0, 31.9, 25.7, 18.0, 17.1 (q, *J* = 2.5 Hz), -4.9, -5.0.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.5 (d, *J* = 8.8 Hz).

HRMS (EI): calcd for C₁₀H₁₆F₃O₂Si⁺ [M-C₄H₉]⁺ 253.0867, found 253.0870.

IR (neat): 2930, 2857, 1720, 1254, 1155, 1075, 835.

5-(trifluoromethyl)oxepan-4-one (272, Table 18, Entry 9)



Was obtained as an oil (26 mg, 65 %) following a modified **GP 5.2** (two further additions of ZrCl₄ (1.3 equiv.) after 30 min and 1 h, followed by stirring during 2 h before quenching). Total 3.9 equiv. ZrCl₄.

¹H-NMR (300 MHz, CDCl₃): δ = 4.14 (dt, *J* = 13.2, 3.9 Hz, 1H), 4.05 (dt, *J* = 12.9, 4.6 Hz, 1H), 3.74–3.55 (m, 2H), 3.53–3.36 (m, 1H), 2.98–2.84 (m, 1H), 2.69 (ddd, *J* = 15.7, 4.6, 3.4 Hz, 1H), 2.17–1.93 (m, 2H).

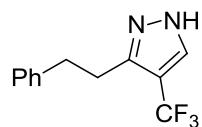
¹³C-NMR (100 MHz, CDCl₃): δ = 202.3, 124.6 (q, *J* = 279.8 Hz), 70.1, 66.2, 54.5 (q, *J* = 25.5 Hz), 46.1 (q, *J* = 1.5 Hz), 26.4 (d, *J* = 2.0 Hz.)

¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.2 (d, *J* = 8.4 Hz).

HRMS (EI): calcd for C₇H₉F₃O₂⁺ [M]⁺ 182.0550, found 182.0549.

IR (neat): 2923, 1723, 1393, 1278, 1126, 1038, 917.

3-phenethyl-4-(trifluoromethyl)-1H-pyrazole (193)



1,1,1-trifluoro-5-phenylpenta-3-one (150 mg, 0.69 mmol, 1 equiv.) was dissolved in toluene (0.7 mL) and *N*-Dimethoxymethyl-*N,N*-dimethylamine (165 mg, 1.38 mmol, 2 equiv.) was added and the mixture was refluxed for 14 h. The solvent was then evaporated in vacuo and the resulting oil was dried for 1 h (< 1 mbar). The crude mixture was then dissolved in EtOH (0.7 mL) and hydrazine monohydrate (174 mg, 3.47 mmol, 5 equiv.) was added. The reaction was refluxed during 3 h, diluted with EtOAc, washed with NaHCO₃ (2 x) and brine. After evaporation of the solvent the product was purified by flash chromatography (hexane/ EtOAc 2:1) to give the pure product as a solid (**193**, 130 mg, 0.54 mmol, 78 %).

¹H-NMR (300 MHz, CDCl₃): δ = 11.35 (s, 1H), 7.70 (s, 1H), 7.44–6.99 (m, 5H), 3.20–2.82 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 145.6 (br s), 140.3, 134.5 (br s), 128.7, 128.4, 126.5, 123.3 (q, *J* = 265.9 Hz), 110.7 (q, *J* = 37.2 Hz), 35.2, 27.5.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -56.2 (s).

HRMS (EI): calcd for C₁₂H₁₁F₃N₂⁺ [M]⁺ 240.0868, found 240.0864.

IR (neat): 3081, 2968, 1523, 1391, 1266, 1138, 1106.

Experiment to prove the conservation of enantiomeric excess:

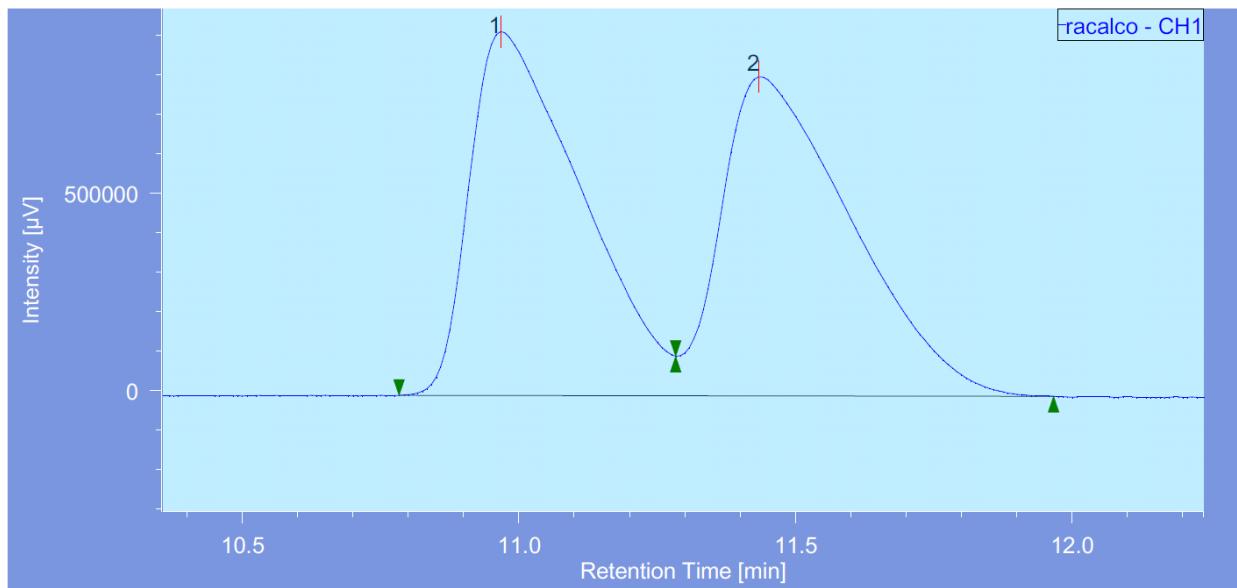
Commercially available (*R*)-(-)-2-Phenylpropionic acid was reduced to the alcohol,²⁰⁹ and then oxidized (DMP)²¹⁰ to the corresponding aldehyde that was immediately used in the homologation reaction using the exact same procedure as for racemic **7**. The crude reaction mixture was quenched at -78°C by addition of MeOH (2 mL) and sat. NaHCO₃, and was finally extracted with hexane and crude enantioenriched **261** was analyzed by chiral SFC (OJ-H, 2 mL/min, 99 % CO₂/1 % MeOH, retention time 11 min, 11.5 min). ee > 99 %

On the other hand, some freshly prepared aldehyde (from the same batch as the one used in the homologation above) was reduced with excess NaBH₄ and the ee of the alcohol was measured on chiral SFC (OB-H, 2 mL/min, 100 % CO₂, retention time 3.2 min, 4.3 min). ee > 99 %

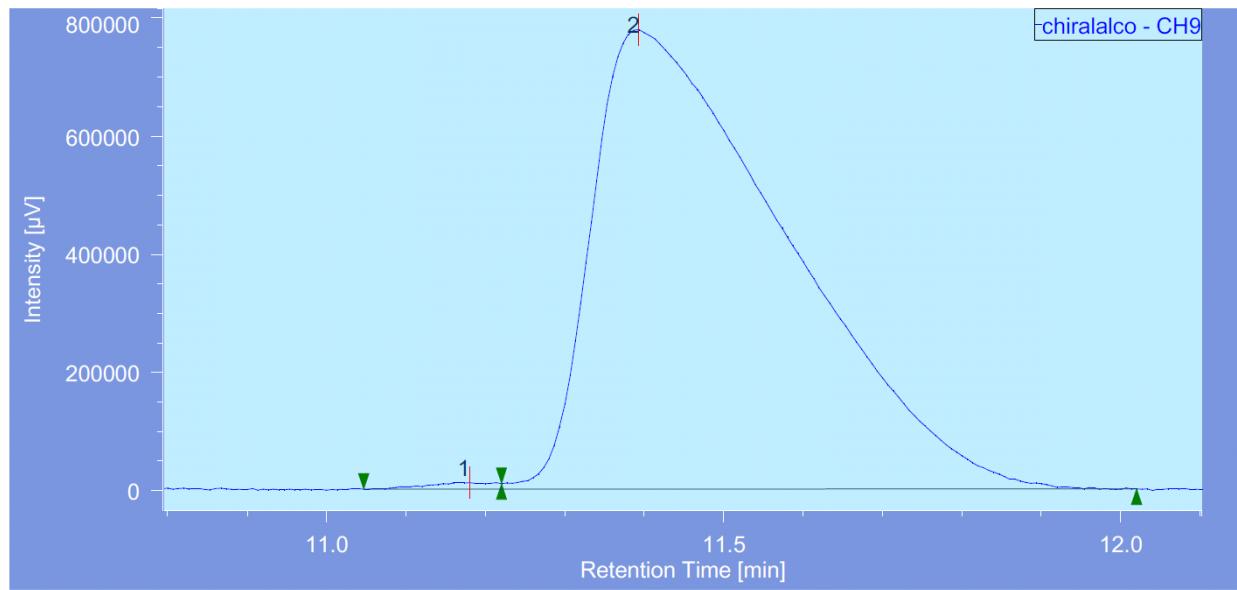
²⁰⁹ A. Chen, L. Ren, C. M. Cradden, *J. Org. Chem.* **1999**, 64, 9704.

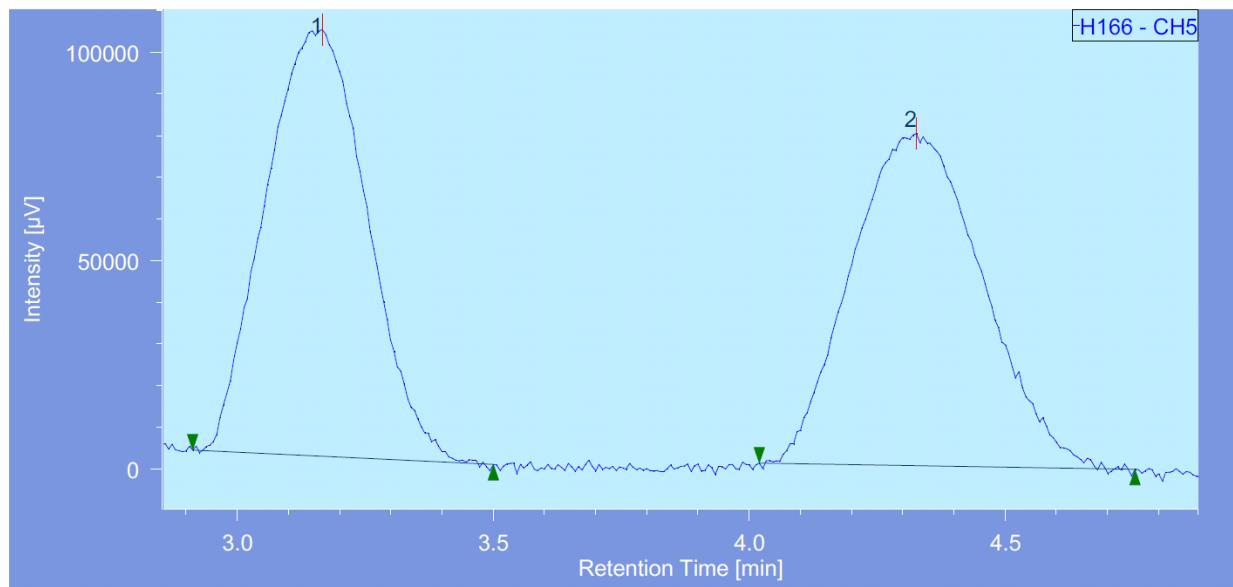
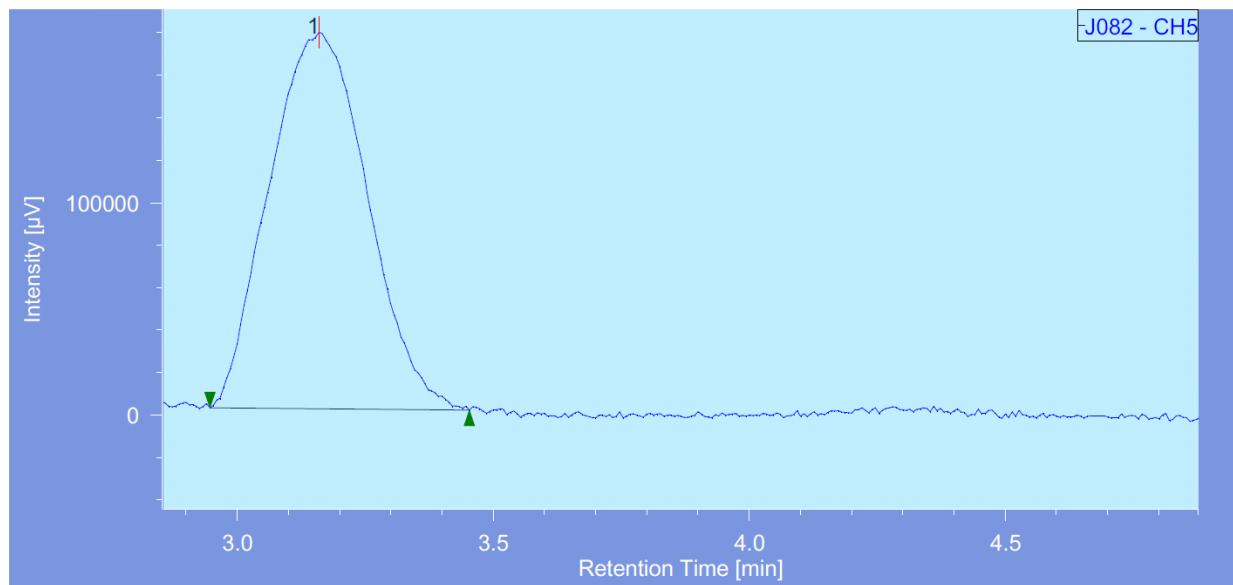
²¹⁰ M. Vogt, S. Ceylan, A. Kirschning, *Tetrahedron* **2010**, 66, 6450.

Racemic alcohol



Enantioenriched alcohol (from aldehyde reduction)

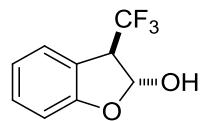


Racemic **261** (trifluoroethylketone)Enantioenriched **261**

General procedure 5.3 (GP 5.3) for the screening of Lewis Acids (Table 21): Trifluoroethylamine hydrochloride (3.0 equiv.) and NaNO₂ (3.6 equiv.) are dissolved in a CH₂Cl₂/water mixture (3 mL/0.1 mL) and stirred for one hour in a sealed Schlenk (10 mL) in an ice bath under Ar atmosphere. The yellow mixture is then cooled to -78 °C in a dry-ice/acetone bath and stirred for 10 min, followed by the addition of salicylaldehyde (**195**, 0.22 mmol) and the Lewis Acid. After 45 min, the mixture is quenched by the addition of MeOH (3 mL) followed by sat. NaHCO₃, extracted with CH₂Cl₂ (3x), dried over MgSO₄ and evaporated in vacuo. The crude product was then analyzed by NMR (yields were determined by ¹⁹F-NMR analysis with trifluorotoluene as a standard).

General procedure 5.4 (GP 5.4) for the homologation of salicylaldehydes (Table 22): Trifluoroethylamine hydrochloride (90 mg, 0.66 mmol, 3.0 equiv.) and NaNO₂ (54 mg, 0.78 mmol, 3.6 equiv.) are dissolved in a CH₂Cl₂/water mixture (3 mL/0.1 mL) and stirred for one hour in a sealed Schlenk (10 mL) in an ice bath under Ar atmosphere. The yellow mixture is then cooled to -78 °C in a dry-ice/acetone bath and stirred for 10 min, followed by the addition of the substrate (0.22 mmol) and BF₃•Et₂O (49 µL, 0.40 mmol, 1.8 equiv.). The reaction mixture is then stirred at this temperature until TLC analysis indicates completion, is then quenched by the addition of MeOH (3 mL) followed by sat. NaHCO₃, extracted with CH₂Cl₂ (3x), dried over MgSO₄ and evaporated in vacuo. After analysis of the crude NMR spectrum, the crude mixture was chromatographed on silica gel (CH₂Cl₂) to afford the pure product.

(2RS,3RS)-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (**196**, Table 22, Entry 1)



Was obtained as an oil (33 mg, 74 %) following **GP 5.4** (stirred for 45 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.41–7.28 (m, 2H), 7.01 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 1H), 6.09 (dd, *J* = 4.4, 2.1 Hz, 1H), 3.92 (qd, *J* = 9.2, 1.8 Hz, 1H), 3.52 (d, *J* = 4.4 Hz, 1H).

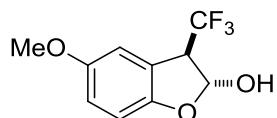
¹³C-NMR (100 MHz, CDCl₃): δ = 158.7, 130.8, 126.1, 125.0 (q, J = 278.4 Hz), 121.9, 118.9 (q, J = 2.1 Hz), 110.5, 99.9 (q, J = 3.8 Hz), 54.5 (q, J = 29.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.4 (d, J = 9.1 Hz)

HRMS (EI): calcd for C₉H₇F₃O₂⁺ [M]⁺ 204.0393, found 204.0394.

IR (neat): 3421, 2970, 1483, 1362, 1237, 1126.

(2RS,3RS)-5-methoxy-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (273, Table 22, Entry 2)



Was obtained as a solid (36 mg, 70 %) following **GP 5.4** (stirred for 45 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 6.91 (s, 1H), 6.89–6.78 (m, 2H), 6.06 (dd, J = 4.5, 1.9 Hz, 1H), 3.88 (qd, J = 9.2, 1.8 Hz, 1H), 3.78 (s, 3H), 3.64 (br s, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 154.9, 152.8, 125.0 (q, J = 278.5 Hz), 119.6 (q, J = 2.1 Hz), 116.4, 111.7, 110.7, 100.2 (q, J = 3.7 Hz), 56.1, 55.0 (q, J = 29.1 Hz).

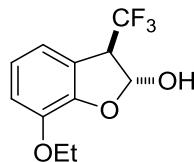
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.2 (d, J = 9.2 Hz)

HRMS (EI): calcd for C₁₀H₉F₃O₃⁺ [M]⁺ 234.0499, found 234.0503.

IR (neat): 3380, 2953, 1492, 1356, 1264, 1118.

MP: 104 °C

(2RS,3RS)-7-ethoxy-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (197, Table 22, Entry 3)



Was obtained as a solid (37 mg, 68 %) following **GP 5.4** (stirred for 30 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.04–6.74 (m, 3H), 6.21 (br s, 1H), 4.43 (s, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.96 (qd, *J* = 9.3, 2.3 Hz, 1H), 1.46 (t, *J* = 7.0 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 147.4, 143.9, 125.1 (q, *J* = 278.4 Hz), 122.4, 120.1 (q, *J* = 2.1 Hz), 117.7, 114.0, 100.7 (q, *J* = 3.8 Hz), 64.4, 54.9 (q, *J* = 29.1 Hz), 14.6.

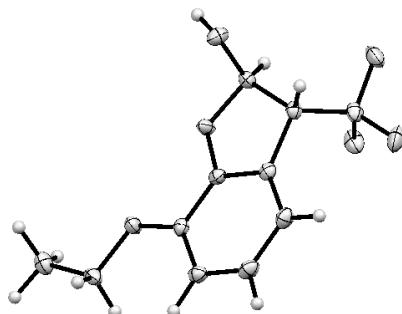
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.2 (d, *J* = 9.2 Hz).

HRMS (EI): calcd for C₁₁H₁₁F₃O₃⁺ [M]⁺ 248.0655, found 248.0655.

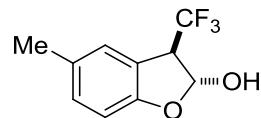
IR (neat): 3200, 2970, 1450, 1215.

MP: 134 °C

Crystal structure. Crystals were grown by slow evaporation from a CHCl₃ solution.



(2RS,3RS)-5-methyl-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (274, Table 22, Entry 4)



Was obtained as a solid (34 mg, 71 %) following **GP 5.4** (stirred for 30 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.16 (s, 1H), 7.14–7.07 (m, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.06 (dd, *J* = 4.6, 2.1 Hz, 1H), 3.87 (qd, *J* = 9.1, 1.9 Hz, 1H), 3.54 (d, *J* = 4.6 Hz, 1H), 2.33 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 156.6, 131.4, 131.2, 126.4, 125.0 (q, *J* = 278.5 Hz), 118.8 (q, *J* = 2.1 Hz), 110.1, 100.1 (q, *J* = 3.8 Hz), 54.6 (q, *J* = 29.1 Hz), 20.8.

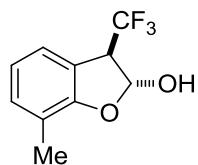
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.3 (d, *J* = 9.2 Hz).

HRMS (EI): calcd for C₁₀H₉F₃O₂⁺ [M]⁺ 218.0550, found 218.0548.

IR (neat): 3294, 2970, 1491, 1350, 1216.

MP: 77 °C

(2RS,3RS)-7-methyl-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (275, Table 22, Entry 5)



Was obtained as an oil (32 mg, 67 %) following **GP 5.4** (stirred for 90 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.24–7.08 (m, 2H), 6.91 (t, J = 7.5 Hz, 1H), 6.09 (dd, J = 4.6, 2.2 Hz, 1H), 3.92 (qd, J = 9.3, 1.9 Hz, 1H), 3.44 (d, J = 4.6 Hz, 1H), 2.26 (s, 3H).

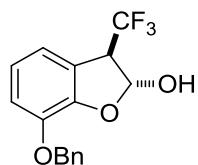
¹³C-NMR (100 MHz, CDCl₃): δ = 157.2, 131.9, 125.1 (q, J = 278.4 Hz), 123.3, 121.8, 120.7, 118.1 (q, J = 2.1 Hz), 99.7 (q, J = 3.8 Hz), 54.9 (q, J = 29.0 Hz), 15.1.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.4 (d, J = 9.2 Hz).

HRMS (EI): calcd for C₁₀H₉F₃O₂⁺ [M]⁺ 218.0550, found 218.0553.

IR (neat): 3418, 2970, 1468, 1262, 1122, 1065.

(2RS,3RS)-7-(benzyloxy)-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (276, Table 22, Entry 6)



Was obtained as a solid (50 mg, 73 %) following **GP 5.4** (stirred for 30 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.50–7.29 (m, 5H), 7.04–6.80 (m, 3H), 6.15 (dd, J = 4.1, 2.2 Hz, 1H), 5.15 (s, 2H), 4.05 (d, J = 4.1 Hz, 1H), 3.91 (qd, J = 9.1, 1.8 Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 147.8, 143.8, 136.5, 128.6, 128.2, 127.7, 125.0 (q, *J* = 278.4 Hz), 122.4, 120.3 (q, *J* = 2.1 Hz), 118.3, 115.5, 100.6 (q, *J* = 3.8 Hz), 71.2, 54.9 (q, *J* = 29.2 Hz).

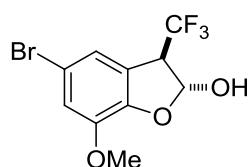
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.2 (d, *J* = 9.2 Hz).

HRMS (EI): calcd for C₁₆H₁₃F₃O₃⁺ [M]⁺ 310.0812, found 310.0811.

IR (neat): 3457, 2924, 1495, 1170, 918.

MP: 103 °C

(2RS,3RS)-5-bromo-7-methoxy-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (277, Table 22, Entry 7)



Was obtained as a solid (37 mg, 54 %) following **GP 5.4** (stirred for 180 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.10 (dt, *J* = 1.7, 0.8 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 6.16 (dd, *J* = 4.0, 2.2 Hz, 1H), 4.03 (d, *J* = 4.0 Hz, 1H), 3.99 – 3.83 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 146.7, 145.2, 124.7 (q, *J* = 278.6 Hz), 121.4 (d, *J* = 2.1 Hz), 120.7, 116.8, 113.8, 100.9 (q, *J* = 3.7 Hz), 56.3, 54.7 (q, *J* = 29.5 Hz).

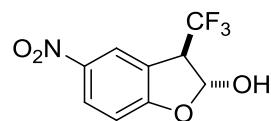
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.1 (d, *J* = 9.0 Hz)

HRMS (EI): calcd for C₁₀H₈BrF₃O₃⁺ [M]⁺ 311.9604, found 311.9604.

IR (neat): 3476, 2970, 1486, 1252, 1074.

MP: 80 °C

(2RS,3RS)-5-nitro-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (278, Table 22, Entry 8)



Was obtained as a solid (31 mg, 57 %) following **GP 5.4** (stirred for 180 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 8.32–8.26 (m, 2H), 7.00 (d, J = 9.5 Hz, 1H), 6.27 (dd, J = 4.2, 2.3 Hz, 1H), 4.01 (qd, J = 9.1, 2.4 Hz, 1H), 3.87 (d, J = 4.2 Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 163.6, 142.9, 127.9, 124.4 (q, J = 278.6 Hz), 122.6, 120.6 (q, J = 2.2 Hz), 110.7, 101.8, 53.8 (q, J = 29.9 Hz).

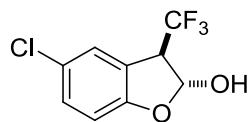
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.2 (d, J = 8.9 Hz).

HRMS (EI): calcd for C₉H₆F₃NO₄⁺ [M]⁺ 249.0244, found 249.0244.

IR (neat): 3418, 2970, 1601, 1517, 1336, 1076.

MP: 136 °C

(2RS,3RS)-5-chloro-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (279, Table 22, Entry 9)



Was obtained as an oil (38 mg, 72 %) following **GP 5.4** (stirred for 90 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.35–7.31 (m, 1H), 7.30 –7.25 (m, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.11 (dd, J = 4.4, 2.2 Hz, 1H), 3.90 (qd, J = 9.1, 1.7 Hz, 1H), 3.60 (d, J = 4.4 Hz, 1H).

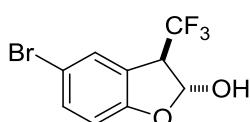
¹³C-NMR (100 MHz, CDCl₃): δ = 157.4, 130.8, 126.8, 126.1, 124.7 (q, J = 278.5 Hz), 120.7 (q, J = 2.2 Hz), 111.6, 100.5 (q, J = 3.7 Hz), 54.5 (q, J = 29.4 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.3 (d, J = 9.0 Hz).

HRMS (EI): calcd for C₉H₆ClF₃O₂⁺ [M]⁺ 238.0003, found 238.0006.

IR (neat): 3445, 2971, 1475, 1265, 1073.

(2RS,3RS)-5-bromo-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (198, Table 22, Entry 10)



Was obtained as a solid (43 mg, 69 %) following **GP 5.4** (stirred for 150 min at -78 °C).

¹H-NMR (300 MHz, CDCl₃): δ = 7.50 – 7.45 (m, 1H), 7.42 (ddd, *J* = 8.5, 2.1, 0.7 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 6.10 (dd, *J* = 4.4, 2.2 Hz, 1H), 3.91 (qd, *J* = 9.1, 1.9 Hz, 1H), 3.61 (d, *J* = 4.3 Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 157.9, 133.7, 129.0, 124.7 (q, *J* = 278.5 Hz), 121.2 (d, *J* = 2.1 Hz), 113.7, 112.2, 100.4 (q, *J* = 3.7 Hz), 54.4 (q, *J* = 29.5 Hz).

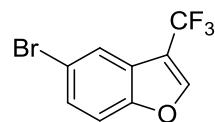
¹⁹F-NMR (282 MHz, CDCl₃): δ = -70.2 (d, *J* = 9.0 Hz)

HRMS (EI): calcd for C₉H₆BrF₃O₂⁺ [M]⁺ 281.9498, found 281.9500.

IR (neat): 3313, 2970, 1471, 1345, 1189, 947.

MP: 79 °C

5-bromo-3-(trifluoromethyl)benzofuran (199)



(2*RS*,3*RS*)-5-bromo-3-(trifluoromethyl)-2,3-dihydrobenzofuran-2-ol (200 mg, 0.707 mmol, **10**) was dissolved in toluene (20 mL) and *p*-toluenesulfonic acid (190 mg, 1 mmol) was added. The mixture was refluxed for 18 h with a Dean-Stark trap. The mixture was cooled down and the solvent evaporated in vacuo. Filtration with pentane over a short silica plug afforded the product as clear oil (149 mg, 80 %).

¹H-NMR (300 MHz, CDCl₃): δ = 7.97 (s, 1H), 7.83 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 1H).

¹³C-NMR (100 MHz, CDCl₃): δ = 154.1, 145.8 (q, *J* = 5.6 Hz), 129.1, 123.7, 122.9, 122.3 (q, *J* = 267.1 Hz), 117.4, 113.5, 113.2 (q, *J* = 38.1 Hz).

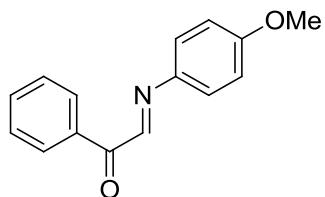
¹⁹F-NMR (282 MHz, CDCl₃): δ = -59.5.

HRMS (EI): calcd for C₉H₄BrF₃O⁺ [M]⁺ 263.9393, found 263.9393.

IR (neat): 2970, 1450, 1105, 802.

General procedure 5.5 (GP 5.5) for imine condensation: Arylglyoxals were produced according to known procedures²¹¹ or purchased from commercial sources. MgSO₄ (10 g) was suspended in 50 mL CH₂Cl₂. Then, the corresponding arylglyoxal monohydrate (11 mmol) and *p*-anisidine (11 mmol) were added in one portion to the stirred suspension. After 1 h the suspension was filtered, and the solvent was evaporated under reduced pressure to give the desired product (quantitative yield). The crude product was used without further purification.

(E)-2-((4-methoxyphenyl)imino)-1-phenylethanone (201)



The title compound was obtained in quantitative yield as a brown solid following **GP 5.5**.

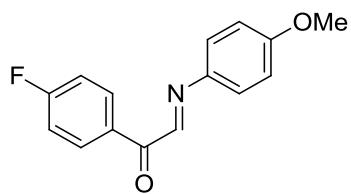
¹H-NMR (300 MHz, CDCl₃): δ = 8.36 (s, 1H), 8.32 – 8.26 (m, 2H), 7.66 – 7.57 (m, 1H), 7.55 – 7.46 (m, 2H), 7.44 – 7.36 (m, 2H), 7.01 – 6.94 (m, 2H), 3.86 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 190.9, 160.6, 154.2, 141.7, 135.5, 133.4, 130.6, 128.3, 123.5, 114.7, 55.6.

HRMS (ESI): calcd for C₁₅H₁₄NO₂⁺ ([M+H]⁺) 240.1019, found 240.1016.

IR (neat): 3061, 2837, 1649, 1574, 1503, 1245, 1024, 829 cm⁻¹.

(E)-1-(4-fluorophenyl)-2-((4-methoxyphenyl)imino)ethanone (280)



²¹¹ (a) M. B. Floyd, M. T. Du, P. F. Fabio, L. A. Jacob, B. D. Johnson, *J. Org. Chem.* **1985**, *50*, 5022. (b) S. S. Bhella, M. Elango, M. P. S. Ishar, *Tetrahedron* **2009**, *65*, 240. (c) K. C. Joshi, V. N. Pathak, M. K. Goyal, *J. Heterocyclic. Chem.* **1981**, *18*, 1651.

The title compound was obtained in quantitative yield as a green solid following **GP 5.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 8.43 – 8.35 (m, 2H), 8.31 (s, 1H), 7.44 – 7.36 (m, 2H), 7.22 – 7.11 (m, 2H), 7.01 – 6.92 (m, 2H), 3.86 (s, 3H).

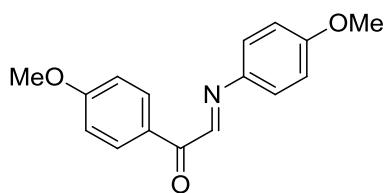
¹³C-NMR (100 MHz, CDCl₃): δ = 189.2, 166.0 (d, *J* = 255.5 Hz), 160.7, 154.1, 141.4, 133.5 (d, *J* = 9.3 Hz), 131.8 (d, *J* = 3.0 Hz), 123.6, 115.5 (d, *J* = 21.7 Hz), 114.7, 55.6.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -104.12 (m).

HRMS (ESI): calcd for C₁₅H₁₃FNO₂⁺ ([M+H]⁺) 258.0925, found 258.0924.

IR (neat): 1694, 1651, 1598, 1581, 1504, 1229, 1158, 824 cm⁻¹.

(E)-1-(4-methoxyphenyl)-2-((4-methoxyphenyl)imino)ethanone (281)



The title compound was obtained in quantitative yield as a red-brown solid following **GP 5.5**.

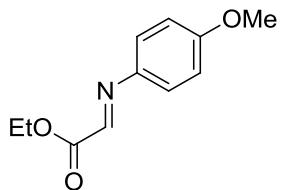
¹H-NMR (300 MHz, CDCl₃): δ = 8.39 – 8.33 (m, 2H), 8.33 (s, 1H), 7.42 – 7.35 (m, 2H), 7.02 – 6.90 (m, 4H), 3.90 (s, 3H), 3.86 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 189.0, 164.0, 160.4, 154.8, 141.9, 133.1, 128.4, 123.4, 114.6, 113.7, 55.6, 55.5.

HRMS (ESI): calcd for C₁₆H₁₆NO₃⁺ ([M+H]⁺) 270.1125, found 270.1121.

IR (neat): 2935, 2838, 1648, 1596, 1504, 1244, 1021, 822 cm⁻¹.

(E)-ethyl 2-((4-methoxyphenyl)imino)acetate (282)



The title compound was obtained in quantitative yield as an oil following **GP 5.5**.

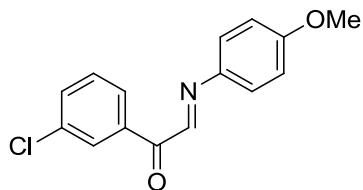
¹H-NMR (300 MHz, CDCl₃): δ = 7.93 (s, 1H), 7.40 – 7.31 (m, 2H), 6.98 – 6.86 (m, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 1H), 1.41 (t, *J* = 7.1 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 163.6, 160.5, 148.0, 141.4, 123.6, 114.5, 61.9, 55.5, 14.2.

HRMS (ESI): calcd for C₁₁H₁₄NO₃⁺ ([M+H]⁺) 208.0968, found 208.0973.

IR (neat): 2979, 2836, 1730, 1508, 1244, 1027, 831 cm⁻¹.

(E)-1-(3-chlorophenyl)-2-((4-methoxyphenyl)imino)ethanone (283)



The title compound was obtained in quantitative yield as a green solid following **GP 5.5**.

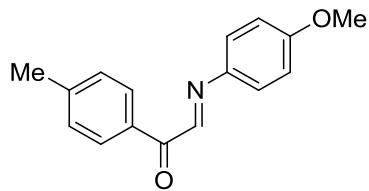
¹H-NMR (300 MHz, CDCl₃): δ = 8.31 (s, 1H), 8.31 – 8.29 (m, 1H), 8.20 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 7.58 (ddd, *J* = 8.0, 2.1, 1.1 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.02 – 6.93 (m, 2H), 3.87 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 189.5, 160.9, 153.6, 141.3, 137.0, 134.5, 133.2, 130.7, 129.6, 128.8, 123.7, 114.7, 55.6.

HRMS (ESI): calcd for C₁₅H₁₃ClNO₂⁺ ([M+H]⁺) 274.0629, found 274.0625.

IR (neat): 3087, 3000, 2949, 2839, 1641, 1561, 1505, 1250, 1163, 827 cm⁻¹.

(E)-2-((4-methoxyphenyl)imino)-1-(*p*-tolyl)ethanone (284)



The title compound was obtained in quantitative yield as a brown solid following **GP 5.5**.

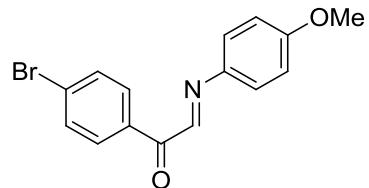
¹H-NMR (300 MHz, CDCl₃): δ = 8.35 (s, 1H), 8.23 – 8.18 (m, 2H), 7.44 – 7.35 (m, 2H), 7.33 – 7.27 (m, 2H), 7.01 – 6.91 (m, 2H), 3.86 (s, 3H), 2.44 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 190.4, 160.4, 154.4, 144.4, 141.8, 133.0, 130.7, 129.1, 123.5, 114.6, 55.6, 21.8.

HRMS (EI/ESI): calcd for C₁₆H₁₆NO₂⁺ ([M+H]⁺) 254.1176, found 254.1172.

IR (neat): 2934, 2836, 1648, 1602, 1503, 1243, 1027, 822 cm⁻¹.

(E)-1-(4-bromophenyl)-2-((4-methoxyphenyl)imino)ethanone (285)



The title compound was obtained in quantitative yield as a green solid following **GP 5.5**.

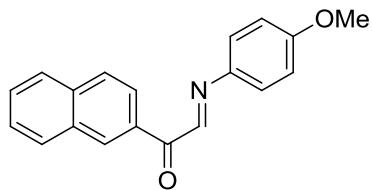
¹H-NMR (300 MHz, CDCl₃): δ = 8.30 (s, 1H), 8.25 – 8.14 (m, 2H), 7.66 – 7.60 (m, 2H), 7.44 – 7.35 (m, 2H), 7.01 – 6.92 (m, 2H), 3.86 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 189.9, 160.8, 153.8, 141.3, 134.2, 132.2, 131.6, 128.7, 123.7, 114.7, 55.6.

HRMS (ESI): calcd for C₁₅H₁₃BrNO₂ ([M+H]⁺) 318.0124, found 318.0128.

IR (neat): 1650, 1582, 1504, 1256, 823 cm⁻¹.

(E)-2-((4-methoxyphenyl)imino)-1-(naphthalen-1-yl)ethanone (286)



The title compound was obtained in quantitative yield as a green solid following **GP 5.5**.

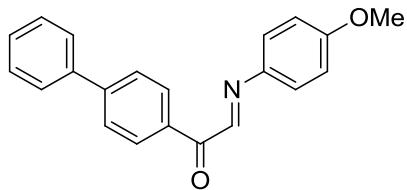
¹H-NMR (300 MHz, CDCl₃): δ = 8.98 (s, 1H), 8.46 (s, 1H), 8.26 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.04 – 7.85 (m, 3H), 7.59 (dd, *J* = 19.1, 8.2, 6.9, 1.4 Hz, 2H), 7.49 – 7.42 (m, 2H), 7.03 – 6.96 (m, 2H), 3.88 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 190.6, 160.6, 154.4, 141.8, 135.8, 133.3, 132.8, 132.4, 130.0, 128.7, 128.2, 127.8, 126.7, 125.6, 123.6, 114.7, 55.6.

HRMS (ESI): calcd for C₁₉H₁₆NO₂⁺ ([M+H]⁺) 290.1176, found 290.1169.

IR (neat): 3048, 1652, 1574, 1504, 1258, 811 cm⁻¹.

(E)-1-((1,1'-biphenyl)-4-yl)-2-((4-methoxyphenyl)imino)ethanone (287)



The title compound was obtained in quantitative yield as an orange solid following **GP 5.5**.

¹H-NMR (300 MHz, CDCl₃): δ = 8.40 (s, 1H), 8.37 (s, 2H), 7.77 – 7.57 (m, 4H), 7.54 – 7.34 (m, 5H), 7.04 – 6.92 (m, 2H), 3.86 (s, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 190.4, 160.6, 154.4, 146.1, 141.7, 140.0, 134.2, 131.2, 129.0, 128.3, 127.3, 127.0, 123.6, 114.7, 55.6.

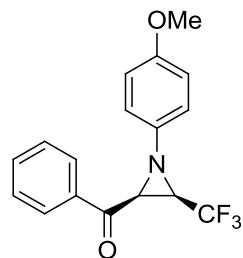
HRMS (ESI): calcd for C₂₁H₁₈NO₂⁺ ([M+H]⁺) 316.1332, found 316.1333.

IR (neat): 3003, 1645, 1592, 1574, 1502, 1246, 833 cm⁻¹.

General procedure 5.6 (GP 5.6) for aziridination (Table 23): To a mixture of 7.5 mL CH₂Cl₂ and 0.25 mL H₂O cooled to 0 °C was added trifluoroethylamine hydrochloride (203 mg, 1.5 mmol) and NaNO₂ (124 mg, 1.8 mmol). After being stirred at this temperature for 1 h, the reaction mixture was cooled to -78 °C. Then, after 20-25 min the appropriate imine (0.5 mmol) and BF₃·OEt₂ (111 µL, 0.9 mmol) were added consecutively. After the indicated time, the reaction was quenched with MeOH and sat. NaHCO₃. The reaction mixture was extracted with CH₂Cl₂ (3x), dried over MgSO₄ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the pure *cis*-isomer.

((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)(phenyl)methanone (202,

Table 23, Entry 1)



The title compound was obtained as an amorphous solid (103 mg, 64 %) following **GP 5.6** (dr 17:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.14 – 8.05 (m, 2H), 7.66 – 7.57 (m, 1H), 7.54 – 7.41 (m, 2H), 7.07 – 6.97 (m, 2H), 6.89 – 6.76 (m, 2H), 3.77 (s, 3H), 3.60 (d, *J* = 6.6 Hz, 1H), 3.14 (dq, *J* = 6.7, 5.6 Hz, 1H).

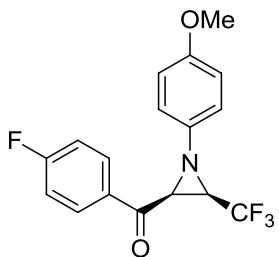
¹³C-NMR (100 MHz, CDCl₃): δ = 190.5, 156.6, 143.5, 135.2, 134.1, 128.8, 128.7, 123.3 (q, *J* = 274.7 Hz), 120.7, 114.7, 55.5, 45.7, 44.4 (q, *J* = 40.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.7 (d, *J* = 5.4 Hz).

HRMS (EI): calcd for C₁₇H₁₄F₃NO₂⁺ (M⁺) 321.0977, found 321.0972.

IR (neat): 2957, 2837, 2359, 1692, 1597, 1240, 1142 cm⁻¹.

(4-fluorophenyl)((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)methanone (288, Table 23, Entry 2)



The title compound was obtained as an amorphous solid (132 mg, 78 %) following **GP 5.6** (dr 19:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.20 – 8.12 (m, 2H), 7.22 – 7.10 (m, 2H), 7.06 – 6.98 (m, 2H), 6.90 – 6.78 (m, 2H), 3.79 (s, 3H), 3.54 (d, *J* = 6.5 Hz, 1H), 3.11 (dq, *J* = 6.6, 5.5 Hz, 1H).

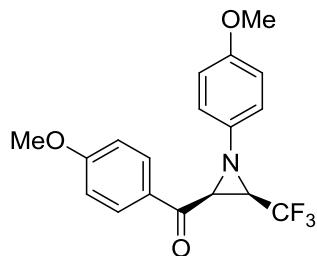
¹³C-NMR (100 MHz, CDCl₃): δ = 189.1, 166.3 (d, *J* = 256.8 Hz), 156.7, 143.3, 131.7 (d, *J* = 2.9 Hz), 131.5 (d, *J* = 9.5 Hz), 123.2 (q, *J* = 274.6 Hz), 120.7, 116.1 (d, *J* = 22.0 Hz), 114.7, 55.6, 45.4, 44.3 (q, *J* = 40.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.8 (d, *J* = 5.5 Hz), -102.6 (m).

HRMS (ESI): calcd for C₁₇H₁₄F₄NO₂ ([M+H]⁺) 340.0955, found 340.0957.

IR (neat): 3003, 1688, 1595, 1509, 1146 cm⁻¹.

(4-methoxyphenyl)((2SR,3RS)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)methanone (289, Table 23, Entry 3)



The title compound was obtained as an amorphous solid (87 mg, 50 %) following **GP 5.6** (dr 12:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.13 – 8.06 (m, 2H), 7.05 – 6.91 (m, 4H), 6.87 – 6.78 (m, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.54 (d, *J* = 6.7 Hz, 2H), 3.09 (dq, *J* = 6.3, 5.5 Hz, 1H).

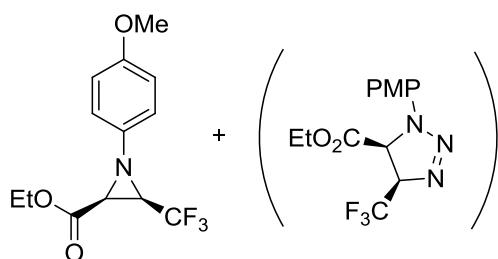
¹³C-NMR (100 MHz, CDCl₃): δ = 188.9, 164.3, 156.6, 143.7, 131.1, 128.4, 123.3 (q, *J* = 274.8 Hz), 120.7, 114.7, 114.0, 55.57, 55.55, 45.5, 44.3 (q, *J* = 40.1 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.8 (d, *J* = 5.3 Hz).

HRMS (ESI): calcd for C₁₈H₁₇F₃NO₃⁺ ([M+H]⁺) 352.1155, found 352.1148.

IR (neat): 1961, 2841, 1681, 1597, 1509, 1241, 1141 cm⁻¹.

(2*S*,3*R*)-ethyl 1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-carboxylate (290, Table 23, Entry 4)



The title compound was obtained as an oil (104 mg total, 83 % purity (17 % cycloaddition product, designed as minor below), 87 mg, 60%) following **GP 5.6** (dr 11:1).

¹H-NMR (300 MHz, CDCl₃): δ = 6.99 – 6.85 (m, 2H), 6.83 – 6.76 (m, 2H), 5.23 (dq, *J* = 8.5, 7.4 Hz, 1H, minor), 4.56 (d, *J* = 8.4 Hz, 1H, minor), 4.40 – 4.17 (m, 2H), 3.79 (s, 3H, minor), 3.75 (s, 3H), 3.05 (d, *J* = 6.6 Hz, 1H), 2.88 (dq, *J* = 6.6, 5.5 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

¹³C-NMR (100 MHz, CDCl₃): δ = 167.8 (minor), 165.8, 157.0 (minor), 156.6, 143.2, 132.5 (minor), 123.1 (q, *J* = 274.4 Hz), 120.5, 117.8 (minor), 114.8 (minor), 114.6, 82.1 (q, *J* = 29.9 Hz, minor), 63.0 (minor), 62.1, 57.9 (minor), 55.5, 43.1 (q, *J* = 40.8 Hz), 41.4, 13.9.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -68.0 (d, *J* = 5.6 Hz, major), -73.2 (d, *J* = 7.7 Hz, minor).

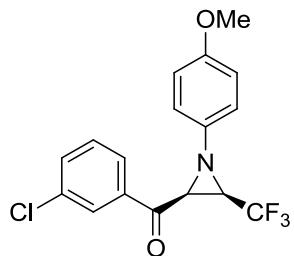
HRMS (ESI): calcd for C₁₃H₁₅F₃NO₃⁺ ([M+H]⁺) 290.0999, found 290.1009.

IR (neat): 2986, 2838, 1751, 1508, 1240, 1143 cm⁻¹.

Spectral data in accordance with literature values.²¹²

²¹² See Reference 184.

**(3-chlorophenyl)((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)methanone
(291, Table 23, Entry 5)**



The title compound was obtained as yellow oil (79 mg, 61 %) following **GP 5.6** on a 0.365 mmol scale (dr 16:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.07 (t, J = 1.7 Hz, 1H), 7.99 (ddd, J = 7.8, 1.6, 1.1 Hz, 1H), 7.59 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.52 – 7.39 (m, 1H), 7.05 – 6.96 (m, 2H), 6.89 – 6.78 (m, 2H), 3.77 (s, 3H), 3.56 (d, J = 6.6 Hz, 1H), 3.14 (dq, J = 6.7, 5.5 Hz, 1H).

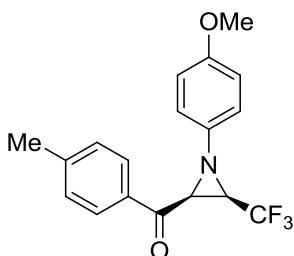
¹³C-NMR (100 MHz, CDCl₃): δ = 189.6, 156.7, 143.2, 136.7, 135.2, 134.1, 130.2, 128.7, 126.8, 123.1 (q, J = 274.7 Hz), 120.7, 114.7, 55.5, 45.5, 44.4 (q, J = 40.2 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.7 (d, J = 5.9 Hz).

HRMS (ESI): calcd for C₁₇H₁₄ClF₃NO₂⁺ ([M+H]⁺) 356.0660, found 356.0647.

IR (neat): 2959, 2837, 1698, 1572, 1508, 1240, 1144 cm⁻¹.

**((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)(*p*-tolyl)methanone (292,
Table 23, Entry 6)**



The title compound was obtained as an amorphous solid (100 mg, 60 %) following **GP 5.6** (dr 16:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.05 – 7.96 (m, 2H), 7.35 – 7.21 (m, 2H), 7.08 – 6.94 (m, 2H), 6.91 – 6.77 (m, 2H), 3.77 (s, 3H, major), 3.57 (d, *J* = 6.6 Hz, 1H), 3.12 (dq, *J* = 6.7, 5.6 Hz, 1H), 2.42 (s, 3H).

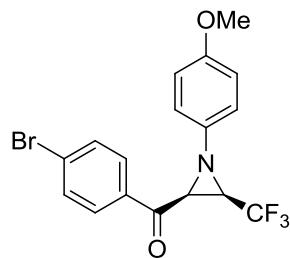
¹³C-NMR (100 MHz, CDCl₃): δ = 190.0, 156.6, 145.2, 143.7, 132.8, 129.5, 128.8, 123.29 (q, *J* = 274.7 Hz), 120.7, 114.6, 55.5, 45.7, 44.4 (q, *J* = 40.1 Hz), 21.8.

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.8 (d, *J* = 5.7 Hz).

HRMS (ESI): calcd for C₁₈H₁₇F₃NO₂⁺ ([M+H]⁺) 336.1206, found 336.1207.

IR (neat): 2963, 2838, 2360, 1685, 1605, 1508, 1240, 1143 cm⁻¹.

**(4-bromophenyl)((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)methanone
(293, Table 23, Entry 7)**



The title compound was obtained as an amorphous solid (94 mg, 47 %) following t GP 5.6 (dr 13:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.01 – 7.93 (m, 2H), 7.69 – 7.56 (m, 2H), 7.06 – 6.95 (m, 2H), 6.90 – 6.78 (m, 2H), 3.78 (s, 3H), 3.53 (d, *J* = 6.6 Hz, 1H), 3.11 (dq, *J* = 6.7, 5.5 Hz, 1H).

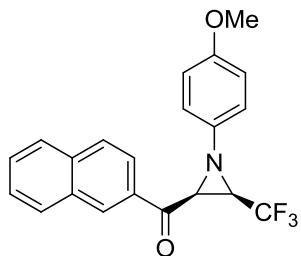
¹³C-NMR (100 MHz, CDCl₃): δ = 189.9, 156.7, 143.2, 134.0, 132.2, 130.2, 129.5, 123.2 (q, *J* = 274.7 Hz), 120.7, 114.7, 55.6, 45.4, 44.4 (q, *J* = 40.1 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.56 (d, *J* = 5.3 Hz).

HRMS (ESI): calcd for C₁₇H₁₄BrF₃NO₂⁺ ([M+H]⁺) 400.0155, found 400.0162.

IR (neat): 1691, 1582, 1508, 1144 cm⁻¹.

**((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)(naphthalen-1-yl)methanone
(293, Table 23, Entry 8)**



The title compound was obtained as an amorphous solid (130 mg, 70 %) following **GP 5.6** (dr 15:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.76 – 8.61 (m, 1H), 8.13 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.03 – 7.84 (m, 3H), 7.60 (dd, *J* = 21.2, 8.1, 6.9, 1.3 Hz, 2H), 7.12 – 7.00 (m, 2H), 6.93 – 6.78 (m, 2H), 3.80 (s, 3H), 3.72 (d, *J* = 6.6 Hz, 1H), 3.22 (dq, *J* = 6.6, 5.5 Hz, 1H).

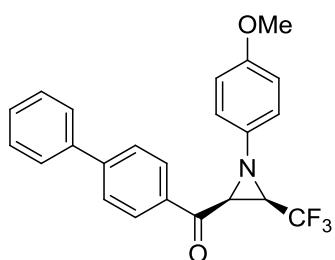
¹³C-NMR (100 MHz, CDCl₃): δ = 190.4, 156.7, 143.6, 136.1, 132.6, 132.4, 131.0, 129.8, 129.1, 128.8, 127.9, 123.3 (q, *J* = 274.7 Hz), 127.0, 123.8, 120.7, 114.7, 55.6, 45.8, 44.5 (q, *J* = 40.1 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.65 (d, *J* = 5.5 Hz).

HRMS (ESI): calcd for C₂₁H₁₇F₃NO₂⁺ ([M+H]⁺) 372.1206, found 372.1197.

IR (neat): 1694, 1624, 1508, 1142 cm⁻¹.

[1,1'-biphenyl]-4-yl((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)methanone (294, Table 23, Entry 9)



The title compound was obtained as an amorphous solid (144 mg, 73 %) following **GP 5.6** (dr 15:1).

¹H-NMR (300 MHz, CDCl₃): δ = 8.28 – 8.12 (m, 2H), 7.76 – 7.67 (m, 2H), 7.67 – 7.59 (m, 2H), 7.53 – 7.31 (m, 3H), 7.11 – 6.97 (m, 2H), 6.92 – 6.78 (m, 2H), 3.79 (s, 3H), 3.62 (d, *J* = 6.6 Hz, 1H), 3.22 – 3.05 (m, 1H).

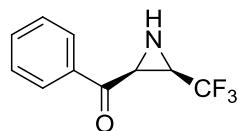
¹³C-NMR (100 MHz, CDCl₃): δ = 190.1, 156.7, 146.8, 143.6, 139.6, 133.9, 129.3, 129.0, 128.5, 127.4, 127.3, 127.2 – 118.8 (m), 120.7, 114.7, 55.6, 45.7, 44.4 (q, *J* = 40.0 Hz).

¹⁹F-NMR (282 MHz, CDCl₃): δ = -67.51 (d, *J* = 5.6 Hz).

HRMS (ESI): calcd for C₂₃H₁₉F₃NO₂⁺ ([M+H]⁺) 398.1362, found 398.1362.

IR (neat): 1682, 1603, 1506, 1143 cm⁻¹.

Phenyl((2*S*,3*R*)-3-(trifluoromethyl)aziridin-2-yl)methanone (203)



To a solution of ((2*S*,3*R*)-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridin-2-yl)(phenyl)methanone (100 mg, 0.31 mmol) in 8 ml CH₃CN was added (NH₄)₂Ce(NO₃)₆ (427 mg, 0.78 mmol) in 2.7 ml H₂O at 0 °C. After 1 h 30 min the reaction was quenched with sat. Na₂SO₃ and sat. NaHCO₃, extracted 3 times with dichloromethane, dried over MgSO₄ and the solvent evaporated under reduced pressure. The residue was purified on silica gel (hexane/ethyl acetate 70:30) to give the product as white solid (50 mg, 75 %).

¹H-NMR (300 MHz, CD₃CN): δ = 8.13 – 8.03 (m, 2H), 7.70 – 7.62 (m, 1H), 7.59 – 7.48 (m, 2H), 3.62 (dd, *J* = 9.8, 6.6 Hz, 1H), 3.35 – 3.11 (m, 1H), 2.24 (br, 1H).

¹³C-NMR (100 MHz, CD₃CN): δ = 191.7, 135.9, 133.7, 128.7, 128.5, 124.6 (q, *J* = 273.2 Hz), 37.6, 35.0 (q, *J* = 39.3 Hz).

¹⁹F-NMR (282 MHz, CD₃CN): δ = -66.94 (d, *J* = 6.2 Hz).

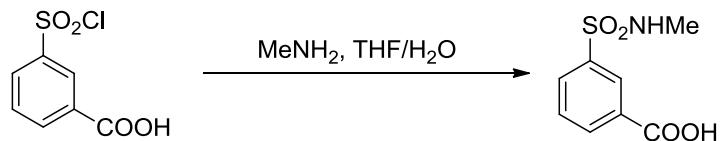
HRMS (ESI): calcd for C₁₀H₉F₃NO⁺ ([M+H]⁺) 216.0631, found 216.0633.

IR (neat): 3196, 1684, 1596, 1132 cm⁻¹.

8.5. Experimental Part to Chapter 6

Preparation of water-soluble diazald 213

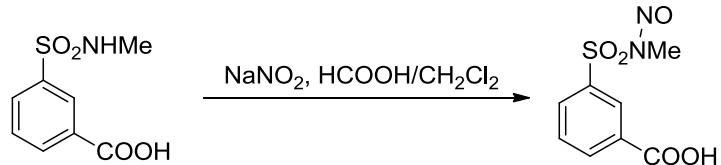
3-(N-methylsulfamoyl)benzoic acid (211)



Commercially available 3-(chlorosulfonyl)benzoic acid (5.00 g, 22.7 mmol) was dissolved in THF (25 mL) and MeNH₂ (8.58 g (41% in water), 113 mmol) was added dropwise at 0 °C. The resulting mixture was slowly warmed to room temperature and the THF was evaporated in vacuo after 1 h. Conc. HCl was added to the remaining mixture and the formed precipitated was collected by filtration and dried in vacuo to give 3-(N-methylsulfamoyl)benzoic acid (**211**) in quantitative yield. It was used in the next step without further purification.

¹H-NMR (300 MHz, DMSO): δ = 8.30 (dd, *J* = 2.4, 1.1 Hz, 1H), 8.17 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.00 (ddd, *J* = 7.8, 1.9, 1.2 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.61 (q, *J* = 5.0 Hz, 1H), 2.41 (d, *J* = 5.0 Hz, 3H).

3-(N-methyl-N-nitrososulfamoyl)benzoic acid (212)



3-(N-methylsulfamoyl)benzoic acid (**211**, 1.5 g, 7.0 mmol) was dissolved in HCOOH (105 mL)/CH₂Cl₂ (45 mL) and cooled down in an ice-bath. To this solution was added NaNO₂ (4.8 g, 70 mmol) portionwise over 1 h behind a blast shield. After the addition was completed, the reaction mixture was stirred at 0 °C for 30 min and quenched by addition to ice-water. The resulting phases

were separated and the aqueous phase was further (2x) extracted with CH_2Cl_2 . The combined organic phases were dried over MgSO_4 and evaporated in vacuo to afford pure 3-(N-methyl-N-nitrososulfamoyl)benzoic acid (**212**, 1.2 g, 4.9 mmol 71%). The product is stable at room temperature but is preferentially stored at 0 °C.

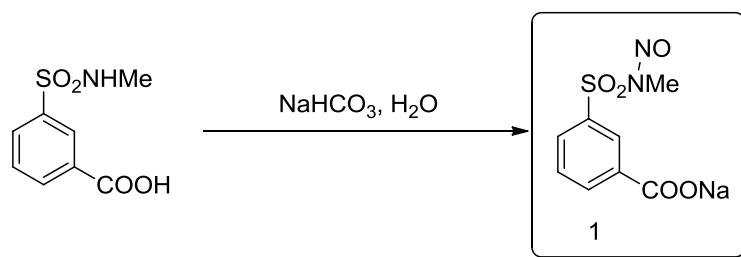
$^1\text{H-NMR}$ (300 MHz, DMSO): $\delta = 13.69$ (s, 1H), 8.41 (s, 1H), 8.33 (d, $J = 7.8$ Hz, 1H), 8.29 – 8.23 (m, 1H), 7.85 (t, $J = 7.8$ Hz, 1H), 3.16 (s, 3H).

$^{13}\text{C-NMR}$ (100 MHz, DMSO): $\delta = 165.9, 137.3, 136.2, 133.2, 132.2, 131.6, 128.5, 30.2$.

HRMS (ESI): calcd for $\text{C}_8\text{H}_9\text{N}_2\text{O}_5\text{S}^+$ ($\text{M}+\text{H})^+$ 245.0227, found 245.0232.

IR (neat): 2980, 2848, 1689, 1513, 1381.

sodium 3-(N-methyl-N-nitrososulfamoyl)benzoate (aqueous solution of **213**)



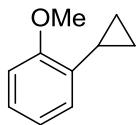
3-(N-methyl-N-nitrososulfamoyl)benzoic acid (**212**, 1.2 g, 4.9 mmol) was suspended in water (37.5 mL) and NaHCO_3 (0.45 g, 5.4 mmol) was added portionwise behind a blast shield. The mixture was vigorously stirred for 45 min until the solid had almost completely dissolved. The remaining small amount of solid was then removed by filtration. The formed solution of reagent **213** in water (approx. 0.13 M) was used as such in the catalytic reactions. The solution was stored at 4 °C and used in the next days due to slow denitrosation in water.

General procedure 6.1 (GP 6.1) for cyclopropanation with different catalysts (Scheme 82): The catalyst (5 mol %, 2.5 mol % for Rh dimers) was dissolved in *p*-methoxystyrene (15 μL , 0.11 mmol) and 6 M aqueous KOH (1 mL) was added in an open flask. To this vigorously, steadily stirred solution (> 1000 rpm) was added an aqueous solution of reagent **1** (2.5 mL, 0.13 M in water, 0.33 mmol, 3 equiv.) over 4 h at room temperature with a syringe pump. After further 30 min, the

solution was diluted with water and extracted three times with CH₂Cl₂. The organic phases were dried over MgSO₄ and evaporated under vacuo. The conversion was determined by analysis of the ¹H-NMR spectrum of the crude reaction mixture (integration of the MeO-signal).

General procedure 6.2 (GP 6.2) for cyclopropanation with Fe(TPP)Cl and reagent 1 (Table 24): FeTPP^{Cl} was dissolved in the substrate (0.22 mmol) and 6 M aqueous KOH was added in an open vial. To this vigorously, steadily stirred solution (> 1000 rpm) was added an aqueous solution of reagent **1** (0.13 M in water) at room temperature with a syringe pump. After further 30 min, the solution was diluted with water and extracted three times with CH₂Cl₂. The organic phases were dried over MgSO₄ and evaporated under vacuo. After NMR-analysis of the crude reaction mixture, the product was purified by flash chromatography (pentane/diethyl ether) to afford the pure product.

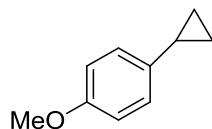
1-cyclopropyl-2-methoxybenzene (295, Table 24, Entry 1)



Was obtained as an oil (26 mg, 80%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

Spectral data are in accordance with the literature.²¹³

1-cyclopropyl-4-methoxybenzene (214, Table 24, Entry 2)

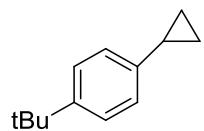


²¹³ G. A. Molander, F. Beaumard, T. K. Niethamer, *J. Org. Chem.* **2011**, *76*, 8126.

Was obtained as an oil (29 mg, 89%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

Spectral data are in accordance with the literature.²¹³

1-(tert-butyl)-4-cyclopropylbenzene (296, Table 24, Entry 3)



Was obtained as an oil (30 mg, 78%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

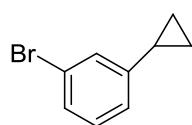
¹H-NMR (300 MHz, CDCl₃): δ = 7.29 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.6, 2H), 1.87 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.31 (s, 9H), 1.02–0.88 (m, 2H), 0.77–0.60 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 148.2, 140.8, 125.3, 125.2, 34.3, 31.4, 14.9, 8.9.

HRMS (EI): calcd for C₁₃H₁₈⁺ (M⁺) 174.1403, found 174.1398.

IR (neat): 2935, 2860, 1508, 812.

1-bromo-3-cyclopropylbenzene (297, Table 24, Entry 4)



Was obtained as an oil (35 mg, 81%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

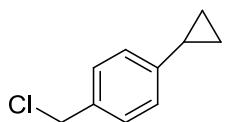
¹H-NMR (300 MHz, CDCl₃): δ = 7.26 (ddd, *J* = 7.8, 2.0, 1.1 Hz, 1H), 7.19 (t, *J* = 1.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.02–6.96 (m, 1H), 1.86 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.05–0.91 (m, 2H), 0.76–0.62 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 146.5, 129.8, 128.8, 128.4, 124.4, 122.5, 15.2, 9.4.

HRMS (EI): calcd for C₉H₉Br⁺ (M⁺) 195.9883, found 195.9889.

IR (neat): 2931, 2858, 1064, 687.

1-(chloromethyl)-4-cyclopropylbenzene (298, Table 24, Entry 5)



Was obtained as an oil (28 mg, 76%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

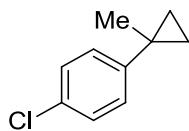
¹H-NMR (300 MHz, CDCl₃): δ = 7.27 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 4.57 (s, 2H), 1.90 (tt, *J* = 8.4, 5.1 Hz, 1H), 1.09–0.91 (m, 2H), 0.70 (dt, *J* = 6.6, 4.7 Hz, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 144.6, 134.5, 128.6, 126.0, 46.3, 15.2, 9.4.

HRMS (EI): calcd for C₁₀H₁₁Cl⁺ (M⁺) 166.0544, found 166.0536.

IR (neat): 2926, 1264, 737, 705.

1-chloro-4-(1-methylcyclopropyl)benzene (299, Table 24, Entry 6)



Was obtained as an oil (27 mg, 74%) following **GP 6.2** with Fe(TPP)Cl (3.1 mg, 0.0044 mmol, 2 mol%), 6 M KOH (2 mL) and addition of **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h.

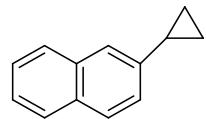
¹H-NMR (300 MHz, CDCl₃): δ = 7.26–7.14 (m, 4H), 1.38 (s, 3H), 0.86–0.79 (m, 2H), 0.78–0.70 (m, 2H).

¹³C-NMR (100 MHz, CDCl₃): δ = 145.6, 131.1, 128.2, 128.2, 25.6, 19.4, 15.6.

HRMS (EI): calcd for C₁₀H₁₁Cl⁺ (M⁺) 166.0544, found 166.0538.

IR (neat): 3001, 2956, 1496, 1112, 731.

2-cyclopropylnaphthalene (300, Table 24, Entry 7)



Was obtained as an oil (26 mg, 70%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL), 100 μ L toluene and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

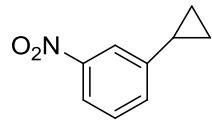
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 7.83\text{--}7.71$ (m, 3H), 7.55 (d, $J = 1.2$ Hz, 1H), 7.49–7.36 (m, 2H), 7.21 (dd, $J = 8.5, 1.8$ Hz, 1H), 2.08 (tt, $J = 8.4, 5.1$ Hz, 1H), 1.12–1.00 (m, 2H), 0.89–0.79 (m, 2H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 141.5, 133.6, 131.9, 127.9, 127.6, 127.3, 126.0, 124.9, 124.7, 123.8, 15.7, 9.2$.

HRMS (EI): calcd for $\text{C}_{13}\text{H}_{12}^+$ (M^+) 168.0934, found 168.0927.

IR (neat): 3080, 3000, 1631, 1598, 1508.

1-cyclopropyl-3-nitrobenzene (301, Table 24, Entry 8)



Was obtained as an oil (23 mg, 64%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL), and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

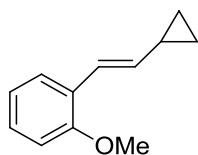
$^1\text{H-NMR}$ (300 MHz, CDCl_3): $\delta = 8.05\text{--}7.91$ (m, 1H), 7.93–7.82 (m, 1H), 7.45–7.33 (m, 2H), 2.00 (tt, $J = 8.5, 5.1$ Hz, 1H), 1.22–0.97 (m, 2H), 0.78 (dt, $J = 6.6, 4.9$ Hz, 2H).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3): $\delta = 148.4, 146.4, 132.1, 129.0, 120.4, 120.4, 15.3, 9.9$.

HRMS (EI): calcd for $C_9H_9NO_2^+$ (M^+) 163.0628, found 163.0629.

IR (neat): 3087, 2868, 1527, 1348.

(E)-1-(2-cyclopropylvinyl)-2-methoxybenzene (302, Table 24, Entry 10)



Was obtained as an oil (30 mg, 78%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL), and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

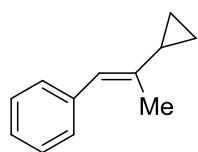
1H -NMR (300 MHz, CDCl₃): δ = 7.36 (dd, J = 7.6, 1.7 Hz, 1H), 7.17 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H), 7.02–6.55 (m, 3H), 5.74 (dd, J = 15.9, 8.9 Hz, 1H), 3.85 (s, 3H), 1.82–1.45 (m, 1H), 1.11–0.70 (m, 2H), 0.52 (dt, J = 6.6, 4.4 Hz, 2H).

^{13}C -NMR (100 MHz, CDCl₃): δ = 156.1, 135.7, 127.5, 126.9, 126.1, 122.0, 120.6, 110.8, 55.5, 15.0, 7.3.

HRMS (EI): calcd for $C_{12}H_{14}O^+$ (M^+) 174.1040, found 174.1039.

IR (neat): 3002, 2835, 1488, 1239.

(E)-(2-cyclopropylprop-1-en-1-yl)benzene (303, Table 24, Entry 10)



Was obtained as an oil (25 mg, 72%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL), and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

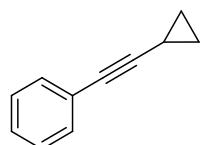
¹H-NMR (300 MHz, CDCl₃): δ = 7.54–7.03 (m, 5H), 6.34 (s, 1H), 1.74 (d, *J* = 1.3 Hz, 3H), 1.67–1.46 (m, 1H), 0.85–0.55 (m, 4H).

¹³C-NMR (100 MHz, CDCl₃): δ = 139.5, 138.6, 128.8, 128.0, 125.7, 123.4, 19.8, 15.2, 4.9.

HRMS (EI): calcd for C₁₂H₁₄⁺ (M⁺) 158.1090, found 158.1094.

IR (neat): 3081, 3008, 1493, 698.

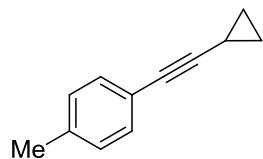
(cyclopropylethynyl)benzene (304, Table 24, Entry 11)



Was obtained as an oil (23 mg, 74%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL) and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

Spectral data are in accordance with the literature.²¹⁴

1-(cyclopropylethynyl)-4-methylbenzene (305, Table 24, Entry 12)



Was obtained as an oil (26 mg, 76%) following **GP 6.2** with Fe(TPP)Cl (4.6 mg, 0.0066 mmol, 3 mol%), 6 M KOH (3 mL) and addition of **213** (8.5 mL, 0.13 M in water, 1.1 mmol, 5 equiv) over 7 h.

Spectral data are in accordance with the literature.²¹⁴

²¹⁴ C. W. Li, K. Pati, G. Y. Lin, S. M. Abu Sohel, H. H. Hung, R. S. Liu, *Angew. Chem. Int. Ed.* **2010**, *49*, 9891.

Experiment to determine the turnover number

FeTPPCl (0.15 mg, 0.1 mol%) was dissolved in *p*-MeO-styrene (30 µL, 0.22 mmol) and 6 M aqueous KOH (2 mL) was added in an open vial. To this vigorously, steadily stirred solution (> 1000 rpm) was added an aqueous solution of reagent **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h at room temperature. After further 30 min, the solution was diluted with water and extracted three times with CH₂Cl₂. The organic phases were dried over MgSO₄ and evaporated under vacuo. The conversion was then determined by ¹H-NMR-analysis of the crude mixture (integration of the MeO-signals), and the turnover number was calculated using the following equation: TON = conversion/mol% catalyst = 60%/0.1% = 600.

Experiment using a water-soluble substrate

FeTPPCl (3.1 mg, 0.0044 mmol, 2 mol%) was dissolved in toluene (100 µL) and 6 M aqueous KOH (2 mL) and 4-vinylbenzoic acid (33 mg, 0.22 mmol) were added in an open vial. To this vigorously, steadily stirred solution (> 1000 rpm) was added an aqueous solution of reagent **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h at room temperature. After further 30 min, the solution was acidified with 1 M HCl and extracted three times with CH₂Cl₂. The organic phases were dried over MgSO₄ and evaporated under vacuo. The ¹H-NMR analysis of the crude mixture showed no conversion of starting material to the product.

Experiment using ethanol as a cosolvent

FeTPPCl (3.1 mg, 0.0044 mmol, 2 mol%) was dissolved in *p*-MeO-styrene (0.22 mmol) and 6 M aqueous KOH (2 mL) and EtOH (3 mL) were added in an open vial. To this vigorously, steadily stirred solution (> 1000 rpm) was added a solution of reagent **213** (5 mL, 0.13 M in water, 0.66 mmol, 3 equiv) over 4 h at room temperature. After further 30 min, the solution was diluted with water and extracted three times with CH₂Cl₂. The organic phases were dried over MgSO₄ and evaporated under vacuo. The conversion (12%) was determined by NMR analysis of the crude product (integration of the MeO-signals).

Curriculum Vitae

Born June 1st 1983 in Fribourg, Switzerland. Married to Stéphanie, one child (Kayla).

04/2008 – present	Doctoral studies in the group of Prof. Dr. ERICK M. CARREIRA, ETH Zürich, Switzerland.
	Title: <i>The in situ Generation of Diazo Compounds: Development of Novel Methods for Organic Synthesis.</i>
09/2006 – 03/2008	Master of Science ETH in Biology (specialization in biological chemistry)
	<u>Master Thesis (Prof. Dr. E. M. Carreira)</u>
	“Catalytic Decarbonylation of Epoxyaldehydes as an Innovative Strategy to Prepare Optically Active Mono- and Disubstituted Terminal Epoxides”
09/2003 – 08/2006	Bachelor of Science ETH in Biology.
1999 – 2003	Collège Saint-Michel, Fribourg
1996 – 1999	Cycle d’orientation de Jolimont, Fribourg
1990 – 1999	Ecole primaire, Arconciel et Fribourg

Awards and Fellowships

05/2011	2011 SCNAT/SCS Chemistry Travel Award.
2008 – 2011	Stipendienfonds der Schweizerischen Chemischen Industrie.
2006	Oskar-Jeger Scholarship from the ETH Zürich

During my doctoral studies, I was three times teaching assistant for an introductory-level organic chemistry laboratory course, responsible for two undergraduate students in the context of their research projects, and responsible for two master students.

Zürich, Mai 2012

Bill Morandi