

**Synthesis and Application of Silylated Pyrrolidines**  
**Enantioselective Organocatalytic Synthesis of  $\alpha$ -Trifluoromethyl**  
 **$\alpha$ -Amino Acid Derivatives**  
**and**  
**Copper-Catalyzed Multicomponent Reactions**

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigte Dissertation

vorgelegt von

Diplom-Chemiker

**Ralph Husmann**

aus Heerlen, Niederlande

Berichter:

Universitätsprofessor Dr. Carsten Bolm

Professor Dr. Sukbok Chang

Tag der mündlichen Prüfung: 03.06.2011

Diese Dissertation ist auf den Internetseiten der Hochschulbibliothek online verfügbar.

## **AACHENER BEITRÄGE ZUR CHEMIE**

(Aachener Beiträge zur Chemie ; Bd. 100)  
Zugl.: Aachen, Techn. Hochsch., Diss., 2011

Ralph Husmann

Synthesis and Application of Silylated Pyrrolidines Enantioselective Organocatalytic Synthesis  
of  $\alpha$ -Trifluoromethyl  $\alpha$ -Amino Acid Derivatives and Copper-Catalyzed Multicomponent Reactions

ISBN: 978-3-86130-382-4

1. Auflage 2011

### **Bibliografische Information der Deutschen Bibliothek**

Die Deutsche Bibliothek verzeichnet diese Publikation in der Deutschen Nationalbibliografie; detaillierte bibliografische Daten sind im Internet über <http://dnb.ddb.de> abrufbar.

Das Werk einschließlich seiner Teile ist urheberrechtlich geschützt. Jede Verwendung ist ohne die Zustimmung des Herausgebers außerhalb der engen Grenzen des Urhebergesetzes unzulässig und strafbar. Das gilt insbesondere für Vervielfältigungen, Übersetzungen, Mikroverfilmungen und die Einspeicherung und Verarbeitung in elektronischen Systemen.

### **Vertrieb:**

1. Auflage 2011  
© Verlagsgruppe Mainz GmbH Aachen  
Süsterfeldstr. 83, 52072 Aachen  
Tel. 0241/87 34 34  
Fax 0241/875577  
[www.Verlag-Mainz.de](http://www.Verlag-Mainz.de)

### **Herstellung:**

Druck und Verlagshaus Mainz GmbH Aachen  
Süsterfeldstraße 83  
52072 Aachen  
Tel. 0241/873434  
Fax 0241/875577  
[www.DruckereiMainz.de](http://www.DruckereiMainz.de)  
[www.Druckservice-Aachen.de](http://www.Druckservice-Aachen.de)

Satz: nach Druckvorlage des Autors  
Umschlaggestaltung: Druckerei Mainz

printed in Germany  
D 82 (Diss. RWTH Aachen University, 2011)

The work presented in this thesis was carried out from April 2007 until December 2010, at the Institute of Organic Chemistry, RWTH Aachen University, under the supervision of Professor Dr. Carsten Bolm. The major part of the work presented in Chapter 2.3 was conducted from October until December 2009, at the Department of Chemistry, KAIST (Korean Advanced Institute of Science and Technology) in Daejeon (Republic of Korea), under the supervision of Professor Dr. Sukbok Chang.

I would like to thank Professor Dr. Carsten Bolm for giving me the opportunity to work on exciting topics under excellent working conditions and his support.

Further thanks go to my second examiner, Professor Dr. Sukbok Chang.

Parts of this work have already been published:

R. Husmann, M. Jörres, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 12549-12552.

R. Husmann, Y. S. Na, C. Bolm, S. Chang, *Chem. Commun.* **2010**, *46*, 5494-5496.

R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping, C. Bolm, *Org. Lett.* **2011**, *13*, 1044-1047.



*“All things are ready if our minds be so.”*

– William Shakespeare –

*for my families*



# Table of Contents

|          |                                                                                                                                 |           |
|----------|---------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>1</b> | <b>Introduction .....</b>                                                                                                       | <b>11</b> |
| 1.1      | Asymmetric Organocatalysis .....                                                                                                | 12        |
| 1.1.1    | Lewis Base Catalysis .....                                                                                                      | 14        |
| 1.1.2    | Lewis Acid Catalysis .....                                                                                                      | 23        |
| 1.1.3    | Brønsted Base Catalysis.....                                                                                                    | 26        |
| 1.1.4    | Brønsted Acid Catalysis.....                                                                                                    | 28        |
| 1.2      | Copper-Catalyzed Multicomponent Reactions .....                                                                                 | 36        |
| 1.2.1    | Copper-Catalyzed Three-Component Coupling Reactions of Terminal Alkynes, Sulfonyl Azides and <i>N</i> -Nucleophiles .....       | 38        |
| 1.2.2    | Copper-Catalyzed Three-Component Coupling Reactions of Terminal Alkynes, Sulfonyl Azides and <i>O</i> -Nucleophiles .....       | 40        |
| 1.2.3    | Copper-Catalyzed Three-Component Coupling Reactions: Miscellaneous Examples.....                                                | 41        |
| 1.2.4    | Copper-Catalyzed Four-Component Coupling Reactions .....                                                                        | 42        |
| <b>2</b> | <b>Results and Discussion .....</b>                                                                                             | <b>45</b> |
| 2.1      | Synthesis and Application of Silylated Pyrrolidines.....                                                                        | 45        |
| 2.1.1    | Research Objective .....                                                                                                        | 45        |
| 2.1.2    | Synthesis of <i>N</i> -Boc-Protected Silylated Pyrrolidines .....                                                               | 46        |
| 2.1.3    | Deprotection of <i>N</i> -Boc Silylated Pyrrolidines .....                                                                      | 50        |
| 2.1.4    | Application of Silylated Pyrrolidines.....                                                                                      | 52        |
| 2.2      | Enantioselective Organocatalytic Synthesis of Quaternary $\alpha$ -Amino Acid Derivatives Bearing a CF <sub>3</sub> Moiety..... | 59        |
| 2.2.1    | Research Objective .....                                                                                                        | 61        |

## Table of Contents

---

|          |                                                                                                                                    |           |
|----------|------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 2.2.2    | Synthesis of Trifluoropyruvate Imines .....                                                                                        | 63        |
| 2.2.3    | Chiral Phosphoric Acid Catalyzed Synthesis of $\alpha$ -Trifluoromethyl $\alpha$ -Amino<br>Acid Derivatives .....                  | 64        |
| 2.3      | Copper-Catalyzed Multicomponent Reactions .....                                                                                    | 73        |
| 2.3.1    | Research Objective .....                                                                                                           | 74        |
| 2.3.2    | In Search of Alternative Nucleophiles for the Copper-Catalyzed Three-<br>Component Coupling Reaction.....                          | 75        |
| 2.3.3    | Nitroolefins as Suitable Electrophiles in the Copper-Catalyzed Four-<br>Component Coupling Reaction.....                           | 77        |
| <b>3</b> | <b>Summary and Outlook.....</b>                                                                                                    | <b>87</b> |
| 3.1      | Synthesis and Application of Silylated Pyrrolidines.....                                                                           | 87        |
| 3.2      | Enantioselective Organocatalytic Synthesis of Quaternary $\alpha$ -Amino Acid Derivatives<br>Bearing a CF <sub>3</sub> Moiety..... | 89        |
| 3.3      | Copper-Catalyzed Multicomponent Reactions .....                                                                                    | 91        |
| <b>4</b> | <b>Experimental Section .....</b>                                                                                                  | <b>95</b> |
| 4.1      | General Methods and Chemicals .....                                                                                                | 95        |
| 4.1.1    | Solvents.....                                                                                                                      | 95        |
| 4.1.2    | Chromatography .....                                                                                                               | 95        |
| 4.2      | Determination of the Physical Data .....                                                                                           | 96        |
| 4.3      | Synthesis of Substrates.....                                                                                                       | 98        |
| 4.4      | Synthesis of <i>N</i> -Boc-Protected Silylated Pyrrolidines .....                                                                  | 98        |
| 4.5      | Deprotection of <i>N</i> -Boc Silylated Pyrrolidines .....                                                                         | 104       |
| 4.6      | Michael Addition Reactions of Aldehydes to Nitroolefins.....                                                                       | 110       |
| 4.7      | Synthesis of Trifluoropyruvate Derived Imines.....                                                                                 | 122       |
| 4.8      | Synthesis of $\alpha$ -Trifluoromethyl $\alpha$ -Amino Acid Derivatives .....                                                      | 124       |
| 4.9      | Synthesis of $\alpha$ -Functionalized Imidates.....                                                                                | 137       |

## Table of Contents

---

|          |                               |            |
|----------|-------------------------------|------------|
| <b>5</b> | <b>Abbreviations.....</b>     | <b>151</b> |
| <b>6</b> | <b>References .....</b>       | <b>155</b> |
| <b>7</b> | <b>Acknowledgements.....</b>  | <b>175</b> |
| <b>8</b> | <b>Curriculum Vitae .....</b> | <b>177</b> |



---

# 1 Introduction

---

The phenomenon of catalysis has been utilized by mankind for many centuries. However, it wasn't until 1811 that Kirchhof conducted the first formal experiment on catalysis. He found that sugar was formed from starch in the presence of a small amount of sulfuric acid which could be recovered after the reaction.<sup>1</sup> Davy discovered that a hot platinum wire maintained the combustion of alcohol or ether vapors in the presence of air without the metal being chemically changed.<sup>2</sup> These findings finally led to the invention of the miner's safety-lamp.<sup>3</sup> Soon after, this heterogeneous process was also described by his cousin who prepared finely-divided platinum that acted in the same manner but at room temperature.<sup>4</sup> Around the same time, Thénard approached the concept of catalysis based on his results obtained from experiments with hydrogen peroxide although he never coined it as such.<sup>5</sup> Dulong and Thénard then further investigated Döbereiner's experiments where a stream of hydrogen gas over platinum sponge could be ignited.<sup>6</sup> Mitscherlich drew some important conclusions about the formation of ether and water from alcohol in the presence of sulfuric acid.<sup>7</sup> All these observations led the influential chemist Berzelius to formulate a new term: catalysis. In 1835, he described it in the following way:<sup>8</sup>

*“This new force, which was unknown until now, is common to organic and inorganic nature. I do not believe that this is a force entirely independent of the electrochemical affinities of matter; I believe, on the contrary, that it is only a new manifestation, but since we cannot see their connection and mutual dependence, it will be easier to designate it by a separate name. I will call this force catalytic force. Similarly, I will call the decomposition of bodies by this force catalysis, as one designates the decomposition of bodies by chemical affinity analysis.”*

The first Nobel Prize in chemistry in the field of catalysis was awarded to Ostwald in 1909. In Ostwald's Nobel lecture, Berzelius was honored as a master in the art of formulating chemical concepts.<sup>9</sup> In 1912, Sabatier (along with Grignard) obtained the same prize for his method of hydrogenating organic compounds in the presence of finely disintegrated metals.<sup>10</sup>

The first organocatalytic transformation was described by Wöhler and Von Liebig. They found the benzoin condensation during their research on bitter almond oil.<sup>11</sup> Zinin further developed this reaction in the laboratories of Von Liebig.<sup>12</sup>

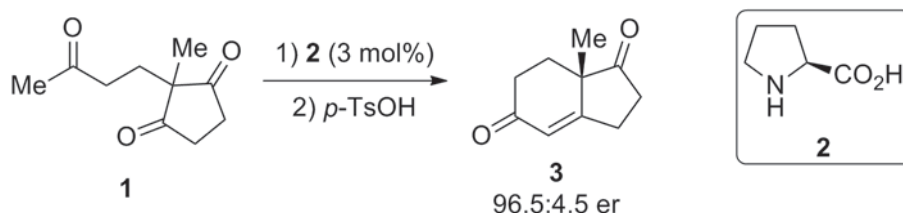
The first asymmetric synthesis was claimed by Marckwald in the year 1904.<sup>13</sup> He was able to decarboxylate 2-ethyl-2-methylmalonic acid in the presence of a chiral base, brucine, to obtain an optically active product. A few years later, Bredig and Fajans found that the decarboxylation of camphorcarboxylic acid in the presence of a chiral catalyst, nicotine, showed clear differences in decomposition rates for the two substrate antipodes, (*R*)- and (*S*)-camphorcarboxylic acid.<sup>14</sup> This can be regarded as the first organocatalytic asymmetric synthesis.

Since these early discoveries, advances in organic synthesis have often depended on advances in catalysis. In particular, the seminal work of Knowles, Noyori and Sharpless;<sup>15</sup> Chauvin, Grubbs and Schrock;<sup>16</sup> Ertl;<sup>17</sup> and of Heck, Negishi and Suzuki,<sup>18</sup> whom were all honored with the Nobel Prize in 2001, 2005, 2007 and 2010, respectively, should be mentioned.

This thesis will give an introduction to the field of asymmetric organocatalysis and copper-catalyzed multicomponent reactions. The synthesis of chiral silylated pyrrolidines and their use as organocatalysts, the application of chiral Brønsted acids in organocatalyzed stereoselective synthesis of  $\alpha$ -amino acids and copper-catalyzed four-component reactions will be described thereafter.

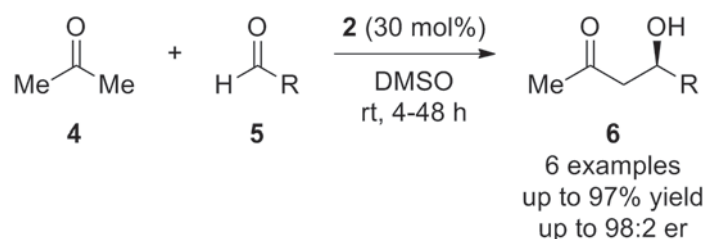
## 1.1 Asymmetric Organocatalysis

After the first report on asymmetric organocatalysis, only a small number of additional examples were described during the twentieth century. Initial experiments on asymmetric alkylation of enamines were conducted by Yamada in 1969.<sup>19</sup> Soon after, a catalytic intramolecular aldol reaction involving enamine intermediates was described by Eder, Sauer and Wiechert at Schering AG,<sup>20a,b</sup> and by Hajos and Parrish at Hoffman-LaRoche.<sup>20c,d</sup> The treatment of triketone **1** with a catalytic amount of (*S*)-proline (**2**) and subsequent acid mediated condensation led to the desired bicyclic compound **3** with an enantiomeric ratio of 94.5:4.5 (Scheme 1).



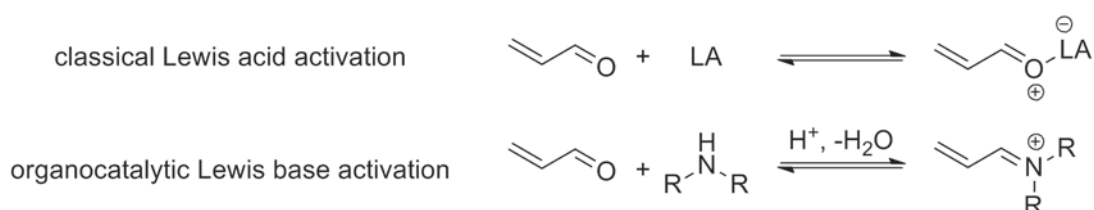
**Scheme 1:** The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

In 2000, List, Lerner and Barbas III reported on the use of (*S*)-proline (**2**) in direct intermolecular asymmetric aldol reactions. They obtained the cross aldol products in good yields and with enantiomeric ratios of up to 98:2 (Scheme 2). A drawback of this protocol is the high amount of catalyst required and its poor solubility in common organic solvents.<sup>21</sup>



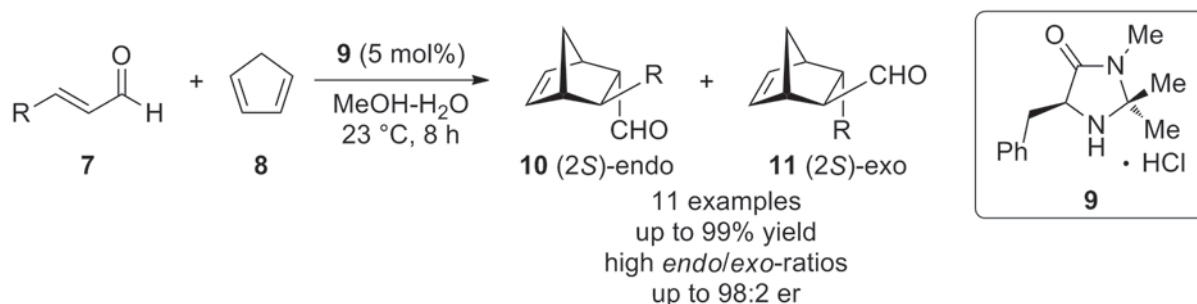
**Scheme 2:** The first organocatalytic intermolecular aldol reaction.

At nearly the same time, MacMillan introduced an enantioselective organocatalytic Diels-Alder reaction. Based on the classic concept of Lewis acid catalysis, they envisaged that the reversible formation of iminium ions from  $\alpha,\beta$ -unsaturated carbonyl compounds and secondary amines might cause a LUMO-lowering activation of the substrate (Figure 1).<sup>22</sup> Interestingly, earlier work on amine-catalyzed asymmetric Diels-Alder cycloadditions by Serebryakov seemed to remain unnoticed.<sup>23</sup>



**Figure 1:** Concepts for carbonyl activation.

Several chiral secondary amines were screened in the Diels-Alder reaction between  $\alpha,\beta$ -unsaturated aldehydes **7** and cyclopentadiene (**8**) and imidazolidinone **9** proved to be most successful (Scheme 3). A wide variety of substrates were tolerated in this transformation, giving the products in good yields, high *endo/exo*- and high enantiomeric ratios.<sup>22</sup>



**Scheme 3:** An organocatalytic Diels-Alder reaction.

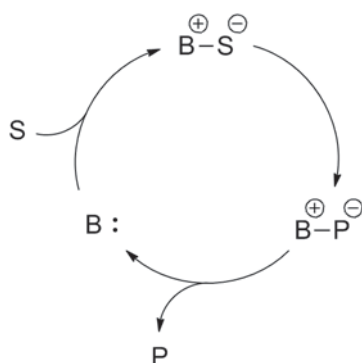
The last two examples account for the beginning of a new era in the field of asymmetric catalysis: organocatalysis. It is generally defined as catalysis with low molecular weight organic molecules where a metal is not part of the active principle. Over the past decade it has become a powerful third strategy next to previously established metal- and biocatalytic methods for the synthesis of optically active compounds.

Given that the field has grown so rapidly and the number of publications concerning the concept of organocatalysis is enormous, it is useful to classify reactions into four groups: Lewis base, Lewis acid, Brønsted base and Brønsted acid catalysis.<sup>24</sup> Not all catalysts can be categorized and some possess acidic and basic properties, making them bi- or multifunctional catalysts. Each case has to be properly assessed to draw conclusions on the mode of activation.

The next subchapters will give an introduction on the four areas. The emphasis will focus on Lewis base and Brønsted acid catalysis as the main part of the later presented experimental work can be classified as such.

### 1.1.1 Lewis Base Catalysis

A simplified principle of Lewis base catalyzed reactions is shown in Figure 2. The Hajos-Parrish-Eder-Sauer-Wiechert reaction and the transformations described by List and MacMillan (see Chapter 1.1) can be designated to this mode of activation. The Lewis base catalyst (B) reacts with substrate (S) through nucleophilic addition to form an active nucleophile or electrophile. This adduct further transforms into the product (P) and the catalyst is released to continue in the subsequent catalytic cycle.<sup>25</sup> Important developments in terms of catalyst design and applications where a covalent interaction of Lewis base catalyst and substrate is crucial will be illustrated in the following subchapter. Importantly, additional interactions like hydrogen bonding often play a pivotal role.



**Figure 2:** General principle of Lewis base catalysis.

Several important C-C bond forming reactions catalyzed by (*S*)-proline have been described since its use as an organocatalyst in the intermolecular aldol reaction in 2000. For example, an aldol reaction between hydroxyacetone and aldehydes to form *anti*-1,2-diols was developed.<sup>26a</sup> Also, ketones and  $\alpha$ -unsubstituted aldehydes were used as acceptors in aldol reactions.<sup>26b</sup> Self-aldolization of acetaldehyde was accomplished by Barbas III.<sup>26c</sup> Moreover, the aldol reaction between two aldehydes,<sup>26d</sup> aldehydes and activated carbonyl acceptors,<sup>26e</sup> dicarbonyls,<sup>26f</sup> and dioxanones (as dihydroxyacetone equivalents) and aldehydes<sup>26g</sup> were established.<sup>26h</sup>

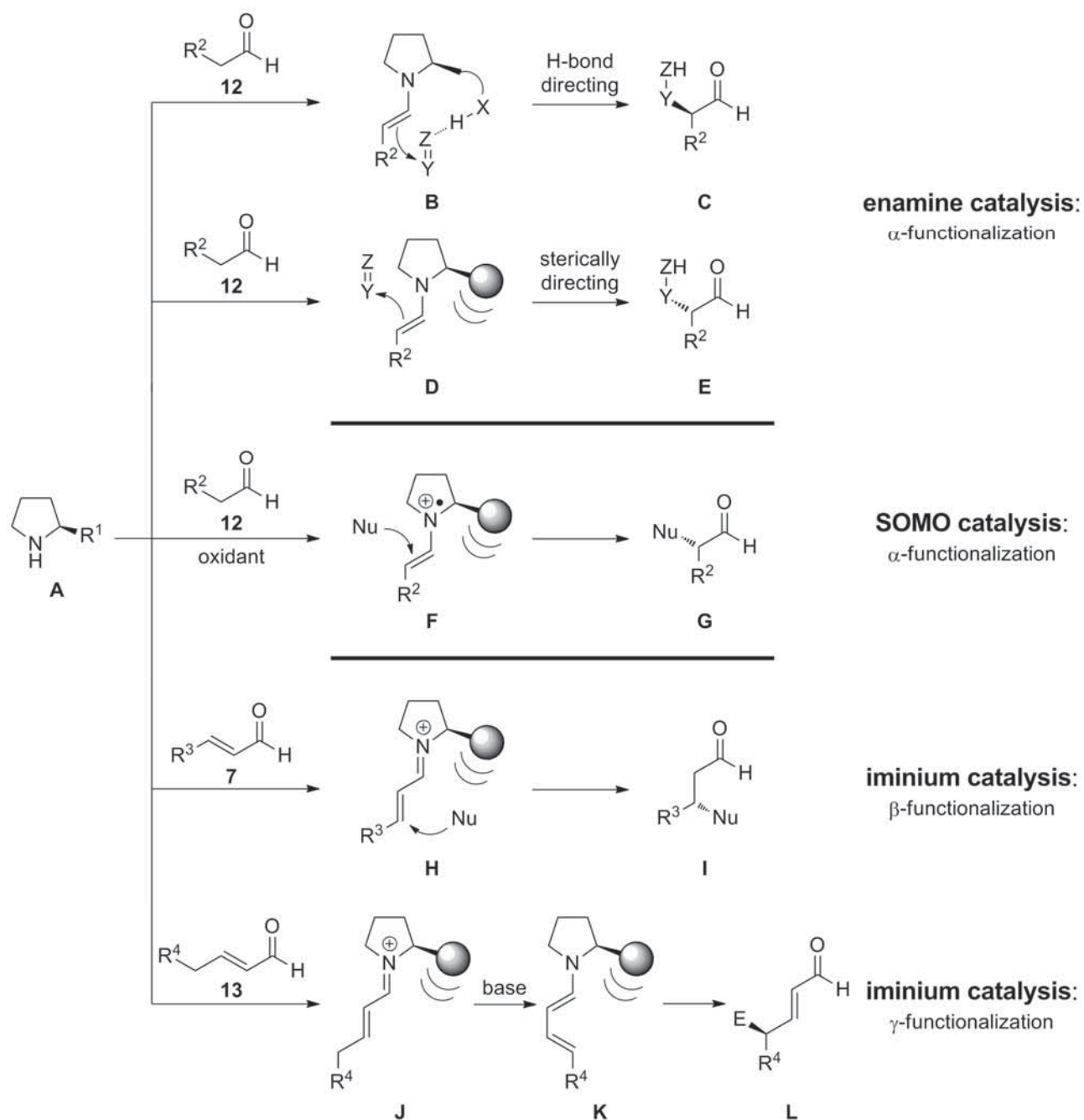
List described the first direct organocatalytic three-component Mannich reaction using (*S*)-proline to give the desired  $\beta$ -amino-ketones in yields of up to 90% and enantiomeric ratios of up to 98:2.<sup>27a</sup> Hydroxyacetone can be employed to form *syn*-1,2-amino alcohols.<sup>27b</sup> Amino acid derivatives were obtained in good yields and high enantioselectivities when preformed *N*-PMP-protected imino ethyl glyoxylate was reacted with aldehydes in the presence of (*S*)-proline.<sup>27c,d</sup> Hayashi reported a one-pot cross-Mannich reaction of aldehydes. Due to the instability of the resulting  $\beta$ -amino aldehydes, the reaction mixture was treated with NaBH<sub>4</sub> to form the corresponding  $\beta$ -amino alcohols.<sup>27e</sup> Westermann and Enders simultaneously disclosed the synthesis of protected amino sugars and derivatives.<sup>27f,g</sup> Another milestone discovery was the (*S*)-proline catalyzed Mannich reaction of acetaldehyde with *N*-Boc-imines. This exceptionally enantioselective reaction led to valuable products with broad synthetic applications.<sup>27h-j</sup>

Another important reaction in organic synthesis is the Michael addition reaction.<sup>28</sup> The first Michael addition using enamine-catalysis with (*S*)-proline was described by List.<sup>29a</sup> The  $\gamma$ -nitro ketones, obtained from cyclohexanone and  $\beta$ -nitrostyrene in good yields and high diastereoselectivities, could not be produced in an enantiomeric ratio exceeding 61.5:38.5. Enders was able to increase this ratio to 88.0:12.0 by changing the solvent from DMSO to MeOH.<sup>29b</sup> Generally, (*S*)-proline catalyzed Michael additions seem to be less enantioselective and therefore many catalysts have been designed to increase the stereoselectivity of these transformations.

In addition to C-C bond formations, C-N and C-O bonds in the  $\alpha$ -position of carbonyl compounds can be connected by (*S*)-proline catalysis.<sup>30</sup> Based on these results, (*S*)-proline can be considered as the basic module for organocatalysts.<sup>31</sup> Many of the organocatalysts known today stem from this natural amino acid but other rationally designed compounds can also serve as Lewis base type catalysts.

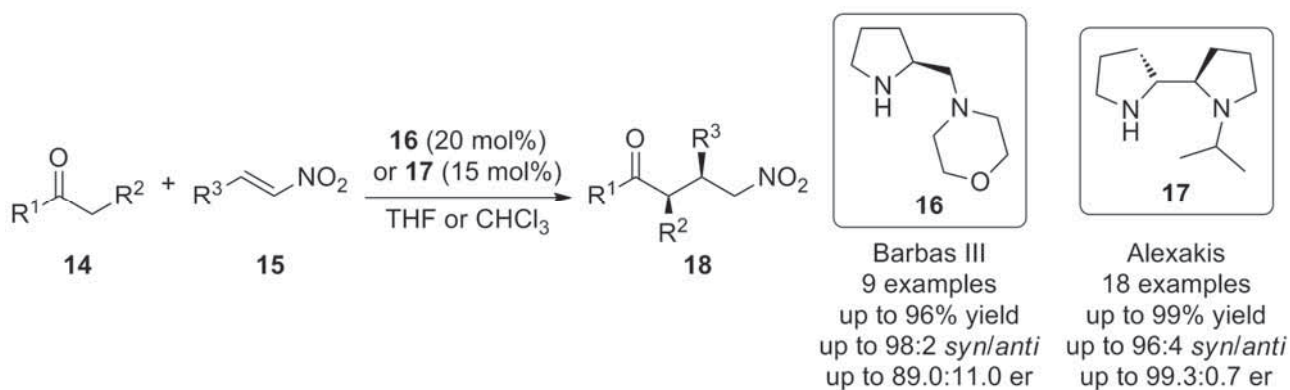
Catalytic reactions performed with Lewis bases are mostly founded on only three modes of activation (Figure 3).<sup>30,32</sup> Enamine catalysis is widely used to effect enantioselective carbonyl  $\alpha$ -functionalization. Two types of catalysts can be distinguished in this case. Once the enamine is

formed, it attracts an electrophile through hydrogen bonding or electrostatic interactions (structure **B**) facilitating a *Re*-face attack to give the (*R*)-product (structure **C**). The other possibility is that one side of the enamine intermediate (structure **D**) is sterically hindered and thus allowing for a preferred *Si*-face attack to give the (*S*)-product (structure **E**).<sup>26h</sup> An alternative view of this mode of activation is given by Seebach.<sup>33</sup> The first example of SOMO catalyzed  $\alpha$ -functionalization was reported by MacMillan.<sup>34</sup> In this case, the enamine is oxidized to give an electrophilic species **F** which reacts with a variety of weakly nucleophilic SOMOphiles. This leads to structure **G**. Another main part of Lewis base catalysis is based on iminium catalysis.<sup>35</sup>  $\alpha,\beta$ -Unsaturated carbonyl compound **7** reacts with the secondary amine to form an iminium ion **H** which is attacked by a nucleophile from the sterically less hindered side to eventually give structure **I**. Recently, some  $\gamma$ -functionalizations of  $\alpha,\beta$ -unsaturated carbonyl compounds **13** that proceed through a dienamine **K** have been realized.<sup>36</sup>



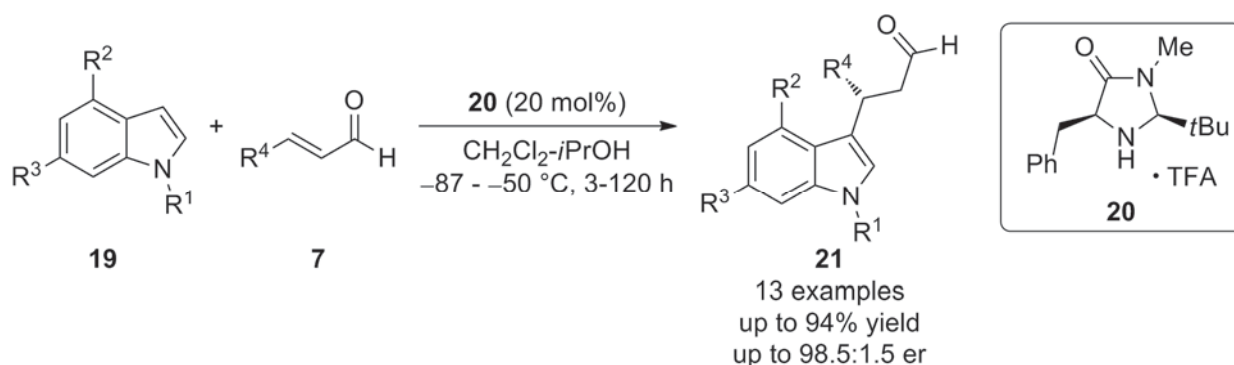
**Figure 3:** Different modes of action in Lewis base catalysis.

Superior results to (*S*)-proline catalyzed Michael additions were achieved with diamines as shown by Barbas III and Alexakis. Both pyrrolidine-based catalysts **16** and **17** were effective to give high yields and satisfactory stereoselectivities in the addition of carbonyl compounds **14** to nitroolefins **15** (Scheme 4).<sup>37a,b</sup> It is interesting that the use of hydroxyacetone also led to the desired 1,4-adducts, but with opposite diastereoselectivity (high *anti/syn*-ratio instead of high *syn/anti*-ratio).<sup>37c</sup>



**Scheme 4:** Michael addition reaction catalyzed by diamines **16** and **17**.

MacMillan utilized his second generation catalyst for iminium activation in a highly stereoselective Friedel-Crafts reaction. First generation catalyst **9** proved to be ineffective in the Friedel-Crafts alkylation of indoles. On the other hand, with imidazolidinone **20** the iminium formation is favored because the nitrogen lone pair is positioned away from the sterically hindered site and thus more accessible than in **9**. Various substrates were tolerated to give the alkylated indoles **21** in good yields (up to 94%) and enantiomeric ratios of up to 98.5:1.5 (Scheme 5).<sup>38</sup>

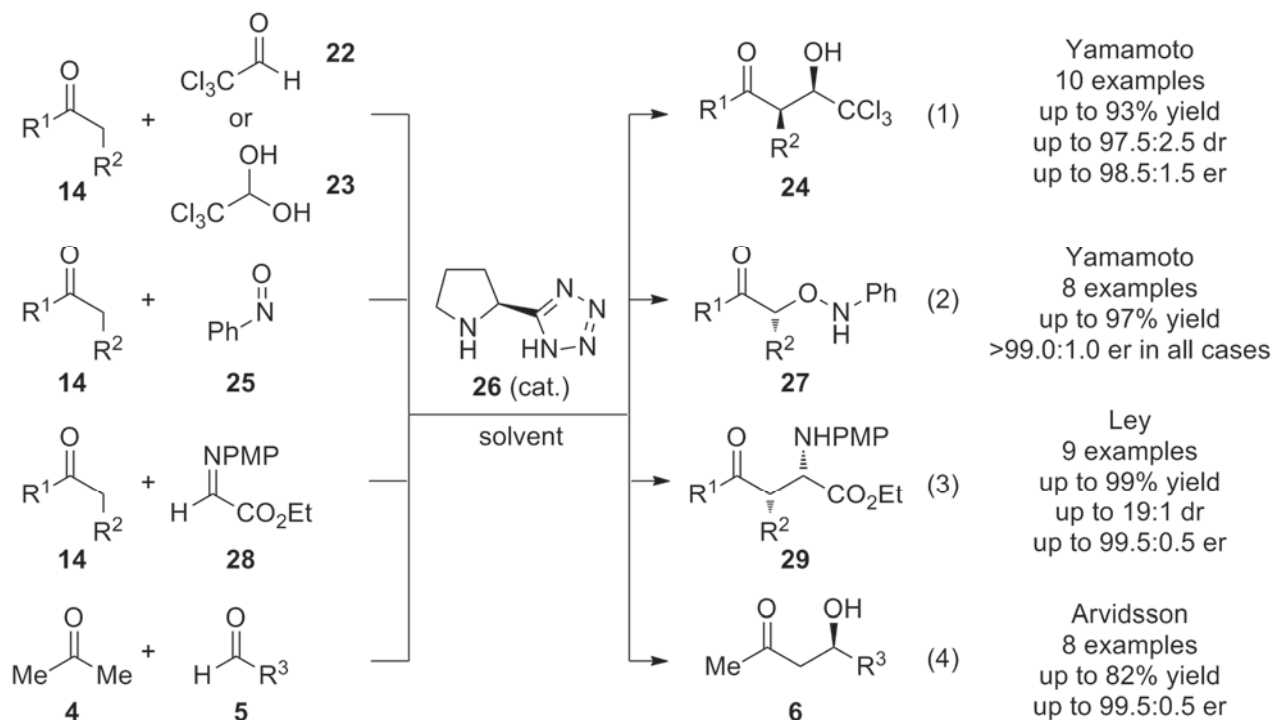


**Scheme 5:** MacMillan's second generation catalyst **20**.

Imidazolidinone **20** has become a widely applicable catalyst for several iminium- or enamine-type transformations, for example the Mukaiyama-Michael reaction,<sup>39a</sup> conjugate hydride reductions,<sup>39b</sup>  $\alpha$ -halogenation of carbonyl compounds<sup>32b</sup> or even organo-cascade reactions.<sup>39c</sup>

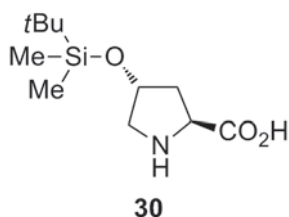
Another versatile catalyst was simultaneously introduced by Yamamoto, Ley and Arvidsson.<sup>40</sup> Tetrazole **26** is easily synthesized starting from (*S*)-proline and has the advantage of better solubility in common organic solvents. This (*S*)-proline analog was successfully applied in an aldol reaction of ketones and chloral (**22**) or chloral hydrate (**23**) (eq. (1) in Scheme 6).<sup>40a</sup> The synthesis of  $\alpha$ -aminooxy carbonyl compounds was also accomplished by Yamamoto (eq. (2)).<sup>40b</sup> Ley successfully employed 5-pyrrolidin-2-yltetrazole (**26**) as an organocatalyst in the Mannich reaction of carbonyl compounds and *N*-PMP-protected imino ethyl glyoxylate **28** (eq. (3)).<sup>40c</sup> Catalyst loadings as low as 5 mol% were used in these reactions. Arvidsson exploited this catalyst in an

aldol reaction (eq. (4)) and performed computational studies in order to explain the increase of reactivity of the tetrazole catalyst.<sup>40d,e</sup> Other transformations like an *O*-nitroso aldol/Michael reaction,<sup>41a</sup> the addition of ketones to nitroolefins<sup>41b</sup> or the conjugate addition of nitroalkanes to enones<sup>41c</sup> have since been reported. Recently, an interesting application of this proline derivative was described. Continuous-flow microreactor systems were used to accelerate aldol and Mannich reactions. This can be especially appealing for industrial applications as reaction scale-up with these systems is straightforward.<sup>41d</sup>



**Scheme 6:** Use of 5-pyrrolidin-2-yltetrazole (**26**) in various transformations.

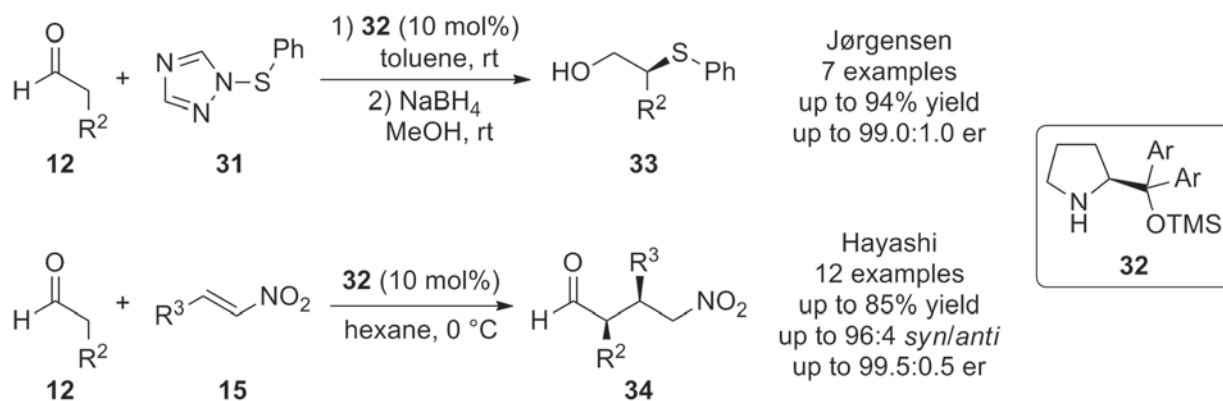
Along the same lines, Hayashi proposed the use of 4-siloxyproline **30** as a more soluble catalyst (Figure 4). When comparing this compound to (*S*)-proline, a much higher reactivity was observed in the  $\alpha$ -aminooxylation of carbonyl compounds, *O*-nitroso aldol/Michael and Mannich reaction. Thus, shorter reaction times and lower catalyst loadings were needed for completion of the transformations without compromising on stereoselectivity.<sup>42</sup>



**Figure 4:** Hayashi's 4-siloxyproline **30**.

Soon thereafter, Jørgensen and Hayashi simultaneously developed undoubtedly the most versatile organocatalyst known today. Jørgensen used TMS-protected diarylprolinol derivative **32** in an

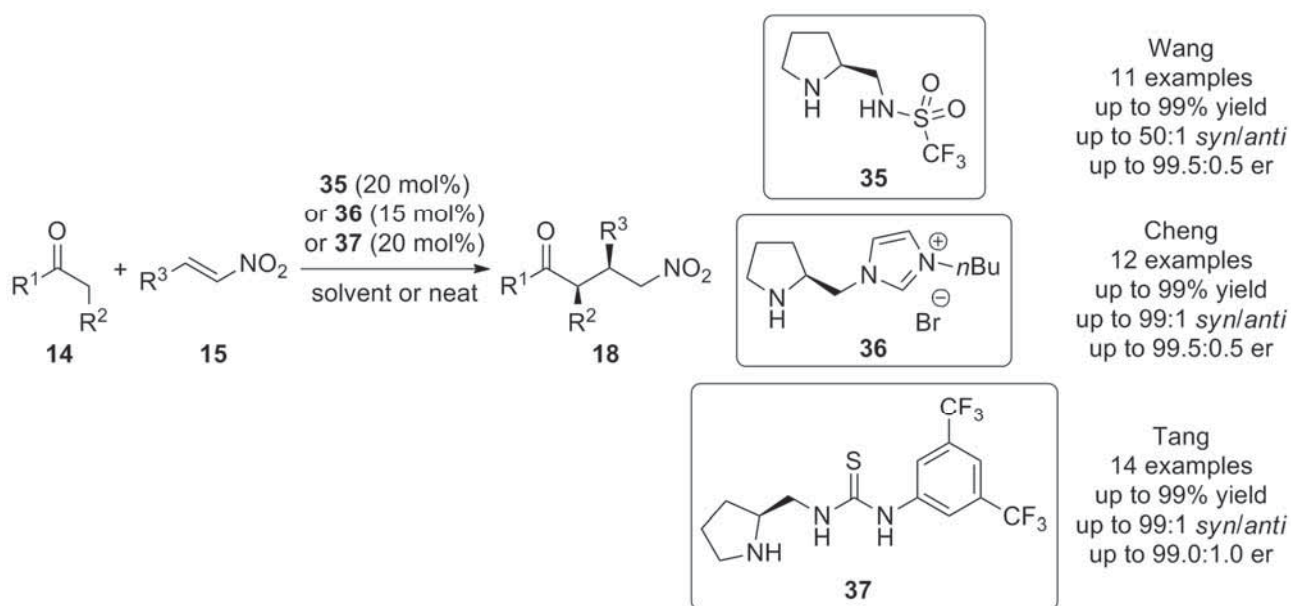
$\alpha$ -sulfenylation reaction of aldehydes (Scheme 7). Due to their instability, it was necessary to reduce the aldehydes *in situ*. The corresponding alcohols **33** were obtained in high yields and excellent enantioselectivities.<sup>43a</sup> Furthermore, Hayashi applied **32** as a catalyst for the asymmetric Michael addition of aldehydes **12** to nitroolefins **15**.<sup>43b</sup>



**Scheme 7:** First applications of the Jørgensen-Hayashi catalyst **32**.

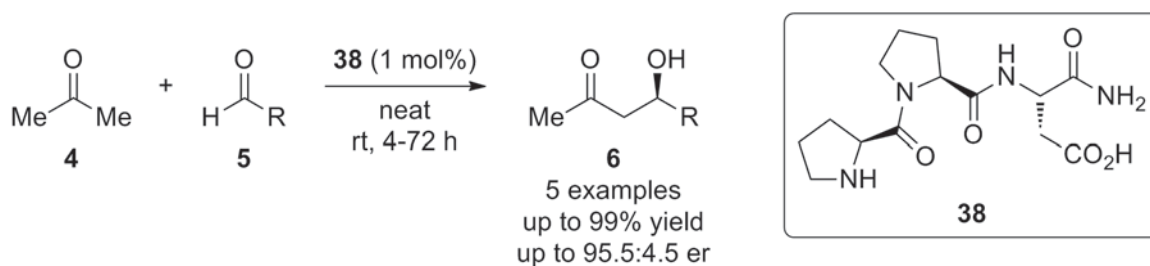
In addition to C-S and C-C bond forming reactions, C-N, C-O, C-F, C-Cl and C-Br bonds in the  $\alpha$ -position of carbonyl compounds have been formed with this remarkable compound. Excellent reviews have reported on the progress that was achieved with the Jørgensen-Hayashi catalyst.<sup>26h,30,32a,44</sup> Other silicon-containing catalysts have also been developed and used in various transformations.<sup>45</sup>

The Michael addition of carbonyl compounds to nitroolefins has become a benchmark reaction for the evaluation of new organocatalysts. Wang showed that pyrrolidine sulfonamide **35** served as an efficient organocatalyst not only in  $\alpha$ -aminooxylation,<sup>46a</sup> Mannich,<sup>46b</sup>  $\alpha$ -sulfenylation<sup>46c</sup> or  $\alpha$ -selenylation<sup>46d</sup> reactions, but also in Michael additions of aldehydes to nitroolefins (Scheme 8).<sup>46e</sup> Cheng studied the effect of chiral ionic liquids and achieved high yields and stereoselectivities with **36**.<sup>47</sup> Bifunctional catalyst **37** was developed by Tang. This pyrrolidine-based thiourea showed remarkable properties especially due to the ability of thioureas to coordinate to the nitro group, thus controlling the orientation of the substrates leading to high stereoselectivity of the product.<sup>48</sup>



**Scheme 8:** Several rationally designed organocatalysts for Michael additions to nitroolefins.

Following the first example of a peptide-catalyzed aldol reaction by Reymond in 2003,<sup>49</sup> Wennemers developed the exquisitely active tripeptide **38** to catalyze the aldol reaction between acetone (**4**) and aldehydes **5** (Scheme 9). This tripeptidic catalyst was found using a strategy for the rapid identification of organocatalyzed bimolecular reactions developed by the same group.<sup>50a</sup> Only 1 mol% of catalyst was used to achieve excellent yields and enantioselectivities of up to 95.5:4.5 er.<sup>50b</sup> A remarkable catalyst loading of only 0.1 mol% was recently published in the conjugate addition of aldehydes to nitroolefins.<sup>51</sup>

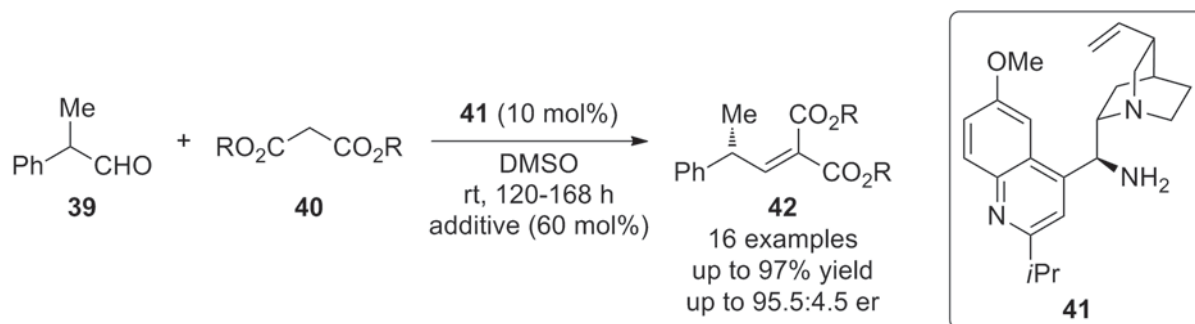


**Scheme 9:** Peptide **38** as organocatalyst in aldol reactions.

Numerous other examples of peptide-catalyzed reactions have been demonstrated and reviewed by Miller.<sup>52</sup>

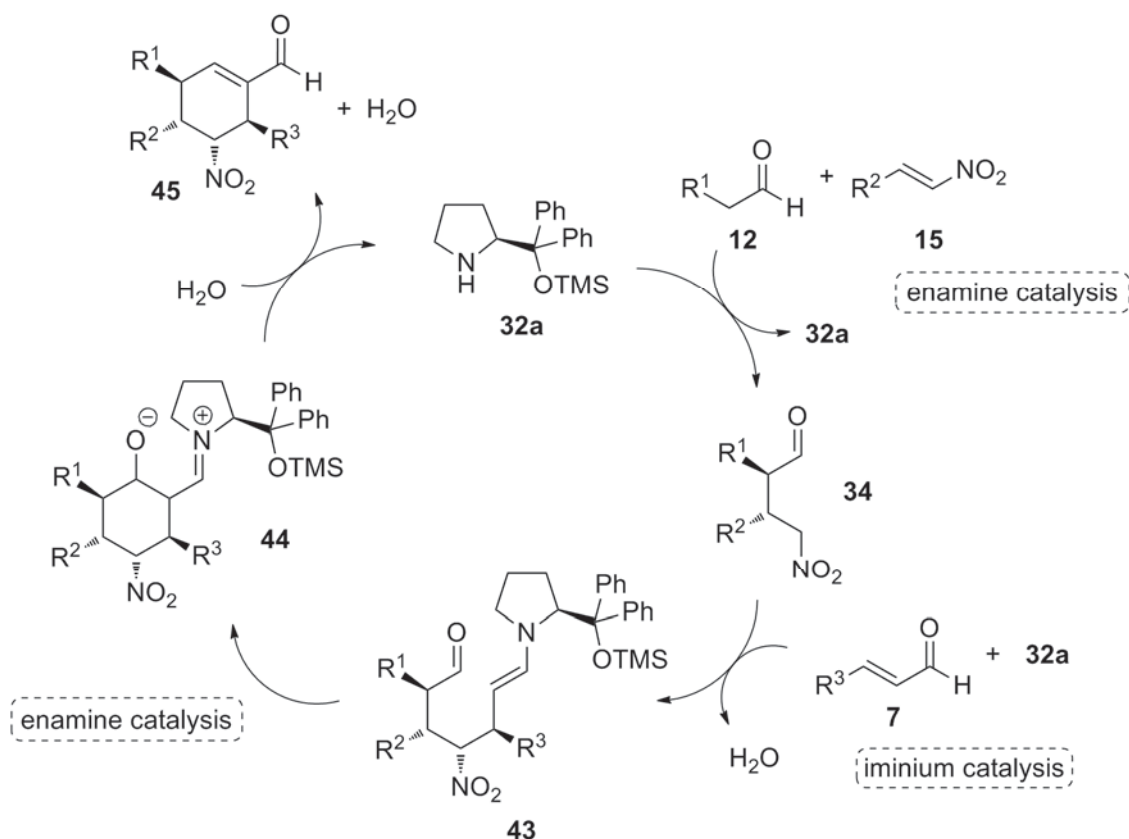
Interestingly, despite the efforts of Knoevenagel, Dakin, Kuhn, Langenbeck, Stork and others concerning enamine- and iminium-type transformations from the late nineteenth and twentieth century,<sup>53</sup> no asymmetric version of the Knoevenagel condensation had been described until recently. Easily synthesized cinchona amine catalysts like **41** were applied in the reaction of racemic  $\alpha$ -branched aldehydes **39** and malonates **40** using benzene-1,3,5-tricarboxylic acid as

additive (Scheme 10). The Knoevenagel condensation products were obtained in high yields and enantiomeric ratios of up to 95.5:4.5.<sup>54</sup>



**Scheme 10:** The first catalytic asymmetric Knoevenagel condensation.

Organocatalysis has not only been used in relatively simple transformations as described above. Enders especially has pioneered the realm of catalytic asymmetric multicomponent domino reactions. In 2006, his group reported on the synthesis of tetra-substituted cyclohexene carbaldehydes using a Michael/Michael/aldol reaction sequence (Figure 5). Jørgensen-Hayashi catalyst **32a** was capable of catalyzing each step of this triple cascade. The first conjugate addition takes place between linear aldehyde **12** and nitroolefin **15**. The catalyst is set free by hydrolysis and can form an iminium ion with  $\alpha,\beta$ -unsaturated aldehyde **7** which in turn reacts in the next Michael addition with **34**. An intramolecular aldol reaction of **43** subsequently forms intermediate **44** and through hydrolysis and elimination of water the 6-membered cycle **45** with four newly formed stereocenters is released and the catalyst enters the next catalytic cycle. A wide variety of substrates was tolerated to give the desired products in moderate yields (up to 58%), good diastereoselectivities (up to 9.9:0.1) and complete enantiocontrol (>99.5:0.5 in all cases).<sup>55</sup>

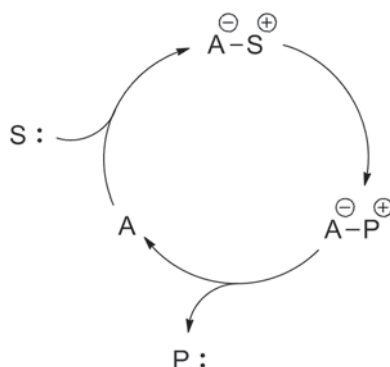


**Figure 5:** Enders' triple cascade cycle.

The last example demonstrates that organocatalysis serves as a powerful tool to construct complicated structures in a highly stereoselective manner. Excellent reviews by Christmann and Enders give an overview on the scope and limitations of organocatalysis in total synthesis.<sup>56</sup> The combination of organocatalysis and photoredox catalysis has lately been introduced by MacMillan and is an emerging field.<sup>57</sup>

### 1.1.2 Lewis Acid Catalysis

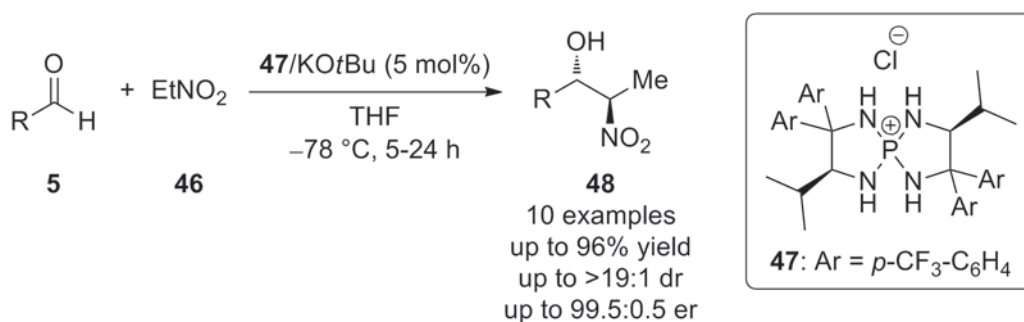
The general principle of Lewis acid catalyzed reactions is depicted in Figure 6. The Lewis acid catalyst (A) reacts with substrate (S) by accepting an electron pair to form an active species which further transforms into the product (P). The catalyst is released to continue in the subsequent catalytic cycle.



**Figure 6:** General principle of Lewis acid catalysis.

Lewis acid catalysis includes catalysis by boron (although considered as metalloid),<sup>58</sup> carbocations,<sup>59</sup> silylium ions (also considered as metalloids)<sup>60</sup> and phosphonium cations.<sup>61</sup> Chiral phosphonium salts have recently been successfully applied in several asymmetric transformations. Although hydrogen bonding probably plays a crucial role in the reaction pathway (thus making it a Brønsted acid catalyst), it will be discussed here.

The *P*-spiro-tetraaminophosphonium salt **47** was synthesized from (*S*)-valine and applied in a Henry reaction between aldehydes **5** and nitroethane (**46**) (Scheme 11). An array of 10 different aldehydes was tolerated to give the nitro alcohols **48** in good yields and excellent stereoselectivities.<sup>62a</sup> Other applications in a direct Mannich-type reaction<sup>62b</sup> and the use of chiral phosphonium salts under phase transfer conditions in the amination of  $\beta$ -ketoesters have been reported.<sup>62c</sup>

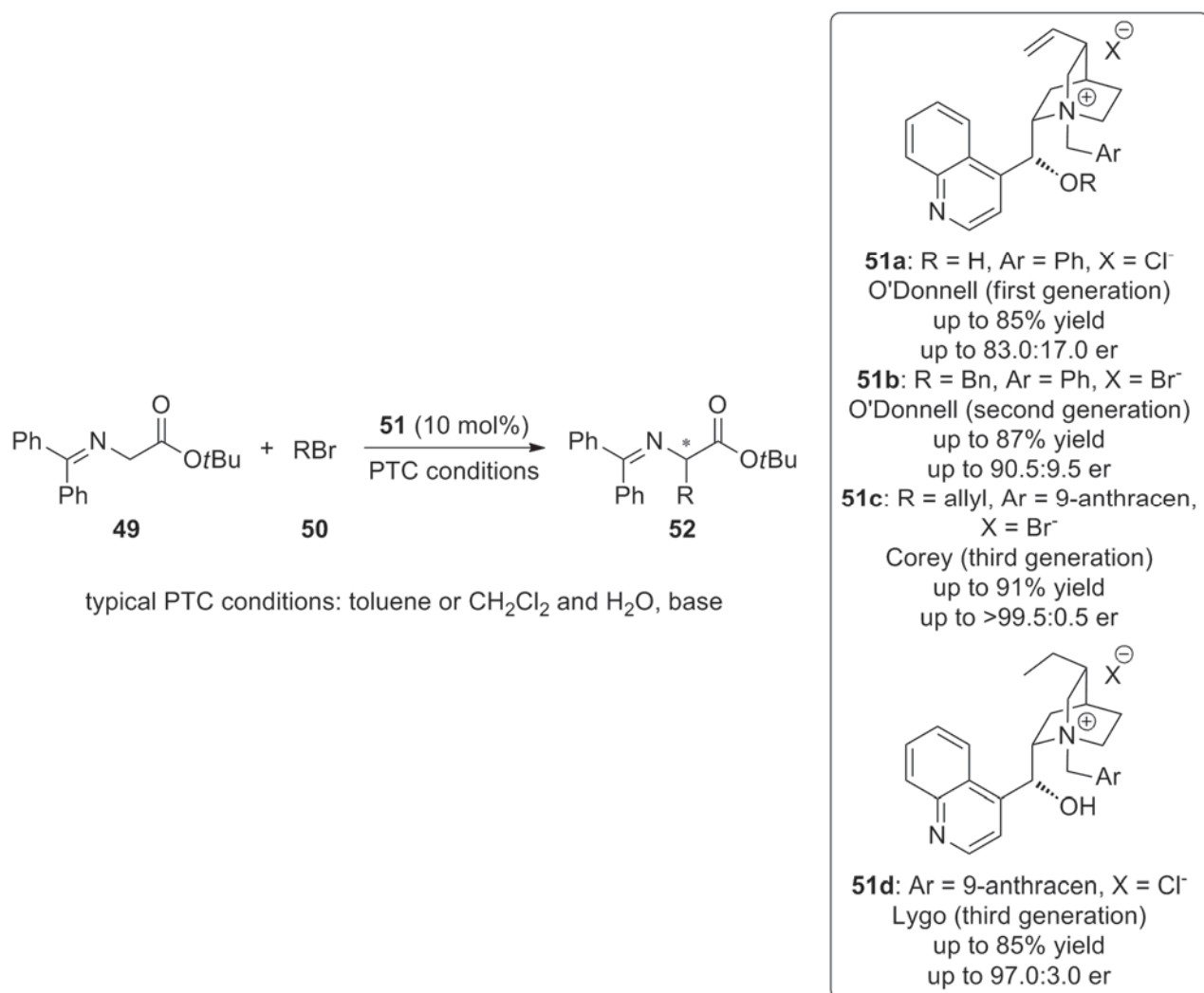


**Scheme 11:** First highly stereoselective phosphonium salt catalyzed Henry reaction.

Another major field in asymmetric organocatalysis is the use of quaternary ammonium salts,  $R_4N^+$ , in phase transfer reactions. Strictly speaking, phase transfer catalysis with fully substituted ammonium cations does not belong in the realm of Lewis acid catalysis. These cations do not possess an empty orbital to accept an electron pair, and thus are not Lewis acids. Nevertheless, it will be shortly introduced here.

The first efficient asymmetric alkylation of an indanone derivative using *N*-benzylcinchoninium chloride was developed by a group at Merck in 1984.<sup>63</sup> The first practical asymmetric synthesis of  $\alpha$ -amino acids using the same approach was introduced by O'Donnell.<sup>64</sup> Lygo and Corey

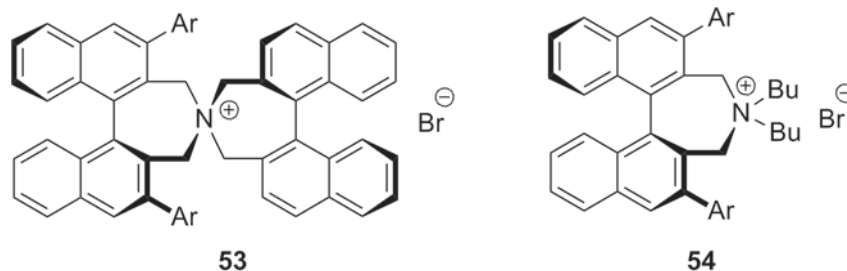
independently further extended this area.<sup>65</sup> Their alkaloid-based catalysts **51** proved effective in the alkylation of glycine Schiff base **49** with alkyl bromides **50** to form the protected  $\alpha$ -amino acids **52** in good yields and high stereoisomeric ratios (Scheme 12). Acidic hydrolysis of **52** afforded the free amino esters. Products with the opposite absolute configuration were obtained by using the cinchonine instead of the cinchonidine **51** derived catalysts without compromising on the stereoselectivities.



**Scheme 12:** Three generations of alkaloid-based phase-transfer catalysts.

Maruoka and Ooi emerged as leaders in this field after their report on newly developed C<sub>2</sub>-symmetric chiral phase-transfer catalyst **53** in 1999 (Figure 7).<sup>66a</sup> The catalyst displayed outstanding activity in alkylation of glycine Schiff base **49** and several other reactions. A particularly remarkable feature of the reactions was the low catalyst loading. Only 1 mol% (instead of the usual 10 mol% for the conventional alkaloid-based catalysts) was sufficient to obtain excellent results in terms of yield and stereoselectivity. A further advance was made with the powerful quaternary ammonium bromide **54**. It possesses straight-chain-alkyl groups and is even

effective with catalyst loadings as low as 0.01-0.05 mol% in the alkylation of **49** to form  $\alpha$ -alkyl and  $\alpha,\alpha$ -dialkyl-amino acids.<sup>66b</sup>

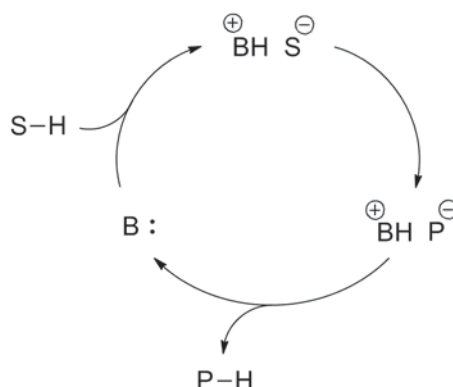


**Figure 7:** Maruoka's phase-transfer catalysts **53** and **54**.

In summary, this type of catalysis enables alkylation and dialkylation of glycine Schiff base to produce natural and unnatural  $\alpha$ -amino acid derivatives and gives rise to numerous other transformations to give products in high yields and stereoselectivities.<sup>67</sup>

### 1.1.3 Brønsted Base Catalysis

The IUPAC definition of a Brønsted base is a molecular entity capable of accepting a hydron (proton) from an acid (*i.e.* a “hydron acceptor”) or the corresponding chemical species.<sup>68</sup> A general picture of Brønsted base catalysis is given in Figure 8. A pro-nucleophile (S-H) is deprotonated by the base to render a species ( $\text{BH}^+\text{S}^-$ ) with enhanced nucleophilicity. This species further transforms into the product (P) and the catalyst is released to continue in the subsequent catalytic cycle. In contrast to Lewis base catalysis, reactions with Brønsted bases rely on non-covalent interactions of the substrate-catalyst adduct in the transition state. A few important asymmetric organocatalytic examples will be described here.



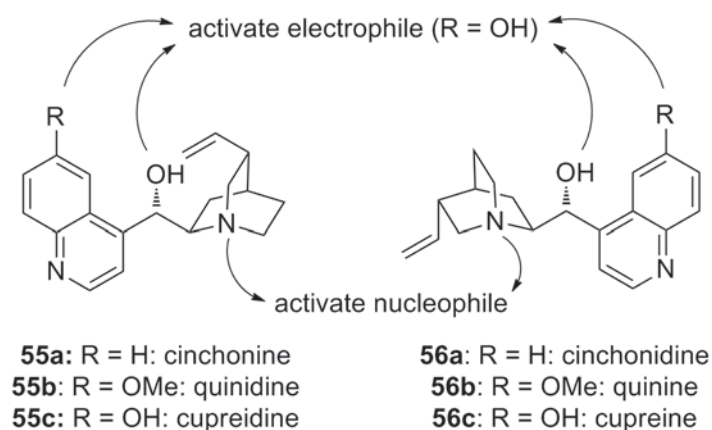
**Figure 8:** General principle of Brønsted base catalysis.

Since the interaction of the Brønsted base catalyst and substrate results in an ion pair and the asymmetric outcome of the reaction relies on the nature of the chiral catalytic component of the

intermediate, effective catalysts often incorporate an additional site with hydrogen-bond donor ability. Nevertheless, these bifunctional Brønsted base/Brønsted acid catalysts will be discussed when the basic center proved crucial for effective catalysis and the catalytic cycle involves a base-promoted deprotonation step. Synergistic activation of the nucleophile and electrophile often leads to highly effective transformations with low catalyst loadings.

Cinchona alkaloids seem to have properties to fulfill these requirements and the first catalytic reaction was described by Bredig almost 100 years ago. He obtained an enantiomeric ratio of only 55.0:45.0 in the hydrocyanation of aldehydes in the presence of quinidine.<sup>69a</sup> In 1960, Pracejus found a stereoselective method to form  $\alpha$ -phenyl propionic acid ester (87.0:13.0 er) when using phenylmethylketene, methanol and only 1 mol% of acetylquinidine.<sup>69b</sup> Various publications by Wynberg<sup>69c</sup> during the second half of the twentieth century showed the broad applicability of cinchona alkaloid based catalysis, with a stereoselective  $\beta$ -lactone synthesis as perhaps the most eminent example.<sup>69d</sup>

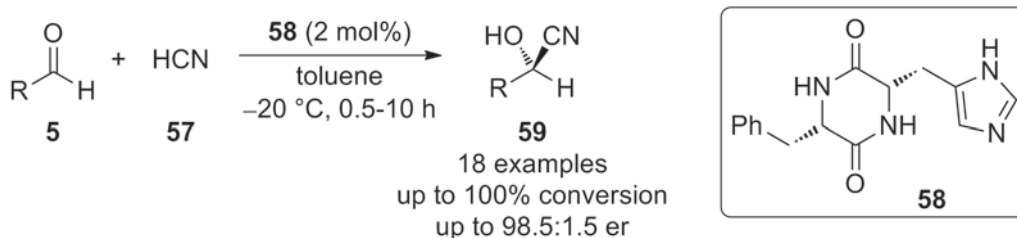
Cinchona alkaloids like **55** and **56** are successful catalyst in numerous asymmetric transformations due to their bifunctional nature (Figure 9). They possess multiple sites suitable for further modification and thus fine-tuning for specific requirements of reactions like the Mannich, Michael, Henry or aza-Henry reaction is possible. Furthermore, few examples of stereoselective C-O-, C-N-, C-S- and C-P-bond forming reactions have been reported.<sup>70</sup> The desymmetrization of cyclic *meso*-anhydrides leading to optically active hemiesters using these types of alkaloids has also been described.<sup>71</sup>



**Figure 9:** Bifunctional cinchona alkaloids.

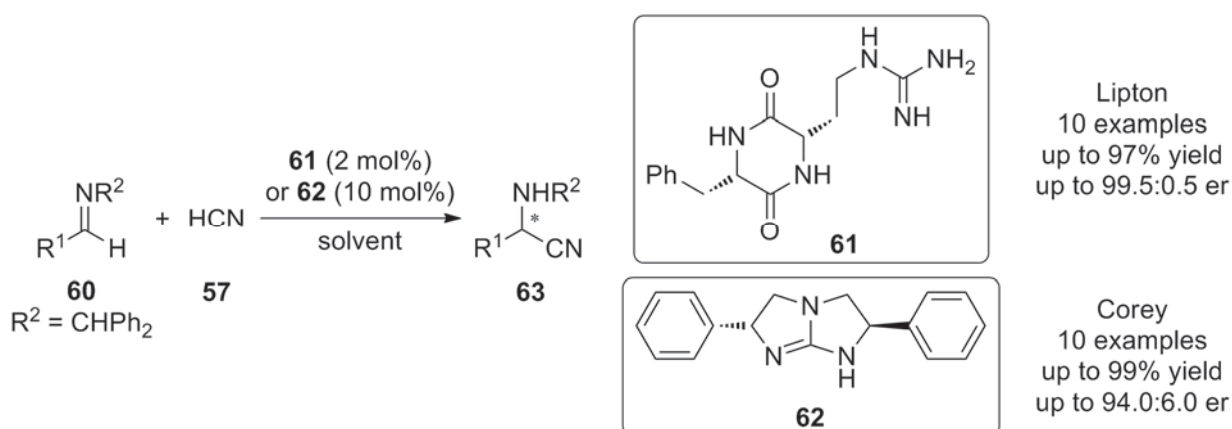
In 1990, Inoue employed a dipeptide in the stereoselective synthesis of cyanohydrins. Cyclo[(*S*)-phenylalanyl-(*S*)-histidyl] (**58**) is easily synthesized starting from the corresponding protected amino acids (benzyloxycarbonyl)-(*S*)-phenylalanine and (*S*)-histidine methyl ester. Use of only 2 mol% of this catalyst in the addition of hydrogen cyanide (**57**) to aldehydes **5** led to enantiomeric

ratios of up to 98.5:1.5 (Scheme 13). After derivatizing the cyanohydrins to the appropriate esters, the conversion and enantiomeric ratio were determined by  $^1\text{H}$  NMR spectroscopy or GC.<sup>72</sup>



**Scheme 13:** Asymmetric addition of hydrogen cyanide to aldehydes catalyzed by dipeptide **58**.

The addition of hydrogen cyanide to imines is part of the oldest method known for the synthesis of  $\alpha$ -amino acids: the Strecker synthesis.<sup>73</sup> Lipton utilized a similar dipeptide as Inoue but with guanidine as basic moiety for the addition of hydrogen cyanide (**57**) to *N*-benzhydryl imines **60** (Scheme 14).<sup>74a</sup> Corey also developed a guanidine-based catalyst for this reaction.<sup>74b</sup> High yields and enantiomeric ratios of the *N*-substituted  $\alpha$ -amino nitriles **63** were obtained in both cases. Treatment with 6N HCl at elevated temperatures gave the corresponding  $\alpha$ -amino acids.



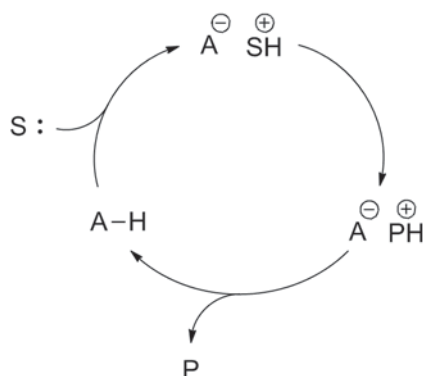
**Scheme 14:** Asymmetric Strecker synthesis catalyzed by guanidine derivatives **61** and **62**.

Interestingly, subsequent studies by Kunz revealed that the results reported by Lipton were not reproducible and that **61** did not induce enantioselective addition of hydrogen cyanide to imines.<sup>75</sup> The characteristics of chiral guanidines comprise high  $\text{p}K_{\text{a}}$  values and the ability to form dual hydrogen bonds which make these type of compounds feasible catalysts for many asymmetric transformations.<sup>76</sup>

#### 1.1.4 Brønsted Acid Catalysis

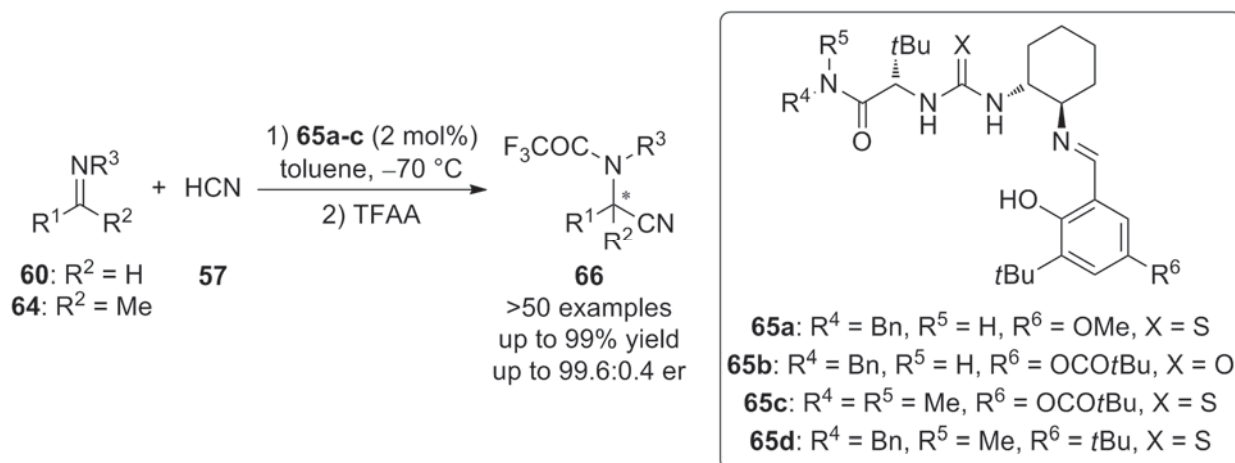
Brønsted acid catalysis is based on non-covalent interactions as well. The general asymmetric Brønsted acid catalysis through directed hydrogen bonding will shortly be introduced in this

section. More specific acid catalysis with chiral Brønsted acids constitutes the main topic of this part. A general picture is delineated in Figure 10. The chiral Brønsted acid (A-H) protonates the substrate (S) and forms a chiral ionic pair that further transforms into the product (P) and releases the catalyst for subsequent action. This asymmetric counterion-directed catalysis (ACDC, a term introduced by List) has become a viable concept in the recent past.<sup>77</sup>



**Figure 10:** General principle of Brønsted acid catalysis.

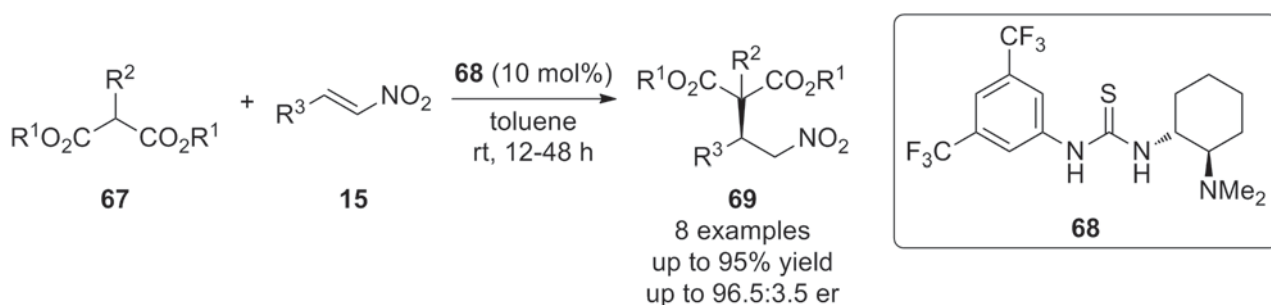
Activation of electrophiles through hydrogen bonding is abundant in the field of biocatalysis.<sup>78</sup> Inspired by this type of activation, Jacobsen introduced a small molecule catalyst capable of forming double hydrogen bonds. Chiral Schiff bases **65a-c** bearing urea or thiourea moieties were able to catalyze the addition of hydrogen cyanide (**57**) to a wide variety of imines forming  $\alpha$ -amino nitriles in high yields and excellent enantiomeric ratios (Scheme 15).<sup>79</sup> The addition to ketimines to form quaternary  $\alpha$ -amino acid derivatives was also achieved.<sup>80</sup> Additional transformations like the Mannich<sup>81a</sup> or aza-Baylis-Hillman<sup>81b</sup> reaction were performed with **65d**.<sup>82</sup>



**Scheme 15:** Jacobsen's catalysts **65a-c** in the asymmetric Strecker reaction.

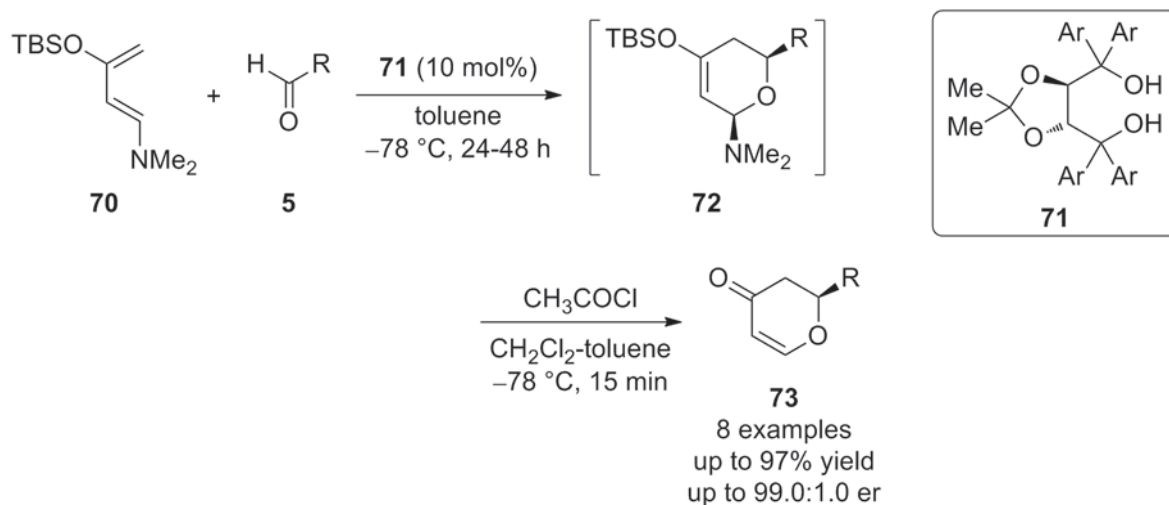
Takemoto reported that a thiourea-based catalyst **68** was effective in the Michael addition of malonates **67** to nitroolefins **15** (Scheme 16). Their investigations showed that the thiourea and tertiary amino group both should be present within the molecule to obtain satisfying rates and

enantioselectivities.<sup>83</sup> Compound **68** thus possesses Brønsted acidic as well as Brønsted basic properties. The electron withdrawing CF<sub>3</sub>-groups make the N-H protons more acidic and therefore better hydrogen bond donors. They also polarize the adjacent H atoms, which in turn facilitates interaction with the sulfur which may make the catalyst more rigid and explain the high stereoselectivities that are achieved with thiourea-based catalysts. Early studies about this paradigm had been conducted by Schreiner.<sup>82a,g,84</sup>



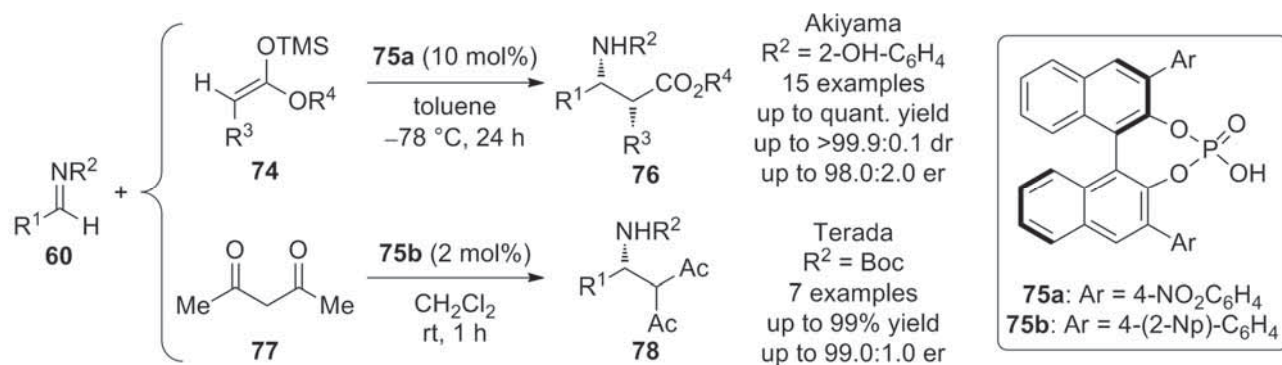
**Scheme 16:** Asymmetric Michael addition catalyzed by Takemoto's catalyst **68**.

The versatile Seebach compound, TADDOL (**71**),<sup>85</sup> was first successfully applied as an organocatalyst in the asymmetric hetero-Diels-Alder reaction. When 1-amino-3-siloxy diene **70** was reacted with aldehyde **5** in the presence of catalyst **71**, cycloadduct **72** was constructed and directly transformed into dihydropyrone **73** upon treatment with acetylchloride (Scheme 17).<sup>86</sup> The diol, derived from tartaric acid, is believed to activate the carbonyl compound by single hydrogen bond donation. Most likely, intramolecular H-bonding increases the acidity of the other O-H bond and the proximity of aryl groups further defines the orientation of substrate by steric and electronic interactions.<sup>58b,82d</sup> These two features, Brønsted acidity and aryl groups allowing for  $\pi$ - $\pi$  interactions with the substrate, are also present in chiral phosphoric acid catalysts.



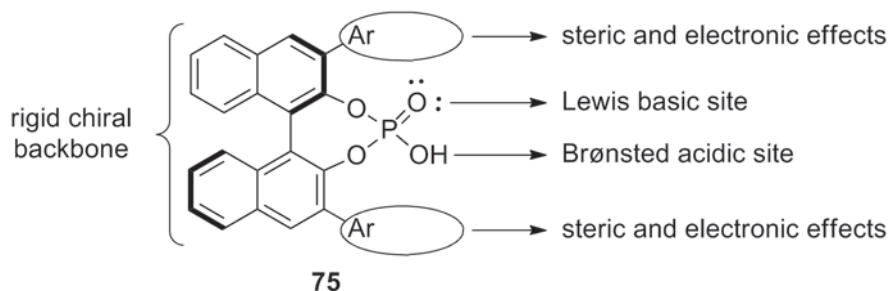
**Scheme 17:** Hetero-Diels-Alder reaction catalyzed by chiral diol **71**.

Phosphoric acids are stronger Brønsted acids than the previously discussed (thio)ureas and diols. In 2004, Akiyama and Terada simultaneously reported the first asymmetric synthesis using BINOL-based phosphoric acids as catalysts. They both performed a Mannich reaction with preformed imines **60** to produce the desired  $\beta$ -amino carbonyl compounds **76** and **78** (Scheme 18).<sup>87</sup>



**Scheme 18:** Mannich reactions catalyzed by chiral phosphoric acids **75a** and **75b**.

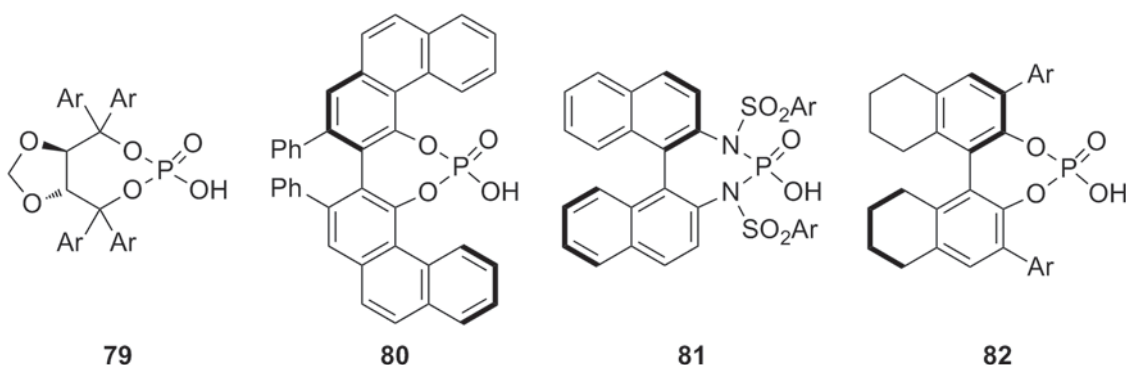
Many more reactions using similar BINOL-derived phosphoric acids have been developed following these two seminal reports. Several features of this type of catalyst proved necessary for efficient asymmetric transformations (Figure 11). The rigid  $C_2$ -symmetric binaphthyl moiety forms the chiral backbone of the molecule. Substituents in the 3,3'-position of this backbone can be adjusted to achieve ideal steric and electronic properties for the desired transformation. Furthermore, both enantiomers of BINOL are commercially available and numerous methods for introducing substituents in the 3,3'-position of the binaphthyl backbone have been described. The key aspect in most cases, however, is the dual function of the phosphoric acid. Its Brønsted acidic and Lewis basic site readily enable substrate activation.<sup>88</sup>



**Figure 11:** Properties of BINOL-based phosphoric acids **75**.

Other chiral phosphoric acid structures have also been developed (Figure 12). For example the TADDOL-based compound **79** was used by Akiyama in a Mukaiyama-type Mannich reaction.<sup>89a</sup> Antilla introduced the vaulted 3,3'-biphenanthrol-based **80** for use in the addition of amides and imides to imines.<sup>89b,c</sup> Another alternative was found by Terada. Phosphorodiamidic acid **81** catalyzed the Mannich reaction albeit with low enantiomeric ratios (up to 78.0:22.0).<sup>89d</sup> A more twisted backbone was obtained when the partially hydrogenated BINOL ( $H_8$ -BINOL) was

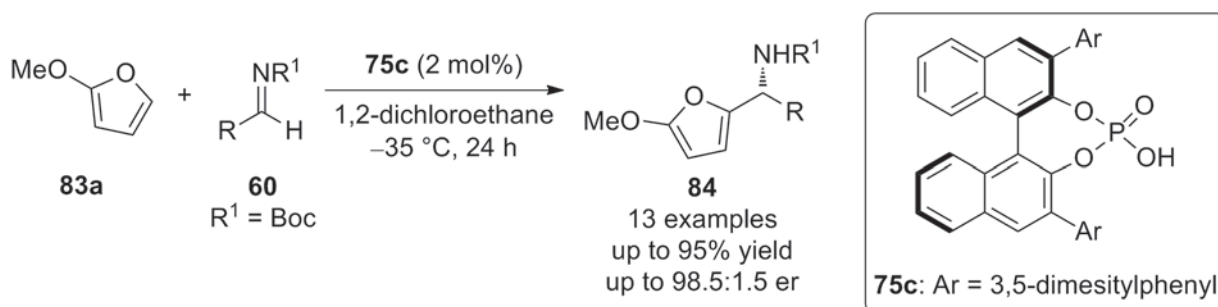
implemented (compound **82**). Gong and others found some exquisite applications for this type of catalyst. Among them are the Biginelli,<sup>89e</sup> hetero-Diels-Alder,<sup>89f</sup> Mannich,<sup>89g,h</sup> and Friedel-Crafts<sup>89i</sup> reaction.



**Figure 12:** Chiral phosphoric acids **79-82**.

Catalysts **79-81** have been moderately successful but not yet found broad application. Catalyst **82** has turned out to be more fruitful in several applications, but derivative **75** is undoubtedly the most versatile Brønsted acid catalyst and will therefore be discussed in more detail.

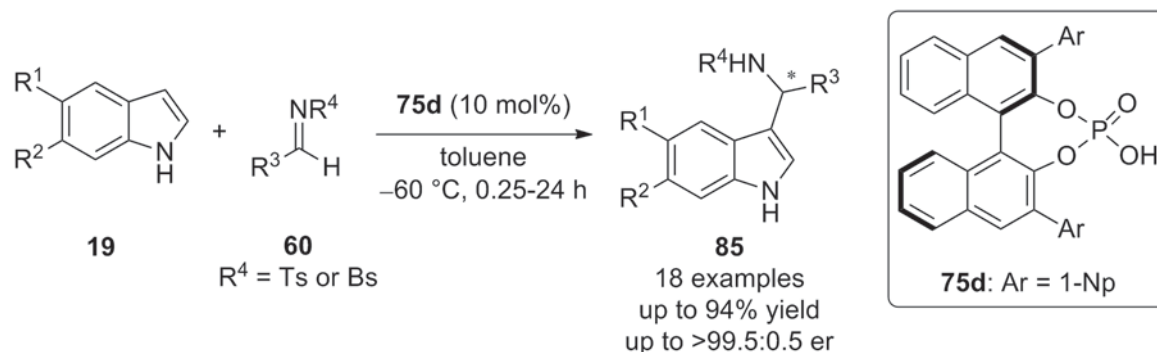
In 2004, Terada employed the sterically hindered 3,5-dimesitylphenyl-substituted catalyst **75c** in the Friedel-Crafts reaction between furan **83a** and *N*-Boc aldimines **60** (Scheme 19). The furan-2-ylamines **84** were obtained in high yields and in a highly enantioselective fashion. It is noteworthy that the reaction could be performed on a 1 g scale with only 0.5 mol% of catalyst without compromising on yield (95%) or enantioselectivity (98.5:1.5 er).<sup>90</sup>



**Scheme 19:** The first asymmetric phosphoric acid catalyzed Friedel-Crafts reaction.

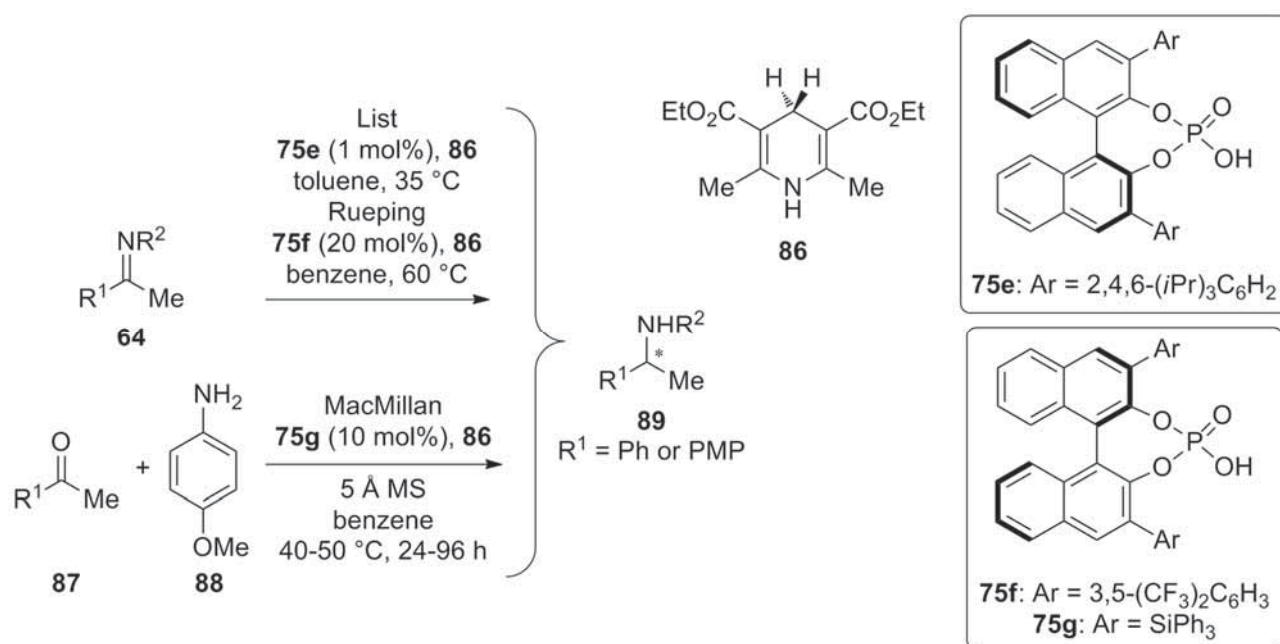
Another interesting chiral phosphoric acid catalyzed Friedel-Crafts reaction towards functionalized indole derivatives was introduced by You (Scheme 20). Imines derived from aromatic aldehydes were the main substrates used, but one aliphatic example was presented (albeit with lower yield and enantioselectivity, 56% and 79.0:21.0 er, respectively). *N*-Tosyl and *N*-brosyl were used as protecting groups on imines **60**. In general, this procedure represents an efficient chiral acid catalyzed method to form 3-indolyl methanamine derivatives **85**.<sup>91a</sup> An interesting chiral phosphoric acid catalyzed Friedel-Crafts reaction of indole and  $\alpha$ -aryl enamides to form quaternary carbon

centers was developed by Zhou.<sup>91b</sup> Also, Friedel-Crafts reactions for the functionalization of pyrroles in the 2-position using the same activation mode were described.<sup>91c,d</sup>



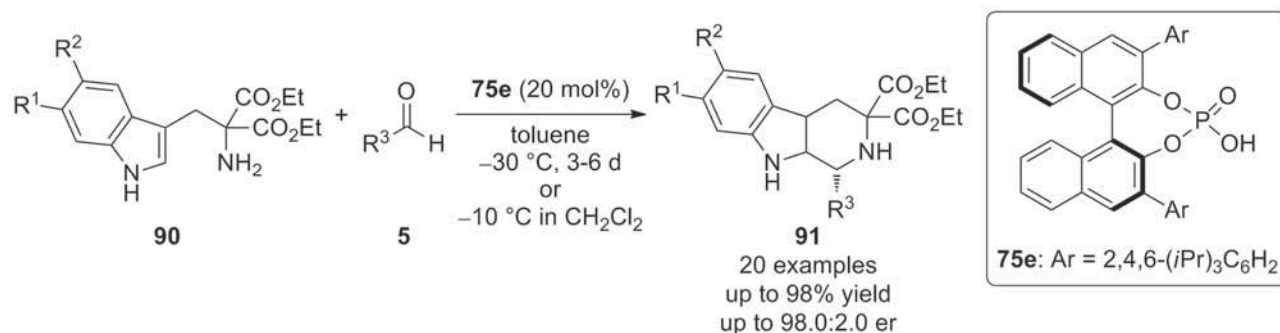
**Scheme 20:** Asymmetric organocatalytic synthesis of indole derivatives **85**.

List and Rueping then simultaneously made a breakthrough in the field with the organocatalytic reduction of ketimines **64** (Scheme 21). List introduced a bulky substituent on the backbone of the phosphoric acid which proved applicable for many transformations (for a detailed study concerning the use of TRIP (**75e**) as an organocatalyst, see Chapter 2.2.3). Merely 1 mol% of catalyst and slightly elevated temperatures (35 °C) in toluene were sufficient for the reduction of a large number of *N*-PMP-protected ketimines **64** (11 examples, up to 98% yield, up to 96.5:3.5 er) in the presence of 1.4 equivalents of Hantzsch ester **86**.<sup>92a</sup> Rueping performed the same reaction and reached somewhat lower enantiomeric ratios of amines **89** (13 examples, up to 91% yield up to 92.0:8.0 er) employing 20 mol% of catalyst **75f** in benzene at 60 °C.<sup>92b</sup> MacMillan disclosed the *ortho*-triphenylsilyl variant **75g** of the BINOL-based catalyst for the reductive amination of ketones **87** (27 examples). Molecular sieves were necessary to trap the water formed during imine formation and which disrupted the hydride reduction step. The desired amines **89** were obtained in yields of up to 92% and enantiomeric ratios of up to 98.5:1.5.<sup>92c</sup>



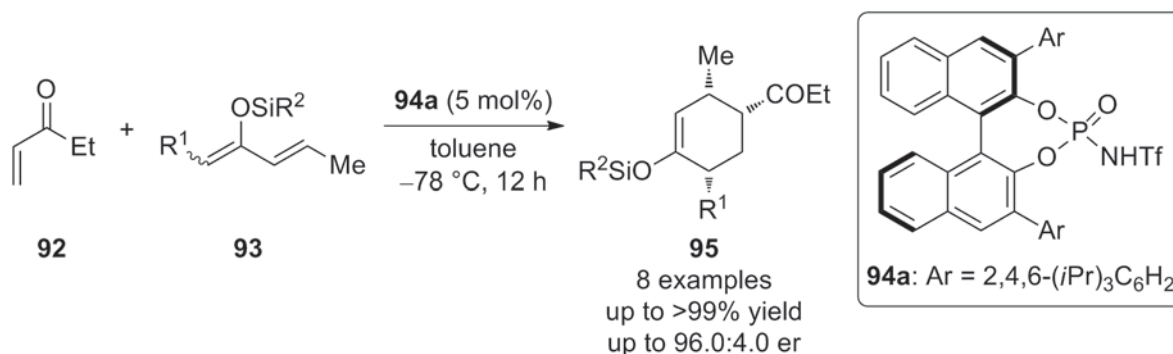
**Scheme 21:** Brønsted acid catalyzed synthesis of enantiomerically enriched amines **89**.

The Pictet-Spengler reaction is a powerful method to form tetrahydroisoquinoline and tetrahydro- $\beta$ -carboline structures. The first acyl-Pictet-Spengler reaction catalyzed by a chiral thiourea was described by Jacobsen.<sup>93a</sup> List then found that also chiral phosphoric acids can catalyze this transformation. At that time, Jacobsen and List both concluded that the use of simple substrates were unsuccessful because they were inactive under the applied conditions. To overcome this limitation, List employed the Thorpe-Ingold effect and used geminally disubstituted tryptamines **90** as substrates that effectively led to the desired carboline derivatives **91** (Scheme 22).<sup>93b</sup> To surmount the disadvantages of the *N*-acyl (Jacobsen) and the two ester groups (List), Hiemstra found that *N*-sulfenyltryptamines are suitable substrates as the sulfenyl group is easily introduced and removed.<sup>93c</sup> These methods were applied in the total synthesis of (+)-yohimbine<sup>93d</sup> and (–)-arboricine<sup>93e</sup> among others. Further breakthroughs like the use of *N*-benzyltryptamines and even tryptamine itself as starting material were established by Hiemstra<sup>93f</sup> and Jacobsen,<sup>93g</sup> respectively.



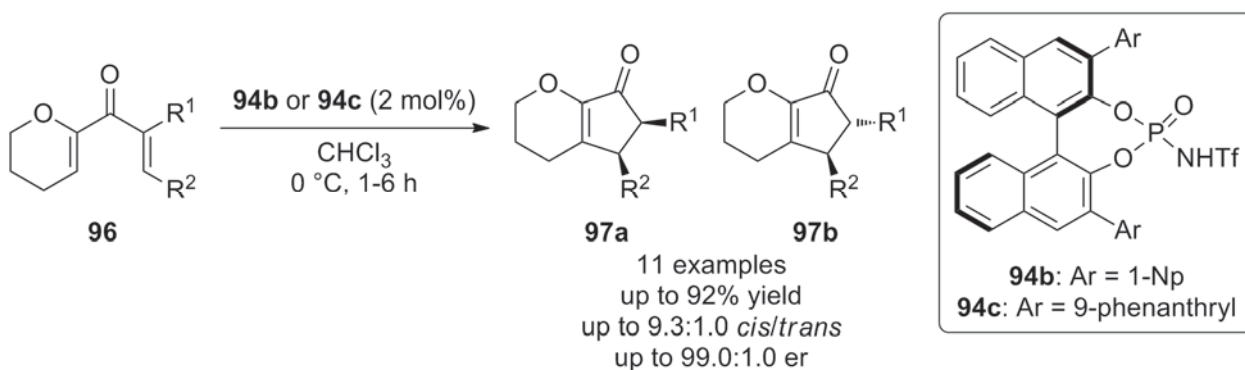
**Scheme 22:** Chiral phosphoric acid catalyzed Pictet-Spengler reaction.

The acidity of the phosphoric acids described above is sufficient to activate reactive substrates, which somewhat constitutes a limitation of this type of catalysis. Stronger acids would be desirable and Yamamoto achieved this by introducing a “NTf” group into the phosphoric acid. *N*-Triflyl phosphoramidate **94a** was used in the Diels-Alder reaction between ethyl vinyl ketone (**92**) and siloxydienes **93** to yield the cyclic adducts **95** in enantioselectivities of up to 96.0:4.0 er (Scheme 23).<sup>94</sup>



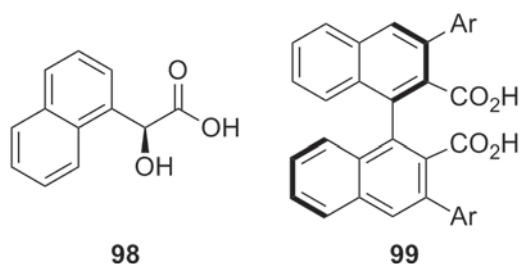
**Scheme 23:** *N*-Triflyl phosphoramidate **94a** in the asymmetric Diels-Alder reaction.

The first activation of a carbonyl compound was also accomplished with *N*-triflyl phosphoramidates. The Nazarov reaction is a versatile method for the synthesis of five-membered rings. The interesting optically pure cyclopentanone products are formed by an electrocyclic reaction (Scheme 24). The major *cis*-products **97a** could be easily isomerized into the *trans*-product **97b** by basic alumina without affecting the enantioselectivity, thus, this method provides access to both diastereomers with high enantioselectivity.<sup>95</sup>



**Scheme 24:** First Brønsted acid catalyzed enantioselective electrocyclic reaction.

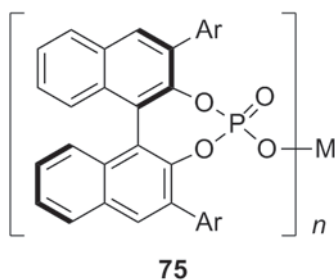
The broad range of applications of chiral phosphoric acid catalyzed reactions also includes *i.a.* aza-ene-type,<sup>96a</sup> Strecker,<sup>96b</sup> Baeyer-Villiger,<sup>96c</sup> aza-Henry,<sup>96d</sup> Kabachnik-Fields<sup>96e,f</sup> and carbonyl-ene<sup>96g</sup> reactions. Weaker Brønsted acids have also been developed for some specific applications concerning acid sensitive substrates. The carboxylic acids **98** and **99** display two examples of such catalysts (Figure 13).<sup>97</sup>



**Figure 13:** Chiral carboxylic acids **98** and **99**.

Brønsted acid catalysis has also become relevant in cascade and multicomponent reactions.<sup>56,88d</sup> Furthermore, the combination of chiral Brønsted acid and metal catalysis has received growing attention. A review by Rueping gives an overview of this exciting area.<sup>98</sup>

Important observations concerning the synthesis and purification methods of the phosphoric acids have been made. In a report by Ishihara, it was shown that both  $\text{Ca}[\mathbf{75}]_2$  and  $\text{H}[\mathbf{75}]$  catalyze a Mannich reaction (Figure 14). Distinct differences were observed when the phosphoric acids were washed with HCl after purification on silica gel. Therefore it is of high importance to affirm whether the reaction is promoted by a metal salt of the phosphoric acid or the phosphoric acid itself.<sup>99</sup>



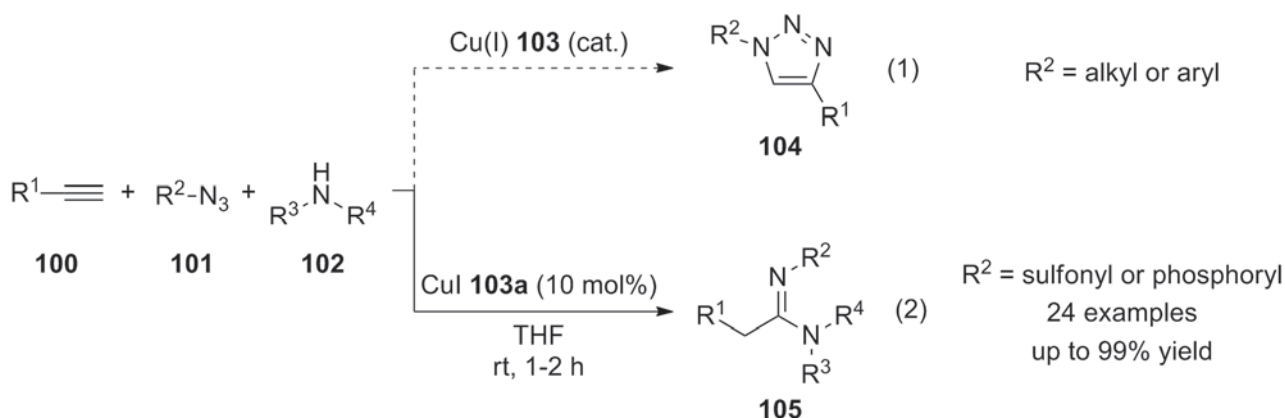
**Figure 14:** Chiral phosphoric acid or its metal salt as catalyst?

Organocatalysis has become a powerful method to construct stereocenters in a highly enantioselective fashion. Although many protocols still have limitations, further studies will most probably bring improvements in these cases. With the toolbox of organocatalysis still growing and the progress of mechanistic insight, it will be exciting to investigate unexplored reactions or even find novel activation modes.

## 1.2 Copper-Catalyzed Multicomponent Reactions

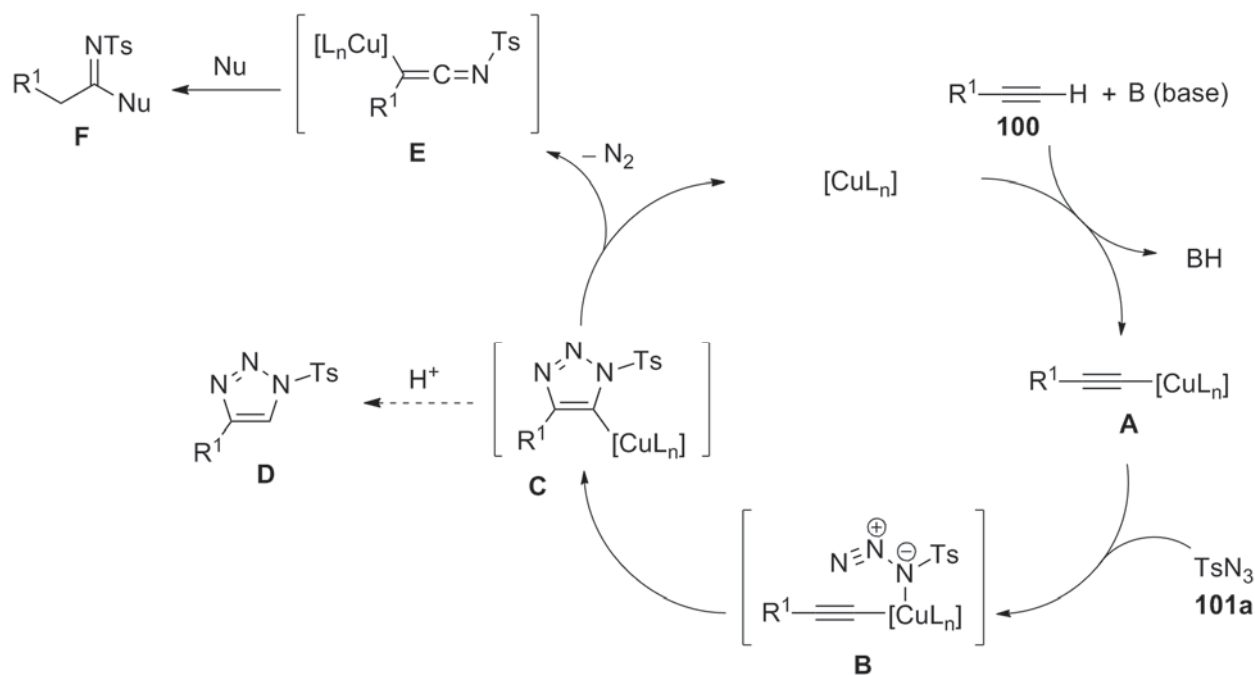
This section will elucidate some important advances in multicomponent reactions (MCRs) and focus on the work by Chang and Fokin who are pioneers in the field of copper-catalyzed multicomponent reactions.

The cycloaddition of azides and alkynes is a very useful method to form triazoles and can be considered as a click reaction.<sup>100</sup> A thermally induced Huisgen addition leads to an approximate 1:1 mixture of 1,4- and 1,5-regioisomers. The copper-catalyzed reaction between terminal alkynes and azides results exclusively in 1,4-disubstituted 1,2,3-triazoles **104** (eq. (1) in Scheme 25).<sup>101</sup> Surprisingly, when Chang utilized sulfonyl instead of alkyl- or aryl-substituted azides and terminal alkynes in the presence of amines and catalytic amount of copper, amidines **105** were produced in high yields. Copper(I) iodide (**103a**) was chosen as catalyst and the reaction had a broad scope in terms of all substrates giving the amidines in yields of up to 99% (eq. (2)).<sup>102a</sup> The use of phosphoryl azides led to phosphoryl amidines.<sup>102b</sup>



**Scheme 25:** Different pathways (1) and (2) depending on azide **101**.

The mechanism of this transformation was intensely studied and is depicted in Figure 15. The initial step is similar to the “regular” copper-catalyzed azide-alkyne cycloaddition (CuAAC). A copper acetylide species **A** is formed when a terminal alkyne is treated with a base in the presence of Cu(I). Only one copper atom is shown although more than one copper atom is most likely involved in the catalytic cycle.<sup>103</sup> After coordination of tosyl azide (**101a**) to **A**, stepwise formation of triazole **C** takes place. Ring-chain isomerization leads to the formation of an active ketenimine **E** which can be trapped with a suitable nucleophile to produce adduct **F**.<sup>104</sup> Ideal trapping conditions to form triazole **D** were developed by Chang and Fokin and others.<sup>105</sup> Thus, by choosing the right basic additives and appropriate temperature, it is possible to control the product distribution.



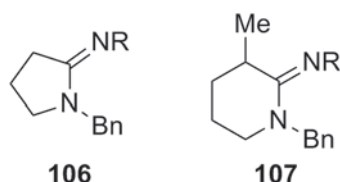
**Figure 15:** Proposed mechanism for the Cu-catalyzed three-component reaction.

The addition of a nucleophile to the active ketenimine species **E** embodies the potential of this reaction. A large number of nucleophiles have been found to form a broad scope of products.<sup>106</sup> The next subsections will introduce some remarkable examples concerning the use of *N*-nucleophiles and *O*-nucleophiles. Thereafter, a few miscellaneous examples will be highlighted and at last four-component reactions will be covered.

### 1.2.1 Copper-Catalyzed Three-Component Coupling Reactions of Terminal Alkynes, Sulfonyl Azides and *N*-Nucleophiles

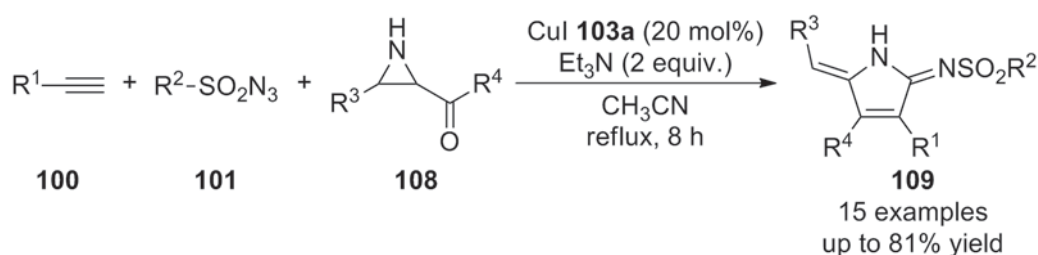
After the first example of a copper-catalyzed three-component coupling reaction of sulfonyl azides, terminal alkynes and *N*-nucleophiles by Chang (see Scheme 25), many more were reported and some will be discussed here.

Cyclic amidines such as **106** and **107** were obtained when 1,*n*-aminoalkynes were reacted with sulfonyl azides in the presence of a copper catalyst (Figure 16). It was found that the reaction did not follow the same path as in the intermolecular version as other metals also catalyzed the transformation.  $Ru_3(CO)_{12}$  showed the highest efficiency and a tandem reaction involving intramolecular hydroamination was proposed.<sup>107</sup>



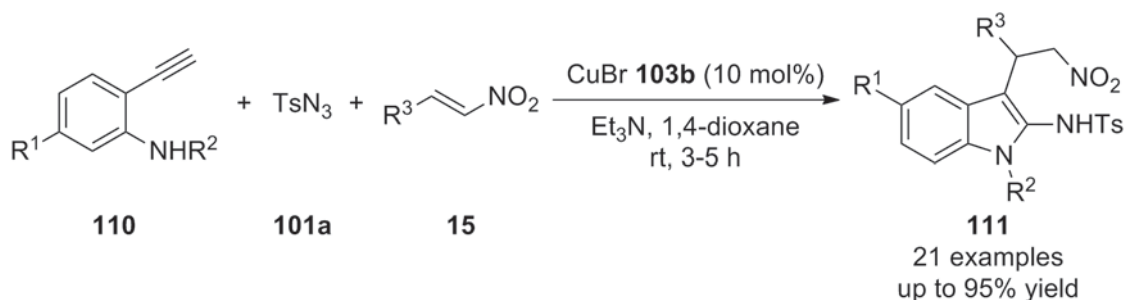
**Figure 16:** Examples of 5- and 6-membered cyclic amidines.

An interesting procedure to form 5-arylidene-2-imino-3-pyrrolines **109** was described by Wang (Scheme 26). 2-Acyl aziridines **108** were selected as coupling partners for the copper catalyzed three-component reaction. Uncyclized products were delivered when the reaction was performed in  $\text{CH}_2\text{Cl}_2$ . Elevated temperatures in acetonitrile were needed to form the desired cyclic products **109** with only trace amounts of uncyclized amidine.<sup>108</sup>



**Scheme 26:** Synthesis of pyrroline-derivatives **109**.

The synthesis of indole-derivatives **111** was achieved by following a similar approach developed by Chang to produce indolines.<sup>109a</sup> A wide variety of 2-ethynylanilines **110** reacted with tosyl azide (**101a**) in the presence of  $\text{CuBr}$  and a base towards the reactive ketenimine following the general mechanism (see Figure 15). The ketenimine was then attacked in an intramolecular fashion to form the indole ring which in turn reacted with a range of nitroolefins **15** to yield the desired products **111** (Scheme 27). The testing of these compounds in biological screening as an HCT-116 inhibitor showed promising results.<sup>109b</sup>

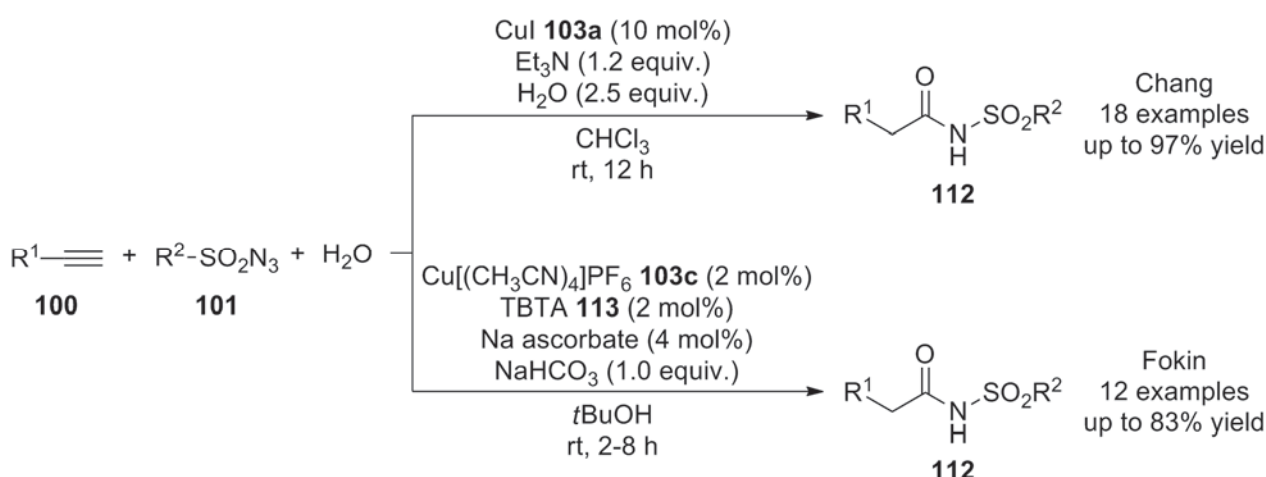


**Scheme 27:** A three-component reaction towards indole-derivatives **111**.

Other examples of this type of multicomponent reaction include the synthesis of 2-imino-1,2-dihydroquinolines and 2-imino-thiochromenes,<sup>110a</sup> the use of ammonium salts as facile coupling partners,<sup>110b</sup> the synthesis of 2-alkylidene-1,2,3,4-tetrahydropyrimidines,<sup>110c</sup> substituted benzimidazoles<sup>110d,e</sup> and *N*-sulfonylacetamidines.<sup>110f</sup>

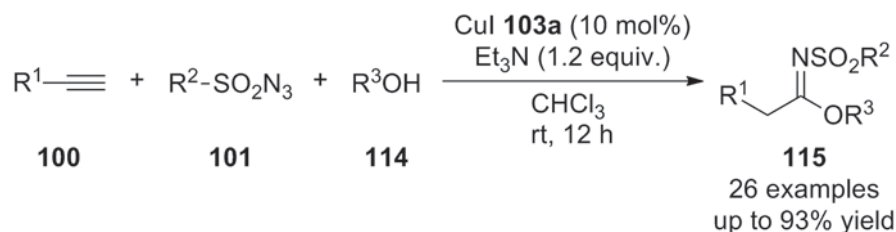
### 1.2.2 Copper-Catalyzed Three-Component Coupling Reactions of Terminal Alkynes, Sulfonyl Azides and *O*-Nucleophiles

An appealing alternative amide synthesis was independently developed by Chang and Fokin. Reactions of terminal alkynes **100** and sulfonyl azides **101** in the presence of triethylamine as base and a catalytic amount of copper(I) iodide delivered the *N*-sulfonyl amides **112** under aqueous conditions (Scheme 28).<sup>111a</sup> Fokin simultaneously reported the same sequence with slightly adjusted conditions. For example, the addition of 2 mol% of TBTA (**113**) accelerated the reaction.<sup>111b,c</sup>



**Scheme 28:** Copper-catalyzed hydrative amide synthesis.

The Pinner reaction constitutes a viable method to form imidates although some limitations such as low yields and limited substrate scope are present.<sup>112</sup> Chang introduced the synthesis of these compounds in high yields using a mild method where terminal alkynes **100**, sulfonyl azides **101** and alcohols **114** react in the presence of triethylamine and catalytic amounts of copper(I) iodide (Scheme 29). Further modifications towards amidines (and subsequent desulfonylation) and *N*-allylic sulfonamides (by Pd-catalyzed rearrangement) were also presented.<sup>113</sup>

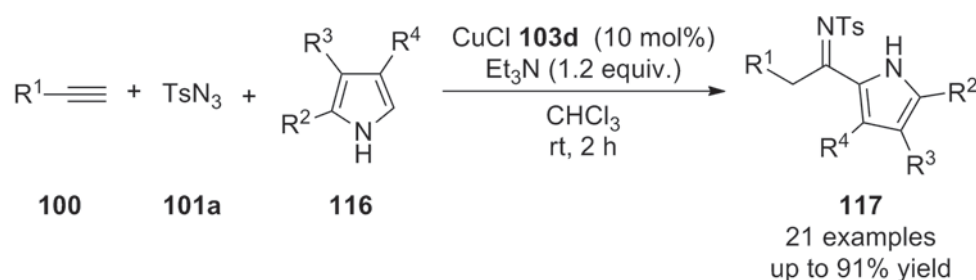


**Scheme 29:** Synthesis of *N*-sulfonylimidates **115**.

Other examples where an *O*-nucleophile was employed were disclosed in the synthesis of 2-iminocoumarins and 2-iminodihydrocoumarins.<sup>114</sup>

### 1.2.3 Copper-Catalyzed Three-Component Coupling Reactions: Miscellaneous Examples

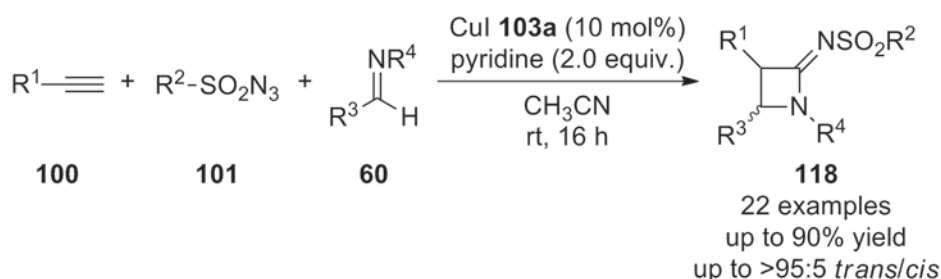
Reaction partners other than nitrogen or oxygen nucleophiles have also been utilized in the copper-catalyzed multicomponent reaction. Chang developed a protocol for the functionalization of pyrrole derivatives under mild conditions (Scheme 30). Copper(I) chloride was found to be the best copper source to catalyze the transformation. A broad scope of substrates reacted to give the target compounds **117** in high yields.<sup>115a</sup>



**Scheme 30:** Copper-catalyzed 2-functionalization of pyrroles under mild conditions.

Only one additional example that leads to the construction of a C–C bond by using a carbon nucleophile to trap the reactive ketenimine intermediate has been described to date. Zhang showed that  $\beta$ -ketoesters were efficient coupling partners in the copper-catalyzed three-component reaction to produce 4-arylsulfonimino-4,5-dihydrofuran derivatives.<sup>115b</sup>

An intriguing example of trapping the ketenimine intermediate, formed as an intermediate after the copper-catalyzed azide-alkyne cycloaddition, was shown by Fokin (Scheme 31). This one-step procedure furnished the four-membered heterocyclic *N*-sulfonylazetidines **118** and was tolerant of a wide variety of alkyne-, azide- and imine-substrates which underlines the versatility of this reaction.<sup>116a</sup> A route towards azetidinium and azetidinimine analogs of  $\beta$ -lactams using different approaches was already described by Ghosez in the 1970s and 1980s.<sup>116b–d</sup>



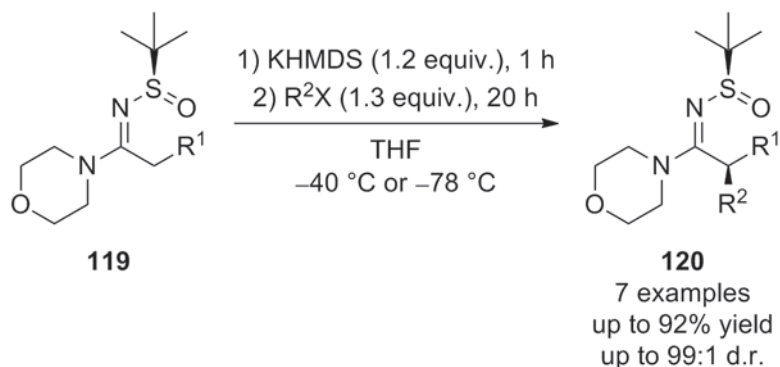
**Scheme 31:** Synthesis of azetidines **118**.

Additional examples in which formal [2+2] cycloadditions of *in situ* generated *N*-sulfonylketenimines takes place were reported by Xu, Wang, Shang and Ma. Xu utilized carbodiimides to deliver 2-(sulfonylimino)-4-(alkylimino)azetidine derivatives.<sup>117a</sup> Phosphorus-

containing amidines were prepared by Wang.<sup>117b</sup> Shang made use of phenolic imines to form an azetidinimine which was attacked by the phenolic oxygen in an intramolecular fashion. This eventually led to benzoxazoline-amidines.<sup>117c</sup> Ma recently reported the synthesis of 2-iminooxetanes that could be further reacted towards functionalized pyrrolidinone and maleimide derivatives.<sup>117d</sup>

### 1.2.4 Copper-Catalyzed Four-Component Coupling Reactions

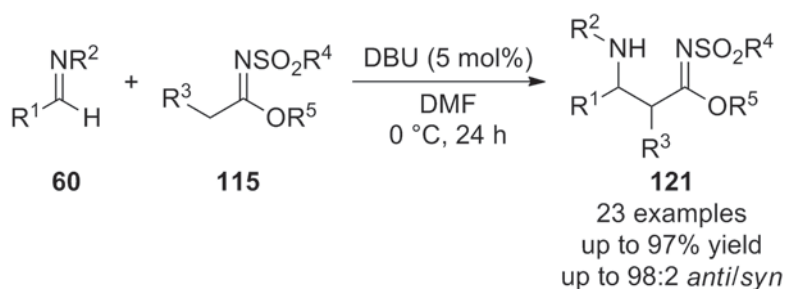
The  $\alpha$ -functionalization of amidines or imidates with different electrophiles represents an interesting approach to form aldol-, Michael-, Mannich-type or other products. Highly diastereoselective reactions of cyclic amidines with aldehydes were investigated by Magnus.<sup>118a</sup> In 2004, Ellman demonstrated the use of the *tert*-butanesulfinyl group as chiral auxiliary in the diastereoselective alkylation of acyclic **119** to afford amidines **120** (Scheme 32). Further transformations of the amidines to aldimines, ketimines and amines that include  $\alpha$ - and  $\beta$ -stereocenters were achieved. Moreover, the asymmetric synthesis of (6*R*,7*S*)-7-amino-7,8-dihydro- $\alpha$ -bisabolene was established.<sup>118b</sup> Few examples of diastereoselective alkylation of phosphoryl amidines were shown by Chang.<sup>102b</sup>



**Scheme 32:** First diastereoselective alkylation of preformed acyclic amidines.

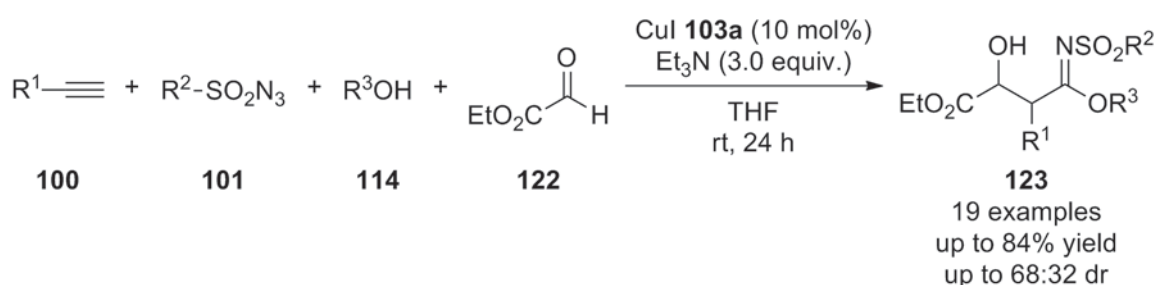
Kobayashi found a highly diastereoselective Mannich-type reaction when sulfonylimidates **115** were treated with catalytic amounts of DBU in the presence of imines **60** (Scheme 33). Bulky groups on the imide part ( $R^4 = 2,5\text{-xylyl}$ ,  $R^5 = i\text{Pr}$ ) proved optimal to reach high yields and diastereoselectivities. Methyl acrylate and azodicarboxylate as Michael acceptors were also successfully employed as electrophiles in this transformation.<sup>119</sup> Chiral *N'*-*tert*-butanesulfinyl imidates represent also suitable substrates for further modification (for example the synthesis of  $\beta$ -amino acid derivatives) as presented by De Kimpe.<sup>120a-c</sup> An enantioselective organocatalytic

Michael reaction between *N*-tosylimidates and Michael acceptors was accomplished by Barbas III.<sup>121</sup>



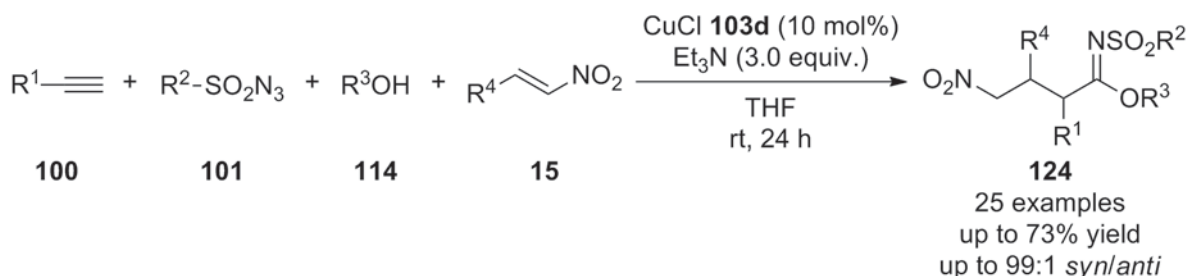
**Scheme 33:** DBU-catalyzed Mannich-type addition of sulfonylimidates **115**.

The first one-pot procedure towards  $\alpha$ -functionalized imidates was developed by Chang. Ethyl glyoxylate (**122**) was the only electrophile (among others tested) that led to the desired four-component adduct. Various terminal aryl alkynes **100**, sulfonyl azides **101**, alcohols **114** and ethyl glyoxylate (**122**) reacted in the presence of triethylamine as base and catalytic amount of copper(I) iodide to furnish  $\alpha$ -aryl- $\beta$ -hydroxy imidates **123** in high yields (Scheme 34).<sup>122</sup>



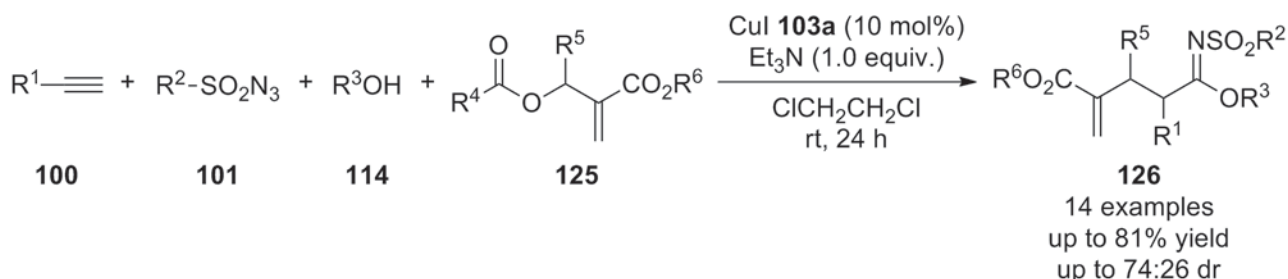
**Scheme 34:** Copper-catalyzed four-component reaction to form  $\alpha$ -functionalized imidates **123**.

Wang reported the use of nitroolefins as suitable electrophiles in a similar copper-catalyzed four-component reaction (Scheme 35). This work was established independently and at the same time as we conducted related experiments at KAIST (see Chapter 2.3 for more details).<sup>123a</sup> Variations of all four substrates were tolerant to the reaction conditions and yielded  $\gamma$ -nitro imidates **124**.<sup>123b</sup>



**Scheme 35:** Copper-catalyzed four-component coupling with nitroolefins.

Morita-Baylis-Hillman adducts **125** also served as electrophiles in the four-component coupling reaction. The substrate scope was broad and gave the desired products **126** in very satisfactory yields (Scheme 36). Furthermore, a possible mechanism was described by Wang.<sup>124</sup>



**Scheme 36:** Copper-catalyzed four-component coupling with Baylis-Hillman adducts.

With many multicomponent reactions already available in the chemist's toolbox, such as the Biginelli (3CR),<sup>125</sup> Hantzsch (4CR),<sup>126</sup> Mannich (3CR),<sup>27i,j,127</sup> Passerini (3CR),<sup>128</sup> Petasis (3CR),<sup>129</sup> Strecker (3CR)<sup>73</sup> and Ugi (4CR) reactions,<sup>130</sup> it has been shown that the multicomponent reaction introduced here is surely an appealing additional example. This relatively new development of multicomponent reactions based on the well-known CuAAC reaction has rapidly grown to a viable method to form highly functionalized products.

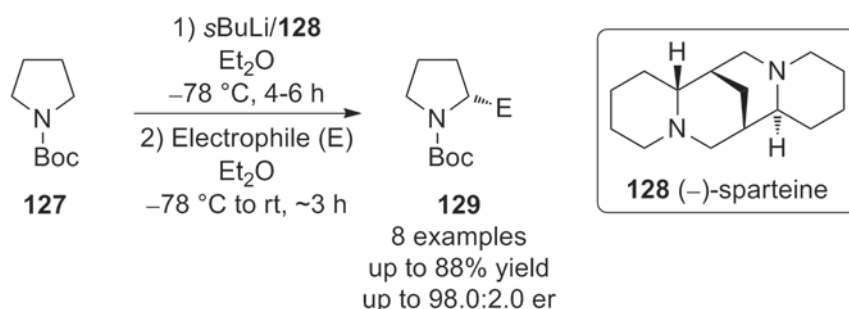
---

## 2 Results and Discussion

---

### 2.1 Synthesis and Application of Silylated Pyrrolidines

The *tert*-butoxycarbonyl (Boc) group can be used to direct  $\alpha$ -lithiation to give a nucleophilic species which can be trapped by electrophiles to provide  $\alpha$ -functionalized carbamates. This approach has often been applied in asymmetric synthesis.<sup>131</sup> The enantioselective synthesis of 2-substituted Boc-pyrrolidines was effected through deprotonation with a combination of *sec*-butyllithium (*s*BuLi) and (–)-sparteine (**128**). Electrophiles like TMSCl, aldehydes, ketones and dimethylsulfate among others were used by Beak to form the desired products **129** in high yields and enantioselectivities (Scheme 37).<sup>132</sup> Intensive studies of this transformation have been conducted by several groups.<sup>133</sup> Moreover, the Boc group is easily installed and removed.<sup>134</sup>



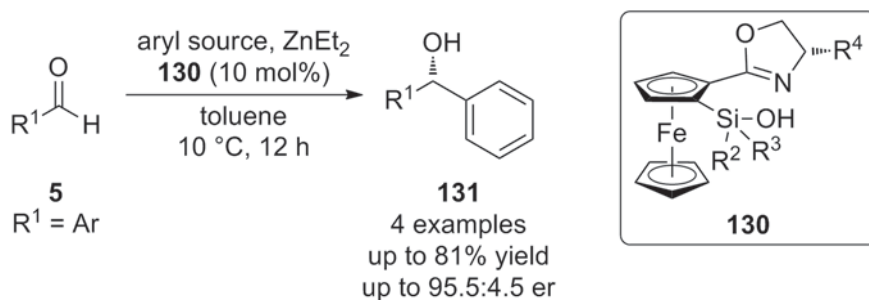
**Scheme 37:** Asymmetric synthesis of 2-substituted pyrrolidines.

This constitutes a convenient method to synthesize silylated pyrrolidines, however, the applications of such structures are quite rare. West utilized 2-dimethylphenylsilyl-substituted pyrrolidines to furnish dihydroxyquinolizidines, which involves a silyl-directed Stevens [1,2]-shift of ammonium ylides as crucial step.<sup>135</sup> Skrydstrup found an alternative synthesis of (*R*)-*N*-Boc-2-(diphenylmethylsilyl)pyrrolidine in the study towards silicon-containing peptide mimics.<sup>136</sup>

#### 2.1.1 Research Objective

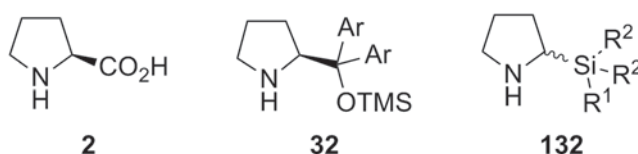
The research objective for this project was based on earlier investigations by Bolm concerning silicon chemistry. Bolm was the first to find a synthetic method to form  $\alpha$ -trialkylsilyl-substituted  $\alpha$ -amino acids through rhodium-catalyzed N-H insertion reactions. These compounds can be

considered as *tert*-leucine analogs and they were successfully implemented in a dipeptide.<sup>137</sup> Other related compounds such as  $\alpha$ -silyl-substituted  $\alpha$ -hydroxyacetic acids,<sup>138a,d</sup> silicon-containing dioxolanones<sup>138b</sup> and silylated 1,2,4-triazin-5-ones<sup>138c</sup> were also synthesized. Planar-chiral ferrocene-based silanols **130** were catalytically used as ligands in zinc-mediated aryl transfer reactions to give diarylmethanols **131** in up to 81% yield and up to 95.5:4.5 er (Scheme 38).<sup>139</sup>



**Scheme 38:** Ferrocene-based silanols **130** as chiral ligands.

The purpose of this research was to synthesize silicon-containing compounds in an enantioselective fashion and to use them as organocatalysts. At the outset of this study it was envisaged that pyrrolidine-based structures **132** could meet those goals (Figure 17). These structures are analogous to the highly versatile organocatalysts (*S*)-proline (**2**) and the Jørgensen-Hayashi catalyst **32**.



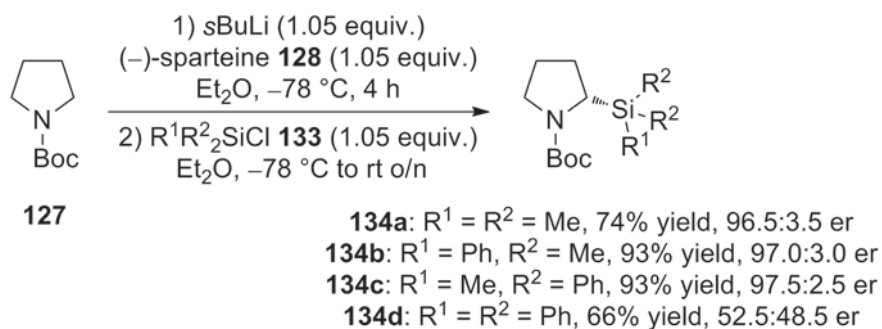
**Figure 17:** Established organocatalysts **2** and **32** and silylated pyrrolidine **132**.

The following subchapters will discuss the synthesis of various *N*-Boc-protected silylated pyrrolidines, the deprotection thereof and their application as organocatalysts.

### 2.1.2 Synthesis of *N*-Boc-Protected Silylated Pyrrolidines

The synthesis of *N*-Boc-pyrrolidine (**127**) was accomplished following a procedure described in the literature. The reaction of readily available pyrrolidine with di-*tert*-butyl pyrocarbonate in the presence of the Steglich-catalyst DMAP delivered the desired product **127** in quantitative yield.<sup>140</sup> The subsequent  $\alpha$ -functionalization was achieved by a slightly adjusted protocol, which was established by Beak, O'Brien and others (see Chapter 2.1). Some important precautions had to be taken into account to obtain reproducible yields and enantioselectivities. The molarity of *s*BuLi should be ascertained by titration prior to use.<sup>141</sup> (–)-Sparteine (**128**) should be distilled before use to remove impurities and water. It was sufficient to treat the chlorosilanes **133** with a base ( $\text{K}_2\text{CO}_3$ )

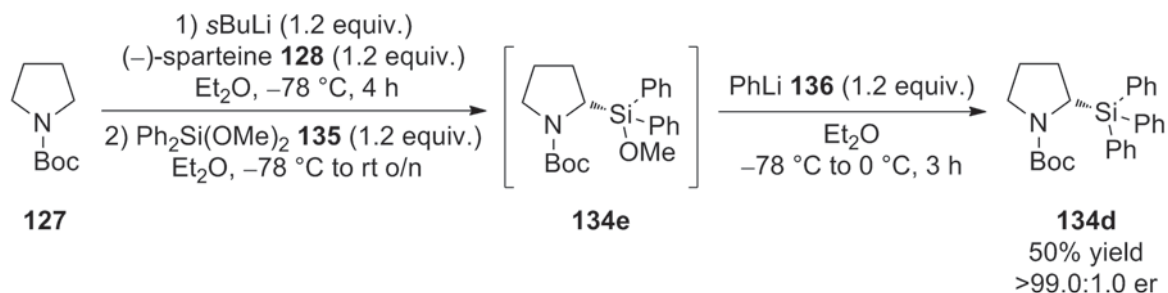
before adding it to the reaction mixture, although distillation proved to be more effective. Possibly present acids and silanols were removed this way.<sup>142</sup> The order of addition was also found to play a key role in the process. First, an ethereal solution of (–)-sparteine (0.75 M) was cooled to –78 °C with the help of an *i*PrOH/dry ice bath. *s*BuLi was then slowly added with a syringe and the mixture was stirred for 15 min. A solution of *N*-Boc-pyrrolidine (**127**) in diethyl ether (1.0 M) was subsequently added and the mixture was stirred at –78 °C for another 4 hours. It was then crucial to add the electrophile slowly. A convenient addition method of the ethereal chlorosilane solution (1.0 M) was effected with the aid of a syringe pump (an addition speed of ~20 mL/h was selected). The substrates were employed with 1.05 equivalents relating to the *N*-Boc-pyrrolidine. Furthermore, the temperature should be maintained at –78 °C overnight and the mixture should be allowed to reach room temperature shortly before the work-up procedure. Eventually, intensive investigations led to an array of silylated pyrrolidines **134a–d** (Scheme 39). The trimethylsilyl-substituted product **134a** was obtained in 74% yield and an enantiomeric ratio of 96.5:3.5, which is in accordance with the literature.<sup>132</sup> The dimethylphenyl derivative **134b** was produced in 93% yield and with a slightly higher enantiomeric ratio than reported by West (97.0:3.0 er compared to 92.5:7.5 er).<sup>135</sup> Reaction with diphenylmethylsilyl chloride turned out to give product **134c** in 93% yield and with the best enantioselectivity (97.5:2.5 er). Surprisingly, the triphenylsilyl-substituted *N*-Boc-pyrrolidine **134d** was accessed in lower yield and almost racemic form. Latter evidence was gained after HPLC analysis of the corresponding benzoyl derivative as no suitable HPLC conditions were found for **134d** (see Chapter 2.1.3 for the derivatization). The low yield and enantiomeric ratio probably occurred due to the low solubility of triphenylsilyl chloride in diethyl ether at such low temperatures. Racemic mixtures of the silylated pyrrolidines **134a–c** were synthesized following the same procedure but with TMEDA instead of (–)-sparteine. The resulting racemic samples were used to find suitable separation conditions for HPLC analysis (see Chapter 4.4 for further details).<sup>143a</sup>



**Scheme 39:** Synthesis of *N*-Boc-protected silylated pyrrolidines **134a–d**.

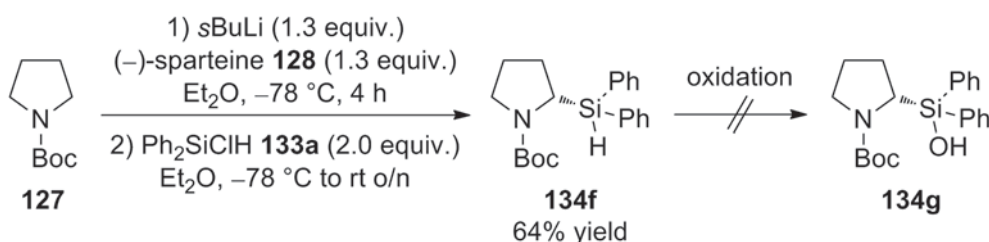
Strohmman found an elegant way to synthesize enantiopure (*S*)-*N*-Boc-2-triphenylsilylpyrrolidine (**134d**). In independent studies it was shown that the use of dimethoxydiphenylsilane (**135**) led to intermediate **134e**, which was not isolated. Subsequent nucleophilic substitution with phenyllithium

(**136**) gave the desired product **134d** in moderate yield (50%, Scheme 40). Enantiopure samples were obtained after recrystallization.<sup>143b</sup>



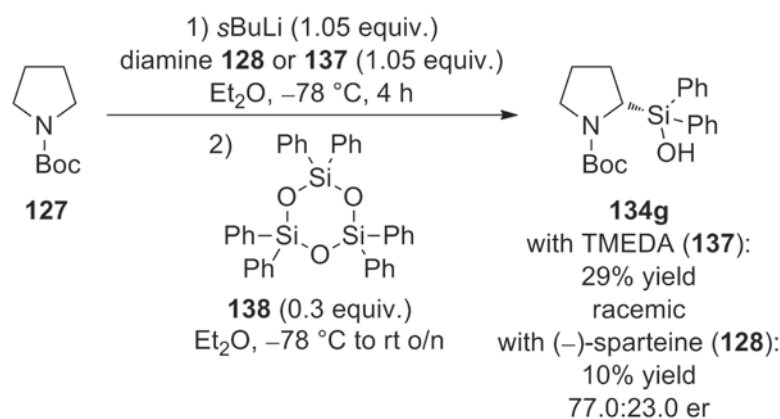
**Scheme 40:** An alternative approach towards *N*-Boc-2-(triphenylsilyl)pyrrolidine (**134d**).

Further studies focused on the synthesis of silanol-containing pyrrolidine derivatives. Preliminary results were obtained by Özçubukçu.<sup>144</sup> Experiments on the synthesis of silane **134f** were reproduced in 64% yield although it was found that the silane was unstable on silica gel and was not obtained in pure form (Scheme 41). The eventual goal was to oxidize the Si-H bond to the desired silanol **134g**. This was envisaged to be accomplished by oxidation methods with for example KMnO<sub>4</sub> (developed by Lickiss)<sup>145a</sup> or Ir-catalysis (developed by Lee and Chang).<sup>145b</sup> Moreover, the impure silane decomposed into a mixture of unidentified compounds and no silanol product was obtained by any means. The free silanol is particularly desirable due to its higher acidity compared to its carbinol analog, which makes it a better hydrogen bond donor with probable advantageous features.<sup>146</sup>



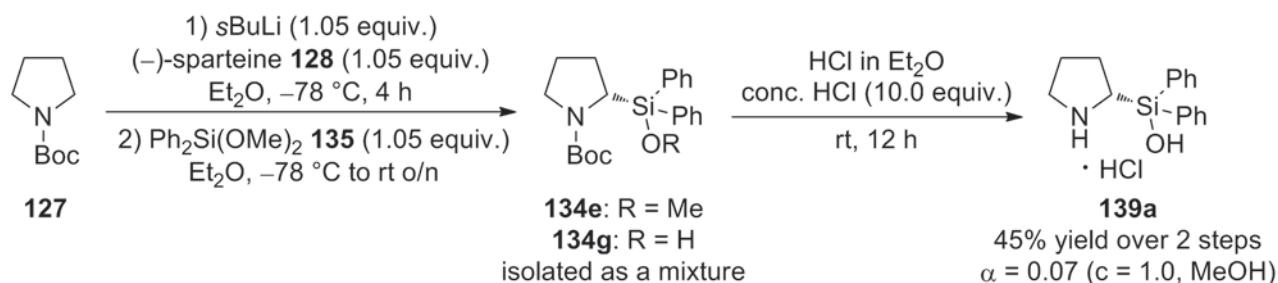
**Scheme 41:** A possible route towards silanol **134g**.

An alternative approach to produce silanol derivatives was undertaken with cyclotrisiloxane **138** as silicon electrophile. Sieburth reported on the application of cyclic diphenyl- and dimethylsiloxanes with primary, secondary and tertiary organolithium reagents to form the corresponding silanols in good yields.<sup>147</sup> Several attempts using this method were conducted but led to the desired product in poor yield (Scheme 42). With TMEDA (**137**) as diamine ligand silanol **134g** was formed in 29% yield and racemic form. Surprisingly, the reaction with (–)-sparteine (**128**) gave the product in only 10% yield with an enantiomeric ratio of 77.0:23.0.



**Scheme 42:** Use of cyclotrisiloxane **138** to form silanol **134g**.

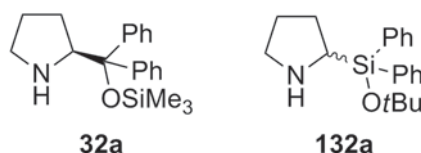
A similar electrophile was employed to test if the yield could be increased compared to the previous method. Trapping the lithiated pyrrolidine, which was generated using the established procedure, with diphenyldimethoxysilane (**135**) yielded a mixture of *N*-Boc-protected 2-(methoxydiphenylsilyl)pyrrolidine **134e** and *N*-Boc-2-(diphenylhydroxy)pyrrolidine (**134g**) (Scheme 43). The mixture was then treated with hydrochloric acid, which led to removal of the Boc-group and hydrolysis of the methylsilyl ether to form the hydrochloric salt **139a**. Intensive investigations about the treatment of *N*-Boc-protected silylated pyrrolidines with acids will be given in the next subchapter. Unfortunately, treatment of **139a** with base afforded a mixture of products and no free amino silanol was observed.



**Scheme 43:** Formation of amino-silanol **139a**.

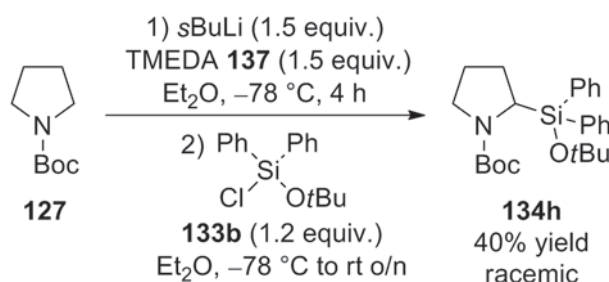
The hydrolysis of the Si-Cl bond constitutes one of the most commonly employed methods to furnish silanols. However, all attempts to make chlorosilyl-substituted pyrrolidines starting from dichlorodiorganosilanes failed.

Experiments towards the synthesis of a “reversed” Jørgensen-Hayashi catalyst **132a** were initiated (Figure 18). This compound might possess similar steric properties compared to the original catalyst but differs in electronic nature mainly due to the presence of silicon in  $\alpha$ -position to the nitrogen.



**Figure 18:** The Jørgensen-Hayashi catalyst **32a** and its reversed analog **132a**.

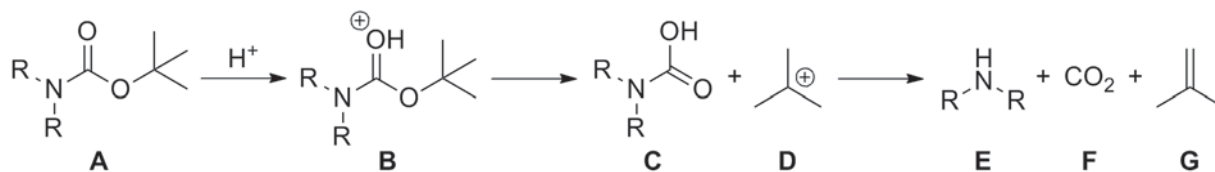
The first step towards this goal was achieved by reacting lithiated pyrrolidine with *tert*-butoxydiphenylsilyl chloride (**133b**).<sup>148</sup> By employing TMEDA (**137**) as achiral diamine ligand in the deprotonation step, product **134h** was formed as a racemic mixture (Scheme 44). Suitable conditions to promote deprotection of the amine without affecting the silyl ether are yet to be found.



**Scheme 44:** The first attempt towards a “reversed” Jørgensen-Hayashi catalyst **134h**.

### 2.1.3 Deprotection of *N*-Boc Silylated Pyrrolidines

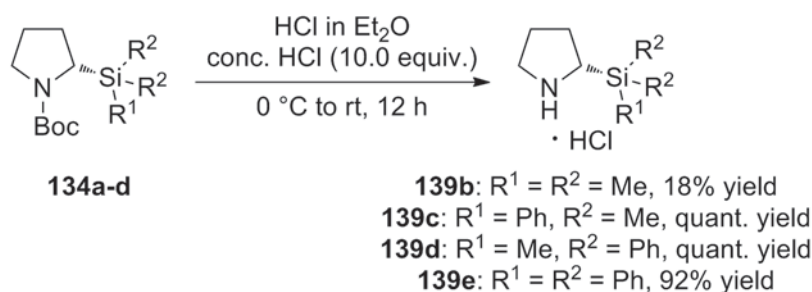
Acid mediated cleavage of the *tert*-butoxycarbonyl group is an established procedure to deprotect *N*-Boc amines and proceeds in three steps (Figure 19).<sup>134b</sup> The carbamate **A** is first protonated at the most basic oxygen to produce carboxonium ion **B**. The second step contains a heterolytic *O-tert*-butyl-bond cleavage to yield neutral species **C** and *tert*-butyl cation **D**. Carbamic acid **C** is unstable and readily decarboxylates to form the free amine **E**. The *tert*-butyl cation **D** is simultaneously deprotonated and gives isobutylene **G**.<sup>149</sup>



**Figure 19:** E<sub>1</sub>-Elimination of the *tert*-butoxycarbonyl group.

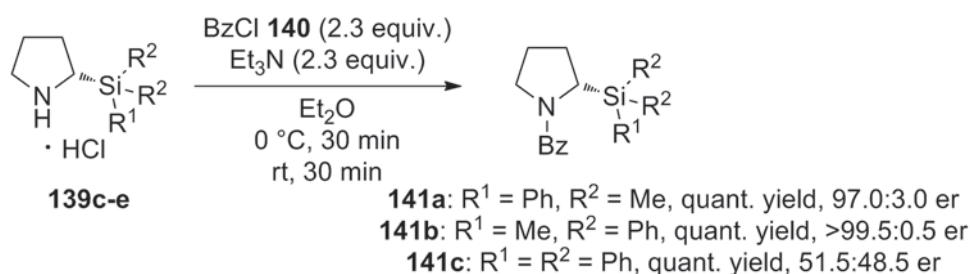
Although trifluoroacetic acid is commonly used for Boc removal, it did not seem the right choice for the *N*-Boc silylated pyrrolidines. Its use resulted in low yield of deprotected pyrrolidine and residues of trifluoroacetic acid in the product (detected by <sup>19</sup>F NMR) could not be removed by basic washing or column chromatography.<sup>150</sup> Experiments with *in situ* generated hydrochlorid acid through hydrolysis of acetylchloride with dry ethanol in dry ethyl acetate did not show promising

results. However, this method was employed by West and Strohmann to afford the hydrochloric salts of the amines.<sup>135,143b</sup> Another deprotection method is thermolysis, but this resulted in decomposition of the substrates.<sup>151</sup> Treatment with hydrochloric acid saturated diethyl ether showed partial deprotection of the substrate and when an excess of concentrated hydrochloric acid was added, full conversion of the *N*-Boc-pyrrolidines was observed. Solving the substrates **134a–d** in hydrochloric acid saturated diethyl ether at 0 °C, subsequent slow addition of 10 equivalents of concentrated hydrochloric acid and stirring for 12 hours was disclosed as optimum. Strangely, the TMS-substituted *N*-Boc-pyrrolidine **134a** yielded only 18% of the desired hydrochloric salt, whereas the other derivatives **134b–d** afforded the products **139c** and **139d** in quantitative yield and **139e** in 92% yield (Scheme 45).<sup>143a</sup> Further efforts to optimize the yield of **139b** were not undertaken.



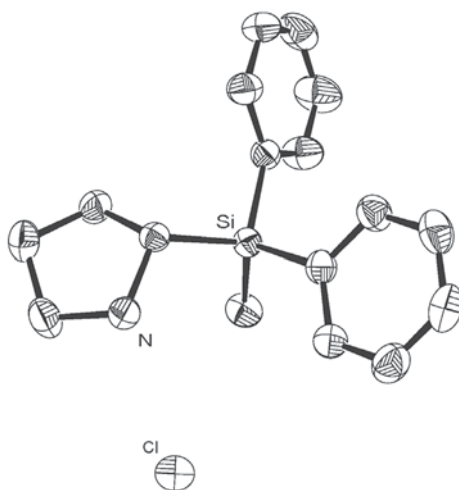
**Scheme 45:** Acid-mediated cleavage of the Boc-group.

Continuative investigations focused on the enantiomeric enrichment of the hydrochloric acids **139c** and **139d** by recrystallization. Numerous methods were tested and unfortunately, no suitable conditions were found to enrich 2-(dimethylphenylsilyl)pyrrolidine hydrochloric salt (**139c**). On the contrary, enantiopure samples of **139d** were obtained when the compound was dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub>/MeOH (9:1) and the solvent was slowly evaporated in a test tube in the course of a few days. The collected crystals were then derivatized to determine the enantiomeric excess by HPLC analysis on a chiral stationary phase (Scheme 46). Therefore, the hydrochloric salt was treated with benzoyl chloride (**140**) in the presence of triethylamine as base to quantitatively yield the *N*-benzoyl-protected silylated pyrrolidines **141a–c**.<sup>143a</sup> Attempts to benzoyl protect amino silanol **139a** remained unfruitful.



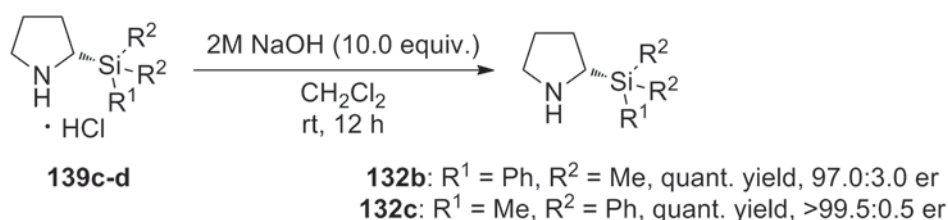
**Scheme 46:** Benzoyl protection of hydrochloric salts **139c–e**.

Moreover, crystals of **139d** were subjected to X-ray structure analysis to confirm the absolute configuration.<sup>152</sup> Indeed, the stereocenter had (*S*)-configuration as shown in Figure 20. The same result was attained by Strohmann.<sup>143</sup>



**Figure 20:** Crystal structure of **139d**.<sup>153</sup> Ellipsoids at the 50% level.

Treatment of the hydrochloric salts **139c** and **139d** with base afforded the corresponding free amines as colorless oils in quantitative yield without loss of stereoinformation (Scheme 47). The enantiopurity of the free amines **132b** and **132c** was affirmed by HPLC analysis after derivatization to the corresponding benzoyl analogs according to the above described procedure (however with 1.3 equivalents of both benzoyl chloride and triethylamine).<sup>143a</sup>

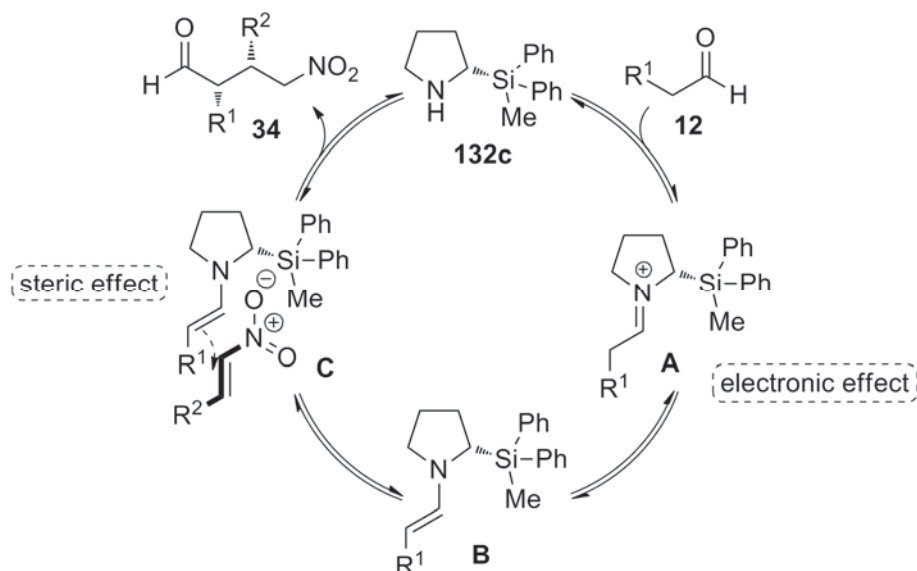


**Scheme 47:** Treatment with base to afford free amines **132b** and **132c**.

## 2.1.4 Application of Silylated Pyrrolidines

Since the first organocatalytic addition of aldehydes to nitroolefins was described by Hayashi, intensive investigations have focused on this transformation (see Chapter 1.1.1). With the enantiopure silylated pyrrolidine **132c** in hand, this Michael addition seemed a good model reaction to test its reactivity and stereinduction. Based on studies in the literature, an action mode for the silicon-containing organocatalyst as depicted in Figure 21 was proposed. The catalytic cycle is initiated by the formation of iminium-type structure **A**. Favorable electronic effects of the silicon

might play a role in stabilizing the positive charge of this structure. Enamine **B** is then formed from intermediate **A**. The *E*-configuration of **B** is preferred due to the bulkiness of the silicon moiety. The silicon also supports the orientation of the incoming electrophile, a nitroolefin, and provides the basis for enantioselective C-C bond formation. Subsequently, the product is released and the catalyst is liberated to enter in the next catalytic cycle.



**Figure 21:** Proposed mechanism for the Michael addition catalyzed by 2-silylated pyrrolidine **132c**.

The initial experiment of the Michael addition of propanal (**12a**) to  $\beta$ -nitrostyrene (**15a**) in THF at room temperature gave a satisfactory yield of 65%, diastereomeric ratio of 64:36 and an enantiomeric ratio of 84.0:16.0. From this promising starting point, solvent screening experiments were conducted. Running the reaction at 0 °C with 10 equivalents of propanal (**12a**) in THF gave the desired  $\gamma$ -nitro aldehyde **34a** in 91% yield and good stereoselectivity (entry 1, Table 1). Diethyl ether was also a suitable solvent for the transformation (entry 2). The reaction performed in 1,4-dioxane gave inferior results (entry 3). In nonpolar solvents such as *n*-hexane, a reaction time of only 5 hours was needed to give the product in high yield and good enantioselectivity (entry 4). Similar results were obtained in toluene after 17 hours (entry 5). Dichloromethane also served as appropriate solvent to give the Michael adduct in 96% yield, 97:3 dr but only 73.5:26.5 er (entry 6). In protic and aprotic polar solvents, the reaction became inefficient in terms of yield and enantioselectivity (entries 7 and 8). The absolute configuration was confirmed by comparison with optical rotation values reported in the literature (see Chapter 4.6 for further details).

**Table 1:** Solvent screening experiments for the Michael addition reaction.

CC(=O)C (12a) + c1ccc(cc1)/C=C/[N+](=O)[O-] (15a)  $\xrightarrow[\text{solvent, } 0^\circ\text{C, time}]{\text{132c (10 mol\%)}}$  CC(=O)C(c1ccc(cc1)C)C[N+](=O)[O-] (34a)

| Entry <sup>a</sup> | Solvent                         | <i>t</i> [h] | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> | <i>er</i> <sup>d</sup> |
|--------------------|---------------------------------|--------------|------------------------|------------------------------|------------------------|
| 1                  | THF                             | 17           | 91                     | 89:11                        | 94.0:6.0               |
| 2                  | Et <sub>2</sub> O               | 17           | 98                     | 94:6                         | 92.5:7.5               |
| 3                  | 1,4-dioxane                     | 17           | 81                     | 91:9                         | 77.5:22.5              |
| 4                  | <i>n</i> -hexane                | 5            | 91                     | 96:4                         | 91.0:9.0               |
| 5                  | toluene                         | 17           | 98                     | 99:1                         | 91.5:8.5               |
| 6                  | CH <sub>2</sub> Cl <sub>2</sub> | 17           | 96                     | 97:3                         | 73.5:26.5              |
| 7                  | <i>i</i> PrOH                   | 17           | 57                     | 91:9                         | 63.5:36.5              |
| 8                  | CH <sub>3</sub> CN              | 17           | 84                     | 89:11                        | 51.0:49.0              |

a) Reaction conditions: **12a** (5 mmol), **15a** (0.5 mmol) and **132c** (0.05 mmol) were stirred in solvent (1.5 mL) at 0 °C.

b) Yield after column chromatography. c) Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude product.

d) Determined by HPLC analysis using a chiral stationary phase (*er* values of the *syn* diastereomer are given).

A subsequent study focused on the substrate scope of this Michael reaction. Several substitution patterns on the phenyl ring of the nitroolefin were employed, but surprisingly gave much lower yields and stereoselectivities. Not only halogen substitution in the 2- and 4-position of β-nitrostyrene (entries 1–3, 6 and 7, Table 2), but also 4-methyl- and 4-methoxy-substituted β-nitrostyrenes and (*E*)-2-(2-nitrovinyl)furan (entries 4, 5 and 8) gave unsatisfactory results. The addition of acid did not improve the outcome of the reaction.<sup>154</sup> Racemic samples for determining appropriate HPLC conditions were synthesized using pyrrolidine as catalyst and dichloromethane as solvent.

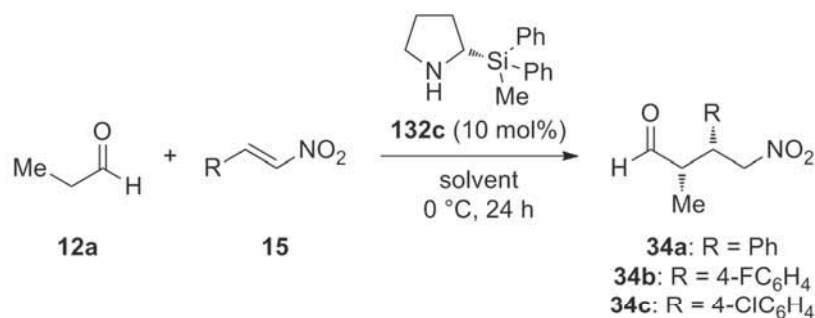
**Table 2:** Substrate scope of the Michael addition reaction with THF as solvent.

$\text{Me-CH}_2\text{-CHO}$  (12a) +  $\text{R-CH=CH-NO}_2$  (15)  $\xrightarrow[\text{THF, 0 } ^\circ\text{C, time}]{\text{132c (10 mol\%)}}$   $\text{Me-CH}_2\text{-CH(R)-CH}_2\text{-NO}_2$  (34b-i)

| Entry <sup>a</sup> | Product              | <i>t</i> [h] | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> | <i>er</i> <sup>d</sup> |
|--------------------|----------------------|--------------|------------------------|------------------------------|------------------------|
| 1                  | X = F ( <b>34b</b> ) | 24           | 45                     | 86:14                        | 92.5:7.5               |
| 2                  | Cl ( <b>34c</b> )    | 17           | 31                     | 68:32                        | 76.0:24.0              |
| 3                  | Br ( <b>34d</b> )    | 24           | 34                     | 92:8                         | 93.0:7.0               |
| 4                  | Me ( <b>34e</b> )    | 21           | 54                     | 95:5                         | 87.0:13.0              |
| 5                  | MeO ( <b>34f</b> )   | 17           | 55                     | 81:19                        | 89.0:11.0              |
| 6                  | F ( <b>34g</b> )     | 17           | 78                     | 85:15                        | 67.0:33.0              |
| 7                  | Cl ( <b>34h</b> )    | 17           | 47                     | 73:27                        | 61.0:39.0              |
| 8                  | ( <b>34i</b> )       | 24           | 40                     | 85:15                        | 82.5:17.5              |

a)–d) as in Table 1.

This undesirable outcome demanded additional solvent screening investigations. The attention was especially drawn to solvent mixtures. A mixture of *n*-hexane and THF, as the two best sole nonpolar and polar solvents, was chosen as starting point. A ratio of 5:1 gave superior results over a 1:1 and 1:5 mixture in the reaction between propanal (**12a**) and  $\beta$ -nitrostyrene (**15a**) (entries 1–3, Table 3). The best result however, was obtained with a solvent mixture of toluene and THF in a 5:1 ratio (entry 4). When 4-fluoro- $\beta$ -nitrostyrene (**15b**) was used as Michael acceptor, the latter mixture also turned out to be the best (entries 5 and 6). Other polar-nonpolar solvent mixtures were tested with 4-chloro- $\beta$ -nitrostyrene (**15c**). When *n*-hexane was used in combination with THF, 1,4-dioxane and phenetole as ethers, the desired product **34c** was formed in high yield and stereoselectivity (entries 7–9). Again, toluene mixed with THF (5:1 ratio) proved most effective to give **34c** in 99% yield, 95:5 dr and 93.0:7.0 er (entry 10). The other solvents investigated showed similar or slightly inferior results, but were not chosen due to practical reasons (entries 11–13).

**Table 3:** Mixed solvent screening experiments for the Michael addition reaction.

| Entry <sup>a</sup>    | Solvent                            | R                                                | Yield [%] <sup>b</sup> | syn:anti <sup>c</sup> | er <sup>d</sup> |
|-----------------------|------------------------------------|--------------------------------------------------|------------------------|-----------------------|-----------------|
| 1                     | <i>n</i> -hexane:THF (5:1)         | Ph ( <b>15a</b> )                                | 97                     | 95:5                  | 93.0:7.0        |
| 2                     | <i>n</i> -hexane:THF (1:1)         | Ph ( <b>15a</b> )                                | 82                     | 91:9                  | 93.5:6.5        |
| 3                     | <i>n</i> -hexane:THF (1:5)         | Ph ( <b>15a</b> )                                | 46                     | 89:11                 | 94.0:6.0        |
| <b>4<sup>e</sup></b>  | <b>toluene:THF (5:1)</b>           | <b>Ph (15a)</b>                                  | <b>96</b>              | <b>95:5</b>           | <b>94.5:5.5</b> |
| 5                     | <i>n</i> -hexane:THF (5:1)         | 4-FC <sub>6</sub> H <sub>4</sub> ( <b>15b</b> )  | 92                     | 96:4                  | 92.0:8.0        |
| <b>6<sup>f</sup></b>  | <b>toluene:THF (5:1)</b>           | <b>4-FC<sub>6</sub>H<sub>4</sub> (15b)</b>       | <b>93</b>              | <b>95:5</b>           | <b>92.5:7.5</b> |
| 7                     | <i>n</i> -hexane:THF (5:1)         | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 96                     | 95:5                  | 92.5:7.5        |
| 8                     | <i>n</i> -hexane:1,4-dioxane (5:1) | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 95                     | 97:3                  | 91.5:8.5        |
| 9                     | <i>n</i> -hexane:phenetole (5:1)   | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 94                     | 99:1                  | 92.0:8.0        |
| <b>10<sup>g</sup></b> | <b>toluene:THF (5:1)</b>           | <b>4-ClC<sub>6</sub>H<sub>4</sub> (15c)</b>      | <b>99</b>              | <b>95:5</b>           | <b>93.0:7.0</b> |
| 11                    | toluene:1,4-dioxane (5:1)          | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 94                     | 97:3                  | 92.0:8.0        |
| 12                    | toluene:phenetole (5:1)            | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 88                     | 97:3                  | 93.0:7.0        |
| 13                    | mesitylene:THF (5:1)               | 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>15c</b> ) | 98                     | 95:5                  | 93.0:7.0        |

a)–d) as in Table 1. The reaction was stopped after e) 17 h; f) 22 h; g) 19 h.

The results shown in Tables 1–3 were obtained in cooperation with Jörres and the experiments were repeated at least once to confirm their reproducibility.<sup>155</sup>

In addition to the 4-fluoro- and 4-chloro-substituted  $\beta$ -nitrostyrenes (entries 6 and 10, Table 3), also 4-bromo- $\beta$ -nitrostyrene (entry 1, Table 4) was tolerated in the Michael addition performed in a 5:1 mixture of toluene and THF. Nitroolefins with electron donating properties on the phenyl moiety gave diastereomeric and enantiomeric ratios above the 93.5:6.5 level and the reaction was completed after 22 hours in these cases (entries 2 and 3). 2-Fluoro- and 2-chloro-substituted  $\beta$ -nitrostyrenes reacted readily to give the desired compounds **34g** and **34h** in high yields and stereoselectivities (entries 4 and 5). When a heterocyclic nitroolefin was employed, the yield and diastereoselectivity were still high, but the enantioselectivity dropped slightly (entry 6). A longer

reaction time was needed when the Michael addition was performed with butanal instead of propanal but no compromises in terms of yields and stereoselectivities were made (entries 7 and 8).<sup>143a</sup>

The hydrochloric salt **139d** did not catalyze the reaction. Catalyst **132b** with the less bulky dimethylphenylsilyl group gave lower stereoselectivities and therefore was not further investigated.

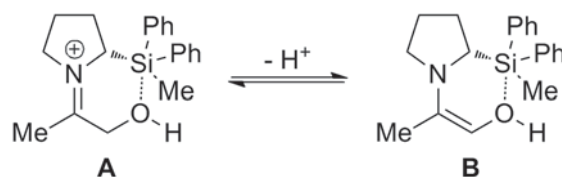
**Table 4:** Substrate scope of the Michael addition reaction with toluene:THF (5:1) as solvent mixture.

| Entry <sup>a</sup> | Product | <i>t</i> [h] | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> | <i>er</i> <sup>d</sup> |
|--------------------|---------|--------------|------------------------|------------------------------|------------------------|
| 1                  |         | 22           | 87                     | 97:3                         | 93.0:7.0               |
| 2                  |         | 22           | 98                     | 96:4                         | 95.5:4.5               |
| 3                  |         | 22           | 93                     | 96:4                         | 93.5:6.5               |
| 4                  |         | 15           | 96                     | 97:3                         | 92.0:8.0               |
| 5                  |         | 15           | 96                     | 92:8                         | 93.0:7.0               |
| 6                  |         | 22           | 88                     | 96:4                         | 89.0:11.0              |
| 7                  |         | 46           | 95                     | 95:5                         | 93.5:6.5               |
| 8                  |         | 48           | 90                     | 94:6                         | 95.0:5.0               |

a)–d) as in Table 1.

This study represents the first effective transformation catalyzed by a silylated pyrrolidine where the silicon is positioned in  $\alpha$ -position to the nitrogen. Similar results were obtained independently by Strohmann.<sup>143</sup>

Attempts to find additional reactions catalyzed by silylated pyrrolidines were subsequently undertaken. It was envisaged that hydroxyacetone might function as a suitable substrate in a Michael reaction. Along the same lines with the activation mode of Alexakis' diamine, iminium and enamine intermediates **A** and **B** can be proposed (Figure 22).<sup>37c</sup> A Lewis base/Lewis acid interaction between oxygen and silicon was hypothesized and should facilitate the formation of enol/enamine **B**. This interplay could “lock” the enamine nucleophile in a rigid transition state to leave only one side sterically unhindered for the incoming electrophile.



**Figure 22:** Proposed activation mode for hydroxyacetone.

Unfortunately, the proposed mechanism was not confirmed by the experiments. The reaction between hydroxyacetone (**14a**) and  $\beta$ -nitrostyrene (**15a**) was performed in ethereal and chlorinated solvents and gave the product **18a** in 59-84% yield with low diastereoselectivity in essentially racemic form (entries 1–3, Table 5). The reaction became sluggish at lower temperature but gave a slightly higher diastereoselective ratio and an enantiomeric ratio of 65.5:34.5 (entry 4).

**Table 5:** Experiments with hydroxyacetone (**14a**) as donor component.

| Entry <sup>a</sup> | Solvent                         | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> | er <sup>d</sup> |
|--------------------|---------------------------------|------------------------|------------------------------|-----------------|
| 1                  | THF                             | 59                     | 75:25                        | racemic         |
| 2                  | Et <sub>2</sub> O               | 84                     | 76:24                        | racemic         |
| 3                  | CH <sub>2</sub> Cl <sub>2</sub> | 63                     | 76:24                        | 52.5:47.5       |
| 4 <sup>e</sup>     | CH <sub>2</sub> Cl <sub>2</sub> | 11                     | 82:18                        | 65.5:34.5       |

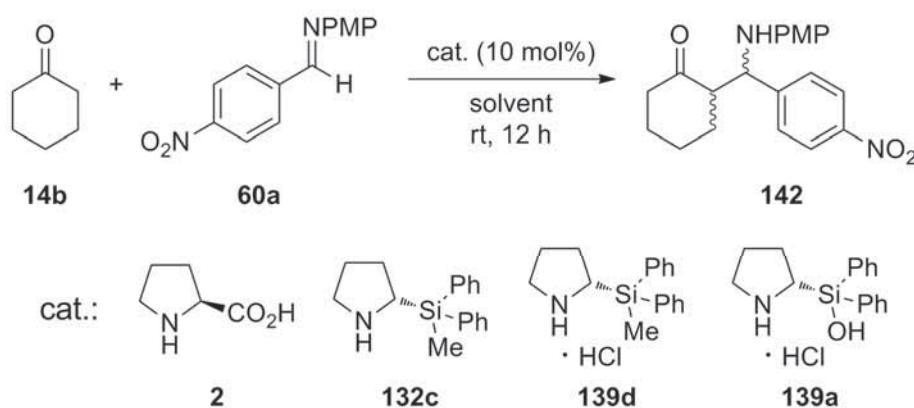
a) Reaction conditions: **14a** (5 mmol), **15a** (0.5 mmol) and **132c** (0.05 mmol) were stirred in solvent (1.5 mL) at rt.

b)–d) as in Table 1. e) Reaction was run for 24 hours at 0 °C.

The Mannich reaction between cyclohexanone (**14b**) and preformed imine **60a** was tested with silylated pyrrolidines **132c**, **139a**, **139d** and (*S*)-proline (**2**). Proline catalyzed the reaction to provide the product in 44% yield, approximately 1:1 dr and 85.5:14.5 er for the *syn* diastereomer (entry 1,

Table 6). Intensive studies by Barbas and Houk revealed that 3-pyrrolidinecarboxylic acid derivatives mainly gave *anti* Mannich products compared to the usually observed *syn* selectivity when proline is employed as catalyst.<sup>156</sup> Surprisingly, both triorganylsilylated pyrrolidines **132c** and **139d** catalyzed the reaction to give the *anti* product, but unfortunately in racemic form (entries 2 and 3). Compound **139a** can be considered as a proline analog, but also in this case no enantioselectivity was observed (entry 4). Perhaps the formation of siloxane upon loss of water inhibits stereoselection in this case. An ongoing project focuses on gaining additional information on the interactions between the catalyst and substrates in order to comprehend the behavior of this type of compounds.

**Table 6:** Mannich reaction with various catalysts.



| Entry <sup>a</sup> | Cat.        | Solvent                         | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> | <i>er</i> <sup>d</sup>                              |
|--------------------|-------------|---------------------------------|------------------------|------------------------------|-----------------------------------------------------|
| 1 <sup>e</sup>     | <b>2</b>    | DMSO                            | 44                     | ~1:1                         | 64.0:36.0 ( <i>anti</i> ); 85.5:14.5 ( <i>syn</i> ) |
| 2 <sup>f</sup>     | <b>132c</b> | neat                            | 53                     | 28:72                        | racemic                                             |
| 3                  | <b>139d</b> | CH <sub>2</sub> Cl <sub>2</sub> | 81                     | 19:81                        | racemic                                             |
| 4                  | <b>139a</b> | CH <sub>2</sub> Cl <sub>2</sub> | 91                     | 18:82                        | racemic                                             |

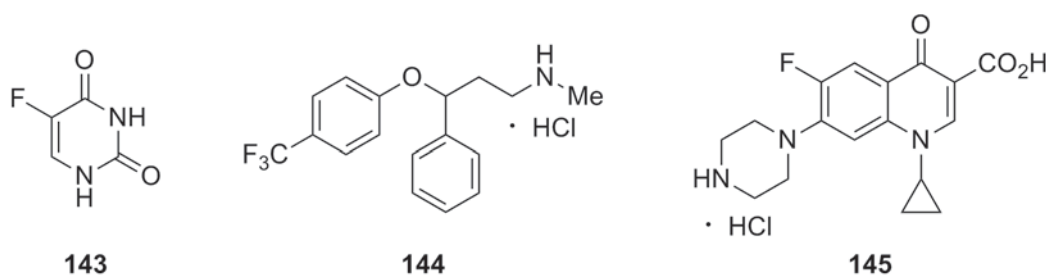
a) Reaction conditions: **14b** (5 mmol), **60a** (0.5 mmol) and catalyst (0.05 mmol) were stirred in solvent (1.5 mL) at rt.

b)–c) as in Table 1. d) Determined by HPLC analysis using a chiral stationary phase. e) 3 mmol; f) 15 mmol of cyclohexanone (**14b**) was used.

## 2.2 Enantioselective Organocatalytic Synthesis of Quaternary $\alpha$ -Amino Acid Derivatives Bearing a CF<sub>3</sub> Moiety

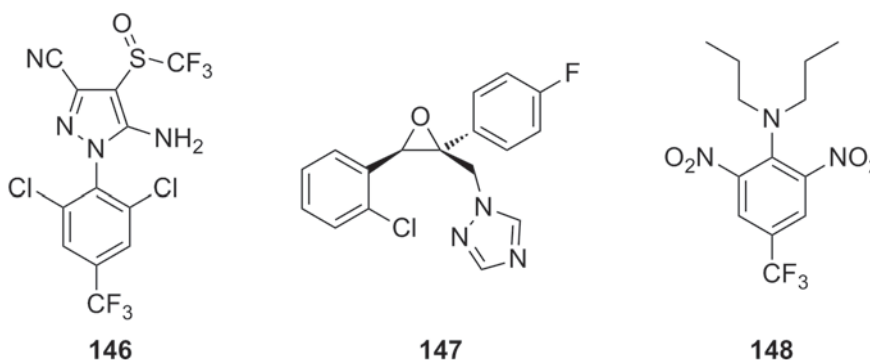
Fluorine is the most electronegative of all the elements and therefore exhibits remarkable features. It is also the 13<sup>th</sup> most abundant element in the earth's crust occurring most importantly in the mineral fluorspar, CaF<sub>2</sub>. Besides plenty other inorganic fluorine-containing compounds, only around 30 naturally occurring organofluorines are known.<sup>157</sup> The number of synthetic compounds

containing a C-F bond, though, is vast and the properties of these structures seem invaluable in pharmaceuticals, crop protection products and at home. Around 20% of all pharmaceuticals contain fluorine and fluoro agrochemicals account for even more than 30% of the total market. 5-Fluorouracil (**143**) was the first fluorine-containing drug introduced in 1957 (Figure 23). The pyrimidine derivate is used as a potent drug for the treatment of cancer. Today, fluoxetine (**144**) (Prozac<sup>®</sup>) and ciprofloxacin (**145**) (Cipro<sup>®</sup>) belong to the best selling prescription drugs bearing at least one fluorine atom. The first is used as antidepressant and latter is an antibacterial agent. These are merely three examples out of a large array of fluorine-containing drugs.<sup>158</sup>



**Figure 23:** Examples of important fluorine-containing drugs.

Three blockbuster agrochemicals are displayed in Figure 24. The first is an insecticide named fipronil (**146**) and was launched in 1993 by Rhône-Poulenc. The triazole-containing epoxiconazole (**147**) was developed by BASF and is used as a fungicide active ingredient. Trifluralin (**148**) represents a herbicide which was first registered in 1963 and despite its suspected carcinogenicity, it is still widely used in some countries.<sup>159</sup>

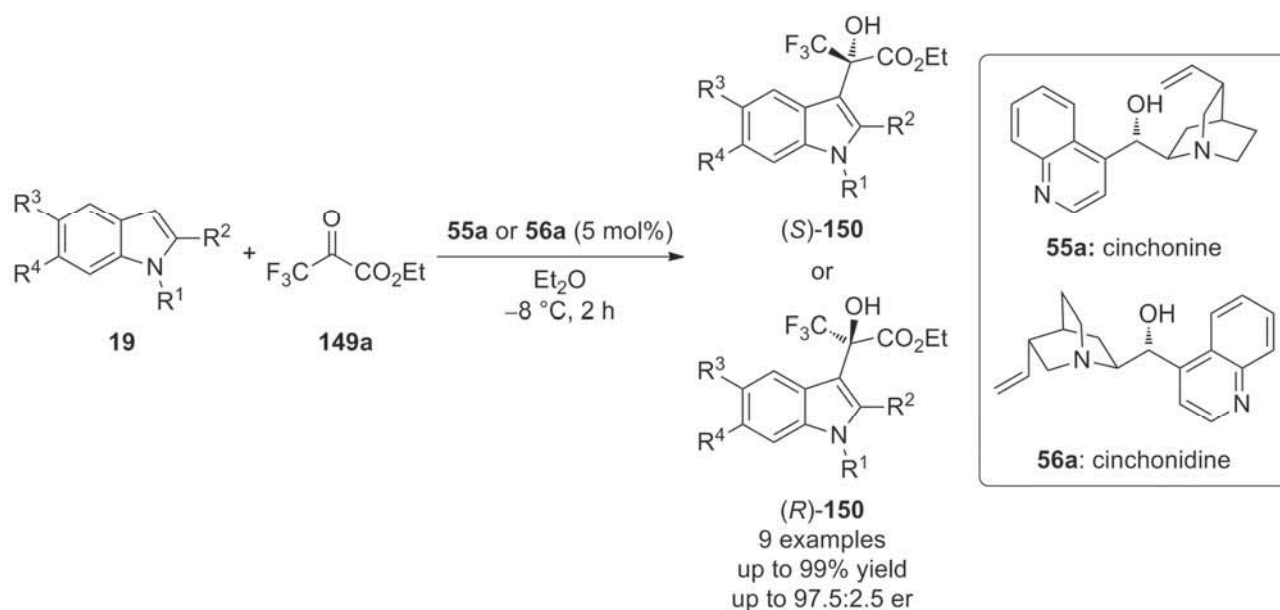


**Figure 24:** Examples of important fluorine-containing agrochemicals.

These examples emphasize the importance of fluorine incorporation in organic compounds. It is evident that fluorine substitution alters the electronic and steric properties of a molecule. Further detailed studies on the effect of such compounds are necessary to improve their efficacy and to reduce their impact on the environment. Moreover, the search for new methods to introduce fluorine into organic structures and the synthesis of new compounds bearing fluorine-containing moieties remain the focus in recent research.<sup>160</sup>

### 2.2.1 Research Objective

Several synthetic methods to generate trifluoromethylated compounds in an enantioselective fashion have been developed.<sup>161</sup> The first organocatalytic Friedel-Crafts reaction of indoles with ethyl trifluoropyruvate was demonstrated by Török and Prakash (Scheme 48). Cinchona alkaloids were found to catalyze the Friedel-Crafts reaction to give the desired alcohols **150** in high yields and enantioselectivities. Cinchonine (**55a**) and cinchonidine (**56a**) proved most effective and provided either enantiomers of the product. Several substituted indole derivatives also reacted without affecting the yield and stereoisomeric outcome of the reaction.<sup>162</sup>

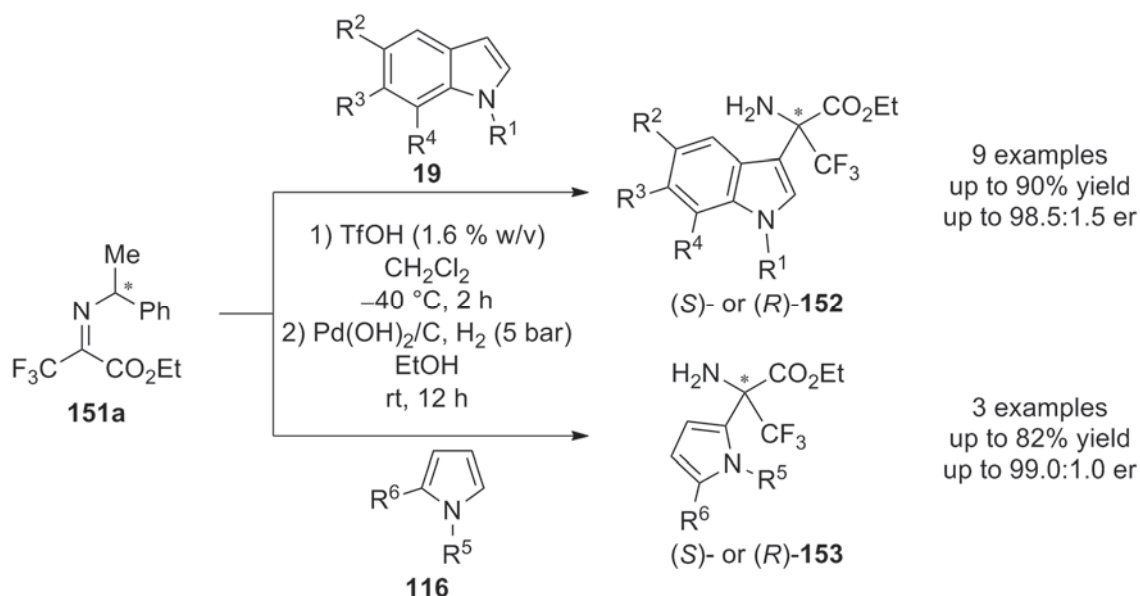


**Scheme 48:** Enantioselective organocatalytic hydroxyalkylation of indoles.

Various other examples of reactions with trifluoromethyl ketones as electrophiles catalyzed by chiral hydrogen donor catalysts have been developed. Among them are a carbonyl-ene reaction<sup>96g</sup> and numerous Friedel-Crafts reactions.<sup>163</sup>

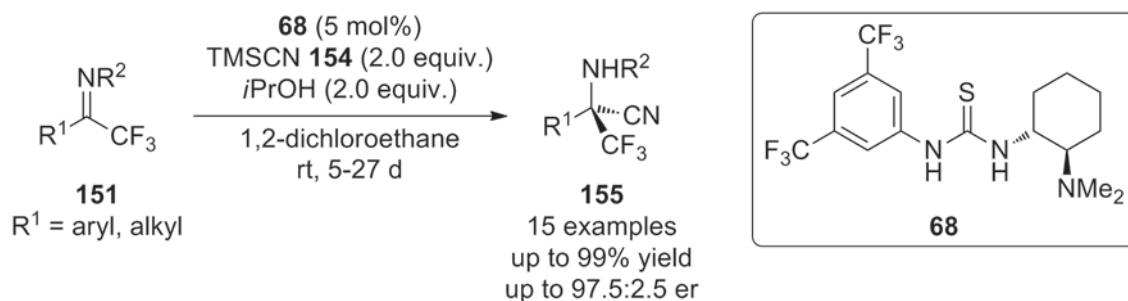
The synthesis of fluorine-containing amino acids has attracted quite some attention in the synthetic community over the past decades. These structures play an important role in biological and peptide chemistry. The unique properties of fluorine including high electronegativity, high lipophilicity and steric size are the main reasons for their broad application in these fields.<sup>164</sup> Several racemic processes to synthesize  $\alpha$ -trifluoromethyl-substituted amino acids have been described.<sup>165</sup> Only a few diastereomeric approaches have been reported so far, but with moderate success.<sup>166</sup> However, a highly selective Friedel-Crafts reaction was developed by Török (Scheme 49). A chiral protecting group was employed to effect a diastereoselective addition to imine **151a**. The strong Brønsted acid TfOH catalyzed the Friedel-Crafts aminoalkylation and subsequent Pd-catalyzed hydrogenolysis

cleaved the benzyl group to yield the target amino esters **152** and **153** in enantiomeric ratios of up to 99.0:1.0. Both enantiomers of the ethyl trifluoropyruvate were accessible to allow the stereoselective synthesis of either enantiomer of the product.<sup>167</sup>



**Scheme 49:** Triflic acid catalyzed aminoalkylation of indoles **19** and pyrroles **116**.

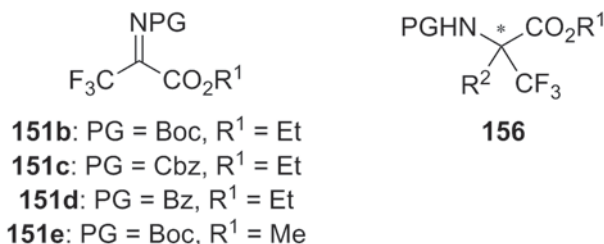
Recently, Enders presented an organocatalytic enantioselective Strecker synthesis of quaternary  $\alpha$ -trifluoromethyl amino nitriles **155** (Scheme 50). Trimethylsilyl cyanide (**154**) was used as a cyanide source. Takemoto's catalyst **68** emerged as the best catalyst for this transformation to give the desired compounds in high yields and enantioselectivities. In some cases, enantiopure samples were obtained after recrystallization. In addition to various phenyl-substituted imines, also alkyl-substituted ones reacted readily. However, the extreme long reaction time of up to 27 days is a disadvantage of this procedure. As representative example, one amino nitrile was deprotected and subsequently hydrolyzed to give the free  $\alpha$ -trifluoromethyl amino acid in 75% yield.<sup>168</sup>



**Scheme 50:** Strecker synthesis of quaternary  $\alpha$ -trifluoromethyl amino nitriles **155**.

The research objective of this project was to develop an organocatalytic enantioselective method to synthesize  $\alpha$ -trifluoromethylated amino acid derivatives **156** (Figure 25). The first goal was to synthesize various imines **151b–e** according to literature procedures.<sup>165b,169</sup> Nucleophilic addition to

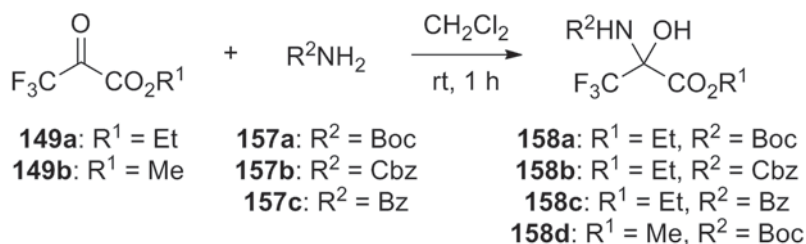
the imine carbon was then envisaged to occur in a stereoselective fashion mediated by a suitable organocatalyst.



**Figure 25:** Trifluoropyruvate derived imines **151b–d** and quaternary  $\alpha$ -trifluoromethyl amino acid derivatives **156**.

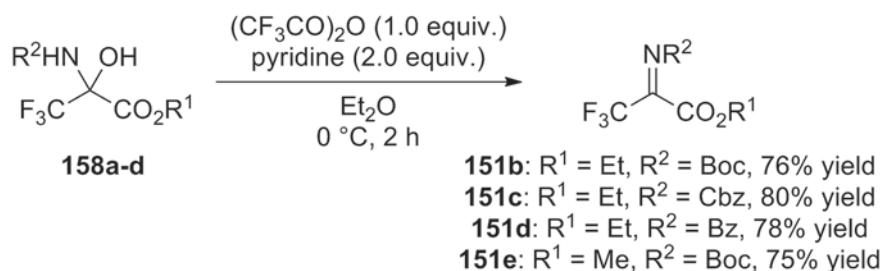
## 2.2.2 Synthesis of Trifluoropyruvate Imines

Trifluoropyruvates **149** served as substrates towards the desired imines. In accordance with literature procedures,<sup>165b</sup> they readily reacted with carbamates **157a**, **157b** and amide **157c** to form the stable hemiaminals **158a–d**. These compounds were obtained as solids in quantitative yield after evaporation of the solvent (Scheme 51).



**Scheme 51:** Synthesis of trifluoromethylated hemiaminals **158**.

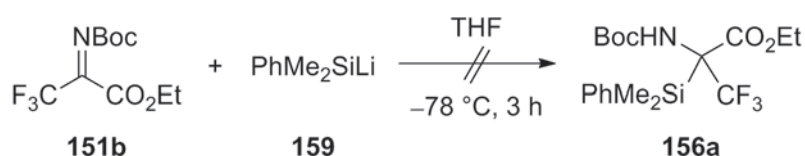
Special caution was needed to conduct the subsequent step towards imines **151**. Hemiaminal **158** was dissolved in diethyl ether and cooled to 0 °C. Trifluoroacetic anhydride and pyridine were simultaneously added with the help of a syringe pump (~2 mL/h).<sup>170</sup> Over a period of two hours a white solid formed, which was quickly filtered off. The filtrate was then treated with dry *n*-hexane and left in a fridge overnight. Pyridinium trifluoroacetate crystals were formed, filtered off and after evaporation of *n*-hexane, the crude products were distilled in high vacuum to give the imines **151b–e** in high yields (Scheme 52). The products are highly hygroscopic and were stored in a glove box to circumvent addition of water that would lead to the hemiaminals **158**.



**Scheme 52:** Dehydration of **158a–d** to form the desired imines **151b–e**.

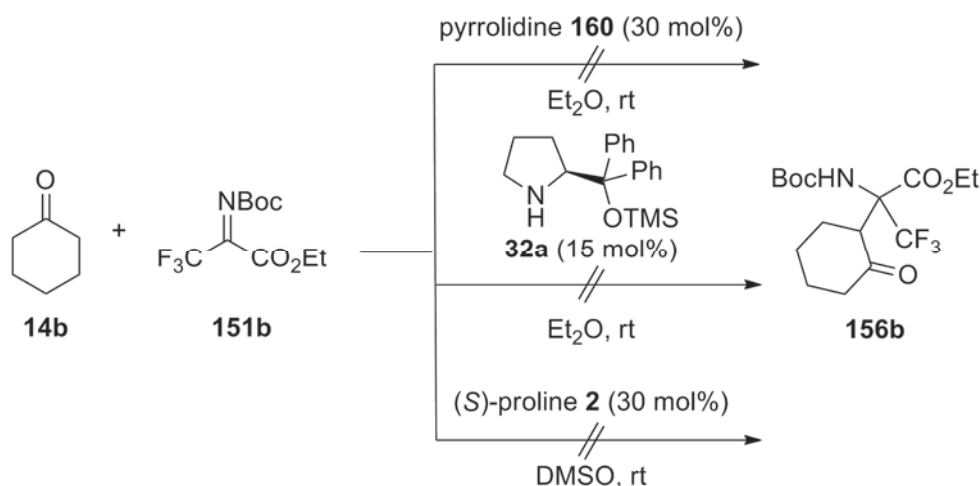
### 2.2.3 Chiral Phosphoric Acid Catalyzed Synthesis of $\alpha$ -Trifluoromethyl $\alpha$ -Amino Acid Derivatives

The development of alternative synthetic methods to produce  $\alpha$ -silyl  $\alpha$ -amino acids is still highly desirable.<sup>137b</sup> A report by Uneyama revealed that organolithium reagents effectively added to trifluoropyruvate imines to give alkylated fluorinated  $\alpha$ -amino acids.<sup>171</sup> Along the same lines, silyllithium species **159** was reacted with *N*-Boc-protected ethyl trifluoropyruvate imine **151b** (Scheme 53). Dimethylphenylsilyllithium (**159**) was prepared from the corresponding chlorosilane and elemental lithium according to literature procedures.<sup>172</sup> Unfortunately, no desired product **156a** was detected, which can be explained by competitive electrophilicity of the ester moiety or even the nitrogen. However, none of these alternative products were isolated. A comprehensive overview on the addition of organometallic compounds to  $\alpha$ -imino esters is given by Kozłowski.<sup>173</sup>



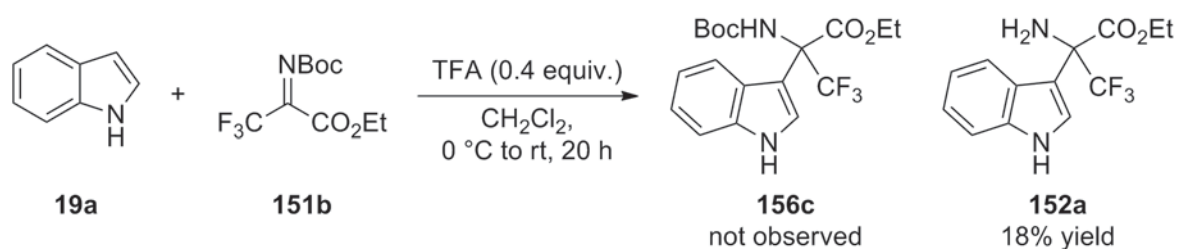
**Scheme 53:** The synthesis of silicon-containing amino acid derivative **156a** failed.

Preliminary experiments using Lewis base catalysis to form  $\alpha$ -trifluoromethyl  $\alpha$ -amino acid derivatives were then undertaken. Cyclohexanone (**14b**) was chosen as carbonyl donor compound with pyrrolidine (**160**), the Jørgensen-Hayashi catalyst **32a** or (*S*)-proline (**2**) as organocatalyst in a Mannich-type reaction (Scheme 54).<sup>174</sup> Additionally, propanal was tested under these conditions. Unfortunately,  $\alpha$ -functionalization of cyclohexanone or propanal was not accomplished in any case.



**Scheme 54:** Various conditions to effect a Mannich reaction were unsuccessful.

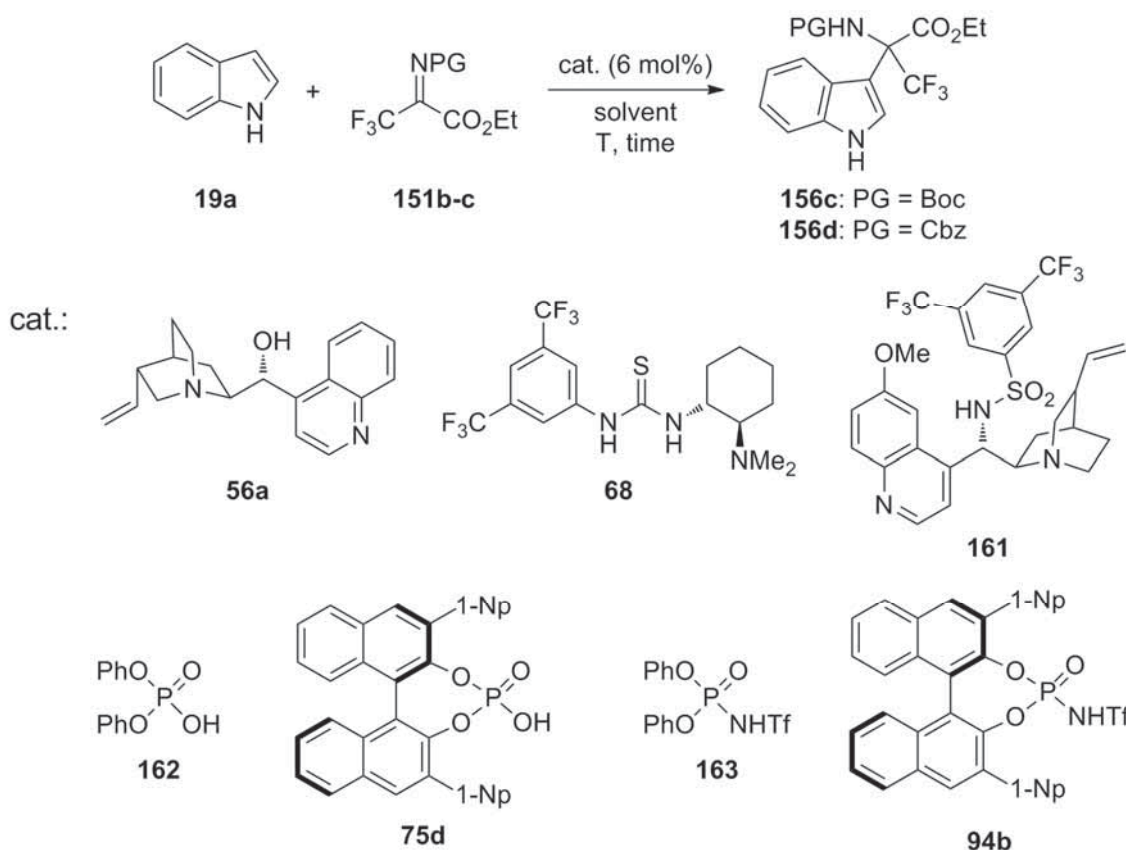
On the contrary, when indole **19a** was used as a nucleophile in the presence of trifluoroacetic acid as a Brønsted acid catalyst, small amounts of aminoalkylated indole were isolated (Scheme 55). The *N*-Boc protecting group was also cleaved during the course of the reaction to give the free amino ester **152a** in 18% yield.



**Scheme 55:** Achiral Brønsted acid catalyzed Friedel-Crafts reaction.

Organocatalytic enantioselective functionalization of indoles has been intensely studied.<sup>175</sup> Brønsted acid catalysts mainly dominate this field. Deng described the Friedel-Crafts reaction of indoles with aryl and alkyl imines in the presence of a cinchona alkaloid derived thiourea.<sup>176a</sup> You used the stronger BINOL-based phosphoric acids to accomplish the same reaction, however an alkyl imine did not react very efficiently and gave the product in moderate enantioselectivity.<sup>91a</sup> Hiemstra also employed chiral phosphoric acids in the Friedel-Crafts reaction of indoles and glyoxylate imines to form  $\alpha$ -amino acid derivatives.<sup>89i</sup> You synthesized  $\alpha$ -amino acid derivatives through a three-component reaction with indoles and *in situ* formed imines in the presence of a chiral phosphoric acid.<sup>176b</sup> Ma followed a similar approach using trifluoroacetaldehyde hemiacetal and amines to form the imines, which reacted with indoles in one-pot.<sup>163b</sup> Other electrophiles have also been utilized in the chiral Brønsted acid catalyzed Friedel-Crafts reaction of indoles. Among them are carbonyl compounds,<sup>163a,c-f</sup>  $\alpha,\beta$ -unsaturated carbonyl compounds<sup>177</sup> and nitroolefins.<sup>178</sup>

Based on these reports and the preliminary result shown in Scheme 55, several other achiral and chiral Brønsted acids were tested in the aminoalkylation reaction with trifluoromethyl-substituted imines. The reaction did not proceed in the absence of a catalyst, even after long reaction times (entry 1 and 2, Table 7). Also, use of 10 mol% cinchonidine (**56a**) did not lead to any desired product (entry 3). When Cbz-protected imine **151c** was reacted with indole in the presence of Takemoto's catalyst **68**, the product was formed in 12% yield, but as a racemic mixture (entry 4). The yield with sulfonamide **161** as catalyst was moderate (54%), but also gave a racemic mixture of the product (entry 5).<sup>179</sup> Diphenyl phosphate (**162**) activated imine **151c** to give 52% yield of the product (entry 6). Chiral phosphoric acid **75d** catalyzed the reaction to afford **156d** in 54% yield with an enantiomeric ratio of 68.0:32.0 at room temperature (entry 7). Stronger phosphoric acid derivative **163** yielded 65% of functionalized indole **156c**, even when the reaction was conducted at  $-40\text{ }^{\circ}\text{C}$  (entry 8).<sup>180</sup> Chiral *N*-triflyl phosphoramidate **94b** was an effective catalyst for the transformation at  $-78\text{ }^{\circ}\text{C}$ , but unfortunately the target compound was produced as an almost racemic mixture (entry 9).<sup>181</sup>

**Table 7:** Screening of various Brønsted acid catalysts in the Friedel-Crafts aminoalkylation of indole (**19a**).

| Entry <sup>a</sup> | PG         | Cat.       | Solvent                             | T [°C]    | t [h]     | Yield [%] <sup>b</sup> | er <sup>c</sup>  |
|--------------------|------------|------------|-------------------------------------|-----------|-----------|------------------------|------------------|
| 1                  | Boc        | -          | Et <sub>2</sub> O                   | rt        | 72        | -                      | -                |
| 2                  | Cbz        | -          | THF                                 | rt        | 72        | -                      | -                |
| 3 <sup>d</sup>     | Boc        | <b>56a</b> | Et <sub>2</sub> O                   | rt        | 72        | -                      | -                |
| 4                  | Cbz        | <b>68</b>  | THF                                 | rt        | 24        | 12                     | racemic          |
| 5                  | Cbz        | <b>161</b> | CH <sub>2</sub> Cl <sub>2</sub>     | rt        | 17        | 54                     | racemic          |
| 6                  | Cbz        | <b>162</b> | CH <sub>2</sub> Cl <sub>2</sub>     | rt        | 14        | 52                     | -                |
| 7                  | <b>Cbz</b> | <b>75d</b> | <b>CH<sub>2</sub>Cl<sub>2</sub></b> | <b>rt</b> | <b>14</b> | <b>54</b>              | <b>68.0:32.0</b> |
| 8                  | Cbz        | <b>163</b> | CH <sub>2</sub> Cl <sub>2</sub>     | -40       | 24        | 65                     | -                |
| 9                  | Cbz        | <b>94b</b> | CH <sub>2</sub> Cl <sub>2</sub>     | -78       | 24        | 91                     | 52.0:48.0        |

a) Reaction conditions: **19a**, **151** (1.2 equiv.) and catalyst (0.06 equiv.) were stirred in solvent (0.1 M) at the indicated temperature. b) Yield after column chromatography. c) The *R*:*S* ratio was determined by HPLC analysis using a chiral stationary phase. d) 10 mol% of catalyst was used.

Additional experiments revealed that the Friedel-Crafts reaction in the presence of a BINOL-derived phosphoric acid was completed after 3 hours at -78 °C. Some solvents were screened with the versatile TRIP catalyst **75e** and the reaction went smoothly in diethyl ether, THF and

dichloromethane to give the product in 94%, 80% and 64% yield, respectively (up to 95.5:4.5 er, entries 1-3, Table 8). The best result in terms of yield and stereoselectivity was obtained with toluene as solvent (99% yield and 96.0:4.0 er, entry 4).

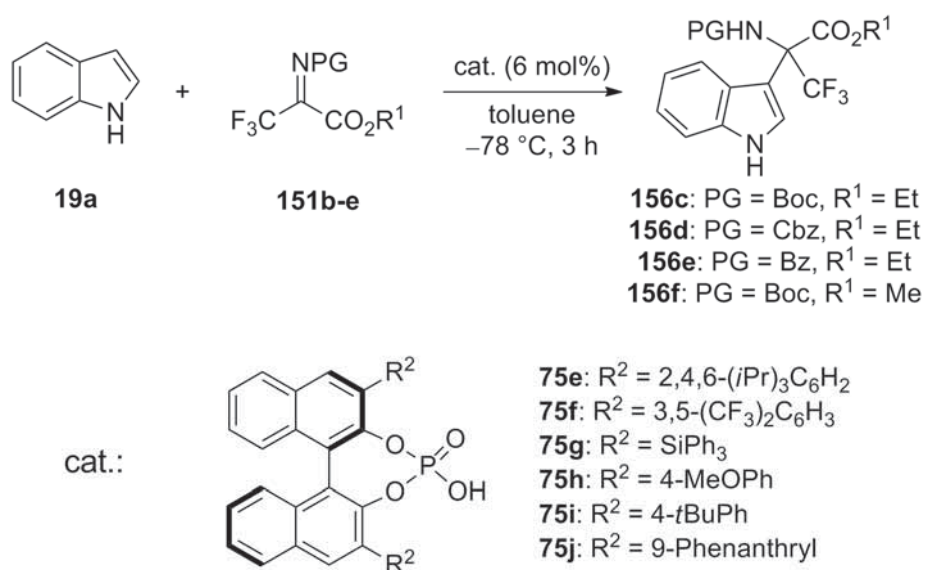
**Table 8:** Solvent screening experiments for the TRIP (**75e**) catalyzed Friedel-Crafts reaction.

Reaction scheme: Indole (**19a**) +  $\text{F}_3\text{C}-\text{C}(\text{NBoc})=\text{CO}_2\text{Et}$  (**151b**)  $\xrightarrow[\text{solvent } -78^\circ\text{C, 3 h}]{\text{75e (6 mol\%)}}$  Product (**156c**)

| Entry <sup>a</sup> | Solvent                         | Yield [%] <sup>b</sup> | er <sup>c</sup> |
|--------------------|---------------------------------|------------------------|-----------------|
| 1                  | Et <sub>2</sub> O               | 94                     | 95.0:5.0        |
| 2                  | THF                             | 80                     | 92.0:8.0        |
| 3                  | CH <sub>2</sub> Cl <sub>2</sub> | 64                     | 95.5:4.5        |
| <b>4</b>           | <b>toluene</b>                  | <b>99</b>              | <b>96.0:4.0</b> |

a)–c) as in Table 7.

Subsequent studies focused on a survey of various chiral phosphoric acids and imines. It turned out that the TRIP catalyst **75e** was by far the best for the reaction of indole (**19a**) with *N*-Boc-protected ethyl trifluoropyruvate imine **151b** (entry 1, Table 9). Alternative substitution patterns on the BINOL backbone made the reaction less efficient (16–78% yield) and less stereoselective (up to 70.0:30.0 er, entries 2–6). In some cases opposite stereomeric induction was observed (entries 2 and 4), although it remained on an unsatisfactory level. Substrates with other protecting groups on the imine nitrogen were also tested. The Cbz protecting group was tolerant to the conditions applied to give the quaternary  $\alpha$ -amino acid derivative **156d** in 71% yield and 86.5:13.5 er (entry 7). Surprisingly, when a benzoyl group was installed in the imine substrate, the product was formed in high yield but as a racemic mixture (entry 8). The use of methyl imino ester **151e** resulted in inferior results compared to the ethyl ester (entry 9).<sup>182</sup> The calcium salt of the TRIP catalyst also catalyzed the reaction between indole and *N*-Boc imine **151b**, however in lower yield (80%) and with slightly lower enantioselectivity (94.5:5.5 er). Racemic mixtures of the products were synthesized with diphenyl phosphate (**162**). The resulting racemic samples were used to find suitable separation conditions for HPLC analysis (see Chapter 4.8).

**Table 9:** Survey of chiral phosphoric acids for the Friedel-Crafts reaction.

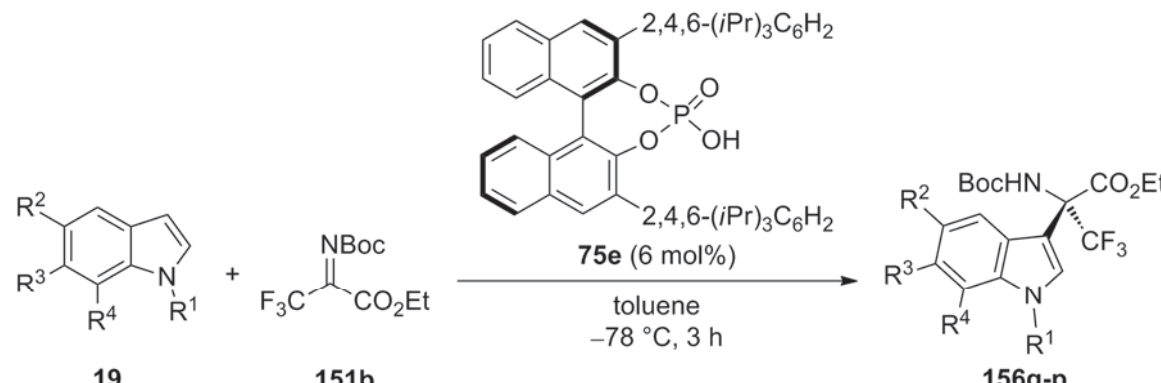
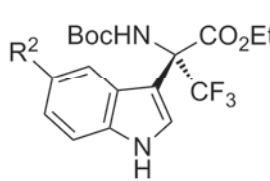
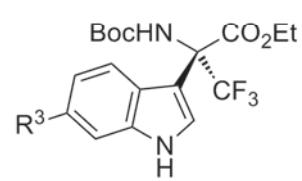
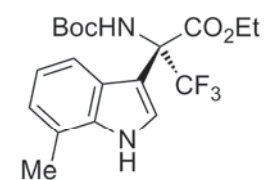
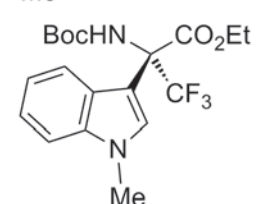
| Entry <sup>a</sup> | Catalyst             | Product     | Yield [%] <sup>b</sup> | er <sup>c</sup> |
|--------------------|----------------------|-------------|------------------------|-----------------|
| 1                  | <b>75e</b>           | <b>156c</b> | 99                     | 96.0:4.0        |
| 2                  | <b>75f</b>           | <b>156c</b> | 16                     | 37.0:63.0       |
| 3                  | <b>75g</b>           | <b>156c</b> | 37                     | racemic         |
| 4                  | <b>75h</b>           | <b>156c</b> | 25                     | 36.5:63.5       |
| 5                  | <b>75i</b>           | <b>156c</b> | 39                     | 70.0:30.0       |
| 6                  | <b>75j</b>           | <b>156c</b> | 78                     | 55.5:44.5       |
| 7                  | <b>75e</b>           | <b>156d</b> | 71                     | 86.5:13.5       |
| 8                  | <b>75e</b>           | <b>156e</b> | 96                     | racemic         |
| 9                  | <b>75e</b>           | <b>156f</b> | 73                     | 91.5:8.5        |
| 10                 | <b>75e</b> (Ca-salt) | <b>156c</b> | 80                     | 94.5:5.5        |

a)–c) as in Table 7.

The optimized conditions were then employed to expand the scope of the reaction (Table 10). It is known that the nucleophilicity of indoles strongly depends on the substitution pattern.<sup>183</sup> It was found that various substitutions were tolerated in the transformation, for example, 5-halogenated indoles gave the products in excellent yields (entries 1-3). However, in the case of 5-bromoindole the yield was slightly lower (85%, entry 3) as compared to the 5-fluoro- and 5-chloro-substituted ones (both 99%, entries 1 and 2). The enantiomeric ratios were all on the same level (96.0:4.0 er for the 5-fluoro and 95.5:4.5 for both the 5-chloro and 5-bromo derivative). Electron rich indoles also reacted readily to give the adducts in 99% yield and with high enantioselectivities (entries 4 and 5). Methyl indole-5-carboxylate needed prolonged reaction time, yielding 65% of product **156l** with an

enantiomeric ratio of 94.5:5.5 after 10 hours (entry 6). With substituents in the 6- and 7-position of the indole (entries 7-9) the reaction went smoothly, giving the best result in terms of enantioselectivity (97.5:2.5 er) for **156n**. *N*-Methyl indole reacted sluggishly and gave the product in poor yield and low enantioselectivity (entry 10). This confirms that the free N-H is necessary for coordination to the Lewis basic oxygen of the phosphoric acid, bringing the substrates in close proximity and allowing them to stereoselectively form a new C-C bond.<sup>91b,d,182</sup> Indoles with substituents in the 2-position did not react under these conditions, probably due to steric hindrance.

**Table 10:** Scope of the TRIP catalyzed Friedel-Crafts reaction.

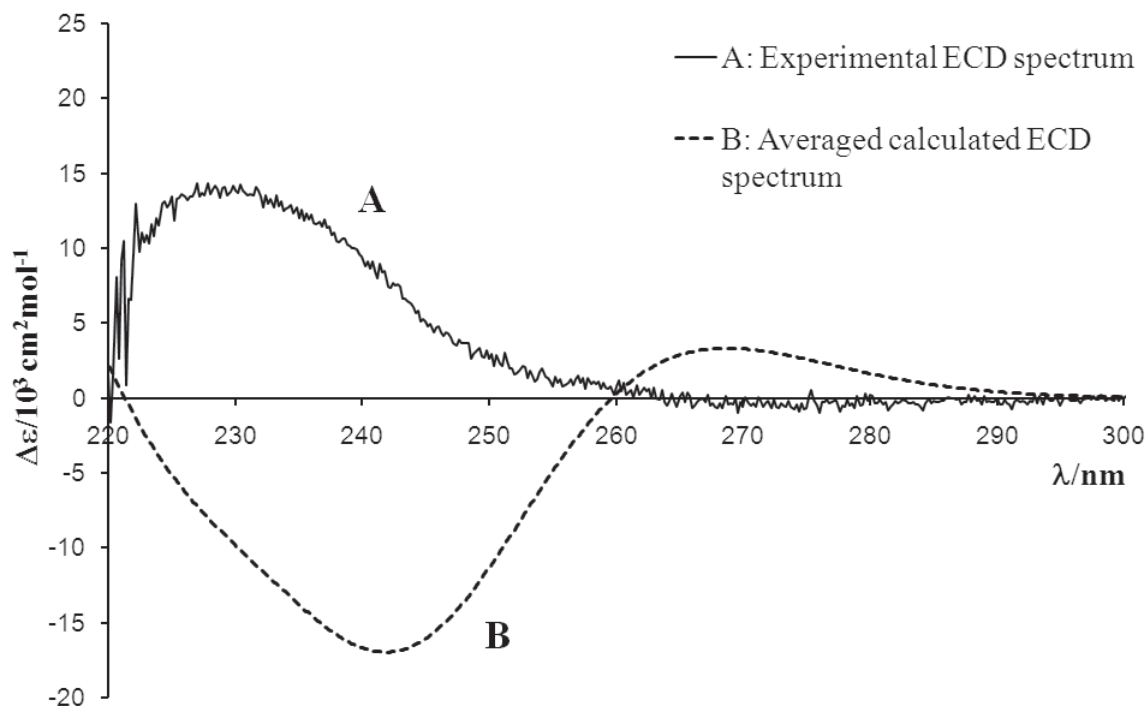
|  |                                                                                     |                                    |                 |           |
|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------|-----------------|-----------|
| Entry <sup>a</sup>                                                                 | Product                                                                             | Yield [%] <sup>b</sup>             | er <sup>c</sup> |           |
| 1                                                                                  |    | R <sup>2</sup> = F ( <b>156g</b> ) | 99              | 96.0:4.0  |
| 2                                                                                  |                                                                                     | Cl ( <b>156h</b> )                 | 99              | 95.5:4.5  |
| 3                                                                                  |                                                                                     | Br ( <b>156i</b> )                 | 85              | 95.5:4.5  |
| 4                                                                                  |                                                                                     | Me ( <b>156j</b> )                 | 99              | 94.0:6.0  |
| 5                                                                                  |                                                                                     | OMe ( <b>156k</b> )                | 99              | 93.0:7.0  |
| 6 <sup>d</sup>                                                                     |                                                                                     | CO <sub>2</sub> Me ( <b>156l</b> ) | 65              | 94.5:5.5  |
| 7                                                                                  |  | R <sup>3</sup> = F ( <b>156m</b> ) | 97              | 95.0:5.0  |
| 8                                                                                  |                                                                                     | Cl ( <b>156n</b> )                 | 98              | 97.5:2.5  |
| 9                                                                                  |  | ( <b>156o</b> )                    | 99              | 94.0:6.0  |
| 10                                                                                 |  | ( <b>156p</b> )                    | 22              | 53.5:46.5 |

a)–c) as in Table 7. d) The reaction was stopped after 10 h.

In compounds with a trifluoromethyl group directly adjacent to a stereogenic center, the possibility of self-disproportionation of enantiomers (SDE) has to be taken into account. Therefore, special care should be taken in collecting the entire product after column chromatography.<sup>184a</sup> SDE was not observed upon sublimation under high vacuum at room temperature.<sup>184b</sup>

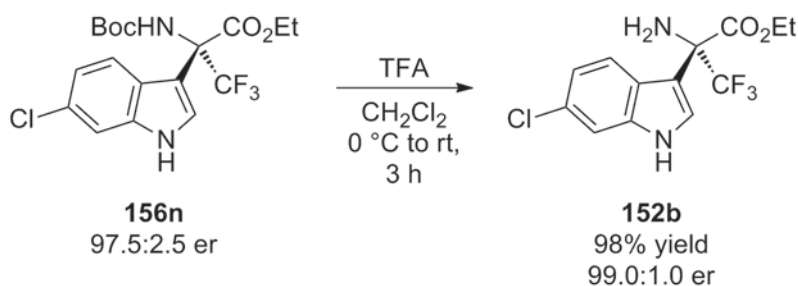
Unfortunately, although most products were solid, no suitable crystal was obtained to perform X-ray crystal structure analysis. An alternative method to determine the absolute configuration was

applied: electronic circular dichroism (ECD) spectroscopy. Hence, a conformational search for a representative example, compound (*S*)-**156c**, was performed using the program Spartan '02.<sup>185</sup> The theoretical ECD spectrum (B in Figure 26) was obtained after geometry optimization of all conformers and TD-DFT<sup>186</sup> calculations applying the B3LYP functional<sup>187</sup> and the 6-311++G\*\* basis set with the program Gaussian09.<sup>188</sup> The experimental ECD spectrum of **156c** (96.0:4.0 er) was recorded at room temperature using a  $1.08 \cdot 10^{-3}$  mol/L solution in acetonitrile (path length 0.1 cm) on an AVIV 62DS circular dichroism spectrometer (A in Figure 26). The experimental spectrum A is close to the mirror image of the Boltzmann weighted spectrum B, disclosing the absolute configuration of **156c** to be assumably *R*. The absolute configuration of the other products **156d** and **156f-p** was also assigned as *R* based on analogy and the same algebraic sign of the optical rotation (see Chapter 4.8). The theoretical calculations and plotting of the theoretical and experimental data were performed by Mersmann.<sup>182</sup>



**Figure 26:** A) Experimental ECD spectrum of **156c**. B) Averaged calculated ECD spectrum of (*S*)-**156c**.

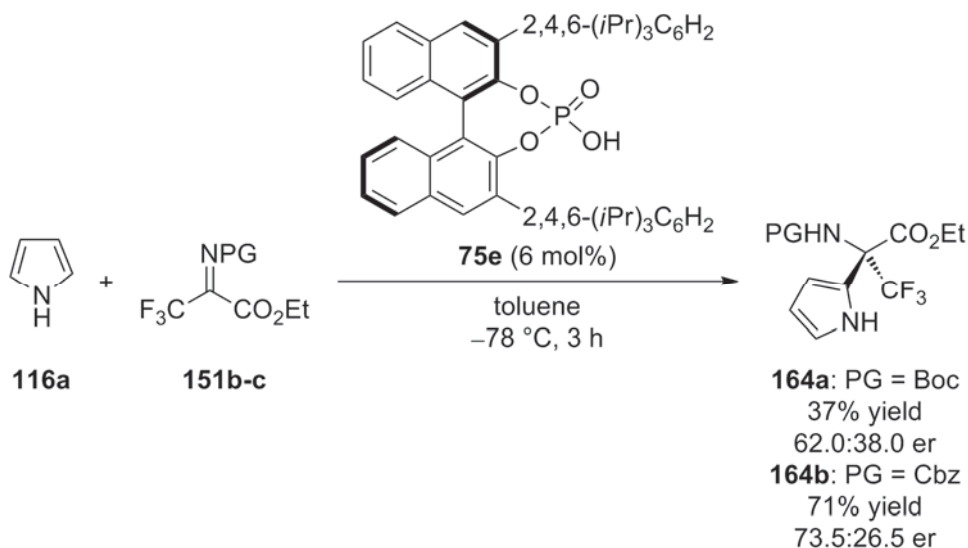
Deprotection of the 6-chloro derivative **156n** was accomplished with an excess of TFA in dichloromethane (Scheme 56). After basic workup, the free amino ester **152b** was obtained in 98% yield and without loss of stereoinformation.<sup>182</sup>



**Scheme 56:** Deprotection of **156n** with TFA to form **152b**.

These results represent the first chiral Brønsted acid catalyzed Friedel-Crafts reaction to form quaternary  $\alpha$ -amino acids bearing a trifluoromethyl group in high yields and enantioselectivities.<sup>182,189</sup>

Promising results were also obtained when pyrrole (**116a**) was employed as nucleophile in the Friedel-Crafts reaction (Scheme 57). Both *N*-Boc- and *N*-Cbz-protected imines **151b** and **151c** reacted towards 2-functionalized pyrroles **164a** and **164b** in moderate to good yields and 62.0:38.0 and 73.5:26.5 er, respectively.



**Scheme 57:** Friedel-Crafts reaction of pyrrole (**116a**).

## 2.3 Copper-Catalyzed Multicomponent Reactions

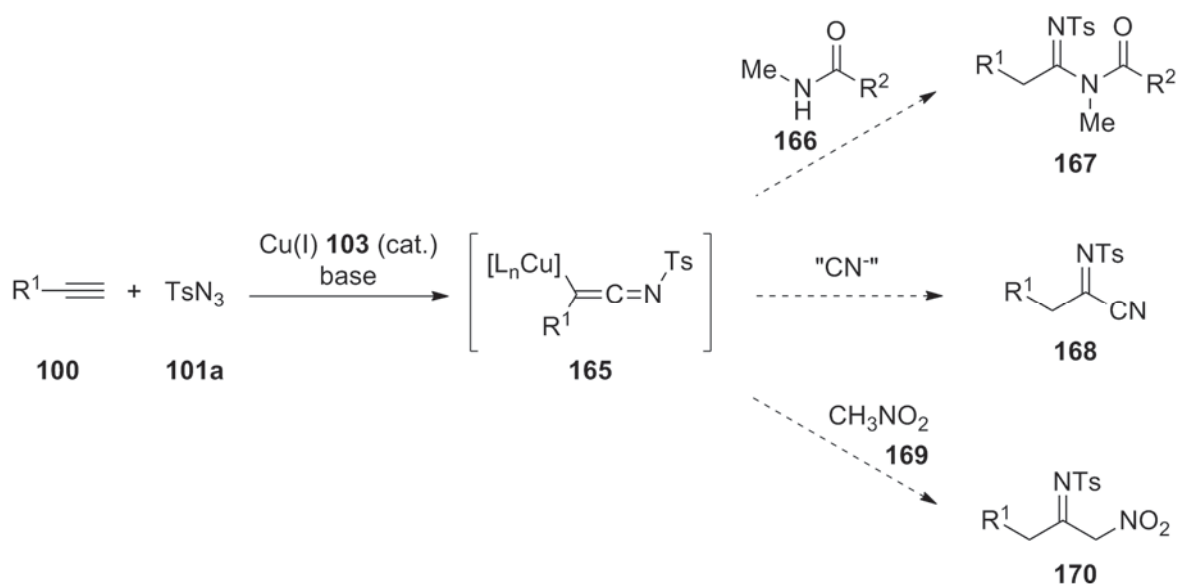
A multicomponent reaction is an important tool to construct complex molecules in one-pot. It is generally defined as a procedure where three or more substrates react to form a product, incorporating all or most of the atoms of the substrates.<sup>190</sup> MCRs are especially interesting because they offer a wide variety of products. The number of potential products increases with the  $X^{\text{th}}$  power of the number of starting materials  $N$ , *e.g.* a three-component reaction potentially gives rise to  $N^3$  products, a four-component reaction to  $N^4$  products and so on. In contrast to multistep synthesis,

this approach is much faster and efficient. MCRs are also of great interest for large scale applications because they can reduce the E factor (kg waste per kg product) and thus it is desirable to further develop this type of reactions.<sup>191</sup>

A project proposal was established in the context of an exchange program supported by the German Academic Exchange Service (DAAD). The project was to be developed at KAIST in the Republic of Korea under the supervision of Chang, and copper-catalyzed multicomponent reactions were chosen as main topic of the project.

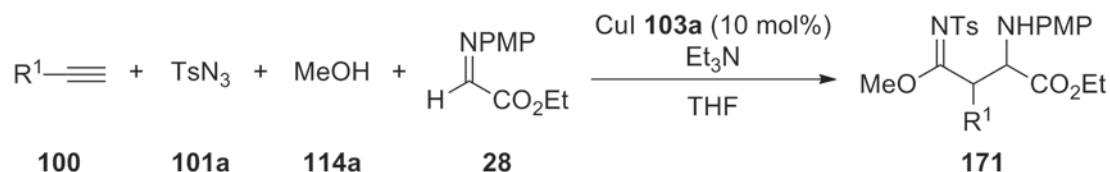
### 2.3.1 Research Objective

Chang developed highly efficient copper-catalyzed three-component reactions to produce amidines, imidates and amides by reacting terminal alkynes, sulfonyl (or phosphoryl) azides and amines, alcohols or water, respectively. Many other applications to form a wide variety of products using this approach have been described since (see Chapter 1.2). Part of this research was to focus on the exploration of alternative nucleophiles with which the intermediate ketenimine **165** could react. *N*-Nucleophiles have been widely used (see Chapter 1.2.1) and it was envisaged that *N*-methyl amides **166** could serve as suitable substrates to form adduct **167** (Scheme 58). Interestingly, very few examples are known where *C*-nucleophiles are utilized (see Chapter 1.2.3). Here, the use of cyanide should be examined to potentially form **168**, which could serve as a precursor for  $\alpha$ -keto acids. Other interesting nucleophiles could be nitroalkanes. They would readily be deprotonated under the reaction conditions and might react with the ketenimine **165** to form  $\beta$ -nitro imines **170**.



**Scheme 58:** Potential alternative *N*- and *C*-nucleophiles in the copper-catalyzed three-component reaction.

As our research on this project started, merely one example of copper-catalyzed four-component reaction involving CuAAC was known. In that case, ethyl glyoxylate served as a suitable electrophile to form  $\alpha$ -functionalized imidates. This project focused on a survey of alternative electrophiles with  $\alpha$ -imino ester **28** as probable example to form the desired adducts **171** (Scheme 59).



**Scheme 59:**  $\alpha$ -Imino ester **28** as electrophile in the copper-catalyzed four-component reaction.

### 2.3.2 In Search of Alternative Nucleophiles for the Copper-Catalyzed Three-Component Coupling Reaction

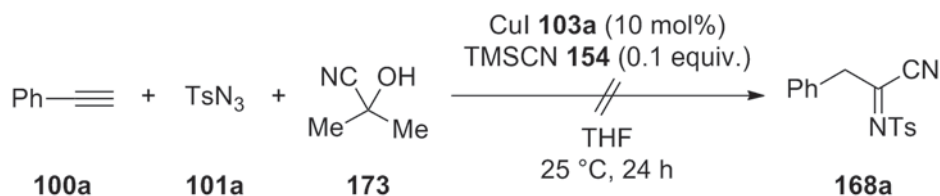
Prior results obtained by Chang showed that the use of amides in the three-component coupling reaction did not lead to the desired compounds. Therefore, more electron rich amides were tested. *N*-Methylamides **166a** and **166b** were reacted with phenylacetylene (**100a**) and tosyl azide (**101a**) (synthesized from tosyl chloride and sodium azide)<sup>192</sup> in the presence of copper(I) iodide in THF but no target compound was formed (entries 1 and 2, Table 11). Furthermore, the addition of bases like triethylamine, DABCO, DMAP or DBU did not lead to the desired product (entries 3–6). Changing the solvent from THF to dichloromethane did not have any effect (entry 7). When 2,6-lutidine was utilized as base, 41% yield of triazole **172** was obtained after column chromatography (entry 8). This is in accordance with the results that were obtained for the synthesis of *N*-sulfonyl-1,2,3-triazoles.<sup>105a</sup>

**Table 11:** *N*-Methyl amides **166a–b** as nucleophiles in the three-component reaction.

| Entry <sup>a</sup> | Base              | Product     | Conversion [%] <sup>b</sup>    |
|--------------------|-------------------|-------------|--------------------------------|
| 1                  | -                 | <b>167a</b> | <1                             |
| 2                  | -                 | <b>167b</b> | <1                             |
| 3                  | Et <sub>3</sub> N | <b>167a</b> | <1                             |
| 4                  | DABCO             | <b>167a</b> | <1                             |
| 5                  | DMAP              | <b>167a</b> | <1                             |
| 6                  | DBU               | <b>167a</b> | decomposition, complex mixture |
| 7 <sup>c</sup>     | Et <sub>3</sub> N | <b>167a</b> | <1                             |
| 8                  | 2,6-lutidine      | <b>172</b>  | 41 <sup>d</sup>                |

a) Reaction conditions: **100a** (0.5 mmol), **101a** (0.6 mmol), **166** (0.6 mmol), **103a** (0.05 mmol) and base (0.6 mmol) were stirred in THF (1.5 mL) at 25 °C. b) The conversion was determined by <sup>1</sup>H NMR spectroscopy of the crude product with 1,1,2,2-tetrachloroethane as internal standard. c) Dichloromethane was used as solvent. d) Yield after column chromatography.

Acetone cyanohydrin (**173**) is a convenient cyanide source and was utilized in the copper-catalyzed three-component reaction in an attempt to synthesize adduct **168a** (Scheme 60).<sup>193a</sup> The addition of catalytic amount trimethylsilyl cyanide (**154**) should accelerate the reaction and presumably deliver a free cyanide anion *in situ*.<sup>193b</sup> Unfortunately, no desired product was obtained.

**Scheme 60:** Attempt to use cyanide as a nucleophile in the three-component reaction.

Additional attempts to form C-C bonds with a *C*-nucleophile in the three-component reaction were undertaken with nitromethane. Nitromethane is deprotonated by triethylamine and thus envisaged to be present as a nucleophilic anion under the basic reaction conditions. Surprisingly, no product was formed with copper(I) sources in various solvents (entries 1-7, Table 12). TBTA (**113**) is often used in copper(I) mediated processes to accelerate the catalysis.<sup>111c</sup> Even the addition of this ligand did

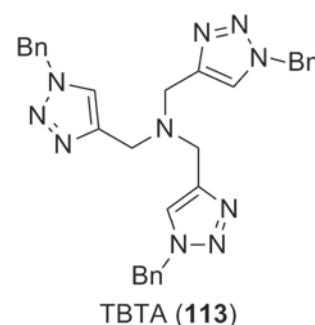
not have an effect on the outcome of the reaction (entries 3 and 4). When Cu(OTf)<sub>2</sub> was used as catalyst, no conversion was observed.

**Table 12:** Nitromethane (**169**) as nucleophile in the three-component reaction.

|                                                                                                                                                                                                                                                                                         |             |            |             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------|-------------|
| $\text{Ph}-\text{C}\equiv\text{C}-\text{H} + \text{TsN}_3 + \text{CH}_3\text{NO}_2 \xrightarrow[\text{solvent, 25 } ^\circ\text{C, 12 h}]{[\text{Cu}] (10 \text{ mol\%}), \text{Et}_3\text{N} (1.2 \text{ equiv.})} \text{Ph}-\text{CH}_2-\text{CH}(\text{NTs})-\text{CH}_2\text{NO}_2$ |             |            |             |
| <b>100a</b>                                                                                                                                                                                                                                                                             | <b>101a</b> | <b>169</b> | <b>170a</b> |

| Entry <sup>a</sup> | [Cu]                 | Solvent                         | Conversion [%] <sup>b</sup> |
|--------------------|----------------------|---------------------------------|-----------------------------|
| 1                  | CuCl                 | CHCl <sub>3</sub>               | <1                          |
| 2                  | CuCl                 | THF                             | <1                          |
| 3 <sup>c</sup>     | CuCl                 | CHCl <sub>3</sub>               | <1                          |
| 4 <sup>c</sup>     | CuCl                 | CH <sub>3</sub> NO <sub>2</sub> | <1                          |
| 5                  | CuI                  | CHCl <sub>3</sub>               | <1                          |
| 6                  | CuI                  | CH <sub>3</sub> NO <sub>2</sub> | <1                          |
| 7 <sup>d</sup>     | CuI                  | THF                             | <1                          |
| 8                  | Cu(OTf) <sub>2</sub> | CHCl <sub>3</sub>               | <1                          |



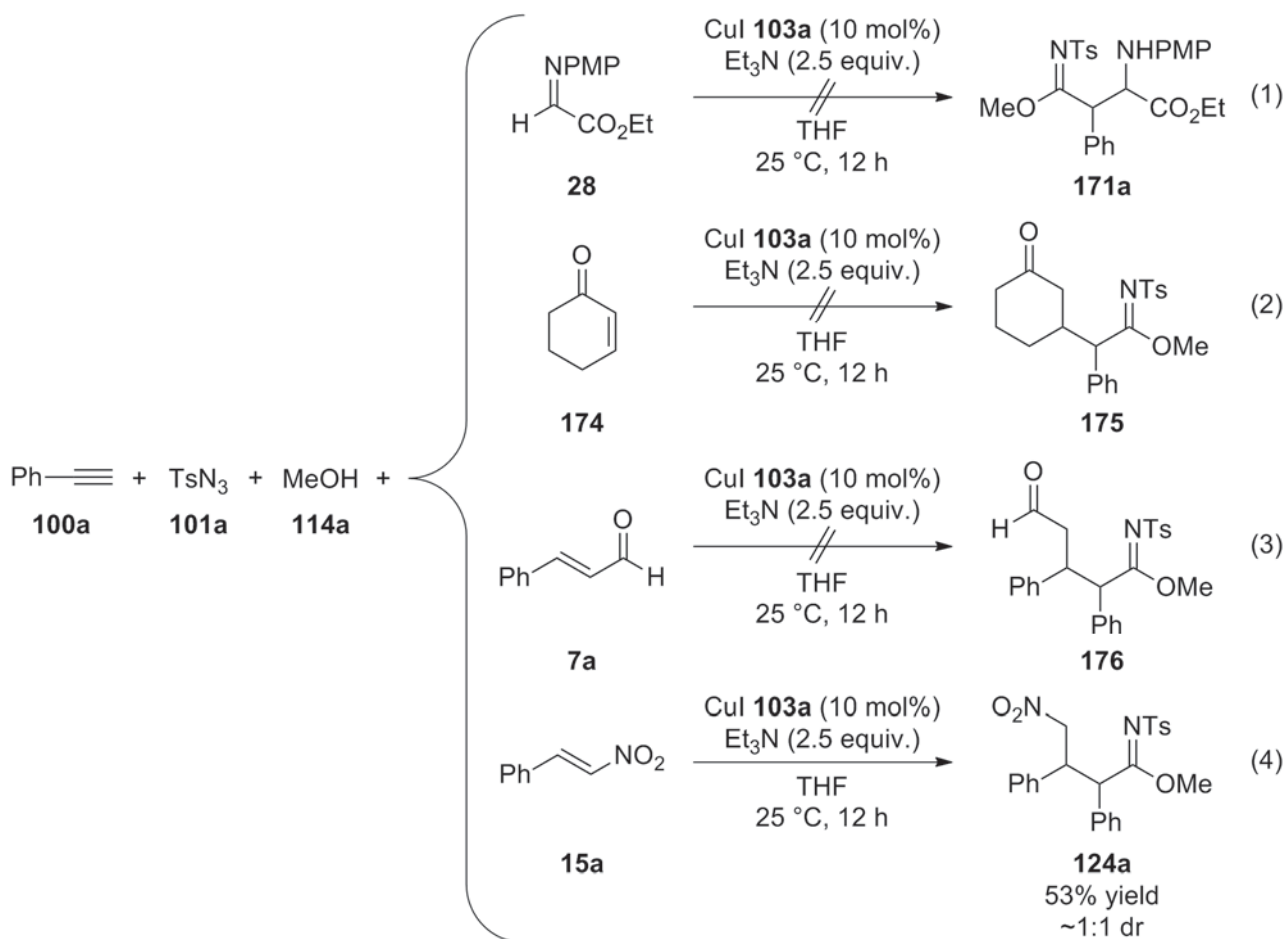
a) Reaction conditions: **100a** (0.5 mmol), **101a** (0.6 mmol), **169** (0.6 mmol), [Cu] (0.05 mmol) and Et<sub>3</sub>N (0.6 mmol) were stirred in solvent (1.5 mL) at 25 °C. b) The conversion was determined by <sup>1</sup>H NMR spectroscopy of the crude product with 1,1,2,2-tetrachloroethane as internal standard. c) 10 mol% of TBTA was added. d) A preformed mixture of CH<sub>3</sub>NO<sub>2</sub>/Et<sub>3</sub>N/THF was added.

The search for alternative nucleophiles in the copper-catalyzed three-component remained unsuccessful and the focus of the research was therefore redirected towards copper-catalyzed four-component reactions.

### 2.3.3 Nitroolefins as Suitable Electrophiles in the Copper-Catalyzed Four-Component Coupling Reaction

Initial experiments on the search for alternative electrophiles were conducted using the reaction conditions for the four-component coupling of terminal alkynes, sulfonyl azides, alcohols and ethyl glyoxylate as described by Chang (see Scheme 34, Chapter 1.2.4).<sup>122</sup> *N*-PMP-protected imine glyoxylate **28** was prepared according to a procedure described in the literature,<sup>194</sup> but its use did not lead to the target compound **171a** (eq. (1) in Scheme 61). Recently, Barbas III used α,β-unsaturated carbonyl compounds in the organocatalyzed α-functionalization of preformed

imidates and this prompted us to further investigate these types of Michael acceptors as electrophiles in the copper-catalyzed four-component reaction.<sup>121</sup> Although cyclohexenone (**174**) and cinnamaldehyde (**7a**) did not react towards the desired four-component product **175** or **176**, respectively (eq. (2) and (3)),  $\beta$ -nitrostyrene (**15a**) was a suitable electrophile and furnished  $\alpha$ -functionalized imidate **124a** in 53% yield in the initial attempt (eq. (4)).



**Scheme 61:** Various electrophiles in the copper-catalyzed four-component reaction.

Additional experiments were then conducted to optimize the yield of this reaction. Copper(I) iodide (**103a**) was disclosed as best Cu(I) source among others tested and gave the desired product in 65% yield after 12 hours in THF (entries 1-4, Table 13). In this case, 13% of the unfunctionalized three-component coupling product was also isolated. Copper(II) triflate catalyzed the transformation as well, but gave the  $\gamma$ -nitro imidate **124a** in only 17% yield (entry 5). Other etheral solvents were tested with copper(I) iodide as catalyst, but this led to lower yields of the product (entries 6 and 7). In a nonpolar solvent like *n*-hexane, the reaction was fully inhibited (entry 8). Chlorinated solvents and protic solvents were also not suitable for the reaction (entries 9-11). Among various amines tested, DBU showed no conversion whereas trioctylamine gave a satisfactory yield of 65% (entries 12 and 13). However, triethylamine was the base of choice due to the lower cost and easier work-up

procedure. When the reaction time was extended to 24 hours with copper(I) iodide as catalyst, triethylamine as base and THF as solvent, the yield improved to 73% and no three-component coupling product was detected (entry 14).<sup>123a</sup>

**Table 13:** Effect of Cu-source, solvent and base on the four-component reaction.

Reaction scheme:  $\text{Ph-C}\equiv\text{C-H} + \text{TsN}_3 + \text{MeOH} + \text{Ph-CH=CH-NO}_2 \xrightarrow[\text{solvent, 25 } ^\circ\text{C, time}]{[\text{Cu}] (10 \text{ mol\%}), \text{base} (3.0 \text{ equiv.})} \text{Product 124a}$

100a      101a      114a      15a      124a

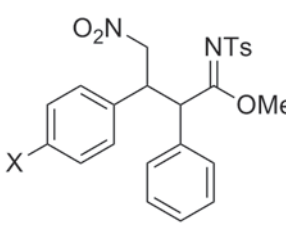
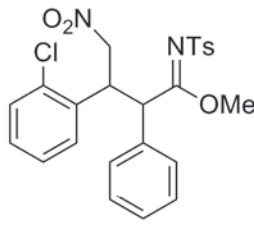
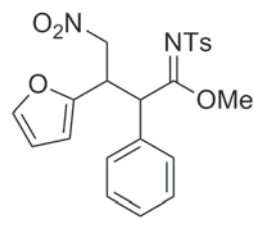
| Entry <sup>a</sup> | [Cu]                 | Solvent                         | Base                   | Time [h]  | Yield [%] <sup>b</sup> |
|--------------------|----------------------|---------------------------------|------------------------|-----------|------------------------|
| 1                  | CuI                  | THF                             | Et <sub>3</sub> N      | 12        | 65 (13) <sup>c</sup>   |
| 2                  | CuCl                 | THF                             | Et <sub>3</sub> N      | 12        | 59                     |
| 3                  | CuBr                 | THF                             | Et <sub>3</sub> N      | 12        | 60                     |
| 4                  | CuCN                 | THF                             | Et <sub>3</sub> N      | 12        | <1                     |
| 5                  | Cu(OTf) <sub>2</sub> | THF                             | Et <sub>3</sub> N      | 12        | 17                     |
| 6                  | CuI                  | Et <sub>2</sub> O               | Et <sub>3</sub> N      | 12        | 41                     |
| 7                  | CuI                  | 1,4-dioxane                     | Et <sub>3</sub> N      | 12        | 58                     |
| 8                  | CuI                  | <i>n</i> -hexane                | Et <sub>3</sub> N      | 12        | <1                     |
| 9                  | CuI                  | CH <sub>2</sub> Cl <sub>2</sub> | Et <sub>3</sub> N      | 12        | 25                     |
| 10                 | CuI                  | CHCl <sub>3</sub>               | Et <sub>3</sub> N      | 12        | 33                     |
| 11                 | CuI                  | MeOH                            | Et <sub>3</sub> N      | 12        | <1                     |
| 12                 | CuI                  | THF                             | DBU                    | 12        | <1                     |
| 13                 | CuI                  | THF                             | Oct <sub>3</sub> N     | 12        | 65                     |
| <b>14</b>          | <b>CuI</b>           | <b>THF</b>                      | <b>Et<sub>3</sub>N</b> | <b>24</b> | <b>73</b>              |

a) Reaction conditions: **100a** (0.6 mmol), **101a** (0.6 mmol), **114a** (2.5 mmol), **15a** (0.5 mmol), [Cu] (0.05 mmol) and base (1.5 mmol) were stirred in solvent (1.5 mL) at 25 °C. b) Yield after column chromatography. c) The yield of unfunctionalized imidate (*i.e.* the three-component coupling product) is given in brackets.

The optimized conditions were then used to investigate the scope of the Michael acceptor **15**. Electronic variations in the 4-position of the phenyl ring of the nitroolefin did not have a great influence on the yield, nor did they affect the *syn:anti* ratio much (entries 1-6, Table 14). When *trans*-2-chloro- $\beta$ -nitrostyrene was used, a slight increase in the *syn:anti* ratio was observed, which can be explained by the higher steric demand close to the newly formed stereocenter (entry 7). This is in agreement with previous findings by Kobayashi.<sup>119</sup> A heterocycle containing electrophile was also tolerated to give the product in 61% yield and 57:43 *syn:anti* ratio (entry 8). The two

diastereoisomers of compound **124f** were separated by column chromatography allowing for unambiguous assignments of the NMR signals to the *syn* and *anti* conformers of the product.<sup>123</sup>

**Table 14:** Copper-catalyzed four-component reaction with variation of nitroolefin **15**.

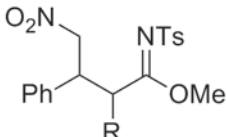
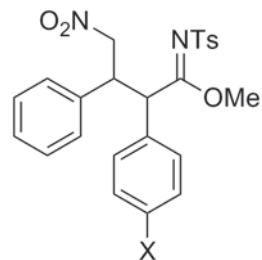
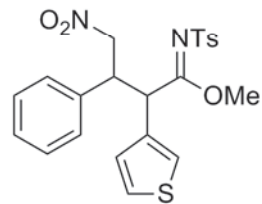
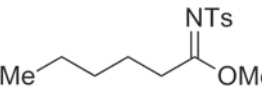
| $  \text{Ph}-\text{C}\equiv\text{C}-\text{H} + \text{TsN}_3 + \text{MeOH} + \text{R}-\text{CH}=\text{CH}-\text{NO}_2 \xrightarrow[\text{THF, 25 } ^\circ\text{C, 24 h}]{\text{CuI } \mathbf{103a} \text{ (10 mol\%)}, \text{Et}_3\text{N (3.0 equiv.)}} \text{O}_2\text{N}-\text{CH}_2-\text{CH}(\text{R})-\text{CH}(\text{Ph})-\text{C}(\text{OMe})=\text{N}-\text{Ts}  $ |                                                                                     |                        |                              |               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------|------------------------------|---------------|
| <b>100a</b>                                                                                                                                                                                                                                                                                                                                                                | <b>101a</b>                                                                         | <b>114a</b>            | <b>15</b>                    | <b>124a-h</b> |
| Entry <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                         | Product                                                                             | Yield [%] <sup>b</sup> | <i>syn:anti</i> <sup>c</sup> |               |
| 1                                                                                                                                                                                                                                                                                                                                                                          |    | X = H ( <b>124a</b> )  | 73                           | 58:42         |
| 2                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     | F ( <b>124b</b> )      | 69                           | 54:46         |
| 3                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     | Cl ( <b>124c</b> )     | 60                           | 56:44         |
| 4                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     | Br ( <b>124d</b> )     | 65                           | 54:46         |
| 5                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     | Me ( <b>124e</b> )     | 58                           | 57:43         |
| 6                                                                                                                                                                                                                                                                                                                                                                          |                                                                                     | MeO ( <b>124f</b> )    | 62                           | 55:45         |
| 7                                                                                                                                                                                                                                                                                                                                                                          |   | ( <b>124g</b> )        | 61                           | 66:34         |
| 8                                                                                                                                                                                                                                                                                                                                                                          |  | ( <b>124h</b> )        | 61                           | 57:43         |

a) Reaction conditions: **100a** (0.6 mmol), **101a** (0.6 mmol), **114a** (2.5 mmol), **15** (0.5 mmol), **103a** (0.05 mmol) and Et<sub>3</sub>N (1.5 mmol) were stirred in THF (1.5 mL) at 25 °C. b) Yield after column chromatography. c) Determined by <sup>1</sup>H NMR spectroscopy.

Subsequent investigations explored the variation of the terminal alkyne. Different substitution patterns on phenylacetylene were tolerated to give the target compounds **124i–l** in good yields and levels of diastereoselectivities of around 3:2 (entries 1-4, Table 15). When a more bulky electron-donating substituent in the 4-position of the phenylacetylene was used, the yield dropped slightly, whereas the *syn:anti* ratio increased little (entry 5). 3-Ethynylthiophene participated smoothly in the four-component reaction (entry 6). As expected, aliphatic terminal alkynes merely reacted towards the unfunctionalized three-component imidate **115a** (entry 7).<sup>122</sup> This can be explained by the lower

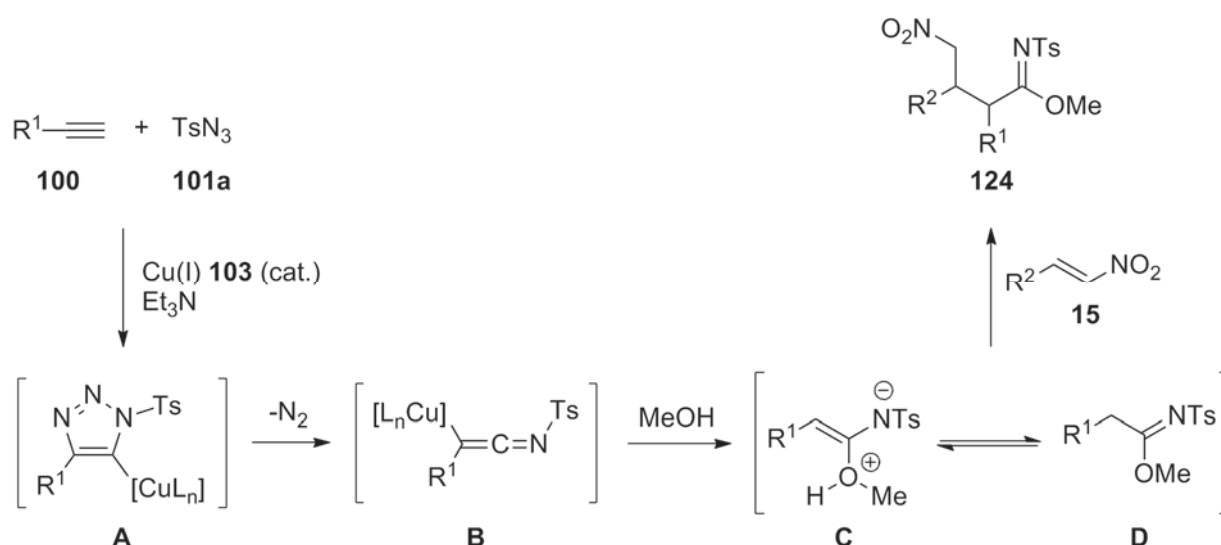
acidity of the  $\alpha$ -proton, thus the electronic nature of compound **115a** inhibits the Michael addition.<sup>123</sup>

**Table 15:** Variation of terminal alkyne **100** in the four-component reaction.

| $  \begin{array}{c}  \text{R}-\text{C}\equiv\text{C} + \text{TsN}_3 + \text{MeOH} + \text{Ph}-\text{CH}=\text{CH}-\text{NO}_2 \xrightarrow[\text{25 } ^\circ\text{C, 24 h}]{\text{CuI } \mathbf{103a} \text{ (10 mol\%)} \\ \text{Et}_3\text{N (3.0 equiv.)} \\ \text{THF}}  \end{array}  $ |                                                                                     |             |                                 |  |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------|---------------------------------|--|-------------------------------------------------------------------------------------|--|
| <b>100</b>                                                                                                                                                                                                                                                                                  | <b>101a</b>                                                                         | <b>114a</b> | <b>15a</b>                      |  | <b>124i-n</b>                                                                       |  |
| Entry <sup>a</sup>                                                                                                                                                                                                                                                                          | Product                                                                             |             | Yield [%] <sup>b</sup>          |  | <i>syn:anti</i> <sup>c</sup>                                                        |  |
| 1                                                                                                                                                                                                                                                                                           |    |             | X = F ( <b>124i</b> )           |  | 67                                                                                  |  |
| 2                                                                                                                                                                                                                                                                                           |                                                                                     |             | Me ( <b>124j</b> )              |  | 64                                                                                  |  |
| 3                                                                                                                                                                                                                                                                                           |                                                                                     |             | CF <sub>3</sub> ( <b>124k</b> ) |  | 73                                                                                  |  |
| 4                                                                                                                                                                                                                                                                                           |                                                                                     |             | PhO ( <b>124l</b> )             |  | 74                                                                                  |  |
| 5                                                                                                                                                                                                                                                                                           |                                                                                     |             | <i>t</i> Bu ( <b>124m</b> )     |  | 56                                                                                  |  |
| 6                                                                                                                                                                                                                                                                                           |   |             | <b>(124n)</b>                   |  | 69                                                                                  |  |
| 7                                                                                                                                                                                                                                                                                           |  |             | <b>(115a)</b>                   |  | 80                                                                                  |  |

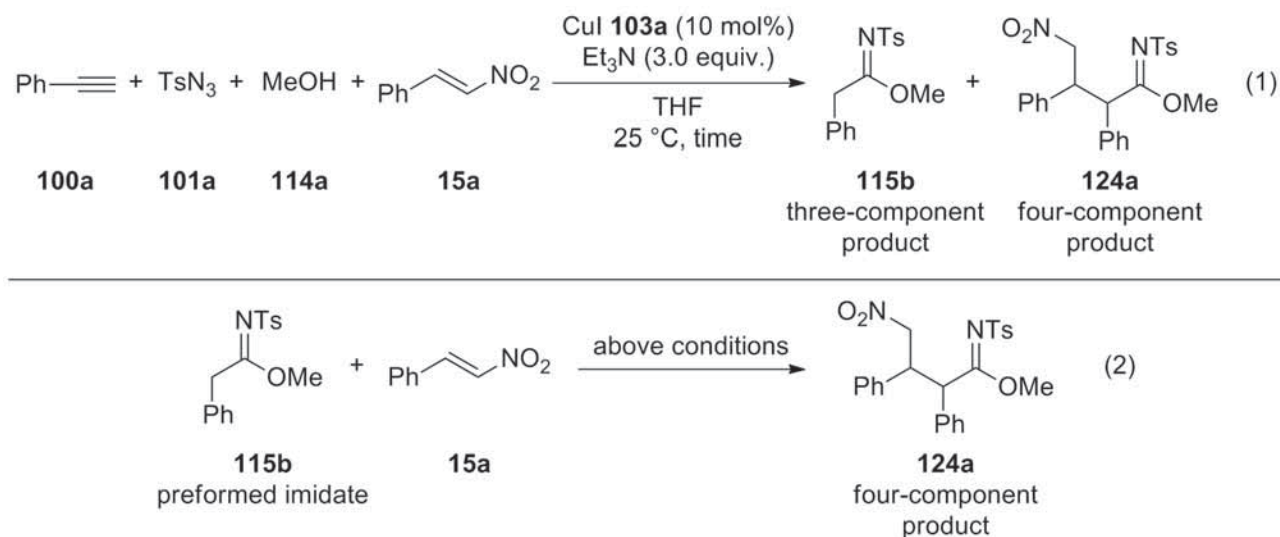
a)–c) as in Table 14.

A plausible mechanism for the copper-catalyzed four-component reaction is depicted in Figure 27. After formation of the triazole **A** by a CuAAC reaction of terminal alkyne **100**, tosyl azide (**101a**), triethylamine and a copper(I) source, a ring-opening rearrangement and loss of nitrogen leads to the ketenimine intermediate **B**. Methanol attacks this electrophilic species to give a Michael donor adduct **C**, which is in equilibrium with structure **D**. In case that the  $\alpha$ -proton is sufficiently acidic, which is not the case when R<sup>1</sup> constitutes an aliphatic moiety (entry 7, Table 15), a Michael addition to nitroolefin **15** can occur and the  $\alpha$ -functionalized four-component product **124** is formed.<sup>123a</sup>



**Figure 27:** Proposed mechanistic pathway for the four-component reaction.

To gain further mechanistic insight, two experimental approaches towards the formation of the four-component product **124a** were set up by Na. The first represented the experimental procedure as described in Table 14 (eq. (1) in Scheme 62). The other approach used preformed imidate **115b** and  $\beta$ -nitrostyrene (**15a**) under the same conditions (eq. (2) in Scheme 62). In all cases, the reaction was stopped after 30 min, 1, 2, 3, 4, 6, 8, 10, 12, 20 and 24 hours, respectively. The yield was then determined by  $^1H$  NMR spectroscopy with 1,1,2,2-tetrachloroethane as internal standard.<sup>123a,195</sup>



**Scheme 62:** Two experimental approaches towards the four-component product **124a**.

The cumulated results obtained by this study are displayed in Figure 28. The data points obtained from equation (1) are shown as  $\blacklozenge$  and  $\blacksquare$ . The dashed grey line represents the formation of the three-component product which is generated prior to the four-component product (unbroken grey line). The four-component product generation starting from the preformed imidate **115b** (data points are displayed as  $\blacktriangle$ , unbroken black line) was very similar to that of the one-pot procedure, suggesting

that the Michael addition of imidate **115** to the nitroolefin **15a** is likely to be the rate-determining step in the copper-catalyzed four-component reaction.<sup>123a</sup>

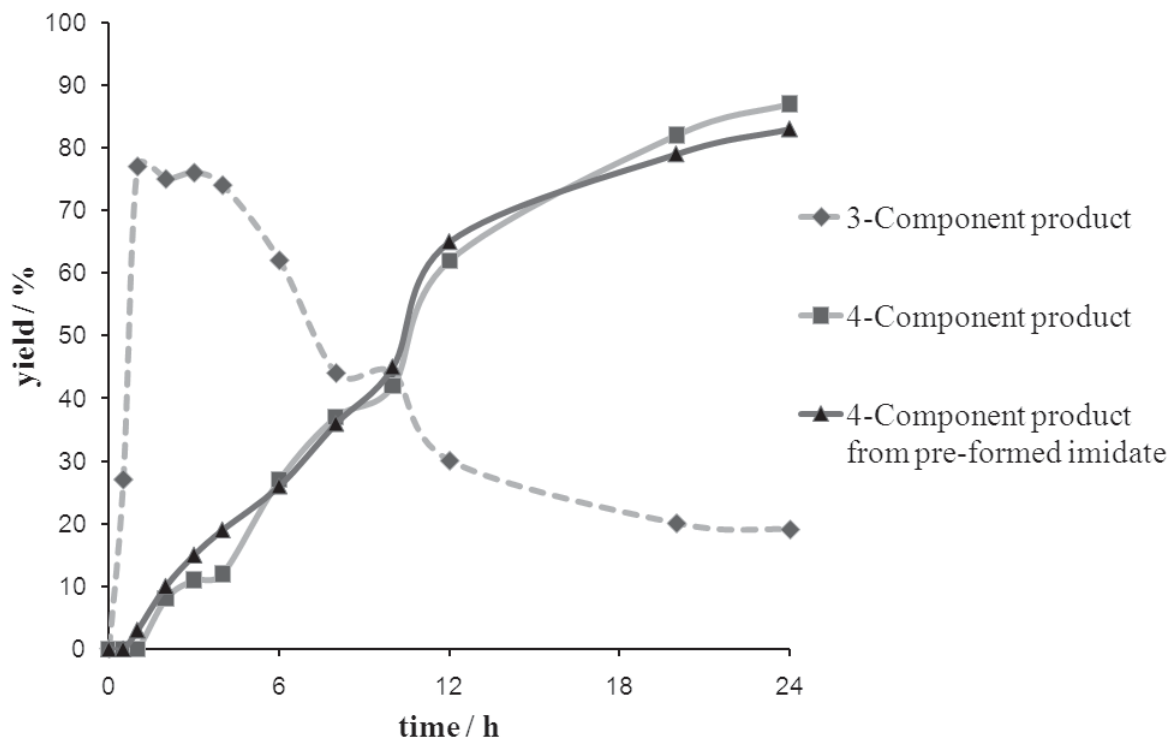
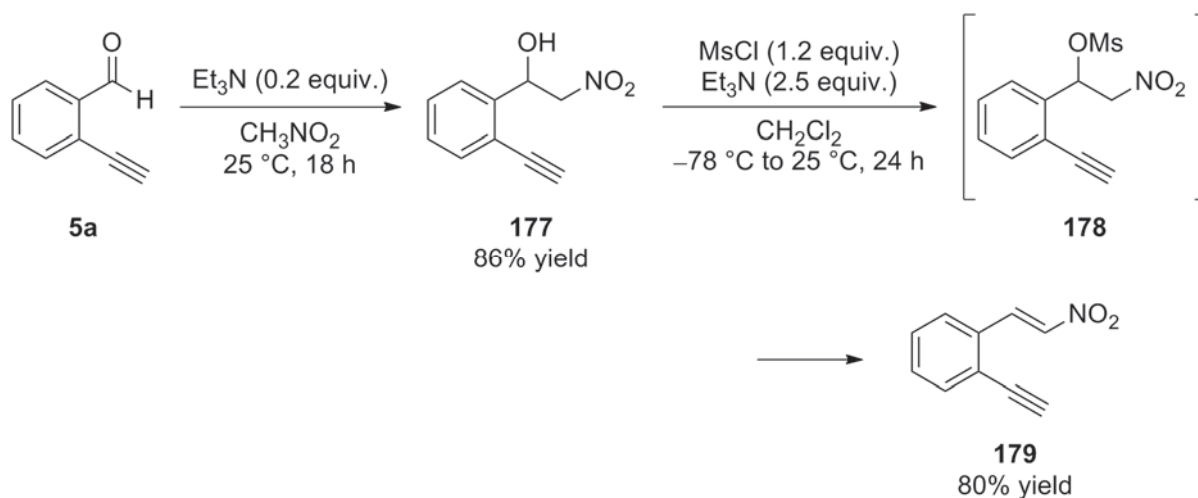


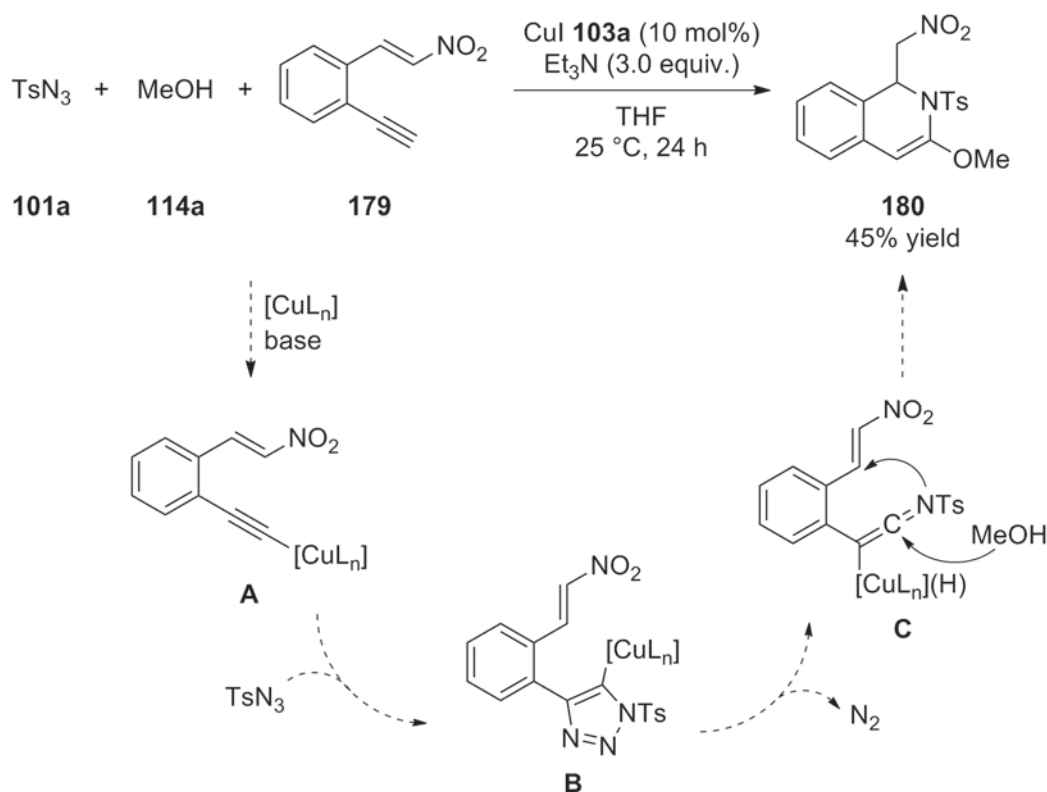
Figure 28: Comparative reaction profiles.

It was envisaged that the bifunctional substrate **179** could lead to an interesting product under the copper-catalyzed multicomponent reaction conditions (Scheme 63). A Henry reaction between 2-ethynylbenzaldehyde (**5a**) and nitromethane in the presence of submolar amounts of triethylamine gave the nitro alcohol **177** in 86% yield. This was immediately converted with mesyl chloride in the presence of a base to form intermediate **178**, which transformed into (*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (**179**).<sup>123a,196</sup>



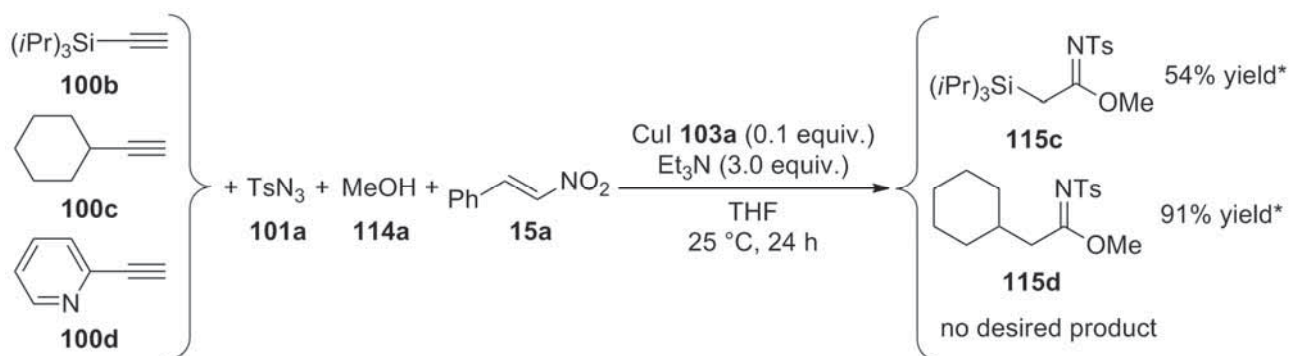
Scheme 63: Synthesis of (*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (**179**).

An interesting intramolecular reaction took place when compound **179** was reacted with tosyl azide (**101a**) and methanol (**114a**) in the presence of triethylamine and copper(I) iodide (**103a**) (Scheme 64). Heterocyclic 1,2-dihydroisoquinoline **180** was obtained in moderate yield and the reaction is assumed to follow the proposed pathway. It involves copper-acetylide species **A** and triazole intermediate **B**. After ketenimine formation, methanol attacks the electrophilic ketenimine carbon center to trigger the subsequent Michael addition reaction, which eventually leads to the target compound.<sup>123a</sup>



**Scheme 64:** Synthesis of 1,2-dihydroisoquinoline **180** including a plausible mechanistic pathway.

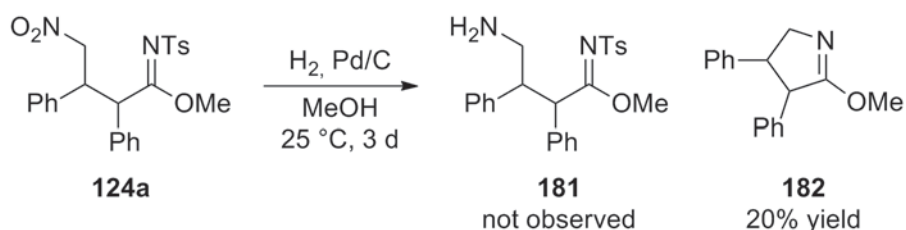
In further investigations to find terminal alkynes that do not bear an aromatic ring or that possess other interesting properties, substrates **100b–d** were tested (Scheme 65). (Triisopropylsilyl)-acetylene (**100b**) and cyclohexylacetylene (**100c**) merely reacted towards the unfunctionalized three-component reaction products **115c** and **115d**, respectively. No multicomponent coupling product was detected when 2-ethynylpyridine (**100d**) was used as substrate.



**Scheme 65:** Alternative terminal alkynes in the copper-catalyzed multicomponent reaction.

\* Determined by <sup>1</sup>H NMR spectroscopy with 1,1,2,2-tetrachloroethane as internal standard.

Surprisingly, in a single attempt to reduce compound **124a** with molecular hydrogen in the presence of catalytic amounts of palladium on carbon, no primary amine **181** was obtained, but cyclized imidate **182** was isolated, albeit in low yield (Scheme 66). Further experiments will be necessary to obtain this interesting product in sufficient quantity as to allow for complete characterization.



**Scheme 66:** Cyclization upon reduction of γ-nitro imidate **124a**.



---

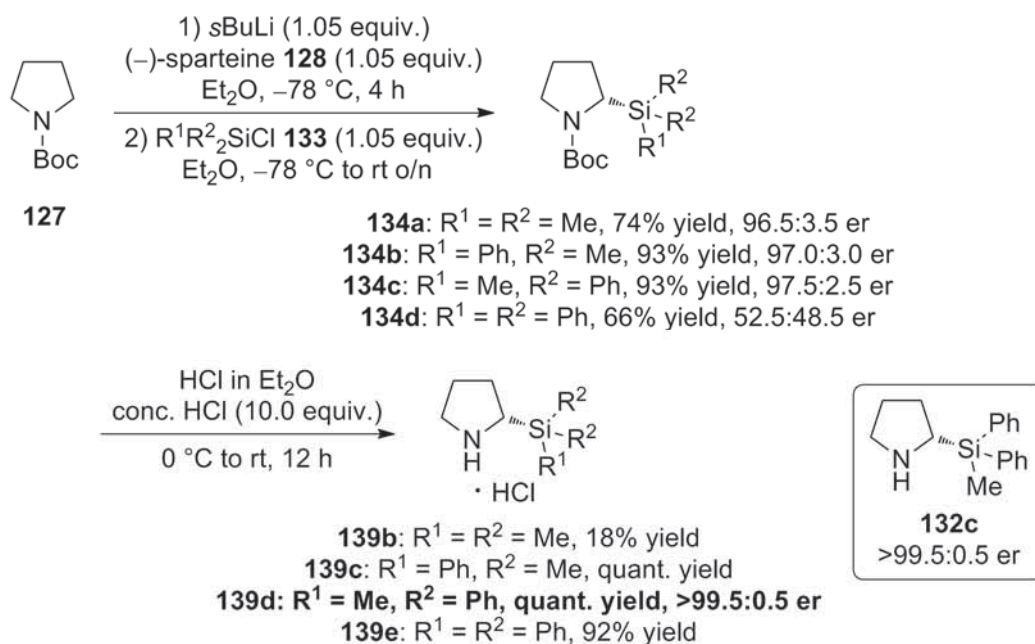
## 3 Summary and Outlook

---

Metal catalysis has been established as a viable concept for efficient transformations in organic chemistry over the past decades. Since 2000, organocatalysis has complemented other fields of catalysis and has become an especially important approach in asymmetric synthesis. This work focused on the asymmetric synthesis of silylated pyrrolidines and their application as organocatalysts. Also, the enantioselective synthesis of quaternary  $\alpha$ -amino acid derivatives bearing a trifluoromethyl moiety by chiral Brønsted acid catalysis was accomplished. The last project concentrated on the development of copper-catalyzed multicomponent reactions.

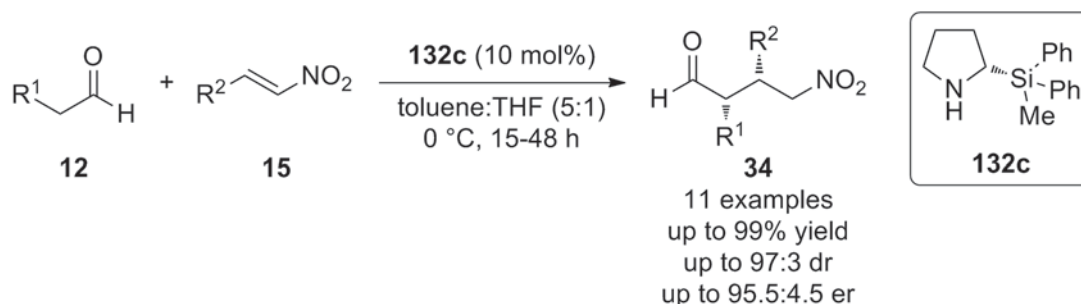
### 3.1 Synthesis and Application of Silylated Pyrrolidines

Silylated pyrrolidines were envisaged as potent organocatalysts due to their similarity to many well-established Lewis base catalysts. Silicon-containing compounds are ubiquitous in organic chemistry, but often in catalysis a bulky silyl group merely serves as a protecting group. An organocatalyst where the silicon is directly attached to the pyrrolidine moiety was prior to this work unprecedented. A synthetic method, originally developed by Beak, was employed to effect asymmetric  $\alpha$ -silylation of *N*-Boc-pyrrolidine (**127**).<sup>131–135</sup> Various triorganylsilyl chlorides **133** reacted after selective deprotonation of *N*-Boc-pyrrolidine (**127**) with *s*BuLi and (–)-sparteine (**128**) to give the target compounds **134a–d** (Scheme 67). High yields and enantioselectivities were obtained in all cases except when triphenylsilyl chloride was applied as an electrophile. Acid mediated deprotection of the *N*-Boc-protected pyrrolidines **134** gave the corresponding hydrochloric salts **139b–e**. (*S*)-(Diphenylmethylsilyl)pyrrolidine hydrochloric salt (**139d**) could be recrystallized to obtain enantiopure samples which were treated with base to afford the corresponding free amine **132c**.<sup>143</sup> A limitation of this method is the use of stoichiometric amounts of (–)-sparteine (**128**). It has not been commercially available for over a year and only few practicable surrogates have been developed.<sup>197</sup>



**Scheme 67:** Asymmetric synthesis of silylated pyrrolidines.

Silylated pyrrolidine **132c** was then successfully applied as organocatalyst in the Michael addition of aldehyde **12** to nitroolefin **15**. The reaction was tolerant towards various substrates to give an array of  $\gamma$ -nitro aldehydes **34** in high yields, dia- and enantioselectivities (Scheme 68).<sup>143</sup>



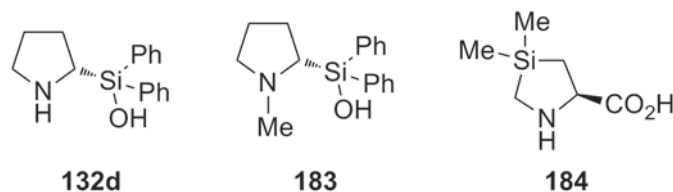
**Scheme 68:** Use of silylated pyrrolidine **132c** as organocatalyst in the Michael addition of aldehyde **12** to nitroolefin **15**.

In conclusion, enantiomerically pure (*S*)-2-(diphenylmethylsilyl)pyrrolidine (**132c**) was synthesized in high yield by asymmetric synthesis. Its absolute configuration was determined by X-ray crystal structure analysis of the HCl salt. This Lewis base type catalyst bearing a silyl group directly attached to the pyrrolidine ring was successfully applied in asymmetric Michael addition reactions. The steric bulk and electronic properties of silicon play a pivotal role in the catalytic cycle.<sup>143</sup> Unfortunately, compound **132c** did not induce enantioselectivity in the Michael reaction between hydroxyacetone and  $\beta$ -nitrostyrene or the Mannich reaction between cyclohexanone and a preformed imine. Further investigations are necessary to fully understand the interactions between the catalyst and substrates.

Initial experiments were conducted to form  $\beta$ -amino silanol **132d** (Figure 29). The proton of this silanol should be more acidic than its carbinol analog, which would make it a stronger hydrogen bond donor. This feature is of great interest in asymmetric catalytic reactions. Moreover, transformation of **132d** with  $\text{BH}_3\cdot\text{THF}$  might lead to a siloxazaborolidine which could be considered as the silicon analog of the established Corey-Bakshi-Shibata catalyst.<sup>198</sup>

Moreover, amino alcohols are effective ligands in metal catalyzed reactions. Tertiary amino silanol **183** might be synthesized by reduction of the corresponding *N*-Boc derivative.<sup>199</sup> This compound could serve as a ligand in various asymmetric transformations, for example in zinc-mediated additions to carbonyl or imine compounds.<sup>200</sup> Zinc could play an additional role of inhibiting siloxane formation as was shown by Strohmann.<sup>201</sup> The desymmetrization of *meso*-anhydrides might also be catalyzed by this type of catalyst.<sup>71</sup>

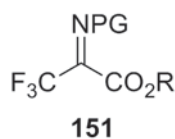
Earlier work focused on the synthesis of silaproline **184**.<sup>202,203</sup> Here, the silicon is positioned  $\beta$  to the nitrogen in the pyrrolidine ring. The synthesis of this amino acid was achieved in its protected form and ongoing work focuses on the cleavage of the protecting group to obtain the free amino acid **184**. It will then be tested in common reactions that are Lewis base catalyzed.



**Figure 29:** Various silicon-containing compounds with potentially interesting properties.

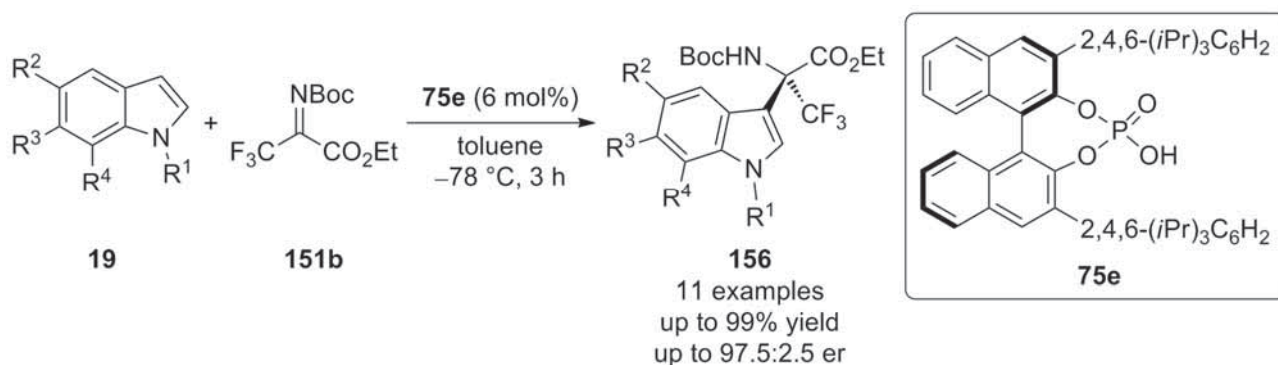
### 3.2 Enantioselective Organocatalytic Synthesis of Quaternary $\alpha$ -Amino Acid Derivatives Bearing a $\text{CF}_3$ Moiety

The second part of this work focused on organocatalytic synthesis of quaternary  $\alpha$ -trifluoromethyl  $\alpha$ -amino acid derivatives. Trifluoropyruvate imines **151** were selected as prochiral precursors for this purpose (Figure 30). They were generated following a method described by Burger.<sup>165b,169</sup>



**Figure 30:** Trifluoropyruvate derived imine **151**.

Chiral phosphoric acids were suitable catalysts in the asymmetric Friedel-Crafts aminoalkylation of indoles **19** (Scheme 69). Excellent yields and enantioselectivities of the protected  $\alpha$ -amino acid **156** were achieved with broad tolerance of indole substitution.<sup>182</sup>

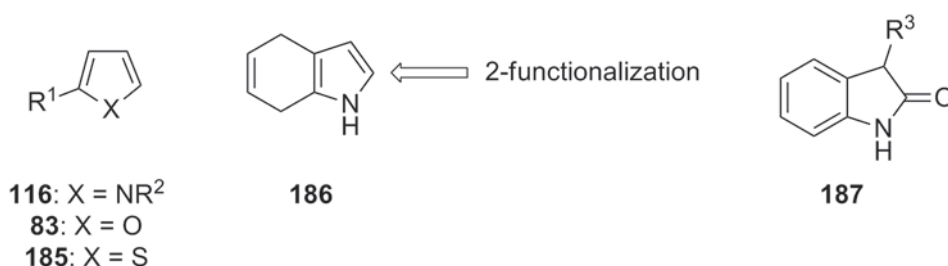


**Scheme 69:** Chiral phosphoric acid catalyzed Friedel-Crafts reaction with trifluoropyruvate derived imines **151b**.

The absolute configuration of a representative example was determined by comparison of calculated and measured ECD spectra and was assigned as *R*. Deprotection of the 6-chloro derivative with TFA was also demonstrated. The corresponding amino ester was obtained in 98% yield without loss of stereoinformation.<sup>182</sup>

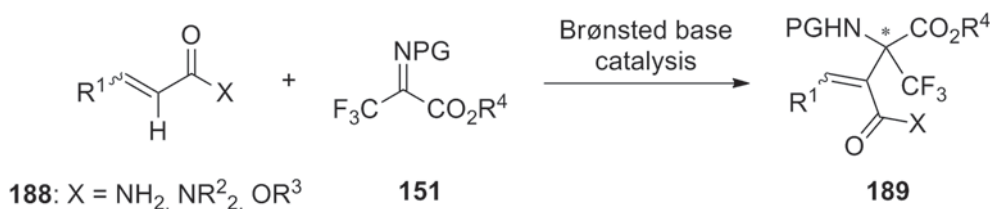
Initial experiments were performed with pyrrole as nucleophile in the Friedel-Crafts reaction. The 2-functionalized pyrroles were furnished in up to 71% yield and up to 73.5:26.5 er. Further investigations will focus on the optimization of this Brønsted acid catalyzed reaction and the use of alternative 5-membered heterocycles like furan **83** and thiophene **185** (Figure 31). Moreover, the Friedel-Crafts reaction of 4,7-dihydroindole (**186**) would be desirable to form 2-functionalized indole derivatives after oxidation.<sup>163f,177g,178b</sup>

Other types of activation might be implemented when oxindole **187** is employed. Various Lewis and Brønsted bases will be tested to effect enantioselective transformations with this substrate. If compound **187** bears a substituent in the 3-position, two adjacent quaternary stereogenic centers would be formed after reaction with trifluoropyruvate imines. The structural motif of oxindole is common in a variety of bioactive molecules and stereoselective organocatalytic synthesis of such fluorine-containing structures would be desirable.<sup>204</sup>



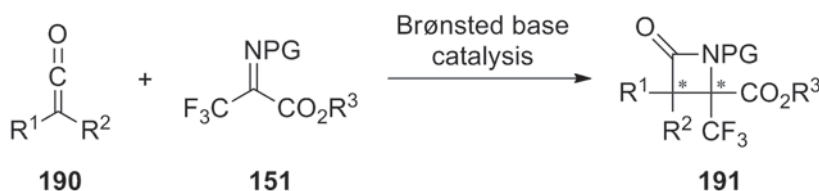
**Figure 31:** Various substrates for Friedel-Crafts reactions and oxindole **187**.

An extremely powerful reaction to form compounds with high functional density is the Morita-Baylis-Hillman reaction.<sup>27j,205</sup> The asymmetric version of an aza-Morita-Baylis-Hillman reaction with trifluoropyruvate imine **151** would be of great interest (Scheme 70). The transformation could be catalyzed by cinchona alkaloids or other Brønsted base catalysts.



**Scheme 70:** The aza-Morita-Baylis-Hillman reaction with trifluoropyruvate imine **151**.

The first asymmetric synthesis of  $\beta$ -trifluoromethyl- $\beta$ -lactones has recently been realized by Ye. A chiral *N*-heterocyclic carbene was used as a catalyst to perform a highly stereoselective formal [2+2] cycloaddition of ketenes and trifluoromethyl ketones.<sup>206</sup> When imines are employed in the Staudinger synthesis,  $\beta$ -lactams are generated and some stereoselective organocatalytic approaches have been demonstrated by Lectka, Fu, Ye and others.<sup>207</sup> The catalysts used in their work or compounds with similar properties might activate the substrates to stereoselectively form  $\beta$ -trifluoromethyl- $\beta$ -lactam derivatives **191** when trifluoropyruvate imine **151** is employed (Scheme 71).

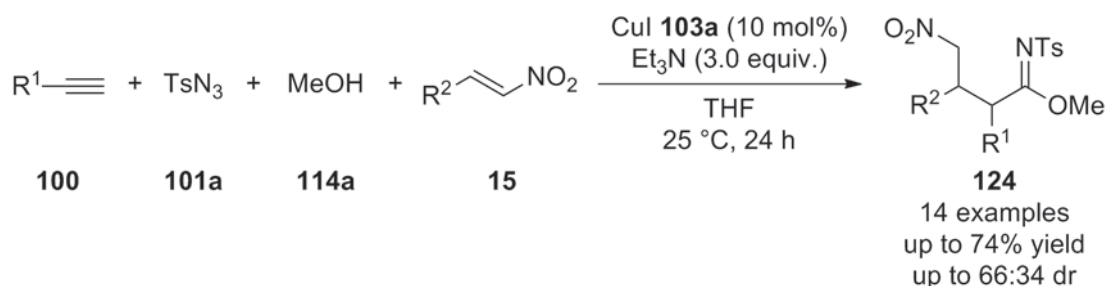


**Scheme 71:** The Staudinger cycloaddition of ketene **190** and trifluoropyruvate imine **151**.

### 3.3 Copper-Catalyzed Multicomponent Reactions

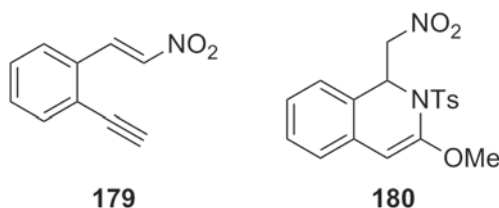
The last project that was described in this work dealt with the development of copper-catalyzed multicomponent reactions.  $\beta$ -Nitrostyrenes **15** were found as suitable electrophiles in a four-component reaction. In this transformation, terminal alkyne **100** and tosyl azide (**101a**) react towards a reactive ketenimine intermediate in the presence of catalytic amounts copper(I) iodide (**103a**) and triethylamine as base. Methanol then attacks the ketenimine to form an imidate which subsequently reacts in a Michael-type addition with the nitroolefin to form the target compound **124** in yields of up to 74% (Scheme 72). The reaction was tolerant of a wide variety of terminal alkynes and nitroolefins. However, alkyl-substituted alkynes merely yielded the unfunctionalized three-

component imidate.  $^1\text{H}$  NMR experiments were performed to further understand the mechanism of this reaction and it was concluded that the Michael addition of the imidate to the nitroolefin is most likely to be the rate-determining step. The reduction of the  $\gamma$ -nitro imidates with molecular hydrogen in the presence of catalytic amounts of palladium on carbon led to an interesting cyclized imidate. This reaction should be further investigated to improve the yield and substrate scope.



**Scheme 72:** Copper-catalyzed four-component reaction to form  $\alpha$ -functionalized imidates **124**.

An interesting intramolecular example was discovered when (*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (**179**) was employed (Figure 32). 1,2-Dihydroisoquinoline derivative **180** was formed in 45% yield under the multicomponent reaction conditions.

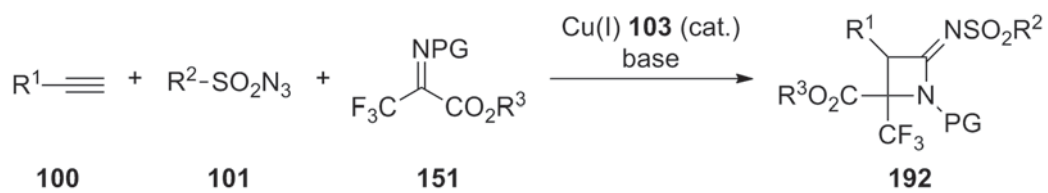


**Figure 32:** (*E*)-1-Ethynyl-2-(2-nitrovinyl)benzene (**179**) and 1,2-dihydroisoquinoline derivative **180**.

Future work could focus on the development of an enantioselective version of this transformation. Preliminary experiments with common chiral ligands for copper-catalysis (*e.g.* bisoxazoline ligands) showed no stereinduction. This means that the copper does not seem to play a crucial role in the stereoselective bond forming process or the product racemizes under the reaction conditions. If the latter can be ruled out, it would be desirable to find a chiral catalyst that does not inhibit the copper-catalyzed imidate formation and leads to the desired stereinduction in the addition step. Recent progress on unifying metal- and organocatalysis may be a promising starting point for this challenge.<sup>98</sup>

Fokin found appropriate conditions for the formal [2+2] cycloaddition of the ketenimine intermediate and aldimines.<sup>116a</sup> Trifluoropyruvate imines **151** might also serve as suitable substrate to form trifluoromethyl-substituted azetidinimines **192** (Scheme 73). Alternatively, when an additional nucleophilic alcohol is added (as in the above described four-component reaction),

$\beta$ -trifluoromethyl imidates might be formed. It would also be desirable to investigate the biological properties of such fluorine-containing compounds.



**Scheme 73:** Copper-catalyzed [2+2] cycloaddition with trifluoropyruvate imine **151**.



---

## 4 Experimental Section

---

### 4.1 General Methods and Chemicals

All air- or moisture-sensitive reactions were carried out under argon using standard Schlenk and vacuum line techniques.<sup>208</sup> Glassware was heated under high vacuum with a heat gun and flushed with argon. Sensitive chemicals were kept under argon in a glove-box or refrigerator.

#### 4.1.1 Solvents

Solvents for anhydrous reactions were dried and purified according to standard techniques.<sup>142</sup>

|                 |                                                                                |
|-----------------|--------------------------------------------------------------------------------|
| Acetone         | HPLC grade acetone was dried over MS 4 Å.                                      |
| Acetonitrile    | was purchased from Sigma-Aldrich and used as supplied.                         |
| Chloroform      | distilled from calcium hydride under an argon atmosphere.                      |
| Dichloromethane | distilled from calcium hydride under an argon atmosphere.                      |
| Diethyl ether   | distilled from sodium (or Solvona) and benzophenone under an argon atmosphere. |
| Methanol        | was purchased from Sigma-Aldrich and used as supplied.                         |
| THF             | distilled from sodium (or Solvona) and benzophenone under an argon atmosphere. |
| Toluene         | distilled from sodium (or Solvona) and benzophenone under an argon atmosphere. |

Dichloromethane, diethyl ether, ethyl acetate, *n*-hexane, methanol and *n*-pentane for column chromatography were distilled before use.

#### 4.1.2 Chromatography

Column chromatography was carried out using silica gel 40-63 µm. Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (silica gel 60 F<sub>254</sub>) and visualized with UV radiation at 254 nm, iodine, by staining with a basic aqueous solution of

potassium permanganate ( $\text{KMnO}_4$ ), an acidic aqueous solution of ammonium molybdate tetrahydrate  $[(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}] \cdot 4\text{H}_2\text{O}$  and cerium sulfate tetrahydrate  $[\text{Ce}(\text{SO}_4)] \cdot 4\text{H}_2\text{O}$  or a solution of ninhydrin in *n*-BuOH/AcOH.

## 4.2 Determination of the Physical Data

### Melting Points

Melting points were measured in open glass capillaries on a Büchi B-540 apparatus and are uncorrected.

### HPLC Analysis

HPLC analysis was performed on an Agilent 1100-series or Agilent 1200-series system using chiral stationary phases from Chiral Technologies Ltd.

### Optical Rotation

Optical rotations were measured on a Perkin Elmer PE-241 instrument at room temperature and are given in  $\text{deg} \cdot \text{cm}^3 \cdot \text{g}^{-1} \cdot \text{dm}^{-1}$ . The measurements were carried out using a light frequency of 589 nm (D-line of a sodium vapor lamp) in a cuvette (length  $d = 10$  cm). The concentration  $c$  is given in  $\text{g} \cdot 100 \text{ mL}^{-1}$ .

### $^1\text{H}$ NMR Spectroscopy

$^1\text{H}$  NMR spectra were recorded on a Varian Mercury 300 (300 MHz), a Varian Inova 400 (400 MHz), a Bruker FT AM 400 (400 MHz) or a Varian Unity 500 (500 MHz) spectrometer and are reported as follows: chemical shift  $\delta$  (ppm) (multiplicity, coupling constant  $J$  (Hz), number of protons). Chemical shifts are referenced to the appropriate solvent peak or  $\delta = 0.00$  ppm for tetramethylsilane.<sup>209</sup> The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet. Coupling constants are given in Hertz to the nearest 0.1 Hz. Unless otherwise stated the  $^1\text{H}$  NMR spectra were recorded at room temperature.

### **<sup>13</sup>C NMR Spectroscopy**

<sup>13</sup>C NMR spectra were recorded on a Varian Mercury 300 (75 MHz), a Varian Inova 400 (100 MHz), a Bruker FT AM 400 (100 MHz) or a Varian Unity 500 (125 MHz) spectrometer. Chemical shifts are quoted in parts per million relative to the appropriate solvent peak or  $\delta = 0.00$  ppm for tetramethylsilane.<sup>209</sup> Coupling constants are given in Hertz to the nearest 0.1 Hz. Assignment of spectra was carried out using DEPT, COSY and HETCOR experiments. Unless otherwise stated the <sup>13</sup>C NMR spectra were recorded at room temperature.

### **<sup>19</sup>F NMR Spectroscopy**

<sup>19</sup>F NMR spectra were recorded on a Varian Mercury 300 (282 MHz) or a Varian Inova 400 (376 MHz) spectrometer. Chemical shifts are quoted in parts per million.

### **<sup>29</sup>Si NMR Spectroscopy**

<sup>29</sup>Si NMR spectra were recorded on a Varian Unity 500 (99 MHz) spectrometer. Chemical shifts are quoted in parts per million.

### **IR Spectroscopy**

IR spectra were recorded on a Perkin-Elmer PE 1760 FT spectrometer. Only adsorption bands with intensity >50% are reported and quoted in wavenumbers (cm<sup>-1</sup>).

### **Mass Spectrometry**

Mass spectra (EI and CI) were obtained on a Varian MAT 212 or a Finnigan SSQ 7000. The peaks are given in *m/z* and the intensity is given as a percentage of the base peak. ESI spectra were acquired on a Thermo Scientific LTQ Orbitrap XL. High resolution mass spectra were recorded on a Finnigan MAT 95 (EI) or a Thermo Scientific LTQ Orbitrap XL (ESI) spectrometer.

## Elemental Analysis

Elemental analysis was performed using a Heraeus CHN-O-Rapid or an Elementar Vario EL instrument. All values are given as mass percentages.

## 4.3 Synthesis of Substrates

The following compounds were synthesized according to literature procedures:

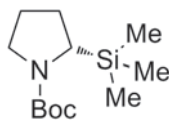
- *N*-PMP-protected imine glyoxylate **28**<sup>194</sup>
- Jørgensen-Hayashi catalyst **32a**<sup>43</sup>
- 4-Methoxy-*N*-(4-nitrobenzylidene)aniline (**60a**)<sup>210</sup>
- Tosyl azide (**101a**)<sup>192</sup>
- *N*-Boc-pyrrolidine (**127**)<sup>140</sup>
- *tert*-Butoxydiphenylsilyl chloride (**133b**)<sup>148</sup>
- Ethyl trifluoropyruvate imines **151b–d**<sup>165b</sup>

## 4.4 Synthesis of *N*-Boc-Protected Silylated Pyrrolidines

### *General Procedure A*

To a solution of (–)-sparteine (**128**) (5.2 g, 22 mmol, 1.05 equiv.) in Et<sub>2</sub>O (30 mL) at –78 °C was added *s*BuLi (16.9 mL, 22 mmol, 1.3 M, solution in cyclohexane:hexane 92:8, 1.05 equiv.) dropwise. After 15 min a solution of *N*-Boc-pyrrolidine (**127**) (3.6 g, 21 mmol) in Et<sub>2</sub>O (20 mL) was added and the reaction mixture was stirred for 4 h. The appropriate silicon electrophile (22 mmol, 1.05 equiv.) in Et<sub>2</sub>O (20 mL) was then added by syringe pump (20 mL/h). The resulting yellow solution was kept at –78 °C overnight and was then stopped by addition of 5% H<sub>3</sub>PO<sub>4</sub>-solution. The aqueous phase was washed with Et<sub>2</sub>O (3x 40 mL) and the combined organic extracts were dried over MgSO<sub>4</sub>, filtered, evaporated *in vacuo* and the crude product was purified by column chromatography.

The same procedure was applied for the synthesis of racemic silylated pyrrolidines using TMEDA instead of (–)-sparteine.

**(S)-N-tert-Butoxycarbonyl-2-(trimethylsilyl)pyrrolidine (134a)**

Prepared from *N*-Boc-pyrrolidine (**127**) and trimethylsilyl chloride according to general procedure A and obtained as a colorless oil in 74% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 95:5; R<sub>f</sub> = 0.24).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 99:1, 0.5 mL/min, *t*<sub>ret</sub>: 8.2 (*R*), 8.6 (*S*) min.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ = 0.02 (s, 9H), 1.43 (s, 9H), 1.65-1.85 (m, 3H), 1.90-2.05 (m, 1H), 3.05-3.32 (m, 2H), 3.35-3.60 (m, 1H) ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 55 °C):** δ = 0.05 (s, 9H), 1.46 (s, 9H), 1.72-1.82 (m, 3H), 1.93-2.06 (m, 1H), 3.11-3.19 (m, 1H), 3.22-3.30 (m, 1H), 3.45-3.57 (m, 1H) ppm.

**<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):** δ = 0.20 (s, 9H), 1.50-1.60 (m, 12H), 1.70-1.83 (m, 1H), 3.09-3.25 (m, 2H), 3.45-3.60 (m, 1H) ppm.

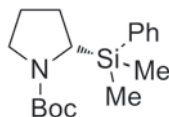
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ = -2.2, 26.0, 27.9, 28.5, 47.0, 47.6, 78.4, 154.9 ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 55 °C):** δ = -2.0, 25.7, 28.1, 28.7, 47.0, 47.9, 78.7, 154.8 ppm.

**<sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):** δ = -1.5, 26.4, 28.8, 29.0, 47.5, 48.5, 78.5, 154.7 ppm.

**MS (CI, methane):** *m/z* (%) = 244 ([M+H]<sup>+</sup>, 1), 200 (7), 186 (25), 172 (100), 142 (9), 114 (20), 101 (2), 73 (4).

The spectroscopic data are in accordance with those reported in the literature.<sup>132</sup>

**(S)-N-tert-Butoxycarbonyl-2-(dimethylphenylsilyl)pyrrolidine (134b)**

Prepared from *N*-Boc-pyrrolidine (**127**) and dimethylphenylsilyl chloride according to general procedure A and obtained as a colorless oil in 93% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 95:5; R<sub>f</sub> = 0.50).

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 99:1, 1.0 mL/min, *t*<sub>ret</sub>: 4.5 (*R*), 5.0 (*S*) min.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 0.38 (s, 6H), 1.44 (s, 9H), 1.49-1.59 (m, 1H), 1.63-1.74 (m, 2H), 1.86-1.95 (m, 1H), 3.01-3.07 (m, 1H), 3.41-3.52 (m, 2H), 7.31-7.38 (m, 3H), 7.51-7.53 (m, 2H) ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = 0.38 (s, 3H), 0.39 (s, 3H), 1.45 (s, 9H), 1.52-1.78 (m, 3H), 1.84-1.98 (m, 1H), 2.99-3.08 (m, 1H), 3.40-3.56 (m, 2H), 7.29-7.37 (m, 3H), 7.49-7.56 (m, 2H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = -3.9, -3.0, 25.6, 28.1, 28.6, 46.8, 47.6, 78.8, 127.6, 128.9, 133.8, 137.9, 154.6 ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = -3.9, -3.0, 25.4, 28.1, 28.6, 46.8, 47.7, 78.7, 127.5, 128.8, 133.8, 137.9, 154.4 ppm.

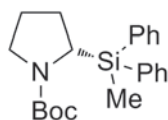
**<sup>29</sup>Si NMR (99 MHz, CDCl<sub>3</sub>):**  $\delta$  = -3.20 ppm.

**IR:**  $\nu$  = 701, 735, 773, 819, 1110, 1168, 1249, 1366, 1405, 1452, 1478, 1689, 2876, 2971 cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 306 ([M+H]<sup>+</sup>, 4), 248 (57), 232 (9), 228 (1), 204 (100), 172 (25), 135 (97), 57 (50).

The spectroscopic data are in accordance with those reported in the literature.<sup>135</sup>

### (*S*)-*N*-*tert*-Butoxycarbonyl-2-(diphenylmethylsilyl)pyrrolidine (**134c**)



Prepared from *N*-Boc-pyrrolidine (**127**) and diphenylmethylsilyl chloride according to general procedure A and obtained as a colorless oil in 93% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 9:1; R<sub>f</sub> = 0.40).

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 99:1, 1.0 mL/min,  $t_{\text{ret}}$ : 5.4 (*R*), 6.1 (*S*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +51.5$  ( $c$  = 1, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 0.67 (s, 3H), 1.15-1.55 (m, 10H), 1.62-1.73 (m, 1H), 1.77-1.90 (m, 1H), 1.92-2.14 (m, 1H), 3.00-3.17 (m, 1H), 3.32-3.60 (m, 1H), 3.85-4.00 (m, 1H), 7.30-7.43 (m, 6H), 7.50-7.65 (m, 4H) ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = 0.68 (s, 3H), 1.33 (s, 9H), 1.44-1.56 (m, 1H), 1.63-1.74 (m, 1H), 1.81-1.91 (m, 1H), 1.97-2.09 (m, 1H), 3.03-3.11 (m, 1H), 3.44-3.55 (m, 1H), 3.90-3.97 (m, 1H), 7.31-7.42 (m, 6H), 7.56-7.61 (m, 4H) ppm.

**<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):**  $\delta$  = 0.67 (s, 3H), 1.21-1.28 (m, 2H), 1.29 (s, 9H), 1.57-1.65 (m, 2H), 2.90-2.99 (m, 1H), 3.30-3.43 (m, 1H), 3.79 (t,  $J$  = 7.6 Hz, 1H), 7.07-7.15 (m, 6H), 7.51-7.58 (m, 4H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = -4.2, -3.4, 24.5, 25.7, 28.3, 28.6, 46.6, 46.6, 78.5, 79.2, 127.5, 129.1, 129.1, 133.8, 134.6, 134.8, 135.4, 154.3, 154.7 ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = -3.7, 25.2, 25.3, 28.5, 28.8, 46.9, 46.9, 78.9, 127.7, 129.0, 129.2, 134.8, 135.0, 135.8, 154.7 ppm.

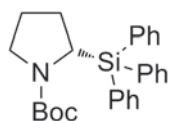
**<sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):**  $\delta$  = -3.0, 26.1, 28.8, 29.6, 47.5, 47.6, 78.8, 127.8, 129.3, 129.4, 135.4, 135.5, 136.8, 154.8 ppm.

**IR:**  $\nu$  = 486, 700, 727, 792, 1109, 1168, 1250, 1366, 1404, 1452, 1478, 1687, 2874, 2973 cm<sup>-1</sup>.

**MS (CI, methane):**  $m/z$  (%) = 369 ([M+H]<sup>+</sup>, 2), 368 ([M]<sup>+</sup>, 7), 310 (31), 290 (10), 296 (12), 266 (17), 235 (30), 234 (100), 197 (13), 105 (2).

**CHN analysis (C<sub>22</sub>H<sub>29</sub>NO<sub>2</sub>Si):** calcd.: C: 71.89, H: 7.95, N: 3.81; found: C: 72.02, H: 8.14, N: 4.30.

### (*S*)-*N*-*tert*-Butoxycarbonyl-2-(triphenylsilyl)pyrrolidine (134d)



Prepared from *N*-Boc-pyrrolidine (**127**) and triphenylsilyl chloride according to general procedure A and obtained as a white solid in 66% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 9:1;  $R_f$  = 0.42).

**Mp.:** 126-129 °C.

**HPLC analysis:** No suitable conditions were found for this compound. The enantiomeric ratio was determined after deprotection and conversion to the corresponding benzoyl-protected derivative.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 1.00-1.30 (m, 10H), 1.63-1.78 (m, 1H), 1.90-2.16 (m, 2H), 3.13-3.28 (m, 1H), 3.40-3.60 (m, 1H), 4.24-4.38 (m, 1H), 7.30-7.49 (m, 10H), 7.54-7.74 (m, 5H) ppm.

**<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):**  $\delta$  = 1.16 (s, 9H), 1.23-1.32 (m, 2H), 1.62-1.80 (m, 2H), 2.95-3.05 (m, 1H), 3.30-3.44 (m, 1H), 4.11-4.23 (m, 1H), 7.06-7.17 (m, 10H), 7.60-7.70 (m, 5H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  = 24.4, 25.8, 28.1, 29.3, 46.1, 46.6, 78.6, 79.4, 127.6, 129.3, 135.0, 136.2, 153.7, 154.4 ppm.

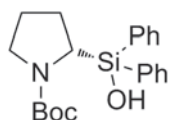
**<sup>13</sup>C NMR (100 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):**  $\delta$  = 26.3, 28.7, 30.5, 46.9, 47.5, 79.0, 128.0, 128.4, 129.5, 130.1, 135.6, 135.7, 136.9, 154.6 ppm.

**IR:**  $\nu$  = 699, 737, 766, 869, 901, 1066, 1105, 1166, 1252, 1364, 1402, 1427, 1678, 2974 cm<sup>-1</sup>.

**MS (CI, methane):**  $m/z$  (%) = 431 ([M+H]<sup>+</sup>, 3), 430 ([M]<sup>+</sup>, 8), 372 (41), 356 (15), 352 (9), 328 (19), 297 (58), 296 (100), 259 (15).

**CHN analysis (C<sub>27</sub>H<sub>31</sub>NO<sub>2</sub>Si):** calcd.: C: 75.48, H: 7.27, N: 3.26; found: C: 75.24, H: 7.06, N: 3.16.

### **(S)-N-tert-Butoxycarbonyl-2-(diphenylhydroxysilyl)pyrrolidine (134g)**



Prepared from *N*-Boc-pyrrolidine (**127**) and diphenyldimethoxysilane (**135**) or cyclotrisiloxane **138** according to general procedure A and obtained as a colorless oil after column chromatography (*n*-pentane:Et<sub>2</sub>O = 4:1; R<sub>f</sub> = 0.41).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 9:1, 0.8 mL/min,  $t_{\text{ret}}$ : 10.9 (*S*), 18.8 (*R*) min.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 1.42 (s, 9H), 1.62-1.72 (m, 2H), 1.83-2.04 (m, 2H), 2.96-3.05 (m, 1H), 3.43-3.51 (m, 1H), 3.54-3.61 (m, 1H), 5.60 (br s, 1H), 7.35-7.46 (m, 6H), 7.65-7.75 (m, 4H) ppm.

**<sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>, 75 °C):**  $\delta$  = 1.18-1.28 (m, 1H), 1.34 (s, 9H), 1.60-1.82 (m, 3H), 2.85-2.94 (m, 1H), 3.22-3.32 (m, 1H), 3.47 (t,  $J$  = 9.0 Hz, 1H), 5.52 (br s, 1H), 7.18-7.25 (m, 6H), 7.77-7.84 (m, 4H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 26.0, 28.3, 28.4, 47.6, 48.7, 79.9, 127.5, 127.6, 129.6, 129.8, 134.1, 134.7, 134.7, 156.1 ppm.

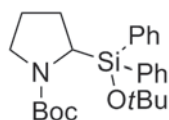
**$^{13}\text{C}$  NMR (100 MHz,  $\text{C}_6\text{D}_6$ , 75 °C):**  $\delta$  = 26.3, 28.8, 29.0, 48.0, 49.8, 79.9, 127.9, 129.9, 130.0, 135.3, 135.4, 136.2, 156.4 ppm.

**IR:**  $\nu$  = 505, 704, 739, 869, 1067, 1116, 1166, 1252, 1310, 1419, 1476, 1681, 2875, 2925, 2972, 3051, 3385  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 370 ( $[\text{M}+\text{H}]^+$ , 2), 352 (5), 312 (51), 296 (15), 292 (2), 268 (100), 236 (31), 199 (90), 77 (10).

**CHN analysis ( $\text{C}_{21}\text{H}_{27}\text{NO}_3\text{Si}$ ):** calcd.: C: 68.26, H: 7.36, N: 3.79; found: C: 67.96, H: 7.36, N: 4.12.

### ***N*-tert-Butoxycarbonyl-2-(tert-butoxydiphenylsilyl)pyrrolidine (134h)**



Prepared from *N*-Boc-pyrrolidine (**127**) and *tert*-butoxydiphenylsilyl chloride (**133b**) according to general procedure A (with TMEDA as diamine ligand) and obtained as a colorless oil in 40% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 9:1;  $R_f$  = 0.41).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 99:1, 0.6 mL/min,  $t_{\text{ret}}$ : 9.2, 10.5 min.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.25 (s, 9H), 1.42 (s, 9H), 1.65-1.90 (m, 2H), 1.95-2.30 (m, 2H), 2.98-3.07 (m, 1H), 3.32-3.64 (m, 1H), 3.85-4.12 (m, 1H), 7.34-7.50 (m, 6H), 7.68-7.90 (m, 4H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 27.3, 27.5, 28.2, 28.4, 31.9, 32.1, 46.2, 48.6, 73.9, 79.0, 127.4, 129.5, 134.4, 135.2, 136.4, 154.6 ppm.

**IR:**  $\nu$  = 703, 757, 892, 1025, 1051, 1114, 1182, 1243, 1366, 1412, 1476, 1664, 2925, 2974, 3068, 3376  $\text{cm}^{-1}$ .

**MS (CI, methane):**  $m/z$  (%) = 426 ( $[\text{M}+\text{H}]^+$ , 4), 368 (22), 352 (8), 324 (21), 296 (57), 292 (39), 268 (7), 255 (5), 236 (100), 199 (29), 139 (9).

**CHN analysis ( $\text{C}_{25}\text{H}_{35}\text{NO}_3\text{Si}$ ):** calcd.: C: 70.55, H: 8.29, N: 3.29; found: C: 71.08, H: 8.21, N: 3.07.

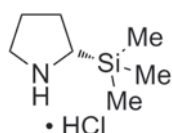
## 4.5 Deprotection of *N*-Boc Silylated Pyrrolidines

### *General Procedure B*

To an ice-cooled solution of silylated *N*-Boc-pyrrolidine **134** in HCl-saturated Et<sub>2</sub>O (0.5 M) was added dropwise aqueous HCl-solution (37%, 10 equiv.). The mixture was allowed to reach room temperature and was stirred overnight. Et<sub>2</sub>O was then evaporated and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the desired product.

The same procedure was applied for the synthesis of racemic silylated pyrrolidines HCl salts.

### (*S*)-2-(Trimethylsilyl)pyrrolidine HCl salt (**139b**)



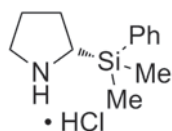
Prepared from (*S*)-*N*-*tert*-butoxycarbonyl-2-(trimethylsilyl)pyrrolidine (**134a**) according to general procedure B and obtained as a white solid in 18% yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 0.24 (s, 9H), 1.60-2.15 (m, 4H), 2.58-2.75 (m, 1H), 3.20-3.40 (m, 2H), 9.07 (br s, 1H), 9.85 (br s, 1H) ppm.

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = -3.0, 25.0, 27.3, 46.1, 49.0 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>135</sup>

### (*S*)-2-(Dimethylphenylsilyl)pyrrolidine HCl salt (**139c**)



Prepared from (*S*)-*N*-*tert*-butoxycarbonyl-2-(dimethylphenylsilyl)pyrrolidine (**134b**) according to general procedure B and obtained as a white solid in quantitative yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 0.62 (s, 3H), 0.63 (s, 3H), 1.67-1.90 (m, 2H), 1.91-2.07 (m, 2H), 2.86-2.98 (m, 1H), 3.18-3.32 (m, 2H), 7.35-7.44 (m, 3H), 7.57-7.63 (m, 2H), 9.09 (br s, 1H), 9.96 (br s, 1H) ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = 0.51 (s, 3H), 0.54 (s, 3H), 1.59-1.96 (m, 4H), 2.81-2.95 (m, 1H), 3.15-3.30 (m, 2H), 7.20-7.32 (m, 3H), 7.46-7.54 (m, 2H), 8.87 (br s, 1H), 9.53 (br s, 1H) ppm.

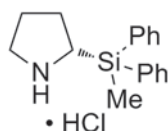
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = -5.7, -4.2, 24.5, 27.1, 46.1, 48.3, 127.5, 129.3, 133.4, 134.0 ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 55 °C):**  $\delta$  = -5.5, -4.1, 24.5, 27.2, 46.2, 48.5, 127.6, 129.4, 133.5, 134.2 ppm.

**<sup>29</sup>Si NMR (99 MHz, CDCl<sub>3</sub>):**  $\delta$  = -3.40 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>135</sup>

### (*S*)-2-(Diphenylmethylsilyl)pyrrolidine HCl salt (**139d**)



Prepared from (*S*)-*N*-*tert*-butoxycarbonyl-2-(diphenylmethylsilyl)pyrrolidine (**134c**) according to general procedure B and obtained as a white solid in quantitative yield.

**Mp.:** 218-219 °C.

**Optical rotation:**  $[\alpha]_D^{22} = +36.0$  ( $c = 1$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 0.92 (s, 3H), 1.68-1.88 (m, 3H), 2.03-2.13 (m, 1H), 2.84-3.04 (m, 2H), 3.23-3.34 (m, 1H), 7.32-7.43 (m, 6H), 7.54-7.61 (m, 2H), 7.67-7.74 (m, 2H), 9.01 (br s, 1H), 9.82 (br s, 1H) ppm.

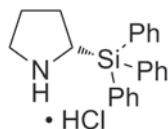
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = -6.0, 25.1, 28.4, 46.5, 46.9, 128.1, 128.2, 130.1, 132.1, 132.5, 134.9, 135.0 ppm.

**IR:**  $\nu = 699, 738, 804, 1018, 1108, 1268, 1400, 1425, 1602, 2702 \text{ cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 268 ([M-Cl]<sup>+</sup>, 1), 267 ([M-HCl]<sup>+</sup>, 2), 239 (7), 197 (8), 150 (7), 105 (6), 70 (100).

**CHN analysis (C<sub>17</sub>H<sub>22</sub>ClNSi):** calcd.: C: 67.19, H: 7.30, N: 4.61; found: C: 67.11, H: 7.36, N: 4.62.

**(S)-2-(Triphenylsilyl)pyrrolidine HCl salt (139e)**



Prepared from (*S*)-*N*-*tert*-butoxycarbonyl-2-(triphenylsilyl)pyrrolidine (**134d**) according to general procedure B and obtained as a white solid in 92% yield.

**Mp.:** 244-245 °C.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 1.64-1.92 (m, 3H), 2.21-2.34 (m, 1H), 2.62-2.92 (m, 2H), 3.57-3.73 (1H), 7.32-7.49 (m, 9H), 7.60-7.71 (m, 6H), 8.15 (br s, 1H), 10.35 (br s, 1H) ppm.

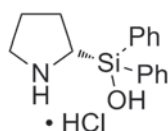
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  = 25.2, 28.8, 45.6, 47.2, 128.5, 130.3, 130.5, 136.3 ppm.

**IR:**  $\nu$  = 699, 743, 1113, 1395, 1428, 1590, 2839 cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 330 ([M-Cl]<sup>+</sup>, 2), 329 ([M-HCl]<sup>+</sup>, 4), 301 (8), 259 (12), 212 (15), 181 (13), 105 (9), 70 (100).

**CHN analysis (C<sub>22</sub>H<sub>24</sub>ClNSi):** calcd.: C: 72.20, H: 6.61, N: 3.83; found: C: 72.10, H: 6.76, N: 3.83.

**(S)-2-(Diphenylhydroxysilyl)pyrrolidine HCl salt (139a)**



Prepared from (*S*)-*N*-*tert*-butoxycarbonyl-2-(diphenylhydroxy)pyrrolidine (**134g**) according to general procedure B and obtained as a white solid.

**Optical rotation:**  $[\alpha]_D^{22} = +0.07$  (c = 1, MeOH).

**<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>):**  $\delta$  = 1.74-2.01 (m, 4H), 3.05-3.19 (m, 2H), 3.26-3.33 (m, 1H), 3.39 (br s, 1H), 7.38-7.50 (m, 6H), 7.61-7.66 (m, 2H), 7.73-7.78 (m, 2H), 8.88 (br s, 1H), 9.55 (br s, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>):**  $\delta$  = 24.6, 27.0, 46.4, 46.9, 127.9, 130.2, 130.2, 133.8, 134.0, 134.2 ppm.

**IR:**  $\nu$  = 695, 712, 737, 876, 915, 986, 1119, 1158, 1370, 1428, 1588, 2920, 3331 cm<sup>-1</sup>.

**HRMS (ESI):**  $m/z$  calcd. for  $C_{16}H_{20}ClNOSi$   $[M-Cl]^+$ : 270.2400, found: 270.4167.

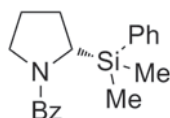
**CHN analysis ( $C_{16}H_{20}ClNOSi$ ):** calcd.: C: 62.83, H: 6.59, N: 4.58; found: C: 62.71, H: 6.67, N: 4.62.

### General Procedure C

To an ice-cooled mixture of silylated pyrrolidine HCl salt **139** (0.075 mmol) in  $Et_2O$  (1.5 mL) was added dropwise  $Et_3N$  (24.0  $\mu L$ , 0.172 mmol, 2.3 equiv.) and benzoylchloride (**140**) (20.0  $\mu L$ , 0.172 mmol, 2.3 equiv.). The reaction mixture was stirred at 0 °C for 30 min and then allowed to reach room temperature (30 min). The reaction was stopped by addition of sat. aqueous  $NaHCO_3$ -solution. The aqueous phase was washed with  $CH_2Cl_2$  (3x 3 mL) and the combined organic extracts were dried over  $MgSO_4$ , filtered, evaporated *in vacuo* and the crude product was purified by column chromatography.

The same procedure was applied for the synthesis of racemic benzoyl-protected silylated pyrrolidines.

### (*S*)-*N*-Benzoyl-2-(dimethylphenylsilyl)pyrrolidine (**141a**)



Prepared from (*S*)-2-(dimethylphenylsilyl)pyrrolidine HCl salt (**139c**) according to general procedure C and obtained as a colorless oil in quantitative yield after column chromatography (*n*-pentane: $Et_2O$  = 7:3;  $R_f$  = 0.21).

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 95:5, 1.0 mL/min,  $t_{ret}$ : 10.3 (*R*), 14.7 (*S*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +193.7$  ( $c = 1$ ,  $CHCl_3$ ).

**$^1H$  NMR (400 MHz,  $CDCl_3$ ):**  $\delta$  = 0.46 (s, 3H), 0.52 (s, 3H), 1.55-1.84 (m, 3H), 1.97-2.06 (m, 1H), 3.04 (dt,  $J$  = 6.4, 10.2 Hz, 1H), 3.33-3.40 (m, 1H), 3.87 (t,  $J$  = 8.9 Hz, 1H), 7.31-7.40 (m, 8H), 7.57-7.62 (m, 2H) ppm.

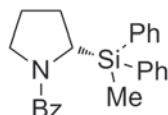
**$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):**  $\delta$  = -3.5, -2.9, 26.8, 28.0, 48.0, 50.9, 127.1, 127.6, 128.0, 129.0, 129.6, 134.0, 137.3, 137.4, 169.2 ppm.

**IR:**  $\nu$  = 485, 664, 701, 752, 790, 885, 1068, 1112, 1252, 1308, 1428, 1607, 1718, 2920, 2966, 3064  $\text{cm}^{-1}$ .

**MS (CI, methane):**  $m/z$  (%) = 309 ( $[\text{M}]^+$ , 7), 294 (14), 232 (100), 204 (1), 174 (1), 135 (6), 105 (9).

**CHN analysis ( $\text{C}_{19}\text{H}_{23}\text{NOSi}$ ):** calcd.: C: 73.74, H: 7.49, N: 4.53; found: C: 73.25, H: 7.50, N: 4.98.

**(S)-N-Benzoyl-2-(diphenylmethylsilyl)pyrrolidine (141b)**



Prepared from (S)-2-(diphenylmethylsilyl)pyrrolidine HCl salt (**139d**) according to general procedure C and obtained as a colorless oil in quantitative yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 1:1;  $R_f$  = 0.40).

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 9:1, 1.0 mL/min,  $t_{\text{ret}}$ : 9.1 (*R*), 11.1 (*S*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +36.0$  ( $c$  = 1,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 0.78 (s, 3H), 1.60-1.73 (m, 2H), 1.85-1.96 (m, 1H), 2.08-2.18 (m, 1H), 2.98-3.07 (m, 1H), 3.30-3.39 (m, 1H), 4.31 (t,  $J$  = 8.8 Hz, 1H), 7.17-7.23 (m, 2H), 7.27-7.49 (m, 9H), 7.60-7.65 (m, 2H), 7.69-7.75 (m, 2H) ppm.

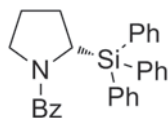
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -2.9, 26.7, 28.5, 46.9, 50.7, 127.0, 127.6, 127.6, 127.9, 129.0, 129.2, 129.5, 134.7, 135.0, 136.2, 137.0, 169.1 ppm.

**$^{29}\text{Si}$  NMR (99 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -6.62 ppm.

**IR:**  $\nu$  = 490, 662, 700, 725, 791, 927, 1068, 1100, 1250, 1425, 1575, 1622, 2871, 2919, 2968, 3049, 3066  $\text{cm}^{-1}$ .

**MS (CI):**  $m/z$  = 372 ( $[\text{M}+\text{H}]^+$ , 43), 371 ( $[\text{M}]^+$ , 57), 356 (38), 322 (17), 294 (100), 266 (7), 197 (10), 105 (13).

**CHN analysis ( $\text{C}_{24}\text{H}_{25}\text{NOSi}$ ):** calcd.: C: 77.58, H: 6.78, N: 3.77; found: C: 77.45, H: 7.13, N: 4.18.

**(S)-N-Benzoyl-2-(triphenylsilyl)pyrrolidine (141c)**

Prepared from (S)-2-(triphenylsilyl)pyrrolidine HCl salt (**139e**) according to general procedure C and obtained as a white solid in quantitative yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 4:1; R<sub>f</sub> = 0.20).

**Mp.:** 159-160 °C.

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 9:1, 1.0 mL/min, t<sub>ret</sub>: 9.0 (*R*), 13.8 (*S*) min.

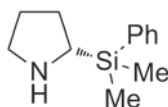
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ = 1.54-1.65 (m, 2H), 1.84-1.96 (m, 1H), 2.06-2.17 (m, 1H), 2.93-3.04 (m, 1H), 3.23-3.31 (m, 1H), 4.57 (t, *J* = 8.7 Hz, 1H), 6.90-6.96 (m, 2H), 7.10-7.22 (m, 3H), 7.23-7.34 (m, 9H), 7.59-7.68 (m, 6H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ = 26.8, 29.4, 45.9, 50.6, 126.9, 127.5, 127.7, 129.2, 129.3, 134.2, 136.1, 136.9, 168.9 ppm.

**IR:** ν = 663, 698, 734, 784, 1103, 1194, 1423, 1617 cm<sup>-1</sup>.

**MS (EI):** *m/z* (%) = 434 ([M+H]<sup>+</sup>, 39), 433 ([M]<sup>+</sup>, 100), 356 (59), 328 (55), 259 (87), 181 (32), 105 (73), 77 (20).

**CHN analysis (C<sub>29</sub>H<sub>27</sub>NOSi):** calcd.: C: 80.33, H: 6.28, N: 3.23; found: C: 80.01, H: 6.37, N: 3.21.

**(S)-2-(Dimethylphenylsilyl)pyrrolidine (132b)**

To a solution of (S)-2-(dimethylphenylsilyl)pyrrolidine HCl salt (**139c**) (0.35 g, 1.70 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was slowly added aqueous NaOH (8.5 mL, 17.0 mmol, 2 M, 10 equiv.). The reaction mixture was stirred overnight. The organic phase was separated and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and evaporated *in vacuo* to afford the title compound as a colorless oil in quantitative yield.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ = 0.34 (s, 3H), 0.34 (s, 3H), 1.34-1.46 (m, 1H), 1.50 (br s, 1H), 1.52-1.75 (m, 2H), 1.80-1.89 (m, 1H), 2.36 (dd, *J* = 7.2, 11.0 Hz, 1H), 2.64-2.73 (m, 1H), 2.97-3.04 (m, 1H), 7.33-7.38 (m, 3H), 7.53-7.58 (m, 2H) ppm.

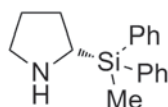
**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta = -5.0, -4.9, 26.5, 28.3, 48.5, 48.9, 127.6, 128.9, 133.8, 136.9$  ppm.

**IR:**  $\nu = 647, 700, 733, 775, 829, 893, 936, 1068, 1112, 1249, 1427, 2823, 2868, 2955, 3048, 3068$   $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 205 ( $[\text{M}]^+$ , 3), 190 (2), 177 (21), 148 (2), 70 (100).

**CHN analysis ( $\text{C}_{12}\text{H}_{19}\text{NSi}$ ):** calcd.: C: 70.18, H: 9.32, N: 6.82; found: C: 69.43, H: 9.37, N: 7.08.

### (S)-2-(Diphenylmethylsilyl)pyrrolidine (**132c**)



Prepared from (S)-2-(diphenylmethylsilyl)pyrrolidine HCl salt (**139d**) following the same procedure as for (S)-2-(dimethylphenylsilyl)pyrrolidine (**132b**) and obtained as a colorless oil in quantitative yield.

**Optical rotation:**  $[\alpha]_D^{22} = +0.7$  ( $c = 1, \text{CHCl}_3$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta = 0.61$  (s, 3H), 1.39 (br s, 1H), 1.49-1.68 (m, 2H), 1.68-1.81 (m, 1H), 1.90-2.04 (m, 1H), 2.69-2.81 (m, 2H), 2.97-3.08 (m, 1H), 7.32-7.44 (m, 6H), 7.56-7.66 (m, 4H) ppm.

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta = -6.0, 26.6, 28.6, 47.3, 49.0, 127.9, 127.9, 129.4, 129.4, 134.9, 135.0, 135.5, 135.7$  ppm.

**IR:**  $\nu = 488, 521, 668, 700, 730, 787, 892, 1067, 1111, 1252, 1386, 1427, 2867, 2956, 3047, 3066$   $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 268 ( $[\text{M}+\text{H}]^+$ , 1), 267 ( $[\text{M}]^+$ , 1), 197 (4), 181 (3), 105 (5), 70 (100).

**CHN analysis ( $\text{C}_{17}\text{H}_{21}\text{NSi}$ ):** calcd.: C: 76.35, H: 7.91, N: 5.24; found: C: 75.95, H: 7.97, N: 5.55.

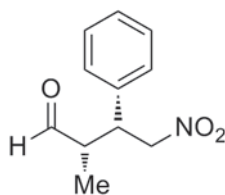
## 4.6 Michael Addition Reactions of Aldehydes to Nitroolefins

### General Procedure D

A solution of silylated pyrrolidine **132c** (13.4 mg, 0.05 mmol, 0.1 equiv.) and the aldehyde (5.00 mmol, 10.0 equiv.) in toluene:THF (5:1, 1.5 mL) was cooled to 0 °C and stirred for 30 min under an

atmosphere of Ar. Then, the nitroolefin (0.50 mmol) was added and the reaction was monitored by TLC analysis. When full conversion was indicated, the reaction was stopped by the addition of aq. 1 M HCl. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x 2 mL), and the combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. After determination of the diastereomeric ratio by <sup>1</sup>H NMR spectroscopy, the product was purified by column chromatography. The enantiomeric ratio was measured by HPLC using a chiral stationary phase.

### (2*S*,3*R*)-2-Methyl-4-nitro-3-phenylbutanal (**34a**)



Prepared from propanal (**12a**) and *trans*-β-nitrostyrene (**15a**) according to general procedure D and obtained as a colorless oil in 96% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3; R<sub>f</sub> = 0.25).

**HPLC analysis:** Chiralcel OD-H, *n*-heptane:*i*PrOH = 9:1, 1.0 mL/min, t<sub>ret</sub>: 25.4 (*syn*, major), 32.6 (*anti*, major), 36.3 (*syn*, minor), 42.8 (*anti*, minor) min.

**Optical rotation:** [α]<sub>D</sub><sup>22</sup> = −37.7 (c = 1, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer):** δ = 0.98 (d, *J* = 7.1 Hz, 3H), 2.72-2.81 (m, 1H), 3.81 (dt, *J* = 5.5, 9.2 Hz, 1H), 4.67 (dd, *J* = 9.3, 12.6 Hz, 1H), 4.80 (dd, *J* = 5.5, 12.6 Hz, 1H), 7.16-7.19 (m, 2H), 7.25-7.36 (m, 3H), 9.70 (d, *J* = 1.7 Hz, 1H) ppm.

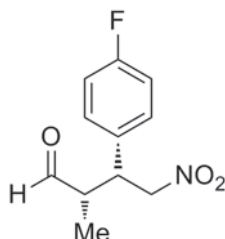
**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, major diastereomer):** δ = 12.1, 44.0, 48.4, 78.0, 127.9, 128.9, 136.4, 202.1 ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, minor diastereomer):** δ = 1.20 (d, *J* = 7.1 Hz, 3H), 2.75-2.85 (m, 1H), 3.81 (dt, *J* = 5.5, 9.2 Hz, 1H), 4.67 (dd, *J* = 9.3, 12.6 Hz, 1H), 4.80 (dd, *J* = 5.5, 12.6 Hz, 1H), 7.16-7.23 (m, 2H), 7.25-7.36 (m, 3H), 9.52 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, minor diastereomer):** δ = 11.6, 44.7, 48.7, 77.3, 127.9, 128.9, 136.8, 202.1 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>37a,211</sup>

**(2*S*,3*R*)-3-(4-Fluorophenyl)-2-methyl-4-nitrobutanal (34b)**



Prepared from propanal (**12a**) and *trans*-4-fluoro- $\beta$ -nitrostyrene (**15b**) according to general procedure D and obtained as a colorless oil in 93% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 1:1; R<sub>f</sub> = 0.30).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 98:2, 0.8 mL/min, *t*<sub>ret</sub> = 35.8 (*syn*, minor), 42.2 (*anti*, major), 47.1 (*anti*, minor), 49.3 (*syn*, major) min.

**Optical rotation:**  $[\alpha]_D^{22} = -36.3$  (*c* = 1, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 0.99 (d, *J* = 7.2 Hz, 3H), 2.69-2.81 (m, 1H), 3.81 (dt, *J* = 5.3, 9.4 Hz, 1H), 4.64 (dd, *J* = 9.6, 12.9 Hz, 1H), 4.79 (dd, *J* = 5.3, 12.7 Hz, 1H), 6.99-7.07 (m, 2H), 7.12-7.19 (m, 2H), 9.69 (d, *J* = 1.5 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 12.0, 43.2, 48.3, 78.1, 115.9 (d, *J* = 21.5 Hz), 129.7 (d, *J* = 8.1 Hz), 132.4 (d, *J* = 3.4 Hz), 162.2 (d, *J* = 245.7 Hz), 202.0 ppm.

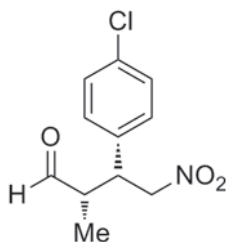
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.21 (d, *J* = 7.2 Hz, 3H), 2.72-2.86 (m, 1H), 3.81 (dt, *J* = 5.3, 9.4 Hz, 1H), 4.64 (dd, *J* = 9.6, 12.9 Hz, 1H), 4.79 (dd, *J* = 5.3, 12.7 Hz, 1H), 6.99-7.07 (m, 2H), 7.12-7.23 (m, 2H), 9.52 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.6, 44.0, 48.7, 77.4, 115.9 (d, *J* = 21.5 Hz), 129.7 (d, *J* = 8.0 Hz), 132.7 (d, *J* = 3.3 Hz), 162.2 (d, *J* = 245.7 Hz), 201.8 ppm.

**IR:**  $\nu$  = 722, 838, 1110, 1162, 1228, 1380, 1435, 1511, 1553, 1604, 1723, 2920 cm<sup>-1</sup>.

**MS (EI):** *m/z* (%) = 225 ([M]<sup>+</sup>, 7), 178 (52), 163 (33), 150 (20), 149 (22), 135 (39), 122 (88), 109 (100), 96 (15), 55 (16).

**CHN analysis (C<sub>11</sub>H<sub>12</sub>FNO<sub>3</sub>):** calcd.: C: 58.66, H: 5.37, N: 6.22; found: C: 58.61, H: 5.44, N: 6.35.

**(2*S*,3*R*)-3-(4-Chlorophenyl)-2-methyl-4-nitrobutanal (34c)**

Prepared from propanal (**12a**) and *trans*-4-chloro- $\beta$ -nitrostyrene (**15c**) according to general procedure D and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 1:1; R<sub>f</sub> = 0.28).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 98:2, 0.5 mL/min,  $t_{\text{ret}}$ : 55.3 (*syn*, minor), 66.5 (*anti*, major), 73.8 (*anti*, minor), 77.6 (*syn*, major) min.

**Optical rotation:**  $[\alpha]_D^{22} = -30.5$  ( $c = 1$ , CHCl<sub>3</sub>).

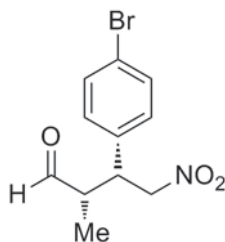
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 0.98 (d,  $J = 7.4$  Hz, 3H), 2.70-2.79 (m, 1H), 3.80 (dt,  $J = 5.2, 9.3$  Hz, 1H), 4.64 (dd,  $J = 9.8, 12.8$  Hz, 1H), 4.80 (dd,  $J = 5.4, 12.8$  Hz, 1H), 7.10-7.15 (m, 2H), 7.29-7.34 (m, 2H), 9.68 (d,  $J = 1.7$  Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 12.1, 43.4, 48.2, 77.8, 129.1, 129.3, 133.8, 135.1, 201.6 ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.20 (d,  $J = 7.1$  Hz, 3H), 2.73-2.84 (m, 1H), 3.80 (dt,  $J = 5.2, 9.3$  Hz, 1H), 4.64 (dd,  $J = 9.8, 12.8$  Hz, 1H), 4.74-4.80 (m, 1H), 7.14-7.19 (m, 2H), 7.29-7.34 (m, 2H), 9.51 (d,  $J = 1.4$  Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.6, 44.0, 48.6, 77.1, 129.1, 129.3, 133.8, 135.4, 201.6 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>211</sup>

**(2*S*,3*R*)-3-(4-Bromophenyl)-2-methyl-4-nitrobutanal (34d)**

Prepared from propanal (**12a**) and *trans*-4-bromo- $\beta$ -nitrostyrene according to general procedure D and obtained as a white solid in 87% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 1:1; R<sub>f</sub> = 0.31).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 98:2, 0.5 mL/min, t<sub>ret</sub> = 64.7 (*syn*, minor), 78.3 (*anti*, major), 86.9 (*anti*, minor), 90.2 (*syn*, major) min.

**Optical rotation:** [ $\alpha$ ]<sub>D</sub><sup>22</sup> = -21.8 (c = 1, CHCl<sub>3</sub>).

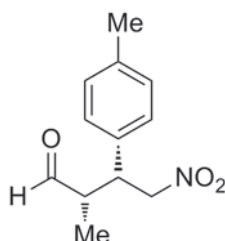
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 1.00 (d, *J* = 7.4 Hz, 3H), 2.71-2.83 (m, 1H), 3.79 (dt, *J* = 5.3, 9.3 Hz, 1H), 4.65 (dd, *J* = 9.5, 12.9 Hz, 1H), 4.80 (dd, *J* = 5.2, 12.9 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 9.69 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 12.3, 43.5, 48.2, 77.8, 122.0, 129.7, 132.1, 135.6, 201.6 ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.21 (d, *J* = 7.4 Hz, 3H), 2.71-2.83 (m, 1H), 3.75-3.84 (m, 1H), 4.61-4.82 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 9.52 (d, *J* = 1.6 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.7, 44.1, 48.6, 77.0, 122.0, 129.7, 132.2, 135.9, 201.6 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>43b</sup>

**(2*S*,3*R*)-2-Methyl-4-nitro-3-(*p*-tolyl)butanal (34e)**

Prepared from propanal (**12a**) and *trans*-4-methyl- $\beta$ -nitrostyrene according to general procedure D and obtained as a colorless oil in 98% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3; R<sub>f</sub> = 0.30).

**HPLC analysis:** Chiralcel OC, *n*-heptane:*i*PrOH = 9:1, 0.8 mL/min, t<sub>ret</sub> = 36.0 (*syn*, major), 39.9 (*anti*, minor), 42.0 (*syn*, minor), 47.0 (*anti*, major) min.

**Optical rotation:**  $[\alpha]_D^{22} = -21.8$  (c = 1, CHCl<sub>3</sub>).

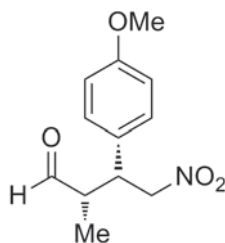
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, major diastereomer)**  $\delta$  = 0.99 (d, *J* = 7.4 Hz, 3H), 2.31 (s, 3H), 2.70-2.80 (m, 1H), 3.78 (dt, *J* = 5.7, 9.1 Hz, 1H), 4.65 (dd, *J* = 9.4, 12.6 Hz, 1H), 4.77 (dd, *J* = 5.5, 12.6 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 9.70 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 12.1, 21.1, 43.7, 48.5, 78.2, 127.8, 129.6, 133.2, 137.7, 202.2 ppm.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.20 (d, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 2.70-2.80 (m, 1H), 3.77 (dt, *J* = 5.7, 9.1 Hz, 1H), 4.73 (dd, *J* = 8.8, 12.6 Hz, 1H), 4.77 (dd, *J* = 6.4, 12.7 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 9.52 (d, *J* = 1.9 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.8, 21.1, 44.6, 48.7, 77.5, 127.8, 129.6, 133.6, 137.8, 202.3 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>212</sup>

**(2*S*,3*R*)-3-(4-Methoxyphenyl)-2-methyl-4-nitrobutanal (34f)**

Prepared from propanal (**12a**) and *trans*-4-methoxy- $\beta$ -nitrostyrene according to general procedure D and obtained as a colorless oil in 93% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 1:1; *R<sub>f</sub>* = 0.30).

**HPLC analysis:** Chiralpak AS, *n*-heptane:*i*PrOH = 7:3, 0.7 mL/min, *t<sub>ret</sub>* = 18.8 (*syn*, major), 22.4 (*anti*, major), 26.1 (*syn*, minor), 30.3 (*anti*, minor) min.

**Optical rotation:**  $[\alpha]_D^{22} = -18.9$  (*c* = 1, CHCl<sub>3</sub>).

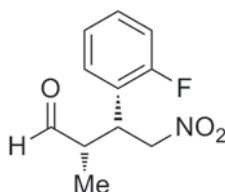
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 0.99 (d, *J* = 7.4 Hz, 3H), 2.66-2.78 (m, 1H), 3.72-3.81 (m, 1H), 3.77 (s, 3H), 4.62 (dd, *J* = 9.4, 12.6 Hz, 1H), 4.76 (dd, *J* = 5.7, 12.6 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 9.68 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 11.9, 43.2, 48.5, 55.1, 78.2, 114.3, 128.3, 129.0, 159.1, 202.4 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.19 (d, *J* = 7.1 Hz, 3H), 2.66-2.80 (m, 1H), 3.72-3.81 (m, 1H), 3.77 (s, 3H), 4.62 (dd, *J* = 9.4, 12.6 Hz, 1H), 4.70-4.78 (m, 1H), 6.85 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.9 Hz, 2H), 9.51 (d, *J* = 1.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.7, 44.2, 48.7, 55.1, 77.7, 114.3, 128.3, 129.1, 159.1, 202.5 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>212</sup>

**(2*S*,3*R*)-3-(2-Fluorophenyl)-2-methyl-4-nitrobutanal (34g)**

Prepared from propanal (**12a**) and *trans*-2-fluoro- $\beta$ -nitrostyrene according to general procedure D and obtained as a colorless oil in 96% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 3:2; *R*<sub>f</sub> = 0.37).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 97:3, 0.8 mL/min, *t*<sub>ret</sub> = 18.5 (*syn*, minor), 21.0 (*syn*, major), 22.2 (*anti*, major), 22.8 (*anti*, minor) min.

**Optical rotation:**  $[\alpha]_D^{22} = -48.8$  (*c* = 1, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 1.01 (d, *J* = 7.2 Hz, 3H), 2.86-2.99 (m, 1H), 4.03 (dt, *J* = 5.7, 9.3 Hz, 1H), 4.72-4.87 (m, 2H), 7.03-7.33 (m, 4H), 9.71 (d, *J* = 1.5 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 12.1, 39.3, 47.2 (d, *J* = 1.9 Hz), 76.8 (d, *J* = 2.7 Hz), 116.0 (d, *J* = 22.1 Hz), 123.7 (d, *J* = 13.5 Hz), 124.6 (d, *J* = 3.5 Hz), 129.8 (d, *J* = 8.6 Hz), 130.4 (d, *J* = 4.5 Hz), 161.0 (d, *J* = 244.6 Hz), 201.9 ppm.

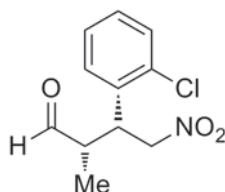
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.22 (d, *J* = 7.2 Hz, 3H), 2.86-2.99 (m, 1H), 4.08-4.16 (m, 1H), 4.72-4.87 (m, 2H), 7.03-7.33 (m, 4H), 9.54 (d, *J* = 1.0 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.5, 38.9 (d, *J* = 1.2 Hz), 47.7 (d, *J* = 1.4 Hz), 76.0 (d, *J* = 2.3 Hz), 116.1 (d, *J* = 22.6 Hz), 123.7 (d, *J* = 13.5 Hz), 124.6 (d, *J* = 3.5 Hz), 129.7 (d, *J* = 4.1 Hz), 129.8 (d, *J* = 8.6 Hz), 161.0 (d, *J* = 244.6 Hz), 201.7 ppm.

**IR:**  $\nu$  = 759, 1113, 1229, 1380, 1436, 1455, 1492, 1555, 1724, 2919 cm<sup>-1</sup>.

**MS (EI):** *m/z* (%) = 225 ([M]<sup>+</sup>, 1), 178 (3), 163 (6), 150 (3), 149 (8), 135 (17), 122 (37), 109 (100), 96 (12), 55 (25).

**CHN analysis (C<sub>11</sub>H<sub>12</sub>FNO<sub>3</sub>):** calcd.: C: 58.66, H: 5.37, N: 6.22; found: C: 58.52, H: 5.59, N: 6.47.

**(2*S*,3*R*)-3-(2-Chlorophenyl)-2-methyl-4-nitrobutanal (34h)**

Prepared from propanal (**12a**) and *trans*-2-chloro- $\beta$ -nitrostyrene according to general procedure D and obtained as a colorless oil in 96% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 3:2; R<sub>f</sub> = 0.37).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 98:2, 0.6 mL/min, *t*<sub>ret</sub>: 32.7 (*syn*, minor), 40.2 (*syn*, major), 44.3 (*anti*, minor), 47.5 (*anti*, major) min.

**Optical rotation:**  $[\alpha]_D^{22} = -62.9$  (*c* = 1, CHCl<sub>3</sub>).

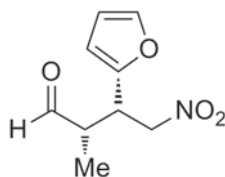
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 1.02 (d, *J* = 7.4 Hz, 3H), 2.92-3.06 (m, 1H), 4.34 (dt, *J* = 5.2, 9.3 Hz, 1H), 4.75-4.91 (m, 2H), 7.19-7.28 (m, 3H), 7.38-7.44 (m, 1H), 9.72 (d, *J* = 1.5 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 12.1, 40.6, 47.7, 76.6, 127.4, 129.0, 129.1, 130.4, 134.3, 134.5, 201.9 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 1.20 (d, *J* = 7.2 Hz, 3H), 2.92-3.06 (m, 1H), 4.46-4.55 (m, 1H), 4.72-4.91 (m, 2H), 7.19-7.31 (m, 3H), 7.38-7.44 (m, 1H), 9.60 (d, *J* = 1.5 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 10.5, 39.7, 47.7, 75.4, 127.3, 128.2, 129.1, 130.5, 134.3, 134.8, 201.6 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>213</sup>

**(2*S*,3*S*)-3-(Furan-2-yl)-2-methyl-4-nitrobutanal (34i)**

Prepared from propanal (**12a**) and (*E*)-2-(2-nitroethenyl)furan according to general procedure D and obtained as a colorless oil in 88% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3; R<sub>f</sub> = 0.42).

**HPLC analysis:** Chiralpak AS-H, *n*-heptane:*i*PrOH = 98:2, 0.9 mL/min,  $t_{\text{ret}} = 42.7$  (*syn*, major), 47.3 (*syn*, minor), 51.7 (*anti*, major), 73.7 (*anti*, minor) min.

**Optical rotation:**  $[\alpha]_D^{22} = -19.5$  ( $c = 1$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta = 1.07$  (d,  $J = 7.2$  Hz, 3H), 2.80 (dq,  $J = 1.0, 7.5$  Hz, 1H), 4.09 (dt,  $J = 6.6, 8.5$  Hz, 1H), 4.69 (dd,  $J = 6.2, 12.9$  Hz, 1H), 4.75 (dd,  $J = 8.5, 12.8$  Hz, 1H), 6.17-6.19 (m, 1H), 6.30 (dd,  $J = 2.0, 3.2$  Hz, 1H), 7.35 (dd,  $J = 0.8, 2.0$  Hz, 1H), 9.70 (d,  $J = 1.0$  Hz, 1H) ppm.

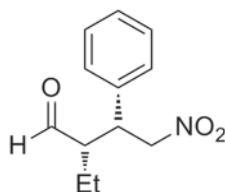
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta = 10.9, 37.6, 47.0, 75.7, 108.7, 110.3, 142.6, 149.9, 201.6$  ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta = 1.21$  (d,  $J = 7.4$  Hz, 3H), 2.81-2.90 (m, 1H), 4.01 (dt,  $J = 5.7, 8.7$  Hz, 1H), 4.69 (dd,  $J = 6.2, 12.9$  Hz, 1H), 4.75 (dd,  $J = 8.5, 12.8$  Hz, 1H), 6.19-6.22 (m, 1H), 6.31 (dd,  $J = 2.0, 3.2$  Hz, 1H), 7.36 (dd,  $J = 0.8, 2.0$  Hz, 1H), 9.63 (d,  $J = 1.5$  Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta = 11.3, 38.3, 47.0, 75.4, 108.5, 110.5, 142.6, 150.1, 201.9$  ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>43b</sup>

### (2*S*,3*R*)-2-Ethyl-4-nitro-3-phenylbutanal (**34j**)



Prepared from butanal and *trans*- $\beta$ -nitrostyrene (**15a**) according to general procedure D and obtained as a white solid in 95% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3;  $R_f = 0.39$ ).

**HPLC analysis:** Chiralcel OD-H, *n*-heptane:*i*PrOH = 95:5, 0.7 mL/min,  $t_{\text{ret}} = 44.0$  (*syn*, major), 46.5 (*anti*, major), 54.1 (*syn*, minor), 88.5 (*anti*, minor) min.

**Optical rotation:**  $[\alpha]_D^{22} = -37.5$  ( $c = 1$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 0.82 (t,  $J$  = 7.5 Hz, 3H), 1.44-1.56 (m, 2H), 2.63-2.72 (m, 1H), 3.79 (dt,  $J$  = 5.1, 9.8 Hz, 1H), 4.63 (dd,  $J$  = 9.6, 12.6 Hz, 1H), 4.72 (dd,  $J$  = 5.1, 12.7 Hz, 1H), 7.15-7.21 (m, 2H), 7.25-7.38 (m, 3H), 9.70 (d,  $J$  = 2.5 Hz, 1H) ppm.

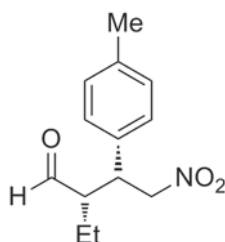
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 10.6, 20.3, 42.6, 54.9, 78.5, 127.9, 128.0, 129.0, 136.8, 203.1 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 0.98 (t,  $J$  = 7.4 Hz, 3H), 1.44-1.56 (m, 2H), 2.52-2.62 (m, 1H), 3.79 (dt,  $J$  = 5.1, 9.8 Hz, 1H), 4.63 (dd,  $J$  = 9.6, 12.6 Hz, 1H), 4.77-4.83 (m, 1H), 7.15-7.21 (m, 2H), 7.25-7.38 (m, 3H), 9.48 (d,  $J$  = 2.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.4, 20.5, 44.0, 54.6, 77.9, 128.1, 128.2, 128.7, 136.3, 203.2 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>37a</sup>

### (2*S*,3*R*)-2-Ethyl-4-nitro-3-(*p*-tolyl)butanal (34k)



Prepared from butanal and *trans*-4-methyl- $\beta$ -nitrostyrene according to general procedure D and obtained as a colorless oil in 90% yield after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3;  $R_f$  = 0.39).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 95:5, 0.8 mL/min,  $t_{ret}$ : 19.2 (*syn*, minor), 21.2 (*anti*, minor), 22.6 (*anti*, major), 23.6 (*syn*, major) min.

**Optical rotation:**  $[\alpha]_D^{22} = -32.9$  ( $c$  = 1, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 0.82 (t,  $J$  = 7.4 Hz, 3H), 1.44-1.56 (m, 2H), 2.31 (s, 3H), 2.60-2.69 (m, 1H), 3.75 (dt,  $J$  = 5.1, 9.9 Hz, 1H), 4.59 (dd,  $J$  = 9.6, 12.6 Hz, 1H), 4.69 (dd,  $J$  = 5.2, 12.6 Hz, 1H), 7.03-7.08 (m, 2H), 7.11-7.17 (m, 2H), 9.70 (d,  $J$  = 2.7 Hz, 1H) ppm.

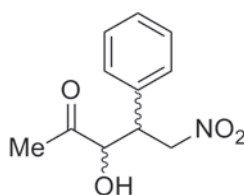
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 10.6, 20.3, 21.0, 42.3, 55.0, 78.6, 127.8, 129.7, 133.6, 137.7, 203.3 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 0.97 (d,  $J$  = 7.4 Hz, 3H), 1.44-1.56 (m, 2H), 2.30 (s, 3H), 2.50-2.59 (m, 1H), 3.75 (dt,  $J$  = 5.1, 9.9 Hz, 1H), 4.59 (dd,  $J$  = 9.6, 12.6 Hz, 1H), 4.71-4.80 (m, 1H), 7.03-7.08 (m, 2H), 7.11-7.17 (m, 2H), 9.47 (d,  $J$  = 3.0 Hz, 1H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 11.4, 20.5, 21.1, 43.8, 54.9, 78.0, 128.0, 129.8, 133.9, 137.9, 203.4 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>154b</sup>

### 3-Hydroxy-5-nitro-4-phenylpentan-2-one (18a)



Prepared from hydroxyacetone (**14a**) and *trans*- $\beta$ -nitrostyrene (**15a**) in solvent (see Table 5) according to general procedure D and obtained as a colorless oil after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3;  $R_f$  = 0.35).

**HPLC analysis:** Chiralcel OD-H, *n*-heptane:*i*PrOH = 9:1, 0.8 mL/min,  $t_{ret}$ : 20.7 (*syn*, minor), 36.2 (*anti*, major), 43.2 (*syn*, major), 79.6 (*anti*, minor) min.

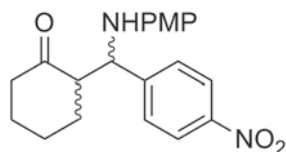
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 2.16 (s, 3H), 3.73 (d,  $J$  = 4.7 Hz, 1H), 4.03 (dt,  $J$  = 3.0, 7.6 Hz, 1H), 4.52 (dd,  $J$  = 3.1, 4.6 Hz, 1H), 4.73 (dd,  $J$  = 7.1, 13.5 Hz, 1H), 5.02 (dd,  $J$  = 8.0, 13.5 Hz, 1H), 7.20-7.40 (m, 5H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):**  $\delta$  = 25.4, 45.6, 76.0, 76.9, 128.4, 128.6, 128.9, 133.7, 206.2 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 2.05 (s, 3H), 3.71-3.75 (m, 1H), 3.79-3.87 (m, 1H), 4.36-4.41 (m, 1H), 4.65 (dd,  $J$  = 8.2, 13.6 Hz, 1H), 4.82 (dd,  $J$  = 6.3, 13.6 Hz, 1H), 7.20-7.40 (m, 5H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):**  $\delta$  = 26.4, 46.8, 76.0, 78.6, 127.9, 128.4, 129.3, 137.1, 207.9 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>37c</sup>

**2-[[[4-Methoxyphenylamino)-4-nitrophenyl]methyl]cyclohexanone (142)**

Prepared from cyclohexanone (**14b**) and imine **60a** in solvent (see Table 6) according to general procedure D and obtained as a colorless oil after column chromatography (*n*-pentane:Et<sub>2</sub>O = 7:3; *R<sub>f</sub>* = 0.35).

**HPLC analysis:** Chiralpak AD, *n*-heptane:*i*PrOH = 87:13, 0.9 mL/min, *t<sub>ret</sub>*: 32.1 (*anti*), 35.6 (*anti*), 40.2 (*syn*), 43.4 (*syn*) min.

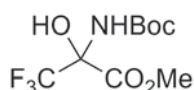
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, major diastereomer):** δ = 1.55-1.81 (m, 3H), 1.83-2.12 (m, 3H), 2.26-2.46 (m, 2H), 2.77-2.88 (m, 1H), 3.66 (s, 3H), 4.50 (br s, 1H), 4.66 (d, *J* = 5.8 Hz, 1H), 6.43-6.49 (m, 2H), 6.63-6.69 (m, 2H), 7.51-7.58 (m, 2H), 8.09-8.15 (m, 2H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, major diastereomer):** δ = 24.3, 27.6, 31.7, 42.2, 55.5, 56.9, 58.5, 114.7, 114.9, 123.4, 128.3, 140.7, 146.8, 150.0, 152.3, 211.7 ppm.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, minor diastereomer):** δ = 1.55-1.81 (m, 3H), 1.83-2.12 (m, 3H), 2.26-2.46 (m, 2H), 2.77-2.88 (m, 1H), 3.66 (s, 3H), 4.50 (br s, 1H), 4.80 (d, *J* = 4.4 Hz, 1H), 6.43-6.49 (m, 2H), 6.63-6.69 (m, 2H), 7.51-7.58 (m, 2H), 8.09-8.15 (m, 2H) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, minor diastereomer):** δ = 24.8, 27.0, 28.7, 42.3, 55.5, 56.2, 57.9, 114.6, 115.4, 123.4, 128.4, 140.7, 146.8, 149.9, 152.5, 210.7 ppm.

The spectroscopic data are in accordance with those reported in the literature.<sup>27a</sup>

**4.7 Synthesis of Trifluoropyruvate Derived Imines****Methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-hydroxypropanoate (158d)**

To a stirred solution of *tert*-butyl carbamate (**157a**) (1.17 g, 10 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added methyl trifluoropyruvate (**149b**) (1.02 mL, 10 mmol) at room temperature. After 1 hour, the

solvent was evaporated *in vacuo* and the product was obtained as white crystals in quantitative yield.

**Mp.:** 80 °C.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ = 1.46 (s, 9H), 3.94 (s, 3H), 5.39 (br s, 1H), 5.75 (br s, 1H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ = −80.73 (s, 3F) ppm.

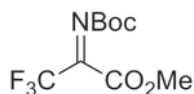
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ = 28.0, 54.7, 81.0 (q, *J* = 32.5 Hz), 82.6, 121.5 (q, *J* = 287.5 Hz), 153.9, 166.7 ppm.

**IR:** ν = 668, 739, 780, 829, 951, 978, 1048, 1121, 1153, 1254, 1369, 1712, 1753 cm<sup>−1</sup>.

**MS (CI, methane):** *m/z* (%) = 274 ([M+H]<sup>+</sup>, 30), 258 (4), 218 (100), 156 (58).

**CHN analysis (C<sub>9</sub>H<sub>14</sub>F<sub>3</sub>NO<sub>5</sub>):** calcd.: C: 39.57, H: 5.17, N: 5.13; found: C: 39.21, H: 5.16, N: 5.15.

### Methyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151e**)



A solution of methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-hydroxypropanoate (**158d**) (2.7 g, 10 mmol) in diethyl ether (50 mL) was cooled to 0 °C under an Ar atmosphere. Simultaneously, pyridine (1.6 mL, 20 mmol, 2.0 equiv.) and trifluoroacetic anhydride (1.4 mL, 10 mmol) were added to the solution with the help of a syringe pump (2 mL/h). The mixture was then stirred for another hour at 0 °C before removing the salts. The filtrate was then treated with *n*-hexane and left in a fridge overnight. The pyridinium trifluoroacetate crystals were filtered off and washed with *n*-hexane. After evaporation of the solvent, the crude product was distilled under high vacuum (*T<sub>b</sub>* = 40 °C at 3.7·10<sup>−1</sup> mbar) to afford a colorless liquid in 75% yield.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ = 1.58 (s, 9H), 3.95 (s, 3H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):** δ = −70.27 (s, 3F) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ = 27.9, 53.9, 85.5, 118.0 (q, *J* = 277.3 Hz), 155.5, 157.0, 166.6 ppm.

**IR:** ν = 686, 731, 844, 975, 1044, 1154, 1205, 1277, 1331, 1373, 1442, 1754, 2985 cm<sup>−1</sup>.

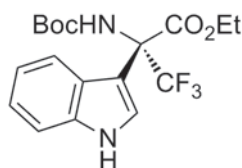
This compound is very hygroscopic and no additional analytical data was obtained.

## 4.8 Synthesis of $\alpha$ -Trifluoromethyl $\alpha$ -Amino Acid Derivatives

### General Procedure E

To a stirred solution of *N*-protected trifluoropyruvate imine **151** (0.075 mmol, 1.2 equiv.) in toluene (0.75 mL) was added TRIP (**75e**) (2.8 mg,  $3.7 \cdot 10^{-3}$  mmol, 0.06 equiv.) at room temperature under an Ar atmosphere. After stirring for 5 min, the reaction mixture was cooled to  $-78$  °C and stirred for additional 10 min. Then, the indole derivative **19** (0.063 mmol) was added. After 3 h, water (3 mL) and  $\text{CH}_2\text{Cl}_2$  (2 mL) were added and the mixture was allowed to reach room temperature. The phases were separated and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3x 3 mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The product was then purified by column chromatography.

### (*R*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(1*H*-indol-3-yl)-propanoate (**156c**)



Prepared from indole (**19a**) and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 4:1;  $R_f$  = 0.27).

**Mp.:** 134 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 9.2 (*S*), 10.4 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +39.8$  ( $c = 0.70$ ,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.20 (t,  $J = 7.1$  Hz, 3H), 1.37 (s, 9H), 4.20-4.32 (m, 2H), 5.92 (br s, 1H), 7.10-7.22 (m, 4H), 7.72 (d,  $J = 8.0$  Hz, 1H), 8.55 (br s, 1H) ppm.

**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):**  $\delta$  =  $-72.12$  (s, 3F) ppm.

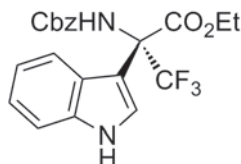
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.8, 28.1, 63.0, 64.9 (q,  $J = 29.4$  Hz), 80.8, 106.8, 111.7, 119.7, 120.3, 122.5, 124.2 (q,  $J = 285.5$  Hz), 124.4, 124.6, 129.9, 136.1, 153.4, 166.5 ppm.

**IR:**  $\nu$  = 746, 872, 917, 978, 1028, 1152, 1188, 1257, 1291, 1369, 1483, 1717, 1751, 3370  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 386 ( $[M+H]^+$ , 46), 330 (11), 313 (7), 270 (17), 257 (52), 239 (10), 213 (95), 143 (26), 116 (9), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for  $C_{18}H_{21}F_3N_2O_4$   $[M+Na]^+$ : 409.1346, found: 409.1335.

**(R)-Ethyl 2-[[[(benzyloxy)carbonyl]amino]-3,3,3-trifluoro-2-(1*H*-indol-3-yl)-propanoate (156d)**



Prepared from indole (**19a**) and ethyl 2-[[[(benzyloxy)carbonyl]imino]-3,3,3-trifluoropropanoate (**151c**) according to general procedure E and obtained as a white solid in 71% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.28).

**Mp.:** 108 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 3:2, 0.5 mL/min,  $t_{ret}$ : 12.6 (*S*), 16.3 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +23.3$  ( $c = 1.16$ ,  $CHCl_3$ ).

**$^1H$  NMR (300 MHz,  $CDCl_3$ ):**  $\delta$  = 1.12 (t,  $J = 7.1$  Hz, 3H), 4.11-4.32 (m, 2H), 5.04 (s, 2H), 6.36 (br s, 1H), 7.05-7.30 (m, 9H), 7.59 (d,  $J = 7.9$  Hz, 1H), 8.62 (br s, 1H) ppm.

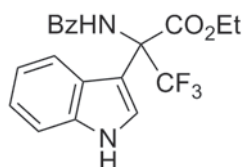
**$^{19}F$  NMR (282 MHz,  $CDCl_3$ ):**  $\delta$  = -71.66 (s, 3F) ppm.

**$^{13}C$  NMR (75 MHz,  $CDCl_3$ ):**  $\delta$  = 13.7, 63.5, 65.0 (q,  $J = 30.0$  Hz), 67.1, 105.7, 111.9, 119.0, 120.3, 124.1 (q,  $J = 285.0$  Hz), 124.4, 124.8, 127.9, 128.1, 128.5, 135.9, 136.0, 153.9, 166.4 ppm.

**IR:**  $\nu$  = 698, 741, 855, 909, 987, 1023, 1185, 1253, 1424, 1460, 1496, 1729, 3390  $cm^{-1}$ .

**MS (EI):**  $m/z$  (%) = 420 ( $[M]^+$ , 85), 347 (22), 303 (47), 270 (4), 239 (16), 213 (5), 143 (14), 116 (5), 91 (100).

**CHN analysis ( $C_{21}H_{19}F_3N_2O_4$ ):** calcd.: C: 60.00, H: 4.56, N: 6.66; found: C: 59.83, H: 4.62, N: 6.65.

**Ethyl 2-benzamido-3,3,3-trifluoro-2-(1*H*-indol-3-yl)propanoate (156e)**

Prepared from indole (**19a**) and ethyl 2-(benzoylimino)-3,3,3-trifluoropropanoate (**151d**) according to general procedure E and obtained as a white solid in 96% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.32).

**Mp.:** 148-151 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 3:2, 0.5 mL/min,  $t_{ret}$ : 17.0, 48.4 min.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.18 (t,  $J$  = 7.2 Hz, 3H), 4.20-4.38 (m, 2H), 7.06-7.18 (m, 2H), 7.26-7.32 (m, 2H), 7.42-7.57 (m, 4H), 7.69 (d, 1H), 7.83-7.87 (m, 2H), 9.05 (br s, 1H) ppm.

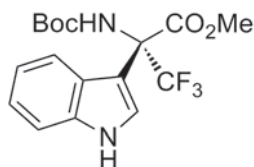
**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -70.77 (s, 3F) ppm.

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.8, 63.3, 65.0 (q,  $J$  = 30.0 Hz), 105.8, 112.1, 119.1, 120.4, 122.4, 124.3 (q,  $J$  = 286.0 Hz), 124.5, 125.0, 127.2, 128.8, 132.2, 133.7, 136.2, 166.0, 166.5 ppm.

**IR:**  $\nu$  = 718, 755, 1031, 1188, 1270, 1339, 1382, 1479, 1510, 1677, 1747, 2920, 3398  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 390 ( $[\text{M}]^+$ , 13), 317 (10), 298 (3), 143 (18), 105 (100), 77 (52).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{20}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 391.1264, found: 391.1267.

**(*R*)-Methyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(1*H*-indol-3-yl)-propanoate (156f)**

Prepared from indole (**19a**) and methyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151e**) according to general procedure E and obtained as a white solid in 73% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.41).

**Mp.:** 125-126 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{ret}$ : 9.5 (*S*), 12.3 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +32.4$  ( $c = 0.24$ ,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta = 1.36$  (s, 9H), 3.80 (s, 3H), 5.87 (br s, 1H), 7.10-7.36 (m, 4H), 7.68-7.73 (m, 1H), 8.46 (br s, 1H) ppm.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta = -72.24$  (s, 3F) ppm.

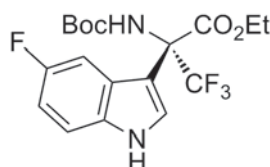
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta = 28.0, 53.5, 65.2$  (q,  $J = 30.9$  Hz), 80.9, 107.1, 111.7, 119.8, 120.6, 122.7, 124.1 (q,  $J = 285.9$  Hz), 124.2, 124.6, 136.0, 153.4, 167.0 ppm.

**IR:**  $\nu = 686, 746, 803, 862, 913, 971, 1010, 1052, 1088, 1117, 1160, 1227, 1256, 1370, 1435, 1460, 1492, 1721, 3319, 3411$   $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 372 ( $[\text{M}]^+$ , 85), 316 (28), 313 (5), 257 (80), 256 (36), 239 (12), 213 (100), 143 (24), 69 (35), 57 (97).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$   $[\text{M}+\text{Na}]^+$ : 395.1189, found: 395.1190.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-2-(5-fluoro-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (156g)**



Prepared from 5-fluoroindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f = 0.32$ ).

**Mp.:** 178-180 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 8.5 (*R*), 10.1 (*S*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +17.6$  ( $c = 0.85$ ,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta = 1.20$  (t,  $J = 7.2$  Hz, 3H), 1.39 (s, 9H), 4.18-4.35 (m, 2H), 5.95 (br s, 1H), 6.83-6.90 (m, 1H), 6.96-7.04 (m, 1H), 7.29-7.35 (m, 2H), 8.68 (br s, 1H) ppm.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta = -123.59$  (s, 1F),  $-72.28$  (s, 3F) ppm.

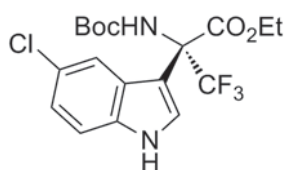
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta = 13.8, 28.1, 63.3, 64.8$  (q,  $J = 29.5$  Hz), 81.0, 104.5 (d,  $J = 25.3$  Hz), 106.4, 110.9 (d,  $J = 26.2$  Hz), 112.3 (d,  $J = 9.8$  Hz), 124.1 (q,  $J = 285.8$  Hz), 125.0 (d,  $J = 10.4$  Hz), 126.3, 132.6, 153.4, 157.9 (d,  $J = 233.6$  Hz), 166.3 ppm.

**IR:**  $\nu$  = 668, 761, 801, 862, 913, 979, 1027, 1074, 1110, 1178, 1266, 1371, 1489, 1583, 1632, 1744, 2934, 2983, 3403  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 404 ( $[\text{M}]^+$ , 59), 348 (15), 331 (10), 288 (18), 275 (56), 231 (100), 161 (32), 134 (9), 57 (95).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{20}\text{F}_4\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 405.1432, found: 405.1436.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-2-(5-chloro-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (156h)**



Prepared from 5-chloroindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as colorless oil in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.32).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 9:1, 0.5 mL/min,  $t_{\text{ret}}$ : 19.5 (*S*), 31.0 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +19.4$  ( $c$  = 0.66,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.20 (t,  $J$  = 7.1 Hz, 3H), 1.40 (s, 9H), 4.18-4.35 (m, 2H), 6.01 (br s, 1H), 6.92-7.26 (m, 3H), 7.63 (s, 1H), 8.75 (br s, 1H) ppm.

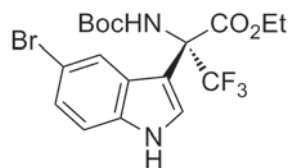
**$^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -72.35 (s, 3F) ppm.

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.8, 28.1, 63.4, 64.8 (q,  $J$  = 29.5 Hz), 81.1, 106.1, 112.6, 118.9, 122.8, 124.0 (q,  $J$  = 285.8 Hz), 125.8, 125.9, 125.9, 134.4, 153.3, 166.3 ppm.

**IR:**  $\nu$  = 759, 797, 872, 894, 979, 1026, 1109, 1164, 1260, 1372, 1490, 1728, 2931, 2983, 3395  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 420 ( $[\text{M}]^+$ , 66), 364 (13), 347 (8), 304 (14), 291 (33), 273 (7), 247 (39), 177 (10), 150 (2), 69 (2), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{20}\text{ClF}_3\text{N}_2\text{O}_4$   $[\text{M}+\text{Na}]^+$ : 443.0956, found: 443.0950.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-2-(5-bromo-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (156i)**

Prepared from 5-bromoindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 85% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.45).

**Mp.:** 174 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{ret}$ : 7.8 (*S*), 9.4 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +17.9$  ( $c$  = 0.97, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 1.19 (t,  $J$  = 7.0 Hz, 3H), 1.42 (s, 9H), 4.15-4.36 (m, 2H), 6.12 (br s, 1H), 6.68-6.80 (m, 1H), 7.08-7.17 (m, 2H), 7.74 (br s, 1H), 8.95 (br s, 1H) ppm.

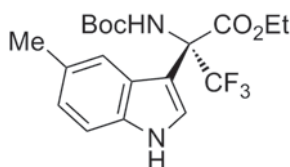
**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  = -72.30 (s, 3F) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  = 13.7, 28.1, 63.6, 64.9 (q,  $J$  = 29.8 Hz), 81.1, 105.2, 113.1, 113.3, 121.6, 123.9 (q,  $J$  = 285.8 Hz), 125.1, 126.1, 126.3, 134.7, 153.4, 166.3 ppm.

**IR:**  $\nu$  = 797, 885, 916, 977, 1022, 1094, 1119, 1156, 1256, 1292, 1369, 1390, 1460, 1489, 1717, 3360 cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 464 ( $[M]^+$ , 20), 408 (5), 391 (2), 335 (18), 317 (4), 291 (27), 221 (4), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for C<sub>18</sub>H<sub>20</sub>BrF<sub>3</sub>N<sub>2</sub>O<sub>4</sub>  $[M+K]^+$ : 503.0190, found: 503.0178.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(5-methyl-1*H*-indol-3-yl)propanoate (156j)**

Prepared from 5-methylindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.40).

**Mp.:** 137 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 7.8 (*S*), 8.9 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +39.2$  ( $c = 1.10$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta = 1.22$  (t,  $J = 7.2$  Hz, 3H), 1.37 (s, 9H), 3.09 (s, 3H), 4.21-4.32 (m, 2H), 5.86 (br s, 1H), 7.00-7.02 (m, 1H), 7.16-7.22 (m, 2H), 7.50 (br s, 1H), 8.37 (br s, 1H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta = -72.09$  (s, 3F) ppm.

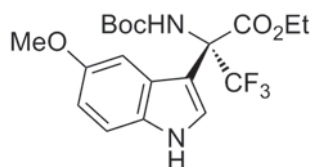
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta = 13.8, 21.6, 28.1, 62.9, 64.9$  (q,  $J = 28.8$  Hz), 80.8, 106.6, 111.3, 119.4, 124.2 (q,  $J = 285.5$  Hz), 124.2, 124.3, 124.9, 129.7, 134.4, 153.4, 166.5 ppm.

**IR:**  $\nu = 794, 869, 909, 977, 1023, 1158, 1256, 1369, 1489, 1722, 3338, 3396$  cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 400 ([M]<sup>+</sup>, 48), 344 (6), 327 (3), 284 (8), 271 (22), 253 (5), 227 (54), 157 (13), 130 (6), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for C<sub>19</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 401.1683, found: 401.1674.

**(*R*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-2-(5-methoxy-1*H*-indol-3-yl)-3,3,3-trifluoropropanoate (**156k**)**



Prepared from 5-methoxyindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f = 0.41$ ).

**Mp.:** 62 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 9.2 (*S*), 10.5 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +42.1$  ( $c = 0.54$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta = 1.23$  (t,  $J = 7.2$  Hz, 3H), 1.37 (s, 9H), 3.85 (s, 3H), 4.27 (q,  $J = 7.1$  Hz, 2H), 5.82 (br s, 1H), 6.85-6.90 (m, 1H), 7.19-7.23 (m, 2H), 7.28-7.30 (m, 1H), 8.33 (br s, 1H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta = -72.14$  (s, 3F) ppm.

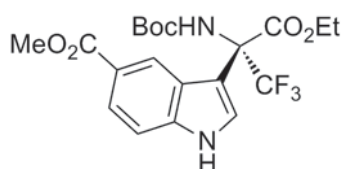
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.9, 28.1, 55.8, 62.9, 64.5 (q,  $J$  = 29.7 Hz), 80.8, 101.7, 106.9, 112.3, 113.0, 124.2 (q,  $J$  = 271.3 Hz), 124.7, 125.2, 131.1, 153.4, 154.4, 166.3 ppm.

**IR:**  $\nu$  = 758, 803, 911, 980, 1032, 1168, 1218, 1261, 1372, 1488, 1583, 1738, 2937, 2983, 3399  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 416 ( $[\text{M}]^+$ , 100), 360 (13), 343 (3), 300 (12), 287 (21), 243 (76), 173 (10), 57 (70).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$ : 417.1632, found: 417.1633.

**(*R*)-Methyl 3-{2-[(*tert*-butoxycarbonyl)amino]-3-ethoxy-1,1,1-trifluoro-3-oxo-propan-2-yl}-1*H*-indole-5-carboxylate (**156l**)**



Prepared from methyl indole-5-carboxylate and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as white crystals in 65% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.39).

**Mp.:** 112-114  $^{\circ}\text{C}$ .

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 4:1, 0.5 mL/min,  $t_{\text{ret}}$ : 18.6 (*R*), 21.6 (*S*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +7.7$  ( $c$  = 2.06,  $\text{CHCl}_3$ ).

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.19 (t,  $J$  = 7.1 Hz, 3H), 1.39 (s, 9H), 3.94 (s, 3H), 4.16-4.36 (m, 2H), 6.17 (br s, 1H), 6.89-6.96 (m, 1H), 7.25-7.28 (m, 1H), 7.74-7.80 (m, 1H), 8.40-8.42 (m, 1H), 9.10 (br s, 1H) ppm.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -72.44 (s, 3F) ppm.

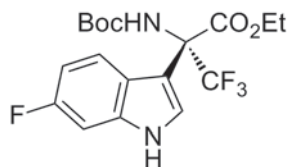
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.7, 28.1, 51.9, 63.5, 64.9 (q,  $J$  = 30.0 Hz), 81.1, 107.2, 111.4, 122.1, 122.1, 123.6, 124.0 (q,  $J$  = 286.0 Hz), 124.3, 126.3, 138.7, 153.5, 166.3, 168.0 ppm.

**IR:**  $\nu$  = 751, 822, 861, 916, 978, 1025, 1115, 1157, 1257, 1369, 1438, 1502, 1620, 1697, 2982, 3329  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 444 ( $[\text{M}]^+$ , 48), 413 (6), 388 (10), 371 (8), 328 (6), 298 (8), 271 (100), 201 (6), 57 (55).

**HRMS (ESI):**  $m/z$  calcd. for  $C_{20}H_{23}F_3N_2O_6$   $[M+Na]^+$ : 467.1400, found: 467.1389.

**(*R*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(6-fluoro-1*H*-indol-3-yl)propanoate (156m)**



Prepared from 6-fluoroindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 97% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.40).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{ret}$ : 8.9 (*S*), 10.2 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +9.5$  ( $c = 1.43$ ,  $CHCl_3$ ).

**$^1H$  NMR (400 MHz,  $CDCl_3$ ):**  $\delta$  = 1.17 (t,  $J = 7.1$  Hz, 3H), 1.39 (s, 9H), 4.17-4.33 (m, 2H), 6.06 (br s, 1H), 6.65 (br s, 1H), 6.83-6.88 (m, 1H), 7.17 (br s, 1H), 7.53-7.57 (m, 1H), 8.79 (br s, 1H) ppm.

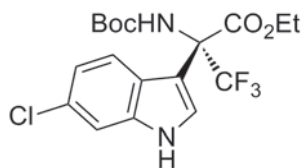
**$^{19}F$  NMR (376 MHz,  $CDCl_3$ ):**  $\delta$  = -72.21 (s, 3F), -120.84 (s, 1F) ppm.

**$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):**  $\delta$  = 13.7, 28.1, 63.4, 65.0 (q,  $J = 30.0$  Hz), 80.9, 97.8 (d,  $J = 26.0$  Hz), 106.1, 108.9 (d,  $J = 24.5$  Hz), 120.1 (d,  $J = 8.1$  Hz), 121.2, 124.1 (q,  $J = 287.5$  Hz), 125.0, 136.3 (d,  $J = 12.5$  Hz), 153.4, 159.8 (d,  $J = 238.6$  Hz), 166.5 ppm.

**IR:**  $\nu$  = 758, 914, 958, 1026, 1162, 1256, 1371, 1492, 1545, 1629, 1728, 2921, 2983, 3401  $cm^{-1}$ .

**MS (EI):**  $m/z$  (%) = 404 ( $[M]^+$ , 53), 348 (17), 331 (3), 288 (11), 275 (44), 257 (8), 231 (48), 161 (19), 134 (7), 73 (2), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for  $C_{18}H_{20}F_4N_2O_4$   $[M+Na]^+$ : 427.1251, found: 427.1246.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(6-chloro-1*H*-indol-3-yl)propanoate (156n)**

Prepared from 6-chloroindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 98% yield after column chromatography (*n*-pentane:ethyl acetate = 4:1;  $R_f$  = 0.31).

**Mp.:** 122 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{ret}$ : 8.9 (*S*), 10.5 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +20.3$  ( $c$  = 1.43, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  = 1.17 (t,  $J$  = 7.2 Hz, 3H), 1.39 (s, 9H), 4.16-4.35 (m, 2H), 6.05 (br s, 1H), 6.92-7.07 (m, 2H), 7.16-7.24 (m, 1H), 7.54 (d,  $J$  = 8.7 Hz, 1H), 8.76 (br s, 1H) ppm.

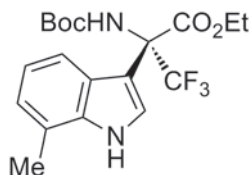
**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta$  = -72.25 (s, 3F) ppm.

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  = 13.7, 28.1, 63.5, 64.9 (q,  $J$  = 30.0 Hz), 81.0, 106.2, 111.5, 120.0, 120.8, 123.2, 124.0 (q,  $J$  = 287.7 Hz), 125.3, 128.4, 136.5, 153.4, 166.4 ppm.

**IR:**  $\nu$  = 669, 759, 912, 1023, 1165, 1216, 1258, 1372, 1491, 1726, 2919, 3439 cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 420 ( $[M]^+$ , 27), 364 (13), 347 (2), 304 (8), 291 (30), 273 (4), 247 (40), 177 (8), 150 (3), 112 (78), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for C<sub>18</sub>H<sub>20</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>4</sub>  $[M+Na]^+$ : 443.0956, found: 443.0952.

**(R)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(7-methyl-1*H*-indol-3-yl)propanoate (156o)**

Prepared from 7-methylindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 99% yield after column chromatography (*n*-pentane:ethyl acetate = 7:3;  $R_f$  = 0.47).

**Mp.:** 182-184 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 9.0 (*S*), 9.9 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +21.9$  ( $c = 0.67$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta = 1.18$  (t,  $J = 7.2$  Hz, 3H), 1.38 (s, 9H), 2.05 (br s, 3H), 4.14-4.33 (m, 2H), 6.05 (br s, 1H), 6.90-7.04 (m, 2H), 7.25-7.28 (m, 1H), 7.49-7.52 (m, 1H), 8.47 (br s, 1H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta = -72.10$  (s, 3F) ppm.

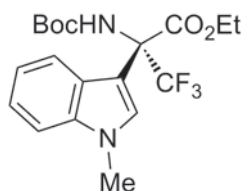
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta = 13.8, 16.2, 28.2, 63.1, 65.0$  (q,  $J = 29.8$  Hz), 80.6, 106.5, 117.1, 120.4, 121.1, 122.8, 124.2 (q,  $J = 285.8$  Hz), 124.2, 125.3, 135.5, 153.3, 166.6 ppm.

**IR:**  $\nu = 731, 777, 860, 907, 982, 1034, 1149, 1190, 1256, 1292, 1370, 1446, 1485, 1711, 1752, 2984, 3355$  cm<sup>-1</sup>.

**MS (EI):**  $m/z$  (%) = 400 ([M]<sup>+</sup>, 75), 344 (14), 327 (5), 284 (14), 271 (48), 227 (100), 157 (15), 130 (5), 57 (43).

**HRMS (ESI):**  $m/z$  calcd. for C<sub>19</sub>H<sub>23</sub>F<sub>3</sub>N<sub>2</sub>O<sub>4</sub> [M+Na]<sup>+</sup>: 423.1502, found: 423.1496.

**(*R*)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(*N*-methyl-1*H*-indol-3-yl)propanoate (156p)**



Prepared from *N*-methylindole and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 22% yield after column chromatography (*n*-pentane:ethyl acetate = 7.5:2.5;  $R_f = 0.56$ ).

**Mp.:** 125 °C.

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 9.9 (*S*), 12.9 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = +3.0$  ( $c = 0.2$ , CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta = 1.23$  (t,  $J = 7.2$  Hz, 3H), 1.37 (s, 9H), 3.79 (s, 3H), 4.27 (q,  $J = 7.1$  Hz, 2H), 5.76 (br s, 1H), 7.12-7.34 (m, 4H), 7.76 (d,  $J = 8.2$  Hz, 1H) ppm.

**<sup>19</sup>F NMR (282 MHz, CDCl<sub>3</sub>):**  $\delta = -72.20$  (s, 3F) ppm.

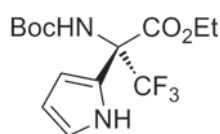
**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.8, 28.0, 33.1, 62.7, 64.9 (q,  $J$  = 31.5 Hz), 80.8, 105.8, 109.7, 120.2, 120.3, 122.3, 124.2 (q,  $J$  = 287.2 Hz), 125.3, 128.6, 136.9, 153.4, 166.3 ppm.

**IR:**  $\nu$  = 675, 741, 774, 858, 901, 976, 1026, 1155, 1252, 1368, 1479, 1702, 1746  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 400 ( $[\text{M}]^+$ , 99), 344 (7), 327 (8), 284 (15), 271 (46), 227 (92), 157 (20), 130 (4), 57 (100).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 401.1683, found: 401.1679.

**(S)-Ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(1*H*-pyrrol-2-yl)-propanoate (164a)**



Prepared from pyrrole (**116a**) and ethyl 2-[(*tert*-butoxycarbonyl)imino]-3,3,3-trifluoropropanoate (**151b**) according to general procedure E and obtained as a white solid in 37% yield after column chromatography (*n*-pentane:ethyl acetate = 8.5:1.5;  $R_f$  = 0.38).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min,  $t_{\text{ret}}$ : 8.3 (*R*), 9.8 (*S*) min.

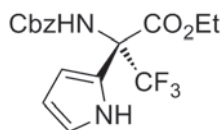
**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.31 (t,  $J$  = 7.2 Hz, 3H), 1.41 (s, 9H), 4.33 (q,  $J$  = 7.1 Hz, 2H), 5.54 (br s, 1H), 6.15-6.19 (m, 1H), 6.31-6.36 (m, 1H), 6.80-6.84 (m, 1H), 9.22 (br s, 1H) ppm.

**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -73.18 (s, 3F) ppm.

**IR:**  $\nu$  = 708, 736, 798, 897, 981, 1027, 1061, 1159, 1290, 1368, 1488, 1736, 2984, 3379  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 336 ( $[\text{M}]^+$ , 24), 280 (9), 263 (12), 220 (15), 207 (100), 163 (35), 139 (4), 57 (50).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{14}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 337.1370, found: 337.1373.

**(S)-Ethyl 2-[[[(benzyloxy)carbonyl]amino]-3,3,3-trifluoro-2-(1H-pyrrol-2-yl)-propanoate (164b)**

Prepared from pyrrole (**116a**) and ethyl 2-[[[(benzyloxy)carbonyl]imino]-3,3,3-trifluoropropanoate (**151c**) according to general procedure E and obtained as a white solid in 71% yield after column chromatography (*n*-pentane:ethyl acetate = 4:1;  $R_f$  = 0.38).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 4:1, 0.6 mL/min,  $t_{ret}$ : 13.6 (*R*), 17.6 (*S*) min.

**$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.24 (t,  $J$  = 7.1 Hz, 3H), 4.28 (q,  $J$  = 6.7 Hz, 2H), 5.10 (s, 2H), 5.75 (br s, 1H), 6.15-6.20 (m, 1H), 6.31-6.36 (m, 1H), 6.80-6.84 (m, 1H), 7.27-7.39 (m, 5H), 9.18 (br s, 1H) ppm.

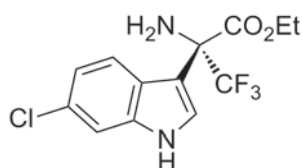
**$^{19}\text{F}$  NMR (282 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = -72.78 (s, 3F) ppm.

**$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 13.7, 63.5, 64.3 (q,  $J$  = 31.4 Hz), 67.7, 108.6, 109.6, 119.9, 121.2, 123.2 (q,  $J$  = 287.0 Hz), 128.2, 128.4, 128.5, 135.5, 154.4, 165.3 ppm.

**IR:**  $\nu$  = 699, 757, 1029, 1062, 1098, 1222, 1259, 1374, 1457, 1504, 1741, 3391  $\text{cm}^{-1}$ .

**MS (EI):**  $m/z$  (%) = 370 ( $[\text{M}]^+$ , 30), 301 (3), 297 (46), 220 (1), 91 (100), 65 (12).

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{17}\text{F}_3\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 371.1213, found: 371.1215.

**(R)-Ethyl 2-amino-2-(6-chloro-1H-indol-3-yl)-3,3,3-trifluoropropanoate (152b)**

To a stirred solution of (*R*)-ethyl 2-[(*tert*-butoxycarbonyl)amino]-3,3,3-trifluoro-2-(6-chloro-1H-indol-3-yl)propanoate (**156n**) (47 mg, 0.112 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) at 0 °C was added trifluoroacetic acid (86  $\mu\text{L}$ , 1.12 mmol, 100 equiv.). The reaction mixture was allowed to reach room temperature in the course of 3 hours and was quenched with so much saturated aq.  $\text{NaHCO}_3$ -solution until the aqueous phase was basic. The phases were separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3x 3 mL). The combined organic extracts were dried over

MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The product was obtained as a colorless oil in 98% yield after column chromatography (*n*-pentane:ethyl acetate = 3:2; R<sub>f</sub> = 0.35).

**HPLC analysis:** Chiralpak AD-H, *n*-heptane:*i*PrOH = 7:3, 0.5 mL/min, t<sub>ret</sub>: 11.4 (*S*), 13.4 (*R*) min.

**Optical rotation:**  $[\alpha]_D^{22} = -8.1$  (c = 1.3, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ = 1.25 (t, *J* = 7.1 Hz, 3H), 2.37 (br s, 2H), 4.22-4.37 (m, 2H), 7.11 (dd, *J* = 1.9, 8.7 Hz, 1H), 7.35-7.38 (m, 2H), 7.73 (d, *J* = 8.7 Hz, 1H), 8.32 (br s, 1H) ppm.

**<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>):** δ = -75.13 (s, 3F) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ = 13.9, 63.0, 64.3 (q, *J* = 29.0 Hz), 110.6, 111.3, 121.2, 121.6, 123.6, 124.3, 124.8 (q, *J* = 285.5 Hz), 128.7, 136.7, 168.9 ppm.

**IR:** ν = 758, 808, 907, 1020, 1166, 1213, 1244, 1337, 1372, 1400, 1456, 1540, 1617, 1738, 2926, 2983, 3408 cm<sup>-1</sup>.

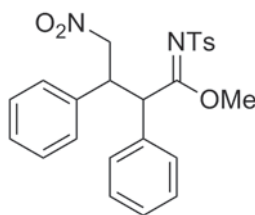
**MS (EI):** *m/z* (%) = 320 ([M]<sup>+</sup>, 72), 304 (34), 247 (100), 177 (35), 152 (40), 142 (22), 117 (70).

**HRMS (ESI):** *m/z* calcd. for C<sub>13</sub>H<sub>12</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 321.0612, found: 321.0616.

## 4.9 Synthesis of α-Functionalized Imidates

### General Procedure F

To a mixture of CuI (**103a**) (9.5 mg, 0.05 mmol, 0.1 equiv.), *p*-toluenesulfonyl azide (**101a**) (118.5 mg, 0.60 mmol, 1.2 equiv.) and nitroolefin **15** (0.50 mmol) in THF (1.5 mL) was slowly added phenylacetylene (**100a**) (66 μL, 0.60 mmol, 1.2 equiv.), methanol (101 μL, 2.5 mmol, 5.0 equiv.) and triethylamine (209 μL, 1.5 mmol, 3.0 equiv.) at room temperature under an N<sub>2</sub> atmosphere. After 24 hours, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (3 mL) and quenched with sat. NH<sub>4</sub>Cl-solution (3 mL) and 1N HCl-solution (3 mL). The mixture was stirred for additional 30 minutes and then the layers were separated. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x 6 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford the desired product.

**Methyl 4-nitro-2,3-diphenyl-*N*-tosylbutanimidate (124a)**

Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 73% yield (58:42 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.37).

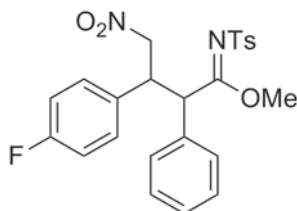
**Mp.:** 161-162 °C.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 2.35 (s, 1.5H), 2.41 (s, 1.5H), 3.48 (s, 1.5H), 3.77 (s, 1.5H), 4.28-4.35 (m, 1.5H), 4.48-4.53 (m, 0.5H), 4.68-4.72 (dd,  $J$  = 4.6, 12.8 Hz, 0.5H), 4.91-4.97 (dd,  $J$  = 10.2, 12.8 Hz, 0.5H), 5.28 (d,  $J$  = 11.6 Hz, 0.5H), 5.52 (d,  $J$  = 11.9 Hz, 0.5H), 7.12-7.18 (m, 5H), 7.29-7.42 (m, 6H), 7.55 (d,  $J$  = 8.3 Hz, 1H), 7.70 (d,  $J$  = 8.3 Hz, 1H), 7.84 (d,  $J$  = 8.3 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 21.3, 21.4, 47.1, 47.2, 51.0, 53.0, 55.4, 56.0, 78.7, 79.0, 126.4, 126.6, 127.8, 127.9, 128.0, 128.1, 128.4, 128.6, 128.8, 128.8, 129.0, 129.1, 129.3, 129.4, 129.4, 134.2, 136.3, 136.6, 138.4, 143.6, 170.9, 172.9 ppm.

**IR:**  $\nu$  = 601, 686, 702, 738, 815, 947, 1017, 1092, 1154, 1254, 1290, 1302, 1379, 1438, 1456, 1496, 1506, 1556, 1597, 1612, 1653  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 452.1406, found: 452.1409.

**Methyl 3-(4-fluorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124b)**

Prepared from *trans*-4-fluoro- $\beta$ -nitrostyrene (**15b**) and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 69% yield (54:46 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.34).

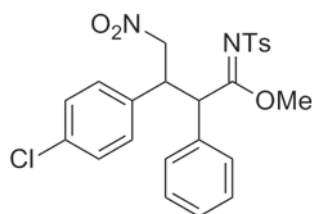
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.35 (s, 1.5H), 2.40 (s, 1.5H), 3.50 (s, 1.5H), 3.78 (s, 1.5H), 4.25-4.34 (m, 1.5H), 4.46-4.52 (m, 0.5H), 4.65-4.70 (m, 0.5H), 4.88-4.94 (dd,  $J$  = 10.5, 12.8 Hz, 0.5H), 5.22 (d,  $J$  = 11.6 Hz, 0.5H), 5.45 (d,  $J$  = 12.0 Hz, 0.5H), 6.81-6.85 (m, 1H), 6.97-7.02 (m, 1H), 7.10-7.19 (m, 3.5H), 7.28-7.43 (m, 4.5H), 7.57 (d,  $J$  = 8.3 Hz, 1H), 7.67 (d,  $J$  = 7.4 Hz, 1H), 7.82 (d,  $J$  = 8.3 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 21.4, 21.4, 46.4, 46.6, 51.1, 53.0, 55.5, 56.1, 78.6, 78.8, 115.7 (d,  $J$  = 21.4 Hz), 115.8 (d,  $J$  = 21.4 Hz), 126.4, 126.6, 128.0, 128.5, 129.0, 129.2, 129.3, 129.4, 129.6 (d,  $J$  = 8.2 Hz), 129.9 (d,  $J$  = 8.1 Hz), 132.1 (d,  $J$  = 3.1 Hz), 132.3 (d,  $J$  = 3.1 Hz), 134.0, 134.1, 138.3, 138.4, 143.4, 143.7, 162.0 (d,  $J$  = 245.5 Hz), 162.3 (d,  $J$  = 245.7 Hz), 170.8, 172.7 ppm.

**IR:**  $\nu$  = 604, 685, 736, 813, 839, 948, 1016, 1092, 1153, 1226, 1289, 1379, 1439, 1512, 1554, 1611 cm<sup>-1</sup>.

**HRMS (EI):**  $m/z$  calcd. for C<sub>24</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 470.1312, found: 470.1313.

### Methyl 3-(4-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124c)



Prepared from *trans*-4-chloro- $\beta$ -nitrostyrene (**15c**) and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 60% yield (56:44 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.43).

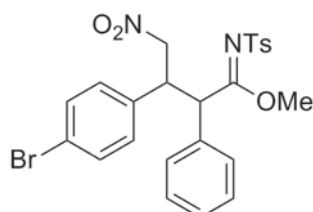
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.37 (s, 1.5H), 2.42 (s, 1.5H), 3.53 (s, 1.5H), 3.79 (s, 1.5H), 4.24-4.35 (m, 1.5H), 4.45-4.52 (m, 0.5H), 4.64-4.70 (dd,  $J$  = 4.5, 12.9 Hz, 0.5H), 4.87-4.95 (dd,  $J$  = 10.4, 12.9 Hz, 0.5H), 5.22 (d,  $J$  = 11.8 Hz, 0.5H), 5.44 (d,  $J$  = 11.8 Hz, 0.5H), 7.06-7.22 (m, 4.5H), 7.24-7.45 (m, 5.5H), 7.56 (d,  $J$  = 8.2 Hz, 1H), 7.66 (d,  $J$  = 6.9 Hz, 1H), 7.82 (d,  $J$  = 8.2 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 21.5, 21.6, 46.6, 46.7, 51.0, 52.9, 55.6, 56.2, 78.4, 78.7, 126.3, 126.6, 128.0, 128.5, 128.8, 128.9, 128.9, 129.0, 129.2, 129.2, 129.3, 129.4, 129.4, 129.5, 133.6, 133.8, 133.9, 134.0, 134.8, 135.0, 138.2, 138.2, 143.3, 143.7, 170.5, 172.4 ppm.

**IR:**  $\nu$  = 681, 743, 813, 915, 946, 1015, 1091, 1152, 1187, 1253, 1292, 1378, 1438, 1493, 1553, 1597  $\text{cm}^{-1}$ .

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{23}\text{ClN}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 487.1089, found: 487.1093.

### Methyl 3-(4-bromophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124d)



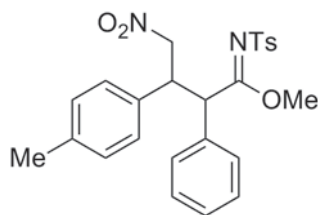
Prepared from *trans*-4-bromo- $\beta$ -nitrostyrene and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 65% yield (54:46 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.37).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 2.38 (s, 1.5H), 2.41 (s, 1.5H), 3.52 (s, 1.5H), 3.78 (s, 1.5H), 4.24-4.31 (m, 1.5H), 4.43-4.50 (m, 0.5H), 4.63-4.67 (dd,  $J$  = 4.5, 12.9 Hz, 0.5H), 4.86-4.92 (dd,  $J$  = 10.4, 12.9 Hz, 0.5H), 5.21 (d,  $J$  = 11.6 Hz, 0.5H), 5.43 (d,  $J$  = 11.7 Hz, 0.5H), 6.99-7.03 (m, 1H), 7.12-7.21 (m, 2.5H), 7.27-7.44 (m, 6.5H), 7.55 (d,  $J$  = 8.4 Hz, 1H), 7.65 (d,  $J$  = 6.9 Hz, 1H), 7.81 (d,  $J$  = 8.3 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 21.5, 21.5, 46.6, 46.7, 50.9, 52.8, 55.6, 56.2, 78.4, 78.7, 121.9, 122.4, 126.4, 126.7, 128.2, 128.6, 129.0, 129.0, 129.3, 129.5, 129.5, 129.7, 129.9, 131.9, 132.0, 133.9, 134.0, 135.5, 135.7, 138.3, 138.4, 143.5, 143.8, 170.6, 172.5 ppm.

**IR:**  $\nu$  = 603, 686, 707, 739, 814, 948, 1012, 1092, 1155, 1184, 1254, 1289, 1378, 1440, 1492, 1554, 1621, 2951  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{23}\text{BrN}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 532.0493, found: 532.0499.

**Methyl 4-nitro-2-phenyl-3-*p*-tolyl-*N*-tosylbutanimidate (124e)**

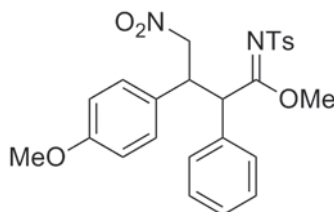
Prepared from *trans*-4-methyl- $\beta$ -nitrostyrene and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 58% yield (57:43 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.41).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 2.04 (s, 1.5H), 2.18 (s, 1.5H), 2.37 (s, 1.5H), 2.42 (s, 1.5H), 3.52 (s, 1.5H), 3.78 (s, 1.5H), 4.26-4.34 (m, 1.5H), 4.49-4.55 (m, 0.5H), 4.67-4.71 (dd,  $J$  = 4.6, 12.6 Hz, 0.5H), 4.90-4.96 (dd,  $J$  = 10.3, 12.6 Hz, 0.5H), 5.29 (d,  $J$  = 11.6 Hz, 0.5H), 5.52 (d,  $J$  = 11.8 Hz, 0.5H), 6.96 (d,  $J$  = 7.9 Hz, 1H), 7.05 (d,  $J$  = 8.1 Hz, 1H), 7.10-7.19 (m, 3.5H), 7.30-7.45 (m, 4.5H), 7.57 (d,  $J$  = 8.3 Hz, 1H), 7.70 (d,  $J$  = 7.1 Hz, 1H), 7.85 (d,  $J$  = 8.3 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 20.9, 21.0, 21.3, 21.4, 46.7, 46.8, 50.9, 52.9, 55.4, 56.0, 78.7, 79.1, 126.4, 126.6, 127.7, 127.8, 127.9, 128.4, 128.8, 129.0, 129.1, 129.3, 129.4, 129.5, 133.2, 133.4, 134.3, 134.4, 137.3, 137.7, 138.4, 138.5, 143.1, 143.6, 171.0, 173.0 ppm.

**IR:**  $\nu$  = 603, 686, 706, 736, 816, 1018, 1092, 1155, 1254, 1288, 1313, 1379, 1439, 1555, 1595, 1613, 2952  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 466.1562, found: 466.1558.

**Methyl 3-(4-methoxyphenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124f)**

Prepared from *trans*-4-methoxy- $\beta$ -nitrostyrene and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 62% yield (55:45 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.37 and 0.27 (*syn* and *anti* diastereoisomer, respectively).

**Mp.:** 99-100  $^{\circ}\text{C}$ .

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *syn* isomer):**  $\delta$  = 2.34 (s, 3H), 3.59 (s, 3H), 3.71 (s, 3H), 4.15-4.22 (m, 1H), 4.55-4.59 (dd,  $J$  = 4.7, 12.6 Hz, 1H), 4.78-4.84 (dd,  $J$  = 10.2, 12.4 Hz, 1H), 5.15 (d,  $J$  = 11.6 Hz, 1H), 6.60 (d,  $J$  = 8.8 Hz, 2H), 6.98 (d,  $J$  = 8.7 Hz, 2H), 7.03-7.11 (m, 3H), 7.21-7.28 (m, 4H), 7.75 (d,  $J$  = 8.4 Hz, 2H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, *syn* isomer):**  $\delta$  = 21.5, 46.6, 53.1, 55.0, 56.1, 79.2, 114.1, 126.7, 127.9, 128.2, 128.5, 129.0, 129.4, 129.4, 134.4, 138.5, 143.7, 158.9, 173.1 ppm.

**IR:**  $\nu$  = 596, 610, 686, 816, 837, 947, 1033, 1092, 1153, 1181, 1254, 1289, 1380, 1439, 1515, 1554, 1612 cm<sup>-1</sup>.

**HRMS (FAB):**  $m/z$  calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup>: 482.1512, found: 482.1512.

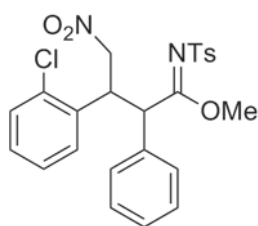
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, *anti* isomer):**  $\delta$  = 2.37 (s, 3H), 3.52 (s, 3H), 3.77 (s, 3H), 4.24-4.29 (m, 2H), 4.45-4.51 (m, 1H), 5.46 (d,  $J$  = 11.6 Hz, 1H), 6.83 (d,  $J$  = 8.7 Hz, 2H), 7.18 (d,  $J$  = 8.6 Hz, 2H), 7.32-7.44 (m, 5H), 7.57 (d,  $J$  = 7.9 Hz, 2H), 7.67 (d,  $J$  = 7.0 Hz, 2H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, *anti* isomer):**  $\delta$  = 21.5, 46.5, 51.2, 55.1, 55.5, 78.9, 114.2, 126.0, 126.5, 128.4, 128.9, 129.0, 129.2, 129.3, 129.4, 134.5, 138.6, 143.2, 159.3, 171.2 ppm.

**IR:**  $\nu$  = 603, 683, 707, 735, 813, 949, 1033, 1092, 1155, 1182, 1254, 1289, 1313, 1344, 1379, 1439, 1514, 1554, 1596, 1612, 2953 cm<sup>-1</sup>.

**HRMS (FAB):**  $m/z$  calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>6</sub>S [M+H]<sup>+</sup>: 482.1512, found: 482.1512.

### Methyl 3-(2-chlorophenyl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124g)



Prepared from *trans*-2-chloro- $\beta$ -nitrostyrene and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 61% yield (66:34 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.36).

**Mp.:** 142-143 °C.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.35 (s, 1.5H), 2.41 (s, 1.5H), 3.50 (s, 1.5H), 3.80 (s, 1.5H), 4.34-4.40 (dd,  $J$  = 4.5, 12.6 Hz, 0.5H), 4.73-4.79 (dd,  $J$  = 4.2, 12.1 Hz, 0.5H), 4.90-5.04 (m, 2H),

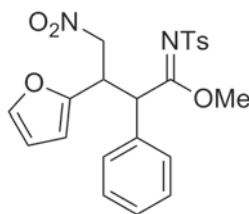
5.47 (d,  $J = 10.9$  Hz, 0.5H), 5.62 (d,  $J = 10.6$  Hz, 0.5H), 7.00-7.06 (m, 1H), 7.12-7.22 (m, 4H), 7.27-7.45 (m, 5H), 7.60 (d,  $J = 8.2$  Hz, 1H), 7.71 (d,  $J = 6.7$  Hz, 1H), 7.82 (d,  $J = 8.4$  Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta = 21.4, 21.5, 43.0, 43.1, 50.7, 52.2, 55.4, 56.1, 78.1, 126.4, 126.7, 127.3, 127.6, 128.1, 128.3, 129.0, 129.0, 129.2, 129.2, 129.3, 129.4, 129.4, 130.1, 133.8, 134.2, 134.3, 134.3, 138.4, 138.5, 143.3, 143.6, 170.8, 172.5$  ppm.

**IR:**  $\nu = 683, 705, 744, 761, 814, 915, 946, 975, 1017, 1037, 1091, 1152, 1187, 1254, 1289, 1378, 1438, 1479, 1495, 1554, 1610\text{ cm}^{-1}$ .

**HRMS (ESI):**  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{23}\text{ClN}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 487.1089, found: 487.1079.

### Methyl 3-(furan-2-yl)-4-nitro-2-phenyl-*N*-tosylbutanimidate (124h)



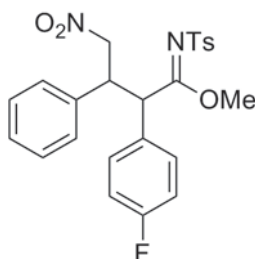
Prepared from (*E*)-2-(2-nitroethenyl)furan and phenylacetylene (**100a**) according to general procedure F and obtained as a yellowish solid in 61% yield (57:43 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f = 0.33$ ).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta = 2.37$  (s, 1H), 2.39 (s, 1.5H), 3.64 (s, 1.5H), 3.79 (s, 1.5H), 4.20-4.26 (dd,  $J = 3.0, 12.8$  Hz, 0.5H), 4.41-4.61 (m, 2H), 4.88-4.96 (dd,  $J = 10.2, 12.9$  Hz, 0.5H), 5.33 (d,  $J = 11.3$  Hz, 0.5H), 5.46 (d,  $J = 11.4$  Hz, 0.5H), 5.92 (d,  $J = 3.3$  Hz, 0.5H), 6.05 (dd,  $J = 1.9, 3.3$  Hz, 0.5H), 6.28 (dd,  $J = 1.9, 3.3$  Hz, 0.5H), 6.33 (d,  $J = 3.2$  Hz, 0.5H), 7.19-7.43 (m, 7H), 7.61 (d,  $J = 6.9$  Hz, 1H), 7.64 (d,  $J = 8.3$  Hz, 1H), 7.78 (d,  $J = 8.3$  Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta = 21.4, 21.4, 40.6, 41.3, 49.6, 50.8, 55.8, 56.1, 76.0, 76.7, 108.3, 109.5, 110.1, 110.4, 126.5, 126.7, 128.1, 128.5, 128.9, 129.0, 129.2, 129.4, 129.4, 129.5, 133.8, 134.3, 138.4, 138.5, 142.5, 142.8, 143.3, 143.6, 148.9, 150.0, 170.9, 172.0$  ppm.

**IR:**  $\nu = 557, 603, 686, 707, 738, 815, 947, 1015, 1092, 1156, 1259, 1289, 1317, 1377, 1439, 1495, 1556, 1595, 1613, 2952\text{ cm}^{-1}$ .

**HRMS (FAB):**  $m/z$  calcd. for  $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6\text{S}$   $[\text{M}+\text{H}]^+$ : 442.1199, found: 442.1195.

**Methyl 2-(4-fluorophenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (124i)**

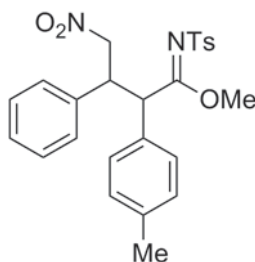
Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 4-fluorophenylacetylene according to general procedure F and obtained as a yellowish solid in 67% yield (61:39 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.38).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 2.35 (s, 1.5H), 2.41 (s, 1.5H), 3.47 (s, 1.5H), 3.78 (s, 1.5H), 4.21-4.31 (m, 1.5H), 4.49-4.56 (m, 0.5H), 4.66-4.71 (dd,  $J$  = 4.7, 12.8 Hz, 0.5H), 4.89-4.95 (dd,  $J$  = 10.1, 12.8 Hz, 0.5H), 5.26 (d,  $J$  = 11.7 Hz, 0.5H), 5.52 (d,  $J$  = 11.6 Hz, 0.5H), 6.81-6.86 (m, 1H), 7.08-7.18 (m, 4.5H), 7.23-7.34 (m, 3.5H), 7.39-7.41 (m, 1H), 7.55 (d,  $J$  = 8.3 Hz, 1H), 7.66-7.69 (m, 1H), 7.83 (d,  $J$  = 8.3 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 21.4, 21.4, 47.2, 47.3, 50.2, 52.2, 55.5, 56.1, 78.6, 78.9, 115.4 (d,  $J$  = 21.3 Hz), 116.3 (d,  $J$  = 21.5 Hz), 126.4, 126.6, 127.9, 128.1, 128.2, 128.7, 128.8, 129.2, 129.4, 130.0 (d,  $J$  = 3.3 Hz), 130.1 (d,  $J$  = 3.4 Hz), 130.8 (d,  $J$  = 8.2 Hz), 131.0 (d,  $J$  = 8.1 Hz), 136.1, 136.4, 138.3, 138.3, 143.3, 143.8, 162.1 (d,  $J$  = 245.9 Hz), 162.8 (d,  $J$  = 247.1 Hz), 170.7, 172.6 ppm.

**IR:**  $\nu$  = 597, 686, 813, 848, 1091, 1153, 1226, 1290, 1380, 1510, 1553, 1611  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{24}\text{H}_{23}\text{FN}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 470.1312, found: 470.1310.

**Methyl 4-nitro-3-phenyl-2-*p*-tolyl-*N*-tosylbutanimidate (124j)**

Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 4-methylphenylacetylene according to general procedure F and obtained as a yellowish solid in 64% yield (59:41 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.42).

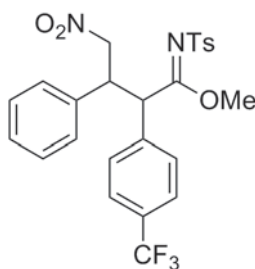
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.18 (s, 1.5H), 2.33 (s, 1.5H), 2.35 (s, 1.5H), 2.41 (s, 1.5H), 3.47 (s, 1.5H), 3.77 (s, 1.5H), 4.27-4.34 (m, 1.5H), 4.50-4.56 (m, 0.5H), 4.66-4.70 (dd,  $J$  = 4.6, 12.7 Hz, 0.5H), 4.90-4.96 (dd,  $J$  = 10.3, 12.8 Hz, 0.5H), 5.25 (d,  $J$  = 11.6 Hz, 0.5H), 5.47 (d,  $J$  = 11.5 Hz, 0.5H), 6.96 (d,  $J$  = 8.0 Hz, 1H), 7.07-7.33 (m, 8.5H), 7.41-7.43 (m, 1H), 7.55-7.59 (m, 1.5H), 7.84 (d,  $J$  = 8.3 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 20.9, 21.0, 21.4, 21.4, 47.1, 50.6, 52.5, 55.4, 56.0, 78.7, 79.0, 126.3, 126.6, 127.7, 128.0, 128.1, 128.6, 128.8, 128.8, 129.1, 129.4, 130.0, 131.0, 131.2, 136.4, 136.7, 137.6, 138.4, 138.7, 143.1, 143.6, 171.2, 173.2 ppm.

**IR:**  $\nu$  = 599, 686, 703, 816, 836, 948, 1018, 1092, 1154, 1187, 1255, 1289, 1313, 1379, 1439, 1495, 1513, 1555, 1601, 1619, 2951 cm<sup>-1</sup>.

**HRMS (EI):**  $m/z$  calcd. for C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 466.1562, found: 466.1558.

**Methyl 4-nitro-3-phenyl-*N*-tosyl-2-(4-trifluoromethylphenyl)butanimidate (124k)**



Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 4-trifluoromethylphenylacetylene according to general procedure F and obtained as a yellowish solid in 73% yield (64:36 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.42).

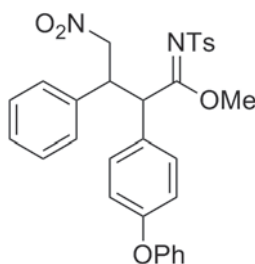
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.35 (s, 1.5H), 2.41 (s, 1.5H), 3.49 (s, 1.5H), 3.79 (s, 1.5H), 4.22-4.36 (m, 1.5H), 4.52-4.58 (dd,  $J$  = 10.7, 12.4 Hz, 0.5H), 4.69-4.74 (dd,  $J$  = 4.7, 12.8 Hz, 0.5H), 4.92-4.97 (dd,  $J$  = 10.1, 12.9 Hz, 0.5H), 5.36 (d,  $J$  = 11.7 Hz, 0.5H), 5.61 (d,  $J$  = 11.9 Hz, 0.5H), 7.09-7.19 (m, 4H), 7.24-7.37 (m, 2.5H), 7.41-7.56 (m, 3.5H), 7.68 (d,  $J$  = 8.2 Hz, 1H), 7.82-7.86 (m, 2H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 21.4, 21.4, 47.0, 50.7, 52.8, 55.7, 56.3, 78.4, 78.8, 123.7 (q,  $J$  = 270.5 Hz), 125.3 (q,  $J$  = 3.6 Hz), 126.3 (q,  $J$  = 3.7 Hz), 126.4, 126.7, 127.9, 128.1, 128.4, 128.9, 128.9, 129.2, 129.5, 129.6, 129.7, 129.8, 130.5, 131.0 (q,  $J$  = 32.3 Hz), 135.8, 136.1, 138.1, 138.3, 143.5, 143.9, 170.0, 171.9 ppm.

**IR:**  $\nu$  = 559, 686, 704, 815, 853, 946, 1018, 1070, 1091, 1128, 1155, 1257, 1327, 1380, 1556, 1609  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{25}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 520.1280, found: 520.1284.

**Methyl 4-nitro-2-(4-phenoxyphenyl)-3-phenyl-*N*-tosylbutanimidate (124l)**



Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 4-phenoxyphenylacetylene according to general procedure F and obtained as a yellowish solid in 74% yield (57:43 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.41).

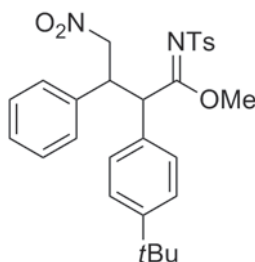
**Mp.:** 129-130 °C.

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 2.36 (s, 1.5H), 2.42 (s, 1.5H), 3.49 (s, 1.5H), 3.80 (s, 1.5H), 4.24-4.37 (m, 1.5H), 4.52-4.57 (dd,  $J$  = 11.0, 12.4 Hz, 0.5H), 4.67-4.71 (dd,  $J$  = 4.6, 12.8 Hz, 0.5H), 4.91-4.96 (dd,  $J$  = 10.2, 12.8 Hz, 0.5H), 5.25 (d,  $J$  = 11.6 Hz, 0.5H), 5.50 (d,  $J$  = 11.8 Hz, 0.5H), 6.79 (d,  $J$  = 8.6 Hz, 1H), 6.88 (d,  $J$  = 7.7 Hz, 1H), 7.02-7.19 (m, 7H), 7.24-7.42 (m, 6H), 7.57 (d,  $J$  = 8.3 Hz, 1H), 7.64 (d,  $J$  = 8.6 Hz, 1H), 7.85 (d,  $J$  = 8.2 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 21.4, 21.5, 47.2, 47.4, 50.3, 52.4, 55.4, 56.1, 78.7, 78.9, 118.5, 118.9, 119.5, 123.4, 123.9, 126.4, 126.7, 127.8, 128.0, 128.1, 128.2, 128.5, 128.7, 128.8, 129.2, 129.4, 129.6, 129.8, 130.4, 130.7, 136.3, 136.6, 138.4, 138.5, 143.2, 143.7, 156.2, 156.6, 156.9, 158.0, 171.0, 172.9 ppm.

**IR:**  $\nu$  = 598, 686, 755, 815, 845, 874, 947, 1017, 1092, 1153, 1242, 1288, 1313, 1378, 1438, 1456, 1488, 1506, 1556, 1589, 1617, 1699  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$   $[\text{M}+\text{H}]^+$ : 544.1668, found: 544.1664.

**Methyl 2-(4-*tert*-butylphenyl)-4-nitro-3-phenyl-*N*-tosylbutanimidate (124m)**

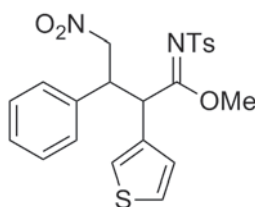
Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 4-*tert*-butylphenylacetylene according to general procedure F and obtained as a yellowish solid in 56% yield (63:37 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.40).

**$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 1.20 (s, 4.5H), 1.33 (s, 4.5H), 2.34 (s, 1.5H), 2.40 (s, 1.5H), 3.47 (s, 1.5H), 3.77 (s, 1.5H), 4.26-4.34 (m, 1.5H), 4.49-4.56 (m, 0.5H), 4.65-4.69 (dd,  $J$  = 4.6, 12.7 Hz, 0.5H), 4.90-4.96 (dd,  $J$  = 10.3, 12.7 Hz, 0.5H), 5.25 (d,  $J$  = 11.5 Hz, 0.5H), 5.47 (d,  $J$  = 11.6 Hz, 0.5H), 7.06-7.17 (m, 5H), 7.23-7.43 (m, 5H), 7.54 (d,  $J$  = 8.3 Hz, 1H), 7.59 (d,  $J$  = 8.3 Hz, 1H), 7.82 (d,  $J$  = 8.3 Hz, 1H) ppm.

**$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):**  $\delta$  = 21.4, 21.5, 31.1, 31.2, 34.3, 34.5, 47.1, 47.2, 50.5, 52.6, 55.4, 56.0, 78.8, 79.0, 125.3, 126.3, 126.4, 126.7, 127.7, 128.0, 128.1, 128.2, 128.6, 128.8, 128.9, 129.1, 129.4, 131.0, 131.1, 136.5, 136.7, 138.5, 138.6, 143.1, 143.6, 150.7, 151.8, 171.2, 173.2 ppm.

**IR:**  $\nu$  = 592, 619, 686, 704, 738, 815, 847, 948, 1018, 1092, 1155, 1185, 1254, 1289, 1314, 1335, 1379, 1438, 1456, 1496, 1556, 1596, 1620, 2868, 2904, 2952, 2967, 3033  $\text{cm}^{-1}$ .

**HRMS (EI):**  $m/z$  calcd. for  $\text{C}_{28}\text{H}_{32}\text{N}_2\text{O}_5\text{S}$   $[\text{M}+\text{H}]^+$ : 508.2032, found: 508.2037.

**Methyl 4-nitro-3-phenyl-2-(thiophen-3-yl)-*N*-tosylbutanimidate (124n)**

Prepared from *trans*- $\beta$ -nitrostyrene (**15a**) and 3-ethynylthiophene according to general procedure F and obtained as a yellowish solid in 69% yield (60:40 *syn:anti*) after column chromatography (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.40).

**Mp.:** 135-136  $^{\circ}\text{C}$ .

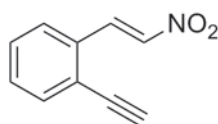
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 2.35 (s, 1.5H), 2.40 (s, 1.5H), 3.47 (s, 1.5H), 3.78 (s, 1.5H), 4.19-4.31 (m, 1H), 4.34-4.38 (m, 0.5H), 4.52-4.57 (m, 0.5H), 4.64-4.68 (m, 0.5H), 4.88-4.94 (m, 0.5H), 5.38 (d,  $J$  = 11.4 Hz, 0.5H), 5.65 (d,  $J$  = 11.8 Hz, 0.5H), 6.99-7.00 (m, 1H), 7.07-7.20 (m, 5H), 7.22-7.33 (m, 3H), 7.36-7.39 (m, 1H), 7.56 (d,  $J$  = 8.3 Hz, 1H), 7.82 (d,  $J$  = 8.1 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 21.4, 21.5, 46.5, 47.1, 47.4, 48.6, 55.4, 56.0, 78.6, 78.7, 124.8, 125.5, 125.6, 126.4, 126.6, 126.9, 127.2, 127.3, 127.8, 127.9, 128.0, 128.2, 128.7, 128.8, 129.2, 129.4, 134.1, 134.3, 136.3, 136.4, 138.2, 138.4, 143.2, 143.7, 170.7, 172.6 ppm.

**IR:**  $\nu$  = 598, 686, 704, 735, 774, 816, 952, 1018, 1092, 1150, 1158, 1185, 1233, 1268, 1315, 1379, 1439, 1456, 1496, 1554, 1596, 1620, 2951, 3032, 3108 cm<sup>-1</sup>.

**HRMS (EI):**  $m/z$  calcd. for C<sub>22</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub> [M+H]<sup>+</sup>: 458.0970, found: 458.0973.

### (*E*)-1-Ethynyl-2-(2-nitrovinyl)benzene (179)



To a stirred mixture of 2-ethynylbenzaldehyde (**5a**) (989 mg, 7.6 mmol) and nitromethane (2.1 mL, 38.1 mmol, 5.0 equiv.) under a N<sub>2</sub> atmosphere was slowly added triethylamine (209  $\mu$ L, 1.5 mmol, 0.2 equiv.) at room temperature. After 16 hours, the solvent was evaporated and the residue was directly subjected to column chromatography (86% yield, *n*-hexane:ethyl acetate = 5:1; R<sub>f</sub> = 0.29). To the resulting Henry-product (841 mg, 4.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) was slowly added MsCl (410  $\mu$ L, 5.3 mmol, 1.2 equiv.) and triethylamine (1.5 mL, 11.1 mmol, 2.5 equiv.). Water (10 mL) was added after 24 hours and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x 10 mL). The combined organic extracts were then washed with 1N HCl (10 mL), dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography to give the desired product as a yellow solid in 80% yield (*n*-hexane:ethyl acetate = 10:1; R<sub>f</sub> = 0.34).

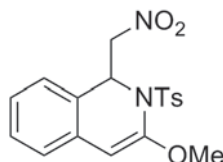
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  = 3.53 (s, 1H), 7.39-7.48 (m, 2H), 7.56-7.63 (m, 2H), 7.73 (d,  $J$  = 13.7 Hz, 1H), 8.45 (d,  $J$  = 13.7 Hz, 1H) ppm.

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):**  $\delta$  = 80.4, 84.6, 123.8, 127.3, 129.2, 131.3, 131.7, 133.9, 136.5, 138.3 ppm.

**IR:**  $\nu$  = 604, 646, 691, 758, 847, 965, 1212, 1257, 1283, 1348, 1477, 1500, 1517, 1593, 1629, 3268 cm<sup>-1</sup>.

**HRMS (EI):**  $m/z$  calcd. for  $C_{10}H_7NO_2$   $[M+H]^+$ : 173.0477, found: 173.0480.

### 3-Methoxy-1-(nitromethyl)-2-tosyl-1,2-dihydroisoquinoline (180)



To a mixture of CuI (**103a**) (9.5 mg, 0.05 mmol, 0.1 equiv.), *p*-toluenesulfonyl azide (**101a**) (118.5 mg, 0.60 mmol, 1.2 equiv.) and (*E*)-1-ethynyl-2-(2-nitrovinyl)benzene (**179**) (87 mg, 0.50 mmol) in THF (1.5 mL) was slowly added methanol (101  $\mu$ L, 2.5 mmol, 5.0 equiv.) and triethylamine (209  $\mu$ L, 1.5 mmol, 3.0 equiv.) at room temperature under a  $N_2$  atmosphere. After 24 hours, the reaction mixture was diluted with  $CH_2Cl_2$  (3 mL) and quenched with sat.  $NH_4Cl$ -solution (3 mL) and 1N HCl-solution (3 mL). The mixture was stirred for additional 30 minutes and then the layers were separated. The aqueous phase was extracted with  $CH_2Cl_2$  (3x 6 mL). The combined organic extracts were dried over  $MgSO_4$ , filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the desired product as a white solid in 45% yield (*n*-hexane:ethyl acetate = 3:1;  $R_f$  = 0.26).

**$^1H$  NMR (400 MHz,  $CDCl_3$ ):**  $\delta$  = 2.32 (s, 3H), 3.73 (s, 3H), 4.27-4.31 (dd,  $J$  = 5.1, 12.5 Hz, 1H), 4.45-4.50 (dd,  $J$  = 10.0, 12.5 Hz, 1H), 5.49 (s, 1H), 6.21-6.25 (dd,  $J$  = 5.2, 10.0 Hz, 1H), 6.96 (d,  $J$  = 7.6 Hz, 1H), 7.10-7.24 (m, 5H), 7.56 (d,  $J$  = 8.4 Hz, 2H) ppm.

**$^{13}C$  NMR (100 MHz,  $CDCl_3$ ):**  $\delta$  = 21.5, 56.4, 57.5, 75.8, 90.1, 124.9, 125.5, 125.7, 126.2, 127.6, 129.0, 129.1, 131.4, 136.2, 144.1, 149.7 ppm.

**IR:**  $\nu$  = 540, 621, 682, 755, 814, 970, 1011, 1088, 1166, 1197, 1245, 1269, 1289, 1354, 1380, 1490, 1556, 1598, 1641  $cm^{-1}$ .

**HRMS (FAB):**  $m/z$  calcd. for  $C_{18}H_{18}N_2O_5S$   $[M+H]^+$ : 374.0936, found: 374.0934.



---

## 5 Abbreviations

---

|        |                                                                            |
|--------|----------------------------------------------------------------------------|
| Ac     | acetyl                                                                     |
| BINOL  | 1,1'-bi-2-naphthol                                                         |
| Bn     | benzyl                                                                     |
| Boc    | <i>tert</i> -butoxycarbonyl                                                |
| br     | broad                                                                      |
| Bs     | brosyl ( <i>p</i> -bromobenzenesulfonyl)                                   |
| Bu     | butyl                                                                      |
| Bz     | benzoyl                                                                    |
| calcd. | calculated                                                                 |
| Cbz    | carboxybenzoyl                                                             |
| CI     | chemical ionization                                                        |
| conc.  | concentrated                                                               |
| CuAAC  | copper-catalyzed azide-alkyne cycloaddition                                |
| d      | days                                                                       |
| DAAD   | Deutscher Akademischer Austausch Dienst (German Academic Exchange Service) |
| DABCO  | 1,4-diazabicyclo[2.2.2]octan                                               |
| DBU    | 1,8-diazabicyclo[5.4.0]undec-7-ene                                         |
| DMAP   | 4-(dimethylamino)pyridine                                                  |
| DMF    | dimethylformamide                                                          |
| DMSO   | dimethyl sulfoxide                                                         |
| dr     | diastereomeric ratio                                                       |
| ECD    | electronic circular dichroism                                              |
| ed.    | edition                                                                    |
| Ed.    | editor                                                                     |
| EI     | electronic ionization                                                      |
| eq.    | equation                                                                   |
| equiv. | equivalents                                                                |
| er     | enantiomeric ratio                                                         |
| ESI    | electrospray ionization                                                    |
| FAB    | fast atom bombardment                                                      |

|                  |                                                                                     |
|------------------|-------------------------------------------------------------------------------------|
| GC               | gas chromatography                                                                  |
| HPLC             | high-performance liquid chromatography                                              |
| HRMS             | high resolution mass spectrometry                                                   |
| <i>i</i> Pr      | isopropyl                                                                           |
| <i>i</i> PrOH    | isopropyl alcohol                                                                   |
| IR               | infrared                                                                            |
| KAIST            | Korea Advanced Institute of Science and Technology                                  |
| KHMDS            | potassium bis(trimethylsilyl)amide                                                  |
| LUMO             | lowest unoccupied molecular orbital                                                 |
| m                | multiplet                                                                           |
| M                | molar (mol/L)                                                                       |
| MCR              | multicomponent reaction                                                             |
| min              | minutes                                                                             |
| Mp               | melting point                                                                       |
| MS               | mol sieves                                                                          |
| NMR              | nuclear magnetic resonance                                                          |
| Np               | naphthyl                                                                            |
| Nu               | nucleophile                                                                         |
| o/n              | overnight                                                                           |
| PG               | protecting group                                                                    |
| PMP              | <i>p</i> -methoxyphenyl                                                             |
| ppm              | parts per million                                                                   |
| q                | quartet                                                                             |
| quant.           | quantitative                                                                        |
| rt               | room temperature                                                                    |
| RWTH             | Rheinisch-Westfälische Technische Hochschule                                        |
| s                | singlet                                                                             |
| sat.             | saturated                                                                           |
| <i>s</i> BuLi    | <i>sec</i> -butyllithium                                                            |
| SDE              | self-disproportionation of enantiomers                                              |
| SOMO             | singly occupied molecular orbital                                                   |
| t                | triplet                                                                             |
| T <sub>b</sub>   | boiling point                                                                       |
| t <sub>ret</sub> | retention time                                                                      |
| TADDOL           | $\alpha,\alpha,\alpha',\alpha'$ -tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol |
| TBS              | <i>tert</i> -butyldimethylsilyl                                                     |

## Abbreviations

---

|             |                                                                                |
|-------------|--------------------------------------------------------------------------------|
| TBTA        | tris[(1-benzyl-1 <i>H</i> -1,2,3-triazol-4-yl)methyl]amine                     |
| <i>t</i> Bu | <i>tert</i> -butyl                                                             |
| Tf          | triflyl (trifluoromethanesulfonyl)                                             |
| TfOH        | triflic acid                                                                   |
| TFAA        | trifluoroacetic anhydride                                                      |
| THF         | tetrahydrofuran                                                                |
| TMEDA       | tetramethylethylenediamine                                                     |
| TMSCl       | trimethylsilyl chloride                                                        |
| TMSCN       | trimethylsilyl cyanide                                                         |
| TRIP        | 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate |
| Ts          | tosyl ( <i>p</i> -toluenesulfonyl)                                             |



---

## 6 References

---

- 1 J. C. C. Schrader in *Journal für Chemie und Physik*, 4. Band (Ed.: J. S. C. Schweigger), Schrag'sche Buchhandlung, Nürnberg, **1812**, pp. 108-110.
- 2 H. Davy, *Phil. Trans. R. Soc. Lond.* **1817**, 107, 77-85.
- 3 A. J. B. Robertson, *Platinum Metals Rev.* **1975**, 19, 64-69.
- 4 E. Davy, *Phil. Trans. R. Soc. Lond.* **1820**, 110, 108-125.
- 5 a) L. J. Thénard, *Ann. Chim. Phys.* **1818**, 8, 306-313. b) J. Wisniak, *Educ. Quim.* **2010**, 21, 60-69.
- 6 a) P. L. Dulong, L. J. Thénard in *Journal für Chemie und Physik*, 9. Band (Ed.: J. S. C. Schweigger), Schrag'sche Buchhandlung, Nürnberg, **1823**, pp. 205-230. b) P. L. Dulong, L. J. Thénard, *Ann. Phys.* **1824**, 76, 83-98. c) G. B. Kauffman, *Platinum Metals Rev.* **1999**, 43, 122-128.
- 7 E. Mitscherlich, *Ann. Phys.* **1834**, 107, 273-282.
- 8 a) J. J. Berzelius, *Jahresbericht über die Fortschritte der Physischen Wissenschaften* **1836**, 15, 237-245. For a translation, see: b) *A Source Book in Chemistry 1400-1900*, 4<sup>th</sup> ed. (Eds.: H. M. Leicester, H. S. Klickstein), Harvard University Press, Cambridge, **1968**, pp. 258-268.
- 9 W. Ostwald, *Annalen der Naturphilosophie* **1910**, 9, 1-25.
- 10 *Catalysis in Organic Chemistry*, (Ed.: P. Sabatier, translated by E. E. Reid), D. Van Nostrand Company, New York, **1922**.
- 11 a) F. Wöhler, J. von Liebig, *Ann. Pharm.* **1832**, 3, 249-282. For an obituary, see: b) H. Kolbe, *J. Prakt. Chem.* **1874**, 428-458.
- 12 a) N. Zinin, *Ann. Pharm.* **1839**, 31, 329-332. b) N. Zinin, *Justus Liebigs Ann. Chem.* **1840**, 34, 186-192. c) For an obituary, see: A. M. Butlerow, A. P. Borodin, *Ber. Dtsch. Chem. Ges.* **1881**, 14, 2887-2908.
- 13 W. Marckwald, *Ber. Dtsch. Chem. Ges.* **1904**, 37, 349-354.
- 14 G. Bredig, K. Fajans, *Ber. Dtsch. Chem. Ges.* **1908**, 41, 752-763.
- 15 a) W. S. Knowles, *Angew. Chem.* **2002**, 114, 2096-2107; *Angew. Chem. Int. Ed.* **2002**, 41, 1998-2007. b) R. Noyori, *Angew. Chem.* **2002**, 114, 2108-2123; *Angew. Chem. Int. Ed.* **2002**, 41, 2008-2022. c) K. B. Sharpless, *Angew. Chem.* **2002**, 114, 2126-2135; *Angew. Chem. Int. Ed.* **2002**, 41, 2024-2032.

- 16 a) Y. Chauvin, *Angew. Chem.* **2006**, *118*, 3824-3831; *Angew. Chem. Int. Ed.* **2006**, *45*, 3741-3747. b) R. H. Grubbs, *Angew. Chem.* **2006**, *118*, 3845-3850; *Angew. Chem. Int. Ed.* **2006**, *45*, 3760-3765. c) R. R. Schrock, *Angew. Chem.* **2006**, *118*, 3832-3844; *Angew. Chem. Int. Ed.* **2006**, *45*, 3748-3759.
- 17 a) G. Ertl, *Angew. Chem.* **2008**, *120*, 3578-3590; *Angew. Chem. Int. Ed.* **2008**, *47*, 3524-3535. For a complete bibliography until 2004, see special issue: b) *J. Phys. Chem. B* **2004**, *108*, 14183-14788.
- 18 a) *Angew. Chem.* **2010**, *122*, 8478; *Angew. Chem. Int. Ed.* **2010**, *49*, 8300. b) X.-F. Wu, P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 9231-9234; *Angew. Chem. Int. Ed.* **2010**, *49*, 9047-9050.
- 19 a) S. Yamada, K. Hiroi, K. Achiwa, *Tetrahedron Lett.* **1969**, *10*, 4233-4236. b) S. Yamada, G. Otani, *Tetrahedron Lett.* **1969**, *10*, 4237-4240.
- 20 a) U. Eder, G. Sauer, R. Wiechert, German Patent DE 2014757, **1971**. b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492-493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496-497. c) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, **1971**. d) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615-1621.
- 21 B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.
- 22 K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244.
- 23 E. P. Serebryakov, A. G. Nigmatov, M. A. Shcherbakov, M. I. Strukhova, *Russ. Chem. Bull.* **1998**, *47*, 82-90.
- 24 J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719-724.
- 25 For a comprehensive review concerning Lewis base catalysis in organic synthesis, see: S. E. Denmark, G. L. Beutner, *Angew. Chem.* **2008**, *120*, 1584-1663; *Angew. Chem. Int. Ed.* **2008**, *47*, 1560-1638.
- 26 a) W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386-7387. b) B. List, P. Porjarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573-575. c) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301-303. d) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798-6799. e) A. Bøgevig, N. Kumaragurubaran, *Chem. Commun.* **2002**, 620-621. f) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2891-2894; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785-2788. g) D. Enders, C. Grondal, *Angew. Chem.* **2005**, *117*, 1235-1238; *Angew. Chem. Int. Ed.* **2005**, *44*, 1210-1212. For a review, see: h) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471-5569.
- 27 a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336-9337. b) B. List, P. Pojarliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827-833. c) A. Córdova, S. Watanabe, F. Tanaka, W.

- Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866-1867. d) W. Notz, F. Tanaka, S. Watanabe, N. S. Chowdari, J. M. Turner, R. Thayumanavan, C. F. Barbas III, *J. Org. Chem.* **2003**, *68*, 9624-9634. e) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805-3808; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677-3680. f) B. Westermann, C. Neuhaus, *Angew. Chem.* **2005**, *117*, 4145-4147; *Angew. Chem. Int. Ed.* **2005**, *44*, 4077-4079. g) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem.* **2005**, *117*, 4079-4083; *Angew. Chem. Int. Ed.* **2005**, *44*, 4079-4083. h) J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453-455. For reviews, see: i) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2008**, *37*, 29-41. j) S. Kobayashi, Y. Mori, J. S. Fossy, M. M. Salter, *Chem. Rev.* **2011**, *111*, 2626-2704.
- 28 For excellent reviews, see: a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171-196. b) O. M. Berner, L. Tedeschi, D. Enders, *Eur. J. Org. Chem.* **2002**, 1877-1894. c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701-1716.
- 29 a) B. List, P. Pojarliev, H. J. Martin, *Org. Lett.* **2001**, *3*, 2423-2425. b) D. Enders, A. Seki, *Synlett* **2002**, 26-28.
- 30 M. Marigo, K. A. Jørgensen, *Chem. Commun.* **2006**, 2001-2011.
- 31 M. Movassaghi, E. N. Jacobsen, *Science* **2002**, *298*, 1904-1905.
- 32 a) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296-18304. b) D. W. C. MacMillan, *Nature* **2008**, *455*, 304-308.
- 33 D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, *Helv. Chim. Acta* **2007**, *90*, 425-471.
- 34 a) T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582-585. b) H.-Y. Jang, J.-B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004-7005.
- 35 a) G. Lelais, D. W. C. MacMillan, *Aldrichim. Acta* **2006**, *39*, 79-87. b) A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416-5470.
- 36 a) S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973-12980. For a review, see: b) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun.* **2011**, *47*, 632-649.
- 37 a) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737-3740. b) A. Alexakis, O. Andrey, *Org. Lett.* **2002**, *4*, 3611-3614. c) O. Andrey, A. Alexakis, G. Bernardinelli, *Org. Lett.* **2003**, *5*, 2559-2561.

- 38 J. F. Austin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 1172-1173.
- 39 a) S. P. Brown, N. C. Goodwin, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 1192-1194. b) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32-33. c) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 15051-15053.
- 40 a) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* **2004**, *116*, 2017-2020; *Angew. Chem. Int. Ed.* **2004**, *43*, 1983-1986. b) N. Momiyama, H. Torii, S. Saito, H. Yamamoto, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5374-5378. c) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558-560. d) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2004**, 1831-1834. e) A. Hartikka, P. I. Arvidsson, *Eur. J. Org. Chem.* **2005**, 4287-4295.
- 41 a) Y. Yamamoto, N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 5962-5963. b) A. J. A. Cobb, D. A. Longbottom, D. H. Shaw, S. V. Ley, *Chem. Commun.* **2004**, 1808-1809. c) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346-5348. d) A. Odedra, P. H. Seeberger, *Angew. Chem.* **2009**, *121*, 2737-2740; *Angew. Chem. Int. Ed.* **2009**, *48*, 2699-2702.
- 42 Y. Hayashi, J. Yamaguchi, K. Hibino, T. Sumiya, T. Urushima, M. Shoji, D. Hashizume, H. Koshino, *Adv. Synth. Catal.* **2004**, *346*, 1435-1439.
- 43 a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804-807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794-797. b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284-4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212-4215.
- 44 a) P.I. Dalko, *Enantioselective Organocatalysis, Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**. b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232-6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138-6171. c) S. Bertelsen, K. A. Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178-2189.
- 45 For a review on silicon-containing organocatalysts, see: L-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243-279.
- 46 a) W. Wang, J. Wang, H. Li, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 7235-7238. b) W. Wang, J. Wang, H. Li, *Tetrahedron Lett.* **2004**, *45*, 7243-7246. c) W. Wang, H. Li, J. Wang, L. Liao, *Tetrahedron Lett.* **2004**, *45*, 8229-8231. d) W. Wang, J. Wang, H. Li, *Org. Lett.* **2004**, *6*, 2817-2820. e) W. Wang, J. Wang, H. Li, *Angew. Chem.* **2005**, *117*, 1393-1395; *Angew. Chem. Int. Ed.* **2005**, *44*, 1369-1371.
- 47 S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3165-3169; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093-3097.

- 48 C.-L. Cao, M.-C. Ye, X.-L. Sun, Y. Tang, *Org. Lett.* **2006**, *8*, 2901-2904.
- 49 J. Kofoed, J. Nielsen, J.-L. Reymond, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445-2447.
- 50 a) P. Krattiger, C. McCarthy, A. Pfaltz, H. Wennemers, *Angew. Chem.* **2003**, *115*, 1763-1766; *Angew. Chem. Int. Ed.* **2003**, *42*, 1722-1724. b) P. Krattiger, R. Kovasy, J. D. Revell, S. Ivan, H. Wennemers, *Org. Lett.* **2005**, *7*, 1101-1103.
- 51 a) M. Wiesner, J. D. Revell, H. Wennemers, *Angew. Chem.* **2008**, *120*, 1897-1900; *Angew. Chem. Int. Ed.* **2008**, *47*, 1871-1874. b) M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6-7.
- 52 a) S. J. Miller, *Acc. Chem. Res.* **2004**, *37*, 601-610. b) E. A. Colby Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759-5812.
- 53 a) E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 172-174. b) E. Knoevenagel, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 738-748. c) B. List, *Angew. Chem.* **2010**, *122*, 1774-1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730-1734.
- 54 A. Lee, A. Michrowska, S. Sulzer-Mossé, B. List, *Angew. Chem.* **2011**, *123*, 1745-1748; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707-1710.
- 55 D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861-863.
- 56 a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590-1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581. b) R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575-2600. c) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167-178. d) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138-1167. e) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem.* **2011**, *123*, 3685-3687; *Angew. Chem. Int. Ed.* **2011**, *50*, 3605-3607.
- 57 D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80.
- 58 a) E. J. Corey, *Angew. Chem.* **2002**, *114*, 1724-1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650-1667. b) H. Yamamoto, K. Futatsugi, *Angew. Chem.* **2005**, *117*, 1958-1977; *Angew. Chem. Int. Ed.* **2005**, *44*, 1924-1942.
- 59 O. Sereda, S. Tabassum, R. Wilhelm, *Top. Curr. Chem.* **2010**, *291*, 349-393.
- 60 H. K. T. Klare, M. Oestreich, *Dalton Trans.* **2010**, *39*, 9176-9184.
- 61 T. Werner, *Adv. Synth. Catal.* **2009**, *351*, 1469-1481.
- 62 a) D. Uraguchi, S. Sakaki, T. Ooi, *J. Am. Chem. Soc.* **2007**, *129*, 12392-12393. b) D. Uraguchi, Y. Ueki, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 14088-14089. c) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem.* **2008**, *120*, 9608-9610; *Angew. Chem. Int. Ed.* **2008**, *47*, 9466-9468.
- 63 U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446-447.

- 64 a) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353-2355. b) M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507-4518. c) I. A. Esikova, T. S. Nahreini, M. J. O'Donnell in *Phase-Transfer Catalysis*, Ed.: M. E. Halpern, American Chemical Society: Washington, DC, **1997**, pp. 89-96.
- 65 a) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414-12415. b) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595-8598.
- 66 a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519-6520. b) M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2005**, *117*, 1573-1575; *Angew. Chem. Int. Ed.* **2005**, *44*, 1549-1551.
- 67 a) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013-3028. b) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506-517. c) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518-525. d) T. Ooi, K. Maruoka, *Angew. Chem.* **2007**, *119*, 4300-4345; *Angew. Chem. Int. Ed.* **2007**, *46*, 4222-4266. e) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2007**, *107*, 5656-5682. f) K. Maruoka, *Asymmetric Phase Transfer Catalysis*, Wiley-VCH, Weinheim, **2008**. g) K. Maruoka, *Org. Process Res. Dev.* **2008**, *12*, 679-697.
- 68 P. Muller, *Pure & Appl. Chem.* **1994**, *66*, 1077-1184.
- 69 a) G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7-23. b) H. Pracejus, *Justus Liebigs Ann. Chem.* **1960**, *634*, 9-22. c) H. Wynberg in *Topics in Stereochemistry*, Eds.: E. L. Eliel, S. H. Wilen, N. L. Allinger, John Wiley & Sons, New York, **1989**, pp. 87-129. d) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc.* **1982**, *104*, 166-168.
- 70 For reviews, see: a) K. Kacprzak, J. Gawroński, *Synthesis* **2001**, 961-998. b) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621-631. c) T. Marcelli, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 7658-7666; *Angew. Chem. Int. Ed.* **2006**, *45*, 7496-7504. d) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229-1279.
- 71 For reviews, see: a) Y. Chen, P. McDaid, L. Deng, *Chem. Rev.* **2003**, *103*, 2965-2983. b) I. Atodiresei, I. Schiffers, C. Bolm, *Chem. Rev.* **2007**, *107*, 5683-5712.
- 72 K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181-185.
- 73 a) A. Strecker, *Ann. Chem. Pharm.* **1850**, *75*, 27-45. For reviews, see: b) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539-1650. c) L. Yet, *Angew. Chem.* **2001**, *113*, 900-902; *Angew. Chem. Int. Ed.* **2001**, *40*, 875-877. d) H. Gröger, *Chem. Rev.* **2001**, *103*, 2795-2827. e) C. Spino, *Angew. Chem.* **2004**, *116*, 1796-1798; *Angew. Chem. Int. Ed.* **2004**, *43*, 1764-1766.
- 74 a) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910-4911. b) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157-160.

- 75 C. Becker, C. Hoben, D. Schollmeyer, G. Scherr, H. Kunz, *Eur. J. Org. Chem.* **2005**, 1497-1499.
- 76 For a review, see: D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488-507.
- 77 a) S. Mayer, B. List, *Angew. Chem.* **2006**, *118*, 4299-4301; *Angew. Chem. Int. Ed.* **2006**, *45*, 4193-4195. b) L. Ratjen, S. Müller, B. List, *Nachrichten aus der Chemie* **2010**, *58*, 640-646.
- 78 W.-D. Fessner, T. Anthonsen, *Modern Biocatalysis: Stereoselective and Environmentally Friendly Reactions*, Wiley-VCH, Weinheim, **2009**.
- 79 a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336-1338; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279-1281. c) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012-10014.
- 80 P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867-870.
- 81 a) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964-12965. b) I. T. Raheem, E. N. Jacobsen, *Adv. Synth. Catal.* **2005**, *347*, 1701-1708.
- 82 For reviews concerning hydrogen-bond mediated asymmetric catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289-296. b) Y. Takemoto, *Org. Biomol. Chem.* **2005**, *3*, 4299-4306. c) C. Bolm, T. Rantanen, I. Schiffrers, L. Zani, *Angew. Chem.* **2005**, *117*, 1788-1793; *Angew. Chem. Int. Ed.* **2005**, *44*, 1758-1763. d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550-1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520-1543. e) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713-5743. f) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516-532. g) S. J. Connon, *Synlett* **2009**, 354-376. h) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593-601. i) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678-20685.
- 83 T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673.
- 84 a) P. R. Schreiner, A. Wittkopp, *Org. Lett.* **2002**, *4*, 217-220. b) A. Wittkopp, P. R. Schreiner, *Chem. Eur. J.* **2003**, *9*, 407-414.
- 85 D. Seebach, A. K. Beck, A. Heckel, *Angew. Chem.* **2001**, *113*, 96-142; *Angew. Chem. Int. Ed.* **2001**, *40*, 92-138.
- 86 Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146.
- 87 a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592-1594; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566-1568. b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356-5357.
- 88 For reviews, see: a) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744-5758. b) M. Terada, *Synthesis* **2010**, 1929-1982. c) D. Kampen, C. M. Reisinger, B. List, *Top. Curr. Chem.* **2010**, *291*,

- 395-456. d) A. Zamfir, S. Schenker, M. Freund, S. B. Tsogoeva, *Org. Biomol. Chem.* **2010**, *8*, 5262-5276.
- 89 a) T. Akiyama, Y. Saitoh, H. Morita, K. Fuchibe, *Adv. Synth. Catal.* **2005**, *347*, 1523-1526. b) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang, J. C. Antilla, *J. Am. Chem. Soc.* **2005**, *127*, 15696-15697. c) Y. Liang, E. B. Rowland, G. B. Rowland, J. A. Perman, J. C. Antilla, *Chem. Commun.* **2007**, 4477-4479. d) M. Terada, K. Sorimachi, D. Uruguchi, *Synlett* **2006**, 133-136. e) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802-14803. f) H. Liu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 6023-6026. g) Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu, L.-Z. Gong, *J. Am. Chem. Soc.* **2007**, *129*, 3790-3791. h) M. Rueping, E. Sugiono, F. R. Schoepke, *Synlett* **2007**, 1441-1445. i) M. J. Wanner, P. Hauwert, H. E. Schoemaker, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.* **2008**, 180-185.
- 90 D. Uruguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804-11805.
- 91 a) Q. Kang, Z.-A. Zhao, S.-L. You, *J. Am. Chem. Soc.* **2007**, *129*, 1484-1485. b) Y.-X. Jia, J. Zhong, S.-F. Zhu, C.-M. Zhang, Q.-L. Zhou, *Angew. Chem.* **2007**, *119*, 5661-5663; *Angew. Chem. Int. Ed.* **2007**, *46*, 5565-5567. c) G. Li, G. B. Rowland, E. B. Rowland, J. C. Antilla, *Org. Lett.* **2007**, *9*, 4065-4068. d) Y.-F. Sheng, Q. Gu, A.-J. Zhang, S.-L. You, *J. Org. Chem.* **2009**, *74*, 6899-6901.
- 92 a) S. Hoffmann, A. M. Seayad, B. List, *Angew. Chem.* **2005**, *117*, 7590-7593; *Angew. Chem. Int. Ed.* **2005**, *44*, 7424-7427. b) M. Rueping, E. Sugiono, C. Azap, T. Theissmann, M. Bolte, *Org. Lett.* **2005**, *7*, 3781-3783. c) R. I. Storer, D. E. Carrera, Y. Ni, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 84-86.
- 93 a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 10558-10559. b) J. Seayad, A. M. Seayad, B. List, *J. Am. Chem. Soc.* **2006**, *128*, 1086-1087. c) M. J. Wanner, R. N. S. van der Haas, K. R. de Cuba, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2007**, *119*, 7629-7631; *Angew. Chem. Int. Ed.* **2007**, *46*, 7485-7487. d) D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.* **2008**, *10*, 745-748. e) M. J. Wanner, R. N. A. Boots, B. Eradus, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *Org. Lett.* **2009**, *11*, 2579-2581. f) N. V. Sewgobind, M. J. Wanner, S. Ingemann, R. de Gelder, J. H. van Maarseveen, H. Hiemstra, *J. Org. Chem.* **2008**, *73*, 6405-6408. g) R. S. Klausen, E. N. Jacobsen, *Org. Lett.* **2009**, *11*, 887-890.
- 94 D. Nakashima, H. Yamamoto, *J. Am. Chem. Soc.* **2006**, *128*, 9626-9627.
- 95 M. Rueping, W. Ieawsuwan, A. P. Antonchick, B. J. Nachtsheim, *Angew. Chem.* **2007**, *119*, 2143-2146; *Angew. Chem. Int. Ed.* **2007**, *46*, 2097-2100.

- 96 a) M. Terada, K. Machioka, K. Sorimachi, *Angew. Chem.* **2006**, *118*, 2312-2315; *Angew. Chem. Int. Ed.* **2006**, *45*, 2254-2257. b) M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, *118*, 2679-2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2617-2619. c) S. Xu, Z. Wang, X. Zhang, X. Zhang, K. Ding, *Angew. Chem.* **2008**, *120*, 2882-2885; *Angew. Chem. Int. Ed.* **2008**, *47*, 2840-2843. d) M. Rueping, A. P. Antonchick, *Org. Lett.* **2008**, *10*, 1731-1734. e) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583-2585. f) X. Cheng, R. Goddard, G. Buth, B. List, *Angew. Chem.* **2008**, *120*, 5157-5159; *Angew. Chem. Int. Ed.* **2008**, *47*, 5079-5081. g) M. Rueping, T. Theissmann, A. Kuenkel, R. M. Koenigs, *Angew. Chem.* **2008**, *120*, 6903-6906; *Angew. Chem. Int. Ed.* **2008**, *47*, 6798-6801.
- 97 a) N. Momiyama, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 1080-1081. b) T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 10054-10055. c) T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380-14381.
- 98 M. Rueping, R. M. Koenigs, I. Atodiresei, *Chem. Eur. J.* **2010**, *16*, 9350-9365.
- 99 M. Hatano, K. Moriyama, T. Maki, K. Ishihara, *Angew. Chem.* **2010**, *122*, 3911-3914; *Angew. Chem. Int. Ed.* **2010**, *49*, 3823-3826.
- 100 For an introduction of the term click chemistry, see: H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056-2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.
- 101 a) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057-3064. b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708-2711; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596-2599. For reviews on click chemistry (especially CuAAC), see: c) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today* **2003**, *8*, 1128-1137. d) V. D. Bock, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2006**, 51-68. e) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249-1262. f) C. Spiteri, J. E. Moses, *Angew. Chem.* **2010**, *122*, 33-36; *Angew. Chem. Int. Ed.* **2010**, *49*, 31-33. g) J. E. Hein, V. V. Fokin, *Chem. Soc. Rev.* **2010**, *39*, 1302-1315.
- 102 a) I. Bae, H. Han, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 2038-2039. b) S. H. Kim, D. Y. Jung, S. Chang, *J. Org. Chem.* **2007**, *72*, 9769-9771.
- 103 a) V. O. Rodionov, V. V. Fokin, M. G. Finn, *Angew. Chem.* **2005**, *117*, 2250-2255; *Angew. Chem. Int. Ed.* **2005**, *44*, 2210-2215. b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210-216. c) M. Ahlquist, V. V. Fokin, *Organometallics* **2007**, *26*, 4389-4391.
- 104 E. J. Yoo, M. Ahlquist, I. Bae, K. B. Sharpless, V. V. Fokin, S. Chang, *J. Org. Chem.* **2008**, *73*, 5520-5528.

- 105 a) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless, S. Chang, *Angew. Chem.* **2007**, *119*, 1760-1763; *Angew. Chem. Int. Ed.* **2007**, *46*, 1730-1733. b) F. Wang, H. Fu, Y. Jiang, Y. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 1830-1834.
- 106 For a review, see: P. Lu, Y. Wang, *Synlett* **2010**, 165-173.
- 107 S. Chang, M. Lee, D. Y. Jung, E. Y. Yoo, S. H. Cho, S. K. Han, *J. Am. Chem. Soc.* **2006**, *128*, 12366-12367.
- 108 S.-L. Cui, J. Wang, Y.-G. Wang, *Org. Lett.* **2007**, *9*, 5023-5025.
- 109 a) E. J. Yoo, S. Chang, *Org. Lett.* **2008**, *10*, 1163-1166. b) Z. Chen, D. Zheng, J. Wu, *Org. Lett.* **2011**, *13*, 848-851.
- 110 a) S.-L. Cui, J. Wang, Y.-G. Wang, *Tetrahedron* **2008**, *64*, 487-492. b) J. Kim, S. Y. Lee, J. Lee, Y. Do, S. Chang, *J. Org. Chem.* **2008**, *73*, 9454-9457. c) W. Lu, W. Song, D. Hong, P. Lu, Y. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1768-1772. d) J. She, Z. Jiang, Y. Wang, *Synlett* **2009**, 2023-2027. e) H. Jin, X. Xu, J. Gao, J. Zhong, Y. Wang, *Adv. Synth. Catal.* **2010**, *352*, 347-350. f) M. Xu, C. Kuang, Z. Wang, Q. Yang, *Synlett* **2010**, 2664-2666.
- 111 a) S. H. Cho, E. J. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 16046-16047. b) M. P. Cassidy, J. Raushel, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 3226-3229; *Angew. Chem. Int. Ed.* **2006**, *45*, 3154-3157. c) T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin, *Org. Lett.* **2004**, *6*, 2853-2855.
- 112 a) A. Pinner, F. Klein, *Chem. Ber.* **1877**, *10*, 1889-1897. For a review, see: b) R. Rogers, D. G. Neilson, *Chem. Rev.* **1961**, *61*, 179-211.
- 113 E. J. Yoo, I. Bae, S. H. Cho, H. Han, S. Chang, *Org. Lett.* **2006**, *8*, 1347-1350.
- 114 a) S.-L. Cui, X.-F. Lin, Y.-G. Wang, *Org. Lett.* **2006**, *8*, 4517-4520. b) Y. Shen, S. Cui, J. Wang, X. Chen, P. Lu, Y. Wang, *Adv. Synth. Catal.* **2010**, *352*, 1139-1144.
- 115 a) S. H. Cho, S. Chang, *Angew. Chem.* **2008**, *120*, 2878-2881; *Angew. Chem. Int. Ed.* **2008**, *47*, 2836-2839. b) Y. Shang, K. Ju, X. He, J. Hu, S. Yu, M. Zhang, K. Liao, L. Wang, P. Zhang, *J. Org. Chem.* **2010**, *75*, 5743-5745.
- 116 a) M. Whiting, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 3229-3233; *Angew. Chem. Int. Ed.* **2006**, *45*, 3157-3161. b) M. de Poortere, J. Marchand-Brynaert, L. Ghosez, *Angew. Chem.* **1974**, *86*, 272-273; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 267-268. c) A. van Camp, D. Goossens, M. Moya-Portuguez, J. Marchand-Brynaert, L. Ghosez, *Tetrahedron Lett.* **1980**, *21*, 3081-3084. d) J. Marchand-Brynaert, M. Moya-Portuguez, D. Lesuisse, L. Ghosez, *J. Chem. Soc., Chem. Commun.* **1980**, 173-174.
- 117 a) X. Xu, D. Cheng, J. Li, H. Guo, J. Yan, *Org. Lett.* **2007**, *9*, 1585-1587. b) S.-L. Cui, J. Wang, Y.-G. Wang, *Org. Lett.* **2008**, *10*, 1267-1269. c) Y. Shang, X. He, J. Hu, J. Wu, M.

- Zhang, S. Yu, Q. Zhang, *Adv. Synth. Catal.* **2009**, *351*, 2709-2713. d) W. Yao, L. Pan, Y. Zhang, G. Wang, X. Wang, C. Ma, *Angew. Chem.* **2010**, *122*, 9396-9400; *Angew. Chem. Int. Ed.* **2010**, *49*, 9210-9214.
- 118 a) P. Magnus, J. Moursounidis, *J. Org. Chem.* **1991**, *56*, 1529-1534. b) T. Kochi, J. A. Ellman, *J. Am. Chem. Soc.* **2004**, *126*, 15652-15653.
- 119 R. Matsubara, F. Berthiol, S. Kobayashi, *J. Am. Chem. Soc.* **2008**, *130*, 1804-1805.
- 120 a) F. Colpaert, S. Mangelinckx, G. Verniest, N. de Kimpe, *J. Org. Chem.* **2009**, *74*, 3792-3797. b) F. Colpaert, S. Mangelinckx, N. de Kimpe, *Org. Lett.* **2010**, *12*, 1904-1907. c) F. Colpaert, S. Mangelinckx, N. de Kimpe, *J. Org. Chem.* **2011**, *76*, 234-244.
- 121 A. Massa, N. Utsumi, C. F. Barbas III, *Tetrahedron Lett.* **2009**, 145-147.
- 122 E. J. Yoo, S. H. Park, S. H. Lee, S. Chang, *Org. Lett.* **2009**, *11*, 1155-1158.
- 123 a) R. Husmann, Y. S. Na, C. Bolm, S. Chang, *Chem. Commun.* **2010**, *46*, 5494-5496. b) W. Song, W. Lu, J. Wang, P. Lu, Y. Wang, *J. Org. Chem.* **2010**, *75*, 3481-3483.
- 124 W. Song, M. Lei, Y. Shen, S. Cai, W. Lu, P. Lu, Y. Wang, *Adv. Synth. Catal.* **2010**, *352*, 2432-2436.
- 125 For reviews, see: a) C. O. Kappe, *Acc. Chem. Res.* **2000**, *33*, 879-888. b) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920-8926.
- 126 For reviews, see: a) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957-4980. b) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451-463.
- 127 For reviews, see: a) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580-591. b) R. G. Arrayás, J. C. Carretero, *Chem. Soc. Rev.* **2009**, *38*, 1940-1948.
- 128 a) L. Banfi, R. Riva in *Organic Reactions*, Vol. 65, Ed.: L. E. Overman, John Wiley & Sons, New York, **2005**, pp. 1-140. b) S. E. Denmark, Y. Fan, *J. Org. Chem.* **2005**, *70*, 9667-9676.
- 129 a) N. A. Petasis, I. Akritopoulou, *Tetrahedron Lett.* **1993**, *34*, 583-586. For a review, see: b) P. F. Kaiser, Q. I. Churches, C. A. Hutton, *Aust. J. Chem.* **2007**, *60*, 799-810.
- 130 For reviews, see: a) I. Ugi, *Angew. Chem.* **1982**, *94*, 826-835; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810-819. b) G. Dyker, *Angew. Chem.* **1997**, *36*, 1777-1779; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1700-1702. c) I. Ugi, *Pure Appl. Chem.* **2001**, *73*, 187-191. d) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133-1144. e) L. A. Wessjohann, D. G. Rivera, O. E. Vercillo, *Chem. Rev.* **2009**, *109*, 796-814.
- 131 For reviews, see: a) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552-560. b) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376-2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282-2316. c) P. O'Brien, J. L. Bilke, *Angew. Chem.* **2008**, *120*, 2774-2776; *Angew. Chem. Int. Ed.* **2008**, *47*, 2734-2736.

- 132 a) S. T. Kerrick, P. Beak, *J. Am. Chem. Soc.* **1991**, *113*, 9708-9710. b) P. Beak, S. T. Kerrick, S. Wu, J. Chu, *J. Am. Chem. Soc.* **1994**, *116*, 3231-3239.
- 133 a) I. Coldham, S. Dufour, T. F. N. Haxell, S. Howard, G. P. Vennall, *Angew. Chem.* **2002**, *114*, 4043-4045; *Angew. Chem. Int. Ed.* **2002**, *41*, 3887-3889. b) I. Coldham, S. Dufour, T. F. N. Haxell, J. J. Patel, G. Sanchez-Jimenez, *J. Am. Chem. Soc.* **2006**, *128*, 10943-10951. c) M. J. McGrath, J. L. Bilke, P. O'Brien, *Chem. Commun.* **2006**, 2607-2609. d) J. L. Bilke, S. P. Moore, P. O'Brien, J. Gilday, *Org. Lett.* **2009**, *11*, 1935-1938. For computational studies, see: e) K. B. Wiberg, W. F. Bailey, *Angew. Chem.* **2000**, *112*, 2211-2213; *Angew. Chem. Int. Ed.* **2000**, *39*, 2127-2129. f) K. B. Wiberg, W. F. Bailey, *J. Am. Chem. Soc.* **2001**, *123*, 8231-8238. g) P.-W. Phuan, J. C. Ianni, M. C. Kozlowski, *J. Am. Chem. Soc.* **2004**, *126*, 15473-15479. h) P. O'Brien, K. B. Wiberg, W. F. Bailey, J.-P. R. Hermet, M. J. McGrath, *J. Am. Chem. Soc.* **2004**, *126*, 15480-15489.
- 134 a) P. Beak, W.-K. Lee, *Tetrahedron Lett.* **1989**, *30*, 1197-1200. b) T. W. Greene, P. G. M. Wuts, *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup> ed., John Wiley & Sons, New York, **1999**.
- 135 J. A. Vanecko, F. G. West, *Org. Lett.* **2002**, *4*, 2813-2816.
- 136 D. Hernández, K. B. Lindsay, L. Nielsen, T. Mittag, K. Bjerglund, S. Friis, R. Mose, T. Skrydstrup, *J. Org. Chem.* **2010**, *75*, 3283-3293.
- 137 a) C. Bolm, A. Kasyan, K. Drauz, K. Günther, G. Raabe, *Angew. Chem.* **2000**, *112*, 2374-2376; *Angew. Chem. Int. Ed.* **2000**, *39*, 2288-2290. For a review, see: b) M. Mortensen, R. Husmann, E. Veri, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 1002-1010.
- 138 a) C. Bolm, A. Kasyan, P. Heider, S. Saladin, K. Drauz, K. Günther, C. Wagner, *Org. Lett.* **2002**, *4*, 2265-2267. b) C. Bolm, S. Saladin, A. Kasyan, *Org. Lett.* **2002**, *4*, 4631-4633. c) C. Bolm, S. Saladin, A. Claßen, A. Kasyan, E. Veri, G. Raabe, *Synlett* **2005**, 461-464. d) C. Bolm, A. Kasyan, S. Saladin, *Tetrahedron Lett.* **2005**, *46*, 4049-4051.
- 139 S. Özçubukçu, F. Schmidt, C. Bolm, *Org. Lett.* **2005**, *7*, 1407-1409.
- 140 A. Thaqi, A. McCluskey, J. L. Scott, *Tetrahedron Lett.* **2008**, *49*, 6962-6964.
- 141 W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879-1880.
- 142 W. L. F. Armarego, C. L. L. Chai, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, **2003**.
- 143 a) R. Husmann, M. Jörres, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 12549-12552. b) J. O. Bauer, J. Stiller, E. Marqués-López, K. Strohfeldt, M. Christmann, C. Strohmann, *Chem. Eur. J.* **2010**, *16*, 12553-12558.
- 144 S. Özçubukçu, doctoral thesis, RWTH Aachen University (Germany), **2007**.

- 145 a) P. D. Lickiss, R. Lucas, *J. Organomet. Chem.* **1995**, 521, 229-234. b) Y. Lee, D. Seomoon, S. Kim, H. Han, S. Chang, P. H. Lee, *J. Org. Chem.* **2004**, 69, 1741-1743.
- 146 For a review on the synthesis and structure of organosilanols, see: V. Chandrasekhar, R. Boomishankar, S. Nagendran, *Chem. Rev.* **2004**, 104, 5847-5910.
- 147 S. McN. Sieburth, W. Mu, *J. Org. Chem.* **1993**, 58, 7584-7586.
- 148 J. W. Gillard, R. Fortin, H. E. Morton, C. Yoakim, C. A. Quesnelle, S. Daignault, Y. Guindon, *J. Org. Chem.* **1988**, 53, 2602-2608.
- 149 R. Brückner, *Reaktionsmechanismen: Organische Reaktionen, Stereochemie, moderne Synthesemethoden*, 2<sup>nd</sup> ed., Spektrum Akademischer Verlag GmbH, Heidelberg, **2003**.
- 150 The same effect was observed by Strohmman. Personal conversation, Dortmund (Germany), 12 November **2010**.
- 151 V. H. Rawal, M. P. Cava, *Tetrahedron Lett.* **1985**, 26, 6141-6142.
- 152 Flack's method was employed: H. D. Flack, *Acta Crystallogr. Sect. A.* **1983**, 39, 876-881.
- 153 Single-crystal X-ray diffraction analysis of **139d**: C<sub>17</sub>H<sub>22</sub>ClNSi, colorless crystals, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>(19), *Z* = 4, *a* = 7.4665(2) Å, *b* = 9.0303(3) Å, *c* = 24.9057(8) Å, *V* = 1679.26(9) Å<sup>3</sup>,  $\rho_{\text{calcd}}$  = 1.202 Mg/m<sup>3</sup>, *T* = 293 K, MoK $\alpha$ ,  $\lambda$  = 0.71073 Å,  $\theta_{\text{max}}$  = 35.3°, data collection: Bruker KAPPA APEX II, structure solution: Xtal3.7 (The Xtal 3.7 System, S. R. Hall, D. J. Du Bolay, R. Olthof-Hazekamp, University of Western Australia, **2001**), refinement on *F*, *R*(*R*<sub>w</sub>) = 0.054(0.040), *S* = 1.571, for 265 parameters and 6144 reflections with *I* > 2 $\sigma$ (*I*), hydrogen atoms located and refined isotropically, residual electron density – 0.724/0.599 e/Å<sup>3</sup>. CCDC-778923 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre, [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).
- 154 The addition of acids is advantageous in some cases as reported by: a) D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, Y. Nagel, C. Nájera, *Eur. J. Org. Chem.* **2007**, 2328-2343. b) Y.-Q. Cheng, Z. Bian, Y.-B. He, F.-S. Han, C.-Q. Kang, Z.-L. Ning, L.-X. Gao, *Tetrahedron: Asymmetry* **2009**, 20, 1753-1758. For a review, see: c) S. Saito, H. Yamamoto, *Acc. Chem. Res.* **2004**, 37, 570-579.
- 155 M. Jörres, diploma thesis, RWTH Aachen University (Germany), **2010**.
- 156 a) S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, 128, 1040-1041. b) H. Zhang, S. Mitsumori, N. Utsumi, M. Imai, N. Garcia-Delgado, M. Mifsud, K. Albertshofer, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2008**, 130, 875-886. For reviews, see ref. 27i,j and 127a.

- 157 G. W. Gribble in *Organofluorines*, Vol. 3, Ed.: A. H. Neilson, Springer, Berlin, **2002**, pp. 121-136.
- 158 For reviews, see: a) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, 5, 637-643. b) C. Isanbor, D. O'Hagan, *J. Fluorine Chem.* **2006**, 127, 303-319. c) K. L. Kirk, *J. Fluorine Chem.* **2006**, 127, 1013-1029. d) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881-1886. e) K. L. Kirk, *Org. Process Res. Dev.* **2008**, 12, 305-321. f) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320-330. g) W. K. Hagmann, *J. Med. Chem.* **2008**, 51, 4359-4369.
- 159 For reviews, see: a) P. Jeschke, *ChemBioChem* **2004**, 5, 570-589. b) P. Maienfisch, R. G. Hall, *Chimia* **2004**, 58, 93-99. c) P. Jeschke, *Pest Manag. Sci.* **2010**, 66, 10-27.
- 160 For special issues on organofluorine chemistry, see: a) *ChemBioChem* **2004**, 5, 557-726. b) *Beilstein J. Org. Chem.* **2008**, 4, No. 11. c) *Beilstein J. Org. Chem.* **2010**, 6, No. 36. d) *Adv. Synth. Catal.* **2010**, 352, 2677-2846.
- 161 For a review on the asymmetric construction of stereogenic carbon centers bearing a trifluoromethyl group, see: J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, 111, 455-529.
- 162 B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, G. K. S. Prakash, *Angew. Chem.* **2005**, 117, 3146-3149; *Angew. Chem. Int. Ed.* **2005**, 44, 3086-3089.
- 163 a) J.-L. Zhao, L. Liu, C.-L. Gu, D. Wang, Y.-J. Chen, *Tetrahedron Lett.* **2008**, 49, 1476-1479. b) G.-W. Zhang, L. Wang, J. Nie, J.-A. Ma, *Adv. Synth. Catal.* **2008**, 350, 1457-1463. c) J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng, J.-A. Ma, *Chem. Commun.* **2009**, 2356-2358. d) J. Nie, G.-W. Zhang, L. Wang, D.-H. Zheng, Y. Zheng, J.-A. Ma, *Eur. J. Org. Chem.* **2009**, 3145-3149. e) W. Kashikura, J. Itoh, K. Mori, T. Akiyama, *Chem. Asian J.* **2010**, 5, 470-472. f) T. Wang, G.-W. Zhang, Y. Teng, J. Nie, Y. Zheng, J.-A. Ma, *Adv. Synth. Catal.* **2010**, 352, 2773-2777.
- 164 a) V. P. Kukhar, V. A. Soloshonok, *Fluorine-containing Amino Acids - Synthesis and Properties*, John Wiley & Sons, Chichester, **1995**. b) K. Uneyama in *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*, Ed.: V. A. Soloshonok, John Wiley & Sons, Chichester, **1999**, pp. 391-418.
- 165 a) S. N. Osipov, N. D. Chkanikov, A. F. Kolomiets, A. V. Fokin, *Russ. Chem. Bull.* **1986**, 35, 1256-1259. b) K. Burger, E. Höß, K. Gaa, *Chem. Ztg.* **1989**, 113, 243-247. c) S. N. Osipov, N. D. Chkanikov, A. F. Kolomiets, A. V. Fokin, *Russ. Chem. Bull.* **1989**, 38, 1512-1515. d) S. N. Osipov, N. D. Chkanikov, Y. V. Shklyayev, A. F. Kolomiets, A. V. Fokin, *Russ. Chem. Bull.* **1989**, 38, 1962-1964. e) K. Burger, K. Gaa, K. Geith, C. Schierlinger, *Synthesis* **1989**,

- 850-855. f) K. Burger, N. Sewald, *Synthesis* **1990**, 115-118. g) S. N. Osipov, N. Sewald, A. F. Kolomiets, A. V. Fokin, K. Burger, *Tetrahedron Lett.* **1996**, *37*, 615-618. h) S. N. Osipov, A. S. Golubev, N. Sewald, T. Michel, A. F. Kolomiets, A. V. Fokin, K. Burger, *J. Org. Chem.* **1996**, *61*, 7521-7528. i) V. A. Soloshonok, V. P. Kukhar, *Tetrahedron* **1997**, *53*, 8307-8314. j) H. Skarpos, D. V. Vorob'eva, S. N. Osipov, I. L. Odinet, E. Breuer, G.-V. Rösenthaller, *Org. Biomol. Chem.* **2006**, *4*, 3669-3674. k) G. T. Shchetnikov, M. A. Zotova, C. Bruneau, P. H. Dixneuf, S. N. Osipov, *Eur. J. Org. Chem.* **2010**, 1587-1592. For reviews, see: l) A. Sutherland, C. L. Willis, *Nat. Prod. Rep.* **2000**, *17*, 621-631. m) X.-L. Qiu, W.-D. Meng, F.-L. Qing, *Tetrahedron* **2004**, *60*, 6711-6745. n) R. Smits, C. D. Cadicamo, K. Burger, B. Koks, *Chem. Soc. Rev.* **2008**, *37*, 1727-1739.
- 166 a) N. Sewald, L. C. Seymour, K. Burger, S. N. Osipov, A. F. Kolomiets, A. V. Fokin, *Tetrahedron Asymmetry* **1994**, *5*, 1051-1060. b) P. Bravo, S. Fustero, M. Guidetti, A. Volonterio, M. Zanda, *J. Org. Chem.* **1999**, *64*, 8731-8735. c) A. Asensio, P. Bravo, M. Crucianelli, A. Farina, S. Fustero, J. G. Soler, S. V. Meille, W. Panzeri, F. Viani, A. Volonterio, M. Zanda, *Eur. J. Org. Chem.* **2001**, 1449-1458. d) F. Lazzaro, A. Gissot, M. Crucianelli, F. de Angelis, L. Bruché, M. Zanda, *Lett. Org. Chem.* **2005**, *2*, 235-237.
- 167 M. Abid, L. Teixeira, B. Török, *Org. Lett.* **2008**, *10*, 933-935.
- 168 D. Enders, K. Gottfried, G. Raabe, *Adv. Synth. Catal.* **2010**, *352*, 3147-3152.
- 169 For a review, see: S. N. Osipov, A. F. Kolomiets, A. V. Fokin, *Russ. Chem. Rev.* **1992**, *61*, 798-815.
- 170 W. Steglich, K. Burger, M. Dürr, E. Burgis, *Chem. Ber.* **1974**, *107*, 1488-1498.
- 171 H. Watanabe, Y. Hashizume, K. Uneyama, *Tetrahedron Lett.* **1992**, *33*, 4333-4336.
- 172 I. Fleming, R. S. Roberts, S. C. Smith, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1209-1214.
- 173 J. S. Dickstein, M. C. Kozlowski, *Chem. Soc. Rev.* **2008**, *37*, 1166-1173.
- 174 For the first organocatalytic enantioselective Mannich reaction of ketimines, see: W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 4576-4578; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476-4478.
- 175 For reviews, see: a) K. A. Jørgensen, *Synthesis* **2003**, 1117-1125. b) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199-1222. c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190-2201. d) M. Bandini, A. Eichholzer, *Angew. Chem.* **2009**, *121*, 9786-9824; *Angew. Chem. Int. Ed.* **2009**, *48*, 9608-9644. e) M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **2010**, *6*, No. 6, DOI:10.3762/bjoc.6.6. f) M. Zeng, S.-L. You, *Synlett* **2010**, 1289-1301. g) V. Terrasson, R. M. de Figueiredo, J. M. Campagne, *Eur. J.*

- Org. Chem.* **2010**, 2635-2655. h) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, 39, 4449-4465.
- 176 a) Y.-Q. Wang, J. Song, R. Hong, H. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, 128, 8156-8157.  
b) Q. Kang, Z.-A. Zhao, S.-L. You, *Tetrahedron* **2009**, 1603-1607.
- 177 a) M. Rueping, B. J. Nachtsheim, S. A. Moreth, M. Bolte, *Angew. Chem.* **2008**, 120, 603-606; *Angew. Chem. Int. Ed.* **2008**, 47, 593-596. b) H.-Y. Tang, A.-D. Lu, Z.-H. Zhou, G.-F. Zhao, L.-N. He, C.-C. Tang, *Eur. J. Org. Chem.* **2008**, 1406-1410. c) A. Scettri, R. Villano, M. R. Acocella, *Molecules* **2009**, 14, 3030-3036. d) P. Bachu, T. Akiyama, *Chem. Commun.* **2010**, 46, 4112-4114. e) G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, C. Vila, *Chem. Eur. J.* **2010**, 16, 9117-9122. f) Z.-K. Pei, Y. Zheng, J. Nie, J.-A. Ma, *Tetrahedron Lett.* **2010**, 51, 4658-4661. g) T. Sakamoto, J. Itoh, K. Mori, T. Akiyama, *Org. Biomol. Chem.* **2010**, 8, 5448-5454.
- 178 a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, 120, 4080-4082; *Angew. Chem. Int. Ed.* **2008**, 47, 4016-4018. b) Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang, S.-L. You, *Chem. Eur. J.* **2009**, 15, 3351-3354.
- 179 Compounds **68** and **161** were synthesized and kindly provided by Schmitt. See: E. Schmitt, doctoral thesis, RWTH Aachen University (Germany), **2010**.
- 180 Compound **163** was synthesized and kindly provided by Raja.
- 181 BINOL-derived phosphoric acids were kindly provided by Sugiono. The free acids were prepared according to: M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard, B. List, *Synlett* **2010**, 2189-2192.
- 182 R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping, C. Bolm, *Org. Lett.* **2011**, 13, 1044-1047.
- 183 S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, 71, 9088-9095.
- 184 a) V. A. Soloshonok, *Angew. Chem.* **2006**, 118, 780-783; *Angew. Chem. Int. Ed.* **2006**, 45, 766-769. b) V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekela, J. S. Hirschi, D. A. Singleton, *J. Am. Chem. Soc.* **2007**, 129, 12112-12113.
- 185 *Spartan, Version 02*; Wavefunction, Inc.: Irvine, CA, **2002**.
- 186 R. Bauernschmitt, R. Ahlrichs, *Chem. Phys. Lett.* **1996**, 256, 454-464.
- 187 a) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785-789. b) B. Miehlich, A. Savin, H. Stoll, H. Preuss, *Chem. Phys. Lett.* **1989**, 157, 200-206. c) A. D. Becke, *J. Chem. Phys.* **1993**, 98, 5648-5652.

- 188 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian09, Revision A.1*, Gaussian, Inc., Wallingford, CT, **2009**.
- 189 For reviews on the synthesis of quaternary carbon stereogenic centers, see: a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402-415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388-401. b) J. Christoffers, A. Baro, *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, Wiley-VCH, Weinheim, **2005**. c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473-1482. d) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583-1614.
- 190 a) J. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**. b) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628-1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602-1634. c) A. Dömling, *Chem. Rev.* **2006**, *106*, 17-89. d) B. B. Touré, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439-4486. e) J. E. Biggs-Houck, A. Younai, J. T. Shaw, *Curr. Opin. Chem. Biol.* **2010**, *14*, 371-382.
- 191 a) R. A. Sheldon, *Green Chem.* **2007**, *9*, 1273-1283. b) R. A. Sheldon, *Chem. Commun.* **2008**, 3352-3365. c) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301-312.
- 192 A. Pollex, M. Hiersemann, *Org. Lett.* **2005**, *7*, 5705-5708.
- 193 a) C. L. Liotta, A. M. Dabdoub, L. H. Zalkow, *Tetrahedron Lett.* **1977**, *18*, 1117-1120. b) E. J. Park, S. Lee, S. Chang, *J. Org. Chem.* **2010**, *75*, 2760-2762.
- 194 E. Borrione, M. Prato, G. Scorrano, M. Stivanello, *J. Heterocycl. Chem.* **1988**, *25*, 1831-1835.
- 195 The <sup>1</sup>H NMR spectroscopic experiments on the copper-catalyzed coupling reactions were performed by Na at KAIST, Daejeon (Republic of Korea).
- 196 This compound was reported but no data was given: B. Tan, X. Zhang, P. J. Chua, G. Zhong, *Chem. Commun.* **2009**, 779-781.
- 197 a) M. J. Dearden, C. R. Firkin, J.-P. R. Hermet, P. O'Brien, *J. Am. Chem. Soc.* **2002**, *124*, 11870-11871. b) P. O'Brien, *Chem. Commun.* **2008**, 655-667. c) D. Stead, P. O'Brien, A.

- Sanderson, *Org. Lett.* **2008**, *10*, 1409-1412. d) G. Carbone, P. O'Brien, G. Hilmersson, *J. Am. Chem. Soc.* **2010**, *132*, 15445-15550.
- 198 For reviews, see: a) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092-2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012. b) R. T. Stemmler, *Synlett* **2007**, 997-998. c) H. Butenschön, *Angew. Chem.* **2008**, *120*, 3544-3547; *Angew. Chem. Int. Ed.* **2008**, *47*, 3492-3495. d) E. J. Corey, *Angew. Chem.* **2009**, *121*, 2134-2151; *Angew. Chem. Int. Ed.* **2009**, *48*, 2100-2117.
- 199 Reduction of *N*-Boc-2-(dimethylphenylsilyl)pyrrolidine (**134b**) and *N*-Boc-2-(diphenylmethylsilyl)pyrrolidine (**134c**) was demonstrated by K. Strohfeldt, doctoral thesis, Julius-Maximilians-Universität Würzburg (Germany), **2004**.
- 200 For a selected example, see: a) I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2320-2331. For reviews, see: b) D. E. Frantz, R. Fässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373-381. c) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963-983.
- 201 a) C. Däschlein, J. O. Bauer, C. Strohmann, *Angew. Chem.* **2009**, *121*, 8218-8221; *Angew. Chem. Int. Ed.* **2009**, *48*, 8074-8077. b) C. Däschlein, C. Strohmann, *Z. Naturforsch., B: J. Chem. Sci.* **2009**, *64b*, 1558-1566.
- 202 R. Husmann, diploma thesis, RWTH Aachen University (Germany), **2007**.
- 203 For the synthesis of protected silaproline, see: a) V. I. Handmann, M. Merget, R. Tacke, *Z. Naturforsch., B: J. Chem. Sci.* **2000**, *55b*, 133-138. b) B. Vivet, F. Cavelier, J. Martinez, *Eur. J. Org. Chem.* **2000**, 807-811.
- 204 For reviews, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209-2219. b) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902-8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758. c) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381-1407.
- 205 For a review, see: D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811-891.
- 206 a) X.-N. Wang, P.-L. Shao, H. Lv, S. Ye, *Org. Lett.* **2009**, *11*, 4029-4031. For reviews on *N*-heterocyclic carbenes as organocatalysts, see: b) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534-541. c) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046-3058; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988-3000. d) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606-5655.
- 207 a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831-7832. b) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, D. Ferraris, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 6626-6635. c) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579. d) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am.*

- Chem. Soc.* **2005**, *127*, 11586-11587. For reviews, see: e) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985-3012. f) D. H. Paull, C. J. Abraham, M. T. Scebra, E. Alden-Danforth, T. Lectka, *Acc. Chem. Res.* **2008**, *41*, 655-663.
- 208 D. F. Shriver, M. D. Drezdson, *The Manipulation of Air-Sensitive Compounds*, Wiley, Chichester, **1986**.
- 209 H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.
- 210 D.-Y. Yang, Y.-S. Chen, P.-Y. Kuo, J.-T. Lai, C.-M. Jiang, C.-H. Lai, Y.-H. Liao, P.-T. Chou, *Org. Lett.* **2007**, *9*, 5287-5290.
- 211 S. Mossé, M. Laars, K. Kriis, T. Kanger, A. Alexakis, *Org. Lett.* **2006**, *8*, 2559-2562.
- 212 O. Andrey, A. Alexakis, A. Tomassini, G. Bernardinelli, *Adv. Synth. Catal.* **2004**, *346*, 1147-1168.
- 213 R.-Y. Yang, C.-S. Da, L. Yi, F.-C. Wu, H. Li, *Lett. Org. Chem.* **2009**, *6*, 44-49.



---

## 7 Acknowledgements

---

Firstly, I would like to express sincere thanks to Prof. Dr. C. Bolm for his continuous support during my doctoral studies. His open door and the freedom he gave me to develop research projects independently provided strong motivation. I appreciate his support in allowing me to visit numerous national and international conferences. I also thank him for initiating my short-term research visit in the group of Prof. Dr. S. Chang at KAIST in the Republic of Korea. This was an invaluable experience both professionally and personally.

Deep appreciation goes out to my supervisor during this visit, Prof. Dr. S. Chang. His openness and kindness and the friendliness of his group made me feel very comfortable. This was the basis for a fruitful research period. For all the help concerning personal issues (and for playing tennis with me) I thank Seok Hwan Kim. I am also grateful to Dr. Eun Ju Park, Sae Hume Park, Ji Young Kim and Seung Eon Lee for their kindness. The chicken masters, Dr. Seung Hwan Cho, Dr. Min Kim, Jinho Kim, Hyun Jin Kim and Jaesung Kwak I thank for interesting discussions and sharing meals at later hours. For conducting mechanistic studies on the four-component reaction I am grateful to Yun Suk Na. I am also very thankful to Prof. Dr. S. Chang for being the second examiner and coming to Aachen for my doctoral exam.

For a fruitful collaboration with AK Rueping I would like to thank Dr. Erli Sugiono and Prof. Dr. M. Rueping. The successful completion of the project described in chapter 2.2 would not have been possible without the supply of chiral phosphoric acids.

I would also like to thank all the members of the Institute of Organic Chemistry for their technical support and analytical services (especially Dr. J. Runsink and Annette Müller for the measurement of NMR spectra, Claudia Schleep for CHN analysis and Christel Dittmer for MS and IR spectra). I thank Prof. Dr. G. Raabe for providing X-ray crystal structures and Stefanie Mersmann for performing theoretical calculations. For assistance with various GC- and HPLC-related problems I would like to thank Cornelia Vermeeren. For repairing and manufacturing of special glassware I am grateful to our glassblowers Hasso Jussen and Christian Muschiol. Frau Voss I would like to thank for helping with daily problems and providing office supplies.

Susi Grünebaum and Pierre Winandy are thanked for their skillful preparation of numerous substrates I used during my research.

I am also grateful to Dr. M. Meske and Dr. Ingo Schiffers for smooth collaboration in all student-related issues and practical courses.

Special thanks go to Anne Nijs, Nick Swisher and Manuel Jörres for critical and careful proof-reading of the manuscript.

All the former and current coworkers of AK Bolm and especially Dr. Iuliana Atodiresei, Astrid Beyer, Dr. Olivia Bistri, Julien Bonnamour, Dr. Julien Buendia, Dr. Mathieu Candy, Dr. Monica Carril, Dr. Gae Young Cho (thank you so much for your help preparing for my Korea visit!), Dr. Arkaitz Correa, Simon Elmore, Dr. Angelika Flock, Marcus Frings, Dr. Bernhard Fügen, Jenna Head, Dr. Andreas Hergesell, Manuel Jörres, Dr. Olga García Mancheño, Dr. Gwion Harfoot, Prof. Dr. Lukas Hintermann, Dr. Johannes Johansson, Anke Krebs, Dr. Rafal Kowalczyk, Dr. Aurélie Labonne, Dr. Agathe Mayer, Christiane Metje, Dr. Matthew McGrath, Dr. Matthew Mortensen, Dr. Masafumi Nakanishi, Anne Nijs, Dr. Funda Oguz, Timon Ortloff, Dr. Salih Özçubukçu, Ankur Pandey, Seong Jun Park, Dr. Miguel Pena, Dr. Belén Rodríguez, Dr. Sandra Saladin, Dr. Ingo Schiffers, Dr. Ellen Schmitt, Dr. Marianne Steurer (Tennismeisterin), Nick Swisher, Isabelle Thomé, Dr. Elisabetta Veri, Dr. Daniel Whelligan, Dr. Lorenzo Zani and Dr. Erik Zuidema I thank for support and a good working atmosphere.

All the research students, Manuel Jörres, Christian Willems, Stephanie Schrade, Bernhard Mausolf and Henning Kayser, are thanked for their enthusiastic participation in several research projects. I also thank Marek(x) Weiler for his contribution during his second year of training and Andrew Seidner for his work during a DAAD RISE internship.

My greatest thanks go out to the 5.07 lab members: Arno Claßen was very helpful with his broad knowledge of all kinds of practical and synthetic approaches; Dr. Jutta Kobayashi for all the philosophical talks and discussions not only about chemistry; Anke Krebs as the most constant force of the lab with hilarious sarcasm; Dr. Ellen Schmitt for her friendship, personal talks, all the nice lunches and great trips with the girls; Maria de Rosa and Isabelle Thomé for short-term stays in the lab. Thank you all!

For support outside the lab I thank all my friends, especially Jan Timper for a great friendship since the first chemistry class, Wolfgang Golser for his continuous support of my work (have fun reading this book!) and Georg Schendzielorz and the Stoppes for their friendship all along.

Finally, I would like to express my deep appreciation and gratitude for Karin and Michael Ladenburger for their support. The same goes for my parents, Mieke and Miel Husmann and my sister Yvette Husmann. For all her patience and love I owe the deepest respect to Christine Ladenburger.

---

## 8 Curriculum Vitae

---

### Personal Data

|                  |                            |
|------------------|----------------------------|
| Name:            | Ralph Maria Willem Husmann |
| Date of birth:   | April 13, 1982             |
| Place of birth:  | Heerlen (Netherlands)      |
| Nationality:     | Dutch                      |
| Personal status: | Single                     |

### Education

|                         |                                              |
|-------------------------|----------------------------------------------|
| August 1988 – June 1994 | “Basisschool St. Josef”, Vaals (Netherlands) |
| August 1994 – June 2000 | “Bernardinuscollege”, Heerlen (Netherlands)  |

### Academic Qualifications

|                              |                                                                                                                                                                        |
|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| April 2001 – March 2007      | Studies in chemistry. Diploma thesis under the supervision of Prof. Dr. C. Bolm, Institute of Organic Chemistry, RWTH Aachen University, Germany.                      |
| October 2005 – December 2005 | Research stay in the group of Prof. S. Al-Hallaj, Illinois Institute of Technology (IIT), Chicago, USA.                                                                |
| October 2009 – December 2009 | Research stay in the group of Prof. S. Chang, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Republic of Korea (financed by a DAAD scholarship). |
| Since April 2007             | Doctoral thesis in the group of Prof. Dr. C. Bolm, Institute of Organic Chemistry, RWTH Aachen University, Germany.                                                    |