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## Synthesis of N-Containing Compounds: Development of Methodology and its Application in Total Synthesis

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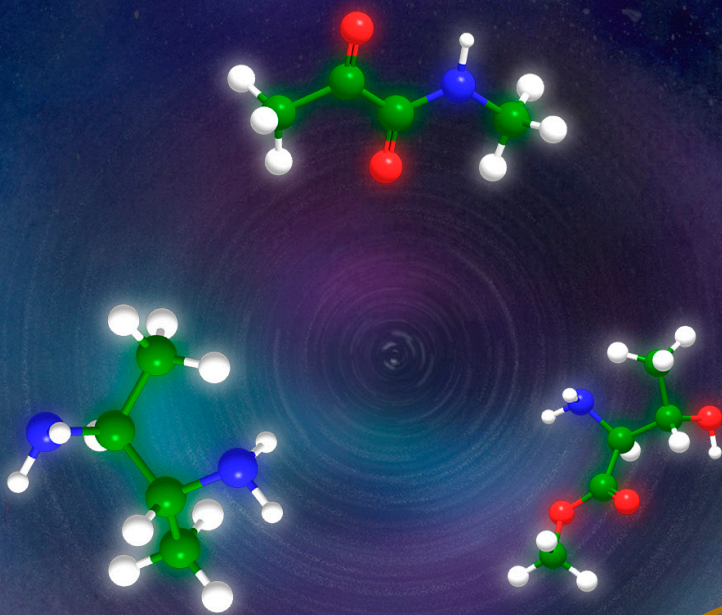
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# Synthesis of *N*-Containing Compounds: Development of Methodology and its Application in Total Synthesis

LU YU | CENTRE FOR ANALYSIS AND SYNTHESIS | LUND UNIVERSITY





# Synthesis of *N*-Containing Compounds: Development of Methodology and its Application in Total Synthesis

Lu Yu



DOCTORAL DISSERTATION

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To be defended at lecture hall C, Kemencentrum. Date 20 september 2019 at 9:00

*Faculty opponent*  
Professor Petri Pihko  
University of Jyväskylä, Finland

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<b>Abstract</b> <p>This thesis aims to develop new synthetic methods and explore the possibilities to apply it in the total synthesis of natural products.</p> <p><i>Chapter 2</i> deals with a mild procedure for the synthesis of <math>\alpha</math>-keto amides by <math>\alpha</math>-oxidation of the corresponding <math>\alpha</math>-keto amines mediated by pyrrolidine and TEMPO. The method can also be applied to the synthesis of <math>\alpha</math>-keto thioamides and <math>\alpha</math>-keto amidines.</p> <p><i>Chapter 3</i> deals with a straightforward synthesis of <i>anti</i>-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic <math>\alpha</math>-amino-<math>\beta</math>-keto esters by using ATH/DKR protocol. In order to highlight the versatility of the methodology, it was applied in an efficient asymmetric synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.</p> <p><i>Chapter 4</i> describes an asymmetric formal hydroamination of enamines approach using Cu-H catalyst for the synthesis of chiral 1,2-diamines. The method provides a straightforward method for the synthesis of chiral 1,2-dialkyl amines in good yields with high level of enantioselectivities for a broad range of substrates and should have significant value for the preparation of molecules bearing a 1,2-diamine motif.</p>		
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# Synthesis of *N*-Containing Compounds: Development of Methodology and its Application in Total Synthesis

Lu Yu



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# List of publications

This thesis is based on the following papers that will be referred to by roman numerals I-IV

**I. Synthesis of  $\alpha$ -keto amide by a pyrrolidine/TEMPO-mediated oxidation of  $\alpha$ -keto amines.**

Lu Yu and Peter Somfai

*Synlett.* **2016**, 27, 2587-2590.

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript.

**II. Enantioselective synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters: application to the total synthesis of (+)-alexine**

Lu Yu and Peter Somfai

*RSC Advances.* **2019**, 9, 2799-2802.

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript.

**III. Regio- and enantioselective formal hydroamination of enamines for the synthesis of 1,2-diamines**

Lu Yu and Peter Somfai

*Angew. Chem. Int. Ed.* **2019**, 58, 8551-8555.

Highlighted in *Synfacts.* **2019**, 15, 0880.

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript.

**IV. Regio- and enantioselective synthesis of 1,2-diamines by formal hydroamination of enamines**

Lu Yu and Peter Somfai

*In manuscript*

I performed all the experimental work, contributed to solving the research problems and wrote the manuscript.

Publication not included in the current thesis:

**Formal synthesis of *ent*-cephalotaxine using a one-pot Parham–Aldol sequence**

Juha H. Siitonen, Lu Yu, Jakob Danielsson, Giovanni Di Gregorio and Peter Somfai

*J. Org. Chem.* **2018**, 83, 11318-11322.

I performed part of the experimental work and contributed to solving the research problems.

# Abbreviations

THF	Tetrahydroofuran
Ac	Acetyl
<i>t</i> -Bu	<i>tert</i> -Butyl
Cbz	Benzyloxycarbonyl
<i>n</i> -PrOH	1-Propanol
Bn	Benzyl
Ms	Methanesulfonyl
COD	1,5-Cyclooctadiene
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Methyl sulfoxide
Ar	Aryl
Ph	Phenyl
Ru	Ruthenium
Ts	Tosyl
atm	Atmosphere
dr	Diastereometric ratio
ee	Enantiomeric excess
er	Enantiomeric ratio
Boc	<i>tert</i> -Butyloxycarbonyl
Pg	Protecting group
Me	Methyl
Et	Ethyl

BRSM	Based on recovered starting material
BOM	Benzyloxymethyl
DMS	Dimethyl sulfide
Ti	Titanium
Pd	Palladium
Zn	Zinc
Rh	Rhodium
Bz	Benzoyl
TMDS	Tetramethyldisiloxane
Mo	Molybdenum
MS	Molecular sieve
TMS	Tetramethylsilane
DTBM	Di(3,5)-di- <i>tert</i> -butyl-4-methoxyphenyl



# 1. Introduction

## 1.1 Organic synthesis

Just as the ancestors who worked out how to build the Great Wall transformed Chinese architecture two thousand years ago, organic synthetic chemists who build molecules on a scale  $10^{10}$  times smaller have transformed everyone's daily life in modern times. Organic synthesis commenced with Wöhler's discovery that ammonium cyanate could be converted into urea in the laboratory in 1828.<sup>1</sup> This scientific breakthrough changed the common perception that there was a clear distinction between molecules from living beings (organic) and those from non-living material (inorganic), encouraged numerous chemists to attempt the synthesis of more and more complex organic molecules.<sup>2</sup> Today, organic molecules touch on all aspects of life, whether as a source of essential drugs, materials, dyes, plastics, detergents, etc<sup>3</sup>. Since organic synthesis is one of the most important ways to obtain these molecules, there is a strong incentive to invest substantial resources in organic synthesis.

For synthesizing an organic molecule, there are three significant steps that must be considered. Firstly, identifying the structure of the target molecule. The target molecule may be prominent pharmaceutical drugs for the treatment on human health, new materials with specific properties of strength and flexibility required by engineers, molecules which could selectively inhibit an enzyme required by a biochemist, or any imaginable structures that might have significant value. Although some of these molecules can be isolated from plants or marine animals, due to the limitation of natural resources, organic synthesis is one of the most important methods to obtain large quantities of valuable natural or non-natural compounds. Secondly, designing appropriate synthetic approaches. Exactly like the architectural blueprint is essential for buildings, a perfect synthetic approach is also highly demanded to make molecules, especially molecules with complex structures. Synthetic planning usually starts with the target molecules and work backward towards the starting materials. This process is referred to as retrosynthetic analysis. The goal of this process is to simplify the target molecule into

simpler precursors through bond-breaking. Such procedure will be repeated until a simple or commercially available starting material is reached. Based on simplifying the structure of the target molecules, more than one possible synthetic pathways might be recognized, and the suitable sequence of synthetic steps could be developed after comparing them logically.<sup>4,5</sup>

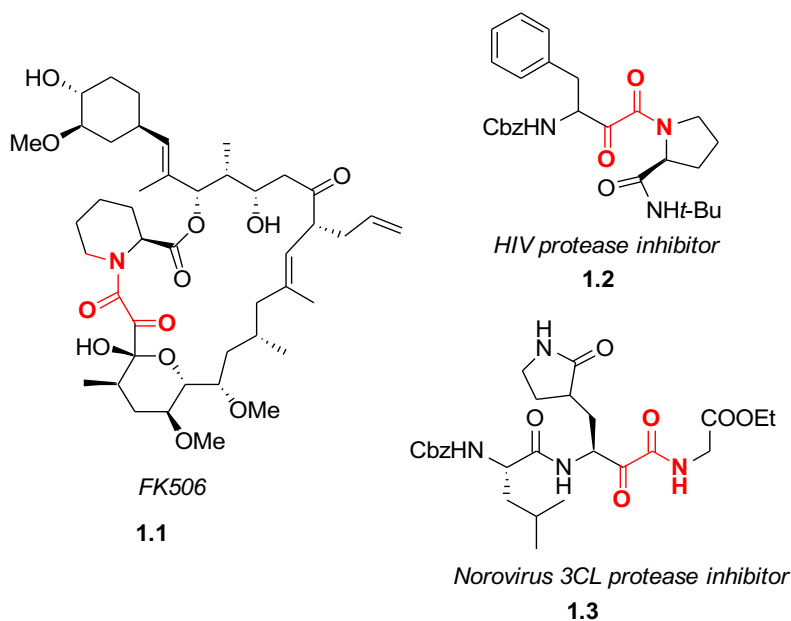
Once we identified the target molecule and the synthetic approaches, next comes the most crucial step: making it. Whether constructing a building or a molecule, tools are essential. In organic synthesis, tools are synthetic methods for different organic compounds in appropriate reaction conditions; for example, the hydroamination to construct C-N bond or the aldol reaction to construct a C-C bond. Development of novel synthetic methodology, one of the main branches of organic synthesis, plays a vital role in accessing the target molecule in an efficient and practical approach. The efficiency of a new methodology can be judged by a variety of metrics, such as yield of the product, the chemo-, regio- and stereoselectivity of the transformation, atom economy, and the number of manipulations.<sup>6,7</sup> The development of new methodology not only provides organic chemists with more available synthetic methods to efficiently accomplish their target products but also promote the development of organic chemistry through increased understanding of fundamental characteristics of molecules or possible reaction mechanisms.

## 1.2 Nitrogen-containing compounds

It is difficult to imagine what the world would be without nitrogen-containing compounds, which are among the most significant structural components of living matters, pharmaceutical agents, agrochemicals, functional materials, and dyes.<sup>8-11</sup> By 2014, analysis of the database of Food and Drug Administration (FDA) approved drugs reveals that 84% of small-molecule drugs contain at least one nitrogen atom.<sup>12</sup> Therefore, the synthesis of such compounds has long been recognized as a crucial topic in organic synthesis. In the past century, numerous elegant methods have been reported for the preparation of a large variety of nitrogen-containing compounds.<sup>13</sup> These synthetic strategies may be divided into two main categories: (a) construction of new carbon-nitrogen bonds and (b) construction of complex nitrogen-containing compounds from structurally simpler nitrogen-containing derivatives through structural modifications.

### 1.3 Synthesis of $\alpha$ -keto amides

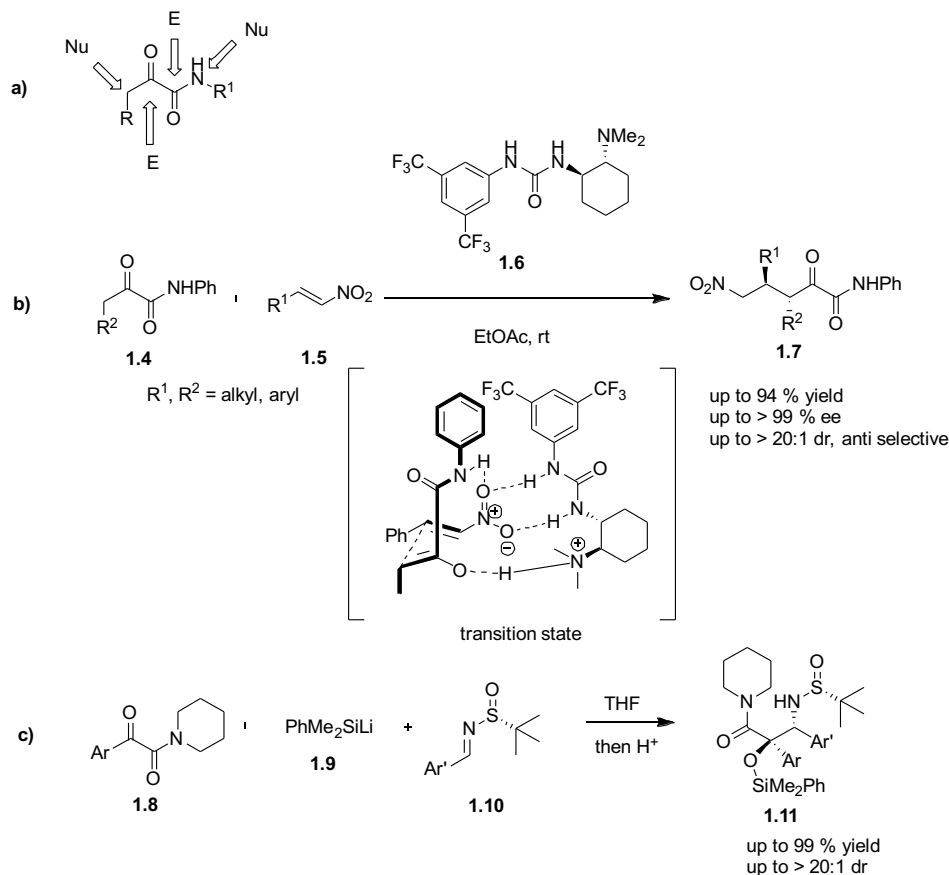
$\alpha$ -Keto amides and their derivatives are important constituents that can be found in many natural products, biologically relevant molecules, drugs, and functional materials. For examples, this structural motif is found in the 23-membered macrolide FK506 (**1.1**) which is an immunosuppressant drug that has been isolated from *Streptomyces tsukubaensis*,<sup>14</sup> whereas some other  $\alpha$ -keto amides containing compounds have been used in developing inhibitors of HIV protease (**1.2**)<sup>15</sup> and norovirus 3CL protease (**1.3**)<sup>16</sup> (Figure 1).



**Figure 1.**  $\alpha$ -Ketoamides containing biologically active compounds

Furthermore, the  $\alpha$ -keto amides are highly versatile and valuable building blocks due to the multiple reactions modes (two potential nucleophilic site and two electrophilic centers, Scheme 1a).<sup>17</sup> For examples,  $\alpha$ -keto amides **1.4** were applied in organocatalytic diastereo- and enantioselective Michael addition with nitroalkenes **1.5**. In this process, amide proton participated in the catalytic transition state and played a critical role in controlling the stereoselectivities of Michael products **1.7**<sup>18</sup> (Scheme 1b). Another example is phenyldimethylsilyllithium (**1.9**) mediated coupling of  $\alpha$ -keto amides **1.8** with *tert*-butanesulfinylimines **1.10** for the synthesis of

enantioenriched  $\alpha$ -(silyloxy)- $\beta$ -amino amides **1.11**, where  $\alpha$ -keto amides **1.8** were utilized as an electrophile.<sup>19</sup> (Scheme 1c)



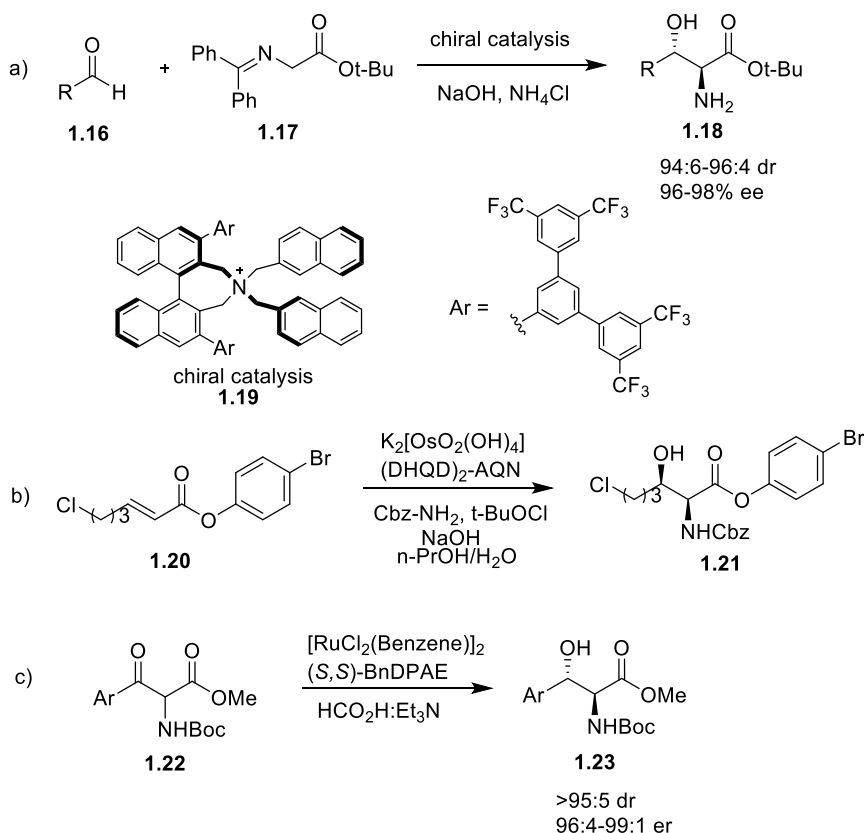
**Scheme 1.** a) Potential reaction sites in  $\alpha$ -keto amides. b) Michael addition of nitroalkenes **1.5** with  $\alpha$ -keto amides **1.4**. c) Silyllithium-initiated coupling of  $\alpha$ -keto amides **1.8** with *tert*-butanesulfinylamines **1.10**.

Due to the significance of this particular structural motif, it is not surprising that several methods have been developed for the preparation of  $\alpha$ -keto amides and its derivatives.<sup>17,20</sup> These synthetic routes can be mainly grouped according to the formation pathway for these compounds (Figure 2): a) oxidation at C(2) of a suitable precursor, b) the oxidative and non-oxidative amination approaches for the construction C(1)-N bond, c) C(1)-C(2)  $\sigma$ -bond construction processes, d) C(2)-R<sup>3</sup> bond-forming processes, e) double-carbonylative amination methods, f) oxidation at C(1) of a suitable precursor at C(1).<sup>17</sup>



pyrrolizidine alkaloids, such as australine **1.14**<sup>23</sup> and castanospermine **1.15**,<sup>24,25</sup> all of which possess significant biological properties, including anti-inflammatory and antibiotic properties, as well as inhibition of some glucosidase enzymes (Figure 3).  $\alpha$ -Amino- $\beta$ -hydroxy ester and its derivatives can also serve as synthetic precursors for other important synthons<sup>26,27</sup> or intermediates for the syntheses of complex natural product<sup>28</sup>.

Due to the importance and applicability of this structural motif, a growing number of methodologies have been developed for the synthesis of  $\alpha$ -amino- $\beta$ -hydroxy esters and their derivatives, especially the synthesis with both diastereomers in high enantioselectivity.<sup>29</sup> During the last decades, with the development of asymmetric synthetic methodologies, several innovative and efficient asymmetric routes towards these subunits have been developed.



**Scheme 2.** Several strategies for the asymmetric synthesis of  $\alpha$ -amino- $\beta$ -hydroxy derivatives

The vast number of asymmetric approaches can conceptually be divided into several strategies:

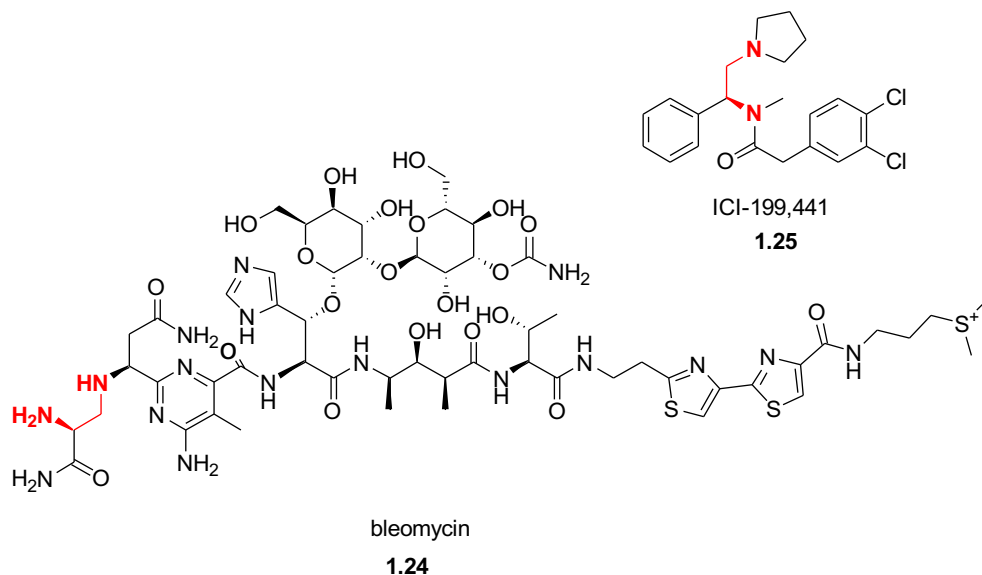
a) the formation of carbon-carbon bond with concomitant formation of two adjacent stereocenters. A representative example is shown in Scheme 2a, the direct aldol reaction of glycine **1.17** for a variety of alkyl aldehyde **1.16** has been developed by use of a phase transfer catalysis **1.19** (Scheme 2a).<sup>30</sup>

b) the installation of one or more heteroatoms onto a pre-existing carbon skeleton. One such strategy is the Sharpless asymmetric aminohydroxylation, in which the oxygen and nitrogen functionalities are appended to the double bond simultaneously (Scheme 2b).<sup>31</sup>

c) the manipulation of a scaffold in which all the heteroatoms are present. An excellent example of this type of strategy is the asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH) of  $\alpha$ -amino- $\beta$ -keto ester **1.22** through dynamic kinetic resolution (DKR). In this sequence, two contiguous stereocenters are constructed in a single operation from a racemic starting material (Scheme 2c).<sup>32,33</sup>

## 1.5 Synthesis of 1, 2-diamines

Another class of scaffolds, which are widely represented in natural products, biologically active compounds, synthetic building blocks, organocatalysts, and ligands, is 1,2-diamines.<sup>34,35</sup> For example, bleomycin **1.24**, isolated from *Streptomyces verticillus*, is an antitumor antibiotic clinically used for the treatment of Hodgkin's lymphoma, tumors of the testis, and carcinomas of skin, head, and neck.<sup>36</sup> The 1-aryl ethylene diamine analogues ICI-199,441 **1.25** have the potential to be useful analgesics, free from the potential for abuse and the adverse side effects of  $\mu$  agonists like morphine (Figure 4).<sup>34</sup> 1,2-Diamines are not only the valuable synthetic intermediate for the preparation of nitrogen-containing complex compounds, but also useful additives to stabilize and activate organometallic reagents and inorganic salts due to its Lewis basic property.<sup>34</sup> As another essential application, chiral 1,2-diamines and their derivatives are particularly useful as organocatalyst or chiral ligand for the stereoselective synthesis.<sup>37</sup>



**Figure 4.** Biologically relevant compounds incorporating the 1,2-diamine moiety.

Conceptually, synthesis of the 1,2-diamines motif can be arranged in several ways. Several examples are selected here to demonstrate the current research progress with the focus on catalytic, asymmetric methods.

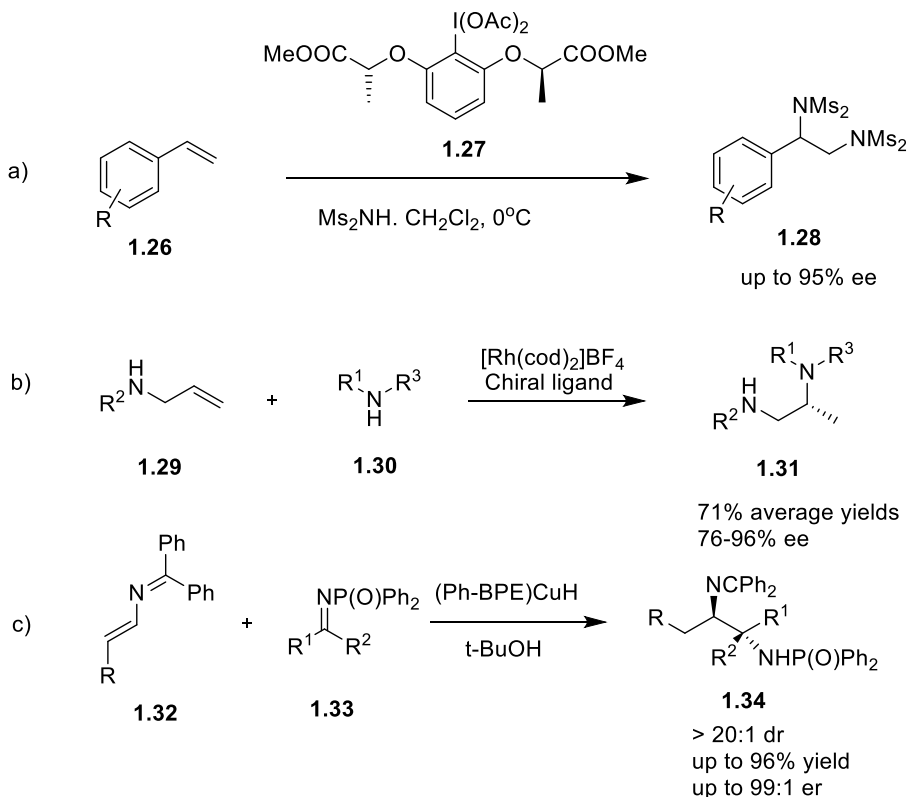
a) the two nitrogen atoms are installed simultaneously onto a preexisting carbon skeleton.<sup>38</sup> As an attractive approach, direct diamination of olefins is probably the most straightforward method for the preparation of 1,2-diamines using readily available alkenes. For example, in 2011, Muñiz has developed an enantioselective diamination of styrene **1.26** using chiral iodine **1.27** as a chiral catalyst and bismesylymide as the nitrogen source.<sup>39</sup> (Scheme 3a)

b) the method that utilizes a compound already containing one of the two final nitrogen atoms of the target 1,2-diamine as the substrate. The ring-opening of aziridine by nitrogen-containing nucleophiles or hydroamination of allylic amines are excellent examples of this strategy.<sup>40,41</sup> In Scheme 3b is shown an enantioselective hydroamination of allylic amine **1.29** using a chiral Rh-Biphep catalyst for the preparation enantioenriched 1,2-diamine.<sup>42</sup>

c) the preparation of 1,2-diamines starting from two nitrogen-containing substrates and involves the formation of a new C-C bond. In this manner, successful methods based on Mannich-type reactions<sup>43,44</sup> and the enantioselective synthesis of 1,2-diamines by Cu-catalyzed reductive couplings of azadienes with aldimines and ketimines have been



disclosed.<sup>45</sup> The Cu-catalyzed process represents a rare example of enantioselective reductive couplings of imines **1.33** to set vicinal heteroatom-substituted stereogenic centers. (Scheme 3c)



**Scheme 3.** Several strategies for the asymmetric synthesis of 1,2-diamine derivatives

## 1.6 The aim of this thesis

This thesis aims to develop new synthetic methods and explore the possibilities to apply it in the total synthesis of natural products.

*Chapter 2* deals with a mild procedure for the synthesis of  $\alpha$ -keto amides by  $\alpha$ -oxidation of the corresponding  $\alpha$ -keto amines mediated by pyrrolidine and TEMPO. The method can also be applied to the synthesis of  $\alpha$ -keto thioamides and  $\alpha$ -keto amidines.

*Chapter 3* deals with a straightforward synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic  $\alpha$ -amino- $\beta$ -keto

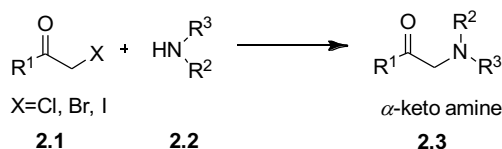
esters by using ATH/DKR protocol. In order to highlight the versatility of the methodology, it was applied in an efficient asymmetric synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.

*Chapter 4* describes an asymmetric formal hydroamination of enamines approach using Cu-H catalyst for the synthesis of chiral 1,2-diamines. The method provides a straightforward method for the synthesis of chiral 1,2-dialkyl amines in good yields with high level of enantioselectivities for a broad range of substrates and should have significant value for the preparation of molecules bearing a 1,2-diamine motif.

## 2. Pyrrolidine-TEMPO mediated oxidation of $\alpha$ -keto amines for the synthesis of $\alpha$ -keto amides

### 2.1 Introduction

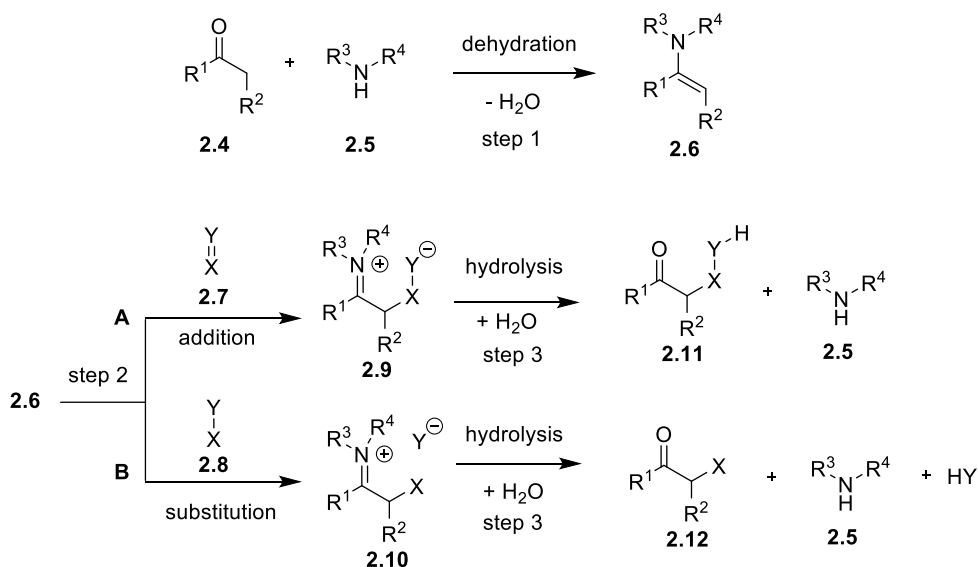
As outlined in the introduction, the development of synthetic methods for the synthesis of  $\alpha$ -keto amides has attracted a growing number of chemists' interest due to the prevalence of this motif in natural products and biologically relevant scaffolds, as well as its utilization in important transformations. Many synthetic methodologies for the preparation of  $\alpha$ -keto amides have been developed over the past decades, however, more efficient and convenient procedures are still highly demanded. This is mainly due to drawbacks of existing methods, such as the dependency of high cost and toxic catalysts, harsh reaction condition, complex procedures for the preparation of the desired starting material or limited range of the desired product. Compared with the other synthetic routes, the  $\alpha$ -oxidation of  $\alpha$ -keto amine has attracted less attention from the synthetic community over the past decade. This approach for the synthesis of  $\alpha$ -keto amides has only been reported as a side product in the Pd/Cu-catalyzed  $\alpha$ -oxidation of  $\alpha$ -keto amines and has not been documented systematically.<sup>46-48</sup> We then became interested in developing the possibility of preparing  $\alpha$ -keto amides through  $\alpha$ -oxidation of readily available  $\alpha$ -keto amines **2.3** which could be easily accessible by S<sub>N</sub>2 substitution between primary amine or secondary amine **2.2** with commercially available  $\alpha$ -halogenated ketone **2.1**.<sup>49</sup> (Scheme 4)



**Scheme 4.** Synthesis of  $\alpha$ -keto amines **2.3**.

## 2.2 Enamine catalysis

The electrophilic substitution reaction in the  $\alpha$ -position of carbonyl compounds via enamine intermediate **2.6** generated by reacting carbonyl **2.4** with a primary or secondary amine **2.5** is called enamine catalysis<sup>50</sup> (Scheme 5). Based on the nature of the electrophile (**2.7** or **2.8**), the enamine can, therefore, undergo two different reaction pathways; nucleophilic addition (Scheme 5A) and nucleophilic substitution (Scheme 5B). In both cases, the formed iminium ions (**2.9** or **2.10**) will then be hydrolyzed to afford the  $\alpha$ -substituted carbonyl product (**2.11** or **2.12**) and regenerated the amine catalyst **2.5**.<sup>50,51</sup>



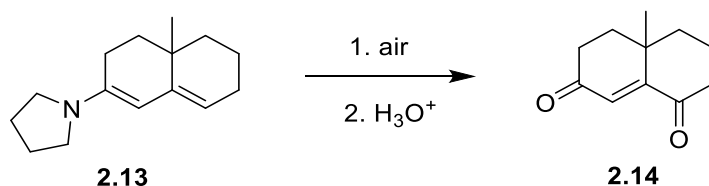
**Scheme 5.** Enamine catalysis.

Over the past two decades, enamine catalysis has proven to be a highly efficient process for the preparation of chiral or non-chiral  $\alpha$ -substituted carbonyl derivatives. This strategy has been applied to asymmetric aldol reactions<sup>52,53</sup>, Mannich reactions<sup>54</sup>, and Michael reactions<sup>55</sup> of aldehydes or ketones when using carbon-oxygen, carbon-nitrogen or carbon-carbon double bond containing electrophiles. In general, a new carbon-carbon bond will be formed in this step. The formation of carbon-hetero bond can also be achieved by using azodicarboxylates<sup>56</sup>, nitrosobenzene<sup>57,58</sup>, and singlet oxygen<sup>59</sup> as electrophiles. In another mode of enamine catalysis, single bond containing electrophiles such as halogenation reagents<sup>60</sup>, benzoyl peroxide<sup>61</sup>, sulfenylation reagents<sup>62</sup>, and other electrophiles<sup>50</sup> can

be added to the  $\alpha$ -position of carbonyl compounds via enamine intermediate catalysis; the overall result being the formation of  $\alpha$ -functionalized carbonyl derivatives.

In addition to the two main reaction pathways, a radical coupling pathway between TEMPO and an enamine radical cations for the preparation of  $\alpha$ -hydroxy carbonyl compounds have been reported by Sibi and Maruoka.<sup>63,64</sup> The enamine radical cations were generated from the enamine intermediate in the presence of a single electron transfer (SET) reagent.

In contrast, the enamine-mediated oxidation of aldehydes and ketones to give the corresponding  $\alpha$ -carbonyl derivatives have received considerably less attention. To the best of our knowledge, the only example reported is the autoxidation of an enamine **2.13** to give the corresponding 1,4-dione **2.14** in 20% yield (Scheme 6).<sup>65</sup> However, the addition of a catalytic amount of  $\text{Fe}^{3+}$  or  $\text{Cu}^{2+}$  to the reaction mixture resulted in a pronounced enhancement of the reaction rate and yield (80-85%). Based on this result, the authors speculated that this autoxidation reaction might proceed via a free-radical process because the metal ions can accept an electron from enamine **2.13** in the chain-initiation step.



**Scheme 6.** Autoxidation of enamine for the synthesis of 1,3-diones.

## 2.3 Results and discussion

As there were no previous reports of the  $\alpha$ -oxidation of  $\alpha$ -keto amines using an enamine intermediate to provide the  $\alpha$ -keto amides, we decide to explore this reaction more thoroughly.

### 2.3.1 Preliminary study of the $\alpha$ -oxidation of an $\alpha$ -keto amine

We started to investigate the  $\alpha$ -oxidation by using  $\alpha$ -keto amines **2.15a** as the benchmark substrate and pyrrolidine (**I**) as the catalyst. To our great delight, treatment of **2.15a** with 5 eq pyrrolidine (**I**) in CH<sub>2</sub>Cl<sub>2</sub> under air resulted in the formation of desired product **2.15** in low yield (23%, Table 1, entry 1). Encouraged by this result, we repeated this reaction under balloon pressure of O<sub>2</sub>, which resulted in a greatly improved conversion, and **2.15** was formed in 63% yield (entry 2). It has been reported that TEMPO can be used as an oxygen source for asymmetric  $\alpha$ -oxyamination of aldehydes through an enamine intermediate in the presence of single electron transfer (SET) reagent.<sup>63,64</sup> We were then interested in running the oxidation under the same condition but adding 1 eq TEMPO. The result revealed that there was no significant effect on the yield of **2.15**, but the reaction rate increased significantly (entries 3 and 4). At the same time, we did not detect any  $\alpha$ -TEMPO-attached product in the crude NMR sample. The same reaction was repeated under air and gave **2.15** in 41% yield and decreased reaction rate (entry 4). Furthermore, only a trace amount of **2.15** was observed when the oxidation was performed under an N<sub>2</sub> atmosphere (entry 5).

**Table 1**  $\alpha$ -oxidation of **2.15**.<sup>[a]</sup>

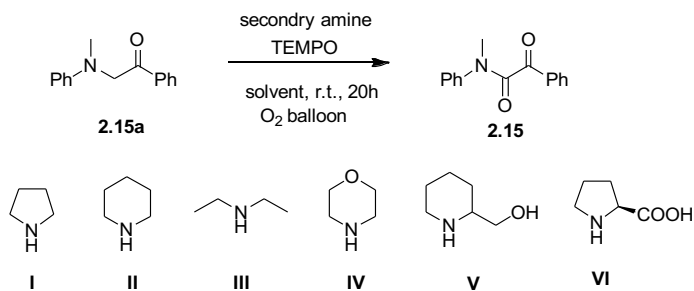
<b>2.15a</b>		<b>2.15</b>	
Entry	Pyrrolidine (eq)	TEMPO (eq)	Yield(%) <sup>[b]</sup>
1	5	--	23 <sup>[c]</sup>
2	5	--	63 <sup>[d]</sup> (11) <sup>[e]</sup>
3	5	1	66 <sup>[d]</sup> (52) <sup>[e]</sup>
4	5	1	41 <sup>[c]</sup> (23) <sup>[e]</sup>
5	5	1	3 <sup>[f]</sup>

[a] Unless noted, the reaction was carried out as follows: the mixture of **2.15** (0.3 mmol, 67.5mg) and pyrrolidine (1.5 mmol, 123  $\mu$ L) were stirred in CH<sub>2</sub>Cl<sub>2</sub> (1mL) under room temperature for 20 h. [b] Yields were determined by GC analysis using naphthalene as an internal standard. [c] Reaction was stirred in a sealed tube under air. [d] O<sub>2</sub> (1 atm) was used in a balloon in this reaction. [e] Yields were determined by GC analysis using naphthalene as an internal standard when this reaction was running 1.5 h. [f] N<sub>2</sub> (1 atm) was used in a balloon in this reaction. TEMPO = 2,2,6,6-Tetramethylpiperidine-1-oxyl.

### 2.3.2 Optimization of reaction conditions

Since it was noted that TEMPO has a beneficial effect on this oxidation, we then continued to optimize the reaction condition using TEMPO as an additive. The results showed that lowering the amount of TEMPO was

**Table 2** Screening of reaction conditions<sup>[a]</sup>



Entry	Amine (eq)	TEMPO (eq)	solvent	Yield <sup>[b]</sup> (%)
1	<b>I</b> (5)	1	CH <sub>2</sub> Cl <sub>2</sub>	66
2	<b>I</b> (5)	0.7	CH <sub>2</sub> Cl <sub>2</sub>	62
3	<b>I</b> (5)	0.4	CH <sub>2</sub> Cl <sub>2</sub>	68
4	<b>I</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	69
5	<b>I</b> (3)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	45
6	<b>I</b> (1)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	13
7	<b>I</b> (0.1)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	Trace
8	<b>I</b> (0)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	0
9	<b>II</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	43
10	<b>III</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	10
11	<b>IV</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	12
12	<b>V</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	Trace
13	<b>VI</b> (5)	0.1	CH <sub>2</sub> Cl <sub>2</sub>	0
14	<b>I</b> (5)	0.1	Toluene	45
15	<b>I</b> (5)	0.1	EtOAc	60
16	<b>I</b> (5)	0.1	THF	46
17	<b>I</b> (5)	0.1	MeOH	50
18	<b>I</b> (5)	0.1	CHCl <sub>3</sub>	56
19	<b>I</b> (5)	0.1	DMF	66
20	<b>I</b> (5)	0.1	DMSO	66
21	<b>I</b> (5)	0.1	1,4-dioxane	44
22	<b>I</b> (5)	0.1	Acetone	22
23 <sup>[c]</sup>	<b>I</b>	0.1	Pyrrolidine	64
24	<b>I</b> (5)	0.1	CH <sub>3</sub> CN	83

[a] Unless noted, the reaction was carried out as follows: the mixture of **1a** (0.3 mmol, 67.5 mg), the secondary amine (1.5 mmol) and TEMPO (0.03 mmol, 4.7 mg) were stirred in the solvent (1 mL) under a balloon pressure of O<sub>2</sub> at room temperature for 20 h. [b] Yields were determined by GC analysis using naphthalene as an internal standard.

[c] 1 mL of pyrrolidine was added as catalysis and solvent.

beneficial and the optimal result, in terms of both the yield and reaction rate, was obtained by using 0.1 eq of the additive (Table 2, entries 1–4). However, decreasing the amount of pyrrolidine was detrimental and resulted in much lower yields of **2.15** (entries 4–7). As expected, no

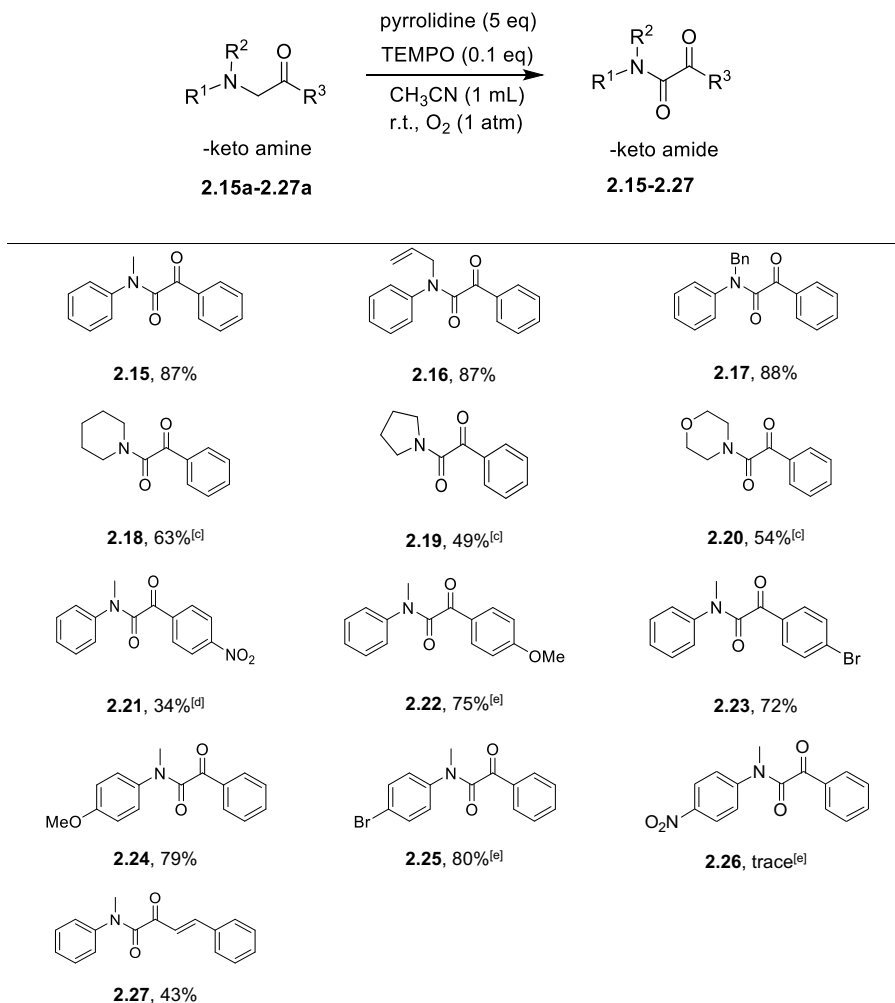
product **2.15** was formed when this reaction was performed without pyrrolidine, suggesting that an enamine intermediate played an important role in the  $\alpha$ -oxidation process (entry 8). Next, a series of commercially available secondary amines were examined to study the influences on the yield. However, pyrrolidine proved to be the most superior among the investigated secondary amines (entries 9-13). Whereas most solvents gave lower or comparable yields to  $\text{CH}_2\text{Cl}_2$  (entries, 14-23), the use of  $\text{CH}_3\text{CN}$  gave **2.15** in 83% yield (entry 24). Finally, our optimal reaction conditions were confirmed as follows: pyrrolidine (5 eq), TEMPO (0.1 eq),  $\alpha$ -keto amine **2.15a** (1 eq), stirred in  $\text{CH}_3\text{CN}$  (1 mL) at room temperature under  $\text{O}_2$  atmosphere. Under the optimized conditions,  $\alpha$ -keto amide **2.15** was afforded in 83% yield.

### 2.3.3 Scope of $\alpha$ -keto amines

With the best reaction condition in hand, the scope of pyrrolidine/TEMPO-mediate  $\alpha$ -oxidation of  $\alpha$ -keto amines **2.15a-2.27a** was then investigated (Table 3). It was found that various *N*-alkyl group, such as methyl, allyl, and benzyl, were well tolerated in this oxidation, giving the corresponding  $\alpha$ -keto amides **2.15-2.17** in good yields. On changing from aryl dialkyl amines to trialkyl amines, the oxidation became significantly slower, and the reaction temperature had to be raised to 50 °C to achieve an acceptable conversion to products **2.18-2.20**. It appears that the oxidation is sensitive to the electronic nature of the substituents in the benzoyl moiety. When the substituent is a strong electron-withdrawing group (*para*-nitro), a complex reaction mixture was obtained at ambient temperature. However, it was possible to isolate the desired product **2.21** in 34% yield when the reaction was repeated at -35 °C. Based on this result, we hypothesized that the oxidation is highly dependent on the rate of the formation of the enamine intermediate. The substrate with *para*- $\text{NO}_2$  benzoyl moiety is more electrophilic compared with non-substituted benzoyl substrate due to its strong electron-withdrawing effect, resulting in a faster condensation with pyrrolidine. Indeed, the presence of electron-donating group e.g. *p*-OMe slows down the oxidation, giving a 75 % yield of **2.22** after heating to 50 °C for 20 h, which also proved our hypothesis. The *para*-bromo substituent gave the product **2.23** in 72 % yield without modification of the optimal



**Table 3** Scope of  $\alpha$ -keto amines. [a][b]

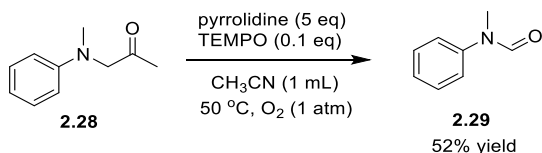


[a] Unless noted, the reaction was carried out as following: the mixture of  $\alpha$ -keto amines (0.3 mmol), pyrrolidine (1.5 mmol) and TEMPO (0.03 mmol, 4.7 mg) with O<sub>2</sub> balloon were stirred in CH<sub>3</sub>CN (1 mL) under room temperature for 20 h. [b] Isolated yields [c] Stirred at 50 °C for 20 h. [d] Stirred at -35 °C for 20 h. [e] Stirred at room temperature for 72 h.

reaction condition. Next, the effect of altering the substituent on the aniline moiety was investigated, and it was found that electron-donating *para*-substituents were tolerated with good yield (**2.24**), whereas weakly electron-withdrawing *para*-bromo derivative reacts much slower but in comparable yield (**2.25**). When subjecting strong electron-withdrawing *para*-NO<sub>2</sub> substituted  $\alpha$ -amine keto substrate in the optimal condition,

only trace **2.26** was detected on TLC after 72 h. Moreover, the substrate containing a cinnamoyl moiety also gave **2.27** in 43 % yield.

Surprisingly, subjecting  $\alpha$ -methyl keto amine **2.28** to the optimal reaction condition at 50°C for 20 h resulted in the formation of **2.29** as a single product. It was believed that the formation of formylamide **2.29** in this case was due to the oxidative cleavage of the carbon-carbon  $\delta$ -bond (Scheme 7).

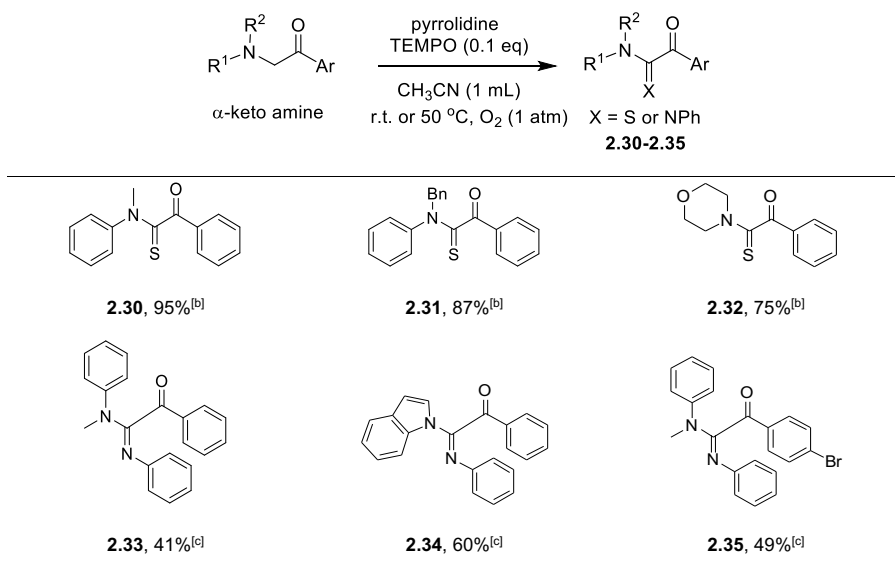


**Scheme 7.** Unexpected formation of formylamide **2.29**.

### 2.3.4 Synthesis of $\alpha$ -keto thioamides and $\alpha$ -keto amidines

Encouraged by these successful examples for the preparation of  $\alpha$ -keto amides, we then turned our attention to the investigation of other oxidants, such as elemental sulfur and nitrosobenzene. If successful, such transformations would result in the formation of  $\alpha$ -keto thioamides and  $\alpha$ -keto amidines, which both have been recognized as important structural motifs.<sup>66-68</sup> As shown in Table 4, oxidation of  $\alpha$ -keto amines by using sulfur (10 eq) afforded desired  $\alpha$ -thioamides **2.30-2.32** in good to excellent yields. When nitrosobenzene (2 eq) was used as the oxidant,  $\alpha$ -keto amidines **2.33-2.35** were also obtained in moderate yields.

**Table 4.** Synthesis of  $\alpha$ -keto thioamide and  $\alpha$ -keto amidines.<sup>[a]</sup>

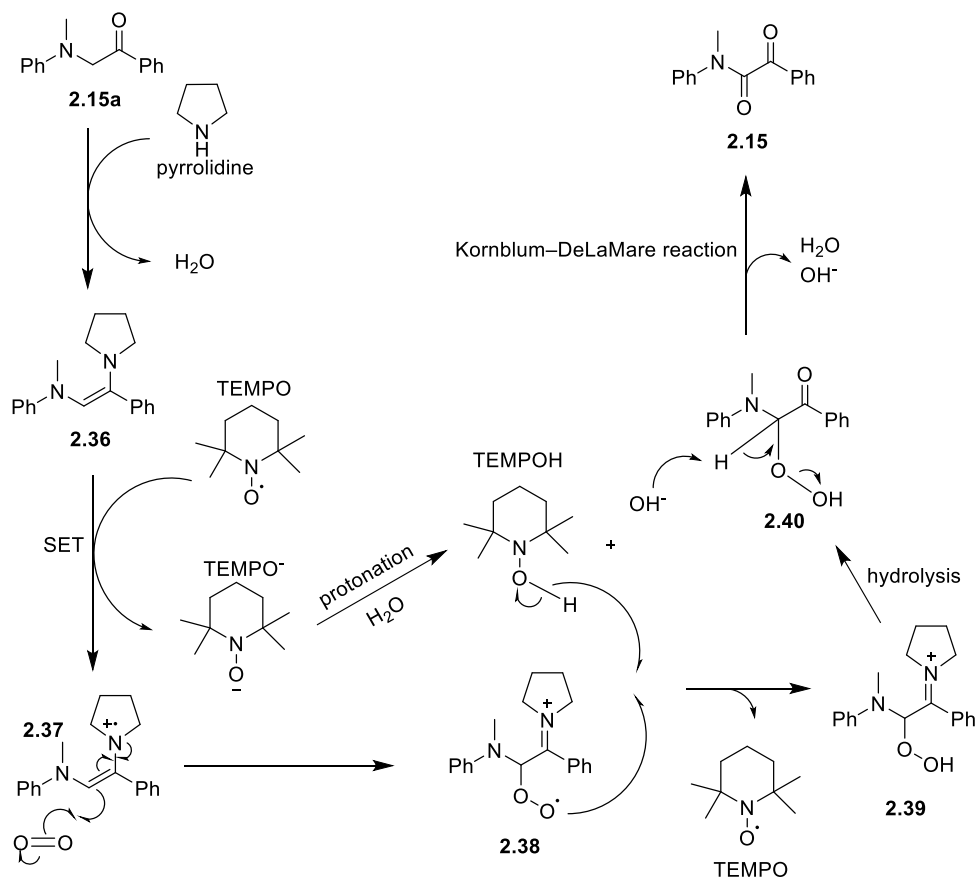


[a] Isolated yields [b] The mixture of  $\alpha$ -keto amines (0.3 mmol), pyrrolidine (1.5 mmol), TEMPO (0.03 mmol, 4.7 mg) and sulfur (10 eq) in  $\text{CH}_3\text{CN}$  (1 mL) were stirred under an argon atmosphere at 50  $^\circ\text{C}$  for 20 h. [c] The mixture of  $\alpha$ -keto amines (0.3 mmol), pyrrolidine (0.3 mmol), TEMPO (0.03 mmol, 4.7 mg) and nitrosobenzene (2 eq) in  $\text{CH}_3\text{CN}$  (1 mL) were stirred under an argon atmosphere at rt for 20 h.

## 2.4 Proposed mechanism for the pyrrolidine/TEMPO-mediated oxidation of $\alpha$ -keto amines

To this end, a hypothesized mechanism of the pyrrolidine/TEMPO-mediated  $\alpha$ -oxidation for the synthesis of  $\alpha$ -keto amide is shown in Scheme 8. In the proposed mechanism the reaction starts by the condensation between  $\alpha$ -keto amine **2.15a** and pyrrolidine **I** to provide the electron-rich enamine **2.36**, which is then transformed into radical cation **2.37** in the presence of TEMPO or  $\text{O}_2$  by single electron transfer (SET) oxidation. The beneficial effect of TEMPO might be attributed to its function as a single electron oxidant which could oxidize the enamines easier than oxygen.<sup>69,70</sup> At the same time, TEMPO $^\cdot$  is formed and is in turn protonated by water, giving TEMPOH and  $\text{OH}^\cdot$ .<sup>71</sup> Intermediate **2.37** can then be trapped by  $\text{O}_2$  to form peroxy radical intermediate **2.38**.<sup>65</sup> Next, the formed TEMPOH serves as H-donor to reduce the peroxy radical **2.38** to the iminium ion intermediate **2.39**, regenerating the TEMPO catalyst.

After hydrolysis of the iminium ion **2.39**, the  $\alpha$ -hydroperoxyl ketone **2.40** can be oxidized to the  $\alpha$ -keto amide **2.15** through a Kornblum-DeLaMare-type reaction.<sup>72</sup> Notably, the possibility of a Kornblum-DeLaMare-type reaction occurring before hydrolysis could not be completely ruled out. According to these results of **2.25-2.26** from Table 3, we hypothesized that the enamine intermediate **2.36** with higher electron-density would be easier to get SET-oxidized by TEMPO to give the corresponding radical cation **2.37**, thus furnishing the  $\alpha$ -keto amide products more efficiently.



**Scheme 8.** Proposed mechanism pathway for the  $\alpha$ -oxidation.

## 2.5 Conclusion

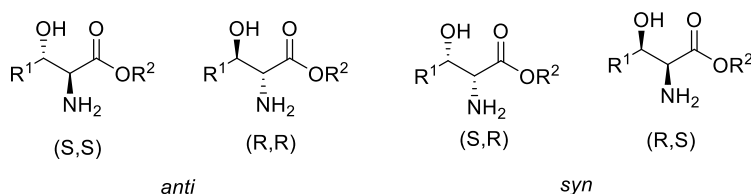
We have developed a fast and convenient procedure for the synthesis of  $\alpha$ -keto amides from easily accessible  $\alpha$ -keto amines by an  $\alpha$ -oxidation mediated by pyrrolidine and TEMPO. The method can also be applied to the synthesis of  $\alpha$ -keto thioamides and  $\alpha$ -keto amidines with moderate to excellent yields. In the end, a suggested mechanism pathway for this novel method is discussed.



### 3. Synthesis of *anti*- $\alpha$ -amino- $\beta$ -hydroxy esters and its application in total synthesis

#### 3.1 Introduction

$\alpha$ -Amino- $\beta$ -hydroxy esters and their derivatives is a crucial structural motif because it is prevalent in a variety of natural products and biologically relevant compounds, as outlined in the introduction. One feature to note about the structural motif is that it includes two vicinal stereocenters and can, therefore, exist as four stereoisomers – with the hydroxyl and amino group *syn* or *anti* to each other and the enantiomers of both relative configurations (Figure 5). These four different stereoisomers often show distinct biological profiles by their interactions with the chiral environment in biological systems. Therefore, it can always be an attractive and challenging area to develop stereodivergent approaches for the synthesis of all possible stereoisomers and individually elucidate their effects in biological systems. In this chapter, we outline our enantioselective approach to the synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters using asymmetric transfer hydrogenation (ATH) coupled with dynamic kinetic resolution (DKR). In order to highlight the versatility of the methodology, it was applied in the asymmetric total synthesis of the polyhydroxylated pyrrolizidine alkaloids (+)-alexine (**3.78**).



**Figure 5.** Four different stereoisomers of  $\alpha$ -amino- $\beta$ -hydroxy ester

## 3.2 Asymmetric hydrogenation (AH) and asymmetric transfer hydrogenation (ATH)

### 3.2.1 Asymmetric hydrogenation (AH)

The asymmetric hydrogenation of prochiral unsaturated substrates, such as alkenes<sup>73,74</sup>, ketones<sup>75-77</sup>, imines<sup>78</sup>, and enamines<sup>79</sup>, is one of the most effective and straightforward methods for the preparation of optically active compounds. This method adds two atoms from hydrogen to one of two faces of unsaturated compounds catalyzed by a small amount of chiral transition metal complexes. The most well-known catalytic system for the asymmetric hydrogenation of various unsaturated compounds is a series of chiral ruthenium catalysts which was developed by Noyori, who was awarded the Nobel prize in chemistry in 2001 for his contribution to this area.<sup>80</sup> The well-developed ruthenium-(*R*)-BINAP dicarboxylate **3.1**,<sup>81-83</sup> ruthenium-(*R*)-BINAP halogen-containing<sup>84,85</sup> complexes **3.2**, and ruthenium-(*R*)-BINAP/diamine<sup>86,87</sup> complexes **3.3** have all been used in asymmetric hydrogenation of functionalized olefins, functionalized ketones, and simple ketones, respectively (Figure 6).

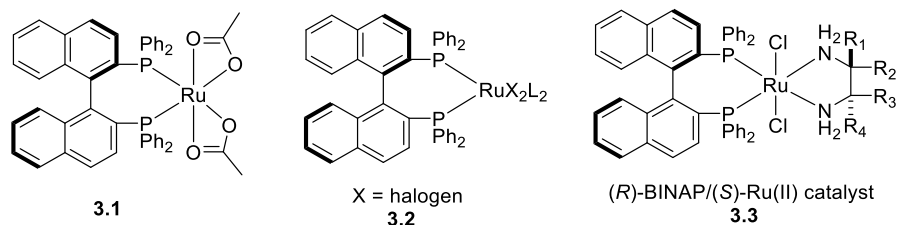
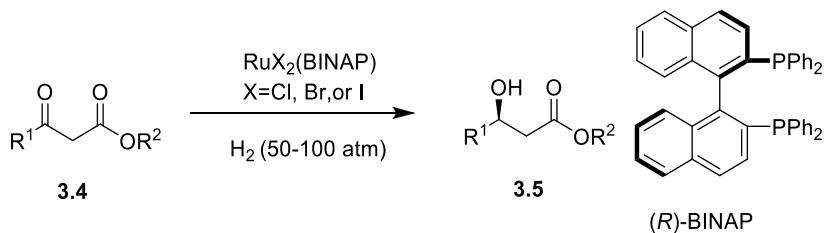


Figure 6. Three kinds of ruthenium-(*R*)-BINAP complexes.

The asymmetric hydrogenation of  $\beta$ -keto ester **3.4** for the preparation of  $\beta$ -hydroxy ester **3.5** could be catalyzed by ruthenium-BINAP halogen-containing complex in high enantiomeric purity (Scheme 9)<sup>88</sup>, wherein the coordinative oxygen in the ester group played an important role to direct the reactivity and stereochemical outcome in an absolute sense.<sup>85,89</sup>



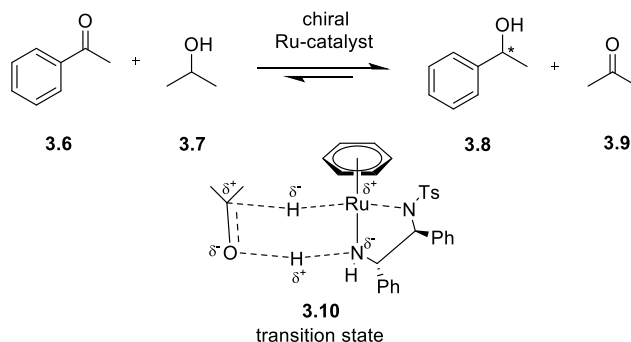


**Scheme 9.** Asymmetric hydrogenation of  $\beta$ -keto ester.

### 3.2.2 Asymmetric transfer hydrogenation (ATH)

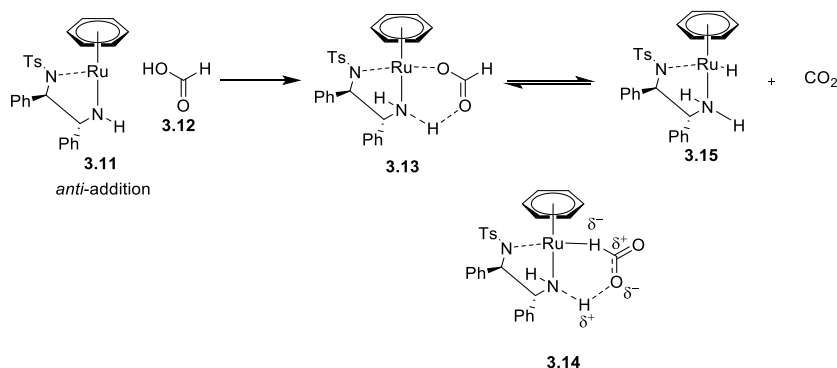
Hydrogenation can broadly divide into two employed strategies: direct hydrogenation with a pressure of  $\text{H}_2$  gas and transfer hydrogenation. Transfer hydrogenation, referring to the homogenous process where a proton and a hydride are transferred from a non- $\text{H}_2$  hydrogen source to the substrate, is a convenient and powerful method to access various hydrogenated compounds. It is an attractive alternative to direct hydrogenation since it doesn't need high pressure therefore doesn't require any specialized equipment or safety measures.<sup>90</sup>

2-Propanol has often been used as hydrogen donor for the asymmetric transfer hydrogenation of ketones and imines because it is stable, easy to handle, non-toxic, and inexpensive.<sup>91</sup> Although the asymmetric transfer hydrogenation using 2-propanol give satisfactory results in terms of both reactivity and selectivity,<sup>92</sup> an inherent drawback of the process is the reversibility due to the fact that this reaction is a concerted process.<sup>93</sup> More specifically, the formed acetone (**3.9**) could also be reduced by the same catalyst using alcohol **3.8** as the hydrogen donor (Scheme 10). Based on this, even though the reduction proceeds with excellent enantiomeric purity of the product, the reverse process lowers the enantioselectivity after prolonged exposure of the reaction system to the catalyst.<sup>94</sup>



**Scheme 10.** Asymmetric transfer hydrogenation of acetophenone using 2-propanol as hydrogen donor.

This drawback is overcome when using formic acid as the hydrogen source for the transfer hydrogenation. Mechanistic studies have suggested that the reaction of formic acid with the ruthenium-ligand complex **3.11** via an *anti*-addition of  $\text{H}^+$  and  $\text{HCOO}^-$  on ruthenium-nitrogen bond in **3.11**, leading to the kinetically favorable complex **3.13** (Scheme 11). Then, the resulting formate complex **3.13** gives rise to the hydride complex **3.15** through decarbonylation. It should be noted that the activated ruthenium-hydride catalyst **3.15** can also participate in the  $\text{CO}_2$  activation through the formation of intermediate **3.14**, giving back formic acid, which makes this process reversible. On account of the reversibility, the  $\text{CO}_2$  should be effectively removed from the catalytic system to avoid the reverse reaction.<sup>93,95</sup>



**Scheme 11.** Possible mechanism for the formation of Ruthenium-hydride catalyst.

### 3.3 Synthesis of $\alpha$ -amino- $\beta$ -hydroxy ester

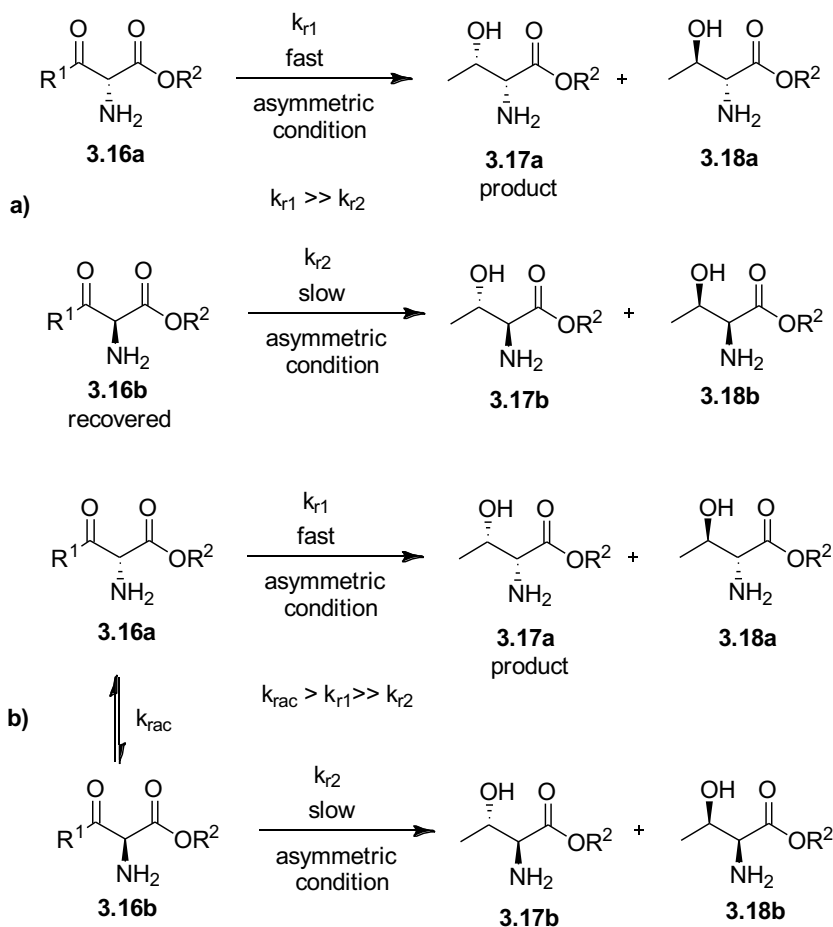
#### 3.3.1 Kinetic resolution (KR) and dynamic kinetic resolution (DKR)

The asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH) of racemic  $\alpha$ -amino- $\beta$ -keto esters coupled with kinetic resolution (KR) or dynamic kinetic resolution (DKR) can give rise to  $\alpha$ -amino- $\beta$ -hydroxy esters with a single stereoisomer out of the four possible stereoisomers. In these approaches, two contiguous stereocenters are constructed in a single operation.

Kinetic resolution is based on that one enantiomer of the substrate reacts much faster than the other under asymmetric condition. As shown in Scheme 12a, under suitable catalytic condition, it is possible that enantiomer **3.16a** react much faster than enantiomer **3.16b** ( $k_{r1} \gg k_{r2}$ ), giving the  $\alpha$ -amino- $\beta$ -hydroxy ester **3.17a** over than **3.18a** through asymmetric transfer hydrogenation or asymmetric hydrogenation. On the other hand, the slower reacting enantiomer **3.16b** of the starting material can be recovered entirely, without any formation of **3.17b** or **3.18b**. The limitation of this strategy is that the theoretical maximum yield of the desired product is 50% due to the recovery of the non-productive starting material.

A more elegant strategy would be if the starting  $\alpha$ -amido- $\beta$ -keto ester was able to racemize, giving rise to a dynamic kinetic resolution (DKR) (Scheme 12b). In this case, if the rate of racemization between **3.16a** and **3.16b** is faster than the reaction ( $k_{rac} > k_{r1} \gg k_{r2}$ ), and the ATH/AH condition is favored to give rise to **3.17a** over than **3.17b**, the asymmetric synthesis of **3.17a** as the only product is possible and the theoretical yield can be 100%.

Hence, the asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH) coupled with dynamic kinetic resolution (DKR) can be used as a powerful technique for the stereoselective synthesis of  $\alpha$ -amino- $\beta$ -hydroxy esters from racemic  $\alpha$ -amino- $\beta$ -keto esters.

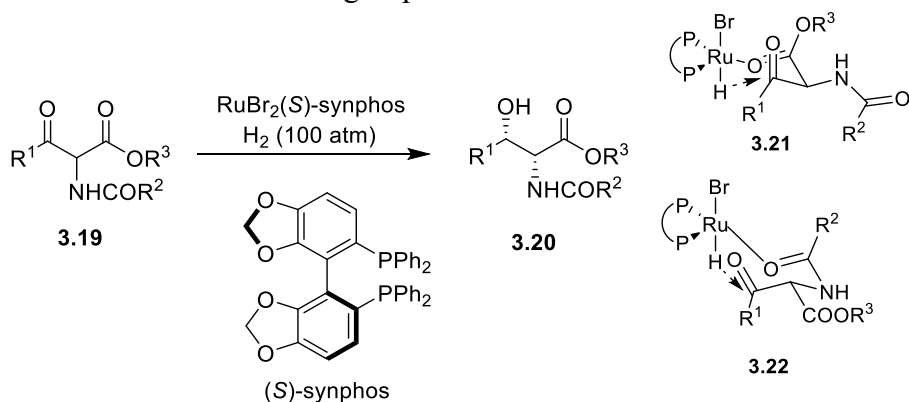


**Scheme 12.** a) Kinetic resolution of  $\alpha$ -amino- $\beta$ -keto ester. b) Dynamic kinetic resolution of  $\alpha$ -amino- $\beta$ -keto ester.

### 3.3.2 Synthesis of *syn*- $\alpha$ -amino- $\beta$ -hydroxy ester via AH/ATH coupled with DKR

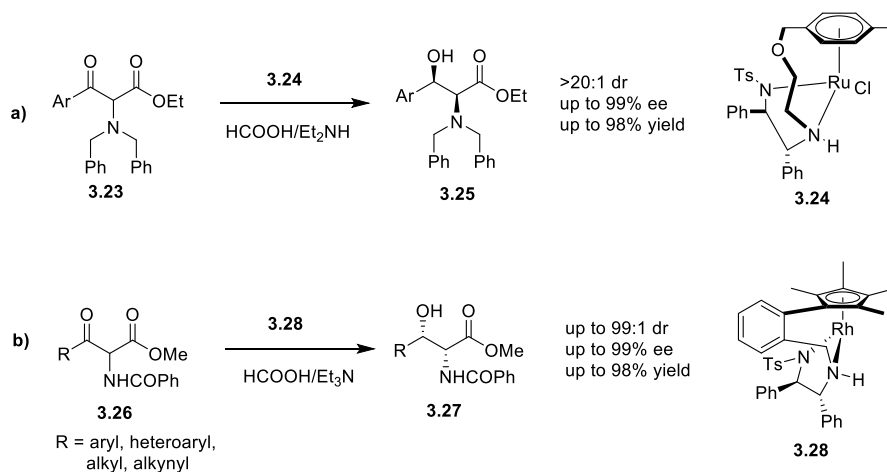
To date, two examples for the enantioselective synthesis of *syn*- $\alpha$ -amino- $\beta$ -hydroxy ester **3.20** using AH/DKR with a ruthenium catalyst and bisphosphine ligand have been reported by Noyori and Genêt.<sup>96-98</sup> The observed enantioselectivity can be accredited to the coordination of the ruthenium complex to the substrate **3.19** in the transition state, where the metal can be coordinated to the ester moiety **3.21** or the carbonyl moiety of the amide **3.22** (Scheme 13).<sup>97,98</sup> Very recently, Zhang reported a highly

Zhang reported a highly diastereo- and enantioselective access to *syn*- $\alpha$ -amido- $\beta$ -hydroxy esters via ruthenium-catalyzed AH coupled DKR which tolerated several functional groups.<sup>99</sup>



**Scheme 13.** Access to *syn*- $\alpha$ -amino- $\beta$ -hydroxy ester via AH/DKR and the proposed transition states.

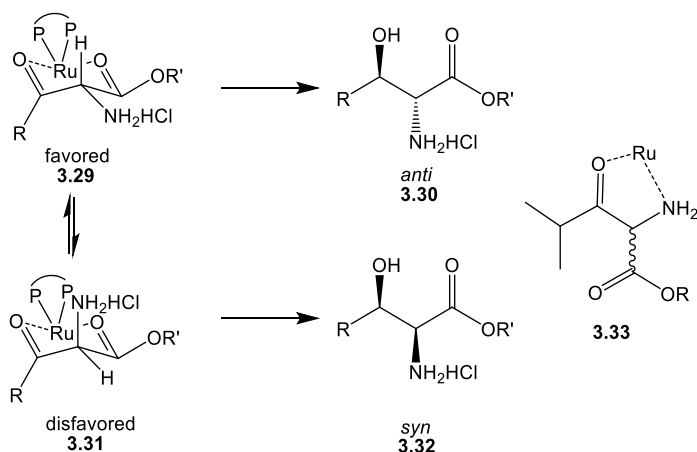
Due to the drawbacks of asymmetric hydrogenation, such as high pressure, specialized equipment, and air-sensitive catalysts being required, the ATH coupled with DKR is more attractive for the synthesis of such compounds. The earlier research was devoted to the ruthenium-catalyzed ATH/DKR of Boc-protected  $\alpha$ -amino- $\beta$ -keto ester using diamine or vicinal amino alcohol as chiral ligands, and formic acid as the hydrogen source.<sup>100,101</sup> These reactions are believed to proceed through a six-membered transition state. In 2017, Wang developed an efficient asymmetric synthesis of enantiomeric pure *syn*-aryl  $\alpha$ -dibenzylamino- $\beta$ -hydroxy esters **3.25** via ATH/DKR using oxo-tethered catalyst **3.24**. It was found that the dibenzyl substituent at the nitrogen atom may play a key role in the stereoselectivity (Scheme 14a).<sup>102</sup> The first rhodium-catalyzed ATH/DKR for the stereoselective synthesis of  $\alpha$ -benzoylamido- $\beta$ -hydroxy ester **3.27** with a tethered rhodium-DPEN complex **3.28** was reported by Ratovelomanana-Vidal and Phansavath in 2018 (Scheme 14b).<sup>103</sup>



**Scheme 14.** Access to *syn*- $\alpha$ -amino- $\beta$ -hydroxy ester via ATH/DKR

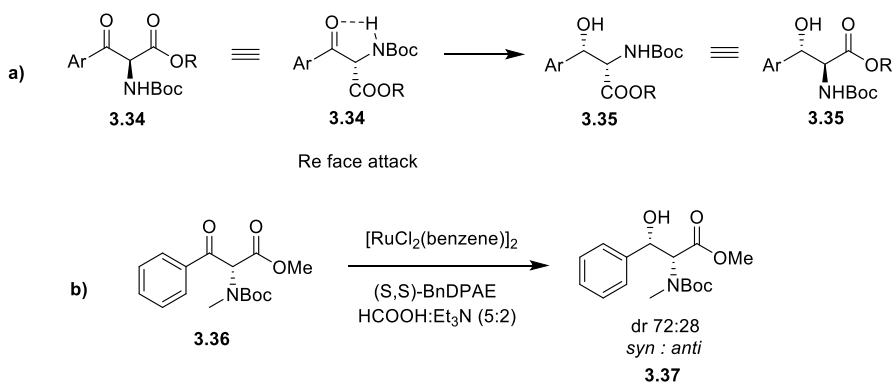
### 3.3.3 Synthesis of *anti*- $\alpha$ -amino- $\beta$ -hydroxy ester via AH/ATH coupled with DKR

Genêt, and subsequently Hamada, disclosed an enantioselective synthesis of *anti*- $\alpha$ -amino- $\beta$ -hydroxy ester through AH/DKR of the hydrochloride salt of  $\alpha$ -amino- $\beta$ -keto esters using a similar ruthenium catalyst and a biphosphine ligand.<sup>98,104,105</sup> Two different rationales for the origin of the observed *anti*-diastereoselectivity are proposed. Genêt suggested the chair-like transition state **3.29** with the ketone and ester carbonyl chelated to the ruthenium and the ammonium salt in a favored equatorial position,<sup>98</sup> while Hamada envisioned this AH through the five-membered transition state **3.33** with the 2-amino substituent as a directing group (Scheme 15).<sup>104</sup> Furthermore, Hamada has also developed a series of methods for the enantioselective synthesis of *anti*- $\alpha$ -amino- $\beta$ -hydroxy esters from hydrochloride salt of  $\alpha$ -amino- $\beta$ -keto ester using other metal catalysts, such as Rh, Ir, and Ni. All protocols give excellent yields, diastereoselectivities and enantioselectivities for a broad range of substrates.<sup>33,106-108</sup>



**Scheme 15.** Stereochemical model for *anti*-stereoselectivity

We commenced our investigation for an ATH/DKR approach towards enantioselective synthesis of *anti*- $\alpha$ -amino- $\beta$ -hydroxy ester.<sup>32,109,110</sup> Excellent results in terms of yields, diastereo- and enantioselectivities were achieved for a wide range of  $\alpha$ -amino- $\beta$ -keto esters **3.34** in organic solvents, emulsions or water system catalyzed by Ru/(*S,S*)-BnDPAE complex. In addition, a model for predicting the stereochemical outcome was proposed. The formation of a cyclic intermediate **3.34** with an intramolecular hydrogen bond between N-H and the carbonyl played an important role to control the addition direction of the hydride (Scheme 16a).<sup>111</sup> In accordance with this hypothesis *syn* diastereomer **3.37** is the major product when using the doubly protected  $\alpha$ -amino- $\beta$ -keto esters **3.36** as the substrate (Scheme 16b).



**Scheme 16.** a) Stereochemical model b) Reduction of doubly protected  $\alpha$ -amino- $\beta$ -keto ester

### 3.4 Aim of the project

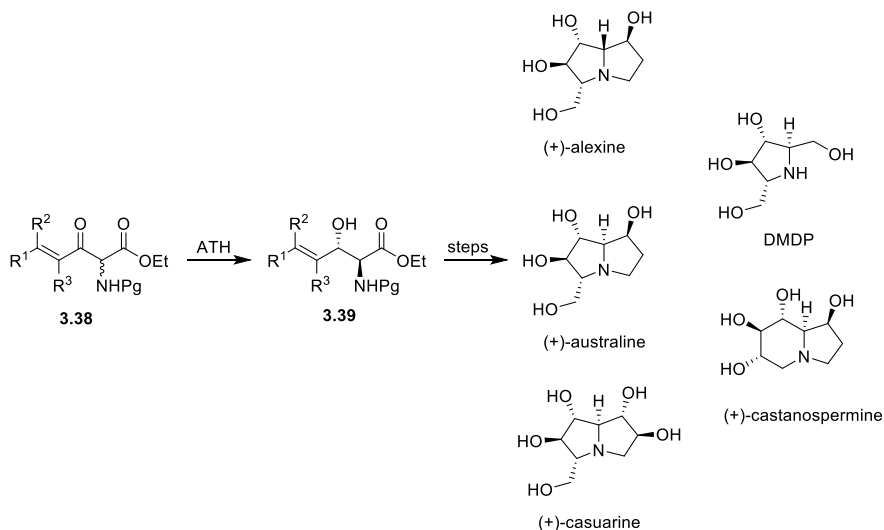
The focus of this project was to investigate a chemoselective 1,2-reduction of 3-alkenyl-2-amido-3-keto esters in preference of a 1,4-reduction of the enone moiety, for the synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters. The existence of a vinylic group in the 3-position of  $\alpha$ -amino- $\beta$ -hydroxy ester allows for additional stereoselective manipulation and a broader application in the total synthesis of polyhydroxylated pyrrolizidine alkaloids.

### 3.5 Development of methodology

#### 3.5.1 *anti*-3-Alkenyl-2-amido-3-hydroxy ester and its application in total synthesis

As already mentioned, the  $\alpha$ -amino- $\beta$ -hydroxy ester is an important structural motif, which can be found in a variety of biologically relevant compounds and can serve as a platform for the preparation of other valuable molecules. Although AH/ATH coupled with DKR is an effective and straightforward approach for the stereoselective synthesis of such compounds, the utilization of this method in synthesis of polyhydroxylated alkaloids, compounds with biological activities,<sup>112,113</sup> is found to be problematic because the scope of substrate is limited to aryl or aliphatic  $\alpha$ -amino- $\beta$ -keto ester. We speculated that this problem could be overcome by incorporation of a vinyl moiety in 3-position of  $\alpha$ -amino- $\beta$ -hydroxy ester. For example, *anti*-3-alkenyl-2-amido-3-hydroxy ester **3.39**, which in turn is derived from easily accessible 3-alkenyl-2-amido-3-hydroxy ester **3.38** through ATH/DKR, can be a key intermediate in the asymmetric total synthesis of polyhydroxylated alkaloids after additional stereoselective manipulation (Scheme 17).

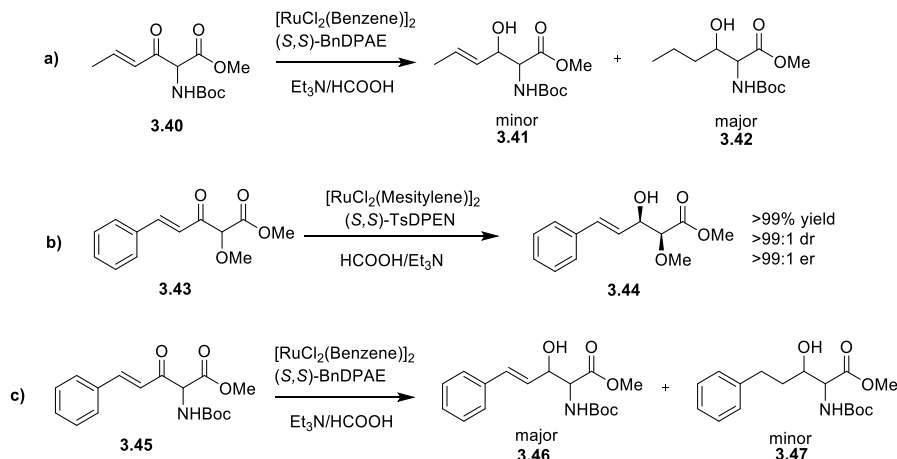




**Scheme 17.** Proposed route from 3-alkenyl-2-amido-3-keto ester to polyhydroxylated alkaloids.

### 3.5.2 Preliminary study

The investigation was initiated by examining the ATH of ester **3.40** using our previously optimized condition, yielding a complex mixture of products, with the major product being  $\alpha$ -amino- $\beta$ -hydroxy ester **3.42**, in which both reduction of the carbon-carbon double bond and the carbonyl group was observed. In addition, substrate **3.40** proved relatively unstable and decomposed after one week even when stored at  $-20^{\circ}\text{C}$ , probably through an intramolecular Michael addition. It has been reported that  $\alpha$ -methoxy- $\beta$ -keto ester **3.43** was successfully applied for the synthesis of allylic *syn*-1,2-diol **3.44** derivatives with excellent yields, distereo- and enantioselectivities through ATH/DKR.<sup>114,115</sup> We, therefore, turned our attention to a similar substrate **3.45**, in hope that the phenyl group might reduce 1,4-reduction. Again, a mixture of desired product **3.46** and over-reduction product **3.47** were obtained; however, the desired product **3.46** was produced as the major product, with low dr (71:29). (Scheme 18)

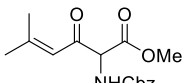
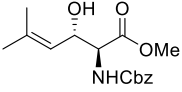
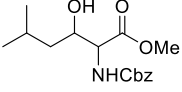
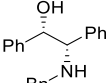
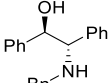
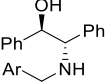
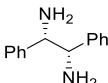
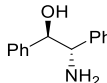
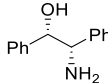


**Scheme 18.** a) and c) Attempted reduction of **3.40** and **3.45**. b) Known reduction of **3.43**.

### 3.5.3 Optimization of reaction conditions

Encouraged by the preliminary findings, we then decided to test the reduction of substrate **3.48a**, in which the conjugate reduction should be hindered. Subjecting **3.48a** to the ATH condition described above resulted in a complex mixture of *anti*-product **3.48**, having low dr and moderate er, and the over-reduced product **3.49** in poor selectivity (Table 5, entry 1). A variety of benzyl protected amino alcohol ligands (**3.51-3.58**) were then explored in hope of improving the chemo-, diastereo-, and enantioselectivity of the reaction, but in all cases the results were not satisfactorily (entries 2-9). We then turned our attention to testing the unprotected ligands **3.59-3.61** (entries 10-12). Ligand **3.61** eventually provided the highest enantioselectivity, although the reaction also gave a mixture of desired product and over-reduction product in a 2.5:1 ratio. It was then decided to explore different ruthenium dimer catalysts together with ligand **3.61** (entries 13-15). It was found that ruthenium dimer catalysts incorporating a substituted arene moiety gave improved chemoselectivity with only trace amounts of the over-reduction product, the best result being obtained with  $[\text{RuCl}_2(\text{mesitylene})]_2$ . (entry 14)

**Table 5** Screening of catalysts and ligands<sup>[a]</sup>

 <b>3.48a</b>	$\xrightarrow[\text{ligand}]{[\text{RuCl}_2(\text{arene})]_2}$ HCOOH:Et <sub>3</sub> N (1.5:3) CH <sub>2</sub> Cl <sub>2</sub> , rt 3.5 - 7 d	 <b>3.48</b> desired product	+	 <b>3.49</b> over-reduction product	
 ( <i>S,S</i> )-BnDPAE <b>3.50</b>	 ( <i>R,S</i> )-BnDPAE <b>3.51</b>	 ( <i>R,S</i> )-BnDPAE <b>3.52-3.58</b>	 ( <i>S,S</i> )-DPEN <b>3.59</b>	 ( <i>R,S</i> )-DPAE <b>3.60</b>	 ( <i>S,S</i> )-DPAE <b>3.61</b>

entry	Ru dimer	Ligand	<b>3.48a</b> (%) <sup>[b]</sup>	<b>3.48</b> (%) <sup>[b]</sup>	<b>3.49</b> (%) <sup>[b]</sup>	dr <b>3.48</b> ( <i>anti:syn</i> ) <sup>[c]</sup>	er ( <i>anti</i> ) <sup>[d]</sup>
1	benzene	<b>3.50</b>	5	50	20	55:45	88.5:11.5
2	benzene	<b>3.51</b>	21	41	16	89:11	7:93
3	benzene	<b>3.52</b> (Ar=2,4,6-trimethylphenyl)	38	14	10	75:25	85.5:14.5
4	benzene	<b>3.53</b> (Ar=1-naphthyl)	25	27	13	84:16	89.5:10.5
5	benzene	<b>3.54</b> (Ar=4-methylphenyl)	35	33	15	87:13	88:12
6	benzene	<b>3.55</b> (Ar=4-methoxyphenyl)	24	43	17	86:14	87.5:12.5
7	benzene	<b>3.56</b> (Ar=4-biphenyl)	trace	50	18	87:13	88:12
8	benzene	<b>3.57</b> (Ar=3,5-di- <i>tert</i> -butyl phenyl)	trace	58	19	74:26	75:25
9	benzene	<b>3.58</b> (Ar=4- <i>tert</i> -butyl phenyl)	trace	50	23	88:12	93.5:6.5
10	benzene	<b>3.59</b>	0	trace	71	—	—
11	benzene	<b>3.60</b>	35	15	5	87:13	12.5:87.5
12	benzene	<b>3.61</b>	trace	50	20	80:20	95:5
13	<i>p</i> -cymene	<b>3.61</b>	33	47	trace	85:15	90.5:9.5
14	mesitylene	<b>3.61</b>	20	65	trace	91.5:8.5	93:7
15	hexamethylbenzene	<b>3.61</b>	34	28	trace	83:17	58:42

[a] Reaction performed with 0.1 eq of [RuCl<sub>2</sub>(arene)]<sub>2</sub>, 0.2 eq of ligand heated in 2-propanol (0.3 mL) at 80 °C for 1 h. After cooling to room temperature, the catalyst was then added to the  $\alpha$ -amino- $\beta$ -keto ester **3.48a** 0.2mmol (1 eq) with HCOOH/EtN<sub>3</sub> (1.5 eq/3 eq) complex. [b] Isolated yields. [c] Determined by NMR spectroscopy of crude reaction mixture. [d] Determined by chiral HPLC analysis (Chiralcel IA).

In order to further improve the reaction outcome, the screening of reaction solvent and catalytic loading were then carried out (Table 6). This revealed that the reaction was compatible with various solvents, while performing the reaction in MeOH or CH<sub>3</sub>CN did not improve the outcome (entries 2-3). On the other hand, the use of other solvents afforded similar results in terms of yields and stereoselectivities as CH<sub>2</sub>Cl<sub>2</sub> (entries 4-8). In all cases the starting material **3.48a** was not fully consumed even after 7 days at room temperature. Since the best result was obtained when using dioxane (entry 8), this solvent was then selected as the reaction solvent for the final optimization of catalyst loading (entries 9-11). It was observed that the

best result, 72% yield of **3.48** with 95:5 dr and 96.5:3.5 er, was obtained when using only 5 mol% of the catalyst (entry 11).

**Table 6** Optimization of reaction condition<sup>[a]</sup>

<p style="text-align: center;"> <b>3.48a</b> <span style="margin-left: 100px;">desired product <b>3.48</b></span> <span style="margin-left: 50px;">over-reduction product <b>3.49</b></span> </p>							
entry	Ru/ligand (mol%)	solvent	<b>3.48a</b> (%) <sup>[b]</sup>	<b>3.48</b> (%) <sup>[b]</sup>	<b>3.49</b> (%) <sup>[b]</sup>	dr <b>3.48</b> ( <i>anti:syn</i> ) <sup>[c]</sup>	er ( <i>anti</i> ) <sup>[d]</sup>
1	20	CH <sub>2</sub> Cl <sub>2</sub>	20	65	trace	91.5:8.5	93:7
2	20	MeOH	49	24	trace	86:14	89.5:10.5
3	20	CH <sub>3</sub> CN	26	37	trace	85:15	85:15
4	20	CH <sub>3</sub> Cl <sub>3</sub>	13	57	trace	94.5:5.5	96:4
5	20	toluene	11	63	trace	93.4:6.6	96:4
6	20	Et <sub>2</sub> O	11	61	trace	94.3:5.6	96:4
7	20	iPrOH	16	58	trace	92.5:7.5	95:5
8	20	dioxane	8	68	trace	93:7	95.5:4.5
9	15	dioxane	11	68	trace	93:7	96:4
10	10	dioxane	15	60	trace	94:6	96:4
11	5	dioxane	12	72	trace	95:5	96.5:3.5

[a] Reaction performed with [RuCl<sub>2</sub>(mesitylene)]<sub>2</sub>, (S,S)-DPAE heated in 2-propanol (0.3 mL) at 80°C for 1 h. After cooling to room temperature, the catalyst was then added to the  $\alpha$ -amino- $\beta$ -keto ester **3.48a** 0.2 mmol (1 eq) with HCOOH/Et<sub>3</sub>N (1.5 eq/3 eq) complex. [b] Isolated yields. [c] Determined by NMR of crude products. [d] Determined by chiral HPLC analysis (Chiralcel IA).

### 3.5.4 Scope of 3-alkenyl-2-amido-3-keto esters

With the optimized conditions in hand, the next step was to evaluate the scope of the reaction. The influence of the ester moiety in the substrate was negligible as the *anti*-3-alkenyl-2-amido-3-hydroxy esters **3.48**, **3.62-3.64** were all produced from corresponding starting materials in good yields and high selectivities, respectively. However, the reaction outcome was highly dependent on the amino protecting group, with *N*-acetyl and *N*-benzoate protected substrates gave the corresponding products **3.66** and **3.67** in lower yields and selectivities compared to **3.48**, while the *N*-Boc protected substrate gave **3.65** with equally good result. The ATH reaction proved to be sensitive to the substitution at the olefin moiety with substrate **3.68a**, having a disubstituted alkene, giving mostly over-reduced products derived from both 1,4- and 1,2-reductions and only minor amounts of **3.68**. Substrates having a trisubstituted and 1,1-disubstituted olefin moiety performed well in the ATH reaction and delivered the corresponding products **3.69** and **3.70** in excellent yields, dr and er. Similarly, products **3.71-3.73**, having a conjugated olefin moiety, were obtained in moderate

yields, dr and er in the reduction, while **3.74a** and **3.75a** did not give the desired products.

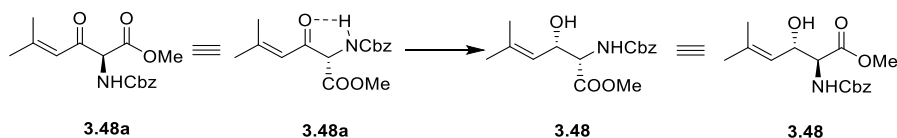
**Table 7** Scope of 3-alkenyl-2-amido-3-keto esters<sup>[a]</sup><sup>[b]</sup><sup>[c]</sup><sup>[d]</sup>

 <b>3.48a, 3.62a-3.75a</b>	<b>3.48, 3.62-3.75</b>
 <b>3.48</b> 6 d, 72%(84%) <sup>[e]</sup> dr 95:5 er 96.5:3.5	 <b>3.62</b> 7 d, 78%(87%) <sup>[e]</sup> dr 96.4:3.6 er 97.5:2.5
 <b>3.65</b> 7 d, 67%(86%) <sup>[e]</sup> dr 97:3 er 97:3	 <b>3.66</b> 7 d, 58%(73%) <sup>[e]</sup> dr 74:26 er 81.7:18.3
 <b>3.69</b> 1 d, 91% dr >95:5 er 98:2	 <b>3.70</b> 1 d, 60% dr >95:5 er 98.5:1.5
 <b>3.73</b> 3 d, 43% (85%) <sup>[e]</sup> dr 92.3:7.7 er 90.1:9.9	 <b>3.74</b> 3 d, n.r.
 <b>3.63</b> 7 d, 66%(79%) <sup>[e]</sup> dr 92.8:7.2 er 97:3	 <b>3.67</b> 2 d, 67%(75%) <sup>[e]</sup> dr 83.7:16.3 er 83.4:16.6
 <b>3.68</b> 2 d, < 10% dr n.d. er n.d.	 <b>3.71</b> 1.5 d, 77% dr 85:15 er 92:8
 <b>3.75</b> 3 d, complex mixture	 <b>3.72</b> 6 d, 61% (92%) <sup>[e]</sup> dr 91:9 er 88.5:11.5

[a] Reaction performed with  $[\text{RuCl}_2(\text{mesitylene})]_2$  (0.025 eq.) and (S,S)-DPAE (0.05 eq.) heated in 2-propanol (0.3 mL) at 80 °C for 1 h. After cooling to room temperature, the catalyst was then added to the 3-alkenyl-2-amido-3-keto esters (0.2 mmol, 1 eq.) and  $\text{HCOOH}/\text{Et}_3\text{N}$  (1.5 eq/3 eq) in dioxane (1 mL). [b] Isolated yields. [c] dr determined by  $^1\text{H}$  NMR analysis of the crude reaction mixture. [d] er determined by chiral HPLC. [e] Isolated yields based on recovered start material. n.d. = not determined. n.r. = no reaction.

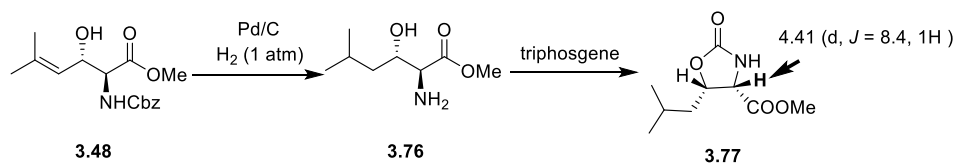
### 3.5.5 Stereochemical model

As described in Section 3.3.3, we believe that the diastereofacial discrimination in this ATH can be rationalized by the formation of a 5-member ring intermediate **3.48a**, where an intramolecular hydrogen bond exists between the *N*-H and the carbonyl group. Subsequently, the hydride from the catalytic complex will attack the carbonyl from the less hindered face, and lead to the formation of *anti*-product **3.48**. (Scheme 19)



**Scheme 19** Stereochemical model

The formation of *anti*-configuration of **3.48** was proved by the synthesis of oxazolidinone **3.77** in two steps. The *J*-coupling constant of the relevant hydrogen is 8.4 Hz, which indicates that the oxazolidinone should be *cis*.<sup>110</sup> (Scheme 20)



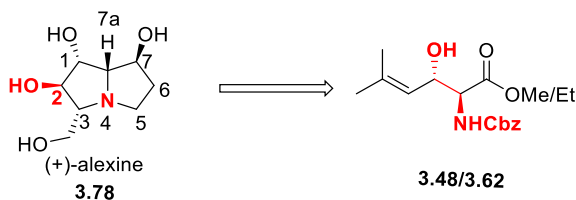
**Scheme 20.** Proof of the *anti*-configuration in **3.48**.

## 3.6 Total synthesis of (+)-alexine

### 3.6.1 Background

Polyhydroxylated pyrrolizidine alkaloids are a group of naturally occurring alkaloids based on the structure of pyrrolidine. Most of these compounds have the potential to be selective glycosidase inhibitors and antiviral or antiretroviral agents.<sup>23,113,116-118</sup> As one of the most important polyhydroxylated pyrrolizidine alkaloids, (+)-alexine **3.78** have been isolated from genera *Alexa*.<sup>119</sup> It exhibits potent inhibitory activity toward

carbohydrate-processing enzymes<sup>120</sup> as well as antiviral and retroviral activities.<sup>117</sup> Therefore, several efforts in its total syntheses have been documented.<sup>121-123</sup> However, many of the earlier synthetic methods used carbohydrates as starting materials, that require several protecting-group manipulations, thereby making the total number of steps relatively high.

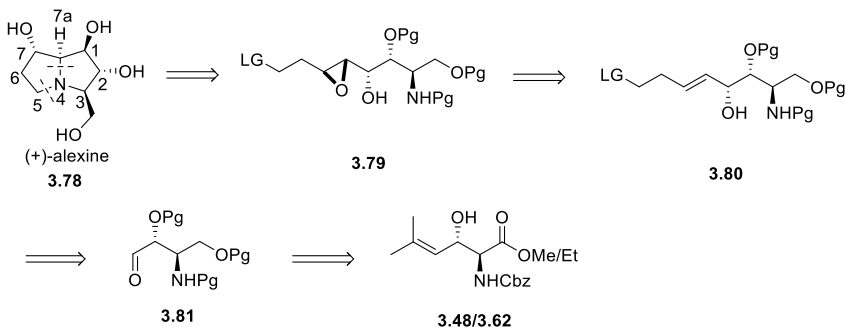


**Scheme 21.** Planned strategy for the synthesis of (+)-alexine

We envisioned that (+)-alexine (**3.78**) could be derived from a divergent route starting from *anti*-3-alkenyl-2-amido-3-hydroxy ester **3.48/3.62**, which we anticipated could be synthesized by using the ATH/DKR of 3-alkenyl-2-amido-3-keto ester. (Scheme 21)

### 3.6.2 Total synthesis of (+)-alexine

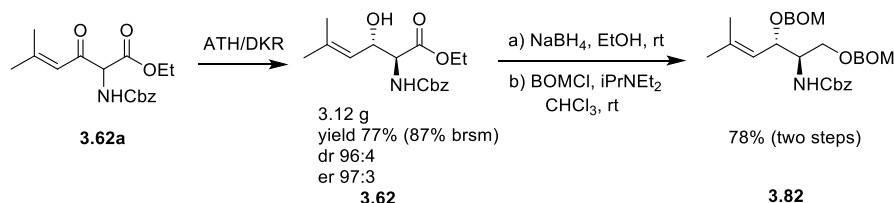
To demonstrate the applicability of the developed methodology it was decided to apply it to an effective total synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine **3.78**. Our retrosynthetic proposal is shown in Scheme 20 and relies on the reported double-cyclization of epoxide **3.79**. The key alkene **3.80** could arise from a Grignard or Barbier reaction of **3.81** followed by an intramolecular metathesis reaction with an alkene. (Scheme 22)



**Scheme 22.** Retrosynthetic analysis of (+)-alexine (**3.78**).

The total synthesis of (+)-alexine is initiated by the scalable ATH/DKR of 3-alkenyl-2-amido-3-keto ester **3.62a**, yielding **3.62** with 87 % (brsm)

yield, 96:4 dr and 97:3 er. Reduction of **3.62** with NaBH<sub>4</sub>, followed by protection of the resulting 1,3-diol provided bis-BOM compound **3.82** in 78% yield over two steps. We opted for the BOM protection group because we had previously shown that a TBS group would mainly result in the formation of the undesired Felkin-Anh product in the subsequent Grignard addition. The BOM protecting group, on the other hand, is more prone to deliver the chelation controlled product.<sup>124</sup> (Scheme 23)



**Scheme 23.** Synthesis of bis-BOM compound **3.82**

Different conditions were evaluated for the 1,2-addition reaction of the aldehyde **3.83** which are derived from compound **3.82** through ozonolysis. It was envisioned that the correct C1 stereochemistry required for (+)-alexine (**3.78**) could be installed by a chelating-controlled addition to **3.83**, in which the ether in BOM and oxygen in aldehyde could chelate with the Grignard reagent and exerts the major stereo-directing effect. On the contrary, a Felkin-Anh controlled nucleophilic addition to aldehyde **3.83**, in which the BOMO moiety act as a large group, is expected to furnish the undesired C1 stereoselectivity. It should also be noted that the  $\beta$ -NH has the possibility to form a hydrogen bond to the aldehyde, thus resulting in a more complicated outcome. Treatment of aldehyde **3.83** with vinyl magnesium bromide at -78 °C afforded compound **3.84** as a mixture of two diastereoisomers in a ratio of 50:50 (Table 8, entry 1). Repeating this reaction at 0 °C result in an improved ratio, but still not satisfactory (entry 2). Next, a bidentate Lewis acid (MgBr•OEt<sub>2</sub>) and a noncoordinating solvent (CH<sub>2</sub>Cl<sub>2</sub>) was used in order to further increase the chelation.<sup>125</sup> However, the ratio still remained rather low (entry 3). Furthermore, when this reaction was repeated in CH<sub>2</sub>Cl<sub>2</sub> and using ZnCl<sub>2</sub> as Lewis acid, the best result was obtained with 58 % yield and 75:25 ratio (entry 3).<sup>126</sup>

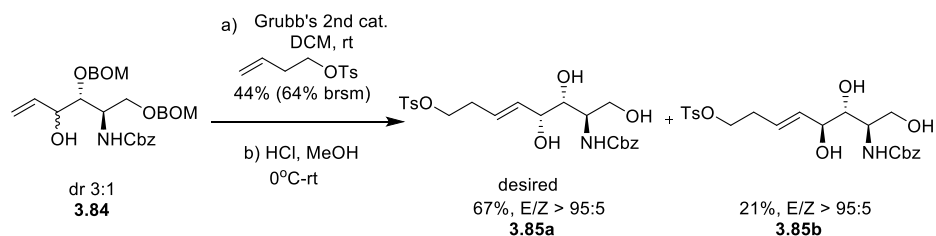


**Table 8.** Diastereoselective vinylation for the synthesis of **3.84**.

entry	solvent	Lewis acid (eq)	temperature (°C)	yield (% two steps) <sup>[a]</sup>	<b>3.84a</b> : <b>3.84b</b> <sup>[b]</sup>
1	THF	--	-78°C	n.d.	50:50
2	THF	--	0-rt	n.d.	67:33
3	DCM	MgBr <sub>2</sub> ·OEt <sub>2</sub> (3)	-78°C - rt	n.d.	67:33
4	DCM	ZnCl <sub>2</sub> (2.5)	-78°C - rt	58	75:25

[a] Isolated yield. [b] Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. n.d. = no determined

Subjecting **3.84**, as a mixture of diastereomers, to 4-butenol *p*-tolyl-sulfonate in the presence of Grubbs' 2nd generation catalyst, followed by hydrolysis of the BOM protecting groups furnished diols **3.85**. Column chromatography of the mixture gave diastereomer **3.85a** in 67% yield and dr > 95 : 5. (Scheme 24)

**Scheme 24.** Metathesis reaction and the separation of **3.85a**.

Next the stage was set for the neighboring group directed epoxidation of **3.85a**. We accomplished the neighboring group directed epoxidation of **3.85a** using Ti(OiPr)<sub>4</sub> and  $\beta$ -hydroperoxy alcohol **3.86**, yielding *anti* epoxide **3.87** in 78% yield as the only detectable isomer.<sup>127</sup> Deprotection of **3.87** (Pd/C, H<sub>2</sub>, MeOH) followed by purification on silica gel afforded (+)-alexine (**3.78**) in 76% yield as a white solid. The <sup>1</sup>H-NMR and <sup>13</sup>C-NMR data, melting point and the optical rotation (mp 160–162° C, [ $\alpha$ ]<sup>20</sup> = +42.1 (c 0.3 in H<sub>2</sub>O)) were in good agreement with the published data for (+)-alexine<sup>119,122</sup> (mp 162–163 °C, [ $\alpha$ ] = +40 (c 0.25 in H<sub>2</sub>O)). (Scheme 25)



In summary, we have applied the ATH/DKR strategy for the operationally straightforward synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic 3-alkenyl-2-amido-3-keto esters. This method is compatible for a broad range of starting material in moderate yields with high chemo-, diastereo-, and enantioselectivities. In addition, the key *anti*-3-alkenyl-2-amido-3-hydroxy esters product was applied in asymmetric total synthesis of alexine **3.78**, which also highlights the versatility of the developed methodology. We believe that the *anti*-3-alkenyl-2-amido-3-hydroxy esters also can serve as an intermediate in the total synthesis of other polyhydroxylated alkaloids containing the *anti*-amino alcohol subunit.

## 4. Formal hydroamination of enamines for the synthesis of chiral 1, 2-diamines

### 4.1 Introduction

The importance and the main synthetic approaches for the 1,2-diamine structural motif have been described in Chapter 1.5. This introduction will mainly focus on the hydroamination, Cu-H catalytic formal hydroamination, and hydroamination for the preparation of 1,2-diamines.

#### 4.1.1 Hydroamination

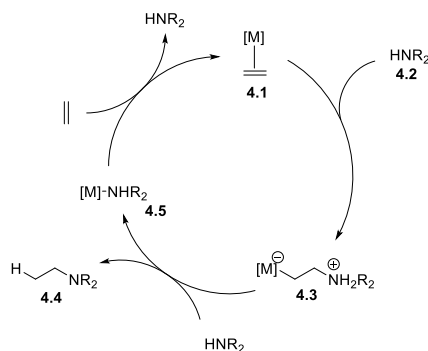
Hydroamination is the direct formation of a C-N bond by the addition of an *N*-H bond across C-C multiple bonds of an alkene, alkyne, diene, allene. This effective strategy has always attracted attention from the scientific community as it allows for relatively simple starting materials to be readily transformed into *N*-containing compounds, such as amines and enamines.<sup>128-130</sup> The addition of nucleophilic *N*-H across a C-C multiple bonds is kinetically difficult because the high electron density of the nucleophile and  $\pi$ -electrons of the C-C multiple bonds repel each other. Therefore, noncatalytic hydroamination always requires either strongly acidic condition<sup>131,132</sup> where the C-C multiple bond is protonated and which is then followed by the addition of an amine, or strongly basic condition<sup>133,134</sup> where the generation of a nucleophilic metal amide makes the attack on the C-C multiple bond easier.

In comparison to noncatalytic hydroamination, metal-catalyzed hydroamination could be achieved under milder conditions, because the coordination of the metal catalysts mimics the action of the proton, and the C-C multiple bond can reduce the electron density of  $\pi$ -system, thus enabling the formation of C-N bond. The mechanistic pathways of metal-

catalyzed hydroamination can roughly be divided into four categories depending on their initiating step.

a) C-C Multiple bond activation (Scheme 26).

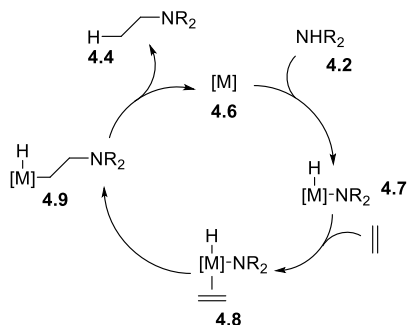
In this mechanism, the C-C multiple bond is activated by coordination to a Lewis-acidic metal complex, and the C-N bond is formed by *anti*-nucleophilic attack of amine **4.2** on the coordinated C-C multiple bond. The carbon-metal bond in **4.3** is then cleaved through direct protonolysis or protonation at the metal center followed by reductive elimination. Finally, the starting catalytic complex **4.1** is regenerated from metal-amine complex **4.5** through ligand exchange with another C-C multiple bond. As an example, Hull reported a rhodium-catalyzed *anti*-Markovnikov-selective hydroamination of homoallylic amine. The proximal Lewis basic amine serves to promote reactivity and enforce regioselectivity through the formation of the favored metallacycle.<sup>135</sup>



**Scheme 26.** C-C multiple bond activation pathway.

b) Amine activation (Scheme 27).

The coordinatively unsaturated metal center activates the amine by ligand exchange or oxidative addition of the N-H bond. The formed amido hydrido complex then coordinates to a C-C multiple bond, followed by migratory insertion of the C-C multiple bond into the M-N bond. After the C-H reductive elimination, the product is liberated. A neutral iridium catalyzed hydroamination of allylic acetate under basic condition probably follows this pathway.<sup>136</sup>



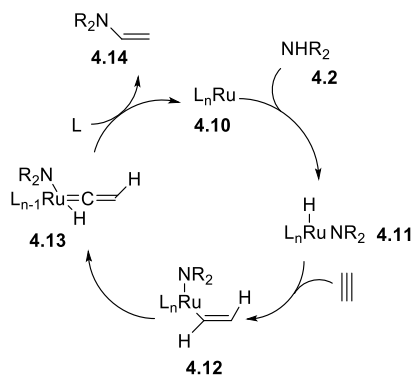
**Scheme 27.** Amine activation pathway

### c) Metal-hydride catalytic complex.

The metal-hydride could be formed by a various way. For example, oxidative addition of carboxylic acid or acidic *N*-H to the metal center has been described. Other methods for the preparation of metal-hydride includes dehydrogenation of alcohols and hydride transfer from silanes. Like the pathway b, the metal-hydride pathway also involves the migratory insertion of the C-C multiple bond into the M-H bond, and the C-N bond is formed in the subsequent reductive elimination step. The Cu-H catalyzed formal hydroamination pathway will be further discussed later in this introduction (See 4.1.2).

### d) Formation of vinylidene complex (Scheme 28).

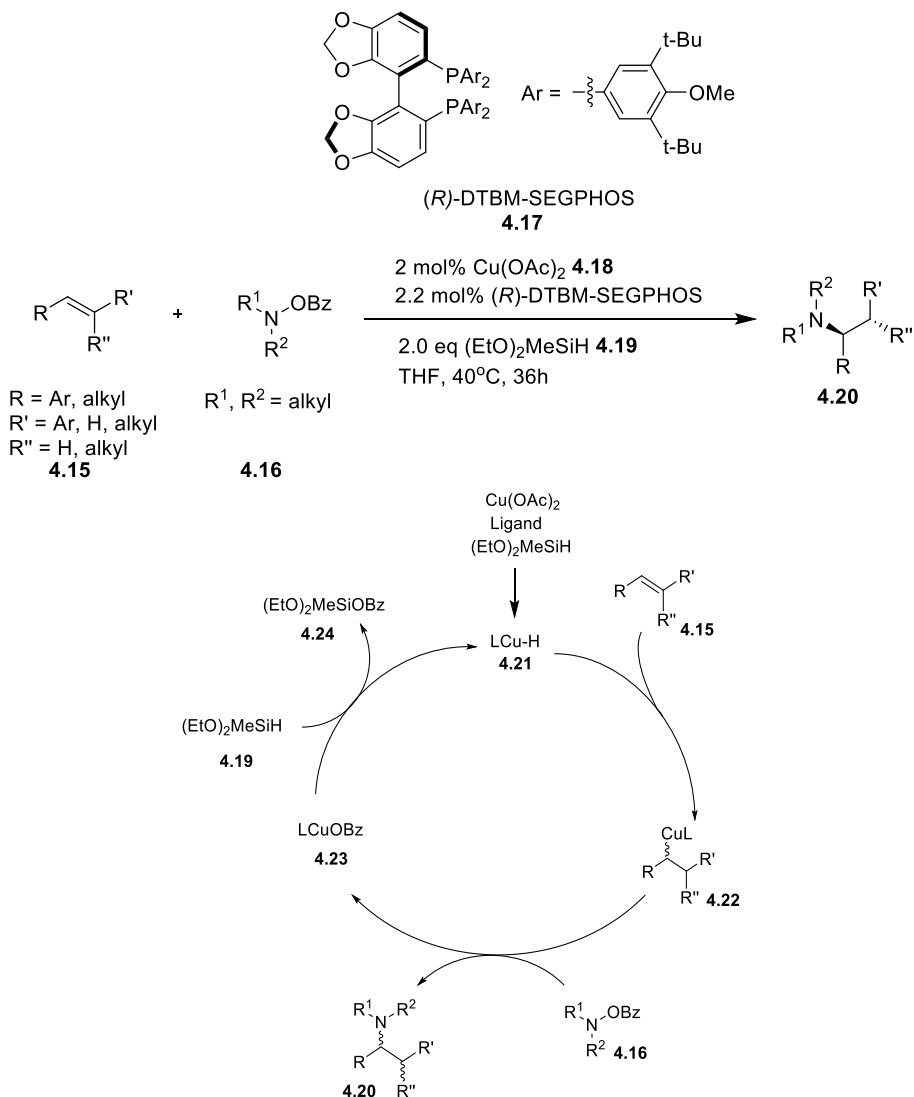
This mechanistic pathway has only been described for the ruthenium-catalyzed hydroamination of alkynes.<sup>137</sup> The catalytic cycle starts with the formation of Ru-H species **4.11** followed by insertion of an alkyne to give intermediate **4.12**. The resulting Ru(II)-vinyl complex **4.12** rearranges to a Ru(IV)-hydride-vinylidene species **4.13** via  $\alpha$ -hydride transfer. Finally, reductive elimination releases the enamine product **4.14** and regenerates the Ru(0) catalyst.



**Scheme 28.** Pathway through the formation of vinylidene

#### 4.1.2 Cu-H catalyzed formal hydroamination

In 2013, the groups of Hirano, Miura<sup>138</sup>, and Buchwald<sup>139</sup> independently developed a copper-catalyzed enantioselective formal hydroamination of alkenes with O-benzoylhydroxylamines in the presence of an excess hydrosilane. Since then, this approach has been well demonstrated for a broad range of alkene and alkyne substrates<sup>140-144</sup>, including vinylsilanes<sup>145</sup>, alkenyl dan boronates (dan = 1,8-diaminonaphthyl)<sup>146</sup>, vinylphosphines<sup>147</sup> and 1-trifluoromethylalkenes<sup>148</sup>. The proposed mechanism of this reaction is shown in Scheme 29. Treatment of Cu(OAc)<sub>2</sub> **4.18** and (*R*)-DTBM-segphos **4.17** likely give rise to a Cu-ligand complex, which was converted into the catalytically competent Cu-H **4.21** through transmetalation with silane **4.19**. Alkene **4.15** inserts into the Cu-H bond to generate the corresponding chiral alkyl-Cu complex **4.22**, which then intercepts hydroxylamine O-benzoate reagent **4.16** via oxidative addition, which is followed by reductive elimination to generate the enantioenriched amine product **4.20** and phosphine-bound Cu benzoate **4.23**. Cu-benzoate **4.23** then undergoes transmetalation with silane **4.19** to regenerate Cu-H **4.21** to complete the catalytic cycle.

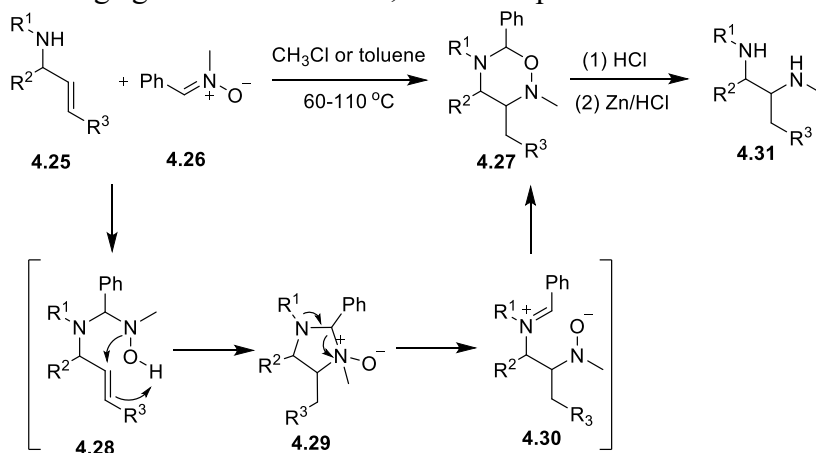


**Scheme 29.** Proposed catalytic cycle of Cu-H catalyzed formal hydroamination

### 4.1.3 Synthesis of 1,2-diamines by applying hydroamination

To date, the catalytic hydroamination reaction has been established as a powerful tool for the rapid synthesis of several types of amines, such as 1,3-amino alcohols,<sup>136</sup>  $\beta$ -aminosilanes,<sup>149</sup> 1, 4-diamines,<sup>135</sup>  $\alpha$ -aminosilanes,<sup>145</sup>  $\alpha$ -trifluoromethylamines,<sup>148</sup> and  $\alpha$ -aminoboronic acid derivatives<sup>146</sup>, which themselves are valuable intermediates in organic and

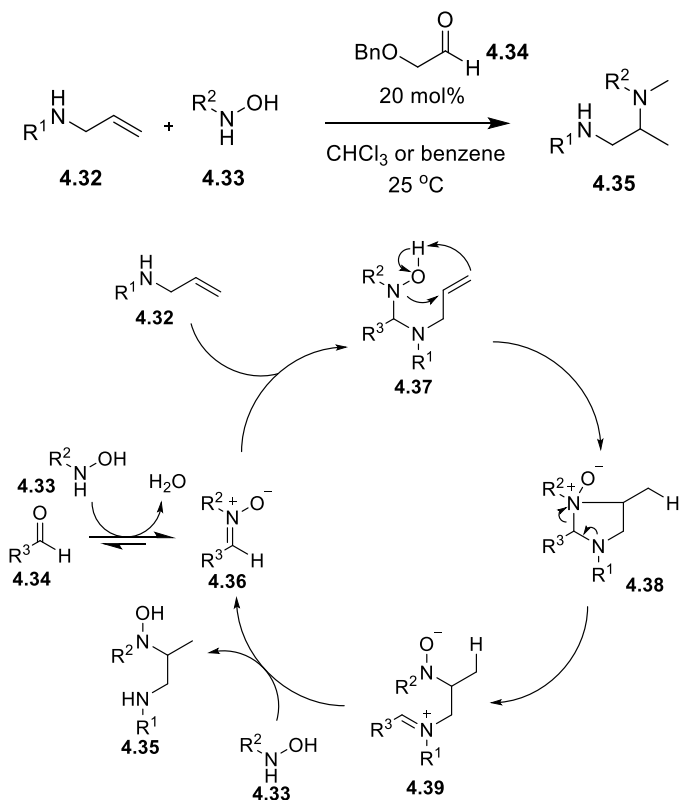
pharmaceutical chemistry. The first example for the synthesis of 1,2-diamines reaction was reported by Knight in 1993 in which the hydroamination procedure was employed (Scheme 30).<sup>150</sup> Nitrones **4.26** were reacted with allylamines **4.25** to afford 1,2,5-oxadiazinanes **4.27** through a retro-Cope elimination process, which was then treated with acid and reducing agent to furnish the 1,2-diamine product.



**Scheme 30.** Synthesis of oxadiazinanes and its conversion into 1,2-diamine

Inspired by Knight's work, Beauchemin later reported aldehyde-catalyzed hydroamination of allylamine for the synthesis of 1,2-diamine (Scheme 31).<sup>41</sup> In this manner, aldehyde **4.34** was used to tether a hydroxylamine **4.33** and an allylic amine **4.32**, which is then followed by an intramolecular retro-Cope elimination to install the 1,2-diamine moiety **4.35**. The proposed mechanism is shown in Scheme 31. Initially, the condensation between aldehyde catalyst **4.34** and hydroxylamine **4.33** give rise to the nitron **4.36**, which is then attacked by allylamine **4.32** to form intermediate **4.37**. Next, the stage is set for the retro-Cope type rearrangement followed by an amination cleavage, leading to the iminium ion **4.39**. Finally, intermediate **4.39** exchange with another hydroxylamine **4.33** to furnish the 1,2-diamine product **4.35** and regenerate the nitron **4.36**. Furthermore, they utilized  $\alpha$ -chiral aldehyde as catalyst to achieve the enantioselective synthesis of 1,2-diamines with moderate to excellent *er*.<sup>151</sup>

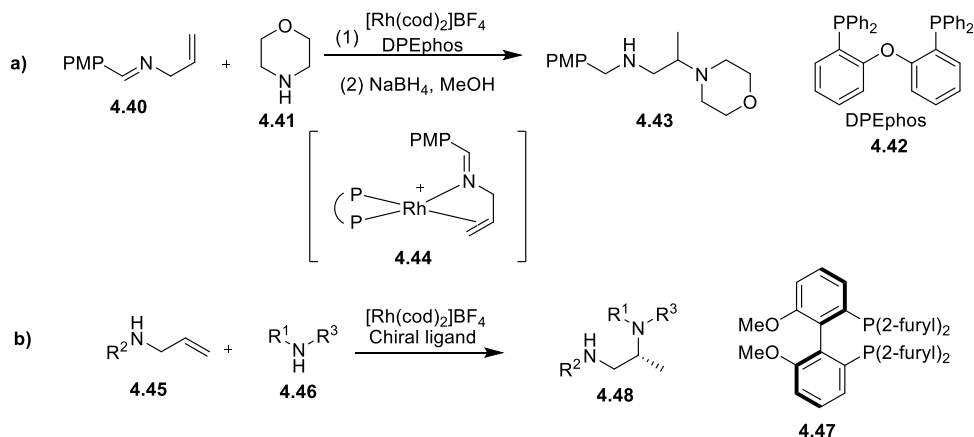




**Scheme 31.** Proposed mechanism for Beauchemin's hydroamination.

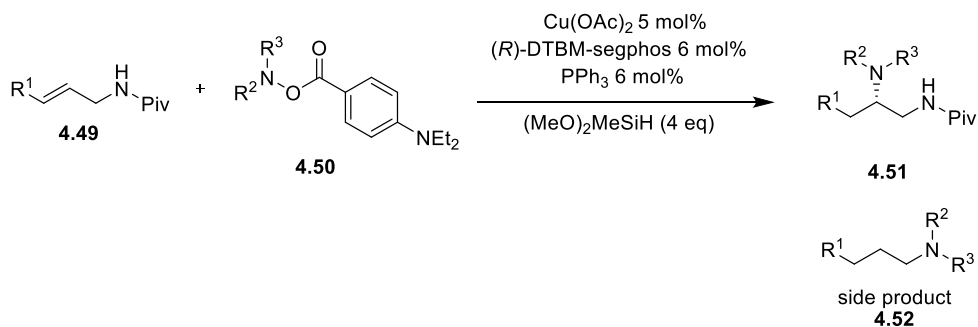
In comparison to organocatalytic methods, metal-catalyzed hydroamination for the synthesis of 1,2-diamines is more challenging, because the Lewis basic amines have a high affinity for transition metals which could lead to the formation of stable amine-metal complexes. However, in 2014, Hull and coworkers reported the first intramolecular hydroamination for the synthesis of 1,2-diamines (Scheme 32a).<sup>152</sup> In their work, a Rh-DPEphos catalyst<sup>153</sup> was used for the hydroamination of an allyl imine with cyclic secondary amines. The presence of the allylic imine moiety could facilitate the hydroamination process because the coordination of both the imine and olefin to the cationic ruthenium complex increase the reactivity of olefin.<sup>152</sup> The reaction proceeds via the C-C multiple bond activation discussed in Section 4.1.1 a. Very recently, they extended their methodology to the asymmetric hydroamination reaction by utilizing the same cationic ruthenium catalyst but using the chiral BIPHEP-type ligand **4.47**. To the best of our knowledge, this is the

first example of the synthesis of enantioenriched 1,2-diamines via a metal-catalyzed hydroamination (Scheme 32b).<sup>42</sup>



**Scheme 32.** Hull's hydroamination of allyl imine/amine for the synthesis of 1,2-diamine.

Just recently, a related method for the synthesis of 1,2-diamines via Cu-H catalyzed formal hydroamination of allylic amines **4.49** was reported by Buchwald (Scheme 33). It was found that the regioselectivity of this reaction is related to the size of  $\text{R}^1$ , where the much lower *rr* was obtained when using primary alkyl substituents  $\text{R}^1$  in comparing to the secondary or tertiary alkyl substituents. The formation of side product **4.52** suggested that a  $\beta$ -elimination followed by a formal hydroamination could take place after the hydrocupration step. In order to prevent the  $\beta$ -elimination, they then investigated different protecting group of allylic amine and found the use of *N*-pivaloyl substrate could give the desired 1,2-diamine product **4.51** with good yield and *er*.<sup>154</sup>



**Scheme 33.** Buchwald's formal hydroamination of allylic amine **4.49** for the synthesis of 1,2-diamine **4.51**.

## 4.2 Aim of the project

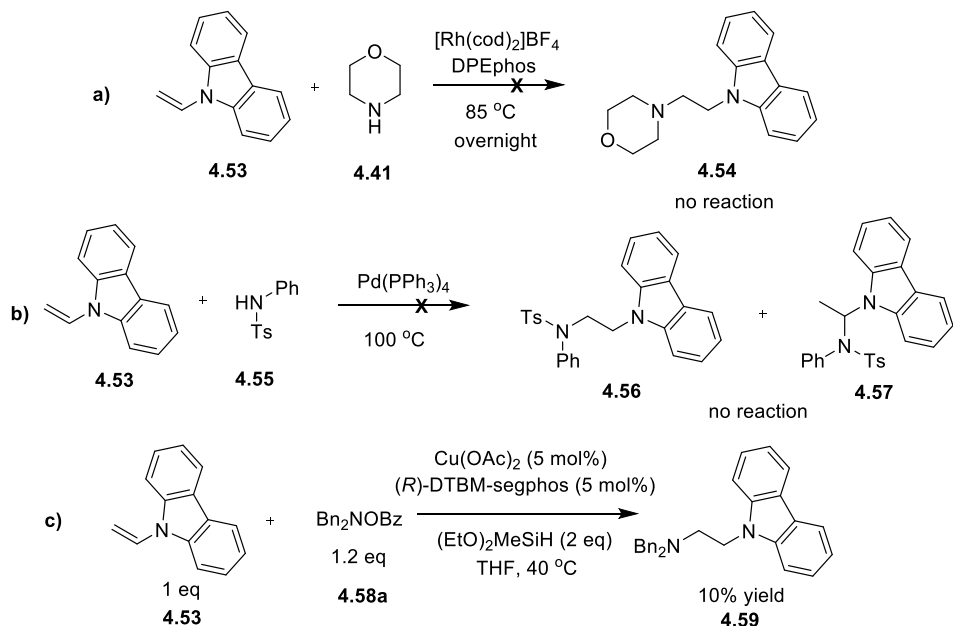
In this project, we were interested in developing a novel approach for the preparation of enantioenriched 1,2-diamines from easily accessible enamines through a Cu-H catalyzed formal hydroamination. We believe that such a reaction would constitute a highly attractive method for the synthesis of this important structural motif.

## 4.3 Results and discussions

### 4.3.1 Preliminary study

Enamines have electron-rich carbon-carbon double bonds due to the resonance donation of the nitrogen lone pair into the C=C  $\pi$ -bond. They have not been employed as substrates in the catalytic hydroamination reaction, perhaps because of the hydrolytic sensitivity of these compounds or their propensity to participate in enamine-imine tautomerization.<sup>79,155</sup> However, if successful, such transformation would result in the formation of 1,2-diamines. At the beginning of this project, we speculated that decreasing the electron density of the enamine by using a conjugated system, in which the hydrolysis and tautomerization of enamine could also be prevented, may favor the desired hydroamination reaction.

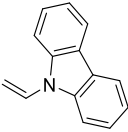
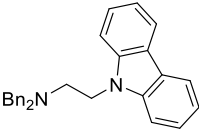
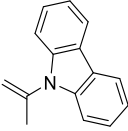
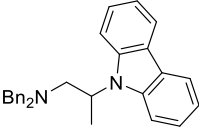
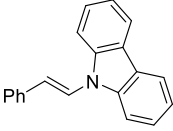
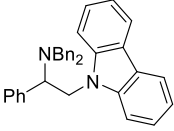
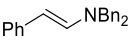
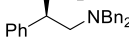
We then chose the stable and commercially available 9-vinylcarbazole **4.53** as the enamine substrate and investigated its hydroamination with different amine source in several reported reaction conditions. We began our investigation with the use of Hartwig's methodology<sup>153</sup> for the hydroamination of **4.53** with morpholine **4.41**. After stirring the reaction at 85 °C overnight, no desired 1,2-diamine **4.54** product was produced and the enamine starting material was recovered (Scheme 34a). Pd(0) has been utilized as the catalyst for the inter- or intramolecular Markovnikov hydroamination of electron-rich vinyl ether substrates.<sup>156,157</sup> However, such conditions are not compatible for the enamine substrates (Scheme 34b). Next, we turned our attention to the Cu-H catalyzed formal hydroamination condition developed by Hirano, Miura<sup>138</sup> and Buchwald<sup>139</sup>. To our great delight, treatment of 9-vinylcarbazole **4.53** with *O*-benzoylhydroxylamine **4.58a** under the reported formal hydroamination conditions lead to the desired *anti*-Markovnikov 1,2-diamine product **4.59** with 10% isolated yield (Scheme 34c).



**Scheme 34.** Investigation of different hydroamination conditions.

These initial results unequivocally demonstrated the potential of the Cu-H formal hydroamination approach and, equally clear, the need for a screening of enamines substrates for the optimization of reaction conditions. Formal hydroamination with  $\alpha$ -methyl enamine **4.60** and  $\beta$ -phenyl enamine **4.62** showed that the substituents on the 9-vinylcarbazole **4.53** had a negative influence on the reaction, probably as a result of their delicate difference in electron density or steric hindrance of carbon-carbon double bond (Table 9, entry 2-3). Surprisingly, the formal hydroamination with an electron-rich dibenzyl enamine **4.64** afforded the 1,2-diamine product **4.65** 28% yield and excellent enantioselectivity. Notably, because the competitive and unproductive reduction of hydroxylamine **4.58a** with silane is also catalyzed by the same Cu-H species,<sup>141</sup> 29 mol% enamine **4.64** remained when the hydroxylamine **4.58a** was fully consumed (entry 4).

**Table 9.** Preliminary screening of enamines<sup>[a]</sup>

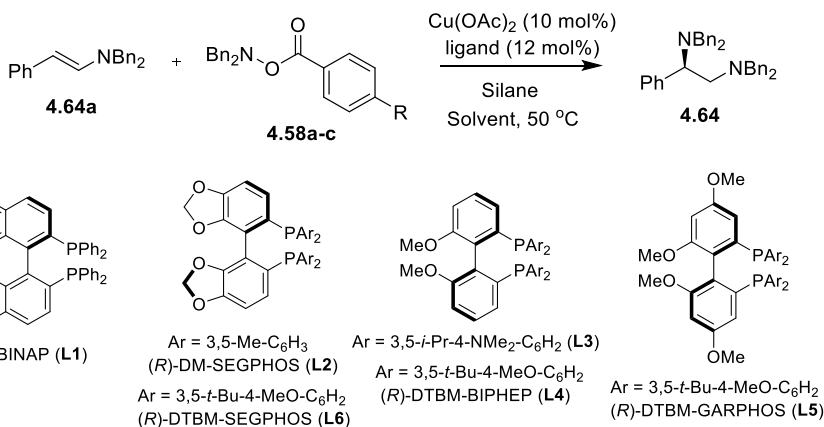
$  \begin{array}{c}  \text{R}^1 \text{---} \text{C} = \text{C} \text{---} \text{N}(\text{R}^2)\text{R}^3 \\    \\  \text{R}^2  \end{array}  + \text{Bn}_2\text{NOBz}  \xrightarrow[\text{THF, 50 } ^\circ\text{C}]{\begin{array}{c} \text{Cu(OAc)}_2 \text{ (5 mol\%)} \\ \text{(R)-DTBM-segphos (5.5 mol\%)} \\ \text{(EtO)}_2\text{MeSiH (2 eq)} \end{array}}  \begin{array}{c}  \text{NBn}_2\text{R}^2 \\    \\  \text{R}^1 \text{---} \text{C} \text{---} \text{C} \text{---} \text{N}(\text{R}^2)\text{R}^3 \\    \\  \text{R}^2  \end{array}  $					
$  \begin{array}{c}  \text{R}^1 \text{---} \text{C} = \text{C} \text{---} \text{N}(\text{R}^2)\text{R}^3 \\    \\  \text{R}^2  \end{array}  + \text{Bn}_2\text{NOBz}  \xrightarrow[\text{THF, 50 } ^\circ\text{C}]{\begin{array}{c} \text{Cu(OAc)}_2 \text{ (5 mol\%)} \\ \text{(R)-DTBM-segphos (5.5 mol\%)} \\ \text{(EtO)}_2\text{MeSiH (2 eq)} \end{array}}  \begin{array}{c}  \text{NBn}_2\text{R}^2 \\    \\  \text{R}^1 \text{---} \text{C} \text{---} \text{C} \text{---} \text{N}(\text{R}^2)\text{R}^3 \\    \\  \text{R}^2  \end{array}  $					
Entry	enamines	products	Time (h)	yield <sup>[b]</sup>	er <sup>[c]</sup>
1	 <b>4.53</b>	 <b>4.59</b>	24	10	--
2	 <b>4.60</b>	 <b>4.61</b>	48	Complex mixture	--
3	 <b>4.62</b>	 <b>4.63</b>	48	n.r.	--
4	 <b>4.64a</b>	 <b>4.64</b>	48	28(64) <sup>[d]</sup>	98:2

[a] Reaction performed with Cu(OAc)<sub>2</sub> (5 mol%), (R)-DTBM-segphos (6 mol%), enamine (1 eq), **4.58a** (1.2 eq) and (EtO)<sub>2</sub>MeSiH (2 eq) in THF (1 mL) at 50 °C. [b] Yield determined by using <sup>1</sup>H NMR spectroscopy and an internal standard. [c] Determined by chiral HPLC. [d] Yield based on recovered enamine determined by using <sup>1</sup>H NMR spectroscopy and an internal standard. n.r. = no reaction.

### 4.3.2 Optimization of reaction condition

With these preliminary results in hand, it is clear that a thorough optimization of the reaction conditions was needed. We chose the formal hydroamination of enamine **4.64a** with hydroxylamine **4.58a** as the model reaction and began the optimization by investigating the ratio of enamine **4.64a** and hydroxylamine **4.58a**. Increasing the amount of hydroxylamine **4.58a** led to similar results with yields and enantioselectivities, and did not result in a full consumption of enamine **4.64a** (Table 10, entry 1-4). Treatment of 1 eq hydroxylamine **4.58a** with 3 eq enamine **4.64a** allows us to skip the consumption problem of enamine, furnish the 1,2-diamines product with improved yield and slightly lower er (entry 4). It has been reported that the use of an electrophilic aminating reagent bearing a more

**Table 10.** Optimization of reaction condition<sup>a]</sup>



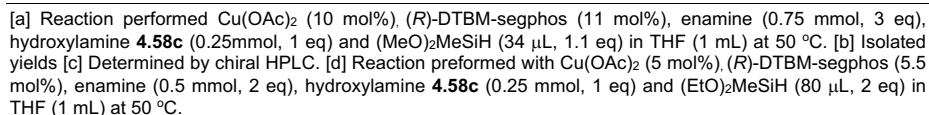
entry	<b>4.62/4.57</b>	ligand	R	solvent	silane (eq)	time (h)	yield(%) <sup>[b]</sup>	er <sup>[c]</sup>
1	1/1.2	<b>L6</b>	H ( <b>4.58a</b> )	THF	DEMS (2)	48	28(64)	98:2
2	1/3	<b>L6</b>	H ( <b>4.58a</b> )	THF	DEMS (2)	48	24(61)	98:2
3	1/5	<b>L6</b>	H ( <b>4.58a</b> )	THF	DEMS (2)	48	40(73)	99:1
4	3/1	<b>L6</b>	H ( <b>4.58a</b> )	THF	DEMS (2)	24	38	94:6
5	3/1	<b>L6</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	24	53	97:3
6 <sup>[d]</sup>	3/1	<b>L6</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	72	47	98:2
7	3/1	<b>L1</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	48	<5	--
8	3/1	<b>L2</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	48	11	n.d.
9	3/1	<b>L3</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	48	26	96:4
10	3/1	<b>L4</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	48	37	99:1
11	3/1	<b>L5</b>	NMe <sub>2</sub> ( <b>4.58b</b> )	THF	DEMS (2)	48	44	98:2
12	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (2)	48	57	96:4
13	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	CH <sub>2</sub> Cl <sub>2</sub>	DEMS (2)	24	n.r.	--
14	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	Et <sub>2</sub> O	DEMS (2)	24	trace	--
15	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	toluene	DEMS (2)	72	43	97:3
16	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	dioxane	DEMS (2)	72	49	96:4
17 <sup>[e]</sup>	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (2)	24	50	97:3
18 <sup>[f]</sup>	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (2)	24	58	96:6
19 <sup>[g]</sup>	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (2)	24	55	95:5
20	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (1.1)	36	61	96:4
21	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (3)	24	52	96:4
22	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DEMS (5)	24	55	95:5
23	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	PMHS (1.1)	48	62	95:5
24	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	(MeO) <sub>3</sub> SiH (1.1)	48	51	96:4
25	3/1	<b>L6</b>	NEt <sub>2</sub> ( <b>4.58c</b> )	THF	DMMS (1.1)	48	69	97:3

[a] Reaction performed Cu(OAc)<sub>2</sub> (10 mol%), (R)-DTBM-segphos (11 mol%), enamine **4.64** (0.25-0.75 mmol, 1-3 eq), hydroxylamine **4.58** (0.25-1.25 mmol, 1-5 eq) and silane in solvent (1 mL) at 50 °C. [b] Yield determined by using <sup>1</sup>H NMR spectroscopy and an internal standard. [c] Determined by chiral HPLC. [d] PPh<sub>3</sub> (11 mol%) was added in reaction as a co-catalyst. [e] Cu(OAc)<sub>2</sub> (5 mol%), (R)-DTBM-segphos (5.5 mol%) were used in reaction. [f] Cu(OAc)<sub>2</sub> (15 mol%), (R)-DTBM-segphos (16.5 mol%) were used in reaction [g] Cu(OAc)<sub>2</sub> (20 mol%), (R)-DTBM-segphos (22 mol%) were used in reaction n.r. = no reaction

electron-rich benzoyl group could enhance reactivity toward the nucleophilic alkyl copper intermediate, thus suppressing the nonproductive consumption of hydroxylamine by the Cu-H intermediate.<sup>141</sup> Indeed, the use of more electron-rich hydroxylamine **4.58b** was beneficial to the reaction efficiency (entry 5). As discovered by Lipshutz, triphenylphosphine could be used as a secondary ligand to enable lower catalyst loading and improve overall reactivity for certain system.<sup>158</sup> However, the addition of 11 mol% PPh<sub>3</sub> to the model system did not improve the results; instead, a decrease in reaction rate was observed (entry 6). Next, we studied the formal hydroamination of enamine **4.64a** and hydroxylamine **4.58b** using different bidentate phosphine ligands. It was found that the use of bulky bidentate phosphine ligands in the reaction has, somewhat counterintuitively, a beneficial effect on the reactivity (entry 7-10). Moreover, both the ligands **L5** and **L6** resulted in increased yields, compared to those obtained when using **L4**, while retaining excellent er values, perhaps indicating a beneficial influence on the reactivity when increasing the electron-donating ability of the biphenyl backbone (entry 5 and 11). The optimization was then continued with (*R*)-DTBM-segphos (**L6**), and the hydroxylamine **4.58c** was selected for further optimization because of the slightly higher yield compared to hydroxylamine **4.58b** (entry 12). Further screening of solvents revealed that performing the reaction in THF was optimal (entry 12-16). Increasing the catalyst loading led to the formation of 1,2-diamine **4.64** in similar yields and er, while a lower yield was obtained when decreasing the catalyst to 5 mol% (entry 17-19). Finally, in order to further improve the reaction outcome, we investigated the type and amounts of silanes. It was shown that using 1.1 eq (MeO)<sub>2</sub>MeSiH (DMMS) as the hydride source had the beneficial influence on the reaction outcome, affording 1,2-diamine **4.64** in 69% yield with 97:3 er (entry 20-25).

### 4.3.3 Scope of enamines

Having identified the optimal reaction conditions, we next investigated the scope and limitation of the Cu-H catalyzed formal hydroamination of a variety of enamines **4.64a-4.77a**, **4.53** with dibenzyl hydroxylamine **4.58c**, and the results are presented in Table 11 and Table 12. The influence of the *N*-substituents in enamines on the reaction outcome was negligible as compounds **4.64a-4.68a** all gave the corresponding dialkylamines **4.64-4.68** with high er value, although the yield of the *N*-methyl indole derivative **4.67** was somewhat lower. In addition, enamines derived from morpholine **4.69a**, 4-piperidinone **4.70a**, and piperazine **4.71a-4.72a** can

Table 11. Scope of enamines<sup>[a][b][c]</sup>

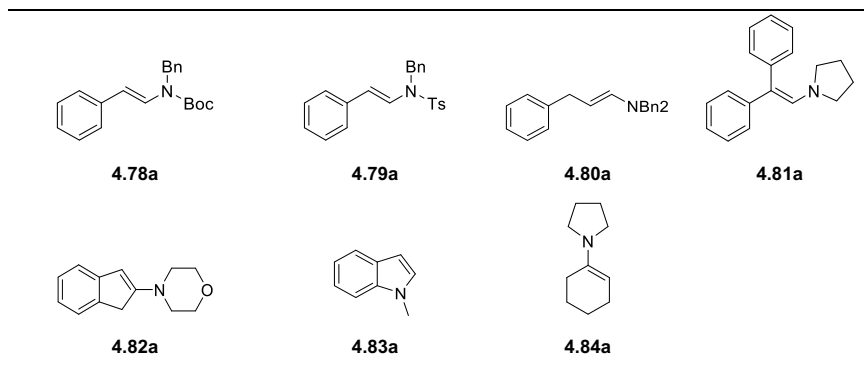
68



the electron-deficient enamine **4.73a** is more suitable for this reaction since the excellent yield was obtained without any loss of enantioselectivity (**4.73**). Enamine **4.77a**, having an ester functional group, performed well in the formal hydroamination reaction and delivered the corresponding diamine ester **4.77** in good yield but as a racemate. It was believed that the formation of racemic diamine product **4.77** in this case was due to the isomerization of the copper enolate intermediate, which was formed through the originally 1,4-addition of enamine **4.77a** by the Cu-H catalyst.<sup>159,160</sup> Furthermore, 9-vinylcarbazole **4.53** could also be hydroaminated under the optimal condition, producing the *anti*-Markovnikov product **4.59** in low yield.

Although several successful examples had been achieved, this Cu-H catalyzed formal hydroamination reactions is not without limitations. When subjecting enamines **4.78a-4.80a** to the reaction conditions, none of the desired diamine products were obtained. Instead, in each case the starting material was recovered unaffected and the hydroxylamine was reduced under the reaction conditions. Attempts to formally hydroaminate the trisubstituted enamines **4.81a-4.82a** proved to be unsuccessful and produced none of the desired product, which might be attributed to unfavorable sterical hindrance in the hydrocupration step. Finally, both *N*-methylindole **4.83a** or 1-pyrrolidino-1-cyclohexene **4.84a** failed to afford the desired products.

**Table 12.** Unsuccessful enamines substrates.

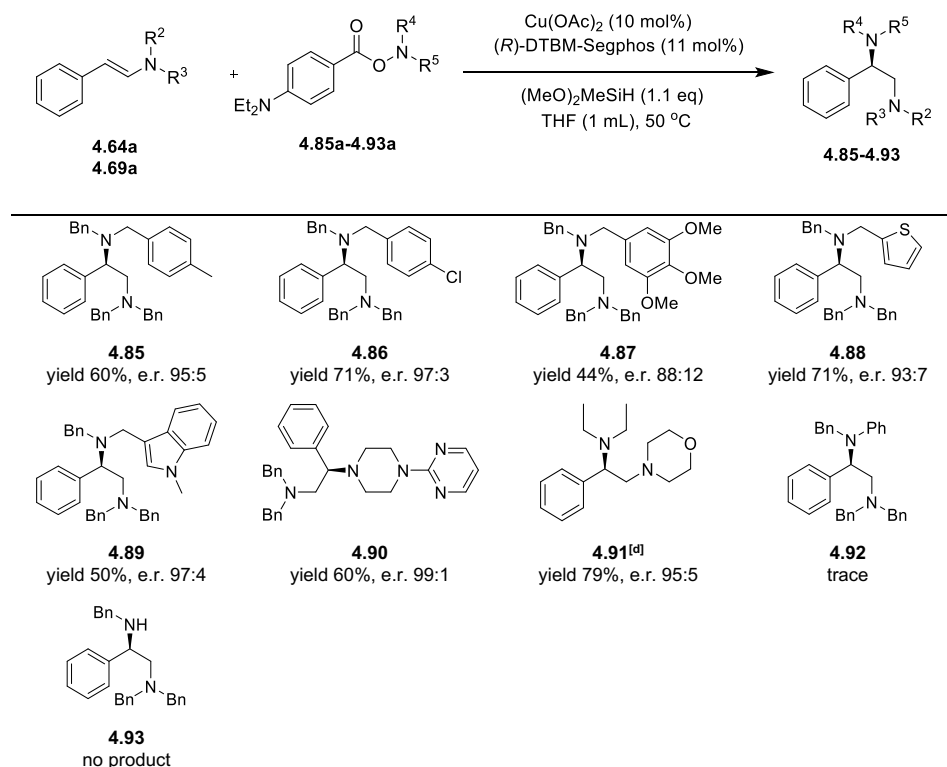


#### 4.3.4 Scope of hydroxylamines

The influence of the hydroxylamines on the reaction outcome was next explored (Table 13). In these reactions, we found that in the presence of enamine **4.64a**, a wide range of hydroxylamines were tolerated. Electron-

rich (**4.85a** and **4.87a**), electron-deficient (**4.86a**) as well as heterocyclic (**4.88a** and **4.89a**) hydroxylamines all gave compatible results compared with the standard substrate, affording the corresponding 1,2-diamines **4.85-4.89** in good yields and high er values. Interestingly, the Lewis basic 1-pyrimidylpiperazine hydroxylamine **4.90a** was also successfully utilized as an electrophilic aminating reagent, providing **4.90** in good yield and excellent enantioselectivity. The dialkyl hydroxylamine **4.91a** also gave desired dialkylamine product **4.91** in good yield and high er value. The absolute configuration of **4.91** was determined to be *R* by comparing its optical rotation ( $[\alpha]_{\text{D}}^{25} = -1.3$  ( $c = 2.00$ ,  $\text{CHCl}_3$ ) with literature data of its enantiomer ( $[\alpha]_{\text{D}}^{25} = +1.3$  ( $c = 2.00$ ,  $\text{CHCl}_3$ )<sup>161</sup>, and the configuration of the other compounds described in this work are assigned in analogy to **4.91**.

**Table 13.** Scope of hydroxylamines.<sup>[a][b][c]</sup>

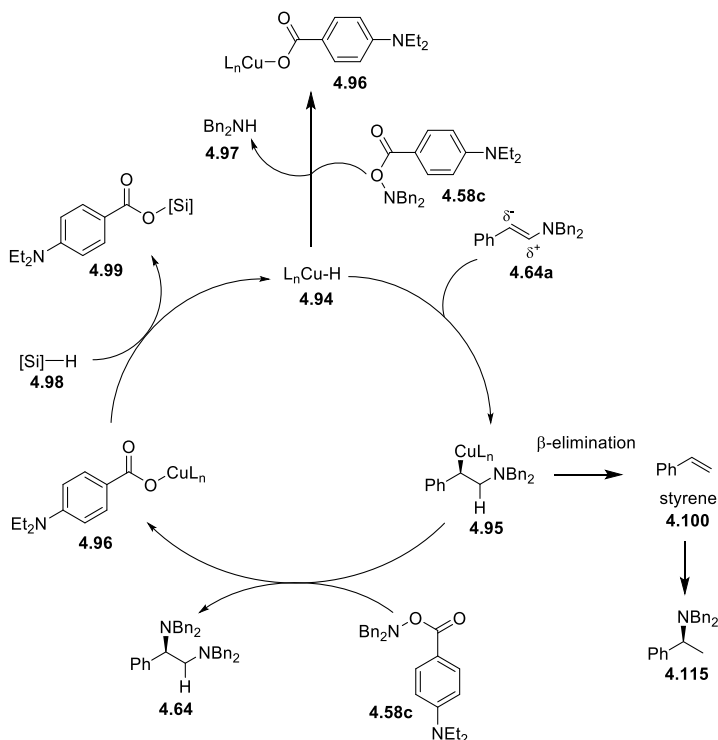


[a] Reaction performed using  $\text{Cu}(\text{OAc})_2$  (10 mol%), (*R*)-DTBM-segphos (11 mol%), enamine **4.64a** (0.75 mmol, 3 eq), hydroxylamine (0.25 mmol, 1 eq) and  $(\text{MeO})_2\text{MeSiH}$  (34  $\mu\text{L}$ , 1.1 eq) in THF (1 mL) at 50 °C. [b] Isolated yields [c] Determined by chiral HPLC. [d] Reaction performed using  $\text{Cu}(\text{OAc})_2$  (5 mol%), (*R*)-DTBM-segphos (5.5 mol%), enamine **4.69a** (0.5 mmol, 2 eq), hydroxylamine (0.25 mmol, 1 eq) and  $(\text{EtO})_2\text{MeSiH}$  (80  $\mu\text{L}$ , 2 eq) in THF (1 mL) at 50 °C.

To our disappointment, *N,N*-benzylaryl hydroxylamine **4.92a** and semi-benzyl hydroxylamine **4.93a** only gave undesired by-product amines, resulting from the reduction of the hydroxylamine by the hydrosilane.<sup>162,163</sup>

#### 4.3.5 Proposed catalytic cycle

Based on the previously proposed mechanism for the CuH-catalyzed hydrofunctionalization reaction of alkenes, a plausible catalytic cycle for the formal hydroamination of enamine was proposed (Scheme 35). Regio- and enantioselective hydrocupration of enamine **4.64a** with the in situ generated copper(I) hydride **4.94** provide the secondary alkylcopper intermediate **4.95**. In the hydroamination of alkenes it has been shown that this step is irreversible and enantio-determining, and it is reasonable to assume that this is also the case for the present reaction.<sup>141,164-166</sup> Oxidation of alkyl copper species **4.95** with hydroxylamine **4.58c** then furnishes the enantioenriched 1,2-diamine **4.64** and releases the copper benzoate **4.96**, which is reconverted into Cu-H catalyst **4.94** upon transmetalation with hydrosilane **4.98**. In this reaction trace amounts of amine **4.115** was detected in the crude reaction mixture. It is believed to be formed by a formal hydroamination of styrene **4.100** resulted from the  $\beta$ -elimination of **4.95**.<sup>144,167</sup> Notably, the competitive reduction of the hydroxylamine **4.58c** is catalyzed by the same Cu-H catalyst **4.94**, furnishing dibenzylamine **4.97** as an undesired by-product.



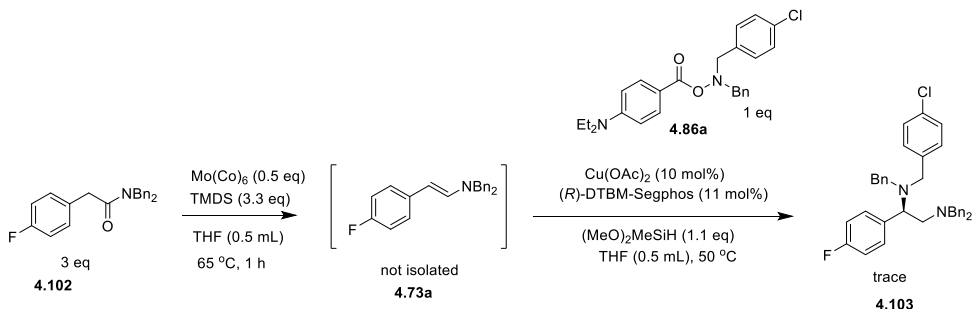
**Scheme 35.** Proposed catalytic cycle

### 4.3.6 One-pot synthesis of 1,2-diamines via formal hydroamination process

Although the Cu-H catalyzed formal hydroamination of enamines provided a novel approach for the enantioselective synthesis of a broad range of 1,2-diamines, the preparation and isolation of unstable enamine substrates limited the overall yields and the scope of targets. Therefore, we were interested in developing a one-pot procedure for the synthesis of chiral 1,2-diamines via the formal hydroamination, which would allow for the in-situ utilization of formed enamine substrates without any purification. At the outset, we spent some time in screening reaction conditions for the formation of enamines that would allow for a subsequent hydroamination.

Tinnis and Adolffson have reported the reductive functionalization of amides into triazolines, 4,5-dihydroisoxazoles, and pyrimidinediones.<sup>168-170</sup> The key step for these transformations were the reduction of amides to enamines using catalytic amounts of Mo(CO)<sub>6</sub> in combination with stable

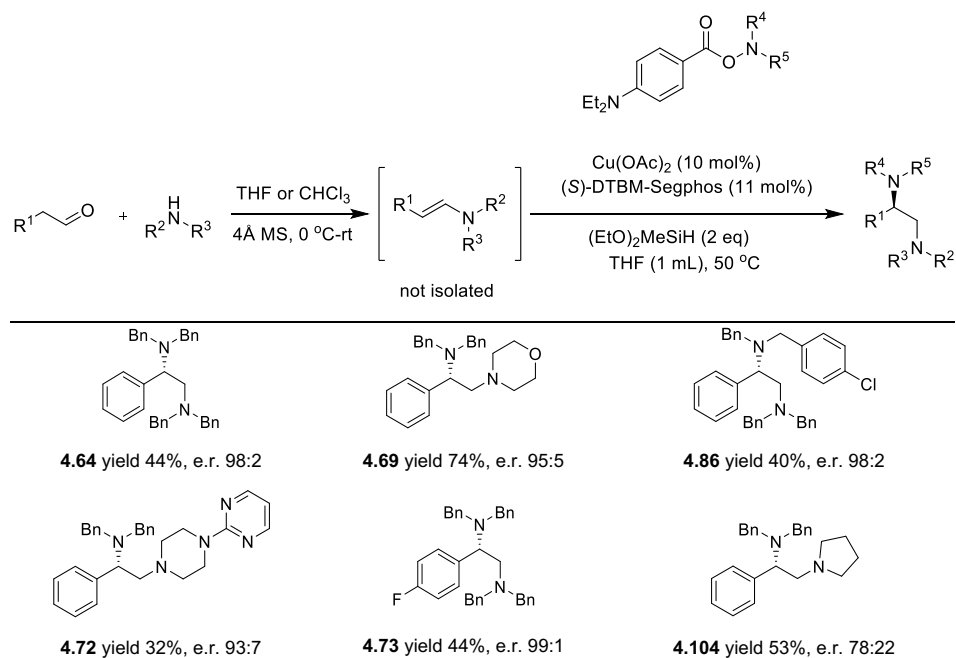
silane 1,1,3,3-tetramethyldisiloxane (TMDS). However, this protocol was not successful in our hands and gave a minute amount of desired 1,2-diamine product, probably due to the mixed catalysts making the reaction elusive (Scheme 36).



**Scheme 36.** One-pot synthesis of 1,2-diamine via Tinnis and Adolfsson's protocol.

To simplify the reaction system, we then turned our attention to an alternative strategy using a mild and fast method for the synthesis of enamines from aldehydes and secondary amines.<sup>171</sup> In this case, the one-pot synthesis of 1,2-diamines via formal hydroamination process was achieved with high level of enantioselectivities and moderate yields (Table 14).

**Table 14.** One-pot synthesis of 1,2-diamines.<sup>[a][b][c]</sup>



[a] Reaction preformed Cu(OAc)<sub>2</sub> (10 mol%), (S)-DTBM-segphos (11 mol%), aldehydes (0.75 mmol, 3 eq), secondary amines (0.83 mmol, 3.3 eq), hydroxylamine (0.25mmol, 1 eq) and (EtO)<sub>2</sub>MeSiH (34 μL, 1.1 eq) in THF (1 mL) at 50 °C. [b] Isolated yields [c] Determined by chiral HPLC.

### 4.3.7 Study towards the formal hydroamination of vinyl ethers

The 1,2-amino alcohol functionality is also a structural element of central importance to organic chemistry and biology due to its wide abundance in biologically active natural products and pharmaceutical drugs.<sup>172</sup> Thus, it is important to have efficient synthetic tools that can be used to access this structural motif. We have developed a catalytic protocol for the asymmetric synthesis of 1,2-diamines via the Cu-H catalyzed formal hydroamination easily accessible enamines. This process is initiated by the regio- and enantioselective hydrocupration of electron-rich enamines, followed by an oxidative addition with hydroxylamine and reductive elimination to furnish the desired 1,2-diamine product. We were then interested in extending this novel methodology to vinyl ether substrates. If successful, such transformation would result in the formation of 1,2-amino alcohol.

Our initial focus was directed toward the formal hydroamination of commercial vinyl butyl ether **4.105**. However, this attempt was unsuccessful and gave *N,N*-dibenzyl-1-phenylethylamine **4.113** as the major product, the result of a hydrocupration,  $\beta$ -elimination of a Cu(I) alkoxide, followed by a hydroamination of the so formed ethylene to give the observed product.<sup>144</sup> Attempt to overcome this problem, we examined this formal hydroamination of a series of vinyl ether substrates **4.106**-**4.109**. Unfortunately, all attempts gave the  $\beta$ -elimination products **4.113**-**4.115**. The lately reported Cu-H catalyzed formal hydroamination of *N*-protect allylic amine revealed that differing in the protecting group on the allylic amine nitrogen played an important role in preventing the  $\beta$ -elimination.<sup>154</sup> To our disappoint, vinyl ester substrates **4.110**-**4.112** all gave complex reaction mixtures under the formal hydroamination condition. (Table 15)

**Table 15.** Formal hydroamination of vinyl ether or vinyl ester

vinyl ether/ester +			Cu(OAc) <sub>2</sub> (5 mol%) ( <i>R</i> )-DTBM-segphos (5 mol%) (EtO) <sub>2</sub> MeSiH (2 eq) THF(1 mL), 50 °C		product
1.5 eq		1 eq			
		<b>4.58a</b>			
entry	vinyl ether/ester	product	entry	vinyl ether/ester	product
1			5		
	<b>4.105</b>	<b>4.113</b>		<b>4.109</b>	<b>4.115</b>
2			6		mess
	<b>4.106</b>	<b>4.113</b>		<b>4.110</b>	
3			7		mess
	<b>4.107</b>	<b>4.113</b>		<b>4.111</b>	
4			8		mess
	<b>4.108</b>	<b>4.114</b>		<b>4.112</b>	

## 4.4 Conclusions

In summary, to the best of our knowledge, we have developed the first regio- and enantioselectivity formal hydroamination of enamines. This method allowed direct access to the 1,2-dialkylamines motifs with moderate to excellent yields and high level of enantioselectivities from readily available starting materials. However, the application of this method to a broader range of enamine substrates was limited due to the instability of these compound. We then developed a one-pot procedure for the formal hydroamination using an in-situ formation of enamines. Although relatively lower yields were obtained in all cases, the high level of enantioselectivities remained and the operation procedure was simplified by avoiding the purification of enamines. In the end, attempts to utilize this method for the synthesis of 1,2-amino alcohol was unsuccessful due to the  $\beta$ -elimination of a Cu(I) alkoxide intermediate.



## 5. Concluding remarks

This thesis deals with the development of new methodology for the synthesis three kinds of *N*-containing compounds, which are  $\alpha$ -keto amides,  $\alpha$ -amino- $\beta$ -hydroxy ester, and 1,2-dialkyl amines. Furthermore, the ATH/DKR protocol for the stereoselective synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters was utilized as a key step for the total synthesis of polyhydroxylated pyrrolizidine alkaloid natural products.

More specifically, a mild procedure for the  $\alpha$ -oxidation of  $\alpha$ -keto amines to give the corresponding  $\alpha$ -keto amides was developed. This method was catalyzed by pyrrolidine and TEMPO, gave moderate to good yields. It was believed that the reaction proceeds through an enamine intermediate that is subsequently oxidized by TEMPO or O<sub>2</sub>. In addition, this method can also be applied to the synthesis of  $\alpha$ -keto thioamides and  $\alpha$ -keto amidines using sulfur and nitrosobenzene as oxidant.

In the second part of the thesis the focus was shifted to the stereoselective synthesis of  $\alpha$ -amino- $\beta$ -hydroxy ester structural motif containing vicinal stereocenters. Based on our previous work, we extended this ATH/DKR protocol to the straightforward synthesis of *anti*-3-alkenyl-2-amido-3-hydroxy esters from the corresponding racemic 3-alkenyl-2-amido-3-keto ester. This method gave moderate to excellent yields, diastereoselectivities and enantioselectivities for a broad range of substrates. In order to highlight the versatility of the methodology, it was applied in an asymmetric total synthesis of the polyhydroxylated pyrrolizidine alkaloid (+)-alexine.

Finally, we developed the first example of the formal hydroamination of electron-rich enamines substrates. This method provided a straightforward and efficient approach for the synthesis of chiral 1,2-dialkyl amines in good yields with high levels of enantioselectivities for a broad range of substrate. In order to simplify the procedure and extending it to a broader substrate range, we developed a one-pot procedure for the formal hydroamination using enamines formed in situ, from the condensation between aldehydes and secondary amines. Unfortunately, formal

hydroamination of vinyl ethers failed to give the desired 1,2-amino alcohol product due to the  $\beta$ -elimination of a Cu(I) alkoxide intermediate.

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# Appendix

## Experimental procedures and NMR data for unpublished compounds

### Compound **2.29**<sup>173</sup>

Pyrrolidine (123  $\mu$ L, 1.5 mmol) was added to a solution of  $\alpha$ -keto-amine **2.28** (0.3 mmol) and TEMPO (4.7 mg, 0.03 mmol) in MeCN (1 mL) under O<sub>2</sub> (balloon pressure) atmosphere. The reaction mixture was then stirred at 50 °C for 20h and the product was monitored by TLC. The reaction mixture was then concentrated and purified by column chromatography (n-heptane/EtOAc 100/20) to afford the corresponding product **2.29** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.50 (s, 1H), 7.48 – 7.39 (m, 2H), 7.34 – 7.26 (m, 1H), 7.23 – 7.15 (m, 2H), 3.35 (d,  $J$  = 0.6 Hz, 3H).

### Compound **3.77**

A mixture of 10% Pd/C (35 mg, 0.033 mmol, 0.1 eq) and **3.48** (107 mg, 0.33 mmol, 1 eq) were dissolved in EtOH (1.4 mL) and EtOAc (2.1 mL) mixed solvent, such mixture was then stirred at room temperature under H<sub>2</sub> atmosphere (1 atm) for 6 h. The mixture was filtered through Celite, and filtrate was concentrated under reduced pressure to yield the crude product **3.76**. The above crude product **3.76** and triphosgene (17 mg, 0.5 mmol, 1.5 eq) was dissolved in CH<sub>2</sub>Cl<sub>2</sub>. Then, iPr<sub>2</sub>NEt was added dropwise at 0 °C and then stirred an additional 1 h at room temperature. The reaction was quenched with saturated NaHCO<sub>3</sub> and the aqueous phase was extracted two times with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated and then subject to flash chromatography (heptane/EtOAc 50/50) to yield the desired product **3.77** (22 mg, 33%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.27 (s, 1H), 4.86 (ddd,  $J$  = 10.6, 8.4, 3.2 Hz, 1H), 4.41 (d,  $J$  = 8.4 Hz, 1H), 3.82 (s, 3H), 1.89 (dddd,  $J$  = 13.6, 6.7, 4.8, 2.4 Hz, 1H), 1.54 (ddd,  $J$  = 14.1, 10.7, 4.9 Hz, 1H), 1.46 – 1.29 (m, 1H), 0.97 (dd,  $J$  = 6.7, 4.1 Hz, 7H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  169.8, 159.3, 58.3, 52.6, 39.1, 24.8, 23.3, 21.4.

### Compound **4.60** and **4.62**

To a screw-capped reaction tube was CuI (0.21 g, 1.12 mmol, 0.1 eq), 9H-carbazole (2.25 g, 13.50 mmol, 1.2 eq) and K<sub>3</sub>PO<sub>4</sub> (4.70 g, 22.48 mmol, 2

eq). The reaction tube was then evacuated and backfilled with N<sub>2</sub> for three times. Vinyl bromide (1.36g, 11.24 mmol, 1eq), ethylenediamine (0.15 mL, 2.25mmol, 0.2 eq) and 1,4-dioxane (1.0 mL) were then added by syringe at room temperature. The reaction tube was then sealed by a screw with a Teflon-lined septum, and the reaction mixture was stirred at 110 °C overnight. The reaction mixture was concentrated and then directly purified by column chromatography (Haptane/EtOAc) to yield the desired product.

#### **4.60**<sup>174</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (dq, *J* = 7.8, 0.9 Hz, 2H), 7.56 – 7.40 (m, 4H), 7.34 – 7.22 (m, 2H), 5.61 (q, *J* = 1.3 Hz, 1H), 5.38 (s, 1H), 2.26 (dd, *J* = 1.3, 0.7 Hz, 3H).

#### **4.62**<sup>174</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.14 (dd, *J* = 8.0, 2.5 Hz, 2H), 7.82 – 7.70 (m, 3H), 7.61 – 7.50 (m, 4H), 7.45 (td, *J* = 7.7, 3.6 Hz, 2H), 7.34 (qd, *J* = 7.1, 2.6 Hz, 3H), 7.11 (dd, *J* = 14.5, 1.9 Hz, 1H).

#### Compound **4.81a**<sup>171</sup>

Molecular sieves (4 Å, 1.1 g) were added to a solution of diphenylacetaldehyde (2 mL, 11.3 mmol, 1 eq) in dry CHCl<sub>3</sub> (15 mL) at room temperature. The solution was cooled to 0 °C, then the pyrrolidine (1.4 mL, 16.9 mmol, 1.5 eq) was added and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then filtered and concentrated under reduced pressure to obtain the pure enamine **4.81a**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 – 7.24 (m, 4H), 7.24 – 7.17 (m, 3H), 7.16 – 7.10 (m, 2H), 7.10 – 7.04 (m, 1H), 6.66 (s, 1H), 3.07 – 2.95 (m, 4H), 1.79 – 1.72 (m, 4H).

#### Compound **4.82a**<sup>175,176</sup>

In a three necked flask, 2-indanone (3 g, 22.7 mmol, 1 eq) was dissolved in dry toluene (20 mL) at room temperature under N<sub>2</sub> atmosphere. Morpholine (4 mL, 45.5 mmol, 2 eq) was then added in one portion, and the reaction system was stirred at 90 °C overnight. The reaction mixture was then filtered and concentrated under reduced pressure to obtain the pure enamine **4.82a** as brown solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33 – 7.21 (m, 1H), 7.13 (dd, *J* = 26.1, 7.5 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 5.60 (s, 1H), 3.84 (t, *J* = 4.9 Hz, 4H), 3.42 (s, 2H), 3.16 (t, *J* = 4.9 Hz, 4H).

Compound **4.92a**<sup>163</sup>

White solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.00 – 7.83 (m, 2H), 7.55 – 7.40 (m, 2H), 7.38 – 7.23 (m, 5H), 7.23 – 7.15 (m, 2H), 7.08 (tt, *J* = 7.2, 1.2 Hz, 1H), 6.69 – 6.60 (m, 2H), 4.77 (s, 2H), 3.43 (q, *J* = 7.1 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H).

Compound **4.93a**<sup>144</sup>

Yellowish solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.03 (t, *J* = 6.4 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.48 – 7.42 (m, 2H), 7.41 – 7.30 (m, 3H), 6.67 – 6.58 (m, 2H), 4.24 (d, *J* = 6.4 Hz, 2H), 3.43 (q, *J* = 7.1 Hz, 4H), 1.21 (t, *J* = 7.1 Hz, 6H).

Compound **4.104**

Colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.47 – 7.42 (m, 5H), 7.41 – 7.37 (m, 2H), 7.36 – 7.30 (m, 6H), 7.28 – 7.22 (m, 2H), 3.97 (t, *J* = 7.0 Hz, 1H), 3.83 (d, *J* = 13.8 Hz, 2H), 3.33 (d, *J* = 13.8 Hz, 2H), 3.12 (d, *J* = 7.1 Hz, 2H), 2.47 (s, 4H), 1.85 – 1.60 (m, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 140.3, 129.0, 128.8, 128.2, 128.0, 127.1, 126.8, 60.1, 57.4, 54.4, 53.9, 23.5.

Compound **4.111**<sup>177</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.89 (d, *J* = 12.8 Hz, 1H), 7.39 – 7.30 (m, 4H), 7.30 – 7.22 (m, 1H), 6.43 (d, *J* = 12.8 Hz, 1H), 2.22 (s, 3H).

Compound **4.112**<sup>178</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58 – 7.46 (m, 2H), 7.43 – 7.31 (m, 3H), 5.51 (d, *J* = 2.2 Hz, 1H), 5.06 (d, *J* = 2.2 Hz, 1H), 2.31 (s, 3H).

Compound **4.113**<sup>179</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 (d, *J* = 7.1 Hz, 4H), 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 2H), 3.61 (s, 4H), 2.54 (q, *J* = 7.1 Hz, 2H), 1.11 (t, *J* = 7.1 Hz, 3H).

Compound **4.114**<sup>180</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.41 (t, *J* = 6.3 Hz, 4H), 7.35 (q, *J* = 7.7, 7.1 Hz, 4H), 7.29 – 7.23 (m, 2H), 3.60 (s, 4H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.56 (p, *J* = 7.4 Hz, 2H), 0.89 (t, *J* = 7.4 Hz, 3H).

Compound **4.115**<sup>139</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.63 – 7.25 (m, 15H), 4.10 (q, *J* = 6.9 Hz, 1H), 3.78 (d, *J* = 13.8 Hz, 2H), 3.64 (d, *J* = 13.8 Hz, 2H), 1.59 (d, *J* = 7.0 Hz, 3H).





# References

- (1) Wöhler, F. Ueber künstliche Bildung des Harnstoffs. *Annalen der Physik* **1828**, 88, 253.
- (2) Yeh, B. J.; Lim, W. A. Synthetic biology: lessons from the history of synthetic organic chemistry. *Nature Chemical Biology* **2007**, 3, 521.
- (3) Nicolaou, K. C. Organic synthesis: the art and science of replicating the molecules of living nature and creating others like them in the laboratory. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences* **2014**, 470 (2163), 20130690.
- (4) Corey, E. J. Robert Robinson Lecture. Retrosynthetic thinking-essentials and examples. *Chem. Soc. Rev.* **1988**, 17 (0), 111.
- (5) Law, J.; Zsoldos, Z.; Simon, A.; Reid, D.; Liu, Y.; Khew, S. Y.; Johnson, A. P.; Major, S.; Wade, R. A.; Ando, H. Y. Route Designer: A Retrosynthetic Analysis Tool Utilizing Automated Retrosynthetic Rule Generation. *Journal of Chemical Information and Modeling* **2009**, 49 (3), 593.
- (6) Trost, B. M. Atom Economy-A Challenge for Organic Synthesis: Homogeneous Catalysis Leads the Way. *Angew. Chem. Int. Ed. Engl.* **1995**, 34 (3), 259.
- (7) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009**, 38 (11), 3010.
- (8) Lawrence, S. A. Amines: Synthesis, properties and applications. *Cambridge University Press, Cambridge* **2004**.
- (9) Ricci, A. Amino group chemistry: from synthesis to the life Science. *Wiley-VCH, Weinheim* **2008**.
- (10) Liu, J.-K. N-Containing Compounds of Macromycetes. *Chem. Rev.* **2005**, 105 (7), 2723.
- (11) Liang, Y.; Liang, Y.-F.; Jiao, N. Cu- or Fe-catalyzed C-H/C-C bond nitrogenation reactions for the direct synthesis of N-containing compounds. *Org. Chem. Front.* **2015**, 2 (4), 403.
- (12) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, 57 (24), 10257.
- (13) Jiao, N. Nitrogenation Strategy for the Synthesis of N-containing Compounds. *Springer* **2017**.
- (14) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M.; Taga, T. Structure of FK506, a novel

- immunosuppressant isolated from *Streptomyces*. *J. Am. Chem. Soc.* **1987**, *109* (16), 5031.
- (15) Slee, D. H.; Laslo, K. L.; Elder, J. H.; Ollmann, I. R.; Gustchina, A.; Kervinen, J.; Zdanov, A.; Wlodawer, A.; Wong, C.-H. Selectivity in the Inhibition of HIV and FIV Protease: Inhibitory and Mechanistic Studies of Pyrrolidine-Containing  $\alpha$ -Keto Amide and Hydroxyethylamine Core Structures. *J. Am. Chem. Soc.* **1995**, *117* (48), 11867.
  - (16) Mandadapu, S. R.; Weerawarna, P. M.; Gunnam, M. R.; Alliston, K. R.; Lushington, G. H.; Kim, Y.; Chang, K.-O.; Groutas, W. C. Potent inhibition of norovirus 3CL protease by peptidyl  $\alpha$ -ketoamides and  $\alpha$ -ketoheterocycles. *Bioorg. Med. Chem. Lett.* **2012**, *22* (14), 4820.
  - (17) De Risi, C.; Pollini, G. P.; Zanirato, V. Recent Developments in General Methodologies for the Synthesis of  $\alpha$ -Ketoamides. *Chem. Rev.* **2016**, *116* (5), 3241.
  - (18) Baslé, O.; Raimondi, W.; Duque, M. d. M. S.; Bonne, D.; Constantieux, T.; Rodriguez, J. Highly Diastereo- and Enantioselective Organocatalytic Michael Addition of  $\alpha$ -Ketoamides to Nitroalkenes. *Org. Lett.* **2010**, *12* (22), 5246.
  - (19) Sun, Z.; Liu, H.; Zeng, Y.-M.; Lu, C.-D.; Xu, Y.-J. Silyllithium-Initiated Coupling of  $\alpha$ -Ketoamides with *tert*-Butanesulfinylimines for Stereoselective Synthesis of Enantioenriched  $\alpha$ -(Silyloxy)- $\beta$ -amino Amides. *Org. Lett.* **2016**, *18* (3), 620.
  - (20) Kumar, D.; Vemula, S. R.; Cook, G. R. Recent Advances in the Catalytic Synthesis of  $\alpha$ -Ketoamides. *ACS Catalysis* **2016**, *6* (8), 4920.
  - (21) Nicolaou, K. C.; Boddy, C. N. C.; Bräse, S.; Winssinger, N. Chemistry, Biology, and Medicine of the Glycopeptide Antibiotics. *Angew. Chem. Int. Ed.* **1999**, *38* (15), 2096.
  - (22) Hamada, Y.; Shioiri, T. Recent Progress of the Synthetic Studies of Biologically Active Marine Cyclic Peptides and Depsipeptides. *Chem. Rev.* **2005**, *105* (12), 4441.
  - (23) Gilles, P.; Py, S.  $\text{SmI}_2$ -Mediated Cross-Coupling of Nitrones with  $\beta$ -Silyl Acrylates: Synthesis of (+)-Australine. *Org. Lett.* **2012**, *14* (4), 1042.
  - (24) Mulzer, J.; Dehmlow, H.; Buschmann, J.; Luger, P. Stereocontrolled total synthesis of the unnatural enantiomers of castanospermine and 1-epi-castanospermine. *J. Org. Chem.* **1992**, *57* (11), 3194.
  - (25) Saul, R.; Ghidoni, J. J.; Molyneux, R. J.; Elbein, A. D. Castanospermine inhibits alpha-glucosidase activities and alters glycogen distribution in animals. *Proceedings of the National Academy of Sciences* **1985**, *82* (1), 93.
  - (26) Misner, J. W.; Fisher, J. W.; Gardner, J. P.; Pedersen, S. W.; Trinkle, K. L.; Jackson, B. G.; Zhang, T. Y. Enantioselective synthesis of the carbacephem antibiotic loracarbef via Mitsunobu and Dieckmann cyclization from an unnatural amino acid. *Tetrahedron Lett.* **2003**, *44* (32), 5991.

- (27) Reetz, M. T. New Approaches to the Use of Amino Acids as Chiral Building Blocks in Organic Synthesis [New Synthetic Methods (85)]. *Angew. Chem. Int. Ed. Engl.* **1991**, 30 (12), 1531.
- (28) Echeverria, P.-G.; Prévost, S.; Cornil, J.; Férard, C.; Reymond, S.; Guérinot, A.; Cossy, J.; Ratovelomanana-Vidal, V.; Phansavath, P. Synthetic Strategy toward the C44-C65 Fragment of Mirabalin. *Org. Lett.* **2014**, 16 (9), 2390.
- (29) Nájera, C.; Sansano, J. M. Catalytic Asymmetric Synthesis of  $\alpha$ -Amino Acids. *Chem. Rev.* **2007**, 107 (11), 4584.
- (30) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. Development of Highly Diastereo- and Enantioselective Direct Asymmetric Aldol Reaction of a Glycinate Schiff Base with Aldehydes Catalyzed by Chiral Quaternary Ammonium Salts. *J. Am. Chem. Soc.* **2004**, 126 (31), 9685.
- (31) Masse, C. E.; Morgan, A. J.; Panek, J. S. An Asymmetric Aminohydroxylation Approach to the Azepine Core of (-)-Balanol. *Org. Lett.* **2000**, 2 (17), 2571.
- (32) Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P. Enantioselective Synthesis of *anti*- $\beta$ -Hydroxy- $\alpha$ -amido Esters via Transfer Hydrogenation. *Org. Lett.* **2010**, 12 (22), 5274.
- (33) Makino, K.; Hiroki, Y.; Hamada, Y. Dynamic Kinetic Resolution Catalyzed by Ir Axially Chiral Phosphine Catalyst: Asymmetric Synthesis of anti Aromatic  $\beta$ -Hydroxy- $\alpha$ -amino Acid Esters. *J. Am. Chem. Soc.* **2005**, 127 (16), 5784.
- (34) Lucet, D.; Le Gall, T.; Mioskowski, C. The Chemistry of Vicinal Diamines. *Angew. Chem. Int. Ed.* **1998**, 37 (19), 2580.
- (35) Viso, A.; Fernández de la Pradilla, R.; Tortosa, M.; García, A.; Flores, A. Update 1 of:  $\alpha,\beta$ -Diamino Acids: Biological Significance and Synthetic Approaches. *Chem. Rev.* **2011**, 111 (2), PR1.
- (36) Galm, U.; Hager, M. H.; Van Lanen, S. G.; Ju, J.; Thorson, J. S.; Shen, B. Antitumor Antibiotics: Bleomycin, Eneidyne, and Mitomycin. *Chem. Rev.* **2005**, 105 (2), 739.
- (37) Kizirian, J.-C. Chiral Tertiary Diamines in Asymmetric Synthesis. *Chem. Rev.* **2008**, 108 (1), 140.
- (38) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. Catalytic Diamination of Olefins via N-N Bond Activation. *Acc. Chem. Res.* **2014**, 47 (12), 3665.
- (39) Röben, C.; Souto, J. A.; González, Y.; Lishchynskiy, A.; Muñiz, K. Enantioselective Metal-Free Diamination of Styrenes. *Angew. Chem. Int. Ed.* **2011**, 50 (40), 9478.
- (40) Chai, Z.; Yang, P.-J.; Zhang, H.; Wang, S.; Yang, G. Synthesis of Chiral Vicinal Diamines by Silver(I)-Catalyzed Enantioselective Aminolysis of N-Tosylaziridines. *Angew. Chem. Int. Ed.* **2017**, 56 (2), 650.
- (41) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. A Catalytic Tethering Strategy: Simple Aldehydes Catalyze

- Intermolecular Alkene Hydroaminations. *J. Am. Chem. Soc.* **2011**, *133* (50), 20100.
- (42) Venable, E. P.; Kennemur, J. L.; Joyce, L. A.; Ruck, R. T.; Schultz, D. M.; Hull, K. L. Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines. *J. Am. Chem. Soc.* **2019**, *141* (2), 739.
- (43) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. Stereocontrolled Synthesis of Vicinal Diamines by Organocatalytic Asymmetric Mannich Reaction of N-Protected Aminoacetaldehydes: Formal Synthesis of (-)-Agelastatin A. *J. Am. Chem. Soc.* **2012**, *134* (17), 7516.
- (44) Yamada, K.-i.; Harwood, S. J.; Gröger, H.; Shibasaki, M. The First Catalytic Asymmetric Nitro-Mannich-Type Reaction Promoted by a New Heterobimetallic Complex. *Angew. Chem. Int. Ed.* **1999**, *38* (23), 3504.
- (45) Shao, X.; Li, K.; Malcolmson, S. J. Enantioselective Synthesis of *anti*-1,2-Diamines by Cu-Catalyzed Reductive Couplings of Azadienes with Aldimines and Ketimines. *J. Am. Chem. Soc.* **2018**, *140* (23), 7083.
- (46) Tang, R.-Y.; Guo, X.-K.; Xiang, J.-N.; Li, J.-H. Palladium-Catalyzed Synthesis of 3-Acylated Indoles Involving Oxidative Cross-Coupling of Indoles with  $\alpha$ -Amino Carbonyl Compounds. *J. Org. Chem.* **2013**, *78* (22), 11163.
- (47) Majji, G.; Rajamanickam, S.; Khatun, N.; Santra, S. K.; Patel, B. K. Generation of bis-Acyl Ketals from Esters and Benzyl Amines Under Oxidative Conditions. *J. Org. Chem.* **2015**, *80* (7), 3440.
- (48) Li, L.; Wang, Q.; Liu, P.; Meng, H.; Kan, X.-L.; Liu, Q.; Zhao, Y.-L. DBU-mediated metal-free oxidative cyanation of  $\alpha$ -amino carbonyl compounds: using molecular oxygen as the oxidant. *Org. Biomol. Chem.* **2016**, *14* (1), 165.
- (49) Soheili, A.; Tambar, U. K. Tandem Catalytic Allylic Amination and [2,3]-Stevens Rearrangement of Tertiary Amines. *J. Am. Chem. Soc.* **2011**, *133* (33), 12956.
- (50) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Asymmetric Enamine Catalysis. *Chem. Rev.* **2007**, *107* (12), 5471.
- (51) List, B. Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res.* **2004**, *37* (8), 548.
- (52) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122* (10), 2395.
- (53) Notz, W.; List, B. Catalytic Asymmetric Synthesis of *anti*-1,2-Diols. *J. Am. Chem. Soc.* **2000**, *122* (30), 7386.
- (54) List, B. The Direct Catalytic Asymmetric Three-Component Mannich Reaction. *J. Am. Chem. Soc.* **2000**, *122* (38), 9336.
- (55) List, B.; Pojarliev, P.; Martin, H. J. Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins. *Org. Lett.* **2001**, *3* (16), 2423.

- (56) List, B. Direct Catalytic Asymmetric  $\alpha$ -Amination of Aldehydes. *J. Am. Chem. Soc.* **2002**, *124* (20), 5656.
- (57) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. The Direct and Enantioselective Organocatalytic  $\alpha$ -Oxidation of Aldehydes. *J. Am. Chem. Soc.* **2003**, *125* (36), 10808.
- (58) Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. Direct Asymmetric Hydroxyamination Reaction Catalyzed by an Axially Chiral Secondary Amine Catalyst. *J. Am. Chem. Soc.* **2006**, *128* (18), 6046.
- (59) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahim, I.; Casas, J. The Direct Amino Acid-Catalyzed Asymmetric Incorporation of Molecular Oxygen to Organic Compounds. *J. Am. Chem. Soc.* **2004**, *126* (29), 8914.
- (60) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. Organocatalytic asymmetric  $\alpha$ -bromination of aldehydes and ketones. *Chem. Commun.* **2005**, , 4821.
- (61) Kano, T.; Mii, H.; Maruoka, K. Direct Asymmetric Benzoyloxylation of Aldehydes Catalyzed by 2-Tritylpyrrolidine. *J. Am. Chem. Soc.* **2009**, *131* (10), 3450.
- (62) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. Enantioselective Organocatalyzed  $\alpha$  Sulfenylation of Aldehydes. *Angew. Chem. Int. Ed.* **2005**, *44* (5), 794.
- (63) Sibi, M. P.; Hasegawa, M. Organocatalysis in Radical Chemistry. Enantioselective  $\alpha$ -Oxyamination of Aldehydes. *J. Am. Chem. Soc.* **2007**, *129* (14), 4124.
- (64) Kano, T.; Mii, H.; Maruoka, K. Metal-Free Direct Asymmetric Aminooxylation of Aldehydes Catalyzed by a Binaphthyl-Based Chiral Amine. *Angew. Chem. Int. Ed.* **2010**, *49* (37), 6638.
- (65) Sudarshan K. Malhotra, J. J. H., and Ann F. Lundin. Autoxidation of Enamines and Schiff Bases of  $\alpha,\beta$ -Unsaturated Ketones. A New Synthesis of Unsaturated 1,4-Diones. *J. Am. Chem. Soc.* **1968**, *90* (23), 6565.
- (66) Martinez-Ariza, G.; McConnell, N.; Hulme, C. One-Pot Two-Step Multicomponent Process of Indole and Other Nitrogenous Heterocycles or Amines toward  $\alpha$ -Oxo-acetamidines. *Org. Lett.* **2016**, *18* (8), 1864.
- (67) Gan, L.; Gao, Y.; Wei, L.; Wan, J.-P. Synthesis of  $\alpha$ -Keto Thioamides by Metal-Free C=C Bond Cleavage in Enaminones Using Elemental Sulfur. *J. Org. Chem.* **2019**, *84* (2), 1064.
- (68) Li, H.-Z.; Xue, W.-J.; Wu, A.-X. Direct synthesis of  $\alpha$ -ketothioamides from aryl methyl ketones and amines via  $I_2$ -promoted  $sp^3$  C-H functionalization. *Tetrahedron* **2014**, *70* (31), 4645.
- (69) Tebben, L.; Studer, A. Nitroxides: Applications in Synthesis and in Polymer Chemistry. *Angew. Chem. Int. Ed.* **2011**, *50* (22), 5034.
- (70) Cao, Q.; Dornan, L. M.; Rogan, L.; Hughes, N. L.; Muldoon, M. J. Aerobic oxidation catalysis with stable radicals. *Chem. Commun.* **2014**, *50* (35), 4524.

- (71) De Sarkar, S.; Studer, A. NHC-Catalyzed Michael Addition to  $\alpha,\beta$ -Unsaturated Aldehydes by Redox Activation. *Angew. Chem. Int. Ed.* **2010**, *49* (48), 9266.
- (72) Kornblum, N.; DeLaMare, H. E. The Base Catalyzed Decomposition of a Dialkyl Peroxide. *J. Am. Chem. Soc.* **1951**, *73* (2), 880.
- (73) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. Iridium Phosphite-Oxazoline Catalysts for the Highly Enantioselective Hydrogenation of Terminal Alkenes. *J. Am. Chem. Soc.* **2009**, *131* (34), 12344.
- (74) Woodmansee, D. H.; Pfaltz, A. Asymmetric hydrogenation of alkenes lacking coordinating groups. *Chem. Commun.* **2011**, *47* (28), 7912.
- (75) Noyori, R.; Ohkuma, T. Asymmetric Catalysis by Architectural and Functional Molecular Engineering: Practical Chemo- and Stereoselective Hydrogenation of Ketones. *Angew. Chem. Int. Ed.* **2001**, *40* (1), 40.
- (76) Xie, J.-H.; Liu, X.-Y.; Xie, J.-B.; Wang, L.-X.; Zhou, Q.-L. An Additional Coordination Group Leads to Extremely Efficient Chiral Iridium Catalysts for Asymmetric Hydrogenation of Ketones. *Angew. Chem. Int. Ed.* **2011**, *50* (32), 7329.
- (77) Meemken, F.; Baiker, A. Recent Progress in Heterogeneous Asymmetric Hydrogenation of C=O and C=C Bonds on Supported Noble Metal Catalysts. *Chem. Rev.* **2017**, *117* (17), 11522.
- (78) Zhu, S.-F.; Xie, J.-B.; Zhang, Y.-Z.; Li, S.; Zhou, Q.-L. Well-Defined Chiral Spiro Iridium/Phosphine-Oxazoline Cationic Complexes for Highly Enantioselective Hydrogenation of Imines at Ambient Pressure. *J. Am. Chem. Soc.* **2006**, *128* (39), 12886.
- (79) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Transition Metal-Catalyzed Enantioselective Hydrogenation of Enamines and Imines. *Chem. Rev.* **2011**, *111* (3), 1713.
- (80) Noyori, R. Asymmetric Catalysis: Science and Opportunities (Nobel Lecture). *Angew. Chem. Int. Ed.* **2002**, *41* (12), 2008.
- (81) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. Asymmetric synthesis of isoquinoline alkaloids by homogeneous catalysis. *J. Am. Chem. Soc.* **1986**, *108* (22), 7117.
- (82) Ohta, T.; Takaya, H.; Noyori, R. Bis(diarylphosphino)-1,1 binaphthyl (BINAP)-ruthenium(II) dicarboxylate complexes: new, highly efficient catalysts for asymmetric hydrogenations. *Inorg. Chem.* **1988**, *27* (3), 566.
- (83) Kitamura, M.; Tokunaga, M.; Noyori, R. Practical synthesis of BINAP-ruthenium(II) dicarboxylate complexes. *J. Org. Chem.* **1992**, *57* (14), 4053.
- (84) Mashima, K.; Kusano, K.-h.; Sato, N.; Matsumura, Y.-i.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T. Cationic BINAP-Ru(II) Halide Complexes: Highly Efficient Catalysts for Stereoselective Asymmetric Hydrogenation of  $\alpha$ - and  $\beta$ -Functionalized Ketones. *J. Org. Chem.* **1994**, *59* (11), 3064.

- (85) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. Homogeneous asymmetric hydrogenation of functionalized ketones. *J. Am. Chem. Soc.* **1988**, *110* (2), 629.
- (86) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. Practical Enantioselective Hydrogenation of Aromatic Ketones. *J. Am. Chem. Soc.* **1995**, *117* (9), 2675.
- (87) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. Preferential hydrogenation of aldehydes and ketones. *J. Am. Chem. Soc.* **1995**, *117* (41), 10417.
- (88) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. Asymmetric hydrogenation of  $\beta$ -keto carboxylic esters. A practical, purely chemical access to  $\beta$ -hydroxy esters in high enantiomeric purity. *J. Am. Chem. Soc.* **1987**, *109* (19), 5856.
- (89) Mashima, K.; Kusano, K.-H.; Ohta, T.; Noyori, R.; Takaya, H. Synthesis of new cationic BINAP-ruthenium(II) complexes and their use in asymmetric hydrogenation. *J. Chem. Soc., Chem. Commun.* **1989**, 1208.
- (90) Wang, D.; Astruc, D. The Golden Age of Transfer Hydrogenation. *Chem. Rev.* **2015**, *115* (13), 6621.
- (91) Noyori, R.; Hashiguchi, S. Asymmetric Transfer Hydrogenation Catalyzed by Chiral Ruthenium Complexes. *Acc. Chem. Res.* **1997**, *30* (2), 97.
- (92) Palmer, M. J.; Wills, M. Asymmetric transfer hydrogenation of C=O and C=N bonds. *Tetrahedron: Asymmetry* **1999**, *10* (11), 2045.
- (93) Ikariya, T.; Blacker, A. J. Asymmetric Transfer Hydrogenation of Ketones with Bifunctional Transition Metal-Based Molecular Catalysts. *Acc. Chem. Res.* **2007**, *40* (12), 1300.
- (94) Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. Kinetic Resolution of Racemic Secondary Alcohols by RuII-Catalyzed Hydrogen Transfer. *Angew. Chem. Int. Ed. Engl.* **1997**, *36* (3), 288.
- (95) Koike, T.; Ikariya, T. Mechanistic Aspects of Formation of Chiral Ruthenium Hydride Complexes from 16-Electron Ruthenium Amide Complexes and Formic Acid: Facile Reversible Decarboxylation and Carboxylation. *Adv. Synth. Catal.* **2004**, *346* (1), 37.
- (96) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T. et al. Stereoselective hydrogenation via dynamic kinetic resolution. *J. Am. Chem. Soc.* **1989**, *111* (25), 9134.
- (97) Ryoji, N.; Makoto, T.; Masato, K. Stereoselective Organic Synthesis via Dynamic Kinetic Resolution. *Bull. Chem. Soc. Jpn.* **1995**, *68* (1), 36.
- (98) Mordant, C.; Dünkelfmann, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. A Versatile Route to *syn*- and *anti*- $\alpha$ -Amino- $\beta$ -Hydroxy Esters from  $\beta$ -Keto Esters by Dynamic Kinetic Resolution with Ru-Synphos Catalyst. *Eur. J. Org. Chem.* **2004**, *2004* (14), 3017.

- (99) Lu, B.; Wu, X.; Li, C.; Ding, G.; Li, W.; Xie, X.; Zhang, Z. Highly Diastereo- and Enantioselective Access to *syn*- $\alpha$ -Amido- $\beta$ -Hydroxy Esters via Ruthenium-Catalyzed Dynamic Kinetic Resolution-Asymmetric Hydrogenation. *J. Org. Chem.* **2019**, *84* (6), 3201.
- (100) Mohar, B.; Valleix, A.; Desmurs, J.-R.; Felemez, M.; Wagner, A.; Mioskowski, C. Highly enantioselective synthesis via dynamic kinetic resolution under transfer hydrogenation using Ru( $\eta^6$ -arene)-N-perfluorosulfonyl-1,2-diamine catalysts: a first insight into the relationship of the ligand's pKa and the catalyst activity. *Chem. Commun.* **2001**, 2572.
- (101) Bourdon, L. H.; Fairfax, D. J.; Martin, G. S.; Mathison, C. J.; Zhichkin, P. An enantioselective synthesis of nitrogen protected 3-arylserine esters. *Tetrahedron: Asymmetry* **2004**, *15* (22), 3485.
- (102) Sun, G.; Zhou, Z.; Luo, Z.; Wang, H.; Chen, L.; Xu, Y.; Li, S.; Jian, W.; Zeng, J.; Hu, B. et al. Highly Enantioselective Synthesis of *syn*- $\beta$ -Hydroxy  $\alpha$ -Dibenzylamino Esters via DKR Asymmetric Transfer Hydrogenation and Gram-Scale Preparation of Droxidopa. *Org. Lett.* **2017**, *19* (16), 4339.
- (103) Zheng, L.-S.; Ferard, C.; Phansavath, P.; Ratovelomanana-Vidal, V. Rhodium-mediated asymmetric transfer hydrogenation: a diastereo- and enantioselective synthesis of *syn*- $\alpha$ -amido- $\beta$ -hydroxy esters. *Chem. Commun.* **2018**, *54* (3), 283.
- (104) Makino, K.; Goto, T.; Hiroki, Y.; Hamada, Y. Stereoselective Synthesis of *anti*- $\beta$ -Hydroxy- $\alpha$ -amino Acids through Dynamic Kinetic Resolution. *Angew. Chem. Int. Ed.* **2004**, *43* (7), 882.
- (105) Mordant, C.; Dünkelfmann, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. Dynamic kinetic resolution: an efficient route to anti  $\alpha$ -amino- $\beta$ -hydroxy esters via Ru-Synphos catalyzed hydrogenation. *Chem. Commun.* **2004**, 1296.
- (106) Makino, K.; Fujii, T.; Hamada, Y. Rhodium-catalyzed asymmetric hydrogenation through dynamic kinetic resolution: asymmetric synthesis of *anti*- $\beta$ -hydroxy- $\alpha$ -amino acid esters. *Tetrahedron: Asymmetry* **2006**, *17* (4), 481.
- (107) Makino, K.; Iwasaki, M.; Hamada, Y. Enantio- and Diastereoselective Hydrogenation via Dynamic Kinetic Resolution by a Cationic Iridium Complex in the Synthesis of  $\beta$ -Hydroxy- $\alpha$ -amino Acid Esters. *Org. Lett.* **2006**, *8* (20), 4573.
- (108) Hamada, Y.; Koseki, Y.; Fujii, T.; Maeda, T.; Hibino, T.; Makino, K. Catalytic asymmetric hydrogenation of  $\alpha$ -amino- $\beta$ -keto ester hydrochlorides using homogeneous chiral nickel-bisphosphine complexes through DKR. *Chem. Commun.* **2008**, 6206.
- (109) Seashore-Ludlow, B.; Saint-Dizier, F.; Somfai, P. Asymmetric Transfer Hydrogenation Coupled with Dynamic Kinetic Resolution in Water: Synthesis of anti- $\beta$ -Hydroxy- $\alpha$ -amino Acid Derivatives. *Org. Lett.* **2012**, *14* (24), 6334.



- (110) Seashore-Ludlow, B.; Villo, P.; Somfai, P. Enantioselective Synthesis of anti- $\beta$ -Hydroxy- $\alpha$ -Amido Esters by Asymmetric Transfer Hydrogenation in Emulsions. *Chem. Eur. J.* **2012**, *18* (23), 7219.
- (111) Restorp, P.; Somfai, P. Diastereoselective Aldol Additions to  $\alpha$ -Amino- $\beta$ -silyloxy Aldehydes. Divergent Synthesis of Aminodiols. *Org. Lett.* **2005**, *7* (5), 893.
- (112) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. Recent Developments of Transition-State Analogue Glycosidase Inhibitors of Non-Natural Product Origin. *Chem. Rev.* **2002**, *102* (2), 515.
- (113) Robertson, J.; Stevens, K. Pyrrolizidine alkaloids. *Nat. Prod. Rep.* **2014**, *31* (12), 1721.
- (114) Cartigny, D.; Püntener, K.; Ayad, T.; Scalone, M.; Ratovelomanana-Vidal, V. Highly Diastereo- and Enantioselective Synthesis of Monodifferentiated syn-1,2-Diol Derivatives through Asymmetric Transfer Hydrogenation via Dynamic Kinetic Resolution. *Org. Lett.* **2010**, *12* (17), 3788.
- (115) Monnereau, L.; Cartigny, D.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. Efficient Synthesis of Differentiated syn-1,2-Diol Derivatives by Asymmetric Transfer Hydrogenation–Dynamic Kinetic Resolution of  $\alpha$ -Alkoxy-Substituted  $\beta$ -Ketoesters. *Chem. Eur. J.* **2015**, *21* (33), 11799.
- (116) Pearson, W. H.; Hines, J. V. Total Syntheses of (+)-Australine and (–)-7-Epialexine. *J. Org. Chem.* **2000**, *65* (18), 5785.
- (117) Romero, A.; Wong, C.-H. Chemo-Enzymatic Total Synthesis of 3-Epiaustraline, Australine, and 7-Epialexine. *J. Org. Chem.* **2000**, *65* (24), 8264.
- (118) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. Polyhydroxylated pyrrolizidine alkaloids from transannular iodoaminations: application to the asymmetric syntheses of (–)-hyacinthacine A1, (–)-7a-epi-hyacinthacine A1, (–)-hyacinthacine A2, and (–)-1-epi-alexine. *Org. Biomol. Chem.* **2013**, *11* (19), 3187.
- (119) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. Isolation from alexa leiopetala and x-ray crystal structure of alexine, (1r,2r,3r,7s,8s)-3-hydroxymethyl-1,2,7-trihydroxypyrrolizidine [(2r,3r,4r,5s,6s)-2-hydroxymethyl-1-azabicyclo[3.3.0]octan-3,4,6-triol], a unique pyrrolizidine alkaloid. *Tetrahedron Lett.* **1988**, *29* (20), 2487.
- (120) Winchester, B. G. Iminosugars: from botanical curiosities to licensed drugs. *Tetrahedron: Asymmetry* **2009**, *20* (6), 645.
- (121) Yoda, H.; Katoh, H.; Takabe, K. Asymmetric total synthesis of natural pyrrolizidine alkaloid, (+)-alexine. *Tetrahedron Lett.* **2000**, *41* (40), 7661.
- (122) Dressel, M.; Restorp, P.; Somfai, P. Total Synthesis of (+)-Alexine by Utilizing a Highly Stereoselective [3+2] Annulation Reaction of an N-Tosyl- $\alpha$ -Amino Aldehyde and a 1,3-Bis(silyl)propene. *Chem. Eur. J.* **2008**, *14* (10), 3072.

- (123) Takahashi, M.; Maehara, T.; Sengoku, T.; Fujita, N.; Takabe, K.; Yoda, H. New asymmetric strategy for the total synthesis of naturally occurring (+)-alexine and (–)-7-epi-alexine. *Tetrahedron* **2008**, *64* (22), 5254.
- (124) Stanton, G. R.; Johnson, C. N.; Walsh, P. J. Overriding Felkin Control: A General Method for Highly Diastereoselective Chelation-Controlled Additions to  $\alpha$ -Silyloxy Aldehydes. *J. Am. Chem. Soc.* **2010**, *132* (12), 4399.
- (125) Carda, M.; Rodríguez, S.; González, F.; Castillo, E.; Villanueva, A.; Marco, J. A. Stereoselective Synthesis of the Naturally Occurring Lactones (–)-Osmundalactone and (–)-Muricatacine Using Ring-Closing Metathesis. *Eur. J. Org. Chem.* **2002**, *2002* (15), 2649.
- (126) Yang, F.; Feng, L.; Wang, N.; Liu, X.; Li, J.; Shen, Y. Practical synthesis of C1–8 fragment of autolytimycin via a chelation-controlled diastereoselective addition of diisopropenylzinc to  $\alpha$ -methoxy aldehyde. *Tetrahedron* **2013**, *69* (45), 9463.
- (127) Adam, W.; Peters, K.; Renz, M. Titanium-Catalyzed Diastereoselective Epoxidations of Ene Diols and Allylic Alcohols with  $\beta$ -Hydroperoxy Alcohols as Novel Oxygen Donors. *J. Org. Chem.* **1997**, *62* (10), 3183.
- (128) Huang, L.; Arndt, M.; Gooßen, K.; Heydt, H.; Gooßen, L. J. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115* (7), 2596.
- (129) Müller, T. E.; Beller, M. Metal-Initiated Amination of Alkenes and Alkynes. *Chem. Rev.* **1998**, *98* (2), 675.
- (130) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **2008**, *108* (9), 3795.
- (131) Schlummer, B.; Hartwig, J. F. Brønsted Acid-Catalyzed Intramolecular Hydroamination of Protected Alkenylamines. Synthesis of Pyrrolidines and Piperidines. *Org. Lett.* **2002**, *4* (9), 1471.
- (132) Dion, I.; Beauchemin, A. M. Asymmetric Brønsted Acid Catalysis Enabling Hydroaminations of Dienes and Allenes. *Angew. Chem. Int. Ed.* **2011**, *50* (36), 8233.
- (133) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. Base-Catalyzed Hydroamination of Olefins: An Environmentally Friendly Route to Amines. *Adv. Synth. Catal.* **2002**, *344* (8), 795.
- (134) Rodríguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. Versatile Indole Synthesis by a 5-endo-dig Cyclization Mediated by Potassium or Cesium Bases. *Angew. Chem. Int. Ed.* **2000**, *39* (14), 2488.
- (135) Ensign, S. C.; Venable, E. P.; Kortman, G. D.; Weir, L. J.; Hull, K. L. Anti-Markovnikov Hydroamination of Homoallylic Amines. *J. Am. Chem. Soc.* **2015**, *137* (43), 13748.
- (136) Kim, S. W.; Wurm, T.; Brito, G. A.; Jung, W.-O.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Hydroamination versus Allylic Amination in Iridium-Catalyzed Reactions of Allylic Acetates with Amines: 1,3-

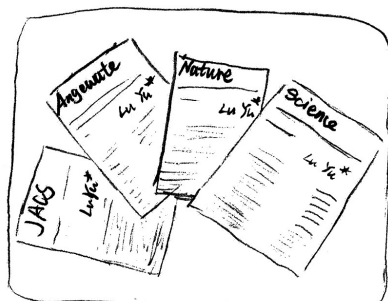
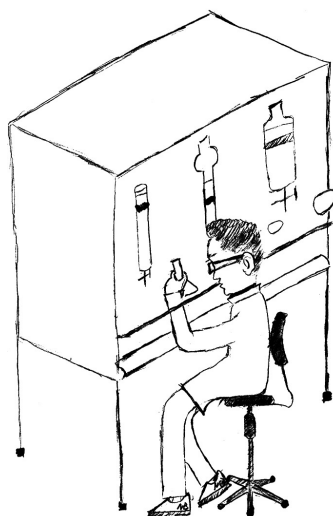
- Aminoalcohols via Ester-Directed Regioselectivity. *J. Am. Chem. Soc.* **2018**, *140* (29), 9087.
- (137) Gooßen, L. J.; Rauhaus, J. E.; Deng, G. Ru-Catalyzed Anti-Markovnikov Addition of Amides to Alkynes: A Regio- and Stereoselective Synthesis of Enamides. *Angew. Chem. Int. Ed.* **2005**, *44* (26), 4042.
- (138) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. Copper-Catalyzed Intermolecular Regioselective Hydroamination of Styrenes with Polymethylhydrosiloxane and Hydroxylamines. *Angew. Chem. Int. Ed.* **2013**, *52* (41), 10830.
- (139) Zhu, S.; Niljianskul, N.; Buchwald, S. L. Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. *J. Am. Chem. Soc.* **2013**, *135* (42), 15746.
- (140) Zhu, S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **2014**, *136* (45), 15913.
- (141) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L. Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. *Science* **2015**, *349* (6243), 62.
- (142) Pirnot, M. T.; Wang, Y. M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem. Int. Ed.* **2016**, *55* (1), 48.
- (143) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L. Copper-catalysed enantioselective stereodivergent synthesis of amino alcohols. *Nature* **2016**, *532*, 353.
- (144) Zhu, S.; Niljianskul, N.; Buchwald, S. L. A direct approach to amines with remote stereocentres by enantioselective CuH-catalysed reductive relay hydroamination. *Nat. Chem.* **2016**, *8*, 144.
- (145) Nootaree, N.; Shaolin, Z.; L., B. S. Enantioselective Synthesis of  $\alpha$ -Aminosilanes by Copper-Catalyzed Hydroamination of Vinylsilanes. *Angew. Chem. Int. Ed.* **2015**, *54* (5), 1638.
- (146) Nishikawa, D.; Hirano, K.; Miura, M. Asymmetric Synthesis of  $\alpha$ -Aminoboronic Acid Derivatives by Copper-Catalyzed Enantioselective Hydroamination. *J. Am. Chem. Soc.* **2015**, *137* (50), 15620.
- (147) Takata, T.; Nishikawa, D.; Hirano, K.; Miura, M. Synthesis of  $\alpha$ -Aminophosphines by Copper-Catalyzed Regioselective Hydroamination of Vinylphosphines. *Chem. Eur. J.* **2018**, *24* (43), 10975.
- (148) Takata, T.; Hirano, K.; Miura, M. Synthesis of  $\alpha$ -Trifluoromethylamines by Cu-Catalyzed Regio- and Enantioselective Hydroamination of 1-Trifluoromethylalkenes. *Org. Lett.* **2019**, *21*, 4284.
- (149) Lardy, S. W.; Schmidt, V. A. Intermolecular Radical Mediated Anti-Markovnikov Alkene Hydroamination Using N-Hydroxyphthalimide. *J. Am. Chem. Soc.* **2018**, *140* (39), 12318.
- (150) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. Retro-Cope eliminations in the synthesis of 1,2,5-oxadiazinanes from allylamines

- and nitrones: a method for the amination of unactivated alkenes. *J. Chem. Soc., Chem. Commun.* **1993**, 169.
- (151) MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts. *Chem. Eur. J.* **2013**, *19* (8), 2597.
  - (152) Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. Regio- and Chemoselective Intermolecular Hydroamination of Allyl Imines for the Synthesis of 1,2-Diamines. *J. Am. Chem. Soc.* **2014**, *136* (32), 11256.
  - (153) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. Rhodium-Catalyzed Anti-Markovnikov Hydroamination of Vinylarenes. *J. Am. Chem. Soc.* **2003**, *125* (19), 5608.
  - (154) Ichikawa, S.; Dai, X.-J.; Buchwald, S. L. Regio- and Enantioselective Synthesis of 1,2-Diamine Derivatives by Copper-Catalyzed Hydroamination. *Org. Lett.* **2019**, *21*, 4370.
  - (155) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. Recent advances in transition metal-catalyzed enantioselective hydrogenation of unprotected enamines. *Chem. Soc. Rev.* **2012**, *41* (11), 4126.
  - (156) Pahadi, N. K.; Tunge, J. A. Catalytic intermolecular hydroamination of vinyl ethers. *Synlett* **2009**, *19*, 3135.
  - (157) Ward, A. F.; Wolfe, J. P. Stereoselective Synthesis of Substituted 1,3-Oxazolidines via Pd-Catalyzed Carboamination Reactions of O-Vinyl-1,2-Amino Alcohols. *Org. Lett.* **2011**, *13* (17), 4728.
  - (158) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. Asymmetric Hydrosilylation of Aryl Ketones Catalyzed by Copper Hydride Complexed by Nonracemic Biphenyl Bis-phosphine Ligands. *J. Am. Chem. Soc.* **2003**, *125* (29), 8779.
  - (159) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. Asymmetric Conjugate Reduction of  $\alpha,\beta$ -Unsaturated Esters Using a Chiral Phosphine-Copper Catalyst. *J. Am. Chem. Soc.* **1999**, *121* (40), 9473.
  - (160) Zhou, Y.; Bandar, J. S.; Buchwald, S. L. Enantioselective CuH-Catalyzed Hydroacylation Employing Unsaturated Carboxylic Acids as Aldehyde Surrogates. *J. Am. Chem. Soc.* **2017**, *139* (24), 8126.
  - (161) Saravanan, P.; Bisai, A.; Baktharaman, S.; Chandrasekhar, M.; Singh, V. K. Synthesis of chiral non-racemic 1,2-diamines from O-acetyl mandelic acid: application in enantioselective deprotonation of epoxides and diethylzinc addition to aldehydes. *Tetrahedron* **2002**, *58* (23), 4693.
  - (162) Niu, D.; Buchwald, S. L. Design of Modified Amine Transfer Reagents Allows the Synthesis of  $\alpha$ -Chiral Secondary Amines via CuH-Catalyzed Hydroamination. *J. Am. Chem. Soc.* **2015**, *137* (30), 9716.
  - (163) Ichikawa, S.; Zhu, S.; Buchwald, S. L. A Modified System for the Synthesis of Enantioenriched N-Arylamines through Copper-Catalyzed Hydroamination. *Angew. Chem. Int. Ed.* **2018**, *130* (28), 8850.

- (164) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L. Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins. *J. Am. Chem. Soc.* **2015**, *137* (46), 14812.
- (165) Tobisch, S. CuH-Catalysed Hydroamination of Styrene with Hydroxylamine Esters: A Coupled Cluster Scrutiny of Mechanistic Pathways. *Chem. Eur. J.* **2016**, *22* (24), 8290.
- (166) Thomas, A. A.; Speck, K.; Kevlishvili, I.; Lu, Z.; Liu, P.; Buchwald, S. L. Mechanistically Guided Design of Ligands That Significantly Improve the Efficiency of CuH-Catalyzed Hydroamination Reactions. *J. Am. Chem. Soc.* **2018**, *140* (42), 13976.
- (167) Xu-Xu, Q.-F.; Liu, Q.-Q.; Zhang, X.; You, S.-L. Copper-Catalyzed Ring Opening of Benzofurans and an Enantioselective Hydroamination Cascade. *Angew. Chem. Int. Ed.* **2018**, *57* (46), 15204.
- (168) Slagbrand, T.; Kervefors, G.; Tinnis, F.; Adolfsson, H. An Efficient One-pot Procedure for the Direct Preparation of 4,5-Dihydroisoxazoles from Amides. *Adv. Synth. Catal.* **2017**, *359* (11), 1990.
- (169) Slagbrand, T.; Volkov, A.; Trillo, P.; Tinnis, F.; Adolfsson, H. Transformation of Amides into Highly Functionalized Triazolines. *ACS Catal.* **2017**, *7* (3), 1771.
- (170) Trillo, P.; Slagbrand, T.; Tinnis, F.; Adolfsson, H. Facile preparation of pyrimidinediones and thioacrylamides via reductive functionalization of amides. *Chem. Commun.* **2017**, *53* (65), 9159.
- (171) Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. Highly Chemoselective Formation of Aldehyde Enamines under Very Mild Reaction Conditions. *J. Org. Chem.* **2006**, *71* (19), 7481.
- (172) Bergmeier, S. C. The Synthesis of Vicinal Amino Alcohols. *Tetrahedron* **2000**, *56* (17), 2561.
- (173) Ma, X.; Deng, S.; Song, Q. Halodifluoroacetates as formylation reagents for various amines via unprecedented quadruple cleavage. *Org. Chem. Front.* **2018**, *5* (24), 3505.
- (174) Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. Palladium-Catalyzed Stereocontrolled Vinylation of Azoles and Phenothiazine. *Org. Lett.* **2002**, *4* (4), 623.
- (175) Blomquist, A. T.; Moriconi, E. J. Enamines of 2-Indanones 1a,b. *J. Org. Chem.* **1961**, *26* (10), 3761.
- (176) Ten Hoeve, W.; Wynberg, H. Synthetic approaches to planar carbon. 2. *J. Org. Chem.* **1980**, *45* (15), 2930.
- (177) Poladura, B.; Martínez-Castañeda, Á.; Rodríguez-Solla, H.; Llavona, R.; Concellón, C.; del Amo, V. General Metal-Free Baeyer-Villiger-Type Synthesis of Vinyl Acetates. *Org. Lett.* **2013**, *15* (11), 2810.
- (178) Liwosz, T. W.; Chemler, S. R. Copper-Catalyzed Enantioselective Intramolecular Alkene Amination/Intermolecular Heck-Type Coupling Cascade. *J. Am. Chem. Soc.* **2012**, *134* (4), 2020.

- (179) Liang, S.; Monsen, P.; Hammond, G. B.; Xu, B. Au/TiO<sub>2</sub> catalyzed reductive amination of aldehydes and ketones using formic acid as reductant. *Org. Chem. Front.* **2016**, 3 (4), 505.
- (180) Adam, R.; Cabrero-Antonino, J. R.; Junge, K.; Jackstell, R.; Beller, M. Esters, Including Triglycerides, and Hydrogen as Feedstocks for the Ruthenium-Catalyzed Direct N-Alkylation of Amines. *Angew. Chem. Int. Ed.* **2016**, 55 (37), 11049.





"There is no compound that can't be purified by a column. If there is, put it on another column."

— Lu Yu

