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DEVELOPMENT OF HIGHLY ENANTIOSELECTIVE ORGANOcatalyzed transformations

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ABSTRACT

Most biologically active organic molecules exist as only one stereoisomer in nature. Therefore, it is of great interest in the field of synthetic organic chemistry, to be able to control the stereoisomeric outcome of any reaction.

This work describes new protocols for highly stereo- and enantioselective transformations of aldehydes catalyzed by derivatives from the naturally occurring amino acid (S)-proline. To further expand the scope of aminocatalysis, we have developed efficient protocols for combining aminocatalysis with transition metalcatalysis, such as copper and palladium. This has further improved the usefulness of amino acids as catalysts by making it available to even more types of transformations.

Keywords: Asymmetric Catalysis, Aldehydes, Proline Derivatives, Transition metals, Friedel-Crafts, Conjugate Addition, Boration, α-Alkylation.
SAMMANDRAG

Många biologiskt aktiva organiska föreningar förekommer som endast en stereoisomer i naturen. Det är därför av stort intresse att inom syntetisk organisk kemi kunna kontrollera stereokemin i en reaktion.

Detta arbete beskriver metoder inom organokatalys för både diastereo- och enantioselektiva reaktioner av aldehyder. Som katalysator har olika derivat av naturligt förekommande aminosyran (S)-prolin använts. För att ytterligare utveckla användningsområdet för aminosyror inom katalys har vi kombinerataminokatalys med katalys av övergångsmetaller, så som koppar och palladium. Detta har ytterligare ökat användbarheten för aminosyror som katalysatorer då det visat sig att de är applicerbara flera typer av reaktioner.
# TABLE OF CONTENTS

ABSTRACT .......................................................................................................................... IV-V

SAMMANDRAG .................................................................................................................... V

LIST OF PAPERS ................................................................................................................ VII

LIST OF ABBREVIATIONS ...................................................................................................... VIII

1. INTRODUCTION ............................................................................................................. 1
   1.1. CHIRALITY ................................................................................................................ 1
   1.2. ASYMMETRIC SYNTHESIS .................................................................................... 2
   1.3. AMINE CATALYSIS ............................................................................................... 3
   1.4. ORGANOCATALYST .............................................................................................. 7

2. IMINIUM TYPE REACTIONS .......................................................................................... 8
   2.1. ENANTIOSELECTIVE FREIDEL-CRAFTS ALKYLATION OF AN \( \alpha,\beta \)-UNSATURATED
        ALDEHYDE ............................................................................................................. 9
   2.2. ORGANOCATALYTIC ASYMMETRIC SYNTHESIS OF 5-HYDROXY- \( \alpha \)-QUATERNARY
        PROLINE DERIVATIVES ........................................................................................... 14

3. DUAL CATALYSIS BY COMBINATION OF TRANSITION METAL
   CATALYSIS AND IMINIUM ACTIVATION....................................................................... 21
   3.1. DUAL CATALYTIC \( \beta \)-ALKYLATION OF \( \alpha,\beta \)-UNSATURATED ALDEHYDES IN THE
        SYNTHESIS OF BISBOLANE SESQUITERPENES ....................................................... 21
   3.2. ENANTIOSELECTIVE DUAL CATALYZED SYNTHESIS OF HOMOALLYLBORONATES ... 28

4. DUAL CATALYSIS BY COMBINATION OF TRANSITION METAL
   CATALYSIS AND ENAMINE ACTIVATION .................................................................... 35
   4.1. ENANTIOSELECTIVE DUAL CATALYZED \( \alpha \)-ALLYLATION OF ALDEHYDES BY
        COMBINATION OF PALLADIUM AND CHIRAL AMINES CATALYSTS ............................ 35

5. CONCLUDING REMARKS .............................................................................................. 42

6. ACKNOWLEDGMENTS .................................................................................................... 43

7. REFERENCES .................................................................................................................. 44
LIST OF PAPERS

This thesis is mainly based on the following papers, herein referred to by their Roman numerals:

Paper I  Chiral Pyrrolidinium Salts as Organocatalysts in the Stereoselective 1,4-Conjugate Addition of N-Methylpyrrole to Cyclopent-1-ene Carbaldehyde
Palle Breistein, Staffan Karlsson and Erik Hedenström

Palle Breistein, Jonas Johansson, Ismail Ibrahim, Shuangzheng Lin, Luca Deiana, Junliang Sun and Armando Córdova.
Manuscript.

Paper III Catalytic Enantioselective β-Alkylation of α,β-Unsaturated Aldehydes by Combination of Transition metal- and Aminocatalysis: Total Synthesis of Bisabolane Sesquiterpenes
Samson Afewerki, Palle Breistein, Kristian Pirttiala, Luca Deiana, Pawel Dziedzic, Ismail Ibrahim and Armando Córdova

Paper IV One-Pot Three-Component Catalytic Enantioselective Synthesis of Homoaatlylborationates
Ismail Ibrahim, Palle Breistein and Armando Córdova

Paper V Direct Enantioselective α-Allylation of Aldehydes by Combination of Transition metal and Amine catalysis
Samson Afewerki, Ismail Ibrahim, Jonas Rydfjord, Palle Breistein and Armando Córdova.
Submitted.
LIST OF ABBREVIATIONS

Ac  acetyl
Bn  benzyl
Boc  tert-butoxycarbonyl
Bpin pinacolato boron
Cbz  benzylxocarbonyl
CHCN  acetonitrile
Cat.  catalyst
DFT  density functional theory
DMSO  dimethyl sulfoxide
DMF  N,N-dimethylformamide
d.r.  diastereoisomeric ratio
E  electrophile
ECA  enantioselective conjugate addition
ee  enantiomeric excess
EtOH  ethanol
GC  gas chromatography
HOMO  highest occupied molecular orbital
HPLC  high performance liquid chromatography
HR-MS  high resolution mass spectroscopy
i-PrOH  iso-propanol
L  ligand
LUMO  lowest unoccupied molecular orbital
MeOH  methanol
NaBH₄  sodium borohydride
n.d.  not determined
NMO  N-methylmorpholine-N-oxide
NMP  N-methylpyrrolidone
Nu  nucleophile
Ph  phenyl
R.T.  room temperature
SOMO  single occupied molecular orbital
TES  triethyl silyl
THF  tetrahydrofuran
TMS  trimethyl silyl
TPAP  tetrapropylammonium perruthenate
Ts  tosyl


1. INTRODUCTION

1.1 Chirality

A chiral molecule is not superimposable on its mirror image. The two make a pair of enantiomers, and if in an equal amount, a racemic mixture. Compounds consisting of only the one enantiomer are enantiomerically pure. Different enantiomers have the same physical and chemical properties in an achiral environment, however they may interact differently with a chiral non-racemic environment.

Most biologically active organic molecules are chiral (e.g. amino acids and sugars). In nature they exist predominantly in only one form as enantiomerically pure. Hence, nature consists of chiral building blocks and thus is a chiral environment in which different enantiomers can behave differently. This is of particular interest and importance in the drug industry. One drastic example of this is the drug Neurosedyn (thaloxide in the USA) (fig 1). The (R)-enantiomer is an efficient sedative, used to treat morning sickness and the S-enantiomer is a potent human teratogen, causing birth defects.

The possible different biological activity of the different enantiomers has created a demand to develop methods to obtain enantiomerically pure compounds.

There are three methods for the preparation of enantiomerically pure compounds: (1) Asymmetric synthesis, (2) resolution of a racemic mixture into its two enantiomers via enzymatic or chemical methods (3) synthetic manipulation of natural products extracted from the chiral pool. Synthetic manipulations of natural products have been an extensively used approach which if conducted in a stereo controllable fashion will give the desired product in high optical purity from inexpensive starting materials. On the downside, this strategy may require several synthetic steps and the starting material may only be available in one enantiomeric form.

![Fig 1. The two enantiomers of Neurosedyn](image)

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![Fig 1. The two enantiomers of Neurosedyn](image)

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1.1 Chirality

A chiral molecule is not superimposable on its mirror image. The two make a pair of enantiomers, and if in an equal amount, a racemic mixture. Compounds consisting of only the one enantiomer are enantiomerically pure. Different enantiomers have the same physical and chemical properties in an achiral environment, however they may interact differently with a chiral non-racemic environment.

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![Fig 1. The two enantiomers of Neurosedyn](image)
1.2 Asymmetric synthesis

A goal within organic synthesis is to find and develop new highly efficient and stereoselective routes to obtain optically active compounds from inexpensive and readily available starting materials. Asymmetric synthesis is an important method for chemists to achieve that goal. Asymmetric synthesis can be achieved either by the use of a chiral auxiliary, a chiral reagent, or by a chiral catalyst.

The use of chiral auxiliaries involves the temporarily stoichiometric attachment of a chiral molecule to induce the chiral environment. This will create a favored side for the approach of the next reactant, either by acting as a steric hinder or as a directing group, creating stereoselectivity. The major drawback of this method is the extra synthetic steps required to attach and detach the chiral auxiliary.

Asymmetric catalysis involves the substoichiometric use of a chiral catalyst to convert a larger amount of achiral substrate to a chiral product, stereoselectively. Chiral catalysts can be further divided into metal catalysis, biocatalysis, organocatalysis and metal and non-metal Lewis acid catalysis.

Asymmetric organocatalysis has several advantages; it is environmentally friendly, inexpensive, often readily available in both enantiomeric forms and applicable to a large number of different reactions. Although the first examples of asymmetric organocatalysis were reported several decades ago (1971), the (S)-proline catalyzed Robinson annulations disclosed by Hajos and Parrish (scheme 1), this area has not been a main focus of research for more than the last decade.\(^5\)

![Scheme 1. The proline catalyzed Robinson annulation by Hajos and Parrish.](image)

Hajos and Parrish achievement was later followed by several intramolecular aldolreactions. For example Woodward developed a (R)-proline-catalyzed aldol reaction in the synthesis of erythromycin.\(^6\) However, it was not until the discovery that proline and its derivatives also can catalyze intermolecular reactions that the potential of this approach was realized.\(^7\)

The concept of catalysis has been developed further into combination of different types of catalysis. This can be used to increase activity and selectivity as well as providing new possibilities for several new applications. One example of this is the 1,4-addition of a propargylated carbon acid to an \(\alpha,\beta\)-unsaturated
aldehyde via iminium activation. Which, followed by a metal catalyzed intramolecular cyclisation and double bond isomerization, furnish the substituted cyclopentene (scheme 2).

\[ \text{Scheme 2. Iminium and Pd catalyzed domino reaction} \]

This thesis deals with organocatalytic asymmetric transformation made possible by amine activation, forming enamin or iminium ion, and dual catalysis whereas a transition metal is used in combination with an organocatalyst to further expand the scope of organocatalytic transformations.

1.3 Amine catalysis

The amine activation of a carbonyl group is one of the most powerful and versatile approaches to asymmetric organocatalysis. This is the condensation of a carbonyl moiety and an secondary amine forming a positively charged iminium ion I (scheme 3). This efficiently lowers the LUMO energy of the system, facilitating nucleophilic additions including conjugate addition for \( \alpha,\beta \)-unsaturated aldehydes. In the case of an isolated \( \pi \) system, the formation of the iminium ion will increase the acidity of the \( \alpha \)-proton causing deprotonation and generation of the enamine II. This will instead raise the HOMO (highest occupied molecular orbital) energy of the system, turning it into an activated nucleophile which can react with a vast variety of electrophiles to furnish intermediate III, which after hydrolysis will yield the \( \alpha \)-functionalized aldehydes or ketones (scheme 3).
Scheme 3. The catalytic cycle of enamine activation.

The conjugated system, as a result of the condensation of a $\alpha,\beta$-unsaturated aldehyde, however will remain as an iminium ion IV, acting as an activated electrophile towards nucleophilic addition in a large number of reactions, e.g. Fridel-Crafts,$^{10}$ Michael-addition,$^{11}$ dipolar addition (scheme 4).$^{12}$

Scheme 4. Reactions catalyzed by iminium formation of an $\alpha,\beta$-unsaturated aldehyde and an secondary chiral amine.
However, recently it has been reported that the condensation of an α,β-unsaturated aldehyde with a secondary amine catalyst can generate the dienamine V (scheme 5), hence becoming a nucleophile, presenting a new method for deriving γ-functionalized α,β-unsaturated aldehydes.\textsuperscript{13}

\[
\begin{align*}
\text{HO-CH=CHR}^1 + R_2^+ N\text{H} &\overset{-\text{H}_2\text{O}}{\rightleftharpoons} \left[ \text{R}_2^+ \text{N} \right] \text{H} \overset{+\text{H}^+}{\rightleftharpoons} \text{E} \overset{+\text{H}_2\text{O}}{\rightarrow} \text{HO-CH=CHR}^1 \\
\end{align*}
\]

\textbf{Scheme 5.} Amine catalysis via dienamine activation.

A fourth aminocatalytic pathway is the formation of a radical in the activated enamine intermediate, SOMO catalysis (single occupied molecular orbital), which will react further in α-position furnishing α-functionalized aldehydes (scheme 6).\textsuperscript{14}

\[
\begin{align*}
\text{HO-CH=CHR}^1 &\overset{-\text{H}_2\text{O}}{\rightarrow} \text{HO-CH=CHR}^1 \overset{-\text{H}^+}{\rightarrow} \text{HO-CH=CHR}^1 \overset{-\text{e}^-}{\rightarrow} \text{HO-CH=CHR}^1 \overset{-\text{H}_2\text{O}}{\rightarrow} \text{HO-CH=CHR}^1 \\
\end{align*}
\]

\textbf{Scheme 6.} Amine catalysis via SOMO activation.
Scheme 7. Domino reaction via enamine/iminium activation.

Combination of enamine/iminium activation cycles has further expanded the scope of amine catalysis.\textsuperscript{15,16} Several examples of different domino reactions have been published. For example, Yamamoto and co-workers have developed a tandem aldol-type Michael addition.\textsuperscript{17} Moreover, our group have reported the catalytic asymmetric domino Mannich/Michael reaction based on this approach (scheme 7).\textsuperscript{18} The catalytic cycle begins with the condensation of the secondary amine catalyst forming the enamine VI followed by the enamine attack on the electrophile which in turn forms the iminium ion intermediate VII. Next the LUMO activated system undergoes an intramolecular Michael cyclisation forming the bicyclic Diels-Alder adduct VIII, which upon hydrolysis forms the product and releases the amine catalyst.
Scheme 8. Domino reaction via iminium/enamine activation.

Another chiral amine catalyzed transformation is the domino iminium/enamine activation reaction (scheme 8) that again begins with the condensation of the α,β-unsaturated aldehyde and the amine to form IX. Next the LUMO activated electrophile is subjected to a nucleophile attack in β-position forming the enamine intermediate X. The newly formed HOMO activated nucleophilic enamine will now attack the electrophile to form intermediate XI. Hydrolysis will deliver the corresponding product and release the catalyst.

1.4 Organocatalysts

Most organocatalysts are derived from amino acids, peptides, alkaloids or synthetic nitrogen-containing molecules. The exceptional enantioselective induction shown by amino acids in their catalytic reactions has led to extensive research within asymmetric catalysis. Among all natural occurring amino acids, proline stands out as the most effective. The extraordinary reactivity of proline is
often explained by the nature of the secondary amine and the five-membered ring structure. This has led to a great variety of proline derivatives where the carboxylic acid moiety has been extensively modified. Though proline naturally occurs in its (S)-form it is also readily available in its (R)-form.

![Chemical structures](image)

**2. IMINIUM TYPE REACTIONS**

In this part we present examples of organocatalytic asymmetric transformations via iminium intermediates, e.g. the Friedels-Crafts alkylation of an \(\alpha,\beta\)-unsaturated aldehyde with \(N\)-methyl pyrrole and the 1,4-addition of amides to \(\alpha,\beta\)-unsaturated aldehydes followed by cyclisation.

As mentioned in the introduction, the formation of iminium species is the condensation of an aldehyde and a secondary or primary amine causing lowered LUMO energy and thereby increased reactivity towards nucleophilic attack.
2.1 Enantioselective Friedel-Crafts alkylation of an $\alpha,\beta$-unsaturated aldehyde.

The first known enantioselective organocatalytic Friedel-Crafts alkylation was reported by MacMillan in 2001.\textsuperscript{20} The addition of $N$-methyl pyrrole 4 to an $\alpha,\beta$-unsaturated aldehyde 1, to furnishing the substituted pyrrole 3, who serves as a valuable synthon for the construction of biomedical agents (scheme 9).\textsuperscript{21}

![Scheme 9. The first aminocatalyzed Friedel-Crafts reaction.](image)

Inspired by these results we decided to further investigate and expand the scope of the amino-catalyzed Friedel-Crafts reaction. Introducing an $\alpha,\alpha$-disubstituted enal to the reaction would create two new stereogenic centers in one step. For this purpose we choose the cyclopent-1-enecarbaldehyde 5. We also investigated the catalytic performance of some organocatalysts that had not been applied in this type of reaction before (scheme 10).
Scheme 10. The Friedel-Crafts reaction catalyzed by various chiral amines.

The reaction of N-methylpyrrole 4 with cyclopent-1-ene carbaldehyde 5 was carried out under aerobic conditions in the presence of catalyst 2, or 7-9 (10 mol%) and a catalytic amount of water, in DMF. The reaction was normally completed within 72 h. The product was obtained as a mixture of all four stereoisomers of 2-(1-methyl-1H-pyrro-2-yl)cyclopentanecarbaldehyde 6 (table 1).

We first investigated catalyst 2a previously used by Paras and MacMillian in a similar transformation (scheme 9).\textsuperscript{20} Catalyst 2a gave moderate cis-6/trans-6 ratio (Table 1, entry 1) but low enantioselectivity. Next we tested the proline derived organocatalysts 7. Catalyst 7a (table1, entry 2) showed promising enantioselectivity but the cis-6/trans-6 ratio was low. Conducting the reaction at lower temperature gave only minor improvements in selectivity (table 1, entries 3-4).
Table 1. The conjugate addition of N-methylpyrrole 4 to cyclopent-1-ene carbaldehyde 5 catalyzed by various organocatalyst.\(^a\)

<table>
<thead>
<tr>
<th>Entry(^a)</th>
<th>Cat.</th>
<th>Co-cat.</th>
<th>Temp. (°C)</th>
<th>cis-6/ trans-6(^b)</th>
<th>cis-(1R,2S)/ trans-(1S,2R)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>HCl</td>
<td>25</td>
<td>27:73</td>
<td>44:56</td>
</tr>
<tr>
<td>2</td>
<td>7a</td>
<td>HCl</td>
<td>25</td>
<td>44:56</td>
<td>68:32</td>
</tr>
<tr>
<td>3</td>
<td>7a</td>
<td>HCl</td>
<td>5</td>
<td>50:50</td>
<td>71:29</td>
</tr>
<tr>
<td>4</td>
<td>7a</td>
<td>HCl</td>
<td>-25</td>
<td>50:50</td>
<td>70:30</td>
</tr>
<tr>
<td>5</td>
<td>7b</td>
<td>HCl</td>
<td>25</td>
<td>30:70</td>
<td>69:31</td>
</tr>
<tr>
<td>6</td>
<td>7a</td>
<td>2HCl</td>
<td>25</td>
<td>35:65</td>
<td>88:12</td>
</tr>
<tr>
<td>7</td>
<td>7b</td>
<td>2HCl</td>
<td>25</td>
<td>44:56</td>
<td>88:12</td>
</tr>
<tr>
<td>8(^d)</td>
<td>7c</td>
<td>HCl</td>
<td>25</td>
<td>51:49</td>
<td>37:63</td>
</tr>
<tr>
<td>9(^e)</td>
<td>8</td>
<td>HCl</td>
<td>25</td>
<td>9:91</td>
<td>54:46</td>
</tr>
<tr>
<td>10(^e)</td>
<td>9</td>
<td>HCl</td>
<td>25</td>
<td>16:84</td>
<td>65:35</td>
</tr>
</tbody>
</table>

\(^a\) All experiments were carried out at the specified temperature for 72h in 2 ml DMF (with 40 µl of water added), using 84 mg (0.88 mmol) of aldehyde 5, 10 mol % of the catalyst and 390 µl (4.4 mmol) of N-methylpyrrole 4.  
\(^b\) The cis-6/trans-6 ratio was determined by GC analysis.  
\(^c\) Enantiomeric ratio was determined by chiral GC analysis of 6 GC β-dex 325 column.  
\(^d\) The reaction was carried out with 80 µl of water added.  
\(^e\) The reaction was carried out with 20 µl of water added.

However, catalyst 7a or 7b with 2.0 equivalents of the acid co-catalyst increased the enantio- and diastereoselectivity in both cases (table 1, entries 6 and 7). Catalysts 8 and 9 both showed high diastereoselectivity however, they only gave moderate to low enantioselectivity (table 1, entries 9 and 10). The amount of acidic co-catalyst in the system seems to influence the stereochemical outcome of the reaction when using the two proline derived catalysts 7a and 7b. The effect of the co-catalyst was investigated further by applying a variety of different pyrrolidinium salts of 7b to our reaction conditions. The results are summarized in table 2.
Table 2. Various co-catalysts were applied with 7b in the conjugate addition of N-methylpyrrole 4 to cyclopent-1-ene carbaldehyde 5.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Co-cat. (HX)n</th>
<th>Cis-6/trans-6b (cis-(1R,2S)-6)</th>
<th>trans-(1R,2R)-6</th>
<th>trans-(1S,2S)-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBr</td>
<td>7:93</td>
<td>54:46</td>
<td>61:39</td>
</tr>
<tr>
<td>2</td>
<td>2HBr</td>
<td>48:52</td>
<td>79:21</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>HI</td>
<td>9:91</td>
<td>48:52</td>
<td>51:49</td>
</tr>
<tr>
<td>4</td>
<td>2HI</td>
<td>3:97</td>
<td>84:16</td>
<td>81:19</td>
</tr>
<tr>
<td>5</td>
<td>TFA</td>
<td>23:77</td>
<td>60:40</td>
<td>63:37</td>
</tr>
<tr>
<td>6</td>
<td>2 TFA</td>
<td>8:92</td>
<td>79:21</td>
<td>75:25</td>
</tr>
<tr>
<td>7</td>
<td>TsOH</td>
<td>24:76</td>
<td>51:49</td>
<td>56:44</td>
</tr>
<tr>
<td>8</td>
<td>2 TsOH</td>
<td>37:63</td>
<td>73:27</td>
<td>74:26</td>
</tr>
<tr>
<td>9</td>
<td>HClO₄</td>
<td>25:75</td>
<td>51:49</td>
<td>55:45</td>
</tr>
<tr>
<td>10</td>
<td>2 HClO₄</td>
<td>26:74</td>
<td>67:33</td>
<td>70:30</td>
</tr>
</tbody>
</table>

a All experiments were carried out at 25 °C for 72h in 2 ml DMF (with 40 μl of water added), using 84 mg (0.88 mmol) of aldehyde 5, 10 mol % of catalyst 7b and 390 μl (4.4 mmol) of N-methylpyrrole 4. The cis-6/trans-6 ratio was determined using a GC EC-1 column. Enantiomeric ratio was measured using a chiral GC β-dex 325 column.

Adding two equivalents of acid to the amine catalyst consequently gave both higher diastere- and enantioselectivity (table 2, entries 1-10). The highest selectivity was achieved when using 2.0 equivalents of HI as a co-catalyst (table 2, entry 4).

Initial experiments showed that the amount of water influenced the stereoselectivity of the reaction. Thus, we investigated this further by using the diiodopyrroloidinium salt of 7b in a series of experiments. The results are summarized in table 3. The best results were obtained when 10-40 μL of water was added (table 3 entries 2-5). Higher or lower levels decreased the selectivity (table 3, entries 1 and 6-7). However, 40μL of added water seemed to be the optimal amount for our reaction conditions.
Table 3. The conjugate addition of N-methylpyrrole 4 to cyclopent-1-ene carbaldehyde 5 catalyzed by 7b using 2HI as co-catalyst with different amounts of water added.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Water (µL)</th>
<th>Cis-6/trans-6(^a)</th>
<th>Cis-(1R,2S)-6/ cis-(1S,2R)-6(^c)</th>
<th>Trans-(1R,2R)-6/ trans-(1S,2S)-6(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>17:83</td>
<td>74:26</td>
<td>82:18</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>9:91</td>
<td>66:34</td>
<td>82:18</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>5:95</td>
<td>63:37</td>
<td>83:17</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>7:93</td>
<td>87:13</td>
<td>78:22</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>3:97</td>
<td>84:16</td>
<td>81:19</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>25:75</td>
<td>78:22</td>
<td>74:26</td>
</tr>
<tr>
<td>7</td>
<td>200</td>
<td>28:72</td>
<td>68:32</td>
<td>65:35</td>
</tr>
</tbody>
</table>

\(^a\) All experiments were carried out at 25 °C for 72h in 2 ml DMF (with different amounts of water added), using 84 mg (0.88 mmol) of aldehyde 5, 10 mol % of catalyst 7b (2HI as co-catalyst) and 390 µl (4.4 mmol) of N-methylpyrrole 4.\(^b\) The cis-6/trans-6 ratio was determined using a GC EC-1 column.\(^c\) Enantiomeric ratio was measured using a chiral GC β-dex 325 column.

The added amount of water has an important role in the organocatalytic cycle. It has been shown earlier that adding water can increase the reaction rate and affect the enantioselectivity e.g. organocatalyzed Diels-Alder and Mannich reaction.\(^2\) Probably in our case, both the amount of water added and the acidity of the co-catalysts used influence the reactivity and selectivity of the reaction.
2.2 Organocatalytic asymmetric synthesis of 5-hydroxy-α-quaternary proline derivatives.

As mentioned in the introduction, domino reactions introducing two or more new stereogenic centers can be a highly efficient route to new complex molecules.

![Organocatalytic asymmetric synthesis of 5-hydroxy-α-quaternary proline derivatives.](image)

*Fig 2. Heterocycles formed by organocatalyzed tandem reactions.*

Substituted chiral proline derivatives are important pharmaceuticals, natural products, organocatalysts and building blocks in chemical synthesis. Development of efficient catalytic enantioselective reactions that furnish polysubstituted proline derivatives bearing an all-carbon quaternary stereogenic center is an attractive approach in asymmetric synthesis. Catalytic enantioselective tandem reactions involving an intramolecular cyclization step can be a powerful method for formation of chiral pyrrolidine and proline derivatives. This strategy has been applied earlier in the synthesis of 3-substituted 5-hydroxyisoxazolidines, where an N-protected hydroxylamine was used as a nucleophile in the tandem reaction of an iminium activated enal (fig 2 (a)). Further on, aminomalonate was used as a nucleophile in the chiral synthesis of a 5-hydroxylproline derivative (fig 2 (b)). However, this method was only applicable on aromatic enals. Up to date, there are only a few reports on the catalytic enantioselective synthesis of a 5-hydroxypyrrolidine bearing a quaternary α-stereogenic carbon. Recently, the enantioselective aminocatalyzed [3+2] dipolar cycloaddition to furnish a proline derivative with a quaternary stereogenic center at 2-position was reported (fig 3).
Fig 3. The [3+2] dipolar addition.

Thus, based on our previous work, we envisioned that the catalytic tandem cyclization reaction between ethyl N-protected α-cyanoglycine esters 10 and enals 1 would deliver the desired chiral 5-hydroxy proline derivative bearing α-quaternary stereocenter (scheme 11).

Scheme 11. The enantioselective organocatalyzed synthesis of 11.

Here we present the aminecatalyzed 1,4-conjugate addition of an N-protected α-cyanoglycine ester 10 to an α,β-unsaturated aldehyde 1 followed by intramolecular cyclization to deliver the chiral substituted proline derivative 11.
Table 4. Initial screening of the tandem 1,4-addition reaction conditions.\(^a\)

![Chemical structures](image)

Table 4. Initial screening of the tandem 1,4-addition reaction conditions.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R)</th>
<th>Cat.</th>
<th>Prod.</th>
<th>Solv.</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv.(^b) (%)</th>
<th>d.r.(^b)</th>
<th>ee(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>MeOH</td>
<td>R.T.</td>
<td>7</td>
<td>90</td>
<td>2:1</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>MeOH</td>
<td>R.T.</td>
<td>7</td>
<td>&gt;98</td>
<td>3:1</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>(-)PrOH</td>
<td>R.T.</td>
<td>7</td>
<td>&gt;98</td>
<td>5:1</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>Toluene</td>
<td>R.T.</td>
<td>9</td>
<td>96</td>
<td>1:1</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>THF</td>
<td>R.T.</td>
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<td>95</td>
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<td>62</td>
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<tr>
<td>6</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>(\text{CHCl}_3)</td>
<td>R.T.</td>
<td>9</td>
<td>90</td>
<td>3:1</td>
<td>13</td>
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<tr>
<td>7</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
<td>95</td>
<td>5:1</td>
<td>94</td>
</tr>
<tr>
<td>8(^e)</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
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<td>5:1</td>
<td>88</td>
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<tr>
<td>9(^f)</td>
<td>Ph</td>
<td>Ph</td>
<td>7d</td>
<td>11a</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
<td>95</td>
<td>4:1</td>
<td>94</td>
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<tr>
<td>10</td>
<td>Ph</td>
<td>(n)-(\text{Pr})</td>
<td>7d</td>
<td>11m</td>
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<td>R.T.</td>
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<td>81</td>
</tr>
<tr>
<td>11</td>
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<td>7d</td>
<td>11m</td>
<td>(-)PrOH</td>
<td>R.T.</td>
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<tr>
<td>12</td>
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<td>Ph</td>
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<td>11f</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
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<td>Me</td>
<td>Ph</td>
<td>7d</td>
<td>11f</td>
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<td>8:1</td>
<td>94</td>
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<td>11f</td>
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<td>4:1</td>
<td>78</td>
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<td>Me</td>
<td>Ph</td>
<td>7h</td>
<td>11f</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
<td>98</td>
<td>8:1</td>
<td>90</td>
</tr>
<tr>
<td>16</td>
<td>Me</td>
<td>Ph</td>
<td>2b</td>
<td>11f</td>
<td>MeOH</td>
<td>-20</td>
<td>13</td>
<td>4</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>17</td>
<td>(t)-(\text{BuO})</td>
<td>Ph</td>
<td>7d</td>
<td>11n</td>
<td>MeOH</td>
<td>R.T.</td>
<td>24</td>
<td>98</td>
<td>2:1</td>
<td>83</td>
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<tr>
<td>18</td>
<td>BnO</td>
<td>Ph</td>
<td>7d</td>
<td>11o</td>
<td>MeOH</td>
<td>R.T.</td>
<td>41</td>
<td>70</td>
<td>6:1</td>
<td>84</td>
</tr>
</tbody>
</table>

\(^a\) Nucleophile 10 (0.2 mmol, 1 equiv.) was added to a stirred solution of aldehyde 1 (0.4 mmol, 2 equiv.), catalyst 7 and acid in solvent (0.4 mL). The reaction was stirred for the given time and temperature. \(^b\) Determined by \(^1\)H NMR analysis. \(^c\) Determined by chiral-phase HPLC analysis. \(^d\) Reaction run
without acid. ° Reaction run with 3-nitrobenzoic acid. † Reaction run with 4-nitrobenzoic acid.

We began investigating the reaction by studying the 1,4-addition of the N-benzoyl protected α-cyanoglycine ester 10a to cinnamic aldehyde 1a using the proline derivative 7d as the catalyst in methanol as solvent, at room temperature. To our delight we found that the reaction proceeded smoothly yielding the desired product 11a (table 4, entry 1) as a mixture of two diastereoisomers. Only the α-anomer was formed in the hemiaminal formation step as determined by 1H NMR analysis of the crude reaction mixture. Adding 2-fluorobenzoic acid (10 mol%) as a co-catalyst improved the diastereoselectivity (table 4 entry 2). Furthermore, solvent screen showed that MeOH gave the best enantioselectivity (table 4, entries 2-6). Lowering the reaction temperature improved the enantioselectivity considerably in the case of MeOH, though decreasing the reaction rate (table 4, entry 7). Finally we performed a catalyst screen and found that the O-protected diphenyl prolinol derivatives 7d and 7h, catalyzed the reaction with highest enantio- and diastereoselectivity (table 4, entries 12-16).

Inspired by these results we proceeded to investigate the importance of the protective groups of the α-cyanoglycine ester 10. We found that benzoyl- 10a and acylprotected 10b α-cyanoglycine esters gave the best results in terms of enantioselectivity (table 4, entries 8 and 14). However, Boc- and Cbz-protected α-cyanoglycine esters showed good selectivity, but were less reactive (table 4, entries 18-19).
Table 5. Scope of the organocatalytic tandem reaction.

Table 5. Scope of the organocatalytic tandem reaction. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>R$^1$</th>
<th>R</th>
<th>Prod.</th>
<th>Yield (%)$^b$</th>
<th>d.r.$^c$</th>
<th>ee (%)$^a$</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>11a</td>
<td>83</td>
<td>5:1</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>4-MeC$_6$H$_4$</td>
<td>11b</td>
<td>88</td>
<td>5:1</td>
<td>92</td>
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<tr>
<td>3</td>
<td>Ph</td>
<td>4-BrC$_6$H$_4$</td>
<td>11c</td>
<td>68</td>
<td>6:1</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>4-ClC$_6$H$_4$</td>
<td>11d</td>
<td>78</td>
<td>4:1</td>
<td>92</td>
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<tr>
<td>5</td>
<td>Ph</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>11e</td>
<td>84</td>
<td>4:1</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>Ph</td>
<td>11f</td>
<td>89</td>
<td>8:1</td>
<td>94</td>
</tr>
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<td>7</td>
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<td>11g</td>
<td>90</td>
<td>12:1</td>
<td>92</td>
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<td>8</td>
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<td>11h</td>
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<td>9</td>
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<td>11i</td>
<td>90</td>
<td>10:1</td>
<td>91</td>
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<td>10</td>
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<td>11j</td>
<td>68</td>
<td>9:1</td>
<td>94</td>
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<td>11</td>
<td>Me</td>
<td>2-ClC$_6$H$_4$</td>
<td>11k</td>
<td>81</td>
<td>&gt;20:1</td>
<td>92</td>
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<tr>
<td>12$^e$</td>
<td>Me</td>
<td>n-Pr</td>
<td>11l</td>
<td>47</td>
<td>2:1</td>
<td>98 (95)$^f$</td>
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</tbody>
</table>

$^a$ Nucleophile 10 (0.2 mmol, 1 equiv.) was added to a stirred solution of aldehyde 1 (0.4 mmol, 2 equiv.), catalyst 7d and acid in solvent (0.4 mL).$^b$
Combined yield of both diastereoisomers. $^c$ Determined by $^1$H NMR analysis. $^d$ Determined by chiral-phase HPLC analysis. $^e$ The reaction was run in i-PrOH $^f$ ee for the minor diastereoisomer.

Next, we investigated the 1,4-addition reactions of 10a and 10b to a number of different aromatic $\alpha,\beta$-unsaturated aldehydes 1. The reactions proceed with high enantioselectivity and good diastereoselectivity (table 5). However, diastereoselectivity was increased in the case of 1,4-addition of 10b to enals 1d and 1f bearing an electron-withdrawing group at the meta- or ortho-position (table 5, entries 9 and 11). The reaction conditions were also applicable to aliphatic enals. However, the best results were obtained when using i-PrOH as solvent (table 5, entry 12).
The 5-hydroxyproline derivative **11** could be transformed into the proline derivative **7i** by removal of the 5-hydroxy group (fig 4). Adding Et₃SiH and BF₃·Et₂O to a -78°C solution of **7i** in CH₂Cl₂ and leaving the reaction to reach room temperature over night gave the proline derivative **7i**. Submitting a diastereomer mixture of **11** to these reaction conditions gave a diastereomer mixture of **7i**.

**Fig 4.** synthesis of 3-substituted α-quaternary proline derivatives.

**Fig 5.** ORTEP picture of the crystalline compound **11j**.

The absolute configuration of the 5-hydroxyproline derivatives **11** was determined by X-ray analysis of **11j** (2S, 3S, 5R) (fig 5).
**Scheme 12.** The proposed mechanism for the amine catalyzed tandem reaction.

Based on the absolute configuration of 11, we propose the reaction mechanism depicted in scheme 12. The α-cyanoglycine 10 ester undergoes enolization and approaches the iminium species I from the less sterically hindered Si-face to form reaction intermediate II which will proceed to enamine III. Subsequent formation of the iminium species IV will after hydrolysis generate intermediate V and the chiral amine catalyst. Intermediate V will undergo Re-facial hemiaminal formation to give the final 5-hydroxyproline derivative 11.
3. DUAL CATALYSIS BY COMBINATION OF TRANSITION METALS AND AMINE CATALYSIS.

One of the more challenging approaches in the field of organocatalysis has been the direct 1,4-alkylation of α,β-unsaturated carbonyls. Normally, the addition of an organometallic reagent to an α,β-unsaturated aldehyde would yield mostly the 1,2 adduct, rather than the desired 1,4 adduct (fig 6).\(^{28}\) This has led us to search for new pathways to control the regioselectivity of 1,4-alkyl addition to α,β-unsaturated aldehydes. The recent breakthroughs in transition metal-catalyzed enantioselective conjugate addition (ECA)\(^{29}\) prompted us to combine transition metal catalysis and chiral amine iminium activation catalysis, creating a new type of enantioselective dual catalysis\(^{30}\).

![Chemical Reaction Diagram](image_url)

**Fig 6.** 1,4-/1,2-Alkylation of α,β-unsaturated aldehydes.

3.2 Dual catalytic β-alkylation of α,β-unsaturated aldehydes in the synthesis of bisbolane sesquiterpenes.

Chiral β-Alkyl substituted aldehydes are constituents of biologically active natural products (e.g., (S)-citronellal) and valuable chiral building blocks in asymmetric synthesis. For example, they can be used as synthons for the total synthesis of sesquiterpenes and polyketides.\(^{31}\) In this context, natural products such as bisabolane sesquiterpenes (e.g., (S)-(+)curcumene 14, (S)-(+)dehydrocurcumene 15, and (S)-(+)tumerone 16 (scheme 13), which exhibit anticancer as well as antimicrobial activities and are used as additives in perfumes, flavors, and cosmetics,\(^{32}\) could be rapidly assembled according to retrosynthetic analysis from (3S)-β-methyl aldehyde (12k).
Scheme 13. Retrosynthetic analysis for syntheses of bisabolan sesquiterpenes 14, 15 and 16.

Our aim was to develop an aminocatalyzed 1,4-alkylation of an α,β-unsaturated aldehyde, with the additional use of transition metal to circumvent the problem of 1,2 addition (scheme 14). Thus, the formation of an iminium species to induce chirality and lower the LUMO energy and simultaneously combine with nucleophilic copper-catalysis to favor the 1,4-addition. This can, as shown in scheme 14, be the key step in the synthesis of several sesquiterpenes.

Scheme 14. The dual catalyzed 1,4-alkylation.
Table 6. Screening of reaction conditions.\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Entry & Cat. & Ligand & Time (h) & Conv. (%) & Ratio 12/13 & e.r.\textsuperscript{a} \\
\hline
1 & - & 17a & 12 & 91 & 3:97 & 50:50 \\
2 & 7d\textsuperscript{a} & - & 9 & 29 & 22:78 & 78:22 \\
3 & 7d & - & 12 & 18 & 84:16 & 77:23 \\
4 & 7d & 17a & 12 & 58 & 62:38 & 96:4 \\
5 & 7e & 17a & 17 & 53 & 8:92 & 61:39 \\
6 & 7f & 17a & 18 & 60 & 48:52 & 90:10 \\
7 & 7g & 17a & 14 & >98 & 10:90 & 47:53 \\
8 & 2a & 17a & 17 & 38 & 8:92 & 47:53 \\
9 & 2b & 17a & 15 & 75 & 12:88 & 62:38 \\
10 & 7d\textsuperscript{f} & 17a & 12 & 45 & 58:42 & 95:5 \\
11 & 7d & 17b & 12 & 38 & 76:24 & 87:13 \\
12 & 7d\textsuperscript{g} & 17c & 8 & 8 & 77:23 & 76:24 \\
13 & 7d & 17d & 11 & 27 & 49:51 & 89:11 \\
14 & 7d & 17e & 12 & 19 & 86:14 & 94:6 \\
15 & 7d & 17f & 9 & 11 & 36:64 & 82:18 \\
16 & 7d\textsuperscript{h} & 17a & 16 & 72 & 34:66 & 88:12 \\
17 & 7d\textsuperscript{i} & 17a & 23 & 24 & 76:24 & 91:9 \\
18 & 7d\textsuperscript{i} & - & 4 & 23 & 16:84 & 71:29 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Ar= 3,5-(CF\textsubscript{3})\textsubscript{2}C\textsubscript{6}H\textsubscript{3}

\textsuperscript{b}Cat. 2 or 7 (25 mol\%) Cu(OTf)\textsubscript{2} (10 mol\%) Et\textsubscript{2}Zn. 17 (20 mol\%) THF 60 °C
a The reaction was carried out under N₂ atmosphere. b Determined by GC analysis of the crude reaction mixtures. c Determined by GC analysis and ¹H NMR analysis of the crude reaction mixture. d Determined by chiral-phase GC analysis. The ee value of products 13 is 0% in all cases. e The reaction was performed without Cu(OTf)₂ catalyst. f 20 mol% 7d. g The ligand was pre-mixed with KOT-Bu and the reaction was performed at R.T. h the reaction was performed at R.T. i CuTC (copper thiophene carboxylate) (2 mol%), 17a (4 mol%) at R.T. j CuCl (10 mol%) at 50°C.

We began investigating the reaction between Et₂Zn and cinnamic aldehyde 1a by using different copper salts and chiral amines 7 and 2 as catalysts. We found that the highest 1,4-selectivity and enantioselectivity was achieved when copper(II) triflate, Cu(OTf)₂, 10 mol% was used as the transition metal co-catalyst and THF as the solvent at 60°C. Key results are shown in Table 6. The reaction proceeded without the chiral amine catalyst 7, but gave mainly the undesired racemic alcohol 13a rather than aldehyde 12a (12a/13a; 3:97; Table 6, entry 1). In the absence of copper, the chiral amine catalyst 7d also gave low regioselectivity (12a/13a; 22:78; Table 6, entry 2), however, 12a was formed in 78:22 e.r. To our delight, the combination of chiral amine 7d and Cu(OTf)₂ switched the 1,2-selective reaction towards a 1,4-selective transformation (12a/13a; 84:16) and gave 12a in 77:23 e.r. (Table 6, entry 3).

In order to improve the conversion of the reaction we decided to add ligands such as organic phosphines and N-heterocyclic carbenes 17 to the copper catalyst.³⁴

In most cases, the reaction was 1,4-selective and gave 12a with good to high enantiomeric ratios. The highest conversion was achieved when PPh₃ 17a was added as the ligand. Of the screened amine catalysts 7 and 2, the protected diarylprolinol 7d catalyzed the asymmetric conjugate addition with the best enantioselectivity. For example, aldehyde 12a was formed with up to 96:4 e.r. (Table 6, entry 4). Lowering the catalyst loading of 7d slightly decreased the e.r. of 12a to 95:5 (Table 6, entry 10). Based on these results, we decided to investigate the scope of the catalytic ECA of organozinc reagent R₂Zn to α,β-unsaturated aldehydes 1 using Cu(OTf)₂ as the metal catalyst, 7d as the chiral amine, and 17a as the additive in THF at 60°C (Table 7).
Table 7. The scope of the dual catalyzed ECA of R:Zn to enals 1.

\[
\begin{align*}
\text{Entry} & \quad \text{R}^1 & \quad \text{R} & \quad \text{Product} & \quad \text{Time (h)} & \quad \text{Yield (%)}^b & \quad \text{Ratio 12/13}^c & \quad \text{e.r.}^d \\
1 & 4-\text{MeOC}_6\text{H}_4 & \text{Et} & 12b & 13 & 83 & 85:15 & 98:2 \\
2 & 2-\text{napht.} & \text{Et} & 12c & 16 & 62 & 64:36 & 98:2 \\
3 & 4-\text{ClC}_6\text{H}_4 & \text{Et} & 12d & 18 & 60 & 63:37 & 95:5 \\
4 & 4-\text{BrC}_6\text{H}_4 & \text{Et} & 12e & 13 & 47 & 78:22 & 96:4 \\
5 & 4-\text{MeC}_6\text{H}_4 & \text{Et} & 12f & 13 & 44 & 75:25 & 98:2 \\
6 & 4-i-\text{PrC}_6\text{H}_4 & \text{Et} & 12g & 9 & 71 & 83:17 & 97:3 \\
7 & 3-\text{ClC}_6\text{H}_4 & \text{Et} & 12h & 9 & 44 & 79:21 & 97:3 \\
8 & 3-\text{MeOC}_6\text{H}_4 & \text{Et} & 12i & 11 & 79 & 80:20 & 98:2 \\
9 & 4-\text{MeOC}_6\text{H}_4 & \text{Me}^e & 12j & 16 & 76 & 91:9 & 98:2 \\
10 & 4-\text{MeC}_6\text{H}_4 & \text{Me}^e & 12k & 14 & 65 & 93:7 & 97:3 \\
11 & n-\text{Bu} & \text{Me}^{i,g} & 12l & 14 & 23^i & 51:49 & 92:8 \\
12 & n-\text{Bu} & \text{Me}^{i,h} & 12l & 16 & 60^i & 80:20 & 83:17 \\
\end{align*}
\]

a The reaction was carried out under N\textsubscript{2} atmosphere. b Isolated yield of 12 after silica gel column chromatography. c Determined by \textsuperscript{1}H NMR analysis of the crude reaction mixture. d Determined by chiral-phase HPLC or chiral GC analyses. The ee value of products 13 is 0%. i Reaction run at 22°C. j Reaction run at 45°C. k Me\textsubscript{2}Zn added at 22°C. l Me\textsubscript{2}Zn added at −78°C. iYield determined by GC.

The dual catalytic ECA of EtZn to enals 1 with an aryl substituent at the β-position proceeded with good 1,4-selectivities and high enantioselectivity to give the corresponding β-alkylated aldehydes 12b–12l (Table 7, entries 1–8). The highest selectivities for the dual catalytic asymmetric reactions were achieved when enals 1 substituted in β-position with a meta- or para-MeOPh group was used as substrates (Table 7, entries 1 and 8). The dual catalytic transformations using MeZn as the reagent was also 1,4-selective and gave the corresponding product 12 with high e.r. value. For example, the ECA of MeZn to the corresponding enals 1 gave the aldehydes 12j and 12k with 98:2 and 97:3 e.r., respectively (Table 7, entries 9 and 10). The dialkylzinc reagent MeZn also worked for aliphatic enals 1 as substrates but gave lower e.r. values (Table 7, entries 11 and 12).
Scheme 15. a) Me₂Zn, cat 7d, Cu(OTf)₂; 17a, THF, 60°C; b) NaBH₄, CH₂Cl₂, MeOH, 0°C; c) TsCl, pyridine, CH₂Cl₂, RT 5h; d) NaI, acetone, reflux 2h; e) 19, THF, 0°C, 1h; f) 20, CHCl₃, reflux 16h; g) Ph₃PMeBr, BuLi, Et₂O; h) tetrapropylammonium perruthenate (TPAP), N-methylmorpholine-N-oxide (NMO), CH₂Cl₂, MS (4 Å), 3h.

Finally, the methodology was applied to the short total synthesis of (S)-(+)-curcumene 14, (E)-(S)-(+)-3-dehydrocurcumene 15, and (S)-(+)-tumerone 16⁵⁰(Scheme 15), which have been targets for the synthetic community. However, there have been fewer enantioselective syntheses to date of tumerone 16. Our syntheses began with the synthesis of aldehyde (S)-12k (97.3 e.r.), derived by dual catalytic ECA of MeZn to enol 1b. The subsequent reduction of 12k, tosylation and nucleophilic displacement gave iodine 18 in 65% overall yield (three steps). Grignard addition of 19 to 18 gave curcumene 14 in 57% yield. The synthesis of dehydrocurcumene 15 began with a Wittig reaction between aldehyde 12k and 20 to give enone 21 in 64% yield. A subsequent Wittig reaction gave dehydrocurcumene 15 in 68% yield. Tumerone 16 was rapidly assembled in 51% overall yield in a procedure involving a Grignard addition of 19 to
aldehyde 12k followed by oxidation with tetrapropylammonium perruthenate (TPAP).\textsuperscript{36} Thus, this synthesis was completed in two purification steps from α,β-
unsaturated aldehyde 1b and delivered the target compound with 97.3 e.r.

\textbf{Scheme 16.} The proposed reaction mechanism of the dual catalytic EGA.

The proposed mechanism is based on the absolute configuration and previous
\textit{DFT} calculations made for the similar dual catalyzed 1,4-conjugate silyl addition\textsuperscript{30}
to α,β-unsaturated aldehydes 1. We propose that the \textit{in situ} generated L-Cu(II)-
alkyl specie 22 approaches the less sterically hindered \textit{Si-face} of the iminium
intermediate I to form II to selectively perform the 1,4-alkylation. The chiral amine
catalyst 7 is recovered after hydrolysis of the iminium specie III as well as the
copper catalyst complex is regenerated by the dialkylzink. Aqueous work up will
yield the desired β-alkyl aldehyde 12.
3.3 Enantioselective dual catalyzed synthesis of homoallylboronates

Our previous results in dual catalysis where we successfully have combined copper catalysis with iminium activation inspired us to expand the concept into new catalytic asymmetric approaches.

The enantioselective synthesis of chiral organoboron compounds is a field of great interest in organic synthesis. This is because of the possibilities of transforming the C-B bond stereospecifically to a C-O, C-N or C-C bond. Thus, the boron moiety may be a valuable precursor for several purposes. Even so, allyl- and homoallylboronates can be used as nucleophiles for additions to carbonyls or imines to give the corresponding alcohols or amines respectively.

A direct approach for the synthesis of homoallylboronates is the 1,6-boration of the 2,4-dienoate 22 which can be a challenging reaction since it requires both high chemo- regio- and enantioselectivity. In fact, performing the copper catalyzed addition of 23 to the dienoate 22 we were only able to obtain the 1,4-adduct 28 (scheme 17).

Scheme 17. The direct boration of the dienoate 22.

However we envisioned that with our new methods in dual catalysis, providing high regio- and enantioselectivity, we could furnish the 1,6-adduct 27 in a three component one-pot fashion incorporating the Wittig reaction. The reaction would proceed via the copper catalyzed amine activated 1,4-addition of bis(pinacolato) diboron (B(pin)) 23 to the α,β-unsaturated aldehyde 1 followed by the addition of the Wittig-reagent 26. However, this type of transformation can still be challenging due to competing 1,2 addition (scheme 18). B(pin) 23 has been successfully employed as boryl reagent in chiral copper-phosphine complex- or bidentate N-heterocyclic carbene-Cu complex-catalyzed enantioselective conjugate addition to α,β-unsaturated carbonyl compounds, alkenes, alkynes and dienes.
We began investigating the dual catalyzed one-pot reaction by using B:pin 23, cinnamic aldehyde 1a and phosphorane 26b different copper salts, chiral amines 7 and phosphine ligands 17. The key results are shown in table 8. We found that the reaction proceeded without the chiral amine catalyst but with poor 1,4-selectivity and low enantioselectivity (table 8, entry 1). Without the addition of the copper catalyst only very low conversion was observed (table 8, entry 2). To our delight, the homoallylboronate could be obtained asymmetrically when using the chiral amines 7 as catalysts in combination with Cu(OTf): as the transition metal co-catalyst and phosphines 17 as ligands in diethyl ether (table 8, entry 7). MeOH (3.0 equiv.) was added to regenerate the copper catalyst and maintaining the catalytic cycle. We was able to isolate the aldehyde intermediate 24, however it was hard to purify due to elimination of the boron group (regenerating the starting material). With the addition of an organic acid (10 mol%) the reaction proceeded with excellent 1,4-additionselectivity (table 8, entries 7 and 9) and high enantioselectivity. Of the investigated chiral amines, the highest reactivity and enantioselectivity was obtained when using 7d as the catalyst, providing the homoallylic product 27a in 65% isolated yield and 97.5:2.5 e.r. (table 8, entry 7). Phosphine 17a proved to be most efficient ligand for our conditions.
Table 8. Screening of reaction conditions.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>17</th>
<th>Cu-salt</th>
<th>Time (h)</th>
<th>Conv. (%)\textsuperscript{b}</th>
<th>e.r.\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>1</td>
<td>60\textsuperscript{d}</td>
<td>50:50</td>
</tr>
<tr>
<td>2</td>
<td>7d</td>
<td>a</td>
<td>-</td>
<td>7</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>7d</td>
<td>a</td>
<td>CuCl</td>
<td>4</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>7d</td>
<td>a</td>
<td>CuBr</td>
<td>4</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>5</td>
<td>7d</td>
<td>a</td>
<td>CuI</td>
<td>4</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>7d</td>
<td>a</td>
<td>CuOAc</td>
<td>4</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>7d</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>1</td>
<td>98</td>
<td>97.5:2.5</td>
</tr>
<tr>
<td>8</td>
<td>7d</td>
<td>a</td>
<td>CuCl\textsubscript{2}</td>
<td>4</td>
<td>&lt;2</td>
<td>n.d.</td>
</tr>
<tr>
<td>9\textsuperscript{e}</td>
<td>7d</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>1</td>
<td>98</td>
<td>69:31</td>
</tr>
<tr>
<td>10</td>
<td>7d</td>
<td>f</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>4</td>
<td>30</td>
<td>80:20</td>
</tr>
<tr>
<td>11</td>
<td>7d</td>
<td>g</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>4</td>
<td>24</td>
<td>63:37</td>
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<td>Cu(OTf)\textsubscript{2}</td>
<td>4</td>
<td>70</td>
<td>85:15</td>
</tr>
<tr>
<td>13</td>
<td>7d</td>
<td>i</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>4</td>
<td>70</td>
<td>90:10</td>
</tr>
<tr>
<td>14</td>
<td>7e</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>1</td>
<td>80</td>
<td>55:45</td>
</tr>
<tr>
<td>15</td>
<td>7h</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>2</td>
<td>95</td>
<td>72:28</td>
</tr>
<tr>
<td>16</td>
<td>7g</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>1</td>
<td>85</td>
<td>53:47</td>
</tr>
<tr>
<td>17</td>
<td>2b</td>
<td>a</td>
<td>Cu(OTf)\textsubscript{2}</td>
<td>7</td>
<td>20</td>
<td>n.d.</td>
</tr>
</tbody>
</table>
a The reaction was carried out under N₂ atmosphere.  
b Conversion to aldehyde 24a as determined by ¹H NMR analysis of the crude reaction mixture.  
c Determined by chiral-phase HPLC analysis of 27a.  
d Without the addition of chiral amine 7, the 1,4-/1,2-addition ratio was 67:33 as determined by ¹H NMR analysis of the crude reaction mixture.  
e Without the addition of 2-fluorobenzoic acid, the 1,4-/1,2- addition ratio was 75:25 as determined by ¹H NMR analysis of the crude reaction mixture.

With these results in hand we decided to expand the scope of the dual catalytic one-pot enantioselective reaction by submitting a variety of α,β-unsaturated aldehydes to our optimized reaction conditions. The reaction proceeded with excellent 1,4-selectivity and high enantioselectivity with aromatic as well as aliphatic enals. Aromatic enals with an electron-withdrawing substituent at para-, ortho-, meta- or para-position showed increased reactivity in the 1,4-boronation step (scheme 19). The subsequent Wittig reaction yielded the desired homoallylboronate in 60-65% yield and 88:12-97:3:2.5 e.r. The moderate yields are due to decomposition of the intermediate 24 through elimination, thus regenerating enal 1.
Scheme 19. The 1,4-boration reaction was run under N\textsubscript{2} atm. in the given temperature, for the given amount of time. \textsuperscript{a} 45 min, 22°C. \textsuperscript{b} 35 min, 22°C. \textsuperscript{c} 60 min, 22°C, 3.0 equiv. of enals 1. \textsuperscript{d} 45 min, 4°C.
Fig 7. Boronation of methyl cinnamate.

The presence of a chiral iminium species formed by the condensation of catalyst 7d and enal 1a in the 1,4-boronation step could be confirmed by \(^1\)H NMR and HRMS analysis of the crude reaction mixture. Subjecting the cinnamic methyl ester, hence excluding the possibilities of iminium formation, to our reaction conditions gave the corresponding racemic 1,4-boron adduct (fig 7). This indicates that the iminium formation is necessary to make the enantioselective dual catalyzed one-pot boration enantioselective.


To determine the absolute configuration of the homoallylboronate 27, we performed a one-pot synthesis of the homoallylic alcohol 29a (scheme 20). Comparison with the literature confirmed that stereochemistry at C5 was \(S \ (\{\alpha\})_{D}^{\circ} = -15.30 \ (c = 1.0, \text{EtOH})\); Lit. (R)-8: \(\{\alpha\})_{D}^{\circ} = +10.40 \ (c = 1.1, \text{EtOH}).^{45}
Scheme 21. The proposed reaction mechanism.

Based on these experiments, the absolute configuration of products 27 and DFT calculations previous made by our group,

\[ \text{Scheme 21. The proposed reaction mechanism.} \]

Thus, the in situ generated L-Cu-Bpin species I approaches the less sterically hindered Si-face (R = aryl) of the β-carbon of the iminium species II. Subsequent C-B formation converts III into IV, which after hydrolysis and addition of MeOH will release the amine catalyst 7 and regenerate the copper catalyst as MeO-Cu-L, and furnish the β-borylaldehyde intermediate 24. Next the in situ Wittig reaction with phosphine 26 gives the final homoallylboronate product 27.

34
4. DUAL CATALYSIS BY TRANSITION METAL CATALYSIS AND ENAMINE ACTIVATION.

4.1. Enantioselective dual catalyzed α-allylation of aldehydes by combination of Palladium and chiral amine catalysts.

Based on our previous work in dual catalyzed α-allylation of aldehydes, we began to investigate the possibility of using a chiral amine catalyst to develop the direct enatiomselective α-allylation (scheme 22). The dual catalytic cycle starts with condensation of the aldehyde 31 and the chiral catalyst 7 which eventually forms the enamine II (scheme 23). The chiral enamine II then reacts in a nucleophile addition to the catalytically generated Pd π-allyl complex I, forming the intermediate III. Subsequently III will undergo hydrolysis and reductive elimination to form the α-allylic aldehyde and regenerate the Pd-catalyst as well as the chiral amine catalyst. However, there is the possibility of racemization via enolization of the product 33 or via the enaminification of intermediate III. The aldehyde product 33 was therefore reduced in situ with NaBH₄ to give alcohol 34.
Scheme 23. The proposed reaction pathway.

Initially we subjected 3-phenylpropionaldehyde 31a and phenylallyl acetate 32a to chiral amine catalysts 7d in the presence of a catalytic amount of Pd(PPh₃)₄ in DMSO at room temperature. To our delight, the direct catalytic enantioselective α-allylation of aldehyde 31a reached 70% conversion after 13 h, affording, after in situ reduction, the desired α-allylated alcohol 34a as a single regiosomer in moderate enantioselectivity (75:25 e.r.) in DMSO (table 9, entry 1). Subsequent optimization studies showed that DMSO gave the highest reactivity whereas DMF gave the highest enantioselectivity (table 9 entries 2-4). Lowering the temperature to +4°C increased the enantioselectivity as well as decreased the reactivity. Performing the reaction in a 1:1 mixture of DMSO and DMF increased the reactivity, with the selectivity remaining at a high level (table 9, entry 8). Initially, Pd(OAc)₂ showed higher selectivity whereas Pd(PPh₃)₄ showed higher reactivity (table 9, 8-11). However, Pd(PPh₃)₄ could catalyze the reaction even at -20°C, giving the desired product in high yield and high stereoselectivity (table 9, entry 11).
We found that the highest reactivity and enantioselectivity was achieved when using chiral amine 7d (20 mol%) in combination with Pd(PPh)$_3$ (5 mol%) as the transition metal co-catalyst in a 1:1 mixture of DMSO and DMF at -20°C. The reaction proceeded with high regio- and enantioselectivity with the use of the O-protected simple commercially available chiral amines 7d and 7h in combination with Pd(PPh)$_3$ (table 9, entry 11-12). Both bromide and chloride of the phenylallyl 32 was tested as alternative leaving groups (table 9, entry 15-16), however none showed higher reactivity than acetate.
Table 9. Screening of reaction conditions. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>LG</th>
<th>Pd-salt</th>
<th>Cat.</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
<th>e.r. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>7d</td>
<td>-</td>
<td>DMSO</td>
<td>22</td>
<td>13</td>
<td>70</td>
<td>75:25</td>
</tr>
<tr>
<td>2</td>
<td>OAc</td>
<td>Pd(OAc)$_2$</td>
<td>7d</td>
<td>PPh$_3$</td>
<td>DMSO</td>
<td>22</td>
<td>29</td>
<td>93</td>
<td>81:19</td>
</tr>
<tr>
<td>3</td>
<td>OAc</td>
<td>Pd(OAc)$_2$</td>
<td>7d</td>
<td>PPh$_3$</td>
<td>NMP</td>
<td>22</td>
<td>112</td>
<td>37</td>
<td>72:5:27:5</td>
</tr>
<tr>
<td>4</td>
<td>OAc</td>
<td>Pd(OAc)$_2$</td>
<td>7d</td>
<td>PPh$_3$</td>
<td>DMF</td>
<td>22</td>
<td>24</td>
<td>63</td>
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</tr>
<tr>
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<td>OAc</td>
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<td>7d</td>
<td>PPh$_3$</td>
<td>DMSO</td>
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<td>48</td>
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<td>85.5:14.5</td>
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<td>Pd(OAc)$_2$</td>
<td>7d</td>
<td>PPh$_3$</td>
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<td>48</td>
<td>43</td>
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<td>7d</td>
<td>PPh$_3$</td>
<td>DMF</td>
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<td>62</td>
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<td>85.5:14.5</td>
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<tr>
<td>8</td>
<td>OAc</td>
<td>Pd(OAc)$_2$</td>
<td>7d</td>
<td>PPh$_3$</td>
<td>DMF:DMSO</td>
<td>4</td>
<td>24</td>
<td>65</td>
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<tr>
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<td>7d</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>4</td>
<td>24</td>
<td>95</td>
<td>83:17</td>
</tr>
<tr>
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<td>7d</td>
<td>PPh$_3$</td>
<td>DMF:DMSO</td>
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<td>40</td>
<td>11</td>
<td>n.d.</td>
</tr>
<tr>
<td>11</td>
<td>OAc</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>7d</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>40</td>
<td>96</td>
<td>96:4</td>
</tr>
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<td>12</td>
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<td>Pd(PPh$_3$)$_4$</td>
<td>7h</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>40</td>
<td>69</td>
<td>97:3</td>
</tr>
<tr>
<td>13</td>
<td>OAc</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>7e</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>48 &lt;2</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>OAc</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>2b</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>48 &lt;2</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Br</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>7d</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>48</td>
<td>40</td>
<td>96:4</td>
</tr>
<tr>
<td>16</td>
<td>Cl</td>
<td>Pd(PPh$_3$)$_4$</td>
<td>7d</td>
<td>-</td>
<td>DMF:DMSO</td>
<td>-20</td>
<td>48</td>
<td>21</td>
<td>88:12</td>
</tr>
</tbody>
</table>

*a* Under N$_2$ atmosphere.  
*b* Determined by $^1$H NMR analysis of the crude reaction mixture.  
*c* determined by chiral-phase HPLC analysis of 34a.
With these results in hand we decided to probe the scope of the direct dual catalytic enantioselective α-allylation by subjecting a variety of aldehydes to our optimized reaction conditions (table 10). The reaction continued to furnish the desired product in high yields and excellent enantioselectivity in up to 83% and 98:2 e.r. respectively (table 10, entry 5).

**Table 10.** Dual Pd- and aminecatalyzed direct α-allylation of various aldehydes 31.\(^a\)

![Reaction scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^1)</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
<th>e.r.(^c)</th>
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<tbody>
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<td>1</td>
<td>Ph</td>
<td>34a</td>
<td>41</td>
<td>80</td>
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</tr>
<tr>
<td>2</td>
<td>n-Hex</td>
<td>34b</td>
<td>41</td>
<td>85</td>
<td>96:4</td>
</tr>
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<td>n-Bu</td>
<td>34c</td>
<td>41</td>
<td>75</td>
<td>97:3</td>
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<tr>
<td>4</td>
<td>n-Pr</td>
<td>34d</td>
<td>41</td>
<td>81</td>
<td>96:4</td>
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<tr>
<td>5</td>
<td>Et</td>
<td>34e</td>
<td>45</td>
<td>83</td>
<td>98:2</td>
</tr>
<tr>
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<td>Me</td>
<td>34f</td>
<td>45</td>
<td>79</td>
<td>96.6:3.4</td>
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<tr>
<td>7</td>
<td>H</td>
<td>34g</td>
<td>48</td>
<td>65</td>
<td>94:6</td>
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<tr>
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<td>CH(_2)CH-</td>
<td>34h</td>
<td>45</td>
<td>70</td>
<td>95:5</td>
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<td>i-Pr</td>
<td>34i</td>
<td>48</td>
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<td>45</td>
<td>83</td>
<td>95:5</td>
</tr>
<tr>
<td>11</td>
<td>BnO(_2)CCH(_2)CH(_2)-</td>
<td>34k</td>
<td>45</td>
<td>45</td>
<td>93:7</td>
</tr>
</tbody>
</table>

\(^a\) The reaction was carried out under N\(_2\) atmosphere with Pd(PPh\(_3\))\(_4\) (5 mol%), 7d (20 mol%) and 31 (3.0 equiv.). \(^b\) Isolated yield of 34 after silica gel chromatography. \(^c\) Determined by chiral phase HPLC analysis of 34.
Table 11. Dual Pd- and amine-catalyzed direct α-allylation by various acetates 30.\(^a\)

![Diagram: Reaction scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
<th>e.r.(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>4-MeOC(_6)H(_4)</td>
<td>34l</td>
<td>48</td>
<td>30</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>(n)-Pr</td>
<td>4-MeOC(_6)H(_4)</td>
<td>34m</td>
<td>48</td>
<td>50</td>
<td>98:2</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>4-ClC(_6)H(_4)</td>
<td>34n</td>
<td>48</td>
<td>78</td>
<td>95.5:4.5</td>
</tr>
<tr>
<td>4</td>
<td>(n)-Pr</td>
<td>4-ClC(_6)H(_4)</td>
<td>34o</td>
<td>48</td>
<td>81</td>
<td>97.5:2.5</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>H</td>
<td>34p</td>
<td>48</td>
<td>56</td>
<td>92:8</td>
</tr>
</tbody>
</table>

\(^a\) The reaction was carried out under \(\text{N}_2\) atmosphere with \(\text{Pd(PPh}_3\)_4\) (5 mol%), \(7d\) (20 mol%) and \(31\) (3.0 equiv.). \(^b\) Isolated yield of 34 after silica gel chromatography. \(^c\) Determined by chiral phase HPLC analysis of 34.

Encourage by these result we went on to investigate how well different allylacetates performed under our reaction conditions. The results are summarized in table 11. However we observed a decrease in reactivity when using phenyl allylacets with an electron-donating group in \(para\)-position (table 11, entries 1 and 2), though the enantioselectivity remained at high levels (table 11, entries 1-5).
Scheme 24. Synthesis of 2-benzylbutane 1,4-diol 36a in 49% overall yield.

In order to establish the absolute configuration of 34 we decided to transform α-allyl alcohol product 34a to the known 2-benzylbutan 1,4-diol 36a, by OsO₄ cleavage of the double bond followed by reduction with NaBH₄ (scheme 24). Comparison of optical rotation with the literature established the absolute configuration as (R)-36a.⁴⁴

The results are in accordance with the proposed mechanism (scheme 23) where the Si-face of the chiral enamine II is shielded by the proline moiety, forcing the Pd π-allyl complex I to approach from the Re-face and finally furnishing the (S)-34 (R⁵ = aryl).

In conclusion we have combined the two catalytic cycles of the Pd π-allyl formation with the chiral enamine activation in order to create an efficient highly regio- and enantioselective route to α-allyl alcohols.
5. CONCLUDING REMARKS

Over the last decade the field of organocatalysis has grown exponentially and proven to be a powerful method for synthesis of chiral compounds of high optical purity. The stereochemistry of the products is controllable by choice of organocatalyst. Simple chiral molecules such as amino acid derivatives can, through iminium or enamine activation or combination of both, catalyze a large number of transformations with great selectivity. We have showed that complex molecules with several stereogenic centers can be obtained from simple achiral molecules in one-pot procedures.

We have also showed that asymmetric aminocatalysis can successfully be combined with transition metal catalysis in dual catalysis. We have combined both iminium and enamine activation with copper- and palladiumcatalysis respectively. We have achieved both β-alkylation and β-boration of α,β-unsaturated aldehydes as well as α-allylation of aldehydes. The combination of aminocatalysis and transition metal catalysis creates new possible transformations in the field of organocatalysis.
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7. REFERENCES

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