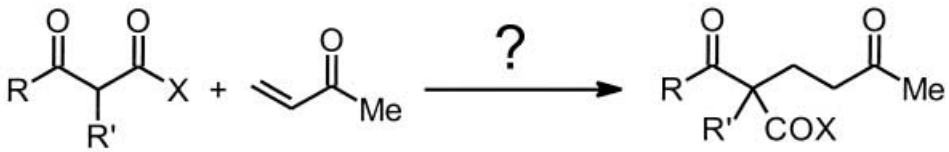
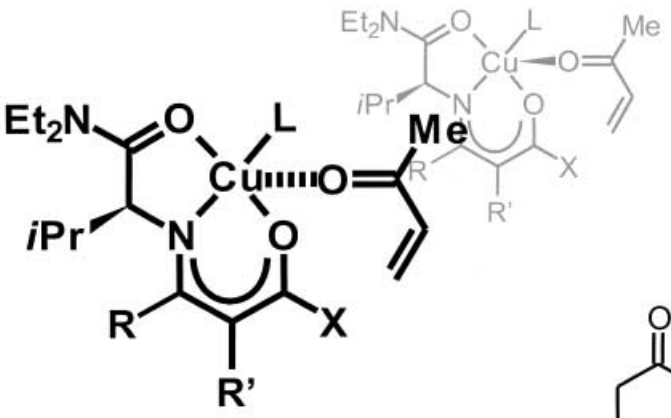
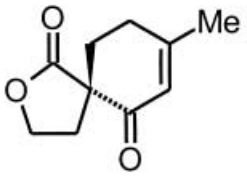
# Quaternary Stereocenters by Asymmetric Michael Reaction

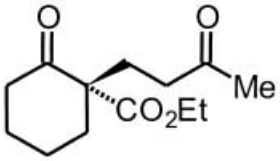



Screening of metal ions and chiral ligands




>99% *ee*

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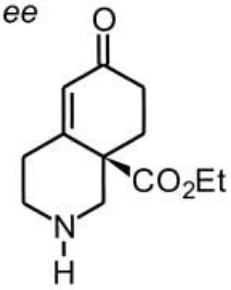


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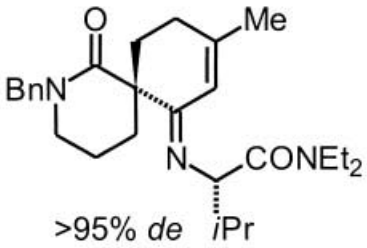
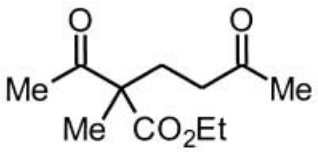



>95% *de*

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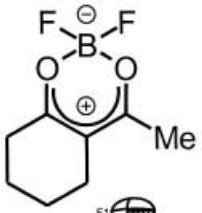


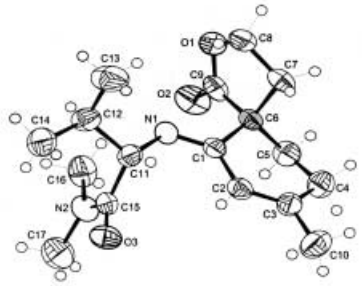

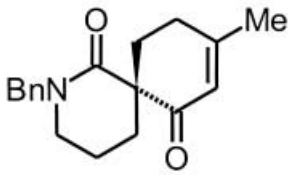


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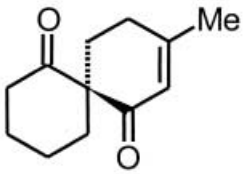


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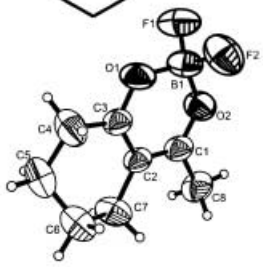



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# Formation of Quaternary Stereocenters by Copper-Catalyzed Michael Reactions with L-Valine Amides as Auxiliaries

**Jens Christoffers*[a]**

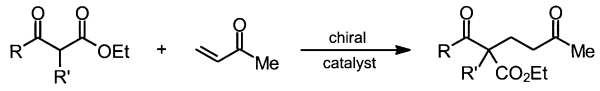
*Dedicated to Professor Karl Heinz Dötz on the occasion of his 60th birthday*

**Abstract:** Extensive investigations of chiral auxiliaries and active metals for Michael addition of 1,3-dicarbonyl compounds with vinyl ketones are summarized. Our efforts result in a widely applicable auxiliary-mediated, copper(II) acetate-catalyzed procedure. For these purposes, L-valine diethylamide is an optimal chiral auxiliary giving quaternary stereocenters with up to 99% *ee* at ambient temperature. No inert or anhydrous conditions are required, the solvent is simply acetone, and the auxiliary can be recovered almost quantitatively after workup.

**Keywords:** amino acid derivative · catalysis · chirality · Michael addition · stereoselectivity

## Introduction

The asymmetric Michael reaction is one of the most powerful tools for stereoselective C–C-bond formation.[1] To date, three catalytic enantioselective methods define the state of the art in this area. In 1992 Ito and co-workers introduced rhodium catalysts with the chiral PhTrap ligand (PhTrap = 2,2′-bis[1-diphenylphosphanyl)ethenyl]-1,1′-biferrocene), which allowed for highly selective (up to 95% *ee*) conversion of $\alpha$-cyano propionates with $\alpha,\beta$-unsaturated ketones and aldehydes.[2] Two years later, Shibasaki et al. reported on efficient heterobimetallic BINOL-based catalysts that are still used today and have no significant competition as far as the formation of tertiary stereocenters by Michael addition is concerned.[3] Unfortunately, these expectations could hardly be extended to synthetic targets with quaternary stereocenters.[4] In recent years, Shibasaki and co-workers attempted to develop air-stable, storable, and reusable catalysts, and in 2000 they first presented a so-called "linked-BINOL" system to respond to the above-mentioned issues.[5] Most recently, however, Sodeoka et al. published the latest ultimate breakthrough in this area. By applying a $Pd^{II}$–BINAP-based catalyst, selectivities of up to 99% *ee* at relatively high temperature (up to $-10\,^{\circ}C$) can be achieved for the construction of quaternary stereocenters (Scheme 1).[6]




1 2 3

Scheme 1. Formation of a quaternary stereocenter in the catalytic asymmetric Michael reaction of $\beta$-ketoester **1** with methyl vinyl ketone (**2**).

The auxiliary-assisted asymmetric Michael reaction represents an important alternative route for generating quaternary stereocenters.[7] This article summarizes our work on this type of C–C-bond formation, which started in 1996 with a combinatorial kind of screening of chiral ligands and transition metal ions to find an efficient procedure capable of constructing quaternary stereocenters at ambient temperature. From these investigations the enamine formation turned out to be essential for our method. Thus, we extended the screening, and in 2000 we were able to develop a new concept in Michael reactions: the combination of copper catalysis and the first utilization of L-valine diethylamide as a readily available and reusable auxiliary. This new concept now allowed for the highly selective construction of quaternary stereocenters at ambient temperature.

## First Screening

From our work on $Fe^{III}$-catalyzed Michael reactions,[8] the following working model was deduced in order to start a search for a new chiral catalyst applicable in asymmetric Michael reactions (Scheme 2). Most transition metals form diketonate complexes with $\beta$-dicarbonyl compounds such as $\beta$-ketoesters **1**. The six-membered ring chelate is planar and particularly stabilized by π-delocalization. The acceptor **2** is

[a] Prof. Dr. J. Christoffers
Institut für Organische Chemie, Universität Stuttgart
Pfaffenwaldring 55, 70569 Stuttgart (Germany)
Fax: (+49) 711-685-4269
E-mail: jchr@po.uni-stuttgart.de

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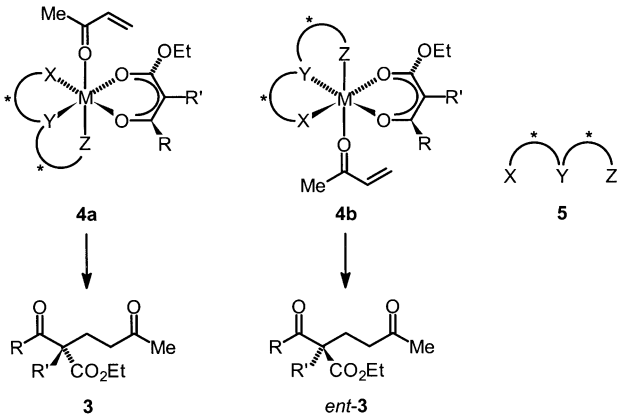


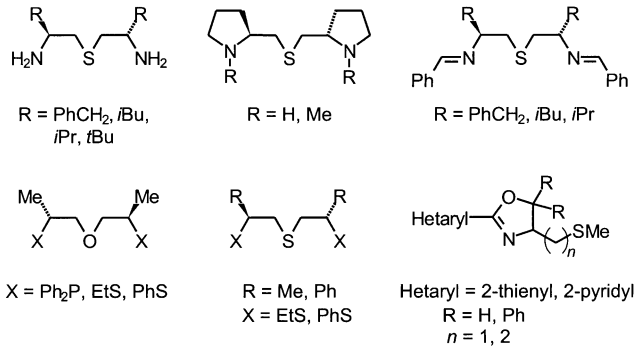

Scheme 2. Diastereofacial differentiation of the *Re* and *Si* site of $\beta$-diketonates with tridentate ligands **5**.

proposed to coordinate at a vacant site to form a species **4** by ligand exchange. The function of the center metal is not only to hold the acceptor in proximity to the donor, but also to activate the acceptor by the Lewis acidity of the metal. Subsequently, the nucleophilic carbon atom of the dionato ligand is alkylated by the coordinating acceptor to form an intermediate from which the product **3** is liberated.

A stereogenic center is generated at the metal with donor and acceptor in a facial situation. If an additional chiral ligand coordinates to one or to all of the three coordination sites at the opposite face of the octahedron, two diastereoisomeric intermediates **4a** and **4b** result. In particular, one could refer to a tridentate chiral ligand of the general type **5** in order to realize a diastereofacial differentiation of the upper and lower site of the diketonate chelate. In the ideal case, the acceptor would prefer one of the coordination isomers **4a** or **4b** and thus, causes a stereoselectivity in the formation of the enantiomeric products **3** and *ent*-**3**.

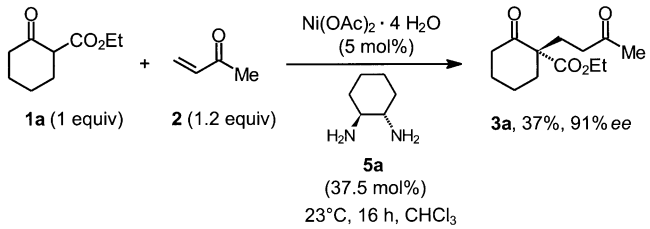
With consideration of this model, a set of novel chiral tridentate ligands (a selection of which is shown in Scheme 3) was prepared from $\alpha$-amino and $\alpha$-hydroxy acids[9] and screened in combination with 14 different active metal salts in model Michael reactions.

Enantioselectivities of only up to 30% *ee* were determined in some cases with $Ni^{II}$, $Co^{II}$, and $Cu^{II}$ salts, thus, we decided to extend our search to a large number of bidentate phosphane, amino- and thioether $C_1$- and $C_2$-symmetrical ligands that




Scheme 3. Tridentate ligands derived from $\alpha$-amino acids and $\alpha$-hydroxy acids.

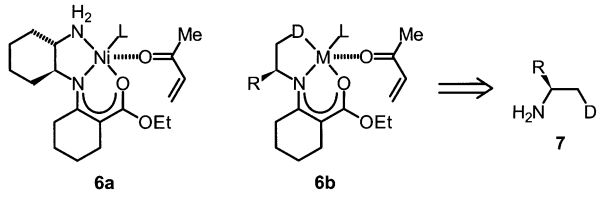
were commercially available and known from the literature. The effective catalytic system finally obtained in 1999 is shown in Scheme 4. Conversion of $\beta$-ketoester **1a** with methyl vinyl ketone (**2**) in the presence of catalytic amounts of




Scheme 4. First $Ni^{II}$-catalyzed Michael reaction exceeding 90% *ee* at ambient temperature with *trans*-cyclohexanediamine **5a** as chiral ligand.

$Ni(OAc)_2 \cdot 4H_2O$ and *trans* (*S*,*S*)-cyclohexanediamine (**5a**) as the chiral ligand gave product **3a** with 91% *ee*.[10] This result was of outstanding importance since it was the first example of a metal-catalyzed Michael reaction forming a quaternary stereocenter with high enantioselectivity at ambient temperature. The efficiency, however, was very low (37% yield), but interestingly corresponded to the amount of chiral ligand used (37.5 mol%; for unknown reasons the Ni to ligand ratio of 1:7.5 turned out to be optimal). It must be mentioned that significant selectivity was obtained only with $Ni^{II}$ acetate. All other metal salts, even $Ni^{II}$ with different counterions, gave worse results. The role of the counterion is actually important and will be discussed later.

The correlation between yield and amount of diamine outlined in Scheme 4 prompted us to develop a new working model of the Ni-catalyzed asymmetric Michael reaction. In order to explain the high stereoselectivity, we proposed in situ enamine formation of the diamine with $\beta$-ketoester **1a**. After deprotonation of the N-H proton, which is acidified by H bonding, this intermediate enamine is able to coordinate as an azadiketonate to $Ni^{II}$ under formation of a six-membered chelate with delocalization of the $\pi$-electron density. Moreover, the second amino function could now form an additional five-membered chelate to the Ni metal. As depicted in Scheme 5, the stereogenic centers of the diamine generate a



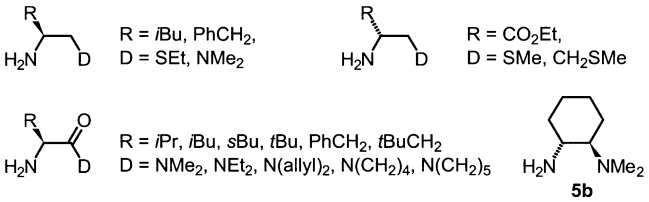

Scheme 5. Proposed intermediate **6a** for the Ni-catalyzed asymmetric Michael reaction, and deduction of a lead structure for a chiral auxiliary **7**.

chiral environment at the Ni center, and as a consequence, the front and back face of the diketonate are subject to diastereofacial differentiation. For steric reasons, we assume coordination and activation of the acceptor **2** from the back face (structure **6a**); this being in accordance with the observed configuration of product **3a** formed with (*S*,*S*)-diamine **5a**. However, it turned out that diamine **5a** is actually disadvanta-

geous, because the second primary amino function is capable of a number of side reactions that are responsible for the low efficiency of the reaction in Scheme 4. The stereochemical model **6a**, however, appeared to be valuable in order to realize high selectivity. We therefore retained the key elements of intermediate **6a** in a new model **6b**. This includes the formation of an additional five-membered chelate ring with a donor function D, which is not a primary amine, and diastereofacial differentiation of the Michael donor by a stereogenic center in this five-membered chelate ring. An azadiketonate **6b** is consequently derived from $\beta$-ketoester **1a** and a chiral primary amine **7** with an additional donor function D.

## Second Screening

The model complex **6b** consequently resulted in the preparation of a variety of primary amines with a second donor function D. First of all, the cyclohexanediamine **5b** with both

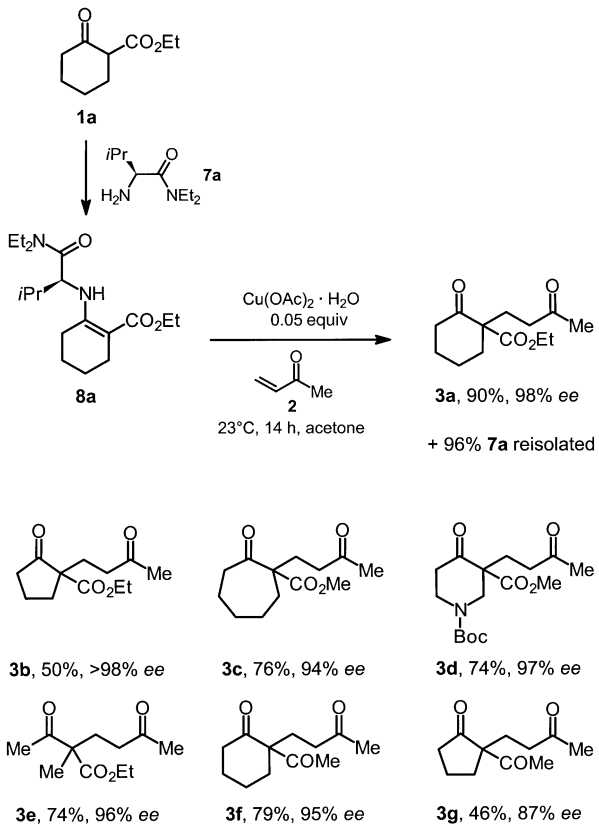



Scheme 6. Chiral auxiliaries investigated in the second screening.

primary and tertiary amino function was among this set (Scheme 6).[11] All other auxiliaries derive from the $\alpha$-amino acids L-phenylalanine, L-leucine, L-isoleucine, L-valine, L-cysteine, L-methionine, L-*tert*-leucine and L-neopentylglycine.[12]

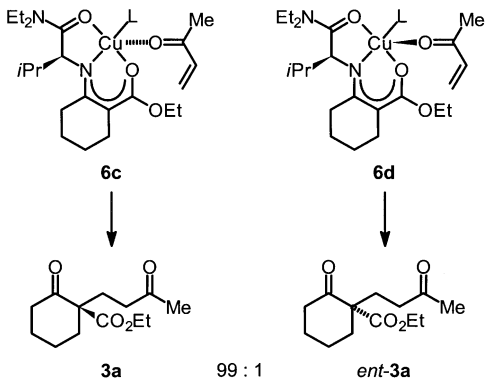
A screening program was initiated with 14 metal salts and ketone **2** as the acceptor. Various enamines, such as **8a**, were prepared from combinations of auxiliaries **7** with 10 different Michael donors and investigated in asymmetric Michael reactions. To our surprise, significant selectivities were now achieved with different metal ions, however, $Cu^{II}$ was found to be optimal.[13] Again, the counterion was crucial and optimal with acetate, since the enamines need to be deprotonated prior to coordination to $Cu^{II}$. Representative results are shown in Scheme 7.

With respect to the auxiliary, L-valine diethylamide (**7a**) turned out to be most effective. The developed procedure is of practical interest: conversion of enamines such as **8a** with **2** in the presence of $Cu(OAc)_2 \cdot H_2O$ (1–5 mol%) proceeds at ambient temperature. Anhydrous or inert conditions are not required, and the solvent is simply acetone. After acidic workup, the products **3a–g** were isolated in generally good yield, with selectivities up to 95–99% *ee*. The auxiliary could be separated from the reaction mixture by extraction and recovered almost quantitatively. The selectivities obtained for these products have, to date, not been exceeded by other methods. A special feature of the copper-catalyzed reaction is the compatibility with donor functions such as the carbamate moiety in product **3d**.[14] Substrates of this type do not convert under the conditions of Shibasaki's heterobimetallic catalysts.




Scheme 7. $Cu^{II}$-catalyzed asymmetric Michael reaction with L-valine diethylamide (**7a**) as auxiliary.

The absolute configuration perfectly agrees with our working model depicted in Scheme 8. Enamines such as **8a** coordinate as tridentate ligands with one six-membered azadiketonate chelate and one five-membered ring to $Cu^{II}$. Because the isopropyl group shields the front face of the planar donor, the acceptor preferentially coordinates to and is activated from the back face of the complex. Thus, L-valine results in *R* configuration of the product **3a**. Scheme 8 also clarifies the successful role of amino acid amides as auxiliaries. The second donor function D coordinates through its carbonyl oxygen to copper, and the role of the amide nitrogen is just to provide electron density to the carbonyl moiety. Actually, $\alpha$-amino acid esters, as earlier introduced by Koga et al.[15] do not show any selectivity in this copper-catalyzed reaction.

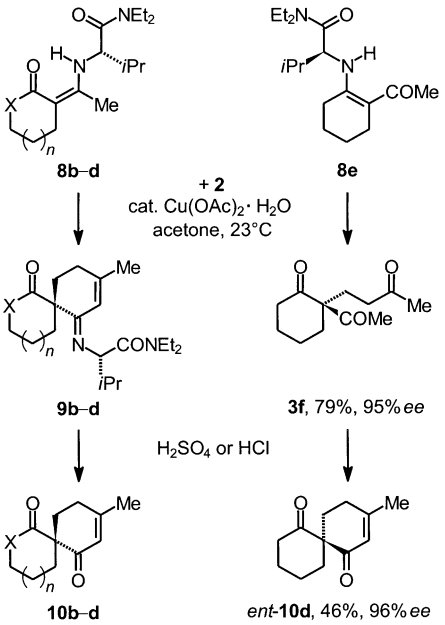



Scheme 8. Proposed origin of the stereoselectivity and absolute configuration in copper-catalyzed, auxiliary-mediated Michael reactions.

## Spirocyclizations

When $\alpha$-acetyllactones[16] or $\alpha$-acetyllactams[17] are converted with auxiliary **7a**, the exocyclic enamines **8b** and **8c** are obtained (Scheme 9). In contrast to the endocyclic cogeners such as **8a**, upon $Cu^{II}$-catalyzed conversion with ketone **2**

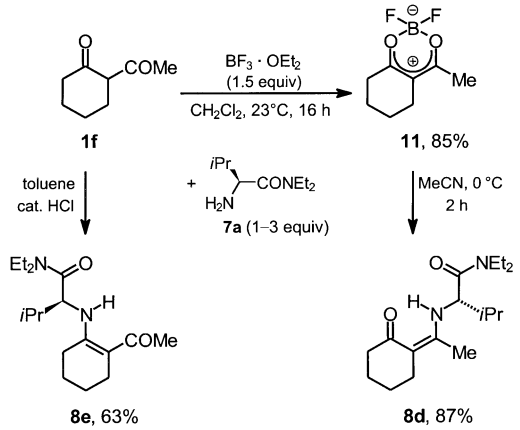



| 8–10 | n | X | 9 yield | de | 10 | ee |
|---|---|---|---|---|---|---|
| b | 0 | O | 54% | >99% | | >99% |
| c | 1 | NBn | 37% | >95% | | >95% |
| d | 1 | $CH_2$ | 46% | 86% | | 87% |

Scheme 9. Formation of *R* and *S* configured spiroketones from exo- and endocyclic enamines **8** with L-valine diethylamide (**7a**) as chiral auxiliary.

these exocyclic enamines give the spirocyclic products **9b** and **9c** in a sequence of Michael reaction and Robinson annulation. The imine moiety exhibits reasonable hydrolytic stability due to a neopentyl situation and is therefore retained in the products **9** (Scheme 9). Acid-catalyzed hydrolysis finally yields the spiroketones **10b** and **10c**.[18] When the exocyclic enamine **8d**, derived from $\alpha$-acetylcylohexanone **1f**, is converted along this sequence spirodiketone **10d** with *S* configuration is obtained. Product **3f**, generated from the endocyclic enamine **8e** is spirocyclized to *ent*-**10d** with the opposite *R* configuration. Evidently, exo- and endocyclic enamines give complementary stereochemical outcomes of the reaction although the same enantiomer of the auxiliary **7a** is applied. This behavior is a direct consequence of the mechanistic picture shown in Scheme 8, and can be assumed to be additional evidence for our stereochemical model.

A precondition for this complementary stereochemistry is, of course, the control of the regioselectivity of enamine formation realized for compound **1f** as depicted in Scheme 10. The endocyclic enamine **8e** results as the thermodynamic product from acid-catalyzed conversion of donor **1f** with auxiliary **7a**. The kinetic, exocyclic enamine **8d** is the product of the aminolysis of diketonato difluoroborate **11**.




Schema 10. Formation of endo- and exocyclic enamines.

## Acknowledgements

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