Enantioselective synthesis of natural products containing tertiary alcohols and contributions to a total synthesis of phorbasin B
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Chapter 1

Methods for the Preparation of Chiral Tertiary Alcohols and Ethers

This chapter gives an introduction on the prominent asymmetric synthesis of tertiary alcohols and ethers and the applications of asymmetric dihydroxylation and epoxidation of olefins in natural product synthesis. The new developments in this field are also summarized.
Chapter 1

1.1 Introduction

Quaternary stereocenters, that means, carbon stereocenters without a carbon-hydrogen bond, are a widely encountered structural motif in natural compounds and pharmaceuticals. Among these quaternary stereocenters, the preparation of chiral enantiopure tertiary alcohols and ethers represents an important, but also a very challenging field. To access these compounds, their asymmetric synthesis is of particular importance, due to the fact that racemic mixtures of tertiary alcohols are difficult to resolve.

Applicable on both small and large scale, the kinetic resolution of a racemic mixture is one of the most common approaches for the production of enantiomerically pure compounds. Many (bio)catalysts have been developed for the kinetic resolution of secondary alcohols via esterification, or hydrolysis of the preformed ester. The (enzymatic) kinetic resolution of tertiary alcohols has turned out to be way more difficult, however, and suffers from low enzyme activities and selectivities. In addition, dynamic kinetic resolution involving in situ racemization of the unwanted enantiomer is not readily achieved in the case of tertiary alcohols. The synthesis of enantiopure secondary alcohols is nowadays also readily accomplished by asymmetric hydrogenation of ketones with transition metals and alcohol dehydrogenases, however, these strategies obviously do not apply for tertiary alcohols.

An additional complication is that chiral tertiary alcohols, and in particular benzylic and allylic tertiary alcohols, are prone to acid-catalyzed racemization via an $S_N1$ pathway and elimination via an $E1$ pathway. All together this makes the development of new approaches for the synthesis of chiral enantiopure tertiary alcohols and ethers an important challenge.

Figure 1. Natural compounds containing tertiary alcohols and ethers
Introduction

Over the past decade, progress has been made in the (asymmetric) synthesis of enantiopure tertiary alcohols not only via established approaches, e.g. the aldol reaction\[7\] and asymmetric hydroxylation\[8\] but also applying new strategies. In 2008, the group of Aggarwal reported a novel method to prepare chiral tertiary alcohols with very high enantiospecificity from enantiopure secondary alcohols via an enantiodivergent conversion\[9\] (Scheme 1). Depending on the use of either a borane or a boronic ester, both enantiomers of a series of benzylic tertiary alcohols were obtained from one enantiomer of the secondary alcohol. Knochel et al., in 2005, presented a highly enantiospecific preparation of tertiary alcohols by copper-mediated allylic S\(\text{N}_2\) substitution.\[10\] Starting from enantiopure allylic pentafluoro benzoates, like 15, allylic substitution was followed by oxidation and Baeyer-Villiger rearrangement. This sequence afforded tertiary alcohol 17 with an \(ee\) of 92-99\% (Scheme 2). Although from a retrosynthetic point of view not always elegant, the “good old” Baeyer-Villiger rearrangement, being strictly stereospecific, is somewhat underestimated.

Apart from these enantiospecific processes, the focus in research has mostly been on catalytic enantioselective processes, the most prominent ones being discussed below.

Scheme 1. Lithiation-borylation of chiral secondary carbamates leading to tertiary alcohols

Scheme 2. Enantiospecific preparation of tertiary alcohol 17 by copper-mediated allylic S\(\text{N}_2\) substitution
1.2 Asymmetric dihydroxylation

Generally, the dihydroxylation of olefins is achieved by oxidation with a transition metal oxo-species. An important landmark in this field is the asymmetric dihydroxylation with OsO₄/dihydroquinine acetate by Sharpless in 1980. In this initial system, stoichiometric amounts of ligand and OsO₄ were required, which made this reaction somewhat unattractive due to the high cost and the toxicity of OsO₄. Subsequently, however, this stoichiometric procedure was transformed into a highly effective catalytic process due to the application of N-methyl morpholine N-oxide as the co-oxidant. Inorganic co-oxidants were investigated as well for the re-oxidation of Os(VI) glycolate in the reaction, and inexpensive K₃Fe(CN)₆ (potassium ferricyanide) turned out to be versatile. According to the supposed mechanism, two competitive catalytic cycles exist in the Sharpless asymmetric dihydroxylation, the primary cycle (desired) affording high ee, and the secondary cycle (undesired) affording low ee (Scheme 3). The use of a two-phase system suppressed the secondary catalytic cycle, and since then K₃Fe(CN)₆ together with the second generation ligands (DHQD)₂PHAL and (DHQ)₂PHAL, and K₂OsO₂(OH)₄ are combined into the known commercial available “AD-mix-α or AD-mix-β”. The absolute configuration of the diol products can be predicted using an empirical model (Scheme 4). In this mnemonic device, the olefin is oriented following the size constrains (R_L = Large substituent, R_M = Medium-sized substituent, and R_S = Small substituent), and then this olefin is dihydroxylated from the top or the bottom face using AD-mix-β or AD-mix-α, respectively.

Scheme 3. Catalytic cycles in the Sharpless catalytic asymmetric dihydroxylation
Introduction

Scheme 4. Sharpless asymmetric dihydroxylation and the prediction of the stereochemistry

Regarding the synthesis of chiral tertiary alcohols, the use of 1,1-disubstituted, trisubstituted and tetrasubstituted olefins are appropriate substrates\cite{13} in the Sharpless asymmetric dihydroxylation, and give good yields and selectivities\cite{16a, 18} (Table 1). An important discovery was that the addition of CH$_3$SO$_2$NH$_2$ accelerated the reaction dramatically,\cite{16a} which is crucial for the application of this reaction for a number of steric hindered and in particular tetrasubstituted olefins,\cite{19} and even $\alpha,\beta$-unsaturated ketones.\cite{20}

<table>
<thead>
<tr>
<th>olefins</th>
<th>AD-mix-H</th>
<th>AD-mix-α</th>
<th>olefins</th>
<th>AD-mix-H</th>
<th>AD-mix-α</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ee</td>
<td>ee</td>
<td></td>
<td>ee</td>
<td>ee</td>
</tr>
<tr>
<td>$\text{Me}$ &amp; 83 (R) &amp; 85 (S) &amp; $\text{Me}$ &amp; 99 (R) &amp; 97 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{OTBS}$ &amp; 93 (R) &amp; 95 (S) &amp; $\text{OTBS}$ &amp; 99 (R) &amp; 97 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{OMe}$ &amp; 99 (R) &amp; 97 (S) &amp; $\text{OMe}$ &amp; 95 (R) &amp; 96 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{H}$ &amp; 99 (R, R) &amp; 97 (S, S) &amp; $\text{H}$ &amp; 99 (R) &amp; 98 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{H}$ &amp; 94 (R) &amp; 93 (S) &amp; $\text{H}$ &amp; 99 (R) &amp; 98 (S)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\text{H}$ &amp; 99 (R) &amp; 98 (S) &amp; $\text{H}$ &amp; 99 (R) &amp; 97 (S)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Table 1. Catalytic asymmetric dihydroxylation of olefins according to Sharpless

Since the first asymmetric dihydroxylation has been reported, the reaction has been studied extensively not only with OsO$_4$,\cite{21} but also with osmium-free methodologies,\cite{22} e.g. permanganate\cite{23} and ruthenium oxide.\cite{24} Different kinds of substrates, for example, divinyl ketones, symmetrical conjugated dienes,\cite{24} dienes
Chapter 1

with isolated double bonds,\(^{26}\) and 1,1-disubstituted allylic alcohols and derivatives have been explored as well.\(^{27}\)

The construction of tertiary alcohols using dihydroxylation of alkenes is a very important approach in natural products synthesis.\(^{28}\) Takano et al. reported the synthesis of (+)-verrucosidin 21 in 1988\(^{29}\) (Scheme 5). In their work, allylic ether 18 was stereoselectively dihydroxylated into diol 19 by OsO\(_4\)/NMO, and this tertiary alcohol subsequently afforded tetrahydrofuran 20 also containing a chiral tertiary alcohol. Paterson et al. accomplished the stereocontrolled introduction of the chiral tertiary hydroxyl groups at C6, C11 and C12 of (+)-(9S)-dihydro-erythronolide A 25 by osmylation\(^{30}\) (Scheme 6). The dihydroxylation of silyl enol ether 22 gave a single \(\alpha\)-hydroxy ketone 23 by using catalytic OsO\(_4\), NMO and quinuclidine. The C11-C12 double bond was not affected even after a longer reaction time. In subsequent work, the authors reduced the C5 ketone followed by TBS deprotection to give tetraol 24. Finally, selective dihydroxylation of the double bond of 24 could be achieved with excess OsO\(_4\) in moderate yield.

![Scheme 5. Synthesis of (+)-verrucosidin 21](image)

In 2000, Armstrong et al. accomplished the synthesis of (+)-zaragozic acid C 28 with four contiguous stereocenters, of which C3 to C6 were constructed by a double Sharpless asymmetric dihydroxylation reaction of diene 26. This double dihydroxylation could not be achieved in one-pot, but took two steps. The first dihydroxylation was performed with Super AD-Mix (commercial AD-Mix supplemented with extra ligand (5 mol%) and OsO\(_4\) (1 mol%)) while in the second step the resulting mixture of regioisomeric triols was subjected to 1 mol% of OsO\(_4\), 5 mol% of (DHQD)\(_2\)-PHAL and 2 eq of NMO to afford the desired pentaol 27\(^{31}\) (Scheme 7).
1.3 Asymmetric epoxidation

The asymmetric epoxidation of olefins is another powerful method to synthesize chiral tertiary alcohols (which need a subsequent stereo-controlled ring-opening process) and ethers. Vanadium and chiral molybdenum catalysts were investigated for asymmetric epoxidation of allylic alcohols in as early as 1970, but the first practical method for asymmetric epoxidation was developed by Sharpless and Katsuki in 1980. The prochiral or chiral allylic alcohols afforded epoxides with high yields and excellent ee by Ti(IV) alkoxide-catalyzed epoxidation with tert-butyl hydroperoxide. Initially, this epoxidation employed a stoichiometric amount of titanium (IV) tetraisopropoxide as well as enantiopure diethyl tartrate (DET). Later, Sharpless’ group developed this methodology into a catalytic asymmetric epoxidation, using 5-10% catalyst. The substrates for the Sharpless asymmetric epoxidation are restricted to allylic alcohols due to the essential coordination of titanium to this hydroxyl group in the reaction. With an empirical model, the enantioselectivity of the Sharpless asymmetric epoxidation can be predicted for prochiral allylic alcohols (Scheme 8). By using (+)- or (-)-tartrate, the system affords reagent controlled epoxidation of the allylic alcohols with good enantioselectivity regardless of the
substitution pattern of the substrate and, an important bonus, high chemoselectivity in the presence of other olefins.

Scheme 8. Sharpless asymmetric epoxidation

In 1990, Jacobsen and Katsuki reported the enantioselective epoxidation of unfunctionalized olefins using (salen)manganese complexes, while more recently unfunctionalized cis-olefins also were used successfully in regioselective and enantioselective epoxidation catalyzed by metalloporphyrins. In 1996, the Shi epoxidation of trans-olefins was disclosed (Scheme 9). Using a fructose-derived ketone as catalyst and oxone as oxidant, trans and trisubstituted olefins could be epoxidized very effectively with high enantioselectivities orthogonal to a variety of functional groups. The pH of the Shi asymmetric epoxidation should be controlled carefully as Baeyer-Villiger reaction decomposes the catalyst at a lower pH and a higher pH the oxone is destroyed.

Scheme 9. The Shi asymmetric epoxidation

Yamamoto developed in 1999 a new chiral vanadium-based catalyst for the asymmetric epoxidation of allylic alcohols with ligand 29 (figure 2), this catalyst gave much higher selectivity than the previous chiral vanadium complexes. More recently, this catalyst system was improved by redesigning the hydroxamic acid-bearing binaphthyl group into a novel α-amino acid-based hydroxamic acid ligand. With ligand 30, the asymmetric epoxidation of allylic alcohols could be carried out at a convenient temperature (0 °C) and a low catalyst loading (1% vanadium). Subsequently, a new C₂-symmetric bishydroxamic acid 31 was designed by the same group. This bidentate ligand solved several practical problems, e.g.
brought success in the asymmetric epoxidation of cis-substituted allylic alcohols, allowed a lower catalyst loading and a high tolerance to air and moisture. In contrast to the ligand-deceleration observed in other vanadium/ligand catalysts, a ligand-accelerated vanadium-catalysed epoxidation of allylic alcohols was reported in the same year by Malkov. Epoxide hydrolysis was successfully suppressed by choosing suitable ligands (Figure 3) and lowering the reaction temperature to $-20^\circ C$ in a mixture of water and methanol.

![Figure 2. Ligands for vanadium-based epoxidation catalysts according to Yamamoto](image)

![Figure 3. Ligands for vanadium-catalysed epoxidation according to Malkov](image)

Building on the vanadium catalyzed asymmetric epoxidation of allylic alcohols with ligand 30, the Yamamoto group also achieved the asymmetric epoxidation of homoallylic alcohols in moderate to good enantioselectivities using ligand 35. To show the utility of this method, it was applied to the total synthesis of $(-)$-$\alpha$- and $(-)$-8-epi-$\alpha$-bisabolol (38 and 39) starting from (S)-limonene. In this synthesis, homoallylic alcohol 36 was epoxidized to give 37 in 84% yield and 90% de (whereas (8R)-37 was obtained in 82% yield and 94% de using L-35). This key epoxide afforded the chiral tertiary alcohol structure in the target compound $(-)$-$\alpha$-bisabolol 38 in a number of steps (Scheme 10).
In recent years, additional progress has been achieved in the asymmetric epoxidation of allylic alcohols and homoallylic alcohols with catalysts based on vanadium as well as other metals, for example, with zirconium(IV), hafnium(IV) and iron. This has been extended to bishomoallylic alcohols and β,β-disubstituted enones. Several reviews have been published on this topic. Tandem reactions for the enantio- and diastereoselective one-pot generation of functionalized epoxy alcohols using titanium-based catalysts have also been summarized.

Chiral enantiopure epoxides are, as noted before, important starting materials for the construction of tertiary alcohols. McDonald prepared oxepanes containing a chiral tertiary alcohol by endo,endo-oxacyclizations of 1,5-diepoxides. The key step in the total synthesis of (+)-madindoline A and (-)-madindoline B, two chiral tertiary alcohols synthesized by Omura and Smith, was achieved by Sharpless asymmetric epoxidation. In their work, the epoxidation of the indole double bond furnished the hydroxyfuroindole ring directly (Scheme 11). In 2002, Curran reported the first asymmetric total synthesis of (20R)-homocamptothecin based on Stille coupling and Sharpless asymmetric epoxidation as key steps. The chiral tertiary alcohol part of 45 resulted from the reductive ring-opening of epoxide 44 (Scheme 12). In 2005, Morimoto reported the total synthesis of (+)-aurilol, a cytotoxic bromotriterpene polyether. In this synthesis, the chiral tertiary alcohols were derived from their corresponding epoxides, prepared in turn by Sharpless epoxidation or Shi epoxidation. (Scheme 13)
1.4 Asymmetric 1,2-Addition of organometallics to ketones

One of the most straightforward ways to prepare chiral enantio-enriched tertiary alcohols is, at least in principle, the asymmetric addition of carbon nucleophiles to ketones. This elementary transformation, and in particular the addition of organometallics, has been studied over a long period. Many kinds of organometallics, e.g. organoboron, organolithium, organosilicon, organoaluminium, diorganozinc and organomagnesium (Grignard) reagents have been used for this purpose.
Ketones, being less reactive than aldehydes, usually require reactive organometallics to afford chiral tertiary alcohols via asymmetric addition. However, the use of Grignard and organolithium reagents causes side reactions like enolization and Meerwein-Ponndorf-Verley-type reduction of the substrate. A way to circumvent these problems is the use of less reactive organozinc reagents with activation of either the carbonyl group or the organozinc reagent, or even both. In 1998, Yus described the first enantioselective addition of Et$_2$Zn and Me$_2$Zn to ketones.$^{[58]}$ With camphor-derived hydroxysulfonamide 52, this system, in the presence of an excess of Ti(O$i$Pr)$_4$, gave a good performance in the 1,2-addition of Et$_2$Zn and Me$_2$Zn to in particular aryl alkyl ketones (Table 2). A practical limitation of this reaction is the long reaction time (4-14 days). Subsequently, different kinds of hydroxysulfonamide ligands were designed for the addition of diethylzinc to ketones (Figure 4). The development of bis(hydroxysulfonamide) 54 assisted the asymmetric addition of Et$_2$Zn and Me$_2$Zn to ketones affording tertiary alcohols with improved yields and excellent ee.$^{[59]}$ The reaction requires as low as 2% catalyst loading and also a much shorter reaction time (in most cases < 2 d). In 2008, Ramón and Yus synthesized the Fréchet dendrimer-based isoborneoldsulfonamide ligand 55 for the continuous-flow synthesis of chiral tertiary alcohols.$^{[60]}$ The catalyst derived from 55 promoted the 1,2-addition of Et$_2$Zn, Me$_2$Zn and in situ generated phenylzinc to simple aryl alkyl ketones giving the products with ee’s up to 99%. A different type of ligand, chiral bifunctional phosphoramide 56, was developed by Ishihara in 2007 (Figure 5).$^{[61]}$ The chiral phosphoramide-Zn(II) complex 57 (1-10 mol%) catalyzed the addition of Ph$_2$Zn and Et$_2$Zn to ketones very efficiently with high enantioselectivities (ee up to 98%).

![Chemical reaction](image)

Table 2. Asymmetric addition of Et$_2$Zn and Me$_2$Zn to ketones with hydroxysulfonamide 52

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et$_2$Zn + R$_3$</td>
<td>89%, 89% ee</td>
</tr>
<tr>
<td>Me$_2$Zn + R$_3$</td>
<td>95%, 83% ee</td>
</tr>
<tr>
<td>Et$_2$Zn + nBu</td>
<td>78%, 86% ee</td>
</tr>
<tr>
<td>Me$_2$Zn + nBu</td>
<td>83%, 81% ee</td>
</tr>
<tr>
<td>Et$_2$Zn + Br</td>
<td>25%, 89% ee</td>
</tr>
<tr>
<td>Me$_2$Zn + Me</td>
<td>36%, 51% ee</td>
</tr>
<tr>
<td>Et$_2$Zn + Me</td>
<td>72%, 31% ee</td>
</tr>
<tr>
<td>Me$_2$Zn + S</td>
<td>42%, 43% ee</td>
</tr>
</tbody>
</table>
In addition to the extensive studies on the Et₂Zn, Me₂Zn and Ph₂Zn addition to ketones, the ethylation and methylation of α-ketoesters and the alkynylation of ketones using organozinc reagents were also investigated.\cite{56}

Due to the advantages of Grignard reagents, being inexpensive, readily available and highly reactive, it has always been one of the most popular choices for carbon-carbon formation. The research on the asymmetric addition of organomagnesium reagents to ketones started in 1953,\cite{63} but initially gave no useful results,\cite{64} until Seebach’s first successful asymmetric addition of Grignard reagents to ketones (Table 3).\cite{65} The TADDOL-derived reagents 59 were prepared by deprotonation of TADDOL with 2 equivalent of a primary alkyl Grignard reagent, and subsequently 1 additional equivalent of Grignard reagent was added to the resulted solution. The chiral tertiary alcohols were formed with the highest selectivity at −100 °C. In this system, steric hindrance either from the Grignard reagent or from the ketone decreased the rate of the reaction drastically. Given the reactivity of Grignard reagents, the control of this addition has always been difficult.
Chapter 1

The state of the art in the preparation of chiral enantio-enriched tertiary alcohols by catalyzed enantioselective addition of carbon nucleophiles to ketones has been summarized in two contributions to Chemical Reviews, in 2008 and 2011. This revealed that the catalytic asymmetric 1,2-addition of Grignard and organolithium reagents to ketones was lacking.

In 2012, Harutyunyan and Minnaard reported the first copper catalyzed enantioselective 1,2-addition of alkyl Grignard reagents to α-methyl-α,β-unsaturated ketones. The reaction was carried out with 5 mol% CuBr·SMe2 and 6 mol% of the ligand rev-Josiphos in tBuOMe at −78 °C (Table 4). This catalyst system does not require the use of stoichiometric amounts of additives though needs β-branched Grignard reagents to obtain tertiary alcohols with excellent enantioselectivities. A complete shift of the, normally overwhelming, selectivity of Cu(I)-organometallics for conjugate addition to 1,2-addition took place using this catalyst/substrate combination. Later, this method was also applied in the catalytic asymmetric addition of Grignard reagents to aryl alkyl ketones and α-bromo-α,β-unsaturated ketones (Scheme 14). The corresponding tertiary alcohols were obtained in good yields and enantioselectivities of up to 98%. This system provides a convenient, though not unrestricted, route to enantio-enriched allylic and benzylic tertiary alcohols which are important classes of building blocks for organic synthesis.

Table 3. Enantioselective addition of primary alkyl Grignard reagents to ketones

<table>
<thead>
<tr>
<th>Ar = Ph, 2-naphthyl</th>
<th>R = primary alkyl groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield (％)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>60% &gt;98% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>60% 98% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>76% 92% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image6.png" alt="Image" /></td>
<td>28% 89% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image7.png" alt="Image" /></td>
<td>75% 98% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image8.png" alt="Image" /></td>
<td>43% 96% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image9.png" alt="Image" /></td>
<td>24% 90% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image10.png" alt="Image" /></td>
<td>53% 66% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image11.png" alt="Image" /></td>
<td>51% 96% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image12.png" alt="Image" /></td>
<td>96%, &gt;99% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image13.png" alt="Image" /></td>
<td>64%, 83% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td><img src="image14.png" alt="Image" /></td>
<td>55%, 71% ee</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

14
A large asymmetric amplification in the catalytic enantioselective 1,2-addition of Grignard reagents to enones was observed during recent studies.\textsuperscript{[71]} This amplification originates from the solubility differences between the enantiopure and the racemic complexes of a transition metal with diphosphine ligands. To understand this amplification phenomenon, structural characterization of the copper complexes of both racemic and enantiopure ferrocenyl diphosphine ligands was carried out.\textsuperscript{[72]}

To investigate the influence of the electronic and steric properties of the ligand in this 1,2-addition, five new chiral ferrocenyl diphosphine ligands of the Josiphos family were synthesized (Figure 6).\textsuperscript{[73]} Some improvement was obtained in the regio- and enantioselectivity of the addition to $\alpha$-H-substituted enones using the ligand 70, containing $\text{tert}$-butyl substituents in the diarylphosphine moiety. The clear message from this study is that the precise structure of the ligand is very critical, with rev-Josiphos (close to) optimal.
Important new developments in this connection were reported very recently and involve the catalytic asymmetric alkylation of acylsilanes[74] and aryl heteroaryl ketones.[75] The alkylation of acylsilanes 72 gives access to aryl- and vinyl-substituted α-hydroxysilanes 73 with quaternary stereocenters in high yields and enantioselectivities (Scheme 15). In this system, β-branched Grignard reagents are not a requirement for high enantioselectivity, the chiral catalyst could be recovered and re-used without loss in activity, and a mixture of two Lewis acids led to the best results.

Scheme 15. Catalytic asymmetric alkylation of acylsilanes 72

1.5 Recent developments

The method reported by Aggarwal et al. in 2008 for the preparation of enantiopure tertiary alcohols from enantiopure secondary alcohols was a new development in this field (Scheme 1).[9] Initially, the reaction worked well only for simple substrates not containing sterically hindered carbamates, boronic esters or aryl groups with electron withdrawing substituents. It was found that erosion of the ee resulted from reversibility of the second step, leading back to the starting lithiated carbamate which is prone to racemization upon warming. The remedy to suppress this dissociation-racemization was the use of either MgBr2/MeOH or less sterically hindered neopentyl boronic esters instead of pinacol boronic esters.[76] In 2013, this lithiation-borylation methodology also afforded access to several α-heterocyclic tertiary alcohols in good to excellent yields and excellent enantioselectivity.[77]

Starting with the enantioselective synthesis of boron-substituted quaternary carbons as well, a different approach was reported in 2010 by Hoveyda for the synthesis of
chiral tertiary alcohols. This was achieved via NHC-Cu-catalyzed enantioselective conjugate boronate additions to trisubstituted alkenes in acyclic α,β-unsaturated carboxylic esters, ketones, and alkyl thioesters. The resulting boron-substituted quaternary stereocenters were oxidized to the corresponding tertiary alcohols (Scheme 16). Meanwhile, the enantioselective synthesis of allylboronates bearing a quaternary boron-substituted stereocenter, as precursors for tertiary allylic alcohols, succeeded. A different NHC-catalyzed intramolecular crossed benzoin reaction was developed by Ema and Sakai in 2009. In their work, bicyclic tertiary alcohols with two consecutive quaternary stereocenters were synthesized with high stereoselectivity (Scheme 17).

![Scheme 16. Hoveyda’s strategy to chiral tertiary alcohols](image)

With a chiral sulfoxide as an auxiliary, Ready et al. showed the asymmetric addition of simple alkynyl, aryl and vinyl organometallics to aryl ketones. Tertiary alcohols are generated in diastereomerically pure form, and enantiopure after removal of the tolyl sulfoxide via reductive lithiation (Scheme 18).

![Scheme 17. Intramolecular crossed benzoin reaction catalyzed by an NHC organocatalyst](image)

An important direction in the construction of enantiopure tertiary alcohols is the
preparation of tertiary homoallyl alcohols. This could be realized by the asymmetric allylation of ketones via different approaches, e.g. Nozaki-Hiyama-Kishi reactions, allylboration, indium-mediated allylations, titanocene-catalyzed Barbier-type allylations and auxiliary-mediated or catalytic allylsilane transfer. In 2005, Soderquist designed 10-Ph-9-BBD reagent \( \text{82} \) (Figure 7), \( B \)-allyl-10-Ph-9-borabicyclo[3.3.2]decanes, for the asymmetric allylboration of ketones to prepare chiral homoallylic tertiary alcohols\( \text{83} \). This new BBD reagent showed high selectivity for a wide range of prochiral ketones. In their subsequent research, \( B \)-allenyl- and \( B \)-(\( \gamma \)-trimethylsilylpropargyl)-10-Ph-9-BBDs (\( \text{83} \) and \( \text{84} \)) were designed for the asymmetric synthesis of propargyl and \( \alpha \)-allenyl tertiary alcohols from ketones\( \text{84} \) and the design of borabicyclodecane (BBD)-derived 1,3-diborylpropenes \( \text{85} \) in 2009 led to selective asymmetric allylboration, first of ketones and subsequently of aldehydes\( \text{85} \). Recently, they also achieved access to highly functionalized tert-carbinols via asymmetric \( \gamma \)-alkoxyallylboration of ketones with \( \text{86} \). Loh, in 2009, developed a highly enantioselective indium(III)-pybox catalyzed ketone-ene reaction (Scheme 19).\( \text{86} \) This asymmetric ketone-ene reaction of methyl trifluoropyruvate \( \text{87} \) with various olefins gave enantioenriched homoallylic alcohols \( \text{90} \) with \( ee \)’s up to 98%. In Laschat’s work, the Evans aldol reaction was employed for the preparation of the required chiral tertiary homoallylic alcohols\( \text{82} \).

Figure 7. BBD reagents developed by Soderquist.

Enantioenriched tertiary allylic alcohols containing a tetrahydrofuran or tetrahydropyrrole are important structural units in natural compounds. A rhodium-catalyzed asymmetric tandem cyclization developed by Xu in 2014 afforded a new access to this kind of heterocyclic tertiary allylic alcohols\( \text{87} \). The reaction was carried out with nitrogen- or oxygen-bridged 5-alkynones and aryloboronic acids in the presence of [Rh(COE)\(_2\)Cl]\(_2\) as the metal precursor and a commercially available chiral BINAP ligand. The corresponding chiral tertiary alcohols were obtained with \( ee \)’s up
to 99%.

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{OMe} \\
\begin{array}{c}
\text{R}^2 \\
\end{array} & + & \begin{array}{c}
\text{R}^1 \\
\end{array} & \xrightarrow{\text{InCl}_3 (10 \text{ mol}\%)} & \begin{array}{c}
\text{AgSbF}_6 (20 \text{ mol}\%) \end{array} & \xrightarrow{4\AA \text{ MS, r.t. ClICH}_2\text{CH}_2\text{Cl}} & \begin{array}{c}
\text{R}^1 \quad \text{F}_3\text{C} \quad \text{OH} \\
\text{OMe} \\
\end{array}
\end{align*}
\]

yield up to 99%, ee up to 98%

Scheme 19. In(III)-pybox catalyzed asymmetric ketone-ene reactions of methyl trifluoropyruvate 87 with olefins

With an improved Rh\(^1\)/BINAP-catalyzed 1,2-addition of organoaluminum reagents to cyclic enones, Zezschwitz et al. in 2013 synthesized 5-7 membered cyclic tertiary allylic alcohols with excellent enantioselectivity and in high yield using only 1 mol% catalyst \[^{88}\] compared to 5 mol% in the previously reported system.\[^{89}\]

In 2007, Cheng published a cobalt-catalyzed diastereoselective reductive [3 + 2] cycloaddition of allenes and enones.\[^{90}\] In this reductive coupling, enones act as the three-carbon nucleophile adding exclusively to the internal double bond of allenes to form cyclopentanols with high diastereoselectivity in the presence of zinc as reducing agent and water as proton source. And in 2012, the authors reported a new synthesis, also catalyzed by cobalt, of bicyclic tertiary alcohols 93 with high regio- and enantioselectivity via [3 + 2] cycloaddition of alkynes and cyclic enones 92 (Scheme 20).\[^{91}\] Cheng’s system provides an advantage from a practical point of view, e.g. the cobalt catalyst is air-stable, relatively inexpensive, zinc is a mild reducing agent, and uses water as proton source.

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^1, \text{R}^2 & = \text{alkyl} \text{ or} \text{ aryl} \\
\text{R}^3, \text{R}^4 & = \text{H} \text{ or} \text{ Me}
\end{align*}
\]

Scheme 20. The enantioselective reductive [3 + 2] cycloaddition of alkynes 93 with cyclic enones 92.

1.6 Conclusion

In this chapter, different approaches for the asymmetric synthesis of tertiary
alcohols and ethers have been introduced. In these approaches, the catalytic asymmetric dihydroxylation and epoxidation of olefins have gained wide acceptance and applications in natural products synthesis. The catalytic asymmetric addition of organometallics to ketones as a straightforward, and from a retrosynthesis point of view preferred, way to prepare enantio-enriched tertiary alcohols attracts more and more attention and has been realized by several transition metal-catalyzed systems. This approach is however far from mature.

1.7 Outline of this thesis

In this thesis, the copper-catalyzed asymmetric 1,2-addition of Grignard reagents to \( \alpha\)-bromo-\( \alpha,\beta \)-unsaturated ketones has been applied in the asymmetric synthesis of dihydrofurans and cyclopentenols and in the total synthesis of (\( R, R, R \))-\( \gamma \)-tocopherol. The second part of this thesis gives an introduction to a novel, protecting group-free, synthesis of the Colorado potato beetle pheromone and efforts on the total synthesis of phorbasin B.

In chapter 2, a novel asymmetric synthesis of dihydrofurans and cyclopentenols has been developed, based on the copper-catalyzed 1,2-addition of Grignard reagents to enones in combination with Sonogashira coupling/cyclization and ring-closing metathesis. Employing this approach, dihydrofurans with an oxygen-containing tertiary stereocenter, and chiral tertiary cyclopentenols are efficiently prepared. The absolute stereochemistry of the products has been established as well.

In chapter 3, based on the asymmetric copper-catalyzed 1,2-addition of Grignard reagents to ketones, (\( R, R, R \))-\( \gamma \)-tocopherol has been synthesized in 36% yield over 12 steps (longest linear sequence). The chiral center in the chroman ring was constructed with 73% e.e. by the 1,2-addition of a phytol-derived Grignard reagent to an \( \alpha \)-bromo enone prepared from 2,3-dimethylquinone.

In chapter 4, a novel synthesis of the aggregation pheromone of the Colorado potato beetle, \( Leptinotarsa decemlineata \), has been developed based on a Sharpless asymmetric epoxidation in combination with a chemoselective alcohol oxidation using catalytic [(neocuproine)PdOAc]\(_2\)OTf\(_2\). Employing this approach, the pheromone was synthesized in 3 steps, 80% yield and 86% ee from geraniol.

Finally, in chapter 5, progress in the asymmetric synthesis of phorbasin B is described. Starting from readily available materials, the required chiral centers of the substituted 2-cyclohexen-1-one part were constructed by Evans aldol reaction and Rubottom reaction, whereas the chiral center in the side chain is provided by copper-catalyzed asymmetric allylic alkylation of a diene bromide.
1.8 References


Chapter 1


Introduction

1404-1411.


