Chemo and enantioselective addition of grignard reagents to ketones and enolizable ketimines
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Chapter 1:
Copper (I)-Diphosphine Catalyst for the Asymmetric Alkylation of Ketones and Ketimines Using Grignard Reagents

Part of this chapter has been published:
1.1. Efficient synthesis of chiral α-tertiary alcohols and amines

Synthetic organic chemistry has had a huge impact in shaping today’s society. One of its most important contributions has been and continues to be the preparation and delivery of drugs. Among them, chiral α-tertiary alcohols are a prevalent motif (Figure 1, top). Their nitrogen counterparts, chiral α-tertiary amines, are also present in some drugs and widespread in natural alkaloids (Figure 1, bottom).

Due to the importance of α-tertiary alcohols and amines, organic chemists have put considerable efforts in designing new and efficient ways to synthesize them (Scheme 1). Hydrogenation is widely used for the preparation of their secondary counterparts by reduction of ketones and ketimines but is not applicable for the synthesis of tetrasubstituted stereocenters. Some elegant approaches have been developed based on the use of configurationally stabilized organolithium intermediates that undergo stereospecific rearrangements. Both these and some other type of rearrangements rely on an already existing chiral center, which, in turn, has to be prepared. Having said that, in some cases it is possible to use achiral/racemic starting materials and obtain enantioenriched products by using a chiral catalyst. Another strategy that makes use of a pre-existing chiral center is the diastereoselective allylic Sn2’ substitution, which can lead to the desired products after oxidation-rearrangement. Cycloaddition reactions are a powerful tool for C-C bond formation and is not surprising that fragments containing N and O atoms have been used to yield the desired chiral tetrasubstituted centers adjacent to those heteroatoms. Nevertheless, there are only a few examples and they are limited to specific cyclic structures. Sharpless asymmetric dihydroxylation and asymmetric epoxidation are yet another option if chiral tertiary alcohols are sought, but the current methodologies require to start with a preformed chiral center in the molecule (Scheme 1).

Figure 1. Chiral α-tertiary alcohols and amines present in natural products and drugs.
bond formation and is not surprising that fragments containing N and O atoms have been used to yield the desired chiral tetrasubstituted centers adjacent to those heteroatoms. Nevertheless, there are only a few examples and they are limited to cyclic structures.\[8\] Sharpless asymmetric dihydroxylation\[^9\] and asymmetric epoxidation\[^10\] are yet another option if chiral tertiary alcohols are sought, but the product of the reaction has to be subsequently transformed in order to obtain them. Kinetic resolution of tertiary alcohols using a variety of (bio)catalysts is a viable method, although it suffers from low (enzyme) activities and selectivities.\[^11\]\[12\] Moreover, dynamic kinetic resolution cannot be readily applied, which makes this approach unpractical. On the other hand, biocatalysis is not developed for the synthesis of chiral α-tertiary amines. These can be accessed by enantioselective C-H amination, but, since no catalyst-controlled procedures have been yet developed, the current methodologies require to start with a preformed chiral center in the molecule (Scheme 1).

**Scheme 1.** Overview of the different approaches for the synthesis of chiral α-tertiary alcohols and amines. R¹ ≠ R² ≠ H. L* = Chiral ligand. M = Metal.

From this summary and related Scheme 1 it might seem that there are multiple ways to synthesize chiral tetrasubstituted carbons with a contiguous oxygen or nitrogen atoms. It is indeed so, but, importantly, most of them are limited to specific
substrates and conditions, often requiring multi-step synthesis of the substrate. There is though a straightforward strategy for the synthesis of chiral tetrakisubstituted centers with O or N atoms in alpha position: the asymmetric addition of nucleophiles to ketones or imines. Since the introduction of stereochemical information and the C-C bond formation take place in the same step this strategy is both atom and step economical (Scheme 1). The concept has long been applied for the addition to aldehydes or imines, which affords chiral α-secondary alcohols and amines. However, ketones and ketimines are comparatively less reactive towards nucleophilic attack. On top of that, the enantiodiscrimination between the two prochiral faces is more difficult due to the similarity of the substituents. Consequently, in spite of being the most studied approach, there are still challenges to solve. Fortunately, one of the advantages of this strategy is its high versatility, for example in the choice of the nucleophile. Stabilized nucleophiles have been introduced using aldol, Strecker and Mannich type reactions, among others. Non-stabilized nucleophiles, on the other hand, allow the introduction of alkyl and aryl groups.

Regarding the latter, a range of organometallic reagents is available to organic chemists for addition to ketones. Grignard reagents, being the benchmark organometallics are arguably the first choice for such transformation, as taught already in Organic Chemistry 1 courses. Nevertheless, performing the catalytic asymmetric variant is a formidable challenge due to their high reactive profile. This, although useful to counteract the lower reactivity of ketones, has a downside: the uncatalyzed reaction, which leads to racemic product (Scheme 2). Moreover, organomagnesium reagents themselves are strong bases, adding the risk of enolization of the corresponding ketones that have hydrogens in α-position. In addition, alkyl Grignard reagents having β-hydrogens bear the risk of reducing the carbonyl substrate via β-hydride transfer (Scheme 2).

![Scheme 2](image)

Scheme 2. Chemo and enantioselectivity problems associated with the catalytic asymmetric addition of Grignard reagents to enolizable ketones.
The first attempts to obtain chiral α-tertiary alcohols by addition of Grignard reagents to ketones required at least one equivalent of a chiral auxiliary. Thus, in Seebach’s report in 1992, the Grignard reagent was made chiral by the use of an equimolar amount of TADDOL. 25 years later, chiral auxiliaries are still used for the asymmetric addition of Grignard reagents to ketones and Ellman’s chiral auxiliary is one of the preferred methods of making chiral amines. The high reactivity of the Grignard reagents discouraged researchers from making this reaction catalytic, establishing instead organozinc (R₂Zn) compounds as the reagents of choice for these transformations. Along these lines, pioneering work was done in 1998 by Dosa and Fu for diphenylzinc and Ramón and Yus for dialkylzinc asymmetric addition to ketones. For the latter, the lower reactivity of dialkyl compared to diarylzinc reagents was compensated by the use of a superstoichiometric amount of titanium isopropoxide additive. In situ formation of organotitanium species is postulated, which has an intermediate reactivity between the highly reactive organomagnesium and the less reactive organozinc reagents. This has been intentionally pursued, either by direct addition of organotitanium reagents or by in situ formation from the parent organometallics (organoaluminium and organomagnesium). It should be taken into account that all of these protocols (based on Zn, Al or Mg) require the use of excess organometallics and superstoichiometric amounts of titanium tetraisopropoxide additive (Scheme 3). Thus, they are catalytic in the chiral ligand but not in the transmetalating metal. The use of organozinc reagents for the catalytic asymmetric addition to ketones has allowed the access to the tetrasubstituted products in good yields and enantioselectivities, but they have some disadvantages. To list some, the already mentioned need of superstoichiometric amounts of titanium tetraisopropoxide additive, as well as long reaction times, high cost, structural limitations, difficulty of preparation and the fact that they transfer only one of the alkyl groups. While the use of Grignard reagents would allow overcoming these drawbacks, prior to 2012 there were no examples of their catalytic asymmetric addition to ketones.
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was to promote the opposite regioselectivity (1,4-addition), the implementation of known from Shibasaki’s work, involving stabilized \[29\] as well as non-stabilized enantioselective addition of nucleophiles to aldehydes and activated ketones was evidence that this could be achieved. For instance, copper(I)-catalyzed such a system for 1,2-addition seemed counterintuitive. There was, however, some evidence that this could be achieved. For instance, copper(I)-catalyzed enantioselective addition of nucleophiles to aldehydes and activated ketones was known from Shibasaki’s work, involving stabilized\[29\] as well as non-stabilized nucleophiles.\[30\] In this regard, they could perform the alkenylation and phenylation of ketones with both organosilanes\[30a\] and organoboranes.\[30b\] Cu(I)F-DTMB-SEGPHOS complex was transmetalated using these organometallics in order to generate the actual nucleophile.

Scheme 3. Catalytic asymmetric alkylation and arylation of ketones promoted by Ti(OiPr)$_4$.

1.2. Development of copper-catalyzed asymmetric 1,2-addition of Grignard reagents to ketones

A fully catalytic system for the enantioselective addition of Grignard reagents was known for the 1,4-addition to α,β-unsaturated ketones and involved copper(I) based complexes as catalysts (Scheme 4).\[28\] Since it was thought that the nature of copper was to promote the opposite regioselectivity (1,4-addition), the implementation of such a system for 1,2-addition seemed counterintuitive. There was, however, some evidence that this could be achieved. For instance, copper(I)-catalyzed enantioselective addition of nucleophiles to aldehydes and activated ketones was known from Shibasaki’s work, involving stabilized\[29\] as well as non-stabilized nucleophiles.\[30\] In this regard, they could perform the alkenylation and phenylation of ketones with both organosilanes\[30a\] and organoboranes.\[30b\] Cu(I)F-DTMB-SEGPHOS complex was transmetalated using these organometallics in order to generate the actual nucleophile.

Scheme 4. Cu/Josiphos catalyzed enantioselective 1,4-addition of Grignard reagents to acyclic enones.\[28\]

A more recent example, and closer to the system under discussion, is the copper(I)-catalyzed enantioselective 1,2-reduction of α,β-unsaturated ketones investigated by Lipshutz et al. Analogously to the copper(I)-catalyzed 1,4-ACA of organometallics.
discussed in the first section, hydrosilylation of α,β-unsaturated ketones 1, employing chiral CuH complexes, benefits from the inherent tendency of Cu(I) to coordinate to the C-C double bond and renders 1,4-addition as the thermodynamically preferred mode of action (Scheme 5, top). This preference was rationalized by the Cu(I)-olefin interaction, which is of soft-soft character. Lipshutz et al. discovered in 2010 that α,β-unsaturated ketones 3, with an α-substituent, undergo the reduction in the 1,2-position, namely the carbonyl group is reduced instead of the conjugated double bond (Scheme 5, bottom). Importantly, in the presence of a chiral ligand, the reduction proceeds enantioselectively. DTMB-SEGPHOS L2 and BIPHEP L3 gave the best results (80-90% ee), although, interestingly, a ferrocenyl type ligand also catalyzed the reaction.

Scheme 5. Copper-catalyzed enantioselective 1,4-reduction and recently developed 1,2-reduction by Lipshutz et al. L* = Chiral ligand.

From a chemical point of view, the 1,2-reduction of the enone involves nucleophilic attack of a hydride to the carbonyl moiety. In theory, nucleophiles other than hydride (e.g. carbon nucleophiles) could also be added to the carbonyl under copper(I) catalysis. Realizing and accomplishing it with Grignard reagents was a great breakthrough in our group in 2012, and shaped the subsequent research. α,β-unsaturated ketones 3 gave a mixture of 1,4-addition, 1,2-addition and 1,2-reduction products upon addition of Grignard reagents, but in the presence of 5 mol % of a copper(I) salt and 6 mol % of rev-Josiphos diphosphine chiral ligand L4, the reaction proceeded with high chemo and enantioselectivity (Scheme 6). For the enantioselectivity to be high some bulkiness around the reactive center was necessary, either on the substrate (R1) or on the Grignard reagent. Thus, β-branched...
Grignard reagents were the best performing ones. Interestingly, less solvating ethers such as tBuOMe and iPr2O gave better results than Et2O.

![Scheme 6](image)

Scheme 6. Cu/rev-Josiphos catalyzed enantioselective 1,2-addition of Grignard reagents to enones.[32]

Next aryl alkyl ketones 6 (Scheme 7) were subjected to the previously successful catalytic conditions.[33] Compared to enones, the problem of regioselectivity is eliminated in this case. However, the addition of Grignard reagents to aryl alkyl ketones, as noted above, often exhibits issues with chemoselectivity, namely the risk of enolization and reduction via β-hydrogen transfer from the corresponding Grignard reagent. The catalytic system based on Cu(I)/rev-Josiphos L4 proved to be powerful for this transformation as well, outcompeting the undesired enolization, the reduction and the uncatalyzed addition reactions. Good to excellent enantioselectivities and yields were obtained in the addition of β-branched 2-ethylbutylmagnesium bromide 7 to a large variety of acetophenone derivatives 6 (Scheme 7). The same trend found earlier for the addition to enones repeated again for aryl alkyl ketones: β-branched Grignard reagents were required in order to obtain products with good enantioselectivities, while linear Grignard reagents led typically to products with moderate ee’s (22-74%). Aryl Grignard reagents led to racemic products, whereas MeMgBr did not react.

![Scheme 7](image)

Scheme 7. Cu/rev-Josiphos catalyzed enantioselective 1,2-addition of 7 to aryl methyl ketones.[33]
1.3. Asymmetric addition of Grignard reagents to acylsilanes

After the success with the asymmetric alkylation of aryl alkyl ketones, it was pondered in our group which substrates were particularly interesting to undergo a similar transformation. One of the chosen ones were acylsilanes 9, with the aim of yielding chiral α-tertiary silylated alcohols (Scheme 8). Replacing the alkyl group by a silyl group in an aryl alkyl ketone had a high impact on the reactivity. Applying the reaction conditions for the addition to aryl alkyl ketones to acylsilane 9 (R = H) an addition: reduction ratio of 1:2 was obtained, while preserving a high enantioselectivity of the addition product 10 (R = H). Screening of various parameters (ligands, solvents, temperatures, and substituents in the silyl moiety) did not provide enhanced addition to reduction ratios. Notably, the use of Lewis acids compatible with Grignard reagents did improve the results, and a 1:1 mixture of BF$_3$·OEt$_2$/CeCl$_3$ was found to be the most beneficial: the addition to reduction ratio improved to 5:1, while the enantioselectivity of the addition product remained high (90% ee). The substrate scope was again wide, with very good yields and enantioselectivities (Scheme 8).

![Scheme 8](image)

The majority of the substituents in the aromatic ring were tolerated and good yields and enantioselectivities, mostly in the range of 90%, were obtained. Remarkably, the substrate scope also included α,β-unsaturated acylsilanes 11, in which the competing 1,4-addition product was not observed, and the corresponding silylated allylic alcohols were obtained in good yields and excellent ee’s. Once again, the addition of β-branched Grignard reagents afforded good enantioselectivities, but it is worth to note that for the first time with this catalytic system high ee’s were
obtained with linear Grignard reagents too. The bulkiness of the silyl group might be the reason for the enhanced enantioselectivity.

The use of the Lewis acid mixture deserves a few more lines, considering that it modifies the original catalytic system. The reduction of ketones has been postulated to be the result of the activation of the carbonyl moiety through coordination with the magnesium atom of the Grignard reagent, followed by β-hydride transfer from the Grignard reagent.[16] In this scenario Lewis acids are expected to prevent the coordination of the magnesium to the oxygen of the C=O, therefore minimizing the reduction and allowing the catalytic pathway. In theory, transmetalation of the Grignard reagent to form organocerium reagents can be envisioned, but when they were prepared and tested only the reduction product was obtained. It is also conceivable that the mixture of Lewis acids leads to the formation of a new Lewis acid, more efficient for this catalytic system. Coordination of the Lewis acid to the copper catalyst, especially in the case of BF₃, is another option, albeit a speculative one.[35]

1.4. Outline of this thesis

The leitmotiv of this thesis has been the use of Grignard reagents for asymmetric alkylation of carbonyl compounds and imines, in order to create chiral tetrasubstituted centers with an heteroatom (O or N) in alpha position. As mentioned above, it was in 2012 when the copper-catalyzed asymmetric 1,2-addition of Grignard reagents to enones and aryl ketones was developed in our group. At my arrival at the group one year later the scope and limits of this new chemistry were being explored. Diarylketones were particularly interesting substrates and thus the efforts devoted to asymmetrically alkylate them, which are summarized in chapter 2. Acyilsilanes were another type of substrate that was being studied in our group (Section 1.3) and the products resulting from their asymmetric alkylation, chiral α-tertiary hydroxysilanes, attracted our attention for their possibility to undergo 1,2-Brook rearrangement. Hence, chapter 3 describes the Brook rearrangement of allylic hydroxysilanes and subsequent trapping of carbonyl electrophiles with full retention of chirality. Chapter 4 covers benzylic hydroxysilanes, which also underwent Brook rearrangement, but in this case only proton could be trapped with retention of chirality. Once the possibilities of Cu(I)-
catalyzed enantioselective addition of Grignard reagents to carbonyls had been explored we entered an unmapped area: the use of our catalytic system for the addition to imines. The first attempts, summarized in chapter 5, focused on the addition of organomagnesium compounds to diarylimines, which could be converted to the corresponding α-tertiary amines, albeit not enantioselectively. The asymmetric addition of Grignard reagents to enolizable imines was eventually achieved with high yields and enantioselectivities and is described in chapter 7. Chapter 6 details the method we developed for an efficient synthesis of enolizable imines. Chapter 8 summarizes the findings on the solution structure of Grignard reagents in tBuOMe and DCM inferred by NMR spectroscopy. Lastly, chapter 9 gives a personal perspective on overcoming the limitations of organometallic reagents.

1.5 References

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[25] In one case it was possible to carry out the reaction using 60 mol% of titanium tetraisopropoxide Ti(OiPr)4 (H. Li, C. García, P. J. Walsh, *Proc. Nat. Acad. Sci. USA* 2004, 101, 5425–5427), and in another case it was reported that Ti(OiPr)4-free 1,2-addition to aromatic ketones is possible when a 3-fold excess of organozinc reagent was used (M. Hatano, T. Miyamoto, K. Ishihara, *Org. Lett.* 2007, 9, 4535-4538.)


If you’re going to try, go all the way. Otherwise, don’t even start.

Charles Bukowski, *Factotum*

In this chapter a new strategy to access chiral tertiary diarylmethanols through copper-catalyzed direct alkylation of (di)(hetero)aryl ketones by using Grignard reagents is described. The low reactivity and the similarity of the enantiotopic faces of bis-aromatic ketones were partially overcome, which resulted in moderate to good yields and enantioselectivities of the addition products.