Synthesis of Enantiopure Chiral Alcohols *via* Addition of Grignard Reagents to Carbonyl Compounds

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Grignard reagents, carbonyl compounds, chiral alcohols, enantioselective catalysis, titanium, copper

ABSTRACT Remarkable progress in the enantioselective addition of Grignard reagents to carbonyl compounds has been made over the past decade. This enantioselective transformation now allows the use of these challenging reactive nucleophiles for the formation of chiral alcohols using catalytic amounts of chiral ligands. This review summarizes the developments in the area.

Introduction

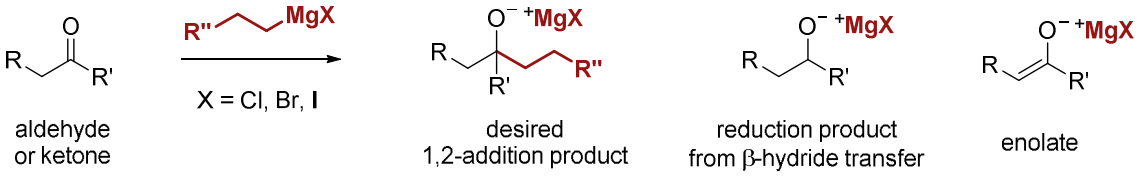
The catalytic asymmetric addition of organometallic reagents to carbonyl compounds is one of the most versatile methods for the synthesis of highly valuable chiral alcohols.[1] Catalytic versions of this key transformation[2] have been studied extensively with organozinc,[3]

organoalumininum[4] and organotitanium[5] reagents – all of them considered organometallic species of low or medium reactivity. The popularity of such approaches is exemplified by even a basic literature search on the catalytic enantioselective addition of diethylzinc to benzaldehyde, which shows more than 200 different ligands that are effective for such a transformation.

Grignard reagents, by comparison to their zinc or aluminum counterparts, offer: a) higher reactivity; b) wider commercial availability; c) increased tunability and d) better atom efficiency since all R groups from the nucleophile are transferred to the substrate. Grignard reagents are amongst the least expensive and most commonly used organometallic reagents in both laboratory and industry. However, they do pose problems for applications in the catalytic enantioselective alkylation of carbonyl compounds and, as such, the catalytic reaction involving their direct addition to carbonyls was not possible until very recently.[6]

The extreme reactivity profile of Grignard reagents makes it difficult for chiral catalysts to outcompete uncatalyzed reactions, frequently leading to racemic alcohol products.

Scheme 1. Chemoselectivity problems associated to the 1,2-addition of Grignard reagents to carbonyl compounds.



Chemoselectivity poses a further challenge since these organometallic reagents are also highly basic and can deprotonate enolizable aldehydes and ketones (Scheme 1). Moreover, alkyl Grignard reagents bearing a hydrogen atom in the β-position bear the risk of reducing the carbonyl substrate *via* β-hydride transfer. These factors help explain why even the direct,

non-enantioselective addition of Grignard reagents to ketones has been a long running challenge. The use of (super)stoichiometric additives to promote the desired reaction pathway (*via* either Lewis acid activation of the ketone or enhancement of the nucleophilicity of the Grignard reagent)[7] was necessary until the recently reported Zn(II)-catalyzed racemic addition of Grignard reagents to ketones.[8]

The above reactivity and chemoselectivity issues have likewise hampered the development of effective methodologies for the enantioselective reaction. Indeed, even enantioselective methodologies using (super)stoichiometric amounts of a chiral ligand are relatively few. The first highly enantioselective catalytic addition of Grignard reagents was reported in 2008 by the group of Harada, for the alkylation reaction of aldehydes.[9] Subsequently in 2014, the group of Yus and Maciá reported the addition of aryl Grignard reagents to more challenging ketones substrates.[10] Both methodologies are catalytic with respect to the chiral ligand but require the super-stoichiometric use of titanium tetraisopropoxide. Another step forward has been made by the groups of Harutyunyan and Minnaard, who proved Cu(I)-based chiral catalysts to be successful for the direct use of Grignard reagents (without additives) as nucleophiles in the catalytic asymmetric alkylations of ketones.[11]

This Perspective outlines efforts towards the synthesis of enantiopure chiral alcohols *via* the addition of Grignard reagents to aldehydes and ketones. Approaches using (super)stoichiometric amounts of chiral additives or ligands as well as recently developed titanium and copper(I)-catalyzed enantioselective additions will be highlighted.

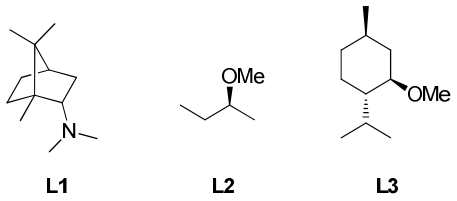
Note that, after the addition reaction step, the generated alkoxide requires protonation to generate the corresponding alcohol. Protonation is typically carried out by addition of water, aqueous NH_4Cl or aqueous HCl. For simplicity, this step has been omitted in all schemes, and only the conditions for the 1,2-addition reaction have been presented.

2. Enantioselective addition of Grignard reagents to carbonyl compounds

To harness the high reactivity of Grignard reagents leading to uncatalyzed reactions and consequently to racemic products and to affect the enantiodiscrimination, the presence of at least one molar equivalent of a chiral substance was required in the early developmental stages of the enantioselective additions to carbonyl derivatives.

The first attempt to perform an enantioselective addition of a Grignard reagent to a carbonyl compound dates from 1940,[12] when Betti and Lucci used *N*,*N*-dimethylbornylamine (**L1**, Figure 1) as solvent in the reaction between benzaldehyde and methylmagnesium iodide. The authors observed small enantiomeric excess in the product of the reaction (1-phenylethanol), which was called into question by Tarbell and Paulson,[13] who could not reproduce this result. Using three different solvents, bornylamine **L1**, *d*-methyl *s*-butyl ether (**L2**) and methyl menthyl ether (**L3**, Figure 1) for the addition of MeMgI to benzaldehyde, optically inactive carbinols were obtained, leading Tarbell and Paulson to conclude that Betti and Lucci's results were due to an optically active impurity in their product derived from the solvent.

Figure 1. Chiral solvents used in the asymmetric addition of Grignard reagents to aldehydes.

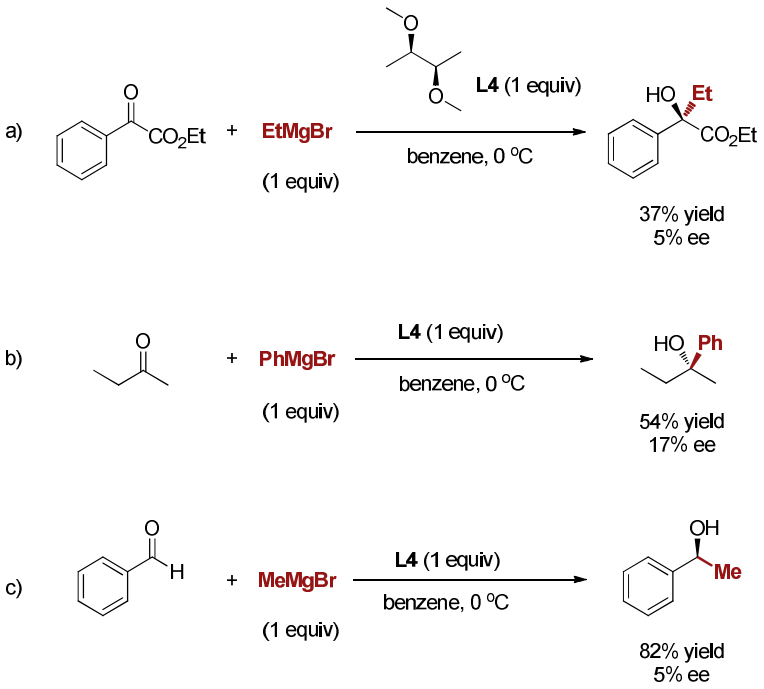


L1 **L2** **L3**

However, the idea that it is possible to affect enantiodiscrimination in the addition of Grignard reagents to carbonyl compounds, in order to obtain enantioenriched carbinols, tantalized organic chemists, and in the following years several groups have used chiral ligands or chiral co-solvents to achieve this goal.

In 1953 Wright's et al. reported the use of the chiral diether **L4** for the asymmetric addition of Grignard reagents to ketoesters (Scheme 2a).[14] The reaction between ethylmagnesium bromide and ethyl benzoyl formate produces the corresponding alcohol in a modest 37% yield and only 5% ee. The ligand **L4** has been also evaluated in the enantioselective addition of Grignard reagents to ketones (Scheme 2b)[15] and aldehydes (Scheme 2c).[16]

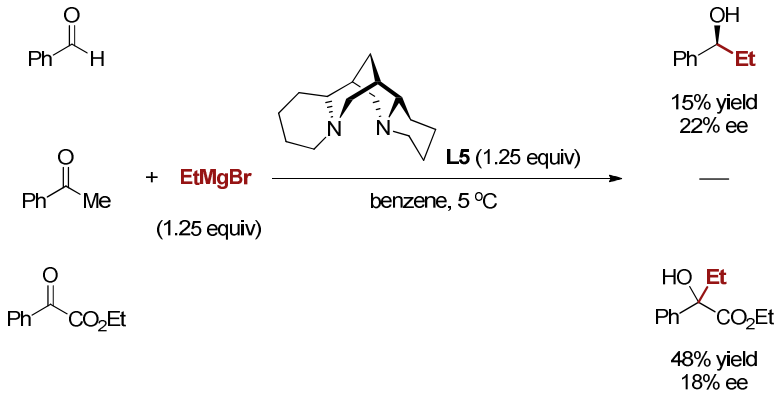
Scheme 2. Addition of Grignard reagents to carbonyl compounds in the presence of chiral diether (L4) by Wright.



The addition of phenylmagnesium bromide to ethyl methyl ketone affords the corresponding product in 54% yield and 17% ee, while the reaction between methylmagnesium bromide and benzaldehyde leads to the corresponding secondary carbinol in 82% yield and 5% ee (which can be increased up to 20% ee when the more reactive Me_2Mg is used instead). The use of an excess of **L4** in these transformations does not enhance the optical purity of the products further. In 1964, Blomberg and Coops explored the use of chiral monofunctional ethers in analogous reactions, obtaining optically inactive carbinols in all cases.[17]

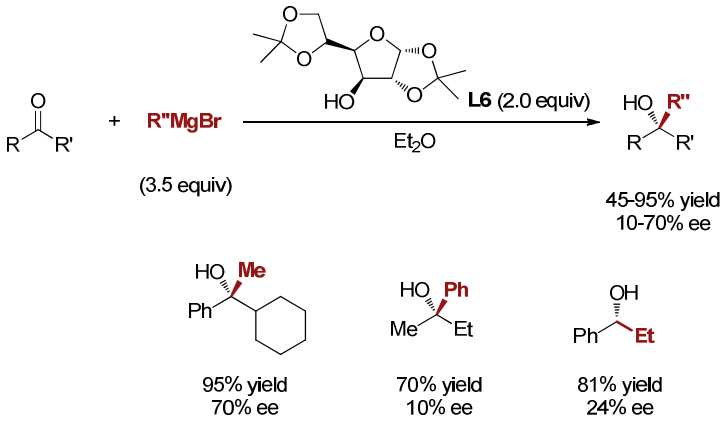
In 1968, Nozaki used (-)-sparteine **L5** in the addition of EtMgBr to benzaldehyde, acetophenone and ethyl benzoylformate in benzene (Scheme 3).[18] Under these conditions, only the more reactive aldehyde and ketoester lead to the corresponding carbinols with slightly improved enantioselectivities respect to those reported by Wright.[14-16]

Scheme 3. Addition of Grignard reagents to carbonyl compounds in the presence of (-)-sparteine (L5) by Nozaki.



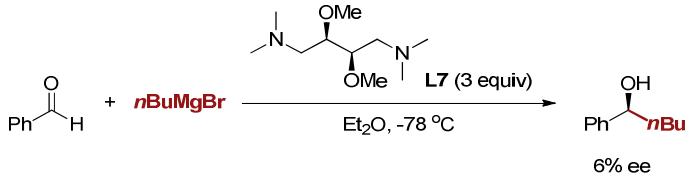
One year later, Inch and co-workers reported improved enantioselectivities for the addition reaction of Grignard reagents to carbonyl compounds using the glucofuranose derivative **L6** (Scheme 4).[19] They evaluated a limited scope of ketones, aldehydes and Grignard reagents and obtained the best results when using MeMgBr or EtMgBr in the addition to aromatic ketones.

Scheme 4. Enantioselective addition of Grignard reagents to ketones in the presence of glucofuranose (L6) by Inch.



The same year, Seebach reported the use of the chiral diamine **L7** for the addition of *n*BuMgBr to benzaldehyde in ether (Scheme 5). A low enantioselectivity (6% ee) is obtained, even when an excess of **L7** (3 equiv) is employed in the reaction.[20]

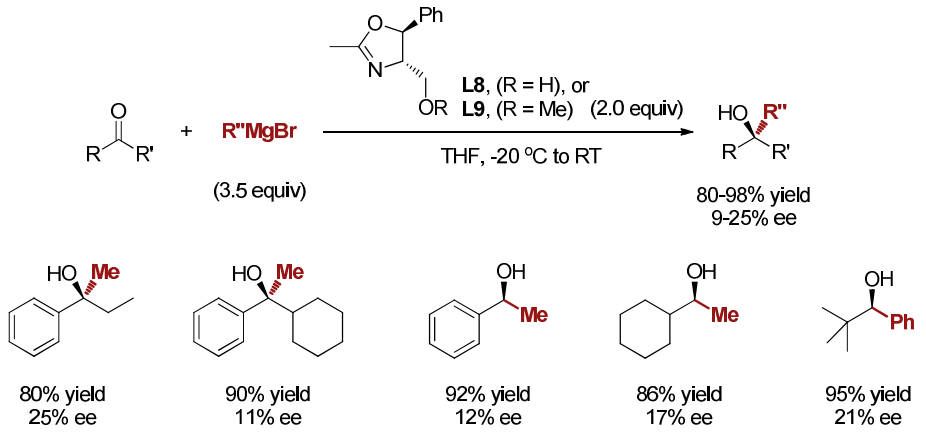
Scheme 5. Addition of *n*BuMgBr to benzaldehyde using chiral diamino diether (L7) by Seebach.



In 1974, Meyers reported the use of the chiral hydroxyoxazoline **L8** and its methyl ether **L9** as ligands in the asymmetric methylation and arylation of aldehydes and ketones.[21] Under these conditions, the corresponding carbinols are obtained in good yields (80-98%) but low enantioselectivities (<25% ee, Scheme 6). In general, the alkoxymagnesium halide formed by deprotonation of **L8** constitutes a better ligand than the methyl ether derivative **L9**.

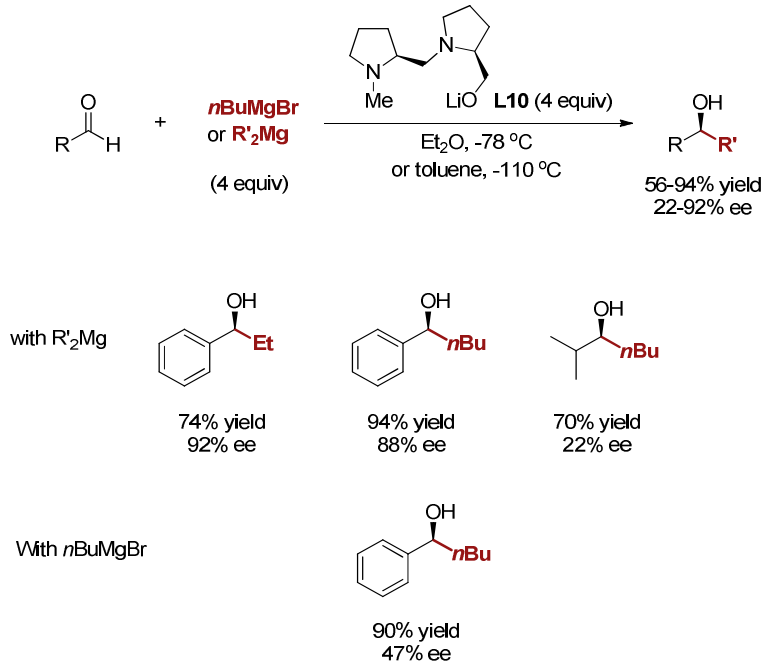
Iffland et al. have evaluated the use of chiral 2-methyltetrahydrofuran (2-MeTHF) as solvent for the addition of Grignard reagents to various aldehydes and ketones.[22] However, low enantioselectivities (2-11% ee) – similar to those obtained by Coops and coworkers using chiral monoethers**Error! Bookmark not defined.** – can be reached under these conditions.

Scheme 6. Addition of Grignard reagents to ketones using chiral oxazolines (L8-9) by Meyers.



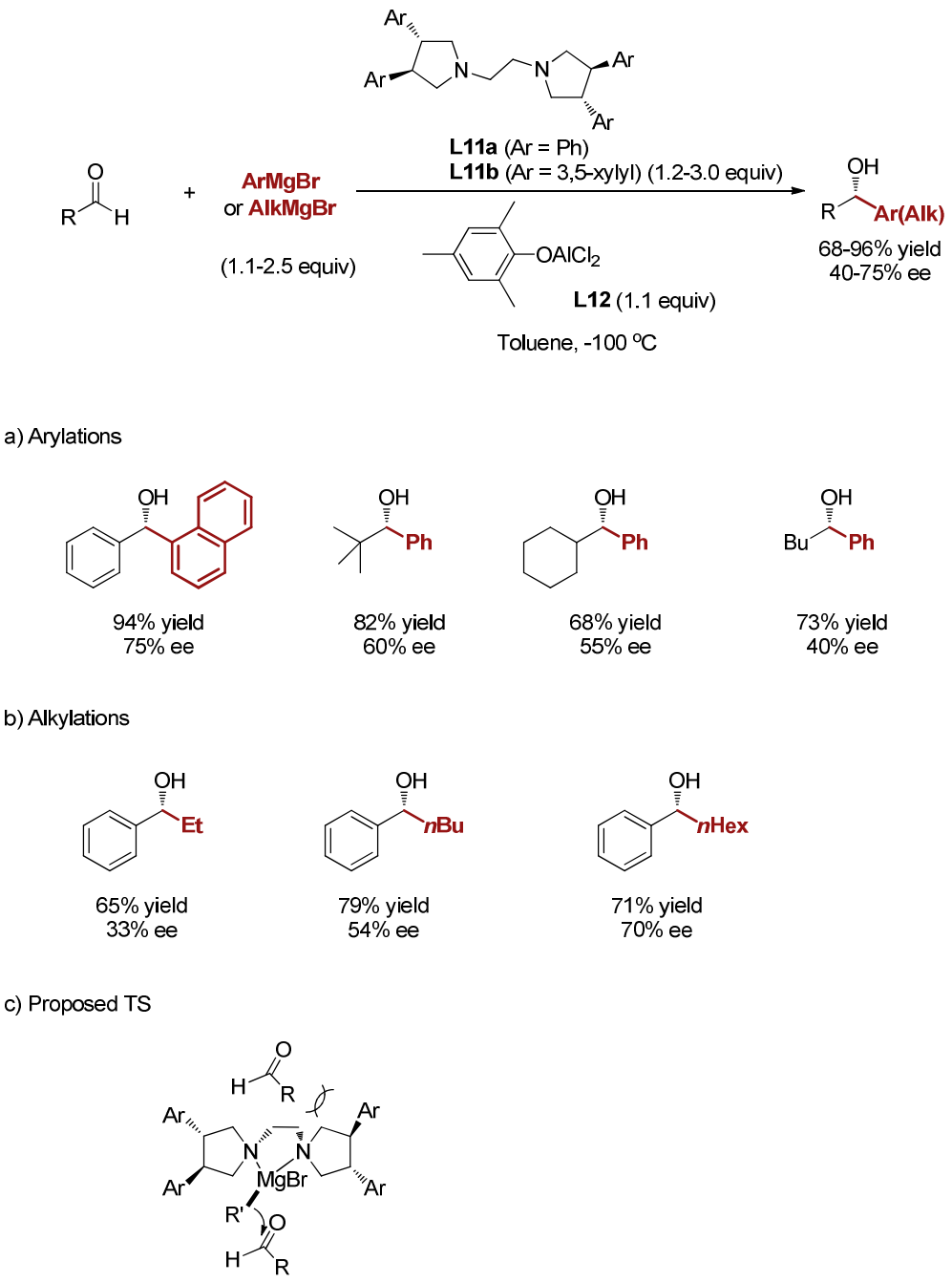
In 1979 Mukaiyama reported improved enantioselectivities for the addition of Grignard reagents to aldehydes using 4 equivalents of the Li salt **L10** as a chiral additive (Scheme 7).[23] Under these conditions, the reaction between benzaldehyde and *n*BuMgBr proceeds with 90% yield and 47% ee. The use of dialkylmagnesium reagents can improve the enantioselectivities of the process; for example, 92% ee is obtained in the addition of Bu_2Mg to benzaldehyde, compared to the 47% ee that *n*BuMgBr provides.

Scheme 7. Alkylation of aldehydes with Grignard and dialkylmagnesium reagents in the presence of chiral diamine alkoxide (L10) by Mukaiyama.



Tomioka and co-workers have reported the use of C_2-symmetric diarylpyrrolidines **L11a-b** (Scheme 8) for the addition of aryl and alkyl Grignard reagents to aldehydes.[24] Good yields (68-96%) and moderate to good enantioselectivities (40-75% ee) are obtained for a narrow scope of aldehydes. Interestingly, the addition of a Lewis acid such as 2,4,6-trimethylphenoxylaluminum dichloride (**L12**,) improves the enantioselectivity in the reaction. For example, the addition of *n*BuMgBr to benzaldehyde improves from 20 to 70% ee in the presence of this aryloxialuminum halide.[24b,c] This methodology allows the use of lower amount of Grignard reagent (1.1 equiv) compared to previous methods. Also, the chiral diamine loading can be reduced from 3 to 1.2 equivalents without any substantial effect in the enantioselectivity. The observed relation between the bulkiness of the Grignard reagent and the enantioselectivity of the addition reaction suggests that the origin of the enantiofacial discrimination are the steric interactions between the aryl group in the chiral diamine and the R group in the aldehyde, as depicted in Scheme 8c.

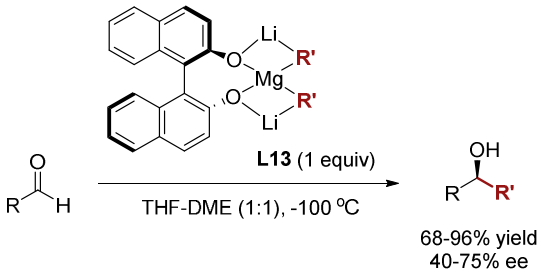
Scheme 8. Enantioselective addition of Grignard reagents to aldehydes in the presence of chiral diamines (L11a-b) and the Lewis acid (L12) by Tomioka.



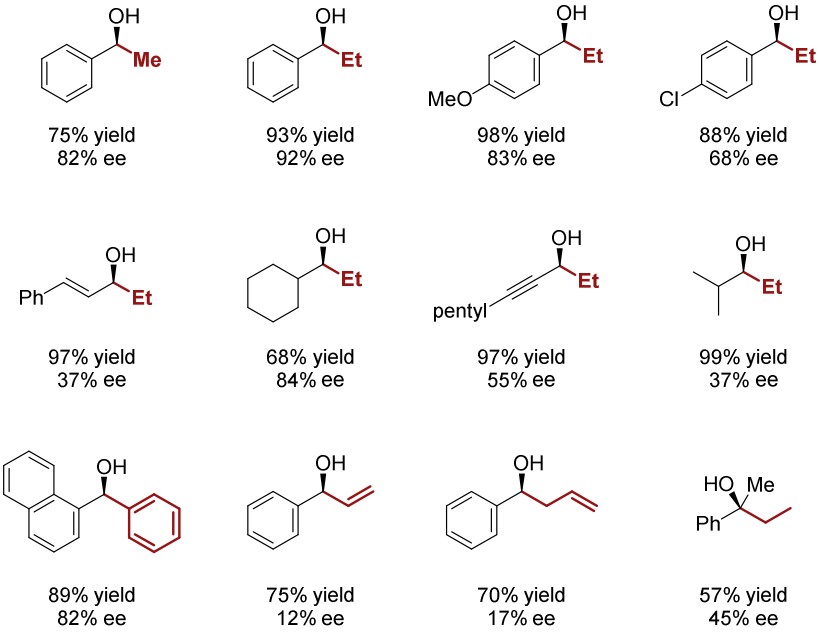
Stoichiometric amounts of the bimetallic chiral reagent **L13** have been also used in the asymmetric addition of Grignard reagents to aldehydes, as reported by Noyori (Scheme 9).[25] The well-defined, coordinatively saturated chiral complex **L13** avoids the aggregation of the

Grignard reagent and allows excellent yields (68-96%) and enantioselectivities (40-75% ee) in the asymmetric addition to aldehydes. This methodology is effective for a broad scope of aromatic (88-98% yield, 68-92% ee), and aliphatic aldehydes (40-99% yield, 37-85% ee). Different dialkyl- and diarylmagnesium reagents can be added successfully, but allyl-, alkenyl- or alkynylmagnesium reagents lead to inferior results (47-76% yield, 4-17% ee).

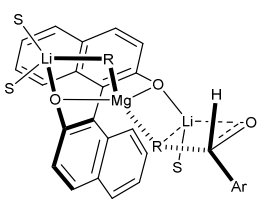
Scheme 9. Enantioselective addition of Grignard reagent to aldehydes and ketones in the presence of complex (L13) by Noyori.



a)

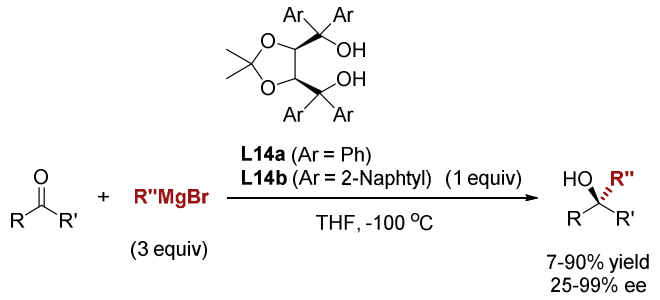


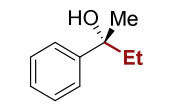
b)



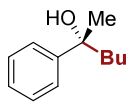
The alkylation of the less reactive acetophenone proceeds with moderate yield (57%) and enantioselectivity (45% ee). The authors have proposed that the activation of the substrate takes place by coordination of a lithium atom with the carbonyl oxygen in the aldehyde, as depicted in the proposed transition state (Scheme 9b).

Scheme 10. Alkylation of ketones in the presence of Mg-TADDOLates by Seebach and Weber.

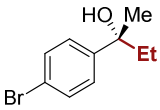




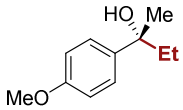
62% yield
98% ee



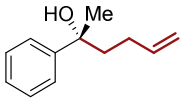
75% yield
98% ee



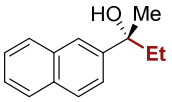
60% yield
98% ee



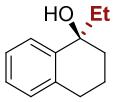
76% yield
92% ee



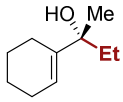
60% yield
98% ee



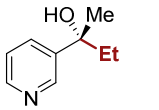
75% yield
98% ee



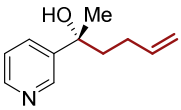
28% yield
89% ee



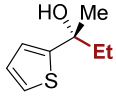
55% yield
71% ee



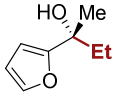
51% yield
96% ee



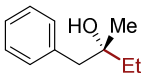
58% yield
86% ee



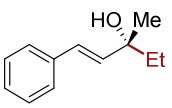
43% yield
96% ee



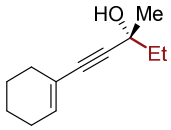
53% yield
66% ee



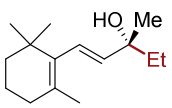
64% yield
83% ee



88% yield
75% ee



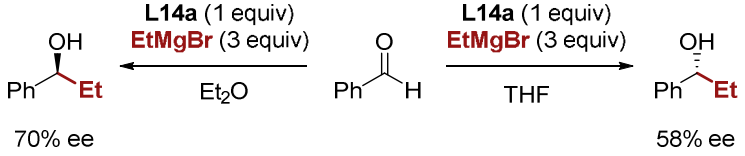
40% yield
70% ee



22% yield
49% ee

In 1992, Seebach and Weber reported a highly efficient system for the enantioselective alkylation of ketones using Grignard reagents, based on the use of stoichiometric amounts of the chiral magnesium alkoxide derived from TADDOL **L14** (Scheme 10).[26] Under these conditions, aryl and heteroaryl ketones lead to their corresponding tertiary carbinols in typically high enantioselectivities (up to 98% ee) and moderated yields. However, alkenyl, alkynyl or aliphatic methyl ketones lead to inferior results (24-70% ee, Scheme 10). In addition, chiral Mg-TADDOLates **L14a,b** can be used in substoichiometric amounts. For example, the addition of *n*BuMgBr to acetophenone in the presence of 0.25 equiv of **L14a** provides the corresponding tertiary alcohol in 84% ee. The behaviour of Seebach and Weber's chiral Mg-TADDOLate **L14a** is particularly interesting in the alkylation reaction of aldehydes. Thus, the addition of ethylmagnesium bromide to benzaldehyde in the presence of **L14a** provides the corresponding (*S*)-carbinol in 60% ee when diethylether is used as solvent but the opposite enantiomer, the (*R*)-carbinol, in 58% ee, when reaction is carried out in THF (Scheme 11).

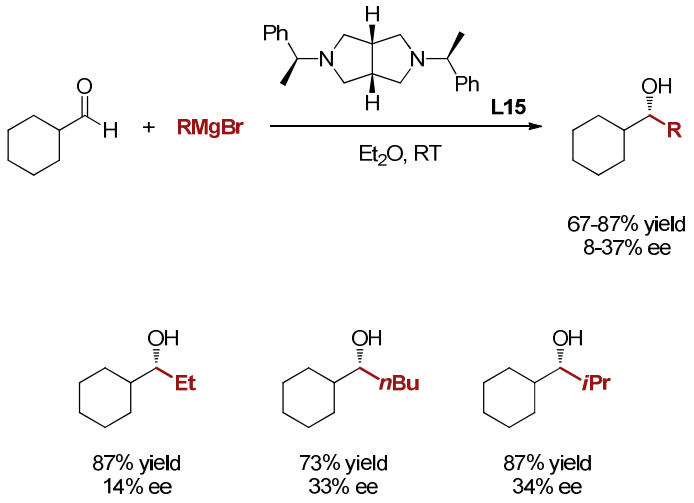
Scheme 11. Alkylation of aldehydes in the presence of Mg-TADDOLate by Seebach and Weber.



In 1994, Markó and co-workers reported the use of the C_2-symmetric diamine **L15** (Scheme 12) in the alkylation reaction of cyclohexane carboxaldehyde.[27] With this methodology, secondary alcohols can be obtained in good yields (67-87%) and modest enantioselectivities (up to 37% ee). The highest enantioselectivities of the series correspond to bulky Grignard reagents. It is worth pointing out that these reactions are carried out at room temperature,

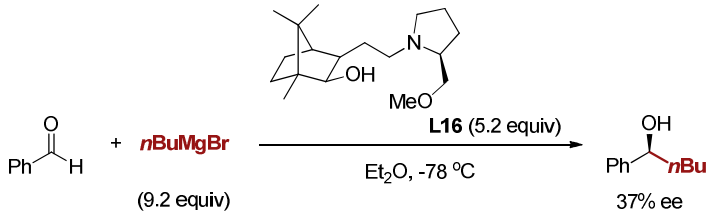
which is quite unusual for the enantioselective addition of Grignard reagents. Interestingly, lower temperatures provided inferior enantioselectivities (9% ee at –40 °C for the addition of *i*PrMgBr, compared to the 42% ee at 35 °C).[28]

Scheme 12. Alkylation of cyclohexane carboxaldehyde at room temperature by Markó.



Knollmuller has evaluated the use of camphor derivatives such as **L6** in the asymmetric addition of *n*BuMgBr to benzaldehyde.[29] A maximum enantiomeric excess of 37% ee is only reached, even in the presence of a great excess of the chiral ligand (Scheme 13).

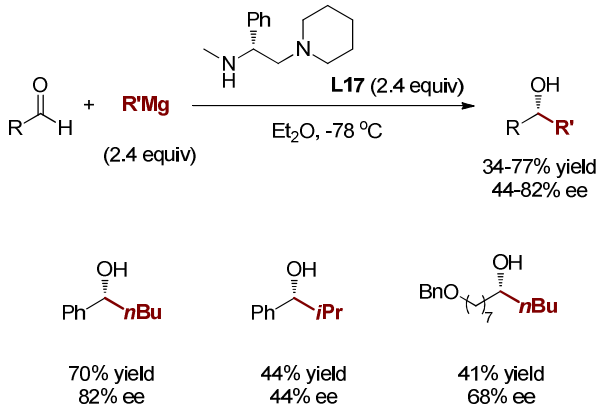
Scheme 13. Alkylation of benzaldehyde in the presence of camphor derivative (L16) by Knollmuller.



Chong et al. have employed chiral organomagnesium amides (COMAs) **L17** in the asymmetric addition of dialkylmagnesium reagents to aldehydes (Scheme 14).[30] Aromatic aldehydes can be transformed into their corresponding secondary alcohols in moderate yields

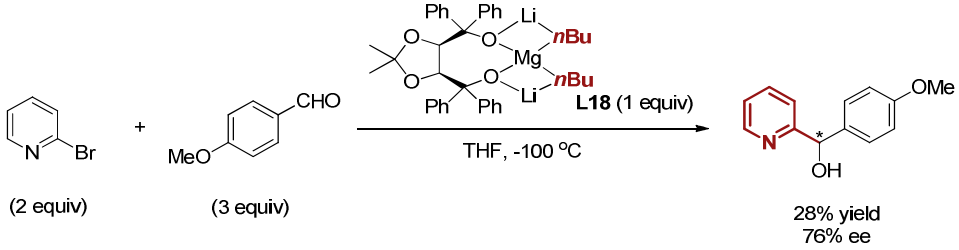
and enantioselectivities (usually 70% yield and up to 82% ee), however highly enolisable aliphatic substrates provide lower yields. The less reactive Me_2Mg also provides lower yields but similar enantioselectivities to its alkyl nucleophilic counterparts.

Scheme 14. Enantioselective alkylation of aldehydes with COMAs by Chong.



Recently, Gros et al. have reported the enantioselective addition of 2-bromopyridine to various aldehydes in the presence of stoichiometric amounts of the Mg-Li-TADDOLate reagent **L18**.[31] Only moderate enantioselectivities and yields can be reached under these reaction conditions, as exemplified in Scheme 15.

Scheme 15. Addition of 2-bromopyridine to aldehydes in the presence of the Mg-Li-TADDOLate (L18) by Gros.



Sixty years have passed since Wright and co-workers discovered that it is possible to use stoichiometric chiral ligands in the enantioselective addition to carbonyl compounds. In this

light, it is remarkable that only the few papers compiled in this section have been reported on the topic, particularly considering the cost-efficiency and availability of Grignard reagents.

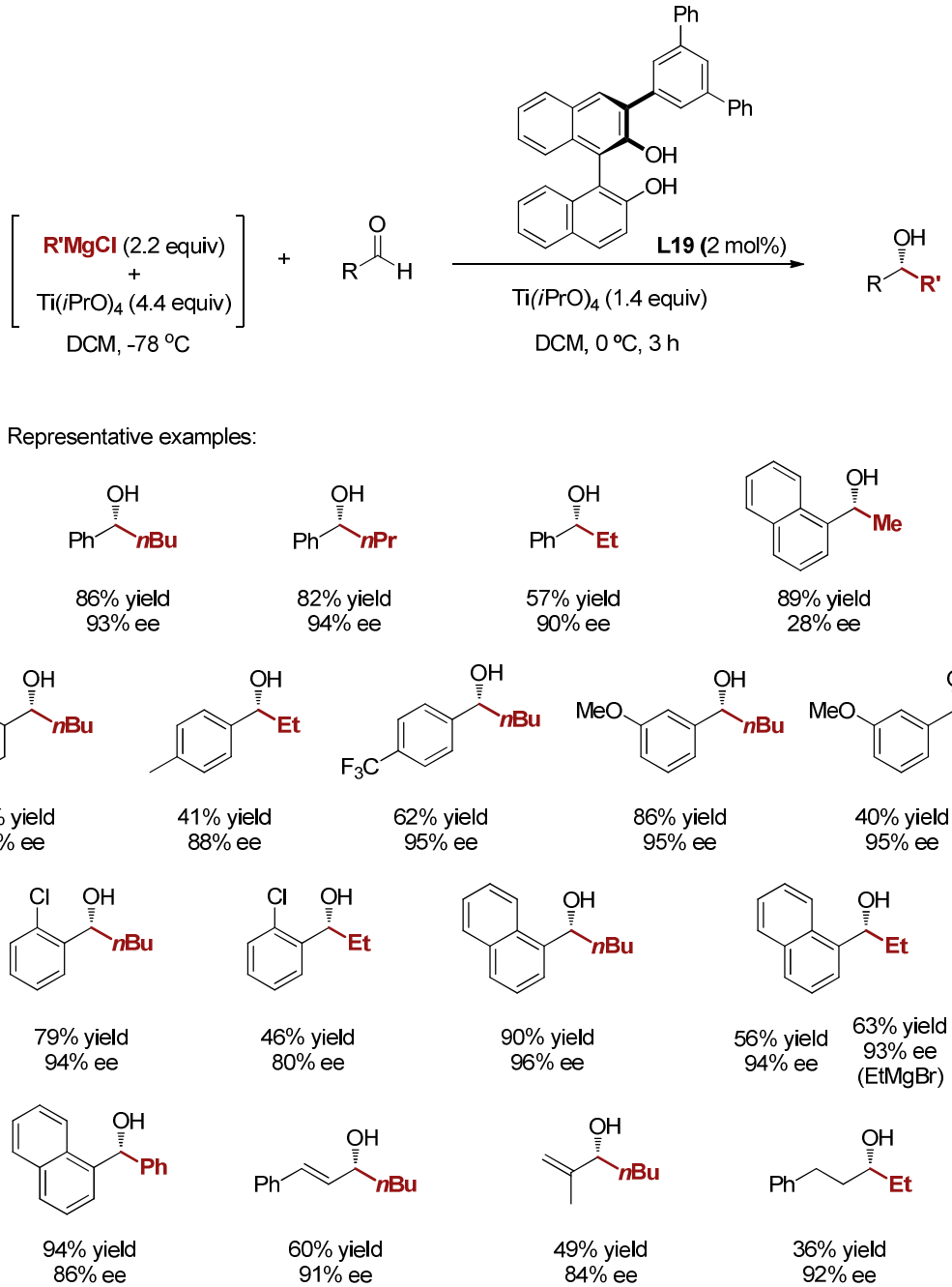
3. Titanium promoted catalytic enantioselective addition of Grignard reagents to carbonyl compounds

Amongst the most used transition metals complexes for enantioselective transformations, those based on titanium stand out for their nontoxicity,[32] high abundance[33] and low cost. In addition, titanium complexes exhibit remarkably diverse chemical reactivity. The rich coordination chemistry of titanium facilitates modulation of complex's properties by modification of the component ligands, which expands the possibilities for control of stereochemistry in various chemical processes.[34]

Enantioselective titanium-mediated transformations have received much attention during the last decade, especially in the area of alkylation, arylation, alkynylation, allylation and vinylation reactions of carbonyl compounds.[35] Since the first enantioselective titanium-promoted addition of diethylzinc to benzaldehyde reported in 1989 by Ohno and Yoshioka, using a chiral disulfonamide as ligand,[36] enantioselective titanium-promoted additions of organozinc and organoaluminum reagents to prochiral aldehydes and ketones have been extensively studied.

However, the use of more reactive organometallic reagents, such as Grignard reagents, in enantioselective titanium-promoted alkylations of carbonyls with catalytic amounts of a chiral ligand was not possible till 2008, with the introduction of ligand **L19** by Harada et al (Scheme 16).**Error! Bookmark not defined.** This report constitutes the first methodology where a Grignard reagent can be used directly (without tedious salt exclusion procedures associated with prior transmetalation to a less reactive organozinc[37] or organotitanium[38] reagent) for the enantioselective catalytic addition to a carbonyl compound.

Scheme 16. (*R*)-DPP-BINOL (L19) catalyzed addition of Grignard reagents to aldehydes by Harada.



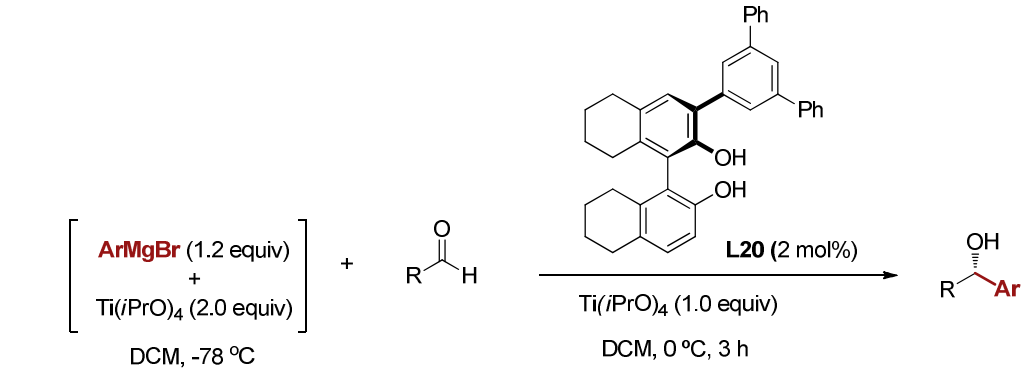
Harada's methodology allows the catalytic alkylation and arylation of aldehydes using Grignard reagents in combination with titanium tetraisopropoxide (Scheme 16). Increasing the amount of chiral ligand from 2 to 4 mol% increases the enantioselectivity of the

corresponding products, although no significant improvement in the reaction yield is observed. The method is applicable to various combinations of aldehydes with both primary alkyl and aryl Grignard reagents but, in order to obtain good levels of enantioselectivity, several practical considerations must be taken into account. Grignard reagents must be previously treated with Ti(*i*PrO)$_4$ at −78 ^{o}C and then slowly added (over 2 h) to the reaction mixture at 0 ^{o}C (Scheme 16). Both organomagnesium chlorides and bromides provide comparable efficiency and selectivity, but the solvent in which the Grignard reagent is prepared influences the reaction outcome. Grignard reagents in Et_2O give better enantioselectivity compared to their analogues in THF.

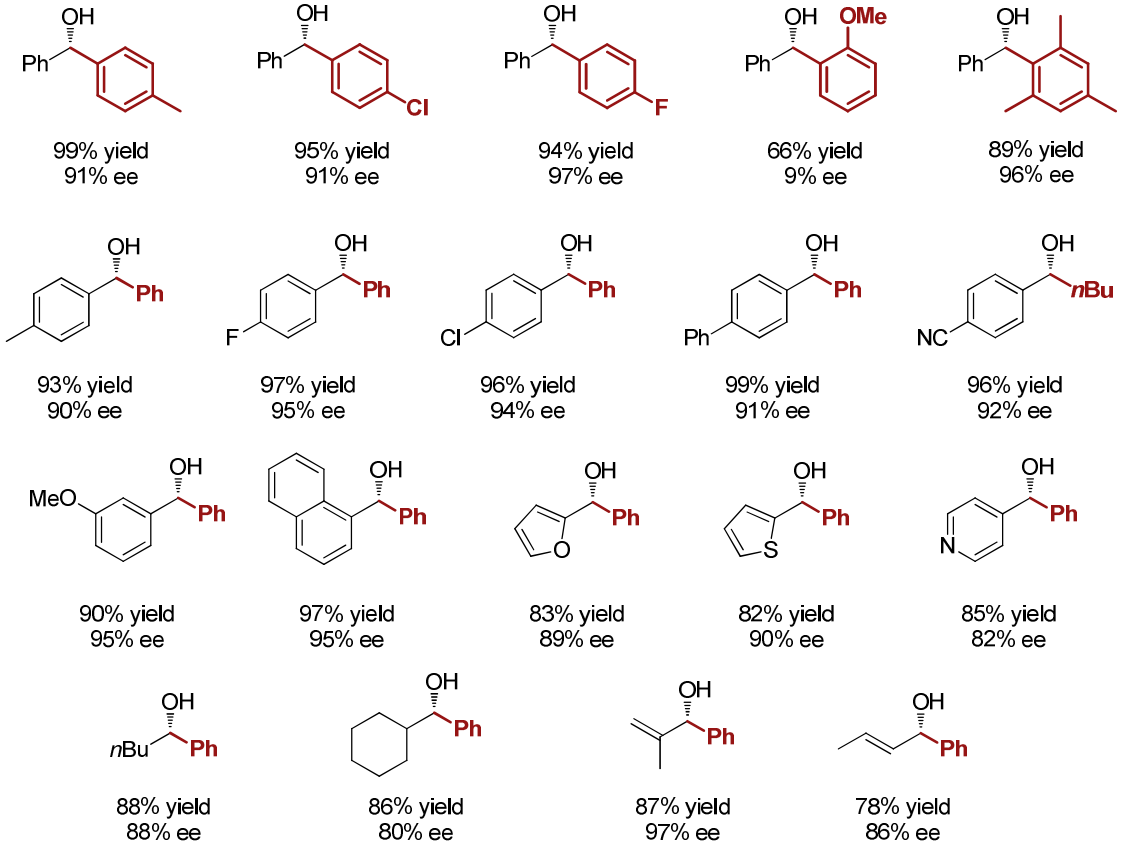
As exemplified in Scheme 16, the addition of primary alkyl nucleophiles to various aromatic aldehydes takes place with good yields (40-90%) and *ee*'s (88-96%), except for the addition of methyl Grignard reagent, which provides low levels of enantioselectivity (28% ee for the addition of MeMgCl to 1-naphthaldehyde). The addition of an aryl nucleophile (PhMgBr) to the aromatic aldehyde 1-napthaldehyde provides good yield (94%) and moderate enantioselectivity (86% ee), while the alkylation of α,β-unsaturated aldehydes provides high enantioselectivity (84-91% ee) and moderate yields (49-60%). This last trend is also observed for the alkylation of aliphatic aldehydes (92% ee and 36% yield for the addition of EtMgCl to 3-phenylpropanal).

The partially hydrogenated ligand (*R*)-DPP-H8-BINOL (**L20**) shows comparable efficiency to **L19** when alkyl Grignard reagents are used as nucleophiles in the addition to aldehydes, but remarkably improved enantioselectivities and yields for aromatic nucleophiles with aromatic and heteroaromatic aldehydes (66-99% yield, 82-97% ee, Scheme 17).[39] The main limitation for **L20** is seen when using *o*-OMeC$_6$H$_4$MgBr, which provides 9% ee and 66% yield in the addition to benzaldehyde. Notably, an excellent enantioselectivity of 96% ee is reached for the addition of the sterically hindered 2,4,6-Me$_3$C$_6$H$_2$MgBr to benzaldehyde.

Scheme 17. (*R*)-DPP-H8-BINOL (L20) catalyzed addition of aromatic Grignard reagents to aldehydes by Harada.



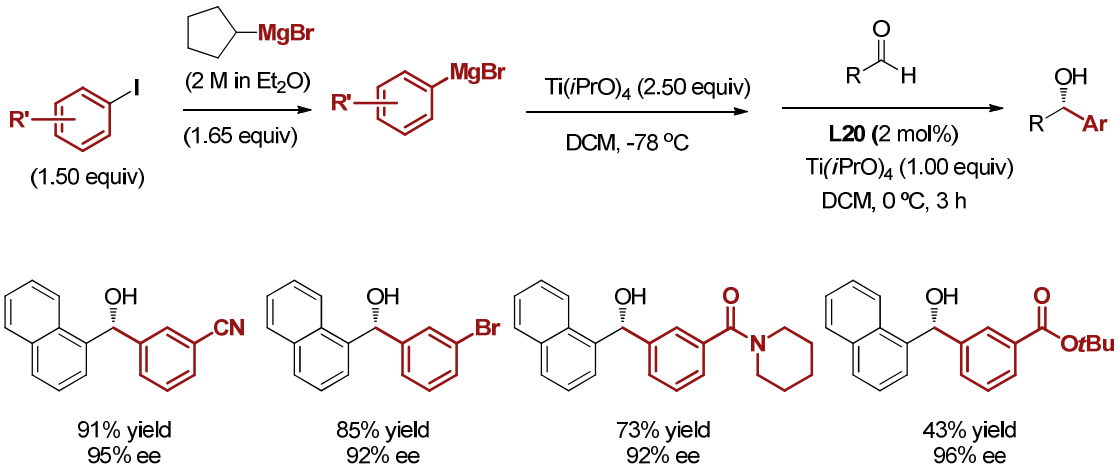
Representative examples:



The substrate scope of **L20** includes α,β-unsaturated aldehydes and aliphatic aldehydes which provide high enantioselectivity (80-97% ee) and moderate to good yields (78-87%) for the addition of PhMgBr (Scheme 17). The experimental procedure for the use of **L20** is

analogous to that previously described for **L19** (slow addition of the Grignard reagent – pretreated with Ti(*i*OPr)$_4$ – over the reaction mixture containing aldehydes, ligand and Ti(*i*OPr)$_4$). When **L20** is used as ligand, however, the total amount of Ti(*i*PrO)$_4$ necessary to obtain good enantioselectivities is lower (3.0 equiv in total versus 5.8 equiv needed for **L19**); also, a lower amount of nucleophile can be used (1.2 equiv *versus* 2.2 equiv needed for **L19**). This methodology also allows for the addition of functionalized Grignard reagents, prepared *in situ* by reaction of the corresponding iodoarene and *c*-C_5H_9MgCl (2M in Et_2O), as per Knochel´s procedure (92-96% ee, 43-91% yield, Scheme 18).[40] Alternatively, the I/Mg exchange can be performed using the readily available *i*PrMgCl (2 M in THF).[41] However, in this case, the solvent (THF) from the Grignard solution must be removed in-vacuo and replaced with DCM prior to addition to the aldehydes in order to obtain good enantioselectivities.

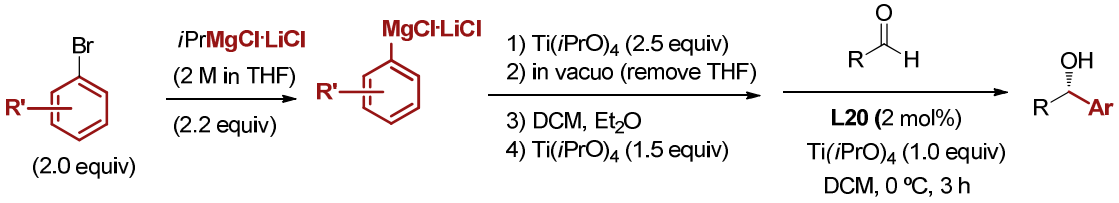
Scheme 18. (*R*)-DPP-H8-BINOL (L20) catalyzed addition of *in situ* prepared functionalized aromatic Grignard reagents to aldehydes, by Harada.



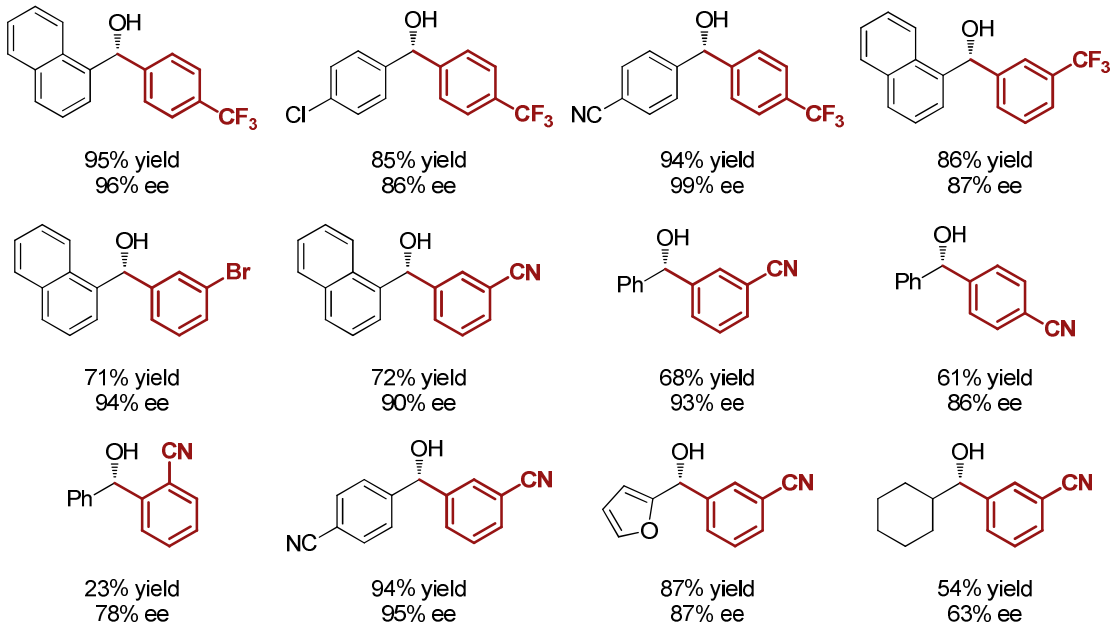
Aryl bromides constitute preferable precursors for the preparation of functionalized Grignard reagents due to their greater stability, wider availability and lower price, in comparison to the corresponding iodoarenes. Harada´s group has applied Knochel´s methodology for the

preparation of functionalized Grignard reagents from aryl bromides (using *i*PrMgBr·LiCl),[42] which, after the strict removal of THF in-vacuo, are suitable nucleophiles for the enantioselective addition to aldehydes using **L20** and Ti(*i*PrO)$_4$ (Scheme 19).[43]

Scheme 19. (*R*)-DPP-H8-BINOL (L20) catalyzed addition of *in situ* prepared functionalized aromatic Grignard reagents to aldehydes, by Harada.



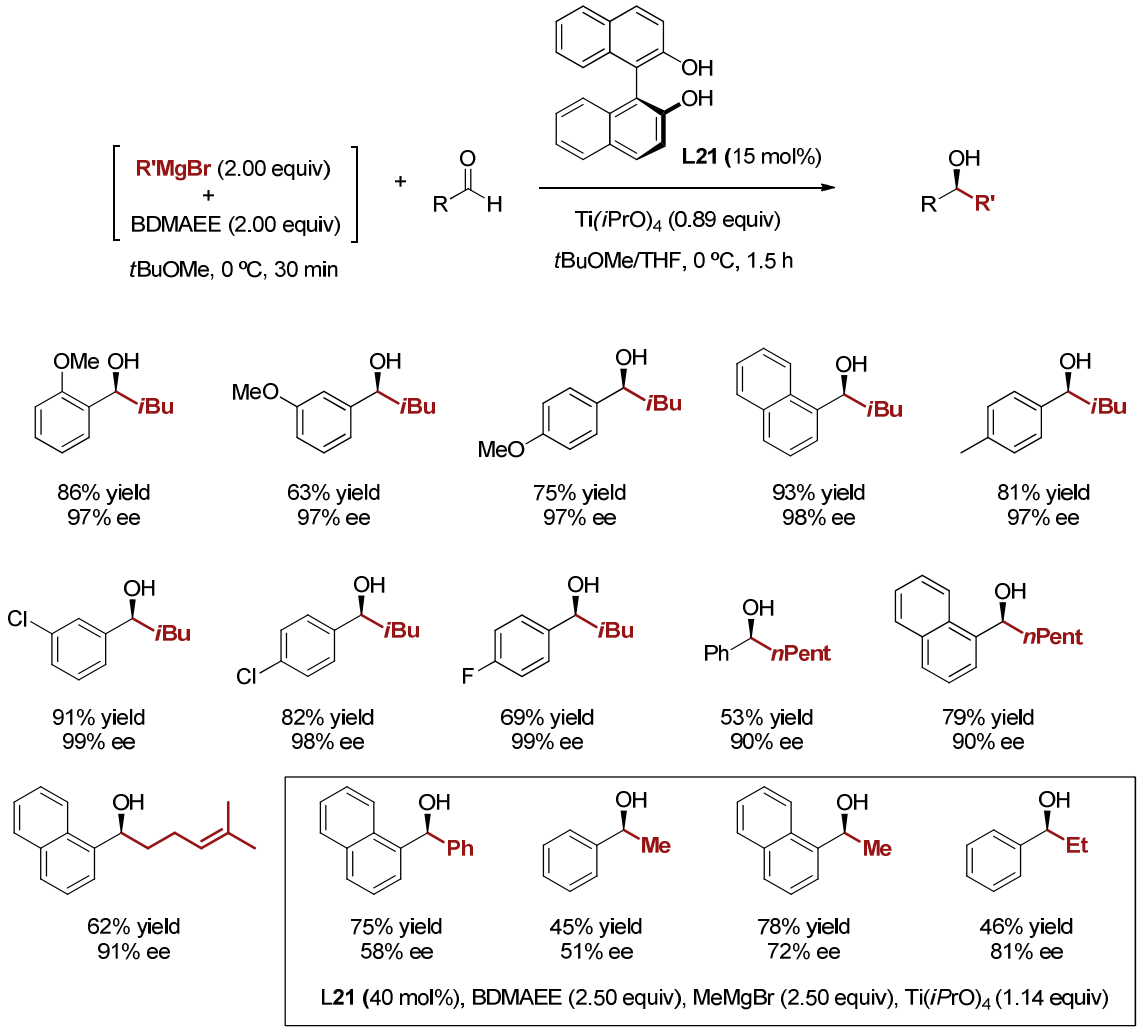
Representative examples:



The method is applicable to aryl bromides bearing CF_3, Br and CN groups, affording a range of chiral functionalized aryl secondary alcohols of synthetic importance in good to high yields and enantioselectivities (84-99% ee, 61-94% yield) when added to aromatic aldehydes (Scheme 19). Unfortunately, the reaction of the aliphatic cyclohexanecarbaldehyde provides the corresponding product in only moderate yield (54%) and enantioselectivity (63% ee).

A significant operational improvement (temperatures of 0 °C, no slow addition of reagents needed and lower amounts of Ti(*i*PrO)$_4$) in comparison with Harada´s methodology has been reported by Da et al., namely by using equimolar amounts of *bis*[2-(*N*,*N*´-dimethylamino)ethyl]ether (BDMAEE) as chelating additive to decrease the high reactivity of the alkyl Grignard reagents (Scheme 20).[44]

Scheme 20. (*S*)-BINOL (L21) catalyzed addition of Grignard reagents to aldehydes, by Da.



The strong basic and chelating BDMAEE traps magnesium salts, such as $MgBr_2$ or Mg(*i*PrO)Br generated in either the Schlenck equilibrium and/or the transmetallation process

with titanium tetraisopropoxide, respectively, as depicted in Scheme 21 (species **C** and **E**). This chelation prevents Lewis acid/base coordination of magnesium salts to the carbonyl group of the aldehyde, which would promote undesired and uncatalyzed reactions generating racemic alcohols.

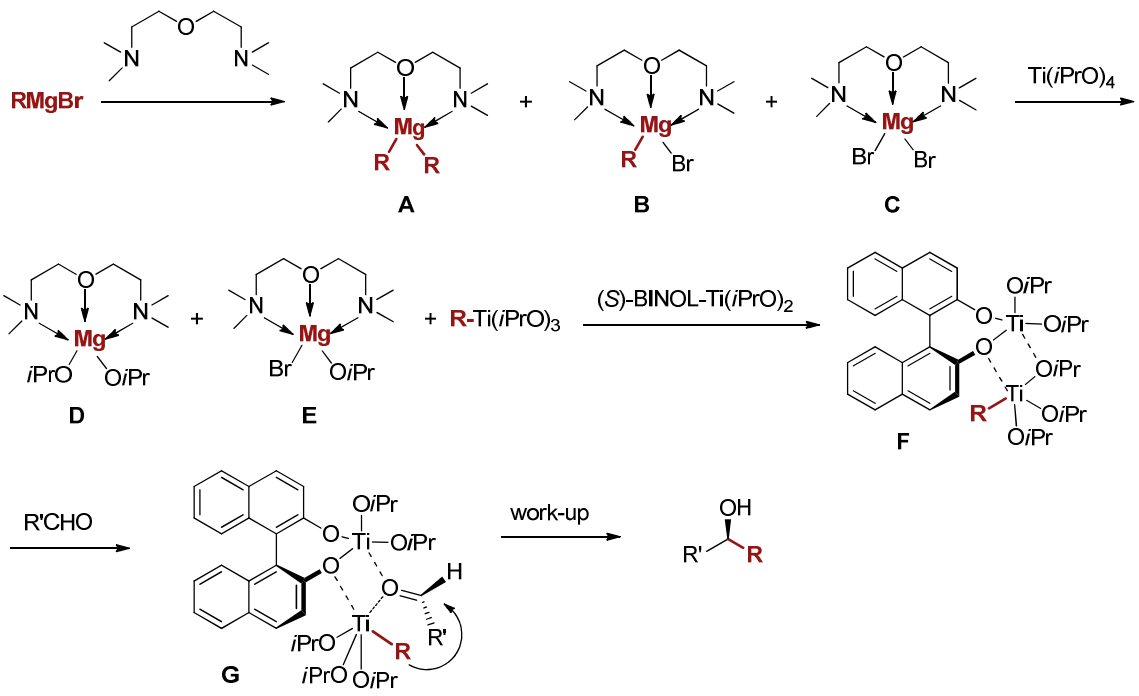
Although elevated ligand loadings (10-20 mol%) are needed to reach higher enantioselectivity (compared to the lower 2 mol% of catalyst **L19** or **L20** required in Harada´s methods), the ligand (*S*)-BINOL is commercially available at a relatively low price.

On the basis of the Schlenk equilibrium, transmetalation of Grignard reagents with Ti(*i*PrO)$_4$, and the investigations of Bolm and Walsh,[45] Da proposes the mechanism shown in Scheme 21 for the reaction. Coordination of BDMAEE to the Grignard reagent generates three possible intermediates **A**-**C**. Importantly, the salt $MgBr_2$ is well chelated by BDMAEE and partly loses its catalytic activity (species **C**). In the presence of Ti(*i*PrO)$_4$, chelates **A** and **B** convert to the chelated salts **D** and **E**, and the reactive intermediate R-Ti(*i*PrO)$_3$. Naturally, **E** is a less reactive Lewis acid than **C**, and R-Ti(*i*PrO)$_3$ is much less reactive than the Grignard reagent itself. This might be the reason why a mixture of RMgBr-BDMAEE-Ti(*i*PrO)$_4$ does not react with an aldehyde in the absence of a chiral catalyst such as **L21**. However, when R-Ti(*i*PrO)$_3$ coordinates the chiral catalyst (*S*)-BINOL-Ti(*i*PrO)$_2$, complex **F** is formed. This species **F** is able to coordinate the aldehyde providing intermediate **G** where steric interactions between R' (aldehyde) and the three bulky isopropoxy groups in R-Ti(*i*PrO)$_3$ moiety are minimised. This configuration will favor the S_i-face addition to the aldehyde.

Da´s method allows the addition of alkyl Grignard reagents to aromatic aldehydes (Scheme 20) in yields that vary from 35-91% and generally good enantioselectivities (70-99% ee). Of particular note is the addition of *i*BuMgBr to aromatic aldehydes (97-99% ee) with 15 mol% of **L21**. Unfortunately, the challenging addition of MeMgBr to aromatic aldehydes provides low enantioselectivities (51-72% ee), even at higher catalyst loadings (40 mol% **L21**).

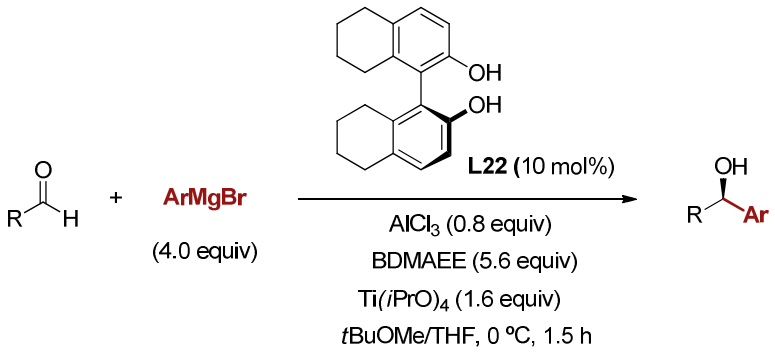
Inferior results when utilising sp^2 hybridised Grignard reagents (both vinyl and aryl) also limit this methodology. For example, the addition of PhMgBr proceeds with low enantioselectivity (54-58% ee) and low yield (58-75%) when aromatic aldehydes are used as substrates, even with high catalyst loadings (40 mol% **L21**).

Scheme 21. The chelated Lewis acidic salts by BDMAEE (A and B species) and the proposed mechanism for the reaction proposed by Da.

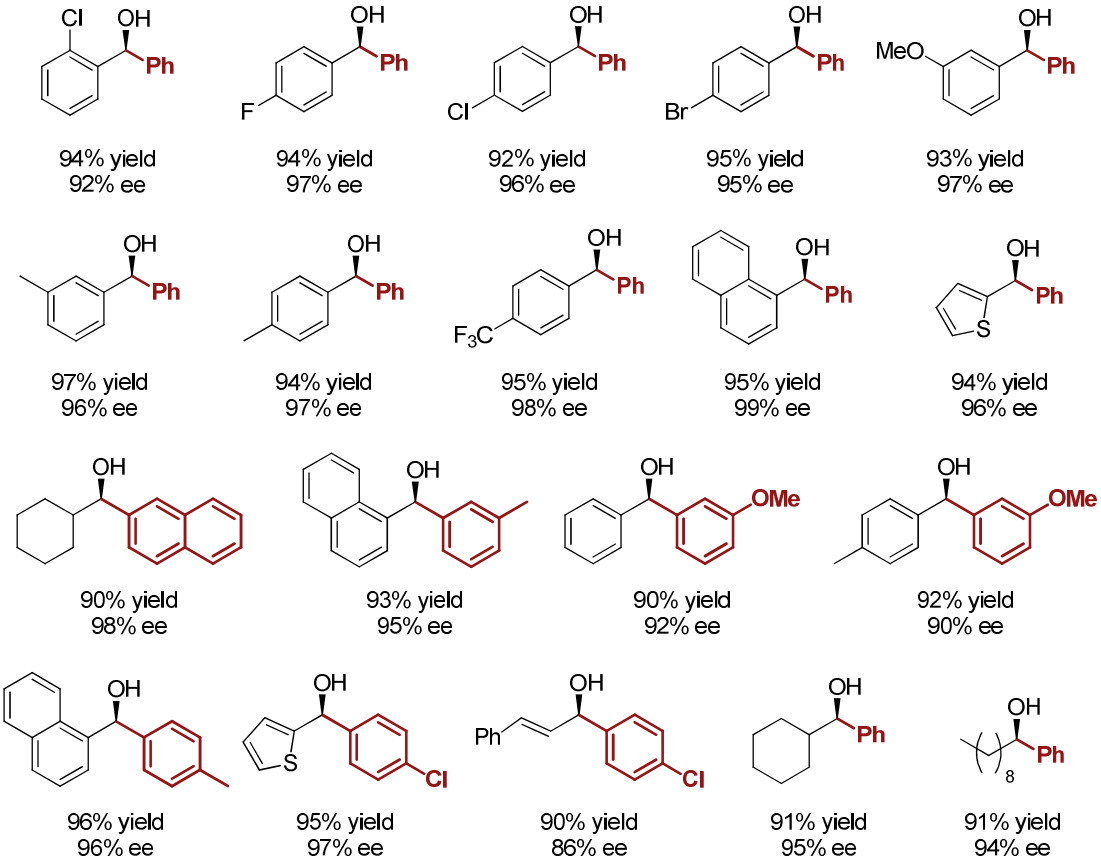


Da et al. have reported an alternative methodology that allows the enantioselective addition of aromatic Grignard reagents to aldehydes. This new strategy involves conversion of Grignard reagents into less reactive triarylaluminum intermediates *in situ* by treatment with $AlCl_3$.[46] Operationally simple, the aryl Grignard reagent is treated with $AlCl_3$ in THF, followed by addition of BDMAEE, ligand **L22**, Ti(*i*PrO)$_4$ and last, the aldehyde. Remarkably highly enantioselectivities (87-98% ee) and good yields (83-97%) are obtained for a variety of aromatic as well as aliphatic aldehydes (Scheme 22).

Scheme 22. (*S*)-H8-BINOL (L22) catalyzed addition of aromatic Grignard reagents to aldehydes, by Da.



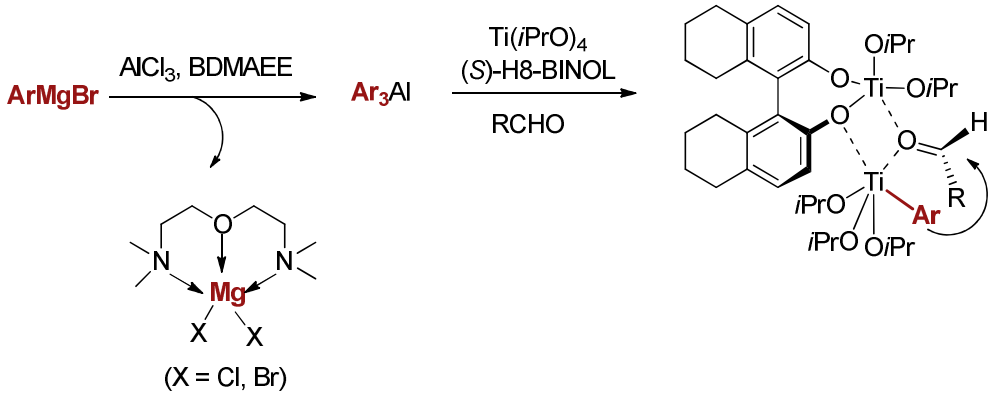
Representative examples:



The authors have proposed the mechanism depicted in Scheme 23 to explain the role of $AlCl_3$ in the reaction. The corresponding $AlAr_3$ species is generated by reaction of the aromatic Grignard reagent with $AlCl_3$. As seen previously, BDMAEE is believed to sequester

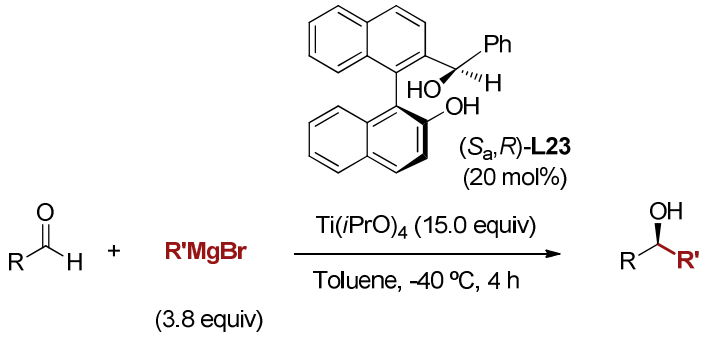
magnesium salts to prevent them from promoting racemic addition to the aldehyde. Transfer of one aryl group from $AlAr_3$ to the (*S*)-H8-BINOL/titanium complex occurs and, after coordination of the aldehyde, enantioselective addition takes place.

Scheme 23. Mechanism for the (*S*)-H8-BINOL (L22) catalyzed addition of aromatic Grignard reagents to aldehydes in the presence of $AlCl_3$ and BDMAEE proposed by Da.

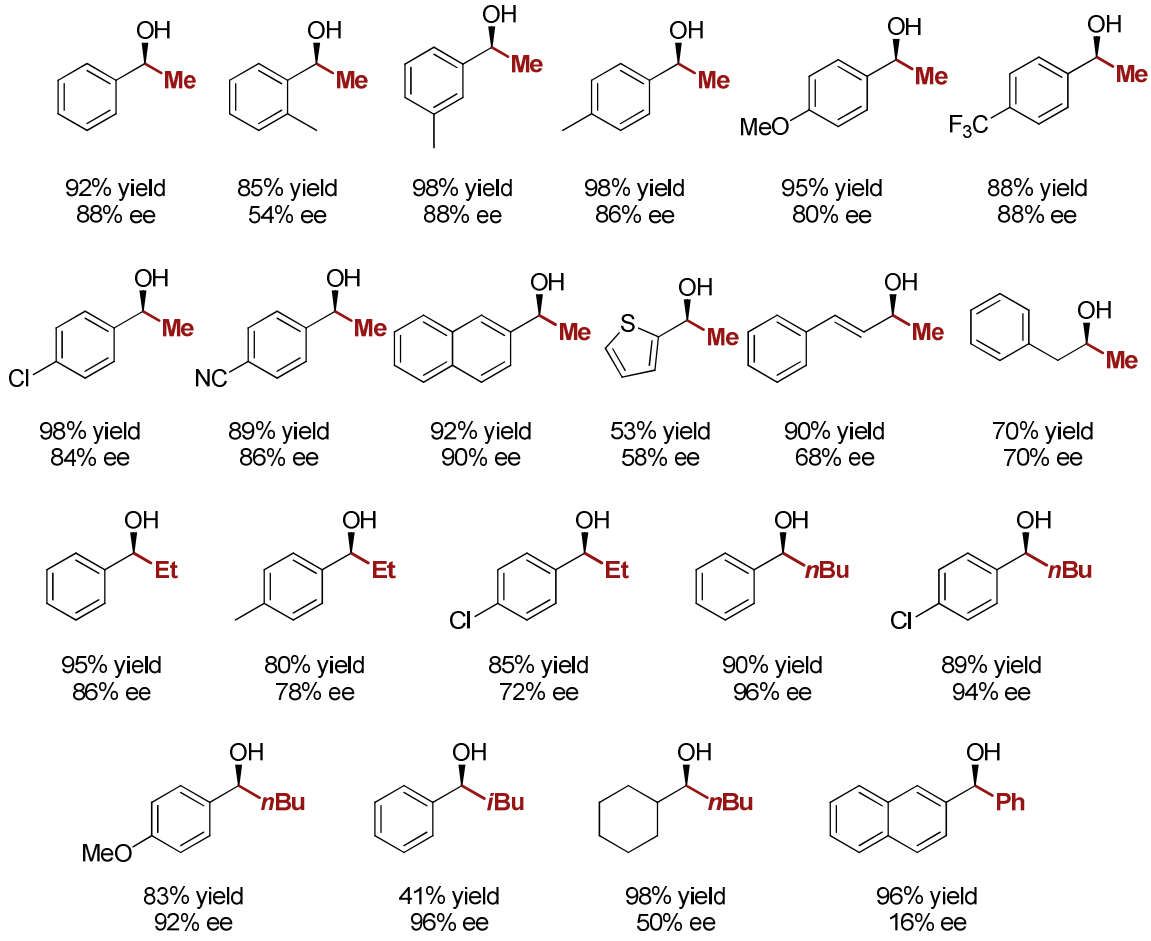


In 2011, Maciá, Yus et al. reported the use of another efficient chiral catalyst[47] for the direct addition of alkylmagnesium bromides to aldehydes in the presence of Ti(*i*PrO)$_4$ (15 equiv) and the chiral ligand (S_a,*R*)-Ph-BINMOL **L23** (20 mol%) at –40 ^{o}C (Scheme 24).[48] Although lower temperatures (–40 ^{o}C) and a larger excess of Ti(*i*PrO)$_4$ are needed, the experimental procedure offers various benefits over previous methodologies; no slow addition protocols are necessary and the entire process can be operated in one-pot (no pre-treatment of the Grignard reagent required). This methodology provides exceptional results (not achievable with previous methodologies) when the challenging methyl Grignard reagent is used as nucleophile. Good yields and enantioselectivities are obtained in the addition reaction of MeMgBr to aromatic (58-90% ee and 85-99% yield) and α,β-unsaturated (68% ee and 90% yield) aldehydes.

Scheme 24. (S_a,*R*)-Ph-BINMOL (L23) catalyzed addition of Grignard reagents to aldehydes, by Maciá and Yus.



Representative examples:



The methylation of *ortho*-methylbenzaldehyde proceeds with a lower enantioselectivity (54% ee), probably due to the steric hindrance close to the reactive site. Other nucleophiles such as ethyl and *n*-butyl perform in a similar fashion to the other methodologies, providing good

yields (81-95%) and enantioselectivities (86-96% ee) in the addition to aromatic aldehydes. The use of *i*BuMgBr provides good enantioselectivity in the addition to benzaldehyde (96% ee) but lower yield (41%)[49] than Da's methodology.[44] The addition of aromatic Grignard reagents proceeds with very low enantioselectivities (16% ee for the addition of PhMgBr to 2-napthaldehyde). It must be noted that, in this methodology, THF has a detrimental effect on enantioselectivity and Et_2O must be used as the Grignard reagent solvent.

Although aliphatic aldehydes only provide moderate enantioselectivities (50-70% ee) with **L23**, the results can be substantially improved by using the analogous ligand (S_a,*R*)-4-Pyridine-BINMOL **L24**, in combination with Ti(*i*PrO)$_4$ (10 equiv) in Et_2O at –20 ^oC (Scheme 25).[50]

This novel catalytic system allows the enantioselective addition of alkyl nucleophiles to alkyl aldehydes, providing chiral aliphatic secondary alcohols – very important motifs in biological systems – in generally good yields (61-99%) and enantioselectivities (60-99% ee).[51] Again, the methodology is suitable for the addition of MeMgBr, which allows the synthesis of versatile chiral methyl carbinol units with unprecedented yields and enantioselectivities in a simple one-pot procedure and under mild conditions.

A further advantage of this methodology is the ability to recover the chiral ligand **L24** from the reaction mixture by simple acid–base extraction (60% recovery yield) which, at the same time, facilitates the isolation and purification of the corresponding products. The recovered ligand **L24** can be reused in subsequent reactions without any loss of activity.

Scheme 25. (S_a,*R*)-4-Py-BINMOL (L24) catalyzed addition of Grignard reagents to aliphatic aldehydes, by Maciá and Yus.

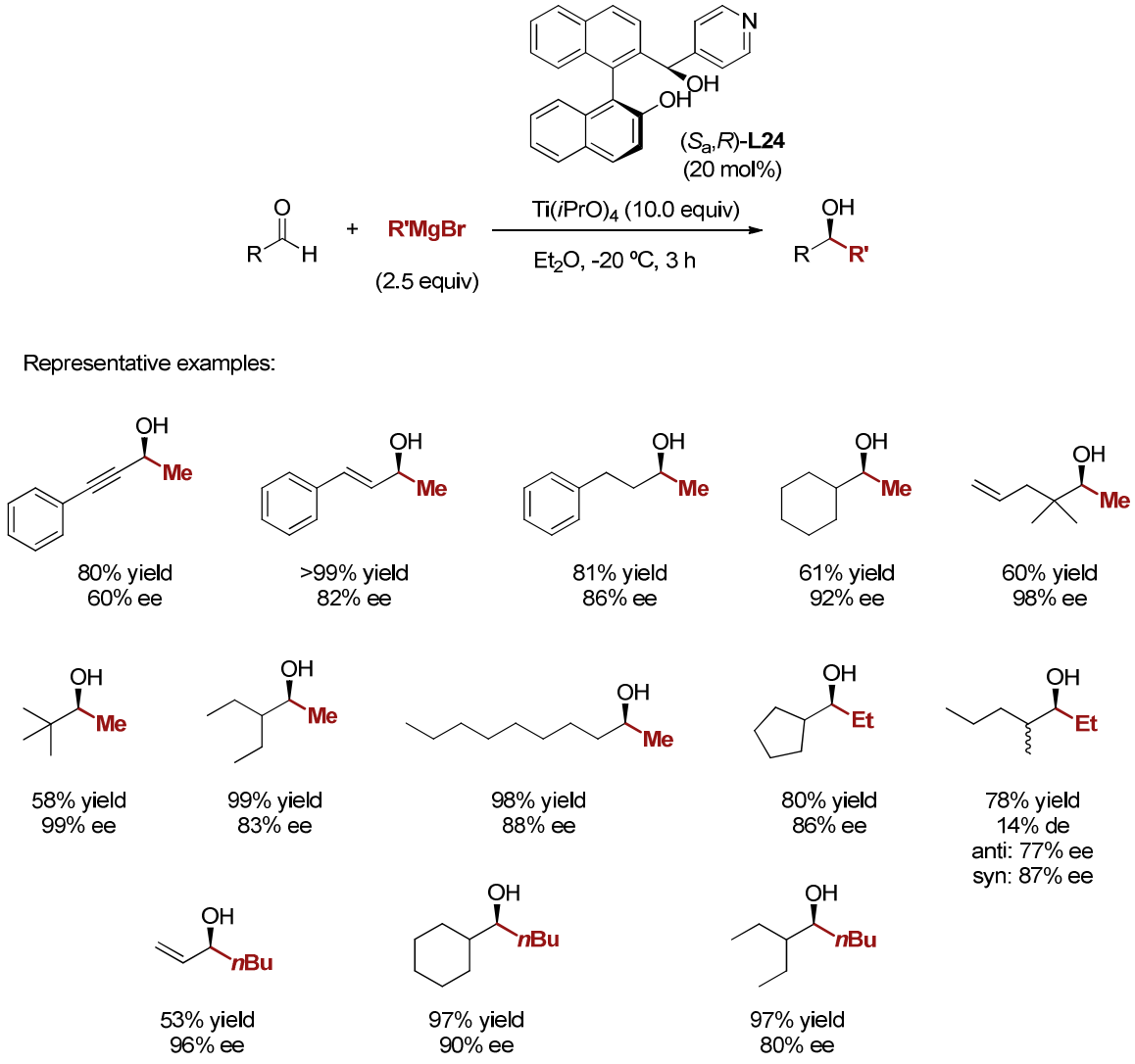
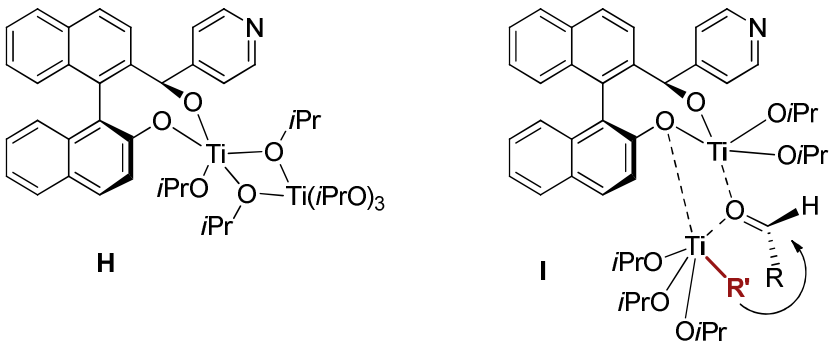


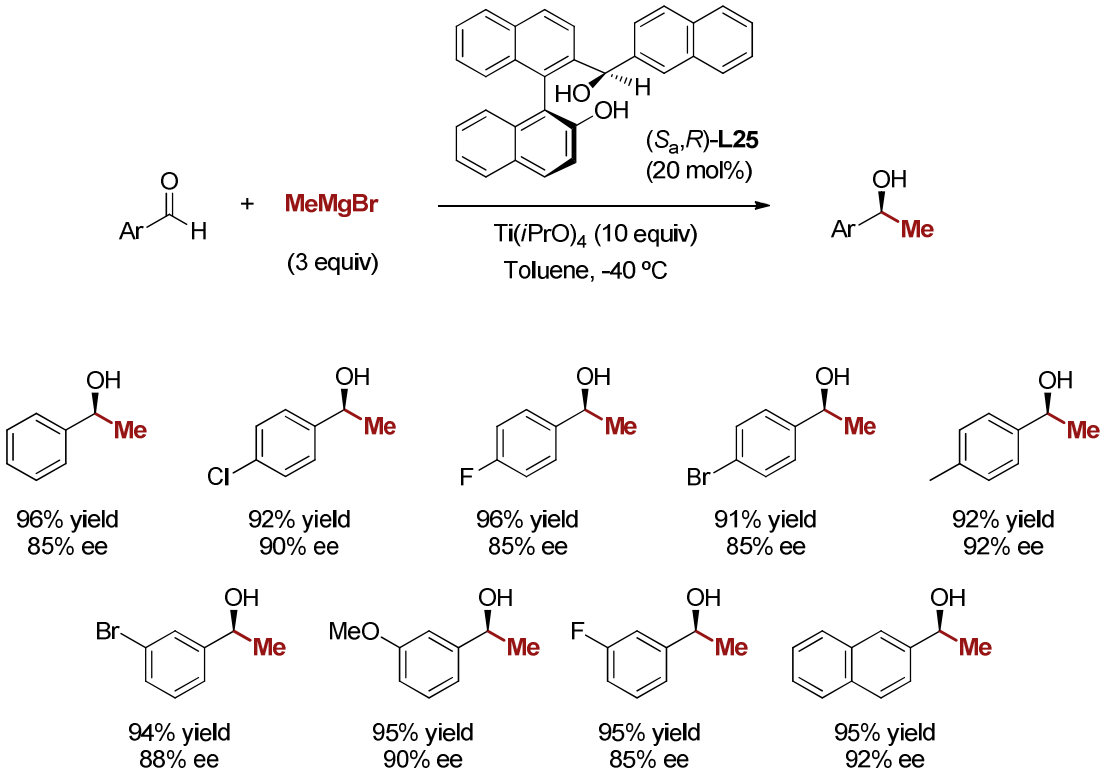
Figure 2. Possible intermediates involved in the catalysis by Maciá and Yus.



By analogy with previous reports on the asymmetric addition of alkyl groups to aldehydes catalyzed by titanium-BINOLate[45] and titanium-TADDOLate[52] species, the group proposes the monomeric bimetallic species **H** and **I** (Figure 2) to be responsible for both conversion and asymmetric induction in the system.

Xu et al. have also employed 2-napthyl-BINMOL ligand **L25** for the addition of MeMgBr to various aromatic aldehydes (Scheme 26).[53] In comparison with the previous example which used **L23**, reduced amounts of MeMgBr (3.0 *vs* 3.8 equiv) and Ti(*i*PrO)$_4$ (10.0 vs 15.0 equiv) can be used; enantioselectivities and yields of the chiral carbinol products obtained are the same (85-90% ee and 91-96% yield).

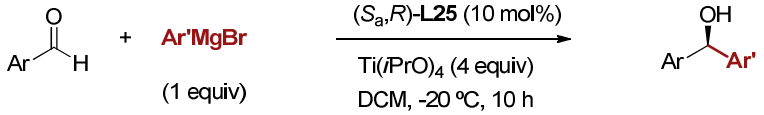
Scheme 26. (S_a,*R*)-2-Naph-BINMOL (L25) catalyzed addition of methylmagnesium bromide to aromatic aldehydes, by Xu.



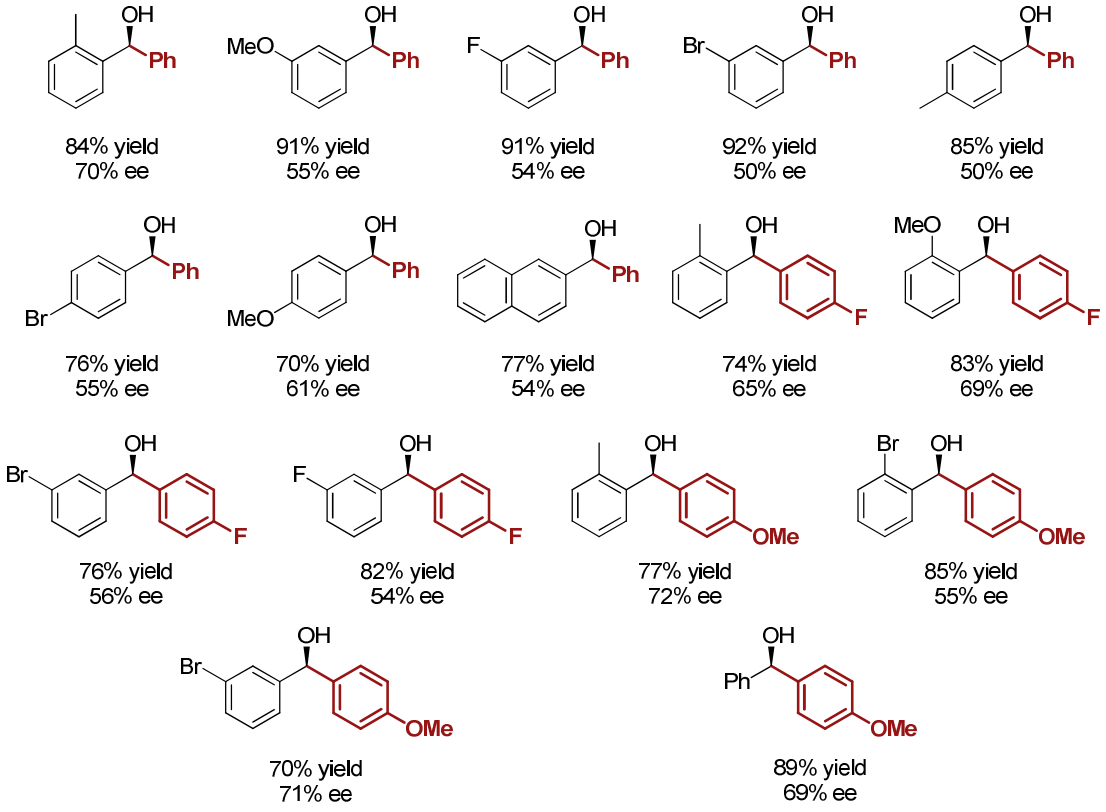
Ligand **L25** is, however, more effective than **L23** for the addition of aryl Grignard reagents to aromatic aldehydes (Scheme 27). With only 10 mol% of **L25**, and working in DCM at –20

°C, the corresponding diarylmethanols are obtained with moderate enantioselectivities (50-71% ee) and yields (70-92%). These results are, however, less satisfactory compared to Harada or Da´s methodologies.[39,43,46]

Scheme 27. (S_a,*R*)-2-Naph-BINMOL (L25) catalyzed addition of aromatic Grignard reagents to aromatic aldehydes by Xu.



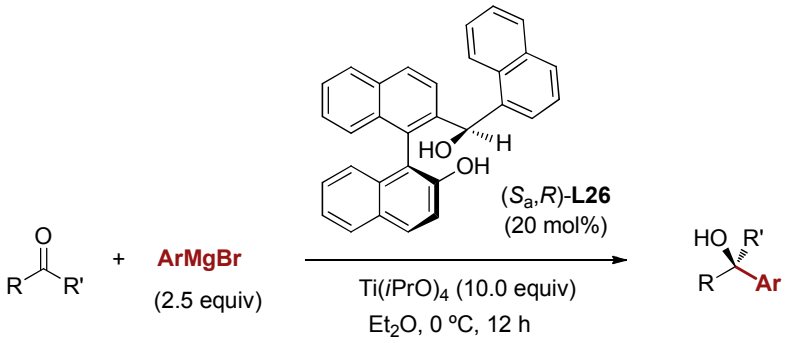
Representative examples:

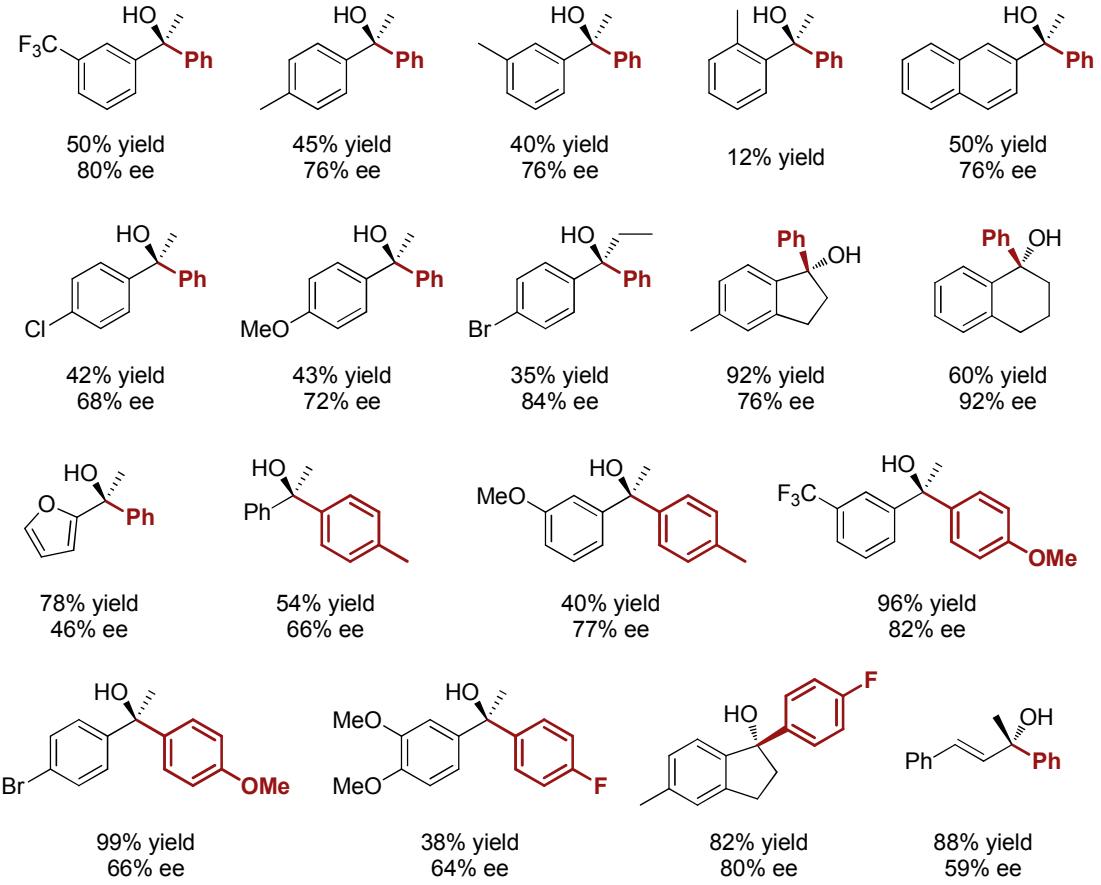


Of all the titanium complexes discussed in this section, only Ar-BINMOL ligands have been applied to the addition of Grignard reagents to the less reactive (and therefore, more challenging) ketone substrate class (Scheme 28).**Error! Bookmark not defined.** Although restricted to the addition of aryl nucleophiles, chiral tertiary alcohols bearing two aryl groups

can be prepared, which represents a major challenge in asymmetric catalysis. The ligand 1-napthyl-BINMOL **L26** (20 mol%) used in combination with Ti(*i*PrO)$_4$ (10 equiv) in Et$_2$O at 0 ^{o}C, allows the addition of a variety of aryl Grignards reagents to various aromatic aldehydes in yields varying from 35-99% and moderate to good enantioselectivities (46-92% ee).

Scheme 28. (S_a,*R*)-1-Naph-BINMOL (L26) catalyzed addition of aromatic Grignard reagents to ketones, by Maciá and Yus.





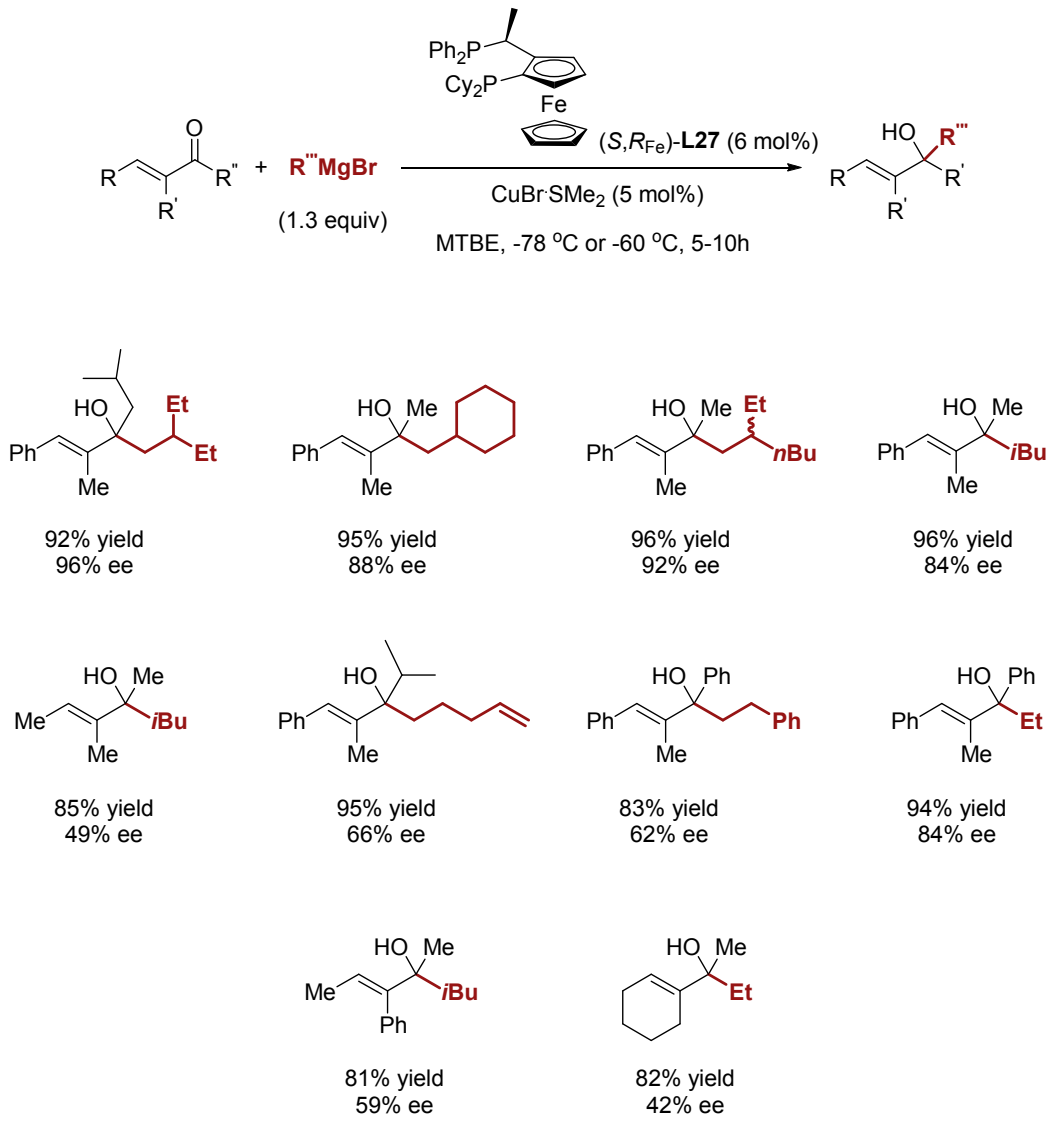
The main limitation of the methodology is bulky substrates, such as 1-(*o*-tolyl)ethanone, which does not provide more than 12% conversion in the addition of PhMgBr.

In the last few years, various groups have reported protocols for the enantioselective titanium promoted addition of Grignard reagents to carbonyl compounds (mainly aldehydes), all utilising BINOL derivatives as chiral ligands for Ti(*i*PrO)$_4$. These procedures are based on *in situ* transmetalation of the Grignard reagent with Ti(*i*PrO)$_4$ to form less reactive intermediates, such as RTi(*i*PrO)$_3$ or the titanate RTi(*i*PrO)$_4$MgX. The mechanistic picture for these transformations is still not clear, but experimental observations and preliminary investigations from different groups point towards the presence of similar intermediates to the ones reported for the titanium promoted catalytic addition of organozinc reagents to carbonyl compounds.[45]

4. Copper(I)-catalyzed enantioselective addition of Grignard reagents to carbonyl compounds

During the past 80 years, following the work of Gilman and Straley in 1934,[54] Cu(I)-based reagents and catalysts have been used to outcompete the 1,2-addition of hard nucleophiles towards the conjugate addition to electron-deficient carbonyl compounds. This exclusive feature of Cu(I)-based catalyst is the main reason for the lack of their application in alkylation reactions of carbonyl compounds. However, this situation has recently changed, owing to reports by the groups of Harutyunyan and Minnaard, who have developed the first Cu(I)-based catalytic system for the asymmetric 1,2-addition of Grignard reagents to α-substituted α,β-unsaturated ketones, in the absence of any other stoichiometric additive (Scheme 29).[55]

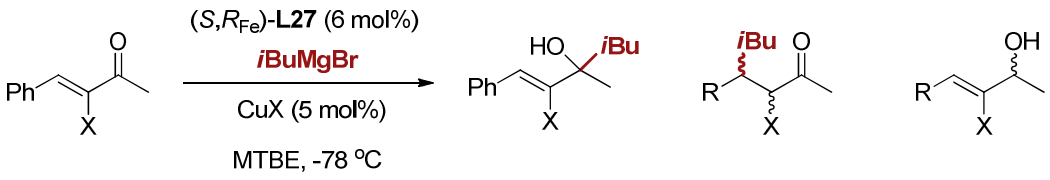
Scheme 29. Catalytic asymmetric 1,2-addition to α,β-unsaturated ketones by Harutyunyan and Minnaard.



The reaction of a Grignard reagent with an α-substituted α,β-unsaturated ketone in the presence of catalytic amounts of a Cu(I) salt but without a chiral ligand, leads to a mixture of 1,2-addition and conjugate addition products. However, when the reaction is carried out in the presence of a diphosphine ligand (BINAP-, Taniaphos- or Josiphos- derivatives) the regioselectivity of the reaction towards the 1,2-addition product increases significantly. An extensive screening of chiral ligands,[56] Cu(I) salts and solvents, have identified the catalytic

system formed by CuBr·SMe_2 and the ferrocenyl diphosphine rev-Josiphos (**L27**) in MTBE as the most suitable to achieve the desired chiral tertiary allylic alcohols with high yields and enantioselectivities. Under the optimal reaction conditions, only 1% of 1,4-addition and 2% of side reaction (reduction) products are formed, and the corresponding allylic alcohols can be obtained in 97% yield and 84% of enantiomeric excess (Scheme 29). This discovery has broken once and for all the old paradigm of the regioselectivity of organocopper compounds towards 1,4-addition. The scope of the reaction has been investigated with several unsaturated ketones and different Grignard reagents (Scheme 29), obtaining, in all cases high 1,2-regioselectivity. Increasing the steric bulk in the substrate (both R and R') or in the Grignard reagent provides higher enantioselectivities. Excellent results can be obtained when β-branched Grignard reagents are used (typically 95% yield and up to 96% ee), while linear Grignard reagents give slightly lower enantioselectivities. When the less reactive MeMgBr is used, only starting material is recovered and the use of the highly reactive PhMgBr leads to racemic 1,2-addition product.

Scheme 30. Study of regio- and enantioselectivity depending on the α-substituent in the enone by Harutyunyan and Minnaard.



X = Me		98 (84% ee)	1	1
Br		97 (90% ee)	1	2
H		51 (32% ee)	49	-
H	EtMgBr	16 (14% ee)	84	-

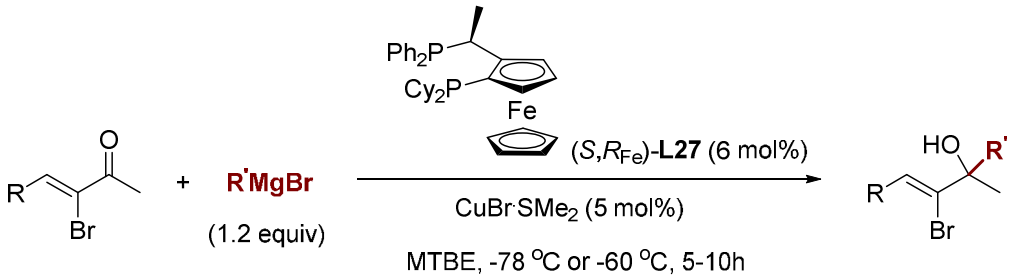
The α-substituent in the enone plays a crucial effect in the outcome of the reaction (Scheme 30). In the absence of an α-substituent (X = H), both regio- and enantioselectivity of the

addition reaction decrease drastically. As mentioned before, also lower regio- and enantioselectivity are obtained with linear Grignard reagent compared to bulky β-branched ones.[57]

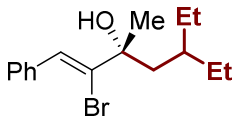
α-Br-unsaturated ketones give excellent results, especially with β-branched Grignard reagents (typically >90% yield and >90% ee, Scheme 31). Lower enantioselectivities are obtained with linear Grignard reagents. Interestingly, magnesium-bromide exchange in the substrate is not detected. To access α-H substituted tertiary allylic alcohols with high enantioselectivity, a further debromination reaction with *t*BuLi can be carried out in excellent yield and with full retention of the enantiomeric excess (Scheme 31b).

Interestingly, the authors have found a dramatic asymmetric amplification effect in this reaction. This phenomenon is the result of the large difference in the solubility of the racemic and the enantiopure chiral Cu-complexes.[58] When scalemic mixtures of the chiral diphopshines are used to form the Cu-complexes in MTBE a significant amount of precipitate is formed. When the supernatant is used as catalyst, the enantioselectivity in the addition of (2-ethylbutyl)magnesium bromide to α-Br-substituted benzylidenacetone is 94% ee in all cases, even when the enantioselectivity of the initial scalemic mixture is only 20% ee. These results are similar to those obtained with the enantiopure catalyst. Slightly lower enantioselectivities are obtained when the supernatant and precipitate mixture are used as catalyst (80-90% ee), indicating that the precipitate is not involved in the catalytic reaction. On the contrary, the precipitate hinders efficient stirring, since longer reaction times are needed in this case to achieve full conversion. The same amplification effect has been observed for other Cu-diphosphine and Pd-complexes.[58]

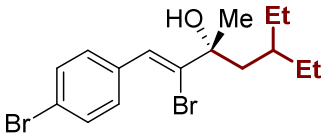
Scheme 31. Catalytic asymmetric addition to α-Br-unsaturated ketones by Harutyunyan and Minnaard.



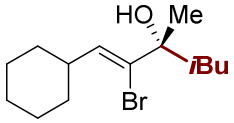
a)



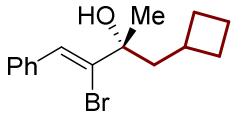
92% yield
98% ee



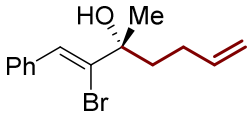
94% yield
92% ee



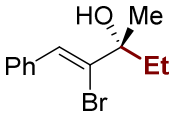
95% yield
94% ee



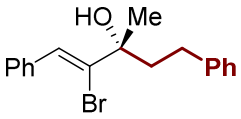
96% yield
82% ee



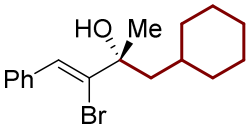
95% yield
66% ee



96% yield
39% ee

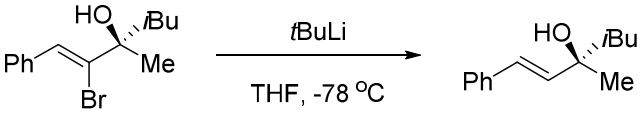


94% yield
72% ee



96% yield
94% ee

b)



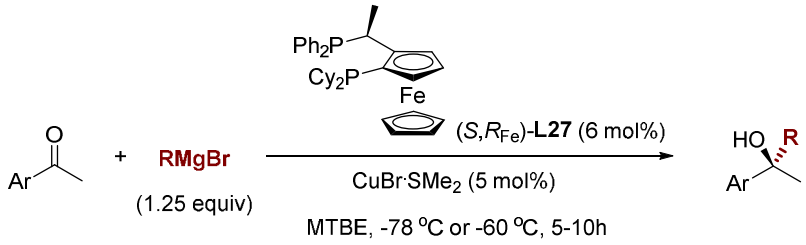
90% ee

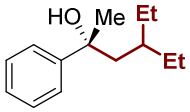
96% yield
90% ee

Harutyunyan and Minnaard´s groups have applied this Cu(I)-phosphine based catalytic system to the alkylation of aryl alkyl ketones with Grignard reagents (Scheme 32).[59] Thus, the corresponding benzylic tertiary alcohols can be formed in high yields and good to

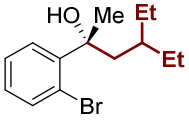
excellent enantioselectivities, with no traces of the uncatalyzed reaction, reduction or enolisation.

Scheme 32. Catalytic asymmetric 1,2-addition to aryl alkyl ketones by Harutyunyan and Minnaard.

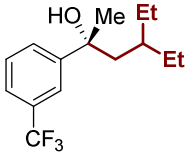




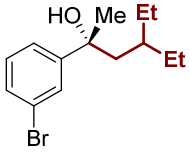
96% yield
82% ee



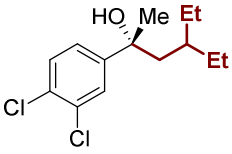
61% yield
95% ee



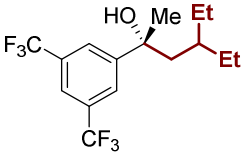
95% yield
96% ee



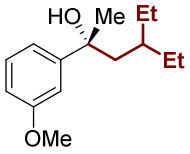
96% yield
90% ee



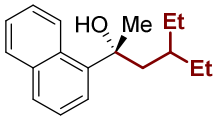
96% yield
96% ee



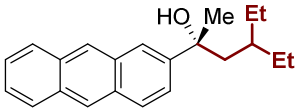
95% yield
98% ee



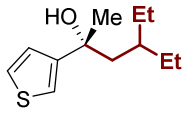
87% yield
54% ee



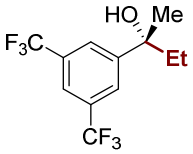
71% yield
95% ee



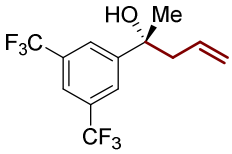
88% yield
80% ee



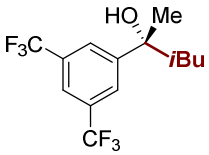
96% yield
76% ee

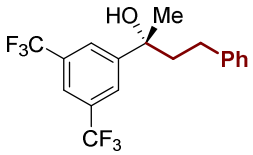


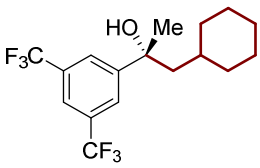
94% yield
22% ee

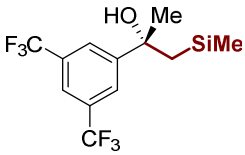


92% yield
44% ee





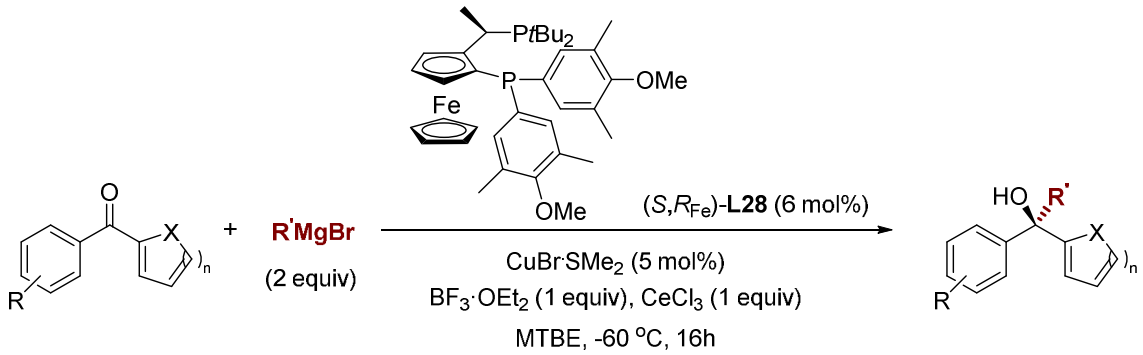


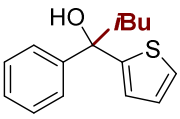


The scope of the reaction includes a broad spectrum of substituted acetophenones although no relationship between the enantioselectivity of the reaction and the stereoelectronic effects of the substituents in the ketone has been observed. As with previous substrates, β-branched Grignard reagents give high enantiomeric excesses, while linear Grignard reagents lead to

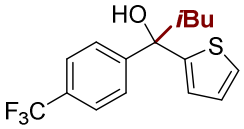
their corresponding tertiary alcohols with lower enantioselection, and MeMgBr is inactive. Tertiary aryl heteroaryl methanols are very interesting motifs broadly present in biologically active structures. Their enantioselective synthesis through the addition of alkyl Grignard reagents to aryl heteroaryl ketones is challenging due to the significantly diminished reactivity of the carbonyl moiety compared to aryl alkyl ketones, and to the small steric and electronic differences between the two aryl substituents, which make the enantiodiscrimination difficult. However, the use of a Cu(I)-phosphine based catalytic system ($CuBr{\cdot}SMe_2$ / Josiphos ligand **L28**) leads to the efficient alkylation of various aryl heteroaryl ketones (Scheme 33).[60] It is worth noting that, in this case, the use of a mixture of Lewis acids, $BF_3{\cdot}OEt_2/CeCl_3$ (1:1) is required to improve the reactivity and outcompete the undesired reduction *via* Meerwein-Pondorf-Verley reaction. The role of these Lewis acids is not clear, but they seem to prevent the coordination of the magnesium ion in the Grignard reagent to the oxygen of the ketone carbonyl, which would promote the undesired β-hydride transfer that generates the corresponding by-product of reduction. Organocerium species are not involved in the reaction, since only starting material is recovered when isobutylcerium is employed for the alkylation reaction. The main drawback of the alkylation of aryl heteroaryl ketones with Grignard reagents is the low stability of both the alkoxide and the corresponding diarylmethanol, leading to the formation of the side product from dehydration during the reaction and the purification. The dehydration can be rationalized by the formation of a very stable conjugated system. For these reason, only moderate isolated yields are obtained in this reaction. Furthermore, low to moderate enantioselectivites are obtained due to difficult enantiodiscrimination. The use of linear Grignard reagents, as well as the presence of other coordinative sites in the aryl moiety of the ketone, lead to a significant decrease in the enantiomeric excess (Scheme 33). Nevertheless, this report represents the first example of direct asymmetric alkylation to diaryl ketones.

Scheme 33. Catalytic asymmetric alkylation of aryl heteroaryl ketones by Harutyunyan and Minnaard.

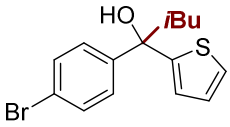




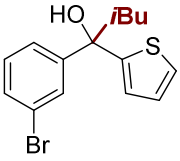
24% yield
69% ee



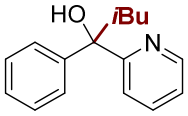
64% yield
50% ee



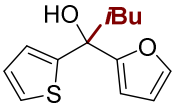
44% yield
56% ee



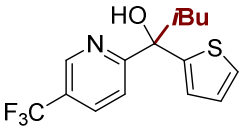
38% yield
42% ee



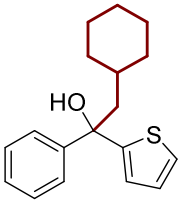
39% yield
22% ee



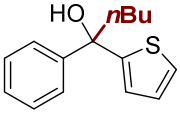
29% yield
16% ee



51% yield
racemic



61% yield
41% ee



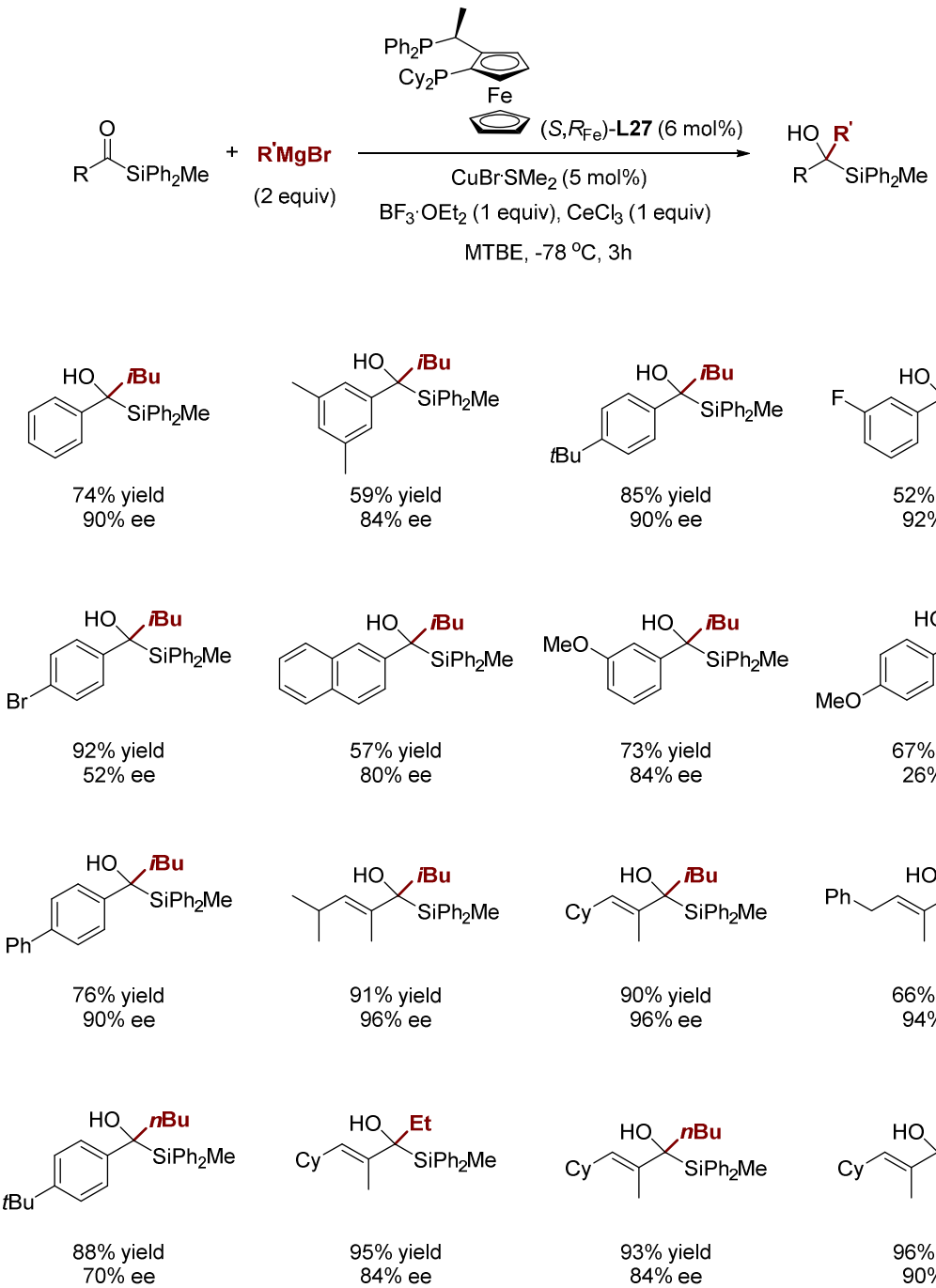
77% yield
13% ee

Encouraged by the increasing applications of silicon containing compounds in medicinal chemistry,[61] acyl silanes have been also evaluated in the alkylation reaction with Grignard reagents (Scheme 34).[62] In spite of several anticipated problems, such as the bulkiness of the

silicon group and the possible side reactions (MVP-type reduction and Brook rearrangement of the corresponding alkoxysilanes), excellent enantiodiscrimination between the two moieties of the carbonyl group, as well as excellent yields are obtained under the catalysis of the Cu(I)-rev-Josiphos **L27** system. The methodology is applicable to various alkyl Grignard reagents, including β-branched and linear ones, and a wide range of acyl silanes (Scheme 34). Both regio- and enantioselectivity of the reaction are strongly dependent on the bulkiness of the silyl moiety. Triphenyl- and triethylsilyl substituted ketones ($SiPh_3$ and $SiEt_3$) provide exclusively the corresponding reduction product, while $SiPh_2Me$ or $SiPhMe_2$ substituents lead to the desired 1,2-addition product, being yields and enantioselectivities slightly higher for the $SiPh_2Me$ analogues.

In the absence of a Lewis acid, the Cu(I)-rev-Josiphos **L27** catalyzes the addition of *i*BuMgBr to phenylsilylketone providing good enantiomeric excess (90% ee) but poor regioselectivitity (1:2, carbonyl addition/MPV reduction). The addition of $BF_3{\cdot}OEt_2$ to the reaction mixture enhances the selectivity up to 3:1, but at the expense of the enantiomeric excess, which drops to 86% ee. However, the mixture of two Lewis acids (stoichiometric $BF_3{\cdot}OEt_2/CeCl_3$ 1:1) leads to the desired tertiary alcohol in good regioselectivity (5:1, carbonyl addition/MPV reduction) and 90% ee. The scope of the reaction includes various substituted aryl acyl silanes and vinyl acyl silanes. In the case of vinyl acyl silanes the conjugate addition of the Grignard reagent constitutes another potential side-reaction, together with the reduction and alkylation pathways. Remarkably, for these substrates, only 0.25 equiv of Lewis acids are required and the undesired 1,4-addition product is not detected by NMR under these conditions. A broad scope of Grignard reagents is suitable for this methodology, including both linear and β-branched, as well as functionalized Grignard reagents. However, MeMgBr leads to racemic product.

Scheme 34. Catalytic asymmetric alkylation of acyl silanes by Harutyunyan and Minnaard.



At this point, it is useful to summarize the general observations on the Cu(I)/chiral diphosphine catalyzed alkylation of ketones with Grignard reagents: a) the substrate scope

includes α-substituted (Me, Br, Ph) α,β-unsaturated acyclic ketones, aryl alkyl ketones, diaryl ketones and acylsilanes; b) the addition reaction of Grignard reagents to α-H-substituted α,β-unsaturated ketones proceeds with lower regio- and stereoselectivity than α-Me-, Ph-, or Br-substituted analogues; c) the addition of MeMgBr and PhMgBr leads to racemic products; d) β-branched Grignard reagents typically add with better stereoselectivity than linear ones; e) only 5 mol% of chiral catalyst loading is necessary; 6) reactions must be carried out in MTBE at -78 ^{o}C; f) the alkylation reaction of diaryl ketones and acylsilanes requires the use of a Lewis acid to avoid the side reduction pathway via β-hydride transfer; g) the Cu(I)-rev-Josiphos complex can be recovered after the reaction and reused many times. Important benefits of the copper(I)-based catalytic system when compared to the previous catalytic methodologies using titanium additives include lower amounts of Grignard reagents, significantly reduced reaction times, low catalyst loadings and, in the case of α-substituted α,β-unsaturated ketones and alkyl aryl ketones, the fact that no additives are needed.

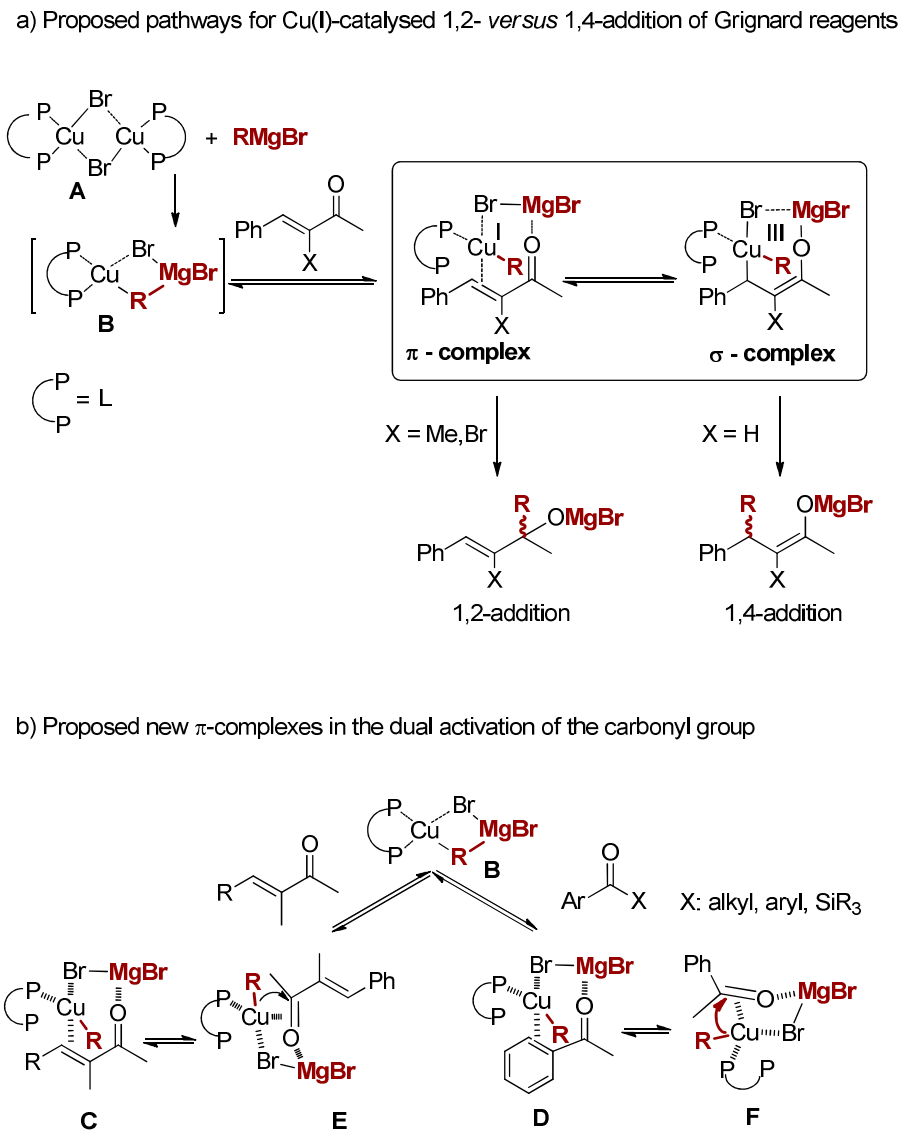
This novel methodology based on Cu(I)-complexes of chiral ferrocenyl-based diphosphine ligands allows the direct use of Grignard reagents in the catalytic asymmetric alkylation reactions of carbonyl compounds. Moreover, when α,β-unsaturated ketones are used as substrates the methodology breaks the 70 year old paradigm in organic chemistry that asserts that Cu(I)-based catalysts direct the addition of the nucleophile to the β-position of the α,β-unsaturated system. Mechanistically, the reason why some copper(I)-based catalysts, similar to those used in previous studies for 1,4-additions of Grignard reagents,[63] prefer the 1,2-addition, is not clear. In order to direct the attack of the Grignard reagents to the 1,2-position of an enone in the presence of a Cu(I)-catalyst, the presence of an α-substituent in the enone is required. Based on experimental and theoretical data, the Cu(I)/Cu(III) redox chemistry has long been proposed to have a role in the Cu(I)-catalyzed 1,4-addition reactions. [64] However neither the Cu(I)-catalyzed 1,2-addition of Grignard reagents to enones, nor the alkylations of

acylsilanes, aryl alkyl, and aryl heteroaryl ketones described above can be rationalised with the existing mechanistic understanding of organocuprate chemistry involving Cu(I)/Cu(III)-intermediates.

To explain the Cu(I)-catalyzed 1,2-addition pathway, the authors have proposed the formation of a monomeric Cu(I) complex **B** from the dimeric species **A** by transmetalation with a Grignard reagent (Scheme 35)similar to that observed in catalytic enantioselective conjugate additions.[65] The formation of a Cu(I) π-complex which is in equilibrium with a Cu(III) σ-complex (formal oxidative addition) has been suggested in the case of 1,2-addition of Grignard reagents to α-substituted α,β-unsaturated ketones.[65] The differences in the stability between Cu(I) π-complex and Cu(III) σ-complex caused by the substitution in α-position, explain the different ratios of 1,2- and 1,4-addition products. The authors suggest that the presence of an α-substituent (Me, Br or Ph) prevents the accumulation of Cu(III) species, favouring the Cu(I) π-complex, followed by direct 1,2-addition to form the product alkoxide.

However, the same Cu(I)-rev-Josiphos catalyst system is used both in the 1,2-alkylation of enones as well as in the alkylation of aryl alkyl ketones. Therefore, an alternative pathway in which the Mg^{2+} and Cu atoms coordinate simultaneously to the oxygen atom and the double bond in the carbonyl moiety (Scheme 35, species **E** and **F**) is proposed.[55,11] This rationalisation is in analogy to the system characterized by Ogle and co-workers for the 1,2-addition of Gillman reagents to aryl alkyl ketones.[66] In the case of α,β-unsaturated ketones, species **E** can be formed directly or after formation of the Cu(I) π-complex. In the case of aryl alkyl ketones, as well as diaryl ketones or acyl silanes, other possible Cu(I) π-complexes with the aromatic ring can be proposed (Scheme 35, species **D**), again in equilibrium with species **F**.

Scheme 35. Proposed mechanism for Cu(I)-catalyzed addition to enones and aryl ketones.



5. Conclusions and future perspective

The number of methodologies available to synthetic chemists for the generation of chiral alcohols with high enantioselectivity by the addition of Grignard reagents to carbonyl compounds has substantially increased in the past decade.

Although a diverse range of catalytic chemical transformations is now available to meet this formidable challenge, there are still limitations to the methodologies and several challenges to overcome. Not only is the development of alternative catalytic methods, based on readily available and less expensive complex catalysts, highly desirable, but also other specific issues need to be addressed. For example, all the currently available methodologies for the addition of Grignard reagents to aldehydes require the use of super stoichiometric amounts of $Ti(iPrO)_4$, which makes the process economically non-efficient and complicates the work up of the reaction. Therefore the implementation of these methodologies in industrial processes is not practical. Similarly, the catalytic enantioselective processes utilizing ketones as substrates are currently restricted to the addition of aryl Grignard reagents (under an excess of $Ti(iPrO)_4$) and bulky β-branched alkyl Grignard reagents (under catalytic amounts of a Cu(I)-complex, but requiring, in certain cases, stoichiometric amounts of Lewis acid additives at low, and industrially impractical, temperatures). These methodologies are still at their early stage of development and need further investigation. Last, and of particular interest, is the development and/or improvement of existing methodologies for the addition of MeMgBr, that provides an easy approach to the methyl-substituted stereogenic centres ubiquitous in natural products.[67]

It is clear that in the near future, the barriers to incorporating chiral alcohols in organic molecules will narrow by the development of new and improved methods for the catalytic enantioselective addition of Grignard reagents to carbonyl compounds. These enantiomerically enriched building blocks are of special interest for their occurrence in natural products, medicines, agrichemicals, polymers and advanced materials.

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ABBREVIATIONS

BDMAEE, bis[2-(N,N´-dimethylamino)ethyl]ether; BINMOL, 1,1´-binaphthalene-2-α-methan-2´-ol; BINOL, 1,1'-Bi-2-naphthol; TADDOL, α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol; COMA, Chiral organomagnesium amides; *c*Hex, cyclohexyl; *c*Pent, cyclopentyl; DCM, Dichloromethane; DME , Dimethoxyethane; MTBE, *Tert*-butylmethyl ether; THF , Tetrahydrofuran; NMR, Nuclear magnetic resonance; DPP, 3,5-Diphenylphenyl.

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