

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

*Juan F. Collados,<sup>a</sup> Ricard Solà,<sup>b</sup> Syuzanna R. Harutyunyan<sup>a,\*</sup> Beatriz Maciá<sup>b,\*</sup>*

<sup>a</sup> Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747AG, Groningen, Netherlands; <sup>b</sup>Division of Chemistry and Environmental Science, Faculty of Science and Engineering, Manchester Metropolitan University, John Dalton Building, Oxford Road, M1 5GD, Manchester, UK. Email: [S.Harutyunyan@rug.nl](mailto:S.Harutyunyan@rug.nl), [B.Macia-Ruiz@mmu.ac.uk](mailto:B.Macia-Ruiz@mmu.ac.uk)

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**

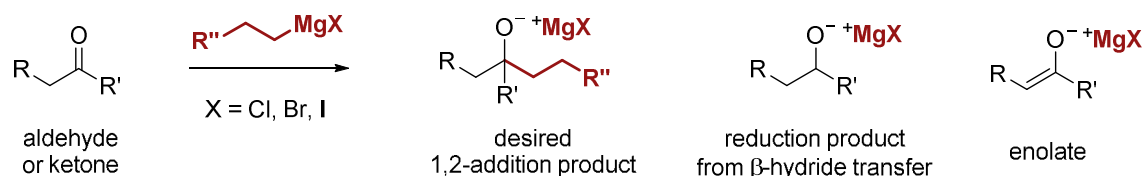
The catalytic asymmetric addition of organometallic reagents to carbonyl compounds is one of the most versatile methods for the synthesis of highly valuable chiral alcohols.<sup>1</sup> Catalytic versions of this key transformation<sup>2</sup> have been studied extensively with organozinc,<sup>3</sup>

organoaluminum<sup>4</sup> and organotitanium<sup>5</sup> 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.<sup>6</sup>

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  $\beta$ -position bear the risk of reducing the carbonyl substrate *via*  $\beta$ -hydride transfer. These factors help explain why even the direct,

1  
2  
3 non-enantioselective addition of Grignard reagents to ketones has been a long running  
4  
5 challenge. The use of (super)stoichiometric additives to promote the desired reaction pathway  
6  
7 (*via* either Lewis acid activation of the ketone or enhancement of the nucleophilicity of the  
8  
9 Grignard reagent)<sup>7</sup> was necessary until the recently reported Zn(II)-catalyzed racemic  
10  
11 addition of Grignard reagents to ketones.<sup>8</sup>  
12

13  
14 The above reactivity and chemoselectivity issues have likewise hampered the development of  
15  
16 effective methodologies for the enantioselective reaction. Indeed, even enantioselective  
17  
18 methodologies using (super)stoichiometric amounts of a chiral ligand are relatively few. The  
19  
20 first highly enantioselective catalytic addition of Grignard reagents was reported in 2008 by  
21  
22 the group of Harada, for the alkylation reaction of aldehydes.<sup>9</sup> Subsequently in 2014, the  
23  
24 group of Yus and Maciá reported the addition of aryl Grignard reagents to more challenging  
25  
26 ketones substrates.<sup>10</sup> Both methodologies are catalytic with respect to the chiral ligand but  
27  
28 require the super-stoichiometric use of titanium tetraisopropoxide. Another step forward has  
29  
30 been made by the groups of Harutyunyan and Minnaard, who proved Cu(I)-based chiral  
31  
32 catalysts to be successful for the direct use of Grignard reagents (without additives) as  
33  
34 nucleophiles in the catalytic asymmetric alkylations of ketones.<sup>11</sup>  
35  
36  
37

38  
39 This Perspective outlines efforts towards the synthesis of enantiopure chiral alcohols *via* the  
40  
41 addition of Grignard reagents to aldehydes and ketones. Approaches using  
42  
43 (super)stoichiometric amounts of chiral additives or ligands as well as recently developed  
44  
45 titanium and copper(I)-catalyzed enantioselective additions will be highlighted.  
46

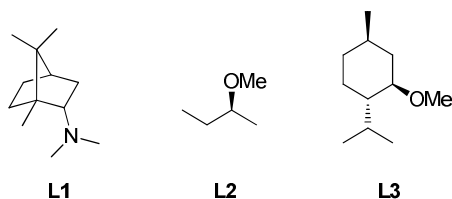
47  
48 Note that, after the addition reaction step, the generated alkoxide requires protonation to  
49  
50 generate the corresponding alcohol. Protonation is typically carried out by addition of water,  
51  
52 aqueous NH<sub>4</sub>Cl or aqueous HCl. For simplicity, this step has been omitted in all schemes, and  
53  
54 only the conditions for the 1,2-addition reaction have been presented.  
55  
56  
57  
58  
59  
60

## 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,<sup>12</sup> 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,<sup>13</sup> 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.

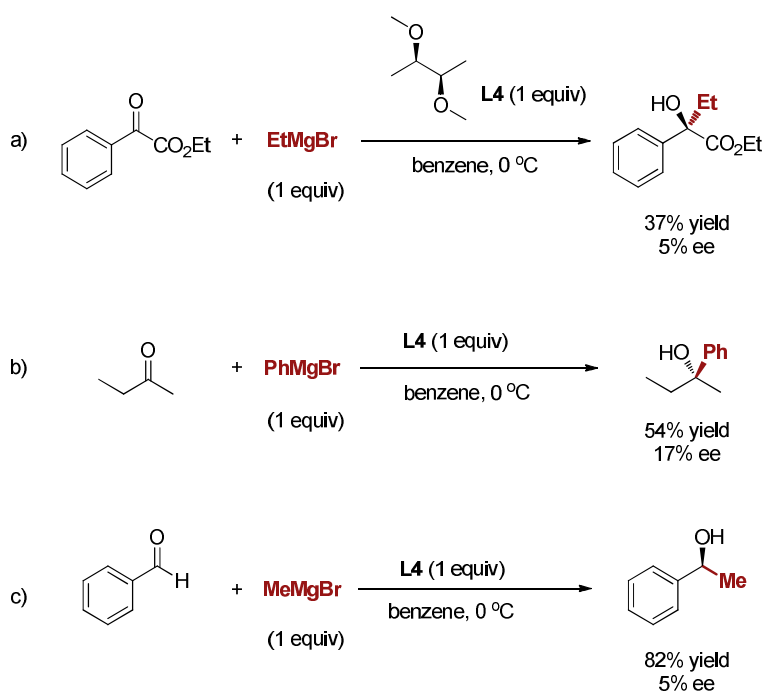
**Figure 1. Chiral solvents used in the asymmetric addition of Grignard reagents to aldehydes.**



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).<sup>14</sup> 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)<sup>15</sup> and aldehydes (Scheme 2c).<sup>16</sup>

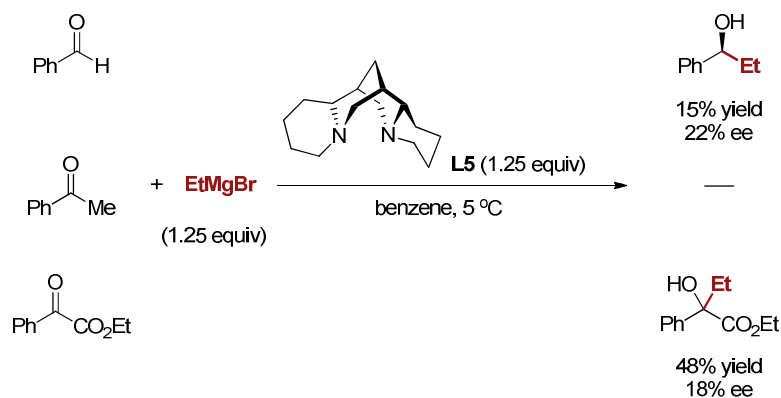
**Scheme 2. Addition of Grignard reagents to carbonyl compounds in the presence of chiral diether (L4) by Wright.**



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<sub>2</sub>Mg 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.<sup>17</sup>

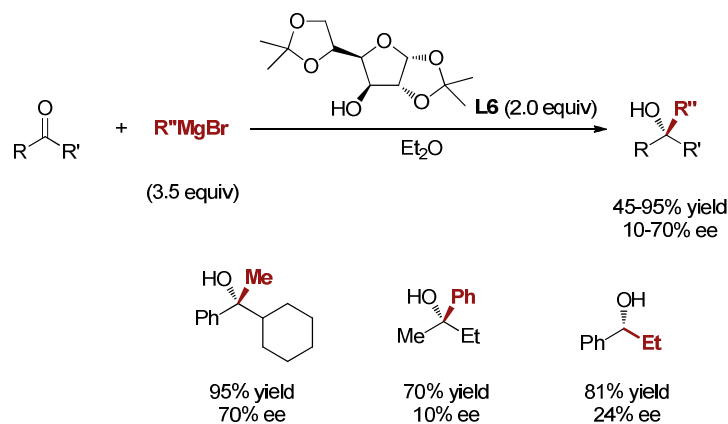
1  
2  
3 In 1968, Nozaki used (-)-sparteine **L5** in the addition of EtMgBr to benzaldehyde,  
4  
5 acetophenone and ethyl benzoylformate in benzene (Scheme 3).<sup>18</sup> Under these conditions,  
6  
7 only the more reactive aldehyde and ketoester lead to the corresponding carbinols with  
8  
9 slightly improved enantioselectivities respect to those reported by Wright.<sup>14-16</sup>  
10  
11

12 **Scheme 3. Addition of Grignard reagents to carbonyl compounds in the presence of (-)-**  
13 **sparteine (L5) by Nozaki.**  
14  
15



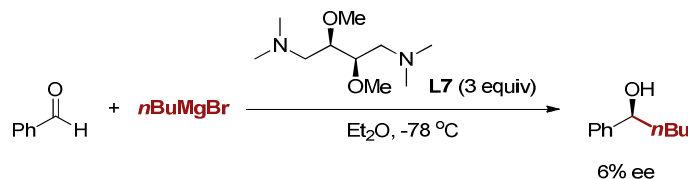
32 One year later, Inch and co-workers reported improved enantioselectivities for the addition  
33  
34 reaction of Grignard reagents to carbonyl compounds using the glucofuranose derivative **L6**  
35  
36 (Scheme 4).<sup>19</sup> They evaluated a limited scope of ketones, aldehydes and Grignard reagents  
37  
38 and obtained the best results when using MeMgBr or EtMgBr in the addition to aromatic  
39  
40 ketones.  
41  
42

43  
44 **Scheme 4. Enantioselective addition of Grignard reagents to ketones in the presence of**  
45 **glucofuranose (L6) by Inch.**  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



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

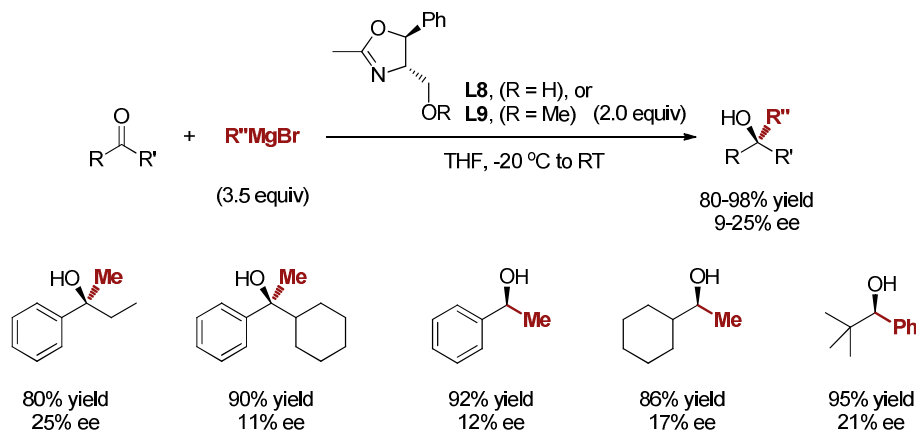
21  
22  
23  
24  
25  
26 **Scheme 5. Addition of *n*BuMgBr to benzaldehyde using chiral diamino diether (**L7**) by**  
27 **Seebach.**



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

44  
45  
46  
47  
48  
49  
50 Iffland et al. have evaluated the use of chiral 2-methyltetrahydrofuran (2-MeTHF) as solvent  
51 for the addition of Grignard reagents to various aldehydes and ketones.<sup>22</sup> However, low  
52 enantioselectivities (2-11% ee) – similar to those obtained by Coops and coworkers using  
53 chiral monoethers **Error! Bookmark not defined.** – can be reached under these conditions.  
54  
55  
56  
57  
58  
59  
60

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

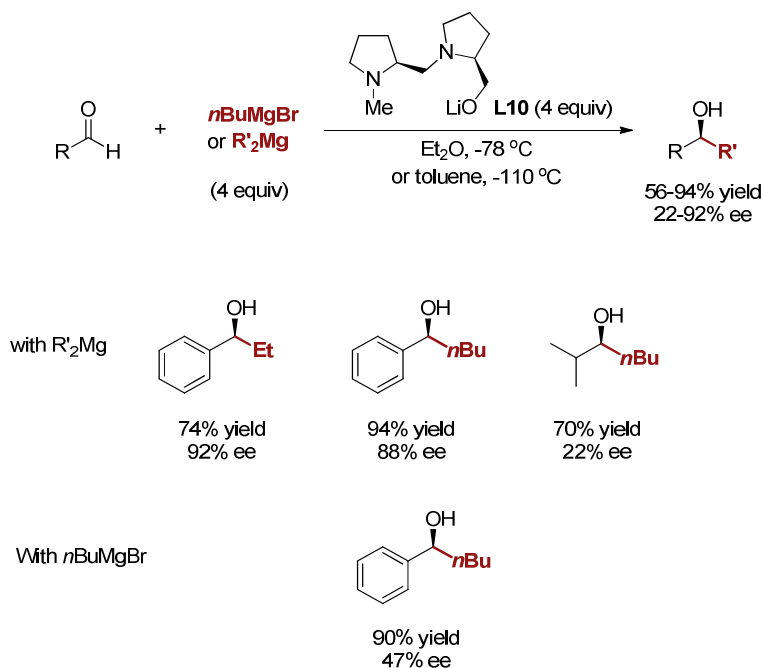


In 1979 Mukaiyama reported improved enantioselectivities for the addition of Grignard reagents to aldehydes using 4 equivalents of the Li salt **L10** as a chiral additive (Scheme 7).<sup>23</sup>

Under these conditions, the reaction between benzaldehyde and  $nBuMgBr$  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  $nBuMgBr$  provides.

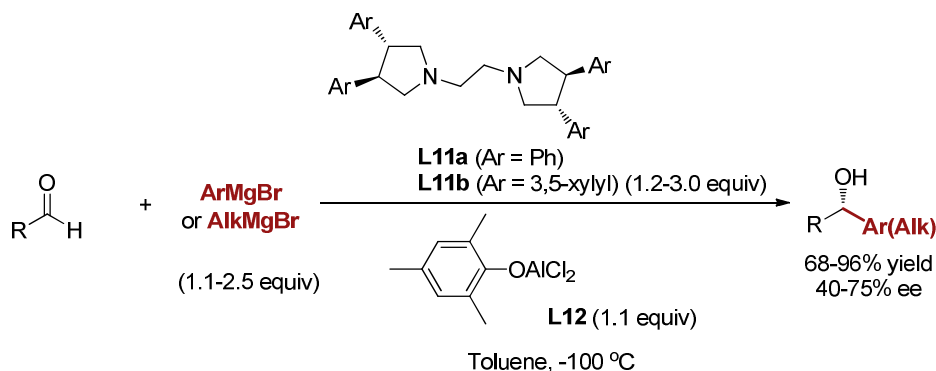
**Scheme 7. Alkylation of aldehydes with Grignard and dialkylmagnesium reagents in the presence of chiral diamine alkoxide (L10) by Mukaiyama.**



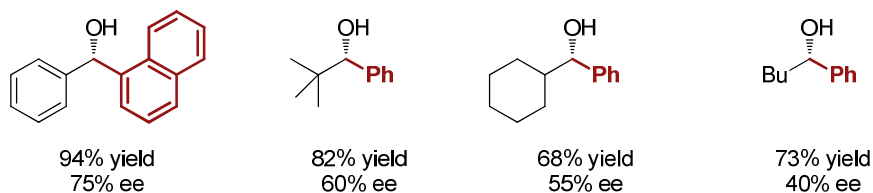


26 Tomioka and co-workers have reported the use of  $C_2$ -symmetric diarylpyrrolidines **L11a-b**  
 27 (Scheme 8) for the addition of aryl and alkyl Grignard reagents to aldehydes.<sup>24</sup> Good yields  
 28 (68-96%) and moderate to good enantioselectivities (40-75% ee) are obtained for a narrow  
 29 scope of aldehydes. Interestingly, the addition of a Lewis acid such as 2,4,6-  
 30 trimethylphenoxyaluminum dichloride (**L12**,) improves the enantioselectivity in the reaction.  
 31 For example, the addition of  $nBuMgBr$  to benzaldehyde improves from 20 to 70% ee in the  
 32 presence of this aryloxialuminum halide.<sup>24b,c</sup> This methodology allows the use of lower  
 33 amount of Grignard reagent (1.1 equiv) compared to previous methods. Also, the chiral  
 34 diamine loading can be reduced from 3 to 1.2 equivalents without any substantial effect in the  
 35 enantioselectivity. The observed relation between the bulkiness of the Grignard reagent and  
 36 the enantioselectivity of the addition reaction suggests that the origin of the enantiofacial  
 37 discrimination are the steric interactions between the aryl group in the chiral diamine and the  
 38 R group in the aldehyde, as depicted in Scheme 8c.  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46  
 47  
 48  
 49  
 50  
 51  
 52  
 53  
 54  
 55  
 56  
 57  
 58  
 59  
 60

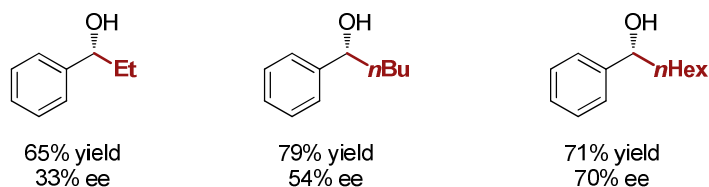
**Scheme 8. Enantioselective addition of Grignard reagents to aldehydes in the presence of chiral diamines (L11a-b) and the Lewis acid (L12) by Tomioka.**



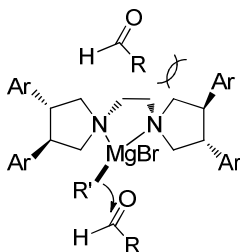
a) Arylations



b) Alkylations



c) Proposed TS

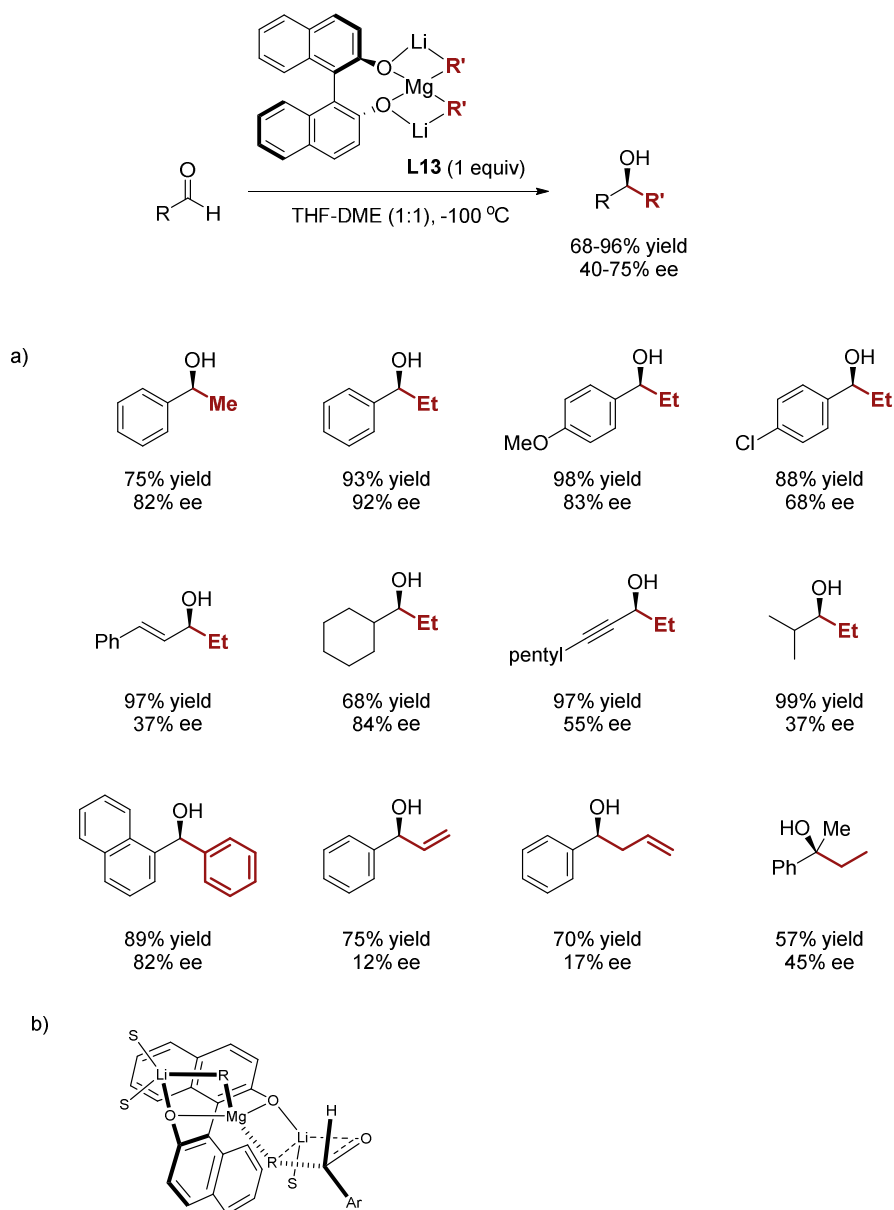


Stoichiometric amounts of the bimetallic chiral reagent **L13** have been also used in the asymmetric addition of Grignard reagents to aldehydes, as reported by Noyori (Scheme 9).<sup>25</sup>

The well-defined, coordinatively saturated chiral complex **L13** avoids the aggregation of the

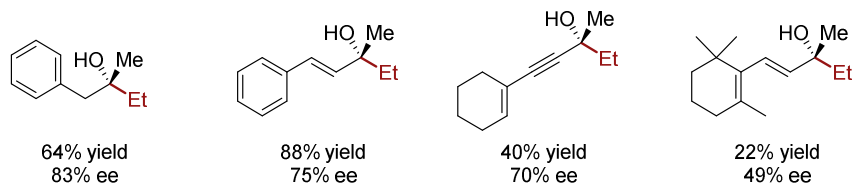
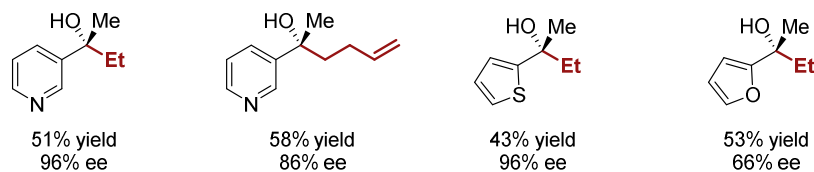
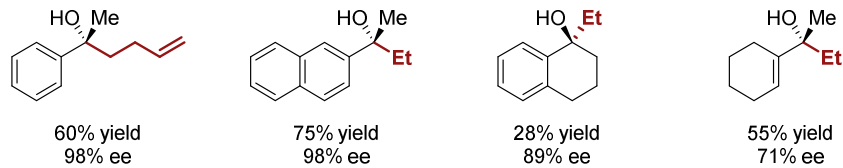
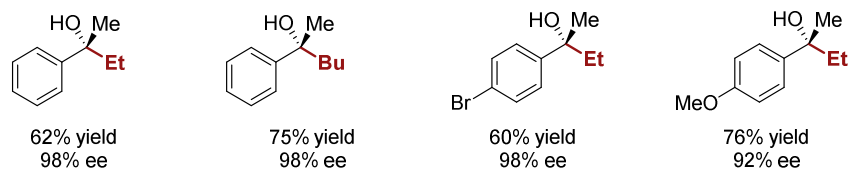
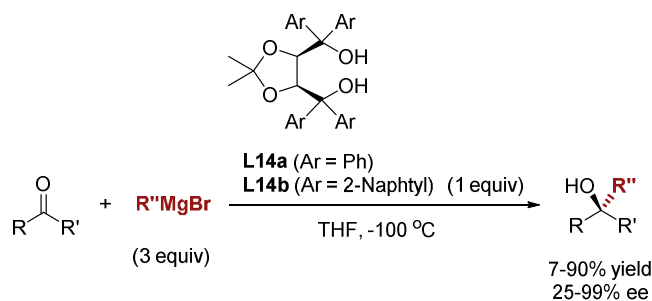
Grignard reagent and allows excellent yields (68-96%) and enantioselectivities (40-75% ee) in the asymmetric addition to aldehydes. This methodology is effective for a broad scope of aromatic (88-98% yield, 68-92% ee), and aliphatic aldehydes (40-99% yield, 37-85% ee). Different dialkyl- and diarylmagnesium 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.**



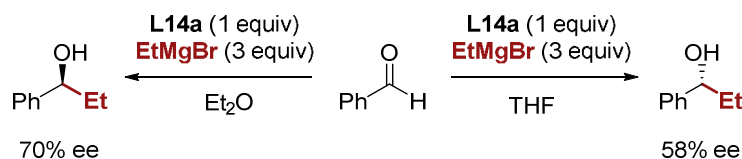
The alkylation of the less reactive acetophenone proceeds with moderate yield (57%) and enantioselectivity (45% ee). The authors have proposed that the activation of the substrate takes place by coordination of a lithium atom with the carbonyl oxygen in the aldehyde, as depicted in the proposed transition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

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



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).<sup>26</sup> 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).

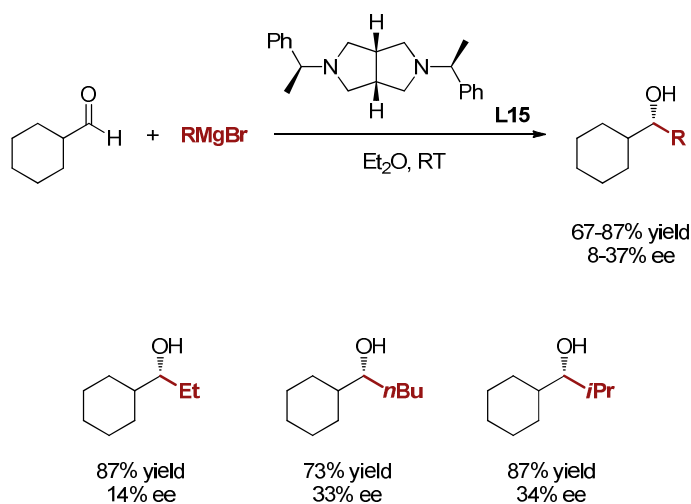
**Scheme 11. Alkylation of aldehydes in the presence of Mg-TADDOLate by Seebach and Weber.**



In 1994, Markó and co-workers reported the use of the *C*<sub>2</sub>-symmetric diamine **L15** (Scheme 12) in the alkylation reaction of cyclohexane carboxaldehyde.<sup>27</sup> 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,

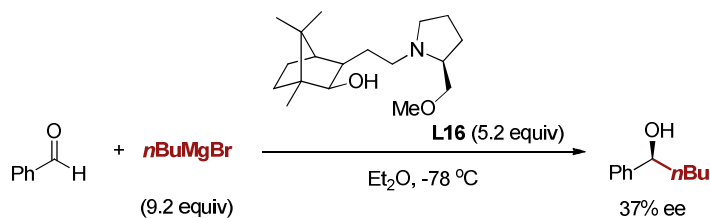
which is quite unusual for the enantioselective addition of Grignard reagents. Interestingly, lower temperatures provided inferior enantioselectivities (9% ee at  $-40\text{ }^{\circ}\text{C}$  for the addition of *i*PrMgBr, compared to the 42% ee at  $35\text{ }^{\circ}\text{C}$ ).<sup>28</sup>

**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.<sup>29</sup> A maximum enantiomeric excess of 37% ee is only reached, even in the presence of a great excess of the chiral ligand (Scheme 13).

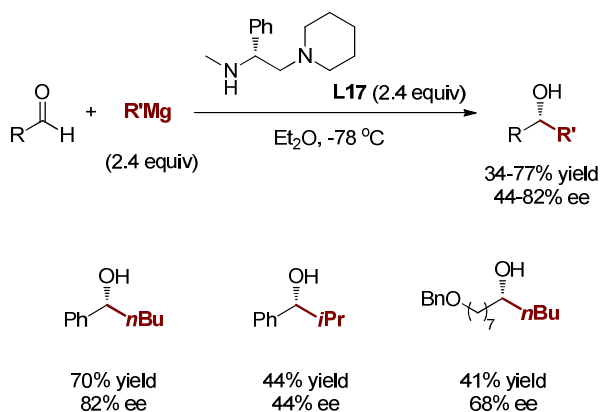
**Scheme 13. Alkylation of benzaldehyde in the presence of camphor derivative (L16) by Knollmuller.**



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

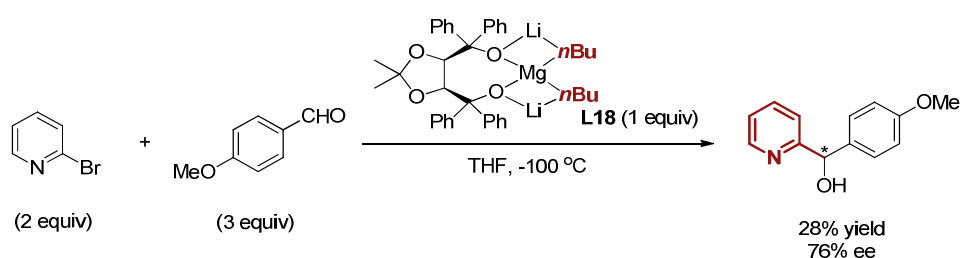
and enantioselectivities (usually 70% yield and up to 82% ee), however highly enolisable aliphatic substrates provide lower yields. The less reactive  $\text{Me}_2\text{Mg}$  also provides lower yields but similar enantioselectivities to its alkyl nucleophilic counterparts.

**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**.<sup>31</sup> 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

1  
2  
3 light, it is remarkable that only the few papers compiled in this section have been reported on  
4  
5 the topic, particularly considering the cost-efficiency and availability of Grignard reagents.  
6  
7

### 8 9 10 **3. Titanium promoted catalytic enantioselective addition of Grignard reagents to** 11 **carbonyl compounds**

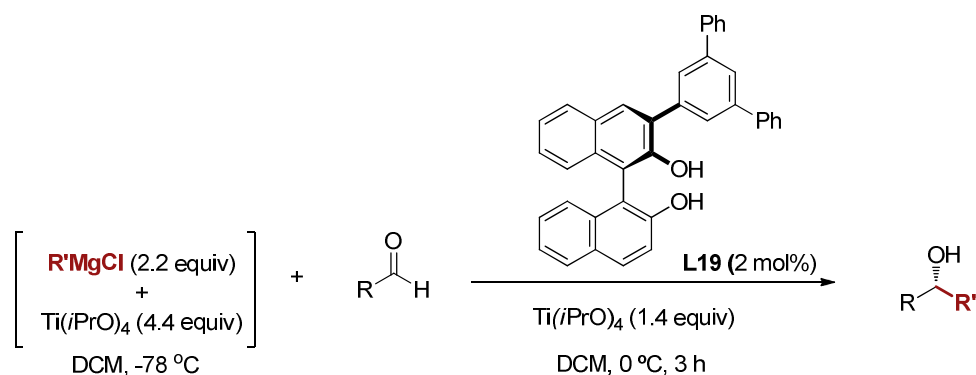
12  
13  
14 Amongst the most used transition metals complexes for enantioselective transformations,  
15  
16 those based on titanium stand out for their nontoxicity,<sup>32</sup> high abundance<sup>33</sup> and low cost. In  
17  
18 addition, titanium complexes exhibit remarkably diverse chemical reactivity. The rich  
19  
20 coordination chemistry of titanium facilitates modulation of complex's properties by  
21  
22 modification of the component ligands, which expands the possibilities for control of  
23  
24 stereochemistry in various chemical processes.<sup>34</sup>  
25  
26

27  
28 Enantioselective titanium-mediated transformations have received much attention during the  
29  
30 last decade, especially in the area of alkylation, arylation, alkynylation, allylation and  
31  
32 vinylation reactions of carbonyl compounds.<sup>35</sup> Since the first enantioselective titanium-  
33  
34 promoted addition of diethylzinc to benzaldehyde reported in 1989 by Ohno and Yoshioka,  
35  
36 using a chiral disulfonamide as ligand,<sup>36</sup> enantioselective titanium-promoted additions of  
37  
38 organozinc and organoaluminum reagents to prochiral aldehydes and ketones have been  
39  
40 extensively studied.  
41  
42

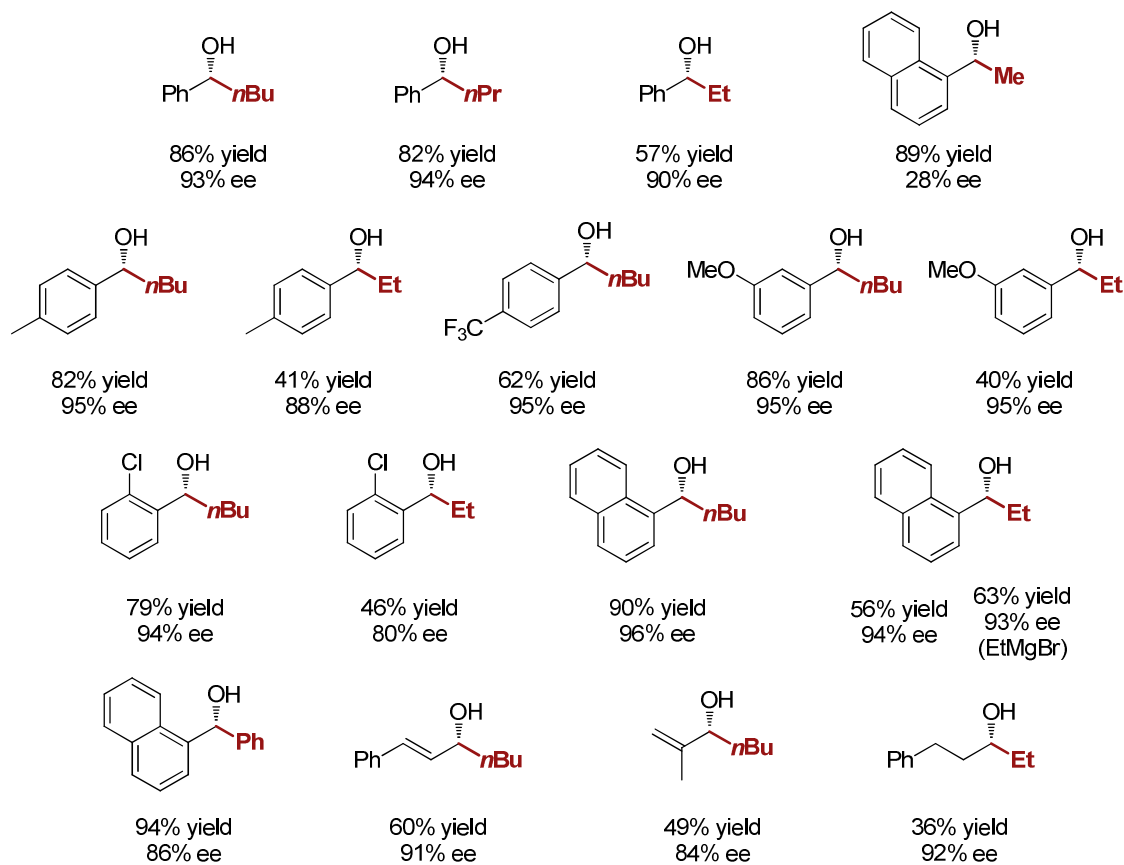
43  
44 However, the use of more reactive organometallic reagents, such as Grignard reagents, in  
45  
46 enantioselective titanium-promoted alkylations of carbonyls with catalytic amounts of a  
47  
48 chiral ligand was not possible till 2008, with the introduction of ligand **L19** by Harada et al  
49  
50 (Scheme 16).**Error! Bookmark not defined.** This report constitutes the first methodology where  
51  
52 a Grignard reagent can be used directly (without tedious salt exclusion procedures associated  
53  
54 with prior transmetalation to a less reactive organozinc<sup>37</sup> or organotitanium<sup>38</sup> reagent) for the  
55  
56 enantioselective catalytic addition to a carbonyl compound.  
57  
58  
59  
60



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



Representative examples:



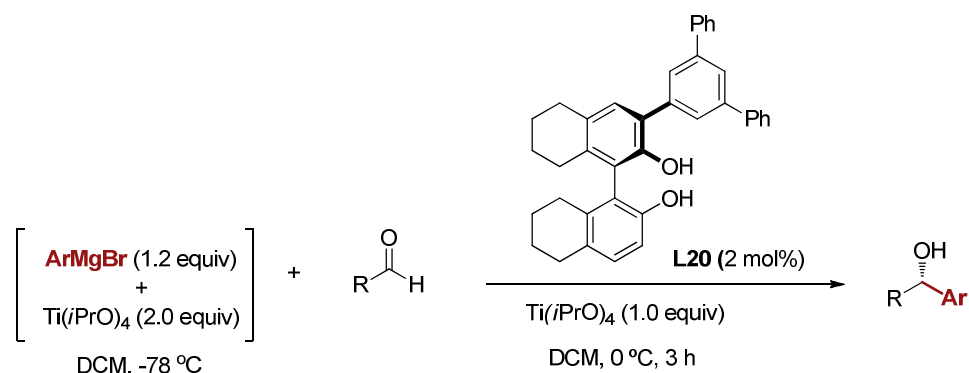
Harada's methodology allows the catalytic alkylation and arylation of aldehydes using Grignard reagents in combination with titanium tetraisopropoxide (Scheme 16). Increasing the amount of chiral ligand from 2 to 4 mol% increases the enantioselectivity of the

1  
2  
3 corresponding products, although no significant improvement in the reaction yield is  
4  
5 observed. The method is applicable to various combinations of aldehydes with both primary  
6  
7 alkyl and aryl Grignard reagents but, in order to obtain good levels of enantioselectivity,  
8  
9 several practical considerations must be taken into account. Grignard reagents must be  
10  
11 previously treated with  $\text{Ti}(i\text{PrO})_4$  at  $-78\text{ }^\circ\text{C}$  and then slowly added (over 2 h) to the reaction  
12  
13 mixture at  $0\text{ }^\circ\text{C}$  (Scheme 16). Both organomagnesium chlorides and bromides provide  
14  
15 comparable efficiency and selectivity, but the solvent in which the Grignard reagent is  
16  
17 prepared influences the reaction outcome. Grignard reagents in  $\text{Et}_2\text{O}$  give better  
18  
19 enantioselectivity compared to their analogues in THF.  
20  
21

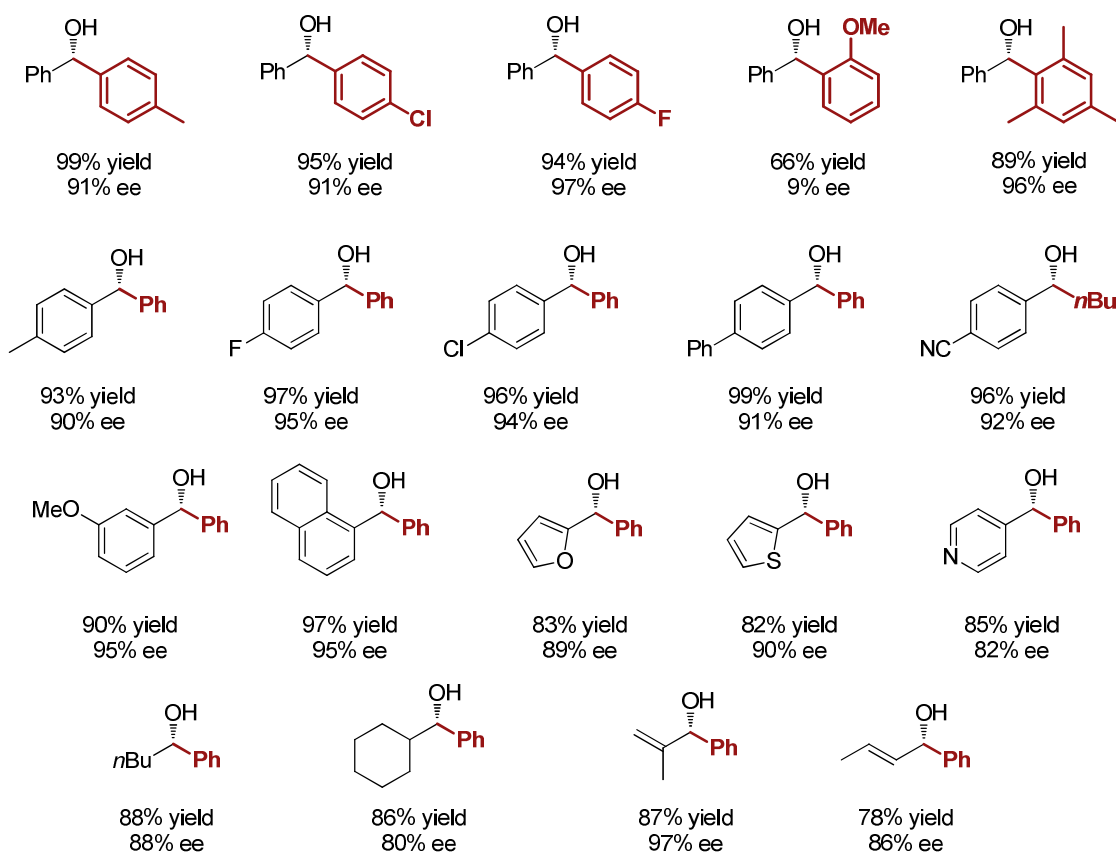
22  
23 As exemplified in Scheme 16, the addition of primary alkyl nucleophiles to various aromatic  
24  
25 aldehydes takes place with good yields (40-90%) and *ee*'s (88-96%), except for the addition  
26  
27 of methyl Grignard reagent, which provides low levels of enantioselectivity (28% *ee* for the  
28  
29 addition of  $\text{MeMgCl}$  to 1-naphthaldehyde). The addition of an aryl nucleophile ( $\text{PhMgBr}$ ) to  
30  
31 the aromatic aldehyde 1-naphthaldehyde provides good yield (94%) and moderate  
32  
33 enantioselectivity (86% *ee*), while the alkylation of  $\alpha,\beta$ -unsaturated aldehydes provides high  
34  
35 enantioselectivity (84-91% *ee*) and moderate yields (49-60%). This last trend is also observed  
36  
37 for the alkylation of aliphatic aldehydes (92% *ee* and 36% yield for the addition of  $\text{EtMgCl}$  to  
38  
39 3-phenylpropanal).  
40  
41

42  
43 The partially hydrogenated ligand (*R*)-DPP-H8-BINOL (**L20**) shows comparable efficiency  
44  
45 to **L19** when alkyl Grignard reagents are used as nucleophiles in the addition to aldehydes,  
46  
47 but remarkably improved enantioselectivities and yields for aromatic nucleophiles with  
48  
49 aromatic and heteroaromatic aldehydes (66-99% yield, 82-97% *ee*, Scheme 17).<sup>39</sup> The main  
50  
51 limitation for **L20** is seen when using  $o\text{-OMeC}_6\text{H}_4\text{MgBr}$ , which provides 9% *ee* and 66%  
52  
53 yield in the addition to benzaldehyde. Notably, an excellent enantioselectivity of 96% *ee* is  
54  
55 reached for the addition of the sterically hindered  $2,4,6\text{-Me}_3\text{C}_6\text{H}_2\text{MgBr}$  to benzaldehyde.  
56  
57  
58  
59  
60

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



Representative examples:

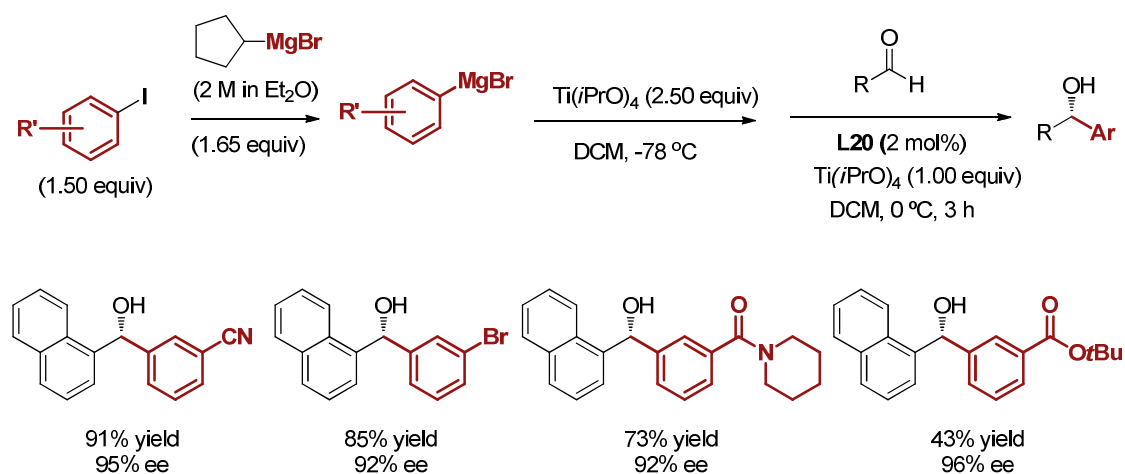


The substrate scope of **L20** includes  $\alpha,\beta$ -unsaturated aldehydes and aliphatic aldehydes which provide high enantioselectivity (80-97% ee) and moderate to good yields (78-87%) for the addition of  $\text{PhMgBr}$  (Scheme 17). The experimental procedure for the use of **L20** is

1  
2  
3 analogous to that previously described for **L19** (slow addition of the Grignard reagent –  
4 pretreated with  $\text{Ti}(i\text{OPr})_4$  – over the reaction mixture containing aldehydes, ligand and  
5  $\text{Ti}(i\text{OPr})_4$ ). When **L20** is used as ligand, however, the total amount of  $\text{Ti}(i\text{PrO})_4$  necessary to  
6 obtain good enantioselectivities is lower (3.0 equiv in total versus 5.8 equiv needed for **L19**);  
7 also, a lower amount of nucleophile can be used (1.2 equiv *versus* 2.2 equiv needed for **L19**).  
8 This methodology also allows for the addition of functionalized Grignard reagents, prepared  
9 *in situ* by reaction of the corresponding iodoarene and *c*- $\text{C}_5\text{H}_9\text{MgCl}$  (2M in  $\text{Et}_2\text{O}$ ), as per  
10 Knochel's procedure (92-96% ee, 43-91% yield, Scheme 18).<sup>40</sup> Alternatively, the I/Mg  
11 exchange can be performed using the readily available *i*PrMgCl (2 M in THF).<sup>41</sup> However, in  
12 this case, the solvent (THF) from the Grignard solution must be removed *in-vacuo* and  
13 replaced with DCM prior to addition to the aldehydes in order to obtain good  
14 enantioselectivities.

15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

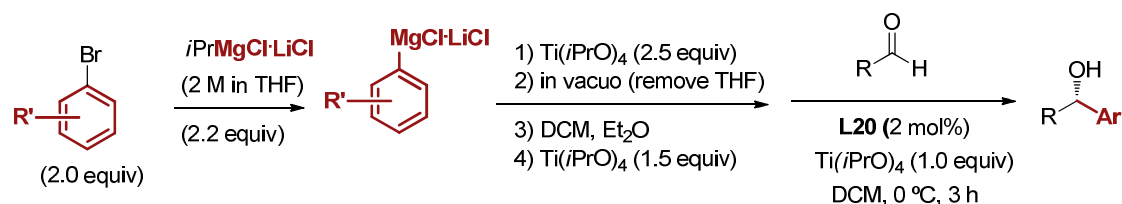
**Scheme 18. (R)-DPP-H8-BINOL (L20) catalyzed addition of *in situ* prepared functionalized aromatic Grignard reagents to aldehydes, by Harada.**



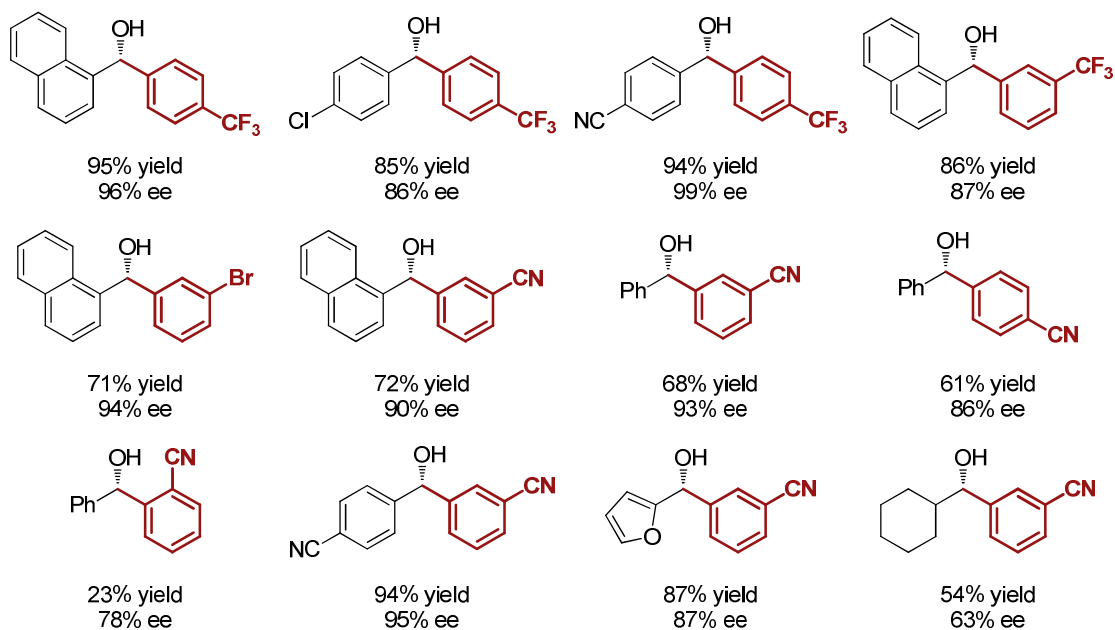
Aryl bromides constitute preferable precursors for the preparation of functionalized Grignard reagents due to their greater stability, wider availability and lower price, in comparison to the corresponding iodoarenes. Harada's group has applied Knochel's methodology for the

preparation of functionalized Grignard reagents from aryl bromides (using  $i\text{PrMgBr}\cdot\text{LiCl}$ ),<sup>42</sup> which, after the strict removal of THF in-vacuo, are suitable nucleophiles for the enantioselective addition to aldehydes using **L20** and  $\text{Ti}(i\text{PrO})_4$  (Scheme 19).<sup>43</sup>

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



Representative examples:

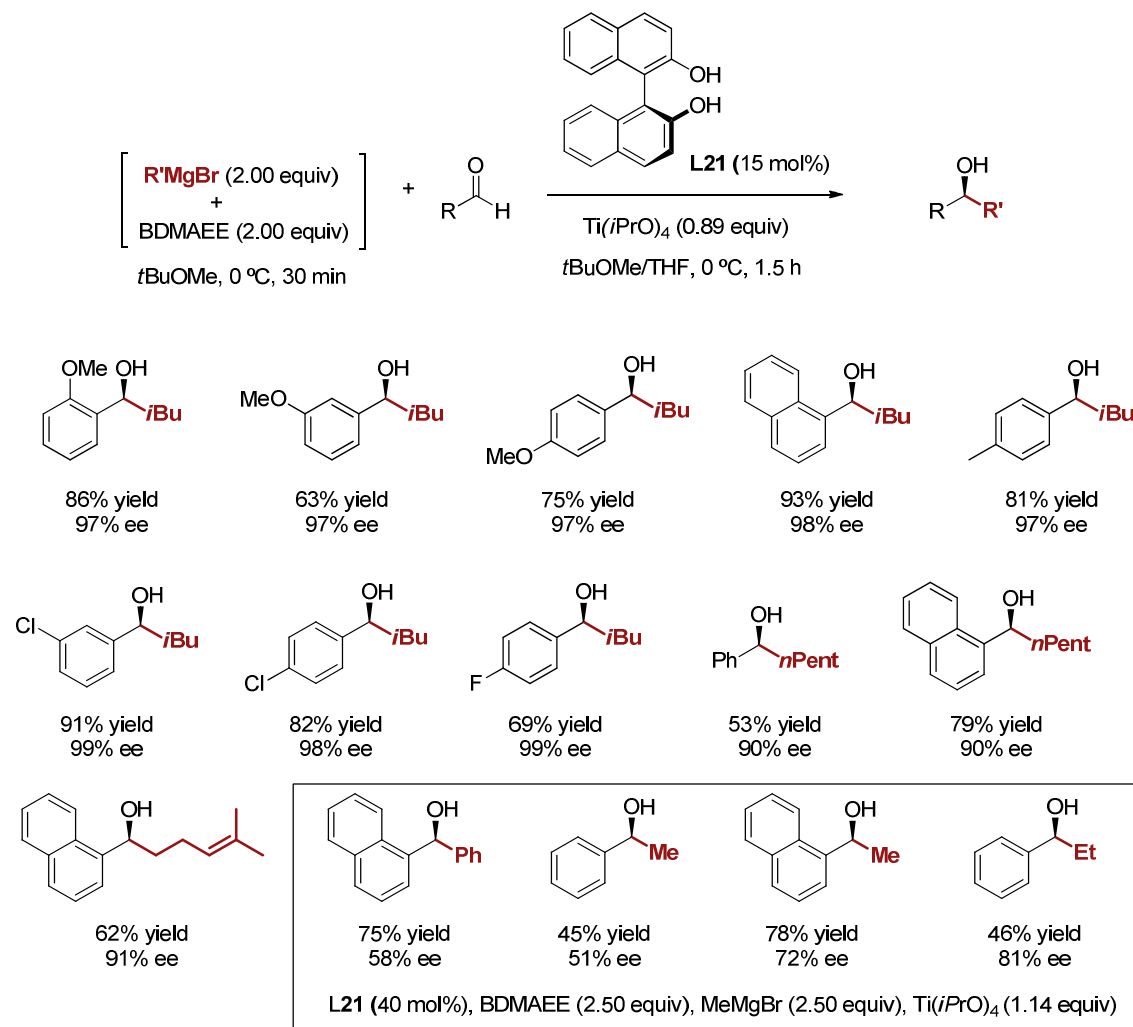


The method is applicable to aryl bromides bearing  $\text{CF}_3$ , Br and CN groups, affording a range of chiral functionalized aryl secondary alcohols of synthetic importance in good to high yields and enantioselectivities (84-99% ee, 61-94% yield) when added to aromatic aldehydes (Scheme 19). Unfortunately, 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  $\text{Ti}(i\text{PrO})_4$ ) 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).<sup>44</sup>

**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  $\text{MgBr}_2$  or  $\text{Mg}(i\text{PrO})\text{Br}$  generated in either the Schlenk equilibrium and/or the transmetalation process

1  
2  
3 with titanium tetraisopropoxide, respectively, as depicted in Scheme 21 (species **C** and **E**).  
4  
5 This chelation prevents Lewis acid/base coordination of magnesium salts to the carbonyl  
6  
7 group of the aldehyde, which would promote undesired and uncatalyzed reactions generating  
8  
9 racemic alcohols.

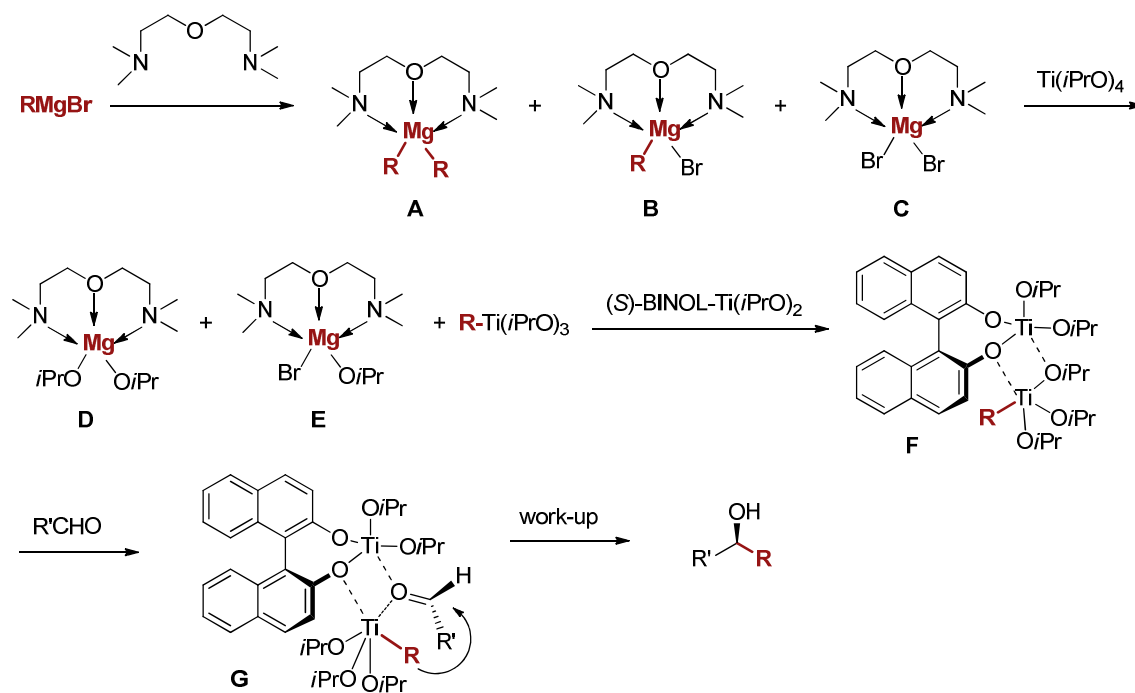
10  
11 Although elevated ligand loadings (10-20 mol%) are needed to reach higher  
12  
13 enantioselectivity (compared to the lower 2 mol% of catalyst **L19** or **L20** required in  
14  
15 Harada's methods), the ligand (*S*)-BINOL is commercially available at a relatively low price.

16  
17 On the basis of the Schlenk equilibrium, transmetalation of Grignard reagents with  $\text{Ti}(i\text{PrO})_4$ ,  
18  
19 and the investigations of Bolm and Walsh,<sup>45</sup> Da proposes the mechanism shown in Scheme  
20  
21 21 for the reaction. Coordination of BDMAEE to the Grignard reagent generates three  
22  
23 possible intermediates **A-C**. Importantly, the salt  $\text{MgBr}_2$  is well chelated by BDMAEE and  
24  
25 partly loses its catalytic activity (species **C**). In the presence of  $\text{Ti}(i\text{PrO})_4$ , chelates **A** and **B**  
26  
27 convert to the chelated salts **D** and **E**, and the reactive intermediate  $\text{R-Ti}(i\text{PrO})_3$ . Naturally, **E**  
28  
29 is a less reactive Lewis acid than **C**, and  $\text{R-Ti}(i\text{PrO})_3$  is much less reactive than the Grignard  
30  
31 reagent itself. This might be the reason why a mixture of  $\text{RMgBr-BDMAEE-Ti}(i\text{PrO})_4$  does  
32  
33 not react with an aldehyde in the absence of a chiral catalyst such as **L21**. However, when  $\text{R-}$   
34  
35  $\text{Ti}(i\text{PrO})_3$  coordinates the chiral catalyst (*S*)-BINOL- $\text{Ti}(i\text{PrO})_2$ , complex **F** is formed. This  
36  
37 species **F** is able to coordinate the aldehyde providing intermediate **G** where steric  
38  
39 interactions between R' (aldehyde) and the three bulky isopropoxy groups in  $\text{R-Ti}(i\text{PrO})_3$   
40  
41 moiety are minimised. This configuration will favor the  $S_i$ -face addition to the aldehyde.

42  
43 Da's method allows the addition of alkyl Grignard reagents to aromatic aldehydes (Scheme  
44  
45 20) in yields that vary from 35-91% and generally good enantioselectivities (70-99% ee). Of  
46  
47 particular note is the addition of *i*BuMgBr to aromatic aldehydes (97-99% ee) with 15 mol%  
48  
49 of **L21**. Unfortunately, the challenging addition of MeMgBr to aromatic aldehydes provides  
50  
51 low enantioselectivities (51-72% ee), even at higher catalyst loadings (40 mol% **L21**).  
52  
53  
54  
55  
56  
57  
58  
59  
60

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).

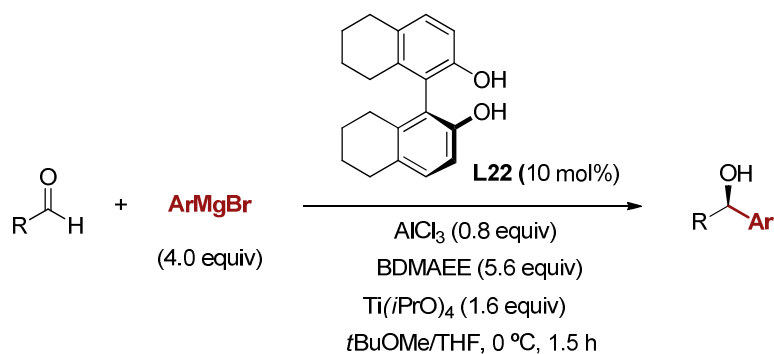
**Scheme 21. The chelated Lewis acidic salts by BDMAEE (A and B species) and the proposed mechanism for the reaction proposed by Da.**



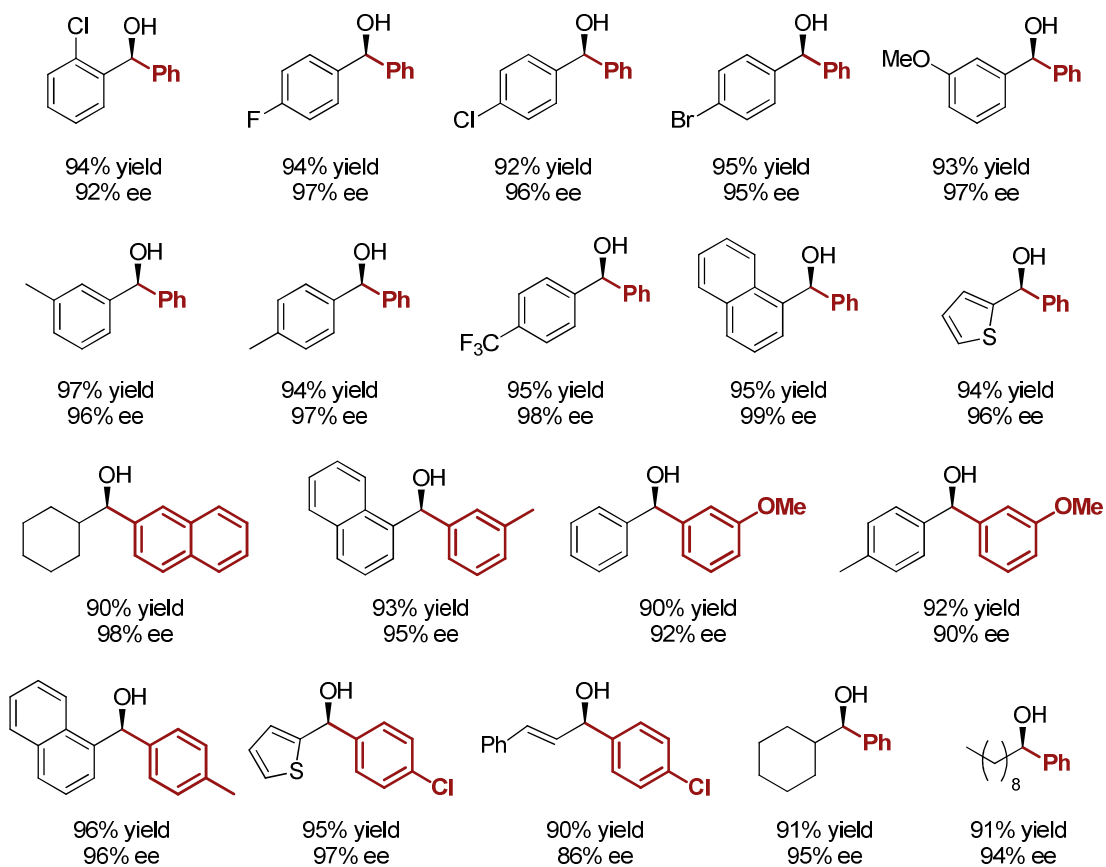
Da et al. have reported an alternative methodology that allows the enantioselective addition of aromatic Grignard reagents to aldehydes. This new strategy involves conversion of Grignard reagents into less reactive triarylaluminum intermediates *in situ* by treatment with  $AlCl_3$ .<sup>46</sup> Operationally simple, the aryl Grignard reagent is treated with  $AlCl_3$  in THF, followed by addition of BDMAEE, ligand L22,  $Ti(iPrO)_4$  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.



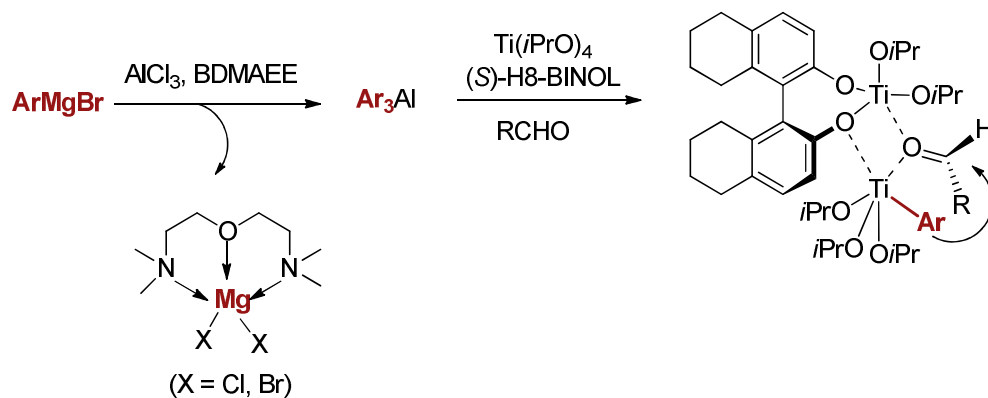
Representative examples:



The authors have proposed the mechanism depicted in Scheme 23 to explain the role of  $\text{AlCl}_3$  in the reaction. The corresponding  $\text{AlAr}_3$  species is generated by reaction of the aromatic Grignard reagent with  $\text{AlCl}_3$ . As seen previously, BDMAEE is believed to sequester

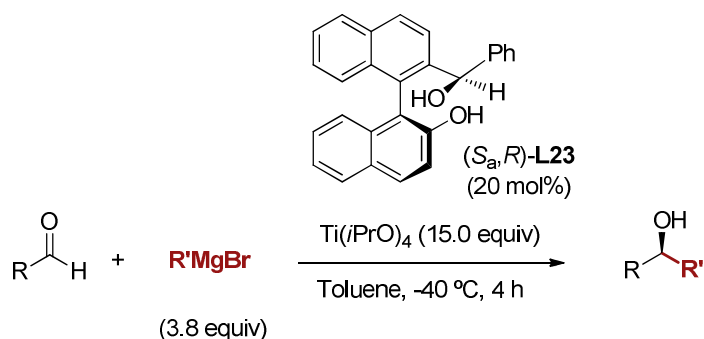
magnesium salts to prevent them from promoting racemic addition to the aldehyde. Transfer of one aryl group from  $\text{AlAr}_3$  to the (*S*)-H8-BINOL/titanium complex occurs and, after coordination of the aldehyde, enantioselective addition takes place.

**Scheme 23. Mechanism for the (*S*)-H8-BINOL (L22) catalyzed addition of aromatic Grignard reagents to aldehydes in the presence of  $\text{AlCl}_3$  and BDMAEE proposed by Da.**

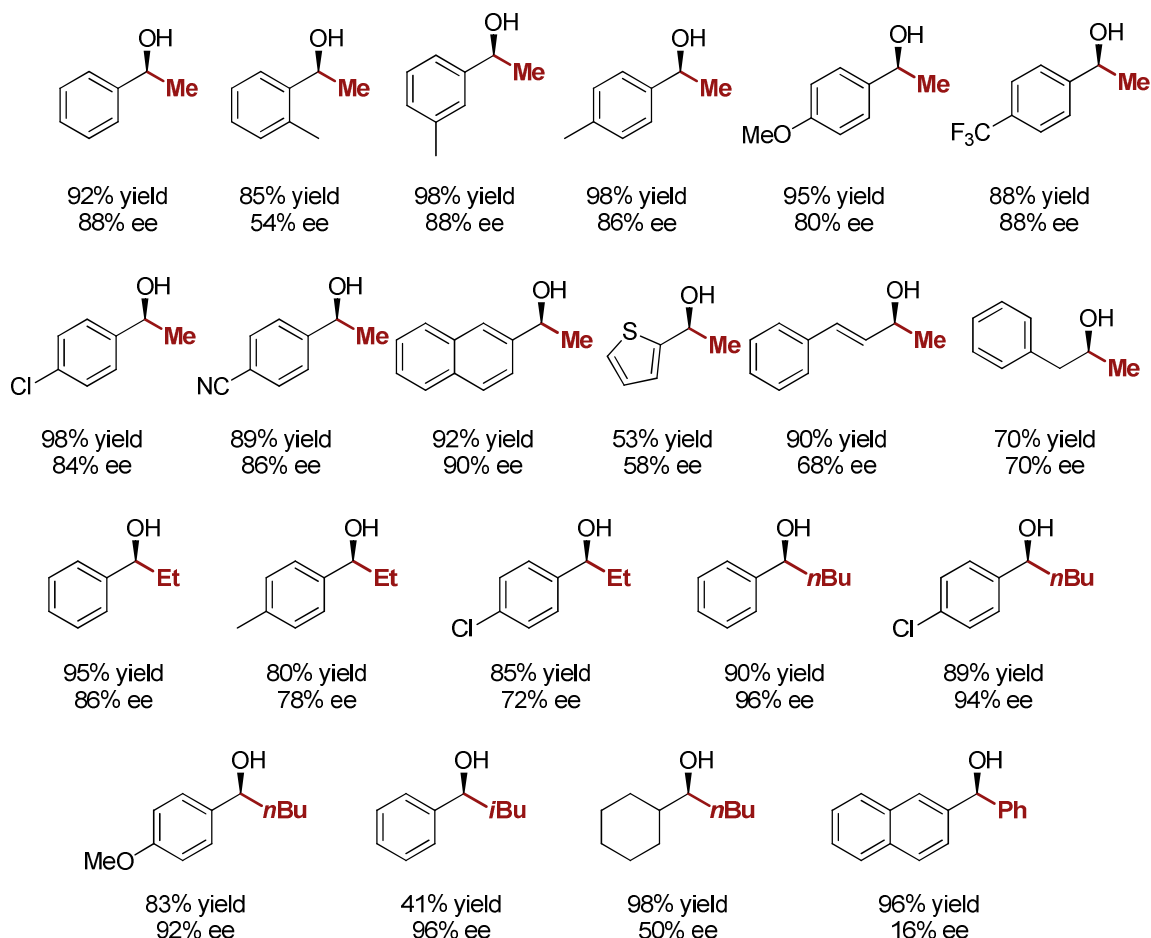


In 2011, Maciá, Yus et al. reported the use of another efficient chiral catalyst<sup>47</sup> for the direct addition of alkylmagnesium bromides to aldehydes in the presence of  $\text{Ti}(i\text{PrO})_4$  (15 equiv) and the chiral ligand (*S<sub>a</sub>,R*)-Ph-BINMOL L23 (20 mol%) at  $-40\text{ }^\circ\text{C}$  (Scheme 24).<sup>48</sup> Although lower temperatures ( $-40\text{ }^\circ\text{C}$ ) and a larger excess of  $\text{Ti}(i\text{PrO})_4$  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  $\text{MeMgBr}$  to aromatic (58-90% ee and 85-99% yield) and  $\alpha,\beta$ -unsaturated (68% ee and 90% yield) aldehydes.

Scheme 24. (*S<sub>a</sub>,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

1  
2  
3 yields (81-95%) and enantioselectivities (86-96% ee) in the addition to aromatic aldehydes.  
4  
5 The use of *i*BuMgBr provides good enantioselectivity in the addition to benzaldehyde (96%  
6  
7 ee) but lower yield (41%)<sup>49</sup> than Da's methodology.<sup>44</sup> The addition of aromatic Grignard  
8  
9 reagents proceeds with very low enantioselectivities (16% ee for the addition of PhMgBr to  
10  
11 2-naphthaldehyde). It must be noted that, in this methodology, THF has a detrimental effect on  
12  
13 enantioselectivity and Et<sub>2</sub>O must be used as the Grignard reagent solvent.  
14  
15

16 Although aliphatic aldehydes only provide moderate enantioselectivities (50-70% ee) with  
17  
18 **L23**, the results can be substantially improved by using the analogous ligand (*S<sub>a</sub>,R*)-4-  
19  
20 Pyridine-BINMOL **L24**, in combination with Ti(*i*PrO)<sub>4</sub> (10 equiv) in Et<sub>2</sub>O at -20 °C (Scheme  
21  
22 25).<sup>50</sup>  
23  
24

25 This novel catalytic system allows the enantioselective addition of alkyl nucleophiles to alkyl  
26  
27 aldehydes, providing chiral aliphatic secondary alcohols – very important motifs in biological  
28  
29 systems – in generally good yields (61-99%) and enantioselectivities (60-99% ee).<sup>51</sup> Again,  
30  
31 the methodology is suitable for the addition of MeMgBr, which allows the synthesis of  
32  
33 versatile chiral methyl carbinol units with unprecedented yields and enantioselectivities in a  
34  
35 simple one-pot procedure and under mild conditions.  
36  
37

38 A further advantage of this methodology is the ability to recover the chiral ligand **L24** from  
39  
40 the reaction mixture by simple acid–base extraction (60% recovery yield) which, at the same  
41  
42 time, facilitates the isolation and purification of the corresponding products. The recovered  
43  
44 ligand **L24** can be reused in subsequent reactions without any loss of activity.  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Scheme 25. (*S<sub>a</sub>*,*R*)-4-Py-BINMOL (L24) catalyzed addition of Grignard reagents to aliphatic aldehydes, by Maciá and Yus.

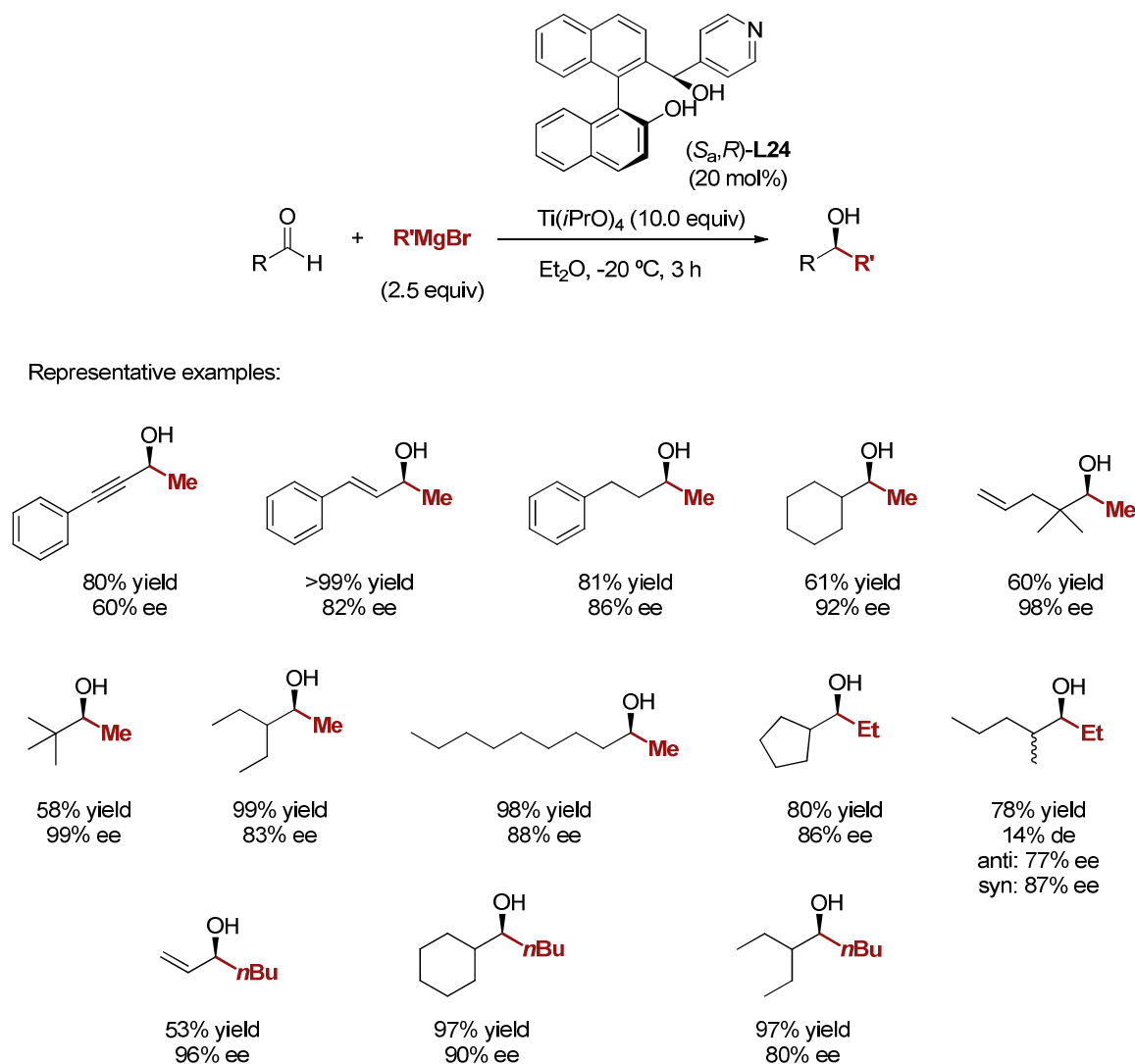
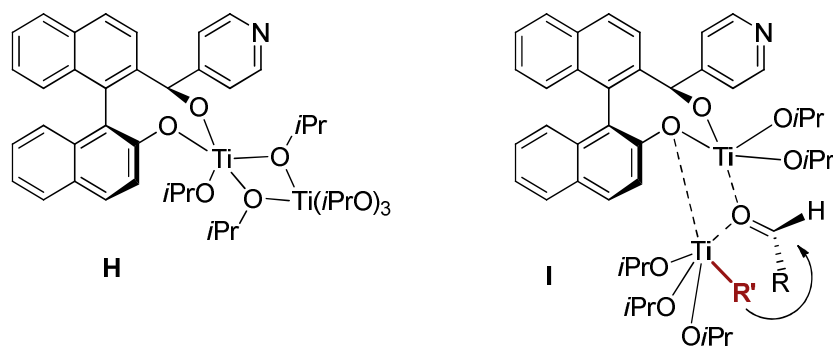


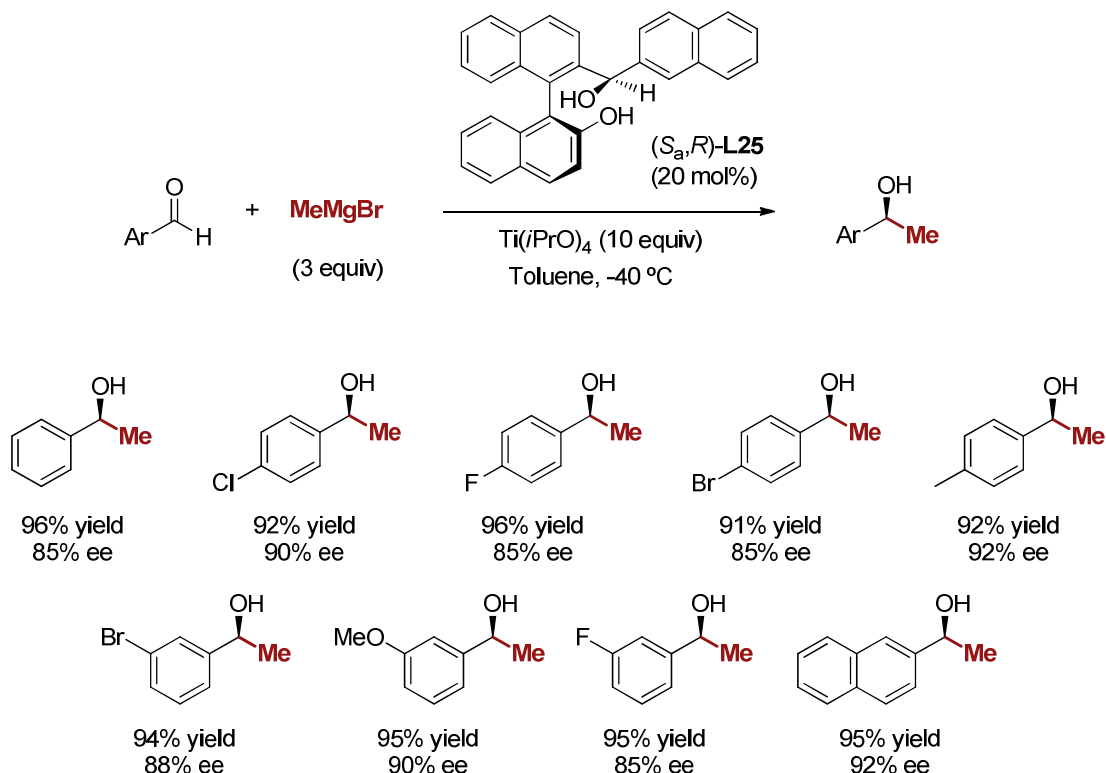
Figure 2. Possible intermediates involved in the catalysis by Maciá and Yus.



By analogy with previous reports on the asymmetric addition of alkyl groups to aldehydes catalyzed by titanium-BINOLate<sup>45</sup> and titanium-TADDOLate<sup>52</sup> 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-naphthyl-BINMOL ligand **L25** for the addition of MeMgBr to various aromatic aldehydes (Scheme 26).<sup>53</sup> In comparison with the previous example which used **L23**, reduced amounts of MeMgBr (3.0 vs 3.8 equiv) and Ti(*i*PrO)<sub>4</sub> (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).

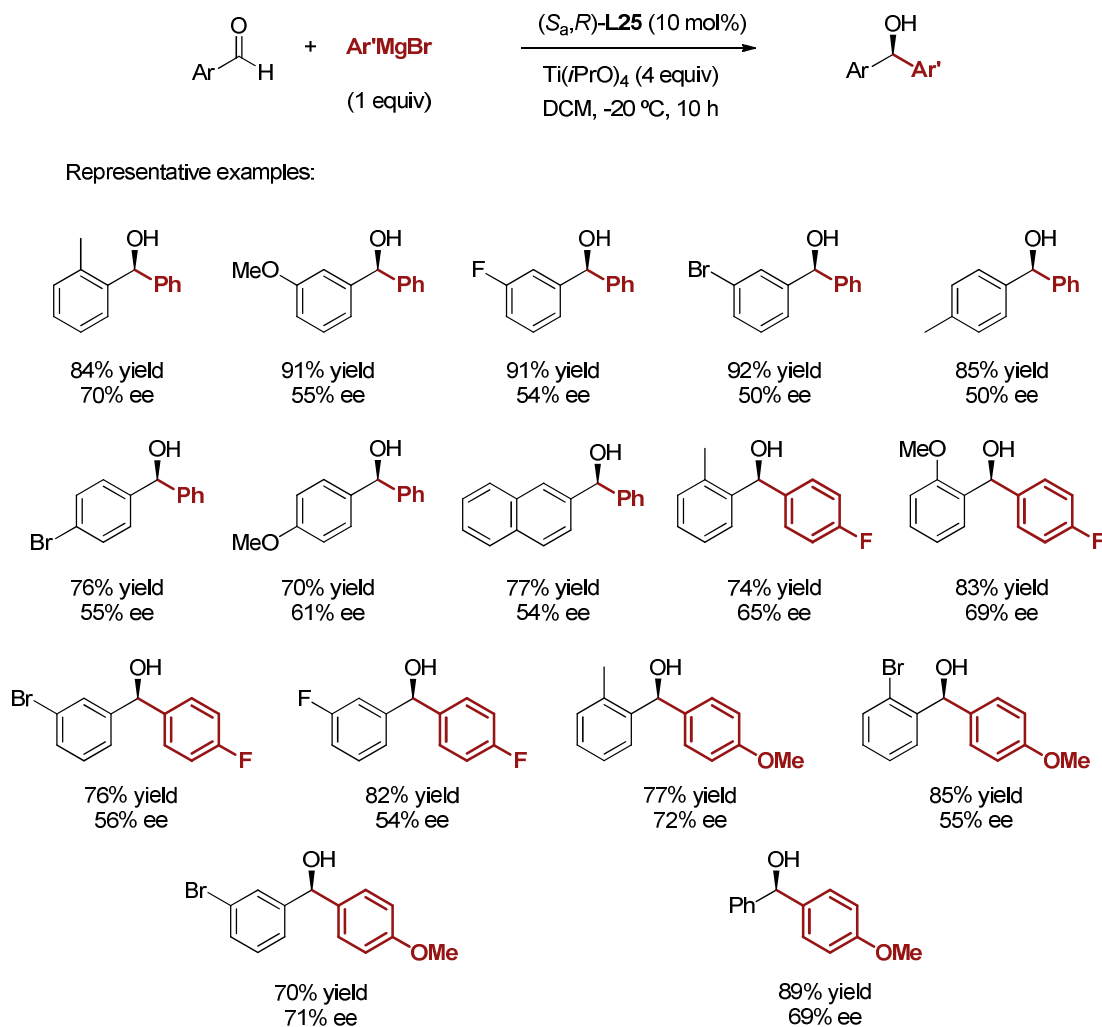
**Scheme 26.** (*S<sub>a</sub>*,*R*)-2-Naph-BINMOL (**L25**) catalyzed addition of methylmagnesium bromide to aromatic aldehydes, by Xu.



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.<sup>39,43,46</sup>

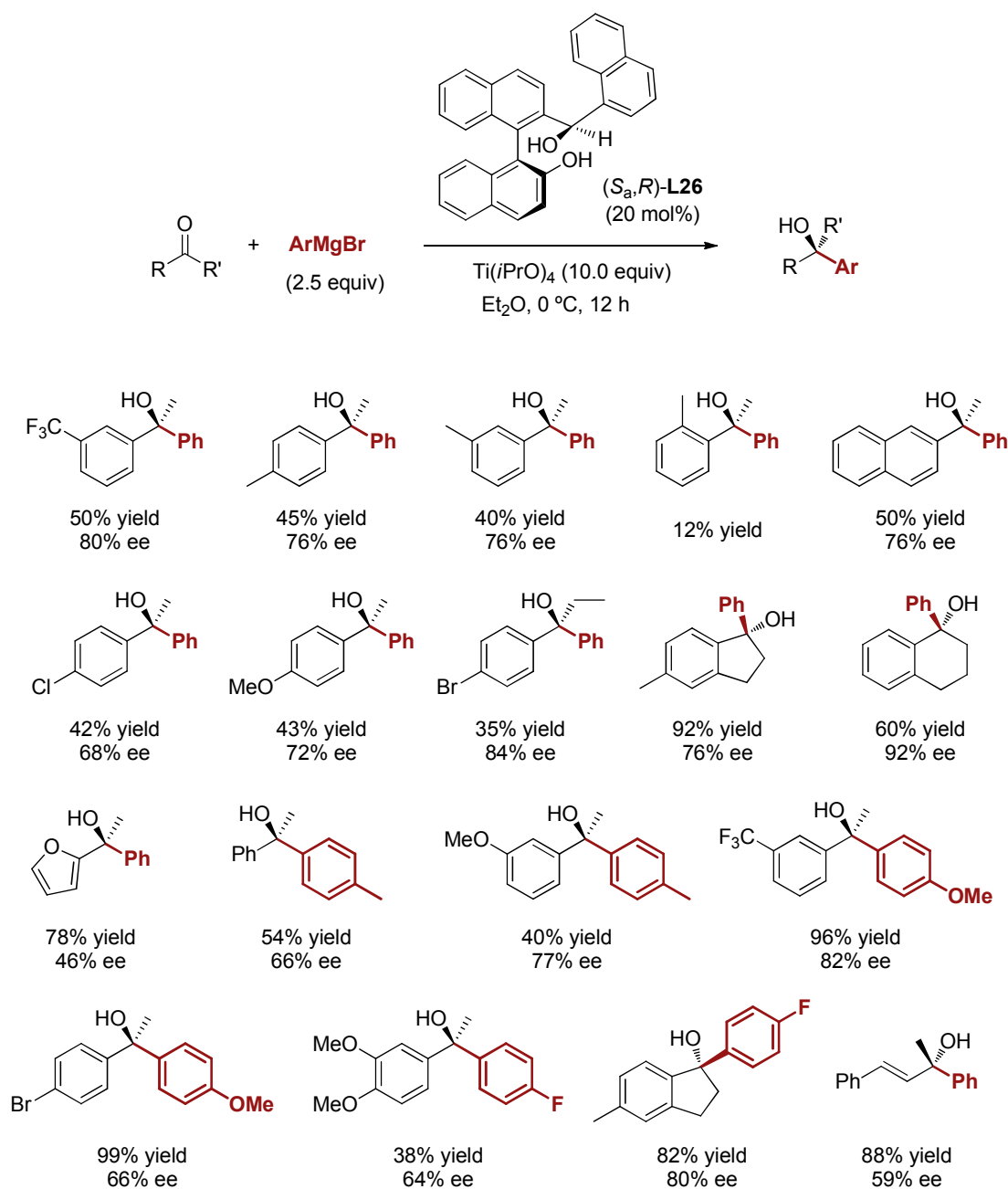
**Scheme 27. (*S<sub>a</sub>*,*R*)-2-Naph-BINMOL (L25) catalyzed addition of aromatic Grignard reagents to aromatic aldehydes by Xu.**



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).<sup>47</sup> 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-naphthyl-BINMOL **L26** (20 mol%) used in combination with  $\text{Ti}(i\text{PrO})_4$  (10 equiv) in  $\text{Et}_2\text{O}$  at  $0^\circ\text{C}$ , 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*<sub>a</sub>,*R*)-1-Naph-BINMOL (L26) catalyzed addition of aromatic Grignard reagents to ketones, by Maciá and Yus.**





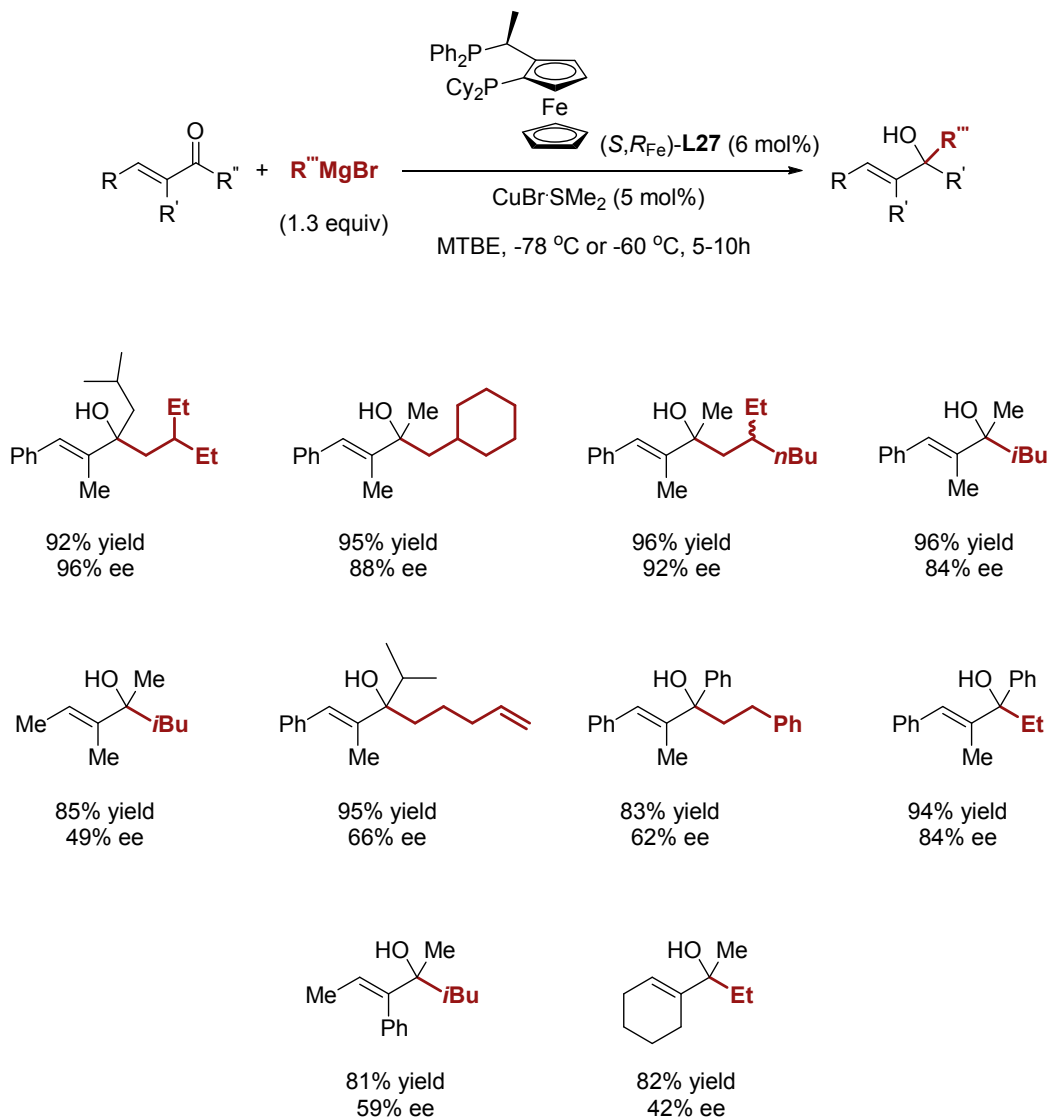
1  
2  
3 The main limitation of the methodology is bulky substrates, such as 1-(*o*-tolyl)ethanone,  
4  
5 which does not provide more than 12% conversion in the addition of PhMgBr.  
6

7  
8 In the last few years, various groups have reported protocols for the enantioselective titanium  
9 promoted addition of Grignard reagents to carbonyl compounds (mainly aldehydes), all  
10 utilising BINOL derivatives as chiral ligands for Ti(*i*PrO)<sub>4</sub>. These procedures are based on *in*  
11 *situ* transmetalation of the Grignard reagent with Ti(*i*PrO)<sub>4</sub> to form less reactive  
12 intermediates, such as RTi(*i*PrO)<sub>3</sub> or the titanate RTi(*i*PrO)<sub>4</sub>MgX. The mechanistic picture for  
13 these transformations is still not clear, but experimental observations and preliminary  
14 investigations from different groups point towards the presence of similar intermediates to the  
15 ones reported for the titanium promoted catalytic addition of organozinc reagents to carbonyl  
16 compounds.<sup>45</sup>  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28

#### 29 **4. Copper(I)-catalyzed enantioselective addition of Grignard reagents to carbonyl** 30 **compounds** 31 32

33  
34 During the past 80 years, following the work of Gilman and Straley in 1934,<sup>54</sup> Cu(I)-based  
35 reagents and catalysts have been used to outcompete the 1,2-addition of hard nucleophiles  
36 towards the conjugate addition to electron-deficient carbonyl compounds. This exclusive  
37 feature of Cu(I)-based catalyst is the main reason for the lack of their application in  
38 alkylation reactions of carbonyl compounds. However, this situation has recently changed,  
39 owing to reports by the groups of Harutyunyan and Minnaard, who have developed the first  
40 Cu(I)-based catalytic system for the asymmetric 1,2-addition of Grignard reagents to  $\alpha$ -  
41 substituted  $\alpha,\beta$ -unsaturated ketones, in the absence of any other stoichiometric additive  
42 (Scheme 29).<sup>55</sup>  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

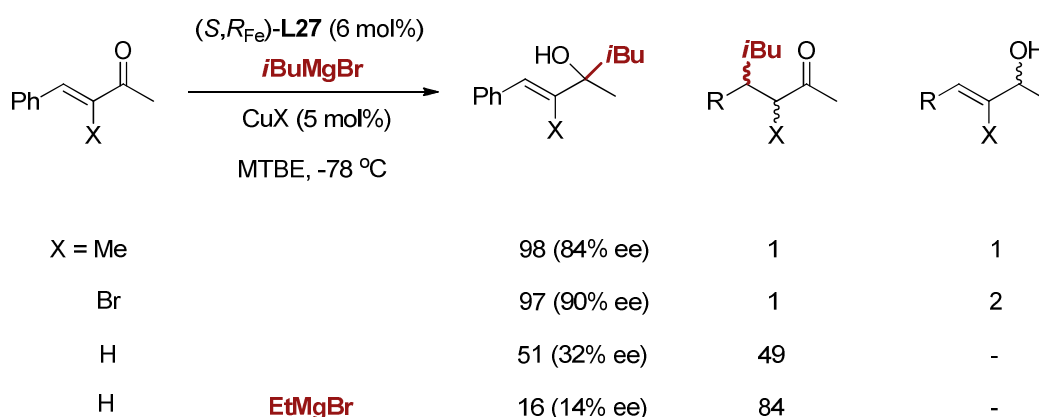
**Scheme 29. Catalytic asymmetric 1,2-addition to  $\alpha,\beta$ -unsaturated ketones by Harutyunyan and Minnaard.**



The reaction of a Grignard reagent with an  $\alpha$ -substituted  $\alpha,\beta$ -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,<sup>56</sup> Cu(I) salts and solvents, have identified the catalytic

1  
2  
3 system formed by CuBr·SMe<sub>2</sub> and the ferrocenyl diphosphine rev-Josiphos (**L27**) in MTBE  
4  
5 as the most suitable to achieve the desired chiral tertiary allylic alcohols with high yields and  
6  
7 enantioselectivities. Under the optimal reaction conditions, only 1% of 1,4-addition and 2%  
8  
9 of side reaction (reduction) products are formed, and the corresponding allylic alcohols can  
10  
11 be obtained in 97% yield and 84% of enantiomeric excess (Scheme 29). This discovery has  
12  
13 broken once and for all the old paradigm of the regioselectivity of organocopper compounds  
14  
15 towards 1,4-addition. The scope of the reaction has been investigated with several  
16  
17 unsaturated ketones and different Grignard reagents (Scheme 29), obtaining, in all cases high  
18  
19 1,2-regioselectivity. Increasing the steric bulk in the substrate (both R and R') or in the  
20  
21 Grignard reagent provides higher enantioselectivities. Excellent results can be obtained when  
22  
23 β-branched Grignard reagents are used (typically 95% yield and up to 96% ee), while linear  
24  
25 Grignard reagents give slightly lower enantioselectivities. When the less reactive MeMgBr is  
26  
27 used, only starting material is recovered and the use of the highly reactive PhMgBr leads to  
28  
29 racemic 1,2-addition product.  
30  
31  
32  
33  
34

35 **Scheme 30. Study of regio- and enantioselectivity depending on the α-substituent in the**  
36 **enone by Harutyunyan and Minnaard.**  
37  
38



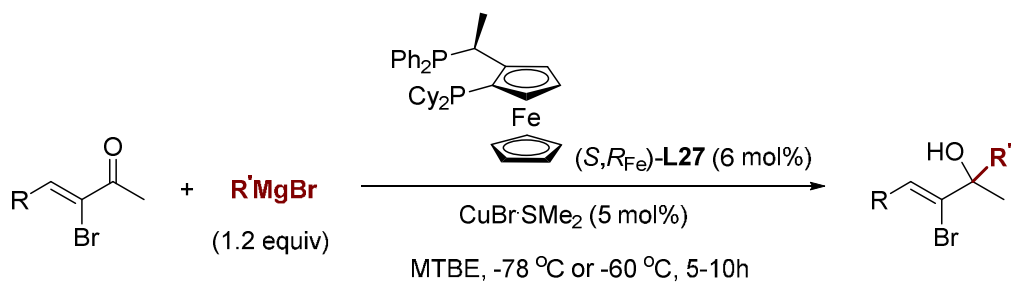
55 The α-substituent in the enone plays a crucial effect in the outcome of the reaction (Scheme  
56  
57 30). In the absence of an α-substituent (X = H), both regio- and enantioselectivity of the  
58  
59  
60

1  
2  
3 addition reaction decrease drastically. As mentioned before, also lower regio- and  
4  
5 enantioselectivity are obtained with linear Grignard reagent compared to bulky  $\beta$ -branched  
6  
7 ones.<sup>57</sup>  
8  
9

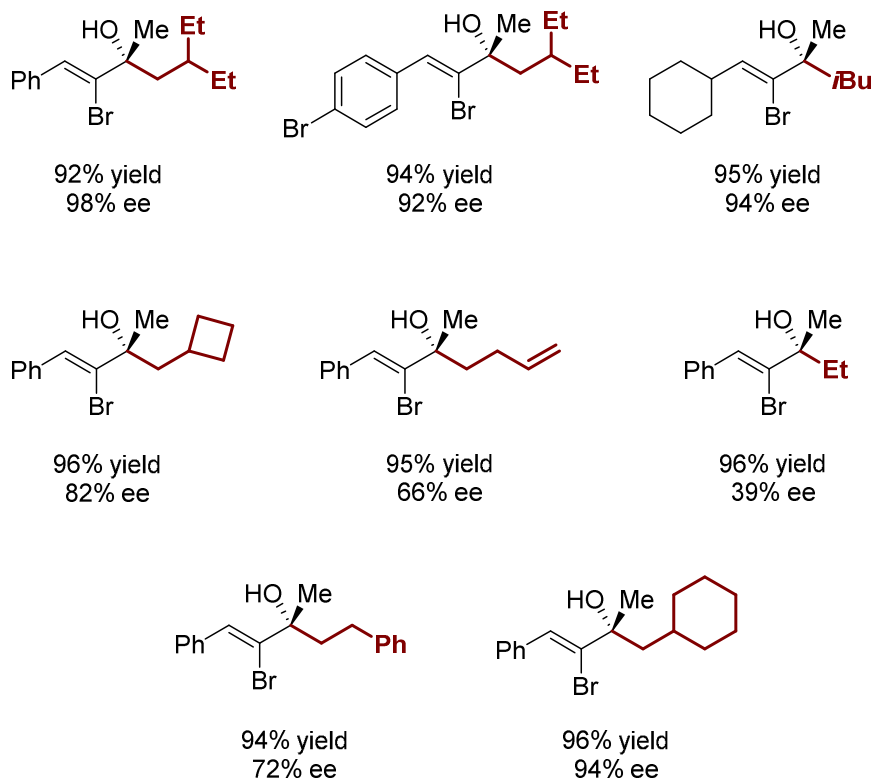
10  $\alpha$ -Br-unsaturated ketones give excellent results, especially with  $\beta$ -branched Grignard  
11  
12 reagents (typically >90% yield and >90% ee, Scheme 31). Lower enantioselectivities are  
13  
14 obtained with linear Grignard reagents. Interestingly, magnesium-bromide exchange in the  
15  
16 substrate is not detected. To access  $\alpha$ -H substituted tertiary allylic alcohols with high  
17  
18 enantioselectivity, a further debromination reaction with *t*BuLi can be carried out in excellent  
19  
20 yield and with full retention of the enantiomeric excess (Scheme 31b).  
21  
22  
23

24  
25 Interestingly, the authors have found a dramatic asymmetric amplification effect in this  
26  
27 reaction. This phenomenon is the result of the large difference in the solubility of the racemic  
28  
29 and the enantiopure chiral Cu-complexes.<sup>58</sup> When scalemic mixtures of the chiral  
30  
31 diphosphines are used to form the Cu-complexes in MTBE a significant amount of precipitate  
32  
33 is formed. When the supernatant is used as catalyst, the enantioselectivity in the addition of  
34  
35 (2-ethylbutyl)magnesium bromide to  $\alpha$ -Br-substituted benzylidenacetone is 94% ee in all  
36  
37 cases, even when the enantioselectivity of the initial scalemic mixture is only 20% ee. These  
38  
39 results are similar to those obtained with the enantiopure catalyst. Slightly lower  
40  
41 enantioselectivities are obtained when the supernatant and precipitate mixture are used as  
42  
43 catalyst (80-90% ee), indicating that the precipitate is not involved in the catalytic reaction.  
44  
45 On the contrary, the precipitate hinders efficient stirring, since longer reaction times are  
46  
47 needed in this case to achieve full conversion. The same amplification effect has been  
48  
49 observed for other Cu-diphosphine and Pd-complexes.<sup>58</sup>  
50  
51  
52  
53

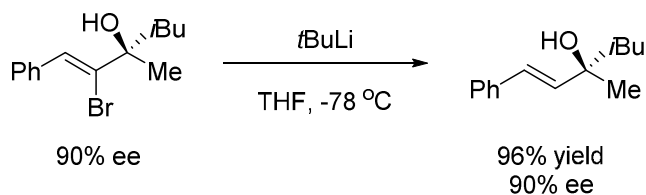
54 **Scheme 31. Catalytic asymmetric addition to  $\alpha$ -Br-unsaturated ketones by**  
55  
56 **Harutyunyan and Minnaard.**  
57  
58  
59  
60



a)



b)

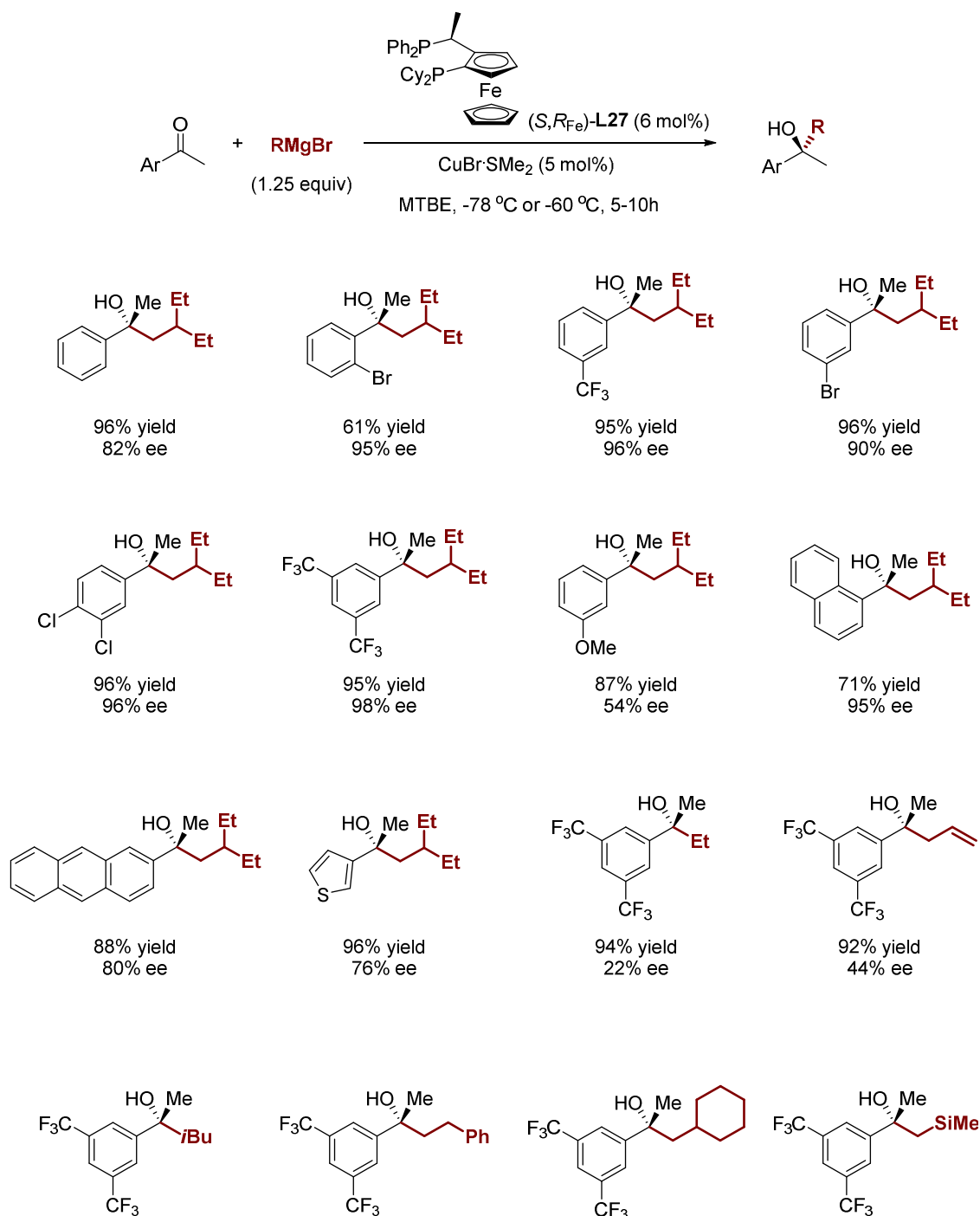


51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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).<sup>59</sup> Thus, the corresponding benzylic tertiary alcohols can be formed in high yields and good to

1  
2  
3 excellent enantioselectivities, with no traces of the uncatalyzed reaction, reduction or  
4  
5 enolisation.  
6  
7

8 **Scheme 32. Catalytic asymmetric 1,2-addition to aryl alkyl ketones by Harutyunyan**  
9 **and Minnaard.**  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

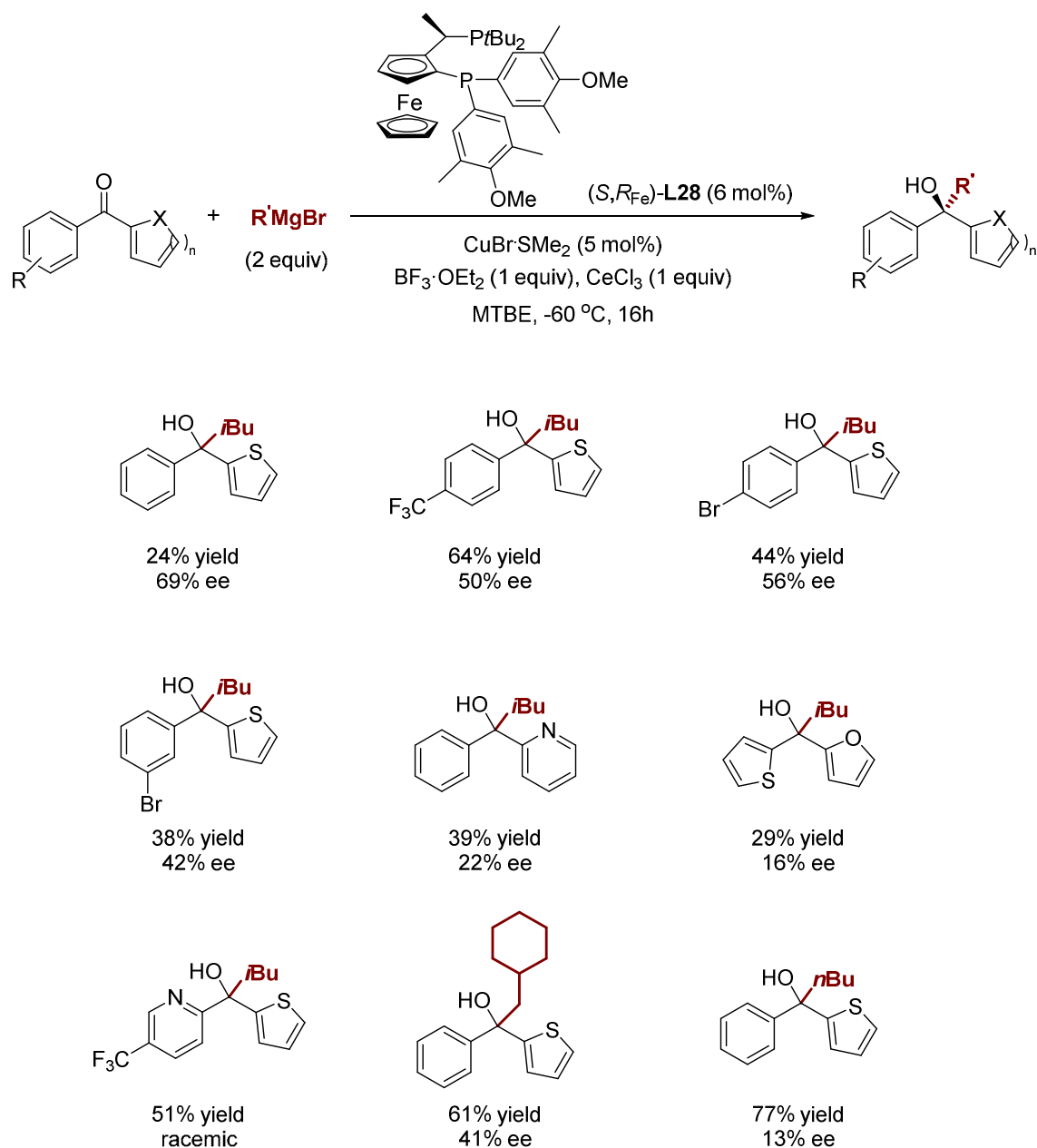


The scope of the reaction includes a broad spectrum of substituted acetophenones although no relationship between the enantioselectivity of the reaction and the stereoelectronic effects of the substituents in the ketone has been observed. As with previous substrates,  $\beta$ -branched Grignard reagents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

1  
2  
3 their corresponding tertiary alcohols with lower enantioselection, and MeMgBr is inactive.  
4  
5 Tertiary aryl heteroaryl methanols are very interesting motifs broadly present in biologically  
6  
7 active structures. Their enantioselective synthesis through the addition of alkyl Grignard  
8  
9 reagents to aryl heteroaryl ketones is challenging due to the significantly diminished  
10  
11 reactivity of the carbonyl moiety compared to aryl alkyl ketones, and to the small steric and  
12  
13 electronic differences between the two aryl substituents, which make the  
14  
15 enantiodiscrimination difficult. However, the use of a Cu(I)-phosphine based catalytic system  
16  
17 (CuBr·SMe<sub>2</sub> / Josiphos ligand **L28**) leads to the efficient alkylation of various aryl heteroaryl  
18  
19 ketones (Scheme 33).<sup>60</sup> It is worth noting that, in this case, the use of a mixture of Lewis  
20  
21 acids, BF<sub>3</sub>·OEt<sub>2</sub>/CeCl<sub>3</sub> (1:1) is required to improve the reactivity and outcompete the  
22  
23 undesired reduction *via* Meerwein-Ponndorf-Verley reaction. The role of these Lewis acids is  
24  
25 not clear, but they seem to prevent the coordination of the magnesium ion in the Grignard  
26  
27 reagent to the oxygen of the ketone carbonyl, which would promote the undesired β-hydride  
28  
29 transfer that generates the corresponding by-product of reduction. Organocerium species are  
30  
31 not involved in the reaction, since only starting material is recovered when isobutylcerium is  
32  
33 employed for the alkylation reaction. The main drawback of the alkylation of aryl heteroaryl  
34  
35 ketones with Grignard reagents is the low stability of both the alkoxide and the corresponding  
36  
37 diarylmethanol, leading to the formation of the side product from dehydration during the  
38  
39 reaction and the purification. The dehydration can be rationalized by the formation of a very  
40  
41 stable conjugated system. For these reason, only moderate isolated yields are obtained in this  
42  
43 reaction. Furthermore, low to moderate enantioselectivities are obtained due to difficult  
44  
45 enantiodiscrimination. The use of linear Grignard reagents, as well as the presence of other  
46  
47 coordinative sites in the aryl moiety of the ketone, lead to a significant decrease in the  
48  
49 enantiomeric excess (Scheme 33). Nevertheless, this report represents the first example of  
50  
51 direct asymmetric alkylation to diaryl ketones.  
52  
53  
54  
55  
56  
57  
58  
59  
60



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

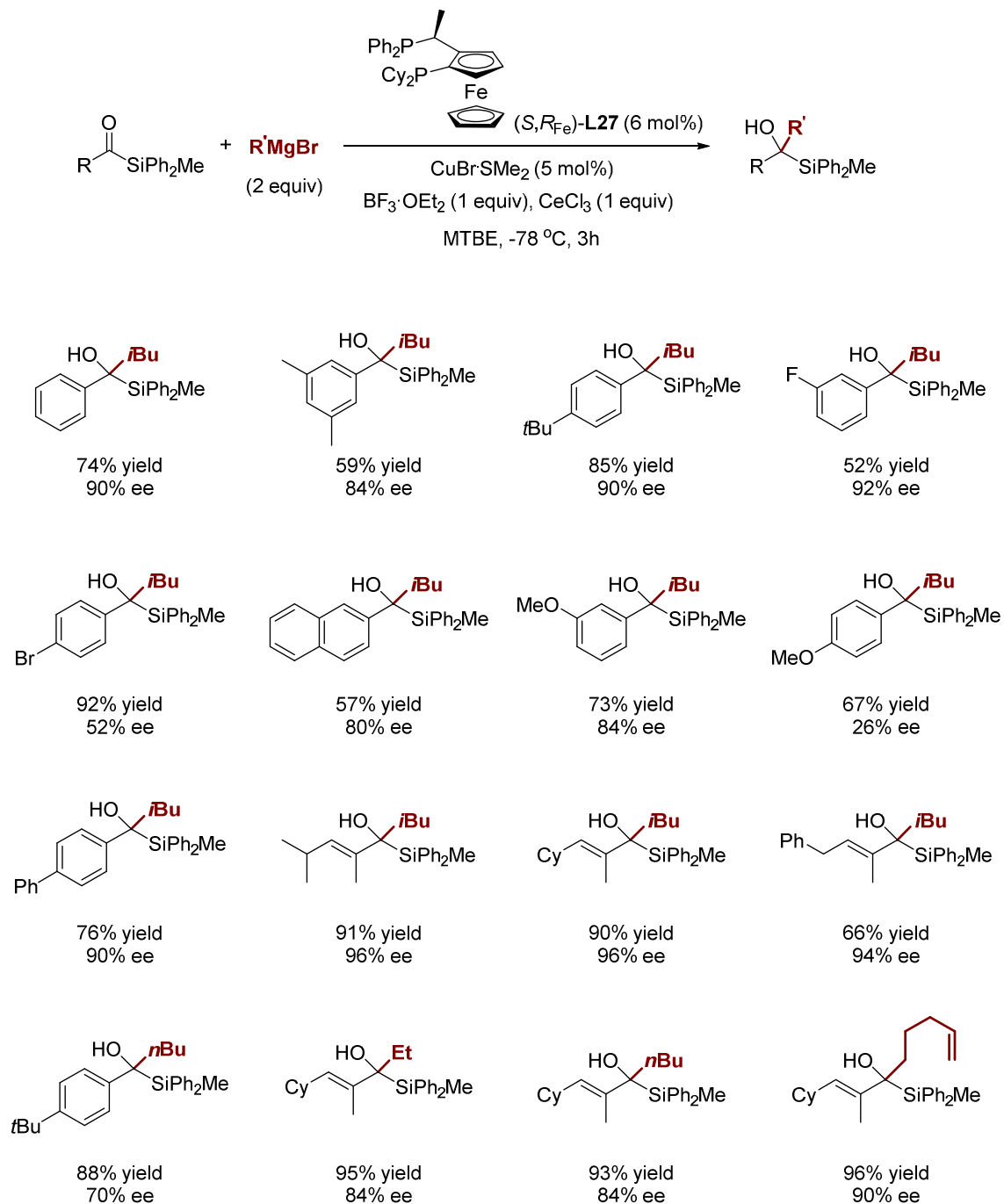


Encouraged by the increasing applications of silicon containing compounds in medicinal chemistry,<sup>61</sup> acyl silanes have been also evaluated in the alkylation reaction with Grignard reagents (Scheme 34).<sup>62</sup> In spite of several anticipated problems, such as the bulkiness of the

1  
2  
3 silicon group and the possible side reactions (MVP-type reduction and Brook rearrangement  
4 of the corresponding alkoxy silanes), excellent enantiodiscrimination between the two  
5 moieties of the carbonyl group, as well as excellent yields are obtained under the catalysis of  
6 the Cu(I)-rev-Josiphos **L27** system. The methodology is applicable to various alkyl Grignard  
7 reagents, including  $\beta$ -branched and linear ones, and a wide range of acyl silanes (Scheme 34).  
8 Both regio- and enantioselectivity of the reaction are strongly dependent on the bulkiness of  
9 the silyl moiety. Triphenyl- and triethylsilyl substituted ketones ( $\text{SiPh}_3$  and  $\text{SiEt}_3$ ) provide  
10 exclusively the corresponding reduction product, while  $\text{SiPh}_2\text{Me}$  or  $\text{SiPhMe}_2$  substituents  
11 lead to the desired 1,2-addition product, being yields and enantioselectivities slightly higher  
12 for the  $\text{SiPh}_2\text{Me}$  analogues.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25

26 In the absence of a Lewis acid, the Cu(I)-rev-Josiphos **L27** catalyzes the addition of  
27 *i*BuMgBr to phenylsilylketone providing good enantiomeric excess (90% ee) but poor  
28 regioselectivity (1:2, carbonyl addition/MPV reduction). The addition of  $\text{BF}_3 \cdot \text{OEt}_2$  to the  
29 reaction mixture enhances the selectivity up to 3:1, but at the expense of the enantiomeric  
30 excess, which drops to 86% ee. However, the mixture of two Lewis acids (stoichiometric  
31  $\text{BF}_3 \cdot \text{OEt}_2/\text{CeCl}_3$  1:1) leads to the desired tertiary alcohol in good regioselectivity (5:1,  
32 carbonyl addition/MPV reduction) and 90% ee. The scope of the reaction includes various  
33 substituted aryl acyl silanes and vinyl acyl silanes. In the case of vinyl acyl silanes the  
34 conjugate addition of the Grignard reagent constitutes another potential side-reaction,  
35 together with the reduction and alkylation pathways. Remarkably, for these substrates, only  
36 0.25 equiv of Lewis acids are required and the undesired 1,4-addition product is not detected  
37 by NMR under these conditions. A broad scope of Grignard reagents is suitable for this  
38 methodology, including both linear and  $\beta$ -branched, as well as functionalized Grignard  
39 reagents. However, MeMgBr leads to racemic product.  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

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

1  
2  
3 includes  $\alpha$ -substituted (Me, Br, Ph)  $\alpha,\beta$ -unsaturated acyclic ketones, aryl alkyl ketones, diaryl  
4 ketones and acylsilanes; b) the addition reaction of Grignard reagents to  $\alpha$ -H-substituted  $\alpha,\beta$ -  
5 unsaturated ketones proceeds with lower regio- and stereoselectivity than  $\alpha$ -Me-, Ph-, or Br-  
6 substituted analogues; c) the addition of MeMgBr and PhMgBr leads to racemic products; d)  
7  $\beta$ -branched Grignard reagents typically add with better stereoselectivity than linear ones; e)  
8 only 5 mol% of chiral catalyst loading is necessary; 6) reactions must be carried out in MTBE  
9 at -78 °C; f) the alkylation reaction of diaryl ketones and acylsilanes requires the use of a  
10 Lewis acid to avoid the side reduction pathway via  $\beta$ -hydride transfer; g) the Cu(I)-rev-  
11 Josiphos complex can be recovered after the reaction and reused many times. Important  
12 benefits of the copper(I)-based catalytic system when compared to the previous catalytic  
13 methodologies using titanium additives include lower amounts of Grignard reagents,  
14 significantly reduced reaction times, low catalyst loadings and, in the case of  $\alpha$ -substituted  
15  $\alpha,\beta$ -unsaturated ketones and alkyl aryl ketones, the fact that no additives are needed.

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32 This novel methodology based on Cu(I)-complexes of chiral ferrocenyl-based diphosphine  
33 ligands allows the direct use of Grignard reagents in the catalytic asymmetric alkylation  
34 reactions of carbonyl compounds. Moreover, when  $\alpha,\beta$ -unsaturated ketones are used as  
35 substrates the methodology breaks the 70 year old paradigm in organic chemistry that asserts  
36 that Cu(I)-based catalysts direct the addition of the nucleophile to the  $\beta$ -position of the  $\alpha,\beta$ -  
37 unsaturated system. Mechanistically, the reason why some copper(I)-based catalysts, similar  
38 to those used in previous studies for 1,4-additions of Grignard reagents,<sup>63</sup> prefer the 1,2-  
39 addition, is not clear. In order to direct the attack of the Grignard reagents to the 1,2-position  
40 of an enone in the presence of a Cu(I)-catalyst, the presence of an  $\alpha$ -substituent in the enone  
41 is required. Based on experimental and theoretical data, the Cu(I)/Cu(III) redox chemistry has  
42 long been proposed to have a role in the Cu(I)-catalyzed 1,4-addition reactions.<sup>64</sup> However  
43 neither the Cu(I)-catalyzed 1,2-addition of Grignard reagents to enones, nor the alkylations of  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

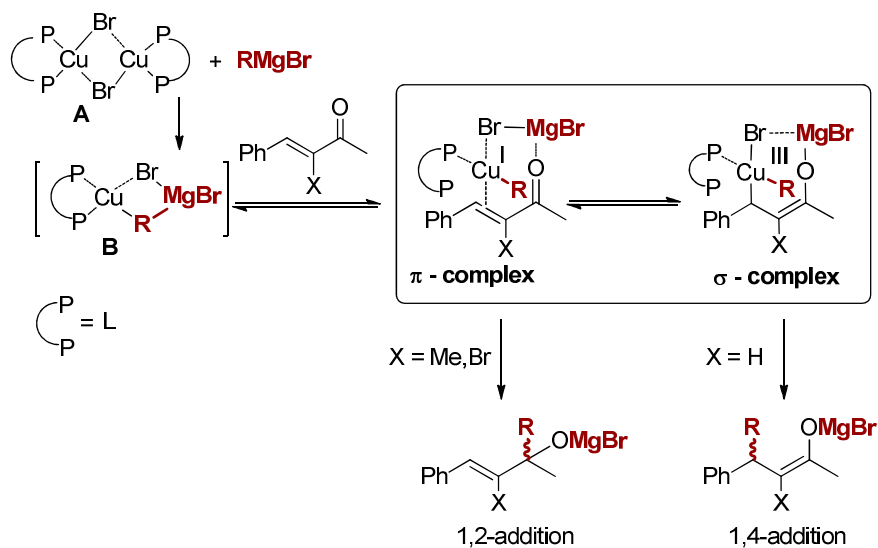
1  
2  
3 acylsilanes, aryl alkyl, and aryl heteroaryl ketones described above can be rationalised with  
4  
5 the existing mechanistic understanding of organocuprate chemistry involving Cu(I)/Cu(III)-  
6  
7 intermediates.  
8

9  
10 To explain the Cu(I)-catalyzed 1,2-addition pathway, the authors have proposed the  
11  
12 formation of a monomeric Cu(I) complex **B** from the dimeric species **A** by transmetalation  
13  
14 with a Grignard reagent (Scheme 35) similar to that observed in catalytic enantioselective  
15  
16 conjugate additions.<sup>65</sup> The formation of a Cu(I)  $\pi$ -complex which is in equilibrium with a  
17  
18 Cu(III)  $\sigma$ -complex (formal oxidative addition) has been suggested in the case of 1,2-addition  
19  
20 of Grignard reagents to  $\alpha$ -substituted  $\alpha,\beta$ -unsaturated ketones.<sup>65</sup> The differences in the  
21  
22 stability between Cu(I)  $\pi$ -complex and Cu(III)  $\sigma$ -complex caused by the substitution in  $\alpha$ -  
23  
24 position, explain the different ratios of 1,2- and 1,4-addition products. The authors suggest  
25  
26 that the presence of an  $\alpha$ -substituent (Me, Br or Ph) prevents the accumulation of Cu(III)  
27  
28 species, favouring the Cu(I)  $\pi$ -complex, followed by direct 1,2-addition to form the product  
29  
30 alkoxide.  
31  
32  
33

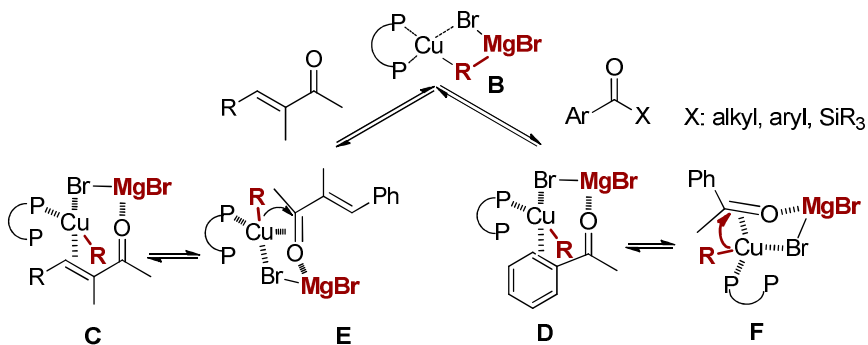
34  
35 However, the same Cu(I)-rev-Josiphos catalyst system is used both in the 1,2-alkylation of  
36  
37 enones as well as in the alkylation of aryl alkyl ketones. Therefore, an alternative pathway in  
38  
39 which the Mg<sup>2+</sup> and Cu atoms coordinate simultaneously to the oxygen atom and the double  
40  
41 bond in the carbonyl moiety (Scheme 35, species **E** and **F**) is proposed.<sup>55,11</sup> This  
42  
43 rationalisation is in analogy to the system characterized by Ogle and co-workers for the 1,2-  
44  
45 addition of Gillman reagents to aryl alkyl ketones.<sup>66</sup> In the case of  $\alpha,\beta$ -unsaturated ketones,  
46  
47 species **E** can be formed directly or after formation of the Cu(I)  $\pi$ -complex. In the case of aryl  
48  
49 alkyl ketones, as well as diaryl ketones or acyl silanes, other possible Cu(I)  $\pi$ -complexes with  
50  
51 the aromatic ring can be proposed (Scheme 35, species **D**), again in equilibrium with species  
52  
53  
54  
55  
56 **F**.  
57  
58  
59  
60

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

a) Proposed pathways for Cu(I)-catalyzed 1,2- versus 1,4-addition of Grignard reagents



b) Proposed new  $\pi$ -complexes in the dual activation of the carbonyl group



## 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.

1  
2  
3 Although a diverse range of catalytic chemical transformations is now available to meet this  
4 formidable challenge, there are still limitations to the methodologies and several challenges  
5 to overcome. Not only is the development of alternative catalytic methods, based on readily  
6 available and less expensive complex catalysts, highly desirable, but also other specific issues  
7 need to be addressed. For example, all the currently available methodologies for the addition  
8 of Grignard reagents to aldehydes require the use of super stoichiometric amounts of  
9  $Ti(iPrO)_4$ , which makes the process economically non-efficient and complicates the work up  
10 of the reaction. Therefore the implementation of these methodologies in industrial processes  
11 is not practical. Similarly, the catalytic enantioselective processes utilizing ketones as  
12 substrates are currently restricted to the addition of aryl Grignard reagents (under an excess of  
13  $Ti(iPrO)_4$ ) and bulky  $\beta$ -branched alkyl Grignard reagents (under catalytic amounts of a Cu(I)-  
14 complex, but requiring, in certain cases, stoichiometric amounts of Lewis acid additives at  
15 low, and industrially impractical, temperatures). These methodologies are still at their early  
16 stage of development and need further investigation. Last, and of particular interest, is the  
17 development and/or improvement of existing methodologies for the addition of  $MeMgBr$ ,  
18 that provides an easy approach to the methyl-substituted stereogenic centres ubiquitous in  
19 natural products.<sup>67</sup>

20  
21 It is clear that in the near future, the barriers to incorporating chiral alcohols in organic  
22 molecules will narrow by the development of new and improved methods for the catalytic  
23 enantioselective addition of Grignard reagents to carbonyl compounds. These  
24 enantiomerically enriched building blocks are of special interest for their occurrence in  
25 natural products, medicines, agrichemicals, polymers and advanced materials.

## 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 AUTHOR INFORMATION

### 54 55 56 **Corresponding Authors** 57 58 59 60

[S.Harutyunyan@rug.nl](mailto:S.Harutyunyan@rug.nl), [B.Macia-Ruiz@mmu.ac.uk](mailto:B.Macia-Ruiz@mmu.ac.uk)

## ACKNOWLEDGMENT

SRH thanks Financial support from The Netherlands Organization for Scientific Research (NWO-Vidi and ECHO to SRH.) and the Ministry of Education, Culture and Science (Gravity program 024.001.035). BM thanks the European Commission for a Marie Curie Career Integration Grant and the EPSRC for a First Grant. G. P. Howell and P. R. Birkett are thanked for helpful comments on the manuscript.

## ABBREVIATIONS

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

## REFERENCES

- <sup>1</sup> (a) Noyori, R.; Kitamura, M. *Angew. Chem.* **1991**, *103*, 34-55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833-856. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757-824. (d) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem.* **2001**, *113*, 3382-3407; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284-3308. (e) Pu, L. *Tetrahedron* **2003**, *59*, 9873-9886.
- <sup>2</sup> Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
- <sup>3</sup> (a) Oguni, N.; Omi, T.; Yamamoto, Y.; Nakamura, A. *Chem. Lett.* **1983**, 841-842. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071-6072. (c) Dosa, P. I.; Fu, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 445-446. (d) Takahashi, H.; Kawakita, T.; Ohno, M.; Yoshioka, M.; Kobayashi, S. *Tetrahedron* **1992**, *48*, 5691-5700. (e) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229-8243. (f) Knochel, P.; Jones, P. *Organozinc Reagents*, Oxford University Press, Oxford, **1999**. (g) García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970-10971. (h) Jeon, S.-J.; Li, H.; García, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448-455. (i) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416-16425. (j) Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139-208. (k) Lemièrre, A.; Côté, A.; Janes, M. K.; Charette, A. B. *Aldrichim. Acta* **2009**, *42*, 71-83. (l) Yus, M.; Ramón, D. J. *Recent Res. Dev. Org. Chem.* **2002**, *6*, 297-378. (m) Ramón, D. J.;



- 1  
2  
3  
4 Yus, M. *Chem. Rev.* **2006**, *106*, 2126–2208. (n) Yus, M.; Ramón, D. J. *Pure Appl. Chem.*  
5 **2005**, *77*, 2111–2119.
- 6 <sup>4</sup> Organoaluminum reagents: (a) You, J.-S.; Hsieh, S.-H.; Gau, H.-M. *Chem. Commun.* **2001**,  
7 1546–1547. (b) Biswas, K.; Prieto, O.; Goldsmith, P. J.; Woodward, S. *Angew. Chem.* **2005**,  
8 *117*, 2272–2274; *Angew. Chem. Int. Ed.* **2005**, *44*, 2232–2234. (c) Wu, K.-H.; Gau, H.-M. *J.*  
9 *Am. Chem. Soc.* **2006**, *128*, 14808–14809. (d) Mata, Y.; Dièguez, M.; Pàmies, O.;  
10 Woodward, S. *J. Org. Chem.* **2006**, *71*, 8159–8165.
- 11 <sup>5</sup> Aryltitanium reagents: Seebach, D.; Beck, A. K.; Roggo, S.; Wonnacott, A. *Chem. Ber.*  
12 **1985**, *118*, 3673–3682.
- 13 <sup>6</sup> (a) Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B.  
14 *Tetrahedron: Asymmetry* **2009**, *20*, 981–998. (b) Richey, H. G. *New Developments: Grignard*  
15 *Reagents*, Wiley, Chichester, UK, **2000**. (c) Wakefield, B. J. *Organomagnesium Methods in*  
16 *Organic Synthesis*, Academic Press, San Diego, CA, **1995**.
- 17 <sup>7</sup> (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.*  
18 **1989**, *111*, 4392–4398. (b) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371–4377.  
19 (c) Richery, H. G., Jr.; DeStephano, J. P. *J. Org. Chem.* **1990**, *55*, 3281–3286. (d) Scheiper,  
20 B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943–3949. (e)  
21 Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440–444. (f)  
22 Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497–500.
- 23 <sup>8</sup> (a) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998–9999. (b)  
24 Hatano, M.; Ito, O.; Suzuki, S.; Ishihara, K. *J. Org. Chem.* **2010**, *75*, 5008–5016. (d) Hatano,  
25 M.; Ito, O.; Suzuki, S.; Ishihara, K. *Chem. Commun.* **2010**, *46*, 2674–2676.
- 26 <sup>9</sup> Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088–1090.
- 27 <sup>10</sup> Fernández-Mateos, E.; Maciá, B.; Yus, M. *Eur. J. Org. Chem.* **2014**, 6519–6526.
- 28 <sup>11</sup> Rong, J.; Pellegrini, T.; Harutyunyan, S. R. *Chem. Eur. J.* **2015**, *21*, 1–14.
- 29 <sup>12</sup> Betti, M.; Lucchi, E. *Bull. Sci. Fac. Chim. Ind. Bologna* **1940**, *1/2*, 2–5. (C.A. *34*, 2354  
30 (1940)).
- 31 <sup>13</sup> Tarbell, D. S.; Paulson, M. C. *J. Am. Chem. Soc.* **1942**, *64*, 2842–2844.
- 32 <sup>14</sup> Cohen, H. L.; Wright, G. F. *J. Org. Chem.* **1953**, *18*, 432–446.
- 33 <sup>15</sup> Allentoff, N.; Wright, G. F. *J. Org. Chem.* **1957**, *22*, 1–6.
- 34 <sup>16</sup> French, W.; Wright, G. F. *Can. J. Chem.* **1964**, *42*, 2474–2479.
- 35 <sup>17</sup> Blomberg, C.; Coops, J. *Recl. Trav. Chim. Pays-Bas* **1964**, *83*, 1083–1095.
- 36 <sup>18</sup> (a) Nozaki, H.; Aratini, T.; Toraya, T. *Tetrahedron Lett.* **1968**, *9*, 4097–4098. (b) Nozaki,  
37 H.; Aratini, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905–913.
- 38 <sup>19</sup> Inch, T. D.; Lewis, G. J.; Sainsbury, G. L.; Sellers, D. J. *Tetrahedron Lett.* **1969**, *10*,  
39 3657–3660.
- 40 <sup>20</sup> Seebach, D.; Dörr, H.; Bastani, B.; Ehrig, V. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*,  
41 982–983.
- 42 <sup>21</sup> Meyers, A. I.; Ford, M. E. *Tetrahedron Lett.* **1974**, *15*, 1341–1344.
- 43 <sup>22</sup> Iffland, D. C.; Davis, J. E. *J. Org. Chem.* **1977**, *42*, 4150–4151.
- 44 <sup>23</sup> Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*,  
45 1455–1460.
- 46 <sup>24</sup> (a) Tomioka, K.; Nakajima, M.; Koga, K. *Chem. Lett.* **1987**, 65–68. (b) Tomioka, K.;  
47 Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 1291–1292. (c) Nakajima, M.; Tomioka,  
48 K.; Koga, K. *Tetrahedron* **1993**, *49*, 9751–9758.
- 49 <sup>25</sup> Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. *Pure Appl. Chem.* **1988**, *60*,  
50 1597–1606.
- 51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 <sup>26</sup> (a) Weber, B.; Seebach, D. *Angew. Chem.* **1992**, *104*, 96-97. (b) Weber, B.; Seebach, D.  
5 *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84-86.
- 6 <sup>27</sup> Markó, I. E.; Chesney, A.; Hollinshead, D. M. *Tetrahedron: Asymmetry* **1994**, *5*, 569-572.
- 7 <sup>28</sup> Mowat, J.; Kang, B.; Fonovic, B.; Dudding, T.; Britton, R. *Org. Lett.* **2009**, *11*, 2057-2060.
- 8 <sup>29</sup> Knollmüller, M.; Ferencic, M.; Gärtner, P. *Tetrahedron: Asymmetry* **1999**, *10*, 3969-3975.
- 9 <sup>30</sup> Yong, K. H.; Taylor, N. J.; Chong, J. M. *Org. Lett.* **2002**, *4*, 3553-3556.
- 10 <sup>31</sup> Catel, D.; Chevalier, F.; Mongin, F.; Gros, P. C. *Eur. J. Org. Chem.* **2012**, 53-57.
- 11 <sup>32</sup> Its nontoxicity has allowed their use for medical purposes (prostheses).
- 12 <sup>33</sup> Titanium is the ninth-most abundant element in the Earth's crust ( $5.65 \times 10^3$  ppm, 0.63% by  
13 mass). See: Lide, D. R. *CRC Handbook of Chemistry and Physics*, 88th edition. Boca Raton,  
14 Florida: Taylor & Francis Group, **2008**.
- 15 <sup>34</sup> (a) Yu, Y.; Ding, K.; Chen, G. in *Acid Catalysis in Modern Organic Synthesis*; Yamamoto,  
16 H. Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, **2008**; Chapter 14, p 721. (b)  
17 Mikami, K.; Terada, M. in *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Vol. 2;  
18 Wiley-VCH: Weinheim, Germany, **2000**; Vol. 2; Chapter 16, p 799. (c) Duthaler, R. O.;  
19 Hafner, A. *Chem. Rev.* **1992**, *92*, 807-832. (d) Cozzi, P. G.; Solari, E.; Floriani, C.; Chiesi-  
20 Villa, A.; Rizzoli, C. *Chem. Ber.* **1996**, *129*, 1361-1368.
- 21 <sup>35</sup> For a recent review on enantioselective titanium-promoted 1,2-additions of carbon  
22 nucleophiles to carbonyl compounds, see: Pellissier, H. *Tetrahedron* **2015**, *71*, 2487-2524.
- 23 <sup>36</sup> (a) Yoshioka, M.; Kawakita, T.; Ohno, M. *Tetrahedron Lett.* **1989**, *30*, 1657-1660. (b)  
24 Takahashi, H.; Kawakita, T.; Yoshioka, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1989**,  
25 *30*, 7095-7098.
- 26 <sup>37</sup> The transmetallation of Grignard reagents with ZnCl<sub>2</sub> affords their corresponding  
27 dialkylzinc derivatives, which can be used in the enantioselective addition to carbonyl  
28 compounds after strict exclusion of the magnesium salts: (a) Seebach, D.; Behrendt, L.; Felix,  
29 D. *Angew. Chem.* **1991**, *103*, 991-992; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1008-1009.  
30 (b) von dem Bussche-Hüennefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719-5730. (c)  
31 Kim, J. G.; Walsh, P. J. *Angew. Chem.* **2006**, *118*, 4281-4284; *Angew. Chem. Int. Ed.* **2006**,  
32 *45*, 4175-4178. (d) Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771-2773. (e)  
33 Soai, K.; Kawase, Y.; Oshio, A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1613-1615.
- 34 <sup>38</sup> Ti(*i*PrO)<sub>3</sub>Ph can be prepared by transmetalation of PhLi with TiCl(*i*PrO)<sub>3</sub> and used in the  
35 enantioselective catalytic addition to aldehydes, after removal of LiCl by centrifugation:  
36 Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473-7484.
- 37 <sup>39</sup> (a) Muramatsu, Y.; Harada, T. *Chem. Eur. J.* **2008**, *14*, 10560-10563. (b) Muramatsu, Y.;  
38 Kanehira, S.; Tanigawa, M.; Miyawaki; Harada, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 19-32.
- 39 <sup>40</sup> Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem.* **1998**, *110*,  
40 1801-1803; *Angew. Chem. Int. Ed.* **1998**, *37*, 1701-1703.
- 41 <sup>41</sup> (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.;  
42 Sapountzis, I.; Vu, V. A. *Angew. Chem.* **2003**, *115*, 4438-4456; *Angew. Chem. Int. Ed.* **2003**,  
43 *42*, 4302-4320.
- 44 <sup>42</sup> (a) Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333-3336. (b) Shi, L.;  
45 Chu, Y.; Knochel, P.; Mayr, H. *J. Org. Chem.* **2009**, *74*, 2760-2764.
- 46 <sup>43</sup> Itakura, D.; Harada, T. *Synlett* **2011**, 2875-2879.
- 47 <sup>44</sup> (a) Da, C.-S.; Wang, J.-R.; Yin, X.-G.; Fan, X.-Y.; Liu, Y.; Yu, S.-L. *Org. Lett.* **2009**, *11*,  
48 5578-5581. (b) Liu, Y.; Da, C.-S.; Yu, S.-L.; Yin, X.-G.; Wang, J.-R.; Fan, X.-Y.; Li, W.-P.;  
49 Wang, R. *J. Org. Chem.* **2010**, *75*, 6869-6878.
- 50 <sup>45</sup> Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336-  
51 10348.
- 52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4 <sup>46</sup> Fan, X.-Y.; Yang, Y.-X.; Zhuo, F.-F.; Yu, S.-L.; Li, X.; Guo, Q.-P.; Du, Z.-X.; Da, C.-S. *Chem. Eur. J.* **2010**, *16*, 7988–7991.
- 5  
6 <sup>47</sup> (a) Gao, G.; Gu, F.-L.; Jiang, J.-X.; Jiang, K.; Sheng, C.-Q.; Lai, G.-Q.; Xu, L.-W. *Chem. Eur. J.* **2011**, *17*, 2698–2703. For other applications of Ar-BINMOLs in asymmetric catalysis, see: (b) Gao, G.; Bai, X.-F.; Yang, H.-M.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Eur. J. Org. Chem.* **2011**, 5039–5046.
- 7  
8  
9  
10 <sup>48</sup> Fernández-Mateos, E.; Maciá, B.; Ramón, D. J.; Yus, M. *Eur. J. Org. Chem.* **2011**, 6851–6855.
- 11  
12 <sup>49</sup> Phenylmethanol is formed in the reaction, probably through a  $\beta$ -hydride elimination process and subsequent reduction of benzaldehyde.
- 13  
14 <sup>50</sup> Fernández-Mateos, E.; Maciá, B.; Yus, M. *Adv. Synth. Catal.* **2013**, 355, 1249–1254.
- 15  
16 <sup>51</sup> (a) Mozga, T.; Prokop, Z.; Chaloupkova, R.; Damborsky, J. *Collect. Czech. Chem. Commun.* **2009**, *74*, 1195–1278. (b) Keinan, E.; Sinha, S. C.; Singh, S. P. *Tetrahedron* **1991**, *47*, 4631–4638. (c) Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480.
- 17  
18  
19  
20 <sup>52</sup> Ito, Y. N.; Ariza, X.; Beck, A. K.; Bohác, A.; Ganter, C.; Gawley, R. E.; Khnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2110.
- 21  
22 <sup>53</sup> Zheng, L.-S.; Jiang, K.-Z.; Deng, Y.; Bai, X.-F.; Gao, G.; Gu, F.-L.; Xu, L.-W. *Eur. J. Org. Chem.* **2013**, *4*, 748–755.
- 23  
24 <sup>54</sup> (a) Gilman, H.; Straley, J. M. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 821–834. (b) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308–2316.
- 25  
26  
27 <sup>55</sup> Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Chem. Commun.* **2012**, *48*, 1478–1480.
- 28  
29 <sup>56</sup> Oost, R.; Rong, J.; Minnaard, A. J.; Harutyunyan, S. R. *Catal. Sci. Technol.* **2014**, *4*, 1997–2005.
- 30  
31 <sup>57</sup> (a) Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Org. Biomol. Chem.* **2012**, *10*, 2878–2884. (b) Wu, Z.; Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J. *Eur. J. Org. Chem.* **2014**, 575–582.
- 32  
33  
34 <sup>58</sup> Caprioli, F.; Madduri, A. V. R.; Minnaard, A. J.; Harutyunyan, S. R. *Chem. Commun.* **2013**, *49*, 5450–5452.
- 35  
36 <sup>59</sup> Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 3164–3167.
- 37  
38  
39 <sup>60</sup> Ortiz, P.; del Hoyo, A. M.; Harutyunyan, S. R. *Eur. J. Org. Chem.* **2015**, 72–76.
- 40  
41 <sup>61</sup> (a) Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388–405. (b) Mortensen, M.; Husmann, R.; Veri, E.; Bolm, C. *Chem. Soc. Rev.* **2009**, *38*, 1002–1010.
- 42  
43 <sup>62</sup> Rong, J.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R. *Angew. Chem.* **2015**, *127*, 3081–3085; *Angew. Chem. Int. Ed.* **2015**, *54*, 3038–3042.
- 44  
45 <sup>63</sup> Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L.; *Chem. Rev.* **2008**, *108*, 2824–2852.
- 46  
47 <sup>64</sup> (a) Hickman, A. J.; Sanford, M. S. *Nature*, **2012**, *484*, 177–185. (b) Youshikai, N.; Nakamura, E. *Chem. Rev.* **2012**, *112*, 2339–2372.
- 48  
49 <sup>65</sup> Harutyunyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 9103–9118.
- 50  
51 <sup>66</sup> Bertz, S. H.; Hardin, R. A.; Heavey, T. J.; Ogle, C. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 10250–10252.
- 52  
53  
54 <sup>67</sup> (a) Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 12904–12906. (b) Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 21–25.
- 55  
56  
57  
58  
59  
60