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Asymmetric Direct 1,2-Addition of Aryl Grignard Reagents to Aryl Alkyl Ketones

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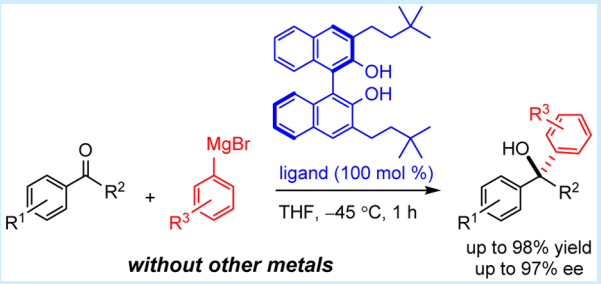
Supporting Information

ABSTRACT: The enantioselective addition of Grignard reagents to ketones was promoted by a BINOL derivative bearing alkyl chains at the 3,3′-positions. This is the first asymmetric direct aryl Grignard addition to ketones reported to date. A variety of tertiary diaryl alcohols could be obtained in high yields and enantioselectivities without using any other metal source.



Enantiopure tertiary alcohols are important structural motifs in organic chemistry and are ubiquitous in natural products and pharmaceutical compounds.[1] The simplest approach to constructing these structures involves the enantioselective 1,2-addition of organometallics to ketones.[2,3] The addition of alkyl groups to ketones has been achieved by developing catalysts using organozinc,[4] titanium,[4] and aluminum.[5] By contrast, the enantioselective addition of readily available Grignard reagents has proven to be more difficult.[6] Recently, copper-catalyzed asymmetric additions of alkyl Grignard reagents were reported.[7] Only a few Grignard reagent additions have been achieved without the use of additional metals, and these reactions have required more than stoichiometric amounts of a chiral ligand to achieve a high enantioselectivity.[8,9]

The addition of aryl groups to ketones was first achieved using an asymmetric reaction of $ZnPh_2$, as reported by Fu et al. in 1998.[10] Over the two subsequent decades, several approaches to obtaining chiral tertiary alcohols have been explored using arylzinc,[11] -titanium,[12] -boron compounds,[13] and -aluminum.[14] These reports showed excellent results; however, they are disadvantaged in their requirement for nucleophile preparation. For example, the preparation of arylzinc reagents from excess $ZnEt_2$ and arylboron compounds required elevated temperatures and long reaction times. Triarylaluminum compounds were prepared from $AlCl_3$ and 3 equiv of aryl Grignard reagents in THF over 12 h. In comparison with these preparations, asymmetric direct aryl Grignard additions to ketones are very simple procedures and efficient methods for reduction of other metal wastes. Although enantioselective catalytic additions of aryl Grignard reagents with excess amounts of $Ti(O^iPr)_4$ were reported recently,[15] to the best of our knowledge, no examples of enantioselective aryl Grignard addition to simple ketones without the use of other metals have yet been described.[16]

We previously reported the enantioselective alkynylation of lithium acetylide to ketones using lithium binaphtholate as a catalyst.[17] Here, we report the first direct asymmetric addition of aryl Grignard reagents to simple ketones using magnesium binaphtholate as a chiral ligand, providing tertiary diaryl alcohols in high yields and enantioselectivities.

Initially, we attempted the addition of a THF solution of 2′-acetonaphthone (**1a**) to phenylmagnesium bromide (**2a**) (3.5 equiv) and (*R*)-BINOL (**3a**) (100 mol %) as a chiral ligand in THF at −45 °C (Table 1, entry 1). In our research, 2 equiv of the Grignard reagent was consumed during deprotonation of the chiral ligand, and more than 1 equiv of the reagent was essential for the reaction with a ketone; therefore, we first used 3.5 equiv of **2a**. The reaction proceeded smoothly to give the tertiary alcohol **4a** in good yield and low ee. The stereoselectivity was improved by investigating other BINOL derivatives. The desired product was obtained in moderate enantioselectivity in the presence of (*R*)-3,3′-diphenyl-1,1′-binaphthol **3b**, which was the best catalyst identified in our previous alkynylation reactions (entry 2). This result suggested that the high stereoinduction of tertiary alcohols was essential for obtaining steric effects at the 3,3′-positions of the BINOL skeleton. We next tested the 2,6-dimethylphenyl-substituted BINOL derivative **3c**, but no enantioselectivity was achieved (entry 3).

BINOLs with substituents at the 3,3′-positions are versatile C_2-symmetric chiral ligands; however, few examples have described the use of compounds bearing alkyl groups in these positions as asymmetric ligands.[18] Therefore, we accepted the challenge associated with synthesizing these new types of BINOL ligands. The BINOL derivatives **3d** and **3e**, bearing benzyl and 1-methoxy-1-methylethyl groups, provided a poor yield and poor enantioselectivity (entries 4 and 5); however, the ligand **3f**, which included 2-methoxy-2-methylpropyl groups, yielded an improved enantioselectivity (entry 6). The ligand **3g** gave almost the same result (entry 7). We next introduced bulky aliphatic chains at the 3,3′-positions of BINOL (entries 8 and 9).

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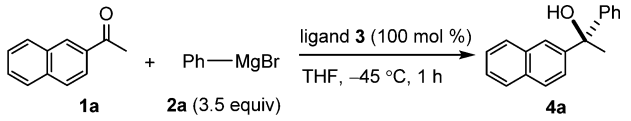
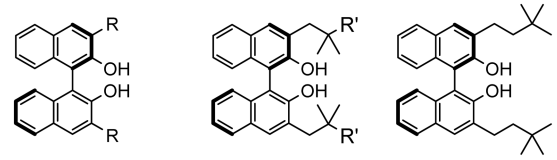
Table 1. Optimization of the Chiral Ligands[a]



1a 2a (3.5 equiv) 4a

entry	3	yield (%)	ee (%)
1	**3a**	87	18
2	**3b**	92	50
3	**3c**	80	2
4	**3d**	81	3
5	**3e**	24	−25
6	**3f**	96	72
7	**3g**	89	72
8	**3h**	95	78
9	**3i**	92	90
10[b]	**3i**	**94**	**93**



R = H (**3a**)
R = Ph (**3b**)
R = 2,6-$Me_2C_6H_3$ (**3c**)
R = Benzyl (**3d**)
R = $C(CH_3)_2OMe$ (**3e**)

R' = OMe (**3f**)
R' = OEt (**3g**)
R' = Me (**3h**)

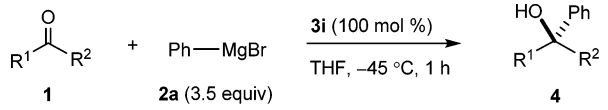
3i

[a]Unless otherwise noted, the reactions were conducted using the following procedure: A THF solution of 2′-acetonaphthone (**1a**) (0.5 mmol) was added to a solution of phenylmagnesium bromide (**2a**) (1.75 mmol) and ligand **3** (0.5 mmol) in THF (1.0 mL) at −45 °C. [b]Phenylmagnesium bromide (**2a**) (1.75 mmol) was added to the solution of 2′-acetonaphthone (**1a**) (0.5 mmol) and ligand **3** (0.5 mmol) in THF (1.0 mL) at −45 °C.

Gratifyingly, we succeeded in improving the enantioselectivity. The tertiary alcohol was obtained in a 92% yield and 90% ee using ligand **3i** with 3,3-dimethylbutyl groups. Furthermore, reactions unrelated to the ligand were partially suppressed by addition of phenylmagnesium bromide (**2a**) to the mixture of 2′-acetonaphthone (**1a**) and the ligand **3i** in THF, yielding the corresponding product in 94% yield and 93% ee (entry 10).[19] In our procedure, the reaction reached completion within 1 h. The reaction time was shorter than the time required for the corresponding aryl organometallics, which generally required over 12 h. Although we used stoichiometric amounts of the chiral ligand **3i**, this ligand was easily recovered and reused.[20]

The conditions optimized for ketone **1a** were applied to the reactions of other simple ketones **1b**–**g** (Table 2). 1′-Acetonaphthone (**1b**) showed a lower chemical yield than **1a**, although the obtained product **4b** displayed an excellent enantioselectivity (entry 2). Although the product **4e** displayed a slightly lower enantioselectivity, the aromatic ketones **1c**–**e** bearing electron-donating and -withdrawing groups smoothly reacted to give the tertiary alcohols **4c**–**e** in very high yields and enantioselectivities (entries 3–5). 2-Naphthyl ethyl ketone (**1f**), which included bulkier R^2 groups than **1a**, reacted with an acceptable enantioselectivity (entry 6). Cyclohexyl methyl ketone (**1g**) gave a high yield with a low ee (entry 7). Therefore, intermolecular interactions such as $\pi-\pi$ stacking between the aromatic ketone and the Grignard reagent appeared to play a key role in the transition state of the 1,2-addition.

Table 2. Various Simple Ketones Were Tested for the Preparation of the Tertiary Alcohols[a]



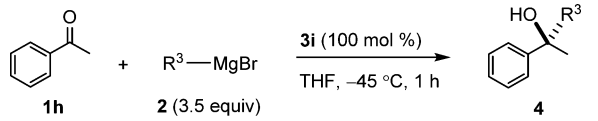
1 2a (3.5 equiv) 4

entry	1	R^1	R^2	4	yield (%)	ee (%)
1	**1a**	2-naphthyl	Me	**4a**	94	93
2	**1b**	1-naphthyl	Me	**4b**	70	96
3	**1c**	4-$MeOC_6H_4$	Me	**4c**	95	91
4	**1d**	4-BrC_6H_4	Me	**4d**	92	91
5	**1e**	4-ClC_6H_4	Me	**4e**	98	86
6	**1f**	2-naphthyl	Et	**4f**	97	86
7	**1g**	^{c}Hex	Me	**4g**	92	30

[a]All reactions were conducted using ketone **1** (0.5 mmol), phenylmagnesium bromide (**2a**) (1.75 mmol), and ligand **3i** (0.5 mmol) in THF (1.0 mL) at −45 °C.

We next investigated the reactions of various Grignard reagents with acetophenone (**1h**) (Table 3). 2-Naphthylmagnesium bromide (**2b**) afforded the product *ent*-**4a** in good yield with a high enantioselectivity (entry 1) with an absolute configuration opposite that of the product **4a** derived from the phenyl addition to 2′-acetonaphthone. The use of **2c** and **2d**, which bore electron-donating groups at the 4′-, and 3′-positions of the aromatic group, slightly decreased the enantioselectivities of the tertiary alcohols *ent*-**4c** and **4h** (entries 2 and 3). A methoxy group at the 2′-position dramatically decreased the ee (entry 4). This effect was attributed to chelation at the metal center. The methyl-substituted Grignard reagents **2f** and **2g** generated the product in a high yield and acceptable ee (entries 5 and 6). Compounds **2h** and **2i**, which bore electron-withdrawing groups, provided a slightly lower chemical yield, but the ee values of the tertiary alcohols **4l** and *ent*-**4e** were excellent (entries 7 and 8). A reaction of cyclohexylmagnesium bromide (**2j**) dramatically decreased the yield of the product, accompanied by a moderate ee (entry 9). The basicity of the aliphatic Grignard reagent was stronger than that of the aromatic reagent; therefore, enolization of the ketone occurred as the main side reaction.

Table 3. Various Grignard Reagents Were Tested for the Preparation of the Tertiary Alcohols[a]



1h 2 (3.5 equiv) 4

entry	2	R3	4	yield (%)	ee (%)
1	**2b**	2-naphthyl	*ent*-**4a**	80	94
2	**2c**	4-$MeOC_6H_4$	*ent*-**4c**	94	84
3	**2d**	3-$MeOC_6H_4$	**4h**	90	87
4	**2e**	2-$MeOC_6H_4$	**4i**	97	6
5	**2f**	4-MeC_6H_4	**4j**	96	88
6	**2g**	2-MeC_6H_4	**4k**	98	90
7	**2h**	4-FC_6H_4	**4l**	83	94
8	**2i**	4-ClC_6H_4	*ent*-**4e**	70	97
9	**2j**	^{c}Hex	*ent*-**4g**	10	59

[a]All reactions were conducted using acetophenone (**1h**) (0.5 mmol), Grignard reagent **2** (1.75 mmol), and ligand **3i** (0.5 mmol) in THF (1.0 mL) at −45 °C.

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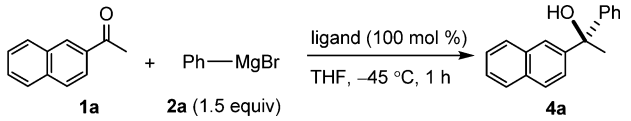
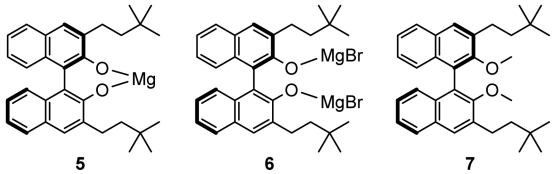
The mechanism underlying the stereoinduction was investigated by examining the structure of the Mg salt of the ligand (Table 4). BINOL derivatives have two oxygen atoms; therefore,

Table 4. Investigation of the Structure of the Mg Salt[a]



entry	ligand	yield (%)	ee (%)
1	**5**	66	26
2	-	77	-
3	**7**	82	0



[a]Ligand **5** was prepared in situ by stirring a 1:1 ratio of **3i** and $^{n}Bu_2Mg$.

two compounds, the monomagnesium salt **5** and the dimagnesium salt **6**, were presumed to be present. Monomagnesium binaphtholate was used as a good asymmetric catalyst and could be readily prepared from BINOL and $^{n}Bu_2Mg$.[21] We tried to use this species in our Grignard addition; however, the product was obtained in a moderate yield and a low ee (entry 1). We attempted a reaction of **1a** and 1.5 equiv of **2a** in the absence of ligand **3i**, and the tertiary alcohol was obtained in 77% yield (entry 2). This chemical yield was lower than that obtained in the presence of the ligand. No enantioselectivity was achieved from the *O*-methylated BINOL derivative **7** (entry 3).

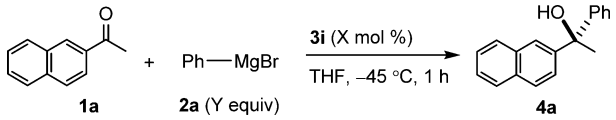
We next examined the relationship between the ee values of the ligand **3i** and those of the product **4a**. No clear nonlinear effects were observed in the 1,2-addition between **1a** and **2a**.[22] Aggregation has been reported in magnesium binaphtholate;[21a,e] however, we assumed that the monomeric species acted as an asymmetric auxiliary in the transition state.

These results suggested that the dimagnesium salt **6** was generated in the reaction and coordinated to the Grignard reagent as a Lewis base to enhance the nucleophilicity. Furthermore, the magnesium atom of **6** was effective in activating the ketone, and substituents at the 3,3′-positions of BINOLs controlled the direction of nucleophilic attack on the prochiral carbon atom. Although further investigations of the mechanism are required to fully understand this method, the transition state appeared to be a monomeric dimagnesium salt **6**.

Finally, we examined the effects of the ratio between the chiral ligand **3i** and the Grignard reagent (Table 5). Interestingly, even 50 mol % of **3i** gave the product in a good yield and an ee of 90% (entry 3); however, reducing the amounts of the chiral ligand tended to reduce the yield and ee (entries 4 and 5). These results suggested that the complex between the Grignard reagent and **3i** was more reactive than the Grignard reagent alone. Therefore, a well-designed BINOL may provide a high ee in a catalytic version of this asymmetric Grignard addition. We are currently investigating the synthesis of more effective BINOL derivative.

In conclusion, we have demonstrated the first example of enantioselective direct aryl Grignard additions to aryl alkyl ketones to afford the tertiary diaryl alcohols. Our protocol is very simple and does not require other metals or long reaction times.

Table 5. Reduction of the Amounts of Chiral Ligand 3i and Phenylmagnesium Bromide (2a)[a]



entry	*X*	*Y*	yield (%)	ee (%)
1	100	3.5	94	93
2	100	3.0	90	92
3	50	2.0	81	90
4	30	1.6	70	64
5	20	1.4	68	47

[a]Each reaction was conducted using 2′-acetonaphthone (**1a**) (0.5 mmol), phenylmagnesium bromide (**2a**) (*Y* equiv), and ligand **3i** (*X* mol %) in THF (1.0 mL) at −45 °C.

Our new BINOL derivative **3i** is easily recyclable and may potentially afford catalytic activity. Further investigations toward achieving BINOL-catalyzed direct Grignard additions are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03379.

Experimental procedures and spectral data for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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(19) Although we screened other solvents, temperatures, and halogen atoms in the Grignard reagent, these results could not be improved. We tested 3.0 equiv of **2a**, and the tertiary alcohol **4a** was obtained in a 90% yield and 92% ee (Table 5, entry 2). Hence, the procedure using entry 10 was deemed to be the best.

(20) The quantitative amounts of all ligand **3** were recovered after asymmetric 1,2-addition. The R_f values of ligand **3i** and product **4a** were 0.74 and 0.15 (hexane/CH_2Cl_2 = 1/1), and the R_f values of all other products **4** were similar to those of **4a**.

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(22) The ee values of the obtained tertiary alcohol **4a** were 55%, 41%, and 19% using ligand **3i** with ee values of 66%, 44%, and 20%, respectively. See the Supporting Information for details.

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