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$AlCl_3$ and BDMAEE: A Pair of Potent Reactive Regulators of Aryl Grignard Reagents and Highly Catalytic Asymmetric Arylation of Aldehydes

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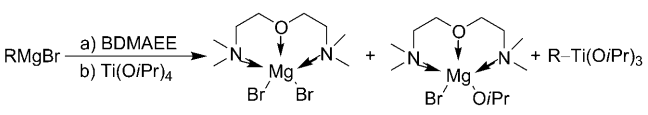
Enantioenriched diarylmethanols are important constituents of many biologically active compounds. As a result, the synthesis by the catalytic asymmetric arylation of aldehydes has generated an enormous amount of attention.[1] The seminal report by Fu and co-workers[2] on the asymmetric addition of diphenylzinc to aldehydes was followed shortly thereafter by the first highly enantioselective method by Pu et al.[3] A more enantioselective method involves the addition of mixed aryl–Zn–alkyl intermediates to aldehydes. These intermediates can be prepared from diphenylzinc[4] or arylboronic acids and diethylzinc[5] as described by Bolm and others.[6] In pursuing an economical procedure, Walsh and co-authors developed a cost-effective protocol starting from inexpensive and readily available arylbromides to prepare arylzinc reagents. *N*,*N*,*N*',*N*'-Tetraethylethylene diamine was used as a potent inhibitor of the Lewis acidic LiCl, which was formed on the transmetallation of the aryllithium to zinc chloride and rapidly promotes the undesired background reaction.[7] Other successful works include salt-free triarylaluminum as nucleophiles by Gau and co-workers,[8] and Ru-catalyzed direct asymmetric arylation with arylboronic acids by Yamamoto, Miyaura, and co-workers.[9]

In comparison to other aryl sources, aryl Grignard reagents are one of the least expensive and most commonly employed organometallic reagents. They are rarely used in the catalytic addition to aldehydes because of their high reactivity.[10] So far only one case has been disclosed by Harada and co-workers,[11] who developed a highly enantioselective protocol based on Grignard reagents. A drawback to their method was the need to add ArMgBr to titanium tetraisoproxide at −78 °C and then to introduce the resulting mixture into the reaction for two hours. Although very useful on a laboratory scale, large-scale reactions at very low temperatures are impractical. A significant operational and economical improvement would be the advancement of a method that could be conducted at room temperature, facilitating large-scale synthesis of highly enantioenriched diarylmethanols. Herein we report a highly asymmetric catalytic addition to aldehydes by using aryl Grignard reagents. The Grignard reagents are converted into triarylaluminum intermediates in situ, and are added to aldehydes with high enantioselectivities. To the best of our knowledge, no such report has been previously disclosed.

We pursued the development of a practical, room-temperature method starting from our recent research on the catalytic asymmetric addition of deactivated alkyl Grignard reagents to aldehydes outlined in Scheme 1.[12] In this reaction, $MgBr_2$ and MgBr(O*i*Pr) are formed. These Lewis acids promote the background reaction to form the racemic product and lower the enantioselectivity of the process. 2,2'-Oxybis(*N*,*N*-dimethylethanamine) (BDMAEE) was used as an additive to chelate the in situ generated Lewis acids $MgBr_2$ and MgBr(O*i*Pr) and to suppress their activity so that the asymmetric catalytic additions are highly enantioselective. However, PhMgBr becomes quite unreactive after coordination of BDMAEE. This result suggested that the chelation significantly decreased the nucleophilicity of PhMgBr. Owing to the inability of the aryl Grignard reagents to transfer aryls to Ti(O*i*Pr)$_4$ in the presence of BDMAEE, we



Scheme 1.

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decided to search for a more electrophilic metal that would be able to accept an aryl group from the deactivated Grignard reagent and arylate the aldehyde. After screening a variety of possibilities, we identified $AlCl_3$. As mentioned earlier, Gau demonstrated that salt-free aryl aluminum reagents could be added to aldehydes with high enantioselectivity. One drawback of Gau's method is that it is difficult to obtain salt-free aryl aluminum reagents.[8]

To examine the possibility of employing aluminum reagents in the asymmetric arylation of aldehydes, 2-chlorobenzaldehyde was used in the presence of (*S*)-BINOL and titanium tetraisoproxide. As shown in Table 1 (entries 1–2), in the absence of $AlCl_3$ or BDMAEE, very low enantioselectivity was observed (<40%). Furthermore, in the absence of $AlCl_3$, the reaction was very slow. In contrast, when the inhibitor BDMAEE and $AlCl_3$ were used together, the enantioselectivity was higher and the reaction reached completion very quickly (Table 1, entry 4). The ratio of $AlCl_3$/BDMAEE/PhMgBr was found to be critical for high enantioselectivity and yield. It was found that 2.7 equivalents of PhMgBr to $AlCl_3$ resulted in the higher enantioselectivity (Table 1, entries 3–5). The enantioselectivity again climbed when the equivalents of BDMAEE was increased (Table 1, entries 6–9), with the best ratio of PhMgBr/BDMAEE/$AlCl_3$ of 2.7:3.5:1 (Table 1, entry 8). An increase in the amount of PhMgBr/BDMAEE/$AlCl_3$ relative to aldehyde led to a slight increase in the enantioselectivity (Table 1, entry 10). The order of introduction of BDMAEE and $AlCl_3$ did not change the enantioselectivity (Table 1, entries 10 and 11).

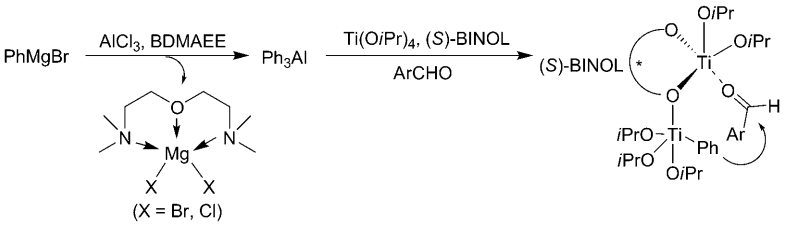
Table 1. Catalytic asymmetric addition of PhMgBr to 2-ClC_6H_4CHO.[a]

Entry	PhMgBr [mmol]	BDMAEE [mmol]	$AlCl_3$ [mmol]	ratio[b]	*ee* [%][c]
1	0.81	0.81	0	2.7:2.7:0	5
2	0.81	0	0.3	2.7:0:1	38
3	0.75	0.75	0.3	2.5:2.5:1	50
4	0.81	0.81	0.3	2.7:2.7:1	54
5	0.90	0.90	0.3	3.0:3.0:1	50
6	0.81	0.3	0.3	2.7:1.0:1	52
7	0.81	0.9	0.3	2.7:3.0:1	65
8	0.81	1.05	0.3	2.7:3.5:1	73
9	0.81	1.2	0.3	2.7:4.0:1	69
10	1.08	1.4	0.4	2.7:3.5:1	77
11	1.08	1.4	0.4	2.7:3.5:1	76[d]

[a] Ratio of (PhMgBr/BDMAEE/$AlCl_3$)/Ti(O*i*Pr)$_4$/(*S*)-BINOL-Ti/aldehyde = 0.3:0.3:0.025:0.25 mmol unless otherwise noted. [b] Ratio of PhMgBr/BDMAEE/$AlCl_3$. [c] Determined by HPLC. [d] First introduction of BDMAEE and then $AlCl_3$ to PhMgBr.

We propose that the role of $AlCl_3$ is to accept the Ph group from the Grignard reagent to generate the intermediate $AlPh_3$, which ultimately transfers the aryl to the aldehyde, as outlined in Scheme 2. The BDMAEE is believed to sequester the magnesium salts to prevent them from promoting the racemic background reaction. Note that $AlPh_3$ has only one open coordination site and [(BINOLate)Ti(O*i*Pr)$_2$] and Ti(O*i*Pr)$_4$ have two. In contrast, the magnesium probably binds the BDMAEE in a tridentate fashion, as shown in Scheme 1. As suggested by the groups of Bolm[5] and Walsh with diamines and lithium,[7] and subsequently by us,[12] BDMAEE chelates the Lewis acids MgX_2 and thus strongly suppresses the undesired reaction catalyzed by MgX_2, which can lead to a poor enantioselectivity. Then $AlPh_3$ transfers phenyl to Ti(O*i*Pr)$_4$ to generate Ph–Ti(O*i*Pr)$_3$, which is supposed to subsequently form a bimetallic nuclear complex with the (*S*)-BINOL-Ti(O*i*Pr)$_2$ and aldehyde.[13]

As mentioned earlier, to develop a truly practical method for the arylation of aldehydes, we examined catalytic asymmetric arylation reactions at room temperature. For high enantioselectivity, however, most catalytic asymmetric reactions must be carried out at low temperature, which can be difficult to accomplish on a large scale. In a study of the affect of temperature on product *ee*, we found that our system gave the highest enantioselectivities at room temperature, in which complete conversion to the diaryl methanol was observed in three hours. Interestingly, lower temperatures resulted in decreased enantioselectivity and longer reaction times (Table 2, entries 1–3). With all these efforts, however, the highest enantioselectivity was only 77%. Considering the reports that optically active H_8-BINOL was more enantioselective than BINOL in the asymmetric catalytic reactions,[8,14] (*S*)-H_8-BINOL was used instead of (*S*)-BINOL. Fortunately, the enantioselectivity increased to 94% (Table 2, entry 4).



Scheme 2. The proposed reaction mechanism.

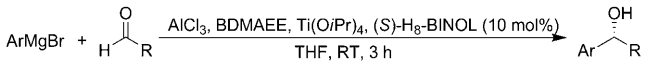
Table 2. The effect of temperature on the catalytic addition.[a]

Entry	Temperature [°C]	Time [h]	*ee* [%][b]
1	RT	3	79
2	0	8	71
3	−20	16	58
4[c]	RT	3	94

[a] Ratio of (PhMgBr/BDMAEE/$AlCl_3$)/Ti(O*i*Pr)$_4$/BINOL-Ti/aldehyde = 0.4:0.4:0.025:0.25 mmol. [b] Determined by HPLC. [c] (*S*)-H_8-BINOL was used instead of (*S*)-BINOL.

Under the optimal conditions in Table 2, entry 4, a series of aldehydes with PhMgBr were screened (Table 3, entries 1–15). Note that the in situ generated $AlPh_3$ intermediate achieved a slightly higher *ee* than that reported for salt-free $AlPh_3$,[8] except with substrates 4-$(MeO)C_6H_4CHO$ and (*E*)-cinnamaldehyde (Table 3, entries 1, 3, and 5–12). Our procedure also resulted in slightly higher enantioselectivity than Harada's procedure (Table 3, entries 1, 3, 5, 8, and 11–13), especially with alkyl aldehydes (Table 3, entry 14).[11] As can be seen in Table 3, in all cases with PhMgBr we obtained $\geq 90\%$ yields. The aromatic and heteroaromatic aldehydes with electron-donating and electron-withdrawing substituents were found to undergo arylation with PhMgBr with excellent enantioselectivities ($\geq 94\%$; Table 3, entries 1–9 and 11–13), in particular, up to 99% *ee* for 1-naphthylaldehyde (Table 3, entry 11). Most significantly, aliphatic aldehydes, including the challenging class of linear aliphatic aldehydes, provided benzylic alcohols with $\geq 94\%$ *ee* (Table 3, entries 14–15).

Table 3. Catalytic asymmetric ArMgBr addition to aldehydes.[a]

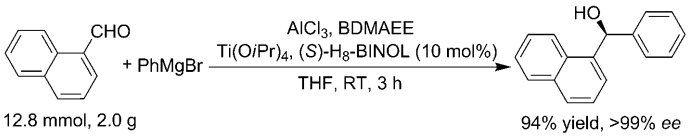


Entry	Ar	R	Yield [%][b]	*ee* [%][c,d]
1	Ph	2-ClC_6H_4	94	94 (92) [90]
2	Ph	4-FC_6H_4	94	97
3	Ph	4-ClC_6H_4	92	96 (95) [94]
4	Ph	4-BrC_6H_4	95	95
5	Ph	3-$(MeO)C_6H_4$	93	97 (96) [95]
6	Ph	4-$(MeO)C_6H_4$	95	95 (97)
7	Ph	3-MeC_6H_4	97	96 (94)
8	Ph	4-MeC_6H_4	94	97 (95) [90]
9	Ph	4-$(CF_3)C_6H_4$	95	98 (96)
10	Ph	(*E*)-PhCH=CH	90	86 (91)
11	Ph	1-naphthyl	95	99 (96) [95]
12	Ph	2-naphthyl	96	95 (94) [91]
13	Ph	2-thienyl	94	96 [90]
14	Ph	*c*-hex[e]	91	95 [80]
15	Ph	$CH_3(CH_2)_8$	91	94
16	2-naphthyl	1-naphthyl	92	95
17	2-naphthyl	*c*-hex[e]	90	98
18	3-tolyl	1-naphthyl	93	95
19	3-$(MeO)C_6H_4$	C_6H_5	90	92
20	3-$(MeO)C_6H_4$	4-MeC_6H_4	92	90
21	4-tolyl	1-naphthyl	96	96
22	4-FC_6H_4	1-naphthyl	94	99
23	4-FC_6H_4	2-naphthyl	96	98
24	4-FC_6H_4	C_6H_5	93	95
25	4-ClC_6H_4	1-naphthyl	92	95
26	4-ClC_6H_4	2-thienyl	95	97
27	benzofuran-5-yl	1-naphthyl	83	87

[a] Ratio of (PhMgBr/BDMAEE/$AlCl_3$)/Ti(O*i*Pr)$_4$/(*S*)-H_8-BINOL-Ti/aldehyde = 0.4:0.4:0.025:0.25 mmol. [b] Isolated yield. [c] Determined by HPLC. [d] The *ee* in the parentheses is referenced from Gau's report,[8] the *ee* in the square bracket is referenced from Harada's report.[11] [e] *c*-Hex = cyclohexane.

Having developed a method for phenyl additions to aldehydes, we wanted to explore the use of substituted and functionalized aryl Grignard reagents. Thus, additional seven different aryl Grignard reagents were screened and all of them achieved high yields and enantioselectivities. We initially employed (2-naphthyl)MgBr and afforded 95–98% enantioselectivities (Table 3, entries 16–17). The *meta*-substituted aryls addition to aldehydes has been rarely reported previously. We used (3-tolyl)MgBr and (3-MeO)C_6H_4MgBr and both of them also provided $\geq 90\%$ enantioselectivities (Table 3, entries 18–20). Three different ArMgBr reagents, with electron-donating or electron-withdrawing *para*-substituents (Table 3, entries 18–26), all gave excellent enantioselectivities and yields, and particularly, the highest enantioselectivity was up to 99%. In addition, the heteroatom-containing (benzofuran-5-yl)MgBr achieved a high *ee* and yield (Table 3, entry 27).

Because of the simple and convenient operation and mild conditions, the reaction was successfully scaled up to 2.0 g with no loss of enantioselectivity or yield, indicating this process has great potential for industrial applications (Scheme 3). To the best of our knowledge, this is the first catalytic asymmetric arylation of an aldehyde with aryl Grignard reagents on a large scale.



Scheme 3.

In summary, we have successfully developed a truly practical catalytic asymmetric arylation of aldehydes by using a variety of aryl and heteroaryl Grignard reagents with enantioselectivities as high as 99%. The key is the use of a combination of $AlCl_3$ and BDMAEE, which play distinct roles in the reaction system. BDMAEE inhibits the undesired background reaction promoted by Lewis acidic MgX_2, whereas $AlCl_3$ serves as an in situ generated aryl intermediate capable of transfer of the aryl to titanium and then to aldehydes under mild conditions. Note that use of in situ generated $AlAr_3$ reagents circumvents the need to isolate salt-free aryl aluminum reagents, greatly simplifying the asymmetric arylation process. In most cases, the in situ generated aryl intermediates resulted in slightly higher enantioselectivities than the salt-free Ar_3Al protocol and the intermediate $ArTi(OiPr)_3$ directly from ArMgBr with Ti(O*i*Pr)$_4$. Furthermore, the fact that the reaction can be conducted at room temperature with inexpensive Grignard reagents facilitates large-scale procedures necessary to produce pharmaceutical intermediates. An additional benefit of this process is that it employs H_8-BINOL, which is commercially available or prepared in one step from enantioenriched BINOL, one of the least expensive chiral ligands in asymmetric catalysis. With these attributes, and the well-recognized biological activity of enantioenriched diarylmethanols, we are confident that this reaction will find application in the pharmaceutical industry.

Experimental Section

General procedure of catalytic asymmetric addition of aryl Grignard reagents to aldehydes: An argon-purged flask was charged with PhMgBr (1.1 mL, 1.0 mmol) in THF (1.1 mL), and then $AlCl_3$ (53 mg, 0.4 mmol) in THF (0.4 mL) was added dropwise. After stirring for 12 h at room temperature, BDMAEE (263 μL, 1.4 mmol) was added. After 30 min, a mixture of (*S*)-H_8-BINOL (7.4 mg, 0.025 mmol) and $Ti(OiPr)_4$ (127 μL, 0.425 mmol) in THF (1 mL) was added. The solution was stirred for 30 min before 2-chlorobenzaldehyde (28.2 μL, 0.25 mmol) was added dropwise. The reaction was stirred at room temperature and monitored by TLC. After completion (3 h), the reaction mixture was quenched with a saturated NH_4Cl aqueous solution and extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give the pure product (51.4 mg, 94% yield, 94% *ee*).

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Keywords: aldehydes · arylation · asymmetric catalysis · asymmetric synthesis · Grignard reaction

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