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Highly Catalytic Asymmetric Addition of Deactivated Alkyl Grignard Reagents to Aldehydes

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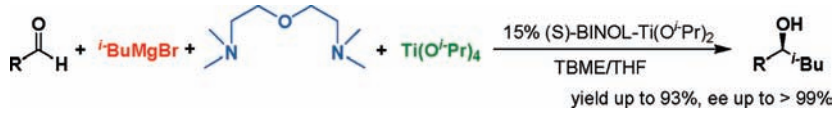
ABSTRACT



Generally used and highly reactive RMgBr reagents were effectively deactivated by bis[2-(*N*,*N*-dimethylamino)ethyl] ether and then were employed in the highly enantioselective addition of Grignard reagents to aldehydes. The reaction was catalyzed by the complex of commercially available (*S*)-BINOL and Ti(O^{i}Pr)$_4$ under mild conditions. Compared with the other observed Grignard reagents, alkyl Grignard reagents showed higher enantioselectivity and they achieved >99% ee.

Asymmetric addition of Grignard reagents to aldehydes is a powerful C−C bond formation reaction to generate chiral secondary alcohols with numerous biologic activities.[1] Because of the high reactivity of Grignard reagents, however, previous investigations were mainly focused on employing more than stoichiometric chiral auxiliaries[2] or chiral cosolvents[3] with modest to high enantioselection at extremely low temperatures. So currently two principal successful highly catalytic enantioselective procedures are involved in achieving optically pure secondary alcohols. The procedures are addition of organozinc to aldehydes[4] and hydrogenation of ketones.[5]

Only recently were two effective catalytic asymmetric protocols disclosed with Grignard reagents. One is that Grignard reagents were transferred into dialkyl or diaryl zinc[6] in advance and then such diorgnozinc reagents were used to add to aldehydes. This protocol essentially is the catalytic

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asymmetric addition of inertial diorganozinc to aldehydes. However, only one R group of R_2Zn can usually be useful, and this makes this protocol less atom economic. Another is that the Grignard reagent must be preconverted into the less reactive $RTi(O^iPr)_3$[7] and then the generated $RTi(O^iPr)_3$ was employed to react with aldehydes under asymmetric catalysis.[8] Weber and Seebach reported the first aryl or alkyl triiospropoxy titanium reagents from Grignard reagents and $ClTi(O^iPr)_3$ at −78 °C.[8a] But the in situ generated salts must be removed by centrifugation in order to afford the high enantioselectivity. More interesting are the reports by Harada and co-worker,[8b,c] in which the alkyl or aryl triiospropoxy titanium was generated by transmetalation of the Grignard reagent with 2.0 or 1.7 times the $Ti(O^iPr)_4$ than the Grignard reagent itself (without consideration of the additional $Ti(O^iPr)_4$ in the mixture of chiral ligand and aldehydes) at −78 °C, respectively. With only 2% chiral catalyst but no removal of the in situ generated salts via metal metathesis, Harada and co-worker achieved up to 97% high enantioselectivity. The drawback of the procedures is that the high loading of Ti compounds and preconversion of the Grignard reagent to $R\text{-}Ti(O^iPr)_3$ at an extremely low temperature are unavoidable.

Therefore, to the best of our knowledge, no direct catalytic asymmetric addition of Grignard reagents to aldehydes has been reported to date. And direct asymmetric reactions are particularly popular at present.[9] This situation makes it considerably interesting, challenging, and highly desirable to develop a direct highly catalytic asymmetric Grignard reaction of aldehydes under mild reaction conditions. Herein we report our result on this topic.

Initially, our effort also began with transferring RMgBr into $R\text{-}Ti(O^iPr)_3$ with $Ti(O^iPr)_4$ in the presence of a series of chiral ligands (Figure 1) under mild conditions for a long term. As can be seen (Table 1), (*S*)-BINOL was the promising ligand among **L1**−**L5** (entries 3−7). However, the enantioselectivity was rather difficult to duplicate even under the identical conditions (entries 1 and 2). So the central problem was to try to effectively decrease the high reactivity of Grignard reagents. We noted that Wang and co-workers reported that Grignard reagents chelated by bis[2-(*N*,*N*-dimethylamino)ethyl] ether (BDMAEE) cannot react with ketones.[10] This result revealed that Grignard reagents can be partly deactivated by some suitable chelating additive reagent.

Therefore five chelating additives were screened. The entire procedure was performed at a mild temperature (see p S4 in the Supporting Information). The results indicated that the diamine ether BDMAEE was satisfied in deactivation of the Grignard reagent reactivity in view of the ee value (Table 1, entries 8−12). With BDMAEE, the enantioselectivity could be easily duplicated (entries 12−13). When 40%

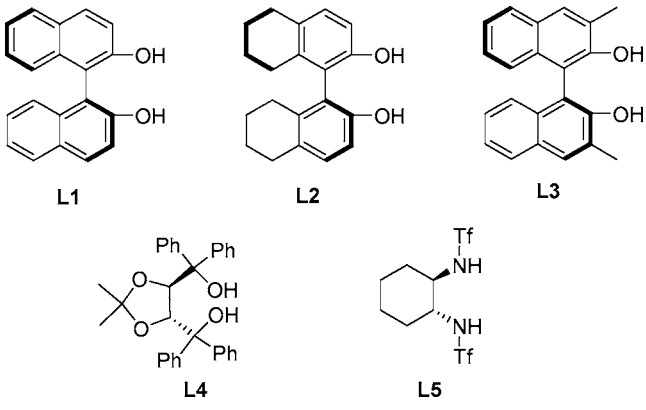

Figure 1. Chiral ligands.

Table 1. The Catalyzed Asymmetric Addition of ^{n}BuMgBr to PhCHO[a]

entry	ligand[b]	Ti[c]	^{n}BuMgBr[d]	additive[e]	sol.[f]	ee (%)[g]
1	**L1**(0.4)	2.8	3.58		THF	50
2	**L1**(0.4)	2.8	3.58		THF	75
3	**L1**(0.1)	2.8	3.85		THF	69
4	**L2**(0.1)	2.8	3.85		THF	60
5	**L3**(0.1)	2.8	3.85		THF	5
6	**L4**(0.1)	2.8	3.85		THF	33
7	**L5**(0.1)	2.8	3.85		THF	6
8	**L1**(0.1)	0.7	1.9	NMM	THF	54
9	**L1**(0.1)	0.7	1.9	TMEDA	THF	50
10	**L1**(0.1)	0.7	1.9	DMAP	THF	45
11	**L1**(0.1)	0.7	1.9	hexamine[h]	THF	48
12	**L1**(0.1)	0.7	1.9	BDMAEE	THF	70
13	**L1**(0.1)	0.7	1.9	BDMAEE	THF	68
14	**L1**(0.4)	0.7	2.5	BDMAEE	THF	98
15	**L1**(0.1)	0.7	1.9	BDMAEE	TBME	78
16	**L1**(0.1)	0.8	1.9	BDMAEE	Et_2O	50
17	**L1**(0.1)	0.8	1.9	BDMAEE	TBME	83
18	**L1**(0.1)	0.5	1.9	BDMAEE	TBME	53
19	**L1**(0.1)	1.0	1.9	BDMAEE	TBME	83
20	**L1**(0.1)	1.2	1.9	BDMAEE	TBME	84
21	**L1**(0.1)	1.4	1.9	BDMAEE	TBME	83
22	**L1**(0.1)	2.28	1.9	BDMAEE	TBME	82
23	**L1**(0.1)	0.84	1.9	BDMAEE	TBME	85

[a] ^{n}BuMgBr was introduced into $Ti(O^iPr)_4$ on the condition of ice-salt bath. The reaction temperature was naturally warmed to be ambient. [b] Data in parentheses are the used amount of ligands equivalent to benzaldehyde. [c] $Ti(O^iPr)_4$. The used amount equivalent to benzaldehyde. [d] The used amount equivalent to benzaldehyde. [e] The same amount of the additive as ^{n}BuMgBr equivalent to benzaldehyde was used. [f] Solvent. The solvent except THF was a cosolvent when THF was the solvent of ^{n}BuMgBr. [g] Determined by chiral HPLC. [h] Hexamine, also named urotropine, is hexamethylenetetramine.

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(*S*)-BINOL was used, 98% ee was achieved (entry 14). Experiments on solvents showed that the bisolvent of TBME (^{t}BuOMe) with THF was optimal (entries 13 and 15−16). The amount of Ti(O^{i}Pr)$_4$ was crucial to the enantioselectivity (entries 15 and 17−23). Low Ti(O^{i}Pr)$_4$ loading led to sharply decreased enantioselectivity. However, Ti(O^{i}Pr)$_4$ over 0.84 equiv gradually and slightly reduced ee values, such as Ti(O^{i}Pr)$_4$ over ^{n}BuMgBr achieved a slightly declined 82% ee (entry 22). So 0.84 equiv of Ti(O^{i}Pr)$_4$ was optimal in view of the enantioselectivity (entry 23).

Ti(O^{i}Pr)$_4$ and ^{n}BuMgBr should undergo transmetalation with each other to generate ^{n}Bu-Ti(O^{i}Pr)$_3$ and Mg(O^{i}Pr)Br ahead of the reaction. Considering the formation of the real catalyst (*S*)-BINOL-Ti(O^{i}Pr)$_2$[7d] should consume 1.0 equiv of Ti(O^{i}Pr)$_4$ but simultaneously generate 2.0 equiv of ^{i}PrOH to BINOL, which will consume 2.0 equiv of ^{n}BuMgBr to BINOL, the real ratio of Ti(O^{i}Pr)$_4$ to ^{n}BuMgBr was 7.4:17, less than 1:2. Apparently much less Ti(O^{i}Pr)$_4$ was used in this novel process in comparison with the previous reports.

BDMAEE-RMgBr can rapidly react with aldehydes without Ti(O^{i}Pr)$_4$, so can RMgBr-Ti(O^{i}Pr)$_4$ without BDMAEE. But if only BDMAEE-RMgBr complex and Ti(O^{i}Pr)$_4$ were introduced into aldehydes without **L1**, no product was observed within 4 h, in which addition of $MgBr_2$ quickly achieved the alcohol. This result denoted that the two additives cooperatively reduced the reactivity of RMgBr. It was assumed that BDMAEE could inhibit the racemic background reaction promoted by the active Lewis acidic salt MgBr(O^{i}Pr). Similar results have been observed previously.[11] Bolm and co-workers disclosed that dimethyl(polyethylene glycol) (DiMPEG, M_w = 2000 g mol^{-1}) could effectively suppress the activity of Ph_2Zn or $ZnBr_2$ in the catalytic asymmetric arylation of aldehydes, which actively catalyzed the racemic background reaction and caused the reaction to give low enantioselectivity.[11a,b] Later, Walsh and co-workers reported that TEEDA (*N*,*N*′,*N*′-tetraethylethylene diamine) successfully circumvented the racemic background reaction promoted by the strong Lewis acidic Li salts in the highly catalytic asymmetric arylation and heteroarylation of aldehydes.[11c−e] Herein, the strong basic and chelating additive BDMAEE should perform the same inhibited function as DiMPEG and TEEDA. Therefore, introduction of BDMAEE successively with Ti(O^{i}Pr)$_4$ into the Grignard reagents led to the in situ generated salt Mg(O^{i}Pr)Br via transmetalation to turn completely into the chelate complex **II** (Figure 2). The complex **II** is much less reactive than the precedingly generated complex **I** by way of Schlenk equilibrium[1d] that can catalyze the Grignard reaction. Thus catalytic activity of the complex **II** was so sharply decreased that it failed to catalyze the in situ generated RTi(O^{i}Pr)$_3$ to react with aldehydes. As a result, the racemic background reaction was effectively inhibited. This result would naturally lead to the highly enantioselective addition of R-Ti(O^{i}Pr)$_3$ to aldehydes which should be catalyzed only by (*S*)-BINOL-Ti(O^{i}Pr)$_2$.

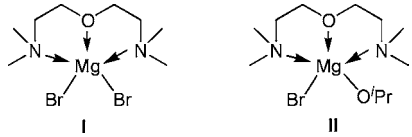
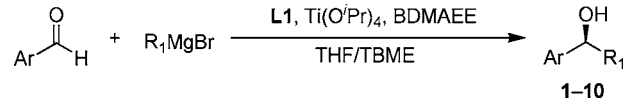


Figure 2. The chelated Lewis acidic salts by BDMAEE.

To check the generality of the Grignard reagents in this protocol, several commonly used RMgBr reagents were screened (Table 2). It can be observed that long-chain alkyl Grignard reagents achieved higher ee than short-chain alkyl, aryl, and vinyl Grignard reagents. The allylMgBr gave no enantioselectivity; however, vinylMgBr gave 33% ee (entry 12). MeMgBr achieved the highest 72% ee under a catalytic condition to date with 40% **L1** (entries 1−3) while EtMgBr achieved up to 93% ee with 30% **L1** (entries 4−6). PhMgBr and BnMgBr both gave moderate ee (entries 8−11). Clearly ^{i}BuMgBr was the most promising Grignard reagent (entries 13−15). Increasing **L1** to 15% gave an improvement of enantioselectivity to 98%. However, further increase in **L1** did not further improve the ee.

Table 2. Addition of Deactivated RMgBr to Arylaldehyde



entry	R1	Ar	**L1**[a]	yield (%)[b]	ee (%)[c]
1	Me	Ph	0.1	33	35
2[d]	Me	Ph	0.4	45	51
3[d]	Me	1-naphth	0.4	78	72
4	Et	Ph	0.1	39	70
5[d]	Et	Ph	0.4	46	81
6[e]	Et	1-naphth	0.3	54	93
7[f]	^{n}Bu	Ph	0.2	68	92
8	Ph	2-naphth	0.1	44	34
9[d]	Ph	2-naphth	0.4	58	54
10[d]	Ph	1-naphth	0.4	75	58
11	Bn	Ph	0.1	46	48
12[d,g]	vinyl	1-naphth	0.4	26	33
13	^{i}Bu	Ph	0.1	65	94
14[h]	^{i}Bu	Ph	0.15	76	98
15[f]	^{i}Bu	Ph	0.2	76	97

[a] The used amount of **L1** is relative to the aldehyde. [b] Isolated yield. [c] Measured by chiral HPLC. [d] 2.5 equiv of BDMAEE, 2.5 equiv of Grignard reagent, and 1.14 equiv of Ti(O^{i}Pr)$_4$ were used. [e] 2.3 equiv of BDMAEE, 2.3 equiv of Grignard reagent, and 1.04 equiv of Ti(O^{i}Pr)$_4$ were used. [f] 2.1 equiv of BDMAEE, 2.1 equiv of Grignard reagent, and 0.94 equiv of Ti(O^{i}Pr)$_4$ were used. [g] **L3** was used. [h] 2.0 equiv of BDMAEE, 2.0 equiv of Grignard reagent, and 0.89 equiv of Ti(O^{i}Pr)$_4$ were used.

Subsequently, several alkylmagnesium bromides were used to add to a series of aldehydes (Table 3). The results proved

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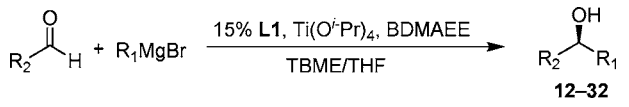
Table 3. Catalytic Asymmetric Addition of RMgBr to Aldehydes[a]



12–32

entry	R_2	R_1	yield (%)[b]	ee (%)[c]
1	2-MeO-C_6H_4	^{i}Bu	86	97
2	3-MeO-C_6H_4	^{i}Bu	63	97
3	4-MeO-C_6H_4	^{i}Bu	75	97
4	1-naphth	^{i}Bu	93	98
5	2-naphth	^{i}Bu	86	97
6	4-tolyl	^{i}Bu	81	97
7	3-Cl-C_6H_4	^{i}Bu	91	>99
8	4-Cl-C_6H_4	^{i}Bu	82	98
9	4-F-C_6H_4	^{i}Bu	69	>99
10	thiophene-2	^{i}Bu	35	94
11	PhCH=CH	^{i}Bu	70	90
12	cyclohexyl	^{i}Bu	27	98[d]
13	phenylethyl	^{n}Bu	23	88[d]
14	1-naphth	^{n}Bu	60	91[e]
15	Ph	*n*-pentyl	53	90
16	2-naphth	*n*-pentyl	77	90[e]
17	1-naphth	*n*-pentyl	79	90
18	1-naphth	*n*-heptyl	52	87[e]
19	2-naphth	*n*-heptyl	46	88[e]
20	4-MeO-C_6H_4	$Me_2C=CHCH_2CH_2$	50	92[e]
21	1-naphth	$Me_2C=CHCH_2CH_2$	62	91
22	2-naphth	$Me_2C=CHCH_2CH_2$	36	90

[a] 2.0 equiv of BDMAEE, 2.0 equiv of Grignard reagent, and 0.89 equiv of Ti(O^iPr)$_4$ were used. [b] Isolated yield. [c] Measured by chiral HPLC. [d] 30% **L1**, 2.3 equiv of BDMAEE, 2.3 equiv of Grignard reagent, and 1.04 equiv of Ti(O^iPr)$_4$ were used. [e] 20% **L1**, 2.1 equiv of BDMAEE, 2.1 equiv of Grignard reagent, and 0.94 equiv of Ti(O^iPr)$_4$ were used.

this protocol very efficient in terms of the enantioselectivity. ^{i}BuMgBr harvested the highest ee in this transformation to date, >99%. And even with alkyl aldehyde, up to 98% ee was achieved. Their low yields are due to the strong basic mixture, which reduced the aldehydes to primary alcohols. The further long-chain alkyl Grignard reagents achieved slightly decreased ee. The Grignard reagent with a remote C=C group in the chain also yielded high enantioselectivity.

In summary, a highly catalytic asymmetric addition of deactivated Grignard reagents to aldehydes is reported in this paper. A variety of commonly used RMgBr reagents were efficiently deactivated by BDMAEE and successfully employed in the asymmetric addition to aldehydes. The highly enantioselective reaction was catalyzed by the chiral complex of commercially available (*S*)-BINOL and Ti(O^iPr)$_4$. From the start to the end of the protocol, no extremely low temperature was used. And in comparison with the previous reports, much smaller amounts of Ti(O^iPr)$_4$ were employed. Among the observed Grignard reagents in this paper, alkyl Grignard reagents gave high enantioselectivities and ^{i}BuMgBr harvested >99% enantioselectivity.

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Supporting Information Available: Experimental procedures, HPLC spectra, and NMR data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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