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Bidentate ligand-catalyzed enantioselective addition of RZnX to benzaldehyde

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ABSTRACT

Enantioselective addition of RZnX (R = alkyl, X = Cl, OAc) was studied using chiral chelating agents, particularly metal-alkoxides. Moderate enantioselectivity was achieved in the presence of magnesium-TADDOLate using RZnOAcMg(OAc)Br as the alkylating agent.

Enantioselective addition of organometallic reagents to aldehydes is one of the fundamental asymmetric reactions and provides enantiorich secondary alcohols, which are building blocks for the synthesis of natural products and pharmaceuticals.[1] Asymmetric addition of alkyllithium and Grignard reagents is a straightforward approach to synthesize optically active alcohols. However due to their high reactivity, catalytic version remained unexplored for a long period of time.[2] Recently Harada and co-workers have reported that high enantioselectivity can be achieved by adding the Grignard reagent to aldehydes in the presence of catalytic amount of (*R*)-DPP-BINOL.[3] In this method, the reactivity of Grignard reagent was quenched by the use of titanium tetraisopropoxide to achieve excellent enantioselectivity. But this method suffers from drawbacks like the need to use large amount of titanium reagent, transmetallation at low temperature, and slow addition. In contrast, organozinc reagents became most popular during last three decades owing to their mild reactivity and excellent chemoselectivity.[4] Among different approaches, catalytic enantioselective addition of diorganozincs to aldehydes is the most studied reaction.[1b,c,5] However lack of wide commercial availability, high cost, and their pyrophoric nature demands an easy in situ preparation of these reagents. Significant efforts have been made by various research groups to circumvent these difficulties,[6] which include preparation of diorganozincs by boron–zinc[7] or iodine–zinc[8] exchange and transmetallation of alkyllithium or Grignard reagents with zinc salts.[9] One of the major drawbacks in the case of in situ preparation of diorganozincs from alkyllithium or Grignard and ZnX_2 is the inherent formation of lithium and magnesium salts, which affects the enantioselectivity.[9c,e] To overcome this difficulty, additional tasks like centrifugation/filtration[9a–c] or the use of complexing agent like *N,N,N,N*-tertaethylethylenediamine have been explored.[9d,e] The reagents of type RZnX (X = Cl, Br, I) which are easily accessible, are good potential alternatives to diorganozincs. Organozinc halides have been used as alkyl-source in a few asymmetric reactions like catalytic enantioselective 1,4-addition[10] and asymmetric Negishi coupling.[11] Recently Woodward and co-workers have shown that arylzinc halides can be used in catalytic enantioselective arylation of aldehydes.[12] In this method ArZnX was first converted in situ to ArZnMe by treatment with stoichiometric $AlMe_3$, which was then treated with the aldehyde in the presence of catalytic amount of chiral β-aminoalcohol to achieve excellent enantioselectivity. To our knowledge, the direct catalytic enantioselective addition of alkylzinc halides or alkylzinc carboxylates to aldehydes is not known.

Alkylzinc halides (RZnX) are known to be weakly active nucleophiles.[4b,13] It should be possible to enhance the reactivity of these reagents by activation with Lewis bases. It was thought that a chiral bidentate chelating agent could coordinate with the zinc center and form reactive tetrahedral complex[14] (Fig. 1), which may react with aldehyde enantioselectively.

$$EtMgBr + ZnCl_2 \xrightarrow[0\ ^{o}C\ to\ rt,\ 1\ h]{THF} \underset{\mathbf{A}}{EtZnCl{\bullet}Mg(Br)Cl} \quad (1)$$

$$EtMgBr + Zn(OAc)_2 \xrightarrow[0\ ^{o}C\ to\ rt,\ 1\ h]{THF} \underset{\mathbf{B}}{EtZnOAc{\bullet}Mg(OAc)Br} \quad (2)$$

$$Et_2Zn + Zn(OAc)_2 \xrightarrow[rt,\ 1\ h]{THF:hexane} \underset{\mathbf{C}}{EtZnOAc} \quad (3)$$

In our initial study, EtZnCl·Mg(Br)Cl (**A**) prepared by the transmetallation[15] of EtMgBr with $ZnCl_2$ (Eq. 1), was reacted with benzaldehyde. In the absence of any additive, **A** reacted with

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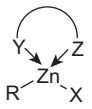
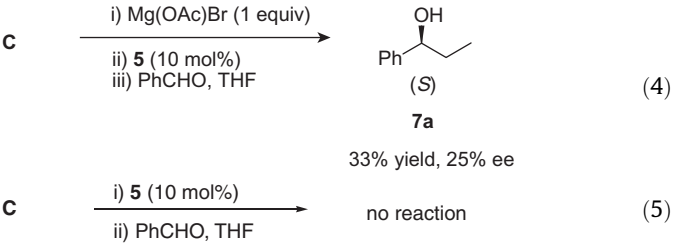


Figure 1. A reactive tetrahedral complex.

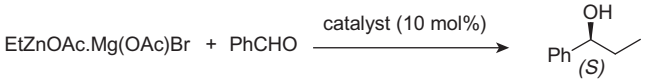
benzaldehyde to give 1-phenyl-1-propanol in 11% yield along with propiophenone (25%) and benzyl alcohol (25%) in 4 h at room temperature (Scheme 1). The formation of byproducts can be explained by Oppenauer oxidation[16] of the intermediate zinc-alkoxide. We then examined the reaction in the presence of various chiral additives (**1–6**). The metal-alkoxides[17] **2** and **4** were prepared separately by the reaction of the corresponding diol with 2 equiv of BuLi, whereas the alkoxides **3**, **5,** and **6** were obtained by treatment with EtMgBr in THF. The catalyst (10 mol %) was mixed with a solution of reagent **A** prior to the addition of benzaldehyde. Although good yields were obtained, negligible enantioselectivity was realized in all the cases.

One of the difficulties in handling the zinc halides is their hygroscopic nature. We decided to use zinc acetate which is nonhygroscopic and can be a good alternative to zinc halides. The reagent EtZnOAc·Mg(OAc)Br (**B**) was prepared by the transmetallation of EtMgBr with zinc acetate[18] (Eq. 2) in THF. The reagent **B** was first reacted with benzaldehyde without any additive. It revealed a reactivity pattern similar to that of **A**. In the presence of chiral chelating agent **1**, racemic 1-phenyl-1-propanol was obtained in 18% yield (Table 1, entry 2). Interestingly, the reaction of **B** in the presence of lithium-TADDOLate **4** provided 31% yield with 13% ee. The corresponding magnesium-TADDOLate **5** furnished 34% yield with 28% ee. Our attempts to isolate the reagent **B** were unsuccessful. To verify the formation of EtZnOAc from EtMgBr and $Zn(OAc)_2$, we prepared magnesium-free EtZnOAc (**C**) from diethylzinc and zinc acetate following the literature procedure[19] (Eq. 3). The reagent **C** was then reacted with benzaldehyde in the presence of stoichiometric amount of Mg(OAc)Br[20] (Eq. 4).



These results were comparable to the ones realized with the reagent **B**. We also found that the presence of MgX_2 was crucial. For example, **C** in the presence of 10 mol % of **5** failed to provide the product (Eq. 5). One of the reasons for moderate selectivity was attributed to MgX_2-promoted background reaction.[21] To overcome this problem, we added complexing agents like 1,4-dioxane or TMEDA. However, this modification proved inconsequential (entries 5 and 6). By changing the solvent from THF to methyl *tert*-butyl ether (MTBE), enantioselectivity increased to 50% (entry 7). When the reaction was carried out at room temperature, the product was isolated in 60% yield but the enantioselectivity was dropped to 39% (entry 8). Similar results were obtained when diethyl ether was used as the solvent (entry 9). Other dimagnesium-alkoxides (**3** and **6)** proved inferior to TADDOL (entries 10 and 11).

Table 1
Enantioselective addition of EtZnOAc·Mg(OAc)Br to benzaldehyde

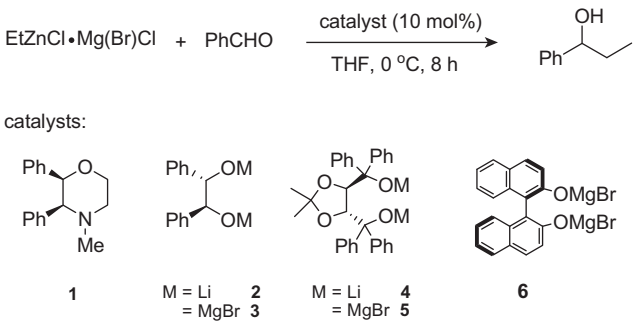


Entry	Catalyst	Solvent[a]	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	None	THF	0	4	29	—
2	**1**	THF	0	8	18	—
3	**4**	THF	0	8	31	13
4	**5**	THF	0	8	34	28
5[d]	**5**	THF	0	8	37	18
6[e]	**5**	THF	0	8	22	21
7	**5**	MTBE	0	8	44	50
8	**5**	MTBE	25	24	60	39
9	**5**	Et_2O	25	24	54	38
10	**3**	MTBE	25	24	45	<5
11	**6**	MTBE	25	24	49	<1

[a] The reactions were carried out at 0.4–0.5 molar concentrations.
[b] Isolated yields of the product.
[c] Determined by comparison of optical rotation with known literature value or chiral GC/HPLC analysis.
[d] One equivalent of 1,4-dioxane was added.
[e] One equivalent of TMEDA was added.

At this stage we are unable to provide a precise model which explains the outcome of stereoselectivity using reagent **B**. However we presume that the oxygen atoms of the metal alkoxide, EtZn(OAc), BrMg(OAc), and PhCHO bind as depicted in Figure 2. The resulting cyclic transition state could be responsible for stereoselection. This would also explain the lack of enantioselectivity with the reagent **A**, which proceeds through MgX_2-catalyzed acyclic pathway.

Heterogeneous reaction mixtures result in the use of solvents other than THF. After extensive optimization, it was found that by adding the Grignard reagent to a suspension of zinc acetate and (−)-TADDOL in THF, a homogenous solution was obtained at



Scheme 1. Addition of EtZnCl·Mg(Br)Cl to benzaldehyde.

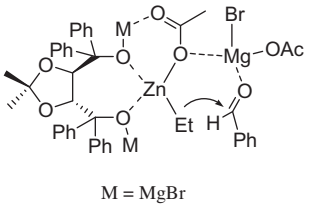
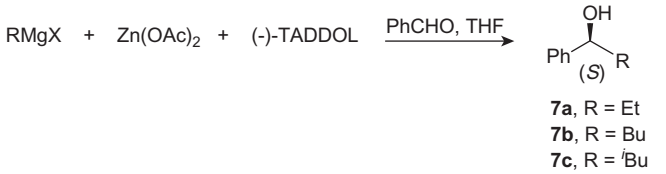


Figure 2. Proposed mechanism for enantioselective alkylation.

Table 2
Enantioselective addition of various RZnOAc·Mg(OAc)X to benzaldehyde



Entry	RMgX[a]	Temp (°C)	Time (h)	Product	Yield[b] (%)	ee[c] (%)
1	EtMgBr	0	8	**7a**	30	40
2[d]	EtMgBr	0	24	**7a**	18	36
3[e]	EtMgBr	0	4	**7a**	60	8
4	BuMgCl	0	8	**7b**	5	0
5	BuMgBr	0	4	**7b**	17	13
6[f]	BuMgI	0	4	**7b**	44	50
7	^{i}BuMgBr	0	8	**7c**	5	16

[a] The stoichiometric ratio of RMgX/Zn(OAc)$_2$:(−)-TADDOL/PhCHO was 1.7:1.5:0.1:1.0, respectively, unless otherwise noted.
[b] Isolated yields of the desired product.
[c] Ee was determined by chiral GC or HPLC analysis.
[d] 0.8 equiv EtMgBr was added with respect to Zn(OAc)$_2$.
[e] 1.2 equiv EtMgBr was added with respect to Zn(OAc)$_2$.
[f] The reaction was carried out in THF/Et$_2$O.

0 °C. This reagent was then reacted with benzaldehyde to obtain 30% yield of the product with 40% ee (Table 2, entry 1). We also studied the effect of stoichiometry of Grignard with respect to zinc acetate. It was found that the rate of the reaction as well as enantioselectivity varied with the change in stiochiometry. Best results were obtained when the ratio was 1:1 (entries 1–3). In terms of halide effect in RMgX, bromide and iodide were found to be better than chloride (entries 4–6). We also examined other Grignard reagents under these conditions. *n*-Butyl and *iso*-butyl magnesium bromide provided 13% and 16% enantioselectivity, respectively, (entries 5 and 7). In the case of ^{t}BuMgCl, no reaction took place at all.

In conclusion, we have found that alkylzinc carboxylates can be used as alkylating agent in enantioselective 1,2-addition to benzaldehyde.[22] These reagents can be attractive alternates to diorganozinc. Detailed study is underway to broaden the scope of the finding.

Acknowledgments

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