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Catalytic Enantioselective Alkylation of Aldehydes by Using Organozinc Halide Reagents

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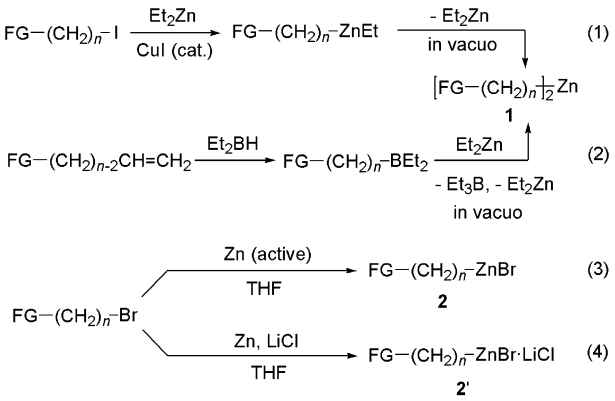
Recent advances in functionalized organometallic reagents have considerably increased the scope of carbon nucleophiles, allowing short and efficient syntheses of polyfunctional target molecules without unproductive protection/deprotection steps.[1] Despite the progress in catalytic enantioselective addition of functionalized aryl groups to aldehydes,[2] very few examples have been reported for the reaction of functionalized alkyl reagents. Knochel and coworkers reported the enantioselective addition of functionalized dialkylzinc reagents, [FG-$(CH_2)_n$]$_2$Zn (**1**), to aldehydes catalyzed by a chiral bis-triflylamide titanium complex.[3,4] The zinc reagents **1** were prepared by CuI-catalyzed I/Zn exchange of the corresponding iodo precursors with Et_2Zn followed by disproportionation of the resulting [FG-$(CH_2)_n$]ZnEt by the subsequent removal of Et_2Zn in vacuo [Scheme 1, Eq. (1)].[3] Alternatively, such reagents can be prepared by hydroboration of the terminal alkene precursors with Et_2BH and subsequent B/Zn transmetalation of the resulting [FG-$(CH_2)_n$]BEt_2 with Et_2Zn followed by the removal of surplus Et_3B and Et_2Zn [Scheme 1, Eq. (2)].[4]



Scheme 1. Preparation of functionalized alkylzinc reagents.

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We were attracted to the possible use of functionalized alkylzinc bromides, FG-$(CH_2)_n$-ZnBr (**2**), in the enantioselective carbonyl addition. The zinc reagents **2** possess superb functional group tolerance.[1] They are readily prepared in an atom-economical manner by oxidative addition of active Rieke-zinc[5] to the alkyl bromides [Scheme 1, Eq. (3)]. More conveniently, the reaction can be carried out with zinc dust in the presence of LiCl to give zinc reagent **2′** complexed with LiCl [Scheme 1, Eq. (4)].[6] Taking advantage of the intrinsic low reactivity, the zinc reagents have been utilized in the formation of carbon–carbon bonds by transition-metal catalysis as represented by the Negishi cross-coupling reaction.[7,1] Recently, Knochel et al. reported that the addition of organozinc halides to aldehydes, ketones, and carbon dioxide is accelerated significantly by mixing them with a stoichiometric amount of $MgCl_2$.[8] However, to date, a catalytic system has not been developed by which functionalized alkylzinc halides undergo enantioselective addition to aldehydes.

Herein, we report the first successful example of catalytic enantioselective alkylation of aldehydes by using functionalized alkylzinc halides **2** and **2′**. The reactivity of the zinc reagents is shown to be enhanced by mixing them with [Ti(O*i*Pr)$_4$] and $MgBr_2$. In the presence of a chiral titanium catalyst derived from (*R*)-DPP-H$_8$-BINOL (**3d**; BINOL = binaphthol, DPP = 3,5-diphenylphenyl; 5 mol%), a variety of functionalized alkylzinc reagents, prepared from readily available bromide precursors, underwent enantioselective addition to aldehydes to give the corresponding functionalized alcohols in high enantioselectivity.

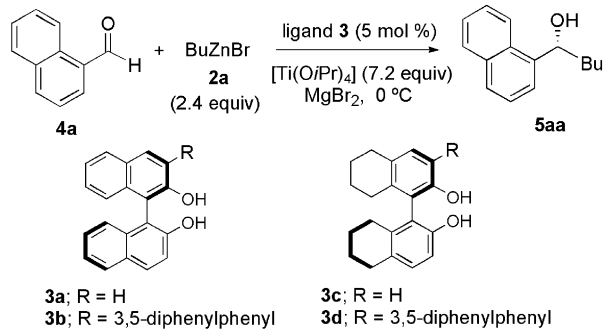
Recent reports from this laboratory showed that Grignard reagents can be used in the enantioselective addition to aldehydes by using titanium(IV) catalysts derived from (*R*)-DPP-BINOL (**3b**) and (*R*)-DPP-H$_8$-BINOL (**3d**) in the presence of excess [Ti(O*i*Pr)$_4$].[9,2l,m] In the present study, we first examined butylation of 1-naphthaldeyde (**4a**) by using *n*BuZnBr (**2a**) under similar conditions. Thus, when **4a** was treated with a commercial THF solution of *n*BuZnBr (2.4 equiv) in the presence of (*R*)-DPP-BINOL (**3b**) (5 mol%) and [Ti(O*i*Pr)$_4$] (7.2 equiv) at 0°C for 24 h, butylation product (*R*)-**5aa** was obtained in 90% *ee* (Table 1, entry 1 and Scheme 2). However, the chemical yield was moderate and aldehyde **4a** was recovered in 42%.

To improve the conversion of the aldehyde, the effect of metal salt additives was examined. Of these, magnesium halides were particularly effective in accelerating the reac-

Table 1. Optimization of reaction conditions for catalytic enantioselective butylation of aldehyde **4a** by using *n*BuZnBr (**2a**).[a]

	Ligand	$MgBr_2$ [equiv]	Solvent	Yield [%]	*ee* [%]
1[b]	**3b**	0	THF	55	90
2	**3b**	2.4	THF	94	55
3	**3b**	2.4	CH_2Cl_2	96	87
4	**3b**	2.4	Et_2O	92	87
5	**3b**	1.2	CH_2Cl_2	97	92
6	**3b**	1.2	toluene	65	88
7	**3b**	0.6	CH_2Cl_2	45	92
8	**3d**	1.2	CH_2Cl_2	95	93
9[c]	**3d**	1.2	CH_2Cl_2	64	82
10[d]	**3d**	1.2	CH_2Cl_2	88	93
11[e]	**3d**	1.2	CH_2Cl_2	87	91
12[f]	**3d**	0	CH_2Cl_2	60	90
13	**3a**	1.2	CH_2Cl_2	58	76
14	**3c**	1.2	CH_2Cl_2	66	71
15[g]	–	1.2	CH_2Cl_2	38	–

[a] Unless otherwise noted, reactions were carried out with **4a** (0.42 M), **2a** (2.4 equiv), $MgBr_2$, $[Ti(OiPr)_4]$ (7.2 equiv), and ligand **3** (5 mol%) at 0°C for 3 h. [b] The reaction was carried out at 0.21 M of **4a** in THF for 24 h. [c] The reaction was carried out with $[Ti(OiPr)_4]$ (3.2 equiv). [d] The reaction was carried out in the presence of LiCl (2.4 equiv). [e] BuZnBr·LiCl prepared in THF from *n*BuBr, Zn, and LiCl was used. [f] $MgCl_2$ (1.2 equiv) was added. [g] The reaction was carried out in the absence of a ligand.

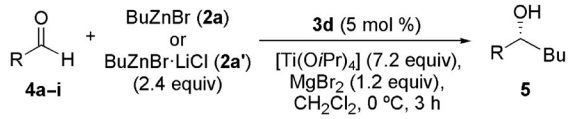


Scheme 2. Catalytic enantioselective butylation of aldehyde **4a** by using BuZnBr (**5a**).

tion.[10] In the presence of $MgBr_2$ (2.4 equiv), **5aa** was obtained in high yield within 3 h, but in decreased enantioselectivity (entry 2). The enantioselectivity was improved by using the mixed reagent of *n*BuZnBr (**2a**), $[Ti(OiPr)_4]$, and $MgBr_2$ after removal of THF in vacuo followed by dissolution in CH_2Cl_2 or in Et_2O (entries 3 and 4). Further improvements in the enantioselectivity were attained by reducing the amount of $MgBr_2$ (1.2–0.6 equiv) (entries 5 and 7) and by using a titanium catalyst derived from (*R*)-DPP-H_8-BINOL (**3d**) (entry 8). The reaction was slow when using less polar toluene as a solvent (entry 6), decreasing the amount of $[Ti(OiPr)_4]$ to 3.6 equiv (entry 9), applying a 4:1 ratio of **2a**/$MgBr_2$ (entry 7), and using $MgCl_2$ instead of the bromide (entry 12). The use of parent BINOL (**3a**) and H_8-BINOL (**3c**) resulted in significant decrease in the product yield and enantioselectivity (entries 13 and 14). It should be noted that, in the absence of the catalyst, butylation proceeded slowly to give racemic **5aa** in moderate yield (entry 15). When *n*BuZnBr·LiCl (**2a′**), prepared either from **2a** and LiCl (entry 10) or from butyl bromide, zinc dust, and LiCl (entry 11),[6] was employed, **5aa** was obtained without a significant decrease in the chemical yield and enantioselectivity.

Under the conditions of entry 8 in Table 1, the scope of the present reaction for aldehydes was examined in the reaction using BuZnBr (**2a**) and BuZnBr·LiCl (**2a′**) (Table 2).

Table 2. Catalytic enantioselective butylation of aldehydes **4** by using *n*BuZnBr (**2a**) or *n*BuZnBr·LiCl (**2a′**).[a]



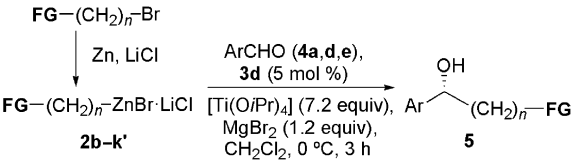
	Aldehyde	Zinc reagent	Product	Yield [%]	*ee* [%]
1	1-NaphCHO (**4a**)	**2a**	**5aa**	95	93
2	PhCHO (**4b**)	**2a′**	**5ba**	87	86
3	*p*-MeC_6H_4CHO (**4c**)	**2a**	**5ca**	86	89
4	*p*-ClC_6H_4CHO (**4d**)	**2a′**	**5da**	92	92
5	*m*-$MeOC_6H_4CHO$ (**4e**)	**2a**	**5ea**	82	91
6	*o*-BrC_6H_4CHO (**4f**)	**2a**	**5fa**	72	44
7	2-ThienylCHO (**4g**)	**2a**	**5ga**	69	78
8[b]				71	86
9	PhCH=CHCHO (**4h**)	**2a**	**5ha**	75	74
10[b]		**2a′**		84	83
11[c]	$PhCH_2CH_2CHO$ (**4i**)	**2a**	**5ia**	51	83

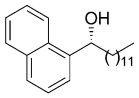
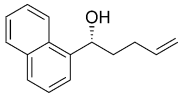
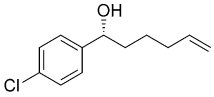
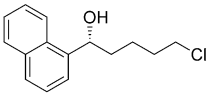
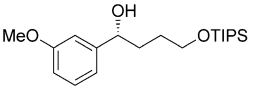
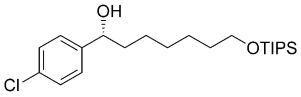
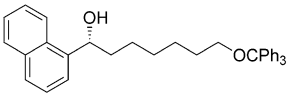
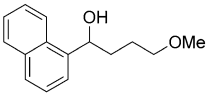
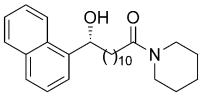
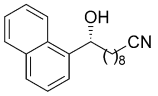
[a] Unless otherwise noted, reactions were carried out with aldehydes **4** (0.42 M), **2a** or **2a′** (2.4 equiv), $MgBr_2$ (1.2 equiv), $[Ti(OiPr)_4]$ (7.2 equiv), and **3d** (5 mol%) in CH_2Cl_2 at 0°C for 3 h. [b] The reaction was carried out with $MgBr_2$ (0.6 equiv) for 21 h. [c] The reaction was carried out with $MgBr_2$ (0.6 equiv) at 5°C for 4 d.

The reaction of benzaldehyde (**4b**) and its *para*- and *meta*-substituted derivatives (**4c–e**) afforded the corresponding butylation products in high yields and in high selectivities (86–92% *ee*) either with **2a** or with **2a′** (entries 2–5). On the other hand, moderate enantioselectivity was observed for *ortho*-substituted derivative **4f** (entry 6). For the reaction of heteroaromatic aldehyde **4g** and α,β-unsaturated aldehyde **4h**, satisfactory yields and selectivities could be attained by applying a 4:1 ratio of **2a** (or **2a′**)/$MgBr_2$ with a longer reaction time (entries 8 and 10). Aliphatic aldehyde **4i** was considerably less reactive. However, the reaction at 5°C for 4 days afforded butylation product **5ia** in relatively high enantioselectivity (entry 11).

Reactions were then carried out with a variety of zinc reagents **2b–k′** that were prepared from bromide precursors by treatment with zinc dust in the presence of LiCl (Table 3).[6] Zinc reagents, prepared from a long-chain alkyl bromide, homoallyl and bis-homoallyl bromide, and an ω-chloroalkyl bromide, all underwent smooth addition to aromatic aldehydes **4** to furnish the corresponding secondary alcohols in high selectivity (86–93% *ee*) (entries 1–4). ω-Silyloxy- and alkoxy-substituted alkylzinc reagents **2f′–h′** also underwent enantioselective addition to give the corresponding mono-protected diols of high 90–92% *ee* (entries 5–7).

Table 3. Catalytic enantioselective addition of functionalized alkyl groups to aldehyde by using zinc reagents **2′**.[a]

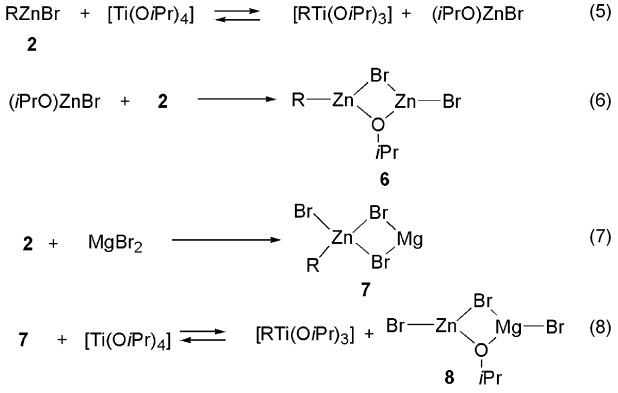


	Aldehyde	RZnBr·LiCl	Product		Yield [%]	*ee* [%]
1	**4a**	$C_{12}H_{23}ZnBr{\cdot}LiCl$ (**2b′**)		**5ab**	76	91
2	**4a**	$CH_2{=}CH(CH_2)_2ZnBr{\cdot}LiCl$ (**2c′**)		**5ac**	96	93
3	**4d**	$CH_2{=}CH(CH_2)_3ZnBr{\cdot}LiCl$ (**2d′**)		**5dd**	81	91
4	**4a**	$ClC_4H_8ZnBr{\cdot}LiCl$ (**2e′**)		**5ae**	91	86
5	**4e**	$TIPSO(CH_2)_3ZnBr{\cdot}LiCl$ (**2f′**)		**5ef**	96	91
6	**4d**	$TIPSO(CH_2)_6ZnBr{\cdot}LiCl$ (**2g′**)		**5dg**	92	90
7	**4a**	$TrO(CH_2)_6ZnBr{\cdot}LiCl$ (**2h′**)		**5ah**	77	92
8	**4a**	$MeO(CH_2)_3ZnBr{\cdot}LiCl$ (**2i′**)		**5ai**	93	3
9	**4a**	$PipCOC_{10}H_{20}ZnBr{\cdot}LiCl$ (**2j′**)		**5aj**	87	85
10	**4a**	$(NC)C_8H_{16}ZnBr{\cdot}LiCl$ (**2k′**)		**5ak**	80	86

[a] Reactions were carried out with aldehydes **4** (0.42 M), **2′** (2.4 equiv), $[Ti(OiPr)_4]$ (7.2 equiv), and **3d** (5 mol %) at 0 °C for 3 h in CH_2Cl_2. [b] Pip = piperidin-1-yl.

An exception was 3-methoxypropyl derivative **2i′**, for which a non-enantioselective reaction was observed (entry 8). It is probable that a background racemic reaction was promoted by an intramolecular coordination of the zinc atom of **2i′** by the neighboring methoxy group. Zinc reagents **2j** and **2k′** bearing a remote tertiary amide and cyano group, respectively, could be used in the present reaction (entries 9 and 10).[11] The corresponding functionalized secondary alcohols were obtained in high yields and good enantioselectivities.

In a relevant enantioselective alkylation of aldehydes with diorganozincs (R_2Zn) in the presence of $[Ti(OiPr)_4]$, it has been proposed that $[RTi(OiPr)_3]$, formed in equilibrium at lower concentration, is an active alkylating agent.[12] By analogy, it is likely that alkylzinc bromides **2** react reversibly with $[Ti(OiPr)_4]$ to generate the alkyltitanium intermediates [Scheme 3, Eq. (5)], which undergo enantioselective addition to aldehydes by the catalysis of a **3d**-based titanium complex. In the absence of $MgBr_2$ additive, the rate of alkylation was slowed down at a relatively lower conversion, resulting in low product yield even after a longer reaction time (24 h; Table 1, entry 1). Although we have no experimental evidence, a possible interpretation for this phenomena is that zinc reagent **2** is consumed additionally by aggregation with (*i*PrO)ZnBr, produced from Equation (5) given in Scheme 3, to form dinuclear zinc complex **6** [Eq. (6)]. In the presence of $MgBr_2$, zinc reagent **2** might form hetero-dinuclear complex **7** as suggested by a recent structural study [Eq. (7)].[13] The observed enhancement in the reaction rate, leading to the rapid conversion of aldehydes within 3 h, might be due to the generation of the alkyltitanium reagent at higher concentration in equilibrium [Scheme 3, Eq. (8)], in which co-produced (*i*PrO)ZnBr is complexed with $MgBr_2$.



Scheme 3. Formation of alkyltitanium species in equilibrium.

In summary, we have demonstrated that alkylzinc bromide reagents can be used in the enantioselective alkylation of aldehydes with a titanium(IV) catalyst derived from a H_8-BINOL derivative in the presence of $[Ti(OiPr)_4]$ and $MgBr_2$. At the low catalyst loading (5 mol%), a variety of functionalized alkylzinc reagents, prepared readily from the corresponding bromide precursors, underwent enantioselective addition to aromatic, heteroaromatic and α,β-unsaturated aldehydes to provide the corresponding functionalized alcohols in high enantioselectivity.

Experimental Section

(*R*)-1-(3-Methoxyphenyl)-4-triisopropylsilanyloxybutan-1-ol (5ef): Typical procedure for enantioselective alkylation of aldehyde by using functionalized zinc reagents **2′** prepared from bromide precursors; A two-layer mixture of $MgBr_2$ in Et_2O (1 mL) was prepared by the reaction of Mg turnings (15 mg, 0.6 mmol) with 1,2-dibromoethane (0.6 mmol, 52 μL). Freshly prepared $TIPSO(CH_2)_3ZnBr{\cdot}LiCl$ (**2f′**) (0.68 M in THF, 1.8 mL, 1.2 mmol)[6] and $[Ti(OiPr)_4]$ (1.07 mL, 3.6 mmol) were added to this mixture at room temperature. After being stirred for 10 min, solvents were removed quickly in vacuo (0.05 mmHg, 2 min) and the resulting oily residue was dissolved in CH_2Cl_2 (1.2 mL) to form clear solution. Then, ligand **3d** (13.1 mg, 0.025 mmol) and *m*-anisaldehyde (**4e**) (68 mg, 0.50 mmol) were added to this solution at 0 °C. After being stirred for 3 h at 0 °C, the reaction mixture was quenched by the addition of aqueous 1 N HCl and extracted with ethyl acetate (3×20 mL). The organic layers were washed successively with aqueous 5% $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (ethyl acetate/hexane 1:99) afforded 167 mg (95% yield, 91% *ee*) of **5ef**. $[\alpha]_D^{25}=21.4$ ($c=1.25$ in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=1.04$–1.15 (m, 21H), 1.62–1.77 (m, 2H), 1.80–1.94 (m, 2H), 2.53 (br, 1H), 3.73–3.78 (m, 2H), 3.82 (s, 3H), 4.71 (dd, $J=4.8$, 8.0 Hz, 1H), 6.80 (ddd, $J=0.8$, 2.6, 8.1 Hz, 1H), 6.94 (m, 2H), 7.24 ppm (t, $J=8.3$ Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta=$ 12.0, 18.0, 29.4, 36.8, 55.2, 63.6, 74.1, 111.2, 112.8, 118.2, 129.3, 146.8, 159.7 ppm; HRMS (FAB): *m/z* calcd for $C_{20}H_{36}O_3Si$: 352.2434; found: 352.2434. Enantioselectivity was determined by HPLC analysis (Chiralcel OD-H column, *i*PrOH/hexane = 2:98; flow rate: 1 mL min^{-1}, $t_R=17.8$ min (major *R* enantiomer); 19.7 min (minor *S* enantiomer). The absolute stereochemistry was assumed by analogy.

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Keywords: alkylation · asymmetric catalysis · asymmetric synthesis · organozinc reagents · titanium

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[10] For other additives (2.4 equiv), the following results were obtained under similar conditions: LiBr; 24% yield, 56% *ee*, $ZnBr_2$; no reaction, $Mg(OiPr)_2$; 32% yield and 61% *ee*.

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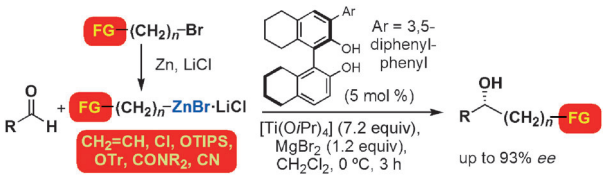

Functionalized alkylzinc halides can be employed in the enantioselective addition to aldehydes by using a titanium(IV) catalyst derived from a H_8-binaphthol derivative in the presence of $[Ti(OiPr)_4]$ and $MgBr_2$. A range of functionalities, including olefin, chlorine atoms, protected alcohols, amides, and cyano groups, are tolerated in the present reaction, providing the corresponding functionalized alcohols in high yields and enantioselectivities (see scheme).

Asymmetric Catalysis

