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Catalytic Asymmetric Aryl Transfer Reactions to Aldehydes with Grignard Reagents as the Aryl Source

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A straightforward synthesis of enantiomerically enriched diarylmethanols involves the addition of an aryl–metal reagent to an aromatic aldehyde, through which a carbon–carbon bond and a stereogenic center are produced simultaneously. Because these alcohols are important constituents and precursors of biologically active compounds, catalytic asymmetric arylation has attracted much attention in recent years.[1] Seebach and Weber reported the first catalytic phenyl transfer reaction with $[Ti(OiPr)_3Ph]$, prepared by transmetalation of PhLi with $[TiCl(OiPr)_3]$ and used after removal of LiCl by centrifugation.[2] Since the works of direct Ph_2Zn addition by Fu et al.,[3] various catalysts have been developed for enantioselective addition of aryl–zinc reagents.[4–6] The scope of aryl groups that can be introduced has been extended significantly by the use of arylboronic acids and their derivatives, either through in situ transformation to aryl–zinc reagents with diethylzinc[7] or through direct catalysis by chiral rhodium complexes.[8] Most recently, Walsh and Kim[9] reported a one-pot method for the generation of aryl–zinc reagents by the reaction of the corresponding aryl bromide with *n*BuLi followed by transmetalation with $ZnCl_2$ and precipitation of the resulting LiCl with tetraethylethylene diamine, and their subsequent catalytic asymmetric addition to aldehydes.[10]

Herein, we report a practical and efficient method for asymmetric arylation of aldehydes by using aryl Grignard reagents in combination with titanium tetraisopropoxide. A variety of diarylmethanols can be obtained in high enantioselectivity by the reaction of aldehydes with the Grignard reagents (1.2 equiv) in the presence of 3-(3,5-diphenylphenyl)-H_8-BINOL (**2**; 2 mol%) and titanium tetraisopropoxide (3 equiv).

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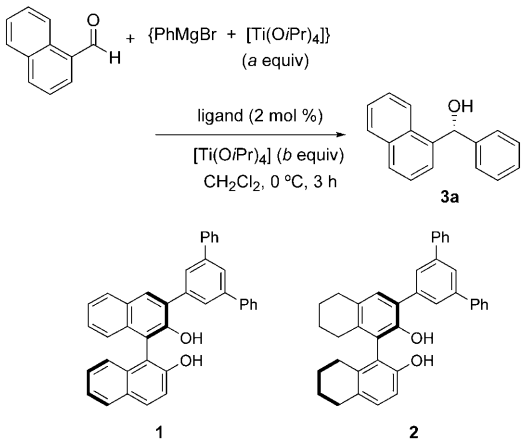
A recent report from this laboratory[11] showed that Grignard reagents can be used in the asymmetric alkylation of aldehydes by using a titanium(IV) catalyst derived from 3-(3,5-diphenylphenyl)-BINOL (**1**) in the presence of excess titanium tetraisopropoxide.[12,13] The reaction protocol involves the slow addition of a mixture of an alkyl Grignard reagent (2.2 equiv) and titanium tetraisopropoxide (4.4 equiv) to a solution of an aldehyde, ligand **1** (2 mol%), and titanium tetraisopropoxide (1.4 equiv) in CH_2Cl_2 at 0°C. In contrast to the high enanatioselectivity obtained in the

Table 1. Asymmetric phenyl transfer reaction of 1-naphthaldehyde using PhMgBr.[a]

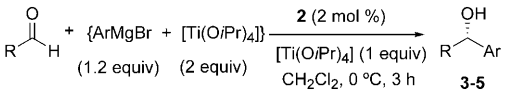


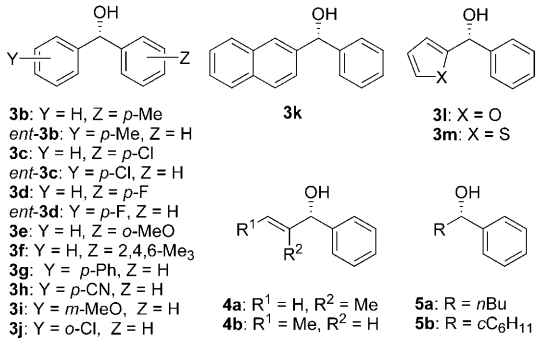
Entry	Ligand	PhMgBr [equiv]	$Ti(OiPr)_4$ (*a* equiv)	(*b* equiv)	Yield[b] [%]	*ee* [%]
1[c]	**1**	2.2	4.4	1.4	94	86
2	**2**	2.2	4.4	1.4	98	94
3	**2**	1.2	2.0	2.0	98	92
4	**2**	1.2	2.0	1.0	97	95
5	**2**	1.2	2.0	0.2	99	91
6	**2**	1.2	1.5	0.2	90	87

[a] Reactions were carried out by adding a solution of PhMgBr (3M in Et_2O) and titanium tetraisopropoxide (*a* equiv) in CH_2Cl_2 (8 mL) to a solution of 1-naphthaldehyde (1 mmol), ligand **1** or **2** (2 mol%), and titanium tetraisopropoxide (*b* equiv) in CH_2Cl_2 (4 mL), over 2 h at 0°C. The reaction mixture was stirred for a further hour before workup. [b] Yield of isolated product. [c] Reference [11].

reaction with alkyl Grignard reagents, inferior selectivity was observed in a phenyl transfer reaction using PhMgBr. Thus, under these conditions, the reaction of 1-naphthaldehyde with PhMgBr gave the corresponding diarylmethanol **3a** in 86% enantiomeric excess (*ee*) (Table 1, entry 1). We have recently reported that **2** showed higher enantioselectivity than **1** in the asymmetric alkylation of aldehydes with Et_2Zn.[14,15] Gratifyingly, the use of **2** as a chiral ligand under similar conditions significantly improved the enantioselectivity, affording **3a** in 94% *ee* and 98% yield (Table 1, entry 2). Further examination of the reaction conditions revealed that phenyl transfer could be carried out with an almost stoichiometric amount of the Grignard reagent (1.2 equiv) and with a total of three equivalents of titanium tetraisopropoxide (Table 1, entry 4). High product yield (97%) and high enantioselectivity (95% *ee*) were obtained under these optimized conditions. Enantioselectivity was decreased by further reduction of the amount of titanium tetraisopropoxide (Table 1, entries 5 and 6).

Table 2. Catalytic asymmetric arylation of aldehydes with Grignard reagents.[a]





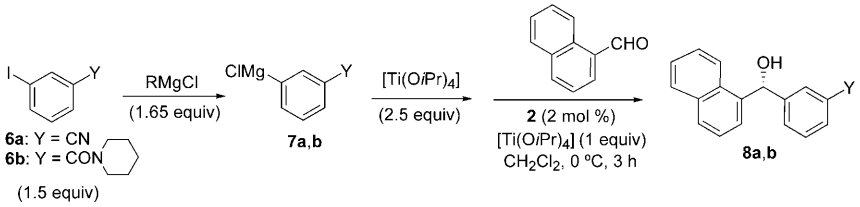
Entry	Aldehyde	ArM[b]	Product	Yield[c] [%]	*ee* [%]
1	PhCHO	*p*-MeC_6H_4MgBr	**3b**	99	91
2	PhCHO	*p*-ClC_6H_4MgBr	**3c**	95	91
3	PhCHO	*p*-FC_6H_4MgBr	**3d**	94	97
4	PhCHO	*o*-$MeOC_6H_4MgBr$	**3e**	66	9
5	PhCHO	2,4,6-$Me_3C_6H_2MgBr$	**3f**	89	96
6	*p*-MeC_6H_4CHO	PhMgBr	*ent*-**3b**	93	90
7	*p*-ClC_6H_4CHO	PhMgBr	*ent*-**3c**	96	94
8	*p*-FC_6H_4CHO	PhMgBr	*ent*-**3d**	97	95
9	*p*-PhC_6H_4CHO	PhMgBr	**3g**	99	91
10	*p*-NCC_6H_4CHO	PhMgBr	**3h**	96	92
11	*m*-$MeOC_6H_4CHO$	PhMgBr	**3i**	90	95
12	*o*-ClC_6H_4CHO	PhMgBr	**3j**	94	90
13	2-naphthylCHO	PhMgBr	**3k**	96	91
14	1-naphthylCHO	PhMgBr	**3a**	97	95
15	1-naphthylCHO	PhLi	**3a**	95	50
16[d]	1-naphthylCHO	PhLi	**3a**	85	95
17	2-furylCHO	PhMgBr	**3l**	83	89
18	2-thienylCHO	PhMgBr	**3m**	85	90
19	CH_2=C(Me)CHO	PhMgBr	**4a**	87	97
20	MeCH=CHCHO	PhMgBr	**4b**	78	86
21	BuCHO	PhMgBr	**5a**	88	88
22	*c*-$C_6H_{11}CHO$	PhMgBr	**5b**	86	80

[a] Reactions were carried out on a 1 mmol scale with **2** (2 mol%) according to the procedure described in the Experimental Section. [b] Commercial solution of the Grignard reagents in Et_2O (1.6–3 M) and PhLi in cyclohexane and Et_2O (0.98 M) were used. [c] Yield of isolated product. [d] PhLi (1.2 equiv) was used after treatment with $MgBr_2$ (1.2 equiv) in Et_2O. See the Supporting Information for more information.

The results of the asymmetric arylation of a variety of aldehydes by using aryl Grignard reagents are summarized in Table 2. High enantioselectivities and yields were obtained in the reaction of benzaldehyde with substituted phenyl Grignard reagents, except for the *o*-methoxy derivative (Table 2, entries 1–5). Notably, excellent enantioselectivity was observed for sterically hindered 2,4,6-$Me_3C_6H_4MgBr$. As shown in Table 2, entries 6–14, the reaction of aromatic aldehydes with PhMgBr generally proceeded in an efficient manner. Slightly lower, yet still acceptable selectivity was obtained for heteroaromatic aldehydes (Table 2, entries 17 and 18). Although the use of PhLi, instead of PhMgBr, resulted in a significant reduction in enantioselectivity (Table 2, entry 15), the organolithium reagent could be employed after conversion into PhMgBr by treatment with $MgBr_2$ (Table 2, entry 16). Note that the reaction was carried out without removing concomitantly produced LiBr,[16] but was simply carried out by mixing PhLi (1.2 equiv) with $MgBr_2$ (1.2 equiv) and titanium tetraisopropoxide (2 equiv), to give **3a** in excellent enantioselectivity. Not only diarylmethanols, but also secondary allylic alcohols **4** and benzylic alcohols **5** could be synthesized enantioselectively by the reaction of α,β-unsaturated aldehydes and aliphatic aldehydes, respectively (Table 2, entries 19–22).

To expand the scope of the reaction, asymmetric transfer of functionalized aryl groups was examined.[17] Recently, Knochel and co-workers have developed a method for the preparation of functionalized Grignard reagents by a halogen–magnesium exchange reaction.[18] According to the reported protocol,[17b] a solution of 3-cyanophenylmagnesium chloride (**7a**) in THF was prepared by treating *m*-iodobenzonitrile (**6a**) with *i*PrMgCl (2 M in THF) at −40 °C, and was

Table 3. Catalytic asymmetric transfer of functionalized aryl groups with Grignard reagents.



Entry	Iodide	RMgCl	Product	Yield [%]	*ee* [%]
1	**6a**	*i*PrMgCl[a]	**8a**	82	61
2	**6a**	cC_5H_9MgCl[b]	**8a**	91	95
3	**6b**	cC_5H_9MgCl[b]	**8b**	76	93

[a] Solution in THF. [b] Solution in Et_2O.

used in the asymmetric arylation of 1-naphthaldehyde (Table 3). The reaction gave diarylmethanol **8a** in high yield but with low enantioselectivity (61% *ee*; Table 3, entry 1). In our previous study, the use of a Grignard reagent in THF resulted in reduced enantioselectivity in comparison with that in Et_2O.[11] Although preparation of the requsite Grignard reagent in Et_2O was unsuccessful with *i*PrMgCl (2 M in Et_2O), it could be prepared efficiently by the use of cC_5H_9MgCl (2 M in Et_2O).[19] Subsequent use in the asymmetric arylation reaction afforded **8a** with a selectivity of 95% *ee* in 91% yield (Table 3, entry 2). Under similar conditions, the reaction of 1-naphthaldehyde with 3-(piperidine-1-carbonyl)phenylmagnesium chloride (**7b**) gave the functionalized diarylmethanol **8b** in high enantioselectivity (Table 3, entry 3).

In summary, we have shown that Grignard reagents can be used in asymmetric arylation of aldehydes in the presence of the chiral titanium catalyst derived from **2** and titanium tetraisopropoxide. The reaction was accomplished within 3 h with a low catalyst loading (2 mol%) and with a slight excess (1.2 equiv) of Grignard reagents. The results show high enantioselectivities and product yields for various combinations of substrates and reagents, including those with functional groups. Work is in progress to investigate the full scope of the reaction.

Experimental Section

Typical procedure for asymmetric arylation with a Grignard reagent (3a; Table 1, entry 4): PhMgBr (0.40 mL, 1.2 mmol; 3 M in Et_2O) was added to a solution of titanium tetraisopropoxide (0.59 mL, 2.0 mmol) in dry CH_2Cl_2 (8 mL) at −78 °C under an argon atmosphere. After being stirred for 10 min at this temperature, the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a solution of **2** (10.5 mg, 0.020 mmol), 1-naphthaldehyde (0.156 g, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) in CH_2Cl_2 (4 mL) at 0 °C under an argon atmosphere. After being stirred for a further hour, the reaction mixture was quenched by the addition of a 1 M solution of HCl and extracted three times with ethyl acetate. The organic layers were washed successively with a 5% aqueous solution of $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo . Flash chromatography (silica gel, 2–20% ethyl acetate in hexane) of the residue gave **3a** as a colorless oil (0.226 g, 97%; 95% *ee*). The *ee* value was determined by HPLC analysis using a Chiralcel OD column (1.5 mL min^{-1}, 10% *i*PrOH in hexane); retention times: 26.8 min (major *R* enantiomer) and 11.4 min (minor *S* enantiomer). The absolute structure of the product was determined based on reported retention times.[8d]

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[19] *i*PrMgCl (2 M in Et_2O) underwent iodine–magnesium exchange reaction rapidly in diethyl ether at −20 °C. However, the resulting Grignard reagent was protonated competitively under these conditions, probably by the reaction with 2-iodopropane. The protonation was not observed when *c*C_5H_9MgCl (2 M in Et_2O) was used. For the use of (*c*C_5H_9)$_2$Mg for the exchange reaction, see reference [18b].

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