Catalytic Enantioselective Arylation of Aldehydes by Using Functionalized Grignard Reagents Generated from Aryl Bromides

Daisuke Itakura, Toshiro Harada*

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan
Fax +81(75)7247514; E-mail: harada@chem.kit.ac.jp

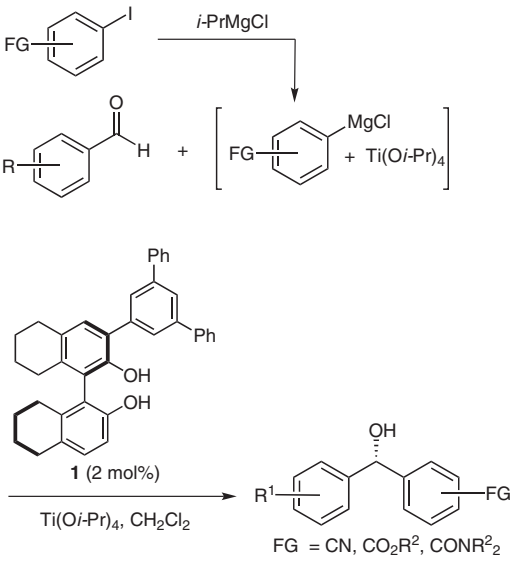
Received 21 September 2011

Abstract: An efficient catalytic method has been developed for the enantioselective synthesis of functionalized diarylmethanols starting from aryl bromides and aldehydes. In the presence of (*R*)-3-(3,5-diphenylphenyl)BINOL (2 mol%) and titanium tetraisopropoxide, functionalized aryl Grignard reagents (FGArMgCl; FG = 3-F_3C, 4-F_3C, 3-Br, 3-CN, 4-CN), prepared in situ by treatment of the bromides with *i*-PrMgCl·LiCl, undergo addition to aldehydes to give the corresponding functionalized diarylmethanols in high enantioselectivities.

Key words: aldehydes, arylation, asymmetric catalysis, magnesium, titanium

Catalytic methods allowing the enantioselective transfer of functionalized aryl groups to aromatic aldehydes has attracted considerable attention in recent years because the resulting functionalized diarylmethanols are in demand as precursors to many biologically active compounds.[1] Because of superior functional-group tolerance and wide commercial availability, arylboronic acids and their derivatives are most often employed as nucleophilic reagents in this transformation directly through chiral transition-metal catalysis[2] or via transmetalation to organozinc derivatives.[3] A variety of functionalized arylzinc halides are commercially available. Catalytic enantioselective aldehyde arylation has also been developed by using the functionalized arylzinc reagents in the presence of Me_3Al.[4]

Recently, we have reported a catalytic enantioselective arylation of aldehydes using Grignard reagents.[5] In the presence of a titanium catalyst derived from DPP-H_8-BINOL (**1**, 2 mol%), mixed titanium reagents derived from aryl Grignard reagents, and titanium tetraisopropoxide undergo addition to aldehydes to give secondary benzylic alcohols with high enantioselectivities.[5b,c] The pioneering work of Knochel and co-workers on the preparation of functionalized Grignard reagents made them available for the catalytic enantioselective addition to aldehydes.[6,7] Indeed, the catalytic aldehyde arylation reaction was successfully applied to the enantioselective synthesis of functionalized diarylmethanols by employing functionalized aryl Grignard reagents prepared in situ by iodine–magnesium exchange of the corresponding aryl iodides with *i*-PrMgCl (Scheme 1).[5c]



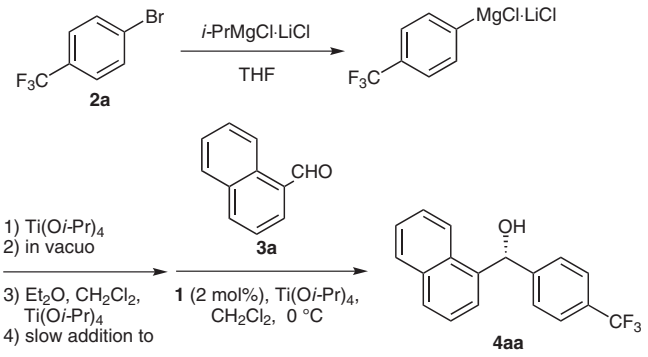
Scheme 1

Aryl bromides would be preferable precursors for the preparation of functionalized Grignard reagents in light of their stability, good availability, and low price in comparison to the corresponding iodides. Therefore, it is desirable to develop a method for the enantioselective synthesis of functionalized diarylmethanols starting from functionalized aryl bromides and aromatic aldehydes. Functionalized arylzinc bromides prepared in situ by $CoBr_2$-catalyzed oxidative addition of zinc metal to aryl bromides[8] were successfully employed in the enantioselective arylation.[4b] Unfortunately, however, good results were reported mostly for α-branched aliphatic aldehydes.

Although bromine–magnesium exchange of aryl bromides is a less efficient process with *i*-PrMgCl, it was recently demonstrated that the exchange reaction becomes feasible when using *i*-PrMgCl·LiCl with enhanced reactivity by virtue of LiCl complexation.[7b,c] In the present study, we were attracted to the possibility of using functionalized Grignard reagents prepared in situ from bromide precursors in the enantioselective arylation of aldehydes catalyzed by a titanium complex of DPP-H_8-BINOL (**1**). Herein, we report the results of our study to probe the scope and limitations of this approach.

We first examined the reaction of 4-bromo(trifluoromethyl)benzene (**2a**) and 1-naphthaldehyde (**3a**) by modifying our previous protocol developed for the enantioselective

SYNLETT 2011, No. 19, pp 2875–2879
Advanced online publication: 09.11.2011
DOI: 10.1055/s-0031-1289854; Art ID: U07011ST

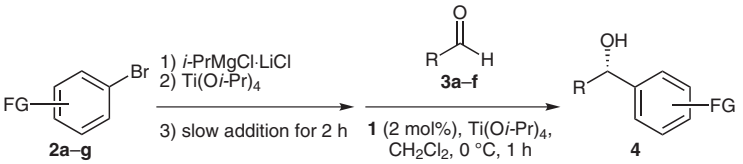


2a	i-PrMgCl·LiCl	yield	ee
1.5 equiv	1.7 equiv	50%	97%
2.0 equiv	2.2 equuiv	95%	96%

Scheme 2

arylation starting from aryl iodides (Scheme 2).[5c] Thus, 4-$F_3CC_6H_4MgCl{\cdot}LiCl$ was prepared by treatment of **2a** (1.5 equiv) with *i*-PrMgCl·LiCl (1.7 equiv) in THF at room temperature for three hours[7b] and then treated with titanium tetraisopropoxide (2.5 equiv). After the removal of THF in vacuo and dissolution in CH_2Cl_2 and Et_2O with additional titanium tetraisopropoxide (1.5 equiv; to replace its partial loss during evacuation of THF), the resulting mixed titanium reagent was slowly added within two hours to a CH_2Cl_2 solution of aldehyde **3a**, **1** (2 mol%), and titanium tetraisopropoxide (1 equiv) at 0 °C. Additional stirring for one hour afforded the corresponding diarylmethanol **4aa** in 97% ee but in moderate yield. When the amount of bromide **2a** and *i*-PrMgCl·LiCl was increased to 2 and 2.2 equivalents, respectively, the chemical yield of **4aa** was improved to 95% while maintaining high enantioselectivity.

Table 1 Enantioselective Arylation of Aldehydes **3a–f** by Using Bromides **2a–g** as Aryl Sources[a]



2a; FG = 4-CF_3 **3a**; R = 1-naphthyl
2b; FG = 3-CF_3 **3b**; R = 4-ClC_6H_4
2c; FG = 3-Br **3c**; R = 4-$(CN)C_6H_4$
2d; FG = 2-Br **3d**; R = Ph
2e; FG = 3-CN **3e**; R = 1-furyl
2f; FG = 4-CN **3f**; R = *c*-hexyl
2g; FG = 2-CN

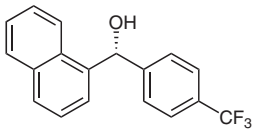
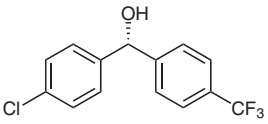
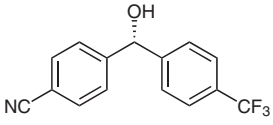
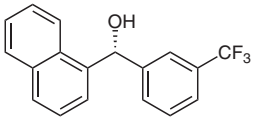
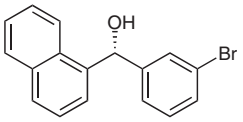
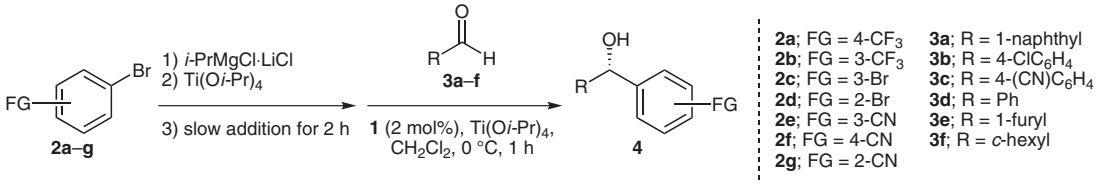
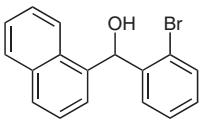
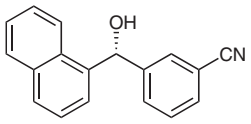
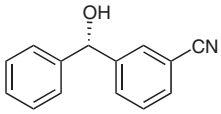
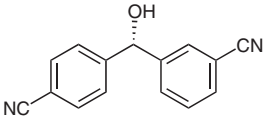
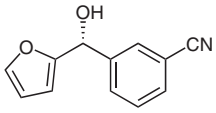
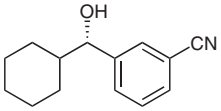
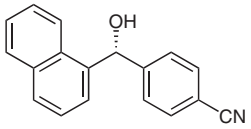
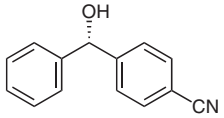
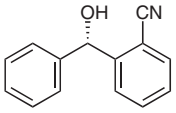
Entry	Bromide **2**	Aldehyde **3**	Product **4**	Yield (%)	ee (%)
1	**2a**	**3a**	 **4aa**	50	97
2[b]				95	96
3[b]	**2a**	**3b**	 **4ab**	85	86
4[b]	**2a**	**3c**	 **4ac**	94	99
5[b]	**2b**	**3a**	 **4ba**	86	87
6	**2c**	**3a**	 **4ca**	71	94

Table 1 Enantioselective Arylation of Aldehydes **3a–f** by Using Bromides **2a–g** as Aryl Sources[a] (continued)



Entry	Bromide **2**	Aldehyde **3**	Product **4**	Yield (%)	ee (%)
7	**2d**	**3a**	 **4da**	50	0
8	**2e**	**3a**	 **4ea**	72	90
9	**2e**	**3d**	 **4ed**	68	93
10	**2e**	**3c**	 **4ec**	94	95
11	**2e**	**3e**	 **4ee**	87	87
12	**2e**	**3f**	 **4ef**	54	63
13[b]	**2f**	**3a**	 **4fa**	80	84
14[b]	**2f**	**3d**	 **4fd**	61	86
15	**2g**	**3d**	 **4gd**	23	78

[a] Unless otherwise noted, reactions were carried out by using Grignard reagents generated by the reaction of bromides **2** (1.5 equiv) with *i*-PrMgCl·LiCl (1.7 equiv, 1.3 M in THF) at r.t. (for **2a**,**b**), at –15 °C for **2c**,**d**, and at 0 °C for **2e**–**g**.
[b] Bromides **2** (2 equiv) and *i*-PrMgCl·LiCl (2.2 equiv) were used in generation of Grignard reagents.

Under similar conditions, the reaction of *p*-substituted benzaldehydes **3b**,**c** with the mixed titanium reagent derived from **2a** provided the corresponding diarylmethanols in high yields and high enantioselectivities (Table 1, entries 3 and 4). Furthermore, the Grignard reagent prepared from *m*-bromo(trifluoromethyl)benzene (**2b**) also underwent enantioselective addition to aldehyde **3a** to give diarylmethanol **4ba** in an efficient manner (Table 1, entry 5). It has been reported that the preparation of (trifluoromethyl)phenyl Grignard reagents by magnesium insertion is dangerous owing to possible runaway reactions.[9,7d] The successful use of this Grignard reagent prepared by bromine–magnesium exchange is of synthetic value in light of the fact that the (trifluoromethyl)phenyl moiety is frequently encountered in pharmaceutical drugs.[10]

Dibromobenzenes undergo selective monoexchange with *i*-PrMgCl·LiCl to give bromophenyl Grignard reagents.[7] 3-Bromophenyl Grignard reagent prepared from 1,4-dibromobenzene (**2c**) could be successfully employed in enantioselective addition to 1-naphthaldehyde **3a** to give **4ca** in high enantioselectivity (Table 1, entry 6). On the other hand, the reaction starting from 1,2-dibromobenzene (**2d**) resulted in nonselective formation of the corresponding adduct **4da** (Table 1, entry 7).[11]

Starting from bromobenzonitriles **2e**,**f**, a variety of diarylmethanol possessing a cyano group could be synthesized in an enantiomerically enriched form. Thus, for example, starting from 3-cyano derivative **2e** (1.5 equiv) and aldehyde **3a**, functionalized diarylmethanol **4ea** was synthesized in 72% and in 90% ee (Table 1, entry 8). Under similar conditions, the mixed titanium reagent underwent enantioselective addition to aromatic aldehydes **3d**,**c** and furfural (**3e**, Table 1, entries 9–11). On the other hand, the reaction of aliphatic aldehyde **3f** resulted in the formation of the corresponding adduct **4ef** in only moderate yield and enantioselectivity (Table 1, entry 12). A mixed titanium reagent derived from 4-bromobenzonitrile (**2f**) also underwent enantioselective addition to aldehyde **3a**,**d** (Table 1, entries 13 and 14) while, on the other hand, that derived from 2-bromobenzonitrile (**2g**) exhibited a reduced product yield and enantioselectivity (Table 1, entry 15). Finally, the attempted reaction of **3a** with a mixed titanium reagent derived from *tert*-butyl 4-bromobenzoate resulted in the formation of complex mixtures of unidentified products.

In summary, we have developed a catatlytic enantioselective arylation of aldehydes using Grignard reagents generated in situ from functionalized aryl bromides. The method is applicable to aryl bromides bearing a CF_3, Br, and CN group at the *meta* and *para* positions, affording enantiomerically enriched functionalized diarylmethanols of synthetic importance at a low catalyst loading (2 mol%).

Typical Procedure for the Synthesis of (*S*)-3-[4-Cyanophenyl(hydroxy)methyl]benzonitrile (4ec, Table 1, Entry 10)

To a 1.3 M THF solution of *i*-PrMgCl·LiCl (1.27 mL, 1.65 mmol) at 0 °C, under an argon atmosphere, was added bromide **2e** (0.273 g, 1.5 mmol). After being stirred for 3 h, the resulting solution of *m*-cyanophenyl Grignard reagent was diluted with CH_2Cl_2 (4 mL) at –78 °C. After addition of Ti(O*i*-Pr)$_4$ (0.74 mL, 2.5 mmol), the solvents were removed under vacuum ($1.3\cdot10^{-4}$ bar, 0 °C), and the residue was dissolved with Et_2O (3.8 mL) and CH_2Cl_2 (10 mL). After addition of Ti(O*i*-Pr)$_4$ (0.44 mL, 1.5 mmol), the resulting mixture was slowly added over a period of 2 h by using a syringe pump to a CH_2Cl_2 (4 mL) solution of ligand **1** (10.5 mg, 0.020 mmol), aldehyde **3c** (0.131 g, 1.0 mmol), and Ti(O*i*-Pr)$_4$ (0.30 mL, 1.0 mmol) at 0 °C. After being stirred for an additional hour, the reaction mixture was quenched by the addition of aq 1 N HCl and extracted three times with EtOAc. The organic layers were washed successively with aq $NaHCO_3$ (5% soln) and with brine, dried (Na_2SO_4), and concentrated in vacuo. Flash chromatography (silica gel, 5–10% EtOAc in toluene) of the residue gave 0.219 g (94% yield) of **4ec**: $[\alpha]_D^{30}$ –9.8 (*c* 1.04, $CHCl_3$; 95% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.8 (1 H, br), 5.89 (1 H, s), 7.44–7.51 (3 H, m), 7.56–7.58 (2 H, m), 7.65 (2 H, d, *J* = 9.0 Hz). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 74.5, 111.8, 112.7, 118.4 (2 C), 127.1, 129.6, 130, 130.9, 131.6, 132.6, 144.2, 147.8. HRMS–FAB: *m/z* calcd for $C_{15}H_{11}N_2O$ [MH^+]: 235.00871; found: 235.0871. The ee value was determined by HPLC analysis using a Chiralpak AS-H column (1 mL/min, 1% *i*-PrOH in hexane); retention times: 14.5 min (major *S* enantiomer) and 11.7 min (minor *R* enantiomer).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by Grant-in-Aid for Scientific Research (No. 20550095) from Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan and by Kyoto Institute of Technology Research Fund.

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(11) The mixed titanium reagent of 2-$MeOC_6H_4MgBr$ and $Ti(O\textit{i}\text{-}Pr)_4$ also underwent nonenantioselective reaction to an aldehyde.[5c] Intramolecular coordination of the *ortho* substituents to the titanium center might be responsible for the poor selectivities.