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Catalytic Enantioselective Synthesis of Diarylmethanols from Aryl Bromides and Aldehydes by Using Organolithium Reagents

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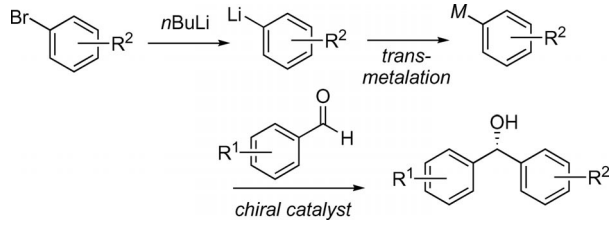
A general method has been developed for preparing enantioenriched secondary alcohols by starting from aryl bromides and aldehydes. Aryl bromides were first treated with BuLi, and the resulting aryllithium reagents were mixed with titanium tetraisopropoxide and magnesium bromide. The reaction of aldehydes with the resulting mixed titanium reagents, in the presence of 3-(3,5-diphenylphenyl)-H_8-BINOL (2 mol-%) and titanium tetraisopropoxide, furnished the corresponding alcohols in high enantioselectivities and in high yields.

Introduction

Enantiomerically enriched diarylmethanols are important constituents and precursors of biologically active compounds. In recent years, the catalytic enantioselective arylation of aldehydes has attracted great attention as a straightforward method for the synthesis of these alcohols by which a carbon–carbon bond and a stereogenic center are produced simultaneously.[1] Several efficient catalytic arylation methods have been developed by using phenyllithium,[2] diphenylzinc,[3] arylboronic acids,[4,5] arylaluminium reagents,[6] arylzinc bromides,[7] and aryl Grignard reagents,[8,9] as aryl sources. However, additional reaction steps are required to prepare these arylation reagents. Some of them are commercially available but often quite expensive. The enantioselective arylation of aldehydes by employing aryllithium reagents generated in situ from common aryl bromides by Br/Li exchange serves as a more practical and versatile method (Scheme 1). Recently, Walsh and coworkers clearly demonstrated the utility and practicality of the approach by developing a chiral amino alcohol catalyzed highly enantioselective, one-pot arylation method in which aryl butylzinc reagents [ArZn(*n*Bu)] were generated from aryl bromides (ArBr) by successive treatment with *n*BuLi, $ZnCl_2$, and additional *n*BuLi.[10,11]

Herein, we wish to report an alternative method in which in situ generated aryllithium reagents are used after mixing with titanium tetraisopropoxide and magnesium bromide. Starting from aryl bromides, a variety of diarylmethanols as well as other benzylic alcohols can be obtained in high enantioselectivity by the reaction of aldehydes with the mixed titanium reagents in the presence of DPP-H_8-BINOL **1** (2 mol-%) and titanium tetraisopropoxide.



Scheme 1. Catalytic enantioselective arylation of aldehydes by using aryl bromides as aryl source.

Results and Discussion

A recent report from this laboratory showed that Grignard reagents can be used in the enantioselective arylation of aldehydes by using a titanium(IV) catalyst derived from DPP-H_8-BINOL **1** (2 mol-%) in the presence of excess titanium tetraisopropoxide [Equation (1)].[8b,8c] The reaction protocol involves the slow addition of a ca. 1:2 mixture of an aryl Grignard reagent (Et_2O solution) and titanium tetraisopropoxide to a solution of an aldehyde, ligand **1** (2 mol-%), and titanium tetraisopropoxide in CH_2Cl_2 at 0 °C. When a mixed titanium reagent derived from PhLi (cyclohexane/Et_2O solution) was used in the reaction of 1-naphthaldehyde under these conditions, the corresponding phenylation product was obtained only in 50% *ee*. However, a high selectivity (95% *ee*) was obtained by using PhLi after treatment with magnesium bromide.[8b,8c] The order of mixing was not critical; treatment of PhLi first with titanium tetraisopropoxide and then with magnesium bromide also afforded the product in 94% *ee* and in 94% yield.

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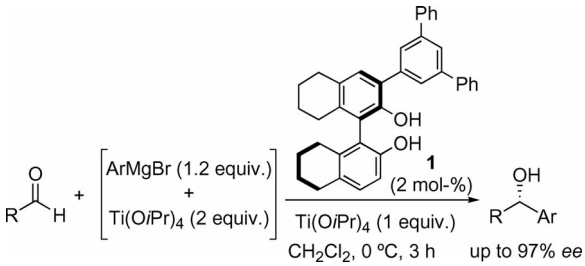
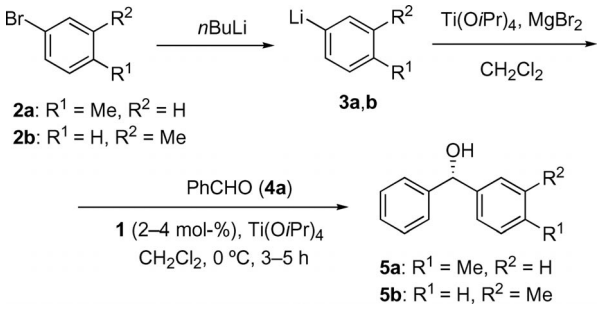


(1)

Based on these results, we examined the arylation of benzaldehyde (**4a**) starting with *p*-bromotoluene (**2a**) [Equation (2)]. Treatment of **2a** (1.5 equiv.) with *n*BuLi (1.5 equiv.) in THF at –78 °C afforded aryllithium **3a**. To avoid an undesirable alkylation of **3a** with concurrently produced butyl bromide, it was mixed successively with titanium tetraisopropoxide (2.5 equiv.) in CH_2Cl_2 and magnesium bromide (1.5 equiv.) in Et_2O at –78 °C. Addition of the resulting mixed titanium reagent to a CH_2Cl_2 solution of **4a**, ligand **1** (2 mol-%), and titanium tetraisopropoxide (1 equiv.) at 0 °C for 2 h followed by additional 1 h of stirring afforded diarylmethanol **5a** in high yield but with a moderate enantioselectivity (75% *ee*) (Table 1, Entry 1). In our previous study, the use of Grignard reagents in Et_2O was necessary to obtain a high enantioselectivity; the use of the reagents in THF caused a significant decrease in enantioselectivity.[8] To circumvent the detrimental effect of THF, the solvent system was modified. Thus, when the mixed titanium reagent derived from aryllithium **3a** was employed after the removal of THF in vacuo and dissolution in CH_2Cl_2 and Et_2O with additional titanium tetraisopropoxide (to replace its partial loss in evacuation of THF), **5a** was obtained with increased enantioselectivity (92% *ee*) and in high yield (Entry 2). Application of this protocol to the reaction of *m*-bromotoluene (**2b**) and **4a** resulted in a slightly lower selectivity (86% *ee*) of the corresponding diarylmethanol **5b** (Entry 3). However, a higher selectivity (up to 92% *ee*) could be attained either by using 4 mol-% of ligand **1** (Entry 4) or by elongation of the time for the slow addition (Entries 5 and 6).



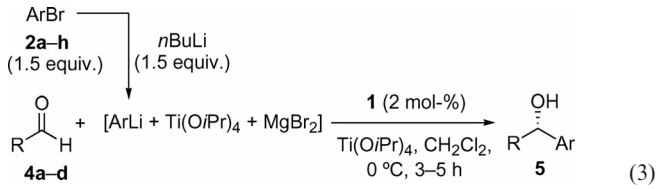
(2)

Under the optimized conditions with 2 mol-% of ligand **1** (i.e., Entry 2 or 6 in Table 1), reactions were carried out for various combinations of aryl bromides **2a**–**h** and aldehydes **4a**–**d** [Equation (3), Table 2]. Not only tolyl bromides **2a**,**b** but also phenyl bromides, bearing a halogen atom (**2c**,**d**) or a methoxy group (**2e**), or 2-naphthyl bromide (**2h**) could be employed in the arylation of **4a** to give the corresponding diarylmethanols **5a**–**e**,**h** in high yields and high enantioselectivities (86–95% *ee*) (Entries 1–5 and 8). Although aryllithium intermediates bearing a cyano group are thermally unstable, mixed titanium reagents derived from bromobenzonitriles **2f**,**g** were stable at room temperature during the slow addition, successfully employed in the reaction of **4a** to furnish functionalized diarylmethanols **5f**,**g** with high enantioselectivity (Entries 6 and 7). The reaction using *n*BuLi in hexane afforded butylation product **5i** with relatively high selectivity (Entry 9). The mixed titanium reagent prepared from **2c** also underwent a highly enantioselective addition to α,β-unsaturated aldehyde **4c** and aliphatic aldehyde **4d** to give allylic alcohol **5k** (96% *ee*) and benzylic alcohol **5l** (96% *ee*), respectively (Entries 11 and 12), whereas a lower selectivity was observed in the reaction of the heterocyclic aldehyde **4b** (Entry 10).

Table 1. Enantioselective arylation of benzaldehyde starting with aryl bromides **2a**,**b**.[a]

Entry	Aryl bromide	**1** [mol-%]	Time [h][b]	Product	Yield [%]	*ee* [%]
1[c]	**2a**	2	2	**5a**	88	75
2	**2a**	2	2	**5a**	95	92
3	**2b**	2	2	**5b**	78	86
4	**2b**	4	2	**5b**	77	90
5	**2b**	2	3	**5b**	93	88
6	**2b**	2	4	**5b**	87	92

[a] Unless otherwise noted, reactions were carried out by treatment of **2a**,**b** (1.5 equiv.) with *n*BuLi (1.5 equiv.) in THF at –78 °C followed by mixing the resulting aryllithium reagents **3** successively with $Ti(OiPr)_4$ (2.5 equiv.) and $MgBr_2$ (1.5 equiv.) and subsequent removal of solvents in vacuo. After dissolution in CH_2Cl_2 and Et_2O with additional $Ti(OiPr)_4$ (1.5 equiv.), the resulting mixed titanium reagents were slowly added to a CH_2Cl_2 solution of benzaldehyde (1 mmol), **1**, and $Ti(OiPr)_4$ (1.5 equiv.). The reaction mixture was stirred further for 1 h before workup. [b] Time for slow addition. [c] The reaction was carried out without removal of THF in vacuo.

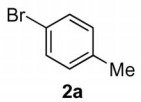
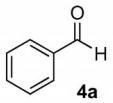
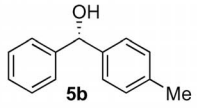
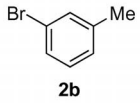
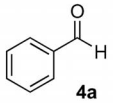
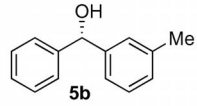
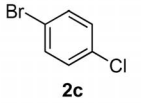
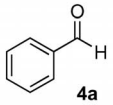
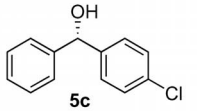
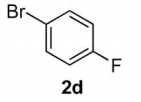
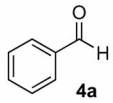
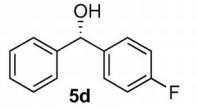
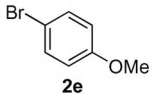
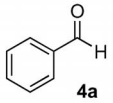
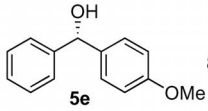
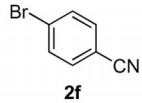
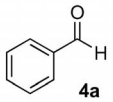
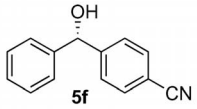
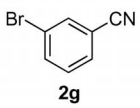
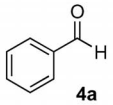
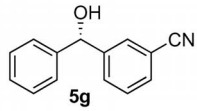
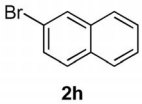
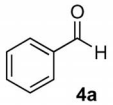
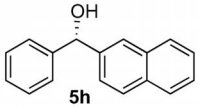
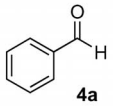
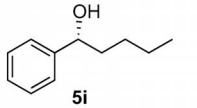
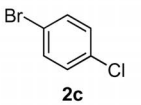
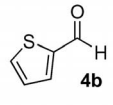
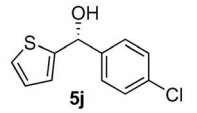
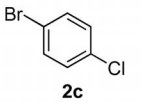
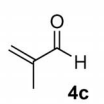
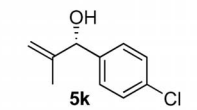
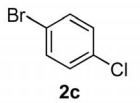
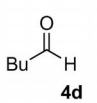
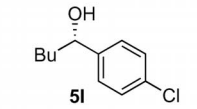


(3)

Conclusions

We have developed a versatile method for the enantioselective arylation of aldehydes starting from readily available aryl bromides. Mixed titanium reagents, derived from aryllithium intermediates, titanium tetraisopropoxide, and magnesium bromide, underwent highly enantioselective addition to aldehydes. The reactions could be carried out at

Table 2. Enantioselective arylation of aldehydes **4a**–**d** by using bromides **2a**–**h** as aryl sources.[a]

Entry	Bromoarene	Aldehyde	Product	Yield (*ee*)[b]
1	 **2a**	 **4a**	 **5b**	94% (92%)
2	 **2b**	 **4a**	 **5b**	87% (92%)
3	 **2c**	 **4a**	 **5c**	80% (95%)
4[c]	 **2d**	 **4a**	 **5d**	82% (93%)
5[c]	 **2e**	 **4a**	 **5e**	89% (89%)
6[c]	 **2f**	 **4a**	 **5f**	62% (88%)
7[c]	 **2g**	 **4a**	 **5g**	60% (89%)
8	 **2h**	 **4a**	 **5h**	81% (86%)
9	BuLi	 **4a**	 **5i**	89% (86%)
10	 **2c**	 **4b**	 **5j**	91% (82%)
11	 **2c**	 **4c**	 **5k**	74% (96%)
12	 **2c**	 **4d**	 **5l**	74% (96%)

[a] Unless otherwise noted, reactions were carried under the conditions similar to those of Entry 2 in Table 1. [b] Determined by chiral-stationary-phase HPLC analysis. [c] The mixed titanium reagents were added over a period of 4 h (Entry 6 in Table 1).

a low catalyst loading (2 mol-%). As demonstrated by the successful use of *m*- and *p*-bromobenzonitrile, a good functional-group tolerance is an additional advantage of the present method.

Experimental Section

(*S*)-Phenyl(*p*-tolyl)methanol (5a). Typical Procedure for the Enantioselective Arylation of Aldehydes by Using Aryl Bromides as Aryl Source: Table 1, Entry 2. To a solution of *p*-bromotoluene (**2a**) (0.257 g, 1.5 mmol) in THF (3 mL) at –78 °C under argon was added *n*BuLi (1.6 M in hexane, 0.955 mL, 1.5 mmol). The resulting solution was stirred at this temperature for 0.5 h. To the resulting solution of *p*-tolyllithium was then added titanium tetraisopropoxide (0.74 mL, 2.5 mmol). The resulting mixed titanium reagent was added with a syringe to a two-layer mixture of $MgBr_2$ in Et_2O (2.5 mL), which was prepared by the reaction of magnesium turnings (36.5 mg, 1.5 mmol) with 1,2-dibromoethane (1.5 mmol, 0.13 mL) at 0 °C under argon. After stirring for 30 min, the solvents were removed under vacuum (0.1 Torr, room temp., 10 min), and the residue was dissolved with Et_2O (3.8 mL) and CH_2Cl_2 (10 mL). After addition of titanium tetraisopropoxide (0.44 mL, 1.5 mmol), the resulting mixture was slowly added by using a syringe pump to a CH_2Cl_2 (4 mL) solution of ligand **1** (10.5 mg, 0.020 mmol), benzaldehyde (**4a**) (0.106 mg, 1.0 mmol), and titanium tetraisopropoxide (0.30 mL, 1.0 mmol) at 0 °C under argon over a period of 2 h. After additional stirring for 1 h, the reaction was quenched by the addition of aqueous 1 N HCl and the mixture extracted three times with ethyl acetate. The combined organic layers were washed successively with aqueous 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (silica gel; 1% ethyl acetate in toluene) of the residue gave 0.186 g (94% yield) of **5a**[12] (92% *ee*): HPLC analysis: Chiralcel OD column, 0.5 mL/min, 5% *i*PrOH in hexane; retention times: 30.9 min [major (*S*) enantiomer], 34.6 min [minor (*R*) enantiomer]. This data is in agreement with published values.[12]

Supporting Information (see footnote on the first page of this article): ^1H NMR spectra and determination of the *ee* values of arylation products **5**.

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