

A Highly Enantioselective and Catalytic Aryl Transfer Reaction Using Mixed Triarylbismuthane and Dialkylzinc Reagents

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Highly enantioselective and catalytic aryl transfer reactions to aromatic aldehydes by using mixed triarylbismuthane and dimethylzinc reagents were studied. In the presence of a chiral β -amino alcohol catalyst, chiral diarylmethanols with up to 97 % ee were obtained.

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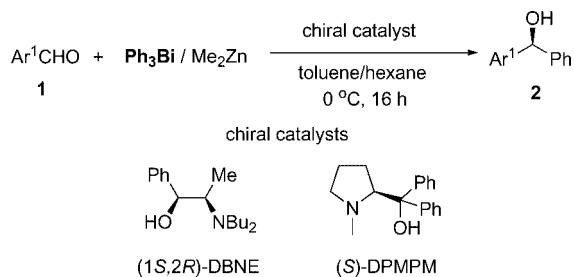
Introduction

Catalytic and asymmetric syntheses are some of the most important tools in modern synthetic organic chemistry.^[1] Among them, the addition of organozinc reagents to carbonyl compounds provides a convenient and promising way to obtain chiral secondary alcohols.^[2] Recently, highly enantioselective phenyl transfer reactions with the use of diphenylzinc^[3,4] and diphenylzinc/diethylzinc^[5,6] were reported. Bolm et al. also reported an aryl transfer reaction by using diethylzinc and aryl boronic acids.^[7,8] Meanwhile, the chemistry of organobismuth reagents is an attractive interest.^[9] Bismuth is the heaviest element of group 15 and, similar to nitrogen and phosphorus, has a pair of electrons in its highest s orbital. Therefore, organobismuth reagents act not only as organometallic reagents but also as basic reagents.^[9a] Control of this reactivity is still a challenge. We report herein a highly enantioselective and catalytic aryl transfer reaction to aldehydes by using mixed triarylbismuthane/dimethylzinc reagents. The enantiomeric excess of the alcohols obtained is up to 97%.

Results and Discussion

The use of a mixed triphenylbismuthane/dimethylzinc reagent in a phenyl transfer reaction was examined (Scheme 1). Triphenylbismuthane (Ph_3Bi) and dimethylzinc (Me_2Zn) were mixed in toluene/hexane, and the mixture was heated at reflux for 10 h. The resulting mixed $\text{Ph}_3\text{Bi}/$

Me_2Zn reagent was treated with various aldehydes in the presence of chiral β -amino alcohol catalysts at 0 °C. As shown in Table 1, the reaction of *p*-tolualdehyde (**1a**) and $\text{Ph}_3\text{Bi}/\text{Me}_2\text{Zn}$ in the presence of (1*S*,2*R*)-*N,N*-dibutyl-norephedrine (DBNE)^[10] gave chiral diaryl methanol **2a** with 93% ee in 96% yield. Me_2Zn seems to be a suitable dialkylzinc reagent in this case. When diethylzinc (Et_2Zn) was used instead of Me_2Zn , a considerable amount of the alkylated product, 1-phenylpropanol, was produced as a by-product. In the absence of dialkylzinc reagents, no reaction occurred. In the conditions examined, the addition of hexane increased the yield of the product. A mixed $\text{Ph}_3\text{BiCl}_2/\text{Et}_2\text{Zn}$ reagent gave diarylmethanol **2a** as the sole product. However, a low level of enantioselectivity (<20% ee) was induced. The use of (*S*)-diphenyl(1-pyrrolidin-2-yl)methanol (DPMPM)^[11] as a chiral catalyst increased the ee value of **2a** to 97% (Table 1, Entry 3). The phenyl transfer reaction to 4-chloro- and 4-bromobenzaldehyde (**1b** and **1c**) gave diarylmethanols **2b** and **2c** in 96 and 97% ee, respectively (Table 1, Entries 4 and 5). Addition to the 2-, 3-, and 4-anisaldehydes (**1d–f**) also proceeded in good yields (93–99%) with high enantioselectivities (84–97% ee) (Table 1, Entries 7–9).



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Scheme 1. An enantioselective phenyl transfer reaction to aldehyde by using a mixed $\text{Ph}_3\text{Bi}/\text{Me}_2\text{Zn}$ reagent.

Table 1. An enantioselective phenyl transfer reaction to aldehyde **1** by using a mixed Ph₃Bi/Me₂Zn reagent.^[a]

Entry	Aldehyde 1		Catalyst	Diarylmethanol 2 ^[b]			
	Ar ¹			Yield [%]	<i>ee</i> [%]	Config.	
1	4-CH ₃ C ₆ H ₄	(1a)	(1 <i>S</i> ,2 <i>R</i>)-DBNE	2a	96	93	<i>S</i>
2 ^[c]					91	90	<i>S</i>
3			(<i>S</i>)-DPMPM		88	97	<i>S</i>
4	4-ClC ₆ H ₄	(1b)		2b	96	96	<i>S</i>
5	4-BrC ₆ H ₄	(1c)		2c	76	97	<i>S</i>
6			(<i>R</i>)-DPMPM		75	97	<i>R</i>
7	2-CH ₃ OC ₆ H ₄	(1d)	(<i>S</i>)-DPMPM	2d	99	84	<i>S</i>
8	3-CH ₃ OC ₆ H ₄	(1e)		2e	93	96	<i>S</i>
9	4-CH ₃ OC ₆ H ₄	(1f)		2f	94	97	<i>S</i>

[a] The reaction were carried out in toluene/hexane, 1:7 at 0 °C. Molar ratio of catalyst/Ph₃Bi/Me₂Zn/**1** = 0.10:2.4:7.2:1.0. For detailed conditions, see Experimental Section. [b] Isolated yield. The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase. The configurations of **2a–c,e–f** were determined by comparison of the sign of the optical rotation value with that of the known compounds. Configuration of **2d** was determined by comparison of the retention time in HPLC analysis with reported values. [c] Molar ratio of catalyst/Ph₃Bi/Me₂Zn/**1** = 0.10:1.2:3.6:1.0.

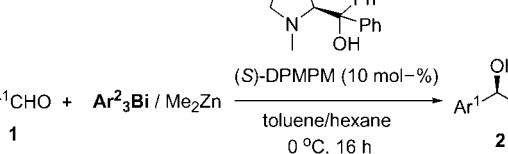
Next, the aryl transfer reaction to aldehydes by using mixed triarylbismuthane and Me₂Zn reagents was examined (Table 2). The addition of the *p*-tolyl group to the aldehydes was achieved with the use of a mixed tris(4-methylphenyl)bismuthane^[12]/Me₂Zn reagent. When the addition to benzaldehyde (**1g**) was examined, diarylmethanol **2a** was obtained in 89% yield and 97% *ee* (Table 2, Entry 1). The addition to 4-bromo- and 4-chlorobenzaldehyde produces corresponding alcohols **2g** and **2h** with 97% *ee* (Table 2, Entries 2 and 3). The reaction with 2-, 3-, and 4-anisaldehyde gave alcohols **2i–k** with 90, 96, and 96% *ee*, respectively (Table 2, Entries 4–6). The tris(4-fluorophenyl)bismuthane/Me₂Zn reagent was found to be a source of the 4-fluorophenyl group (Table 2, Entries 7–9). Corresponding di-

arylmethanols **2l–n** were obtained in 75–92% yield and 83–94% *ee*.

In these aryl transfer reactions using mixed triarylbismuthane and Me₂Zn reagents, the active species is still unknown. Because of the different reactivity of a mixed Ph₃BiCl₂/Et₂Zn reagent and the reaction conditions used, the formation of hypervalent bismuth is highly unlikely. One of the plausible species is the transmetalation product, an arylalkylzinc species, and/or a diarylzinc species. However, the reported transmetalation-type reactions, including the formation of a heterodinuclear complex of triorganobismuth, are few. The reaction with palladium^[13] and rhodium^[14] complexes, copper salts,^[15] aryllithium^[16] and alkylsodium^[17] reagents was reported. To the best of our knowledge, no reports exist of a metal exchange reaction between dialkylzinc and organobismuth reagents. Formation of *ate* complexes are also possible.^[16b] Thus, this report shows the nucleophilic use of the organo group in triorganobismuthane(III).^[18]

In addition, we also tried to use a mixed phenylbismuth dicarboxylate (**3**)^[19]/Et₂Zn reagent (Scheme 2). In the presence of 30 mol-% of (*R*)-DPMPM, the phenyl transfer reaction to 4-bromobenzaldehyde (**1c**) gave diarylmethanol **2c** with 92% *ee* in 73% yield.

Table 2. An enantioselective aryl transfer reaction to aldehyde **1** using a mixed Ar₃Bi/Me₂Zn reagent.



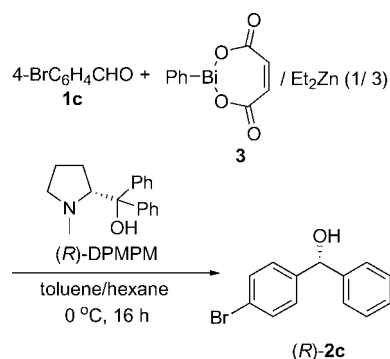
Reaction scheme showing the asymmetric addition of an aldehyde (**1**) to a diarylbismuthane (Ar^2_3Bi) catalyzed by (S)-DPMPM (10 mol-%) in toluene/hexane at 0 °C for 16 h, yielding a diarylmethanol (**2**).

Entry	Aldehyde 1		Ar^2	Diarylmethanol 2 ^[a]		
	Ar^1			Yield [%]	ee [%]	Config.

1	C_6H_5	(1g)	4- $\text{CH}_3\text{C}_6\text{H}_4$	2a	89	97	<i>R</i>
2	4- ClC_6H_4	(1b)		2g	88	97	<i>S</i>
3	4- BrC_6H_4	(1c)		2h	93	97	<i>S</i>
4	2- $\text{CH}_3\text{OC}_6\text{H}_4$	(1d)		2i	89	90	<i>S</i>
5	3- $\text{CH}_3\text{OC}_6\text{H}_4$	(1e)		2j	89	96	<i>S</i>
6	4- $\text{CH}_3\text{OC}_6\text{H}_4$	(1f)		2k	91	96	<i>S</i>

7	C_6H_5	(1g)	4- FC_6H_4	2l	92	94	<i>R</i>
8	4- ClC_6H_4	(1b)		2m	75	83	<i>S</i>
9	4- BrC_6H_4	(1c)		2n	86	86	<i>S</i>

[a] Isolated yield. The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase. The configurations of **2a,g,k–l** were determined by comparison of the sign of the optical rotation value with that of the known compounds. The configurations of **2h–j,m,n** were tentatively assigned by the configuration of the catalyst.^[11]



Scheme 2.

Conclusions

We developed mixed triarylbi-muthanes and Me_2Zn reagents for the aryl transfer reaction to aromatic aldehydes in the presence of chiral β -amino alcohol catalysts to give highly enantiomerically enriched diarylmethanols in good yield.

Experimental Section

General Procedure for the Asymmetric Aryl Transfer Reaction to Aldehydes with Triarylbi-muthane/ Me_2Zn Reagents: Under a nitrogen atmosphere, triarylbi-muthane (2.4 mmol) was dissolved in dry toluene (7 mL). Dimethylzinc (1.0 M in hexane, 7.2 mmol) was added to the solution, and the reaction mixture was heated at reflux for 10 h. After the mixture was cooled to 0 °C, a solution of the chiral catalyst (0.10 mmol) in toluene (1 mL) was added to the mixture. After 15 min of stirring, the aldehyde (1.00 mmol) was added to the mixture, and the mixture was stirred for 16 h at 0 °C. The reaction was quenched by the addition of hydrochloric acid (1 M, 10 mL). After the addition of saturated aqueous NaHCO_3 (15 mL), the mixture was filtered through celite and extracted with AcOEt. The extract was dried with Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by preparative silica gel TLC produced the optically active secondary alcohol. The *ee* value was determined by HPLC analysis on a column fitted with a chiral stationary phase (Chiralcel OD-H, OB-H, or Chiralpak AD-H).

Asymmetric Aryl Transfer Reaction to *p*-Bromobenzaldehyde (1c) with a Mixed (*Z*)-2-Phenyl-1,3,2-dioxabismepin-4,7-dione (3) and Me_2Zn Reagent: For details see Scheme 2. Under a nitrogen atmosphere, diethylzinc (1.0 M in hexane, 2.7 mmol) was added to the suspension of (*Z*)-2-phenyl-1,3,2-dioxabismepin-4,7-dione (3, 360 mg, 0.90 mmol) in toluene (2.7 mL). The mixture was heated at reflux for 6 h. After the mixture was cooled to 0 °C, a solution of (*R*)-DPMPM (24.1 mg, 0.0900 mmol) and aldehyde 1c (55.5 mg, 0.30 mmol) in toluene (2.7 mL) was added. The mixture was stirred for 14 h at 0 °C. The reaction was quenched by the addition of hydrochloric acid (1 M, 5 mL). After the addition of saturated aqueous NaHCO_3 (10 mL), the mixture was filtered through celite and extracted with AcOEt. The extract was dried with MgSO_4 and concentrated under reduced pressure. Purification of the residue by preparative silica gel TLC (benzene/AcOEt, 20:1) produced (*R*)-(4-bromophenyl)phenylmethanol (2c) (57.3 mg, 0.22 mmol). The yield was 73%, with an estimated *ee* value of 92%.

Supporting Information (see footnote on the first page of this article): Experimental details and characteristic data of diarylmethanols 2 are described.

Acknowledgments

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