Ester-Mediated Nucleophilic Aromatic Substitution of 2,3-Alkylidenedioxybenzoic Esters by Aryl Lithium Reagents

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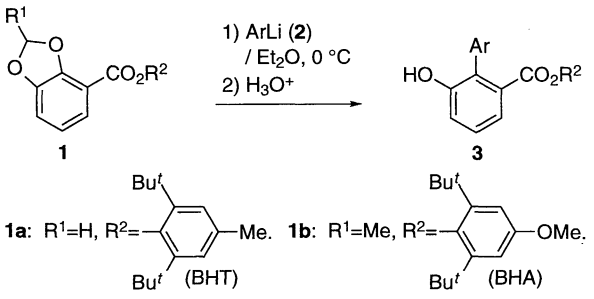
Treatment of 2,6-di-*tert*-butyl-4-methylphenyl 2,3-methylenedioxybenzoate with several aryllithium reagents in diethyl ether at 0 °C affords 6-hydroxy-1,1'-biphenyl-2-carboxylates in good to excellent yields. Reaction of an (*S*)-(–)-2,3-ethylidenedioxybenzoic ester with 2-methoxy-4,6-dimethylphenyllithium induces *R* axial twist with not less than 81% diastereoselectivity in the biphenyl coupling.

The construction of unsymmetrical biaryl units,[1] especially those bearing oxygenated functionalities on the *ortho*-positions, has attracted much attention because of the wide spectrum of biological activities exhibited by a lot of natural products containing such molecular arrangement.[2] We have reported that an ester function of benzoates highly activates an elimination of its *ortho*-alkoxy group for nucleophilic aromatic substitution (S_NAr) by various nucleophiles.[3] Thus, treatment of 2-alkoxybenzoic or 1-alkoxy-2-naphthoic ester with arylmagnesium or -lithium reagents provides a convenient route for the synthesis of biarylcarboxylic esters in excellent yields.[4] Furthermore, chirality of the leaving alkoxy group or the ester moiety induces axial twist in the biaryl coupling to afford atropisomeric biaryls with varying stereoselectivities.[5,6] Herein, we report an extension of the ester-mediated S_NAr reaction to that of 2,3-alkylidenedioxybenzoic esters **1** with aryllithium reagents **2** to give 6-hydroxy-1,1'-biphenyl-2-carboxylates **3** in good to excellent yields (Scheme 1).



Scheme 1.

In typical run, an ethereal solution (4.0 cm^3) of benzoic ester **1a** (367 mg, 1.00 mmol) was added at 0 °C to a solution of 2-methoxyphenyllithium **2a**; **2a** had been prepared by treatment of 1-bromo-2-methoxybenzene (494 mg, 2.64 mmol) in diethyl ether (4.5 cm^3) with butyllithium (1.60 mol dm^{-3} in hexane; 1.60 cm^3, 2.56 mmol) at –45 °C for 1 h. The reaction mixture was stirred at 0 °C for 1 h and worked up as usual. Preparative TLC of the product on silica gel with hexane–ethyl acetate (14:1) afforded 6-hydroxy-2'-methoxy-1,1'-biphenyl-2-carboxylate **3a** in an excellent yield (entry 1 in Table 1). 2-Methoxybenzyl alcohol **6** was also obtained from the reaction in 74% yield

Table 1. S_NAr Reaction of benzoate **1a** with aryllithium **2**[a]

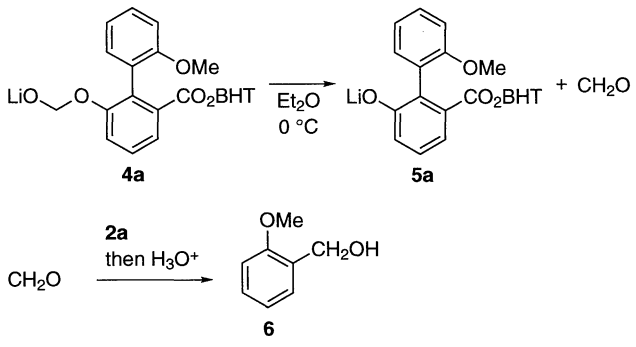
Entry	ArLi (**2**)	Time / h	**3**	Yield / %[b]
1	2-$MeOC_6H_4Li$ (**2a**)	1	**3a**	90
2	C_6H_5Li (**2b**)	1	**3b**	93
3[c]	C_6H_5MgBr (**2b'**)	24	**3b**	57
4	2-MeC_6H_4Li (**2c**)	3	**3c**	63
5	2-MeO-4,6-$(Me)_2C_6H_2Li$ (**2d**)	24	**3d**	62
6	1-NaphthylLi (**2e**)	3	**3e**	69

[a]Reactions were carried out by using *ca.* 2.5 equiv. of **2**. [b]Isolated yield based on **1a**. [c]Reaction was carried out at ambient temp. Benzyl ether **7** was also obtained in 28% (see Chart 1).

(Scheme 2). This suggests that the initially formed alkoxide **4a** readily decomposes to the phenolate **5a** liberating formaldehyde, which in turn reacts with the lithium reagent **2a** to give **6** in the use of excess (*ca.* 2.5 equiv.) of **2a**.

Replacement of phenylmagnesium bromide **2b'** for the phenyllithium **2b** required a longer reaction period at ambient temperature to cause the S_NAr reaction in somewhat reduced yield of the coupling product **3b** (entry 3). This is due to a side-reaction in which the concurrent attack of the Grignard reagent to the methylene carbon yields the benzyl ether **7** (Chart 1).

In the next step, our interest was directed toward the asymmetric biaryl coupling by use of a chiral 2,3-alkylidenedioxybenzoate. Thus, enantiomerically pure 2,3-ethylidenedioxybenzoic acid **8** (Chart 1) was prepared for the first time by



Scheme 2.

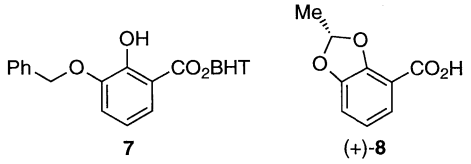


Chart 1.

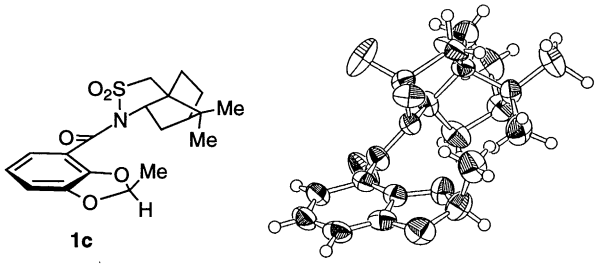
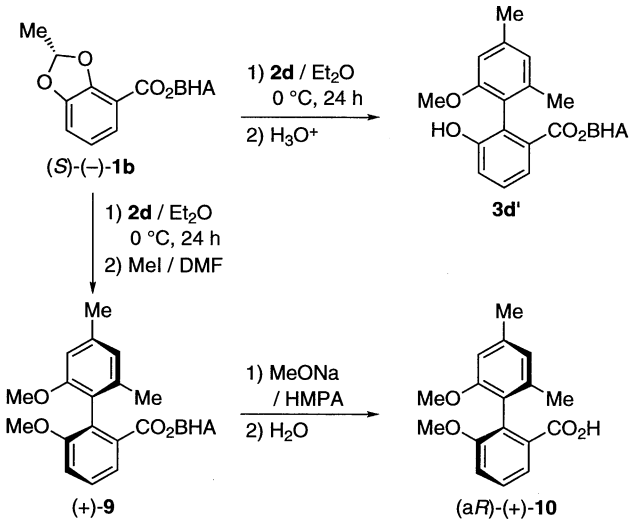


Figure 1. Absolute stereostructure and ORTEP drawing of **1c**.

adopting the Nishida's procedure,[7] and the absolute stereochemistry of the acid (+)-**8** was determined to be *S* by X-ray crystallography of the amide **1c** prepared from (–)-camphorsultam and (+)-**8** (Figure 1).[8,9] The chiral acid (*S*)-**8** was converted to the 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA) ester (*S*)-(–)-**1b**,[8] which was then treated with lithium reagent **2d** in diethyl ether at 0 °C for 24 h (Scheme 3). After aqueous workup, the reaction mixture was subjected to chiral HPLC analysis,[10] which indicated that non-racemic biphenylcarboxylate **3d'** as the product was rather labile to racemization even at ambient temperature. In fact, a racemic benzoate **3d'** was isolated in 61% yield by the conventional procedure.

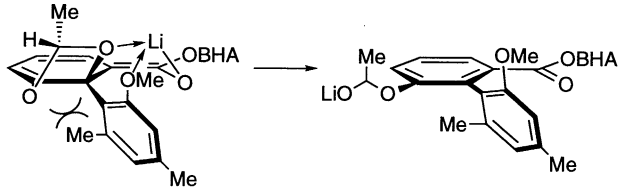
It should be noted that 2,2'-dihydroxy-6,6'-dimethylbiphenyl[11] or a series of 2,2'-dialkoxy-6,6'-dihydroxybiphenyls[12] are thermally far more stable to racemization than the above non-racemic benzoate. Thus, it is interesting that the apparently bulky CO_2BHA moiety in combination with the 6-hydroxy substituent of 2,2',6,6'-tetrasubstituted biphenyl **3d'** is not effective enough to prevent the pivotal rotation of the biphenyl linkage, and further studies on the racemization mechanism are underway. Therefore, a control reaction of ester (*S*)-**1b** with lithium reagent **2d** under the same conditions as above was quenched by addition of a solution of an excess of iodomethane in DMF to convert the lithium phenolate to the methyl ether, giving after usual workup (+)-2',6-dimethoxy-4',6'-dimethyl-1,1'-biphenyl-2-carboxylate (+)-**9** in 60% yield with 81% ee (Scheme 3),[13] the % ee value obtained being the minimum estimation of the diastereoselectivity in the asymmetric biaryl coupling reaction of the substrate (*S*)-**1b**



Scheme 3.

with lithium reagent **2d**. Treatment of the benzoate (+)-**9** with sodium methoxide in HMPA at 80 °C for 9 h liberated carboxylic acid (+)-**10** without notable racemization: $[\alpha]_D^{22}$ +66.9° (*c* 1.02, $CHCl_3$), the absolute configuration of which was assigned to be a*R*.[6]

The stereochemical course of the asymmetric biphenyl coupling can be rationalized based on the addition-elimination mechanism, in which the lithium reagent **2d** attacks the benzoate **1b** from the opposite side of the methyl substituent to avoid steric repulsion (Scheme 4).[14]



Scheme 4.

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References and Notes

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8 (*S*)-(+)-**8**: $[\alpha]_D^{22}$ +10.8° (*c* 1.77, $CHCl_3$). (*S*)-(–)-**1b**: $[\alpha]_D^{20}$ –4.51 (*c* 1.22, $CHCl_3$).
9 Crystal data for **1c**: $C_{19}H_{24}NO_5S$, M = 378.47, monoclinic, $P2_1$, a = 8.991(1) Å, b = 7.586(1) Å, c = 13.383(1) Å, β = 91.994(9)°, V = 912.2(2) Å^3, Z = 2, D_c = 1.367 g/cm^3, D_m = 1.367 g/cm^3, crystal size 0.4 × 0.4 × 0.2 mm^3, R = 0.045 (Rw = 0.044), λ(MoKα) = 0.71069 Å, μ = 2.07 cm^{-1}, unique reflection = 2266.
10 HPLC: column, Daicel Chiralpak AD; eluent, 3% i-PrOH in hexane.
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