

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

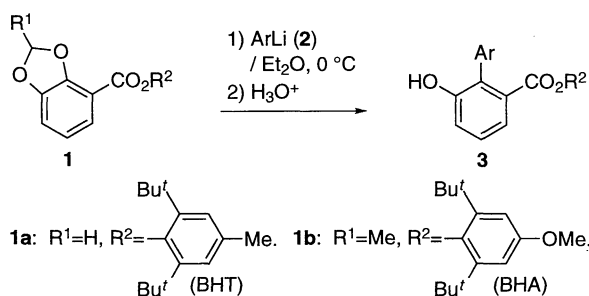
Nobuyuki Koike, Tetsutaro Hattori, Ayanobu Takeda, Yoshikazu Okaishi, and Sotaro Miyano*

Department of Biochemistry and Engineering, Faculty of Engineering, Tohoku University, Aramaki-Aoba, Aoba-ku, Sendai 980-77

(Received March 27, 1997; CL-970228)

Treatment of 2,6-di-*tert*-butyl-4-methylphenyl 2,3-methylene-dioxybenzoate 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 cm³) 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 cm³) with butyllithium (1.60 mol dm⁻³ in hexane; 1.60 cm³, 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

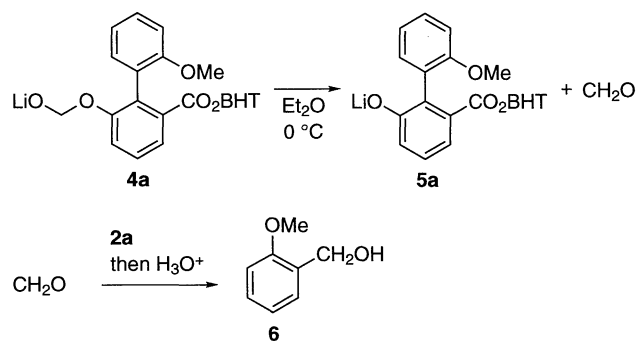
Entry	ArLi (2)	Time / h	3	Yield / % ^b
1	2-MeOC ₆ H ₄ Li (2a)	1	3a	90
2	C ₆ H ₅ Li (2b)	1	3b	93
3 ^c	C ₆ H ₅ MgBr (2b')	24	3b	57
4	2-MeC ₆ H ₄ Li (2c)	3	3c	63
5	2-MeO-4,6-(Me) ₂ C ₆ H ₂ Li (2d)	24	3d	62
6	1-NaphthylLi (2e)	3	3e	69

^aReactions were carried out by using *ca.* 2.5 equiv. of **2**. ^bIsolated yield based on **1a**. ^cReaction 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.

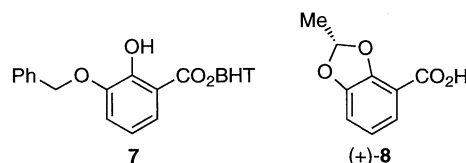


Chart 1.

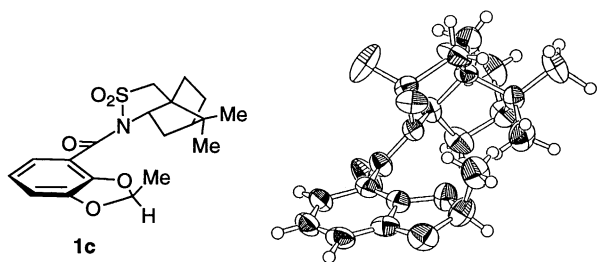
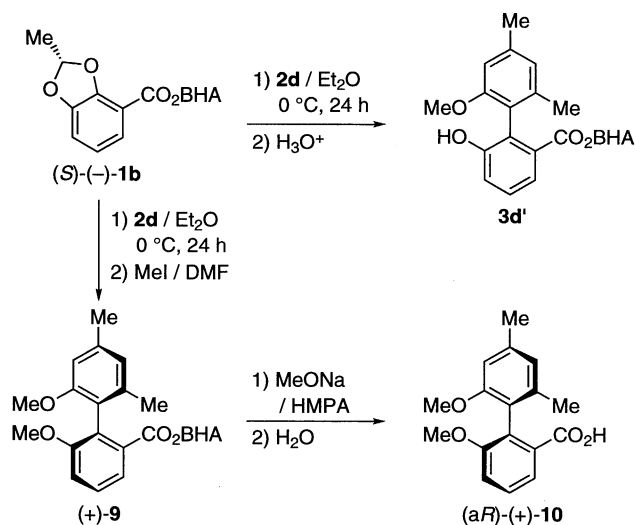


Figure 1. Absolute stereostructure and ORTEP drawing of **1c**.

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.

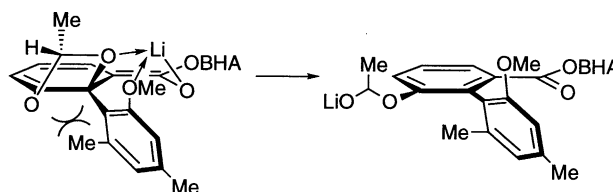
It should be noted that 2,2'-dihydroxy-6,6'-dimethylbiphenyl¹¹ or a series of 2,2'-dialkoxy-6,6'-dihydroxybiphenyls¹² are thermally far more stable to racemization than the above non-racemic benzoate. Thus, it is interesting that the apparently bulky CO₂BHA moiety in combination with the 6-hydroxy substituent 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 (+)-**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: $[\alpha]_D^{22} +66.9^\circ$ (*c* 1.02, CHCl₃), the absolute configuration of which was assigned to be *aR*.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.

We are grateful to Professor Hiroshi Ohrui and Dr. Yoshihiro Nishida of our university for valuable discussions. We thank the Ministry of Education, Science and Culture for financial support (Grant-in-Aid No. 08405058 and No. 07555587).

References and Notes

- 1 G. Bringmann, R. Walter, and R. Weirich, *Angew. Chem., Int. Ed. Engl.*, **29**, 977 (1990).
- 2 For example, G. François, G. Bringmann, J. D. Phillipson, L. A. Assi, C. Dochez, M. Rübenacker, C. Schneider, M. Wéry, D. C. Warhurst, and G. C. Kirby, *Phytochemistry*, **35**, 1461 (1994).
- 3 T. Hattori, T. Satoh, and S. Miyano, *Synthesis*, **1996**, 514.
- 4 T. Hattori, H. Tanaka, Y. Okaishi, and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 235.
- 5 T. Hattori, H. Hotta, T. Suzuki, and S. Miyano, *Bull. Chem. Soc. Jpn.*, **66**, 613 (1993).
- 6 T. Hattori, N. Koike, and S. Miyano, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2273.
- 7 Y. Nishida, M. Abe, H. Ohrui, and H. Meguro, *Tetrahedron: Asymmetry*, **4**, 1431 (1993).
- 8 (*S*)-(–)-**8**: $[\alpha]_D^{22} +10.8^\circ$ (*c* 1.77, CHCl₃). (*S*)-(–)-**1b**: $[\alpha]_D^{20} -4.51$ (*c* 1.22, CHCl₃).
- 9 Crystal data for **1c**: C₁₉H₂₄NO₅S, M = 378.47, monoclinic, P2₁, a = 8.991(1) Å, b = 7.586(1) Å, c = 13.383(1) Å, β = 91.994(9)°, V = 912.2(2) Å³, Z = 2, D_c = 1.367 g/cm³, D_m = 1.367 g/cm³, crystal size 0.4 × 0.4 × 0.2 mm³, R = 0.045 (R_w = 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.
- 11 H. Moorlag and A. I. Meyers, *Tetrahedron Lett.*, **34**, 6993 (1993).
- 12 T. Harada, S. Ueda, T. Yoshida, A. Inoue, M. Takeuchi, N. Ogawa, and A. Oku, *J. Org. Chem.*, **59**, 7575 (1994).
- 13 HPLC: column, Daicel Chiralcel OD-H; eluent, 0.3% i-PrOH in hexane.
- 14 T. Hattori, N. Koike, Y. Okaishi, and S. Miyano, *Tetrahedron Lett.*, **37**, 2057 (1996).