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Asymmetric Desymmetrization of 2,2′,6,6′-Tetrahydroxybiphenyl through Annulation with Enantiomerically Pure Bis(mesylate)

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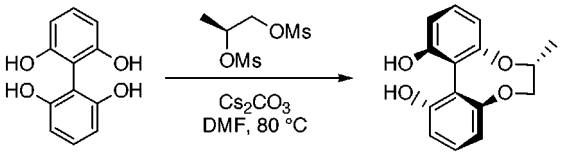
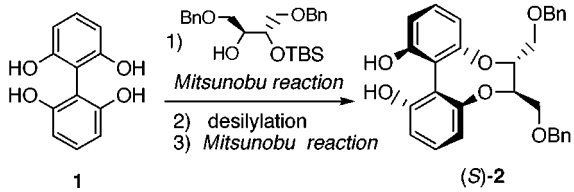
ABSTRACT



2,2′,6,6′-Tetrahydroxybiphenyl undergoes a facile annulation reaction with bis(mesylate) derived from (*S*)-1,2-propanediol in the presence of Cs_2CO_3 to give the corresponding asymmetric desymmetrization product of *S* axial chirality with exclusive diastereoselectivity. The desymmetrization product can be utilized as a versatile chiral building block in asymmetric synthesis of axially chiral 6,6′-disubstituted 2,2′-biphenyldiols.

Enantiotopic group selective reaction of prochiral difunctional compounds, or asymmetric desymmetrization, has recently emerged as a powerful strategy for asymmetric synthesis.[1] The reaction affords enantiomerically enriched compounds with differentiated functional groups which serve as versatile chiral building blocks in asymmetric synthesis of complex molecular frameworks. Although the application of asymmetric desymmetrization was previously limited to the construction of stereogenic centers, the potential of the strategy in the construction of axial chirality of biaryls has recently been disclosed.[2,3] We reported that, through stepwise etherification of 2,2′,6,6′-tetrahydroxybiphenyl (**1**) with 1,4-di-*O*-benzyl-L-threitol under Mitsunobu conditions, the hydroxy groups of **1** are differentiated in an enantioselective manner to furnish desymmetrized biphenyldiol (*S*)-**2** (Scheme 1).[2d,e] Taking advantage of the differentiated functionalities, one can synthesize a variety of axially chiral biaryls in an enantiomerically pure form from chiral building block (*S*)-**2**.

Scheme 1



(1) For review on the nonenzymatic method, see: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Gais, H.-J. *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, p 589. (c) Harada, T.; Oku, A. *Synlett* **1994**, 95. For recent reports, see: (d) Harada, T.; Nakamura, T.; Kinugasa, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 7594 and references therein. For enzymatic methods, see: (e) Wong, C. H.; Whitesides, G. H. *Enzymes in Synthetic Organic Chemistry*; Baldwin, J. E., Magunus, P. D., Eds.; Pergamon: Oxford, 1994; p 41.

(2) (a) Harada, T.; Ueda, S.; Yoshida, T.; Inoue, A, Takeuchi, M.; Ogawa, N.; Oku, A. *J. Org. Chem.* **1994**, *59*, 7575. (b) Harada, T.; Yoshida, T.; Inoue, A.; Takeuchi, M.; Oku, A. *Synlett* **1995**, 283. (c) Harada, T.; Ueda, S.; Tuyet, T. M. T.; Inoue, A.; Fujita, K.; Takeuchi, M.; Ogawa, N.; Oku, A.; Shiro, M. *Tetrahedron* **1997**, *53*, 16663. (d) Harada, T.; Tuyet, T. M. T.; Hashimoto, K.; Hatsuda, M.; Oku, A. *Synlett* **1997**, 1426. (e) Tuyet, T. M. T.; Harada, T.; Hashimoto, K.; Hatsuda, M.; Oku, A. *J. Org. Chem.* **2000**, *65*, 1335.

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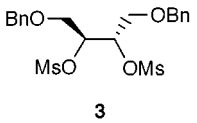
We wish to report herein a single-step asymmetric desymmetrization of prochiral tetrol **1** by annulation with a chiral bis(mesylate). The new method is developed on the basis of consideration of the origin of stereoselectivity in the previous three-step method and significantly reduces the number of synthetic steps to chiral 6,6′-disubstituted 2,2′-biphenyldiols,[4] demonstrating the practicality of the asymmetric desymmetrization-based approach.

We first examined the annulation of tetrol **1** and threitol-derived bis(mesylate) **3** (1.0 equiv) by using a base such as K_2CO_3, Cs_2CO_3, or $KN(SiMe_3)_2$ (80−100 °C, DMF). However, the reactions gave annulation product (*S*)-**2** in low yield (<20%). Alkenyl mesylate ($BnOCH_2C(OMs)C{=}CHCH_2OBn$) was obtained as a major byproduct (33−55% yield), but the formation of initial etherification product **4** was not detected. The formation of the alkenyl mesylate suggests that secondary bis(mesylate) **3** underwent competing substitution and elimination. On the other hand, the absence of **4** implies that the second intramolecular etherification proceeded smoothly.



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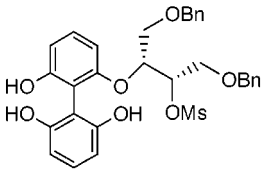

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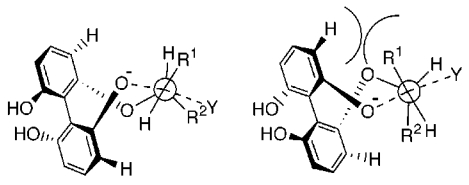
We have previously proposed a transition state model (Figure 1) which rationalizes the stereoselectivity of intramolecular Mitsunobu etherification.[2e] While a severe interaction between a benzene ring and a benzyloxymethyl group (R^1) attached to the reaction site destabilizes transition state **6a** leading to an unobserved (*R*)-diastereomer, such repulsive interaction does not exist in **5a** leading to (*S*)-**2**. According to this model, vicinal substituent R^2 does not play a major role in stereoselection. Therefore, annulation of tetrol **1** with a bis(mesylate) derived from enantiomerically pure 1,2-alkanediols ($R^1CH(OH)CH_2OH$) is promising because the initial intramolecular etherification would proceed on the primary mesylate without competing with elimination and because the resulting intermediate would undergo stereoselective intramolecular etherification through transition state **5b** in preference to **6b**.



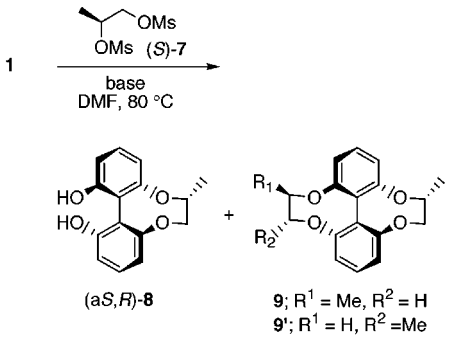
5a,b **6a,b**

a; R^1, R^2 = $BnOCH_2$, Y = Ph_3P^+-O
b; R^1 = alkyl , R^2 = H, Y = MsO

Figure 1. Transition state model for intramolecular etherification.

Mesylation (CH_3SO_2Cl, Et_3N, CH_2Cl_2) of commercially available (*S*)-1,2-propanediol gave crystalline bis(mesylate) (*S*)-**7** (mp 68−69 °C) in 86% yield. Annulation of tetrol **1** was first examined by using K_2CO_3 as a base (Scheme 2).

Scheme 2



(a*S*,*R*)-**8** **9**; R^1 = Me, R^2 = H
9′; R^1 = H, R^2 =Me

Slow addition of the bis(mesylate) (1.0 equiv) during 4 h to a mixture of **1** and K_2CO_3 (2.3 equiv) in DMF (0.1 M) at 80 °C afforded annulation product (a*S*,*R*)-**8**[5] in 30% yield without formation of a (a*R*,*R*)-diastereomer (Table 1, entry 1). Bis-annulation proceeded to some extent, affording a mixture of **9** and **9′** (ca. 1:1) as minor products. Cs_2CO_3 has been used as an efficient base in etherification of mesylates.[6] The use of the base under similar conditions gave an improved yield of (a*S*,*R*)-**8** (entry 2). The amount of the bis-annulation products was increased when 1.3 equiv of (*S*)-**7** was employed (entry 3). The efficiency of annulation was also affected by the concentration (entries 2, 4, and 5); the optimum yield of 68% was obtained in the reaction conducted at 0.03 M.[7] The enantiomeric annulation product (a*R*,*S*)-**8** was prepared in 66% yield by using bis(mesylate) (*R*)-**7** under these optimized conditions (entry 6).

Table 1. Annulation of Tetrol **1** with Bis(mesylate) **7**[a]

			yield (%)	
entry	base	concn[b] (M)	**8**	**9** + **9′**
1	K_2CO_3	0.1	30	7
2	Cs_2CO_3	0.1	52	8
3[c]	Cs_2CO_3	0.1	34	23
4	Cs_2CO_3	0.05	65	6
5	Cs_2CO_3	0.03	68	8
6[d]	Cs_2CO_3	0.03	66	7

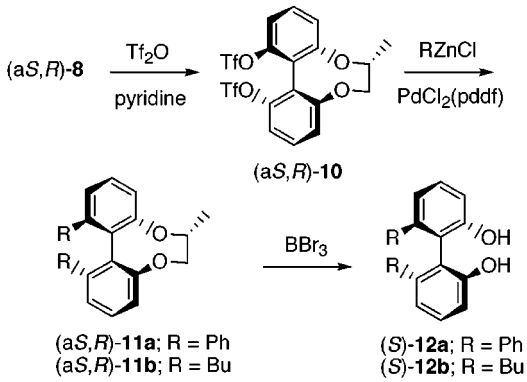
[a] Unless otherwise noted, reactions were carried out by adding a DMF solution of (*S*)-**7** (1.0 equiv) slowly during a 4−5 h period to a stirred mixture of **1** and a base (2.3 equiv) in DMF at 80 °C. [b] Concentration of **1** in DMF. [c] 1.3 equiv of bis(mesylate) was employed. [d] (*R*)-**7** was used.

Desymmetrization product **8** was successfully transformed to enantiomerically pure 6,6′-disubstituted 2,2′-biphenyldiols

(3) For a similar approach, see: Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.

12 via palladium-catalyzed cross-coupling of the corresponding bis(triflate) **10** (Scheme 3). Treatment of (a*S*,*R*)-**8** with

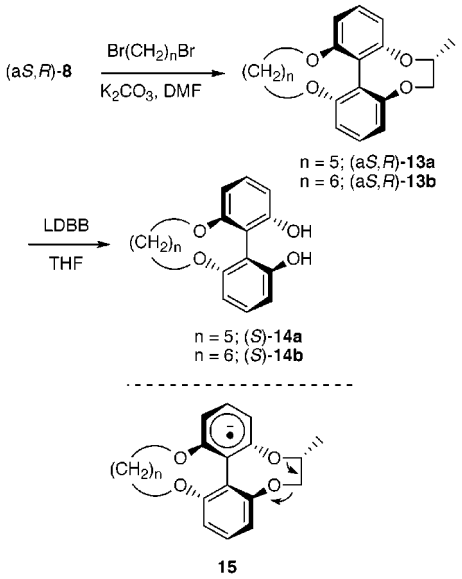
Scheme 3



triflic anhydride in pyridine gave (a*S*,*R*)-**10** in 88% yield. In the presence of $PdCl_2$(dppf) (5 mol %), cross-coupling of (a*S*,*R*)-**10** with PhZnCl (4 equiv) proceeded smoothly at 65 °C in THF to afford diphenylation product (a*S*,*R*)-**11a** in 95% yield.[2e] Subsequent removal of the chiral auxiliary with BBr_3 furnished enantiomerically pure quaterphenyldiol (*S*)-**12a** (91% yield, 99% ee).[8] Application of the same reaction sequence to enantiomeric desymmetrization product (a*R*,*S*)-**8** afforded (*R*)-**12a** (99% ee).[8] Thus, asymmetric synthesis of both (*S*)- and (*R*)-**12a** was achieved in four steps starting from prochiral tetrol **1**. Similarly, cross-coupling of (a*S*,*R*)-**11** with BuZnCl followed by BBr_3 treatment furnished 6,6′-dibutyl derivative (*S*)-**12b** (97% ee)[8] in 79% yield.

Chiral 2,2′-biphenyldiols with $-O(CH_2)_nO-$ bridges at the 6- and 6′-positions (such as **14a**,**b**) are useful ligands for chiral Lewis acids.[9] For these diols, the dihedral angle between benzene rings is controlled by the length of the alkylene chain, allowing for optimization of the chiral environment of the resulting Lewis acid complexes.[10] Treatment of (a*S*,*R*)-**8** with 1,5-dibromopentane and 1,6-dibromohexane in the presence of K_2CO_3 in DMF at 80 °C gave bis-annulation products (a*S*,*R*)-**13a** (75%) and (a*S*,*R*)-**13b** (78%), respectively (Scheme 4). Selective C−O bond cleavage is required to remove the chiral auxiliary. For this purpose, reductive cleavage using lithium 4,4′-di(*tert*-butyl)biphenylide (LDBB)[11] was found to be effective. Treatment of (a*S*,*R*)-**13a** and -**13b** with LDBB (4 equiv) in THF at 0 °C cleanly afforded enantiomerically pure biphenyldiols (*S*)-

Scheme 4



(4) For asymmetric synthesis of axially chiral biaryls, see the following. (a) Review: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Review: Bringmann, G.; Walter, R.; Weirich, R. *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, p 567. (c) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1375. (d) Hattori, T.; Hotta, H.; Suzuki, T.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 613. (e) Miyano, S.; Koike, N.; Hattori, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1899. (f) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989. (g) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993. (h) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 9, 2655. (i) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 3259. (j) Meyers, A. I.; McKennon, M. J. *Tetrahedron Lett.* **1995**, *36*, 5869. (k) Meyers, A. I.; Meir, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853. (l) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732. (m) Uemura, M.; Kamikawa, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2697. (n) Kamikawa, K.; Watanabe, T.; Uemura, M. *Synlett* **1995**, 1040. (o) Watanabe, T.; Kamikawa, K.; Uemura, M. *Tetrahedron Lett.* **1995**, *37*, 6695. (p) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375. (q) Osa, T.; Kashiwagi, Y.; Yanagisawa, Y.; Bobbitt, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2535. (r) Itoh, T.; Chika, J.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J. *J. Org. Chem.* **1996**, *61*, 3700. (s) Nakajima, M.; Miyoshi, I.; Kanayama, K.; Hashimoto, S.; Noji, M.; Koga, K. *J. Org. Chem.* **1999**, *64*, 2264.

(5) The symbol "a" indicates the axial chirality. Thus, "a*S*,*R*" shows that the compound has a*S*-axial chirality and an *R*-stereogenic center.

(6) (a) Wang, S. S.; Gisin, B. B.; Winter, D. P.; Makofske, R.; Kulesha, I. D.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1977**, *42*, 1286. (b) Kruinzinga, W. H.; Strijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1981**, *46*, 4321.

(7) **Procedure for the preparation of (a*S*,*R*)-8:** To a stirred suspension of tetrol **1** (1.77 g, 8.12 mmol) and Cs_2CO_3 (6.08 g, 18.67 mmol) in DMF (232 mL) at 80 °C was added slowly a solution of bis(mesylate) (*S*)-**7** (1.89 g, 8.12 mmol) in DMF (81 mL) during 4 h. The resulting suspension was stirred further for 12 h at this temperature. Most of the solvent was removed by distillation under reduced pressure. The residue was poured into aqueous 1 N HCl and extracted twice with ether. The organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (5−40% ethyl acetate in hexane) gave 1.43 g (68%) of (a*S*,*R*)-**8** and 0.19 g (8%) of a 1:1 mixture of **9** and **9′**. (a*S*,*R*)-**8**: mp 230−231 °C (recrystallized from ethanol and hexane); $[\alpha]^{27}_D$ 174 (*c* 1.15, THF); ^{1}H NMR (500 MHz, d_6-acetone) δ 1.31 (3H, d, J = 6.5 Hz), 3.72 (1H, dd, J = 10.8 and 12.0 Hz), 4.28 (1H, m), 4.43 (1H, dd, J = 3.6 and 12.0 Hz), 6.77−6.84 (4H, m), 7.24−7.29 (2H, m), 8.28 (2H, br s); ^{13}C NMR (125.8 MHz, d_6-acetone) δ 17.51, 79.89, 81.86, 112.98, 113.06, 114.96, 115.01, 117.36, 117.47, 130.28, 130.39, 155.82 (2C), 161.70, 162.16; FT-IR (KBr disk) 3250 (br), 1047, 1018, 798 cm^{-1}; MS *m*/*z* (relative intensity) 258 (M^+, 100), 243 (10), 229 (22); HRMS calcd for $C_{15}H_{14}O_4$ 258.0892, found 258.0879. Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.57; H, 5.52.

(8) The ee value was established by HPLC analyses using a Chiracel AD column with 90:10:0.09 hexane:2-propanol:acetic acid as a mobile phase at a flow rate of 1 mL/min.

(9) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479.

(10) Recently, a theoretical treatment of the results reported in ref 9 has appeared: Gao, D.; Schefzick, S.; Lipkowitz, K. B. *J. Am. Chem. Soc.* **1999**, *121*, 9481.

(11) (a) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152. (b) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (c) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1983**, *48*, 4705. (d) Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866.

14a (88%, 99% ee)[8] and (*S*)-**14b** (97%, 97% ee),[8] respectively. The reaction proceeded probably through a mechanism involving selective cleavage of the most strained secondary C−O bond of anion radical intermediate **15** with the liberation of propene.

In summary, a straightforward and practical method for asymmetric synthesis of axially chiral biaryldiols was developed based on asymmetric desymmetrization. Prochiral tetrahydroxybiphenyl **1** underwent a facile annulation reaction with readily available bis(mesylate) **7** in the presence of Cs_2CO_3 to give the corresponding asymmetric desymmetrization product **8** in one step as a single diastereomer. Desymmetrization product **8** was utilized as a versatile chiral building block in the synthesis of enantiomerically pure axially chiral biaryldiols **12a**,**b** and **14a**,**b**. The application of the method to other prochiral biarylpolyols is underway and will be reported in due course.

Acknowledgment. We thank the Nagase Science and Technology Foundation for financial support of this work.

Supporting Information Available: Experimental details and full characterization data for compounds **9**, **10**, and **11a**,**b**−**14a**,**b**. This material is available free for charge via the Internet at http://pubs.acs.org.

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