A Novel and Facile Racemization of Chiral 1,1′-Biaryl-2,2′-dicarboxylic Acids

Masanori Hatsuda,† Hajime Hiramatsu,‡ Shin-ichi Yamada,† Toshiaki Shimizu,† and Masahiko Seki*,†

Product & Technology Development Laboratory and Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd., 3-16-89, Kashima, Yodogawa-ku, Osaka 532-8505, Japan

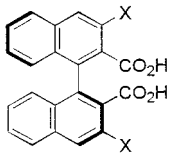
m-seki@tanabe.co.jp

Received January 30, 2001

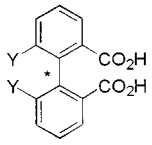
Introduction

Enantiomerically pure 1,1′-biaryl-2,2′-dicarboxylic acids **1** have received considerable attention as chiral building blocks for such valuable compounds as chiral catalyst for asymmetric epoxidation.[1] While some excellent asymmetric syntheses of **1** have been developed, they still have such drawbacks as need for expensive chiral catalyst or covalently bound chiral auxiliary for inducing high stereoselectivities.[2] Consequently, a number of enantiomerically pure 1,1′-biaryl-2,2′-dicarboxylic acids have still been prepared by the conventional optical resolution.

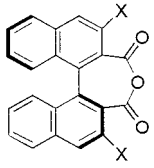
We have recently reported a practical synthesis of a C_2-symmetric chiral binaphthyl ketone **2**, an efficient catalyst for asymmetric epoxidation (Scheme 1).[3] The key step of the synthesis involves an optical resolution of (±)-1,1′-binaphthyl-2,2′-dicarboxylic acid (±)-**1a** with (*R*)-1-cyclohexylethylamine used as a resolving agent to obtain (*R*)-**1a**. To enhance the efficiency of the optical resolution, an effective racemization of the unwanted enantiomer (*S*)-**1a** has been highly desirable. However, (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*S*)-**1a** is too configurationally stable to racemize even at 210 °C in tetralin.[4]



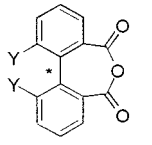
(*S*)-**1a**: X = H
(*S*)-**1b**: X = Cl



(*S*)-**1c**: Y = OMe
(*R*)-**1d**: Y = Me
(*R*)-**1e**: Y = NO_2



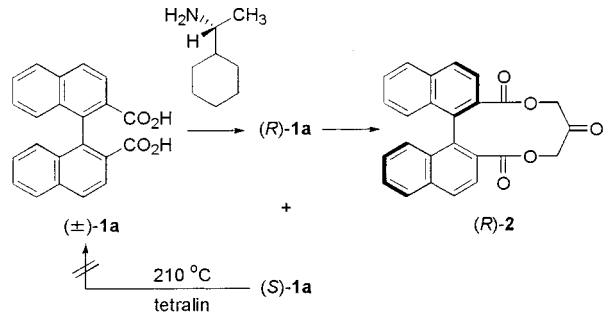
(*S*)-**3a**: X = H
(*S*)-**3b**: X = Cl



(*S*)-**3c**: Y = OMe
(*R*)-**3d**: Y = Me
(*R*)-**3e**: Y = NO_2

Concerning the racemization of the biaryl derivatives, bridged biaryls have been reported to be configurationally more labile than the corresponding ring-opened ones.[5] We thus envisioned a possibility to effect the racemization of (*R*)- or (*S*)-**1** by heating more planar acid anhydride

Scheme 1



Scheme 2

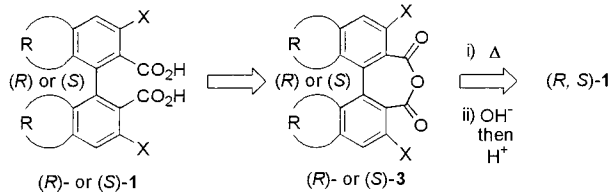
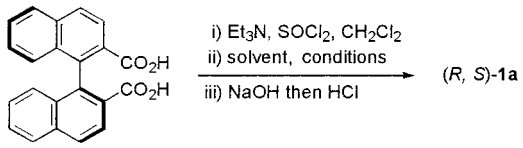


Table 1. Racemization of (*S*)-1a



(*S*)-**1a**
(*R* / *S* = 0 : 100)

		conditions			
entry	solvent	*T* (°C)	period (h)	yield (%)	*R*/*S*[a]
1	toluene	110	6	96[a]	0:100
2	xylene	140	3	91[a]	1:99
3	mesitylene	165	64	84[a]	21:79
4	tetralin	210	40	83[b]	44:56

[a] Determined by HPLC. [b] Isolated yield.

* To whom correspondence should be addressed.
† Product & Technology Development Laboratory.
‡ Discovery Research Laboratory.

(1) (a) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491. (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc.* **1996**, *118*, 11311. (c) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 5943. (d) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

(2) (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153. (b) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655. (c) Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723.

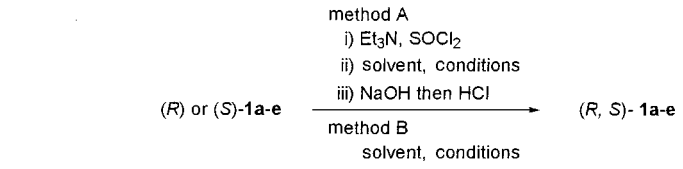
(3) Seki, M.; Yamada, S.; Kuroda, T.; Imashiro, R.; Shimizu, T. *Synthesis* **2000**, 1677.

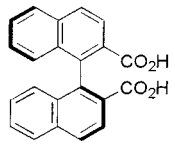
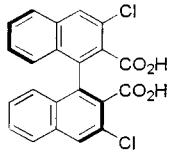
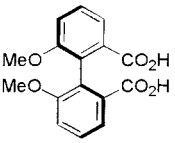
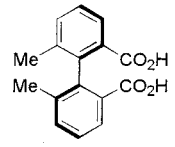
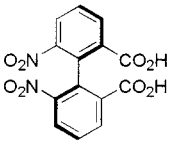
(4) Hall, D. M.; Turner, E. E. *J. Chem. Soc.* **1955**, 1242.

(5) (a) Bringmann, G.; Hartung, T.; Gobel, L.; Schupp, O.; Ewers, C. L. J.; Schoner, B.; Zagst, R.; Peters, K.; von Schnering, H. G.; Bruschka, C. *Liebigs Ann. Chem.* **1992**, 225. (b) Bringmann, G.; Schoner, B.; Schupp, O.; Peters, K.; Peters. E.-M.; von Schnering, H. G. *Liebigs Ann. Chem.* **1994**, 91. (c) Bringmann, G.; Hartung, T.; Krocher, O.; Gulden, K.-P. *Tetrahedron* **1994**, *50*, 2831. (d) Bringmann, G.; Busse, H.; Dauer, U.; Gussregen, S.; Stahl, M. *Tetrahedron* **1995**, *51*, 3149. (e) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525. (f) Bringmann, G.; Heubes, M.; Breuning, M.; Gobel, L.; Ochse, M.; Schoner, B.; Schupp, O. *J. Org. Chem.* **2000**, *65*, 722. (g) Bringmann, G.; Hinrichs, J.; Kraus, J.; Wuzik, A.; Schulz, T. *J. Org. Chem.* **2000**, *65*, 2517.

10.1021/jo0101196 CCC: $20.00
Published on Web 05/19/2001

Table 2. Racemization of Chiral 1,1′-Biaryl-2,2′-dicarboxylic Acids 1a−e



entry	substrate (*R* / *S*)	method	solvent	conditions *T*(°C)	conditions period (h)	yield (%)[a]	*R* / *S*[b]
1	 (*S*)-**1a** (0 : 100)	A	tetralin	210	40	83	44 : 56
2		B	tetralin	210	40	-[d]	1 : 99
3	 (*S*)-**1b** (0 : 100)	A	tetralin	210	24	80	45 : 55[c]
4		B	tetralin	210	24	33	9 : 91[c]
5	 (*S*)-**1c** (0 : 100)	A	1,4-dioxane	85	9	91	36 : 64
6		B	1,4-dioxane	85	24	-[d]	15 : 85
7	 (*R*)-**1d** (99 : 1)	A	DME	85	24	100	50 : 50
8		B	DME	85	24	-[d]	99 : 1
9	 (*R*)-**1e** (99 : 1)	A	1,4-dioxane	108	18	76	50 : 50
10		B	1,4-dioxane	108	36	-[d]	98 : 2

[a] Isolated yield. [b] Determined by HPLC unless otherwise noted. [c] Determined by comparing the specific rotation of (S)-**1b** with that of the pure material. [d] Not determined.

derivatives (*R*)- or (*S*)-**3** (Scheme 2). We report herein a successful result that enabled the facile racemization of (*R*)- or (*S*)-**1** through conversion to the acid anhydrides (*R*)- or (*S*)-**3** and subsequent heating and hydrolysis.

Results and Discussion

Our initial study was focused on the racemization of 1,1′-binaphthyl-2,2′-dicarboxylic acid (*S*)-**1a** (Table 1). Treatment of (*S*)-**1a** with triethylamine and thionyl chloride provided the acid anhydride (*S*)-**3a**. The crude (*S*)-**3a** was subjected immediately to the racemization under various conditions. Although any racemization did not take place by heating (*S*)-**3a** in refluxing toluene or xylene, partial racemization (*R*/*S* = 0:100 to 21:79) was observed when (*S*)-**3a** was heated in mesitylene at 165 °C for 64 h (Table 1, entries 1−3). Encouraged by this result, the reaction was conducted at a higher temperature and for a longer period in tetralin (210 °C, 40 h) to effect further racemization. After alkaline hydrolysis of the reaction mixture, almost racemized dicarboxylic acid (*R*,*S*)-**1a** (*R*/*S* = 44:56) was isolated in 83% yield based on (*S*)-**1a** (Table 1, entry 4). To the best of our knowledge, this represents the first example for the racemization of 1,1′- binaphthyl-2,2′-dicarboxylic acid **1a**.

The procedure through heating the acid anhydride (method A) was then applied to the racemization of other 1,1′-biaryl-2,2′-dicarboxylic acids (*R*)- or (*S*)-**1b**−**e** involving 1,1′-biphenyl-2,2′-dicarboxylic acid derivatives (*R*)- or (*S*)-**1c**−**e** (Table 2). Attempts to effect the direct racemization of the dicarboxylic acids by heating (method B) were also investigated for the control experiments. 3,3′-Dichloro-1,1′-binaphthyl derivative (*S*)-**3b** racemized faster

(reflux in tetralin, 24 h) than that of (*S*)-**3a** to provide, after hydrolysis, (*R*,*S*)-**1b** in good yield (80% yield, *R*/*S* = 0:100 to 45:55) (Table 2, entry 3). In contrast, direct racemization of the dicarboxylic acid (*S*)-**1b** failed to be accompanied by considerable decomposition (reflux in tetralin, 24 h, 33% yield, *R*/*S* = 0:100 to 9:91) (Table 2, entry 4). While 3,3′-dimethoxy-1,1′-biphenyl-2,2′-dicarboxylic acid (*S*)-**1c** racemized when heated in refluxing 1,4-dioxane for 24 h (*R*/*S* = 100:0 to 85:15), the corresponding acid anhydride (*S*)-**3c** racemized more rapidly than (*S*)-**1c** (reflux in 1,4-dioxane, 9 h, *R*/*S* = 0:100 to 36:64) (Table 2, entry 5 vs entry 6). Although the enantiomeric purity of 3,3′-dimethyl derivative (*R*)-**1d** did not vary at all in refluxing DME in the course of 24 h, the corresponding acid anhydride (*R*)-**3d** completely racemized under the same reaction conditions (*R*/*S* = 99:1 to 50:50) (Table 2, entry 7 vs entry 8). It should be noted that 3,3′-dinitro derivative (*R*)-**1e**, which might be dangerous when heated at high temperature, could racemize by heating the acid anhydride (*R*)-**3e** in refluxing 1,4-dioxane for 18 h (*R*/*S* = 99:1 to 50:50) (Table 2, entry 9).

To explain the facile racemization of the acid anhydrides **3**, isolation and X-ray crystallographic analysis of **3** were conducted. Among the acid anhydrides (*R*)- or (*S*)-**3a**−**e** derived from the dicarboxylic acids (*R*)- or (*S*)-**1a**−**e**, 3,3′-dichloro-1,1′-binaphthyl derivative (*S*)-**3b** formed sufficiently large prisms suitable for the X-ray crystallographic study. The dihedral angle between the two naphthalene rings of the acid anhydride (*S*)-**3b** (56.45°) proved to be much narrower than that of the corresponding dicarboxylic acid (*S*)-**1b** (88.80°).[6] The acid anhydride (*S*)-**3b** is thus more planar than the corresponding dicarboxylic acid (*S*)-**1b**. There is another significant feature in the acid anhydride (*S*)-**3b**. The carbon atoms of each naphthalene ring in (*S*)-**3b** are not in the same plane in contrast with those of (*S*)-**1b**. The naphthalene rings of the acid anhydride (*S*)-**3b** therefore have a highly strained helicene-like distorted structure. In good agreement with the reported correlation of the planarity and the ring strain of the biaryl derivatives with the ease for racemization,[5] the X-ray crystallographic results might provide structural evidences for the facile racemization of the acid anhydrides (*R*)- or (*S*)-**3a**−**e** compared to the dicarboxylic acids (*R*)- or (*S*)-**1a**−**e**.

In conclusion, we have demonstrated for the first time that 1,1′-biaryl- 2,2′-dicarboxylic acids can be efficiently racemized through heating the corresponding acid anhydrides under comparably mild conditions. This method is efficient in terms of versatility, good yields, simple operation and use of inexpensive reagents. The present racemization procedure, when combined with the conventional optical resolution, should permit a more practical access to the enantiomerically pure 1,1′-biaryl-2,2′-dicarboxylic acids **1** of recent synthetic importance.

(6) X-ray data for the compounds **1b** and **3b** have been deposited to the Cambridge Crystallographic Data Centre.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded with tetramethylsilane as an internal standard. Optical rotations were measured at the indicated temperature with a sodium lamp (D line, 589 nm). Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol−heat or visualized by UV light where feasible. All solvents and reagents were used as received. The preparation of optically active **1a**,[3] **1b**,[1c] **1c**,[7] **1d**,[8] and **1e**[9] were conducted according to the reported procedures.

A Typical Procedure for the Racemization of Biaryls: Racemization of (*S*)-1a. To a solution of (*S*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*S*)-**1a** (1.03 g, 3.0 mmol) and Et_3N (668 mg, 6.6 mmol) in CH_2Cl_2 (21 mL) was added $SOCl_2$ (419 mg, 3.3 mmol) at 0 °C. After being stirred for 2 h at 25 °C, the reaction mixture was treated with water, and the organic layer was dried ($MgSO_4$) and evaporated. The residue was suspended in tetralin (21 mL) and was heated at 210 °C for 40 h. After evaporation of the solvent, the residue was treated with NaOH (480 mg, 12 mmol) in THF (6 mL) and water (6 mL) at 50 °C for 4 h. The mixture was acidified (pH = 1) by adding concentrated HCl and extracted with EtOAc. The extracts were combined, washed with water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc/AcOH = 50:50:1) to give racemized 1,1′-binaphthyl-2,2′-dicarboxylic acid (*R*,*S*)-**1a** (850 mg, 83% yield, *R*/*S* = 44:56). The enantiomeric purity was determined by HPLC (Chiralcel OD (Daicel), hexane/EtOH/TFA=90:10:0.1, 1.0 mL/min, 35 °C, 254 nm). Racemization of (*S*)-**1b**,**c** and (*R*)-**1d**,**e** was carried out by using the same procedure as that of (*S*)-**1a** except the reaction solvent, temperature and period (see Table 2). Determination of the enantiomeric purity of (*S*)-**1c** and (*R*)-**1d**,**e** was carried out by the use of the same procedure as that of (*S*)-**1a**. The enantiomeric purity of (*S*)-**1b** was determined by comparing the specific rotation with that of the pure material [$[\alpha]^{25}_D$ −111 (*c* 1.0, MeOH)].

***(S)*-2,6-Dichlorodinaphtho[2,3-*c*:3′,2′-*e*]oxepin-2,7-dione (3b).** To a solution of (*S*)-3,3′-dichloro-1,1′-binaphthyl-2,2′-dicarboxylic acid **1b** (200 mg, 0.486 mmol) and Et_3N (0.15 mL, 1.07 mmol) in CH_2Cl_2 (2.4 mL) was added $SOCl_2$ (69 mg, 0.584 mmol) in CH_2Cl_2 (0.58 mL) at 0 °C over 15 min. After being stirred for 11 h at 25 °C, the reaction mixture was treated with 10% aqueous citric acid and extracted with CH_2Cl_2. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/EtOAc = 20:1 to 10:1) to give the acid anhydride **3b** (145 mg, 76% yield) as colorless crystals: mp 248−258 °C dec; $[\alpha]^{20}_D$ +68 (*c* 0.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.64 (ddd, *J* = 1.3, 6.7, 8.9 Hz, 2H), 7.36 (ddd, *J* = 1.3, 6.7, 8.9 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H); IR (KBr) 1800, 1777 cm^{-1}; SIMS *m*/*z* 393 (M^+ + H). Anal. Calcd for $C_{22}H_{10}Cl_2O_3$: C, 67.20; H, 2.56. Found: C, 66.77; H, 2.51.

Supporting Information Available: ORTEP figures and table of X-ray crystallographic data of compounds (*S*)-**1b** and (*S*)-**3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0101196

(7) Leffler, J. E.; Graybill, B. M. *J. Phys. Chem.* **1959**, *63*, 1457.
(8) Kanoh, S.; Muramoto, H.; Kobayashi, N.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3659.
(9) Miyano, S.; Handa, S.; Shimizu, K.; Tagami, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1943.