Pergamon

Tetrahedron Letters, Vol. 37, No. 30, pp. 5343-5346, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01089-1

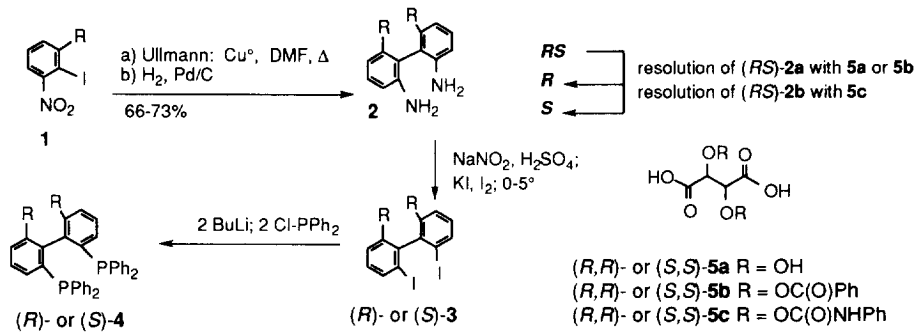
An Efficient Access to (*R*)- and (*S*)-6,6'-Dimethoxy-2,2'-diiodo-1,1'-biphenyl

Marco Cereghetti,* Rudolf Schmid, Peter Schönholzer and Alain Rageot

F.Hoffmann-La Roche Ltd., Pharmaceuticals Division, Preclinical Research, CH-4002 Basel, Switzerland

***Abstract**: In a better procedure than the known for (rac)-**2a**, the diamine (rac)-**2b** was resolved for the first time with the new resolving agent (R,R)- and (S,S)-2,3-di(phenylaminocarbonyl)tartaric acid (**5c**) (40-45% weight yields; >99% ee). The diamines (R)- or (S)-**2a** and **2b** were converted with >98% stereochemical retention into the diiodides (R)- and (S)-**3a** and **3b** and subsequently, without loss of optical purity, diphenylphosphinated to the known diphosphines (R)- and (S)-**4a** and **4b**.* Copyright © 1996 Elsevier Science Ltd

Chiral biaryls are valuable auxiliaries in a large number of efficient stereodifferentiating reactions. Their significance has been highlighted in various reviews.[1] Particularly, the C_2-symmetric diphosphines BINAP[2], **4a**[3], **4a** (Ph = cyclohexyl)[4], **4b**[5] and their analogues[6] are known as highly efficient ligands for transition metal-catalyzed asymmetric transformations. For this class of bidentate diphosphine ligands, the most convenient access proved to be the resolution of the corresponding racemic diphosphine oxides [2,3d,4-6] with O,O'-dibenzoyltartaric acid (**5b**)[7-9]. In analogy to similar work by Murdoch in the binaphthyl series[11], our efforts have focused on the improvement of the synthesis of enantiomerically pure 6,6'-dimethyl-2,2'-diiodo-1,1'-biphenyl (**3a**) and on the establishment of a synthesis for the 6,6'-dimethoxy analogue **3b** (*Scheme 1*). These enantiomerically pure diiodides are highly useful intermediates for the preparation of **4a**[3c] and **4b** and of analogues thereof[12].

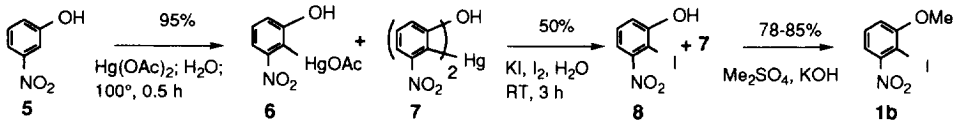


Scheme 1 **a: R = Me; b: R = OMe**

The enantiomers (*R*)- and (*S*)-**2a**, obtainable by resolution of diamine (*rac*)-**2a** with tartaric acid (**5a**) or dibenzoyltartaric acid (**5b**)[13], can be converted into the 2,2'-diiodo derivatives (*R*)-**3a** and (*S*)-**3a** by diazotization and treatment with potassium iodide[14]. Reported yields however are low or not specified. We report here that addition of 0.5 to 1 equiv. of iodine to the potassium iodide solution has a very remarkable effect on both

the product yield and product pattern in the iodination reaction[15]. Thus, reaction of e.g. (*R*)-**2a** (98-99% ee) ($NaNO_2$, H_2SO_4, KI, I_2, 0-5°) afforded a 75% yield of (*R*)-**3a**, while normal conditions ($NaNO_2$, H_2SO_4, KI, 0-5°) afforded a mixture of (*R*)-**3a**, the corresponding monoiodide and 2,2'-dimethylbiphenyl, from which only 28% of (*R*)-**3a** was isolated. It has also been reported that the enantiomer (*R*)-**3a** could be converted by consecutive treatment of (*R*)-**3a** with BuLi and chlorodiphenylphosphine at low temperature to optically pure (*R*)-**4a**[3c]. Applying an accurate ee-determination based on chiral stationary phase GC and HPLC methods[16] on starting materials, intermediates and on diphosphines or diphosphine oxides we evaluated an overall racemization of less than 2% for the two-step sequence (**2a** ⇒ **3a** ⇒ **4a**).

Racemic 6,6'-dimethoxy-2,2'-diaminobiphenyl [(*rac*)-**2b**] was synthesized by Ullmann coupling of 2-iodo-3-nitroanisol (**1b**) (obtained according to *Scheme 2*)[17a-c] followed by catalytic reduction of the nitro to the amino functions. This sequence as well as the conversion of (*rac*)-**2b** to diiodide (*rac*)-**3b** is known[17b-d], but to our knowledge no resolutions in this series have been described so far.



Scheme 2

With the new resolving agent *(R,R)*- or (*S,S*)-(2,3-di[(phenylamino)carbonyl]tartaric acid (**5c**), recently developed for the resolution of racemic diphosphine oxides[10], we obtained an exceptionally efficient resolution of the racemic diamine (*rac*)-**2b**. In contrast to the expected classical diastereomeric (1:1) salt formation, we isolated a (1:2) base/acid associate (NMR; X-ray). Thus, treatment of (*rac*)-**2b** with (*S,S*)-**5c** afforded the less soluble associate (*S*)-**2b**/(*S,S*)-**5c** in 80-90% yield of theory and in better than 99% de (CSP-HPLC analysis) after one or two crystallizations from ethyl acetate[18]. The more soluble mismatched (*R*)-**2b**-/(*S,S*)-**5c** (1:2) associate crystallized rather sluggishly and in low yield only from a mother liquid highly enriched in (*R*)-**2b**[18]. Attempts to resolve (*rac*)-**2b** with (*S*)-[(phenylamino)carbonyloxy]propionic acid[8,9], with (*R,R*)-(**5a**), or with (*R,R*)-**5b** failed.

The resolution of (*rac*)-**2b** with **5c** is remarkably efficient and highly selective. A comparably efficient resolution of (*rac*)-**2a** with this resolving agent (**5c**) could not be achieved. In this case we did obtain a crystalline associate, but its de was very low.

An enzymatic resolution of (*rac*)-2,2'-dihydroxy-6,6'-diiodobiphenyl ((*rac*)-**3b**, R = OH instead of OMe), obtained by demethylation of (*rac*)-**3b** with boron tribromide[17d], was investigated as an alternative entry into the optically active series. Although high ee's could be achieved in a monoacetylation reaction[19], this was considered much less practical than the chemical resolution of diamine (*rac*)-**2b**.

X-ray structural analysis of the (*S*)-**2b**/(*S,S*)-**5c** (1:2) associate revealed the presence of three water molecules in the unit cell (*Fig. 1*)[20]. The central water molecule is firmly bonded in a slightly distorted tetrahedral geometry through hydrogen bonds to the two diamino functions, which it bridges, and to the two distant water molecules. The diamino functions and the two distant water molecules form further hydrogen bonds with oxygen atoms of neighbouring **5c** molecules. The interplanar angle Θ of the least-squares planes of the biphenyl system is 79.7°.

The (*R*)-**2b**/(*R,R*)-**5c** and the (*S*)-**2b**/(*S,S*)-**5c** associates were decomposed by treatment with diluted NaOH to afford quantitatively the optically active diamines (*R*)- and (*S*)-**2b**. These in turn were converted by diazotization/iodination into the diiodides (*R*)- and (*S*)-**3b** (60-80% yield, > 98% ee) using the above described protocol.

In conclusion, a practical and efficient procedure for the preparation of the optically active diiodides (*R*)- and (*S*)-**3b** has been made available. Therefrom, the diphosphines **4b** and analogues thereof are accessible in one-step conversions in yields of 70-85%[12,21]. Naturally the same approach to the (*R*)- and (*S*)-diiodides **3a** and diphosphines **4a** is feasible, but restrained by the inferior resolution of (*rac*)-**2a**[13].

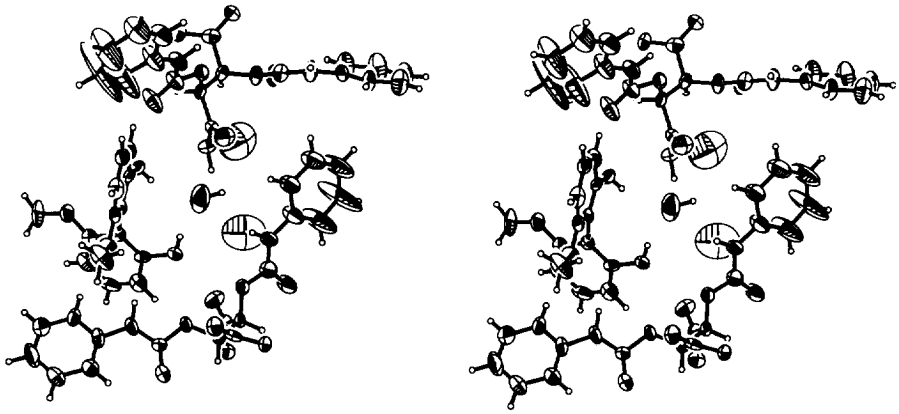


Fig. 1. ORTEP stereoscopic drawing of the molecular structure of the (*S*)-**2b**/(*S,S*)-**5c** (1:2) associate including three H_2O molecules.

References and Notes

* Present address: Dr. Marco Cereghetti, Rheintalweg 5, CH-4125 Riehen, Switzerland

1. a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salavadori, P. *Synthesis* **1992**, 503; b) Takaya, H.; Ohta, T.; Mashima, K.; Noyori, R. *Pure and Appl. Chem.* **1990**, *62*, 1135; c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345; d) Otsuka, S.; Tani, H. *Synthesis* **1991**, 665; e) Otha, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, T. *J. Org. Chem.* **1995**, *60*, 357; f) Trost, B.M. *Angew. Chem.* **1995**, *107*, 285; g) Whitesell, J.K. *Chem. Rev.* **1989**, *89*, 1581.
2. a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932; b) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245; c) Noyori, R. *Chem. Soc. Rev.* **1989**, *18*, 187.
3. a) Schmid, R.; Cereghetti, M.; Heiser, B.; Schönholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897; b) Hansen, H.-J.; Schmid, R.; to *F.Hoffmann-La Roche Ltd.*, Eur. Pat. 104375 (6.8.1983) (*Chem. Abstr.* **1984**, *101*, 111196s); c) Frejd, T.; Klingstedt, T. *Acta Chem. Scand.* **1989**, *43*, 670; see also: Frejd, T.; Klingstedt, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1021; d) Miyashita, A.; Nagano, K.; Abe, T.; Abe, M.; Ojima, T.; Nohira, H.; Takaya, H.; Noyori, R. 51th Annual Meeting of the Chemical Society of Japan, Kyoto, April 1986, Abstr. ITO6, p.1267.
4. a) Chiba, T.; Miyashita, A.; Nohira, H.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 2351; b) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1; c) Miyashita, A.; Karino, H.; Shimamura, J.; Chiba, T.; Nagano, K.; Nohira, H.; Takaya, H. *Chem. Lett.* **1989**, 1849.
5. a) Schmid, R.; Foricher, J.; Cereghetti, M.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370; b) Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 51.
6. a) Murata, M.; Morimoto, T.; Achiwa, K. *Synlett* **1991**, 827; b) Murata, M.; Yamamoto, N.; Yoshikawa, K.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 2767; c) Yamamoto, N.; Murata, M.; Morimoto, T.; Achiwa, K. *Chem. Pharm. Bull.* **1991**, *39*, 1085; d) Yoshikawa, K.; Yamamoto, N.; Murata, M.; Awano, K.; Morimoto, T.; Achiwa, K. *Tetrahedron: Asymmetry* **1992**, *3*, 13.
7. For the optical resolution of racemic phosphine oxides with **5b** see: a) Brunner, H.; Pieronczyk, W. *Angew. Chem. Int. Ed.* **1979**, *18*, 620; b) Brunner, H.; Pieronczyk, W.; Schönhammer, B.; Streng, K.; Bernal, I.; Korp, J. *Chem. Ber.* **1981**, *114*, 1137; c) Döbler, C.; Kreuzfeld, H.-J. *J. Prakt. Chem.* **1981**, *323*, 667; d) Minami, T.; Okada, Y.; Nomura, R.; Hirota, S.; Nagahara, Y.; Fukuyama, K. *Chem. Lett.* **1986**, 613; e) Jap. Pat. 62/12787 (21.1.1987), *IHARA Chemical Industry Co.*; f) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012; g) Horner, L.; Balzer, W.D. *Tetrahedron Lett.* **1965**, 1157; h) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629; i) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth. Coll. Vol. VIII* **1993**, 57. For BINAPO, camphorsulfonic acid has also been reported as a resolving agent[2c].

8. In some cases where resolution of racemic bis(diphenylphosphine oxides) with **5b** failed, we recognized an enhanced resolving power of the corresponding phenylcarbamates. In analogy to a commercially available resolving agent for amines[9], we developed the new resolving agent **5c**, the phenylcarbamates of (*R,R*)- and (*S,S*)-**5a**[10]. With this agent (**5c**), but not with **5b**, the diphosphine oxides (*rac*)-2,2'-bis[di-(3-tolyl)phosphoryl]-1,1'-binapthyl [(*rac*)-mTolBINAPO], reported to be resolved by CSP-HPLC only [see Kumobayashi, H.; Taketomi, T.; to Takasago Int. Corp., Eur. Pat. Appl. 0 403 188 (19.12.1990)], and (rac)-2,2'-dimethyl-6,6'-bis[di-(4-tolyl)phosphoryl]-1,1'-biphenyl were separated into their optical antipodes.
9. a) Brown, E.; Viot, F.; LeFloc'h, Y. *Tetrahedron Lett.* **1985**, *26*, 4451; (*S*)-(-)-[(Phenylamino)carbonyloxy]propionic acid can be obtained from JANSSEN-CHIMICA. b) Salvadori, P.; Pini, D.; Rosini, C.; Ucello-Baretta, G.; Bertucci, C. (*J. Chromat.* **1988**, *450*, 163) used this agent, linked to γ-aminopropylsilanized silicagel, as chiral stationary phase in HPLC.
10. Cereghetti, M.; Rageot, A.; to *F.Hoffmann-La Roche Ltd.*, Eur. Pat. 511 558 (4.11.1992). 2,3-Di(phenylaminocarbonyl)tartaric acid (**5c**). This agent was prepared by reacting dibenzyl (*R,R*)- and (*S,S*)-tartrate with phenylisocyanate and hydrogenolysis of the resulting product. (*R,R*)-**5c**: mp. 203-204°, $[\alpha]_D^{20°}$ -94.8 (c = 1, EtOAc), $[\alpha]_D^{20°}$ -84.3 (c = 1, DMSO); (*S,S*)-**5c**: mp. 201.5-202°, $[\alpha]_D^{20°}$ +98.3 (c = 1, EtOAc), $[\alpha]_D^{20°}$ +86.4 (c = 1, DMSO), $[\alpha]_D^{20°}$ +71.1 (c = 1, MeOH).
11. a) Brown, K.J.; Berry, M.S.; Watermann, K.C.; Lingenfelter, D.; Murdoch, J.R. *J. Am. Chem. Soc.* **1984**, *106*, 4717; b) Brown, K.J.; Murdoch, J.R. *J. Am. Chem. Soc.* **1984**, *106*, 7843; c) Brown, K.J.; Berry, M.S.; Murdoch, J.R. *J. Org. Chem.* **1985**, *50*, 4345; d) Uehara, A.; Kubota, T.; Tsuchiya, R. *Chem. Lett.* **1983**, 441.
12. Cereghetti, M.; Arnold, W.; Broger, E.A.; Rageot, A.; following contribution in this issue.
13. The resolution of (*rac*)-**2a** is considered rather tedious. Indeed the resolution of (*rac*)-**2a** with (*R,R*)- or (*S,S*)-**5a** as well as (*R,R*)- or (*S,S*)-**5b** required up to five recrystallizations and afforded optically pure **2a** in 13-20% weight yields only; see: a) Meisenheimer, J.; Höring, M. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 1425; b) Lew, D.; Amer, I. *Tetrahedron: Asymmetry* **1993**, *4*, 2147; c) Marxen, T.L.; Johnson, B.J.; Nilsson, P.V.; Pignolet, L.H. *Inorg. Chem.* **1984**, *23*, 4663; d) Suda, H.; Motoi, M.; Fujii, M.; Kanoh, S.; Yoshida, H. *Tetrahedron Lett.* **1979**, *20*, 4565.
14. a) Bell, F. *J. Chem. Soc.* **1934**, 835; b) Mislow, K.; Glass, M.A.W.; O'Brien, R.E.; Rutkin, P.; Steinberg, D.H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455.
15. Such a procedure had been previously developed in the binaphthyl series; Coffen, D.L.; Rossiter, B.E.; *Hoffmann-La Roche Inc.*, unpublished results; cf. also Coffen, D.L.; Schaer, B.; Bizzarro, F.T.; Cheung, J.B. *J. Org. Chem.* **1984**, *49*, 296.
16. ee-Analyses for all 6,6'-dimethoxy- and 6,6'-dimethyl compounds, except for **3a**, were performed on commercial CSP-HPLC columns (e.g. Chiralpak AD 305; Daicel). In case of (*rac*)-**3a**, enantiomer separation was successful by CSP-GC only; see: Walther, W.; Cereghetti, M. *J. High Res. Chromat.* **1991**,*14*, 57; and unpublished results of Schärer, J.; Glinz, E.; Ranalder, U.B; Cereghetti, M. *F.Hoffmann-La Roche Ltd.*
17. a) Wawzonek, S.; Wang, S.C. *J. Org. Chem.* **1951**, *16*, 1271; b) Baker, W.; Barton, J.W.; McOmie, J.F.W. *J. Chem.* Soc. **1958**, 2658; c) Blatchy, J.M.; Gardner, D.V.; McOmie, J.F.W.; Watts, M.L. *J. Chem. Soc.* **1968**, 1545; d) Hine, J.; Ahn, K. *J. Org. Chem.* **1987**, *52*, 2089.
18. (*S*)-**2b** / (*S,S*)-**5c** (1:2) associate (less soluble): mp. 145-150°, $[\alpha]_D^{20°}$ +40.8 (c = 1, MeOH);
(*R*)-**2b** / (*S,S*)-**5c** (1:2) associate (more soluble): mp. 143-149°, $[\alpha]_D^{20°}$ +60.8 (c = 1, MeOH).
19. In a screening, thirty commercial enzymes were tested for enantioselective acetylation of (*rac*)-2,2'-dihydroxy-6,6'-diiodobiphenyl using vinyl acetate as acetylating agent. Lipase TOYOBO was the only active enzyme generating exclusively the (*R*)-monoacetate (95% ee; no diacetate formation). Unpublished results of Wirz, B. *F.Hoffmann-La Roche Ltd.* For the resolution of 2,2'-dihydroxy-1,1'-binaphthalene with lipase TOYOBO see: Inagaki, M.; Hiratake, J.; Nishioka, T.; Oda, J. *Agric. Biol. Chem.* **1989**, *53*, 1879.
20. Coordinates and thermal parameters of the X-ray structure have been deposited at the *Crystallographic Data Centre*, Cambridge, University Chemical Lab., Cambridge CB2 1EW, England.
21. (*R*)-**2a**, δ_{Me} 1.97 ppm; $[\alpha]_D^{20°}$ -39.1 (c=1, 1N HCl); mp: 159-160.5° (cf. also [14b]); (*R*)-**3a**, δ_{Me} 2.01 ppm; $[\alpha]_D^{20°}$ -22.9 (c = 1, EtOH); mp: 93° (cf. also [14b,3c]); (*R*)-**4a**, δ_{Me} 1.40 ppm; $[\alpha]_D^{20°}$ -42.0 (c = 1, $CHCl_3$), mp. 211.5-213° (cf. also [3a,c]); (*R*)-**2b**, δ_{Me} 3.71 ppm; $[\alpha]_D^{20°}$ +32.8 (c = 1, $CHCl_3$); mp: 86.0-86.9°; (*R*)-**3b**, δ_{Me} 3.74 ppm; $[\alpha]_D^{20°}$ +55.1 (c = 1, $CHCl_3$), mp: 163-167°; (*R*)-**4b**, δ_{Me} 3.15 ppm; $[\alpha]_D^{20°}$ +42.3 (c = 1, $CHCl_3$), mp. 213-214° (cf. also [5a]).

(*Received in Germany* 19 *December* 1996; *revised* 22 *May* 1996; *accepted* 31 *May* 1996)