

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

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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 C₂-symmetric diphosphines BINAP², **4a**³, **4a** (Ph = cyclohexyl)⁴, **4b**⁵ and their analogues⁶ are known as highly efficient ligands for transition metalcatalyzed 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 series¹¹, 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 thereof¹².



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 iodide¹⁴. 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 reaction¹⁵. Thus, reaction of e.g. (R)-2a (98-99% ee) (NaNO₂, H₂SO₄, KI, I₂, 0-5°) afforded a 75% yield of (R)-3a, while normal conditions (NaNO₂, H₂SO₄, 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 methods¹⁶ on starting materials, intermediates and on diphosphines or diphosphine oxides we evaluated an overall racemization of less than 2% for the two-step sequence ($2a \Rightarrow 3a \Rightarrow 4a$).

Racemic 6,6'-dimethoxy-2,2'-diaminobiphenyl [(rac)-2b] was synthesized by Ullmann coupling of 2iodo-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.



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 oxides¹⁰, 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 acetate¹⁸. 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)-2b¹⁸. 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 reaction¹⁹, 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)-2a¹³.



Fig. 1. ORTEP stereoscopic drawing of the molecular structure of the (S)-2b/(S,S)-5c (1:2) associate including three H₂O molecules.

References and Notes

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 (*R*)-2b / (S,S)-5c (1:2) associate (more soluble): mp. 143-149°, [α]_D^{20°} +60.8 (c = 1, MeOH).
- 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.Hotfmann-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.
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