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Synthesis of Atropisomeric 2,2'-Bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BICHEP) and Its Use in Rh(I)-catalyzed Asymmetric Hydrogenation of Prochiral Olefins

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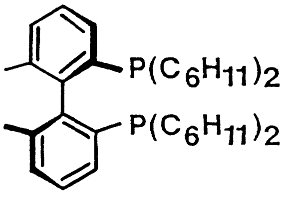
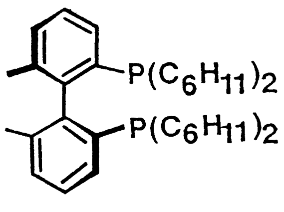
The atropisomeric bis(dialkylarylphosphine) ligands, (*R*)-(-)- and (*S*)-(+)-2,2'-bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl (BICHEP) (**1**) have been newly synthesized, whose Rh(I) complexes are highly efficient catalysts for asymmetric hydrogenations of ethyl α-(benzamido)cinnamate and dimethyl itaconate in up to 98% yields and 98-99% enantiomeric excess.

Substantial effectiveness of the axially dissymmetric diphosphines such as BINAP,1) NAPHOS,2) BDPAB,3) NBDP,4) and MABP5) has been ubiquitously proved in transition metal-catalyzed asymmetric reactions. Currently, much efforts have been focused on molecular design and synthesis of new atropisomeric diphosphines which have a number of interesting characteristics such as molecular pliability. Optically pure 2,2'-bis(diphenylphosphino)-6,6'-dimethyl-1,1'-biphenyl (**2**), an atropisomeric *bis(triarylphosphine)*, has been prepared6) and used as a chiral ligand for Rh(I)-catalyzed enantioselective hydrogenation of α-(acylamino)acrylic acids, though the efficiency is not satisfactory. The complex has also been used for asymmetric conversion of allylamines to enamines by 1,3-hydrogen migration.7) Since biphenyl-based diphosphines are important class of compounds as chiral ligands, more extensive and systematic studies have been required. On relevance of our previous works8) on the effective optical

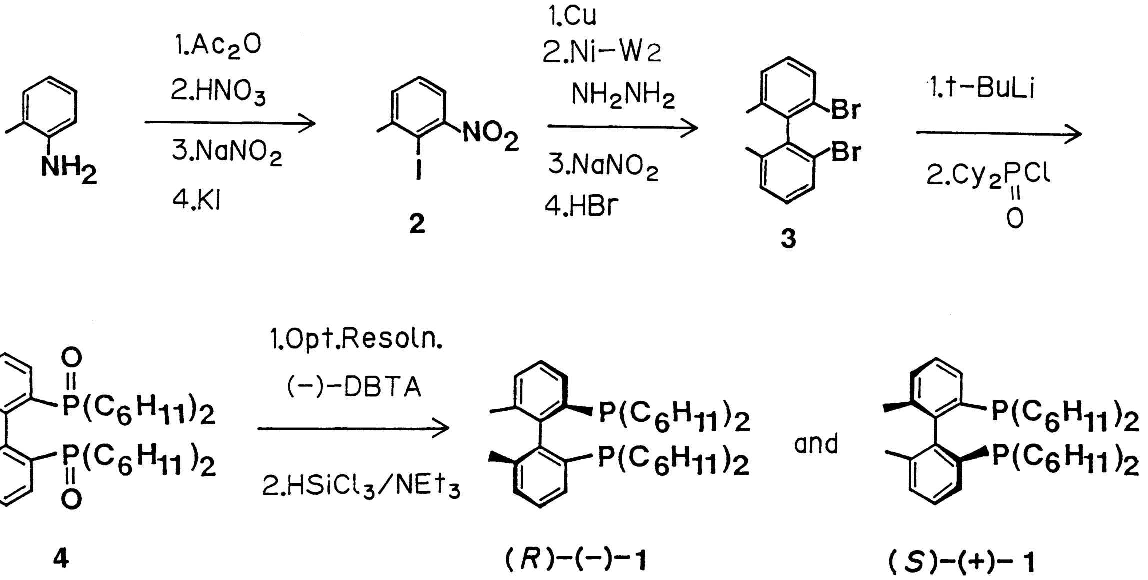


(*R*)-(-)-1



(*S*)-(+)-1

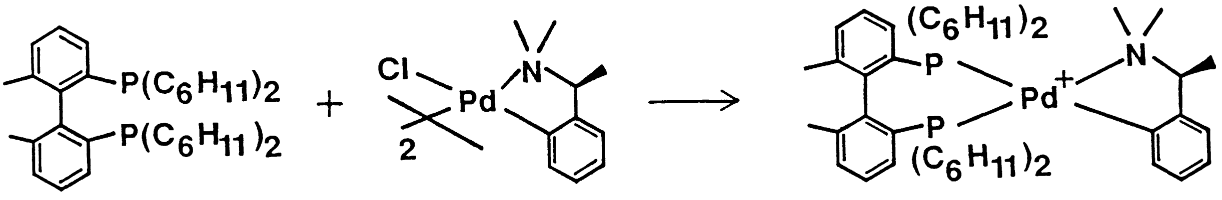
resolution of racemic **2**, our interests have been further extended to the synthesis of new atropisomeric bis(dialkylarylphosphine) **1** having biphenyl framework. In this paper we report the synthesis of (*R*)-(-)- and (*S*)-(+)-2,2'-bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl (**1**) (hereafter abbreviated to BICHEP), and describe their high efficiency in Rh(I)-catalyzed asymmetric hydrogenation of α-(benzamido)cinnamic acid and itaconic acid esters. Optically pure BICHEP (**1**) was prepared starting from *o*-toluidine as outlined in the Scheme. 2-Amino-3-nitrotoluene derived from *o*-toluidine was quantitatively converted into 2-iodo-3-nitrotoluene (**3**) by diazotization followed by iodination. Starting from **3**, racemic dibromide **4** was prepared in an overall yield of 36% by means of Ullmann coupling, catalytic reduction using hydrazine over Ni-W_2, and then Sandmeyer reaction.



Dilithiation of **4** with *t*-butyllithium at -78 °C followed by the treatment with dicyclohexylphosphinyl chloride resulted in the formation of diphosphine dioxide **5** (abbreviated to BICHEPO) in 34% yield.

Effective optical resolution of BICHEPO was attained by using optically active (2*R*,3*R*)-(-)- or (2*S*,3*S*)-(+)-2,3-*O*-dibenzoyltartaric acid [(-)-DBTA or(+)-DBTA] as a resolving agent.9) When a solution of (-)-DBTA in a mixture of ethyl acetate and chloroform (ca. 18:1 ratio) was added into a stirred boiling solution of (+)-**5** in chloroform, less soluble diastereomer precipitated as white crystals in a few minutes. A single recrystallization of these white solids from a mixture of ethyl acetate and chloroform (ca. 15:1 ratio) afforded a diastereomerically pure complex of (*S*)-(+)-**5** and (-)-DBTA in 64% yield of theory. The optically pure antipode, (*R*)-(-)-**5**, which was recovered from the mother liquor by the treatment with aqueous base, was isolated in 58% yield of theory after a couple of recrystallizations.

Stereospecific reduction of the resolved BICHEPO to desired optically pure BICHEP was performed without any racemization in 85% yield by heating with a large excess of trichlorosilane and triethylamine in xylene, initially at 120 °C for 3 h and then at 130 °C for 2 h. The product was then purified by means of silica-gel short column-chromatography under N_2 atmosphere using benzene as an eluent. A couple of recrystallizations of the resulting white crystalline solid from ethyl acetate led to an optically pure BICHEP.$^{10)}$ Enantiomeric purities of BICHEP were determined by NMR measurements of its diastereomeric complexes **6** obtained from the reaction of (R)-**1** or (S)-**1** with (+)-di-μ-chlorobis[(S)-N,N-dimethyl(1-phenylethyl)amine-2C,N]dipalladium(II),[(S)-**6**].$^{11)}$



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^{31}P-NMR (161 MHz) of the Pd complex of (R)-(-)-**1** obtained in situ exhibited only two sets of doublet assignable to the two unequivalent phosphorus atoms at 31.1 (J_{P-P} 36.2 Hz) and 12.5 ppm, respectively. Another Pd complex of (S)-(+)-**1** showed two sets of doublet at 30.1 (J_{P-P} 36.2) and 11.1 ppm. Based on these ^{31}P-NMR analyses, the enantiomeric purities of BICHEP, obtained via optical resolution at BICHEPO stage, were determined to be in the range of 99.5-100%.

The absolute configuration of (+)-**5** was determined by comparison of its chiroptical properties with those of **2** whose absolute configurations have been determined by X-ray crystallography.$^{7)}$ CD spectrum of (+)-**5** in ethanol exhibited a strong positive maximum at 230 and a weaker negative maximum at 293 nm giving nearly identical Cotton curve with (S)-(+)-**2**, while the antipode (-)-**5** gave a complete mirror-image curve having signal maxima at the same wavelengths as (+)-**5**. Comparison of the CD spectrum of (+)-**5** particularly on the shape and the signs of the major Cotton effects with that of (S)-(+)-**2** confirmed that this (+)-enantiomer has the S configuration. These observed strong and clear Cotton effects appear to be characteristic of the phosphino-substituted twisted biphenyl and binaphthyl systems.$^{7,12)}$

One of the most interesting and important features of BICHEP is that its Rh(I) complex creates excellent chiral-recognition ability for enantioface differenciating reactions. Thus, the optically pure BICHEP ligand was tested for asymmetric hydrogenation of prochiral olefins. The cationic Rh(I) complex, prepared from the reaction of $[Rh(norbornadiene)_2]ClO_4$ with an equimolar amount of optically pure (R)-BICHEP in methylene chloride, was used as a hydrogenation catalyst without any further purification. The cationic Rh(I) complex has been found to possess excellent catalytic activity and enantioselectivity for the asymmetric hydrogenation both of ethyl (*Z*)-α-(benzamido)cinnamate and dimethyl itaconate affording *N*-benzoyl-(*S*)-phenylalanine ethyl ester and dimethyl (*R*)-α-methylsuccinate in 98 and 99% ee, respectively.[13)] In contrast, the analogous cationic Rh(I) complex having the bis(triarylphosphine) ligand **2** was reported to have poor enantioselectivity and show low catalytic activity for asymmetric hydrogenation of ethyl (*Z*)-α-(benzamido)cinnamate (14% ee).[6)] Further potential applicability of BICHEP as a chiral ligand in catalytic asymmetric reactions are now actively under investigation.

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10) (*S*)-(+)-BICHEP [(*S*)-(+)-**1** : mp 168-172 °C; $[\alpha]_D$ +119.5° (*c* 0.83, CH_2Cl_2); MS (75eV, EI) 574(M^+); ^{1}H-NMR (CCl_4) 0.8-2.2 ppm (m, CH_3, C_6H_{11}, 50H), 7.1-7.3 (m, C_6H_5, 6H); ^{31}P-NMR (CD_2Cl_2) -9.7 ppm (upfield of external H_3PO_4).
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13) The reactions were run with substrate (1.0-2.0 mmol)/catalyst in 95:1 ratio in 20 ml ethanol at 5 atm of initial H_2 pressure, and completed within half an hour at room temperature. The conversions determined by ^{1}H-NMR were in the range of 95-100%. Optical yields were calculated with respect to the values reported.[1)]

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