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Synthesis of Chiral 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) via a Novel Nickel-Catalyzed Phosphine Insertion

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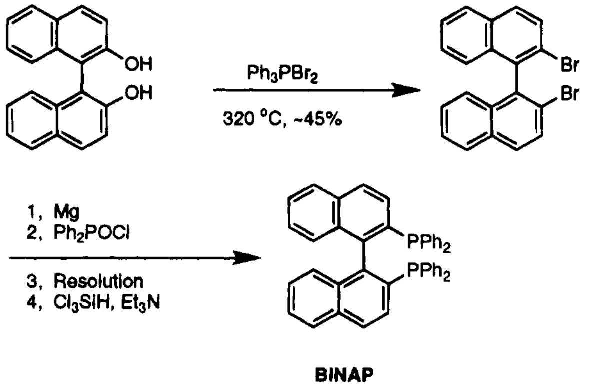
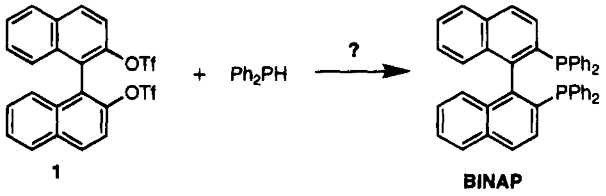
2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), introduced in the early 1980's,[1] has become one of the most successful chiral ligands for catalytic asymmetric induction.[2] Its wide application has been somewhat limited due to the scarce supply and expense of BINAP and up to now, there has been only one reported practical synthesis of chiral BINAP (Scheme 1).[3] This practical route has several drawbacks, including (1) a low-yielding bromination reaction at 240−320 °C with evolution of hot hydrogen bromide, (2) a resolution late in the sequence that results in a low overall yield (14%) for the entire sequence. Due to these drawbacks, which make the chemistry difficult and dangerous to run on large scale, we sought a simple and efficient approach to BINAP.

Scheme 1



Scheme 2



The most attractive approach would be to react the easily accessible chiral ditriflate of 1,1′-binaphthol **1**[4] with diphenylphosphine giving BINAP directly (Scheme 2).[5] As far as we know, there is no literature example of an aryl triflate to aryl phosphine conversion using diphenylphosphine as a reagent.[6,7] There are many problems associated with this strategy. Using nucleophilic replacement chemistry (such as $LiPPh_2$, $KPPh_2$ etc.),[6] the phosphorus atom would likely attack the sulfur of the triflate group instead of the carbon center. A transition metal-catalyzed approach offers the best hope, but one potential problem could be catalyst poisoning by the large excess of phosphine ligands present such as the starting material diphenylphosphine, intermediates, and the product BINAP.[8] In order to minimize catalyst poisoning, it is imperative to choose a transition metal which will not bind BINAP. One of the most suitable candidates is nickel,[9] which is smaller and harder (based on hard−soft acid−base theory) than second or third row transition metals such as palladium, rhodium, ruthenium, platinum, etc.[10] Consequently, we concentrated on using a nickel-catalyzed coupling reaction between ditriflate of 1,1′-binaphthol **1** and diphenylphosphine. We screened numerous readily available nickel catalysts {$NiCl_2$, $NiBr_2$, $NiCl_2$/dppm, $NiCl_2$/dppb, $NiCl_2$/dppf, $NiCl_2$dppp, $NiCl_2$dppe, $NiCl_2(Ph_3P)_2$, $Ni(CO)_2(Ph_3P)_2$, $Ni(Ph_3P)_4$, $Ni[(PhO)_3P]_4$},[11] and found that several catalyzed BINAP formation. After optimization, we found that heating a mixture of chiral ditriflate of binaphthol **1**, diphenylphosphine, and DABCO with 10 mol % [bis(diphenylphosphino)ethane]nickel dichloride in DMF at 100 °C for 2−3 days provided the desired chiral BINAP in 75% yield. After the starting material was completely consumed, the dark brown reaction solution was cooled to 0 °C and filtered. The purity of the isolated BINAP was 95−97 area % by HPLC (at 220 nm) with the major impurity being the monooxide of BINAP (1−3%).[3,12] There was no racemization during the coupling reaction.

The monooxide of BINAP **3** formed by BINAP oxidation by oxygen and from coupling with diphenylphosphine oxide, a 5% impurity in the diphenylphosphine reagent. With vigorous deoxygenation, its level could be reduced to 1−3% (Scheme 3).

We were not able to observe intermediate **2**, indicating that the second coupling step was much faster than the

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[1] (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Toriumi, K.; Ito, T.; Takaya, H.; Souchi, T.; Noyori, R. *Acta Crystallogr. Sect. B: Struct. Sci.* **1982**, *B32*, 807. (c) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245.

[2] (a) Ojima, I. *Catalytic Asymmetric Synthesis*, VCH: New York, New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1994.

[3] (a) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. (b) Takaya, H.; Akutaguwa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20.

[4] (a) Kawashima, M.; Hirata, R. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2002. (b) Tanaka, K.; Okada, T.; Toda, F. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1147. (c) Toda, F.; Tanaka, K. *J. Org. Chem.* **1988**, *53*, 3607. (d) Dolle, R. E.; Schimidt, S. J.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1987**, 904. (e) Vondenhof, M.; Mattay, J. *Tetrahedron Lett.* **1990**, *31*, 985.

[5] For reaction of ditriflate **3** with diphenylphosphine oxide to give the mono phosphine oxide, see: (a) Kurz, L.; Lee, G.; Morgans, D., Jr.; Waldyke, M. J.; Ward, T. *Tetrahedron Lett.* **1990**, *31*, 6321. (b) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

[6] Aguiar, A. M.; Greenberg, H. J.; Rubenstein K. E. *J. Org. Chem.* **1963**, *28*, 2091.

[7] Examples of cross-couplings using phosphine−boranes are known: (a) Imamoto, T.; Oshiki, Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244. (b) Imamoto, T. *Pure Appl. Chem.* **1993**, *65*, 655.

[8] Tamao, K.; Kumada, M. *The Chemistry of the Metal-Carbon Bond*, V4; John Wiley & Sons Ltd.: New York, New York, 1987: pp 820−887.

[9] (a) Cassar, L.; Foà, M. J. *Organomet. Chem.* **1974**, *74*, 75. (b) Morvillo, A.; Turco, A. *J. Organomet. Chem.* **1982**, *224*, 387. (c) Cramer, R.; Coulson, D. R. *J. Org. Chem.* **1975**, *40*, 2267.

[10] (a) Parshall, G. W. *J. Am. Chem. Soc.* **1974**, *96*, 2360. (b) Otsuka, S.; Nakamura, A.; Yoshida, T.; Naruto, M.; Ataka, K. *J. Am. Chem. Soc.* **1973**, *95*, 3180. (c) Braterman, P. S.; Cross, R. J.; Yong, G. B. *J. Chem. Soc. Dalton Trans.* **1976**, 1306. (d) Komiya, S.; Albright, T. A.; Hoffmann, R.; Kochi, J. K. *J. Am. Chem. Soc.* **1977**, *99*, 8440.

[11] dppm = bis(diphenylphosphino)methane; dppb = 1,4-bis(diphenylphosphino)butane; dppf = 1,1′-bis(diphenylphosphino)ferrocene; dppp = 1,3-bis(diphenylphosphino)propane; dppe = 1,2-bis(diphenylphosphino)ethane.

[12] Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177.

0022-3263/94/1959-7180$04.50/0

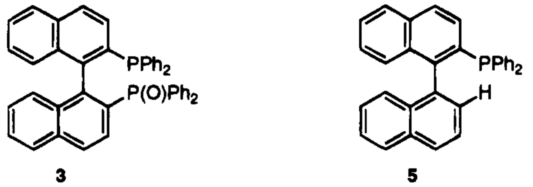
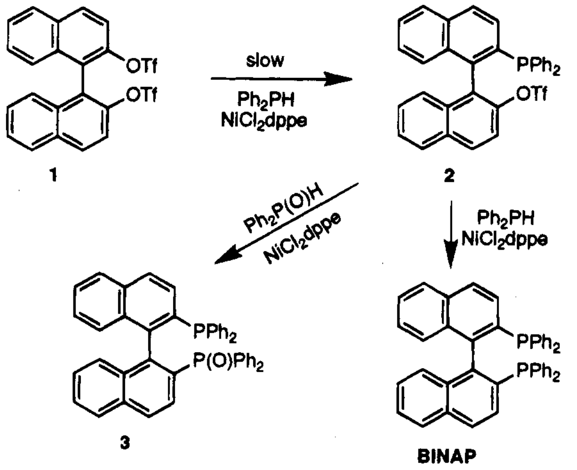
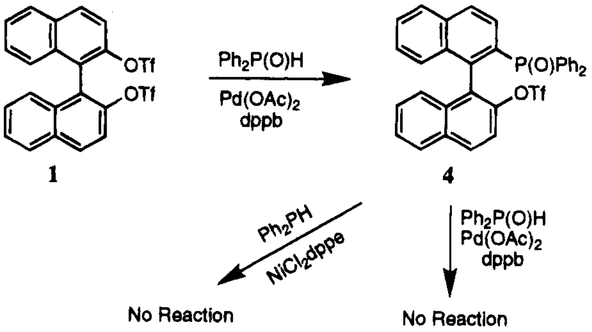


Figure 1. Reaction byproducts.

Scheme 3



Scheme 4



first one, possibly due to internal coordination of the nickel catalyst. Besides $NiCl_2$dppe, the coupling reaction with most other nickel catalysts mentioned above also gave some desired product; in contrast, palladium catalysts [Ph_2PH, $Pd(OAc)_2$, dppb] gave no reaction at all. It is interesting to note that if we did the first coupling reaction of triflate **1** with diphenylphosphine oxide under palladium-catalyzed conditions, the resulting intermediate **4** did not react further with diphenylphosphine under our nickel ($NiCl_2$dppe)-catalyzed conditions (Scheme 4). Steric hindrance of the phosphine oxide was most likely responsible for the failure of the second coupling reaction [$Ph_2PH/NiCl_2$dppe, or $Ph_2P(O)H/Pd(OAc)_2$, dppb], since double cyanation or carbonylation of ditriflate **1** can occur under nickel- or palladium-catalyzed conditions.[5,13]

Other reaction conditions were also critical. As solvent, only DMF gave satisfactory results. Less polar solvents such as ethanol, toluene, dioxane gave no reaction at all, while DMSO was not suitable for this reaction due to oxidation.[14] Acetonitrile and *N*-methylpyrrolidinone gave slow reactions and poor conversion. The choice of amine base and amount of the base strongly influenced the reaction selectivity and the reaction rate.[13] Originally, we used diisopropylethylamine as a base, and while the reaction went to completion, two major impurities were generated: one of them was the monoxide of BINAP **3** and the other was the monoreduced product **5** (Figure 1). Both impurities were significantly reduced when triethylamine was used instead of diisopropylethylamine. Numerous other organic bases were also tried (pyridine, (dimethylamino)pyridine, 2,6-di-*tert*-butylpyridine, DBU, DABCO) and DABCO was found to give the best result.[15]

In summary, we have found a simple and efficient way to prepare chiral BINAP using a novel nickel-catalyzed diphenylphosphine coupling reaction.

Experimental Section

NMR (^1H, ^{13}C, ^{31}P) were recorded with a Bruker AM-250 with $CDCl_3$ as solvent. The reactions and products were assayed by HPLC (Spectra-Physics P4000) using a Zorbax Rx-C8 column with water and acetonitrile as eluting solvents. The melting point is uncorrected. Rotation was measured on a Perkin-Elmer 241 polarimeter. Anhydrous DMF, $NiCl_2$dppe, diphenylphosphine (Ph_2PH), and 1,4-diazabicyclo[2.2.2]octane (DABCO) were all purchased from Aldrich and used without further purification. The reactions were run under the positive pressure of nitrogen, and all the reagents were degassed by vacuum and then purged with nitrogen. Resolution of binaphthol and preparation of the ditriflate of binaphthol were carried out using the literature procedures.[4a,e]

Preparation of (*R*)-(+)-BINAP. To a solution of $NiCl_2$dppe (530 mg, 1 mmol) in DMF (20 mL) was added diphenylphosphine (1 mL, 5.75 mmol) at room temperature, and then the resulting solution was heated at 100 °C. After heating at 100 °C for 30 min, a solution of chiral ditriflate of binaphthol (5.50 g, 10 mmol, 95% ee) and DABCO (4.5 g, 40 mmol) in DMF (30 mL) was added at once, the resulting dark green solution was kept at 100 °C, and three additional portions of diphenylphosphine (3 × 1 mL) were added at 1, 3, and 7 h later. The reaction was kept at 100 °C until the starting material ditriflate of binaphthol was completely consumed (2–3 days), and then the dark brown solution was cooled down to 0–5 °C with an ice bath. The desired product was filtered and the filter cake was washed with methanol (2 × 10 mL) and dried under vacuum. The isolated product (4.95 g, 75%) was a white crystalline compound with chemical purity around 95–97 area % (HPLC, 220 nm) with one major impurity as a monooxide of BINAP (1–3 %). The isolated BINAP was identical to commercial BINAP (Aldrich) as judged by HPLC and the ^1H, ^{13}C, and ^{31}P NMR were identical to the literature data:[3,16] mp 237–241 °C, $[\alpha]_D = +207°$ (benzene, *c* 0.5), [lit. ref $[\alpha]^{20}_D = +217°$ (benzene, *c* 0.5) 98.4 % ee]. Anal. Calcd. for $C_{44}H_{32}P_2$: C, 84.86; H, 5.17; P, 9.95. Found: C, 84.69; H, 5.17; P, 10.01.

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(13) Ohta, T.; Ito, M.; Inagaki, K.; Takaya, H. *Tetrahedron Lett.* **1993**, *34*, 1615.

(14) (a) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908. (b) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460.

(15) (a) Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7548. (b) Komiya, S.; Abe, Y.; Yamamoto, A.; Yamamoto, T. *Organomet.* **1983**, *2*, 1467. (c) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.

(16) The Aldrich Library of ^{13}C and ^1H FT NMR Spectra; Aldrich: Milwaukee, WI, 1993; Vol. 2, p 1663.