Pergamon

Tetrahedron Letters 40 (1999) 1095–1098

TETRAHEDRON LETTERS

Preparation of 2-Amino-2'-Hydroxy-1,1'-Binaphthyl and *N*-Arylated 2-Amino-1,1'-Binaphthyl Derivatives via Palladium-Catalyzed Amination

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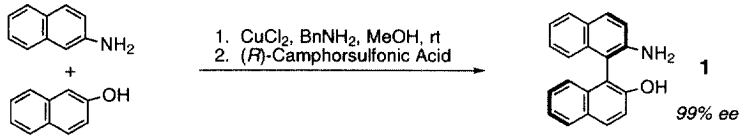
Received 9 November 1998; revised 7 December 1998; accepted 8 December 1998

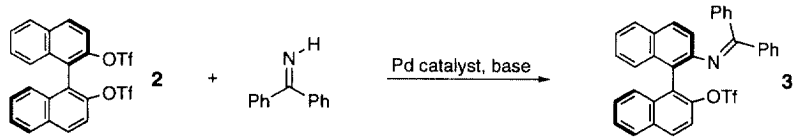
Abstract. Palladium-catalyzed amination reactions were carried out with 2-triflato-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (**5**) and benzophenone imine followed by hydrolysis of the imine and hydrogenolysis of the benzyl protecting group to afford 2-amino-2'-hydroxy-1,1'-binaphthyl (**1**). Arylamines were also coupled successfully with **5** under similar conditions.

Optically pure binaphthyl derivatives have achieved prominent stature through their use as chiral ligands in metal-catalyzed processes.[1] Among the most notable ligands are BINOL and BINAP which have found broad application partly due to their relatively facile preparations and commercial availability.[1] A more recent addition to the family of axially chiral ligands is 2-amino-2'-hydroxy-1,1'-binaphthyl (**1**) which has typically been prepared by the route developed by Kocovsky's group, as shown in Eq 1.[2] Despite the few synthetic steps involved in its preparation, this ligand has seen limited use so far.[3] One of the most elegant applications of this ligand was its use as the chiral backbone in Carreira's titanium(IV) Schiff base aldol catalyst.[4]



(1)

We desired to carry out the Pd-catalyzed amination reaction[5] on a binaphthyl triflate derivative to facilitate access to this class of binaphthyl ligands. We hoped that such a process would allow for their preparation from an optically pure and commercially available precursor as well as circumvent the need to use carcinogenic 2-naphthylamine as a starting material. We first examined coupling reactions with the bis-triflate of BINOL (**2** in Eq 2). However, our efforts were met with minimal success, regardless of the phosphine ligand used. Attempting to couple **2** with benzophenone imine[6] typically resulted in sluggish formation of **3** with substantial hydrolysis of the triflates, in addition to formation of undesired side products.[7]



(2)

We then examined binaphthyl triflate **5** as a potential coupling partner in the amination reaction. BINOL was transformed into triflate **5** in 75% yield with a single isolation (recrystallization from ethanol) using a three step process (Eq 3).[8,9] While carrying out the coupling reaction between **5** and benzophenone imine with BINAP

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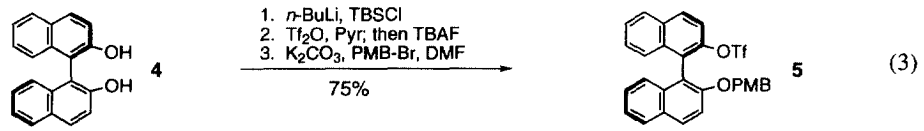
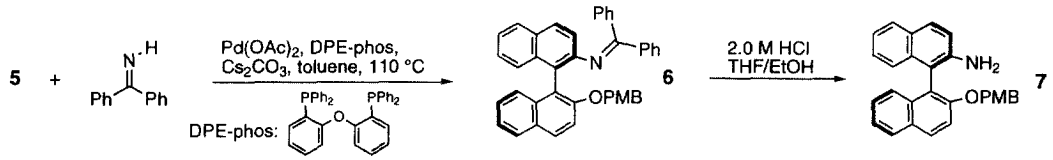


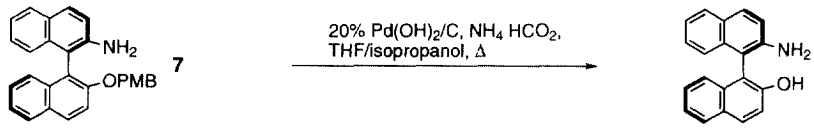
(3)

or DPPF led to significant amounts of reduction and hydrolysis of **5**, we were pleased to find that switching to DPE-phos[10] as the ligand resulted in a highly efficient process (Scheme 1). Using 3 mol% $Pd(OAc)_2$, 4.5 mol% DPE-phos with Cs_2CO_3 as base in toluene at 110 °C afforded **6** in about 90% crude yield by ^1H NMR spectroscopy.[11] Following an aqueous workup, the crude material was subjected to acidic hydrolysis conditions to cleave the imine. Product **7** was recrystallized from isopropanol in 87% yield for the two steps (**5**–**7**).[12] The exclusion of water from reagents (particularly the Cs_2CO_3) was essential for optimal results in the Pd-catalyzed amination step. We found that addition of powdered 4 Å molecular sieves to the reaction mixture (freshly activated by flame drying under vacuum) greatly improved the reliability of the conversion of **5** to **6**.

Scheme 1

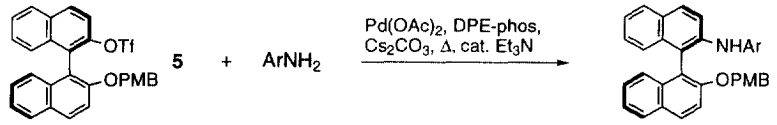


The 4-methoxybenzyl (PMB) group of **7** was readily cleaved by hydrogenolysis with Pearlman's catalyst under transfer hydrogenation conditions (Eq 4). After removal of the $Pd(OH)_2$ by filtration through celite, **1** was isolated in optically pure form by recrystallization from 3:1 hexane/toluene in 94% yield and in 61% yield for the overall process (starting from BINOL).[13] No racemization of the binaphthyl had occurred during the sequence (**4** to **1**) as verified by chiral HPLC.[14]



(4)

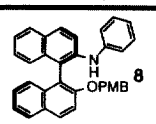
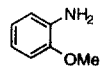
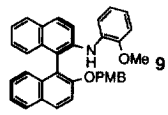
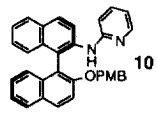
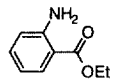
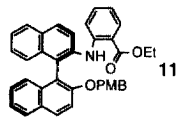
As shown in Table 1, various aromatic amines were combined with **5** under similar conditions as those employed for benzophenone imine. The reactions were carried out with 5 mol% $Pd(OAc)_2$ and 7.5 mol% DPE-phos (Eq 5) and were performed neat to accelerate the rate of the reactions. After an aqueous workup, the diarylamine products were isolated in good chemical yield by chromatography on silica gel.[15] The PMB group masking the phenols of **8**–**11** was cleaved in greater than 90% yield in a manner analogous to **7**.



(5)

In summary, we have applied the Pd-catalyzed amination reaction to the efficient construction of 2-amino-2'-hydroxy-1,1'-binaphthyl and *N*-arylated derivatives.[16] This approach utilizes BINOL, which is an optically pure starting material and commercially available at a moderate cost.[17] This methodology should aid in the development of new chiral ligands derived from the 2-amino-2'-hydroxy-1,1'-binaphthyl backbone.

Table 1

Entry	$ArNH_2$	Product	Temperature	Time	Yield[a]
1		 **8**	90 °C	30 h	90%
2		 **9**	90 °C	32 h	89%
3		 **10**	90 °C	20 h	83%
4		 **11**	110 °C	16 h	73%

[a] Isolated yields are reported as an average of two trials.

Acknowledgment. We thank the NSF (CHE-9421982) and NIH (GM58160) for financial support, and the NIH for providing R.A.S. with a postdoctoral fellowship.

References and Footnotes

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(3) Vyskocil, S.; Jaracz, S.; Smrcina, M.; Stícha, M.; Hanus, V.; Polásek, M.; Kocovsky, P. *J. Org. Chem.* **1998**, *63*, 7727–7737.

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(6) We found it more effective to prepare benzophenone imine by treatment of bromobenzene with *n*-butyllithium at -78 °C in THF for 45 min followed by addition of benzonitrile and warming to rt, rather than the conventional method of using the Grignard reagent.

(7) DPPF gave the best results, affording product in 35% yield after 48 h at 110 °C.

(8) The 4-methoxybenzyl (PMB) protecting group was chosen for its high lability to hydrogenolysis and for improving the solubility properties of the imine product. If the benzyl group was substituted for a methyl protecting group, the imine product was found to be highly insoluble in most organic solvents.

(9) **(*R*)-2-Triflato-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (5)**. To a solution of (*R*)-BINOL (5.73 g, 20.0 mmol) in 60 mL of THF at 0 °C was added a 1.6 M solution of *n*-butyllithium (13.8 mL, 22.0 mmol) in hexane slowly. A white suspension formed which was stirred rapidly for 20 min. Then *tert*-butyldimethylsilyl chloride (3.32 g, 22.0 mmol) was added via cannula in 20 mL of THF. The reaction mixture became homogeneous and was stirred at 0 °C for 10 min before warming to rt. The reaction mixture was poured onto 150 mL of saturated aqueous $NaHCO_3$ and extracted with 200 mL of EtOAc. The organic layer was washed with 150 mL of saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was redissolved in 60 mL of pyridine and cooled to 0 °C and triflic anhydride (5.05 mL, 30.0 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 30 min and was then warmed to rt. After stirring the solution for 1 h at rt, a 1 M solution of TBAF (26.0 mL, 26.0 mmol) in THF was slowly added to the reaction mixture. The reaction mixture was stirred at rt for 7 h and then was poured onto 150 mL of 2 M aqueous HCl to be extracted with 250 mL of 1:1 hexane/EtOAc. The organic layer was washed twice more with 150 mL of 2 M aqueous HCl, once with 150 mL of saturated aqueous $NaHCO_3$, and once with 150 mL of saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material and K_2CO_3 (5.53 g, 40.0 mmol) were taken up in 30 mL of DMF. Freshly prepared 4-methoxybenzyl bromide (5.23 g, 26.0 mmol) was added and the reaction mixture was stirred at rt for 6 h. To the reaction

mixture was added 200 mL of 1:1 hexane/EtOAc followed by slow addition of 150 mL of 2 M aqueous HCl. The organic layer was separated and was washed once with 150 mL of 2 M aqueous NaOH followed by 150 mL of saturated aqueous NaCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was crystallized from 50 mL of EtOH as white cubes (8.05 g, 75%). mp = 91–92 °C; $[\alpha]_D^{22}$ –31.6 (*c* = 0.98, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 154.2, 145.5, 133.5, 132.4, 130.8, 130.0, 129.0, 128.9, 128.1, 128.0, 127.9, 127.2, 127.2, 126.9, 126.6, 125.0, 124.6, 123.8, 120.3, 119.4, 116.1, 114.8, 113.6, 109.2, 70.6, 55.2.

(10) Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327–5330.

(11) Triethylamine was added to the reactions to aid in the initial reduction of the $Pd(OAc)_2$. The reactions were typically conducted at 1 M with respect to **5**. Diluting the reactions further led to significantly slower rates of reaction.

(12) **(*R*)-2-Amino-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (7).** A flask containing **5** (5.39 g, 10.0 mmol), distilled benzophenone imine (5.03 mL, 30.0 mmol), $Pd(OAc)_2$ (67.3 mg, 0.300 mmol), bis[2-(diphenylphosphino)phenyl] ether (DPE-phos) (242 mg, 0.450 mmol), 4 Å powdered molecular sieves (4.00 g), and triethylamine (348 μL, 2.50 mmol) in 10 mL of toluene was purged with a gentle stream of Ar for 20 min while stirring the mixture at rt. After this time, Cs_2CO_3 (4.89 g, 15.0 mmol) was added under a heavy stream of argon. The reaction mixture was then heated to 110 °C under an Ar atmosphere for 18 h. The reaction mixture was then cooled to rt and diluted with 100 mL of EtOAc. The organic solution was washed with 100 mL of saturated aqueous NaCl. The organic solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in 70 mL of THF and 70 mL of EtOH to be treated with 14 mL of 2 M aqueous HCl. The solution was stirred for 1 h and then was concentrated *in vacuo*. The residue was diluted with 150 mL of EtOAc and was washed with 100 mL of 2 M aqueous sodium hydroxide. The organic layer was washed with 100 mL of saturated aqueous NaCl. The organic solution was dried over anhydrous Na_2SO_4 and was concentrated *in vacuo*. The product was isolated as a white solid (3.54 g, 87%) by crystallization from 100 mL of *i*-PrOH. mp = 145–147 °C; $[\alpha]_D^{22}$ +63.0 (*c* = 1.0, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 154.4, 142.1, 134.2, 133.7, 129.9, 129.7, 129.4, 129.0, 128.7, 128.2, 128.0, 127.9, 126.8, 126.2, 125.2, 124.4, 124.2, 122.1, 120.7, 118.2, 117.1, 113.8, 113.6, 71.3, 55.2.

(13) **(*R*)-2-Amino-2'-hydroxy-1,1'-binaphthyl (1).** To a solution of **7** (1.22 g, 3.00 mmol) in 30 mL of THF and 60 mL of *i*-PrOH was added 20% $Pd(OH)_2$ on carbon (418 mg, 0.300 mmol) and ammonium formate (3.78 g, 60.0 mmol). The reaction mixture was heated to a reflux for 1 h. The reaction was then allowed to cool to rt and was diluted with 100 mL of CH_2Cl_2. The reaction mixture was passed through a short column of celite, washing the celite with another 50 mL of CH_2Cl_2. The filtrate was concentrated *in vacuo*. The product was crystallized as white needles (805 mg, 94%) from 30 mL of hexane and 10 mL of toluene. mp = 168–169 °C; $[\alpha]_D^{22}$ +40.0 (*c* = 1.00, CH_2Cl_2).

(14) The optical purity of **1** was assayed by HPLC using a chiralcel OD column. For a flow rate of 0.5 mL/min and eluent composition of 80% *i*-PrOH and 20% hexane, **1** eluted at 22.7 min and *ent*-**1** eluted at 20.8 min.

(15) **General Procedure for preparation of *N*-arylated binaphthyl derivatives.** A flask containing **5** (269 mg, 0.500 mmol), the aniline (2.50 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), DPE-phos (20.2 mg, 0.0375 mmol), and triethylamine (125 μL) was purged under a gentle stream of Ar for 20 min while stirring the mixture at rt. After this time, Cs_2CO_3 (244 mg, 0.750 mmol) was added under a heavy stream of Ar. The reaction mixture was then heated to the desired temperature under an Ar atmosphere for the amount of time specified in Table 1. The reaction mixture was then cooled to rt and diluted with 30 mL of EtOAc. The organic solution was washed twice with 20 mL of 1 M aqueous HCl, once with 20 mL of saturated aqueous $NaHCO_3$, and once with 20 mL of saturated aqueous NaCl. The organic solution was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was isolated by chromatography on silica gel.

(*R*)-2-Aminophenyl-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (8). The product was isolated as a white solid (217 mg, 90%) by flash chromatography on silica gel using 9:1 hexane/EtOAc (with 5% triethylamine) as eluent. mp = 58–59 °C; $[\alpha]_D^{22}$ +55.0 (*c* = 1.0, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 154.1, 143.2, 139.2, 134.2, 133.8, 129.8, 129.5, 129.3, 129.2, 129.0, 128.5, 128.4, 127.9, 127.8, 126.8, 126.1, 125.0, 124.9, 124.0, 123.0, 121.0, 119.8, 118.9, 118.7, 118.5, 116.2, 113.5, 70.8, 55.1.

(*R*)-2-(1-Amino-2-methoxyphenyl)-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (9). The product was isolated as a white solid (231 mg, 90%) by flash chromatography on silica gel using 9:1 hexane/EtOAc (with 5% triethylamine) as eluent. mp = 58–60 °C; $[\alpha]_D^{22}$ +20.0 (*c* = 1.0, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 154.3, 148.8, 138.9, 134.3, 134.2, 133.8, 133.1, 129.6, 129.5, 129.3, 129.3, 128.3, 127.8, 127.8, 126.6, 126.1, 125.2, 125.2, 123.9, 123.0, 120.6, 120.1, 120.1, 119.9, 118.9, 116.2, 115.6, 113.5, 110.6, 71.0, 55.5, 55.1.

(*R*)-2-(2-Aminopyridyl)-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (10). Modified the general procedure by adding 0.500 mL of toluene and 0.250 mL of triethylamine as solvent. The workup was modified by simply diluting the reaction mixture with 30 mL of EtOAc, washing with 20 mL of a saturated aqueous NaCl solution, drying over anhydrous Na_2SO_4, and concentrating *in vacuo*. The product was isolated as a white solid (409 mg, 85%) by flash chromatography on silica gel using 4:1 hexane/EtOAc as eluent. mp = 60–63 °C; $[\alpha]_D^{22}$ +31.0 (*c* = 1.0, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 155.7, 154.0, 148.2, 137.4, 136.7, 133.9, 133.7, 130.2, 130.1, 129.5, 129.0, 128.4, 128.4, 128.0, 127.9, 126.9, 126.2, 125.6, 124.9, 124.1, 123.9, 122.0, 120.6, 119.5, 116.0, 115.0, 113.5, 108.8, 70.7, 55.1.

(*R*)-2-(Ethyl 2-aminobenzoate)-2'-(4-methoxybenzyloxy)-1,1'-binaphthyl (11). Modified general procedure above by carrying out on double the scale (1.00 mmol scale of **5**). The product was isolated as a white solid (411 mg, 74%) by flash chromatography on silica gel using 15:1 hexane/EtOAc as eluent. mp = 64–65 °C; $[\alpha]_D^{22}$ –50.0 (*c* = 1.0, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 158.7, 154.1, 147.1, 143.9, 137.3, 134.2, 133.8, 133.3, 131.3, 130.6, 129.6, 129.4, 129.2, 128.2, 127.8, 127.8, 126.4, 126.1, 125.8, 125.1, 125.0, 124.2, 123.6, 122.2, 119.9, 116.9, 115.4, 114.4, 113.4, 113.0, 70.6, 60.2, 55.1, 14.2.

(16) Compounds **5–11** gave satisfactory elemental analysis.

(17) We have recently purchased optically pure BINOL from Environmental Science Center Limited, Yokohama, Japan for under $3/g.