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Improved Syntheses of Phosphine Ligands by Direct Coupling of Diarylbromophosphine with Organometallic Reagents

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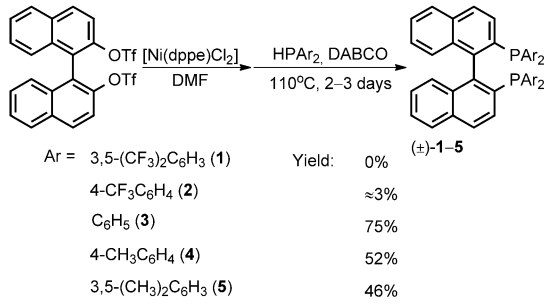
In memory of Jonathan B. Spencer

Ligand synthesis lies at the heart of modern organometallic chemistry. The design and synthesis of new ligands plays a key role in the development of highly efficient asymmetric catalysis. Among those thousands of various ligands that have been synthesized so far, phosphine ligands are undoubtedly the most used ligands in both asymmetric catalysis and Pd catalysis.[1]

During our continued mechanistic studies of homogeneous hydrogenation,[2] the preparation of chiral phosphine ligands with systematically tuned electronic properties is essential. For instance, we synthesized a series of BINAP-type phosphine ligands **1–5** (Scheme 1; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) to investigate the interplay between the electronic properties of ligands and substrates and how this affects the enantioselection of rhodium-catalyzed asymmetric hydrogenation reactions.[2c] BINAP is one of the most efficient ligands for chiral induction and has been most extensively studied in asymmetric catalysis since it was developed by Noyori et al in 1980.[3] We therefore chose BINAP as the model ligand and began to tune the electronic properties of the four phenyl rings.[4]



Scheme 1. Syntheses of ligands **1–5** using the Merck method. Conditions: triflate (1.0 equiv), $XPAr_2$ (1.05 equiv), $[Ni(dppe)Cl_2]$ (0.2 equiv), DABCO (8.0 equiv) in DMF (10 mL mmol^{-1} triflate); heating at 100 °C for 2–3 days.

The first practical synthesis of BINAP was reported by Noyori et al. in 1986 with an overall yield of 14 %.[5] An improved method was reported by Cai et al. (Merck Inc.) in 1994 involving a nickel-catalyzed coupling reaction between the chiral ditriflate of BINOL and diphenylphosphine. The yield of this significantly shorter route was as high as approximately 75 %.[6] A modified version of Cai's method was later developed by Laneman et al (Monsanto) in 1997,[7] which also involves chiral BINOL ditriflate (BINOL = 1,1′-binaphthalene-2,2′-diol) but has the advantage of using industrially available diphenylchlorophosphine as a starting material. We initially chose the Merck method for the syntheses of ligands **1–5** due to its short sequence (Scheme 1). When the phenyl rings were substituted by electron-donating groups, such as *p*-tolyl (ligand **4**) or *m*-xylyl (ligand **5**) groups, the substituted BINAPs were obtained in moderate yields (52 % for ligand **4** and 46 % for ligand **5**). However, when electron-withdrawing groups (such as CF_3) were introduced to the phenyl ring, this method gave either only a trace amount of the desired products or none at all. The Monsanto method was also tested for the syntheses of ligands 1 and 2 but no desired products were obtained.

We then turned to Noyori's method for the syntheses of the oxides of ligands **1** and **2**. Binaphthylmagnesium bromide was coupled with bis[3,5-bis(trifluoromethyl)-phenyl]-phosphinyl chlorides to afford phosphine oxide **1a** (Scheme 2). The complex product mixture was subjected to silica gel chromatography and all the products were isolated and characterized. The products were, in order of elution, 1,1′-binaphthylene (**7**; 6 %), tris[3,5-bis(trifluoromethyl)phenyl]phosphine oxide (**8**; 17 %), 2,2′-dibromo-1,1′-binaphthyl (**6**; 3 %), 2,2′-bis(bis[3,5-bis(trifluoromethyl)phenyl])phosphinyl-1,1′-binaphthyl (**1a**; 18 %), bis[3,5-bis(trifluoromethyl)phenyl]phosphinic acid (**9**; 5 %) and bis(binaphthyl)diphosphine oxide **10** (40 %; see the Supporting Information for characterization data) (Scheme 2). Interestingly, when the reaction was carried out at room temperature, **8** and **10** became the main products and **1a** was not found in the mixture. The formation of **8** indicated the presence of a nucleo-

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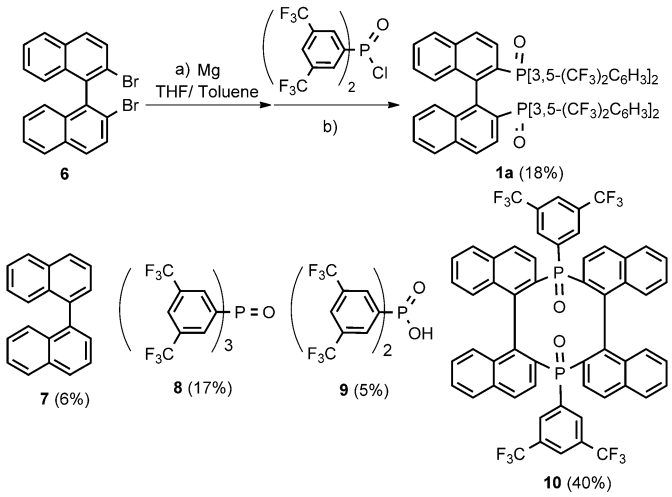
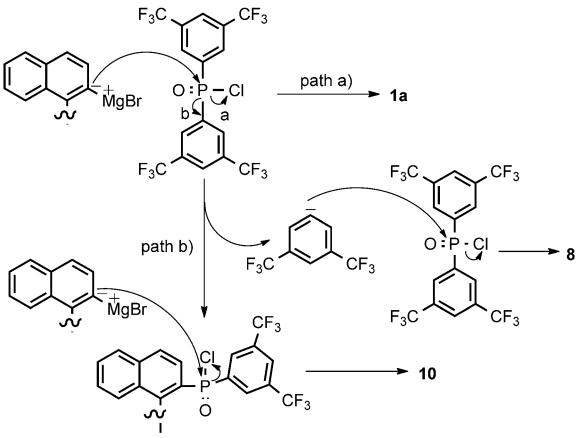


Scheme 2. Synthesis of electron-withdrawing BINAP-type phosphine oxide. Conditions: a) Mg (3.8 mmol), 2,2′-dibromo-1,1′-binaphthyl (1.9 mmol) in THF/toluene (15 mL, 1:4) at 75 °C for 2 h; b) bis[3,5-bis(trifluoromethyl)phenyl]phosphinyl chloride (4.55 mmol) in 5 mL THF added at 60 °C for 3 h.

phile $(CF_3)_2C_6H_3^-$ during the reaction process, and the formation of **10** showed the cleavage of both the P–Cl and P–C bonds of $Ar_2P(O)Cl$. At this stage, both the formation of **8** and **10** can be readily explained by invoking a reaction pathway in which $(CF_3)_2C_6H_3$ acts as a competitive leaving group versus chloride when diarylphosphinyl chloride is attacked by nucleophiles (Scheme 3).

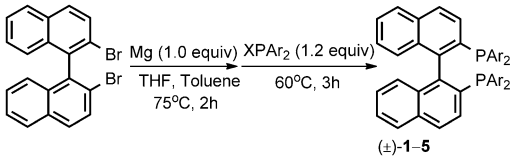


Scheme 3. Proposed reaction pathways (a and b) in the synthesis of **1a**.

Although the mechanism of this reaction requires further studies, the proposed competing pathway involving either $(CF_3)_2C_6H_3$ or halide as the leaving group prompted us to test a better leaving group instead of chloride to improve the yield. Therefore, we decided to prepare bis[3,5-bis(trifluoromethyl)phenyl]phosphinyl(V) bromide as the starting material for the coupling reaction.

Diarylphosphinous(III) bromide ($BrPAr_2$) was successfully prepared without chloride impurities. However, oxidation of this compound always afforded a mixture of bromophosphine oxide and the hydrolyzed product, which are not easy to purify. We therefore decided to investigate whether diarylphosphinous bromide is sufficiently reactive to be used directly to couple with binaphthylmagnesium bromide. We were pleased to find that the coupling reaction between binaphthylmagnesium and bis[3,5-bis(trifluoromethyl)phenyl] phosphinous(III) bromide afforded ligand **1** in 70% yield (Table 1, entry 1). Ligands **2–5** were also synthesized in good yields using the same method (Table 1, entries 2–5). To the best of our knowledge, this is the first report to show that Grignard reagents can react with phosphinous(III) halides directly to afford BINAP-type phosphine ligands. In contrast, reactions between diarylphosphinous chloride and binaphthyl-magnesium bromide give only trace amounts or no desired products.

Table 1. Direct Grignard coupling reactions for the syntheses of BINAP-type phosphines.[a]



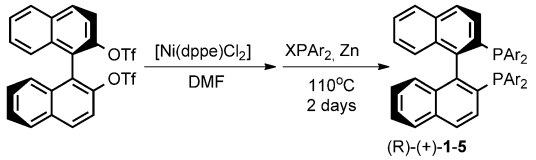
Entry	Ar	Product	X = Br Yield [%][b]	X = Cl Yield [%][b]
1	3,5-$(CF_3)_2C_6H_3$	(±)-**1**	70	≈5
2	4-$CF_3C_6H_4$	(±)-**2**	72	–[c]
3	C_6H_5	(±)-**3**	68	–[c]
4	4-$CH_3C_6H_4$	(±)-**4**	78	–[c]
5	3,5-$(CH_3)_2C_6H_3$	(±)-**5**	75	–[c]

[a] Reaction conditions: Mg (1.0 equiv) in THF/toluene (1:1), heating at 75 °C for 2 h; then $XPAr_2$ (1.2 equiv) added at room temperature and heated to 60 °C for 3 h. [b] Isolated product yield based upon an average of two runs. [c] No detectable product.

This success promoted us to revisit the Monsanto method. Although diarylchlorophosphine is reactive in coupling with BINOL triflate catalyzed by nickel catalyst in the Monsanto method,[7] only the syntheses of electron-rich BINAP derivatives were possible (Table 2, entries 1 and 2). Therefore, we replaced diarylchlorophosphine with diarylbromophosphine for this coupling reaction to see if the higher reactivity of bromophosphine is also beneficial for this process. We found that the yields of all electron-rich phosphine ligands were considerably improved (Table 2, entries 3–5). Electron-deficient ligands **1** and **2** were also obtained by using corresponding diarylbromophosphines, albeit with low yields (Table 2, entries 1 and 2). Thus, a series of chiral BINAP derivatives (*R*)-(+)-**1–5** were made available using (*R*)-(+)-BINOL triflates as starting materials.

Next, we turned our attention to Buchwald's dialkylbiarylphosphine ligands, which were the most broadly used for Pd catalysis.[8a] A variety of Pd-catalyzed carbon–nitrogen,[8]

Table 2. Nickel-assisted coupling reactions for the syntheses of chiral BINAP-type phosphines.[a]



(R)-(+)-**1-5**

Entry	Ar	Product	X = Br Yield [%][b]	X = Cl Yield [%][b]
1	3,5-$(CF_3)_2C_6H_3$	(*R*)-(+)-**1**	28	–[c]
2	4-$CF_3C_6H_4$	(*R*)-(+)-**2**	33	–[c]
3	C_6H_5	(*R*)-(+)-**3**	62	52
4	4-$CH_3C_6H_4$	(*R*)-(+)-**4**	66	46
5	3,5-$(CH_3)_2C_6H_3$	(*R*)-(+)-**5**	64	50

[a] Reaction conditions: triflate (1.0 equiv), $XPAr_2$ (1.2 equiv), [Ni(dppe)Cl_2] (0.5 equiv), Zn powder (1.5 equiv) in DMF (5 mL mmol^{-1} triflate); heating at 110 °C for 2 days. [b] Isolated product yield based upon an average of two runs. [c] No detectable product.

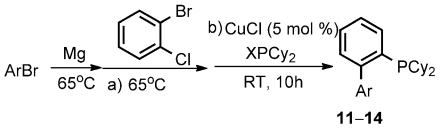
carbon–oxygen,[9] and carbon–carbon[8,10] bond-forming processes critically depend on the use of these ligands. Although several elegant synthetic strategies for making these ligands have been developed, syntheses of a particular ligand can still suffer from relatively low yields.[11] We wondered if the use of bromophosphine instead of chlorophosphine could lead to improved preparation of dialkylbiarylphosphine ligands.

The original one-pot experimental procedure was strictly followed, with the exception of the last step in which dicyclohexylbromophosphine was added instead of its chloro counterpart. The very bulky ligand **11** was obtained in 86% yield, which was comparable to the literature procedure (Table 3, entry 1).[12] Interestingly, for the less bulky ligands **12**–**14**, the product yields were all significantly improved (Table 3, entries 2–4).[11a] It was previously proposed[11a] that the arylmagnesium halide first underwent *cine*-substitution to benzyne to result in an *ortho*-metalated biphenyl derivative; this intermediate then reacted with dialkylhalophosphine to give the desired phosphine. We speculate that the higher reactivity of bromophosphine might speed up the nucleophilic substitution process and make better use of the short-lived intermediate, thus enhancing the reaction yields.

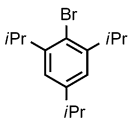
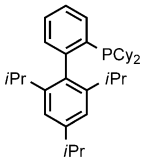
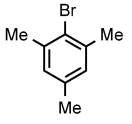
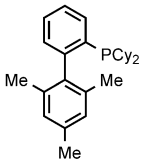
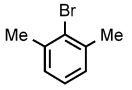
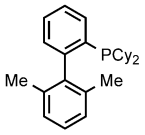
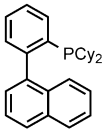
Preparation of electron-deficient biphenyl-based phosphine ligand **15** was also carried out in moderate success (Scheme 4). Bis[3,5-bis(trifluoromethyl)phenyl]-phosphinous bromide was used in the coupling step and **15** was obtained in 46% yield.[13]

In summary, we have discovered that diarylbromophosphine is much more effective than diarylchlorophosphine and can be used to directly couple with binaphthylmagnesium bromide to afford BINAP derivatives. Diarylbromophosphines can also be employed in the nickel-catalyzed coupling reaction with BINOL triflate, giving better yields than their chloro counterparts, especially for the syntheses of electron-deficient phosphine ligands. Finally, we have applied this strategy to prepare several Buchwald's dialkylbiarylphosphine ligands with improved yields.

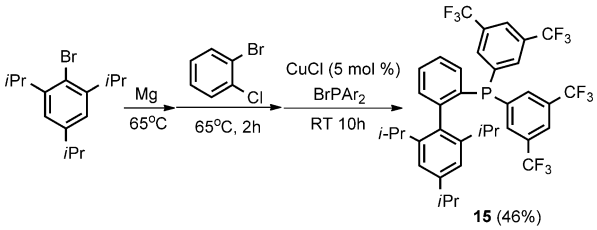
Table 3. Syntheses of Buchwald's dialkylbiaryl phosphine ligands.[a]



11–**14**

Entry	ArBr	Product		X = Br Yield [%][b]	X = Cl Yield [%][b]
1			**11**	86	83
2			**12**	85	53
3			**13**	83	53
4			**14**	68	36

[a] Reaction conditions: a) ArBr (1.0 equiv), Mg (1.0 equiv), bromochlorobenzene (1.0 equiv) in THF (2 mL mmol^{-1} ArBr), heating at 65 °C for 2 h; b) CuCl (0.05 equiv), $XPCy_2$ (1.2 equiv) at room temperature for 10 h. [b] Isolated product yield based upon an average of two runs.



15 (46%)

Scheme 4. Synthesis of an electron-deficient biphenyl-based phosphine ligand. Conditions: a) ArBr (1 equiv), Mg (1.0 equiv), bromochlorobenzene (1.0 equiv) in THF (2 mL mmol^{-1} ArBr), heating at 65 °C for 2 h; b) CuCl (0.05 equiv), $BrPAr_2$ (Ar = 3,5-$(CF_3)_2CH_3$) (1.2 equiv) at room temperature for 10 h.

Acknowledgements

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Keywords: BINAP · chirality · electron-deficient compounds · ligand design · ligand effects · P ligands

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