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A Novel (2,2-Diarylvinyl)phosphine/Palladium Catalyst for Effective Aromatic Amination

Ken Suzuki,[a,*] Yoji Hori,[a] Takenobu Nishikawa,[a] and Tohru Kobayashi[a]

[a] Takasago International Corporation, Corporate Research & Development Division, 1-4-11, Nishi-Yawata, Hiratsuka, Kanagawa 254-0073, Japan
Fax: (+81)-463-25-2093; e-mail: ken_suzuki@takasago.com

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Abstract: A new series of diarylvinylphosphine ligands was designed and synthesized. A catalyst system, consisting of the ligands and palladium species, effectively catalyzed the coupling reaction of aryl bromides and chlorides with amines to afford the corresponding products in good to excellent yields. The efficiency is likely derived from an interaction between the palladium center and the *cis*-aryl moiety on the diarylvinylphosphine ligand stabilizing a catalytic intermediate during the coupling reaction.

Keywords: amination; cross-coupling; ligand design; P ligands; palladium

The palladium-catalyzed coupling reaction of aryl halides with amines has become one of the most powerful methods for the synthesis of aromatic amines.[1] Initial efforts towards the coupling reaction with applicable aryl halides have used generally available phosphine ligands such as (o-tolyl)$_3$P and BINAP.[2] Although aryl bromides have successfully been used for the coupling reaction, employment of less active aryl chlorides has had limited success. Considering applications for industrial processes, the choice of aryl chloride is extremely significant because of its lower cost, better availability and lower toxicity. Recently, there has been a noteworthy advance in the reaction of aryl chlorides using newly discovered ligands that sharply improve the effectiveness of the coupling reaction.[3–8] For example, Buchwald,[3] Hartwig,[4] Beller[5] and Koie[6] as well as others[7,8] reported excellent ligands such as biphenylphosphine, pentaarylferrocenylphosphine, diadamantylbutylphosphine and tris-*tert*-butylphosphine. These advances have led us to develop a new catalyst.

Characteristics that these ligands have in common are electron-richness and steric hindrance. To synthesize a more effective phosphine ligand by strengthening these characteristics, we investigated vinylphosphine **1** due to its three vacant positions, although ligand **1** has not been previously used for this coupling (Figure 1). Based on the vinylphosphine structure, a new ligand, diarylvinylphosphine **2** was designed. A substituent group (R^1) at the α-position on phosphine **2** was introduced to make the ligand more sterically hindered around the phosphorus atom. To increase electron density of the ligand, the β-position was substituted by two aryl moieties (Ar) with electron-donating groups, which were conjugated to the phosphorus atom through the vinyl moiety. Accordingly, we synthesized a series of diarylvinylphosphines **3**–**9**, which are white solids and stable to air and moisture (Figure 2).[9]

First, the effect of substituent groups on the ligands was examined in the reaction of 4-*tert*-butylbromobenzene with diphenylamine in toluene using 1 mol% of Pd(OAc)$_2$ and 4 mol% of the ligand as shown in Table 1. As is the case with alkylphosphines reported previously,[3–8] entries 2–5 show that alkylphosphines **3b**–**d** are more active than arylphosphine **3a**. Introduction of two electron-donating groups at the *para*-position of the aryl moiety on phosphines **4a**–**c** afforded excellent coupling product yields, but a longer reaction time was needed with ligands **3b**–**d** (entries 6–8). Although the reason is unclear, ligand **5** resulted in a poor yield. Ligands **8** and **9**, with phenyl and isopropyl groups introduced into the α-position for bulkiness, gave low yields (entries 12 and 13). Contrary to

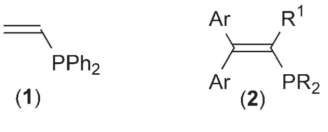
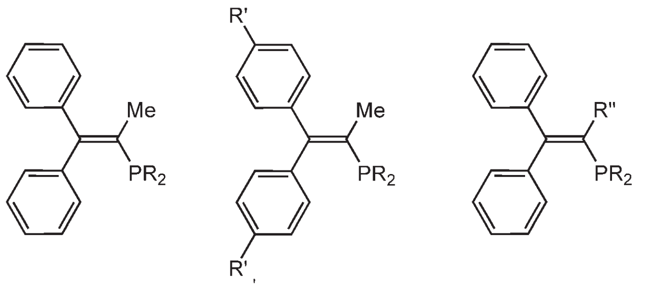


Figure 1. Structures of vinylphosphines.



(**3a**): R = Ph
(**3b**): *i*-Pr
(**3c**): Cy
(**3d**): *t*-Bu

(**4a**): R' = NMe$_2$, R = Ph
(**4b**): Cy
(**4c**): *t*-Bu
(**5**): OMe, Ph
(**6**): F, Ph

(**7**): R'' = H, R = Ph
(**8**): *i*-Pr, Cy
(**9**): Ph, Cy

Figure 2. A series of diarylvinylphosphines.

Table 1. Effect of substituent groups of the diarylvinylphosphines.[a]

Entry	Ligand	Time [h]	Yield[b] [%]	Entry	Ligand	Time [h]	Yield[b] [%]
1	–	8	<1	8	**4c**	8	88
2	**3a**	8	88	9	**5**	8	25
3	**3b**	3	97	10	**6**	8	26
4	**3c**	3	97	11	**7**	8	45
5	**3d**	3	89	12	**8**	8	40
6	**4a**	8	85	13	**9**	8	40
7	**4b**	3	87	14	**1**	8	1

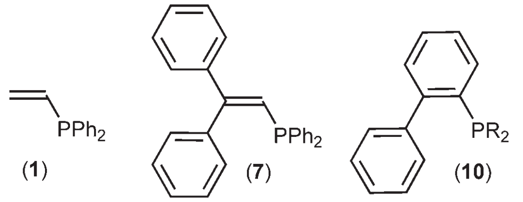
[a] *Reaction conditions:* 4-*tert*-butylbromobenzene (1.1 equivs.), diphenylamine (1.0 equiv.), Pd(OAc)$_2$, (1 mol%), ligand (4 mol%), NaO-*t*-Bu (1.2 equivs.), toluene, 100 °C.

[b] Yields were determined by GC analysis.

our original expectations, we found that the simple phosphines **3b–d** were more effective.

Then we examined the reaction with vinylphosphine **1** under the same reaction conditions, which gave the coupling product in 1% yield (entry 14). A comparison of entry 11 with entry 14 indicates that the phenyl group at the β-position of ligand **7** strongly affects the activity (Figure 3).

Buchwald's group reported ligand **10** as being effective for coupling reactions, and suggested that this effectiveness is related to an interaction between the *ortho*-phenyl group on ligand **10** and the palladium center.[10] Considering the fact that ligand **7** has a similar structure to ligand **10**, it must be proved that the vinyl moiety on ligand **7** could work as a spacer to control the spatial relationship between the *cis*-phenyl group at the β-position and the phosphorus atom. As the result, we believe that an interaction between the palladium center and the *cis*-phenyl group stabilizes the catalyst in the unstable step when an actual catalyst species is generated. At the same time, steric repulsion, which is caused by the *cis*-phenyl moiety and that is around the palladium center, could accelerate a reductive elimination step.



(**1**) (**7**) (**10**)

Figure 3. Structures of phosphines.

Next, we examined the general coupling reaction of aryl halides with amines using ligand **3c**, which was one of the most effective in our series of ligands. Results are summarized in Table 2. Reactions of *para*- and *ortho*-substituted aryl bromides with primary amines in the presence of 2 mol% of ligand **3c** and 1 mol% of Pd(OAc)$_2$ proceeded to selectively give the secondary amines in 89% and 90% yield, respectively (entries 1 and 2). The tertiary amine was also obtained by the reaction of anisyl bromide with dibenzylamine. The catalyst system that consists of ligand **3c**/Pd was active for the reaction of aryl chlorides. In entry 4, the reaction of chlorobenzene with diphenylamine gave triphenylamine in 95% yield under the same conditions. Both electron-rich and electron-poor aryl chlorides could be converted to the corresponding products (entries 5 and 6).

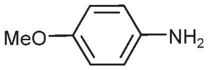
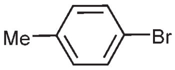
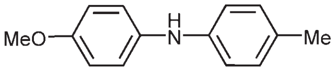
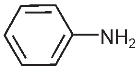
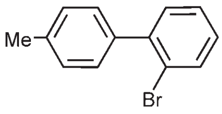
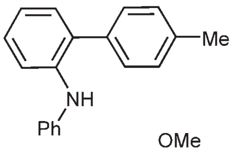
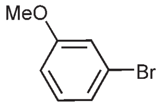
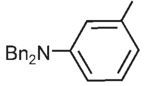
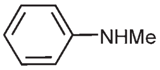
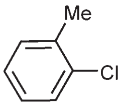
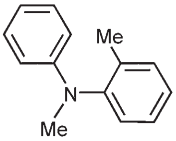
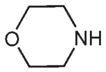
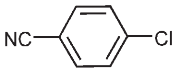
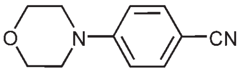
In summary, we have demonstrated that the catalyst system using the new series of diarylvinylphosphine ligands was effective for the coupling reaction of aryl bromides and chlorides with amines, and gave the desired product in good to excellent yields. Our current efforts focus on expanding the scope of aromatic amination and the related coupling reactions.

Experimental Section

Typical Procedure for the Amination

Amine (1.0 equiv.) and aryl halide (1.1 equivs.) were added to a solution of Pd(OAc)$_2$ (1.0 mol%), the ligand (2.0–4.0 mol%) and NaO-*t*-Bu (1.2 equivs.) in toluene (0.5 M) at room temperature under an argon atmosphere. Then the mixture was stirred at 100 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with toluene, and washed with water and brine, and the organic layer was extracted from the aqueous layer with toluene. The combined organic phase was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel to afford the coupling product.

Table 2. Arylamination using ligand **1c**/Pd.[a]

Entry	Amine	Aryl halide	Product	Yield[b] [%]
1				89
2				90
3	Bn$_2$NH			80
4	Ph$_2$NH	PhCl	Ph$_3$N	95
5				81
6[c]				90

[a] *Reaction conditions:* aryl halide (1.1 equivs.), amine (1.0 equivs.), Pd(OAc)$_2$, (1 mol%), ligand (2 mol%), NaO-*t*-Bu (1.2 equivs.), toluene, 100 °C.

[b] Isolated yields.

[c] Aryl halide (1.0 equiv.) and amine (1.1 equivs.) were employed.

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