

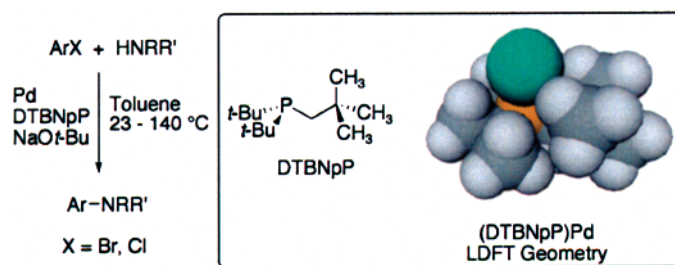
Bulky Alkylphosphines with Neopentyl Substituents as Ligands in the Amination of Aryl Bromides and Chlorides

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Di(*tert*-butyl)neopentylphosphine (DTBNpP) in combination with palladium sources provided catalysts with comparable or better activity for the Hartwig–Buchwald amination of aryl bromides than tri(*tert*-butyl)phosphine (TTBP) under mild conditions. DTBNpP also provided effective catalysts for amination reactions of aryl chlorides at elevated temperatures. Further replacement of *tert*-butyl groups with neopentyl substituents resulted in less effective ligands for amination reactions. Computationally derived cone angles showed that replacement of a *tert*-butyl group with a neopentyl group significantly increased the cone angle of the phosphine. The larger cone angle of DTBNpP than TTBP appears to correlate with the higher activity of catalysts derived from DTBNpP in the amination of aryl bromides. TTBP is a stronger electron donor than DTBNpP, which may explain the higher activity for TTBP-derived catalysts toward aryl chlorides.

Introduction

The palladium-catalyzed coupling of aryl halides with amines and other nitrogen derivatives developed by Hartwig and Buchwald (Hartwig–Buchwald (H–B) coupling) has become widely used in organic synthesis as well as in fine chemical manufacturing of pharmaceutical precursors, electronic materials, and agricultural chemicals.^{1–5} While the initial catalyst systems developed for aryl amination were based on mono- and bidentate triarylphosphines, recent research has shown that

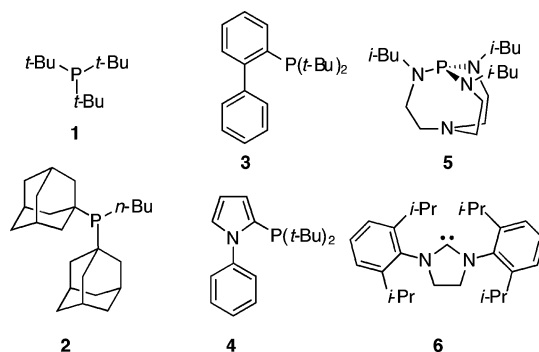


FIGURE 1. Commonly used ligands in H–B amination reactions.

electron-rich, sterically demanding ligands, such as trialkylphosphines (i.e., **1**, **2**, Figure 1),^{6–12} dialkylphosphinous acids,¹³ dialkylarylphosphines (i.e., **3**, **4**),^{8,14–21} bicyclic triaminophosphines (**5**),^{22–24} and imidazol-2-ylidenes and imidazolin-2-

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ylidenes (**6**),^{8,25–29} provide optimal activity and generality for the H–B coupling reaction. Sterically demanding ligands promote ligand dissociation, which is the rate-limiting step in the oxidative addition of aryl bromides to L₂Pd⁰ complexes (L = sterically demanding alkylphosphine), while it is a reversible step prior to rate-limiting oxidative addition of aryl chlorides.³⁰ Electron-rich ligands promote oxidative addition, which is particularly important with less reactive aryl bromides and chlorides. Oxidative addition is the rate-limiting step in the amination of aryl halides.³¹

While it is clear that a combination of steric demand and strong electron-donating ability in the ligand provides highly active catalysts for the H–B amination and other palladium-catalyzed cross-coupling reactions, the relative importance of these elements has not been carefully examined. We have recently reported a study of the roles of steric and electronic ligand parameters in determining catalyst activity in the aqueous-phase Suzuki–Miyaura coupling of aryl bromides.³² Computationally determined cone angles were found to be a good predictor of catalyst activity, while ligand electronic parameters

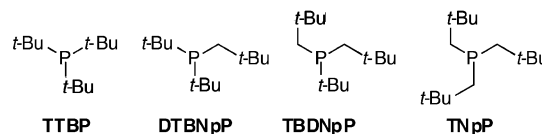


FIGURE 2. Bulky alkylphosphine ligands employed in this work.

determined from the CO stretching frequencies of LNi(CO)₃ complexes gave a poor correlation with activity. We are thus interested in how these findings might relate to other synthetically important cross-coupling reactions. In addition, we sought to explore ligands with even larger cone angles than those explored in our previous studies.

We were motivated to explore neopentyl-substituted phosphines for several reasons. Di-*tert*-butylneopentylphosphine (DTBNpP, Figure 2), which will soon be available in bulk scale,³³ can be easily handled as a 10% solution or as an air-stable phosphonium salt and is economically competitive with other ligands, since it is not encumbered by licensing issues. Most importantly, the series of ligands in Figure 2 would allow us to further address questions about the relative importance of steric and electronic parameters in determining catalyst activity. Finally, although neopentyl-substituted phosphines have been used in coordination chemistry for over 30 years, they have received little attention as ligands in catalysis.^{34–38} The lone example of the use of a neopentylphosphine in a cross-coupling reaction that we have found involved the unsuccessful application of trineopentylphosphine to the coupling 3-bromothiophene with a primary amine.³⁹

The neopentyl substituent provides a different set of steric and electronic factors than the *tert*-butyl group. Tolman⁴⁰ initially estimated the cone angle of trineopentylphosphine (TNpP) to be approximately 180°, comparable to the 182° cone angle he determined for tri-*tert*-butylphosphine (TTBP), which would suggest that neopentyl and *tert*-butyl substituents have similar steric demands. Computationally determined cone angles reported herein show that substitution of neopentyl groups for *tert*-butyl substituents increases the cone angle of the ligand significantly, however. Replacement of a *tert*-butyl group with a neopentyl group decreases the electron-donating ability of the phosphine.⁴¹ Thus, the neopentylphosphines would allow us to explore trialkylphosphines with larger cone angles than TTBP, although these ligands would have decreased electron-donating abilities. We hypothesized that the increased cone angle would give more effective catalysts for couplings of aryl bromides, while the decreased electron-donating ability of the ligands would not be a significant issue. We expected that the decreased electron-donating ability of the neopentylphosphines might result in less effective catalysts toward aryl chlorides.

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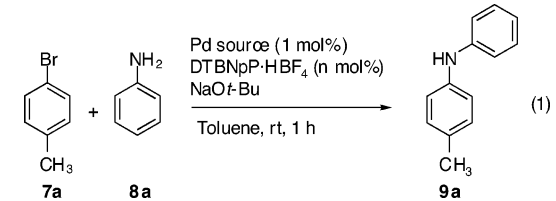
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TABLE 1. Pd/DTBNpP·HBF₄ Catalyzed Coupling of Aniline and 4-Bromotoluene^a


Pd source	L/Pd ratio	yield of 9a ^b (%)
Pd(OAc) ₂	1:1	0
Pd ₂ (dba) ₃	1:1	>99
Pd ₂ (dba) ₃	2:1	>99
Pd ₂ (dba) ₃	0.75:1	73

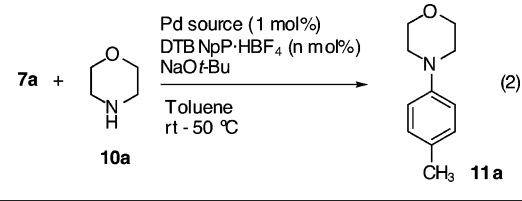
^a 4-Bromotoluene (1 equiv), aniline (1.25 equiv), NaO-*t*-Bu (1.1 equiv), Pd (1 mol %), DTBNpP·HBF₄ (0.75–2 mol %), toluene, rt, 1 h. ^b GC yield determined using response factors obtained from authentic samples of the product.

Herein, we report an evaluation of the ability of mixed neopentyl *tert*-butylphosphines (Figure 2) to give active catalysts for the H–B coupling of aryl bromides and chlorides with primary and secondary amines. DTBNpP was found to give comparable or better levels of activity in the coupling of aryl bromides. This ligand also gave effective catalysts toward the coupling of aryl chlorides. We also report calculated cone angles and electronic properties for these neopentyl ligands based on DFT-optimized geometries using an approach recently developed by us.³² The role of steric and electronic parameters in determining catalyst efficiency is discussed.

Results

DTBNpP as a Ligand in the H–B Coupling. Initial optimization of the reaction was carried out with the HBF₄ salt of DTBNpP (DTBNpP·HBF₄) in combination with Pd(OAc)₂ and Pd₂(dba)₃ as catalyst precursors in the model coupling of 4-bromotoluene with aniline in toluene using 1 mol % of palladium at room temperature (eq 1). Pd(OAc)₂ was ineffective as a catalyst precursor in this reaction, presumably because there is no mechanism to reduce the Pd²⁺ precursor to the Pd⁰ active species (Table 1). Pd₂(dba)₃ was an effective precatalyst for this reaction. Complete conversion to product was seen after 1 h with DTBNpP/Pd ratios of 1:1 or 2:1, while at a 0.75:1 DTBNpP/Pd ratio, the reaction had not reached completion in the same time frame. In contrast, the TTBP/Pd(dba)₂ catalyst system gave optimal activity with a 0.8:1 L/Pd ratio.⁶ Higher L/Pd ratios required elevated temperatures to proceed with TTBP.

A similar reaction optimization study was carried out with morpholine as the amine (eq 2). At room temperature, the coupling of 4-bromotoluene and morpholine required much longer reaction times (18 h) to near completion (Table 2). In contrast to the results with aniline, Pd(OAc)₂ gave a more effective catalyst than did Pd₂(dba)₃. The increased effectiveness of Pd(OAc)₂ as a catalyst precursor for coupling of morpholine compared to aniline can be explained by the ability of morpholine to reduce the Pd²⁺ precursor by coordination followed by β-hydride elimination. The reason for the low activity of the catalyst derived from Pd₂(dba)₃ compared to Pd(OAc)₂ is not clear at this time, though. At 50 °C, the coupling was complete after 1 h using the Pd(OAc)₂/DTBNpP·HBF₄ catalyst system, while using Pd₂(dba)₃ as the palladium source again gave a

TABLE 2. Pd/DTBNpP·HBF₄-Catalyzed Coupling of Morpholine and 4-Bromotoluene^a


Pd source	L/Pd ratio	T (°C)	time (h)	yield of 11a ^b (%)
Pd ₂ (dba) ₃	1:1	23	18	40
Pd(OAc) ₂	1:1	23	18	90
Pd ₂ (dba) ₃	1:1	50	1	33
Pd ₂ (dba) ₃	1:1	50	4	90
Pd(OAc) ₂	0.75:1	50	1	99
Pd(OAc) ₂	1:1	50	1	99
Pd(OAc) ₂	2:1	50	1	99

^a 4-Bromotoluene (1 equiv), morpholine (1 equiv), NaO-*t*-Bu (1.5 equiv), Pd (1 mol %), DTBNpP·HBF₄ (0.75–2 mol %), toluene. ^b GC yield determined using response factors obtained from authentic samples of the product.

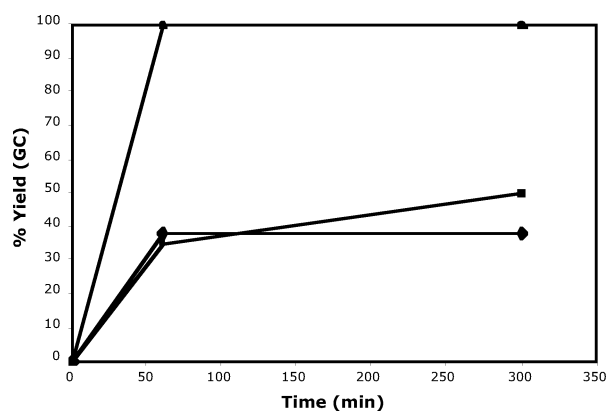


FIGURE 3. Conversion profiles for L/Pd₂(dba)₃-catalyzed (0.5 mol % of Pd, 1:1 L/Pd) coupling of 4-bromoanisole and *N*-methylaniline at room temperature: TTBP (square), DTBNpP (triangle), TBDNpP (open circle), TNpP (diamond). The curves for DTBNpP and TBDNpP overlap, reaching 100% yield prior to the first observation at 60 min.

slower rate of conversion to product. At 50 °C, the Pd(OAc)₂/DTBNpP·HBF₄ catalyst system was insensitive to the L/Pd ratio over the range of 0.75:1 to 2:1.

Ligand Comparison. With optimal conditions determined for the Pd/DTBNpP·HBF₄ system, we wanted to compare the activity of catalysts derived from the four ligands in Figure 2. For these studies, the free phosphines were used, rather than the phosphonium salts. Control reactions showed that comparable activity was achieved with both ligand precursors, as was originally shown by Fu.⁴² The rate of product formation in the coupling of 4-bromoanisole, a deactivated aryl bromide, and *N*-methylaniline at room temperature was determined for catalysts derived from Pd₂(dba)₃ (0.5 mol % of Pd, 1:1 L/Pd) and TTBP or the neopentylphosphines (DTBNpP, TBDNpP, TNpP). The conversion profiles determined by GC analysis of the reaction mixtures are shown in Figure 3. Complete conversion was seen for the DTBNpP and TBDNpP catalyst systems when the first measurement was made after 1 h. In the reactions using TTBP and TNpP, only 40% conversion to product was observed after 1 h at room temperature. Allowing the reaction

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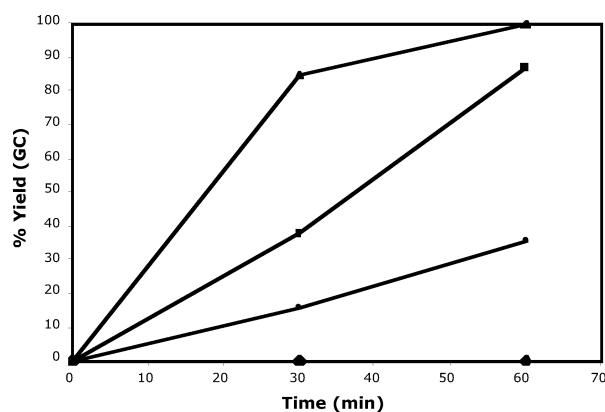


FIGURE 4. Conversion profiles for L/Pd(OAc)₂-catalyzed (1 mol % of Pd, 1:1 L/Pd) coupling of 4-bromoanisole and morpholine at 50 °C: TTBP (square), DTBNpP (triangle), TBDNpP (circle), TNpP (diamond).

to proceed for an additional 4 h resulted in a slight increase in yield for the TTBP system to 50%, while the TNpP system gave no further conversion after 1 h.

A similar comparison of the activity of the catalysts derived from the ligands was carried out in the coupling of morpholine and 4-bromoanisole at 50 °C with catalysts derived from the ligands and Pd(OAc)₂ (1 mol %, 1:1 L/Pd, Figure 4). Again, the catalyst derived from DTBNpP gave the fastest rate of conversion to product. This catalyst system gave nearly complete conversion to product (90%) after 30 min and had converted completely to product after 1 h. The TTBP system also gave nearly complete conversion (87%) after 1 h but had given only a 38% yield after 30 min. Unlike the *N*-methylaniline case, TBDNpP gave a much less active catalyst than either DTBNpP or TTBP reaching only 36% conversion to product after 1 h. Over this time period, no product was seen in the reaction catalyzed by TNpP/Pd(OAc)₂.

Synthetic Scope for the Amination of Aryl Bromides with DTBNpP. The catalyst derived from DTBNpP and Pd₂(dba)₃ was applied to the coupling of aryl bromides and aniline derivatives at room temperature using 1 mol % of palladium (eq 3, Table 3). The phosphonium tetrafluoroborate salt of DTBNpP was used for most reactions in a 1:1 ratio with palladium. The catalyst system gave similar yields for electron-deficient and electron-rich substrates, although the yield was somewhat lower for the very electron-rich **7e** (entry 6). 2-Bromotoluene (**7f**) gave a similar yield to sterically undemanding aryl bromides (entry 7), but the more sterically hindered **7g** required higher catalyst loading (2 mol %) and temperature (50 °C) to reach completion. Sterically hindered anilines **8c** and **8d** could be coupled with **7c** at room temperature, although the yields were lower than were achieved with aniline (entries 9 and 10). Coupling of **8c** with **7g** at 50 °C using 2 mol % of palladium gave the tetra-*ortho*-substituted diarylamine product in 75% yield (entry 12). An attempt to couple **7g** and **8d** was unsuccessful, however.

The DTBNpP catalyst system was also effective for the coupling of aryl bromides with *N*-methylaniline (**10a**) and diphenylamine (**10b**). The scope of aryl halides tolerated with **10a** was similar to that found with aniline (Table 4). Changing from electron-deficient aryl halides, such as **7a**, to the very electron-rich aryl halide (**7e**) had no significant effect on product yield, although reactions with the more electron-rich substrates took longer (6 h vs 1 h). Coupling with the more hindered

secondary amine **10a** did result in more sensitivity to the steric demand of the aryl bromide than was seen with aniline. 2-Bromotoluene (**7f**) gave a similar yield to unhindered aryl bromides, but no product was formed with 2-bromo-*m*-xylene (**7g**) at 80 °C after 16 h (entries 7 and 8). Coupling of unhindered aryl bromides **7b** and **7d** with diphenylamine (**10b**) gave yields comparable to those obtained with **10a** (entries 9 and 10). Diphenylamine was more sensitive to steric bulk than **10a**, however. Coupling of **10b** with **7f** gave only a 54% yield after 6 h, despite using a higher catalyst loading (1 mol %, entry 11).

Secondary aliphatic amines were also effective substrates with the DTBNpP/Pd catalyst system. For these reactions, Pd(OAc)₂ was used as the palladium source on the basis of our initial studies. Coupling of morpholine (**12a**) with aryl bromides ranging from electron rich to electron deficient gave excellent yields of the corresponding *N*-aryl morpholine at 50 °C (eq 5, Table 5). The sensitivity to the steric demand of the aryl halide was similar to that seen with *N*-methylaniline. A good yield was obtained with mono-*ortho*-substituted aryl bromides **7f** and **7i** (entries 5 and 6), but no product was formed with 2-bromo-*m*-xylene. Acyclic dialkylamines (**12b**) gave yields comparable to those seen with morpholine. In neither case was any evidence of hydrodehalogenation seen in GC analyses of the reaction mixtures. Attempts to arylate primary alkylamines were unsuccessful.

Amination of Aryl Chlorides. Good to excellent yields of coupled products were obtained in the amination of aryl chlorides using DTBNpP as the ligand at elevated temperatures (eq 6). High temperatures, higher catalyst loadings, or both were required in the coupling reactions of aryl chlorides in comparison with those of aryl bromides. Coupling of aniline with non-activated or deactivated aryl chlorides required temperatures ≥120 °C (Table 6). Little activity was observed below this temperature, even with higher catalyst loadings. Both 4-chlorotoluene (**14b**) and 2-chlorotoluene (**14d**) gave good yields of diarylamine at 120 °C using 1 mol % of Pd/DTBNpP (entries 1 and 3). In the case of 4-chloroanisole (**14c**), it was necessary to raise the temperature to 140 °C to achieve complete conversion using 1 mol % of Pd.

N-Methylaniline, morpholine, and dibutylamine could be coupled with aryl chlorides at lower temperatures than aniline, although higher catalyst loadings were required in some cases (Table 6). 4-Chlorobenzonitrile (**14a**), an activated aryl chloride, could be coupled with *N*-methylaniline (**10a**) or morpholine (**12a**) at 50 and 80 °C, respectively (entries 4 and 7), using the same catalyst loadings as were used for aryl bromides (0.5 and 1 mol %, respectively). In the coupling of 4-chlorotoluene (**14b**) with *N*-methylaniline **10a**, it was necessary to raise the reaction temperature to 100 °C and increase the catalyst loading to 1 mol % (entry 5). 4-Chloroanisole (**14c**) required increasing the catalyst loading to 5 mol %. Performing the coupling of **14c** and **10a** at 120 °C using 1 mol % of Pd/DTBNpP gave only a low conversion to product. Morpholine and dibutylamine could be coupled with **14b** and **14c** at 80 °C using 2 and 5 mol % of Pd, respectively (entries 8–11). Again, attempts to carry out these reactions at higher temperature with lower catalyst loading were not successful.

Ligand Steric and Electronic Properties. In an effort to understand how the structure of the neopentyl ligands affects their ability to give active catalysts for the H–B reaction, electronic and steric parameters of the ligands were determined.

TABLE 3. DTBNpP/Pd₂(dba)₃-Catalyzed Coupling of Aryl Bromides and Aniline Derivatives^a

$$\text{ArBr} + \text{Ar}'\text{NH}_2 \xrightarrow[\text{Toluene, rt, 3-4 h}]{\text{Pd}_2(\text{dba})_3 (0.5 \text{ mol}\%), \text{DTBNpP} \cdot \text{HBF}_4 (1 \text{ mol}\%), \text{NaO}t\text{-Bu}}$$

$$\text{Ar}-\text{N}(\text{H})-\text{Ar}' \quad (3)$$

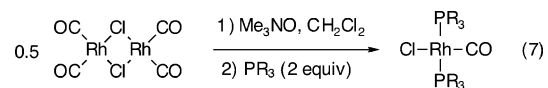
7a: Ar = 4-FC₆H₅
 7b: Ar = 4-CF₃C₆H₅
 7c: Ar = 4-MeC₆H₅
 7d: Ar = 4-MeOC₆H₅
 7e: Ar = 4-Me₂NC₆H₅
 7f: Ar = 2-MeC₆H₅
 7g: Ar = 2,6-Me₂C₆H₄

8a: Ar' = Ph
 8b: Ar' = 4-anisyl
 8c: Ar' = mesityl
 8d: Ar' = 2,6-diisopropylphenyl

entry	ArBr	Ar'NH ₂	product	yield (%) ^b	entry	ArBr	Ar'NH ₂	product	yield (%) ^b
1	7a	8a		84	7	7f	8a		79
2	7b	8a		96	8	7g	8a		77 ^c
3	7c	8a		86	9	7c	8c		60
4	7d	8a		92	10	7c	8d		47
5	7d	8b		89	11	7f	8c		78
6	7e	8a		78	12	7g	8c		75 ^c

^a Aryl bromide (0.8 mmol), aniline (1.0 mmol), NaO-*t*-Bu (0.85 mmol), Pd (1 mol %), DTBNpP·HBF₄ (1 mol %), toluene (2 mL), rt, 3–4 h. ^b Average isolated yield of two runs. ¹H and ¹³C NMR spectral data were consistent with previously reported data. ^c Reaction ran at 50 °C with 2 mol % of Pd/DTBNpP.

The electron-donating ability of the ligands was estimated from the carbonyl stretching frequencies of the corresponding *trans*-L₂Rh(CO)Cl complexes.⁴³ The rhodium complexes were prepared from [Rh(CO)₂(μ-Cl)]₂ by trimethylamine *N*-oxide promoted ligand substitution (eq 7). The crude reaction mixtures were analyzed by FT-IR spectroscopy to determine the carbonyl stretching frequency (Table 7).



Replacing a *tert*-butyl group with a neopentyl substituent decreased the electron-donating ability of the phosphine. The DTBNpP complex gave a CO stretching frequency that was 18 cm⁻¹ higher than that of the TTBP complex, indicating that DTBNpP is less electron donating than TTBP. Each subsequent replacement resulted in a smaller increase in the stretching frequency (7 and 4 cm⁻¹, respectively). The TBDNpP complex gave a stretching frequency that was identical to the reported value for the (*i*-Pr)₃P complex (1946 cm⁻¹).⁴³ The stretching

frequency for the TNpP complex was slightly lower than that of (*n*-Bu)₃P, showing that the electron-donating ability of the neopentyl group is only slightly stronger than that of a simple *n*-alkyl group, based on these measurements.

We have previously shown that the geometries and frequencies of transition-metal complexes^{32,44} can be predicted reliably at the local density functional theory (LDFT) level.⁴⁵ Geometries were optimized at the LDFT level with the polarized double- ζ DZVP2 basis set on all atoms except Pd.⁴⁶ We used the Stuttgart relativistic pseudopotential and the associated basis set for Pd.⁴⁷ There are 28 electrons in the core of the ECP and the basis set for Pd is contracted to [6s5p3d]. The LDFT calculations were done with the potential fit of Vosko, Wilk, and Nusair for the correlation functional⁴⁸ and the exchange functional of Slater.⁴⁹

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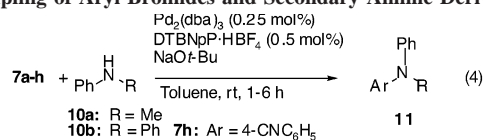
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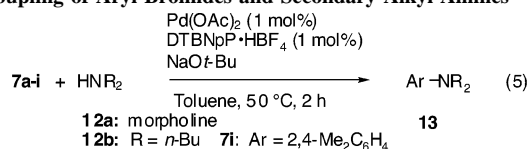
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TABLE 4. DTBNpP/Pd₂(dba)₃-Catalyzed Coupling of Aryl Bromides and Secondary Aniline Derivatives^a

entry	ArBr	Ar'NH ₂	product	yield (%) ^b	entry	ArBr	Ar'NH ₂	product	yield (%) ^b
1	7h	10a		99	7	7f	10a		90
2	7a	10a		93	8	7g	10a		0 ^c
3	7b	10a		93	9	7c	10b		97
4	7c	10a		93	10	7d	10b		83
5	7d	10a		89	11	7f	10b		44 ^d
6	7e	10a		89					

^a Aryl bromide (0.8 mmol), amine (1 mmol), NaO-*t*-Bu (1 mmol), Pd₂(dba)₃ (5 μmol), DTBNpP·HBF₄ (10 μmol), toluene (2 mL), rt, 1–6 h. Reaction times were not optimized. ^b Average isolated yield of two runs. ¹H and ¹³C NMR spectral data were consistent with previously reported data. ^c 80 °C, 1 mol % of Pd, 1 mol % of DTBNpP·HBF₄, 16 h. ^d rt, 1 mol % of Pd, 1 mol % of DTBNpP·HBF₄, 4 h.

TABLE 5. DTBNpP/Pd₂(dba)₃-Catalyzed Coupling of Aryl Bromides and Secondary Alkyl Amines^a

entry	ArBr	Ar'NH ₂	product	yield (%) ^b	entry	ArBr	Ar'NH ₂	product	yield (%) ^b
1	7b	12a		93	5	7f	12a		93
2	7c	12a		89	6	7i	12a		88
3	7d	12a		97	7	7c	12b		86
4	7e	12a		89	8	7d	12b		96

^a Aryl bromide (0.8 mmol), amine (1 mmol), Na-*t*-OBu (1 mmol), Pd(OAc)₂ (1 mol %), DTBNpP·HBF₄ (1 mol %), toluene (2 mL), 50 °C, 2 h. Reaction times were not optimized. ^b Average isolated yield of two runs. ¹H and ¹³C NMR spectral data were consistent with previously reported data.

The bond energies were calculated at the gradient-corrected level at the LDA-optimized geometries with the B3LYP exchange-correlation functional with the above basis sets.^{50,51} The cone angles were calculated from the LDA-optimized geometries for the (phosphine)Pd⁰ complex by using the STERIC program, and the volumetric parameters for the atoms therein with the Pd atom set at the origin.^{52,53}

The LDFT-optimized structures of the monosphosphine complexes are shown in Figure 5. For the structures with a neopentyl group, the CH₂ group bonded to P is rotated in the optimized structures so as to maximize the distance of the H atoms from the Pd. This orientation leads to the *tert*-butyl fragment being oriented toward the Pd center. Other orientations were studied and shown to be of significantly higher energy. This orientation

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TABLE 6. DTBNpP/Pd-Catalyzed Amination of Aryl Chlorides^a

$\text{ArCl} + \text{HNR}'\text{R}'' \xrightarrow[\text{50-140 } ^\circ\text{C}]{\text{Pd source (0.5-5 mol\%), DTBNpP}\cdot\text{HBF}_4 \text{ (0.5-5 mol\%), NaOt-Bu, Toluene or xylene}}$ $\text{Ar-NR}'\text{R}''$ (6)

14a: R = 4-CN
 14b: R = 4-Me
 14c: R = 4-OMe
 14d: R = 2-Me

entry	ArCl	HNRR'	mol % Pd	temp (°C)	time (h)	Product	yield (%) ^b
1	14b	8a	1	120 ^c	3		82
2	14c	8a	1	140 ^c	4		89
3	14d	8a	1	120 ^c	4		95
4	14a	10a	0.5	50	5		96
5	14b	10a	1	100	2		70
6	14c	10a	5	100	18		99
7	14a	12a	1	80 ^d	24		70
8	14b	12a	2	80 ^d	18		86
9	14c	12a	5	80 ^d	24		79
10	14b	12b	2	80 ^d	17		98
11	14c	12b	5	80 ^d	20		86

^a Aryl chloride (0.8 mmol), amine (0.82–1 mmol), Na-*t*-OBu (1 mmol), Pd₂(dba)₃ (0.5–5 mol % of Pd), DTBNpP·HBF₄ (1 equiv/Pd), toluene (2 mL), 50 °C, 2 h. Reaction times were not optimized. ^b Average isolated yield of two runs. ¹H and ¹³C NMR spectral data were consistent with previously reported data. ^c Xylene used as solvent. ^d Pd(OAc)₂.

TABLE 7. Steric and Electronic Properties of Neopentylphosphines

ligand	$\nu_{\text{Rh-CO}}$ (cm ⁻¹) ^a	θ_{DFT}^c (deg)	θ_T^d (deg)	P–Pd bond energy ^e (kcal/mol)	$R(\text{Pd-H})^f$ (Å)	LPd(0)	
						HOMO ^g (eV)	GAP ^h (eV)
TTBP	1921	194	182	37.3	2.69	4.51	3.33
DTBNpP	1939	198		35.8	2.41	4.50	3.27
TBDNpP	1946	210		35.2	2.32	4.52	3.24
TNpP	1950	227	180	33.7	2.38	4.46	3.16
(<i>i</i> -Pr) ₃ P	1946 ^b	182	160	38.7	2.93	4.64	3.47
(<i>n</i> -Bu) ₃ P	1953 ^b	177	132	39.2	3.06	4.66	3.48
Ph ₃ P	1978 ^b	173	145	37.1	3.07	4.91	3.42

^a Carbonyl stretching frequency measured in solution of in situ prepared *trans*-(L)₂Rh(CO)Cl complex. ^b Literature values. ^c Cone angle values determined from LDFT-optimized LPd(0) structures using the STERIC program. ^d Cone angle values determined by Tolman. ^e Calculated at the DFT level with the B3LYP exchange-correlation functional at the LDA-optimized geometries. ^f Closest nonbonded Pd–H distances. For the neopentyl-substituted compounds this is for the methyl groups showing agostic interactions. ^g HOMO energy at the B3LYP level. ^h GAP = |E(HOMO) – E(LUMO)|.

results in the neopentyl substituent having a large steric demand. Thus, the cone angle for DTBNpP of 198° is larger than the value for TTBP of 194° showing a larger steric demand for the former ligand (Table 7). Further replacement of *tert*-butyl groups

with neopentyl substituents resulted in a continued increase in the cone angle. As can be seen in the space filling structures in Figure 5, the three neopentyl groups of TNpP shield a significant amount of the Pd atom.

The DFT-optimized geometries resulted in a significantly larger calculated cone angle for TNpP than was estimated by Tolman. We have found a general trend for the cone angles obtained from LDFT-optimized structures to be larger than those estimated by Tolman. In some cases, these differences can be significant and result in different trends than were predicted by Tolman, such as TTBP compared with DTBNpP. Tolman, in determining his cone angle values, chose ligand conformations that minimize the cone angle. In contrast, the computed geometries are allowed to adopt the lowest energy conformation, which in many cases is not the one with the smallest cone angle. The nature of these conformational effects on cone angles will be discussed in more detail in a forthcoming paper detailing our computational approach to obtaining cone angle values.

The projection of the *tert*-butyl groups of the neopentyl substituents toward the metal center leads to the potential for agostic interactions. There are two such interactions in the DTBNpP and TBDNpP complexes and three in the TNpP complex (Table 7). These agostic interactions have smaller bond distances and hence increased interactions for the more sterically demanding TBDNpP and TNpP ligands than for smaller ligands such as DTBNpP or TTBP. The Pd–P bond strengths decrease with increasing cone angle as would be expected from the steric repulsion effects, with the exception of PPh₃. The bond strengths all are lower than we previously reported for Ph₃P and TTBP³² due to the use of a different exchange-correlation functional. The highest bond strength is found for the least sterically hindered ligand, P(*n*-Bu)₃.

Discussion

DTBNpP in combination with palladium sources gave a highly effective catalyst for the Hartwig–Buchwald amination of aryl bromides at room temperature. The activity was superior to that of catalysts derived from TTBP in direct comparisons of reaction profiles. In contrast, TNpP was a less effective ligand for these coupling reactions than either TTBP or DTBNpP. TBDNpP gave catalysts with activities comparable to DTBNpP or TTBP depending on the amine substrate. Although a direct comparison was not performed, the DTBNpP catalyst system gave comparable yields in the amination of aryl bromides to those reported for catalysts derived from biphenylphosphine **3** using similar catalyst loadings and shorter reaction times.¹⁵

In the case of aryl chlorides, DTBNpP again gave effective catalysts for the amination reactions at elevated temperatures. Similar palladium loadings were required with DTBNpP and TTBP, but the DTBNpP catalyst system required higher temperatures than TTBP to achieve similar yields.⁶ The temperatures required for amination of aryl chlorides using DTBNpP are comparable or lower than those required with adamantylphosphine **2**,^{11,12} although higher catalyst loadings are required in most cases for the DTBNpP system. The DTBNpP catalyst system generally required higher temperatures than catalysts derived from biphenylphosphine **3** for aminations of aryl chlorides.^{15,17}

We have previously shown that calculated cone angles were a good predictor of catalyst activity for a family of water-soluble alkylphosphines in the Suzuki coupling of aryl bromides.³² In this work, we find that with cone angles greater than 200°,

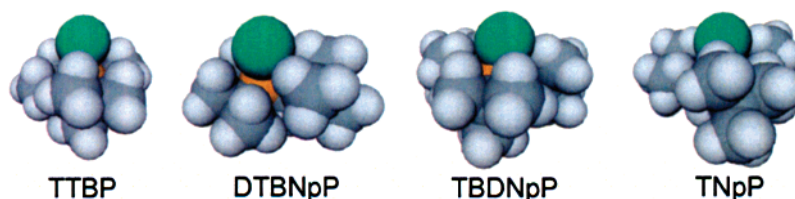


FIGURE 5. Space-filling models of LDFT-optimized geometries for LPd^0 complexes (H = light gray, C = dark gray, P = gold, Pd = green).

catalyst efficiency appeared to decrease with increasing cone angle. In our prior work, we found that catalyst activity increased upon increasing the cone angle over the range of 185 to 194°. Although our prior work dealt with the Suzuki coupling, Hartwig has shown that ligands with smaller cone angles than TTBP, such as tricyclohexylphosphine or $(n\text{-Bu})_3\text{P}$, gave less active catalysts in the H–B coupling.⁸ The sum of these results suggests that the optimal cone angle for these reactions falls between 190° and 200°, whereas ligands with larger or smaller cone angles give less effective catalyst systems.

If the cone angle is less than 180°, then the two ligands in a linear L_2Pd complex will not have a significant steric repulsion and can reach their optimal Pd–L bond distances. Ligand dissociation to give coordinatively unsaturated will not be promoted by ligands of this size. For ligands with cone angles greater than 180°, steric interactions between the ligands will lead to a lower bond energy, assuming equal electronic contribution, resulting in more facile ligand dissociation. For ligands with substantially larger cone angles than 180°, ligand dissociation should be even more facile. The steric demand of the ligand may block incoming substrates from approaching the metal center, however. In addition, the weaker metal–phosphine bond energies may result in catalysts with poor stability. Thus, TBDNpP and TNpP, with cone angles larger than 200°, may be too large to serve as effective ligands in cross-coupling reactions.

The activity of catalysts derived from the neopentylphosphines also decreases with increasing CO stretching frequency of *trans*- $L_2Rh(CO)Cl$ complexes. The significance of this correlation is unclear, since steric and electronic properties of these phosphines are directly coupled. Replacement of a *tert*-butyl group with a neopentyl group increases the cone angle of the phosphine, while decreasing its electron donating ability. TTBP is more electron donating than DTBNpP, but has a smaller cone angle. DTBNpP gave more active catalysts for H–B amination of aryl bromides than TTBP. This result suggests that the cone angle could be more important in determining catalyst activity toward aryl bromides than the electronic properties of the ligands. Of course, it must be noted that the differences in cone angle and especially the CO stretching frequencies are relatively small. In the case of aryl chlorides, we see a reversal in the relative activity of catalysts derived from TTBP and DTBNpP from that seen with aryl bromides. The increased activity of the catalyst derived from TTBP seems to correlate to the increased electron-donating ability of this ligand compared to DTBNpP.

There is very little change in the calculated ionization potential from Koopmanns' theorem (the negative of the HOMO energy) for the substitution of a *tert*-butyl group by a neopentyl substituent so the ionization potential for these systems is not a good measure of the change in the electron-donating ability of the ligand. This observation is consistent with prior computational studies on nickel phosphine complexes. The GAP,

defined as $|E(\text{HOMO}) - E(\text{LUMO})|$, does decrease with substitution of a *tert*-butyl substituent by a neopentyl group tracking the change in frequencies and thus may serve as another means to estimate the electronic parameter. The GAP at the DFT level correlates reasonably well with the first excitation energy.^{54,55} A smaller GAP is consistent with it being easier to excite an electron from the HOMO to the LUMO. This value is lower than the ionization process as the LUMO has a negative eigen value. This correlation is consistent with a single electron excitation process correlating with increased reactivity. The HOMO values show little variation among the ligands, but the LUMO values do vary with substituent. We note that the reactivity changes occur over less than an order of magnitude. Assuming the same preexponential factor, at room temperature, the differences in activation energy must be less than 1.4 kcal/mol, which is consistent with the small differences in the electronic parameters of the various phosphines.

The different contributions of steric and electronic properties suggest a different rate-limiting step in the catalytic cycle for aryl bromides and chlorides. In the coupling of aryl chlorides, oxidative addition is likely to be the rate-limiting step.³¹ More electron-donating ligands would be expected to promote oxidative addition. Oxidative addition is likely not to be the rate-limiting step in the case of aryl bromides. The key step in the case of aryl bromides may well be the initial ligand dissociation to give the highly reactive $LPd(0)$ species. Hartwig³⁰ has shown that ligand dissociation is the rate-limiting step in the oxidative addition of aryl bromides to palladium(0) complexes of bulky alkylphosphines, while the mechanism for aryl chlorides involved reversible ligand dissociation followed by rate limiting oxidative addition. Increased steric demand would be expected to favor ligand dissociation, although the low activity of catalysts derived from TBDNpP and TNpP may indicate that they are either too large or not strongly electron-donating enough, or possibly a combination of both factors, to provide effective catalysts.

Conclusion

DTBNpP is a commercially available, sterically demanding, electron-rich alkylphosphine that provides effective catalysts for the Hartwig–Buchwald amination of aryl bromides and chlorides. DTBNpP provides catalysts with higher activity in the amination of aryl bromides than TTBP. DTBNpP is effective toward aryl chlorides but requires higher temperatures than TTBP. Studies of the steric and electronic properties of the ligands show that the cone angle likely dominates the activity in coupling of aryl bromide, whereas the electron-donating ability of the phosphines becomes more important with aryl

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chlorides. In couplings of aryl bromides, the ligand steric demand appears to be a key parameter with the optimal cone angle being between 190° and 200°. While steric bulk remains important in the coupling of aryl chlorides, electronic factors likely play a much more important role in determining catalyst activity.

Experimental Section

Typical Procedure for the Coupling of Aryl Bromides and Aniline Derivatives. Pd₂(dba)₃ (2–4 μmol), DTBNpP (10% solution in toluene) or DTBNpP·HBF₄ (4–8 μmol, 1 equiv/Pd), sodium *tert*-butoxide (0.85 mmol), and toluene (2 mL) were added to a round-bottom flask in a glovebox. Upon removal of the septum-sealed flask from the drybox, the aryl bromide (0.80 mmol) and aniline derivative (**8** or **10**, 0.82–1.0 mmol) were added by syringe and the reaction was allowed to stir for 1–6 h at room temperature until judged complete by GC. The reaction mixture was then adsorbed on silica gel and purified by flash chromatography eluting with a mixture of hexane and ethyl acetate.

Typical Procedure for the Coupling of Aryl Chlorides and Aniline Derivatives. Pd₂(dba)₃ (2–20 μmol), DTBNpP (10% solution in toluene) or DTBNpP·HBF₄ (4–40 μmol, 1 equiv/Pd), sodium *tert*-butoxide (0.85 mmol), and solvent (toluene or xylene, 2 mL) were added to a round-bottom flask in a glovebox. Xylene was used in place of toluene for reactions carried out at temperatures above 100 °C. Upon removal of the septum-sealed flask from the drybox, the aryl chloride (0.80 mmol) and aniline derivative (**8** or **10**, 0.82–1.0 mmol) were added by syringe. The flask was placed in a preheated oil bath at the indicated temperature and stirred for 2–24 h until judged complete by GC. The reaction mixture was then adsorbed on silica gel and purified by flash chromatography eluting with a mixture of hexane and ethyl acetate.

Typical Procedure for the Coupling of Aryl Bromides and Secondary Alkylamines. Pd(OAc)₂ (10 μmol), DTBNpP (10%

solution in toluene) or DTBNpP·HBF₄ (10 μmol, 1 eq/Pd), sodium *tert*-butoxide (1.5 mmol), and toluene (2.5 mL) were added to a round-bottom flask in a glovebox. Upon removal of the septum-sealed flask from the drybox, the aryl bromide (1.0 mmol) and amine **12a** or **12b** (1.0 mmol) were added by syringe and the reaction was allowed to stir for 2 h at 50 °C. The reaction mixture was then adsorbed on silica gel and purified by flash chromatography eluting with a mixture of hexane and ethyl acetate.

Typical Procedure for the Coupling of Aryl Chlorides and Secondary Alkylamines. Pd(OAc)₂ (10–50 μmol), DTBNpP (10% solution in toluene) or DTBNpP·HBF₄ (10–50 μmol, 1 equiv/Pd), sodium *tert*-butoxide (1.5 mmol), and toluene (2.5 mL) were added to a round-bottom flask in a glovebox. Upon removal of the septum-sealed flask from the drybox, the aryl chloride (1.0 mmol) and amine **12a** or **12b** (1.0 mmol) were added by syringe. The flask was placed in a preheated oil bath at 80 °C and stirred until judged complete by GC. The reaction mixture was then adsorbed on silica gel and purified by flash chromatography eluting with a mixture of hexane and ethyl acetate.

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Supporting Information Available: Detailed experimental data, product characterization data, calculated optimized molecular geometries in Å as well as total and zero point energies in au, and ¹H and ¹³C NMR spectra of the compounds in Tables 3–6. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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