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A Tuned Bicyclic Proazaphosphatrane for Catalytically Enhanced *N*-Arylation Reactions with Aryl Chlorides

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The *N*-arylation of various amines with aryl chlorides proceeded in good-to-excellent yields in the presence of P[N{(*p*-NMe_2)$C_6H_4CH_2$}CH_2CH_2]$_3$N (**1e**, a new electron-rich proazaphosphatrane ligand) and small amounts of $Pd_2(dba)_3$ (dba = dibenzylideneacetone). This catalytic system was also very effective for the synthesis of carbazoles.

Introduction

Amination reactions involving the formation of a carbon–nitrogen bond such as reductive amination, electrophilic amination, and Buchwald–Hartwig *N*-arylation are fundamentally important organic transformations.[1] Especially important is the Buchwald–Hartwig *N*-arylation, a valuable reaction for carbon–nitrogen bond formation through the palladium-catalyzed cross-coupling of various amines with aryl halides.[2] In 1983, Migita and co-workers developed this *N*-arylation methodology for the coupling of Bu_3SnNEt_2 with aryl bromides in the presence of $PdCl_2$[P(*o*Tol)$_3$]$_2$ (*o*Tol = *o*-tolyl).[3] Significantly improved catalytic systems for *N*-arylation reactions have subsequently been developed by Buchwald,[4] Hartwig,[5] and others.[6] Organotin-free palladium-catalyzed *N*-arylation reactions of various amines with aryl halides in the presence of bulky bases such as *t*BuOK[5a] and lithium hexamethyldisilazide (LiHMDS)[7] were introduced by the Buchwald and Hartwig groups. These results constitute the first generation of Buchwald–Hartwig catalytic systems containing phosphine ligands.

The [$Pd_2(dba)_3$]/P(*o*Tol)$_3$ (dba = dibenzylideneacetone) catalytic system is limited to the cross-coupling of secondary amines with aryl bromides containing *para* electron-withdrawing substituents and *ortho* substituents.[5a] However, a [$Pd_2(dba)_3$]/P(*o*Tol)$_3$ catalytic system displayed only low activity for the coupling of primary amines and aryl bromides.[4a] In contrast, a $Pd_2(dba)_3$/BINAP [BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl] catalytic system showed improved catalytic activity for the cross-coupling of primary amines with both electron-rich and electron-poor aryl bromides.[4a] Also, the (DPPF)$PdCl_2$ [DPPF = 1,1′-bis(diphenylphosphanyl)ferrocene] catalytic system showed high activity for the cross-coupling of primary amines with both electron-donating and -withdrawing aryl halides.[4a] The Buchwald group also developed a highly efficient C–N bond-formation methodology that utilizes cheap and normally unreactive aryl chlorides with primary and secondary amines in the presence of $Pd(OAc)_2$/DBPF [DBPF = 1,1′-bis(di-*tert*-butylphosphanyl)ferrocene][4b] and $Pd(dba)_2$/P(*t*Bu)$_3$.[8] Recently, the $Pd_2(dba)_3$/$Ph_5FcP(tBu)_2$ (Fc = ferrocenyl) and $Pd(OAc)_2$/$Ph_5FcP(tBu)_2$ catalytic systems were found to improve the reactivity of various aryl chlorides with primary and secondary amines at 70–100 °C; 4-chlorobenzonitrile was reactive at 45 °C.[9a] Although a variety of amines tend to be facile for general palladium-catalyzed *N*-arylation reactions of aryl bromides and iodides under mild conditions, aryl chlorides readily underwent this transformation only with relatively large quantities of catalyst or under harsh conditions.[8,9]

The synthesis of a growing family of bicyclic proazaphosphatranes has led to the investigation of their catalytic properties as ligands in a variety of organic transformations (e.g., Suzuki,[10] Stille,[11] α-arylation,[12] Morita–Baylis–Hillman,[13] and Hiyama[14] reactions). Proazaphosphatranes lend themselves to electronic tuning of the phosphorus atom by variation of the organic substituent at each PN_3 nitrogen atom. Several years ago, the Verkade group investigated the palladium-catalyzed *N*-arylation reactions of primary and secondary amines with aryl halides in the presence of $Pd(OAc)_2$/**1a** or $Pd_2(dba)_3$/**1a**.[15] However, the palladium-catalyzed *N*-arylation with aryl chlorides showed high activity only with a relatively large quantities of cata-

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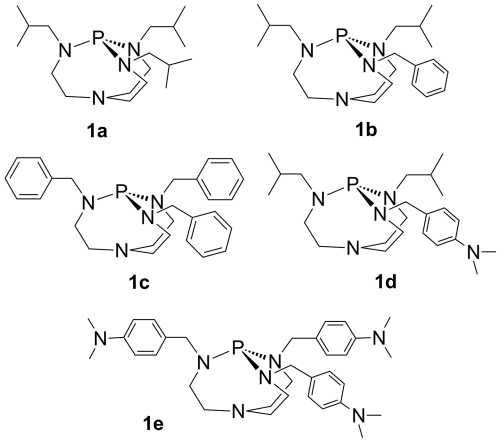
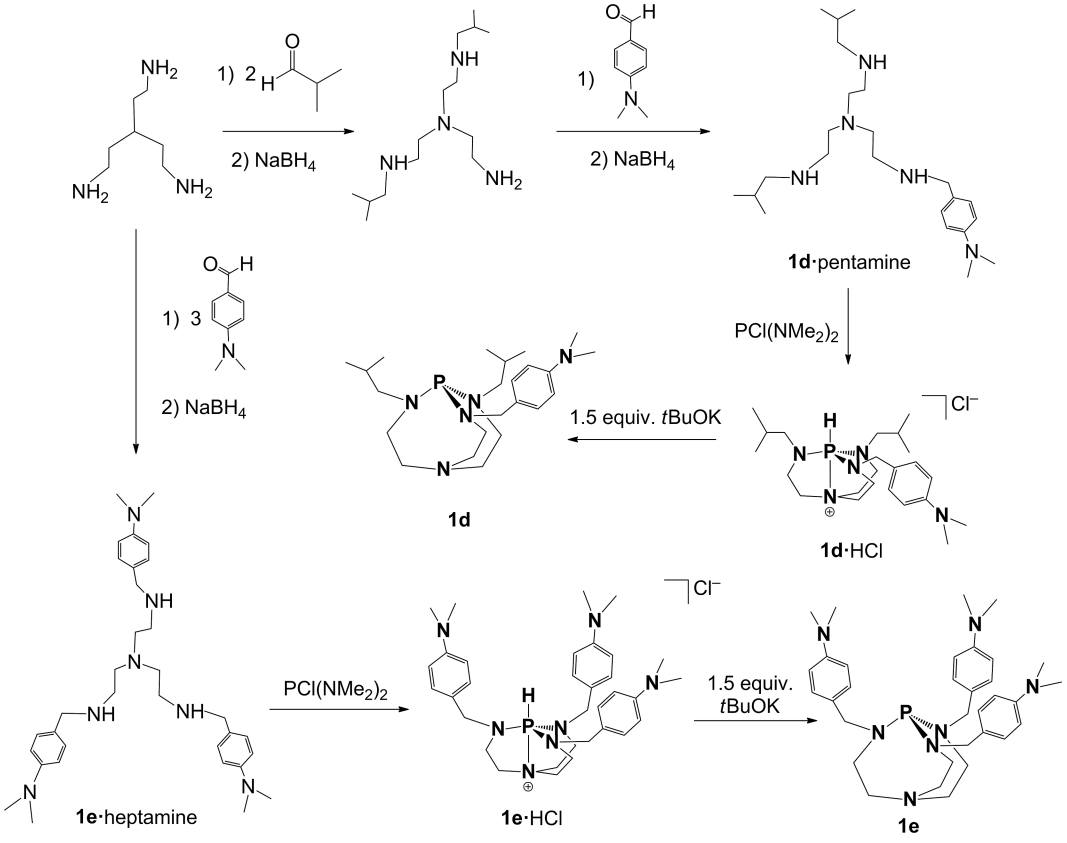


lyst or under harsh conditions.[15b,15c,15d] In the present study, benzyl- and isobutyl-substituted bicyclic proazaphosphatrane ligands (**1a**, **1b**, and **1c**) were synthesized according to previously reported procedures,[16] and **1d** and **1e** were prepared in a manner analogous to the procedure for the known compounds (see Scheme 1). Herein, we also compare the catalytic activity of a series of bicyclic proazaphosphatrane ligands **1a**–**1e** in the palladium-catalyzed *N*-arylation of a variety of amines with a broad range of aryl chlorides.

Results and Discussion

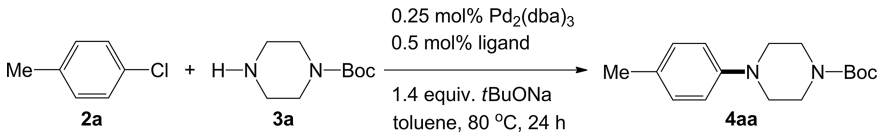
We initially focused on the cross-coupling of 4-methylchlorobenzene (**2a**) with *N*-Boc-piperazine (**3a**; Boc = *tert*-butyloxycarbonyl) as a model reaction for the optimization of the catalyst (Table 1). Previously, the Verkade group investigated the $Pd_2(dba)_3$/**1a** catalyzed cross-coupling of aryl chlorides with *N*-Boc-piperazine in the presence of *t*BuONa at 100 °C for 24 h.[15c] Although these results showed effective cross-coupling of aryl chlorides in high yields, the reaction conditions were harsh compared with those of other catalytic systems.[8,9] To optimize our catalytic system, we performed the reaction in Table 1 at 40 °C for 72 h and at 80 °C for 24 h in the presence of *t*BuONa. As shown in Table 1, ligand **1e** is considerably more efficient than **1a**–**1d** under both sets of reaction conditions (Table 1, Entries 1–10). Therefore, we selected proazaphosphatrane **1e** as the ligand of choice for further studies. Apparently, the catalytic activities of **1a**–**1e** decrease as the electron richness of the phosphorus atom decreases as isobutyl groups are substituted with benzyl substituents. The catalytic activity also increases as the benzyl groups are substituted by the more electron-rich *para*-dimethylaminophenyl substituents.

Next, we performed the coupling of the secondary cyclic amine **3a** with various aryl chlorides (Table 2). The optimized reaction conditions were 0.25 mol-% of $Pd_2(dba)_3$ and 0.05 mol-% of ligand **1e** with *t*BuONa at 80 °C for 24 h.



Scheme 1. Synthetic routes for **1d** and **1e**.

Table 1. Survey of Buchwald–Hartwig *N*-arylation reactions of *N*-Boc-piperazine with 1-chloro-4-methylbenzene in the presence of **1a**–**1e**.[a]

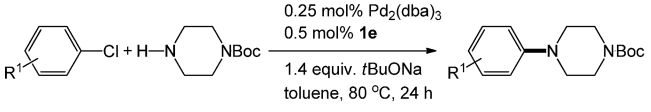


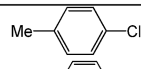
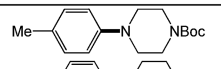
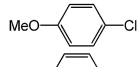
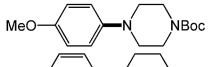
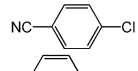
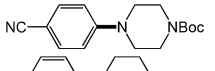
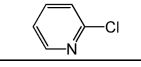
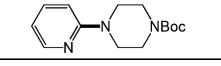
Entry	Ligand	Temperature [°C]	Time [h]	Yield [%][b]
1	**1a**	40	72	48
2	**1b**	40	72	37
3	**1c**	40	72	5
4	**1d**	40	72	57
5	**1e**	40	72	87
6	**1a**	80	24	61
7	**1b**	80	24	53
8	**1c**	80	24	15
9	**1d**	80	24	69
10	**1e**	80	24	92

[a] Reaction conditions: 1-chloro-4-methylbenzene (1 mmol), 1-Boc-piperazine (1.2 mmol), $Pd_2(dba)_3$ (0.25 mol-%), **1a**–**1e** (0.5 mol-%), *t*BuONa (1.4 mmol), toluene (3.0 mL). [b] Isolated yields after silica gel column chromatography.

Under these reaction conditions, aryl chlorides of the electron-neutral, -donating, -withdrawing, and heteroaryl types gave the expected products in excellent isolated yields (90–99%) within 24 h at 80 °C (Table 2, Entries 1–4). These results with small amounts of $Pd_2(dba)_3$ and **1e** as well as a moderate reaction temperature contrast with the harsher ones we reported previously for the $Pd_2(dba)_3$/**1a** catalytic system.[15b,15c]

Table 2. $Pd_2(dba)_3$/**1e**-catalyzed *N*-arylation of 1-Boc-piperazine with various aryl chlorides.[a]

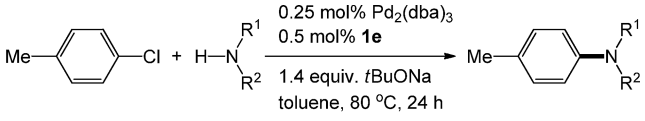


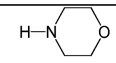
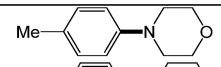
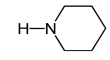
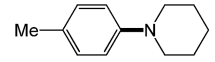
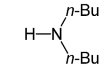
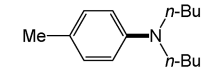
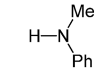
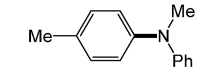
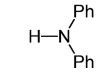
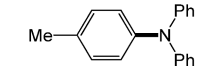
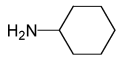
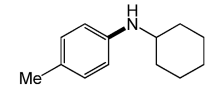
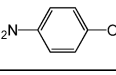
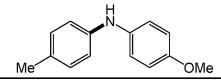
Entry	Aryl chloride		Product	Yield [%][b]
1		**2a**		**4aa**, 92
2		**2b**		**4ba**, 96
3		**2c**		**4ca**, 99
4		**2d**		**4da**, 90

[a] Reaction conditions: aryl chloride (1 mmol), 1-Boc-piperazine (1.2 mmol), $Pd_2(dba)_3$ (0.25 mol-%), **1e** (0.5 mol-%), *t*BuONa (1.4 mmol), toluene (3.0 mL), 80 °C, 24 h. [b] Isolated yields after silica gel column chromatography.

We then assessed the reactivity of various amines including cyclic secondary amines (**3b** and **3c**), noncyclic secondary amines (**3d**, **3e**, and **3f**), and primary amines (**3g** and **3h**) with the electron-neutral aryl chloride **2a** in the presence of $Pd_2(dba)_3$ and **1e** (Table 3). All of the amine substrates provided good-to-excellent yields of *N*-arylated products.

Table 3. $Pd_2(dba)_3$/**1e**-catalyzed *N*-arylation of various primary and secondary amines with 1-chloro-4-methylbenzene (**2a**).[a]



Entry	Aryl chloride		Product	Yield [%][b]
1		**3b**		**4ab**, 91
2		**3c**		**4ac**, 80
3		**3d**		**4ad**, 86
4		**3e**		**4ae**, 86
5		**3f**		**4af**, 91
6		**3g**		**4ag**, 81
7		**3h**		**4ah**, 96

[a] Reaction conditions: 1-chloro-4-methylbenzene (1 mmol), amine (1.2 mmol), $Pd_2(dba)_3$ (0.25 mol-%), **1e** (0.5 mol-%), *t*BuONa (1.4 mmol), toluene (3.0 mL), 80 °C, 24 h. [b] Isolated yields after silica gel column chromatography.

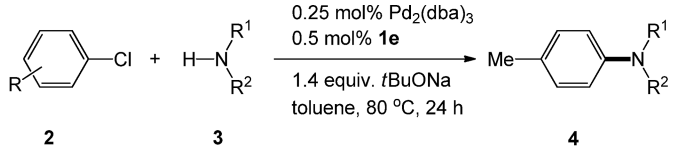
Our next category of amine substrates for investigation included secondary amines containing alkyl or aryl substituents for reactions with electron-neutral, -donating, and -withdrawing aryl chlorides and also a heteroaryl chloride in the presence of $Pd_2(dba)_3$ and **1e**.

The reactions of all the chlorides with the secondary aniline *N*-methylaniline (**3e**) to give diarylamines are depicted in Table 4. The expected products were obtained in good-to-excellent isolated yields (**4be**, **4ce**, **4ee**, and **4ie**, 86–97%). The products of the reactions of the chlorides with diphenylamine (a secondary amine) are also given in Table 4 (**4bf**, **4ef**, and **4if**). Previously, the coupling of diphenylamine with aryl chlorides required high catalyst loading, higher than that for dialkylamines and alkyl arylamines.[15b] Gratifyingly, we found that our protocol gave similar outcomes for dibutylamine (**3d**) and *N*-methylaniline (**3e**), for which the expected products were formed in excellent isolated yields (**4bd**, **4cd**, **4dd**, **4hd**, **4be**, **4ce**, **4ee**, and **4ie**, 88–97%). Notably, the $Pd_2(dba)_3$/**1e** catalytic system is useful for *N*-arylation reactions despite steric congestion of the substrates.

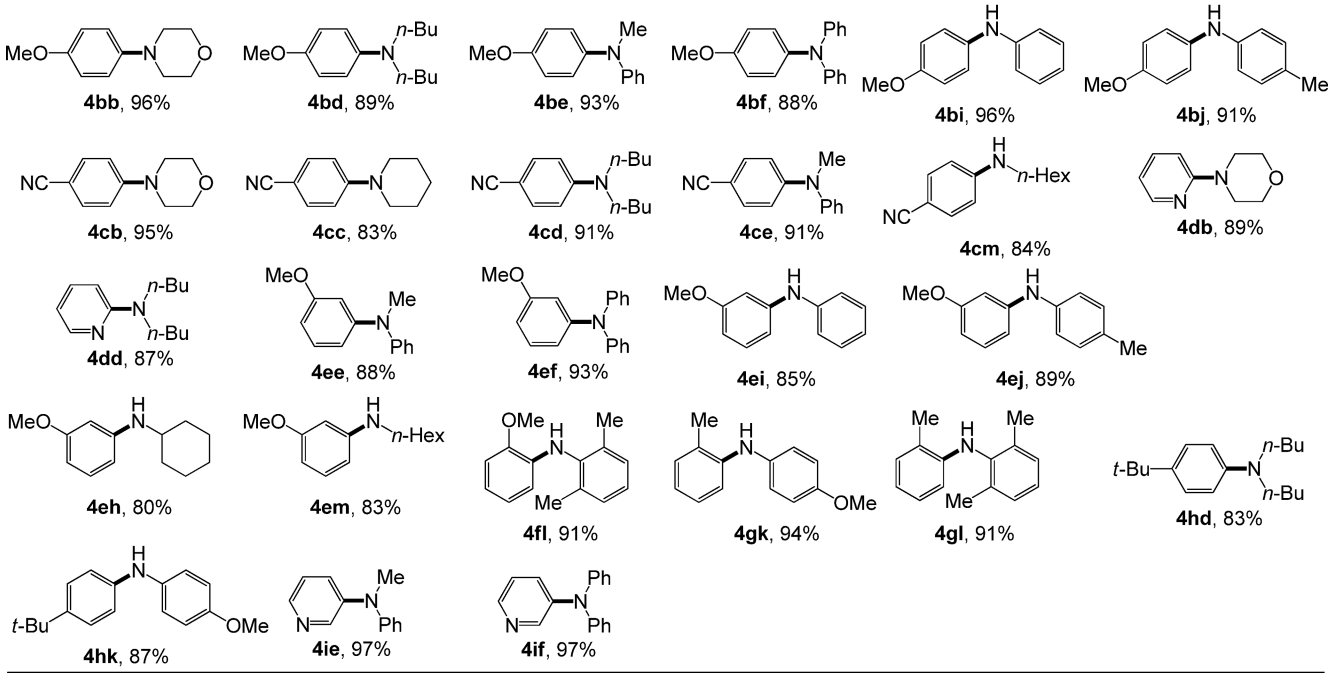
As seen with **4bi**, **4bj**, **4cm**, **4ei**, **4ej**, **4eh**, **4em**, and **4hk** in Table 4, the reactions of aryl chlorides with primary amines proceed in high yields (85–97%). Substituted aryl anilines are notably more reactive than aniline itself. Thus, although the reaction of *ortho*-substituted anilines resulted in 91–94% product yields (**4fl**, **4gk**, and **4gl**), the analogous reactions with aniline proceeded in only 86 or 85% yield (**4bi** and **4ei**, respectively). The results of the reactions of aryl chlorides with primary aliphatic amines as well as secondary aliphatic amines are also summarized in Table 4 (**4bd**, **4cd**, **4cc**, **4cd**, **4da**, **4db**, **4dd**, **4eh**, **4em**, and **4hd**, 80–89%). The coupling of aryl chlorides with aliphatic amines had previously required a relatively large amount of the palladium complex and ligand **1a** to produce low yields of products.[15b] Again, we found the expected products in excellent isolated yields with our low-catalyst-loading system. For example, although the product of the reaction of 3-methoxychlorobenzene with *n*-hexylamine was obtained in 43% yield with **1a**,[15b] the analogous reaction with **1e** proceeds in much better yield (**4em**, 83%).

By our methodology reported herein, a one-step synthesis of carbazoles was readily achieved under mild conditions with good-to-excellent yields (Table 5). Various primary amines were successively reacted with 2,2-dichlorobiphenyl. Under our conditions, a broad range of primary amines, including electron-neutral, electron-rich, and electron-poor amines, were easily coupled to produce the expected products in good-to-excellent isolated yields (Table 5, Entries 1–14; 83–98%). Additional observations of note are that our palladium loading (0.25 mol-%) is one-half that previously reported for $Pd_2(dba)_3$-catalyzed carbazole synthesis, and the reaction temperature is lower.[17] Furthermore, unreactive primary amines, including electron-poor **3u** and aliphatic **3v** and **3w**, gave rise to unexpectedly higher yields of

Table 4. $Pd_2(dba)_3$/**1e**-catalyzed *N*-arylation of various primary and secondary amines with a variety of aryl chlorides.[a,b]

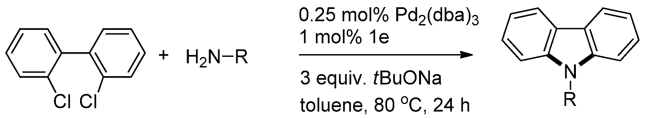


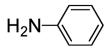
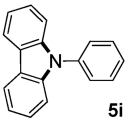
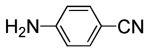
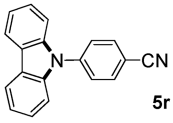
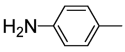
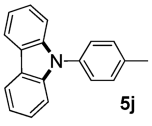
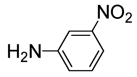
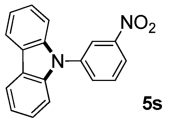
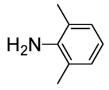
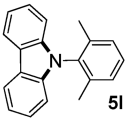
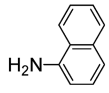
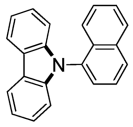
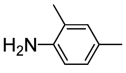
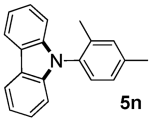
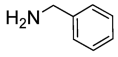
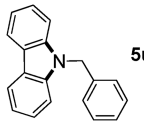
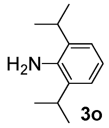
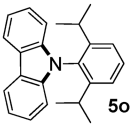
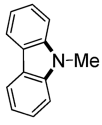
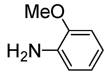
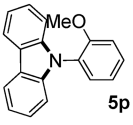
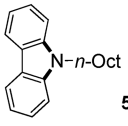
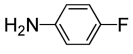
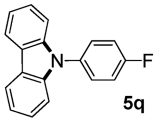
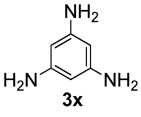
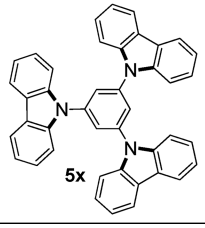
2 **3** **4**



[a] Aryl chloride (1 mmol), amine (1.2 mmol), $Pd_2(dba)_3$ (0.25 mol-%), **1e** (0.5 mol-%), *t*BuONa (1.4 mmol), toluene (3.0 mL), 80 °C, 24 h. [b] Isolated yields after silica gel column chromatography.

Table 5. Pd/**1e**-catalyzed *N*-substituted carbazole synthesis from various primary amines and 2,2′-dichlorobiphenyl.[a,b]



Entry	Amine	Product	Yield [%][b]	Entry	Amine	Product	Yield [%][b]
1	 **3i**	 **5i**	91	8	 **3r**	 **5r**	90[c]
2	 **3j**	 **5j**	96	9	 **3s**	 **5s**	89[c]
3	 **3l**	 **5l**	92	10	 **3t**	 **5t**	98
4	 **3n**	 **5n**	94	11	 **3u**	 **5u**	87[c]
5	 **3o**	 **5o**	88	12	H_2N–Me **3v**	 **5v**	83[c]
6	 **3p**	 **5p**	92	13	H_2N–*n*-Oct **3w**	 **5w**	84[c]
7	 **3q**	 **5q**	89	14	 **3x**	 **5x**	92[d]

[a] Reaction conditions: 2,2′-dichlorobiphenyl (0.5 mmol), aniline (0.6 mmol), $Pd_2(dba)_3$ (0.25 mol-%), **1e** (1 mol-%), *t*BuONa (1.5 mmol), toluene (3.0 mL). [b] Isolated yields after silica gel column chromatography. [c] 2.5 mol-% of $Pd_2(dba)_3$ was employed. [d] 1.5 mmol of 2,2′-dichlorobiphenyl and 4.5 mmol of *t*BuONa were employed.

N-substituted carbazoles than we obtained previously under mild conditions.[17]

Conclusions

We have developed an efficient $Pd_2(dba)_3$/**1e**-catalyzed *N*-arylation protocol for a wide range of amines with a variety of aryl chlorides. Good-to-excellent yields of secondary and tertiary amine derivatives (38 products in 80–99% isolated yields) were achieved in single *N*-arylations. Similar isolated yields (83–98%) of 14 carbazoles were obtained for double *N*-arylations with the same catalytic system.

Experimental Section

General Information: All reactions of air- and moisture-sensitive materials were performed under dinitrogen with standard Schlenk-type glassware on a dual-manifold Schlenk line in a glovebox. Dinitrogen was deoxygenated with activated Cu catalyst and dried with Drierite. All reagents were purchased from Aldrich and used as supplied unless otherwise indicated. All solvents were dried by distillation from sodium diphenyl ketyl under dinitrogen and stored over activated 3-Å molecular sieves. NMR solvents such as $CDCl_3$ and C_6D_6 were dried with activated 4-Å molecular sieves and used after vacuum transfer to a Schlenk tube equipped with a Young valve. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded with samples in $CDCl_3$ [internal standard at δ = 7.24 ppm ($CDCl_3$) and at δ

= 7.15 ppm (C_6D_6) for ^{1}H spectra; at δ = 77.0 ppm ($CDCl_3$) and 128.0 ppm (C_6D_6) for ^{13}C spectra; and at δ = 0.00 ppm for 85% phosphoric acid added as an external standard for ^{31}P spectra] with a 400 MHz NMR spectrometer. HRMS data were recorded with a Shimadzu LCMS 2010 instrument. Column chromatography was performed by flash column techniques with 300–400 mesh silica gel.

Compound 1d: A mixture of diisobutyltren [6.46 g, 32.0 mmol; tren = tris(2-aminoethyl)amine] and 4-(dimethylamino)benzaldehyde (5.22 g, 35.0 mmol) in methanol (100 mL) was stirred overnight at room temp. To the stirring reaction mixture was slowly added $NaBH_4$ (1.82 g, 48.0 mmol), and stirring was continued for 2 h. The desired product **1d**·pentamine was obtained in 83.7% (10.5 g) yield as a colorless oil after purification. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.14 (d, J = 11 Hz, 2 H), 6.66 (d, J = 11 Hz, 2 H), 3.67 (s, 2 H), 2.90 (s, 6 H), 2.53 (m, 12 H), 2.35 (d, J = 8.9 Hz, 4 H), 1.64 (m, 2 H), 1.40 (br s, 3 H), 0.85 (d, J = 8.8 Hz, 12 H) ppm. ^{13}C NMR ($CDCl_3$, 100.63 MHz): δ = 149.7, 129.0, 128.5, 112.7, 58.20, 54.61, 54.47, 53.56, 47.93, 47.10, 40.75, 28.38, 20.70 ppm. HRMS: calcd. for $C_{23}H_{45}N_5$ $[M + H]^+$ 392.3753, found 392.3751. To a solution of $PCl(NMe_2)_2$ in 30 mL of CH_2Cl_2 generated in situ from PCl_3 (0.24 mL, 2.75 mmol) and $P(NMe_2)_3$ (1.00 mL, 5.50 mmol) was added dropwise a solution of **1d**·pentamine (3.23 g, 8.25 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was maintained at room temp. overnight, and then all volatiles were removed under reduced pressure. The residue was washed three times with Et_2O and dried under reduced pressure to give the desired product **1d**·HCl (3.25 g, 86.4%) as a yellow powder. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 6.93 (d, J = 11 Hz, 2 H), 6.62 (d, J = 11 Hz, 2 H), 6.15 (s, 0.5 H), 4.49 (s, 0.5 H), 3.88 (d, J = 22 Hz, 2 H), 3.44 (m, 6 H), 3.06 (m, 4 H), 2.58 (m, 12 H), 1.74 (m, 2 H), 0.84 (d, J = 3.0 Hz, 6 H), 0.82 (d, J = 2.7 Hz, 6 H) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 149.8, 127.9 (d), 123.9 (d), 112.3, 55.23 (d), 50.48 (d), 46.65 (d), 40.16, 39.26 (d), 38.35 (d), 34.31, 26.57 (d), 19.67 ppm. ^{31}P NMR ($CDCl_3$, 161.79 MHz): δ = –7.87 ppm. HRMS: calcd. for $C_{23}H_{43}N_5P$ $[M - Cl]^+$ 420.3256; found 420.3260. A solution of **1d**·HCl (1.21 g, 2.65 mmol) and *t*BuOK (0.89 g, 7.95 mmol) in tetrahydrofuran (THF, 30 mL) was stirred for 1 h at room temp., and then the volatile compounds were removed under reduced pressure. Compound **1d** was extracted with *n*-hexane, and then all volatiles were removed under vacuum to give the desired monomeric **1d** (0.83 g, 74.5%) as a yellow gel. ^{1}H NMR (C_6D_6, 400.13 MHz): δ = 7.35 (d, J = 11 Hz, 2 H), 6.65 (d, J = 11 Hz, 2 H), 4.16 (d, J = 12 Hz, 2 H), 2.72 (m, 16 H), 2.53 (s, 6 H), 1.80 (m, 2 H), 0.99 (d, J = 2.9 Hz, 6 H), 0.96 (d, J = 3.0 Hz, 6 H) ppm. ^{13}C NMR (C_6D_6, 100.63 MHz): δ = 150.1, 129.8 (d), 129.3 (d), 113.1, 58.12 (d), 53.13 (d), 51.64, 51.53 (d), 46.74 (d), 45.21 (d), 40.49, 28.77 (d), 20.90 (d), 20.86 (d) ppm. ^{31}P NMR (C_6D_6, 161.79 MHz): δ = 129.7 ppm. HRMS: calcd. for $C_{23}H_{43}N_5P$ $[M+ H]^+$ 420.3256; found 420.3254.

Compound 1e: To a 250 mL round-bottomed flask containing a magnetic stirring bar and a septum was added tren (10.3 g, 70.2 mmol) followed by methanol (80 mL). Another 250 mL round-bottomed flask containing a magnetic stirring bar and a septum was charged with 4-(dimethylamino)benzaldehyde (34.5 g, 231.7 mmol) to which was added methanol (150 mL). The solution of 4-(dimethylamino)benzaldehyde was added dropwise to the solution of tren at room temp. overnight. To this reaction mixture in a water bath at room temp. was slowly added $NaBH_4$ (3.99 g, 105.3 mmol), and then the reaction mixture was stirred for 2 h at room temp. To the reaction mixture was added distilled water (40 mL), and the mixture was stirred for 3 h at room temp. The reaction mixture was extracted with dichloromethane, the organic phase was dried with Na_2SO_4, and then the solution was filtered and evaporated under reduced pressure with a rotary evaporator to give the desired product **1e**·heptamine (37 g, 96.5%) as a yellow-orange oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.11 (d, J = 8.0 Hz, 6 H, Ph), 6.64 (d, J = 8.0 Hz, 6 H, Ph), 3.63 (s, 6 H, $NCH_2C_6H_4NMe_2$), 2.89 (s, 18 H, NMe_2), 2.61 (t, J = 6.0 Hz, 6 H, NCH_2CH_2NH), 2.52 (t, J = 6. 0 Hz, 6 H, NCH_2CH_2NH) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 149.6, 129.0, 128.3, 128.3, 112.6, 54.32, 53.35, 46.93, 40.66 ppm. HRMS: calcd. for $C_{33}H_{52}N_7$ $[M + H]^+$ 546.4284; found 546.4280. In a manner analogous to the procedure for **1d**·HCl, the desired precursor **1e**·HCl was prepared from a dichloromethane solution of $PCl(NMe_2)_2$ (3.44 mmol) and **1e**·heptamine (1.88 g, 3.44 mmol) in 96.3% yield (2.02 g) as a yellow powder. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 6.94 (d, J = 8.60 Hz, 6 H, Ph), 6.59 (d, J = 8.56 Hz, 6 H, Ph), 6.36 (s, 0.5 H), 5.14 (s, 0.5 H), 3.96 (d, J = 16.95 Hz, 6 H, $NCH_2C_6H_4NMe_2$), 3.36 (m, 6 H, NCH_2CH_2NP), 2.93 (m, 6 H, NCH_2CH_2NP), 2.87 (s, 9 H, NMe_2) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 150.1, 128.5, 124.4 (d), 112.6, 50.75 (d), 46.83 (d), 40.47, 38.89 (d) ppm. ^{31}P NMR (161.79 MHz, $CDCl_3$): δ = –7.98 ppm. In a manner analogous to the procedure for **1d**, product **1e** was prepared from a THF solution of **1e**·HCl (2.3 g, 3.77 mmol) and *t*BuOK (1.27 g, 11.3 mmol) in 72.1% yield (1.56 g) as a yellow sticky oil. ^{1}H NMR ($CDCl_3$, 400.13 MHz): δ = 7.44 (d, J = 8.56 Hz, 6 H, Ph), 6.67 (d, J = 8.60 Hz, 6 H, Ph), 4.32 (d, J = 9.04 Hz, 6 H, $NCH_2C_6H_4NMe_2$), 2.88 (m, 6 H, NCH_2CH_2NP), 2.69 (m, 6 H, NCH_2CH_2NP), 2.55 (s, 18 H, NMe_2) ppm. ^{13}C NMR (100.63 MHz, $CDCl_3$): δ = 150.1, 129.9 (d), 128.4 (d), 113.1 (d), 54.13 (d), 52.80 (d), 45.27 (d), 40.52 ppm. ^{31}P NMR (161.79 MHz, $CDCl_3$): δ = 127.4 ppm. HRMS: calcd. for $C_{33}H_{49}N_7P$ $[M+ H]^+$ 574.3787; found 574.3785.

Although **1d** and **1e** are quite stable to atmospheric oxidation, they and their hydrochloride salts are somewhat sensitive to moisture. It may be assumed that ligands **1d** and **1e** (even as their corresponding oxides) are less toxic than $O=P(NMe_2)_3$, which is more volatile.[18]

Representative Procedure for *N*-Arylation Reactions with Aryl Chloride: An oven-dried 10 mL vial equipped with a magnetic stirring bar and a septum was charged with ligand (0.5 mol-%) inside a nitrogen-filled drybox. After the removal of the vial from the drybox, toluene (3 mL) was added. To an oven-dried 10 mL round-bottomed flask equipped with a magnetic stirring bar and a septum inside a nitrogen-filled drybox was added $Pd_2(dba)_3$ (0.25 mol-%) and NaO^tBu (1.4 mmol). After the removal of the flask from the drybox, the ligand/toluene (3 mL) solution, aryl chloride (1.0 mmol), and amine (1.2 mmol) were added, and stirring was continued under the specified reaction conditions. The reaction mixture was then cooled to room temp., adsorbed onto silica gel, and then purified by column chromatography (ethyl acetate/hexanes as eluent). Isolated yields are the average of two runs.

Supporting Information (see footnote on the first page of this article): ^{1}H, ^{13}C, and ^{31}P NMR and mass spectra of all of the products.

Acknowledgments

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