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Expedited Palladium-Catalyzed Amination of Aryl Nonaflates through the Use of Microwave-Irradiation and Soluble Organic Amine Bases

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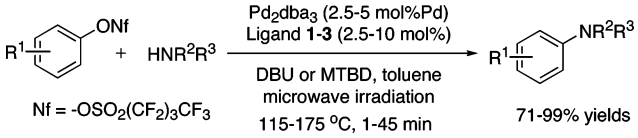

Microwave-assisted, palladium-catalyzed C−N bond-forming reactions with aryl/heteroaryl nonaflates and amines using the soluble amine bases DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene) and ligands (**1**−**3**) resulted in good to excellent yields (71−99%) of arylamines in short reaction times (1−45 min).

The palladium-catalyzed cross-coupling of aryl halides and sulfonates with amines has become a common method in organic synthesis.[1] Recent efforts in this area have focused on the development of more active catalyst systems that operate at lower catalyst loadings and with shorter reaction times.[2] Despite many improvements to the substrate scope through the use of weak inorganic bases such as K_3PO_4, Cs_2CO_3, or K_2CO_3, many of these processes still require from 2 to 24 h to go to completion, a problem that has been addressed through the use of microwave irradiation.[2c,3]

The emergence of microwave technology as a tool for increasing reaction rates is well documented.[4] Microwave-assisted reactions are extremely attractive to synthetic organic chemists due to their ability to shorten reaction times and in some cases improve regio- and/or chemoselectivity.[5] Reactions that previously required hours to run to completion can now be finished within minutes.[6]

In most cases, palladium-catalyzed C−N bond-forming reactions using microwave irradiation employ highly polar solvents and strong bases.[7] Consequently, base-sensitive functional groups are not tolerated, limiting the use and applications of these protocols. The use of insoluble inorganic bases (e.g., Cs_2CO_3) has improved the substrate scope; however, efficient stirring and heating can be problematic. Moreover, there are limited examples of palladium-catalyzed amination of aryl sulfonates using microwave-irradiation.[7c,8] We thought that by employing a soluble organic amine base, we could improve the functional group tolerance and provide more efficient heating and stirring in microwave-assisted Pd-catalyzed C−N bond-forming reactions of aryl nonaflates (nonaflate = $-OSO_2(CF_2)_3CF_3$).[9,10] Herein, we report a general system to effect this using a palladium catalyst comprised of Pd_2dba_3/**1**−**3** and weak organic amine bases DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) and MTBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene). These catalytic systems successfully couple aryl/heteroaryl nonaflates and aryl/heteroarylamines with excellent functional group tolerance and fast reaction times, producing arylamines in good to excellent yields.

XPhos **1**, a bulky electron-rich monophosphine ligand that has been successfully employed in C−N bond-forming reactions of aryl sulfonates and halides, was used in our initial study which examined the coupling of electronically neutral 4-*tert*-butylphenyl nonaflate and aniline (Table 1).[2c] Reactions that employed DBU and MTBD gave the best results with this catalytic system (Table 1, entries 3−5). Guanidine bases possessing a free N−H moiety such as TBD or TMG failed to give any of the desired diarylamine (Table 1, entries 8 and 9). In contrast, with hindered secondary amine TMP as base, the desired arylated amine was produced in an 80% yield (Table 1, entry 6). With DBU, toluene was the best solvent for this reaction.[11] Slightly higher reaction temperatures were required when using *N*,*N*-DMF as the solvent (Table 1 entries 13 and 14). Further, efficient coupling in the absence of solvents was achieved in 1 min providing the diarylamine in 87% yield (Table 1, entry 3).[12]

(1) Reviews: (a) Jiang, L.; Buchwald, S. L. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.: De Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; p 699. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051.

(2) (a) Shen, Q.; Shashank, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (b) Lee, D.-Y.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1169. (c) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(3) (a) Anderson, K. W.; Mendes-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563 (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (c) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359.

(4) (a) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653. (b) Olofsson, K.; Hallberg, A.; Larhed, A. In *Transition Metal Catalysis and Microwave Flash Heating in Organic Chemistry*; Loupy, A., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 379.

(5) (a) De La Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903. (b) Xu, G.; Wang, Y. G. *Org. Lett.* **2004**, *6*, 985.

(6) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250.

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(8) Microwave-assisted amination of aryl triflates with alkylamines in the absence of a catalyst and base has been accomplished; however, arylamines failed and base-sensitive functional groups were not tolerated: Xu, G.; Wang, Y. G. *Org. Lett.* **2004**, *6*, 985.

(9) Hayes, B. L. *Microwave Synthesis*: *Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002.

(10) Aryl/heteroaryl nonaflates are generally more stable toward hydrolysis than the corresponding triflate and can easily be prepared from the corresponding phenol by reacting with perfluoro-1-butanesulfonyl fluoride. See ref 3a and the Supporting Information for more details.

(11) DBU and MTBD are good microwave absorbers, which allows the reactions to attain higher temperatures faster in nonpolar solvents such as toluene.

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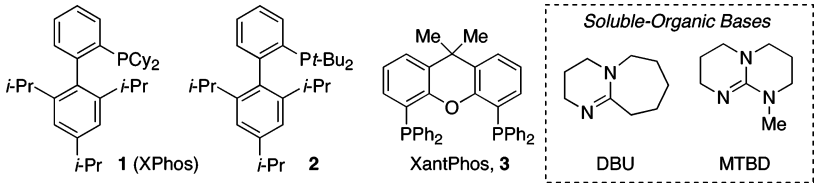
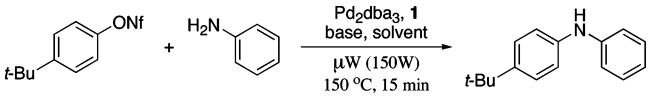


FIGURE 1. Supporting ligands and soluble organic amine bases used in this study.

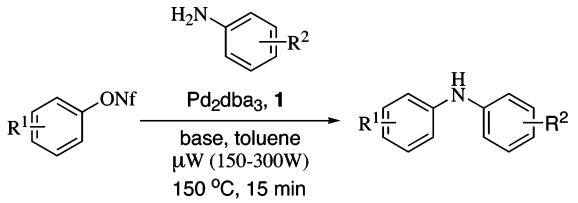
TABLE 1. Screen of Bases and Solvents for the Palladium-Catalyzed Amination of 4-*tert*-Butylphenyl Nonaflate[a]

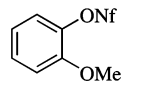
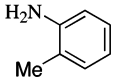
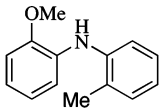
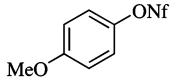
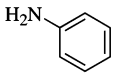
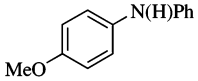
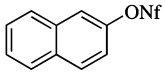
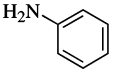
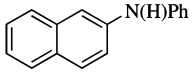


entry	base[b]	solvent	conv (%)	yield (%)[c]
1	TEA	none	>99	0
2	DABCO	none	>99	0
3	DBU	none	>99	87[d]
4	DBU	toluene	>99	99
5	MTBD	toluene	>99	85
6	TMP	toluene	>99	80
7	Proton Sponge	toluene	37	25
8	TBD	toluene	12	0
9	TMG	toluene	10	0
10	TMPMG	toluene	90	89
11	DBU	1,4-dioxane	56	35
12	DBU	1,4-dioxane	>99	38[e]
13	DBU	DMF	92	86
14	DBU	DMF	>99	92[f]
15	DBU	DMSO	94	52

[a] Reaction conditions: 1.0 equiv of Ar-ONf, 1.3 equiv of amine, 2.5 equiv of base, 0.05 equiv of **1**, 0.0125 equiv of Pd_2dba_3, 2 mL of solvent/mmol of Ar-ONf. [b] TEA = triethylamine, DABCO = 1,4-diazabicyclo-[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MTBD = 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene, TMP = 2,2,6,6-tetramethylpiperidine, Proton Sponge = 1,8-bis(dimethylamino)naphthalene, TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine, TMPMG = *N*,*N*,*N*′,*N*′-tetramethyl-*N*″-(phenylmethyl)guanidine. [c] GC yield. [d] Reaction was complete in 1 min; isolated yield. [e] Reaction was conducted at 175 °C for 15 min. [f] Reaction was conducted at 175 °C for 5 min.

TABLE 2. Palladium-Catalyzed Amination of Electron-Rich and Electron−Neutral Aryl Nonaflates[a]



Entry	Aryl Nonaflate	Amine	Product	Yield (%)[b]
1				99
2				99[c]
3				99[d]

[a] Reaction Conditions: 1.0 equiv of Ar-ONf, 1.3 equiv of amine, 2.5 equiv of DBU, 0.06 equiv of **1**, 0.015 equiv of Pd_2dba_3, 2 mL of toluene/mmol of Ar-ONf. [b] Yields (isolated) represents an average of two runs. [c] MTBD was used as the base. [d] **2** was used.

With DBU as the base, the amination of various aryl nonaflates with anilines was explored. For combinations of unactivated electron-rich and electron-neutral aryl nonaflates, ligand **1** was used (Table 2). The coupling of an ortho-substituted aryl nonaflate and aniline was accomplished in 15 min providing excellent yields of the corresponding diarylamine (Table 2, entries 1). Interestingly, use of MTBD as the base for the amination of electron-rich 4-methoxyphenyl nonflate with aniline was crucial to the success of the reaction.

Aryl nonaflates and anilines featuring an assortment of functional groups (e.g., −CN, $-NO_2$, $-CO_2Me$, −C(O)Me) coupled successfully under similar reaction conditions with use of **2**, the more hindered analogue of XPhos **1**, or XantPhos **3** (Table 3). When functional groups were present in the ortho position of the aryl nonaflate, it was essential that the bidentate ligand **3** be employed (Table 3, entries 1−2 and 7). The amination of 2-chlorophenyl nonaflate with aniline is particularly useful since it can be used in the synthesis of carbazoles through C−H activation, a process that has been demonstrated by several research groups (Table 3, entry 7).[13] Interestingly, the use of **3** as a supporting ligand was unsuccessful for reactions of anilines and the nonaflates derived from 3-hydroxy acetophenone or *N*-methyl-5-hydroxyindole. In these instances, a protocol with use of **2** provided the products in excellent yield (Table 3, entries 4 and 6). The synthesis of heterocyclic compounds is important due to their common place in numerous pharmaceutical and natural products. Heteroaryl nonaflates derived from 3-hydroxypyridine and 5-hydroxyquinoline react efficiently with aniline providing the *N*-heteroarylamines in 93% and 80% yields, respectively (Table 3, entries 8 and 9).

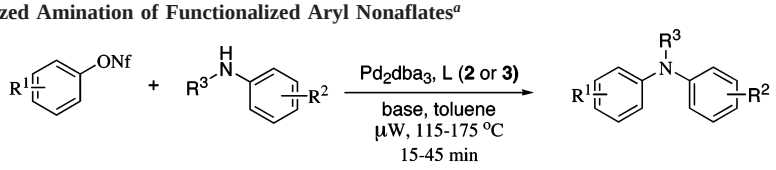
One of the limitations of using DBU as the base is that it was only effective in the coupling of primary anilines to aryl nonaflates; *N*-alkyl anilines, benzophenone imine, and amides proved to be less successful substrates. Fortunately, through the use of MTBD, an effective base in the coupling of aryl nonaflates and anilines in the initial optimization/base study (Table 1), the substrate scope was expanded to include a variety of nitrogen nucleophiles.[14] Under these new reaction conditions, *N*-methyl aniline could be coupled with a functionalized aryl nonaflate (Table 3, entry 3), using **3** as the supporting ligand. Further, benzophenone imine could be combined successfully with an assortment of aryl nonaflates, including heteroaryl nonaflates and functionalized aryl nonaflates (Table 4). As we

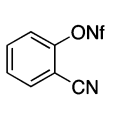
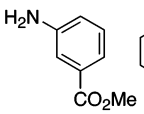
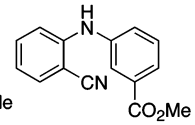
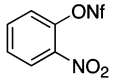
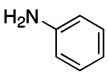
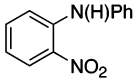
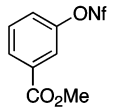
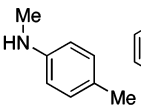
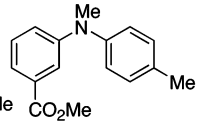
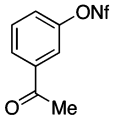
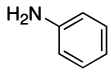
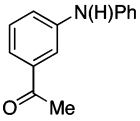
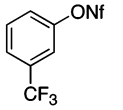
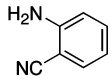
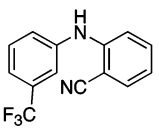
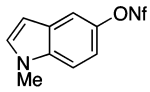
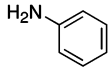
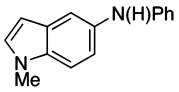
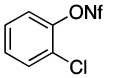
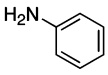
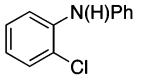
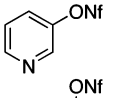
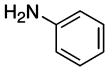
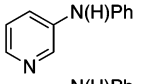
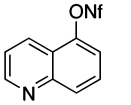
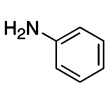
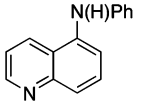
(12) When DBU was used as the base/solvent for more challenging substrate combinations, decomposition of the aryl nonflate predominated.

(13) (a) Ferreira, I. C. F. R.; Queiroz, M. R. P.; Kirsch, G. *Tetrahedron* **2002**, *58*, 7943. (b) Ferreira, I. C. F. R.; Queiroz, M. R. P.; Kirsch, G. *Tetrahedron* **2003** *59*, 3737.

(14) For a comparison of the basicity of organic amines, see: Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, I. A. *J. Org. Chem.* **2005**, *70*, 1019.

TABLE 3. Palladium-Catalyzed Amination of Functionalized Aryl Nonaflates[a]



Entry	Nonaflate	Amine	Product	L	T(°C)/ t (min)	Yield (%)[b]
1				**3**	150/20	94
2				**3**	115/45	84[c]
3				**3**	175/30	94[c]
4				**2**	125/30	81
5				**3**	175/15	85
6				**2**	150/30	99
7				**3**	150/30	93[c]
8				**2**	150/15	93
9				**3**	175/15	80

[a] Reaction conditions: 1.0 equiv of Ar-ONf, 1.3 equiv of amine, 2.5 equiv of DBU, 0.10 equiv of ligands **2** or **3**, 0.025 equiv of Pd_2dba_3, 2 mL of toluene/mmol of Ar-ONf. [b] Yield (isolated) represents an average of two runs. [c] MTBD used as the base.

have previously described, benzophenone imine is an effective ammonia equivalent and the initially formed coupling product can be easily converted to the corresponding free amine with use of aqueous HCl or NH_2OH−HCl (Table 4, entries 1, 2, and 4).[15] For these processes, **3** was the most effective supporting ligand. Aryl nonflates containing an ester or nitrile group in the meta position were successfully combined with benzophenone imine (Table 4, entries 1 and 2). Additionally, heteroaryl nonaflates coupled successfully to benzophenone imine in good to excellent yields within 30 min (Table 4, entries 3 and 4); previously, these processes could take up to 24 h to go to completion and/or required a strong inorganic base.[15]

Further expanding the substrate scope, an aliphatic primary amide is combined with 2-naphthyl nonaflate providing the secondary *N*-aryl amide in 92% yield (Table 4, entry 5). Primary amides benzamide and 3-chlorobenzamide were efficiently combined with 3-trifluoromethylphenyl nonaflate and 2-cyanophenyl nonaflate, respectively, using **3** as the supporting ligand (Table 4, entries 6 and 7).

We have shown that through the use of ligand **3** and MTBD as the base, various heterocyclic amines were coupled successfully to aryl/heteroaryl nonaflates (Table 4, entries 8−11). Of note, 2-aminopyrimidine and 2-amino-*N*-methylbenzimidazole were successfully combined with 3-pyridyl and 5-quinolyl nonaflates, respectively, providing the diheteroarylamines in high yields within 30 min (Table 4, entries 10 and 11). Previously, efficient palladium-catalyzed C−N bond-forming reactions of heteroarylamines required long reaction times (15−23 h) and a weak inorganic base.[16]

In conclusion, we have developed a fast and efficient protocol for the microwave-assisted, palladium-catalyzed coupling of aryl/heteroaryl nonaflates and anilines, amides, benzophenone imine, and heteroarylamines. This method expands the utility of microwave-assisted C−N bond-forming processes by allowing substrates with a broad scope of functional groups, both on the amine and aryl nonaflate, to be utilized. Additionally, the use of a soluble, weak amine base is beneficial in preserving the homogeneity of the reaction mixture for more efficient heating and stirring. Further investigations are underway to apply this system in microwave-assisted palladium-catalyzed C−N bond-forming reactions of aryl halides and aryl tosylates.

Experimental Section

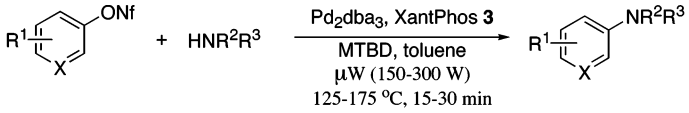
General Procedure for Tables 2−4. An oven-dried disposable microwave tube containing a stir bar was charged with Pd_2dba_3 and ligand. The vessel was sealed with a plastic microwave septum and then evacuated and backfilled with argon; this sequence was repeated two additional times. The aryl/heteroaryl nonaflate (1.0 equiv), amine (1.3 equiv), DBU or MTBD (2.5 equiv), and toluene (2 mL/mmol) were successively added via syringe (aryl/heteroaryl nonaflates or amines that were solids at room temperature were added prior to the evacuation and backfill sequence). The vessel was submitted to microwave irradiation with stirring until the starting aryl/heteroaryl nonaflate had been completely consumed as judged by GC analysis. The mixture was cooled to room temperature and then diluted with water and ethyl acetate. The organic layer was separated, dried over anhydrous $MgSO_4$, and concentrated. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes mixtures). The typical procedure is given for *N*-methyl-*N*-(3-carboxymethyl)-aniline (Table 3, entry 3) and (2-ethyl-2*H*-pyrazol-3-yl)naphthalen-2-ylamine (Table 4, entry 9.)

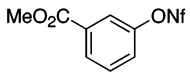
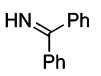
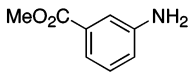
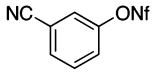
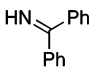
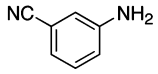
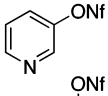
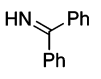
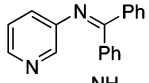
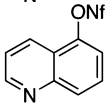
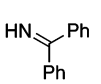
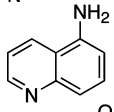
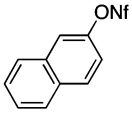
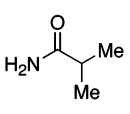
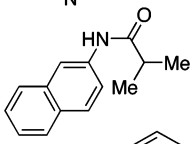
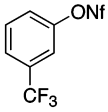
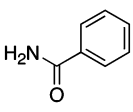
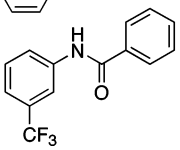
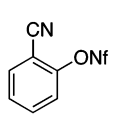
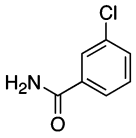
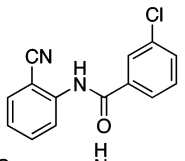
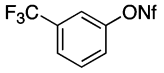
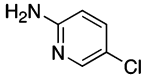
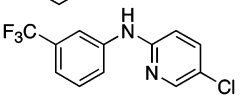
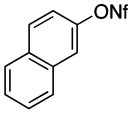
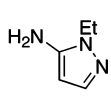
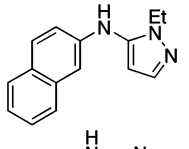
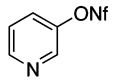
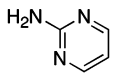
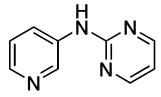
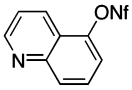
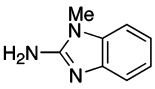
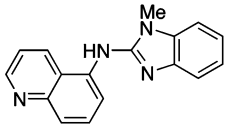
***N*-Methyl-*N*-(3-carboxymethyl)aniline (Table 3, Entry 3).** Using the general procedure, a mixture of 3-carboxymethylphenyl

(15) Wolfe, J. P.; Ahman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(16) Yin, J.; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481.

TABLE 4. Palladium-Catalyzed Imination, Amidation, and Amination of Aryl/Heteroaryl Nonaflates[a]



Entry	Nonaflate	Amine	Product	Yield (%)[b]
1				72[c,e,j]
2				80[f,j]
3				95[d]
4				81[d,i]
5				92[h]
6				91[g]
7				92[g]
8				82[h]
9				71[g]
10				80[h]
11				99[g]

[a] Reaction conditions: 1.0 equiv of Ar-ONf, 1.3 equiv of amine, 2.5 equiv of MTBD, 0.10 equiv of XantPhos **3**, 0.025 equiv of Pd_2dba_3, 2 mL of toluene/mmol of Ar-ONf. [b] Yield (isolated) represents an average of two runs. [c] 0.06 equiv of XantPhos **3** and 0.015 equiv of Pd_2dba_3 used. [d] 125 °C, 30 min. [e] 140 °C, 20 min. [f] 150 °C, 15 min. [g] 150 °C, 30 min. [h] 175 °C, 30 min. [i] Isolated as the free amine after hydrolysis of the imine with HCl (1.0 M). [j] Isolated as the free amine after hydrolysis of the imine with $NH_2OH-HCl$.

nonaflate (177 mg, 0.250 mmol), Pd_2dba_3 (5.8 mg, 0.0063 mmol), XantPhos (14.5 mg, 0.0250 mmol), *N*-methyl-*p*-toluidine (41 μL, 0.33 mmol), and MTBD (90 μL, 0.63 mmol) in toluene (0.5 mL) was subjected to microwave irradiation for 30 min at 175 °C. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:4) to give the title compound as a yellow oil (56 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.15 (m, 1H), 7.06 (d, J = 8 Hz, 2H), 6.94 (d, J = 8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 149.8, 146.4, 133.8, 131.3, 130.6, 129.3, 124.2, 121.8, 120.5, 117.6, 52.5, 40.8, 21.3. IR (neat, cm^{-1}) 2949, 1721, 1598, 1511, 1446, 1348, 1106, 753. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.07; H, 6.65.

(2-Ethyl-2*H*-pyrazol-3-yl)naphthalen-2-ylamine (Table 4, Entry 9). Using the general procedure, a mixture of 2-naphthyl nonaflate (107 mg, 0.250 mmol), Pd_2dba_3 (5.8 mg, 0.0063 mmol), XantPhos (14.5 mg, 0.0250 mmol), 5-amino-1-ethylpyrazole (36 mg, 0.33 mmol), and MTBD (90. μL, 0.63 mmol) in toluene (0.5 mL) was subjected to microwave irradiation for 30 min at 150 °C. The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/hexanes, 1:2) to give the title compound as an off-white solid (44 mg, 74%). Mp 78−79 °C. ^{1}H NMR (400 MHz, d^4-MeOH) δ 7.69−7.72 (m, 2H), 7.53 (d, J = 8.4 Hz, 1H), 7.47 (d, J = 2 Hz, 1H), 7.31 (t, J = 6.4 Hz, 1H), 7.20 (t, J = 6 Hz, 1H), 7.13 (t, J = 7.2 Hz, 1H), 7.02 (d, J = 2 Hz, 1H), 6.08 (d, J = 2 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, d^4-MeOH) δ 144.4, 142.7, 139.8, 136.3, 130.3, 130.2, 128.7, 127.6, 127.4, 124.1, 119.0, 109.5, 99.1, 43.6, 15.6. IR (neat, cm^{-1}) 3248, 1632, 1462,1403, 928, 747. Anal. Calcd for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37. Found: C, 75.73; H, 6.45.

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Supporting Information Available: Experimental procedures as well as characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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