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An Efficient Silane-Promoted Nickel-Catalyzed Amination of Aryl and Heteroaryl Chlorides

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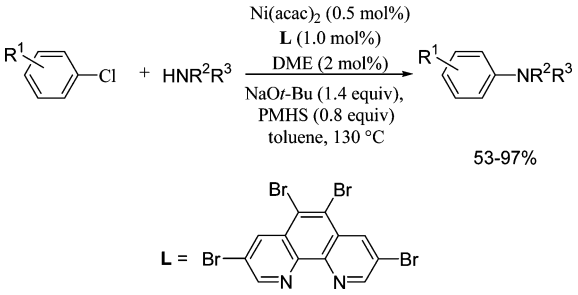

A new silane-promoted nickel-catalyzed amination of aryl chlorides with 0.5 mol % of $Ni(acac)_2$, 1 mol % of 3,5,6,8-tetrabromo-1,10-phenanthroline, and polymethylhydrosiloxane was developed. A broad range of aryl and heteroaryl chlorides can be coupled with secondary amines and anilines to give the desired (het)arylamines in good to excellent yields. The reaction is sensitive to the nature and amount of the silane promoter.

1. Introduction

The synthesis of aromatic amines has attracted much attention due to their important applications as natural products, pharmaceuticals, agrochemicals, dyes, and polymers.[1] Therefore, the development of efficient methods for the formation of new aryl−nitrogen bonds is a matter of particular interest for organic chemists.

Among many synthetic methods,[2] palladium-catalyzed amination of aryl halides and related substrates has been one of the most widely used preparations of aryl amines.[3,4] Buchwald and Hartwig, as well as other groups, have developed palladium catalysts and ligands for the cross-coupling of amines, hydrazines, imines, and ammonia with aryl halides or sulfonates. A particular effort has been devoted to the elaboration of amination reactions for cheap and readily available aryl and heteroaryl chlorides, using novel phosphine ligands.[5] On the other hand, nickel-catalyzed amination reactions have received less attention. Buchwald has reported the amination of aryl chlorides in the presence of $Ni(cod)_2$ (cod = cyclooctadiene) and 1,1′-bis-(diphenylphosphino)ferrocene (dppf) or 1,10-phenanthroline.[6]

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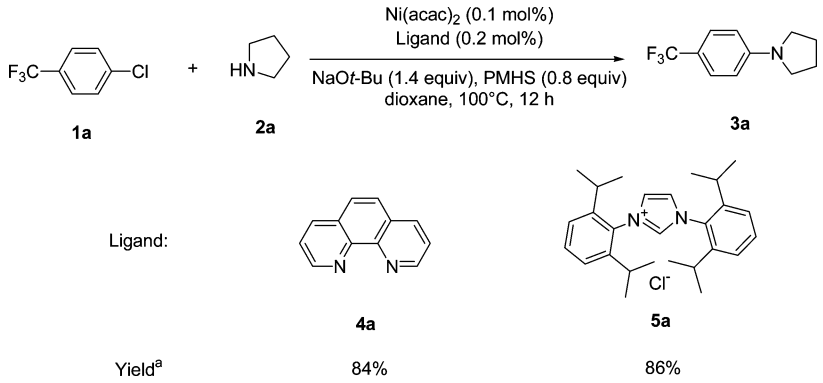
SCHEME 1. Ni-Catalyzed Cross-Coupling of 1-Chloro-4-trifluoromethylbenzene (1a) and Pyrrolidine (2a)



[a] Yields were determined by GC analysis with *n*-tetradecane as internal standard and comparison with an authentic sample of the product.

This methodology was extended by using a heterogeneous Ni-(0)/C catalyst,[7] 2,2′-bipyridine[8] or *N*-heterocyclic carbenes (NHC)[9] as ligands for Ni(0), or employing sulfoximines instead of amines.[10] However, these reactions require high amounts of nickel (5−10 mol %) and either unstable and expensive Ni(0)-sources like $Ni(cod)_2$ or Ni(II)-precursors and reagents like NaH or MeMgBr, which are incompatible with several functional groups. Considering the nature of the ligands importance in palladium-catalyzed amination reactions, we presumed that the scope of a nickel-catalyzed amination reaction can be improved and extended by the development of a more active catalyst system.

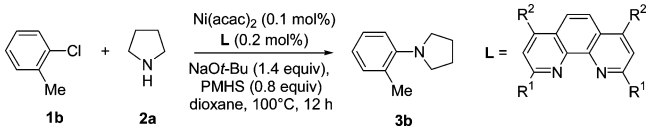
Preliminary studies showed that polymethylhydrosiloxane (PMHS) can be successfully employed as a reducing agent in a nickel-catalyzed amination by using convenient and stable Ni-(II)-precursors like $Ni(acac)_2$. Herein, we wish to detail the investigation of various ligand classes in the nickel-catalyzed amination of aryl chlorides, as well as the influence of solvents and additives on the outcome of this reaction oriented to the catalytic system optimization.

2. Results and Discussion

Influence of the Ligand. For the selection of the most efficient catalyst system, the reaction between 1-chloro-4-trifluoromethyl-benzene (**1a**) and pyrrolidine (**2a**) was chosen as a model. This reaction was performed in the presence of various classes of ligands, using 0.1 mol % of $Ni(acac)_2$ and PMHS as a promoter (Scheme 1).

As expected, without a ligand the amination reaction yielded no detectable amount of product. Various phosphines like tricyclohexylphosphine, bidentate phosphines, or electron-rich biphenyl phosphines, which were successfully employed in palladium-catalyzed aminations or nickel-catalyzed cross-coupling reactions,[3,11] afforded very low yields of the desired product (typically 5−10%) along with unreacted starting material and traces of the corresponding arene, resulting from the reduction of the starting aryl halide. Similarly, diethyl phosphite[12] and PYBOX ligands[13] gave unsatisfactory yields. The best results were obtained with the phenanthroline ligands **4a**[6] and the *N*-heterocyclic carbene **5a**[9] (Scheme 1), which both furnished product **3a** in over 80% yield. Other *N*,*N*-ligands like 2,2′-bipyridine[8] or 9*H*-4,5-diazafluorene[14] gave inferior results.

SCHEME 2. Ni-Catalyzed Cross-Coupling of 2-chlorotoluene (1b) and Pyrrolidine (2a)



To further optimize the catalytic system, we focused on the two most promising ligand classes: *N*,*N*-ligands based on phenanthroline (**4a**) and NHC ligands, using 2-chlorotoluene (**1b**) as a more demanding substrate (Scheme 2).

Generally, lower yields of the aryl amine **3b** were obtained in this test reaction, due to the lower substrate reactivity. Electron-rich phenanthrolines gave the product **3b** in 5−12% yield (in Scheme 2: $R^1 = H$, and $R^2 = OMe$,[15] 9% yield; $R^1 = H$ and $R^2 = N$-pyrrolidino, 5% yield; and 4,5-(methylenedioxy)-phenanthroline,[16] 12% yield), while the parent phenanthroline (**4a**, $R^1 = R^2 = H$) afforded an 11% yield of **3b**. Thus, the higher electron density in the phenanthroline aromatic system was not a decisive factor for the catalytic activity. 2,9-Disubstituted phenanthrolines, like 2,9-dimethylphenathroline ($R^1 = Me$, $R^2 = H$), demonstrated almost no catalytic activity. Similarly, low yields were obtained with several types of NHC ligands. On the other hand, 4,7-aryl- or halogen-substituted phenanthrolines, such as 4,7-diphenyl-1,10-phenathroline[18] (bathophenanthroline, $R^1 = H$, $R^2 = Ph$) and 4,7-dichloro-1,10-phenanthroline ($R^1 = H$, $R^2 = Cl$)[19] lead to higher yields of **3b**

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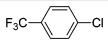
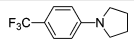
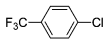
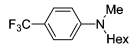
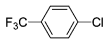
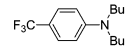
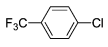
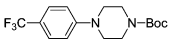
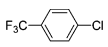
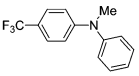
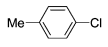
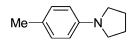
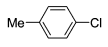
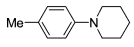
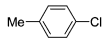
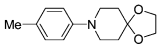
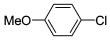
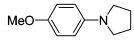
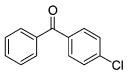
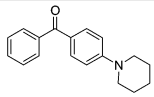
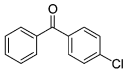
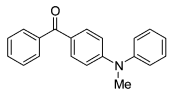
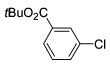
TABLE 1. Nickel-Catalyzed Amination of Aryl Chlorides[a]

Entry	Aryl chloride	Amine	Product	Yield[b]
1	 1a	 2a	 3a	95%
2	 1a	 2b	 3c	96%
3	 1a	 2c	 3d	79%
4	 1a	 2d	 3e	62%
5	 1a	 2e	 3f	62%
6	 1c	 2a	 3g	85%
7	 1d	 2a	 3h	83%
8	 1d	 2f	 3i	87%
9	 1d	 2g	 3j	82%
10	 1b	 2a	 3b	83%
11	 1e	 2a	 3k	82%
12	 1f	 2f	 3l	81%
13	 1f	 2e	 3m	92 %(94)[c]
14	 1g	2a	3n	95%
15	1g	2b	3o	87%
16	1h	2a	3p	97%
17	1i	2f	3q	91%
18	1i	2h	3r	53%[d]
19	1i	2i	3s	71%
20	1j	2f	3t	96%

[a] Reaction conditions: 1 mmol of aryl halide, 1.2 mmol of amine, 1.4 mmol of NaO*t*Bu, 0.8 mmol of PMHS, 0.005 mmol of $Ni(acac)_2$, 0.01 mmol of 3,5,6,8-tetrabromo-1,10-phenanthroline (**4b**), 0.02 mmol of DME, 1.5 mL of toluene in a sealed tube, 130 °C, 18 h. [b] Isolated yields of analytically pure product. [c] This reaction was run in 25 mmol scale. [d] The reaction time was 42 h.

(17−19%). These results prompted us to test 3,5,6,8-tetrabromo-1,10-phenanthroline (**4b**), which can be easily prepared in one step from 1,10-phenanthroline.[20] This highly substituted phenanthroline was found to be the most efficient ligand, providing the *N*-(*o*-tolyl)-pyrrolidine (**3b**) in the test reaction in 31% yield.[21]

Influence of the Solvent/Additives. In the previous experiments, we found dioxane to be a good solvent for the amination reaction. However, due to its toxicity, dioxane is not convenient for large-scale applications. The amination of 2-chlorotoluene (**1b**) in pure toluene resulted in low conversion and yield (<5%). We examined various mixtures of toluene with cosolvents. Use of dioxane/toluene mixtures improved yields up to 22%. Better results were obtained with 1,2-dimethoxyethane (DME). Addition of 2 mol % of DME led to a 39% yield of product **3b** (based on the aryl chloride **1b**). The addition of pyridine, *N*,*N*,*N*′,*N*′-tetramethylethylendiamine (TMEDA), or triethyleneglycol dimethyl ether (triglyme) did not result in significantly higher yields, compared to DME.

Optimization of the Silane Promoter, Base, and the Source of Ni. Several different siloxanes were screened as promoters in the coupling of 2-chlorotoluene (**1b**) and pyrrolidine (**2a**), using the optimized conditions. PMHS and cyclotetra(methylhydrosiloxane) gave the best results (39% and 40% yield of **3b**) compared with yields below 20% for other siloxanes. The amount of 0.8 equiv of PMHS (to aryl halide) proved to be optimal. Siloxanes, not possessing a Si−H bond, did not promote the amination at all and only unreacted 2-chlorotoluene (**1b**) was recovered, which shows the necessity of the reduction of Ni(II) to Ni(0). We assume also that siloxanes influence the catalytic activity of nickel by forming siloxane-bridged nickel clusters,[22] and thus stabilizing the active catalytic species in

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(21) Attempts to further functionalize **4b** by nickel- or palladium-catalyzed amination reactions, including the conditions reported here, were not successful, so that only the unreacted compound was recovered. This indicates that this ligand itself must be involved in this amination reaction. See the Supporting Information for experimental details.

(22) (a) Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B.; Lewis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5824.

solution.[23] A variety of bases were also examined and, not surprisingly, the sterically hindered sodium alkoxides gave the best yields (39% with NaO*t*Bu, and 38% with NaO*t*Am). Other tested bases afforded yields lower than 10%. The use of soluble Ni(II) salts, such as nickel(II) 2-ethylhexanoate, gave the same results as $Ni(acac)_2$, while the amination of 2-chlorotoluene (**1b**) with poorly soluble $NiCl_2$ or $NiBr_2$ proceeded in lower yield. Better yields and full conversion of the aryl chloride in this reaction could be achieved by increasing the reaction temperature to 130 °C (49% yield) and the catalyst loading to 0.5 mol % (73% at 100 °C, 83% at 130 °C).

Amination of Aryl Chlorides. Using the optimized conditions ($Ni(acac)_2$ (0.5 mol %), 3,5,6,8-tetrabromo-1,10-phenanthroline (**4b**, 1 mol %), PMHS (0.8 equiv), NaO*t*Bu (1.4 equiv), DME (2 mol %) in PhMe, 130 °C, 18 h), a broad range of substrates could be involved in this amination reaction, as shown in Table 1.

Both electron-poor (entries 1−4, 6, 12−15, and 20) and electron-rich (entry 11) aryl chlorides could be coupled with secondary cyclic or acyclic amines to provide the products in good to excellent yields. The only side product observed (typically <5 %) was the corresponding arene, which results from the reduction of the starting aryl halide. The sterically hindered ortho-substituted aryl chlorides[3,11] reacted with various amines without difficulty giving 83−97% yields (entries 6, 10, and 16). Moreover, substrates containing functional groups, such a non-enolizable ketone (entries 12 and 13), an ester (entries 14 and 15), a protected aldehyde (entries 16, 17, and 19), or a sulfonamide (entry 20) were converted to the aryl amines in 71−96% yields.

Acyclic amines, such as *N*-hexyl-*N*-methylamine (**2b**), dibutylamine (**2c**), or *N*-methyl-benzylamine (**2i**) (entries 2, 3, 15, and 19), as well as cyclic amines, e.g., 1,2,3,4-tetrahydroquinoline (**2h**) (entry 18), were coupled efficiently. By using the standard conditions, secondary anilines coupled with aryl halides affording the desired products in 62−92% yields (entries 5 and 13).

Surprisingly, while pyrrolidine (**2a**) or piperidine (**2f**) efficiently reacted with 4-chlorotoluene (**1d**) in 83−87% yields (entries 7 and 8), the reaction with morpholine gave toluene as a major product with only traces of the expected aryl amine. Other aryl chlorides reacted with morpholine similarly. Attempts to involve primary alkyl amines or anilines in this reaction failed, indicating a fast catalyst deactivation. This may be due to the formation of catalytically inactive nickel-species such as bis-(amino)- or bis-amido-bridged complexes, as was formerly observed for palladium-catalyzed amination reactions.[24]

Amination of Heteroaryl Chlorides. As nitrogen-containing heterocycles possessing amino substituents often are of particular pharmaceutical interest,[1b] we have extended the scope of the nickel−phenanthroline−PMHS catalytic system to the amination of heteroaryl chlorides. As shown in Table 2, chloropyridines, quinolines, and benzoxazoles give the amination products in 55−98% yields, using the previously developed conditions.

2-Chloropyridine (**6a**) was reacted with cyclic or acyclic secondary amines in up to 92% yield (entries 1, 2, and 3). Higher yields (80−98%) were observed in the amination of 3-chloropyridine (**6b**) (entries 4, 5, and 6). Using an electron-rich pyridine **6c**, the aryl amine **7g** was obtained in 55% yield (entry 7). 2-Chloroquinoline (**6e**) reacted with secondary amines furnishing products in 90−98% yields (entries 8 and 9). The reaction of 2-chlorobenzoxazole (**6e**) proceeded comparably well with various amines such as the piperidine derivative **2k** (entry 11, 83% yield) or aminoalkylamine **2*l*** (entry 12, 84% yield).

TABLE 2. Nickel-Catalyzed Amination of Heteroaryl Chlorides[a]

Entry	Aryl chloride	Amine	Product	Yield[b]
1	**6a**	**2a**	**7a**	80%
2	**6a**	**2f**	**7b**	92%
3	**6a**	**2j**	**7c**	64%
4	**6b**	**2a**	**7d**	89%
5	**6b**	**2f**	**7e**	98%
6	**6b**	**2j**	**7f**	80%
7	**6c**	**2f**	**7g**	55%
8	**6d**	**2a**	**7h**	98%
9	**6d**	**2g**	**7i**	90%
10	**6e**	**2a**	**7j**	82%
11	**6e**	**2k**	**7k**	83%
12	**6e**	**2l**	**7l**	84%

[a] Reaction conditions: 1 mmol of heteroaryl halide, 1.2 mmol of amine, 1.4 mmol of NaO*t*Bu, 0.8 mmol of PMHS, 0.005 mmol of $Ni(acac)_2$, 0.01 mmol of **4b**, 0.02 mmol of DME, 1.5 mL of toluene, sealed tube, 130 °C, 18 h. [b] Isolated yield of analytically pure product.

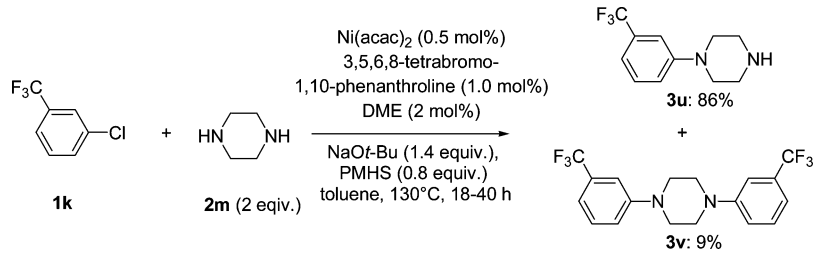
Monoarylation of Piperazine. We studied the mono- and bisarylation of piperazine (**2m**), using the standard conditions with 1-chloro-3-trifluoromethylbenzene (**1k**) as a substrate (Scheme 3). A particularly interesting synthetic target is the monoarylated piperazine **3u** due to its high affinity to 5-HT_1- and VMAT-receptors[25] as well as a promising antimalarial activity.[26]

(23) The utility of PMHS as an additive has previously been described, see: (a) Koike, T.; Mori, A. *Synlett* **2003**, *12*, 1850. (b) Gallagher, W. P.; Maleczka, R. E. *Synlett* **2003**.

(24) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534.

(25) (a) Zlatovic, M. V.; Sukalovic, V. V.; Schneider, C.; Roglic, G. M. *Bioorg. Med. Chem.* **2006**, *14*, 2994. (b) Partilla, J. S.; Dempsey, A. G.; Nagpal, A. S.; Blough, B. E.; Baumann, M. H.; Rothmann, R. B. *J. Pharmacol. Exp. Ther.* **2006**, *319*, 237.

SCHEME 3. Ni-Catalyzed Arylation of Piperazine



This reaction demonstrated a useful selectivity: by using 2 equiv of piperazine (**2m**) the monoarylated amine **3u** can be obtained almost exclusively in 86% yield after 18 h at 130 °C (Scheme 3). The bisarylated adduct could be prepared in moderate yield (53%) and selectivity only if an excess (4 equiv) of the aryl chloride **1k** was used and the reaction time was prolonged to 40 h. Such selectivity can be useful for the selective preparation of monoarylated piperazines, avoiding protection−deprotection steps.

Conclusion. In summary, we have developed a practical protocol for the silane-promoted nickel-catalyzed amination of aryl chlorides. The $Ni(acac)_2$/3,5,6,8-tetrabromophenanthroline/PMHS catalyst system is efficient in loadings of 0.1−0.5 mol % and affords high yields in the arylation and heteroarylation of secondary cyclic or acyclic amines or anilines. The reaction has a broad scope and could be applied to a variety of electron-poor aryl chlorides as well as heteroaryl chlorides. Electron-rich and sterically hindered aryl chlorides could be coupled so far only with cyclic secondary amines. Good to excellent yields were obtained with the vast majority of substrates. The use of the toluene/DME solvent system proved to be the most beneficial. Further studies are underway to expand the reaction scope to primary amines, and to understand the role of PMHS in the formation of the catalytically active system.

3. Experimental Section

General Procedure for the Amination Reaction. A 25 mL sealed tube, equipped with a Teflon screw cap, was loaded with NaO*t*Bu (135 mg, 1.4 mmol), $Ni(acac)_2$ (1.3 mg, 0.005 mmol), 3,5,6,8-tetrabromophenanthroline **4b** (5.0 mg, 0.01 mmol), 1,2-dimethoxyethane (2 μL, 0.02 mmol), and toluene (1.5 mL). PMHS (0.05 mL, 0.8 mmol) was added and the mixture was stirred for 15 min at 25 °C. The amine (1.2 mmol) and the aryl chloride (1.0 mmol) were added. The tube was sealed with a Teflon screw cap and the mixture heated to 130 °C for the specified time. The reaction mixture was cooled to room temperature, diluted with ether (15 mL), filtered through a short pad of Celite, and concentrated in vacuo. The crude product was purified by column chromatography.

***N*-Hexyl-*N*-methyl-4-trifluoromethylaniline (3c).** The general procedure was used to couple 4-chlorotrifluoromethylbenzene (**1a**) (181 mg, 1.0 mmol) and *N*-hexyl-*N*-methylamine (**2b**) (138 mg, 1.2 mmol). After column chromatography (pentane/ether 40:1) the title compound was isolated as a colorless oil (250 mg, 96%). ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C) δ 7.44 (d, J = 8.8 Hz, 2 H), 6.67 (d, J = 8.8 Hz, 2 H), 3.35 (t, J = 7.6 Hz, 2 H), 2.98 (s, 3 H), 1.61−1.57 (m, 2 H), 1.36−1.31 (m, 6 H), 0.91 (t, J = 6.7 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 150 MHz, 25 °C) δ 151.0, 126.2 (q, J = 7.5 Hz), 125.1 (q, J = 270.0 Hz), 116.7 (q, J = 32.6 Hz), 110.6, 52.3, 38.1, 31.5, 26.6, 26.5, 22.5, 13.8. MS (EI, 70 eV) *m*/*z* (%) 259 (11) [M^+], 240 (3), 189 (11), 188 (100), 172 (4). HRMS *m*/*z* calcd for $C_{14}H_{20}NF_3$ 259.1548, found 259.1549. IR (cm^{-1}) 2930 (w), 2859 (w), 1616 (s), 1534 (m), 1485 (w), 1317 (vs), 1186 (m), 1158 (m), 1103 (vs), 1062 (vs), 1006 (w), 939 (w), 822 (s) 640 (w).

3-(Pyrrolidin-1-yl)benzoic Acid *tert*-Butyl Ester (3n). The general procedure was used to couple 3-chlorobenzoic acid *tert*-butyl ester (**1g**) (213 mg, 1.0 mmol) and pyrrolidine (**1a**) (85 mg, 1.2 mmol). After column chromatography (pentane/ether 10:1) the title compound was isolated as a colorless oil (234 mg, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.32−7.28 (m, 2 H), 7.24−7.22 (m, 2 H), 6.75−6.71 (m, 1 H), 3.37−3.32 (m, 4 H), 2.04 (qn, J = 3.3 Hz, 4 H), 1.62 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 166.6, 147.8, 132.7, 128.8, 116.3, 115.5, 112.3, 80.5, 47.7, 28.2, 25.5. MS (EI, 70 eV) *m*/*z* (%) 247 (19) [M^+], 191 (100), 191 (92), 174 (13), 135 (12). HRMS *m*/*z* calcd for $C_{15}H_{21}NO_2$ 247.1572, found 247.1572. IR (cm^{-1}) 2932 (m), 1721 (s), 1597 (s), 1574 (w), 1498 (s), 1453 (m), 1341 (s), 1245 (s), 1172(s), 1134 (s), 949 (m), 853 (m), 736 (vs).

1-[4-(Pyrrolidine-1-sulfonyl)phenyl]piperidine (3t). The general procedure was used to couple 1-(4-chlorobenzenesulfonyl)-pyrrolidine (**1j**) (246 mg, 1.0 mmol) and piperidine (**2f**) (102 mg, 1.2 mmol). After column chromatography (pentane/ether 1:1) the title compound was isolated as a colorless solid (291 mg, 96%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.64 (ddd, J = 9.6, 2.9, 2.5 Hz, 2H), 6.88 (ddd, J = 9.6, 2.9, 2.5 Hz, 2H), 3.33−3.39 (m, 4H), 3.21−3.17 (m, 4H), 1.75−1.58 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 154.0, 129.3, 124.1, 113.8, 48.7, 47.8, 25.4, 25.1, 24.2. MS (EI, 70 eV) *m*/*z* (%) 294 (90) [M^+], 224 (18), 207 (44), 176 (79), 160 (100). HRMS *m*/*z* calcd for $C_{15}H_{22}N_2O_2S$ 294.1402, found 294.1409. IR (cm^{-1}) 2937 (m), 2851 (m), 1587 (s), 1505 (m), 1449 (m), 1360 (m), 1327 (vs), 1247 (s), 1155 (vs), 1125 (vs), 1092 (vs), 1062 (s), 1004 (vs), 917 (s), 813 (s). Mp 142.7−144.5 °C.

3-(*N*-Butyl-*N*-methylamino)pyridine (7f). The general procedure was used to couple 3-chloropyridine (**6b**) (114 mg, 1.0 mmol) and *N*-butyl-*N*-methylamine (**2j**) (105 mg, 1.2 mmol). After column chromatography (CH_2Cl_2/ether 1:1) the title compound was isolated as a colorless oil (132 mg, 80%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 8.09 (d, J = 3.1 Hz, 1H), 7.90 (dd, J = 4.6, 1.1 Hz, 1H), 7.07 (dd, J = 8.6, 4.6 Hz, 1H), 6.90 (ddd, J = 8.6, 3.1, 1.1 Hz, 1H), 3.29 (t, J = 7.5 Hz, 2H), 2.91 (s, 3H), 1.59−1.49 (m, 2H), 1.39−1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 145.0, 137.1, 134.7, 123.4, 118.0, 52.0, 37.9, 28.6, 20.2, 13.9, 14.1. MS (EI, 70 eV) *m*/*z* (%) 164 (11) [M^+], 121 (100), 106 (3), 93 (4), 78 (7). HRMS *m*/*z* calcd.for $C_{10}H_{16}N_2$ 164.1313, found 164.1319. IR (cm^{-1}) 3040 (w), 2956 (m), 2930 (m), 2871 (m), 1582 (vs), 1493 (vs), 1425 (m), 1364 (s), 1243 (s), 1185 (m), 1112 (m), 1087 (m), 1050 (m), 1004 (m), 928 (m), 789 (vs), 706 (vs).

1-(3-Trifluoromethylphenyl)piperazine (3u).[23] The general procedure was used to couple 3-chlorotrifluoromethylbenzene (**1k**) (181 mg, 1.0 mmol), piperazine (**2m**) (172 mg, 2.0 mmol), and NaO*t*Bu (270 mg, 2.4 mmol). After column chromatography (CH_2Cl_2/ether 1:1) the title compound was isolated as a yellow oil (198 mg, 86%). ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C) δ 7.34 (t, J = 7.94 Hz, 1H), 7.10−7.04 (m, 3H), 3.25−3.18 (m, 4H), 3.04 (dd, J = 9.5, 5.1 Hz, 4 H), 1.95 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz, 25 °C) δ 151.8, 129.5, 119.2 (q, J = 32.2 Hz), 117.4 (q, J = 270.4 Hz),

(26) Molyneaux, C.-A.; Krugliak, M.; Ginsburg, H.; Chibale, K. *Biochem. Pharmacol.* **2005**, *71*, 61.

118.9, 115.9 (q, $J = 3.9$ Hz), 112.3 (q, $J = 3.9$ Hz), 49.8, 45.9. MS (EI, 70 eV) *m*/*z* (%) 230 (71) [M^+], 211(100), 161 (34), 173 (12), 145 (41).

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

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