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Efficient Synthesis of *N*-Aryl-Aza-Crown Ethers via Palladium-Catalyzed Amination

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N-Aryl-aza-crown ethers were efficiently prepared by reaction of an aza-crown ether with an aryl bromide via a palladium-catalyzed amination. The combination of $Pd_2(dba)_3$ and a biphenyl-based electron-rich bulky monophosphine is effective for catalyzing the coupling of 1-aza-15-crown-5 with both electron-deficient and electron-rich aryl bromides under mild conditions. *N*-Aryl-aza-crown ethers were produced in 75−91% yields. *N*-Aryl-aza-crown ethers with *o*-aryl substituents can also be synthesized using this catalyst system, albeit in lower yields (∼40%).

Introduction

Macrocyclic ionophores based on crown ethers have been intensively studied for applications in many areas due to their selective affinity for cations.[1] When one or more of the oxygen donor atoms are replaced with nitrogen atoms, aza-crown macrocycles result. Aza-crown ethers have different cation binding properties from crown ethers, and can be derivatized for incorporation of functional moieties for specific applications.[2] Notably, *N*-aryl-aza-crown ether derivatives are widely used in construction of fluoroionophores for signaling recognition events as sensors and switches, owing to the direct electronic communication between the fluorophore and a metal ion encapsulated within the crown ether.[3] The synthesis of *N*-aryl-aza-crown ethers is generally accomplished in multiple steps from aniline derivatives through a low-yielding ring closure step.[2−4] The direct aromatic nucleophilic substitution reactions between aza-crown ethers and aryl halides require high pressure, and are successful only when the aryl halides is activated.[5]

Recently, Witulski reported[6] a new approach for the synthesis of *N*-aryl-crown ethers by reaction of an aza-crown ether with an aryl bromide via palladium-catalyzed amination chemistry.[7] Using the catalyst system Pd/PPh_3 at 100 °C in toluene, *N*-aryl- and *N*-heteroaryl-aza-crown ethers were prepared in good yields from aryl- and heteroaryl bromides, respectively.[6] It was mentioned by the author,[6] however, that the protocol is limited to electron-deficient arenes and heteroarenes. He noted that attempts to couple bromobenzene and 1-aza-18-crown-6 were unsuccessful. In our effort toward the construction of ion sensor materials based on the conductivity of controlled-length and end-capped oligoanilines[8] and well-defined, high molecular weight and processible polyanilines,[9] we hoped to develop a more general protocol for the efficient synthesis of *N*-aryl-aza-crown ethers via palladium-catalyzed amination chemistry. Herein, we present our progress toward that goal.

Results and Discussion

We have recently developed a series of biphenyl-based electron-rich bulky monophosphine ligands (Figure 1), **1**−**6**, and we have demonstrated that they are quite useful in palladium-catalyzed C−N, C−C, and C−O bond-forming reactions.[10] These functionalized dicyclohexyl- and di-*tert*-butylphosphinobiphenyl ligands can now be easily prepared by a one-pot procedure from relatively inexpensive starting materials in useful amounts.[11] Here we report that *N*-aryl-1-aza-15-crown-5 ethers can be prepared efficiently from the reactions of 1-aza-15-crown-5 ether with aryl bromides that are catalyzed by the combination of $Pd_2(dba)_3$ and the phos-

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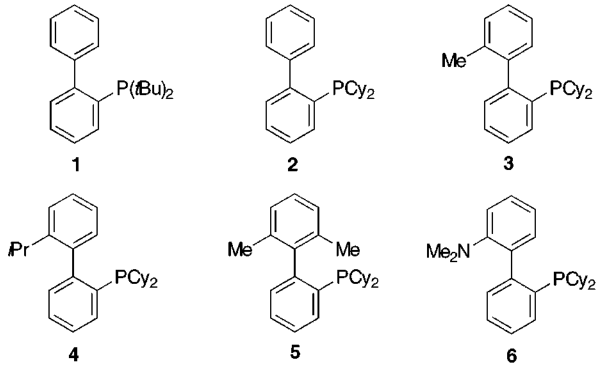

Figure 1. Biphenyl-based electron-rich bulky monophosphine ligands.

phines **1**−**6**. The new protocol is suitable for both electron-poor and electron-rich aryl bromides, and for aryl bromides with ortho-substituents (Table 1).

Our first attempts (Table 1, entries 1−4) to use **1** as a supporting ligand in combination with 1 mol % $Pd_2(dba)_3$ for coupling 1-aza-15-crown-5 with aryl bromides at 100 °C produced the corresponding *N*-aryl-aza-crown ethers in low yields (15−40%). It was encouraging, however, that electron-poor, -neutral, and -rich aryl bromides were all observed to produce the corresponding *N*-aryl-aza-crown ethers. The low yields were thought to be the result of steric hindrance, imposed by the bulky *tert*-butyl groups of ligand **1** and the cyclic secondary amine of aza-crown ether, around the palladium center of an intermediate species that is important to the catalytic cycle.[12] It was previously shown that, for very sterically demanding substrates, dicyclohexylphosphinobiphenyl ligands are superior to the analogous *tert*-butyl ligands.[10] Accordingly, it was reasoned that replacement of the *tert*-butyl groups with less sterically demanding cyclohexyl groups should improve the yields of the coupling reactions with aza-crown ethers. Indeed, when the cyclohexyl-substituted ligand **2** was employed as the supporting ligand, the corresponding *N*-aryl-aza-crown ethers (Table 1, entries 5−8) were obtained in higher yields (52−60%) than obtained with **1** under the same conditions. Notably, the yield of product formation from electron-rich 4-bromoanisole was substantially increased, from 15% to 53%.

We next screened the dicyclohexyl phosphine ligands, **3**−**6**, which contain substituents on the phenyl ring not substituted by phosphorus, for the coupling reaction of 1-aza-15-crown-5 and 1-bromo-4-*tert*-butylbenzene under similar conditions. These ligands were previously found to be important for palladium-catalyzed C−N, C−C, and C−O bond-forming reactions of certain substrate combinations.[10] We found the yields were further improved, from 55% (Table 1, entry 6) to 71−86% (Table 1, entries 9−12). Of the ligands tested, commercially available **6**, which contains a dimethylamino group on the phenyl ring not substituted by phosphorus, gave the best result. It is noted that all the above reactions were carried out at 100 °C using a ligand/Pd ratio of 3/1. Later, we found similar results can be obtained for **6** when the reactions were carried out either at lower temperature (Table 1, entry 13) or using a lower L/Pd ratio (Table 1, entry 14). With the combination of **6** and $Pd_2(dba)_3$ ($L/Pd = 3$), a variety of aryl bromides and 1-aza-15-crown-5 can be successfully coupled at 80 °C to form the corresponding *N*-aryl-aza-crown ethers in good yields (75−91%, Table 1, entries 15−20). Even the very electron-rich substrate 4-bromo-*N*,*N*-dimethylaniline can be coupled in 84% yield (Table 1, entry 18), and meta-substituted aryl bromides (Table 1, entries 19, 20) reacted as efficiently as para-substituted ones.

When ortho-substituted aryl bromides were used as substrates, reactions did not proceed to completion when the conditions (1 mol % $Pd_2(dba)_3$, $L/Pd = 3$ and 80 °C) that are successful for meta- and para-substituted aryl bromides were applied for 24 h. When 2 mol % $Pd_2(dba)_3$ and a reaction temperature of 100 °C were employed, the aryl bromides were completely consumed; however, a substantial amount of reduced product arenes were formed. Better results were obtained using 2 mol % $Pd_2(dba)_3$ and a reaction temperature of 80 °C, and a variety of ortho-substituted aryl bromides were successfully coupled to give the desired products in modest yields (~40%, Table 1, entries 21−26). When more challenging substrates such as 1-bromo-2,4-dimethoxybenzene and 2-bromo-*m*-xylene were reacted, desired products were only observed in low yields (~10%, Table 1, entries 27, 28). Poor yields were also obtained when weak bases were used instead of NaO*t*-Bu. For an example, when 1-bromo-4-*tert*-butylbenzene was reacted with 1-aza-15-crown-5 at 100 °C using 2 mol % $Pd_2(dba)_3$ in the presence of either Cs_2CO_3 or K_3PO_4, the desired product was detected only in ca. 14% yield based on GC analysis.

Summary and Conclusions

In summary, using the combination of $Pd_2(dba)_3$ with the biphenyl-based electron-rich bulky monophosphines, a variety of *N*-aryl-aza-crown ethers can be conveniently prepared through direct reactions of the commercially available aza-crown ethers with aryl bromides under mild conditions. Both electron-poor and rich aryl bromides as well as hindered aryl bromides are suitable substrates. This new methodology should find wide applications in many areas associated with crown and aza-crown ethers, including the construction of sensors and switches based on fluorescence and conductivity. We are currently working to expand the scope of this methodology and to apply it for the construction of oligo- and polyaniline frameworks containing crown ether moiety as sensing materials.

Experimental Section

General Considerations. All reactions were carried out under an argon or nitrogen atmosphere in oven-dried glassware. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Toluene was distilled under nitrogen from molten sodium. Aryl halides were purchased from commercial sources and were used without further purification. Aza-crown ethers were purchased from Aldrich Chemical Co., carefully dried, and stored and handled in a Vacuum Atmospheres glovebox with a nitrogen atmosphere. The biphenyl-based monophosphine ligands **1**−**6** were prepared as previously described.[11] $Pd_2(dba)_3$ was purchased from Strem Chemical Co. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co.; the bulk of this material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (1−2 g) were removed from the glovebox in glass vials, stored in the air in a desiccator filled with anhydrous calcium sulfate, and weighed

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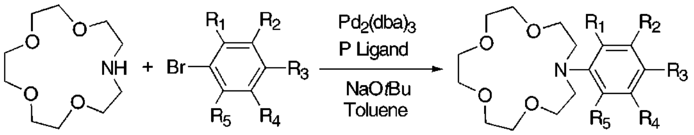
Table 1. Palladium-Catalyzed Synthesis of *N*-Aryl-Aza-Crown Ether[a]



entry	R_1	R_2	R_3	R_4	R_5	ligand	$Pd_2(dba)_3$ mol %	L/Pd	temp (°C)	yield[b] (%)
1	H	H	H	H	H	**1**	1	3	100	30
2	H	H	t-Bu	H	H	**1**	1	3	100	23
3	H	H	CF_3	H	H	**1**	1	3	100	41
4	H	H	OMe	H	H	**1**	1	3	100	15
5	H	H	H	H	H	**2**	1	3	100	60
6	H	H	t-Bu	H	H	**2**	1	3	100	55
7	H	H	CF_3	H	H	**2**	1	3	100	52
8	H	H	OMe	H	H	**2**	1	3	100	53
9	H	H	t-Bu	H	H	**3**	1	3	100	72
10	H	H	t-Bu	H	H	**4**	1	3	100	71
11	H	H	t-Bu	H	H	**5**	1	3	100	80
12	H	H	t-Bu	H	H	**6**	1	3	100	86
13	H	H	t-Bu	H	H	**6**	1	3	80	87
14	H	H	t-Bu	H	H	**6**	1	1	100	88
15	H	H	CF_3	H	H	**6**	1	3	80	75
16	H	H	OMe	H	H	**6**	1	3	80	80
17	H	H	Ph	H	H	**6**	1	3	80	80
18	H	H	NMe_2	H	H	**6**	1	3	80	84
19	H	OMe	H	H	H	**6**	1	3	80	83
20	H	Me	H	Me	H	**6**	1	3	80	91
21	Me	H	H	H	H	**6**	2	3	80	41
22	CF_3	H	H	H	H	**6**	2	3	80	40
23	OMe	H	H	H	H	**6**	2	3	80	40
24	Et	H	H	H	H	**6**	2	3	80	31
25	Me	H	H	Me	H	**6**	2	3	80	43
26	Cl	H	H	H	H	**6**	2	3	80	40
27	OMe	H	OMe	H	H	**6**	2	3	80	15[c]
28	Me	H	H	H	Me	**6**	2	3	80	10[c]

[a] Reactions were run in toluene for 24 h with 1.0 equiv of ArBr, 1.14 equiv of aza-crown ether, and 1.4 equiv of NaO*t*Bu. Concentration: 2 mL toluene/mmol ArBr. Reaction times have not been optimized. [b] Yields represent isolated yields (average of two runs) of compounds estimated to be >95% pure by ^{1}H NMR, GC analysis, or combustion analysis. [c]Estimated yields based on GC analysis.

in the air. Yields in Tables 1 refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC analysis or combustion analysis.

General Procedure. Biphenyl-based monophosphine (0.060 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.010 mmol), and sodium *tert*-butoxide (135 mg, 1.40 mmol) were placed in a dried, resealable Schlenk tube, which was fitted with a Teflon screwcap, evacuated, and backfilled with argon. The tube was sealed and brought into a glovebox with a nitrogen atmosphere. A stock solution of aza-crown ether in toluene (2.0 mL, 0.57 M, 1.14 mmol) was added via syringe. The sample was sealed and taken out of the box. The Teflon screwcap was replaced with a rubber septum. Aryl bromide (1.00 mmol) was added via syringe. The tube was purged with argon for 3 min, and then the septum was replaced with the Teflon screwcap. The tube was sealed, and its contents were heated at 80 °C or 100 °C with stirring for 24 h. The reaction mixture was analyzed by GC and GC-MS. The reaction mixture was then cooled to room temperature, taken up in dichloromethane (60 mL), filtered through Celite, and concentrated in a vacuum. The crude product was purified by flash column chromatography on silica gel using ethyl acetate as an eluting solvent.

***N*-Phenyl-1-aza-15-crown-5 (Table 1, entry 1).** The general procedure was used to couple 1-aza-15-crown-5 with bromobenzene, using **1** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **1**. The title compound was isolated as a pale yellow oil (89 mg, 30%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.16 (m, 2H), 6.67−6.62 (m, 3H), 3.75 (t, $J = 6.2$ Hz, 4H), 3.69−3.62 (m, 12H), 3.59 (t, $J = 6.2$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 129.3, 115.7, 111.3, 71.4, 70.3, 20.2, 68.6, 52.6; IR (film, cm^{-1}) 2936, 2866, 1598, 1572, 1505, 1470, 1449, 1385, 1355, 1294, 1249, 1227, 1192, 1126, 1036, 989, 941. GC-MS (M$^+$) Calcd for $C_{16}H_{25}NO_4$: 295. Found: 295. Anal. Calcd for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53. Found: C, 65.35; H, 8.59.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 2).** The general procedure was used to couple 1-aza-15-crown-5 with 1-bromo-4-*tert*-butylbenzene, using **1** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **1**. The title compound was isolated as a pale yellow oil or solid (81 mg, 23%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, $J = 9.1$ Hz, 2H), 6.60 (d, $J = 9.1$ Hz, 2H), 3.74 (t, $J = 6.2$ Hz, 4H), 3.68−3.62 (m, 12H), 3.56 (t, $J = 6.2$ Hz, 4H), 1.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 138.2, 126.1, 110.9, 71.4, 70.3, 70.2, 68.8, 52.6, 33.8, 31.7; IR (film, cm^{-1}) 3090, 3041, 2951, 2897, 2865, 1614, 1560, 1520, 1469, 1385, 1362, 1294, 1269, 1249, 1230, 1207, 1193, 1128, 1006, 986, 942. GC-MS (M$^+$) Calcd for $C_{20}H_{33}NO_4$: 351. Found: 351. Anal. Calcd for $C_{20}H_{33}NO_4$: C, 68.34; H, 9.46. Found: C, 68.46; H, 9.54.

***N*-(4-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 3).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromobenzenotrifluoride, using **1** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **1**. The title compound was isolated as a light yellow oil (149 mg, 41%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 3.75 (t, $J = 6.0$ Hz, 4H), 3.68−3.60 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 126.6, 125.2, 117.2, 110.8, 71.5, 70.4, 70.2, 68.3, 52.8; ^{19}F NMR (280 MHz, $CDCl_3$) δ −57.1; IR (film, cm^{-1}) 3057, 2942, 2868, 1616, 1570, 1531, 1472, 1452, 1394, 1355, 1331, 1295, 1249, 1200, 1163, 1118, 1071, 986, 940. GC-MS (M$^+$) Calcd for $C_{17}H_{24}NO_4F_3$: 363. Found: 363. Anal. Calcd for $C_{17}H_{24}NO_4F_3$: C, 56.19; H, 6.66. Found: C, 56.30; H, 6.59.

***N*-(4-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 4).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromoanisole, using **1** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **1**. The title compound was isolated as a yellow-brown oil (49 mg, 15%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, $J = 9.1$ Hz, 2H), 6.61 (d, $J = 9.1$ Hz, 2H), 3.73 (s, 3H), 3.72 (t, $J = 6.0$ Hz, 4H), 3.68−3.61 (m, 12H), 3.53 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.8, 142.3, 114.9, 112.7, 71.3, 70.3, 70.2, 68.9, 55.9, 52.8; IR (film, cm^{-1}) 3044, 2933, 2865, 1514, 1466, 1449, 1382, 1354, 1283, 1246, 1192, 1126, 1040, 985, 940. GC-MS (M^+) Calcd for $C_{17}H_{27}NO_5$: 325. Found: 325. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36. Found: C, 63.05; H, 8.41.

***N*-Phenyl-1-aza-15-crown-5 (Table 1, entry 5).** The general procedure was used to couple 1-aza-15-crown-5 with bromobenzene, using **2** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **2**. The title compound was isolated as a pale yellow oil (177 mg, 60%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 1.

***N*-(4-*t*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 6).** The general procedure was used to couple 1-aza-15-crown-5 with 1-bromo-4-*tert*-butylbenzene, using **2** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **2**. The title compound was isolated as a pale yellow oil or solid (193 mg, 55%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 7).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromobenzenotrifluoride, using **2** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **2**. The title compound was isolated as light yellow oil (189 mg, 52%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 3.

***N*-(4-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 8).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromoanisole, using **2** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **2**. The title compound was isolated as a yellow-brown oil (172 mg, 53%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 4.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 9).** The general procedure was followed by using **3** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **3**. The title compound was isolated as a pale yellow oil or soild (253 mg, 72%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 10).** The general procedure was followed by using **4** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **4**. The title compound was isolated as a pale yellow oil or soild (250 mg, 71%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 11).** The general procedure was followed by using **5** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **5**. The title compound was isolated as a pale yellow oil or soild (281 mg, 80%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 12).** The general procedure was followed by using **6** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a pale yellow oil or soild (302 mg, 86%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 13).** The general procedure was followed by using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a pale yellow oil or soild (306 mg, 87%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-*tert*-Butylphenyl)-1-aza-15-crown-5 (Table 1, entry 14).** The general procedure was followed by using **6** as the supporting ligand. The reaction was conducted at 100 °C with 1.0 mol % $Pd_2(dba)_3$ and 2.0 mol % **6**. The title compound was isolated as a pale yellow oil or soild (309 mg, 88%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 2.

***N*-(4-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 15).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromobenzenotrifluoride, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a light yellow oil (273 mg, 75%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 3.

***N*-(4-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 16).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromoanisole, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a yellow-brown oil (260 mg, 80%). The identity and purity of the isolated compound were verified by comparison of its ^1H and ^{13}C NMR spectra and GC and GC-MS chromatograms to those obtained for the compound prepared as described in Table 1, entry 4.

***N*-(4-Biphenyl)-1-aza-15-crown-5 (Table 1, entry 17).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromobiphenyl, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a light yellow oil (297 mg, 80%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, $J = 8.4$ Hz, 2H), 7.45 (d, $J = 9.1$ Hz, 2H), 7.36 (t, $J = 8.1$ Hz, 2H), 7.21 (t, $J = 7.4$ Hz, 1H), 6.70 (d, $J = 9.1$ Hz, 2H), 3.76 (t, $J = 6.0$ Hz, 4H), 3.66−3.59 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 141.1, 128.7, 128.5, 127.9, 126.2, 125.9, 111.7, 71.5, 70.3, 70.2, 68.6, 52.7; IR (film, cm^{-1}) 3076, 3028, 2939, 2868, 1613, 1578, 1525, 1487, 1449, 1387, 1354, 1286, 1248, 1203, 1128, 1042, 984, 942. GC-MS (M^+) Calcd for $C_{22}H_{29}NO_4$: 371. Found: 371. Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87. Found: C, 71.40; H, 7.99.

***N*-(4-Dimethylaminophenyl)-1-aza-15-crown-5 (Table 1, entry 18).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromo-*N*,*N*-dimethylaniline, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a light yellow oil (284 mg, 84%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.77 (d, $J = 9.1$ Hz, 2H), 6.63 (d, $J = 9.1$ Hz, 2H), 3.72 (t, $J = 6.0$ Hz, 4H), 3.68−3.61 (m, 12H), 3.52 (t, $J = 6.0$ Hz, 4H), 2.80 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 140.8, 116.1, 113.0, 71.3, 70.3, 70.2, 69.1, 52.7, 42.5; IR (film, cm^{-1}) 3047, 2941, 2865, 2790, 1614, 1518, 1470, 1450, 1383, 1354, 1323, 1296, 1249, 1224, 1193, 1127, 1007, 985, 947. GC-MS (M^+) Calcd for $C_{18}H_{30}N_2O_4$: 338. Found: 338. Anal. Calcd for $C_{18}H_{30}N_2O_4$: C, 63.88; H, 8.93. Found: C, 63.77; H, 8.91.

***N*-(3-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 19).** The general procedure was used to couple 1-aza-15-crown-5 with 3-bromoanisole, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as a light yellow oil (270 mg, 83%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (t, $J = 8.1$ Hz, 1H), 6.29−6.18 (m, 3H), 3.76 (s, 3H), 3.74 (t, $J = 6.0$ Hz, 4H), 3.67−3.61 (m, 12H), 3.56 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 148.9, 129.9, 104.7, 100.4, 98.1, 71.4, 70.3, 70.2, 68.6, 55.2, 52.7; IR (film, cm^{-1}) 2939, 2868, 1611, 1573, 1499, 1469, 1384, 1354, 1329, 1291, 1251, 1208, 1171, 1128, 1056, 1012, 989, 930. GC-MS (M^+) Calcd for $C_{17}H_{27}NO_5$: 325. Found: 325. Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.75; H, 8.36. Found: C, 62.91; H, 8.26.

***N*-(3,5-Dimethylphenyl)-1-aza-15-crown-5 (Table 1, entry 20).** The general procedure was used to couple 1-aza-15-crown-5 with 5-bromo-*m*-xylene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 1.0 mol % $Pd_2(dba)_3$ and 6.0 mol % **6**. The title compound was isolated as light yellow oil (294 mg, 91%): ^1H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.28 (s, 2H), 3.73 (s, 3H), 3.72 (t, $J = 6.0$ Hz, 4H), 3.68−3.62 (m, 12H), 3.56 (t, $J = 6.0$ Hz, 4H), 2.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 138.7, 117.8, 109.3, 71.4, 70.3, 70.2, 68.7, 52.5, 22.0; IR (film, cm^{-1}) 3044, 2939, 2910, 2865, 1599, 1484, 1450, 1390, 1354, 1298, 1251, 1198, 1128, 1058, 988, 931. GC-MS (M^+) Calcd for $C_{18}H_{29}NO_4$: 323. Found: 323. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04. Found: C, 67.07; H, 9.18.

***N*-(2-Methylphenyl)-1-aza-15-crown-5 (Table 1, entry 21).** The general procedure was used to couple 1-aza-15-crown-5 with 2-bromo*o*-toluene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (127 mg, 41%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, $J = 7.8$ Hz, 1H), 7.16−7.09 (m, 2H), 6.94 (t, $J = 7.2$ Hz, 1H), 3.70−3.59 (m, 16H), 3.30 (t, $J = 6.0$ Hz, 4H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 134.3, 131.1, 126.2, 123.3, 122.7, 71.0, 70.7, 70.4, 70.3, 54.0, 18.6; IR (film, cm^{-1}) 3060, 3016, 2940, 2863, 2735, 1597, 1578, 1492, 1450, 1354, 1295, 1251, 1216, 1128, 986, 937. GC-MS (M^+) Calcd for $C_{17}H_{27}NO_4$: 309. Found: 309. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80. Found: C, 65.96; H, 8.67.

***N*-(2-Trifluoromethylphenyl)-1-aza-15-crown-5 (Table 1, entry 22).** The general procedure was used to couple 1-aza-15-crown-5 with 2-bromo-benenotrifluoride, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (145 mg, 40%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.61−7.47 (m, 3H), 7.19 (t, $J = 7.8$ Hz, 4H), 3.70−3.59 (m, 16H), 3.33 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 132.7, 127.3, 127.1, 127.0, 124.8, 122.3, 71.0, 70.8, 70.7, 70.6, 59.2; ^{19}F NMR (280 MHz, $CDCl_3$) δ −60.4; IR (film, cm^{-1}) 3068, 2940, 2864, 1602, 1582, 1494, 1453, 1356, 1315, 1252, 1214, 1128, 1110, 1055, 1036, 988, 936. GC-MS (M^+) Calcd for $C_{17}H_{24}NO_4F_3$: 363. Found: 363. HRMS-EI (M^+) Calcd for $C_{17}H_{24}NO_4F_3$: 363.1657. Found: 363.1647. Anal. Calcd for $C_{17}H_{24}NO_4F_3$: C, 56.19; H, 6.66. Found: C, 56.43; H, 6.85.

***N*-(2-Methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 23).** The general procedure was used to couple 1-aza-15-crown-5 with 2-bromo-anisole, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (130 mg, 40%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, $J = 7.5$ Hz, 1H), 6.96−6.81 (m, 3H), 3.82 (s, 3H), 3.69−3.62 (m, 16H), 3.47 (t, $J = 6.0$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 140.0, 122.2, 120.8, 120.7, 111.7, 71.1, 70.7, 70.5, 70.3, 55.6, 53.1; IR (film, cm^{-1}) 2910, 2874, 1644, 1593, 1499, 1456, 1352, 1292, 1241, 1182, 1122, 1054, 1024, 940. GC-MS (M^+) Calcd for $C_{17}H_{27}NO_5$: 325. Found: 325. HRMS-EI (M^+) Calcd for $C_{17}H_{27}NO_5$: 325.1889. Found: 325.1894.

***N*-(2-Ethylphenyl)-1-aza-15-crown-5 (Table 1, entry 24).** The general procedure was used to couple 1-aza-15-crown-5 with 1-bromo-2-ethylbenzene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (101 mg, 31%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 7.5$ Hz, 1H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.03 (t, $J = 7.5$ Hz, 1H), 3.70−3.58 (m, 16H), 3.28 (t, $J = 6.0$ Hz, 4H), 2.72 (q, $J = 7.5$ Hz, 2H), 1.20 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 140.9, 129.1, 126.2, 124.1, 123.6, 71.1, 70.8, 70.5, 70.4, 55.0, 23.8, 15.1; IR (film, cm^{-1}) 3058, 3019, 2930, 2868, 2734, 1596, 1577, 1489, 1449, 1354, 1295, 1251, 1212, 1128, 986, 938. GC-MS (M^+) Calcd for $C_{18}H_{29}NO_4$: 323. Found: 323. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04. Found: C, 66.92; H, 8.89.

***N*-(2,5-Dimethylphenyl)-1-aza-15-crown-5 (Table 1, entry 25).** The general procedure was used to couple 1-aza-15-crown-5 with 4-bromo-*m*-xylene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (139 mg, 43%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.02 (d, $J = 8.0$ Hz, 1H), 7.00 (s, 1H), 6.76 (d, $J = 8.0$ Hz, 1H), 3.70−3.59 (m, 16H), 3.28 (t, $J = 6.0$ Hz, 4H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 135.7, 131.0, 130.9, 124.0, 123.3, 71.0, 70.8, 70.4, 70.3, 54.0, 21.3, 18.2; IR (film, cm^{-1}) 3039, 3015, 2939, 2863, 2731, 1609, 1575, 1504, 1450, 1354, 1295, 1250, 1128, 1000, 937. GC-MS (M^+) Calcd for $C_{18}H_{29}NO_4$: 323. Found: 323. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04. Found: C, 66.75; H, 8.98.

***N*-(2-Chlorophenyl)-1-aza-15-crown-5 (Table 1, entry 26).** The general procedure was used to couple 1-aza-15-crown-5 with 2-bromochlorobenzene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was isolated as light yellow oil (132 mg, 40%). Note: The product was contaminated by a small amount of *N*-(2-bromophenyl)-1-aza-15-crown-5 resulting from the reaction of the aryl chloride. The yield therefore should be lower than the reported. Attempts to further purify the title compound were unsuccessful. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.14 (m, 3H), 6.92 (t, $J = 8.1$ Hz, 1H), 3.75−3.59 (m, 16H), 3.47 (t, $J = 6.2$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 130.8, 129.7, 127.1, 123.9, 115.7, 71.0, 70.7, 70.6, 70.4, 53.5; IR (film, cm^{-1}) 3059, 2930, 2860, 1596, 1588, 1505, 1480, 1448, 1354, 1295, 1278, 1251, 1216, 1126, 1053, 1039, 988, 938. GC-MS (M^+) Calcd for $C_{16}H_{24}NO_4Cl$: 329. Found: 329. HRMS-EI (M^+) Calcd for $C_{16}H_{24}NO_4Cl$: 329.1394. Found: 329.1387.

***N*-(2,4-Dimethoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 27).** The general procedure was used to couple 1-aza-15-crown-5 with 1-bromo-2,4-dimethoxybenzene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was not isolated. It was observed by GC/GC-MS in an estimated 15% yield. GC-MS (M^+) Calcd for $C_{18}H_{29}NO_6$: 355. Found: 355.

***N*-(2,6-Dimethylphenyl)-1-aza-15-crown-5 (Table 1, entry 28).** The general procedure was used to couple 1-aza-15-crown-5 with 2-bromo-*m*-xylene, using **6** as the supporting ligand. The reaction was conducted at 80 °C with 2.0 mol % $Pd_2(dba)_3$ and 12.0 mol % **6**. The title compound was not isolated. It was observed by GC/GC-MS in an estimated 10% yield. GC-MS (M^+) Calcd for $C_{18}H_{29}NO_4$: 323. Found: 323.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for *N*-(2-methoxyphenyl)-1-aza-15-crown-5 (Table 1, entry 23). This material is available free of charge via the Internet at http://pubs.acs.org.

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