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Cu-Catalyzed Carbon-Heteroatom Coupling Reactions under Mild Conditions Promoted by Resin-Bound Organic Ionic Bases

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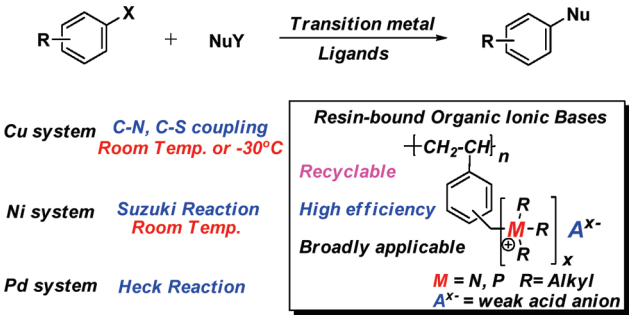

Resin-bound organic ionic bases (RBOIBs) were developed in which tetraalkyl-ammonium or phosphonium cations are covalently attached to solid resins. The application tests showed that the performance of the tetraalkyl-ammonium-type RBOIBs is slightly better than that of the corresponding Cs salts in Cu-catalyzed C−N cross-couplings, while the tetraalkylphosphonium-type RBOIBs are significantly better than all the inorganic bases. With these newly developed RBOIBs, room-temperature Cu-catalyzed C−N coupling with various nonactivated aryl iodides and even aryl bromides can be readily accomplished. Moreover, RBOIBs can be easily recycled and reused for a number of times without much drop of activity. The good performances of RBOIBs are proposed to arise from the relatively weak binding forces between the cationic polymer backbone and basic anions, as opposed to the strong metal−anion interactions in the inorganic bases. Further applications of RBOIBs in Ni-catalyzed Suzuki-type couplings at room temperature, Cu-catalyzed C−N couplings at −30 °C, a Pd-catalyzed Heck reaction at 60 °C, and Cu-catalyzed C−S couplings at room temperature demonstrate that RBOIBs are generally applicable bases with improved performance for many other types of organic transformations.

1. Introduction

Copper-catalyzed carbon-heteroatom cross-coupling reactions have been established as important tools for synthesis of medicinally active compounds and agrochemicals.[1] These reactions were originally carried out under harsh conditions that required high temperatures and stoichiometric quantities of the copper salts.[2] Recently, by the use of chelating ligands such as β-diketones,[3] 1,2-diamines,[4] phenanthrolines,[5] amino acids,[6] and others,[7] milder and selective carbon-heteroatom coupling reactions have been developed with Cu as catalyst. With certain tailor-made ligands, even room-temperature (rt) couplings have been accomplished

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for aryl iodides with aliphatic amines,[8] amides,[9] malonates,[10] and alkoxy diboron reagents.[11] By contrast, there have been scant experimental reports for Cu-catalyzed cross-coupling reactions at room temperature for nonactivated aryl bromides.[12]

In a recent study we showed that the selection of base has an important effect on Cu-catalyzed C−N coupling reactions.[12] This phenomenon can be explained by a mechanism in which the amine group coordinated to (Ligand)Cu^{I} must be deprotonated before the oxidation addition step[13] (or before the single-electron transfer step[14]). The commonly used bases in Cu catalysis are inorganic ionic salts (e.g., K_3PO_4, Cs_2CO_3) that are poorly ionized in organic solvents and therefore, impede the necessary deprotonation step. To overcome this problem, we designed new organic ionic bases composed of tetraalkyl-ammonium or phosphonium cations and basic anions (e.g., $(nBu_4P^+)_2CO_3^{2-}$).[12] These organic ionic bases were found to enable Cu-catalyzed C−N cross-coupling reactions of nonactivated aryl bromides at room temperature.

The organic ionic bases are not without disadvantages. First, these bases are relatively expensive to obtain. Second, the organic ionic bases are found to be fairly hygroscopic and have to be stored and used under strictly dry conditions. These disadvantages may hamper the utility of the organic ionic bases in both Cu-catalyzed couplings and other base-mediated organic reactions. To overcome these disadvantages, we now describe resin-bound organic ionic bases (abbreviated as RBOIB below) in which the cations are replaced by tetraalkyl-ammonium or phosphonium cations covalently bound to hydrophobic polymers. Though various tests, we found that the new RBOIBs are stable in the air. They are easily prepared and inexpensive, and these bases can promote Cu-catalyzed C−N coupling reactions of nonactivated aryl bromides at room temperature and other organic transformations. More interestingly, unlike the traditional inorganic bases, RBOIBs can be easily recycled and reused.

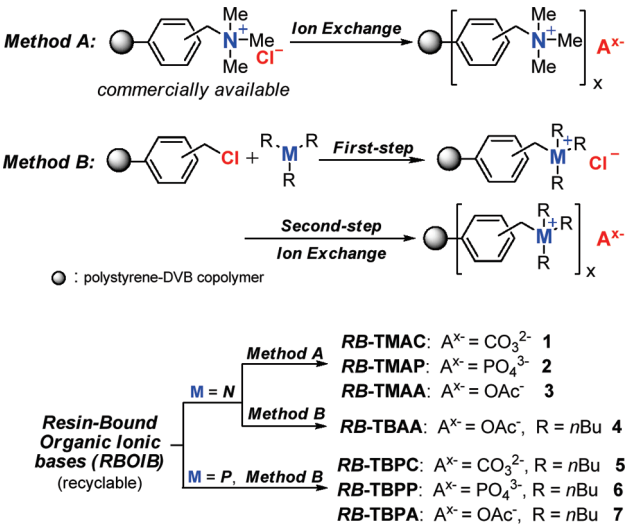

FIGURE 1. Methods for preparing RBOIBs.

2. Results and Discussion

2.1. Synthesis of RBOIBs. Figure 1 shows the RBOIBs synthesized in the present study. They can be prepared through the ion exchange reaction of commercially available Amberlite IRA-400 resins with Na_2CO_3, Na_3PO_4, or NaOAc (Method A). Alternatively, they can be prepared by Method B[15] that involves the reaction of Merrifield resin with nBu_3N or nBu_3P followed by ion exchange. These new RBOIBs resemble traditional basic anion exchange resins. However, two features are unique for the new materials. First, the anions in the new RBOIBs are not OH^- but weaker and less nucleophilic basic anions. The OH-type anion exchange resin does not have much utility in Cu-catalyzed coupling reactions. Second, and more importantly, the tetraalkylphosphonium cations, which have seldom been used for the anion exchange resins, are found to be crucial for RBOIBs to exhibit good performances in mediating organic reactions. Note that in addition to Amberlite or Merrifield resins, some other types of solid supports such as silica or polyacrylic materials can also be considered to make RBOIBs. Comparison of the properties of RBOIBs made from different solid supports is beyond the scope of the present study and will be studied in our following research.

2.2. Solvent Effects on RBOIB-Mediated rt C−N Couplings. To test the performance of the newly developed RBOIBs in comparison to traditional inorganic bases, we have examined the room temperature coupling of benzylamine with

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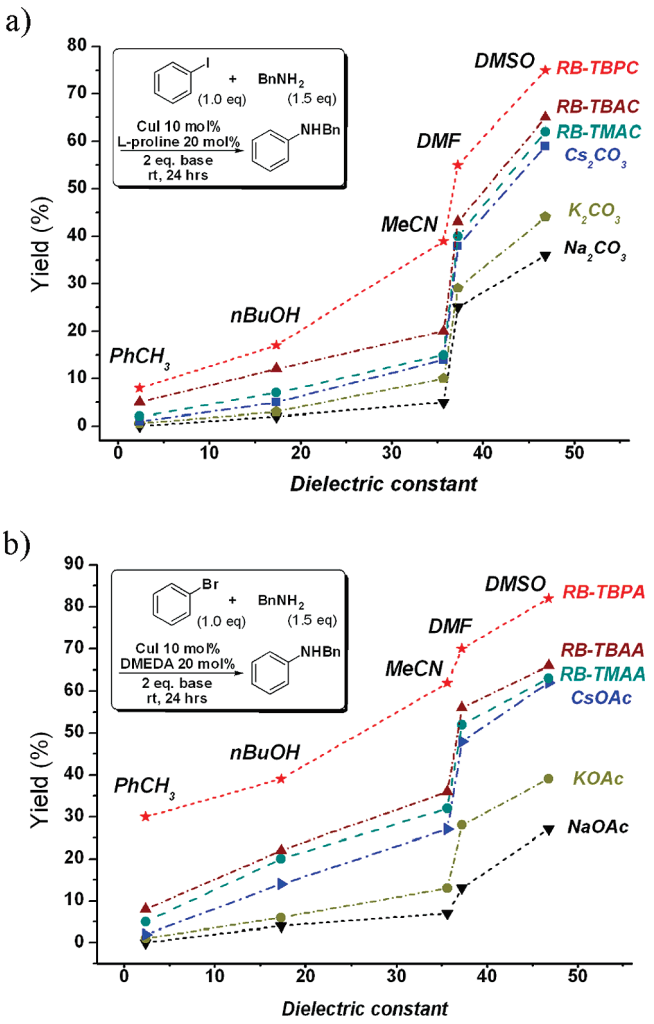

FIGURE 2. Effect of bases on rt C−N coupling of benzylamine with (a) iodobenzene and (b) bromobenzene.

aryl halides. When iodobenzene was tested, RBOIBs with PO_4^{3-}, CO_3^{2-}, and OAc^- anions could all promote the room temperature coupling (Figure 2a). For instance, the coupling yield with the CO_3^{2-} salt of the tetrabutylphosphonium type polymer (**RB-TBPC**) was 78% in DMSO, whereas the yields with the CO_3^{2-} salts of the tetraalkylammonium type polymers (**RB-TBAC** and **RB-TMAC**) were ca. 65%. By comparison, the yield with Cs_2CO_3 was 58%, and the yields with K_2CO_3 and Na_2CO_3 were significantly lower. Note that the above reaction was achieved with L-proline, whereas ligands such as 2-isobutyrylcyclohexanone were required in the previous protocols for Cu-catalyzed C−N coupling at room temperature.[8] Also note that the reaction yield was strongly dependent on the solvent polarity. From DMSO to toluene, the yield decreased considerably from 78% to <10% with RB-TBPC. This observation may be attributed to the fact that DMSO is a better ion pair separating solvent with respect to toluene and other employed solvents. Besides, DMSO can well swell the solid support and enhance accessibility to its inner site. All the other bases showed similar trends, but the use of RBOIBs always afforded significantly higher yields than with inorganic bases.

As to the more challenging substrate (i.e., bromobenzene), the OAc^- salt must be used, because the PO_4^{3-} and CO_3^{2-}

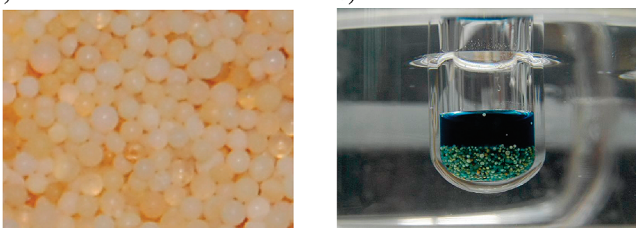

FIGURE 3. RBOIB (**RB-TBPA**) (a) before and (b) after the Cu-catalyzed C−N cross-coupling reaction.

types of RBOIBs were not active enough to promote the reaction. The most powerful base was found to be **RB-TBPA**, which afforded a yield of 82% in DMSO (Figure 2b). On the other hand, the yields with the OAc^- salts of the tetraalkylammonium type polymers (**RB-TBAA** and **RB-TMAA**) were around 65%. The performance of CsOAc was similar to that of the tetraalkylammonium type polymers, but the yields with KOAc and NaOAc were significantly lower.[16] Again, the reaction yield was strongly dependent on the solvent polarity, and RBOIBs always afforded significantly higher yields than the inorganic bases.

2.3. Recycling of RBOIBs. Note that in our previous work the yield for the room temperature coupling of benzylamine with bromobenzene was 92%, where the base was tetrabutylphosphonium malonate. This observation may indicate that the performance of free organic ionic bases is slightly better than that of RBOIBs, presumably because the free organic ionic bases are fully soluble in the organic solvents whereas RBOIBs are insoluble resins (Figure 3). Nonetheless, it is important to aware that most inorganic bases are not soluble in the organic solvents either. Therefore, the use of RBOIBs does not bring about more operation problems than the inorganic bases. On the other hand, three major advantages can be identified for the RBOIBs: (1) RBOIBs exhibit significantly improved performances than the Cs, K, and Na salts (Figure 2). (2) RBOIBs are made from inexpensive resins and cheap Na salts (e.g., NaOAc or Na_2CO_3). The estimated cost of a RBOIB is much lower than that of the corresponding Cs salt. (3) The resin can be readily recycled and reused for a number of times (Table 1). This property may allow the RBOIB to be applied to some large scale syntheses where the inorganic bases are not effective enough. The successful recycle of RBOIBs also indicates that RBOIBs do not decompose when mediating the reaction.

2.4. Scope of rt C−N Coupling. As to the generality of the RBOIB-promoted C−N couplings at room temperature, a number of aryl iodides and bromides were examined with a variety of amine nucleophiles (Tables 2 and 3). Both electron-rich and electron-poor aryl iodides or bromides can be successfully converted bearing a range of functional groups. Heterocycle-containing substrates can also be tolerated in the coupling. The amine nucleophiles include primary and secondary amines, *N*-heterocycles, and even anilines. The coupling yields were mostly good to excellent. Note that Cu-catalyzed C−N cross-coupling of nonactivated aryl bromides at room temperature[12] has been achieved only recently by use of organic ionic bases, whereas the traditional inorganic

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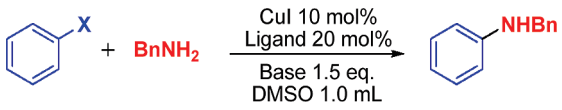
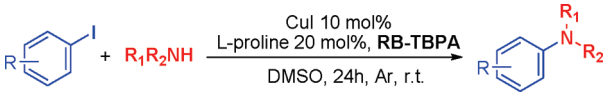
TABLE 1. Yields after Several Rounds of Recycle When using RBOIBs[a]



X	base	1	2	3	4	5	6	7	8	9	10
X = I	**RB-TBPA**	95%	92%	90%	93%	94%	92%	91%	85%	85%	79%
X = Br	**RB-TBPA**	81%	80%	73%	71%	85%	78%	76%	71%	74%	68%

[a]Recycle method: After each round of cross-coupling reaction, the resin was collected by filtration. The resin was washed three times with DMSO and then three times with EtOH. Next the resin was treated with 1 mol/L NaOAc aqueous solution for 24 h. The final material was washed with pure water and EtOH, and then dried at 40 °C under vacuum for 24 h before the next use. Note that due to the magnetic stirring, the resins were pulverized after several rounds of recycling. However, this does not make filtration or recycling difficult in our hands. GC yield. [b]

TABLE 2. Yields for Cu-Catalyzed C−N Couplings of Aryl Iodides with Amines at rt[a]



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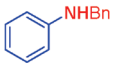
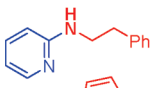
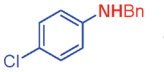
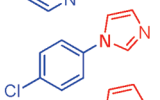
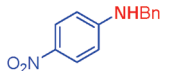
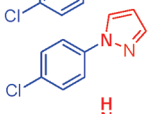
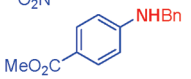
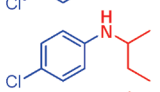
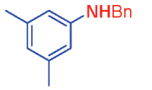
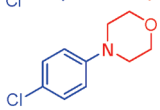
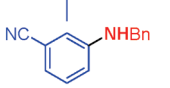
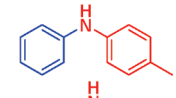
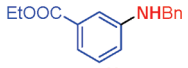
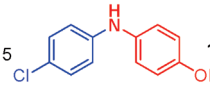
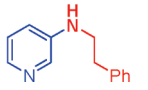
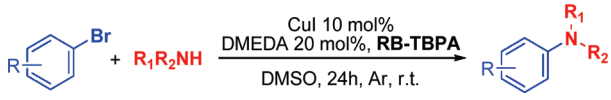
1		**1a** 92	9		**1i** 88
2		**1b** 93	10		**1j** 74
3		**1c** 90	11		**1k** 71
4		**1d** 92	12		**1l** 74
5		**1e** 95	13		**1m** 86
6		**1f** 90	14		**1n** 74
7		**1g** 97	15		**1o** 78
8		**1h** 70			

[a]Conditions: ArI (0.5 mmol), amine (0.75 mmol), ligand (20 mol %), **RB-TBPA** (0.34 g, 1.5 equiv), DMSO (1.0 mL).

TABLE 3. Yields for Cu-Catalyzed C−N Couplings of Aryl Bromides with Amines at rt[a]



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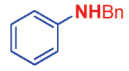
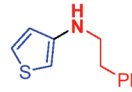
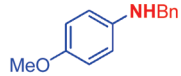
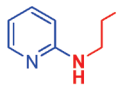
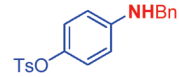
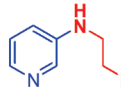
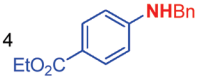
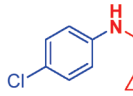
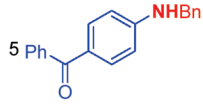
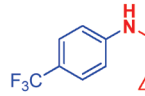
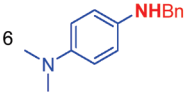
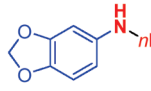
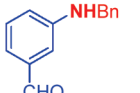
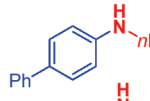
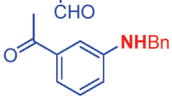
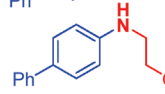
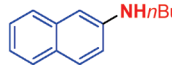
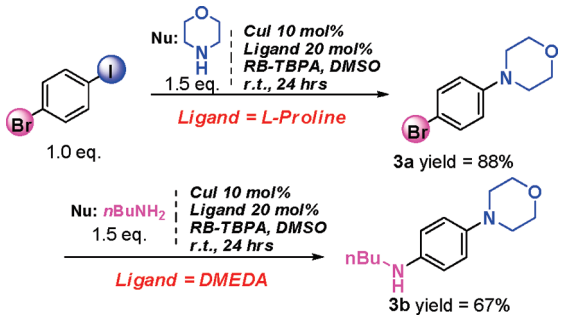
1		**1a** 82	10		**2i** 61
2		**2a** 66	11		**1i** 49
3		**2b** 84	12		**1h** 76
4		**2c** 75	13		**2j** 70
5		**2d** 67	14		**2k** 71
6		**2e** 71	15		**2l** 65
7		**2f** 66	16		**2m** 83
8		**2g** 72	17		**2n** 80
9		**2h** 82			

[a]Conditions: ArBr (0.5 mmol), amine (0.75 mmol), ligand (20 mol %), **RB-TBPA** (0.34 g, 1.5 equiv), DMSO (1.0 mL).

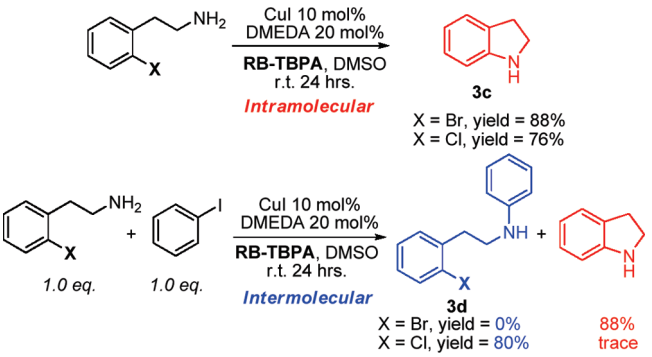
bases (except for CsOAc that can give ca. 60% yields) cannot afford acceptable yields at room temperature. These results show again that the RBOIBs can be more powerful than inorganic bases. Note that with our current catalyst systems, more challenging substrates (such as acyclic secondary amines) cannot undergo the C−N cross-coupling even at elevated temperatures, presumably because these substrates require the use of more sophisticated ligands instead of L-proline and DMEDA. We will study these more difficult substrates with other ligands in our following research.

The above protocols of room temperature C−N cross-coupling reactions may find applications in organic synthesis. By changing ligands, sequential amination reactions can be achieved at the C−I bond and then at the C−Br bond both under very mild conditions at room temperature (Scheme 1). With **RB-TBPA** it is even possible to achieve C−N cross-coupling of an aryl chloride at room temperature (Scheme 2). Previously the same C−Cl activation reaction had to be accomplished at 60−70 °C by using Cs_2CO_3 or K_2CO_3 as base.[17] Interestingly, for the chlorinated substrate the course

SCHEME 1. Selective Amination Reactions



SCHEME 2. Intra- and Intermolecular Amination



of the reaction could be diverted toward intermolecular amination in the presence of an aryl iodide, whereas for the brominated substrate the intramolecular cyclization is still favored.

2.5. Mechanistic Considerations. To understand why RBOIBs are more active than the inorganic bases, we need to point out that deprotonation of the N−H group and/or coordination of the deprotonated nucleophile to Cu could be a rate-limiting step in C−N couplings (Figure 4a). This proposal was supported by our previous experiments with free organic ionic bases showing that variation of the base could dramatically change the reaction rate of the cross coupling.[12] Therefore, optimization of the base is as important as optimization of the ligand for the cross-coupling reaction. As for RBOIBs, our experiments showed that they are not soluble. Thus, the deprotonation step can only take place at the surface of the RBOIBs (and also in the case of inorganic bases). Because of the large size of the tetraalkylammonium or phosphonium cations, it is understandable that the basic anions on the surface of RBOIBs are only loosely bound to the polymer backbone (Figure 4b). By contrast, the basic anions are tightly coordinated by the metal cations on the surface of an inorganic base. The outcome is that the surface of RBOIBs is much more active than that of the inorganic bases, so that RBOIBs can mediate the deprotonation step more efficiently than inorganic bases. Furthermore, some other factors may also explain the advantages of RBOIBs over inorganic bases including the accessibility of the inner sites of RBOIBS.

2.6. Applications to Other Transition Metal-Catalyzed Reactions. More experiments indicate that RBOIBs can

(17) (a) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164. (b) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

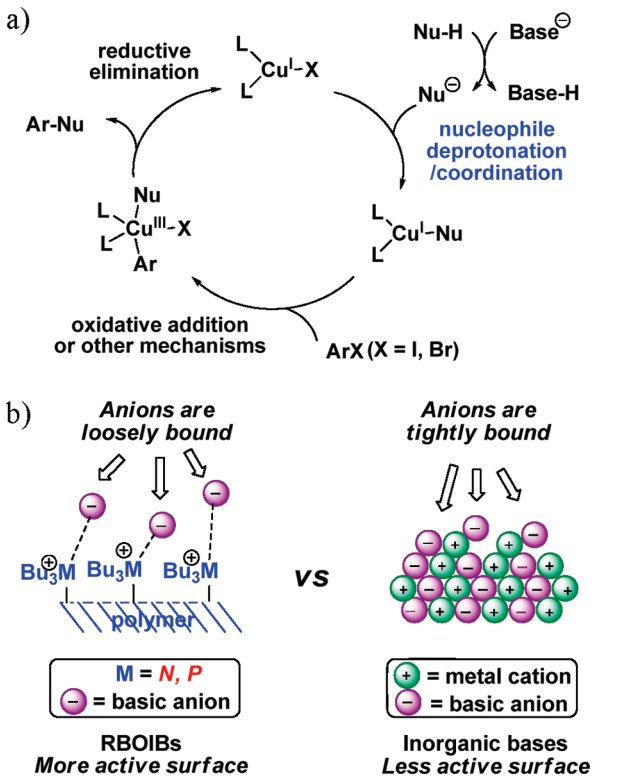
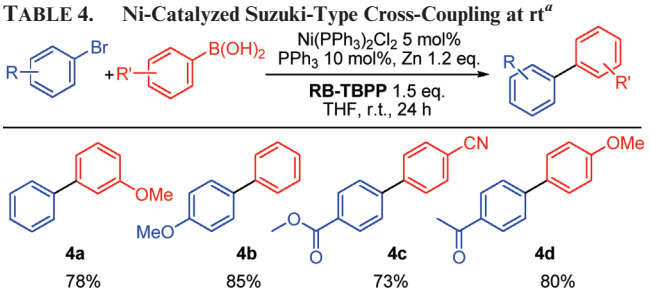


FIGURE 4. (a) Catalytic cycle of the C−N cross-coupling reaction. (b) Compare the surfaces of RBOIBs and inorganic bases.

TABLE 4. Ni-Catalyzed Suzuki-Type Cross-Coupling at rt[a]

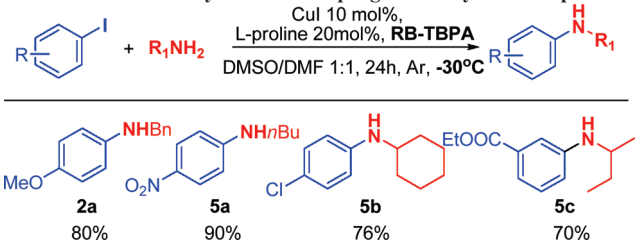


[a]Conditions: ArBr (0.25 mmol), boronic acid (0.5 mmol), **RB-TBPP** (0.15 g, 2 equiv), THF (1.0 mL).

improve performance for many other types of organic transformations in general. Table 4 shows that the phosphate salt of tetrabutyl-phosphonium-type resin (i.e., **RB-TBPP**) can promote the Ni-catalyzed Suzuki-type cross-coupling at room temperature. Previous protocols for the same cross-coupling used K_3PO_4 as base and required the reaction to proceed at elevated temperatures (e.g., 80 °C).[18] To achieve room temperature Ni-catalyzed Suzuki-type reactions, previous studies used either air-sensitive $Ni(COD)_2$ as catalyst or *n*-BuLi as reductant.[19] These conditions are less favorable as compared to the present room temperature protocol that uses inexpensive and air-stable $Ni(PPh_3)_2Cl_2$ as catalyst and Zn as reductant.

(18) (a) Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem.* **1997**, *62*, 8024. (b) Percec, V.; Golding, G. M.; Smidrkal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.
(19) Tang, Z.-Y.; Hu, Q.-S. *J. Org. Chem.* **2006**, *71*, 2167.

TABLE 5. Cu-Catalyzed C−N Couplings at a Very Low Temperature[a]



[a]Conditions: ArI (0.5 mmol), amine (0.75 mmol), **RB-TBPA** (0.34 g, 1.5 equiv), DMSO/DMF (0.5:0.5 mL).

SCHEME 3. Use of RBOIBs in Pd-Catalyzed Heck Reaction

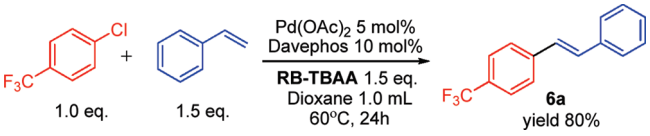
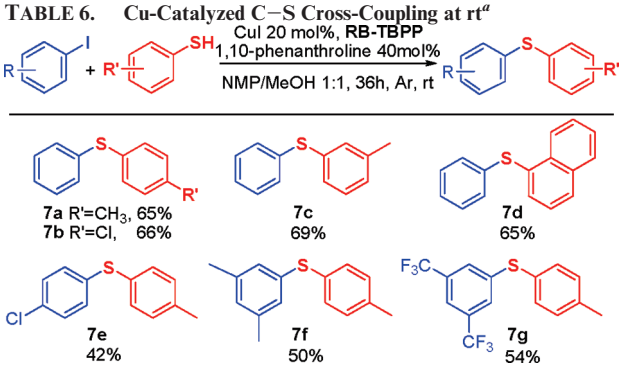


TABLE 6. Cu-Catalyzed C−S Cross-Coupling at rt[a]



[a]Conditions: ArI (1.0 mmol), thiol (0.5 mmol), **RB-TBPP** (0.34 g, 1.5 equiv), NMP/MeOH (0.5:0.5 mL).

It is important to note that the RBOIBs can mediate chemical reactions at various temperatures. For instance, Table 5 shows that **RB-TBPA** can promote Cu-catalyzed C−N cross-coupling reactions with common aryl iodides at −30 °C. Compared to the previous protocols that required at least room temperature to achieve the same reactions,[20] these results demonstrated that RBOIBs not only are bases with better performance, but also can be used at low temperatures. Moreover, Scheme 3 shows a Pd-catalyzed Heck cross-coupling at 60 °C, indicating that RBOIBs are stable and can be used for Pd-catalyzed transformations as well as reactions at elevated temperatures.[21]

Finally, Table 6 shows an interesting discovery that the Cu-catalyzed C−S cross-coupling reaction can now be accomplished at room temperature when a RBOIB is used as the base. Previously, Cu-catalyzed C−S couplings had to be carried out at fairly high temperatures ranging from 60 to 120 °C[22] even when some special ligands such as β-keto ester[23] and 1,1,1-tris(hydroxymethyl)ethane[24] were used. The fact that in the presence of **RB-TBPP**, a common ligand (i.e., 1,10-phenanthroline) can already promote room temperature C−S couplings provides an additional example for the advantageous effect of using RBOIBs. Note that in the control experiments with K_2CO_3, K_3PO_4, Cs_2CO_3, and t-BuOK as the base under the same conditions in Table 6, the C−S coupling yields were lower than 10%.

3. Conclusion

In summary, recent studies showed that organic ionic bases of tetraalkyl-ammonium or phosphonium salts are better than the traditional inorganic bases in some Cu-catalyzed cross-coupling reactions.[25] However, their high synthetic costs and hygroscopic property may limit their application. To solve these problems we developed in this study resin-bound organic ionic bases (RBOIBs) that are inexpensive to prepare and very easy to use. The following conclusions can be made on the basis of our experimental examinations:

First, the performance of the tetraalkyl-ammonium-type RBOIBs is slightly better than that of the corresponding Cs salts in Cu-catalyzed C−N cross-couplings, whereas the tetraalkylphosphonium-type RBOIBs are significantly better than all the inorganic bases.

Second, room-temperature Cu-catalyzed C−N coupling with various nonactivated aryl bromides can be readily accomplished with the RBOIBs, and RBOIBs can be easily recycled and reused for a number of times without much drop of activity.

Finally, RBOIBs can be used to improve the performance of other types of organic transformations as demonstrated by Ni-catalyzed Suzuki-type couplings at room temperature, Cu-catalyzed C−N couplings at −30 °C, a Pd-catalyzed Heck reaction at 60 °C, and Cu-catalyzed C−S couplings at room temperature.

4. Experimental Section

General Procedure for Preparation of RBOIB (A). The Amberlite IRA-400 resin purchased commercially contains the functional group of $-N^+(CH_3)_3Cl^-$. Its average moisture content is 42−48% and its complete exchange capacity is >3.6 mmol/g (dry). The particle diameter is 0.40−0.70 mm. The resin was packed in an exchange-column and flushed with 1 mol/L HCl. Then, the resin was washed with water. A solution of 1 mol/L inorganic base was used to exchange with the anion in the resin until all the Cl^- was exchanged. The flow rate was about 2−3 mL min^{-1}. Finally, the resin was washed by water.

(20) Previous Cu-catalyzed cross-couplings below r.t. required special substrates that could involve an ortho-substituent effect. See: Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050.

(21) For recent examples of Pd-catalyzed Heck reaction, see: (a) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (c) Cui, X.; Li, Z.; Tao, C.-Z.; Xu, Y.; Li, J.; Liu, L.; Guo, Q.-X. *Org. Lett.* **2006**, *8*, 2467.

(22) For examples of Cu-catalyzed C−S bond formation, see: (a) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (b) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254. (c) Rout, L.; Sen, T.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583. (d) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Chem.—Eur. J.* **2007**, *13*, 5100.

(23) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863.

(24) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609.

(25) The selection of base has also been known to be very important in many previous studies on organic transformations. For examples, see: (a) Tzalis, D.; Knochel, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 1463. (b) Rodriguez, A. L.; Christopher, K.; Wolfgang, D.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (c) Alcazar-Roman, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 12905. (d) Taillefer, M.; Rahier, N.; Hameau, A. *Chem. Commun.* **2006**, 3238. (e) Shekhar, S.; Hartwig, J. F. *Organometallics* **2007**, *26*, 340.

RB-TMAC (1). Following procedure A, the anion of the resin was exchanged by CO_3^{2-} from Na_2CO_3 solution. A small puce resin was obtained.

RB-TMAP (2). Following procedure A, the anion of the resin was exchanged by PO_4^{3-} from Na_3PO_4 solution. A small puce resin was obtained.

RB-TMAA (3). Following procedure A, the anion of the resin was exchanged by OAc^- from NaOAc solution. A small puce resin was obtained.

General Procedure for Preparation of RBOIB (B). The Merrifield resin was swelled in DMF for 24 h. An overdried three-neck round-bottom flask with a reflux condensing tube, a constant pressure funnel and a stir bar was charged with the Merrifield resin. The device was evacuated and backfilled with argon. Under a counter flow of argon, DMF was added by syringe and alkylamine was added to the constant pressure funnel. The flask was heated to 80−110 °C. Then alkylamine or alkylphosphine was added dropwise. The reaction was allowed to stir for 48 h. After the reaction, the resin was filtered, and washed with water and ethanol three times.

RB-TBAA (4). Following procedure B, tributylamine (80 mL) was allowed to react with Merrifield resin (20 g, 50−100 mesh) at 80 °C for 48 h. After exchanged with OAc^- from NaOAc solution, a small buff resin was obtained. The average moisture content is 43.8%. The loading value is 2.1 mmol/g (dry) and the particle diameter is 0.40−0.70 mm. Elemental analysis: C/N = 27.8 (w/w), N: 2.756%.

RB-TBPC (5). Following procedure B, tributylphosphine (80 mL) was allowed to react with Merrifield resin (20 g, 50−100 mesh) at 100 °C for 48 h. After exchanged with CO_3^{2-} from Na_2CO_3 solution, a small buff resin was obtained. The average moisture content is 42.5%. The loading value is 2.2 mmol/g (dry) and the particle diameter is 0.20−0.60 mm.

RB-TBPP (6). Following procedure B, tributylphosphine (80 mL) was allowed to react with Merrifield resin (20 g, 50−100 mesh) at 100 °C for 48 h. After exchanged with PO_4^{3-} from Na_3PO_4 solution, a small buff resin was obtained. The average moisture content is 44.6%. The loading value is 2.2 mmol/g (dry) and the particle diameter is 0.20−0.60 mm.

RB-TBPA (7). Following procedure B, tributylphosphine (80 mL) was allowed to react with Merrifield resin (20 g, 50−100 mesh) at 100 °C for 48 h. After exchanged with OAc^- from NaOAc solution, a small yellow resin was obtained. The average moisture content is 43.2%. The loading value is approximately equal 2.2 mmol/g (dry) and the particle diameter is 0.20−0.60 mm. Elemental analysis: C/P = 9.87 (w/w), P: 7.275%.

General Procedure for C−N Coupling (A). CuI (9.5 mg, 0.05 mmol, 10 mol %), L-proline (11.5 mg, 0.1 mmol, 20 mol %), **RB-TBPA** (0.34 g, 0.75 mmol, 1.5 equiv) and any remaining solids (aryl iodide) were added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine, aryl iodide (if liquid) and DMSO (1.0 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir under argon at room temperature (25 ± 3 °C) for 24 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

General Procedure for C−N Coupling (B). CuI (9.5 mg, 0.05 mmol, 10 mol %), **RB-TBPA** (0.34 g, 0.75 mmol, 1.5 equiv) and any remaining solids (aryl bromide) were added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, DMEDA (12 μL, 0.10 mmol, 20%), amine, aryl iodides (if liquid) and DMSO (1.0 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir under argon at room temperature (25 ± 3 °C) for 24 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

N-Benzylaniline (1a):[12] Following procedure A (B), iodobenzene (bromobenzene) (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a light yellow solid (92% (82%) yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.28 (m, 5H), 7.22−7.15 (m, 2H), 6.75−6.69 (m, 1H), 6.65−6.62 (m, 2H), 4.33 (d, 2H), 4.03 (br, 1H).^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.1, 139.4, 129.2, 128.6, 127.5, 127.2, 117.5, 112.8, 48.3.

N-Benzyl-4-chloroaniline (1b):[26] Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a yellow solid (101 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.23 (m, 5H), 7.09 (d, 2H, J = 8.6 Hz), 6.53 (d, 2H, J = 8.6 Hz), 4.28 (s, 2H), 4.10 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.6, 138.9, 128.7, 127.4, 127.3, 122.1, 133.9, 113.9, 48.3.

N-Benzyl-4-nitroaniline (1c):[27] Following procedure A, 1-iodo-4-nitrobenzene (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a yellow solid (103 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, 2H, J = 8.4 Hz), 7.37−7.26 (m, 5H), 6.57 (d, 2H, J = 8.4 Hz), 4.60−4.26 (br, 1H), 4.43 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 153.0, 138.4, 137.4, 128.9, 127.8, 127.3, 126.4, 111.3, 47.6.

Methyl 4-(benzylamino)benzoate (1d):[28] Following procedure A, methyl 4-iodobenzoate (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a white solid (110 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 2H, J = 8.7 Hz), 7.33−7.25 (m, 5H), 6.58 (d, 2H, J = 8.7 Hz), 4.51 (br, 1H), 4.37 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 167.3, 151.8, 138.4, 131.6, 128.8, 127.5, 127.4, 118.7, 111.7, 51.5, 47.7.

N-Benzyl-3, 5-dimethylaniline (1e):[26] Following procedure A, 1-iodo-3,5-dimethylbenzene (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a light-yellow solid (100 mg, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.16 (m, 5H), 6.37 (s, 1H), 6.26 (s, 2H), 4.27 (s, 2H), 3.83 (br, 1H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.3, 139.6, 138.8, 128.5, 127.5, 127.1, 119.6, 110.7, 48.4, 21.5.

3-(Benzylamino)benzonitrile (1f):[26] Following procedure A, 3-iodobenzonitrile (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a yellow solid (94 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 5H), 7.21−7.17 (m, 1H), 6.94 (d, 1H, J = 7.5 Hz), 6.79 (d, 2H, J = 6.9 Hz), 4.36 (br, 1H), 4.31 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.2, 138.1, 128.8, 127.6, 127.3, 120.9, 119.4, 117.2, 115.0, 112.9, 47.8.

Ethyl 3-(Venzylamino)benzoate (1g) Following procedure A, ethyl 3-iodobenzoate (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a white solid (123 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.18 (m, 8H), 6.77 (s, 1H), 4.35−4.30 (m, 4H), 4.19 (br, 1H), 1.36 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 166.9, 148.1, 138.9, 129.2, 128.7, 127.5, 127.4, 118.6, 117.0, 113.6, 60.8, 48.2, 14.3. HRMS (ESI) Calcd for $C_{16}H_{17}NO_2$, 255.1259; Found, 255.1260.

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N-Phenethylpyridin-3-amine (1h). Following procedure A (or B), 3-iodopyridine (or 3-bromopyridine) (0.5 mmol) was allowed to react with 2-phenylethanamine (0.75 mmol) for 24 h. The product was isolated as a white solid (I, 70%; Br, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, 1H, J = 2.1 Hz), 7.95 (d, 1H, J = 4.5 Hz), 7.32 (t, 2H, J = 7.3 Hz), 7.23 (dd, 3H, J = 15.5, 7.3 Hz), 7.07 (dd, 1H, J = 8.2, 4.7 Hz), 6.90−6.82 (m, 1H), 3.78 (br, 1H), 3.41 (t, 2H, J = 6.9 Hz), 2.92 (t, 2H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 143.9, 138.8, 138.7, 136.1, 128.7, 128.6, 126.6, 123.7, 118.6, 44.5, 35.3. HRMS (ESI) calcd for $C_{13}H_{14}N_2$, 198.1157; Found, 198.1156.

N-phenethylpyridin-2-amine (1i):[29] Following procedure A (or B), 2-iodopyridine (or 2-bromopyridine) (0.5 mmol) was allowed to react with 2-phenylethanamine (0.75 mmol) for 24 h. The product was isolated as a white solid (I, 88%; Br, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, 1H, J = 5.0 Hz), 7.42−7.30 (m, 1H), 7.25−7.22 (m, 2H), 7.21−7.20 (m, 3H), 6.58−6.54 (m, 1H), 6.36 (d, 1H, J = 8.4 Hz), 4.51 (br, 1H), 3.58−3.53 (dd, 2H, J = 12.9, 7.0 Hz), 2.94−2.90 (d, 2H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 158.6, 148.2, 139.2, 137.4, 128.8, 128.6, 126.4, 112.9, 106.8, 43.3, 35.7.

1-(4-Chlorophenyl)-1*H*-imidazole (1j):[30] Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with imidazole (0.75 mmol) for 24 h. The product was isolated as a yellow solid (66 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H), 7.46 (d, 2H, J = 8.0 Hz), 7.34 (d, 2H, J = 8.0 Hz), 7.28−7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 135.9, 135.5, 133.2, 130.7, 130.0, 122.7, 118.3.

1-(4-Chlorophenyl)-1H-pyrazole (1k):[31] Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with pyrazole (0.75 mmol) for 24 h. The product was isolated as a yellow solid (63 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, 1H, J = 1.9 Hz), 7.71 (s, 1H), 7.63 (d, 2H, J = 8.7 Hz), 7.40 (d, 2H, J = 8.7 Hz), 6.46 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 141.3, 138.7, 131.8, 129.5, 126.6, 120.3, 107.9.

N-Sec-butyl-4-chloroaniline (1l). Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with butan-2-amine (0.75 mmol) for 24 h. The product was isolated as a yellow liquid (68 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, 2H, J = 8.2 Hz), 6.47 (d, 2H, J = 8.2 Hz), 3.42 (br, 1H), 3.33 (dq, 1H, J = 12.1, 6.3 Hz), 1.62−1.53 (m, 1H), 1.51−1.40 (m, 1H), 1.14 (d, 3H, J = 6.3 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.3, 129.0, 121.1, 114.1, 50.0, 29.5, 20.1, 10.3. HRMS (ESI) calcd for $C_{10}H_{14}ClN$, 183.0815; found, 183.0810.

4-(4-Chlorophenyl)morpholine (1m):[32] Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with morpholine (0.75 mmol) for 24 h. The product was isolated as a white solid (85 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, 2H, J = 8.5 Hz), 6.82 (d, 2H, J = 8.5 Hz), 3.85 (s, 4H), 3.11 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 149.9, 129.0, 124.9, 116.9, 66.8, 49.3.

4-Methyl-*N*-phenylaniline (1n):[33] Following procedure A, iodobenzene (0.5 mmol) was allowed to react with *p* -toluidine (0.75 mmol) for 24 h. The product was isolated as a white solid (68 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, 2H, J = 8.2 Hz), 7.08 (d, 2H, J = 8.0 Hz), 7.00−6.99 (m, 4H), 6.87 (t, 1H, J = 7.3 Hz), 5.59 (br, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 143.9, 140.3, 130.9, 129.8, 129.3, 120.3, 118.9, 116.9, 20.6.

4-Chloro-*N*-(4-methoxyphenyl)aniline (1o):[34] Following procedure A, 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with 4-methoxyaniline (0.75 mmol) for 24 h. The product was isolated as a white solid (91 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, 2H, J = 8.4 Hz), 7.03 (d, 2H, J = 8.1 Hz), 6.85 (d, 2H, J = 8.4 Hz), 6.79 (d, 2H, J = 8.1 Hz), 5.45 (br, 1H), 3.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 155.6, 143.9, 135.2, 129.1, 123.9, 122.5, 116.6, 114.7, 55.5.

N-Benzyl-4-methoxyaniline (2a):[35] Following procedure B, 1-bromo-4-methoxybenzene (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a colorless liquid (70 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 4H), 7.26−7.24 (m, 1H), 6.78−6.76 (m, 2H), 6.61−6.59 (m, 2H), 4.27 (s, 2H), 3.38 (br, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 152.2, 142.3, 139.6, 128.6, 127.5, 127.1, 114.9, 114.2, 55.8, 49.3.

4-(Benzylamino)phenyl 4-methylbenzenesulfonate (2b). Following procedure B, 4-bromophenyl 4-methylbenzene sulfonate (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a white solid (148 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, 2H, J = 7.7 Hz), 7.32−7.25 (m, 7H), 6.75 (d, 2H, J = 8.1 Hz), 6.47 (d, 2H, J = 8.1 Hz), 4.26 (s, 2H), 4.09 (br, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.7, 144.9, 141.1, 138.7, 132.6, 129.6, 128.7, 128.6, 127.5, 127.4, 123.2, 113.1, 48.4, 21.7. HRMS (ESI) calcd for $C_{20}H_{19}NO_3S$, 353.1086; found, 353.1084.

Ethyl 4-(Benzylamino)benzoate (2c):[26] Following procedure B, ethyl 4-bromobenzoate (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a white solid (95 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, 2H, J = 8.8 Hz), 7.35−7.27 (m, 5H), 6.59 (d, 2H, J = 8.8 Hz), 4.49 (br, 1H), 4.38 (s, 2H), 4.30 (q, 2H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 166.8, 151.7, 138.4, 131.5, 128.8, 127.5, 127.4, 119.1, 111.6, 60.2, 47.7, 14.5.

(4-(Benzylamino)phenyl)(phenyl)methanone (2d):[36] Following procedure B, (4-bromophenyl)(phenyl)methanone (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a white solid (96 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (m, 4H), 7.51−7.49 (m, 1H), 7.45−7.41 (m, 2H), 7.34−7.25 (m, 5H), 6.61 (d, 2H, J = 8.3 Hz), 4.67 (br, 1H), 4.40 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 195.1, 151.8, 139.1, 138.2, 132.9, 131.2, 129.4, 128.8, 128.0, 127.5, 127.3, 126.4, 111.5, 47.6.

N′-Benzyl-N″,N″-dimethylbenzene-1,4-diamine (2e):[12] Following procedure B, 4-bromo-*N*,*N*-dimethylaniline (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a yellow solid (80 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.30 (m, 4H), 7.24 (t, 1H, J = 8.0 Hz), 6.73 (d, 2H, J = 7.6 Hz), 6.61 (d, 2H, J = 7.6 Hz), 4.26 (s, 2H), 3.51 (br, 1H), 2.80 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 144.1, 140.8, 139.9, 128.5, 127.5, 127.0, 115.8, 114.3, 49.4, 42.2.

3-(Benzylamino)benzaldehyde (2f). Following procedure B, 3-bromobenzaldehyde (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 36 h. The product was isolated as a yellow liquid (68 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.36−7.29 (m, 6H), 7.20 (d, 1H, J = 7.3 Hz), 7.12 (s, 1H), 6.86 (d, 1H, J = 8.0 Hz), 4.37 (s, 2H), 4.27 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 192.8, 148.6, 143.4, 138.6, 137.5, 129.7, 128.7, 127.5, 120.2, 119.2, 111.6, 48.1. HRMS (ESI) calcd for $C_{14}H_{13}NO$, 211.0907; found, 211.0902.

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1-(3-(Benzylamino)phenyl)ethanone (2g):[37] Following procedure B, 1-(3-bromophenyl)ethanone (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a yellow liquid (81 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.31 (m, 4H), 7.28−7.20 (m, 4H), 6.78 (m, 1H), 4.34 (s, 2H), 4.24 (br, 1H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 166.9, 148.1, 138.9, 129.1, 128.6, 127.5, 127.3, 118.6, 117.0,113.6, 60.8, 48.2, 14.3.

N-Butylnaphthalen-2-amine (2h). Following procedure B, 2-Bromonaphthalene (0.5 mmol) was allowed to react with butan-1-amine (0.75 mmol) for 24 h. The product was isolated as a colorless liquid (81 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, 1H, J = 8.0 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.33 (t, 1H, J = 7.5 Hz), 7.16 (t, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 8.5 Hz), 6.81 (s, 1H), 3.97 (br, 1H), 3.21 (t, 2H, J = 7.1 Hz), 1.70−1.67 (m, 2H), 1.50−1.42 (m, 2H), 0.98(t, 3H, J = 7.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.0, 135.3, 128.8, 127.6, 127.5, 126.3, 125.9, 121.8, 118.0, 104.4, 43.8, 31.5, 20.3, 13.9. HRMS (ESI) calcd for $C_{14}H_{17}N$, 199.1361; found, 199.1355.

N-Phenethylthiophen-3-amine (2i). Following procedure B, 3-bromothiophene (0.5 mmol) was allowed to react with 2-phenylethanamine (0.75 mmol) for 24 h. The product was isolated as a white solid (62 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.28 (m, 2H), 7.21 (m, 2H), 7.12−7.10 (dd, 1H, J = 5.1, 3.0 Hz), 6.56−6.54 (d, 1H, J = 5.1 Hz), 5.97−5.95 (d, 1H, J = 3.0 Hz), 3.56−3.20 (br, 1H), 3.34−3.31 (t, 2H, J = 7.0 Hz), 2.92−2.88 (t, 2H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.3, 139.3, 128.7, 128.6, 126.4, 125.1, 119.9, 95.8, 47.3, 35.5. HRMS (ESI) calcd for $C_{12}H_{13}NS$, 203.0769; found, 203.0762.

4-Chloro-N-(cyclopropylmethyl)aniline (2j):[38] Following procedure B, 1-bromo-4-chlorobenzene (0.5 mmol) was allowed to react with cyclopropylmethanamine (0.75 mmol) for 24 h. The product was isolated as a white solid (63 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, 2H, J = 8.4 Hz), 6.51 (d, 2H, J = 8.4 Hz), 3.77 (br, 1H), 2.91 (d, 2H, J = 6.8 Hz), 1.07 (m, 1H), 0.54 (m, 2H), 0.23−0.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 147.0, 129.0, 121.7, 113.8, 49.1, 10.8, 3.4.

N-(Cyclopropylmethyl)-4-(trifluoromethy)aniline (2k). Following procedure B, 1-bromo-4-(trifluoromethyl)benzene (0.5 mmol) was allowed to react with cycloproylmethanamine (0.75 mmol) for 24 h. The product was isolated as a yellow solid (71 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, 2H, J = 8.2 Hz), 6.58 (d, 2H, J = 8.2 Hz), 4.11 (br, 1H), 2.98 (d, 2H, J = 6.9 Hz), 1.10−1.07 (m, 1H), 0.57 (d, 2H, J = 7.2 Hz), 0.25 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 158.8, 126.6, 126.5, 118.4(q), 111.7, 48.5, 10.7, 3.5. HRMS (ESI) calcd for $C_{11}H_{12}F_3N$, 215.0922; found, 215.0927.

N-Hexylbenzo[d][1,3]dioxol-5-amine (2l):[39] Following procedure B, 5-bromobenzo[d][1,3]dioxole (0.5 mmol) was allowed to react with hexan-1-amine (0.75 mmol) for 24 h. The product was isolated as a white solid (72 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (d, 1H, J = 8.3 Hz), 6.23 (s, 1H), 6.02 (d, 1H, J = 8.3 Hz), 5.85 (s, 2H), 3.27 (br, 1H), 3.02 (t, 2H, J = 7.1 Hz), 1.57 (dd, 2H, J = 8.3, 7.1 Hz), 1.38−1.31 (m, 6H), 0.89 (t, 3H, J = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 148.3, 144.3, 139.4, 108.6, 104.3, 100.5, 95.8, 45.1, 31.6, 29.5, 26.8, 22.6, 14.0.

N-Hexylbiphenyl-4-amine (2m). Following procedure B, 4-bromobiphenyl (0.5 mmol) was allowed to react with hexan-1-amine (0.75 mmol) for 24 h. The product was isolated as a white solid (105 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, 2H, J = 7.6 Hz), 7.43 (d, 2H, J = 7.8 Hz), 7.37 (t, 2H, J = 7.6 Hz), 7.23 (m, 1H), 6.65 (d, 2H, J = 7.8 Hz), 3.67 (br, 1H), 3.13 (t, 2H, J = 7.0 Hz), 1.64−1.59 (m, 2H), 1.47−1.32 (m, 6H), 0.9 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 147.9, 141.3, 129.9, 128.6, 127.9, 126.5, 125.9, 112.9, 44.0, 31.6, 29.5, 26.8, 22.6, 14.0. HRMS (ESI) Calcd for $C_{18}H_{23}N$, 253.1830; Found, 253.1824.

2-(Biphenyl-4-ylamino)ethanol (2n). Following procedure B, 4-bromobiphenyl (0.5 mmol) was allowed to react with 2-aminoethanol (0.75 mmol) for 24 h. The product was isolated as a white solid (85 mg, 80% yield). ^{1}H NMR (400 MHz, d-DMSO): δ = 7.54 (d, 2H, J = 7.7 Hz), 7.41 (d, 2H, J = 8.3 Hz), 7.37 (t, 2H, J = 7.7 Hz), 7.21(t, 1H, J = 7.3 Hz), 6.67 (d, 2H, J = 8.3 Hz), 5.67 (t, 1H, J = 5.4 Hz), 4.71 (t, 1H, J = 5.4 Hz), 3.59 (q, 2H, J = 5.7 Hz), 3.14 (q, 2H, J = 5.7 Hz). ^{13}C NMR (100 MHz, d-DMSO, δ ppm): 134.9, 127.0, 115.1, 113.7, 113.5, 112.0, 111.7, 98.8, 46.0, 31.9. HRMS (ESI) calcd for $C_{14}H_{15}NO$, 213.1154; found, 213.1148.

4-(4-Bromophenyl)morpholine (3a):[40] Following procedure A, 1-bromo-4-iodobenzene (0.5 mmol) was allowed to react with morpholine (0.75 mmol) for 24 h. The product was isolated as a white solid (89 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, 2H, J = 8.7 Hz), 6.81 (d, 2H, J = 8.7 Hz), 3.92−3.82 (t, 4H, J = 4.7 Hz), 3.20−3.04 (t, 4H, J = 4.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 151.0, 132.0, 117.5, 112.5, 66.6, 49.3.

N-Butyl-4-morpholinoaniline (3b). Following procedure B, 4-(4-bromophenyl)morpholine (0.44 mmol) was allowed to react with butan-1-amine (0.66 mmol) for 24 h. The product was isolated as a white solid (73 mg, 67% yield after two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 2H), 6.59 (s, 2H), 3.84 (m, 4H), 3.01 (m, 7H), 1.59−1.47 (m, 2H), 1.43−1.37 (m, 2H), 0.95 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 143.4, 118.4, 113.8, 67.1, 51.3, 44.5, 41.0, 31.8, 20.3, 13.9. HRMS (ESI) calcd for $C_{14}H_{22}N_2O$, 234.1732; found, 234.1726.

Indoline (3c):[6e] Following procedure B, 2-(2-chlorophenyl)-ethanamine or 2-(2-bromophenyl)ethan-amine (0.5 mmol) was reacted for 48 h or 24 h. The product was isolated as a colorless liquid (76% or 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, 1H, J = 7.3 Hz), 7.00 (t, 1H, J = 7.7 Hz), 6.69 (t, 1H, J = 7.3 Hz), 6.62(d, 1H, J = 7.7 Hz), 3.58 (br, 1H). 3.51 (t, 2H, J = 8.4 Hz), 3.00 (t, 2H, J = 8.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 151.5, 129.2, 127.1, 124.6, 118.6, 109.4, 47.3, 29.8.

N-(2-Chlorophenethyl)aniline (3d). Following procedure B, 2-(2-chlorophenyl)-ethanamine (0.5 mmol) was allowed to react with iodobenzene for 24 h. The product was isolated as a colorless liquid (92 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, 1H, J = 7.3 Hz), 7.19−7.15 (m, 5H), 6.70 (t, 1H, J = 7.3 Hz), 6.62 (d, 2H, J = 7.9 Hz), 3.72 (br, 1H), 3.41 (m, 2H), 3.03 (t, 2H, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 146.8, 135.9, 133.1, 129.8, 128.6, 128.2, 126.8, 125.8, 116.4, 111.8, 42.3, 32.4. HRMS (ESI) calcd for $C_{14}H_{14}ClN$, 231.0815; found, 231.0823.

Experimental Procedures for Ni-Catalyzed Suzuki reaction. $Ni(PPh_3)_2Cl_2$ (5 mol %), PPh_3 (10 mol %), boronic acid (0.5 mmol), Zn (1.2 e.q), **RB-TBPP** (1.5 equiv) and any remaining solids (aryl bromide) were added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, THF and aryl bromide (if liquid) were added to the tube by syringe. The tube was sealed and the mixture was allowed to stir under argon at room temperature for 24 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate, the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

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3-Methoxybiphenyl (4a):[41] Following procedure, bromobenzene (0.25 mol) was allowed to react with 3-methoxyphenylboronic acid (0.50 mmol) for 24 h. The product was isolated as a colorless liquid (36 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (d, 2H, J = 7.5 Hz), 7.43 (t, 2H, J = 7.4 Hz), 7.37−7.33 (m, 2H), 7.18 (d, 1H, J = 7.5 Hz), 7.13 (s, 1H), 6.90 (d, 1H, J = 8.0 Hz), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 158.9, 141.7, 140.1, 128.7, 127.7, 126.4, 126.2, 118.6, 111.9, 111.6, 54.3.

4-Methoxybiphenyl (4b):[42] Following procedure, 4-bromoanisole (0.25 mol) was allowed to react with phenylboronic acid (0.50 mmol) for 24 h. The product was isolated as a white solid (39 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 4H), 7.41 (d, 2H, J = 7.6 Hz), 7.30 (m, 1H), 6.97 (d, 2H, J = 8.5 Hz), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl3, δ ppm): 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3.

Methyl 4′-Cyanobiphenyl-4-carboxylate (4c):[43] Following procedure, methyl 4-bromobenzoate (0.25 mol) was allowed to react with 4-cyanophenylboronic acid (0.50 mmol) for 24 h. The product was isolated as a white solid (43 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 2H, J = 8.0 Hz), 7.78−7.70 (m, 4H), 7.66 (d, 2H, J = 8.0 Hz), 3.96(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 166.6, 144.5, 143.4, 132.7, 130.3, 130.2, 127.9, 127.2, 118.6, 111.8, 52.3.

1-(4′-Methoxybiphenyl-4-yl)ethanone (4d):[44] Following procedure, 1-(4-bromophenyl)ethanone (0.25 mol) was allowed to react with 4-methoxyphenylboronic acid (0.50 mmol) for 24 h. The product was isolated as a white solid (45 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, 2H, J = 8.2 Hz), 7.64 (d, 2H, J = 8.2 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.5 Hz), 3.86 (s, 3H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 197.7, 159.9, 145.4, 135.3, 132.3, 128.9, 128.4, 126.6, 114.4, 55.4, 26.6.

General Procedure for C−N Coupling at Low Temperature. CuI (9.5 mg, 0.05 mmol, 10 mol %), L-proline (11.5 mg, 0.1 mmol, 20 mol %), **RB-TBPA** (0.34 g, 0.75 mmol, 1.5 equiv) and any remaining solids (aryl iodide) were added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine, aryl iodide (if liquid) and DMSO/DMF (0.5:0.5 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir under argon at −30 °C for 24 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

N-Benzyl-4-methoxyaniline (2a):[35] Following general procedure, 1-iodo-4-methoxybenzene (0.5 mmol) was allowed to react with benzylamine (0.75 mmol) for 24 h. The product was isolated as a colorless liquid (85 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 4H), 7.26−7.24 (m, 1H), 6.78−6.76 (m, 2H), 6.61−6.59 (m, 2H), 4.27 (s, 2H), 3.38 (br, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 152.2, 142.3, 139.6, 128.6, 127.5, 127.1, 114.9, 114.2, 55.8, 49.3.

N-Butyl-4-nitroaniline (5a):[45] 1-iodo-4-nitrobenzene (0.5 mmol) was allowed to react with butan-1-amine (0.75 mmol) for 24 h. The product was isolated as a yellow liquid (87 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, 2H, J = 8.0 Hz), 6.51 (d, 2H, J = 8.0 Hz), 4.57 (s, 1H), 3.21 (t, 2H, J = 8.0 Hz), 1.66−1.60 (m, 2H), 1.49−1.39 (m, 2H), 0.97 (t, 3H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):153.5, 137.7, 126.5, 110.9, 43.1, 31.2, 20.1, 13.8.

4-Chloro-*N*-cyclohexylaniline (5b):[8c] 1-chloro-4-iodobenzene (0.5 mmol) was allowed to react with cyclohexanamine (0.75 mmol) for 24 h. The product was isolated as a white solid (79 mg, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, 2H, J = 8.3 Hz), 6.49 (d, 2H, J = 8.3 Hz), 3.52 (br, 1H), 3.22−3.17 (m, 1H), 2.04−2.01 (m, 2H), 1.74 (m, 2H), 1.63 (m, 1H), 1.23−1.09(m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 145.9, 129.0, 121.2, 114.1, 51.8, 33.3, 25.8, 24.9.

Ethyl 3-(Sec-butylamino)benzoate (5c). ethyl 3-iodobenzoate (0.5 mmol) was allowed to react with butan-2-amine (0.75 mmol) for 24 h. The product was isolated as a white solid (77 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, 1H, J = 7.6 Hz), 7.25 (s, 1H), 7.19 (t, 1H, J = 7.8 Hz), 6.73 (d, 1H, J = 7.9 Hz), 4.34 (q, 2H, J = 7.1 Hz), 3.63 (br, 1H), 3.44 (m, 1H), 1.62−1.43 (m, 2H), 1.37 (t, 3H, J = 7.1 Hz), 1.16 (d, 3H, J = 6.3 Hz), 0.95 (t, 3H, J = 7.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm):167.1, 147.7, 131.4, 129.1, 117.8, 117.3, 113.7, 60.7, 49.7, 29.6, 20.1, 14.3, 10.3. HRMS (ESI) calcd for $C_{13}H_{19}NO_2$, 221.1416; found, 221.1414.

Experimental Procedures for Pd-Catalyzed Heck Reaction. A oven-dried vacuum tube with a glass cap and a stir was charged with $Pd(OAc)_2$ (5 mol %), Davephos (10 mol %) and **RB-TBAA** (1.5 equiv). The tube was evacuated and backfilled with argon or nitrogen (this sequence was repeated three times). Under a counter flow of argon, 1-chloro-4-trifluoromethyl- benzene (0.5 mmol), styrene (0.75 mmol) along with 1,4-dioxane (1.0 mL) was added to the tube. The mixture was allowed to stir at 60 °C for 24 h. After reaction, the mixture was cooled to room temperature and diluted with ethyl acetate, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

(E)-1-Styryl-4-(trifluoromethyl)benzene (6a):[46] 1-chloro-4-trifluoromethyl- benzene (0.50 mmol) was allowed to react with styrene (1.0 mmol) for 24 h. The product was isolated as a white solid (99 mg, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60−7.57 (m, 4H), 7.53 (d, 2H, J = 7.8 Hz), 7.38 (t, 2H, J = 7.5 Hz), 7.32−7.28 (t, 1H, J = 7.3 Hz), 7.19 (d, 1H, J = 16.4 Hz), 7.11 (d, 1H, J = 16.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 140.8, 136.6, 131.2, 128.3, 127.1, 129.2 (q, ^2J(C,F) = 32.4 Hz), 128.8, 126.8, 126.5, 125.5 (q, ^3J(C,F) = 3.8 Hz), 124.2 (q, ^1J(C,F) = 272 Hz).

Experimental Procedure for C−S coupling. CuI (19 mg, 20 mol %), 1,10-phenanthroline (23 mg, 40 mol %), **RB-TBPP** (1.5 equiv) and any remaining solids (aryl iodides) were added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counter flow of argon, amine, aryl iodides (if liquid) and NMP/MeOH (0.5:0.5 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir under argon at room temperature (25 ± 3 °C) for 36 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate, and the solvent was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel and the product was dried under high vacuum for at least 0.5 h.

4-Methylphenyl Phenyl Sulfide (7a):[47] 4-methylbenzenethiol (0.50 mmol) was allowed to react with iodobenzene (1.0 mmol) for 36 h. The product was isolated as a colorless liquid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H), 7.09−7.18 (m, 3H), 7.20−7.29 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.2, 126.4, 129.0, 129.7, 130.0, 131.4, 132.3, 137.2, 137.5.

4-Chlorophenyl Phenyl Sulfide (7b):[24] 4-chlorobenzenethiol (0.50 mmol) was allowed to react with iodobenzene (1.0 mmol) for 36 h. The product was isolated as a pale yellow liquid (66% yield).

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^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24−7.28 (m, 4H), 7.28−7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 127.3, 129.2, 129.3, 131.3, 131.9, 132.9, 134.6, 135.1.

3-Methylphenyl Phenyl Sulfide (7c):[47] 3-methylbenzenethiol (0.50 mmol) was allowed to react with iodobenzene (1.0 mmol) for 36 h. The product was isolated as a colorless liquid (69% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 1H), 7.15−7.24 (m, 4H), 7.27−7.33 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.4, 126.9, 128.0, 128.4, 129.1, 129.2, 130.8, 131.9, 135.3, 136.2, 139.1.

1-Naphthalenyl Phenyl Sulfide (7d):[47] naphthalene-1-thiol (0.50 mmol) was allowed to react with iodobenzene (1.0 mmol) for 36 h. The product was isolated as a pale yellow liquid (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10−7.20 (m, 5H), 7.37−7.42 (m, 1H), 7.46−7.50 (m, 2H), 7.63−7.65(m, 1H), 7.81−7.86 (m, 2H), 8.35−8.39 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 125.6, 125.8, 126.1, 126.4, 126.9, 128.6, 129.0, 129.1, 129.2, 131.2, 132.5, 133.6, 134.2, 136.9.

(4-Chlorophenyl)(p-tolyl)sulfane (7e):[48] 4-methylbenzenethio (0.50 mmol) was allowed to react with 1-chloro-4-iodobenzene (1.0 mmol) for 36 h. The product was isolated as a white solid (42% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3H), 7.13−7.18 (m, 4H), 7.22 (d, 2H, J = 8.0 Hz), 7.29 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.3, 129.3, 130.4, 130.8, 131.0, 132.5, 132.6, 136.1, 138.2.

(3,5-Dimethylphenyl)(p-tolyl)sulfane (7f). naphthalene-1-thiol (0.50 mmol) was allowed to react with 1-iodo-3,5-dimethylbenzene (1.0 mmol) for 36 h. The product was isolated as a pale yellow liquid (50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H), 2.34 (s, 3H), 6.84 (s, 1H), 6.92 (d, 2H, J = 2.0 Hz), 7.12 (d, 2H, J = 2.0 Hz), 7.26 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm): 21.3, 21.3, 128.1, 128.7, 130.1, 131.9, 132.0, 136.3, 137.3, 138.9. HRMS (ESI) calcd for $C_{15}H_{16}S$, 228.0973; found, 228.0964.

(3,5-Bis(trifluoromethyl)phenyl)(p-tolyl)sulfane (7g). 4-methylbenzenethiol (0.50 mmol) was allowed to react with 1-iodo-3,5-bis(trifluoromethyl)benzene (1.0 mmol) for 36 h. The product was isolated as a colorless liquid (54% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H), 7.24 (d, 2H, J = 8.0 Hz), 7.40 (m, d, 2H, J = 8.0 Hz), 7.52 (s, 2H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.4, 119.3 (m), 123.0 (q, J = 272.0 Hz), 127.18 (m), 129.0, 131.0, 132.3 (q, J = 33 Hz), 134.5, 140.1, 142.8. HRMS (ESI) calcd for $C_{15}H_{10}F_6S$, 366.0407; found, 366.0406.

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Supporting Information Available: Experimental details and compound spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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