Homogeneous Catalysis

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Room-Temperature Copper-Catalyzed Carbon–Nitrogen Coupling of Aryl Iodides and Bromides Promoted by Organic Ionic Bases**

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Transition-metal-catalyzed couplings provide important tools in modern organic synthesis.[1] The bases commonly employed for these couplings are salts of alkaline or alkaline-earth metals (e.g. K_3PO_4, NaO*t*Bu, and Cs_2CO_3). They are thought to facilitate the otherwise slow transmetalation (e.g. in Suzuki couplings), reductive elimination (e.g. in Heck couplings), or nucleophile deprotonation/coordination (e.g. in carbon–heteroatom couplings). At present, the choice of base remains empirical. Problems are often encountered for the couplings in less polar solvents where most inorganic bases are poorly soluble. To solve these problems we propose the use of organic ionic bases composed of organic cations and basic anions.[2] These bases are well soluble in organic solvents. More importantly, they exhibit novel useful reactivities.

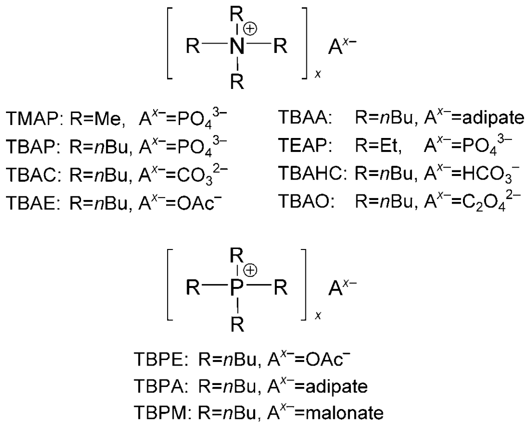

Figure 1. Structures of the organic ionic bases in this study.

Figure 1 shows the organic ionic bases synthesized in the present study. Most of them are new compounds.[3] They were prepared mainly through the reaction between an equimolar quantity of tetraalkylammonium or -phosphonium hydroxide and the appropriate acid. To demonstrate the advantage of using organic ionic bases, we report novel room-temperature (RT) Cu-catalyzed C–N couplings[4] promoted by these bases.

Our work starts with the coupling of aryl iodides with amines. Recently Buchwald et al. reported the first protocol for this coupling at room temperature;[5] other research groups have described related work.[6] In the present study we have examined different organic ionic bases. We found that TMAP and TEAP do not mediate the coupling (Figure 2a) at room temperature (25 ± 1 °C), although they are both well soluble. Significant yields (ca. 40–80%) are obtained when TBAP is used, indicating the importance of choosing a bulky cation. When the cation is fixed as $\mathrm{N}n\mathrm{Bu}_4^+$, the yield varies dramatically with different anions. These observations reveal that solubility alone does not explain the utility of organic ionic bases.

The best yield (95%) is obtained with TBAA, which is a carboxylate base. Remarkably, the use of a very simple and cheap ligand (i.e. L-proline as opposed to 2-isobutyrylcyclohexanone in the previous protocol[5]) is sufficient for the reaction to proceed in high yields at room temperature. Also, the current protocol is not sensitive to water (see Scheme 1, footnote [a]). Application of the optimized protocol to diverse aryl iodides (Scheme 1) was successful. Both electron-rich and electron-poor aryl iodides show high to excellent yields when coupled with aliphatic amines.

Side products may arise from the reaction of the nucleophile with the tetraalkylammonium cation. However, GC–MS analysis of the reaction mixtures from the described coupling reactions shows no such side products (see the Supporting Information). To further minimize this potential problem, we examined the organic ionic bases having tetraalkylphosphonium as the cation; they are known to be much more stable than tetraalkylammonium salts.[7] Remarkably, the phosphonium bases perform even much better than the ammonium bases. For the coupling of PhI with $BnNH_2$ at room temperature, TBPE can drive the reaction to completion within approximately 30 min (Figure 2c) whereas TBAA requires roughly 24 h. Additional evidence for the extremely facile C–N coupling is the fact that TBPE can promote the amination of aryl iodides even at 0 °C in 5 h (Scheme 2).

The unprecedented facility of the coupling implies that even aryl bromides may be activated at room temperature. Indeed TBPE promotes the coupling of PhBr with $BnNH_2$ at room temperature (70% yield). Further tests of other phosphonium bases show that TBPM gives the best result

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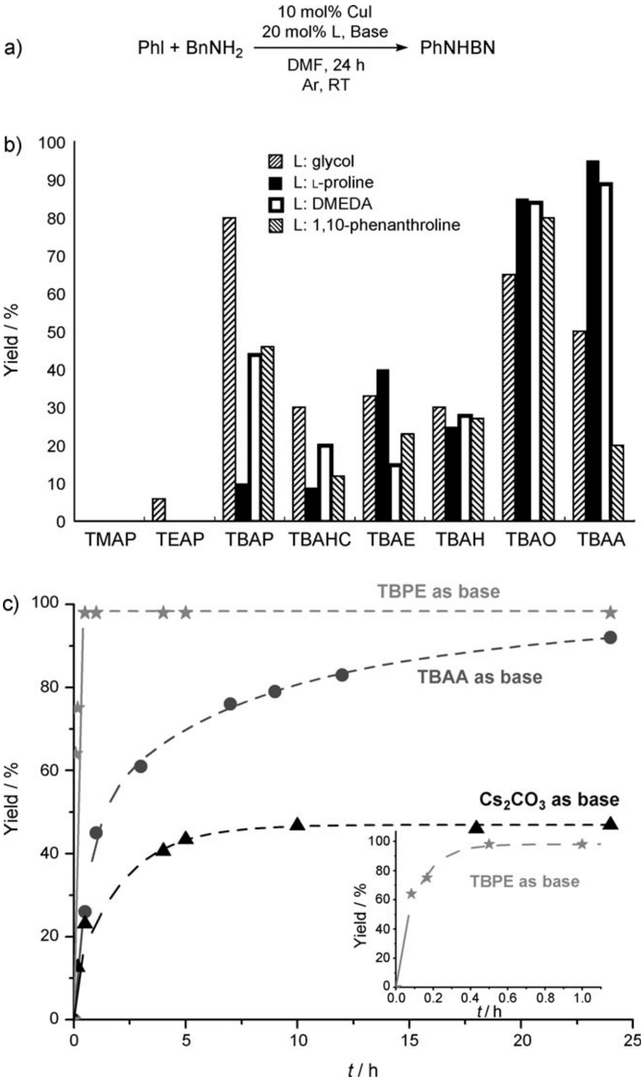
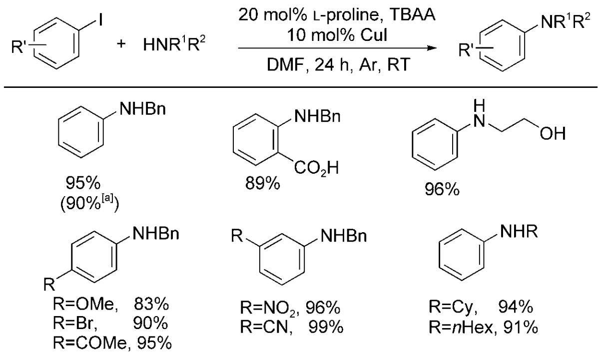
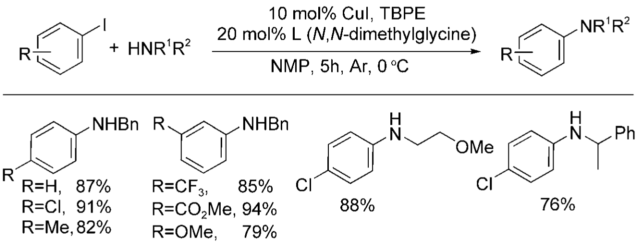


Figure 2. a) Coupling reaction used in this study. b) Effect of base and ligand on the C–N coupling at room temperature. The ratio for $PhI/BnNH_2$/base = 1.0:1.5:2.0. c) Rates of the $PhI–BnNH_2$ coupling reaction; L = L-proline.

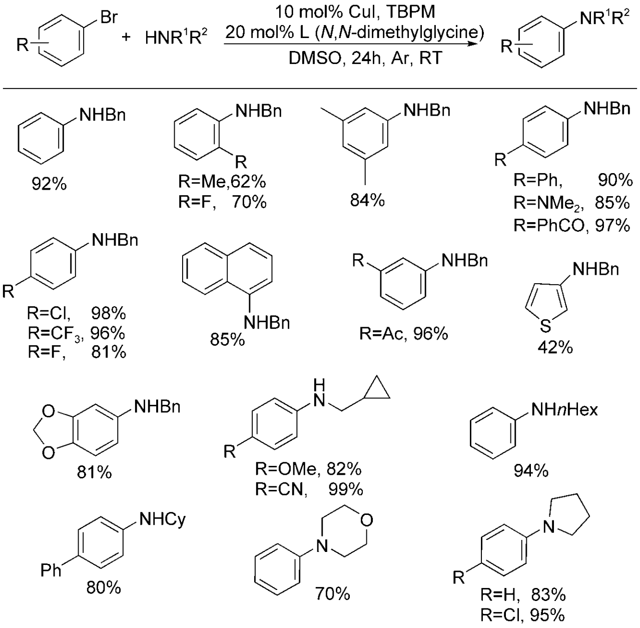


Scheme 1. Products and yields obtained from the coupling of aryl iodides with amines at room temperature. Reaction conditions: ArI (0.5 mmol), amine (0.75 mmol), TBAA (0.75 mmol), DMF (0.5 mL). [a] 1 equiv water was added.



Scheme 2. Products and yields obtained from the coupling of aryl iodides with amines at 0 °C. Reaction conditions: ArI (0.5 mmol), amine (0.75 mmol), TBPE (1 mmol), N-methylpyrrolidone (0.5 mL).

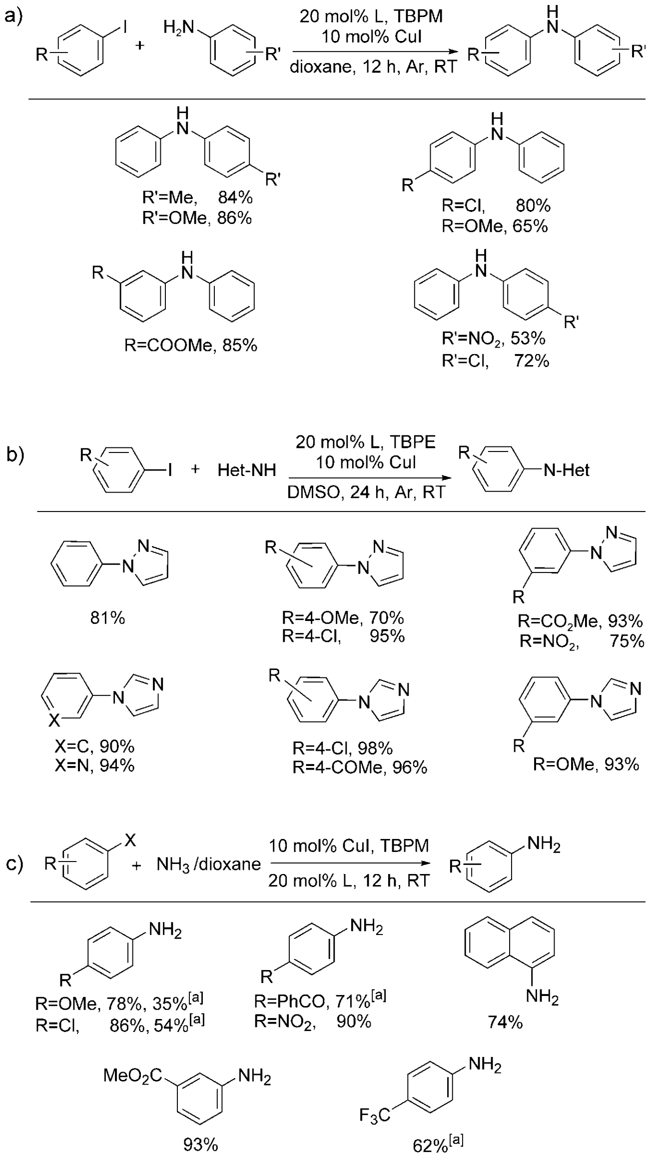
(92 % yield). The ligand (*N*,*N*-dimethylglycine) for this coupling is still a very simple one. As to the generality of the reaction, both electron-rich and electron-poor aryl bromides can be successfully converted (Scheme 3). Various primary and secondary amines can be used. *ortho* Substitution can also be tolerated to some extent. The coupling yields are usually over 80 %. Thus we show the first example for the Cu-catalyzed coupling of nonactivated aryl bromides at room temperature.[8]



Scheme 3. Products and yields obtained from the coupling of aryl bromides with amines at toom temperature. Reaction conditions: ArBr (0.5 mmol), amine (0.75 mmol), TBPM (0.75 mmol), DMSO (0.5 mL).

Other notable applications of the phosphonium bases include: 1) room-temperature coupling of aryl iodides with anilines[9] and N-heterocycles,[10] and 2) room-temperature synthesis of anilines[11] from aryl iodides and even bromides (Scheme 4). These transformations have not been achieved before at room temperature. Control experiments show that the couplings do not proceed at room temperature with traditional inorganic bases.

To explain the significant favorable effect of organic ionic bases, we recognize that the function of the base in the C–N



Scheme 4. Products and yields for other Cu-catalyzed C–N couplings at room temperature. Reaction conditions: a) ArI (0.75 mmol), aniline (0.5 mmol), ligand = 2,2′-biphenol, TBPM (0.75 mmol), dioxane (0.3 mL). b) ArI (0.75 mmol), N-heterocycle (0.5 mmol), ligand = *N,N*-dimethylglycine, TBPE (1.25 mmol), DMSO (0.5 mL). c) ArI (0.5 mmol), ligand = *N,N*-dimethylglycine, TMPM (0.75 mmol), NH_3/dioxane (1.5 mL, 0.5 M). [a] ArBr (0.5 mmol) was used instead of ArI.

couplings is to deprotonate the nucleophile.[12] This step has been shown to be crucial in Cu-catalyzed couplings,[13,14] and the rate of the coupling was calculated to be linearly dependent on the concentration of the Cu^I complex with the deprotonated nucleophile.[12] To optimize the catalysis one must use bases that promote deprotonation the most efficiently. As discussed above, good solubility is not enough to make a good base.

Table 1: Conductivity of various bases (0.01 M) in organic solution (15 °C, 1 atm).[a]

Base	In DMF [µs cm^{-1}]	In THF [µs cm^{-1}]	Base	In DMF [µs cm^{-1}]	In THF [µs cm^{-1}]
Li_2CO_3	2.63	0	TBAP	1237	21.70
Na_2CO_3	2.75	0	TBAC	1229	19.00
K_2CO_3	14.00	0	TBAHC	716	8.76
Cs_2CO_3	24.00	0.021	TBAA	1028	2.11
Na_3PO_4	3.92	0	TBAE	721	1.28
K_3CO_3	13.10	0	TBPA	780	7.40
TMAP	185	1.01	TBPE	758	2.73
TEAP	740	2.88	TBPM	842	9.48

[a] The conductivities of pure DMF and THF are 0.72 and 0 µs cm^{-1}, respectively.

We propose that the performance of the bases may be related to their different ionization abilities. Thus the electric conductivities for various bases were measured (Table 1).[13] The inorganic bases exhibit very low conductivities in DMF and almost zero conductivity in THF, indicating that they do not ionize easily in organic solvents. Among these bases Cs_2CO_3 shows the highest conductivity, which explains why Cs_2CO_3 performs better than Na and K bases in Cu-catalyzed couplings.[15] By comparison, the organic ionic bases exhibit much higher conductivities, meaning that they ionize readily. Interestingly, the conductivity varies greatly between organic ionic bases. A more bulky organic cation leads to greater conductivity. The anion also exerts an influence. The large difference in conductivities explains why these organic ionic bases have dissimilar performances. Thus, it is the ionization ability that accounts for the advantage of using organic ionic bases.

In summary, we have synthesized a series of novel organic ionic bases that promote Cu-catalyzed C–N couplings of aryl iodides and even bromides at room temperature which are either difficult or cannot accomplished with traditional alkaline bases. Good solubility alone does not explain the performance of the organic ionic bases. Conductivity measurements indicate that the usefulness of organic ionic bases may be attributed to their good ionization ability in organic solvents. The results indicate the important, yet overlooked value of using organic ionic bases in transition-metal-catalyzed transformations and/or other organic reactions.[16]

Experimental Section

Representative procedure (Scheme 3): A mixture of CuI (9.5 mg, 0.05 mmol, 10 mol %), *N,N*-dimethylglycine (10.3 mg, 0.1 mmol, 20 mol %), TBPM (465 mg, 0.75 mmol), and the (solid) aryl bromide was added to a vacuum tube filled with argon. The tube was evacuated and backfilled with argon (this procedure was repeated three times). Under a counterflow of argon, the amine, aryl bromides (if liquid), and DMSO (0.5 mL) were added by syringe. The tube was sealed and the mixture was allowed to stir under argon at ambient temperature (25 ± 1 °C) 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 before it was weighed and characterized by NMR spectroscopy.

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