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Highly Selective Room-Temperature Copper-Catalyzed C−N Coupling Reactions

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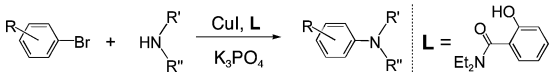
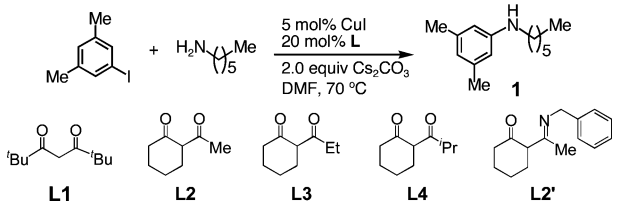
Recent progress in Ullmann coupling has led to the emergence of several protocols utilizing supporting ligands to achieve efficiency at moderate reaction temperatures.[1] In 2003, we introduced *N*,*N*-diethylsalicylamide as a supporting ligand, making it possible to carry out copper-catalyzed coupling of aryl bromides with aliphatic amines under mild conditions (Scheme 1).[2] Since that

Scheme 1. Copper-Catalyzed Amination of Aryl Bromides



report, several new ligands have been introduced to promote copper-catalyzed amination reactions, most notably amino acids[3] and amino alcohols.[4] Despite this progress, long reaction times and inefficient transformation of functionalized substrates remain as limitations of the method. Often, the problems can be traced to catalyst deactivation through competitive N- or O-arylation of the ligand. A report by Song on the use of dipivaloylmethane (**L1**) in the Ullmann-type coupling of phenols[5] raised the possibility for creating a more robust catalyst system where the delocalized enolate form of β-diketone **L1** would be less prone to arylation.[6]

We tested **L1** as a ligand for copper-catalyzed C−N bond formation in the reaction between 5-iodo-*m*-xylene and *n*-hexylamine. While no coupling occurred at 70 °C in the absence of ligand, addition of 20% of **L1** resulted in the formation of the desired coupling product **1** in 75% yield after 10 h. This encouraged



us to test a variety of β-diketones and led to the discovery that commercially available 2-acetylcyclohexanone (**L2**) was an excellent ligand. Other 2-acylcyclohexanones were also found to be highly effective, with activity increasing in the order acetyl (**L2**) < propionyl (**L3**) < isobutyryl (**L4**). Replacing the acetyl group of **L2** with an acetimidoyl group (ligand **L2′**) led to a markedly lower catalytic activity, suggesting that the diketone, rather than the ketoimine, was the actual ligand.

Given the high rates observed, we examined coupling reactions at room temperature. A test reaction using 5% CuI and 20% **L2** reached full conversion after 2.5 h, while with **L4** the reaction time was reduced to 1.5 h. The kinetic profiles of these reactions were measured by reaction calorimetry at 25 °C (Figure 1). While the coupling did not approach completion with *N*,*N*-diethylsalicylamide or **L1**, 88% and 98% conversion of aryl iodide was achieved after only 60 min using **L2** and **L4**, respectively.

For the catalyst comprised of CuI/**L4**, Ullmann coupling of a series of para-substituted iodobenzenes was examined, with substituents ranging from electron-donating *p*-OMe to electron-withdrawing *p*-CN (Figure 2). Although the rates were somewhat lower for electron-rich substrates, in all cases complete conversion was reached in <2 h at 25 °C.

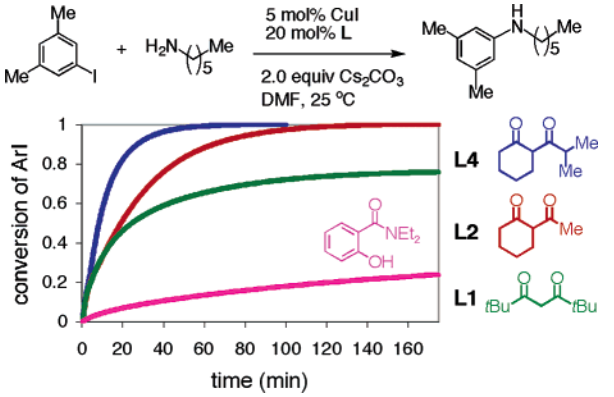


Figure 1. Kinetic profiles of C−N coupling reactions using β-diketones.

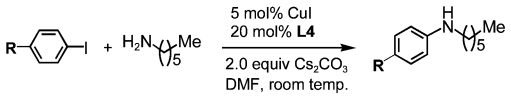


Figure 2. Comparison of reaction times: electronic effect. R = OMe, 110 min; Me, 90 min; H, 70 min; Cl, 50 min; CN, 40 min.

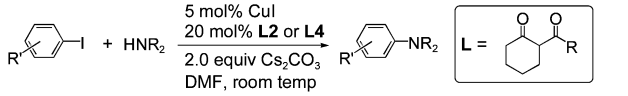
The CuI/**L4** catalyst system was found applicable to a wide range of substrate combinations (Table 1). Although in many instances good yields were obtained using **L2** (Table 1, entries 1, 2, 4, and 5), the faster reaction rates and broader substrate scope afforded by **L4** justify its one-step synthesis.[7] The CuI/**L4** catalyst system showed high selectivity in the presence of a number of potentially reactive functional groups. For the BOC-monoprotected 1,4-diaminobutane, the coupling took place exclusively at the unprotected terminus (entry 2). High yields were achieved in the presence of −COOH and −Br substituents (entries 3, 4). Both 3-iodoaniline and 4-iodophenol were transformed efficiently at room temperature (entries 6, 7). Even the coupling of the more hindered cyclohexylamine and pyrrolidine (entries 8, 9) was achieved in 6−7 h.

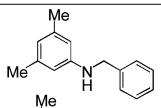
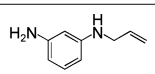
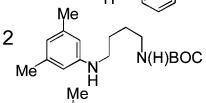
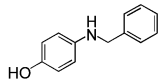
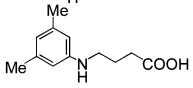
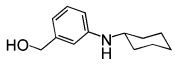
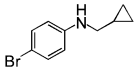
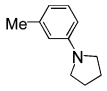
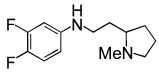
The CuI/**L4** catalyst was found to be equally successful in the coupling of heterocycle-containing substrates. While the reactions were generally slower, both activated (Table 2, entries 1−4) and nonactivated (entries 5, 6) heterocyclic iodides underwent smooth coupling at room temperature. In addition, double-amination of 1,4-diiodobenzene with 2-thienylethylamine proceeded in only 3 h (entry 8).

Application of the CuI/**L4** catalyst to the intramolecular amination of bromide- and chloride-containing substrates is illustrated in Scheme 2. In the case of aryl bromide **2** (X = Br), the intramolecular nature of the reaction allows for the rapid (30 min) formation of indoline **3** at room temperature. We note, however, that complete conversion was achieved in 3 h in the absence of ligand. In contrast, no cyclization of **2** (X = Cl) took place in the

10.1021/ja063063b CCC: $33.50

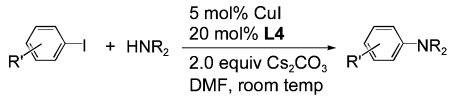
Table 1. Room-Temperature Amination of Aryl Iodides[a]

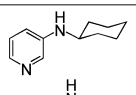
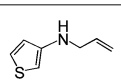
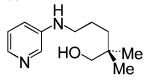
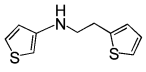
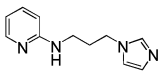
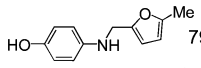
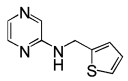
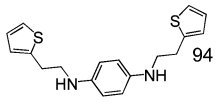


entry	product	% yield (time)	entry	product	% yield (time)[b]
1		96 (2 h) 94 (3 h)[c]	6		90 (6 h)
2		98 (4 h) 97 (6 h)[c]	7		80 (8 h)[e]
3		88[d]	8		88 (7 h)
4		98 (2 h) 96 (3 h)[c]	9		90 (6 h)
5		98 (1h) 98 (1h)[c]			

[a] Reaction conditions: ArI (1.0 mmol), amine (15. mmol), Cs_2CO_3 (2.0 mmol), CuI (0.05 mmol, 5 mol %), and ligand (0.2 mmol, 20 mol %) in 0.5 mL of DMF at room temperature under argon; ligand **L4** was used unless otherwise indicated. [b] Isolated yield, average of two runs. [c] **L2** was used. [e] Using 2.6 mmol of Cs_2CO_3. [d] 6 h at 50 °C.

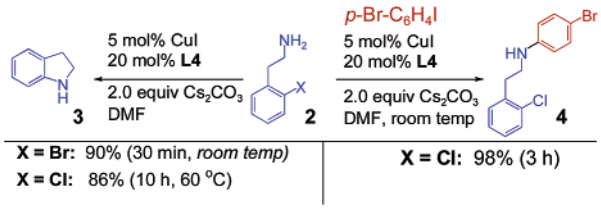
Table 2. Amination of Heterocycle-Containing Substrates[a]



entry	product	% yield (time)	entry	product	% yield (time)
1		90 (10 h)	5		83 (17 h)
2		85 (20 h)	6		82(17 h)
3		90 (20 h)	7		79 (14 h)[b]
4		99 (0.5 h)	8		94 (3 h)[c]

[a] Reaction conditions same as in Table 1. [b] Using 3.0 mmol of Cs_2CO_3. [c] Using 0.5 mmol of 1,4-diiodobenzene and 1.5 mmol of amine.

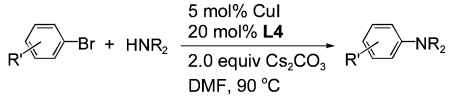
Scheme 2. Intra- vs Intermolecular Amination

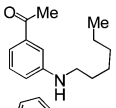
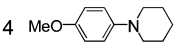
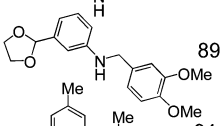
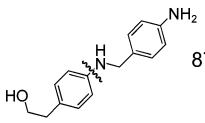
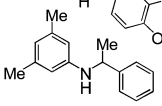


absence of ligand at 60 °C, while addition of **L4** allowed the reaction to take place at this temperature in 10 h. For **2** (X = Cl), the course of the reaction could be diverted toward intermolecular cross-coupling in the presence of an aryl iodide (product **4**).

In addition to aryl iodides, aryl bromides could undergo amination at 90 °C. Less sterically hindered substrates (Table 3, entries 1, 2) could be coupled in as little as 3−6 h, while 10 h was required for the more sterically encumbered α-branched amine

Table 3. Copper-Catalyzed Amination of Aryl Bromides[a]



entry	product	% yield (time)	entry	product	% yield (time)
1		92 (3 h)	4		90 (16 h)[b,c]
2		89 (6 h)	5		87 (12 h)[b]
3		94 (10 h)[b,c]			

[a] Reaction conditions: ArBr (1.0 mmol), amine (1.5 mmol), Cs_2CO_3 (2.0 mmol), CuI (0.05 mmol, 5 mol %), and **L4** (0.2 mmol, 20 mol %) in 0.5 mL of DMF at 20 °C under argon. [b] Using K_3PO_4 (2 mmol, 425 mg). [c] At 100 °C.

(entry 3). We were pleased to find that raising the temperature to 100 °C allowed for the coupling of an aryl bromide with a cyclic secondary amine (entry 4), a very challenging substrate combination.[8] When several reactive functional groups were present, the reaction occurred selectively at the alkylamine (entry 5). This approach can potentially circumvent the need for protecting group manipulations in the synthesis of complex molecules.

In summary, a general protocol for room-temperature coupling of aryl iodides with amines has been described. The catalyst is easily formed in situ by combining CuI with cyclic β-diketone ligand **L2** or **L4**. With the exception of substrates bearing a coordinating group ortho to the halide,[9] the rate acceleration afforded by these catalysts is unprecedented for Ullmann-type coupling reactions and allows for a number of substrates to be transformed in as little as 2−4 h at *room temperature*. This process nicely complements palladium-based methods for the selective N-arylation of aliphatic amines.

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

References

(1) For recent reviews of copper-catalyzed cross-coupling reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364.
(2) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796.
(3) (a) Ma, D. W.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453−2455. (b) Cai, Q.; Zhu, W.; Zhang, H.; Zhang, Y. D.; Ma, D. W. *Synthesis* **2005**, 496−499.
(4) (a) Lu, Z. K.; Twieg, R. J.; Huang, S. P. D. *Tetrahedron Lett.* **2003**, *44*, 6289−6292. (b) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903−918.
(5) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623−1626.
(6) A limited number of studies on copper-catalyzed C-arylation of malonates and β-diketones have appeared: (a) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269−272. (b) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607−5622. (c) Jiang Y.; Wu, N.; He, M. *Synlett* **2005**, 2731−2734.
(7) See Supporting Information.
(8) For some earlier examples, see: Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164−5173.
(9) For recent examples, see: (a) Cai, Q.; Zou, B. L.; Ma, D. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276−1279. (b) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, *124*, 10451−10455.

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