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A General and Efficient Copper Catalyst for the Amidation of Aryl Halides

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Abstract: An experimentally simple and inexpensive catalyst system was developed for the amidation of aryl halides by using 0.2−10 mol % of CuI, 5−20 mol % of a 1,2-diamine ligand, and K_3PO_4, K_2CO_3, or Cs_2CO_3 as base. Catalyst systems based on *N,N′*-dimethylethylenediamine or *trans-N,N′*-dimethyl-1,2-cyclohexanediamine were found to be the most active even though several other 1,2-diamine ligands could be used in the easiest cases. Aryl iodides, bromides, and in some cases even aryl chlorides can be efficiently amidated. A variety of functional groups are tolerated in the reaction, including many that are not compatible with Pd-catalyzed amidation or amination methodology.

Introduction

Transition metal catalyzed C−N bond-forming processes are extensively utilized in the medicinal chemistry and process development groups of pharmaceutical companies and in academic laboratories. Despite significant improvements in the palladium-catalyzed *N*-arylation of amines,[1] some limitations still remain. For example, aryl halides containing free N−H groups[2] as well as certain heterocyclic halides[3] are difficult amination substrates. The palladium-catalyzed arylation of amides, another important class of nitrogen nucleophiles, is encumbered by further limitations. Most notably, the amidation of electron-rich or ortho-substituted electronically neutral aryl halides is difficult.[4] Moreover, the high cost of palladium invites less expensive alternatives.[5] Finally, removal of palladium residues from polar reaction products, particularly in the late stage of the synthesis of a pharmaceutical substance, can be challenging.

Both the Ullmann reaction (copper-catalyzed *N*-arylation of amines)[6] and the related Goldberg reaction (copper-catalyzed *N*-arylation of amides)[7] predate the palladium-catalyzed amination methodology by many decades. While applications of the Ullmann and Goldberg reactions in academic and industrial laboratories are well-documented,[8] the methods have remained relatively undeveloped. The necessity to use temperatures as high as 210 °C,[9] highly polar solvents, and often large amounts of copper reagents, as well as the modest yields often realized, have undoubtedly prevented these reactions from being employed to their full potential. An important alternative has been reported recently where aryl boronic acids are used as arylating agents instead of aryl halides.[10] Unfortunately, the method suffers from high cost and poor availability of functionalized boronic acids, as well as relatively limited scope of the process.

The traditional protocols for the Goldberg amidation reaction prescribe simple copper salts or often copper metal as the catalyst. It is surprising that very few reports have focused on deliberate use of ligands to facilitate the copper-catalyzed aryl amidation reaction.[11] We have previously disclosed Ullmann-type methodology for the *N*-arylation of imidazoles using a 1,10-

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(2) Examples are rare and include the following: (a) Ward, Y. D.; Farina, V. *Tetrahedron Lett.* **1996**, *37*, 6993. (b) Willoughby, C. A.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*, 7181. (c) Batch, A.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 872. (d) Prashad, M.; Hu, B.; Lu, Y.; Draper, R.; Har, D.; Repic, O.; Blacklock, T. J. *J. Org. Chem.* **2000**, *65*, 2612. (e) Link, J. T.; Sorensen, B.; Liu, G.; Pei, Z.; Reilly, E. B.; Leitza, S.; Okasinski, G. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 973.

(3) (a) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133. (b) Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731.

(4) (a) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035. (b) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (c) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.

(5) Ni-catalyzed amination of aryl chlorides: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (b) Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron* **1999**, *55*, 12829. (c) Lipshutz, B. H.; Ueda, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4492.

(6) *N*-Arylation of anilines: (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Gauthier, S.; Fréchet, J. M. J. *Synthesis* **1987**, 383. (c) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496. (d) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791. *N*-Arylation of alkylamines: (e) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459. (f) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475. (g) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. Arylation of ammonia: (h) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251.

(7) (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Freeman, H. S.; Butler, J. R.; Freedman, L. D. *J. Org. Chem.* **1978**, *43*, 4975. (c) Dharmasena, P. M.; Oliveira-Campos, A. M.-F.; Raposo, M. M. M.; Shannon, P. V. R. *J. Chem. Res. (S)* **1994**, 296. (d) Ito, A.; Saito, T.; Tanaka, K.; Yamabe, T. *Tetrahedron Lett.* **1995**, *36*, 8809. (e) Sugahara, M.; Ukita, T. *Chem. Pharm. Bull.* **1997**, *45*, 719. (f) Lange, J. H. M.; Hofmeyer, L. J. F.; Hout, F. A. S.; Osnabrug, S. J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101.

(8) For a review, see: Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(9) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86.

(10) Lam, P. Y. S.; Deudon, S.; Hauptman, E.; Clark, C. G. *Tetrahedron Lett.* **2001**, *42*, 2427 and references therein.

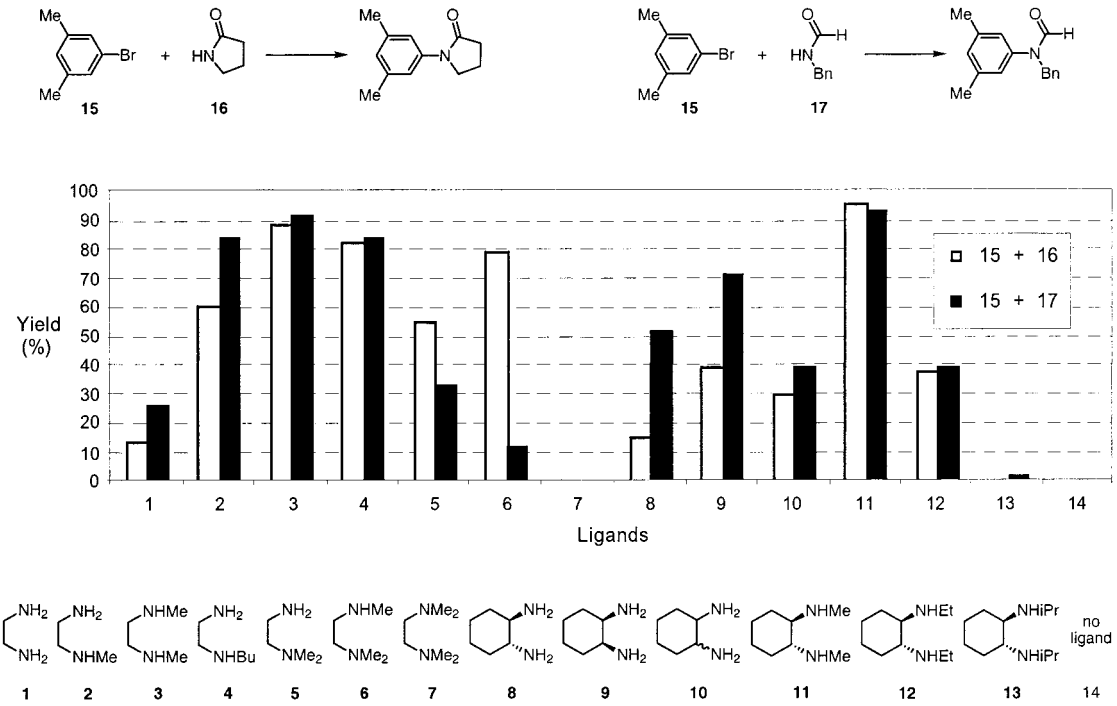
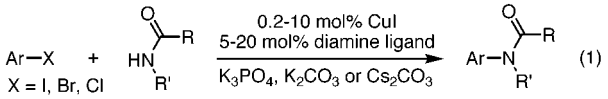


Figure 1. Effect of various diamine ligands on the efficiency of the aryl amidation reaction. The reactions were performed with 5 mol % of CuI, 10 mol % of ligand, 1.0 equiv of aryl bromide **15**, 1.2 equiv of amide **16** or **17**, and 2 equiv of K_2CO_3 in toluene. All experiments have been performed twice and the resulting GC yields have been averaged. The conversion of the aryl halide was also determined by GC and in all cases was found to be 0−10% higher than the GC yield. Reaction conditions: coupling of **15** and **16**, 100 °C for 22 h; coupling of **15** and **17**, 110 °C for 22 h.

phenanthroline/$(CuOTf)_2$·benzene catalyst system.[12] This led us to examine the efficiency of other chelating nitrogen ligands in copper-catalyzed carbon−nitrogen bond-forming processes. We recently demonstrated that the combination of air-stable CuI and inexpensive 1,2-diamine ligands in the presence of K_3PO_4 or K_2CO_3 comprises an extremely efficient and general catalyst system for the *N*-amidation of aryl and heteroaryl iodides and bromides, and in some cases even unactivated aryl chlorides (eq 1).[13] Since then we have examined this process in more

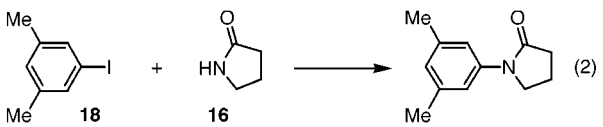


detail and have significantly extended the reaction scope using *N*,*N*′-dimethylethylenediamine and *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine as ligands. Herein, we report in full the results of this investigation.

Results and Discussion

In our initial disclosure we showed that *trans*-1,2-cyclohexanediamine (**8**) was an excellent ligand for coupling amides with aryl iodides. In fact, a variety of 1,2-diamine ligands are effective. In the easiest examples even ethylenediamine can be employed. The structure of the 1,2-diamine ligands has a pronounced effect on their ability to facilitate the copper-catalyzed aryl amidation reactions. A set of 13 ligands was screened for the coupling of aryl bromide **15** with two different amides, **16** and **17**. The two reactions were performed at slightly different temperatures, 100 and 110 °C, to ensure partial conversion of the aryl bromide and therefore better comparison of the ligand effects. As shown in Figure 1, both of the coupling reactions show similar trends with respect to the structure of the diamine ligands. The degree of substitution and consequently the steric bulk of the diamine ligands play the most important role. The *N*,*N*′-dimethyl diamines **3** and **11** have higher activity than the unsubstituted diamines **1**, **8**, **9**, and **10**. On the other hand, bulky *N*-substituents on the ligands, e.g., the isopropyl (**13**) and even ethyl groups (**12**), decrease the rate of aryl amidation reaction. Further substitution at the nitrogen center leads to a completely inactive ligand (e.g., TMEDA (**7**)). The ligand **11** and the commercially available ligand **3** are recommended in most cases. Ligand **11** is slightly more active than **3**; the difference becomes significant in more difficult reactions such as in the amidation of aryl chlorides (see below).

To determine if a chelating ligand is a prerequisite for the success of our amidation protocol, we evaluated a monodentate ligand, *n*-hexylamine. The coupling of aryl iodide **18** and amide **16** (eq 2) in the presence of 5 mol % of CuI in toluene at 80 °C



was unaffected by the addition of 20 mol % of *n*-hexylamine and provided 12−15% yield of the product (Table 1, entries 1 and 2). Significant rate enhancement was observed, however,

(11) (a) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1299. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. See also: (c) Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670. (d) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (e) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973.

(12) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

(13) (a) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. See also: (b) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

Table 1. *N*-Arylation of 2-Pyrrolidinone with Amine Additives[a]

entry	amine additive	amount of amine	solvent	conversion of ArI **18**, %	yield,[b] %
1	none	none	PhMe	19	15
2	*n*-HexNH_2	20 mol %	PhMe	17	12
3	*n*-HexNH_2	7 equiv	none	>99	98[c]
4	*i*-Pr_2NH	7 equiv	none	11	8

[a] Performed with 5 mol % of CuI, 1.0 equiv of aryl iodide **18**, 1.2 equiv of amide **16**, and 2.0 equiv of K_3PO_4 at 80 °C for 23 h. [b] Average yield (GC) for two runs. [c] Isolated yield (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR.

Table 2. Arylation of *N*-Methylformamide with Various Copper Sources[a]

entry	copper source	conversion of ArI, %	yield,[b] %
1	Cu powder (bronze)	89	86
2	CuI	97	97
3	CuCl	95	93
4	CuSCN	92	85
5	Cu_2O	94	91
6	$CuCl_2$	58	55
7	$CuSO_4 \cdot 5H_2O$	81	79
8	CuO	3	<0.5
9	$Cu(OAc)_2$	75	71
10	$Cu(acac)_2$	85	83

[a] Performed with 5 mol % of Cu, 10 mol % of ligand **3**, 1.0 equiv of aryl iodide **18**, 1.2 equiv of *N*-methylformamide, and 2.0 equiv of K_3PO_4 in toluene at 80 °C for 7 h. [b] Average yield (GC) for two runs.

if *n*-hexylamine was used as the solvent (98% yield; entry 3). Interestingly, a more hindered amine, diisopropylamine, failed to accelerate the aryl amidation reaction (entry 4). We speculate that the equilibrium leading to the copper−amine complex is unfavorable unless a large excess of an unhindered amine is used. If that is indeed the case, the role of a chelating diamine ligand could simply be to increase the stability constant of the catalytically active copper−amine complex. Further studies are required to ascertain this hypothesis.

A brief study of several readily available copper compounds as alternative catalyst precursors was also carried out. As shown in Table 2, copper metal, Cu_2O, CuI, and CuCl (among others) produced acceptable results in the arylation of *N*-methylformamide. For more difficult substrates, the air-stable and inexpensive CuI gave the best results. Consequently, CuI was chosen as the catalyst precursor for subsequent experiments although it is conceivable that other copper compounds could be used with comparable or greater success for some of the reactions. It is interesting to note that copper compounds in various oxidation states are catalytically active and presumably are transformed to the same active catalyst under the reaction conditions.[14]

The choice of the base plays a more important role than the nature of the copper precatalyst. Amidation of aryl iodides proceeds best with K_3PO_4 as the base; the reaction is much slower if K_2CO_3 is used instead. In contrast, many amidation reactions of aryl bromides, which typically react more slowly than aryl iodides, fail in the presence of K_3PO_4. In those cases, complete conversion of the aryl bromide can nevertheless be achieved if K_3PO_4 is replaced with a weaker base such as K_2CO_3. Further insight into this interesting phenomenon was provided by an experiment where a solution of a strong base,

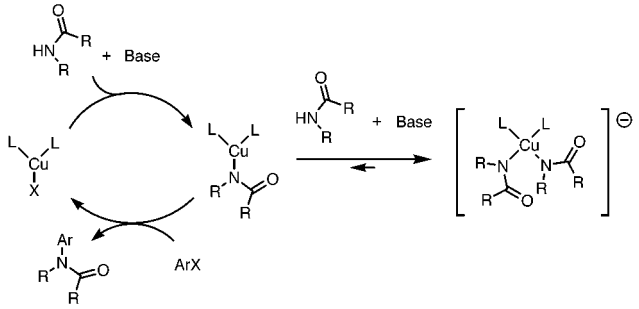
(14) Weston, P. E.; Adkins, H. *J. Am. Chem. Soc.* **1928**, *50*, 859.

Table 3. Base Effects on the Efficiency of the Aryl Amidation Reaction

entry	base	amount of base, equiv	conditions[a]	conversion of ArI,[b] %	yield, %
1	KHMDS	1.2[c]	90 °C, 4 h	<1	<1[b]
2	KHMDS	1.2 (slow)[d]	90 °C, 4 h	98	92[e]
3	NaOtBu	1.2[c]	90 °C, 21 h	10	3[b]
4	phosphazene[f]	2.0[c]	90 °C, 21 h	96	93[e]

[a] Performed with 5 mol % of CuI, 10 mol % of ligand **11**, 1.0 equiv of aryl iodide **18**, and 1.2 equiv of amide **16** in toluene. [b] Measured by GC (average of two runs). [c] Base was added in a single portion. [d] A solution of the base in toluene was added dropwise over 4 h using a syringe pump. [e] Isolated yields (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR. [f] *tert*-Butyliminotris(pyrrolidino)phosphorane.

Scheme 1

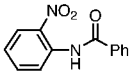
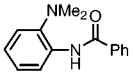
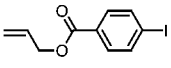
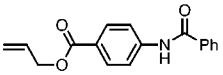
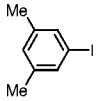
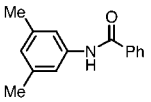
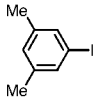
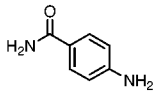
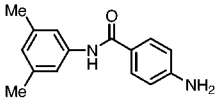
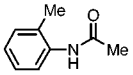
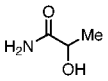
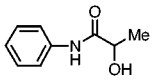


KHMDS, was slowly added to a reaction mixture including aryl iodide **18** and amide **16** (eq 2; Table 3). Nearly complete conversion of the aryl iodide and 92% yield of the *N*-arylated amide was observed (entry 2). However, less than 1% conversion of the aryl iodide was detected if KHMDS was added in a single portion (entry 1). These observations suggest that the rate of deprotonation of the amide has to match the rate of the amidation reaction. If an excess of the deprotonated amide is formed, it impedes the desired aryl amidation reaction presumably via formation of an unreactive cuprate complex (Scheme 1). A similar suggestion has been provided by Bacon and Karim to explain the effects of imide/copper ratio on the efficiency of the arylation of potassium phthalimide.[15]

Comparison of the pK_{HA} values of the amide substrate and the bases used in the arylation reaction reveals another interesting relationship (Table 3). KHMDS (pK_{HA} = 26 in DMSO,[16] entry 1) and NaOtBu (pK_{HA} = 32 in DMSO,[17] entry 3) both fail in the arylation of 2-pyrrolidinone (pK_{HA} = 24 in DMSO).[17] On the other hand, a phosphazene base, *tert*-butyliminotris(pyrrolidino)phosphorane (pK_{BH^+} = 18 in DMSO),[18] is a proficient base and provides 93% yield of the desired *N*-aryl amide (entry 4). This suggests that the pK_{HA} of the base employed in the arylation reaction should be below the pK_{HA} of the amide substrate unless the base is delivered gradually as the reaction proceeds (entry 2). A similar rationale can be applied to inorganic bases such as K_3PO_4 or K_2CO_3. Presumably, these bases are thermodynamically very strong in aprotic solvents;[19] nevertheless, their extremely low solubility in nonpolar organic solvents ensures the rates of deprotonation that are optimal for the arylation of amides.

(15) Bacon, R. G. R.; Karim, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 272.
(16) Grimm, D. T.; Bartmess, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 1227.
(17) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(18) Extrapolated from pK_{BH^+} = 28 (in acetonitrile) reported by: Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1361.
(19) Although we are not aware of any reported pK_{HA} values for K_3PO_4 or K_2CO_3 in non-hydrogen-bond-donor solvents, the hydroxide has pK_{HA} = 31 in DMSO.[17]

Table 4. Coupling of Aryl Iodides with Primary Amides[a]

Entry	Aryl iodide	Amide	Product	Ligand	Amount of CuI (mol%)	Conditions	Solvent	Yield[b]
1				**8**	1	110 °C, 23 h	dioxane	69%
2				**3**	5	80 °C, 7 h	toluene	88%
3				**8**	1	110 °C, 23 h	dioxane	96%
4				**8**	1	110 °C, 23 h	dioxane	86%
5				**3**	5	25 °C, 7 h	THF	99%[c], 10%[d]
6				**19**[e]	5	25 °C, 46 h	dioxane	90%
7				**8**	1	110 °C, 23 h	dioxane	98%
8				**3**	5	80 °C, 23 h	DMF	95%
9				**3**	5	60 °C, 23 h	DMF	90%

[a] Performed using 10 mol % of ligand, 1.0 equiv of aryl iodide, 1.2 equiv of amide, and 2 equiv of K_3PO_4. [b] Isolated yields (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR. [c] With 1 equiv of water and 1.5 equiv of Cs_2CO_3 as base. [d] Without water; using 1.5 equiv of Cs_2CO_3 as base; average yield (GC) for two runs. [e] Racemic *trans*-*N*-(4-methylphenyl)-1,2-cyclohexanediamine; reaction was performed with 2 equiv of Cs_2CO_3 as base.

The scope of the copper-catalyzed aryl amidation reaction was explored by using 0.2−10 mol % of the air-stable CuI as the copper source, 5−20 mol % of a diamine ligand, and K_3PO_4, Cs_2CO_3, or K_2CO_3 as the base. The reactions of aryl iodides with primary amides are detailed in Table 4. The amidation of aryl iodides can be successfully performed by using various 1,2-diamine ligands. Although the *N*,*N*′-dimethyl diamines such as the commercially available ligand **3** generally provide higher reaction rates, the ligand **8** has an advantage of significantly lower price. Cs_2CO_3 and K_3PO_4 are far more efficient bases for the amidation of aryl iodides than is K_2CO_3. In most cases, K_3PO_4 is the recommended base[20] as it is less expensive than Cs_2CO_3. The amidation reactions can be carried out at 60−110 °C and with benzamide even at room temperature (entries 5 and 6). Interestingly, the arylation of benzamide is dramatically accelerated by addition of water (1 equiv) to the reaction mixture (entry 5). We speculate that a small amount of water increases the rate of the arylation reaction by solubilizing the base, Cs_2CO_3, and thus facilitating deprotonation of benzamide. Arylation of other amides is less sensitive to water, and coupling of the less reactive (more hindered) substrates is in fact inhibited by water, which is expected if the rate of deprotonation of the amide exceeds the rate of the aryl amidation reaction (see Scheme 1).

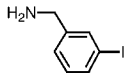
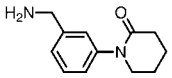
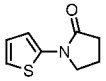
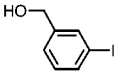
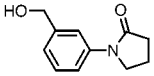
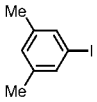
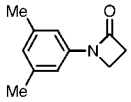
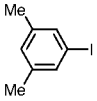
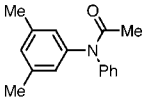
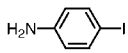
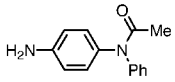
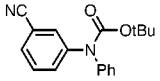
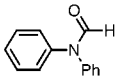
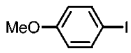
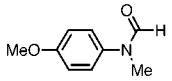
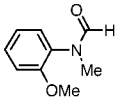
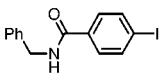
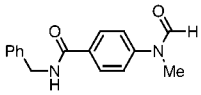
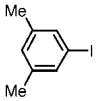
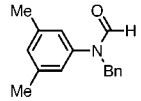
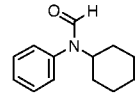
A variety of functional groups are tolerated in the aryl amidation reaction (Table 4). Of particular interest are entries 7 (free NH_2 in nitrogen nucleophile) and 4 (allyl ester) in which substrates not compatible with the Pd-catalyzed methodology are transformed in high yield. A strongly electron-donating substituent at the ortho position of the aryl iodide (entry 3) has no deleterious effects in contrast to the Pd-catalyzed aryl amidation reaction.[4] Notably, the amido group in lactamide (entry 9) can be selectively arylated in the presence of the potentially chelating hydroxy group. Although amidation of 1-nitro-2-iodobenzene proceeded in only 69% yield if ligand **8** and dioxane were used (entry 1), a much cleaner reaction took place utilizing ligand **3** and toluene (88% yield, entry 2). Generally, amidation of aryl iodides can be performed in a wide spectrum of aprotic solvents encompassing toluene, dioxane, THF, and even DMF. The arylations of highly polar amides, acetamide and lactamide (entries 8 and 9), actually proceed better if DMF rather than toluene is used as the solvent.

The practical benefits of the copper-diamine-catalyzed amidation methodology must be briefly noted. Although the reactions are moderately sensitive to oxygen and have to be performed under an inert atmosphere, there is no need to use glovebox techniques nor to purify the commercially available reagents. Most of the reactions are extremely clean; no reduction or homocoupling of the aryl halide, which often takes place in the Pd-catalyzed cross-coupling reactions, is normally observed. Another notable feature of the process is the low molecular weight of diamine ligands, for example, only 88.15 g/mol in the case of ligand **3**. This is a definite advantage if the cost per mole of the ligand is considered.

The reactions of aryl iodides with secondary amides (Table 5) were conducted under conditions similar to those in Table 4. Lactams (entries 1−4) and formamides (entries 8−12) are excellent substrates. In addition, *N*-acetyl and *N*-Boc anilines provide good yields of the arylated products despite slightly lower reactivity (entries 5−7). In the case of *N*-methylformamide, the reaction could be carried out with 0.2 mol % of CuI (S/C = 500) and proceeded in 98% yield. The commercial mixture of the cis and trans diastereomers of 1,2-cyclohexanediamine[21] could be used instead of the pure trans-isomer **8**

(20) The quality of K_3PO_4 is important. See the Experimental Section for more information.

Table 5. Coupling of Aryl Iodides with Secondary Amides[a]

Entry	Aryl iodide	Amide	Product	Amount of CuI (mol%)	Ligand	Conditions	Solvent	Yield[b]
1				5	**3**	100 °C, 18 h	PhMe	95%
2				1	**8**	110 °C, 23 h	dioxane	97%
3				5	**3**	80 °C, 3 h	PhMe	93%
4				1	**8**	110 °C, 23 h	dioxane	93%
5				1	**8**	110 °C, 23 h	dioxane	93%; 88%[c]
6				1	**8**	110 °C, 23 h	dioxane	81%
7				5	**8**[d]	110 °C, 25 h	PhMe	92%
8				5	**1**	80 °C, 4h	PhMe	93%
9				0.2	**8**[e]	110 °C, 23 h	dioxane	99%
10				1	**8**	110 °C, 23 h	dioxane	95%
11				1	**8**	110 °C, 23 h	dioxane	96%
12				1	**8**	110 °C, 23 h	dioxane	99%
13				5	**8**[d]	110 °C, 25 h	PhMe	63%[f]
14				5	**3**	110 °C, 23 h	PhMe	87%[g], 67%[h]

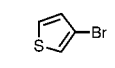
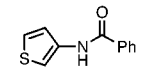
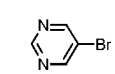
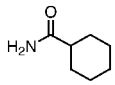
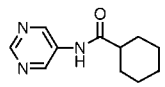
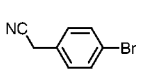
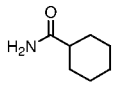
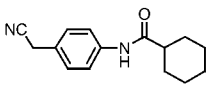
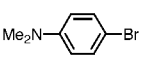
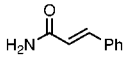
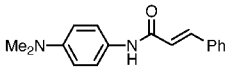
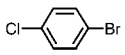
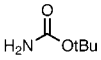
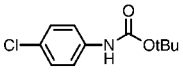
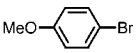
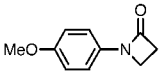
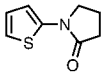
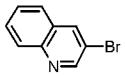
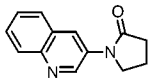
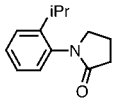
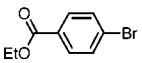
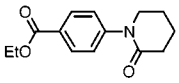
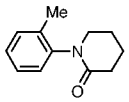
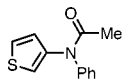
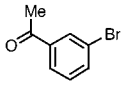
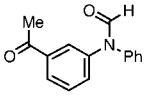
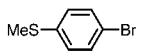
[a] Performed using 10 mol % of ligand, 1.0 equiv of aryl iodide, 1.2 equiv of amide, and 2 equiv of K_3PO_4. [b] Isolated yields (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR. [c] The commercial mixture of the cis and trans diastereomers of ligand **8** was used. [d] With 20 mol % of ligand. [e] With 5 mol % of ligand. [f] *trans-N,N′*-Diphenyl-1,2-cyclohexanediamine was also isolated in 5% yield. [g] With 20 mol % of ligand **3** and 3.0 equiv of amide substrate; isolated yield (average of 2 runs). [h] With 10 mol % of ligand **3** and 1.2 equiv of amide substrate; GC yield (average of 2 runs).

as the ligand with comparable results (entry 5). The amidation reaction tolerates a variety of functional groups including the nitrile (entry 7), free NH_2 (entries 1 and 6), and aliphatic OH (entry 3). The selective amidation of an aryl iodide containing an aliphatic amino group (entry 1) is particularly interesting since we have recently reported a method for selective copper-catalyzed *N*-arylation of aliphatic amines using copper(I) iodide and an *O*-donor ligand (ethylene glycol or an ortho-substituted phenol).[6g] Therefore, it is possible to reverse the selectivity of the copper-catalyzed C−N bond-forming reactions simply by choosing an appropriate ligand. We hypothesize that this remarkable change in selectivity is due to differences in the σ-donating ability of the 1,2-diamine (presumably neutral, moderately donating) and *O*-donor (presumably anionic, strongly donating) ligands; a more detailed study is in progress.

A high level of selectivity was also observed in the amidation of an aryl iodide containing another amide group (Table 5, entry 11). Unfortunately, this result has less desirable implications as well; namely, acyclic *N*-alkylamides other than *N*-alkylformamides are problematic arylation substrates. Even *N*-alkyl-

(21) The mixture of the cis and trans diastereomers of 1,2-cyclohexanediamine is very inexpensive because it is a byproduct in the preparation of Nylon.

Table 6. Amidation of Aryl Bromides[a]

Entry	Aryl bromide	Amide	Product	Amount of CuI (mol%)	Ligand	Solvent	Yield[b]
1				10	**8**	Dioxane	97%[c]
2				10	**3**	Dioxane	86%[c,d]
3				5	**3**	PhMe	83%
4				5	**11**	PhMe	99%
5				5	**3**	PhMe	79%
6				1	**11**	Dioxane	90%
7				10	**8**	Dioxane	96%[c]
8				2	**3**	Diglyme	98%[e]
9				5	**11**	PhMe	94%
10				5	**3**	PhMe	94%
11				5	**3**	PhMe	49%[f], 25%[g]
12				10	**8**	Dioxane	81%[c]
13				5	**11**	PhMe	91%
14				5	**3**	PhMe	95%

[a] Performed with 10 mol % of ligand, 1.0 equiv of aryl bromide, 1.2 equiv of amide, and 2 equiv of K_2CO_3 at 110 °C for 15−24 h. [b] Isolated yields (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR. [c] With 2 equiv of K_3PO_4 as base. [d] With 1.2 equiv of aryl bromide and 1.0 equiv of amide. [e] At 120 °C for 24 h. [f] With 20 mol % of ligand; isolated yield (average of 2 runs). [g] With 10 mol % of ligand, GC yield.

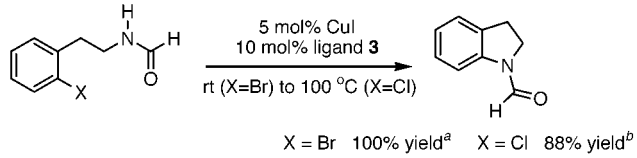
formamides react poorly if the alkyl substituent is bulky enough (entry 13). Moreover, significant *N*-arylation of the diamine ligand (≥5% with respect to the aryl halide) is observed if hindered, unreactive amide substrates are used. The resulting *N*-arylated diamines are less catalytically active then the starting diamine,[22] which further aggravates the reactions involving hindered amides. Slightly improved yields can be obtained by using a higher concentration (20 mol %) of the diamine ligand (entries 13 and 14). In the case of *N*-methyl acetamide (entry 14), the yield of the desired *N*-arylated amide can be further improved by increasing the amount of the amide substrate to 3 equiv. Interestingly, the reactivity of acyclic *N*-alkylamides and hindered amides is equally problematic in the Pd-catalyzed amidation methodology.

Aryl bromides react more slowly than aryl iodides and typically require heating at 110 °C for 24 h (Table 6). The best conditions for most substrates utilize 5 mol % of CuI, K_2CO_3 as the base, toluene as the solvent, and 10 mol % of *N*,*N*′-dimethylated diamines **3** or **11** as the ligands. In the easiest cases, a combination of CuI, ligand **8**, K_3PO_4, and dioxane could be used as well (entries 1, 7, and 12).[23] The reaction is applicable

(22) We have found that only reactions of aryl iodides with benzamide are significantly accelerated by *N*-aryl-1,2-diamines as ligands (Table 4, entry 6).

(23) In contrast to reactions with K_2CO_3 as the base, the coupling of aryl bromides with unhindered amides (particularly primary amides and lactams) utilizing K_3PO_4 as the base is very poor (<10% yield) if less than about 10 mol % or in some cases even 20 mol % of CuI is used. We tentatively

Scheme 2. Intramolecular Aryl Amidation[a]



X = Br 100% yield[a] X = Cl 88% yield[b]

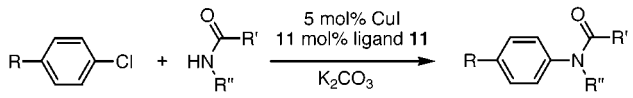
[a] Performed with 1.5 equiv of Cs_2CO_3 as base and 1 equiv of water in THF at 25 °C for 4 h. [b]With 2 equiv of K_2CO_3 as base in toluene at 100 °C for 23 h.

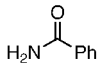
to primary amides and unhindered secondary amides including an α,β-unsaturated amide (entry 4), *tert*-butyl carbamate (entry 5), and a sensitive β-lactam (entry 6). The aryl bromide can contain strongly electron-donating para substituents (entries 4 and 6), and moderately C−H acidic groups as well (entries 3 and 13). The bromo group in 4-bromo-1-chlorobenzene can be selectively amidated in the presence of the chloro substituent (entry 5). While *p*-bromothioanisole is an excellent substrate (entry 14), the *o*-bromothioanisole reacts extremely slowly.[24] This is an unexpected result since chelating aryl halides are usually the best substrates for copper-catalyzed coupling reactions.[25] Significant steric hindrance in the aryl halide can be tolerated if the amide coupling partner is not hindered. For example, 2-bromo-1-isopropylbenzene reacted with 2-pyrrolidinone to give 94% yield of the product (entry 9). Unfortunately, when slightly more hindered amide substrates are used, hindrance in the aryl bromide coupling partner is poorly tolerated (entry 11). A variety of heteroaryl bromides are excellent substrates, including 3-bromoquinoline (entry 8) and 5-bromopyrimidine (entry 2), as well as both 2- and 3-bromothiophene (entries 1, 7, and 12), the latter a substrate only moderately amenable to Pd-catalyzed amination.

The 1,2-diamine ligands can be used to facilitate intramolecular amidation reactions.[26] For example, five-membered-ring formation via intramolecular amidation of an aryl bromide in the presence of ligand **3** could be performed at room temperature in quantitative yield (Scheme 2). In contrast, only a trace of the desired product was observed even at 80 °C if no ligand was added to the reaction mixture. Even an aryl chloride provided an 88% yield of the cyclized product with ligand **3**, although heating at 100 °C for 23 h was necessary.[27] These preliminary results indicate that intramolecular amidation reactions are more facile than the corresponding intermolecular versions, which has been observed for the analogous Pd-catalyzed amidation reactions as well.[28]

We have also begun studies on intermolecular amidation of aryl chlorides using 5 mol % of CuI, 11 mol % of the ligand **11**, and an excess (4 equiv) of the aryl chloride as the solvent (Table 7). For aryl chlorides, ligand **11** performs much better than related diamine **3**. The reaction of *p*-chlorotoluene with benzamide occurred in 93% yield after 23 h at 110 °C (entry 1). The corresponding reaction with 2-pyrrolidinone was slower; nevertheless, it still proceeded in 95% yield at 130 °C (entry 2). Functionalized aryl chlorides provided lower yields of the desired *N*-aryl amides (entries 3 and 4). Although further work is required to improve the reaction conditions and to expand the reaction scope, the coupling reactions reported here are already performed at temperatures that are significantly lower than in the very few cases of copper-catalyzed amidation of aryl chlorides reported previously.[29]

Table 7. Amidation of Aryl Chlorides



Entry	R	Amide	Conditions[a]	Yield[b]
1	Me		110 °C, 23 h	93%
2	Me		130 °C, 23 h	95%
3	MeO		130 °C, 23 h	51%
4	MeO_2C		110 °C, 23 h	62%

[a] Performed neat with 4 equiv of ArCl. [b] Isolated yields (average of 2 runs); >95% purity as determined by GC and ^{1}H NMR.

Conclusion

We have developed a general, mild, and experimentally simple method for the amidation of aryl halides, a radically improved version of the classic Goldberg reaction. The best results are realized by using the inexpensive and air-stable copper(I) iodide and *N*,*N*′-dimethylated 1,2-diamine ligands **3** or **11** as the pre-catalyst. In some cases, other 1,2-diamine ligands including ethylenediamine (**1**) and 1,2-cyclohexanediamine (**10**) can be utilized as a very inexpensive alternative to ligands **3** and **11**. We believe that this catalyst system provides an excellent complement to the Pd-catalyzed methodology, particularly if aryl halides containing strongly electron-donating groups or free N−H groups have to be amidated. Efforts to expand the scope of the method to other nitrogen nucleophiles and to improve the reactivity of hindered amides in combination with mechanistic studies are in progress in our laboratory.

Experimental Section

General Comments. All yields refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC. The procedures described in this section are representative, and thus the yields for the individual reactions may differ slightly from the average yields reported in Tables 4−7. Compounds

attribute this peculiar result to formation of an unreactive cuprate complex (Scheme 1) in the presence of an excessively strong base, K_3PO_4. If this is indeed the case, increasing the amount of CuI in the reaction mixture compensates for the amount of copper removed from the catalytic cycle into the unreactive cuprate complex, and thus keeps the catalytic cycle operating.

(24) Only about 10% GC yield and 28% conversion of aryl bromide was obtained in the arylation of *N*-methylformamide. 2-Pyrrolidinone provided about 40% GC yield of the *N*-arylated product and 66% conversion of 2-bromothioanisole.

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(26) Kametani, T.; Ohsawa, T.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 290.

(27) After the completion of this work, a mild procedure for intramolecular amidation of aryl bromides and aryl iodides utilizing CuI (2 equiv except for one case with 10 mol %) and cesium acetate (5 equiv) in DMSO was reported: Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231.

(28) (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525. (b) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417. (c) Brown, J. A. *Tetrahedron Lett.* **2000**, *41*, 1623. For intramolecular C−O bond formation, see: (d) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

(29) (a) Renger, B. *Synthesis* **1985**, 856. (b) Greiner, A. *Synthesis* **1989**, 312.

described in the literature were characterized by comparing their ^{1}H and ^{13}C NMR spectra to the previously reported data. All new compounds were further characterized by elemental analysis.

The quality of the inorganic bases, particularly K_3PO_4, is quite important. The best results were obtained with K_3PO_4 available from Fluka (catalog number 04347, Riedel-de Haën product; free-flowing, fine granules of uniform size). We also tried several reactions with the K_3PO_4 purchased from Alfa Aesar (particles of variable size ranging from fine powder to large chunks) and obtained comparable results in all cases except for entry 8 in Table 5 where use of the Alfa Aesar product failed. The particle size of K_3PO_4 is very important; most reactions worked best if the granular product available from the commercial sources was used directly. Some reactions (particularly, the arylation of 2-pyrrolidinone) were in fact inhibited if K_3PO_4 was ground with a mortar and pestle. We found only one reaction (Table 5, entry 7) that worked slightly better if finely ground K_3PO_4 was used. We believe that these observations are best explained by variable kinetic basicity of different K_3PO_4 samples, which should be heavily influenced by the particle size of this heterogeneous base. K_2CO_3 (powder, −325 mesh) was purchased from Aldrich. Although K_3PO_4 and K_2CO_3 were weighed out in the air, care was taken to minimize exposure to air due to the hygroscopicity of these bases, particularly during very humid periods of the year.

Representative Procedures: *N*-(2-Methylphenyl)acetamide (Table 4, entry 8). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), acetamide (90 mg, 1.5 mmol), and K_3PO_4 (430 mg, 2.03 mmol), evacuated, and backfilled with argon. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %), 2-iodotoluene (128 μL, 1.01 mmol), and dimethylformamide (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 80 °C for 23 h. The resulting pale brown suspension was allowed to reach room temperature and filtered through a 0.5 × 1 cm pad of silica gel eluting with 10 mL of ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (2 × 15 cm; hexanes−ethyl acetate 1:4; 15 mL fractions). Fractions 8−16 provided 143 mg (95% yield) of the known[30] product as pale yellow fine needles.

***N*-(3-Hydroxymethylphenyl)-2-pyrrolidinone (Table 5, entry 3).** A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %) and K_3PO_4 (430 mg, 2.03 mmol), evacuated, and backfilled with argon. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.10 mmol, 10 mol %), 3-iodobenzyl alcohol (128 μL, 1.01 mmol), 2-pyrrolidinone (94 μL, 1.24 mmol), and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 80 °C for 3 h. The resulting white suspension was allowed to reach room temperature and filtered through a 0.5 × 1 cm pad of silica gel eluting with 10 mL of ether−methanol (5:1). The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (2 × 20 cm; dichloromethane−methanol 25:1; 15 mL fractions). Fractions 14−19 provided 180 mg (93% yield) of the product as a white solid. Mp 120−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (m, 1H), 7.55−7.50 (m, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.17−7.12 (m, 1H), 4.68 (d, J = 5.8 Hz, 2H), 3.86 (t, J = 7.0 Hz, 2H), 2.65 (t, J = 5.8 Hz, 1H), 2.60 (t, J = 8.0 Hz, 2H), 2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 141.8, 139.3, 128.9, 123.0, 119.0, 118.5, 64.9, 48.9, 32.7, 17.9. IR (neat, cm^{-1}): 3331, 1663. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.05; H, 6.81.

***trans*-*N*-(4-Dimethylaminophenyl)-3-phenylpropenamide (Table 6, entry 4).** A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol %), 4-(dimethylamino)-1-bromobenzene (201 mg, 1.00 mmol), *trans*-cinnamamide (178 mg, 1.21 mmol), and K_2CO_3 (280 mg, 2.03 mmol), briefly evacuated, and backfilled with argon. Racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine[31] (16 μL, 0.10 mmol, 10 mol %) and toluene (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 23 h. The resulting bright yellow suspension was allowed to reach room temperature and then filtered through a 0.5 × 1 cm pad of silica gel eluting with 1:1 ethyl acetate−dichloromethane (10 mL). The filtrate was concentrated and the residue was dissolved in 10 mL of dichloromethane and purified by flash chromatography on silica gel (2 × 20 cm, ethyl acetate−dichloromethane 1:4, 15 mL fractions). Fractions 10−20 provided 261 mg (98% yield) of the desired product as a bright yellow solid. Mp 171−173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75−7.65 (m, 2H), 7.53−7.43 (m, 4H), 7.36−7.28 (m, 3H), 6.72−6.66 (m, 2H), 6.58 (d, J = 15.5 Hz, 1H), 2.90 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 147.9, 141.3, 134.8, 129.6, 128.7, 127.8, 121.7, 121.3, 113.0, 40.8. The ^{13}C NMR spectrum contains two overlapping signals. IR (neat, cm^{-1}): 3236, 1652. Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81. Found: C, 76.68; H, 6.82.

***N*-(4-Methylphenyl)-2-pyrrolidinone (Table 7, entry 2).** A Schlenk tube was charged with CuI (20 mg, 0.11 mmol, 5.1 mol %) and K_2CO_3 (600 mg, 4.34 mmol), evacuated, and backfilled with argon. Racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (35 μL, 0.22 mmol, 11 mol %), 2-pyrrolidinone (155 μL, 2.04 mmol), and 4-chlorotoluene (1.0 mL, 8.4 mmol) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 23 h. The resulting dark brown suspension was cooled to room temperature and filtered through a 0.5 × 1 cm pad of silica gel eluting with 10 mL of ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (2 × 20 cm; hexanes−ethyl acetate 1:4; 15 mL fractions). Fractions 7−15 provided 336 mg (94% yield) of the known[32] product as white crystals.

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

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