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The Copper-Catalyzed *N*-Arylation of Indoles

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Abstract: A general method for the *N*-arylation of indoles using catalysts derived from CuI and *trans*-1,2-cyclohexanediamine (**1a**), *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (**2a**), or *N,N′*-dimethyl-ethylenediamine (**3**) is reported. *N*-Arylindoles can be produced in high yield from the coupling of an aryl iodide or aryl bromide with a variety of indoles.

Introduction

The Ullmann-type[1] coupling of aryl halides with indoles represents a straightforward, inexpensive approach to *N*-arylindoles.[2] These copper-catalyzed reactions traditionally have required high temperatures, generally 140 °C or more, and often the use of two or more equivalents of the aryl halide to obtain optimal yields. The palladium-catalyzed *N*-arylation of indoles is an alternative method that addresses the problems of extreme reaction temperatures.[3] Problems, however, such as C-3 arylation, and an intolerance of several important functional groups have also limited this method. Further, because of the relatively high cost of palladium, mild alternatives using inexpensive metals are desirable. Copper-catalyzed methods reported for the arylation of nitrogen heterocycles using mild conditions include the use of arylboronic acids,[4] aryl bismuth,[5] and aryl lead[6] reagents. These methods using alternative arylating agents, derived from the corresponding aryl halide, are restricted in terms of the level of substitution tolerated on either the aryl or indole substrates. Additionally, the toxicity of bismuth and lead compounds and the cost of arylboronic acids detracts from their appeal. The nucleophilic aromatic substitution of aryl halides, activated by electron-withdrawing substituents, with indole represent an alternate route to *N*-arylindoles for some substrate combinations.[7]

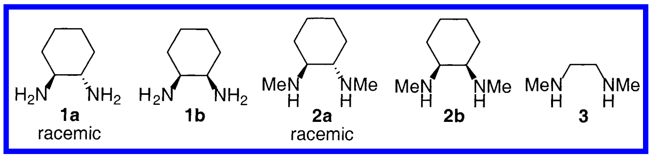

Figure 1. Diamine ligands used for the *N*-arylation of indoles.

We have previously found that the use of 1,10-phenanthroline as a ligand for copper could provide more active catalysts for the *N*-arylation of imidazoles.[8] Goodbrand also observed a similar acceleration in the arylation of diarylamines to form triarylamines.[9] To discover a more active and general catalyst system for the *N*-arylation of indoles, we explored the use of simple chelating ligands for copper. We soon found that copper catalysts derived from copper iodide and simple diamine ligand **1** (Figure 1) could efficiently catalyze the coupling of aryl halides with amides (Goldberg coupling) and *N*-H heterocycles in excellent yields under relatively mild conditions and with low quantities of copper.[10] Moreover, the reaction of a variety of substituted indoles with aryl iodides was explored. Reactions of carbazole, 7-azaindole, 5-cyano-, and 5-aminoindole proceeded in high yield. Hindered indoles (those substituted in the 2- and 7-position) were shown to provide the desired products in moderate yields. In this paper, we report in full our investigations of the *N*-arylation of indoles and disclose an improved copper catalyst system. Our new protocol employs ligands **2a** and **3**, with the latter being commercially available, for the coupling of a variety of indoles with substituted aryl iodides and bromides.

Results and Discussion

In our initial report, the *N*-arylation of indoles utilized 1−5 mol % CuI, 10−20 mol % ligand **1a**,[11] K$_3$PO$_4$ as base and

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(1) For a general review, see Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(2) (a) Khan, M. A.; Polya, J. B. *J. Chem. Soc. C* **1970**, 85. (b) Harbert, C. A.; Plattner, J. J.; Welch, W. M.; Weissman, A.; Koe, B. K. *J. Med. Chem.* **1980**, *23*, 635. (c) Lexy, H.; Kauffmann, T. *Chem. Ber.* **1980**, *113*, 2755. (d) Unangst, P. C.; Connor, D. T.; Stabler, S. R.; Weikert, R. J. *J. Heterocyclic Chem.* **1987**, *24*, 811. (e) Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3279. (f) Murakami, Y.; Watanabe, T.; Hagiwara, T.; Akiyama, Y.; Ishii, H. *Chem. Pharm. Bull.* **1995**, *43*, 1281.

(3) (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (d) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481. (e) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

(4) (a) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941. (b) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757. (c) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233. (d) Yu, S.; Saenz, J.; Srirangam, K. *J. Org. Chem.* **2002**, *5*, 1699.

(5) (a) Barton, D. H. R.; Finet, J.-P.; Khamsi, J. *Tetrahedron Lett.* **1998**, *29*, 1115. (b) Sorenson, R. J. *J. Org. Chem.* **2000**, *65*, 7747.

(6) (a) Lopez-Alvarado, P.; Avendano, C.; Menendez, J. C. *J. Org. Chem.* **1995**, *60*, 5678. (b) Elliott, G. I.; Konopelski, J. P. *Org. Lett.* **2000**, *20*, 3055.

(7) (a) Smith, W. J., III; Sawyer, J. S. *Tetrahedron Lett.* **1996**, *37*, 299. (a) Maiorana, S.; Baldoli, C.; Del Buttero P.; Di Ciolo, M.; Papagni, A. *Synthesis* **1998**, 735. (c) Smith, W. J., III; Sawyer, J. S. *Heterocycles* **1999**, *51*, 157.

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

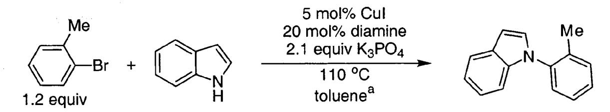
(9) Goodbrand, H. B.; Hu N.-X. *J. Org. Chem.* **1999**, *64*, 670.

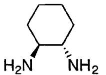
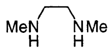
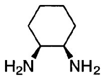
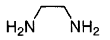
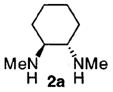
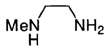
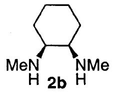
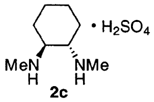
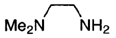
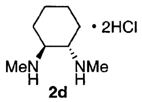
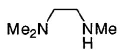
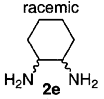
(10) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

(11) We would like to thank Arran Chemical Company for a generous gift of ligand **1a**.

10.1021/ja027433h CCC: $22.00 © 2002 American Chemical Society

Table 1. Screening of Diamine Ligands for the *N*-Arylation of Indole



ligand	% yield[b] 4h	% yield[b] 24h	ligand	% yield[b] 4h	% yield[b] 24h
 **1a** racemic	66	93[c]	 **3**	52	99[d]
 **1b**	59	88	 **4**	22	96
 **2a** racemic	52	98[d]	 **5**	52	90
 **2b**	39	90[e]	 **6**	52	90
 **2c** racemic	55	94	 **7**	5	43
 **2d** racemic	19	85	 **8**	8	71
 **2e** *cis/trans* mixture	41	80[f]	 **9**	<1	2

[a] All reactions: [indole] = 1 M in toluene. [b] In all cases, the conversion of indole was 1−10% higher than the above GC yields (dodecane as an internal standard). [c] With 9−10% mono *N*-arylation of ligand. [d] With 3−5% mono *N*-arylation of ligand. [e] With 10% mono *N*-arylation of ligand. [f] A large amount of mono *N*-arylation of the diamine mixture (∼16−17%) was observed.

dioxane as solvent.[10] Despite the success of this system, limitations remained. For example, in difficult cases, the *N*-arylation of **1a** was found as a side reaction. In turn, the overall reaction rate slowed, and incomplete conversion of the substrates was often observed. Thus, the search for other possible ligands and conditions for this arylation chemistry was undertaken. Initially, during a survey of the effect of different solvents on the reaction efficiency, it was determined that toluene was a superior solvent to dioxane. Since this is a process-friendly substitution, toluene was employed in the majority of new examples in this paper, although other solvents such as ether, THF, DMF, and DME can be utilized.

A series of ligands were examined for the reaction of 2-bromotoluene with indole and the most active ligands are shown in Table 1. We were very pleased to find that several diamines, in addition to the previously studied **1a**, could efficiently catalyze this transformation in toluene. This was somewhat of a surprise as previous screening in dioxane did not provide such uniform improvement. Ligands **2a**[12] and **3**, both bearing *N,N′*-dimethyl groups on nitrogen, provided marginally the best yields. The main advantage of using **2a** or **3** was that less ligand *N*-arylation (3−5%) was observed in comparison to reactions using **1a** (9−10%). The use of greater than one equivalent of the respective aryl halide can help in achieving good yields of the desired product even when some ligand arylation is observed. However, it is ideal to minimize these side reactions because of the resulting loss of active catalyst.[13] Further, **2a** and **3** appear to be better ligands for CuI; the combination of 10 mol % **2a** with 5 mol % CuI in toluene forms a completely homogeneous solution at 80 °C, while the identical experiment with **1a** shows undissolved CuI remaining. Sulfuric acid or hydrochloric acid salts of **2a** showed similar to slightly lower reactivity when compared to the free base.[14] Use of the cis dimethylated ligand (**2b**) showed reduced activity and increased ligand arylation (10%), a possible explanation being that the *cis*-diamine (one axial amino group and one equatorial amino group) is more sterically hindered than the *trans*-diamine (both amino groups equatorial) because of a 1,3-diaxial interaction. This would result in a more hindered copper complex with lower catalytic activity. When the relatively inexpensive cis/trans mixture (**2e**) of 1,2-diaminocyclohexane was used, a significant amount of competitive ligand arylation was found (16−17%). The use of tri- (**8**) or tetramethyl (**9**) substituted ethylenediamine resulted in lower activity. Presumably, the increased level of substitution at nitrogen leads to reduced binding efficiency. In several cases (ligands **2d**, **4**, **7**, and **8**), a comparison of the progress of the reaction (GC yield) after 4 h and 24 h revealed the existence of an induction period.[15] For example, the use of ligand **4** (Table 1) provided only 22% GC yield of the desired product after 4 h but yet gave a 96% yield after a 24 h reaction time.

The ligand study in Table 1 provided evidence that the use of *N,N′*-dimethyldiamine ligands allows for higher yield and less *N*-arylation of ligand compared to reactions using **1**. With this in mind, a more thorough comparison of ligands **1a** and **2a** was undertaken (Table 2). In all cases, **2a** was a superior ligand to **1a** in terms of catalytic activity or yield of the coupling product. For example, as shown in entry 2, a 96% yield of product from the coupling of 4-bromotoluene with indole was observed, while in entry 1 a much lower yield (57%, GC) was found. Interestingly, only a modest improvement in yield (91% versus 88%) was found for the coupling of 2-bromotoluene with indole using **2a** (entry 4). The use of 5-nitroindole as a substrate provided a 38% GC yield (entry 5) of the desired product with **1a**, while a clean reaction with 96% yield was found with **2a** (entry 6). Likewise, significant improvements were found with the **2a** derived catalyst (entries 8 and 10) when the relatively hindered 2-phenylindole and 7-methylindole were combined with iodobenzene. One explanation for the above improvement is that less ligand arylation occurs, and therefore faster reactions result, when **2a** was employed.

An effort was made to determine the impact of the source of copper on the arylation process (Table 3). In the coupling of indole with 4-bromotoluene, Cu(0) (copper bronze) was equally effective as Cu(I) (copper iodide),[16] while Cu(II) sources

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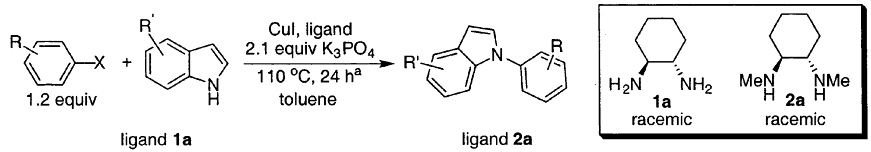
(12) The synthesis of **2a** followed a modified procedure by Seebach (see Experimental Section). Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999.

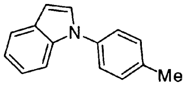
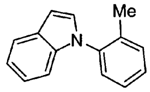
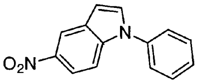
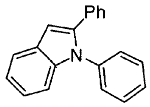
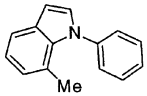
(13) Ligand screening has shown that *N*-aryl-1,2-diamines (mono or bis) are poor ligands for the *N*-arylation of indole.

(14) While they are not recommended as a first choice, in some cases their use may be easier vis á vis long-term storage than for the free base.

(15) Induction periods were observed and are currently being studied in similar amide arylation chemistry: Strieter, E. R.; Buchwald, S. L. Massachusetts Institute of Technology, 2002. Unpublished results.

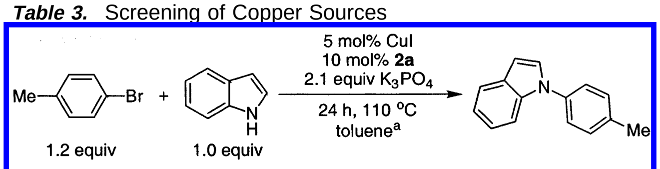
Table 2. A Comparison of Ligands **1a** and **2a** for the Arylation of Indoles



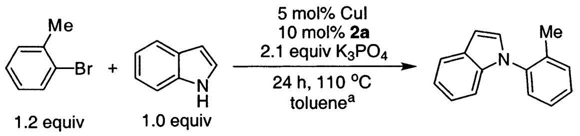
ligand **1a**				ligand **2a**				
entry	conditions	% yield (isol)	arylated[b] **1a** (%GC)	entry	conditions	% yield (isol)	arylated[b] **2a** (%GC)	product
1	(ArBr) 1% CuI 5% **1a**	57[c] (GC)	2[c]	2	(ArBr) 1% CuI 5% **2a**	96	1	
3	(ArBr) 5% CuI 20% **1a**	88	9	4	(ArBr) 5% CuI 20% **2a**	91	5	
5	(ArI) 5% CuI 20% **1a**	38[d] (GC)	n.d.[d]	6	(ArI) 5% CuI 10% **2a**	96	<1	
7	(ArI) 5% CuI 20% **1a**	74	5	8	(ArI) 5% CuI 10% **2a**	92	2	
9	(ArI) 5% CuI 20% **1a**	75	7	10	(ArI) 5% CuI 20% **2a**	85	3	

[a] All reactions: [indole] = 1 M in toluene unless otherwise noted. [b] Yields refer to the average of two isolated yields of >95% purity as determined by GC and ^{1}H NMR. "Arylated" refers to the mono *N*-arylated product (GC yield). [c] Using 5 mol % CuI and 20 mol % **1a** a 95% isolated yield with 3% ligand arylation was found. [d] Multiple GC peaks were found, with the extent of ligand arylation not being determined.

Table 3. Screening of Copper Sources



copper source	% conv	% yield
CuI	100	100
Cu (bronze)	100	100
Cu(OAc)$_2$	100	92
CuCl$_2$	94	80
Cu(OMe)$_2$	99	92



copper source	% conv	% yield
CuI	100	95
Cu (bronze)	60	45

[a] All reactions: [indole] = 1 M in toluene.

(acetate, chloride, and methoxide) gave a lower yield. However, with the slightly more challenging substrate combination, 2-bromotoluene and indole, CuI was superior.

In an attempt to probe the generality of the method, the reaction of aryl halides with a wide variety of 2-, 3-, and 5-substituted indoles, presenting an assortment of functional groups, was conducted (Table 4). The reaction time (24 h unless otherwise specified) was not optimized. With the catalyst system derived from **2a**, the reaction of hindered 2-*i*Pr-indole (entry 1) with iodobenzene could be effected in good yield. The use of 3-substituted indole substrates was straightforward, with tryptamine (entry 4), melatonin (entry 5), tryptophol (entry 6), and 5-methoxytryptamine (entry 8) giving excellent selectivity[17] in arylation of the indole nitrogen. The functional groups present in these cases highlight the mild and remarkably chemoselective nature of the method. Selective couplings in the presence of these functional groups with palladium-based systems have not yet been reported. Thus, this protocol complements existing palladium- or copper-catalyzed *N*-arylation methods.[18] While the arylation of ethyl indole-3-carboxylate (entry 2) and 2,3-dimethylindole (entry 9) proceeds smoothly, the arylation of ethyl 2-methylindole-3-carboxylate proceeded to only 63% conversion even with increased quantities of copper catalyst.[19] One reason that this reaction may be problematic is the necessity to use DMF as a reaction solvent because of the insolubility of the substrate in toluene. We were pleased to find that comparable

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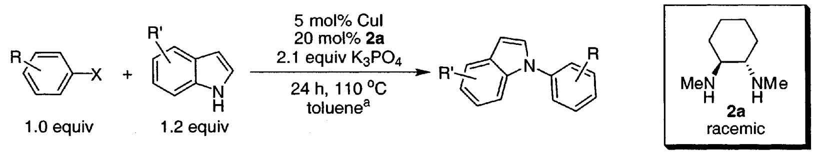
(16) CuI (98% purity, purchased from Strem) was of a fine powdered quality.

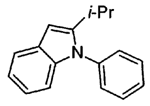
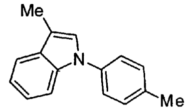
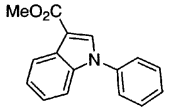
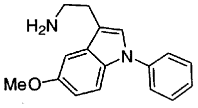
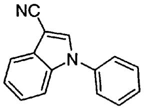
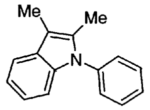
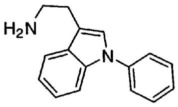
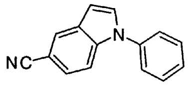
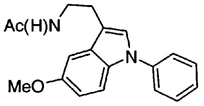
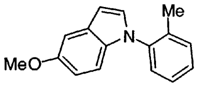
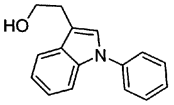
(17) Tryptamine (entry 4), melatonin (entry 5), and 5-methoxytryptamine (entry 8) gave a single regioisomer by GC/MS of the crude reaction mixture. However, the reaction employing tryptophol (entry 6) as a substrate gave 7% of the respective bis-arylated byproduct (GC/MS).

(18) For reviews on Pd-catalyzed amination, see (a) Muci, A. R.; Buchwald, S. L. Practical Palladium Catalysts for C-N and C-O Bond Formation. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, p. 133. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (d) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576* (1−2), 125. For an example of a new copper-catalyzed amination method, see (e) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(19) Optimized conditions: 10 mol % CuI, 25 mol % **2a**, K$_2$CO$_3$, DMF, 110 °C (63% conversion).

Table 4. The Reaction of Aryl Halides with Substituted Indoles Utilizing Ligands **2a** and **3**



entry	X	product	% yield	entry	X	product	% yield
1	I		70[b]	7	Br		85[e]
2	I		96[c]	8	Br		76[c]
3	I		92	9	I		98
4	I		90	10 11	I I		98 99[f]
5	I		77[c]	12	I		86
6	I		90[d]				

Yields refer to the average of two isolated yields of >95% purity as determined by GC and ^{1}H NMR. [a] All reactions: [indole] = 1 M in toluene unless otherwise noted. [b] With 10% CuI and 20% **2a**. [c] With 10 mol % of **2a**. [d] GC/MS of the crude reaction mixture showed 7% of the bis-arylated adduct. [e] With 1 mol % CuI and 5 mol % **2a**. [f] With 20 mol % **3**.

results for the arylation of 5-cyanoindole can be realized using commercially available ligand **3** (entry 11) as an alternative to **2a** (entry 10).

A systematic variation of the aryl halide was also undertaken (Table 5) to provide *N*-arylindoles functionalized in the *para*, *meta*, or *ortho* positions. With the simplest case (entry 1), the coupling could be achieved using 0.2% CuI and 1% **2a** to provide a 98% yield of the desired product. While the reaction of hindered 1-bromo-2-isopropylbenzene with indole was facile (entry 2), the coupling of 2-substituted indoles with 2-substituted bromides was significantly slower.[20] Not all substrates examined require 110 °C for complete reaction; for example, in three separate cases aryl iodides were successful coupling partners with indole at 80 °C in good yield (entries 3, 7, and 9). Ligand **3** again provides a comparably efficient catalyst to the **2a**/CuI system (entries 5 and 11). Particularly interesting examples include three cases where good yields are achieved when 2° amide groups are present on the aryl iodide (entries 12−14). No example of the use of this type of substrate in Pd-catalyzed C−N coupling has so far appeared in the literature. In particular, the *N*-allyl amide (entry 14) would probably be a difficult substrate. This is due to the likelihood of competitive π-allyl-Pd formation[21] as well as the incompatability of the secondary amide. The *N*-arylation of indole with 3-bromopyridine (entry 15), 2-amino-5-bromopyridine (entry 16), and with 4-bromoisoquinoline (entry 17) demonstrates the utility of the method with halo-pyridine substrates.

Some limitations in the method were found when easily ionizable functional groups such as phenols or benzoic acids were present as substituents on the arene. For example, the coupling of 4-iodotoluene with 5-hydroxyindole proceeded (80% conversion of the indole) with the above conditions, but the *N*- to *O*-arylation ratio was determined to be only 5:1. The reaction of 4-bromo- or 2-bromobenzoic acid with indole using the above conditions failed to give any conversion to product even when an extra equivalent of base was allowed for deprotonation of the acid. A possible explanation is that coordination of the resulting phenolate or aryl carboxylate to copper resulted in inactivation of the catalytic species. A second explanation could be that the phenolate or aryl carboxylate would have limited solubility. It is a testament to this method that examples involving sterically hindered indoles (2-*i*Pr) and halides (1-bromo-2-isopropylbenzene) were successful. However, a poor conversion to product was found when *both* coupling partners had substitution in the 2-position.

Conclusion

In summary, a method for the coupling of substituted aryl bromides and iodides with indoles in a general fashion is reported. With our preliminarily reported coupling conditions, utilizing ligand **1a**, the reaction of 4-bromotoluene and indole

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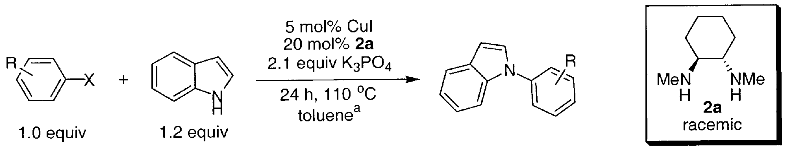
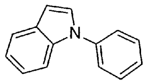
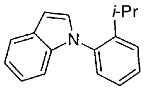
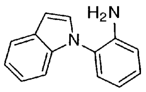
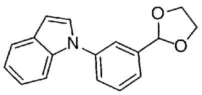
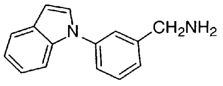
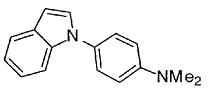
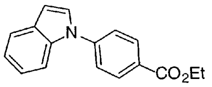
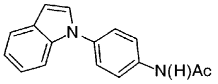
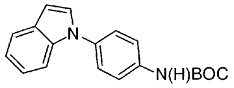
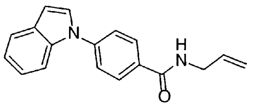
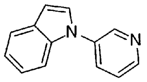
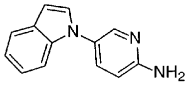
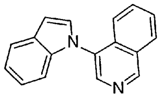
(20) Following conditions of Table 5: Reaction of 2-methylindole with 2-bromotoluene gave no conversion. Reaction of 2-methylindole with 2-iodotoluene gave 10% conversion. Reaction of 2-methylindole with 2-bromoanisole gave only 47% conversion.

(21) For a review on allylic protecting groups and their removal with palladium see Guibe, F. *Tetrahedron* **1998**, *54*, 2967.

Table 5. The Reaction of Substituted Aryl Halides with Indole Utilizing Ligands **2a** and **3**



entry	X	product	% yield
1	I		98[b]
2	Br		86[c]
3	I		88[d]
4	Br		72
5	Br		64[e]
6	Br		78
7	I		90[d]
8	Br		93
9	I		90[d]
10	Br		90
11	Br		92[e]
12	I		72
13	I		75
14	I		83
15	Br		93
16	Br		78
17	Br		72

Yields refer to the average of two isolated yields of >95% purity as determined by GC and ^{1}H NMR. [a] All reactions: [indole] = 1 M in toluene unless otherwise noted. [b] With 0.2 mol % CuI, 1 mol % **2a** for 48 h. [c] [indole] = 2 M. [d] Reaction run at 80 °C. [e] With 20 mol % **3**.

was the only transformation of an aryl bromide that provided the desired product in high yield. With the improved conditions, a variety of aryl bromides were found to be suitable substrates. Functional groups on the aryl halide or the indole that can be tolerated under these coupling conditions include amine (alkyl or aryl), amide, cyano-, nitro-, ester, allyl, and hydroxyl groups. The key development in this improved copper-catalyzed method was the use of *N*,*N*′-dimethyl-1,2-diamine ligands **2a** and **3**, with diamine **3** being commercially available. This method, we believe, now constitutes the state of the art in accomplishing this important transformation. Considering the ubiquity of the indole nucleus in pharmaceutically interesting compounds[22] and natural products,[23] this method should find widespread use. Studies on the arylation of other nitrogen heterocycles as well as the improvement of this methodology are currently underway in our laboratories.

General Procedure for the *N*-Arylation of Indoles. [24] To a resealable Schlenk tube, or alternatively a screw-cap test tube, was added CuI (5 mol %), the indole (1.2 mmol), and K_3PO_4 (2.1 mmol), and the reaction vessel was fitted with a rubber septum. The vessel was evacuated and back-filled with argon and this evacuation/back-fill procedure was repeated one additional time. Dodecane[25] (45 μL, 0.20 mmol), the aryl halide (1.0 mmol), trans-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (10−20 mol %), and toluene (1 mL) were then successively added under a stream of argon. The reaction tube was quickly sealed and the contents were stirred while heating in an oil bath at 110 °C (the reaction time was not optimized as all reactions were run for 24 h unless otherwise noted). The reaction mixture was cooled to ambient temperature, diluted with ethyl acetate (2−3 mL), and filtered through a plug of silica gel, eluting with additional ethyl acetate (10−20 mL). The filtrate was concentrated and the resulting residue was purified by column chromatography to provide the desired product.

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

JA027433H

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(22) Negwer, M. In *Organic-Chemical Drugs and their Synonyms: (An International Survey)*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994.

(23) Southon, I. W.; Buckingham, J. In *Dictionary of Alkaloids*; Saxton, J. E., Ed.; Chapman and Hall: London, 1989.

(24) The quality of K_3PO_4 is extremely important for reproducible results to be obtained. High quality K_3PO_4 was used as purchased from Fluka. Alternatively, K_3PO_4 purchased from Alfa Aesar could be ground to a fine powder that provided reproducible results for the several reactions where it was used.

(25) Dodecane was used in the above reactions as an internal GC standard.