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Highly Efficient Copper-Catalyzed *N*-Arylation of Nitrogen-Containing Heterocycles with Aryl and Heteroaryl Halides

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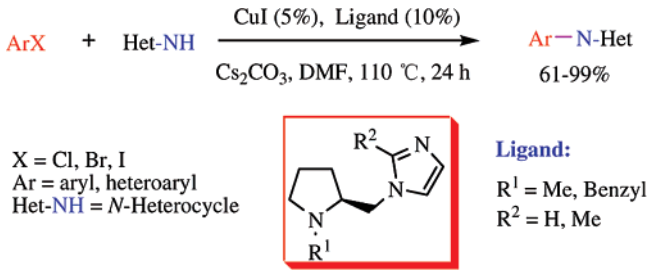

New (*S*)-pyrrolidinylmethylimidazole ligands **(4a−c)** have been readily synthesized in a straightforward fashion from least expensive starting materials in short steps in high yields. Relatively mild and highly efficient CuI-catalyzed *N*-arylation procedures for imidazoles with aryl and heteroaryl bromides or chlorides have been developed in the presence of **4a** and Cs_2CO_3. It is important to note that the protocol could tolerate functional groups such as ester, nitrile, nitro, ketone, free hydroxyl, and free primary amine on the aryl halide. The protocol could also be applicable to other π-electron-rich nitrogen heterocycles (pyrrole, pyrazole, indole, benzimidazole, and triazole), affording the *N*-arylazoles in good to excellent yields.

Introduction

N-Arylazoles (e.g., *N*-arylpyrroles, *N*-arylpyrazoles, *N*-arylindoles, *N*-arylimidazoles, *N*-aryltriazoles, etc.) are ubiquitous in biochemical, biological, and medicinal structure and function.[1] Traditionally, these compounds have been synthesized via SNAr (nucleophilic aromatic substitution) of *N*-H containing π-electron-rich nitrogen heterocycles with electron-deficient aryl halides, which limits its scope,[2] or via the classical Ullmann-type coupling with aryl halides, which generally suffers from important limitations such as high reaction temperatures (often 150 °C or as high as 200 °C), the use of stoichiometric amounts of copper reagents, moderate yields, and poor substrate generality, sometimes preferentially with aryl iodides or aryl halides activated by electron-withdrawing or *o*-carboxylic acid groups.[3] It is therefore not surprising that great efforts have recently been directed toward the development of a mild as well as highly efficient method for constructing *N*-arylazole units.[4] For example, mild conditions have been reached by using other types of cross-coupling reagents instead of aryl halides as substrates, such as aryllead triacetates,[5] aryl siloxanes,[6] triphenylbismuths,[7] arylstannanes,[8] diaryliodonium salts,[9] or recently arylboronic acids.[10] However, these methodologies normally need additional

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steps to convert aryl halides into the corresponding reagents, and thus are limited by the high cost and poor availability of functionalized substrates. In addition, the synthesis of some reagents may involve the use of highly toxic materials and/or unstable reagents.[11] Therefore, the use of aryl halides as an electrophilic coupling partner should resolve many of these issues. Recently, several Pd-catalyzed C−N formation methods have been discovered, which, upon using some sterically hindered phosphine ligands, allowed cross-couplings of aryl halides with *N*-H heterocycles to proceed under relatively mild conditions.[12] Notably, the economic attractiveness of copper has led to a resurgence of interest in Ullmann-type coupling reactions since Buchwald discovered and developed the Cu-catalytic path for *N*-arylation of heterocycles with aryl halides in the presence of diamine ligands.[4,13] Indeed, some efficient ligands have been disclosed in these coupling reactions, including amino acids,[14] diamines,[15] diimines,[16] aminoarenethiolate,[17] phosphine ligands,[18] 2-aminopyrimidine-4,6-diol,[19] and 8-hydroxyquinoline.[20] Quite recently, particularly noteworthy is the use of 4,7-dimethoxy-1,10-phenanthroline for the copper-catalyzed *N*-arylation of imidazoles, which could tolerate an array of functional groups on the aryl halides.[21]

While many significant results have been achieved for the Cu-catlyzed *N*-arylation of a variety of nitrogen heterocycles through the use of those ligands mentioned above, relatively little progress has been made for the coupling of imidazoles. The majority of aryl halides investigated to date, already limited in examples, were aryl iodides.[13b,c,14a,15a,18a] Very few examples of the coupling of imidazoles with aryl bromides or of a hindered substrate or of functional substrates have been disclosed,[14b,c,16,18b−21] and in some cases the electron-withdrawing groups and/or higher reaction temperatures even have to be required.[15a,17,19] Therefore, the development of new ligand structures for copper-catalyzed cross-coupling protocols constitutes an area of considerable interest.

Recently, our laboratory reported the effective simple copper salt catalyzed *N*-arylation of imidazole with arylboronic acids in protic solvents.[22] Thus it was a natural extension for us to explore novel catalytic systems for preparing a variety of *N*-arylazoles through the coupling reaction of aryl halides. L-Proline has been shown to be a suitable auxiliary for the CuI-catalyzed C−N bond formation between *N*-containing heterocycles and aryl iodides or electron-deficient aryl bromides. However, for electron-rich or neutral aryl bromides, low conversions were observed due to the severe self-coupling of L-proline with aryl bromides at higher reaction temperatures (about 110 °C).[14a,b] It is reasonable to assume that the bidentate L-proline ligand might be modified structurally by the *N*-alkylation of the pyrrolidine ring to inhibit such a self-coupling reaction, resulting in the improvement of catalytic performance. In addition, such a modification of L-proline might improve the solubility of the ligand. On the other hand, imidazoles themselves have proved to be an outstanding class of ligands, being capable of forming a broad variety of metal complexes that are able to catalyze a great number of reactions. These prompted us to explore the synthesis of a new class of pyrrolidine-derived diamine ligands in which the carboxyl group of L-proline was replaced by an imidazole ring (**4a**−**c**) and to evaluate their scope as ligands in the CuI-catalyzed *N*-arylation of π-electron-rich nitrogen heterocycles.

Results and Discussion

While not being commercially available, (*S*)-pyrrolidinylmethylimidazoles (**4a**−**c**) are stable and easily synthesized from least expensive starting materials in high yields and on a multigram scale. Following Scheme 1, the synthesis of **4** is a straightforward process starting from (*S*)-pyrrolidin-2-ylmethanol (**1**), which is easily prepared from L-proline.[23] Treatment of **1**

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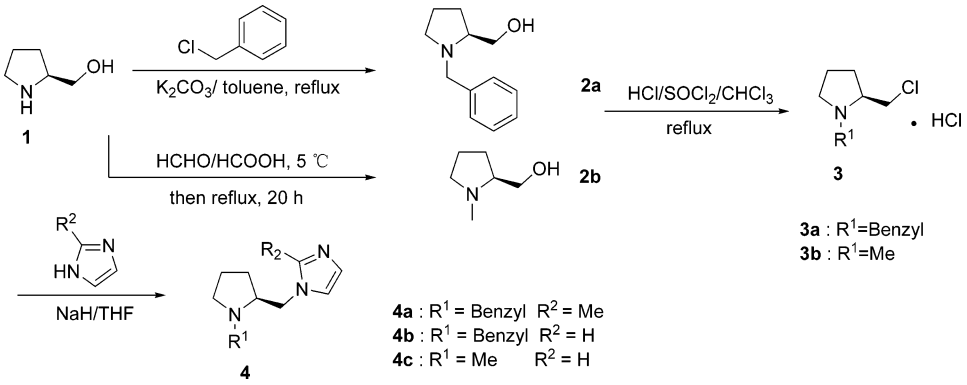
SCHEME 1. Synthesis of (*S*)-Pyrrolidinylmethylimidazoles



with benzyl chloride afforded **2a**[24] or treatment with formic acid and aqueous formaldehyde gave **2b**,[25] followed by treatment with $SOCl_2$/HCl to yield **3**.[26] Thus the chloride displacement of **3** with imidazole provided the desired ligands (**4a**−**c**).

N-Arylimidazoles have not only been recurrent templates in medicinal chemistry[27−36] but also important building blocks for the synthesis of imidazolium quaternary salts used as key precursors to *N*-heterocyclic carbenes (NHCs) as well as ionic liquids.[37] Furthermore, the arylation of imidazoles is still a long-standing problem, which is far from being satisfactorily solved. We therefore chose to focus initial studies on the evaluation of the behavior of (*S*)-pyrrolidinylmethylimidazole **4** in the synthesis of *N*-arylimidazoles. This was determined during a preliminary survey of reaction conditions with use of bromobenzene and imidazole as model arylating agents shown in Table 1. While 5 mol % of CuI and 10 mol % of **4a** were employed in the presence of 2 equiv of Cs_2CO_3, a series of reaction solvents (e.g., toluene, dioxane, *n*-butanol, DMF, and DMSO) were first investigated (entries 1−6). Thus we found that more polar solvents are favorable for the catalytic reaction, which is in agreement with the previously reported results.[14a,b,18b,19] Among the solvents tested, DMF was clearly the best choice, and DMSO and *n*-butanol provided slightly lower yields, while less polar solvents like toluene and 1,4-dioxane delivered little desired coupling product (compare entries 1−5). Although recent reports demonstrate that in some cases the addition of a trace amount of water could improve the reaction efficiency,[10f,20,38] in our catalytic system a negative effect was observed in the presence of either **4a** or **4c**, while the effect of water was almost ignored in the presence of **4b** (entries 5, 6,and 16−19). After screening a variety of bases (e.g., Na_2CO_3, K_2CO_3, K_3PO_4, and Cs_2CO_3), we found that Cs_2CO_3 gave the best result of 96% yield in DMF (compare entries 5 and 11−13). The results from the ligand survey in combination with CuI are also summarized in Table 1, and **4a** and **4c** were found to be particularly effective ligands, whereas **4b** afforded 85% yield (entries 5, 16, and 18). In addition, lowering the amount of CuI to 2.5 mol % led to incomplete consumption of bromobenzene after 24 h of heating (50% yield, Cu/**4a** = 1:2, entry 10). Further experiments showed that a 24 h reaction time period was the optimal choice (entries 5, 14, and 15).

In an effort to obtain an optimum CuI/ligand ratio, we found that a 1:2 CuI/**4a** ratio is the best choice, while a 1:1 and a 2:1 CuI/**4a** ratio provided yields of 86% and 43%, respectively (entries 5, 8, and 9). It should be noted that no significant effect on reactivity was observed when further raising the ratio of CuI/**4a** from 1:2 to 1:4 while the process still required the same time period although the product yield was improved slightly from 96% to 98% (entry 7).

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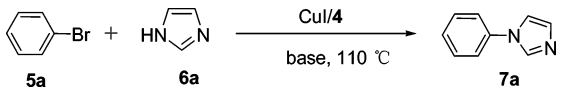
TABLE 1. Some Representative Results from the Screening of Reaction Conditions for the *N*-Arylation of Imidazole with Bromobenzene[a]



5a 6a 7a

entry	amount of ligand [mol %]	amount of CuI [mol %]	reaction time [h]	solvent	base	yield (%)[b]
1	**4a** (10)	5	24	toluene	Cs_2CO_3	*c*
2	**4a** (10)	5	24	dioxane	Cs_2CO_3	*c*
3	**4a** (10)	5	24	DMSO	Cs_2CO_3	71
4	**4a** (10)	5	24	*n*-butanol	Cs_2CO_3	82
5	**4a** (10)	5	24	DMF	Cs_2CO_3	96
6	**4a** (10)	5	24	DMF−H_2O	Cs_2CO_3	84[d]
7	**4a** (20)	5	24	DMF	Cs_2CO_3	98
8	**4a** (5)	5	24	DMF	Cs_2CO_3	86
9	**4a** (2.5)	5	24	DMF	Cs_2CO_3	43
10	**4a** (5)	2.5	24	DMF	Cs_2CO_3	50
11	**4a** (10)	5	24	DMF	K_3PO_4	90
12	**4a** (10)	5	24	DMF	K_2CO_3	32
13	**4a** (10)	5	24	DMF	Na_2CO_3	*c*
14	**4a** (10)	5	40	DMF	Cs_2CO_3	98
15	**4a** (10)	5	12	DMF	Cs_2CO_3	48
16	**4b** (10)	5	24	DMF	Cs_2CO_3	87
17	**4b** (10)	5	24	DMF−H_2O	Cs_2CO_3	87[d]
18	**4c** (10)	5	24	DMF	Cs_2CO_3	94
19	**4c** (10)	5	24	DMF−H_2O	Cs_2CO_3	84[d]

[a] Reaction conditions: **5a** (1.2 mmol), **6a** (1.0 mmol), base (2.0 mmol) in the presence of ligand **4** and CuI in 2.0 mL of solvent at 110 °C under N_2 atmosphere. [b] Isolated yields (average of two runs) based on **6a**. [c] Little coupling product was determined. [d] DMF (2.0 mL) and H_2O (0.1 mL) as solvent.

After optimized reaction conditions were obtained, the scope of the process with respect to aryl halide structure was investigated by using our catalyst system generated in situ from 5 mol % of CuI and 10 mol % of **4a** in the presence of 2 equiv of Cs_2CO_3 in DMF at 110 °C under N_2, and the results are summarized in Table 2. We were delighted to find that the *N*-arylation of imidazole with a variety of aryl bromides could be conducted smoothly to give the corresponding products in good to excellent yields (61−99%) (entries 1−14). It should be pointed out that the reaction of deactivated 4-bromoanisole (**5i**) could afford a good product yield (88%) (entry 9). Generally, Ullmann-type condensations were sensitive to steric hindrance near the halogen atom, and there are rare examples describing the Cu-catalyzed couplings of imidazole with sterically hindered aryl halides. Our catalytic system could be applied to imidazole *N*-arylation with ortho or pseudo-ortho substituted aryl bromides shown in entries 6−8. It is worth noting that the reaction of the notoriously recalcitrant hindered and deactivated 2-bromoanisole (**5h**) with imidazole even proceeded in 64% yield (entry 8). Generally, the synthesis of 1-naphthalen-1-yl-1*H*-imidazole (**7g**) requires more reactive 1-iodonaphthalene or arylboronic acid,[15a,21,22] or even in the presence of stoichiometric amounts of ligand.[39] In contrast, this study demonstrates that 1-bromonaphthalene (**5g**) was efficiently coupled with imidazole to give **7g** in 66% yield (entry 7). Regrettably, in this way, the coupling of more hindered mesityl bromide could not be accomplished smoothly under our standard conditions, affording a very low yield.

Substrates that contain certain functional groups have proven to be persistently problematic in the *N*-arylation of imidazoles. First, some functional groups themselves might be decomposed at higher reaction temperatures, for example, the partial hydrolysis of the ester to benzoic acid and of the nitrile to amide.[20,21] We were pleased to find that our catalytic system could tolerate a variety of functional groups such as ester, nitrile, ketone, and nitro (entries 1−3, 20, and 21). Another problematic situation in this area is the competition from the formation of C(aryl)−N and C(aryl)−O bonds when there is a free OH or NH directly bound to the aromatic ring that contains the halide.[4,40] Generally, free hydroxyl and primary amine groups should be protected before carrying out the *N*-arylation of imidazoles.[41] It is important to note that this protocol could almost exclusively carry out the selective *N*-arylation of 2-bromophenol (**5k**), 4-bromophenol (**5*l***), 4-bromoaniline (**5m**), 3-bromoaniline (**5n**), and 2-amino-5-bromopyridine (**5o**) to provide the corresponding *N*-arylimidazoles in good yields (entries 11−15), avoiding the formation of diaryl ethers and diarylamines. In addition, we also found that the *N*-arylation with *p*-dibromobenzene (**5j**) afforded exclusively the mono *N*-arylimidazole product in an excellent yield and no trace of the dicoupled product was detected when a 1.2:1 ratio of *p*-dibromobenzene to imidazole was employed (entry10).

By using the catalyst system based on **4a**, the coupling reactions of aryl chlorides such as 2-chloropyrimidine (**5s**), 4-chloronitrobenzene (**5t**), and 4-chlorobenzonitrile (**5u**) could also deliver the corresponding *N*-arylated products in excellent yields (entries 19−21). Further exploration revealed that some heteroaryl halides were compatible with these reaction conditions, giving satisfactory yields (75−97% yields) (entries 15−19). It may be noted that only a few papers have described the Cu-catalyzed *N*-arylation of imidazoles with heteroaryl halides in the presence of ligand.[14c,19,42]

To date the development of chemistry that could emanate from a single method for each of the major classes of nitrogen-containing heterocycles (e.g., pyrroles, pyrazoles, indazoles, imidazoles, triazoles, etc.) has been seriously inhibited. In an endeavor to expand the scope of the methodology, the protocol based on the use of our new catalytic system was also applied to other π-electron-rich nitrogen heterocycles (Table 3). It is worth noting that these optimized conditions were also suitable for the *N*-arylation of other imidazole derivatives. For example, the coupling reaction of 1*H*-benzimidazole (**6b**) with bromobenzene afforded the corresponding *N*-arylated product in 75% yield (entry 1). Sterically hindered 2-(1*H*-imidazol-2-yl)-1*H*-imidazole (**6c**) could be selectively monoarylated in 62% yield (entry 2). We were pleased to discover that the arylation of pyrazole and pyrrole with bromobenzene was accomplished through the application of a general reaction procedure to afford the *N*-arylated products in 87% and 72% yield, respectively (entries 3 and 4). Moreover, the yield of 1-phenyl-1*H*-pyrrole (**7x**) could be improved from 72% to 98% while iodobenzene was used in place of bromobenzene at relatively low temperature (90 °C) (entries 4 and 5). While the use of 1,2,4-triazole and indole was disappointing with bromobenzene, providing only very low

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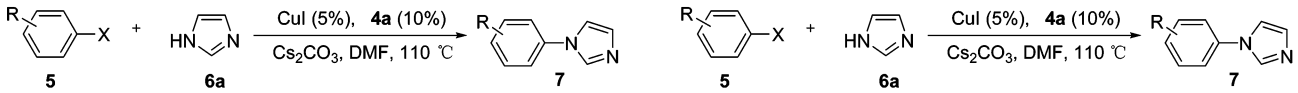
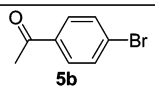
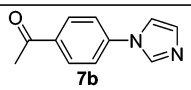
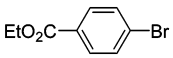
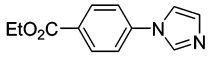
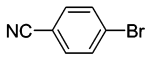
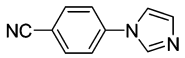
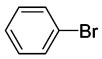
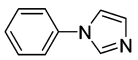
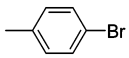
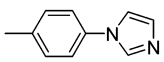
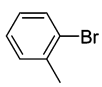
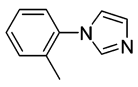
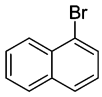
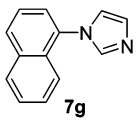
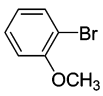
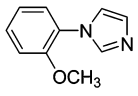
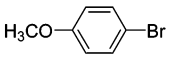
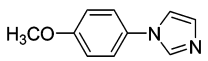
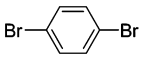
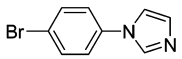
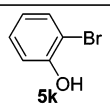
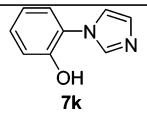
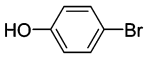
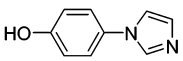
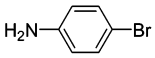
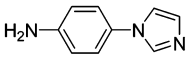
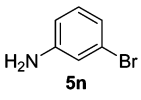
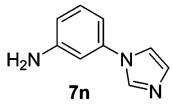
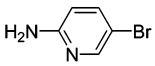
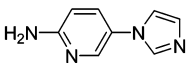
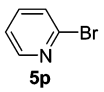
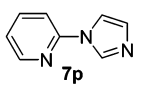
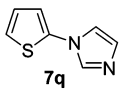
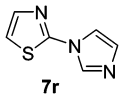
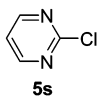
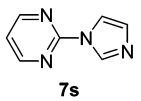
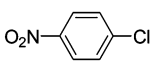
(41) Collman, J. P.; Wang, Z.; Zhong, M.; Zeng, L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1217−1221.

(42) Son, S. U.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778−779.

TABLE 2. Catalytic *N*-Arylation of Imidazole with Aryl or Heteroaryl Halides by CuI/4[a]



Entry	Aryl or heteroaryl halide	Product	Yield[b]
1	 **5b**	 **7b**	99
2	 **5c**	 **7c**	61
3	 **5d**	 **7d**	95
4	 **5a**	 **7a**	96
5	 **5e**	 **7e**	89
6	 **5f**	 **7f**	78
7	 **5g**	 **7g**	66
8	 **5h**	 **7h**	64[c]
9	 **5i**	 **7i**	88
10	 **5j**	 **7j**	87

Entry	Aryl or heteroaryl halide	Product	Yield[b]
11	 **5k**	 **7k**	61[c]
12	 **5l**	 **7l**	70
13	 **5m**	 **7m**	82
14	 **5n**	 **7n**	85
15	 **5o**	 **7o**	83
16	 **5p**	 **7p**	98
17	 **5q**	 **7q**	75
18	 **5r**	 **7r**	85
19	 **5s**	 **7s**	97
20	 **5t**	**7t**	98
21	**5u**	**7d**	92

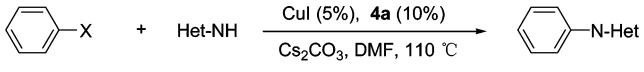
[a] Reaction conditions: **5** (1.2 mmol), **6a** (1.0 mmol), 2.0 mmol of Cs_2CO_3 in the presence of 10 mol % of ligand **4a** and 5 mol % of CuI in 2.0 mL of DMF at 110 °C under N_2 atmosphere for 24 h. [b] Isolated yields (average of two runs) based on **6a**. [c] 48 h at 110 °C.

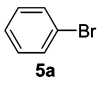
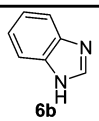
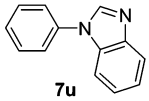
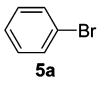
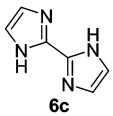
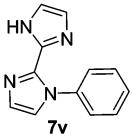
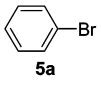
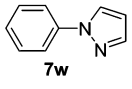
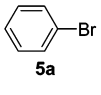
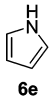
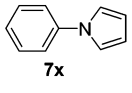
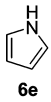
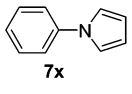
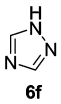
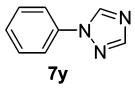
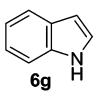
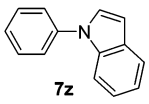
product yields, these reactions could smoothly proceed with iodobenzene to give **7y** and **7z** in 96% and 98% yields, respectively (entries 6 and 7).

Conclusion

We have disclosed that (*S*)-pyrrolidinylmethylimidazole **4a**, which has been readily synthesized in a straightforward fashion from inexpensive L-proline and imidazoles in short steps, acted as a highly efficient ligand for the Cu-catalyzed *N*-arylation of imidazoles with aryl or heteroaryl halides. The system is effective for aryl bromides, and to a less extent, for aryl chlorides. Particularly noteworthy are our protocols could tolerate an array of functional groups such as ester, nitrile, nitro, ketone, free hydroxyl, and free primary amine on the aryl halide. To the best of our knowledge, our catalytic process is among the most efficient approaches to the *N*-arylation of imidazoles with aryl halides so far reported. The protocol could also be applicable to the *N*-arylation of other π-electron-rich nitrogen heterocycles (pyrrole, pyrazole, indole, benzimidazole, and triazole). We believe that this catalyst system could provide an excellent complement to the Pd- or Cu-catalyzed methods that have already been utilized in a number of applications. This

TABLE 3. Catalytic *N*-Arylation of Azoles with Aryl Halides by CuI/4a[a]



Entry	ArX	Het-NH	Product	Yield[b]
1	 5a	 6b	 7u	75
2	 5a	 6c	 7v	62
3	 5a	 6d	 7w	87
4	 5a	 6e	 7x	72
5	 5v	 6e	 7x	98[c]
6	 5v	 6f	 7y	96[c]
7	 5v	 6g	 7z	98

[a] Reaction conditions: **5** (1.2 mmol), **6** (1.0 mmol), 2.0 mmol of Cs_2CO_3 in the presence of 10 mol % of ligand **4a** and 5 mol % of CuI in 2.0 mL of DMF at 110 °C under N_2 atmosphere for 24 h. [b] Isolated yields (average of two runs) based on **6**. [c] 24 h at 90 °C.

work should find wide application among synthetic and medicinal chemists in industry and academics.

Experimental Section

Procedure for the Preparation of Ligands 4a−c: (*S*)-(1-Benzylpyrrolidin-2-yl)methanol ((*S*)-2a). A mixture of (*S*)-pyrrolidin-2-yl-methanol (**1**) (2.02 g, 20 mmol), benzyl chloride (3.80 g, 30 mmol), and anhydrous potassium carbonate (2.76 g, 20 mmol) in 15 mL of toluene was refluxed with stirring under nitrogen for 16 h. Dilute hydrochloric acid was then added until the aqueous layer was strongly acidic. The aqueous layer was separated, shaken with ether, basified with ammonium hydroxide, and extracted with methylene chloride. The organic layer was dried over $MgSO_4$, and the solvent was then removed under reduced press. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (10/1) to afford (*S*)-(1-benzylpyrrolidin-2-yl)methanol as a viscous oil (3.52 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63−1.71 (m, 2H), 1.77−1.86 (m, 1H), 1.88−1.96 (m, 1H), 2.23−2.30 (m, 1H), 2.67−2.73 (m, 1H), 2.92−2.97 (m, 1H), 3.10 (br s, 1H), 3.32 (d, J = 13.2 Hz, 1H), 3.41 (dd, J = 2.0, 4.0 Hz, 1H), 3.44 (dd, J = 2.0, 4.0 Hz, 1H), 3.94 (d, J = 13.2 Hz, 1H), 7.20−7.32 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 27.6, 54.3, 58.5, 61.9, 64.3, 126.8, 128.1, 128.6, 139.1 ppm. MS (ESI$^+$) m/z 192.4 [M + 1] $^+$.

(*S*)-1-Benzyl-2-(chloromethyl)pyrrolidine Hydrochloride ((*S*)-3a). A solution of (*S*)-(1-benzylpyrrolidin-2-yl)methanol **((*S*)-2a)** (3.82 g, 20 mmol) in 20 mL of $CHCl_3$ at −4 °C was saturated with HCl gas and dried by bubbling through a H_2SO_4 trap. Then thionyl chloride (8 mL, 110 mmol) was added dropwise at the same temperature. The temperature was slowly raised to 20 °C, and the reaction mixture was then refluxed for 2 h. Chloroform and an excess of thionyl chloride were removed under reduced pressure. Active charcoal and 25 mL of methanol were then added to the residue, and the mixture was refluxed for 1 h and filtered through celite; the operation was repeated three times. After removal of methanol, the orange oil was crystallized by addition of THF to afford (*S*)-1-benzyl-2-(chloromethyl)pyrrolidine hydrochloride as a white solid (3.94 g, 80%). ^{1}H NMR (400 MHz, D_2O): δ 2.00−2.15 (m, 2H), 2.18−2.24 (m, 1H), 2.41−2.45 (m, 1H), 3.37−3.43 (m, 1H), 3.51−3.57 (m, 1H), 3.85−3.94 (m, 2H), 4.07−4.13 (m, 1H), 4.37 (d, J = 12.8 Hz, 1H), 4.64 (d, J = 12.8 Hz, 1H), 7.60 (s, 5H) ppm. ^{13}C NMR (100 MHz, D_2O): δ 24.4, 30.2, 45.2, 57.6, 61.2, 70.2, 132.1, 132.3, 132.9, 133.5 ppm. MS (ESI$^+$) m/z 210.3 [M − Cl] $^+$.

(*S*)-(1-Methylpyrrolidin-2-yl)methanol ((*S*)-2b). (*S*)-Pyrrolidin-2-yl-methanol (**1**) (2.02 g, 20 mmol) was added to 4 mL of formic acid at 5 °C, followed by 3 mL of 40% aqueous formaldehyde. When the initial vigorous evolution of carbon dioxide had subsided, the whole was refluxed for 20 h. The mixture was acidified with 5 N hydrochloric acid (5 mL), and evaporated in vaccuo to afford a dark gum. The residue was dissolved in a minimum quantity of water, saturated with sodium hydroxide, and extracted with chloroform. The combined extracts were dried over K_2CO_3, and chloroform was then removed under reduced pressure. The fraction, bp 49−50 °C/2 mm, on redistillation gave (*S*)-(1-methylpyrrolidin-2-yl)methanol as colorless oil (1.50 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63−1.88 (m, 4H), 2.19−2.25 (m, 1H), 2.28−2.34 (m, 1H), 2.31 (s, 3H), 3.00−3.05 (m, 1H), 3.39 (dd, J = 4.0, 2.8 Hz, 1H), 3.41 (dd, J = 4.0, 2.8 Hz, 1H), 3.47 (br s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 27.5, 40.8, 57.5, 61.9, 66.4 ppm. MS (ESI$^+$) m/z 116.2 [M + 1] $^+$.

(*S*)-1-Methyl-2-(chloromethyl)pyrrolidine Hydrochloride ((*S*)-3b). This compound was prepared following the same procedure as described above for (*S*)-**3a**. Starting material is from (*S*)-(1-methylpyrrolidin-2-yl)methanol ((*S*)-**2b**). (*S*)-**3b** was obtained in 85% yield as a white solid. ^{1}H NMR (400 MHz, D_2O): δ 2.08−2.18 (m, 2H), 2.21−2.30 (m, 1H), 2.41−2.48 (m, 1H), 3.09 (s, 3H), 3.29−3.36 (m, 1H), 3.78−3.84 (m, 1H), 3.92−3.98 (m, 1H), 4.02 (dd, J = 5.2, 3.6 Hz, 1H), 4.13 (dd, J = 5.2, 3.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, D_2O): δ 24.4, 29.9, 43.1, 44.6, 59.9, 71.8 ppm. MS (ESI$^+$) m/z 134.3 [M − Cl] $^+$.

(*S*)-1-((1-Benzylpyrrolidin-2-yl)methyl)-2-methyl-1*H*-imidazole ((*S*)-4a). To a solution of 2-methyl-1*H*-imidazole (2.46 g, 30 mmol) in 100 mL of THF was added NaH (2.4 g, 60 mmol) at 0 °C. After the mixture was stirred for 0.5 h, (*S*)-1-benzyl-2-(chloromethyl)pyrrolidine hydrochloride ((*S*)-**3a)** (6.15 g, 25 mmol) was added. The temperature was slowly raised to 25 °C, and the reaction mixture was stirred at 40 °C for 10 h and was allowed to warm to room temperature. The mixture was then filtered through celite and washed well with 20 mL of THF. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (15/1) to afford (*S*)-**4a** as a pale yellow oil (5.10 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52−1.57 (m, 1H), 1.69−1.72 (m, 2H), 1.84−1.89 (m, 1H), 2.28−2.32 (m, 1H), 2.35 (s, 3H), 2.88−2.90 (m, 1H), 2.98−3.01 (m, 1H), 3.44 (d, J = 12.6 Hz, 1H), 3.69 (dd, J = 7.2, 5.4 Hz, 1H), 3.72 (dd, J = 7.2, 5.4 Hz, 1H), 3.75 (d, J = 12.6 Hz, 1H), 6.89 (s, 2H), 7.26−7.34 (m, 5H)

ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.2, 22.9, 28.9, 50.3, 54.7, 59.9, 63.6, 119.8, 126.8, 127.0, 128.3, 128.7, 139.2, 144.6 ppm. HRMS (EI) calcd for $[C_{16}H_{21}N_3]^+$ 255.1735, found 255.1730. Anal. Calcd: C 75.26, H 8.29, N 16.46. Found: C 74.33, H 8.45, N 15.75.

(*S*)-1-((1-Benzylpyrrolidin-2-yl)methyl)-1*H*-imidazole ((*S*)-4b). This compound was prepared following the same procedure as described above for (*S*)-**4a**. Starting material is from (*S*)-**3a** and imidazole. (*S*)-**4b** was obtained in 85% yield as a pale yellow oil after purification by column chromatography on silica gel eluting with ethyl acetate/methanol (15/1). ^{1}H NMR (600 MHz, CD_3OD): δ 1.52−1.57 (m, 2H), 1.66−1.68 (m, 1H), 1.87−1.91 (m, 1H), 2.28−2.31 (m, 1H), 2.89−2.95 (m, 2H), 3.39 (d, J = 13.2 Hz, 1H), 3.78 (d, J = 13.2 Hz, 1H), 3.94 (dd, J = 6.0, 4.8 Hz, 1H), 3.96 (dd, J = 6.0, 4.8 Hz, 1H), 6.96 (s, 1H), 7.17 (s, 1H), 7.23−7.26 (m, 1H), 7.30−7.34 (m, 4H), 7.70 (s, 1H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ 23.9, 29.6, 51.8, 55.7, 60.6, 65.0, 121.5, 128.2, 128.6, 129.4, 130.2, 139.1, 140.4 ppm. HRMS (EI) calcd for $[C_{15}H_{19}N_3]^+$ 241.1579, found 241.1586. Anal. Calcd for $C_{15}H_{19}N_3$: C 74.65, H 7.94, N 17.41. Found: C 74.32, H 8.00, N 17.29.

(S)-1-((1-Methylpyrrolidin-2-yl)methyl)-1*H*-imidazole ((*S*)-4c). This compound was prepared following the same procedure as described above for (*S*)-**4a**. Starting materials are from (*S*)-**3b** and imidazole. (*S*)-**4c** was obtained in 82% yield as a pale yellow oil after purification by column chromatography on silica gel eluting with ethyl acetate/methanol (1/4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44−1.50 (m, 1H), 1.60−1.67 (m, 2H), 1.78−1.88 (m, 1H), 2.19−2.25 (m, 4H), 2.46−2.52 (m, 1H), 3.01−3.06 (m, 1H), 3.81 (dd, J = 6.0, 4.8 Hz, 1H), 3.85 (dd, J = 6.0, 4.8 Hz, 1H), 6.93 (s, 1H), 7.00 (s, 1H), 7.48 (s, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 22.4, 28.8, 40.8, 50.4, 57.3, 65.3, 119.4, 128.7, 137.4 ppm. HRMS (FAB) calcd for $[C_9H_{15}N_3 + H]^+$ 166.1344, found 166.1352. Anal. Calcd: C 65.42, H 9.15, N 25.43. Found: C 64.19, H 9.76, N 24.77.

General Procedure for the Catalytic *N*-Arylation of Nitrogen-Containing Heterocycles with Aryl Halides. A flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (9.6 mg, 0.05 mmol), ligand (0.1 mmol), Cs_2CO_3 (0.652 g, 2.0 mmol), nitrogen-containing heterocycle (1.0 mmol), aryl or heteroaryl halide (1.2 mmol), and DMF (2 mL) under N_2. A rubber septum was replaced with a glass stopper, and the system was then evacuated twice and back filled with N_2. The reaction mixture was stirred for 30 min at room temperature, and then heated to 110 °C for 24 h. The reaction mixture was then cooled to ambient temperature, diluted with 2−3 mL of ethyl acetate, filtered through a plug of silica gel, and washed with 10−20 mL of ethyl acetate. The filtrate was concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product.

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Supporting Information Available: Detailed experimental procedures for the synthesis of *N*-arylazoles, characterizational NMR spectral data (^{1}H and ^{13}C) of *N*-arylazoles and compounds **4a**−**c, 3a**,**b**, and **2a**,**b**; copies of ^{1}H and ^{13}C NMR spectra for compounds **4a**−**c, 3a**,**b, 2a**,**b**, and **7a**−**z**. This material is available free of charge via the Internet at http://pubs.acs.org.

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