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Per-6-amino-β-cyclodextrin as an Efficient Supramolecular Ligand and Host for Cu(I)-Catalyzed *N*-Arylation of Imidazole with Aryl Bromides

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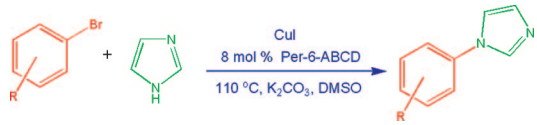

Per-6-amino-β-cyclodextrin (per-6-ABCD), acting simultaneously as a supramolecular ligand for CuI and host for aryl bromides, catalyzes *N*-arylation of imidazole with aryl bromides under mild conditions. This simple method proceeds with excellent yield for the coupling of imidazole with various substituted aryl bromides demonstrating good tolerance of other functionalities.

Nitrogen-containing heterocycles such as *N*-arylimidazoles find extensive applications in medicinal,[1] biological,[2] natural products,[3] and *N*-heterocyclic carbene chemistry.[4] Traditionally, this moiety has been prepared by nucleophilic aromatic substitution of an activated aryl halide with heterocycles by copper-mediated coupling or via Ullmann-type coupling.[5] These protocols often require use of stoichiometric amounts of copper reagents[6] which lead to environmental problems such as waste disposal, harsher conditions (exposure of substrates to high temperature for extended periods of time), and low tolerance of other functional groups. In some instances palladium[7] catalysts have been employed, but this protocol is not general for the *N*-arylation of imidazoles due to its toxicity, high cost, and specificity to ligands. This factor coupled with economic attractiveness of copper has led to a resurgence of interest in the Ullmann-type coupling reaction.[8] Stoichiometric reagents such as aryllead triacetate,[9] arylboronic acids,[10] triarylbismuths,[11] hypervalent arylsiloxanes,[12] diaryl iodonium salts,[13] arylstannanes,[14] and copper triflate-benzene[15] are used in Cu-mediated *N*-arylation. However, many of them have inherent disadvantages as they are toxic, unstable, and difficult to access. In some cases only one of the multiple aryl groups is transferred to the heterocycle. This difficulty can be overcome by employing stable and readily available aryl halides as the electrophilic coupling partners. Recently *N*-arylation has been applied to many heterocycles and various organic ligands such as amino acids,[16] aliphatic diamines,[17] Schiff bases,[18] ethylene glycol,[19] diethyl salicylamide,[20] oxime-phosphine containing ligands,[21] aminoarene

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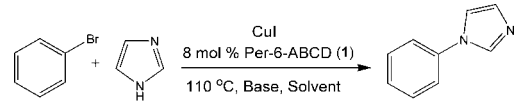
thiolate,[22] 2-aminopyrimidine-4,6-diol,[23] hydroxyquinoline,[24] (*S*)-pyrrolidinylmethylimidazoles,[25] 4,7-dimethoxy-1,10-phenanthroline,[26] 2-oxocyclohexane carboxylate,[27] fluorapatite,[28] benzotriazole,[29] DMEDA,[16b] pipecolinic acid,[30] phosphoramidite,[31] *N*-hydroxyimides,[32] copper salts,[33] and D-glucosamine,[34] have been employed in Cu-mediated *N*-arylation. However, a more practical ligand-promoted Cu-catalyzed chemistry needs to be developed as many of the earlier methods are not general for *N*-arylation. Also only limited studies are available for the coupling of imidazoles with aryl bromides and even they are restricted only to less hindered substrates.[26,34,18b]

Cyclodextrins are cyclic oligomers which catalyze a wide range of chemical reactions through the formation of a reversible host−guest complex.[35] Functionalization of CDs improves their properties and enhances their capability for complexation with metal ions resulting in manifold increase in their applications in catalysis.[36] Amino-CDs are homogeneous CD derivatives modified by persubstitution at the primary face with amino pendant groups and this manifests combined hydrophobic and electrostatic binding of guest molecules relative to native CDs. They are employed as biomimetic catalysts in Kemp elimination,[37a] deprotonation,[37b] and chiral recognition processes.[37c] As amino-functionalized organic moieties[17,34] are widely employed as ligands for *N*-arylation of imidazoles, it is proposed to utilize per-6-amino-β-cyclodextrin (per-6-ABCD) as a ligand for Cu-catalyzed arylation. The hydrophobic cavity of cyclodextrin is also expected to act as a binding site for aryl halide, which will catalyze the reaction. Herein we report our preliminary investigations on the use of per-6-ABCD as an efficient ligand in Cu(I)-catalyzed *N*-arylation of imidazole with aryl bromides.

TABLE 1. Optimization of Reaction Conditions in Cu(I)-Catalyzed *N*-Arylation of Imidazole 3 with Bromobenzene 2a[a]



2a 3 4a

entry	ligand	base	solvent	catalyst	conversion[b] (%)
01	none	K_2CO_3	DMSO	CuI	4
02	per-6-ABCD		DMSO	CuI	nil
03	α-CD	K_2CO_3	DMSO	CuI	3
04	β-CD	K_2CO_3	DMSO	CuI	2
05	per-6-ABCD	Cs_2CO_3	DMSO	CuI	91
06	per-6-ABCD	K_3PO_4	DMSO	CuI	75
07	per-6-ABCD	K_2CO_3	DMSO	CuI	99
08	per-6-ABCD	K_2CO_3	DMF	CuI	55
09	per-6-ABCD	K_2CO_3	ACN	CuI	58
10	per-6-ABCD	K_2CO_3	MeOH	CuI	52
11	per-6-ABCD	K_2CO_3	DMSO−water[c]	CuI	87
12	per-6-ABCD	K_2CO_3	water	CuI	20
13	per-6-ABCD	K_2CO_3	DMSO	CuBr	65
14	per-6-ABCD	K_2CO_3	DMSO	CuCl	49
15	per-6-ABCD[d]	K_2CO_3	DMSO	CuI	
16	per-6-ABCD[e]	K_2CO_3	DMSO	CuI	
17	per-6-ABCD[f]	K_2CO_3	DMSO	CuI	35
18	per-6-ABCD[g]	K_3CO_3	DMSO	CuI	51

[a] Reaction conditions: bromobenzene **2a** (1.2 mmol), imidazole **3** (1 mmol), CuI (0.2 mmol), ligand (8%), and base (2.1 mmol) in 2 mL of solvent at 110 °C for 24 h. [b] Analyzed by GC. [c] DMSO and water are in a 1:1 ratio. [d] 50 °C. [e] 80 °C. [f] Time 6 h, [g] time 12 h.

Imidazole **3** and bromobenzene **2a** are chosen as model substrates to optimize the reaction conditions such as amount of ligand, base, solvent, copper source, and reaction temperature. Without any ligand, treatment of **3** with **2a** using K_2CO_3 as base and CuI as copper source in DMSO affords very poor conversion, yielding only 4% of **4a** (Table 1, entry 1). In the absence of base, reaction fails completely (entry 2). When native α- and β-cyclodextrins are used as ligands, there is very little reaction indicating that per-6-ABCD has a major role as an efficient supramolecular ligand (entries 3 and 4). Bases such as Cs_2CO_3, K_3PO_4, and K_2CO_3 are found to facilitate this coupling reaction and among them K_2CO_3 is the best. Solvents such as DMF, ACN, MeOH, and DMSO are investigated and it is found that polar solvents are more favored. With DMF, ACN, and MeOH, yields are comparatively low. Consequently DMSO is chosen as the medium of choice for this coupling. Though the reaction is very slow in water, use of a DMSO−water (1:1 v/v %) mixture results in affordable (87%) yield indicating that this

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coupling process is fairly insensitive to the presence of water and no special precautions are required to exclude moisture from this reaction. Also when per-6-ABCD is used, the coupling is insensitive to air and hence there is no need to maintain an inert atmosphere, which is the problem with previous studies.[18,32] Readily available copper salts such as CuI, CuBr, and CuCl afford satisfactory results in this reaction in agreement with the previous reports[23,34] illustrating that copper compounds are catalytically active and give better conversion.

This arylation is also found to be highly sensitive to reaction temperature and time. At lower temperatures (50 and 80 °C), the reaction totally fails and with lower reaction time (6 and 12 h) only low to moderate yield is obtained (entries 15 to 18). These preliminary results reveal that per-6-ABCD acts as a good ligand with optimum conditions such as the presence of mild base (K_2CO_3) and CuI as the copper source in DMSO solvent at 100−110 °C for 24 h.

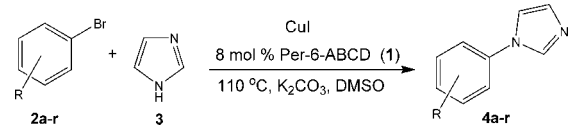
The scope of this coupling reaction is further expanded to diverse aryl bromides (**2b**−**r**) with **3** and the results are listed in Table 2.

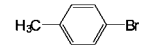
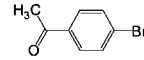
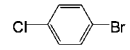
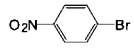
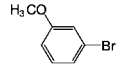
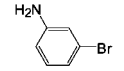
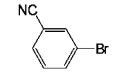
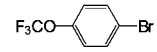
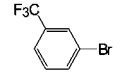
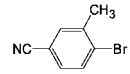
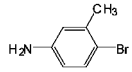
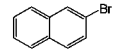
The results indicate clearly that this protocol is general and is applicable for reactions of a wide variety of electron-rich and electron-deficient aryl bromides with **3** and the yields are also good. Substrates possessing electron-rich groups such as *p*-bromotoluene, *o*-bromotoluene, and *m*-bromoanisole afford coupling products in good yield, but with long reaction time (up to 24 h). In contrast, bromoarenes having electron-withdrawing groups (such as *p*-$COCH_3$, *p*-NO_2, *p*- and *m*-CN, *p*-CF_3 and *p*-OCF_3 groups) proceed faster to give excellent yields. It is noteworthy that the present protocol also tolerates many other functional groups including nitrile and amino groups as hydrolyzed products are not observed with ***2l*** (entry 12). Imidazole **3** can be selectively arylated in the presence of a free amino group (entry 13). And also this reaction is less sensitive to steric factors and gives good yield as is evident in all ortho-substituted bromoarenes. However, with increasing steric crowding, as in 2-bromomesitylene, the reaction fails. Fused ring compounds such as 1-bromo and 2-bromonaphthalenes react smoothly with **3** giving excellent yields. Among the aryl halides, the coupling proceeds very readily with aryl bromides giving excellent yield of the corresponding *N*-aryl derivative. Heteroaryl bromides, namely 2-bromopyridine, 2-bromothiophene, and 5-bromopyrimidine (entries 16, 17, and 18), react smoothly giving an excellent yield. Control experiments suggest that among aryl halides, the coupling proceeds readily with aryl chlorides also (in addition to bromides and iodides), but is inert with aryl fluorides.

To expand the scope of this protocol further, other nitrogen-containing heterocycles such as pyrrole, pyrazole, triazole, indole, benzimidazole, and hindered imidazoles like 2-methylimidazole are coupled with bromobenzene to give the corresponding *N*-arylated products in good yield (Table 3). Among the heterocycles, indole reacts slowly and requires a longer reaction time. All other *N*-heterocycles and sterically hindered 2-methylimidazole give excellent yields.

A plausible three-step mechanism for the copper-catalyzed *N*-arylation of **3** (Scheme 1) is proposed in accordance with previous reports.[23,26b,29,38] per-6-ABCD reacts with CuI to produce a Cu-chelated complex (**I**) via interaction between amino groups of per-6-ABCD and CuI. Subsequent oxidative addition of aryl bromide bound inside the CD cavity via hydrophobic interaction leads to intermediate **II**. Treatment of imidazole with **II** in presence of potassium carbonate generates complex **III**. Subsequent reductive elimination of **III** gives *N*-arylated product **4** regenerating the active Cu(I) species. The catalytic role of **1**, i.e., the inclusion of bromoarene within the CD cavity, and reaction taking place inside the cavity is also evidenced by carrying out control experiments on the same

TABLE 2. ***N*-Arylation of Imidazole 3 with Aryl Bromides in the Presence of CuI and per-6-ABCD**



Entry	Aryl bromide		Product	Time (h)	% Yield[b]
1		2a	4a	24	98
2		2b	4b	24	96
3		2c	4c	24	95
4		2d	4d	18	94
5		2e	4e	24	99
6		2f	4f	18	87
7		2g	4g	18	90
8		2h	4h	36	90
9		2i	4i	18	98
10		2j	4j	18	92
11		2k	4k	18	93
12		2l	4l	18	85
13		2m	4m	24	81
14		2n	4n	24	86
15		2o	4o	24	90
16		2p	4p	24	92
17		2q	4q	24	97
18		2r	4r	24	98

a General reaction conditions: imidazole (1 mmol), ArBr (1.2 mmol), CuI (0.2 mmol), per-6-ABCD (0.1 mmol), and K_2CO_3 (2.1 mmol) in DMSO (2 mL) at 110 °C. *b* Isolated yield.

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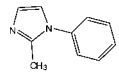
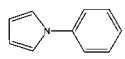
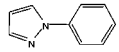
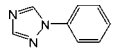
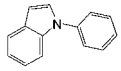
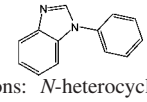
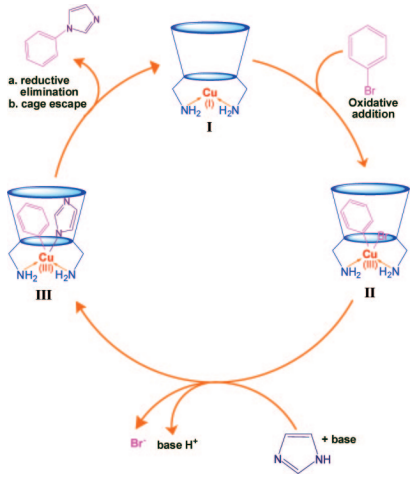
TABLE 3. CuI/per-6-ABCD Catalyzed *N*-Arylation of Various Nitrogen Heterocycles

Entry	*N*-Heterocycle	*N*-arylated products	Time (h)	% Yield[b]
1			24	86
2			24	92
3			24	98
4			24	98
5			24 36	63 93
6			24	99

a General reaction conditions: *N*-heterocycle (1 mmol), ArBr (1.2 mmol), CuI (0.2 mmol), per-6-ABCD (0.1 mmol), and K_2CO_3 (2.1 mmol) in DMSO (2 mL) at 110 °C. [b] Isolated yields.

SCHEME 1. Proposed Mechanism for CuI Catalyzed *N*-Arylation of Imidazole 3 in Presence of per-6-ABCD 1



reaction in the presence of adamantane (which forms a more stronger inclusion complex with CD).[39] As adamantane competes with aryl bromide to complex with CD, a decrease in conversion (40%) is noticed.

In summary, we have demonstrated that per-6-amino-β-cyclodextrin (per-6-ABCD), a natural sugar derivative, acts as an efficient ligand for the cheapest and commercially viable CuI as catalyst in *N*-arylation of imidazole with a wide range of aryl and heteroaryl bromides providing excellent yields under milder conditions. per-6-ABCD also functions as an excellent supramolecular host facilitating inclusion of aryl halide and imidazole cooperatively. This procedure is not only capable of coupling hindered substrates, but also tolerates an array of other functional groups such as nitrile, nitro, and free amines present in aryl bromide. This methodology avoids an inert atmosphere, which is a common requisite with earlier works. This protocol thus may find widespread use for the preparation of *N*-arylated products and, despite the limiting use of DMSO as solvent, will be a great value addition in the pharmaceutical industry.

Experimental Section

General Prodedure for *N*-Arylation of Imidazole with Aryl Bromides. A Schlenk tube equipped with a Teflon stopcock are charged with a magnetic stir bar, K_2CO_3 (572 mg, 2.1 mmol), CuI (0.38 mg, 0.20 mmol, 20 mol %), and per-6-amino-β-cyclodextrin (100 mg, 0.08 mmol, 8 mol %). DMSO (1 mL) was added at room temperature. Then a solution of bromobenzene (188 mg, 1.2 mmol) and imidazole (68 mg, 1.0 mmol) in DMSO (1 mL) was added. The tube was sealed and the mixture was allowed to stir for 24 h at 110 °C. Water (5 mL) was added to the reaction mixture after completion of the reaction. Then it was extracted with ethyl acetate (3 × 20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated by vacuum. The residue was purified by column chromatography on silica gel, using hexane/ethyl acetate (1:3) as eluant, to give an oil of 1-phenylimidazole **4a** (164 mg, 98%)

1-Phenyl-1*H*-imidazole (4a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87(s, 1H), 7.51−7.46 (m, 2H), 7.40 −7.34 (m, 3H), 7.29 (br s, 1H), 7.21 (br s, 1H); ^{13}C NMR (75 MHz) δ 137.1, 135.5, 130.1, 129.7, 127.4, 121.3, 118.2. GC-MS *m*/*z* 144.0 (M^+).

Acknowledgement. Financial assistance from the Department of Science and Technology (DST), New Delhi, India is gratefully acknowledged.

Supporting Information Available: Characterization for products (^{1}H and ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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