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Copper(I)-Catalyzed Intramolecular Direct C-Arylation of Azoles with Aryl Bromides

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A concise route to access 5*H*-imidazo[2,1-*a*]isoindole heterofused compounds by copper(I)-catalyzed intramolecular coupling of non-activated aryl bromides with azoles is reported. With CuI as catalyst, 1,10-phenanthroline as ligand, and K_3PO_4 as base, the reactions of 1-(2-bromobenzyl)-1*H*-imidazoles in DMF/*o*-xylene (1∶1, *V*∶*V*) at 145 ℃ afford the corresponding substituted 5*H*-imidazo[2,1-*a*]isoindoles in high yields via intramolecular C-arylation.

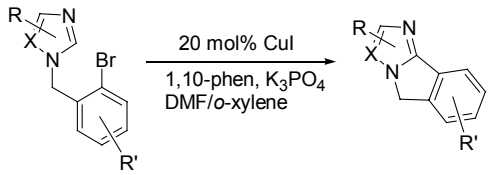
Keywords copper, intramolecular C-arylation, azole, aryl bromides

Introduction

The transition-metal-catalyzed C—H activation for regioselective formation of aryl-aryl bond is a powerful method which has attracted substantial interest over the past century.[1] When we talk about the formation of aryl-aryl bonds, we often regard as inseparable with expensive transition metals such as Rh,[2] Ru[3] and Pd.[4] However, in recent years impressive progress has been made using much cheaper and less toxic copper salts as convenient alternative catalysts for the formation of aryl-aryl bonds.[5] Daugulis and his co-workers[6] developed a general method for copper-catalyzed arylation of sp^2 C—H bonds with pK_a's below 35 in heterocycles as well as polyfluoro-benzenes.[6b,6c] Moreover, a variety of electron-rich and electron-poor heterocycles such as pyrimidine,[6] azoles,[7] thiophenes, benzofuran, pyridine oxides, pyridazine, and caffeine[8] could be arylated. Recently, intramolecular direct arylation of several electron-rich azoles with aryl iodides for the synthesis of a wide range of valuable heterofused molecules was performed by SanMartin *et al*.[9a] Different from formation of azoles ring species by multicomponent reactions[10] or palladium-catalyzed arylation of carbon-hydrogen bonds,[11] this protocol provided a simple and economical way to synthesize biologically relevant tri- and tetra-cyclic fused azoles.

However, this method still suffered from some limitations: Firstly, the system was only efficient with aryl iodides, under the same conditions it was totally unreactive with aryl bromides; secondly, the regioselectivity and functional group tolerance were significantly limited owing to the use of strong bases like LiOBu-*t*. Herein, we report the synthesis of a series of heterocycle-fused azole derivatives by copper(I)-catalyzed intramolecular C—H arylation of azoles with aryl bromides under mild base and compatible ligand (Scheme 1).

Scheme 1 General strategy



Results and Discussion

As it could be seen in Table 1, our preliminary studies focused on the conversion of 1-(2-bromobenzyl)-1*H*-imidazole (**1**) into 5*H*-imidazo[2,1-*a*]isoindole (**2**) as the model reaction. Initially, we tested CuI/LiOBu-*t*/*o*-xylene to catalyze this reaction with aryl bromides, however, same to San Martin's description,[9a] there was no desired product observed (Table 1, Entry 1). Curiously, combination of 1,10-phenanthroline as ligand and organic base, such as LiOBu-*t* or KoBu-*t* reported by

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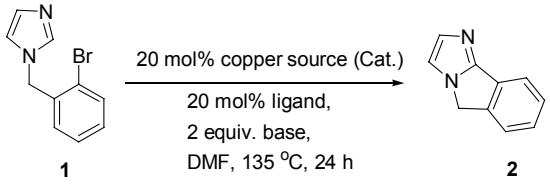
[1] The two authors contributed equally to this work.

Table 1 Screening reaction conditions for catalytic arylation



1 2

Entry[a]	Copper source	Ligand	Base	Yield[b]/%
1	CuI	—	LiOBu-*t*	0
2	CuI	1,10-Phen	LiOBu-*t*	0
3	CuI	1,10-Phen	KOBu-*t*	0
4	CuI	1,10-Phen	K_2CO_3	36
5	CuI	1,10-Phen	Cs_2CO_3	47
6	CuI	1,10-Phen	K_3PO_4	56
7	CuI	Hacac	K_3PO_4	34
8	CuI	TMEDA	K_3PO_4	12
9	CuI	*L*-Proline	K_3PO_4	0
10	CuI	—	K_3PO_4	0
11	—	1,10-Phen	K_3PO_4	0
12	CuBr	1,10-Phen	K_3PO_4	34
13	CuCl	1,10-Phen	K_3PO_4	27
14	Cu_2O	1,10-Phen	K_3PO_4	11

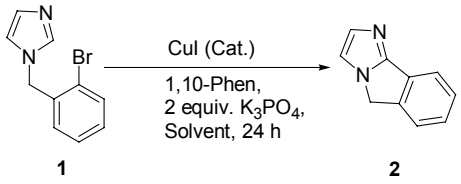
[a] The Schlenk test tube was charged with 20 mol% of Cu salt, 20 mol% of ligand (when it is added) and 2 equiv. of base. All reactions were run in non-anhydrous solvent at 135 ℃ in N_2 for 24 h. [b] Yield of isolated product.

Daugulis and co-workers for the Cu-catalyzed arylation of aromatic C—H bond,[6a] completely failed to lead to the formation of product under the reaction conditions (Table 1, Entries 2 and 3). The success of C—H arylation reactions might be related not only to the strength of the base but also to the solubility of both the base itself[12] and the metal halides byproducts which are formed during the processes.

Fortunately, the reaction occurred when we tried mild inorganic base, and the reactivity was better with K_3PO_4 as the base (Table 1, Entry 6) than with K_2CO_3 and Cs_2CO_3 (Table 1, Entries 4 and 5). In addition to base, some ligands extensively employed in the copper-catalyzed C-arylation were screened.[13] Notably, the reaction using 1,10-phenanthroline was more effective in comparision with Hacac (34%), TMEDA (12%), *L*-proline (0%) and without ligand (0%) (Table 1, Entries 7—10). As expected, no coupling reaction took place when the reaction was carried out without the metal catalyst (Table 1, Entry 11). Among the readily available copper(I) compounds screened, including Cu_2O, CuCl, CuBr and CuI, the air-stable CuI had the best performance (Table 1, Entries 6 and 12—14).

To increase product yield, the influences of the solvent, catalyst loading and temperature were further investigated. As displayed in Table 2, the moderate results were obtained in DMF or *o*-xylene with 20 mol% CuI, 20 mol% Phen and 2 equiv. K_3PO_4 (Table 2, Entries 1 and 2). Further studies showed that utilization of mixed solvent (Table 2, Entries 3 and 4) could afford **2b** in higher yield. Finally, the best result in terms of yield was achieved using DMF∶*o*-xylene (1∶1, *V*∶*V*) and 0.2 equivalent of CuI at 145 ℃ (Table 2, Entry 6). An attempt to lower and enhance temperature or the amount of CuI to 10 mol% (Table 2, Entries 5—12) resulted in less efficiency.

Table 2 Optimization of the reaction conditions



1 2

Entry[a]	Solvent	Catalyst loading/mol%	Temp/℃	Yield[b]/%
1	DMF	20	135	56
2	*o*-xylene	20	135	34
3	DMF/*o*-xylene (1∶2)	20	135	60
4	DMF/*o*-xylene (2∶1)	20	135	49
5	DMF/*o*-xylene (1∶1)	20	135	72
6	DMF/*o*-xylene (1∶1)	20	145	87
7	DMF/*o*-xylene (1∶1)	20	155	76
8	DMF/*o*-xylene (1∶1)	20	125	37
9	DMF/*o*-xylene (1∶1)	5	145	24
10	DMF/*o*-xylene (1∶1)	10	145	54
11	DMF/*o*-xylene (1∶1)	15	145	62
12	DMF/*o*-xylene (1∶1)	25	145	87

[a] Conditions: the Schlenk test tube was charged with CuI, 20 mol% phen and 2 equiv. K_3PO_4. All reactions were run in non-anhydrous solvent in N_2 for 24 h. [b] Yield of isolated product.

On the basis of the above results, we concluded that the optimized conditions for intramolecular coupling were combination of DMF/*o*-xylene (1∶1) at 145 ℃ for 24 h using two equivalents of K_3PO_4 as the base in the presence of a catalyst that was generated *in situ* from CuI (20 mol%) and 1,10-phenanthroline (Phen, 20 mol%).

With the optimized conditions in hand, the scope of the procedure with respect to other substrates was studied. As shown in Table 3, azoles derivatives without substituting group or with electron donating group (*i.e.* methyl-, phenyl-) exhibited greater reactivity, affording the desired arylation products in good to excellent yields (Table 3, Entries 1—7). This protocol was also applied to less acidic substrates (DMSO pK_a's above 35) such as 1-(2-bromobenzyl)-4-nitro-1*H*-imidazole (**8a**), 1-(2-bromobenzyl)-1*H*-pyrazole (**9a**), but both gave negligible results (Table 3, Entries 8 and 9). It could be explained according to the mechanism disclosed by Daugulis and co-workers that the reactions proceed by initial deprotonation of a relatively acidic sp^2 C—H. C—H bond DMSO pK_a's below 35 is necessary for copper-cata-

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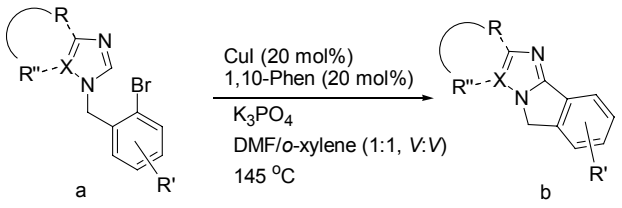
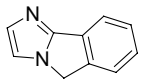
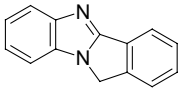
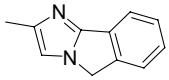
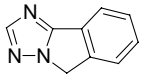
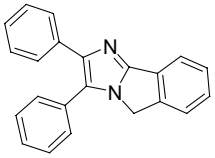
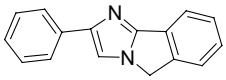
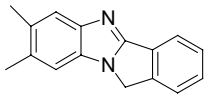
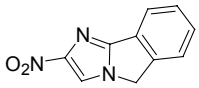
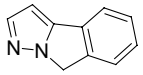
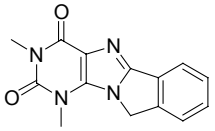
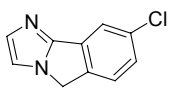
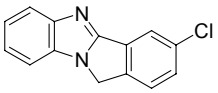
Table 3 Intramolecular copper-catalysed C—H arylation of azoles with aryl bromides



Entry[a]	Product		Isolated yield[b]/%
1		**1b**	87
2		**2b**	85
3		**3b**	95
4		**4b**	77
5		**5b**	67
6		**6b**	58
7		**7b**	65
8		**8b**	0
9		**9b**	0
10		**10b**	0
11		**11b**	62
12		**12b**	60

[a] Conditions: the Schlenk test tube was charged with 20 mol% CuI, 20 mol% phen and 2 equiv. K_3PO_4 in DMF∶*o*-xylene (1∶1, *V*∶*V*). All reactions were run in non-anhydrous solvent in N_2 at 145 ℃ for 24 h. [b] Yield of isolated product.

lyzed direct arylation. We then applied our protocol to 9-(2-bromo-benzyl)-1,3-dimethyl-1*H*-purine-2,6(3*H*,9*H*)-dione (**10a**), unfortunately, only substrate was recovered (Table 3, Entry 10). When 1-(2-Bromo-4-chloro-benzyl)-1*H*-imidazole (**11a**) and 1-(2-Bromo-4-chloro-benzyl)-1*H*-benzoimidazole (**12a**) were used as substrates, the yields of **11b** and **12b** were got in 62% and 60% (Table 3, Entries 11 and 12).

Conclusions

In conclusion, we have shown an effective protocol for the intramolecular direct C—H arylation of azoles with aryl bromides in the presence of less expensive copper salt catalyst and mild inorganic bases. Meanwhile, the reactions are efficient affording the coupled products with good to excellent yields. To the best of our knowledge, it is the first example of copper-mediated C—H functionalization with aryl bromides to build fused azoles derivatives. The method also provides an easy access to the synthesis of 5*H*-imidazo[2,1-*a*]-isoindoles heterofused compounds which are not readily available by conventional methods. This synthetic approach may find applications in straightforward preparation of other novel fused heterocycles. Further studies to extend the application of this method to other functionalized compounds construction are currently in progress in our laboratories.

Experimental

A Bruker AM-300 MHz instrument (Brucker, Switzerland) was used to acquire ^{1}H NMR spectra with TMS as internal standard. Chloroform-D was used as solvents. Low resolution mass spectra (LRMS) were recorded on an HP-5989A instrument (HP, U.S.A.). An Elementar Vario ELIII instrument (Elementar, Germany) was used to acquire data of elemental analysis. Melting points were determined with WRS-2A.

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Solvents were dried by refluxing for at least 24 h over CaH_2 (DMF), or sodium (*o*-xylene), and freshly distilled prior to use. All syntheses and manipulations were carried out under N_2 atmosphere.

General procedure for preparation of compounds (1b—7b, 11b, 12b)

A flame-dried Schlenk test tube with a magnetic stirring bar was charged with CuI (38 mg, 0.2 mmol), 1,10-phenanthroline (36 mg, 0.2 mmol), K_3PO_4 (424 mg, 2.0 mmol), **1a**—**7a** (1.0 mmol) and DMF/*o*-xylene (1∶1) (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 10 min at room temperature, and then heated at 145 ℃ for 24 h. The reaction mixture was then cooled to ambient temperature, diluted with 3—4 mL of CH_2Cl_2, filtered through a plug of silica gel, and washed

with 10—20 mL of CH_2Cl_2. The combined organic extracts were concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product **1b**—**7b**, **11b**, **12b**.

5*H*-Imidazo[5,1-*a*]isoindole (1b)[9a] White solid. M.p. 195—198 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.00 (s, 2H, CH_2), 7.18 (s, 1H, ArH), 7.24 (dd, J=7.5, 7.5 Hz, 1H, ArH), 7.37 (dd, J=8.1, 8.1 Hz, 1H, 1H, ArH), 7.39 (d, J=7.5 Hz, 1H, ArH), 7.55 (d, J=7.2 Hz, 1H, ArH), 7.72 (s, 1H, ArH); MS *m*/*z*: 156.07 $[M+H]^+$. Anal. calcd for $C_{10}H_8N_2$: C 76.90, H 5.16, N 17.94; found C 76.77, H 5.11, N 17.84.

11*H*-Isoindolo[2,1-*a*]benzimidazole (2b)[9a] White solid. M.p. 190—192 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.03 (s, 2H, CH_2), 7.24—7.29 (m, 3H, ArH), 7.45—7.54 (m, 3H, ArH), 7.80—7.90 (m, 1H, ArH), 8.08 (d, J=7.5 Hz, 1H, ArH); MS *m*/*z*: 207.1 $[M+H]^+$. Anal. calcd for $C_{14}H_{10}N_2$: C 81.53, H 4.89, N 13.58; found C 81.44, H 4.91, N 13.47.

2-Methyl-5*H*-imidazo[2,1-*a*]isoindole (3b) White solid. M.p. 182—185 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (s, 3H, CH_3), 4.95 (s, 2H, CH_2), 6.82 (s, 1H, ArH), 7.33—7.44 (m, 2H, ArH), 7.58—7.66 (m, 2H, ArH); MS *m*/*z*: 171.8 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}N_2$: C 77.62, H 5.92, N 16.46; found C, 77.54, H 5.99, N 16.40.

5*H*-[1,2,4]Triazolo[5,1-*a*]isoindole (4b)[9a] White solid. M.p. 98—100 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.28 (s, 2H, CH_2), 7.53—7.56 (m, 2H, ArH), 7.69—7.72 (dd, J=3, 3.9 Hz, 1H, ArH), 7.83—7.86 (dd, J=3.9, 3.6 Hz, 1H, ArH), 8.17 (s, 1H, ArH); MS *m*/*z*: 158.1 $[M+H]^+$. Anal. calcd for $C_9H_7N_3$: C 68.78, H 4.49, N 26.74; found C 68.78, H 4.51, N 26.53.

2,3-Diphenyl-5*H*-imidazo[2,1-*a*]isoindole (5b) Yellow solid. M.p. 143—146 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.06 (s, 2H, CH_2), 6.88—6.90 (m, 1H, ArH), 7.17—7.25 (m 7H, ArH), 7.36—7.43 (m, 5H, ArH), 7.95 (s, 1H, ArH); MS *m*/*z*: 310.1 $[M+H]^+$. Anal. calcd for $C_{22}H_{16}N_2$: C 85.69, H 5.23, N 9.08; found C 85.64, H 5.17, N 9.05.

2-Phenyl-5*H*-imidazo[2,1-*a*]isoindole (6b) Yellow solid. M.p. 172—175 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.22 (s, 2H, CH_2), 6.05—6.42 (m, 6H, ArH), 7.67—7.82 (m, 4H, ArH); MS *m*/*z*: 234.1 $[M+H]^+$. Anal. calcd for $C_{16}H_{12}N_2$: C 82.73, H 5.21, N 12.06; found C 82.47, H 5.27, N 12.01.

7,8-Dimethyl-11*H*-isoindolo[2,1-*a*]benzimidazole (7b)[9a] White solid. M.p. 221—224 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 6H, $2CH_3$), 5.43 (s, 2H, CH_2), 6.46—6.50 (s, 1H, ArH), 6.95 (s, 1H, ArH), 7.15—7.57 (m, 3H, ArH), 7.67 (s, 1H, ArH); MS *m*/*z*: 235.1 $[M+H]^+$. Anal. calcd for $C_{16}H_{14}N_2$: C 82.02, H 6.02, N 11.96; found C 82.04, H 6.03, N 11.98.

8-Chloro-5*H*-imidazo[2,1-*a*]isoindole (11b)[9b] White solid. M.p. 197—199 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.78 (s, 2H, CH_2), 7.14 (s, 1H, ArH), 7.17 (s, 1H, ArH), 7.21 (dd, J=8.2, 2.1 Hz, 1H, ArH), 7.29 (d, J=8.0 Hz, 1H, ArH), 7.73 (d, J=2.0 Hz, 1H, ArH). MS *m*/*z*: 191.0 $[M+H]^+$.

3-Chloro-11*H*-benzo[4,5]imidazo[2,1-*a*]isoindole (12b)[9b] Yellow solid. M.p. 192—194 ℃ (from hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.12 (s, 2H, CH_2), 7.01 (s, 1H, ArH), 7.05 (s, 2H, ArH), 7.38—7.50 (m, 1H, ArH), 7.52 (s, 1H, ArH), 7.70 (d, J=7.5 Hz, 2H, ArH). MS *m*/*z*: 241.5 $[M+H]^+$.

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