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Facile synthesis of 2-bromoindoles by ligand-free CuI-catalyzed intramolecular cross-coupling of *gem*-dibromoolefins

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ABSTRACT

A mild and efficient synthesis of 2-bromoindoles by ligand-free CuI-catalyzed intramolecular cross-coupling of *gem*-dibromoolefins was developed. Reactions were carried out in toluene at room temperature and the corresponding 2-bromoindoles were obtained in excellent yields.

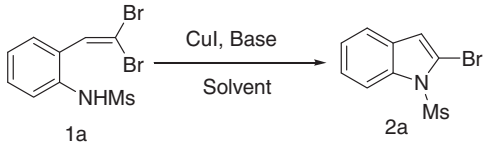
Halogenated indoles are valuable synthetic intermediates as well as important motifs in many biologically active molecules.[1,2] A number of methods have been developed for their syntheses.[3] Among these transformations, the treatment of the parent indoles with an electrophilic halogen source is the most straightforward strategy. Halogens,[3e,h] *N*-halosuccinimides,[3c,d,f] phosphoryl halides/imidazole,[3b,i] and copper (II) halides[3a,g] are commonly used agents for the halogenation of indoles. 3-Halogenated indoles can be easily obtained as the halogenation of indoles normally takes place preferentially at the 3-position.[3e] In contrast, 2-halogenated indoles are less accessible by these methods. The preparation of 2-halogenated indoles usually requires lithiation with strong bases such as *t*-butyllithium followed by treatment of halogenating electrophiles.[3e] These harsh conditions limit its synthetic application due to the poor regioselectivity and poor functional group compatibility. Therefore, there is a need to develop a mild and practical method for the formation of 2-halogenanted indoles.

Gem-dibromoolefins have been found to be versatile intermediates for various transformations, and great effort has been made on their synthetic applications.[4] For instance, amides,[4d,5d] yamides,[4a] ketene *N*,*N*-acetals,[4b] 2-substitute benzofused heterocycles,[4c,e–n,5b,h] and other important classes of compounds[4c,5a] have been efficiently synthesized from *gem*-dihaloolefins. However, to the best of our knowledge, there is no example of constructing indoles from *gem*-dihaloolefins under ligand-free copper catalysis conditions.[6] In our continuous studies of 1,1-dibromoolefins,[5] we found that 2-bromoindoles can be readily prepared in an intramolecular coupling manner. Herein, we describe a mild, efficient, and practical method for the synthesis of 2-bromoindoles from N-protected *ortho*-(*gem*-dibromovinyl)aniline under copper-catalyzed conditions in the absence of ligands.

In the preliminary experiments, treatment of *N*-[2-(2,2-dibromoethenyl)phenyl]methanesulfonamide (**1a**)[7] with catalytic amount of CuI was tested to screen the reaction conditions, and the results are summarized in Table 1.

Initially, the reaction of **1a** with CuI was conducted under Lautens's conditions[4c] (Table 1, entry 1), and **2a** was obtained in 68%

Table 1
Intramolecular coupling reaction of dibromoolefins[a]



1a 2a

Entry	Catalyst	Base	Solvent	*T* (°C)	Yield[b] (%)
1	CuI	K_3PO_4	THF	80	68
2	CuI	K_3PO_4	Toluene	80	73
3	CuI	K_3PO_4	DMF	80	48
4	CuI	K_3PO_4	CH_3CN	80	45
5	CuI	K_2CO_3	Toluene	80	41
6	CuI	Cs_2CO_3	Toluene	80	33
7	CuI	TEA	Toluene	80	49
8	CuI	K_3PO_4	Toluene	80	51[c]
9	CuI/DMEDA	K_3PO_4	Toluene	80	64
10	CuI	K_3PO_4	Toluene	25	90
11	CuBr	K_3PO_4	Toluene	25	42
12	CuCl	K_3PO_4	Toluene	25	34
13		K_3PO_4	Toluene	25	0

[a] Reaction conditions: **1a** (1.0 mmol), base (2.0 mmol) and CuI (0.1 mmol) in solvent (5 mL) at N_2 atmosphere for 8 h. TEA = triethylamine, DMF = *N*,*N*-dimethylformamide, DMEDA = *N*,*N*′-dimethylethylenediamine.
[b] Isolated yields.
[c] 24 h.

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yield. After various bases and solvents were tested, K_3PO_4 and toluene were found to be the most efficient combination. When the temperature was lowered to 25 °C, the yield was significantly improved (Table 1, entry 10), and the addition of a ligand like DMEDA (Table 1, entry 9) was not necessary. Other readily available Cu(I) halides are less efficient in catalyzing the reaction (Table 1, entries 11 and 12). We then screened different protecting groups of the aniline, and the results are summarized in Table 2. Methanesulfonyl was found to be the most suitable protecting group for the transformation possibly due to the coordinating ability of the internal sulfonamide and relatively easy deprotonation of 'NH' by a base (Table 2, entry 1).

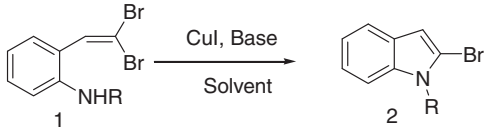
On the basis of these findings, a wide variety of 2-bromoindoles were prepared in excellent yields from *N*-methanesulfonyl protected 2-(*gem*-dibromovinyl)anilines under the optimized conditions: CuI as the catalyst, K_3PO_4 as the base, and toluene as the solvent at room temperature. The results are summarized in Table 3.

Gem-dibromoolefins with both the electron-donating (Table 3, entries 7–9, 12) and the electron-withdrawing substitutions (Table 3, entries 10 and 11) on the aromatic ring afforded the cyclized products in excellent yields. Substitutions next to *gem*-dibromoolefin moiety (Table 3, entry 4) or next to *N*-Ms group (Table 3, entry 12) did not impact the reaction either. Halogen substitutes on the aromatic ring were also well tolerated, giving polyhalogenated indoles. It thus provides an attractive route for further transformation of 2-bromoindoles into natural and unnatural products with indole moieties (Table 3, entries 2–6).[9]

Since suitable *ortho* substitutes have been shown to promote Ullmann-type couplings,[10] a possible mechanism for the formation of 2-bromoindoles is proposed in Scheme 1. Sulfonamide **1** reacts with CuI in the presence of base K_3PO_4 to form intermediate **I**. The 'Cu' atom in intermediate **I** is coordinated with the sulfonamide N and O atoms. Then intramolecular oxidative insertion of the coordinated copper to the dibromoolefin group provides **II**, which then undergoes reductive elimination to give the target product **2**.

In summary, we have developed a practical and efficient method for the synthesis of 2-bromoindoles. The CuI catalyzed intramolecular cross-coupling reactions proceed smoothly at room temperature without the addition of ligands. The desired 2-bromoindoles are obtained in excellent yields. This method provides a facile construction of 2-bromoindoles under mild conditions from *N*-[2-(2,2-dibromoethenyl)phenyl]methanesulfonamides.

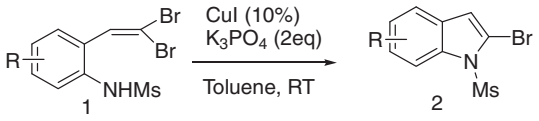
Table 2
Screening of N-protecting groups[a]

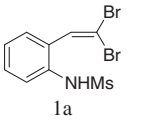
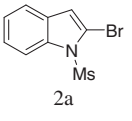
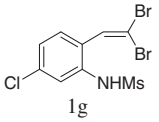
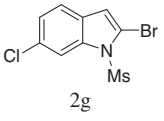
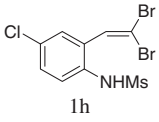
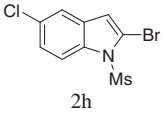
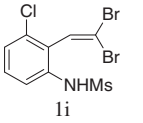
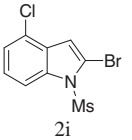
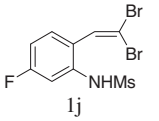
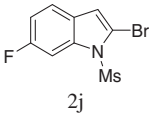
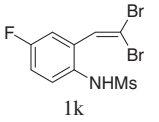
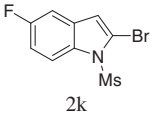
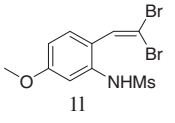
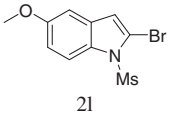
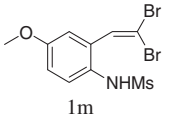
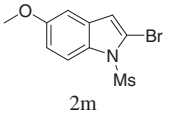
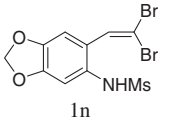
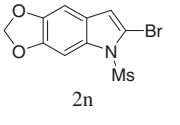
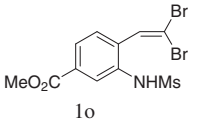
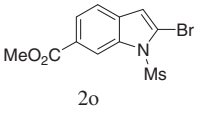
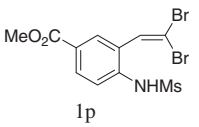
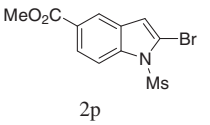
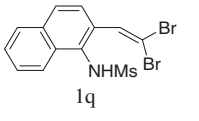
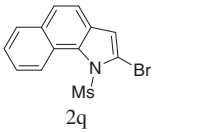


Entry	Substrate/R	Product/yield[b] (%)
1	**1a**/mesyl	**2a**/90
2	**1b**/*p*-toluenesulfonyl	**2b**/88
3	**1c**/acetyl	**2c**/n.d.[c]
4	**1d**/trifluoroacetyl	**2d**/n.d.[c]
5	**1e**/benzoyl	**2e**/trace (40[d])
6	**1f**/ethyloxycarbonyl	**2f**/n.d.[c]

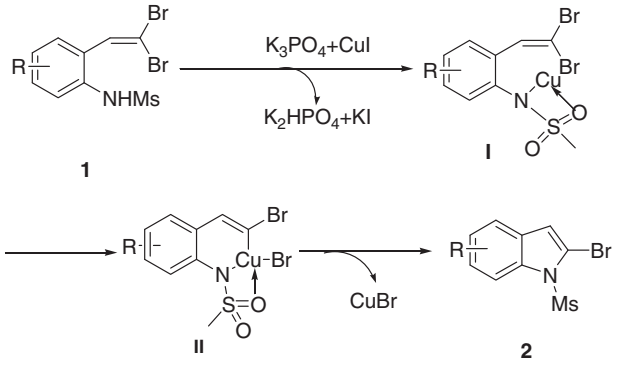
[a] Reaction conditions: **1** (1.0 mmol), K_3PO_4 (2.0 mmol) and CuI (0.1 mmol) in toluene (5.0 mL) at room temperature for 8 h.
[b] Isolated yield.
[c] No desired products.
[d] 80 °C.

Table 3
CuI catalyzed synthesis of 2-bromo indoles[a,8]



Entry	Substrate	Product	Yield[b] (%)
1	 1a	 2a	90
2	 1g	 2g	99
3	 1h	 2h	99
4	 1i	 2i	97
5	 1j	 2j	90
6	 1k	 2k	87
7	 1l	 2l	92
8	 1m	 2m	93
9	 1n	 2n	84
10	 1o	 2o	90
11	 1p	 2p	88
12	 1q	 2q	82

[a] Reaction conditions: **5** (1.0 mmol), K_3PO_4 (2.0 mmol) and CuI (0.1 mmol) in toluene (5.0 mL) at room temperature for 8 h.
[b] Isolated yield.



Scheme 1. A proposed mechanism for the copper catalyzed formation of 2-bromoindoles.

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6. While this manuscript was being prepared, a related formation of 2-bromoindole was published on-line: Wang, Z.-J.; Yang, J.-G.; Yang, F.; Bao, W. *Org. Lett.* **2010**, *12*, 3034.
7. A general procedure[4f–h] for the preparation of *gem*-dibromovinylaniline substrates: To a solution of 2-nitrobenzaldehyde (5.0 g, 33 mmol) and CBr_4 (21.9 g, 66 mmol) in DCM (200 mL) at 0 °C was added dropwise a solution of PPh_3 (34.6 g, 132 mmol) in DCM (100 mL) by an addition funnel. The addition rate was controlled so that the internal temperature was at 1–5 °C. After addition, the mixture was stirred for another 0.5 h before warmed to rt, and stirred for an additional 1 h. The reaction mixture was filtered through a short plug of silica gel (80 g), and was washed with a copious amount of DCM until no product was found. Solvent was removed under vacuum to give a mixture of the desired intermediate and triphenylphosphine oxide. To the mixture was added EtOH (95%, 200 mL) and $SnCl_2{\cdot}H_2O$ (37.2 g, 165 mmol). The suspension was heated at 100 °C (reflux) for 1 h, and then cooled to rt. After most of the ethanol was removed under vacuum, H_2O (100 mL) and EtOAc (150 mL) were added. To the resulting mixture, solid K_2CO_3 was added carefully until pH >10. The EtOAc layer was separated from the heterogeneous mixture, and the aqueous phase was extracted with EtOAc until it was free of the product (3×100 mL). The combined organic solution was washed with brine and dried over Na_2SO_4/K_2CO_3. Solvent was removed under vacuum and the residue was redissolved in Et_2O. The resulting precipitated $Ph_3P(O)$ was removed. The residue was subjected to silica gel chromatography using using 10% EtOAc in petroleum ether giving 2-(2,2-dibromovinyl)-phenylamine (**3a**, 7.3 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.18 (t, J = 7.7 Hz, 1H), 6.80 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 3.71 (br, 2H). To a solution of **3a** (7.3 g, 26 mmol) and pyridine (4.2 ml, 52 mmol) in DCM (30 mL) was added dropwise MsCl (3.0 mL, 39 mmol) 0 °C. The mixture was warmed slowly to rt, stirred for an additional 12 h, and diluted with EtOAc (50 mL). The mixture was washed with $NaHSO_4$ (20%, 2×50 mL), $NaHCO_3$ (50 mL), brine (50 mL), and dried over anhydrous Na_2SO_4. The crude mixture was purified by column chromatography on silica gel to afford the product **1a** as a white solid (9.23 g, 100%). ^1H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 7.79 (s, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.45–7.35 (m, 2H), 7.31 (t, J = 7.3 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 134.79, 134.75, 131.60, 129.53, 129.48, 126.07, 125.88, 92.08, 40.01; HRMS (ESI) calcd for $C_9H_{10}Br_2NO_2S$ ($[M+H]^+$): 355.8779; found: 355.8781.
8. *A general procedure for the preparation of 2-bromo indoles*: To a 25-mL roundbottomed flask was charged with **1a** (355.1 mg, 1 mmol), K_3PO_4 (424.5 mg, 2 mmol) and CuI (19.0 mg, 0.1 mmol). After the flask was evacuated and backfilled with N_2 (this procedure was repeated three times), toluene (5 mL) was added. The flask was evacuated and backfilled with N_2 again. Then the mixture was stirred at room temperature for 8 h. When **1a** was consumed, the mixture was diluted with EtOAc (20 mL) and filtered through Celite. The crude material was purified by column chromatography on silica gel to afford **2a** (245.6 mg, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.53–7.47 (m, 1H), 7.34–7.23 (m, 2H), 6.84 (s, 1H), 3.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.21, 129.36, 124.94, 124.04, 120.10, 114.72, 114.59, 109.42, 41.76; HRMS (ESI) calcd for $C_9H_9BrNO_2S$ ($[M+H]^+$): 273.9537; found: 273.9533.
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