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$CuSO_4$-Catalyzed Tandem $C(sp^3)$−H Insertion Cyclization of Toluenes with Isonitriles to Form Indoles

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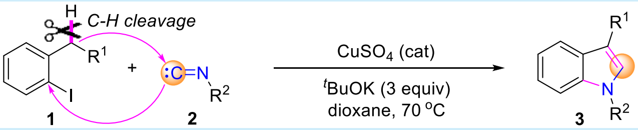
Supporting Information

ABSTRACT: A $CuSO_4$-catalyzed tandem benzylic C−H insertion cyclization of toluene derivatives and isonitriles is described. The naturally abundant salt $CuSO_4$ serves as a low-cost ligand-free redox catalyst. This reaction provides a practical modular synthesis of *N*-aryl indoles from isonitriles.



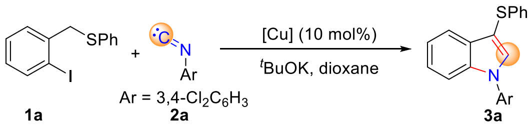
The transition-metal-promoted cleavage of inert bonds such as C−H and C−C bonds has been well-established in recent years. The noble metals including Rh, Pd, Ru, Ir, and so on have been widely used as catalysts with special strategies using directing groups or Haller−Bauer-type cleavage for the activation of these inert bonds.[1] The cleavage of undirected and unactivated C−H bonds remains a challenge in organic synthesis. The base-assisted C−H cleaving [3 + 2] addition−elimination has been a powerful method for the construction of five-membered heterocycles.[2,3] In this work, isonitriles have been found to be a remarkable C−N donor for *N*-aryl indoles.[4,5] The combination of base-promoted benzylic C−H cleavage[6] and copper-catalyzed carbanion-radical redox relay[7] enables this reaction. Catalytic inexpensive naturally abundant $CuSO_4$ promotes the modular synthesis of *N*-aryl indoles from toluene derivatives and isonitriles.

The reaction conditions have been explored by using the conversion of **1a** and **2a** to **3a** as the model reaction (Table 1). Initially, various copper salts were screened as catalysts. $Cu(OAc)_2$, CuI, $CuCl_2$, $Cu(acac)_2$, and $Cu(NCCH_3)_4PF_6$ were all found to be less active in comparison with $CuSO_4$, an inexpensive naturally abundant copper salt (entries 1−6). Further investigation shows that either a lower temperature or a lower amount of isonitrile **2a** can increase the reaction yields (entries 6−11). Dehalogenation and intramolecular cyclization side products were noticed at higher temperatures with more base. No conversion was observed for reactions in the absence of a base or $CuSO_4$ (entries 12 and 13). The reaction conditions identified in entry 11 were chosen as the standard conditions for further investigations.

The isonitrile scope was explored using the reaction of **1** to **3** (Scheme 1). Several *N*-aryl isonitriles bearing representative halo, alkyl, aryl, and hetero substituents were subjected to the standard reaction conditions, and the corresponding indoles were obtained.

Bromo and iodo groups were found to be tolerant of the reaction conditions (**3c**, **3g**, **3j**, and **3m**). The structure of indole product was confirmed by the X-ray analysis of **3m**. The scope of 2-iodotoluenes was examined using isonitrile **2a** as the reactant (Scheme 1). Both arylthio- and alkylthio-substituted toluenes were substrates for this reaction (**3n**−**q** and **3r**−**v**). Other substituents such as phenyl and heteroatom-containing groups were found to be less reactive (**3w**−**y**). The outstanding reactivity of arylthio- or alkylthio-substituted toluenes is a reflection of the possible radical reaction pathway due to the stability of the thio groups to adjacent radicals. The gram-scale synthesis afforded 2.25 g of **3b** in 84% yield.

Table 1. Reaction Conditions



entry[a]	[Cu]	2a (equiv)	temp (°C)	3a (%)[b]
1	$Cu(OAc)_2$	3	90	6
2	CuI	3	90	10
3	$CuCl_2$	3	90	24
4	$Cu(acac)_2$	3	90	28
5	$Cu(NCCH_3)_4PF_6$	3	90	36
6	$CuSO_4$	3	90	44
7	$CuSO_4$	3	70	61
8	$CuSO_4$	3	60	45
9	$CuSO_4$	3	75	56
10	$CuSO_4$	2	70	80
11[b]	$CuSO_4$	2	70	81
12[b]	none	2	70	0
13[c]	$CuSO_4$	2	70	0

[a]Conditions: **1a** (0.5 mmol), **2a** (2− to 3 equiv), ^{t}BuOK (5 equiv), dioxane (2 mL), argon, 5 h, isolated yields. [b]^{t}BuOK (3 equiv). [c]No ^{t}BuOK.

The general scope for toluene derivatives and isonitriles is demonstrated (Scheme 1). Toluenes bearing removable protecting groups such as TIPSO (**3z**), MOMO (**3B**), and $MeSCH_2O$ (**3C**) were converted to corresponding indoles

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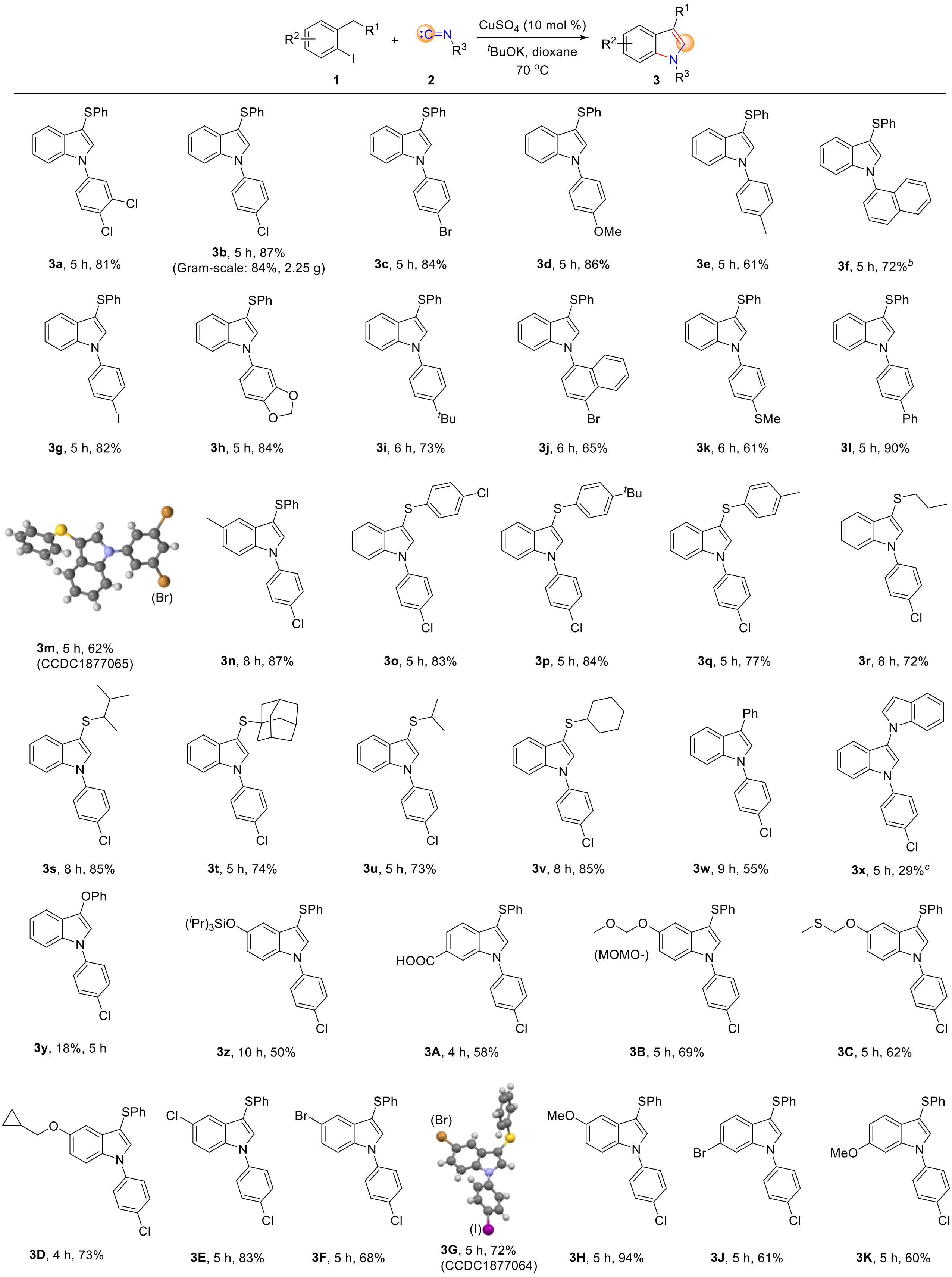
Scheme 1. Reaction Scope[a]



[a] Conditions: **1** (0.5 mmol), **2** (1 mmol), ^{t}BuOK (1.5 mmol), dioxane (2 mL), isolated yield. [b] Isonitrile (1.25 mmol). [c] [Cu] (20 mol %).

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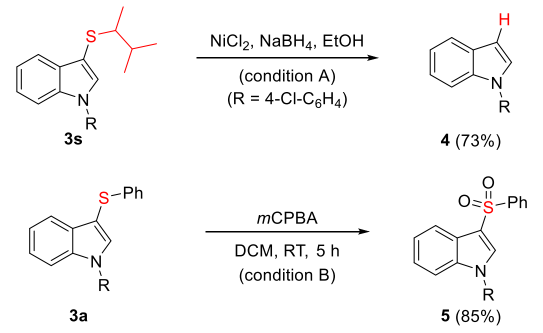
without altering these protecting groups. Carboxylic acid is also tolerated (**3A**). Other substituents including iodo, bromo, and chloro groups were also tolerated (**3D–J**). The structure of the representative indole **3G** was confirmed by X-ray analysis.

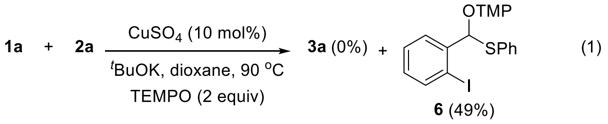
The thio groups are removable in most indole products. For example, the alkylthio group in indole **3s** is reduced to C3–H indole **4** in 73% (Scheme 2). In another case, **3a** was oxidized to 3-sulfonyl indole **5**. 3-Alkylthioindoles can be directly used for cross-coupling.[8]

Scheme 2. Synthetic Applications[a]

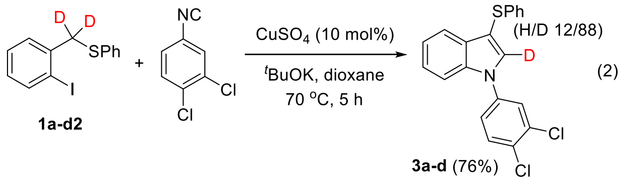


[a]Conditions A: $NiCl_2$ (6.8 equiv), $NaBH_4$ (6.8 equiv), EtOH, reflux, 12 h. Conditions B: *m*CPBA (3 equiv), CH_2Cl_2, r.t., 5 h.

To explore the reaction mechanism, control experiments were performed. In the radical trapping experiment, **1a**-OTEMP adduct **6** was isolated in 49% yield (eq 1), indicating



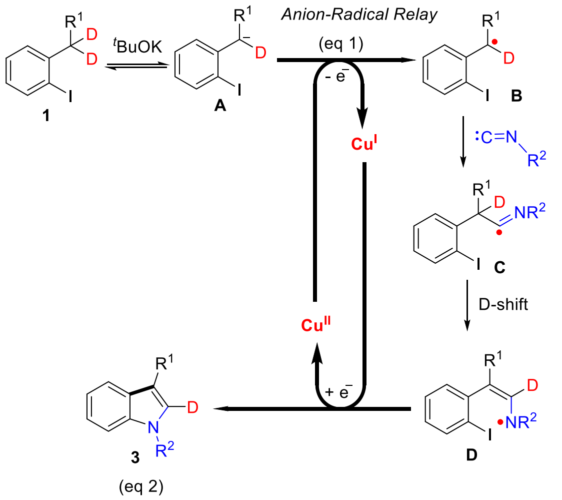
that a benzylic radical might be involved. Benzyl radical addition to nitriles and carbonyls has been proposed.[2,3] The isotope labeling experiment shows 88% D-incorporation at C2 (eq 2).



The reaction mechanism is proposed in Scheme 3. The ^{t}BuOK-promoted C–H cleavage affords carbanion **A**, which can possibly pass either an anionic addition to isonitrile or a redox anion-radical relay to radical **B**. The control experiment is consistent with this reaction passing through a radical pathway (eq 1).[3] The detailed mechanism for the redox anion-radical relay has been previously reported. The oxidation of **A** by Cu(II) affords radical **B**, followed by the addition to isonitrile to form **C**, followed by the 1,2-D-shift to **D** (eq 2). The D-shift step should not be involved with the transfer of the deuterium atom by ^{t}BuOD because the formation of a more active oxygen radical from carbon radical **C** is not allowed. The addition–elimination via either **D** affords **3**. The detailed reaction mechanism is unclear and still underway.

In conclusion, we have developed a $CuSO_4$-catalyzed indole synthesis from the C(sp^3)–H cleaving cyclization of toluene derivatives and isonitriles. The combination of the base-promoted benzylic C–H cleavage and the copper-catalyzed carbanion–radical redox relay enables this reaction. Catalytic amount of inexpensive naturally abundant $CuSO_4$ ensure the modular synthesis of *N*-aryl indoles from abundant toluene derivatives and isonitriles.

Scheme 3. Proposed Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03751.

Experimental procedures, full analysis data for compounds, and copies of nuclear magnetic resonance spectra (PDF)

Accession Codes

CCDC 1877064–1877065 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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