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Synthesis of Indoles via Electron-Catalyzed Intramolecular C−N Bond Formation

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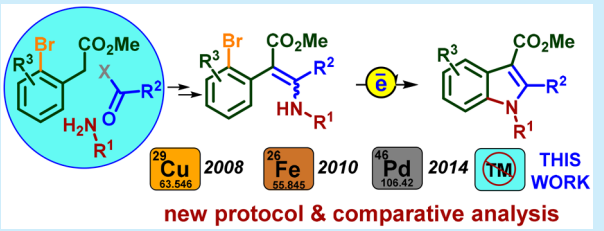
Supporting Information

ABSTRACT: A new protocol for the preparation of *N*-substituted indole-3-carboxylates has been developed. The key C−N bond formation occurs under transition-metal-free conditions employing a *t*-BuOK/DMF system without special initiators or additives. Across a number of substrates, indoles were afforded in yields higher or comparable to those obtained under transition-metal-catalyzed conditions. While demonstrating high functional group tolerance, new conditions are particularly attractive for manufacturing halogenated indoles that cannot be made in a pure form using other metal-based catalytic methods.



Developed over the past century, transition-metal-catalyzed cross-coupling reactions have revolutionized organic synthesis and incredibly expanded our opportunities to construct complex valuable organic molecules. These greatly efficient synthetic methodologies are currently in high demand in everyday synthetic practice, including on an industrial scale.[1] Despite their preeminent status among modern synthetic methods, the transition-metal-catalyzed reactions are associated with several drawbacks: high cost and toxicity of transition metals and ligands and trace metal contaminations in the final products. The latter represents a serious practical concern in the pharmaceutical industry and organic electronics and require extra metal-removing steps, which are usually time-demanding and expensive.[2] Moreover, transition-metal-catalyzed cross-coupling reactions of polyhalogenated substrates often suffer from a partial dehalogenation.[3]

To address the above-mentioned shortcomings, much attention has been paid recently to the development of transition-metal-free cross-coupling reactions, especially those employing the same starting materials (usually haloarenes) and giving the same products as the transition-metal-catalyzed reactions.[2a] Remarkably attractive protocols for the formation of carbon−carbon[4] and carbon−heteroatom[5] bonds in a transition-metal-free manner have been developed over the past several years.

In the absence of a transition metal, the activation of carbon−halogen bond can be achieved by a single-electron transfer (SET) from an electron donor.[2a,6] Although transition-metal-free cross-coupling reactions were proposed to occur by a way of radical or radical ion species, the true mechanism sometimes remains unclear and may vary depending on the substrates and reaction conditions.[2a,4−6] In search of a general mechanistic model, Studer and Curran have introduced a paradigm "electron is a catalyst".[7] For electron-catalyzed cross-coupling reactions, an electron formally acts as a catalyst instead of a transition metal.

The indole structural motif is widespread in natural and synthetic biologically active compounds.[8] For decades, this foundational heterocycle remains a privileged scaffold in drug discovery research. It is important to note that among the FDA-approved drugs currently in the market, 17 are indole-containing compounds.[9] Many methods for preparing indoles,[10] especially those recently developed, involve the use of palladium-[11] and copper-catalyzed reactions[12] and have the above shortcomings. Another approach based on oxidative cyclizations mediated by hypervalent iodine compounds[13] suffers from the use of toxic reagents, generation of a large amount of waste, and low regioselectivity. Therefore, alternative pathways to construct biologically relevant indole targets are highly appealing.

Previously, we disclosed an efficient strategy toward N-functionalized 1*H*-indole-3-carboxylates **1** via a Cu-[14] or Fe-catalyzed[15] intramolecular cyclization of 3-amino-2-(2-bromophenyl)acrylates **2** (Figure 1A). Compound **2** is easily accessed from (2-bromophenyl)acetate, methyl formate, and primary amine (Figure 1B).[14a] Several years later, this disconnection was used for the synthesis of 2-substituted analogues, employing a Pd catalyst.[16] Substituted indole-3-carboxylic acids are common building blocks for the synthesis of biologically relevant indole compounds such as CPI-1205,[17] a highly potent and selective inhibitor EZH2, that is currently in clinical trial as an anticancer agent, and SPD 304,[18] an inhibitor of tumor necrosis factors α (Figure 1C). Compared to other approaches,[19] our strategy is advantageous due to its modular character and wide scope, which enables the systematic variations of $N_{(1)}$ and $C_{(2)}$ substituents. Utilizing the same disconnection, herein we present the first electron-catalyzed indole synthesis and a comparative analysis of

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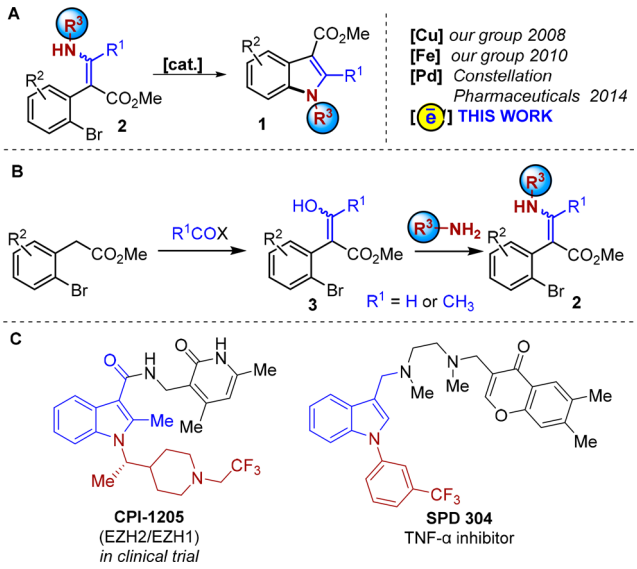


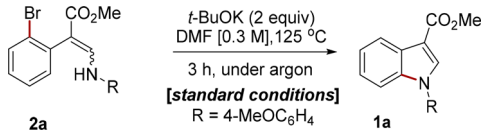
Figure 1. Approaches to *N*-substituted indole-3-carboxylates (A) and their precursors (B); examples of biologically active compounds (C).

different reaction conditions for an intramolecular C−N bond formation to afford indoles. The procedure is compatible with polyhalogenated and sterically congested substrates, which are challenging under transition-metal-catalyzed conditions.

To optimize the reaction conditions, we selected **2a** as a model substrate, prepared from 4-methoxyaniline and methyl 2-(2-bromophenyl)-2-formylacetate (**3a**), following our previously reported procedure.[14a] The substrate **2a** was obtained as a mixture of *Z*- and *E*-isomers; however, as demonstrated previously,[14] both of them can be easily converted to the indole product. Testing of various base/solvent combinations and varying of temperatures and reaction times revealed that *t*-BuOK (2 equiv) in DMF gave the best result, and after 3 h at 125 °C under an argon atmosphere, the indole **1a** was obtained in almost quantitative isolated yield (Table 1, entry 1). Notably, the use of *t*-BuONa or K_2CO_3 led to a decrease in the yield (entries 2 and 3). When the reaction occurred with less than 2 eqiuv of *t*-BuOK or at a lower temperature, the yield of **1a** was also decreased (entries 4 and 5). A slighter lower yield was observed when the reaction time was shortened (entry 6). Among the other solvents tested, only DMSO gave a synthetically useful, though considerably lower, yield (entries 7−10). Remarkably, indole **1a** was obtained in only 24% yield when DMAc was used instead of DMF (entry 8). Unlike published examples of electron-catalyzed intramolecular C−N coupling,[5] the formation of indole **1a** proved to be effective without the addition of a small-organic-molecule promoter.[6] The use of degassed solvents and inert atmosphere were, however, crucial to achieving a high efficiency (entry 11).

Having established the optimized conditions (Table 1, entry 1), we set out to investigate the reaction scope. First, we examined the substrates **2b−q**, derived from esters **3a−f** and substituted anilines (Scheme 1). Optimization of the initial

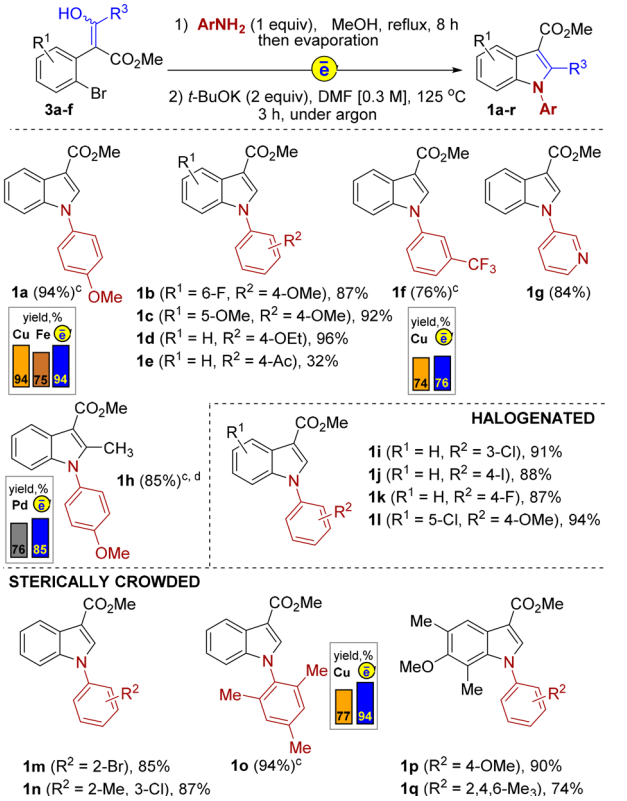
Table 1. Optimization of the Reaction Conditions for the Synthesis of Indoles[a]



entry	deviation from the standard conditions	yields[b] (%)
1	none	100 (94)
2	*t*-BuONa instead of *t*-BuOK	24
3	K_2CO_3 instead of *t*-BuOK	56
4	1 equiv of *t*-BuOK instead of 2 equiv	67
5	110 °C instead of 125 °C	68
6	2 h instead of 3 h	87
7	DMSO instead of DMF	75
8	DMAc instead of DMF	24
9	NMP instead of DMF	60
10	*o*-xylene instead of DMF	traces
11	without argon atmosphere	27

[a]Performed on a 0.1 mmol scale. [b]Yields determined by ^{1}H NMR using an internal standard. Yield of isolated product shown in parentheses. See the SI for details.

Scheme 1. Scope of the Reaction: Anilines[a,b]



[a]Performed on 0.1 mmol scale as a semione-pot procedure; [b]Yields are isolated yields calculated over two steps from **3**. [c]Yields under Cu, Fe, and Pd catalysis were taken for comparison from refs 14a, 15, and 16, respectively. [d]Compound **2h** was obtained following ref 16; cyclization time = 8 h.

step revealed that quantitative formation of **2** from **3** and any amine employed could be achieved by refluxing their mixture in MeOH for 8 h. The whole process was designed as a semione-pot procedure; initially, obtained compounds **2b−q** were subsequently used in the cyclization step after simple removal of the solvent. Yields are calculated over two steps from esters **3**. The method showed generality with respect to substrates possessing various substitution. The electronic nature of the substituents in the benzene ring does not affect the yield (e.g., **1c** vs **1l**). Also, cyclization of sterically crowded

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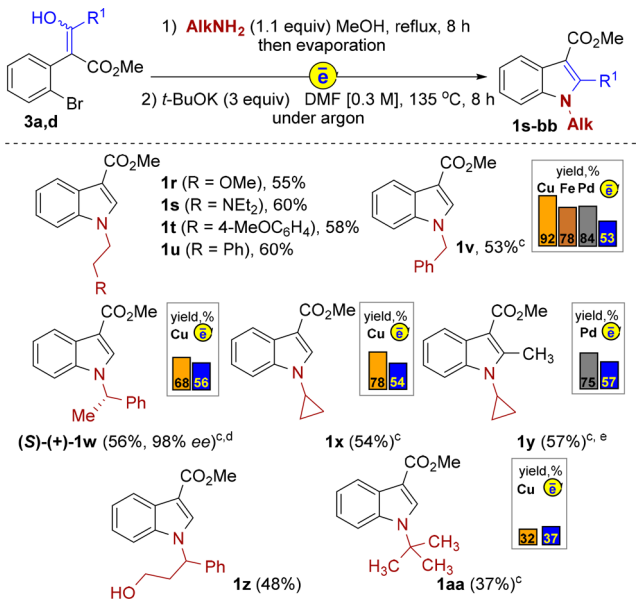
substrates proceeded effectively, delivering the 7-substituted indoles **1p,q** in excellent yields. The process can employ differently substituted anilines, including those containing *ortho*-substituents and being considered as sterically demanding (indoles **1m−o,q**). Importantly, using the chloro-, bromo-, and even iodo-substituted substrates allowed the preparation of the corresponding halogenated indoles **1i,j,l−n** in excellent yields with no traces of dehalogenation products. Indoles bearing fluoro substituents (**1b,f,k**) were also obtained. Despite the appeal of halogenated products, their preparation leaves a significant gap in the scope of most Pd-catalyzed reactions.[3] For instance, cyclization of a Cl analogue of **2** under Pd-catalyzed conditions was accompanied by a partial dechlorination.[16] While Cu- and electron-catalyzed conditions normally are compatible with chloro substituents, reactions of bromo and iodo substrates occur with a pronounced decrease of yields.[5,12,14] Thus, the formation of halogenated indoles without loss of yield is an attractive feature of our new conditions. Finally, cyclization of substrates containing the base-sensitive acetyl group allowed us to obtain **1e**, though in a modest yield. Using our new protocol, *N*-arylindoles **1a,f,h,o** were afforded in better or comparable yields to those reported using the same substrates under Cu-,[14] Fe-,[15] and Pd-catalyzed[16] conditions (Scheme 1).

Unfortunately, when these conditions were applied to **2** derived from alkylamines, *N*-alkylindoles were formed in low yields with most of the starting materials being recovered. Therefore, an additional screening of the reaction conditions was performed.[20] When 3 equiv of *t*-BuOK was employed at a higher temperature and for a prolonged reaction time, indoles **1r−aa** were obtained in moderate but still synthetically useful yields (Scheme 2). Indoles containing tertiary amine (**1s**) and hydroxy (**1z**) functionalities as well as the cyclopropyl moiety (**1x,y**) were tolerated. Remarkably, the protocol is suitable for

Scheme 2. Scope of the Reaction: Alkylamines[a,b]

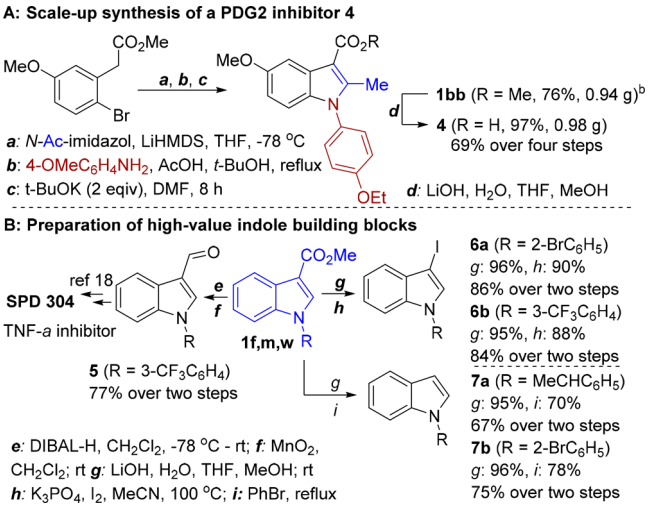


[a]Performed on a 0.1 mmol scale as a semione-pot procedure. [b]Yields are isolated yields calculated over two steps from **3**. [c]Yields under Cu, Fe, and Pd catalysis were taken for comparison from refs14a, 15, and 16, respectively. [d]See the SI for details. [e]Compound **2y** was obtained following ref 16.

the preparation of nonracemic chiral indoles as demonstrated by the synthesis of **1w** from (*S*)-(−)-α-methylbenzylamine without the loss of ee.[20] Utilizing highly bulky *tert*-butylamine proved problematic: **1aa** was obtained in only 37% yield.[21]

The developed conditions have been applied in a gram-scale preparation of a PDG2 inhibitor **4**[22] (Scheme 3A). Starting

Scheme 3. Transition-Metal-Free Preparation of Indoles Based on Indole-3-carboxylates



from methyl *o*-(bromophenyl)acetate, formation of the acid **4** was accomplished in four steps in an overall 69% yield.[20] The key step afforded a 76% yield of the ester **1bb**. Standard reduction/oxidation and hydrolysis/decarboxylation sequences[20] and the Larrosa decarboxylative iodination[23] applied to esters **1f,m,w** provided transition-metal-free routes for indoles **5−7** of high synthetic value[24] (Scheme 3B). Aldehyde **5**, the key intermediate for the preparation of SPD 304, was previously obtained via a Cu-catalyzed N-arylation.[18]

Having developed new cyclization conditions, we compared[20] them to those previously disclosed.[14−16] Neither conditions are ideal, and their ranges of applicability complement each other. While the electron-catalyzed conditions are perfect for the preparation of *N*-aryl and particularly halogenated indole-3-carboxylates, they proved less effective for *N*-alkylated counterparts. Synthesis of indoles with *tert*-alkyl substituents is especially difficult.

To test other halogenated substrates and provide some insight into the mechanism of cyclization, additional experiments were carried out.[20] While an iodine-substituted substrate gave the corresponding indole quantitatively, only a trace amount of the product was obtained with its F and Cl analogues. The addition of TEMPO, a common trapping reagent for free radicals, completely inhibited the cyclization. Similarly, 7,7′,8,8′-tetracyanoquinodimethane, a single-electron scavenger, deactivates the reaction. Although several possible mechanistic scenarios can be envisioned,[20] the above features, as well as the fact that oxygen-free solvent and atmosphere are mandatory, allow us to presume that a single-electron-transfer process and/or a formation of radical species might be involved in this transformation. The radical nature of the reaction was also supported by EPR experiments.[20]

On the basis of the Studer−Curran proposal,[7] the following tentative catalytic cycle has been proposed for the indole formation (Scheme 4). The reaction begins with the initial

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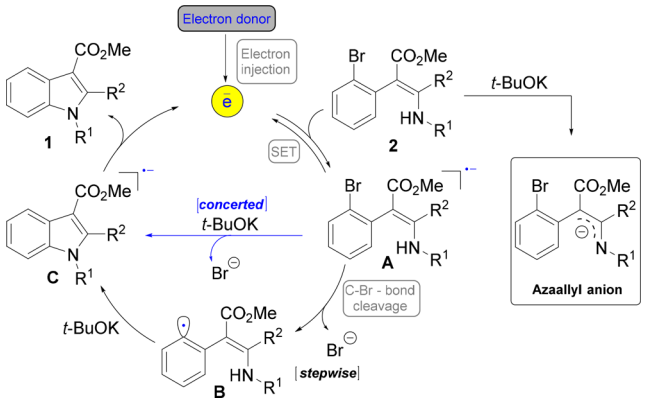
Scheme 4. Proposed Mechanistic Cycle



injection of an electron providing the actual catalyst, the electron. Either the *t*-BuOK/DMF system[25] or an azaallyl anion derived from **2** upon deprotonation can serve as the electron donor to initiate the process. Next, the reduction of **2** via a single-electron transfer generates the corresponding radical anion **A**, which upon fragmentation delivers the radical **B** alongside with bromide-ion. The following intramolecular trapping of **B** with the *N*-nucleophilic moiety generates the radical anion **C**. Finally, **C** acts as an electron donor for the next molecule of substrate **2**, thus giving the product **1** and liberating the electron back to the catalytic cycle. This sequence is like the $S_{RN}1$ mechanism.[26] Alternatively, **C** can be formed from **A** via a concerted pathway without the generation of **B**, which is similar to the $S_{RN}2$ mechanism.[26b] Although the mechanism of this cyclization remains to be elucidated, the high selectivity observed for polyhalogenated substrates suggests the latter pathway to be the more likely. Moreover, the conversion of **A** to **C** appears to be a rate-determining step in the whole cyclization.

In summary, we have disclosed a new synthetic strategy for *N*-functionalized indole-3-carboxylates, based on electron-catalyzed intramolecular C−N bond formation. The protocol uses the *t*-BuOK/DMF system for the cyclization of 3-amino-2-(2-bromphenyl)acrylate, affording the corresponding indoles in moderate to excellent yields. Unlike the transition-metal-based methods, the electron-catalyzed conditions are suitable for the synthesis of halogenated indoles without traces of dehalogenation products. While avoiding the use of expensive catalysts, this method is appealing for rapid generation of diverse libraries of indole containing compounds in drug discovery. The extension of this transition-metal-free methodology of indole synthesis and further mechanistic study are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02784.

Detailed experimental procedures, additional optimization data, mechanistic consideration, additional experiments, characterization of compounds, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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