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Cu-mediated C2-dehydrogenative homocoupling of indoles via C–H activation assisted by a removable *N*-pyrimidyl group

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ABSTRACT

A Cu-mediated regioselective, dehydrogenative homocoupling of indoles was developed using $AgNO_3$ as the additive. The easily installed and removed *N*-pyrimidyl group exerted complete C2 regiocontrol via C–H activation. A series of indole substrates underwent cross-dehydrogenative-homocoupling. This work developed an effective approach for the synthesis of 2,2′-biindole core of a number of chemicals fundamentally important in material and pharmaceutical chemistry.

Indoles are ubiquitous core structural motifs of biologically active natural and unnatural products.[1] Due to their importance in medicinal chemistry and drug discovery, direct functionalization of the indole nucleus has attracted continuous interest of synthetic chemists. In particular, recently emerged transition-metal-mediated direct C–H functionalization enables a direct cross-coupling of unactivated indoles and becomes an ideal and attractive alternative to the conventional cross-coupling technology with organic halides or organometallic reagents.[2–8] Moreover, this approach has opened the door to less-studied C2-functionalization. For example, a variety of methods assisted with a pyrimidine group have enabled the chlorination,[2] amination,[3] alkylation,[4] arylation,[5] alkenylation,[6] cyanation,[7] and acylation[8] of indoles' C2 position.

As critical indole derivatives, 2,2′-biindoles are found in a plethora of biologically active microbial natural products, such as rebeccamycin, staurosporine, ent-staurosporine, tjipanazoles, etc.[9] and plant alkaloids[9c] (Fig. 1). They are also functional moieties of biologically active synthetic molecules such as (−)-K252a[10] and anion sensor organic materials.[11] Commonly used methods for the preparation of 2,2′-biindoles include the Madelung cyclization of *o*-toluidide derivatives,[12] the intramolecular hydroamination of the corresponding 2-ethynylanilines,[13] and the coupling of the corresponding indole derivatives.[14] However, these methods usually suffer from lengthy steps and are not amenable for preparing multiple analogs. The development of an efficient new synthetic route to 2,2′-biindole derivatives is therefore of importance to chemical and drug industries. In this regard, the selective C2 homocoupling of indoles remains poorly developed, although direct homocoupling of some (hetero)arenes, such as arenes, thiophenes, furans, indolizines, azoles, and pyridines,[15] has been achieved. Earlier, Black and Keller reported oxidative coupling of several polysubstituted electron-rich indoles mediated by concentrated nitric acid or thallium trifluoroacetate.[16] In both cases, C3 substitutions were required to achieve the regioselective C2 coupling. Later, Carretero reported four examples of palladium catalyzed intermolecular dehydrogenative homocoupling to form 2,2′-biindoles with the assistance of a removable *N*-(2-pyridyl)sulfonyl group[17] (Scheme 1a). More recently, Miura and co-workers disclosed the copper-mediated regioselective homocoupling of thiophenes and indoles via directed C–H cleavage[18] (Scheme 1b). In this work, only four biindoles were obtained with yields of 35–55%. Herein, we report the development of non-precious copper mediated homocoupling of indoles directed by the removable pyrimidine group via C–H activation. This approach allowed regioselective cross-coupling of commercially available indole substrates at the C2 position to give the symmetrical 2,2′-biindole products with good yields under the easy-to-operate air atmosphere.

Initially, we attempted the reaction of substrate **1a** in the development of transition-metal catalyzed C–H activation/nitration[19,20] to regioselectively synthesize 2-nitroindole. Although

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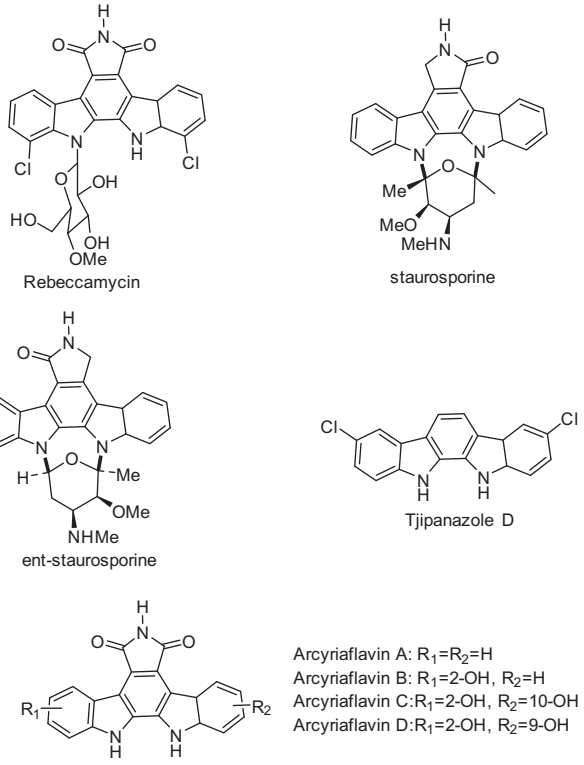
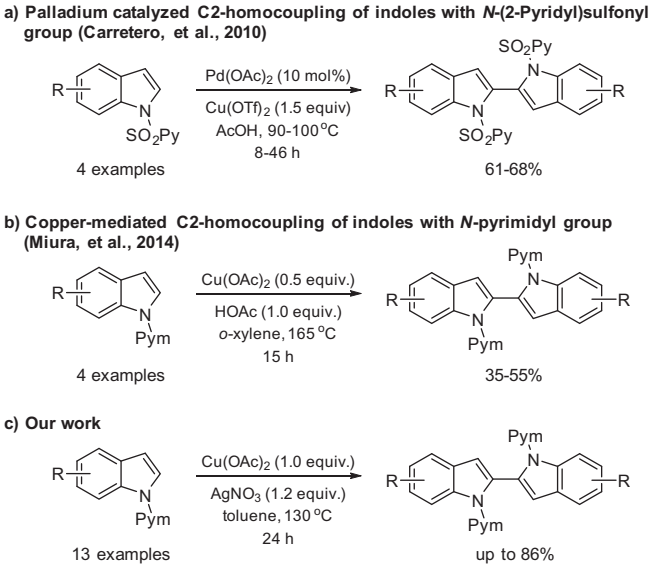


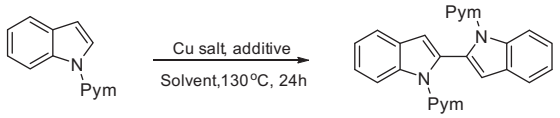
Figure 1. Selected 2,2′-biindole containing natural products.

the desired nitration product was not observed under reaction conditions, a significant amount of homocoupling product, biindole **2a**, was detected (entry 1, Table 1). We then moved our attention to the synthesis of this high value product. A few solvents that are commonly used for such transition metal catalyzed/mediated C–H activation reactions were screened, and among them toluene exhibited the highest efficacy for the homocoupling (entries 1–4). The yield was further improved by increasing $Cu(OAc)_2$ to 1 equiv (entry 5). On the other hand, replacing $AgNO_3$ with $AgNO_2$ decreased the reaction yield by 13% (entry 6). The currently



Scheme 1. Metal-catalyzed or mediated C2 homocoupling of indole via C–H activation.

Table 1
Optimization of reaction conditions for C2 homocoupling of **1a**[a]



Entry	Cu salt	$AgNO_3$ (equiv)	Solvent	Yield (%) of **2a**
1	$Cu(OAc)_2$	1.5	TCP	42[b]
2	$Cu(OAc)_2$	1.5	DCE	9[b]
3	$Cu(OAc)_2$	1.5	CH_3CN	37[b]
4	$Cu(OAc)_2$	1.5	Toluene	51[b]
5	$Cu(OAc)_2$	1.5	Toluene	67
6	$Cu(OAc)_2$	1.5	Toluene	54[c]
7	**$Cu(OAc)_2$**	**1.2**	**Toluene**	**82**
8	$Cu(OAc)_2$	/	Toluene	41
9	/	1.2	Toluene	n.r.
10	$Cu(OAc)_2$	1.2	Toluene	75[d]
11	$Cu(OAc)_2$	1.2	Dioxane	70
12	$Cu(OAc)_2$	1.2	Toluene/CH_3CN	63

[a] Reaction conditions (unless otherwise noted): **1a** (0.2 mmol), $Cu(OAc)_2$ (1 equiv), $AgNO_3$ (1.2 equiv), solvent (1 ml), air, 130 °C, 24 h. Yields were determined by crude NMR analysis using internal standard.
[b] $Cu(OAc)_2$ (0.5 equiv).
[c] $AgNO_2$ was used instead of $AgNO_3$.
[d] The reaction was run at 110 °C.

optimal conditions led to a yield of 82% of **2a** (entry 7) when a less amount of $AgNO_3$ was used in the reaction. Without $AgNO_3$, the reaction yield reduced to the half (41%), which indicates the importance of $AgNO_3$ in promoting the homocoupling (entry 8). Further screening of four additional silver salts failed to identify more active additive, and the results were shown in ESI. Without $Cu(OAc)_2$, the reaction was not occurred at all (entry 9). Decreasing temperature or switching to other solvents all led to the lower yields (entries 10–12).

With the optimized reaction conditions in hand, we then extended the reaction with a range of indole substrates. As illustrated in Table 2, this reaction was compatible with functionalized *N*-pyrimidyl substituted indoles bearing additional substitutions at C4-, C5- or C6-position, and afforded 2,2′-biindoles in good to excellent yields with a high regioselectivity. Electron-donating (methyl-, **2b** and **2f**; benzyloxy-, **2c**; methoxy-, **2e**) and electron-withdrawing groups (nitro-, **2g**) on *N*-Pyrimidyl indoles had insignificant effects on the synthesis of 2,2′-biindole products. Notably, halogen substitutions (fluoro-, **2h** and **2l**; chloro-, **2i** and **2m**; bromo-, **2d** and **2j**) on the indoles tended to give much higher yields than others regardless of their electronegativity. Iodo-substituted indole substrate gave a low yield of product (**2k**), which might come from the liability of iodo-substitution under the reaction conditions. Indole substrates with C7 substitutions led to no to low conversion in the reaction (data not shown), probably due to the steric hindrance between the C7 substitution and the pyrimidyl ring. This interaction might affect the formation of the cyclic organic metal intermediate after C–H activation.

Next, we removed the directing group from the homocoupling product (Scheme 2). Upon treatment of pyrimidyl substituted biindole product **2i** with NaOEt in dimethylsulfoxide (DMSO) at 110 °C, the corresponding N–H biindole **3i** was obtained with a yield of 82%. After condensation with (dimethylamino)-acetaldehyde diethyl acetal in acetic acid, natural product indolo[2,3-*b*]carbazole alkaloid, tjipanazoles D, was obtained in 65% yield.[9d]

According to the previous studies,[18] we proposed the mechanism of this reaction (Scheme 3). The C–H activation event in **1a** takes place at the Cu(II) stage leading to the formation of a five membered cyclocopper(II) intermediate **I**. A second C–H activation