

# Copper-Catalyzed Coupling of Indoles with Dimethylformamide as a Methylenating Reagent

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**Abstract:** By using *N,N*-dimethylformamide (DMF) as a methylenating reagent, the copper-catalyzed C–H activation of indole was demonstrated as an efficient and facile protocol for synthesizing 3,3'-diindolylmethane (DIM) and its derivatives. The results indicate that copper chloride was the best catalyst among the investigated transition metal salts, which affords an excellent regioselectivity and good yield when *tert*-butyl hydroperoxide (TBHP) was used as an oxidant.

**Keywords:** C–C coupling; C–H activation; copper; diindolylmethanes; methylenation

Alkylated indoles occur widely in bioactive natural products and therapeutic drug molecules. For example, 3,3'-diindolylmethane (DIM) and its derivatives are used as dietary supplements, which can promote healthy estrogen metabolism in humans by converting both estrone and estradiol to their respective 2-hydroxy derivatives (non-carcinogenic metabolites).<sup>[1]</sup> In addition, DIM is an effective inhibitor of human prostate cancer cells. Several research groups have made important contributions for its synthesis.<sup>[2]</sup> For instance, Jaisankar et al.<sup>[3]</sup> reported an eco-friendly route by using hexamethylenetetramine as a methylene donor in the presence of an ionic liquid. Li et al.<sup>[4]</sup> demonstrated the synthesis of this compound by using tetramethylethylenediamine (TMEDA) as a methylene donor catalyzed by Cu(II). Recently, a new route *via* C-3 selective alkylation was proposed by Cheng.<sup>[5]</sup> However, all of these methods use either commercially unavailable reagents, a high catalyst

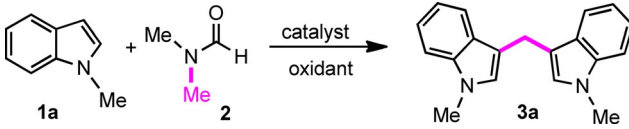
loading, or harsh reaction conditions. Thus, new routes for the efficient synthesis of DIM and its derivatives are highly desired.

Dimethylformamide (DMF) is widely used as a polar solvent in various reactions. Recently, the chemical transformation of DMF to multipurpose building blocks has drawn much attention.<sup>[6]</sup> In fact, DMF as a reaction precursor has been widely studied in a range of reactions,<sup>[7]</sup> including formylation,<sup>[8]</sup> amination,<sup>[9]</sup> and cyanation.<sup>[10]</sup> However, DMF serving as a methylation reagent is less studied.

In a previous work from some of us,<sup>[11]</sup> DMF was successfully used as a methylation reagent for the synthesis of methylated ketones. This stimulated us to explore the possibility of using DMF as a methylenating reagent. Herein, we demonstrate that the direct methylenation of indoles by using DMF as a methylene source is an efficient method for synthesizing DIM and its derivatives.

To this purpose, firstly, *N*-methylindole **1a** was used as a substrate for screening the conditions for this coupling transformation. A solution of **1a** and TBHP in DMF was stirred at 140 °C for 14 h with copper powder (10 mol%) as a catalyst. To our delight, the target product **3a** was obtained in a yield of 54% (Table 1, entry 1). Control experiments revealed that both the copper catalyst and the oxidant were indispensable for the reaction (Table 1, entries 2 and 3). Next, we surveyed several copper salts, and CuCl was found to be the best, leading to the target product in a 90% yield (Table 1, entries 4–7). With these good results in hand, we further surveyed other transition metal chlorides as a catalyst for this reaction. However, all of them exhibited a low catalytic activity (Table 1, entries 8–11). Moreover, on replacing DMF by DMSO, **3a** was not obtained (Table 1, entry 12). In

**Table 1.** Optimization of reaction conditions.<sup>[a]</sup>



Entry	Methylenation reagent	Catalyst	Oxidant	Yield [%] <sup>[b]</sup>
1	DMF	Cu powder	TBHP	54
2	DMF	–	TBHP	0
3	DMF	Cu powder	–	0
4	DMF	CuCl <sub>2</sub>	TBHP	79
5	DMF	CuCl	TBHP	90
6	DMF	CuBr	TBHP	70
7	DMF	CuI	TBHP	64
8	DMF	NiCl <sub>2</sub>	TBHP	47
9	DMF	CoCl <sub>2</sub>	TBHP	52
10	DMF	FeCl <sub>2</sub>	TBHP	54
11	DMF	FeCl <sub>3</sub>	TBHP	33
12	DMSO	CuCl	TBHP	0
13	DMF	CuCl	K <sub>2</sub> S <sub>2</sub> O <sub>8</sub>	5
14	DMF	CuCl	DTBP	23
15	DMF	CuCl	BPO	39
16	DMF	CuCl	AgNO <sub>3</sub>	2
17	DMF	CuCl <sup>[c]</sup>	TBHP	63

<sup>[a]</sup> Reaction conditions: indole (1.0 mmol) was added to a mixture of catalyst (0.1 mmol), TBHP (3.0 mmol), and DMF (3.0 mL), and the mixture was stirred at 140°C for 14 h.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> The amount of CuCl was 0.05 mmol.

view of the fact that oxidants played a key role in this reaction, several commonly used oxidants were evaluated (Table 1, entries 5 and 13–16), and TBHP was proved to be the best as it promoted the reaction to form the desired compound in the highest yield of 90% (Table 1, entry 5). Concerning the catalyst loading, the yield decreased to 63% if it was lowered to 5 mol% (Table 1, entry 17). Thus, the optimal reaction conditions were obtained as follows: CuCl (10 mol%), TBHP (3 equiv.), and DMF as the methylenation reagent at 140°C for 14 h.

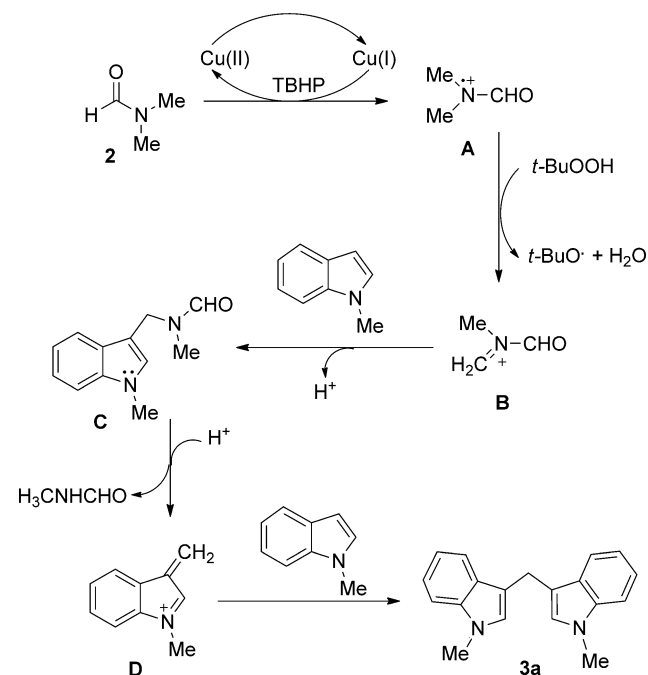
Under the optimized reaction conditions, we studied the substrate scope of the reaction. As can be seen from Table 2, the coupling reaction between a series of *N*-substituted indoles (**1a–r**) proceeded smoothly to afford **3a–r** in a good to excellent yields. Substrates having electron-donating substituents, such as Me or OMe, afforded the corresponding products in satisfactory yields (Table 2, **3a–3g**). In particular, the coupling of *N*-methylindoles bearing functional groups, such as OH and OBn, still proceeded successfully (Table 2, **3h–3j**). When indoles containing electron-withdrawing groups were employed for the reaction, to our delight, the target products were also obtained in good yields (Table 2, **3k–3o**). Even *N*-

benzylindoles were still viable substrates (Table 2, **3p–3r**). However, *N*-Boc- and *N*-sulfonated indoles both failed to give the desired products. In the case of *N*-Boc-indole, the starting material disappeared, but for *N*-sulfonated indole, no reaction happened and the starting material could be recovered.

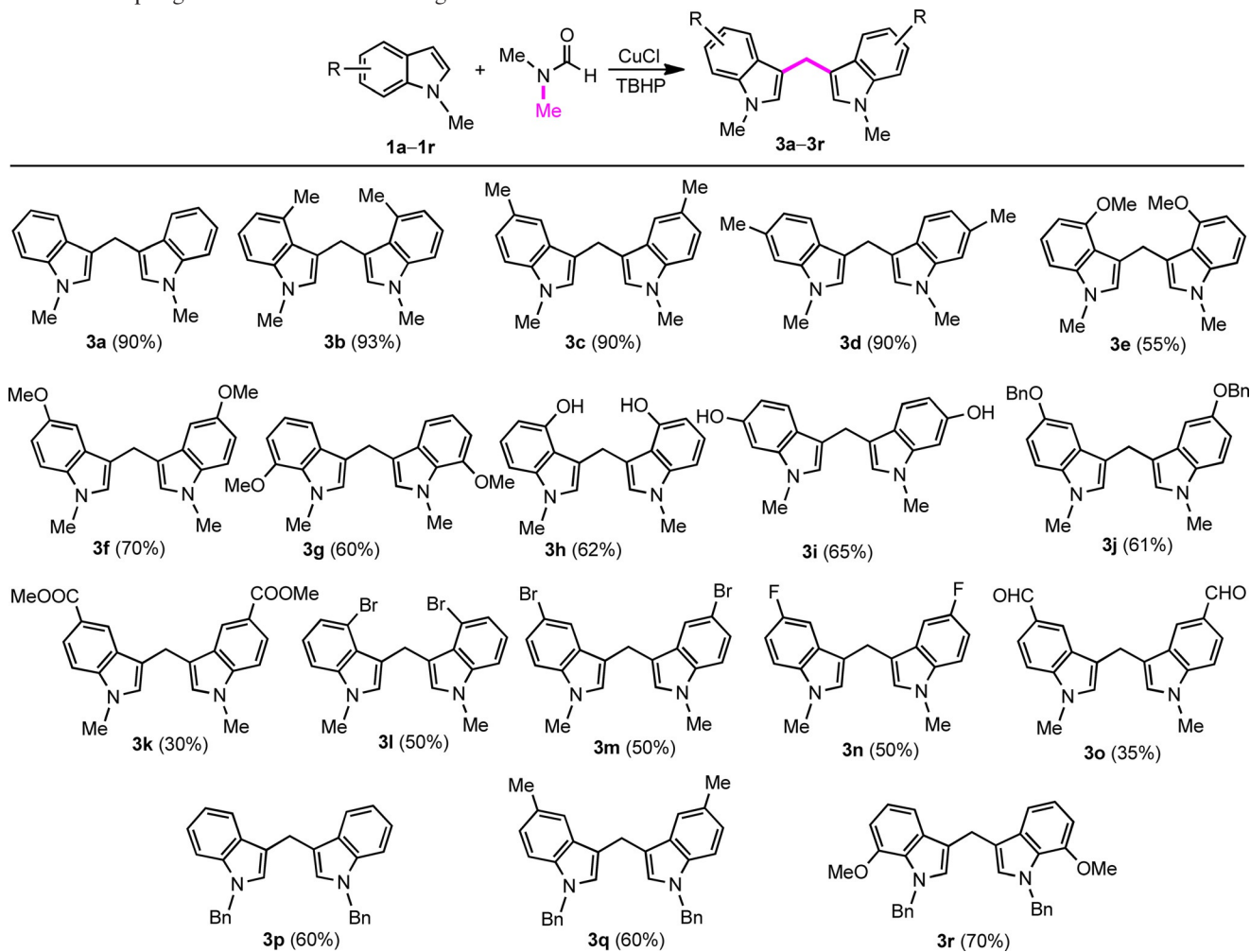
For all of the substrates, the C–C coupling occurred exclusively between the C-3 position of the indole and the methyl carbon of DMF, leading to the formation of DIM and its derivatives in a highly regioselective manner. Moreover, the tolerance of the reaction to functional groups in the indole derivatives, such as chloro, nitro, and methoxy, provides an opportunity for further chemical transformations.

To probe the possible mechanism of this reaction, additional experiments were carried out. In view of the fact that DMF can decompose easily into formaldehyde,<sup>[12]</sup> the methylene unit in the transformation under question could result from formaldehyde. To examine this possibility, the reaction for the formation of **3e** was implemented by adding polyformaldehyde (1 equiv.). However, the product **3e** was obtained in the same yield as that obtained without adding polyformaldehyde. Thus, the possibility of formaldehyde as the intermediate of the reaction can be excluded. In addition, when a radical scavenger such as TEMPO or BHT was added, no reaction was observed, suggesting that radicals are possibly involved as reaction intermediates.

Based on the results, a mechanism for the formation of the coupling product is proposed as shown in Scheme 1. The reaction starts with a single-electron



**Scheme 1.** A possible mechanism for the title reaction using **3a** as an example.

**Table 2.** Coupling of indoles with DMF to give DIMs.<sup>[a]</sup>

<sup>[a]</sup> Reaction conditions: indole (1.0 mmol) was added to a mixture of CuCl (0.1 mmol), TBHP (3.0 mmol), and DMF (3.0 mL), and the mixture was stirred at 140 °C for 14 h.

transfer from **2** to Cu(II) to give the intermediate **A** and Cu(I). Then, hydrogen atom abstraction in **A** by TBHP affords the iminium **B**. Subsequent electrophilic substitution leads to the formation of the compound **C**. The transfer of the lone pair of nitrogen in indole possibly affords azafulvalene **D**, which is ready for accepting another indole to generate the final product (Scheme 1).

In summary, an efficient Cu-catalyzed protocol for the synthesis of DIM and its derivatives has been developed. The easily available copper catalyst, the abundant and cheap DMF as a carbon source, the broad scope of substrates, and the relatively mild reaction conditions are significant practical advantages for this new process.

## Experimental Section

### General Procedure

The reaction was carried out in an autoclave containing a Teflon tube (10.0 mL). The catalyst (0.1 mmol), indole (1.0 mmol), TBHP (3.0 mmol), and DMF (3.0 mL) were added to the reactor. After this, the autoclave was sealed, and the mixture was stirred at 140 °C in an oil bath for 14 h. After cooling to room temperature, the autoclave was opened carefully in a fume hood. Then, water (60.0 mL) was added, and the product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15.0 mL). The organic layers were collected, washed with brine (1 × 20.0 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated on a rotatory evaporator under atmospheric pressure. The desired product was purified by column chromatography on silica gel using a mixture of ethyl acetate and petroleum ether as an eluent.

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