



# Acid-catalyzed efficient Friedel–Crafts reaction of indoles with *N*-Boc amins



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## ABSTRACT

An effective Friedel–Crafts reaction between *N*-Boc amins and *N*-Boc indoles catalyzed by copper(II) trifluoromethanesulfonate has been developed. The less accessible *N*-Boc imines could be generated in situ from *N*-Boc amins. The reaction was achieved in moderate to good yields under mild conditions.

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## 1. Introduction

As one of the most important bicyclic aromatic heterocyclic compounds, indoles are present in many classes of organic compounds in the biological and medicinal field,<sup>1</sup> widely distribute in the natural compounds and exist in a number of drugs currently on the market (Fig. 1).<sup>2</sup> Considerable efforts have been devoted to the modification of the indoles with various functional groups. Wherein, most of reports are focus on C-3 position of the indole structure, this outcome is a result of the high nucleophilic reactivity at the 3-position of the heterocyclic compound.<sup>3</sup> The Friedel–Crafts alkylation of indoles with imine substrates is a completely atom-economical reaction that provides a very useful approach to 3-indolylalkylamine derivatives, which represent a key structure motif in many biologically active compounds.<sup>4</sup> However, there are still some challenges in the direct reaction of indoles with imines owing to the poor electrophilicity of the imines, and bis(indolyl) methane compounds were trend to generate in acid-catalyzed Friedel–Crafts reactions as by-products.<sup>5</sup> Consequently, some imine substrates containing electron-withdrawing groups at nitrogen

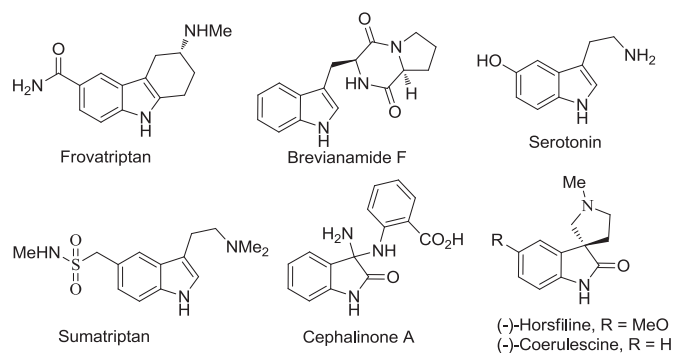


Fig. 1. Examples of drugs and nature products.

atom were developed, and then *N*-sulfonyl and *N*-sulfinyl imines have been widely used in the Friedel–Crafts reactions with indoles to afford corresponding products.<sup>6</sup>

*N*-Boc imines performed well in Friedel–Crafts reaction due to the high reactivity, and have been attracted numerous attentions.<sup>7</sup> However, their application are limited owing to the instability and the difficulty of synthesis. Therefore, *N*-Boc imines were usually generated in situ from the appropriate precursors, such as  $\alpha$ -amido sulfides and  $\alpha$ -amido sulfones.<sup>8</sup> Most recently, Masson and co-

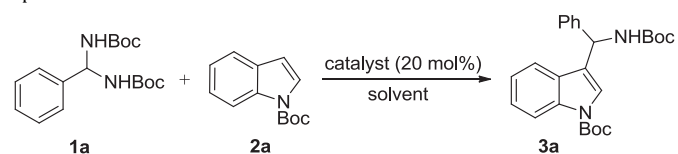
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workers realized *N*-iodosuccinimide promoted Friedel–Crafts reaction of indoles with *N*-Boc imines which generated in situ from  $\alpha$ -amido sulfides and obtained the desired products in good yields.<sup>8b</sup> Maruoka and co-workers developed a novel method that *N*-Boc imines can be generated in situ from *N*-Boc amins, and the less accessible or unprecedented *N*-Boc imines could be generated from the corresponding amins.<sup>9</sup> Most important, *N*-Boc amins are readily accessible from commercially available reagents and can be isolated as a stable and easily handled solid under mild conditions. They are insensitive to air, moisture and light, so the application would be expansive. For instance, this substrates showed highly reactivity in synthesis of versatile nitrogen-containing compounds.<sup>10</sup> On the other hand, the asymmetric Friedel–Crafts reaction of indoles with *N*-tosyl substituted imines could be catalyzed by a chiral copper-bisoxazoline complex.<sup>11</sup> Therefore, we attempt to use the *N*-Boc amins as imine surrogates in the Friedel–Crafts reaction involving indoles, which would be a mild and nontoxic approach to synthesize versatile and powerful heterocyclic compounds.

## 2. Results and discussion

We initially studied the reaction of di-*tert*-butyl (phenylmethylene)dicarbamate (**1a**) with *tert*-butyl 1*H*-indole-1-carboxylate (**2a**) to optimize the reaction conditions. The results are summarized in Table 1. There was no product was observed when the reaction was performed without any catalyst (entry 1), and then different catalysts were examined. Among the Lewis acid screened, the copper(II)-trifluoromethanesulfonate [Cu(OTf)<sub>2</sub>] provided the desired adduct **3a** in 71% yield (entry 5). The other copper salts also gave the products **3a**, but the yield was lower than that using Cu(OTf)<sub>2</sub> (entries 2–6). When the catalyst loading was decreased to 10 mol %, the yield of **3a** would reduce (entries 5 and 6). Meanwhile, when the trifluoroacetic acid (TFA) was used, we got

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



Entry	Catalyst	Solvent	Temp (°C)	Yield (%) <sup>b</sup>
1	—	CH <sub>2</sub> Cl <sub>2</sub>	rt	—
2	CuI	CH <sub>2</sub> Cl <sub>2</sub>	rt	55
3	CuBr <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	50
4	CuCl <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	53
5	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	71
6 <sup>c</sup>	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	67
7 <sup>c</sup>	TFA	CH <sub>2</sub> Cl <sub>2</sub>	rt	63
8	TFA	CH <sub>2</sub> Cl <sub>2</sub>	rt	69
9	TfOH	CH <sub>2</sub> Cl <sub>2</sub>	rt	57
10	Cu(OTf) <sub>2</sub>	DCE	rt	61
11	Cu(OTf) <sub>2</sub>	toluene	rt	68
12	Cu(OTf) <sub>2</sub>	CH <sub>3</sub> CN	rt	62
13	Cu(OTf) <sub>2</sub>	CH <sub>3</sub> OH	rt	49
14	Cu(OTf) <sub>2</sub>	THF	rt	57
15	Cu(OTf) <sub>2</sub>	Dioxane	rt	45
16	Cu(OTf) <sub>2</sub>	EtOAc	rt	51
17 <sup>d</sup>	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	65
18 <sup>e</sup>	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	rt	72
19	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0	59
20	Cu(OTf) <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	40	65

<sup>a</sup> Unless stated otherwise, the reactions were carried out with **1a** (1.5 equiv), **2a** (0.15 mmol, 1.0 equiv), and catalyst (20 mol%) in solvent (1.0 mL) for 3 days.

<sup>b</sup> Isolated yield of **3a** after column chromatography.

<sup>c</sup> 10 mol % catalyst was employed.

<sup>d</sup> The reaction time was 2 days.

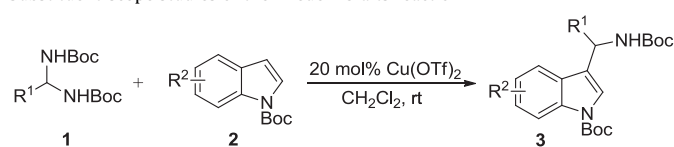
<sup>e</sup> The reaction time was 4 days.

the similar results (entries 7 and 8). The trifluoromethanesulfonic acid could give the desired product in moderate yield (entry 9).

Next the effect of solvent on the reaction was investigated (Table 1 entries 10–16 and entry 5). Using dichloromethane as solvent afforded the desired product **3a** in a better yield (entry 5). Nevertheless, the other solvents such as dichloroethane (DCE), toluene, acetonitrile, methanol, tetrahydrofuran, 1,4-dioxane, ethyl acetate gave product **3a** in moderate yields (entries 10–16 vs 5). Appropriate prolonged reaction time would improve the yield of **3a**, while further increasing the reaction time did not provide an obvious improvement of chemical yield (entries 5, 17 and 18). The temperature screening indicated that room temperature was the suitable condition (entries 5, 19 and 20). Thus, the best optimized conditions for this reaction has been established, Cu(OTf)<sub>2</sub> as catalyst in CH<sub>2</sub>Cl<sub>2</sub> at room temperature for 3 days.

With the optimal reaction conditions in hand, the substrate scope of the reaction was then investigated. A variety of *N*-Boc amins with differently substituted indoles were subjected to the optimal reaction conditions. The results are shown in the Table 2. It is satisfactory that all the substrates provided the desired products in moderate to good yields, and showing good functional group tolerance. Particularly less accessible *N*-Boc imine that with alkyl and phenemyl substituent were performed well and obtained the addition products in moderate yields (entries 2–4). A range of electron-donating and electron-withdrawing group substituted amins were viable in this reaction. In view of the electronic effect of this transformation, in general, electron-donating groups substituted *N*-Boc amins showed higher reactivity and gave slightly higher yields than electron-withdrawing groups substituted ones (entries 5–17). In details, when the phenyl group was substituted with fluorine, we had gained the desired compounds in higher yields than other halogen (entries 7–14). It was pleased to found that when the nitro-group substituted *N*-Boc

**Table 2**  
Substituent-scope studies of the Friedel–Crafts reaction<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Yield (%) <sup>b</sup>
1	C <sub>6</sub> H <sub>5</sub>	H	<b>3a</b>	71
2	C <sub>2</sub> H <sub>5</sub>	H	<b>3b</b>	68
3	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	H	<b>3c</b>	59
4	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	H	<b>3d</b>	65
5	2-MeC <sub>6</sub> H <sub>4</sub>	H	<b>3e</b>	74
6	4-MeOC <sub>6</sub> H <sub>4</sub>	H	<b>3f</b>	73
7	4-BrC <sub>6</sub> H <sub>4</sub>	H	<b>3g</b>	62
8	3-BrC <sub>6</sub> H <sub>4</sub>	H	<b>3h</b>	59
9	2-BrC <sub>6</sub> H <sub>4</sub>	H	<b>3i</b>	65
10	3,5-Br <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	<b>3j</b>	58
11	4-FC <sub>6</sub> H <sub>4</sub>	H	<b>3k</b>	73
12	2-FC <sub>6</sub> H <sub>4</sub>	H	<b>3l</b>	70
13	2-ClC <sub>6</sub> H <sub>4</sub>	H	<b>3m</b>	60
14	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	H	<b>3n</b>	56
15	2-naphthyl	H	<b>3o</b>	55
16	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	<b>3p</b>	75
17	3-CF <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	<b>3q</b>	72
18	C <sub>6</sub> H <sub>5</sub>	5-Me	<b>3r</b>	68
19	C <sub>6</sub> H <sub>5</sub>	6-Me	<b>3s</b>	71
20	C <sub>6</sub> H <sub>5</sub>	5-Br	<b>3t</b>	58
21	C <sub>6</sub> H <sub>5</sub>	6-Br	<b>3u</b>	62
22	C <sub>6</sub> H <sub>5</sub>	5-MeO	<b>3v</b>	72
23	C <sub>6</sub> H <sub>5</sub>	6-MeO	<b>3w</b>	76

<sup>a</sup> The reactions were carried out with **1** (1.5 equiv), **2** (0.15 mmol, 1.0 equiv), and Cu(OTf)<sub>2</sub> (20 mol%) in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) at rt for 3 days.

<sup>b</sup> Isolated yield of **3** after column chromatography.

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