



## Trifluoromethanesulfonic acid-catalyzed solvent-free bisindolylolation of trifluoromethyl ketones



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### ABSTRACT

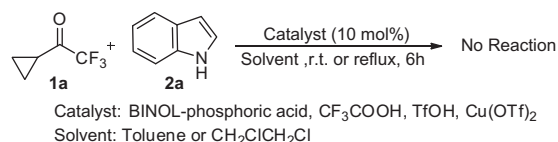
A trifluoromethanesulfonic acid-catalyzed solvent-free bisindolylolation reaction of indoles with alkyl and aryl trifluoromethyl ketones has been developed. The trifluoromethyl-substituted bisindolylalkane derivatives were synthesized in moderate to excellent yields.

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Bisindolylalkane is an important structural unit of natural products. Recent studies have shown that bisindolylalkanes and their derivatives exhibit a wide range of bioactivities.<sup>1,2</sup> Therefore, the synthesis of those useful compounds has attracted great attentions. Several methodologies were developed by synthetic organic chemists.<sup>3–5</sup> The most convenient and straightforward ways for synthesizing bisindolylalkane compounds are Lewis or Brønsted acid-catalyzed addition reactions of indoles with carbonyl compounds.<sup>3</sup> In addition, transition-metal-catalyzed procedures also appeared.<sup>4</sup> Among them, several eco-friendly solvent-free protocols have been developed.<sup>5</sup>

On the other hand, the introduction of fluorine or fluoro-containing substitutes into organic molecules, such as the trifluoromethyl group, often increases their bioactivities.<sup>6</sup> In our everlasting effort of studying the chemical transformation of fluorinated synthetic building blocks,<sup>7</sup> we are interested in investigating the reactions of trifluoromethyl ketones with indoles and synthesizing of fluorine-containing indole derivatives with potential biological activities.

Due to the strong electron-withdrawing nature of the trifluoromethyl group, it can effectively stabilize the  $\alpha$ -C–O bond of intermediate trifluoromethyl-substituted tertiary alcohols.<sup>8</sup> So, it is not easy to make bisindolylalkanes from trifluoromethyl ketone



**Scheme 1.** Preliminary investigation of the reaction of ketone **1a** with indole.

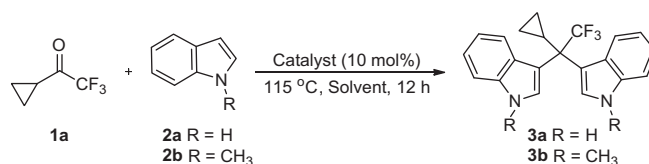
through an acid-catalyzed pathway. Only a few publications mentioned the preparation of trifluoromethyl substituted bisindolylalkane compounds.<sup>8a,9</sup> Recently, Sasaki and co-workers reported a Brønsted acid catalyzed stepwise reaction between trifluoromethyl- $\alpha,\beta$ -ynones and indoles to afford unsymmetrical trifluoromethyl-substituted bisindolylpropynes.<sup>8a</sup> For the relatively unreactive alkyl trifluoromethyl ketones, however, the similar transformation has not been reported so far. Herein, we describe a trifluoromethanesulfonic acid catalyzed bisindolylolation reaction of alkyl and aryl trifluoromethyl ketones under solvent-free condition.

We were particularly interested in synthesizing trifluoromethyl- and cyclopropyl-containing bisindolylalkane compounds. Thus, the initial study began with the examination of the reaction of trifluoromethyl cyclopropyl ketone **1a** with indole **2a**.<sup>10</sup> No reaction took place between **1a** and **2a** at room temperature in the presence of various Lewis or Brønsted acid catalysts in different solvents. Even being refluxed for 6 h, only trace amount of product was observed when  $\text{Cu}(\text{OTf})_2$  or TfOH was used as catalyst, and most of **1a** and **2a** were left unchanged (Scheme 1). However, Ma and co-workers

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



Entry	R	Catalyst	Additive	Solvent	Yield <sup>b</sup> (%)
1	CH <sub>3</sub>	BINOL-phosphoric acid	—	Toluene	—
2	CH <sub>3</sub>	CF <sub>3</sub> COOH	—	CH <sub>2</sub> ClCH <sub>2</sub> Cl	—
3	CH <sub>3</sub>	TfOH	—	CH <sub>2</sub> ClCH <sub>2</sub> Cl	26
4	CH <sub>3</sub>	TfOH	—	Toluene	53
5	CH <sub>3</sub>	TfOH	—	1,4-Dioxane	34
6	CH <sub>3</sub>	TfOH	—	CH <sub>3</sub> CN	8
7	CH <sub>3</sub>	Cu(OTf) <sub>2</sub>	—	Toluene	35
8	CH <sub>3</sub>	Cu(OTf) <sub>2</sub>	—	CH <sub>2</sub> ClCH <sub>2</sub> Cl	50
9	CH <sub>3</sub>	AgOTf	—	CH <sub>2</sub> ClCH <sub>2</sub> Cl	22
10	CH <sub>3</sub>	Sc(OTf) <sub>3</sub>	—	CH <sub>2</sub> ClCH <sub>2</sub> Cl	50
11	CH <sub>3</sub>	TfOH	4 Å MS (500 mg)	Toluene	50–73 <sup>c,d</sup>
12	CH <sub>3</sub>	TfOH	Na <sub>2</sub> SO <sub>4</sub> (30 mol %)	Toluene	80 <sup>d</sup>
13	CH <sub>3</sub>	TfOH	Na <sub>2</sub> SO <sub>4</sub> (30 mol %)	Toluene	88 <sup>d,e</sup>
14	CH <sub>3</sub>	TfOH	Na <sub>2</sub> SO <sub>4</sub> (30 mol %)	Solvent-free	92 (85) <sup>d</sup>
15	H	TfOH	Na <sub>2</sub> SO <sub>4</sub> (30 mol %)	Solvent-free	69 (66) <sup>d</sup>

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** or **2b** (0.6 mmol), catalyst (0.02 mmol, 10 mol %), 0.25 mmol **1a**/mL solvent, stirred at 115 °C for 12 h in a sealed tube.

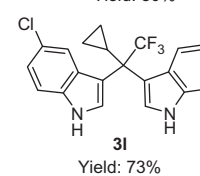
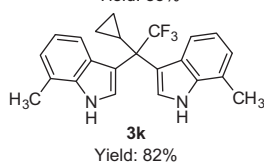
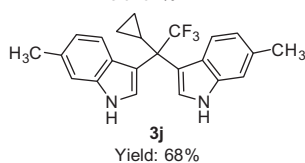
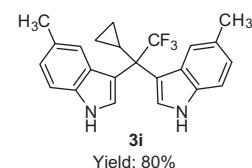
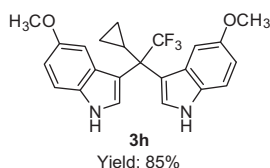
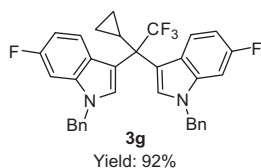
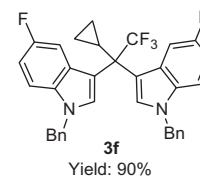
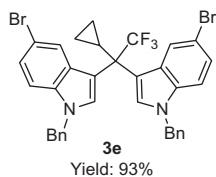
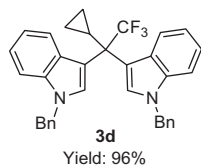
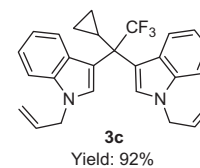
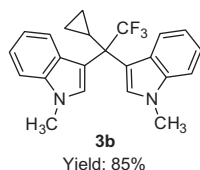
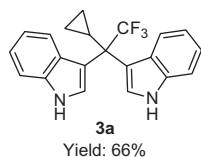
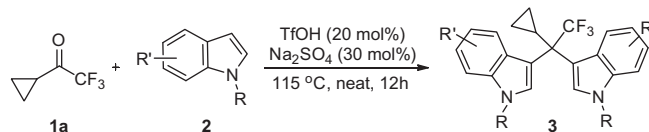
<sup>b</sup> Yields were determined by <sup>19</sup>F NMR using 1-fluoronaphthalene as an internal standard; isolated yields are listed in parentheses.

<sup>c</sup> Poor reproducibility of experiments using 4 Å MS as additive.

<sup>d</sup> 20 mol % TfOH (0.04 mmol) was used.

<sup>e</sup> More concentrated reaction mixture: 2.0 mmol **1a**/mL solvent.

**Table 2**  
Scope of TfOH-catalyzed bisindolylolation of trifluoromethyl cyclopropyl ketone<sup>a,b</sup>



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