

# Tunable Brønsted Acidity-Dependent Alkylation and Alkenylation of Indoles

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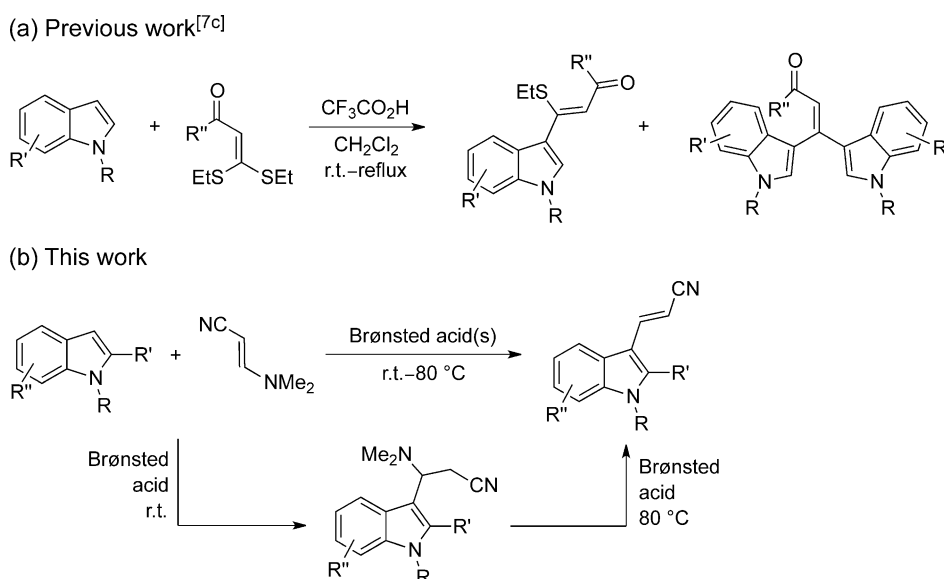
**Abstract:** The Brønsted acid-mediated alkylation and alkenylation of indoles were efficiently achieved by means of 3-(dimethylamino)acrylonitrile. Regulating the acidity of the reaction medium with *para*-toluenesulfonic acid monohydrate (*p*-TsOH·H<sub>2</sub>O) and/or acetic acid (HOAc) led to versatile formation of 3-alkylated and 3-alkenylated indole derivatives under mild conditions. The 3-alkylated indole products could be nearly quantitatively transformed to the corresponding separable (*E*)- and (*Z*)-3-alkenylated indoles.

**Keywords:** alkenylation; alkylation; Brønsted acids; 3-(dimethylamino)acrylonitrile; indoles

Indole derivatives are a very important class of nitrogen heterocyclic compounds with potential bioactivity<sup>[1a]</sup> and have been used in the manufacture of pharmaceuticals or as synthons in organic synthesis.<sup>[1b]</sup> As the C–H cross-coupling reaction is emerging as the most straightforward route to form a carbon-carbon bond,<sup>[2]</sup> C–H functionalization of indoles is considered as a concise method to access diverse indole derivatives.<sup>[3]</sup> Transition metal-catalyzed C–H alkylation<sup>[4]</sup> and alkenylation<sup>[5]</sup> of indoles have recently gained considerable attention for the preparation of functionalized indoles, but organocatalytic transformations<sup>[3b,c]</sup> seem to be more applicable for indole functionalization. Organocatalytic Friedel–Crafts alkylation of indoles has been well-documented, while non-metal mediated alkenylation of indoles has not been made much progress. To date, only a few reports on Brønsted acid-mediated indole alkenylation have been recorded by using functionalized alkynes and

polarized alkenes as the alkenylating reagents.<sup>[6,7]</sup> Indoles reacted with ynamides in the presence of trifluoromethanesulfonyl imide to afford 3-vinylindoles.<sup>[6]</sup> In trifluoroacetic acid, 1-dimethylamino-2-nitroethylene was condensed with indoles to yield 3-(2-nitrovinyl)indoles.<sup>[7a]</sup> Recently, we found that trifluoroacetic acid could promote the alkenylation of indoles with  $\alpha$ -oxoketene dithioacetals to form alkenylated mono- and bisindoles (Scheme 1a).<sup>[7c]</sup>

$\alpha$ -Oxoketene dithioacetal is structurally featured with two electron-donating thioalkyls and an electron-withdrawing carbonyl attached at its C=C bond, exhibiting a push-pull electronic effect to facilitate its protonation by a Brønsted acid.<sup>[7c]</sup> 3-(Dimethylamino)acrylonitrile (Me<sub>2</sub>NCH=CHCN) was reported to react with 6-(methylamino)isocytosine in glacial acetic acid under heating to form an alkenylated intermediate species,<sup>[8]</sup> but no detailed study on its involvement in the direct olefination has been conducted. Based on the structural and electronic features of  $\alpha$ -oxoketene dithioacetals [ $\beta,\beta$ -(bisalkylthio)-substituted  $\alpha,\beta$ -unsaturated carbonyl derivatives] and (dimethylamino)acrylonitrile and their potential applications in organic synthesis,<sup>[9]</sup> they cannot be considered as the same type of push-pull reagents. However, intrigued by the push-pull effect of such a structural element, we envisioned that 3-(dimethylamino)acrylonitrile as a polarized alkene might also undergo a reaction similar to that as shown in Scheme 1, (a). Due to the well-established synthetic protocols to convert nitriles to amines, aldehydes, carboxylic acids, and amides,<sup>[10]</sup> the reactions of indoles with Me<sub>2</sub>NCH=CHCN may provide versatile indole derivatives or be used to introduce relevant functional groups in organic synthesis. Herein, we report the tunable Brønsted acid-mediated alkylation and alkenylation of indoles by 3-(dimethylamino)acrylonitrile [Scheme 1, (b)].



**Scheme 1.** Brønsted acid-mediated functionalization of indoles.

Initially, *N*-methylindole (**1aa**) was treated with 3-(dimethylamino)acrylonitrile (**2**) in the presence of acetic acid in  $\text{CH}_2\text{Cl}_2$  at ambient temperature, and no reaction was observed. Other weak acids such as  $\text{PhCO}_2\text{H}$ ,  $\text{HCO}_2\text{H}$  and  $\text{ClCH}_2\text{CO}_2\text{H}$  did not promote

the reaction either (Table 1, entries 1–4). Using the stronger dichloroacetic acid led to the alkylation and alkenylation products **3aa** (9%), **4aa** (8%), **5a** (<1%), and **6a** (14%) with predominant formation of dimeric indole **1aa'** (Table 1, entry 5). Increasing the acid

**Table 1.** Brønsted acidity-dependent reaction of *N*-methylindole (**1aa**) with 3-(dimethylamino)acrylonitrile (**2**).<sup>[a]</sup>

Entry	Acid/ $pK_a$ (equiv.)	Conversion <sup>[b]</sup> [%]	Yield <sup>[b]</sup> [%]			
			<b>3aa</b>	<b>4aa</b>	<b>5a</b>	<b>6a</b>
1	HOAc/4.76 <sup>[11a]</sup> (20)	–				
2	$\text{PhCO}_2\text{H}$ /4.20 <sup>[11b]</sup> (2)	–				
3	$\text{HCO}_2\text{H}$ /3.75 <sup>[11c]</sup> (20)	–				
4	$\text{ClCH}_2\text{CO}_2\text{H}$ /2.86 <sup>[11a]</sup> (2)	–				
5	$\text{Cl}_2\text{CHCO}_2\text{H}$ /1.30 <sup>[11a]</sup> (2)	78	9	8	<1	14
6	$\text{Cl}_2\text{CHCO}_2\text{H}$ /1.30 <sup>[11a]</sup> (10)	> 99	50	35	<1	4
7	$\text{Cl}_2\text{CHCO}_2\text{H}$ /1.30 <sup>[11a]</sup> (10)	100 <sup>[c]</sup>	28	26	41	3
8	$\text{Cl}_2\text{CHCO}_2\text{H}$ /1.30 <sup>[11a]</sup> (10)	100 <sup>[d]</sup>	10	56	17	1
9	$\text{Cl}_3\text{CCO}_2\text{H}$ /0.63 <sup>[11a]</sup> (2)	98	48	8	<1	12
10	$\text{CF}_3\text{CO}_2\text{H}$ /0.23 <sup>[11a]</sup> (2)	97	35	8	<1	18
11	$\text{CF}_3\text{CO}_2\text{H}$ /0.23 <sup>[11a]</sup> (10)	97	7	4	<1	<1
12	$\text{MeSO}_3\text{H}$ /–1.92 <sup>[11d]</sup> (2)	78	36	15	<1	18
13	$\text{MeSO}_3\text{H}$ /–1.92 <sup>[11d]</sup> (10)	72	29	9	<1	2
14	<i>p</i> -TsOH· $\text{H}_2\text{O}$ /–6.62 <sup>[11e]</sup> (2)	99	83 (80) <sup>[e]</sup>	5	<1	10

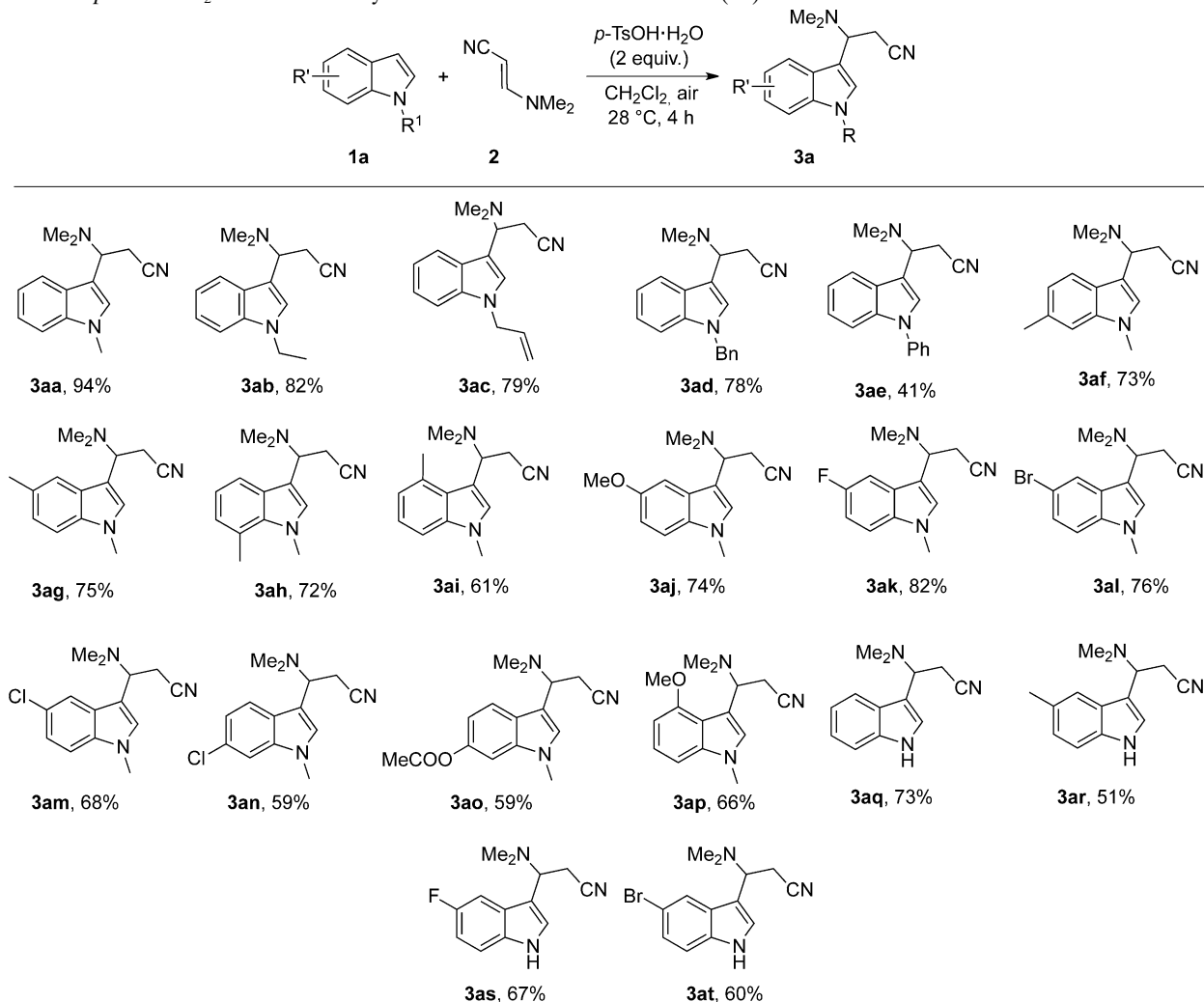
<sup>[a]</sup> Reaction conditions: **1aa** (0.5 mmol), **2** (0.5 mmol),  $\text{CH}_2\text{Cl}_2$  (2 mL), air, 28 °C, 4 h.

<sup>[b]</sup> Conversion of **1aa** and yields of **3–6** were determined by HPLC analysis.

<sup>[c]</sup> 48 h.

<sup>[d]</sup> 40 °C.

<sup>[e]</sup> Isolated yield given in parentheses.

**Table 2.** *p*-TsOH·H<sub>2</sub>O-mediated alkylation of 2-unsubstituted indoles (**1a**) with **2**.<sup>[a,b]</sup>

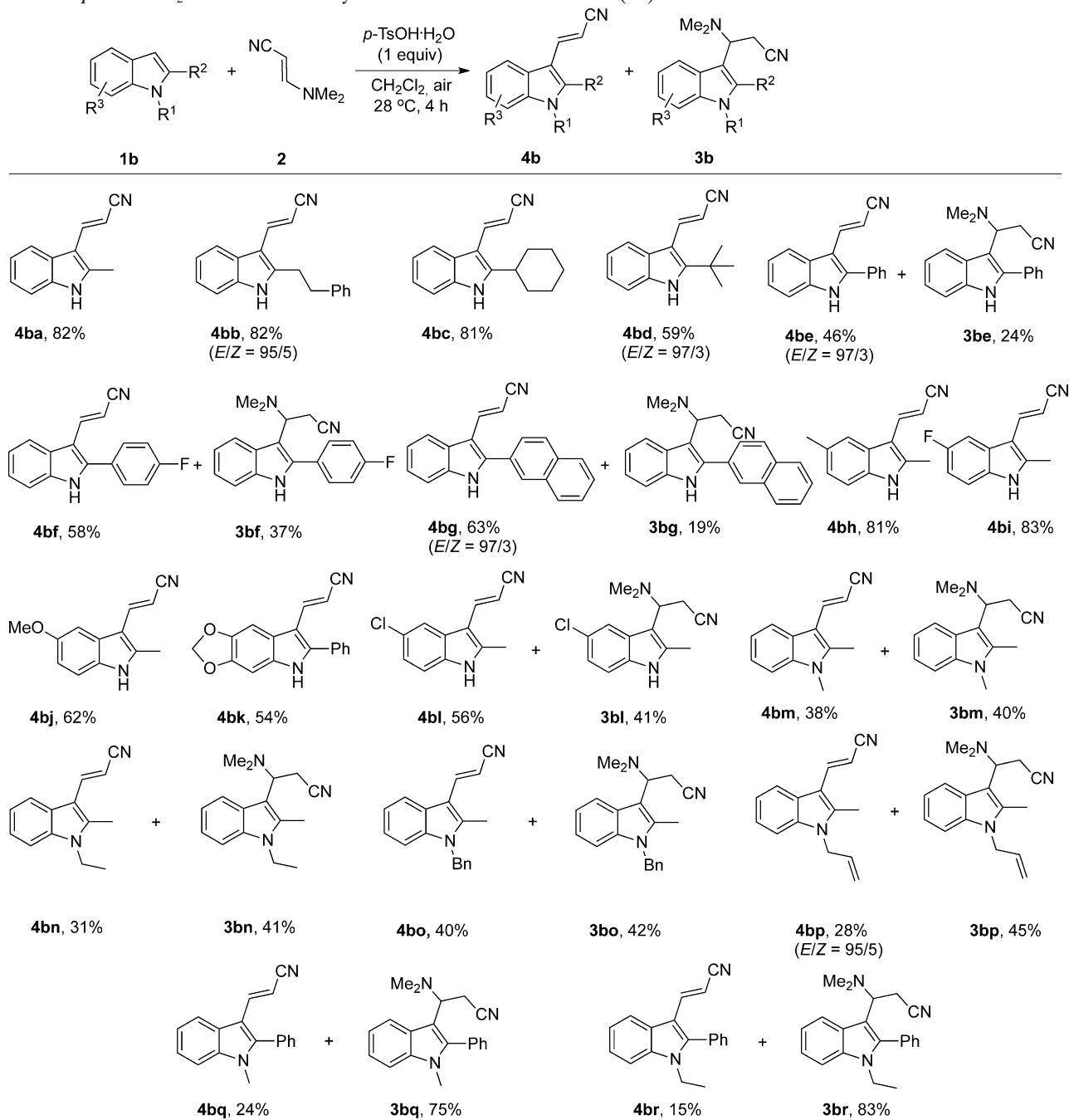
<sup>[a]</sup> Reaction conditions: **1a** (0.75 mmol), **2** (0.5 mmol), *p*-TsOH·H<sub>2</sub>O (1.0 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), air, 28 °C, 4 h.

<sup>[b]</sup> Yields refer to the isolated products.

loading enabled the reaction to reach completion, producing **3aa** (50%) and **4aa** (35%) as the major products (Table 1, entry 6). Extending the reaction time remarkably enhanced the yield of the dimeric **4aa**, i.e. **5a** (41%) (Table 1, entry 7). Higher temperature (40 °C) facilitated formation of the alkenylation product **4aa** (56%) (Table 1, entry 8). Further increasing the acid strength of the added Brønsted acids – trichloroacetic acid ( $pK_a=0.63$ <sup>[11a]</sup>), trifluoroacetic acid ( $pK_a=0.23$ <sup>[11a]</sup>), and methanesulfonic acid ( $pK_a=-1.92$ <sup>[11d]</sup>), reduced the reaction efficiency, and increasing the acid concentration resulted in more dimeric indole<sup>[12]</sup> (Table 1, entries 9–13). Unexpectedly, by means of *p*-TsOH·H<sub>2</sub>O ( $pK_a=-6.62$ <sup>[11e]</sup>) as the added acid **3aa** was obtained in 80% isolated yield (Table 1, entry 14). These results have revealed that the acidity of the reaction medium remarkably affects the product formation, and heating facilitates further transformations of the alkylation product.

In order to obtain the alkylation products of type **3**, the reaction conditions of **1aa** with **2** in the presence of *p*-TsOH·H<sub>2</sub>O were optimized (see Table S1 in the Supporting Information). It was found that a catalytic amount of the acid, e.g., 20 mol%, did not efficiently promote the alkylation of **1aa** by **2**. Dichloromethane and 1,2-dichloroethane (DCE) were tested as the suitable solvents. Eventually, the reaction conditions were optimized to: **1aa** reacted with **2** in a 1.5:1.0 molar ratio in the presence of 2 equiv. of *p*-TsOH·H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature for 4 h. The indole substrate scope was explored as shown in Table 2. Through increasing the steric hindrance of the NR moiety in **1a** from methyl to benzyl, the yields of the target products **3aa–3ad** varied from 94% to 78%, and a phenyl group obviously reduced the yield of **3ae** to 41%. Variation of the methyl substituent at the 5-, 6-, and 7-positions on the aryl backbone of **1a** slightly affected formation of the products **3af–3ah**

**Table 3.** *p*-TsOH·H<sub>2</sub>O-mediated alkenylation of 2-substituted indoles (**1b**) with **2**.<sup>[a,b]</sup>



<sup>[a]</sup> Reaction conditions: **1b** (0.5 mmol), **2** (0.5 mmol), *p*-TsOH·H<sub>2</sub>O (0.5 mmol), CH<sub>2</sub>Cl<sub>2</sub> (2 mL), air, 28 °C, 4 h.

<sup>[b]</sup> Yields refer to the isolated products. The *E/Z* ratios were determined by <sup>1</sup>H NMR analysis.

(72–75%), only a 4-methyl group exhibited an obvious steric effect on the generation of **3ai** (61%). Substituents such as methoxy, fluoro, bromo, chloro and ester groups were tolerated. The *N*-unprotected indole underwent the same reaction to form **3aq** (73%), while substituted 1*H*-indoles demonstrated a lower reactivity to form **3ar–3at** in moderate yields (51–67%). It is noted that dimeric *N*-methylindole, i.e., **1aa'**, reacted with **2** under the same conditions to

afford **3aa** in 72% yield, suggesting that *in-situ* generation of the dimeric indole did not favor the reaction, and compatible acidity of the reaction medium should be regulated for the desired reaction.

2-Substituted indoles were then applied as the substrates to explore the generality of the protocol. Unexpectedly, 3-alkenylated indoles were obtained as the major products. The alkenylation conditions were screened by testing the reaction of 2-methylindole

(**1ba**) with **2** (see Table S2 in the Supporting Information). The alkenylation product, i.e., **4ba**, was thus obtained in 82% yield from the 1:1 molar ratio reaction of **1ba** with **2** in the presence of 1.0 equiv. of *p*-TsOH·H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature for 4 h (Table 3). Under the optimal conditions, the reactions of 2-(2-phenyl)ethyl- and 2-cyclohexylindoles also formed the target products **4bb** (82%) and **4bc** (81%). Increasing the steric hindrance of the 2-substituents (*tert*-butyl, phenyl, 4-fluorophenyl, and 2-naphthyl) in **1b** lessened formation of the corresponding 3-alkenylated indoles, and led to the minor occurrence of the alkylation reaction. Methyl, fluoro, alkoxy, and chloro groups were tolerated as the substituents on the aryl backbones of 2-methyl- and 2-phenylindole substrates, and **4bh–4bl** were produced in 54–83% yields. However, 1,2-disubstituted indoles reacted with **2** to afford 3-alkenylation products **4bm–4br** (15–40%) as the minor products with predominant formation of the corresponding 3-alkylation products **3bm–3br** (40–83%).

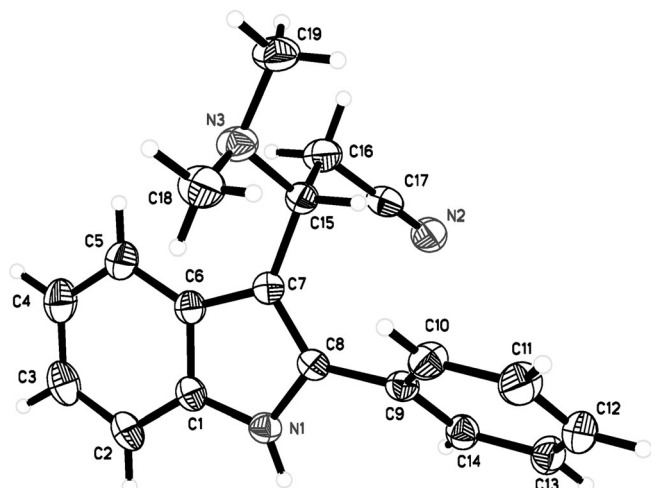


Figure 1. Molecular structure of compound **3be**.

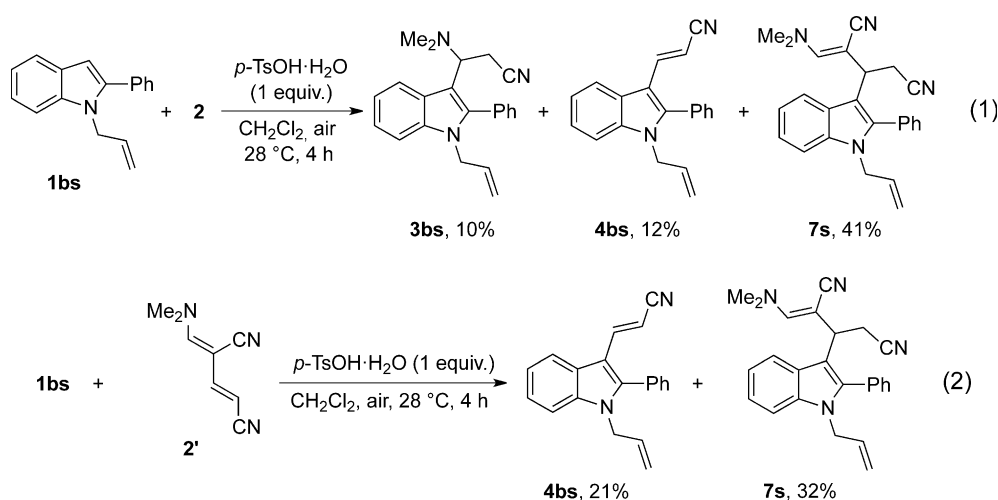
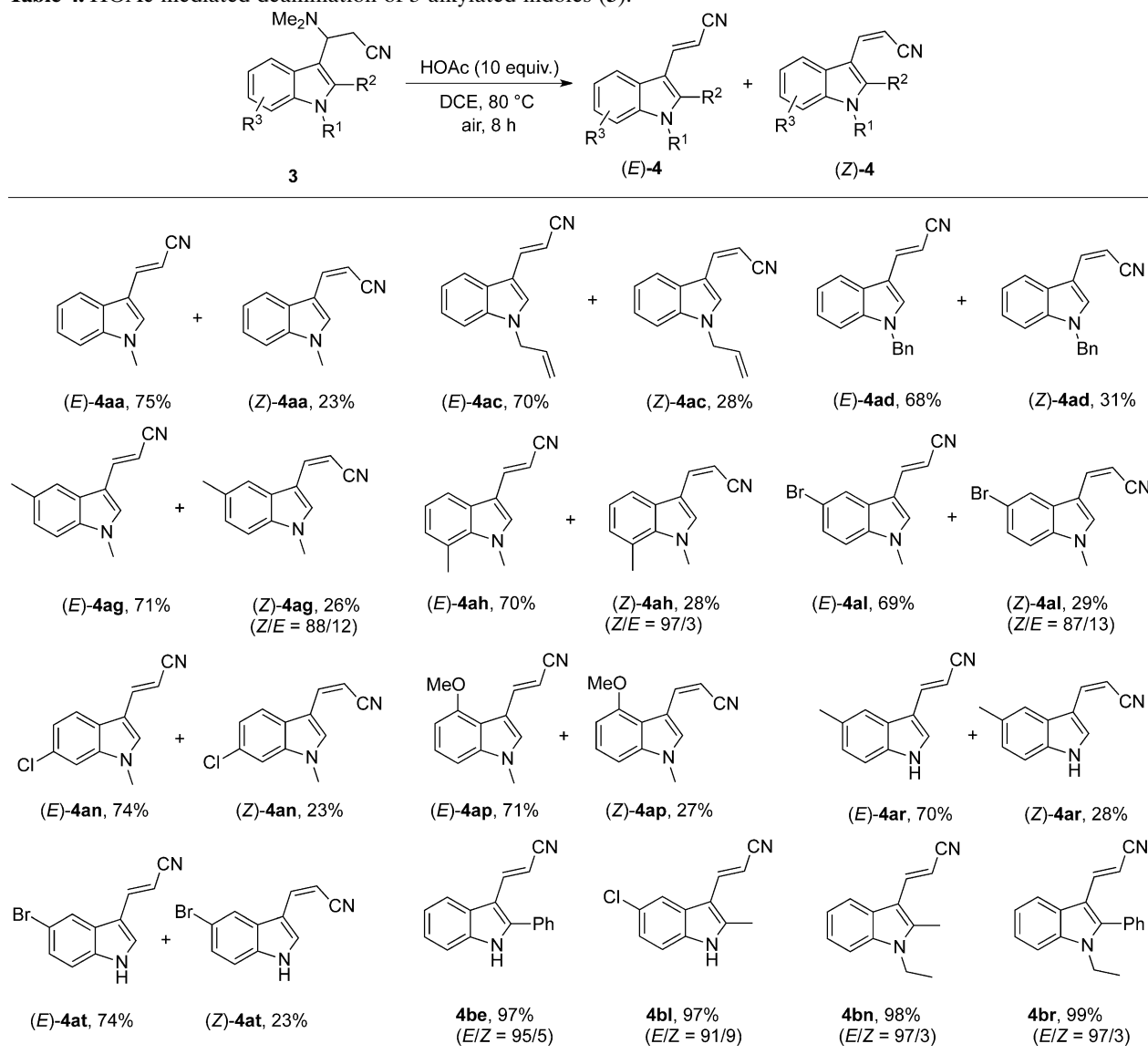


Figure 2. Molecular structure of compound **4bl**.

Interestingly, the reaction of 2-phenyl-*N*-allylindole (**1bs**) with **2** formed the alkylation product **3bs** (10%) and alkenylation product **4bs** (12%) as well as **7s** (41%) [Eq. (1)]. A polarized diene, e.g., **2'**,<sup>[13]</sup> prepared from acid-mediated self-condensation of **2**, was then used to react with **1bs**, giving **4bs** (21%) and **7s** (32%) [Eq. (2)]. Compound **7s** could be further decomposed to **4bs** (49%) and **2'** under the same conditions. These results have demonstrated the involvement of *in-situ* generated **2'** in the overall reaction as shown in Eq. (1). It is noteworthy that (*E*)-3-alkenylated indoles were usually formed as the sole alkene products in most cases (Table 3). The molecular structures of **3be** and **4bl** were further identified by X-ray single crystal structure determinations (Figure 1 and Figure 2).<sup>[14]</sup> The alkenylation product **4bl** exhibits an unambiguous (*E*)-configuration in the solid state.

**Table 4.** HOAc-mediated deamination of 3-alkylated indoles (**3**).<sup>[a,b]</sup>



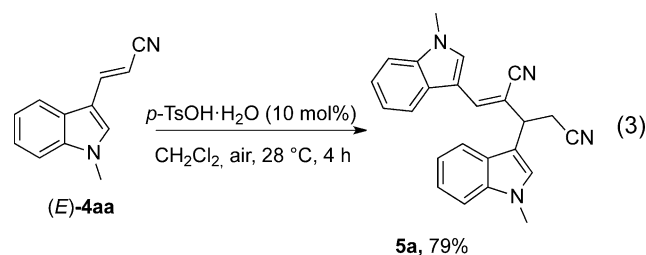
<sup>[a]</sup> Reaction conditions: **3** (0.5 mmol), HOAc (5.0 mmol), DCE (2 mL), air, 80 °C, 8 h.

<sup>[b]</sup> Yields refer to the isolated products. The *E/Z* ratios were determined by <sup>1</sup>H NMR analysis.

Due to the importance of alkenylated indoles in organic synthesis,<sup>[3]</sup> their concise synthesis has been strongly desired.<sup>[15]</sup> To our delight, 3-alkylated indole **3aa** underwent HOAc-mediated deamination to form 3-alkenylated indole **4aa** in a quantitative yield (see Table S3 in the Supporting Information for reaction condition screening). After work-up, (*E*)-**4aa** and (*Z*)-**4aa** were isolated in 75% and 23% yields, respectively (Table 4). Under the same conditions, a variety of 3-alkylated indoles of type **3** efficiently reacted to produce the corresponding 3-alkenylated indole derivatives. For 2-unsubstituted 3-alkylated indole substrates **3a**, their reactions afforded indole derivatives of type **4a** in 97–99% yields with (*E*)-**4a** (68–75%) as the major products and separable (*Z*)-**4a** (23–31%) as the minor products. 2-Substituted 3-alkylated indoles of

type **3b** were exclusively converted to alkenylated indoles of type **4b** (97–99%) with predominant formation of (*E*)-**4b** (*E/Z* ratio: 91/9–97/3).

The transformation of **4aa** was exemplified by treating it with 10 mol% *p*-TsOH·H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at ambient temperature to give **5a** in 79% yield [Eq. (3)]. It is obvious that the acidity of the reaction medium de-



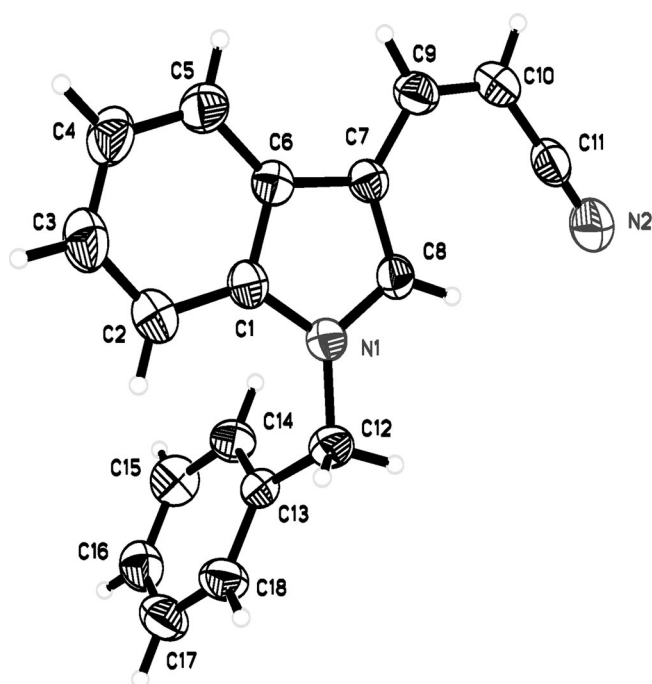


Figure 3. Molecular structure of compound (Z)-4ad.

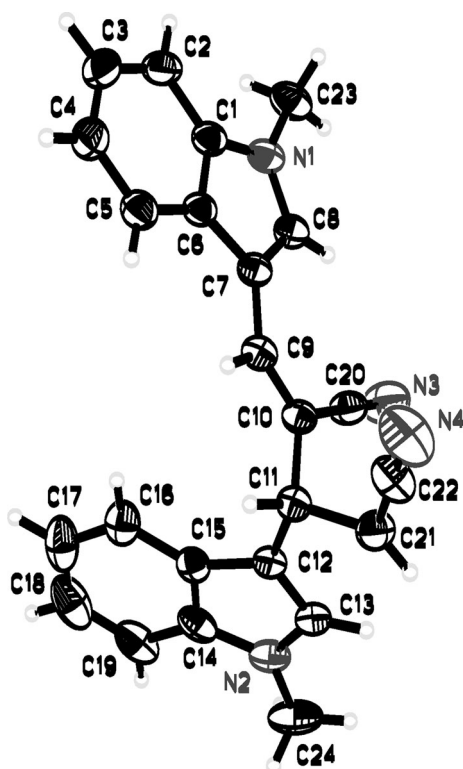


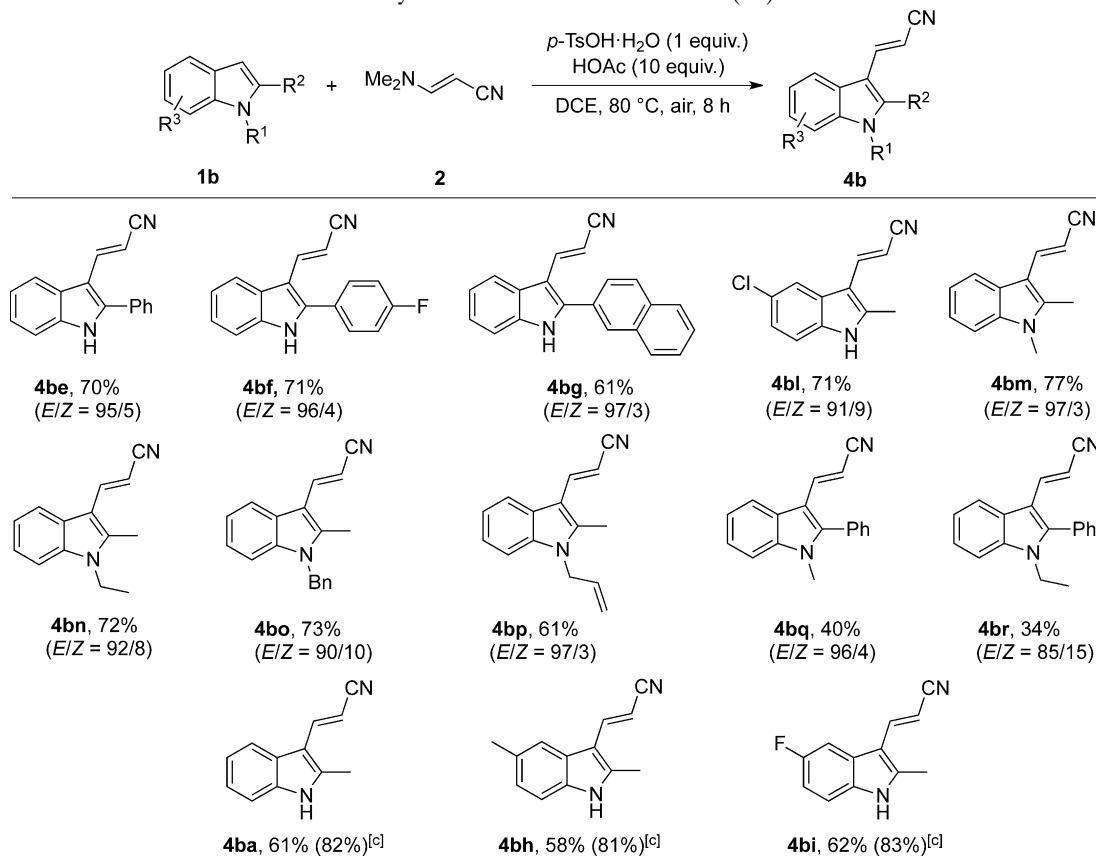
Figure 4. Molecular structure of compound 5a.

termines the formation of the 3-alkylation and alkenylation indole products from the reactions of **1** with **2**. The molecular structures of (Z)-4ad and 5a were

also elucidated by the X-ray crystallographic determinations (Figure 3 and Figure 4).<sup>[14]</sup>

Although 18 examples of the *p*-TsOH·H<sub>2</sub>O-mediated direct olefination of 2-substituted indoles (**1b**) with β-(dimethylamino)acrylonitrile (**2**) at room temperature are given (Table 3), in the cases synthesizing **4be** (46%), **4bf** (58%), **4bg** (63%), **4bl** (56%), **4bm** (38%), **4bn** (31%), **4bo** (40%), **4bp** (28%), **4bq** (24%), and **4br** (15%) considerable amounts of C-3 alkylation products of type **3** could be formed. Thus, the reactions of the corresponding problematic substrates were performed at 80 °C in the presence of excess HOAc (Table 5). Under these relatively harsh conditions, **4be** (70%), **4bf** (71%), **4bg** (61%), **4bl** (71%), **4bm** (77%), **4bn** (72%), **4bo** (73%), **4bp** (61%), **4bq** (40%), and **4br** (34%) were obtained, respectively, demonstrating an obvious improvement of the product yields in most of the cases. Detailed investigation was carried out as follows by regulating acidity of the reaction medium (Table 5). Treatment of 2-phenylindole in the presence of a mixture of HOAc and *p*-TsOH·H<sub>2</sub>O (10:1) in DCE at 80 °C for 8 h formed **4be** in 70% yield, while the same reaction conducted under the conditions as shown in Table 3 gave **4be** in 46% yield. In addition, reacting 2-phenylindole with 1.0 or 2.0 equiv. of *p*-TsOH·H<sub>2</sub>O without addition of HOAc under the same conditions only produced **4be** in 42–45% yields. These results reveal that the acidity of the medium played a key role in determining the reaction efficiency. In a similar fashion, **4bf** was obtained in 71% yield. The increased steric hindrance of the 2-substituent reduced the product yield (61% for **4bg**). Multisubstituted 2-methyl-5-chloroindole also underwent the reaction to afford **4bl** (71%). For *N*-substituted 2-methylindoles, their reactions gave the target products **4bm–4bp** in good yields (61–77%), whereas the same products were only obtained in 28–40% yields under the conditions as shown in Table 3. The sterically hindered *N*-alkyl-2-phenylindoles could not efficiently react to form **4bq** (40%) and **4br** (34%). In most of the cases, the target alkene products were obtained in much higher yields than those achieved by conducting the same reactions with 1.0 equiv. of *p*-TsOH·H<sub>2</sub>O as the sole added acid in DCE at ambient temperature (Table 3). In all the cases, (*E*)-3-alkenylated indoles were predominantly formed. It is noteworthy that 2-unsubstituted **1aa** reacted with **2** in the presence of the same mixed acids to form **4aa** (40%), **5a** (10%), and **6a** (31%), suggesting that the present one-pot procedure is more suitable for the direct synthesis of 3-alkenylated indoles from the 2-substituted indole substrates. However, the mixed acids-mediated method was applied for the synthesis of **4ba** (61%), **4bh** (58%), and **4bi** (62%) (Table 5), only resulting in lower yields for the target products as compared with those (81–83%) achieved from the same reactions performed under the condi-

**Table 5.** Mixed acids-mediated alkenylation of 2-substituted indoles (**1b**) with **2**.<sup>[a,b]</sup>



<sup>[a]</sup> Reaction conditions: **1b** (0.5 mmol), **2** (0.5 mmol), *p*-TsOH·H<sub>2</sub>O (0.5 mmol), HOAc (5.0 mmol), DCE (2 mL), air, 80 °C, 8 h.

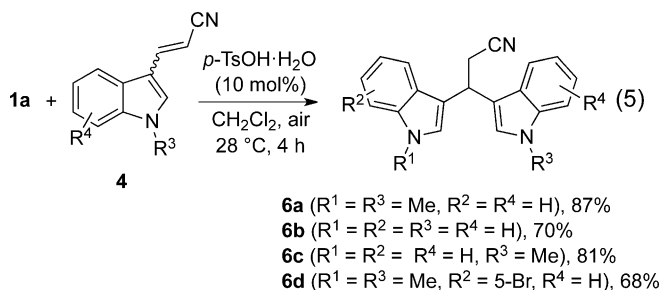
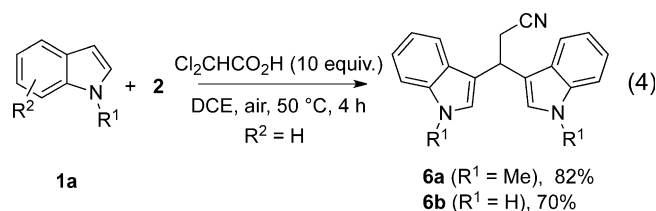
<sup>[b]</sup> Yields refer to the isolated products. The *E/Z* ratios were determined by <sup>1</sup>H NMR analysis.

<sup>[c]</sup> Yield in the parentheses were obtained under the conditions as shown in Table 3 (**1b**, 0.5 mmol with removing); **2**, 0.5 mmol; *p*-TsOH·H<sub>2</sub>O, 0.5 mmol; CH<sub>2</sub>Cl<sub>2</sub>, 2 mL; air, 28 °C, 4 h).

tions as shown in Table 3. These results suggest that the harsher conditions for those problematic substrates are not very suitable for the 2-substituted indole substrates which can undergo efficient direct alkenylation with **2** under the mild conditions. It should be noted that the reactions of 5-nitroindole, *N*-methyl-5-nitroindole, 2-methyl-5-nitroindole, and *N*-acetylindole did not react under the various conditions as shown in Table 2, Table 3 and Table 5. Treatment of 5-methoxyindole, 5-cyanoindole, *N*-methyl-5-cyanoindole, *N*-Boc-indole, or 2-methylindole under the stated conditions only led to complicated reactions.

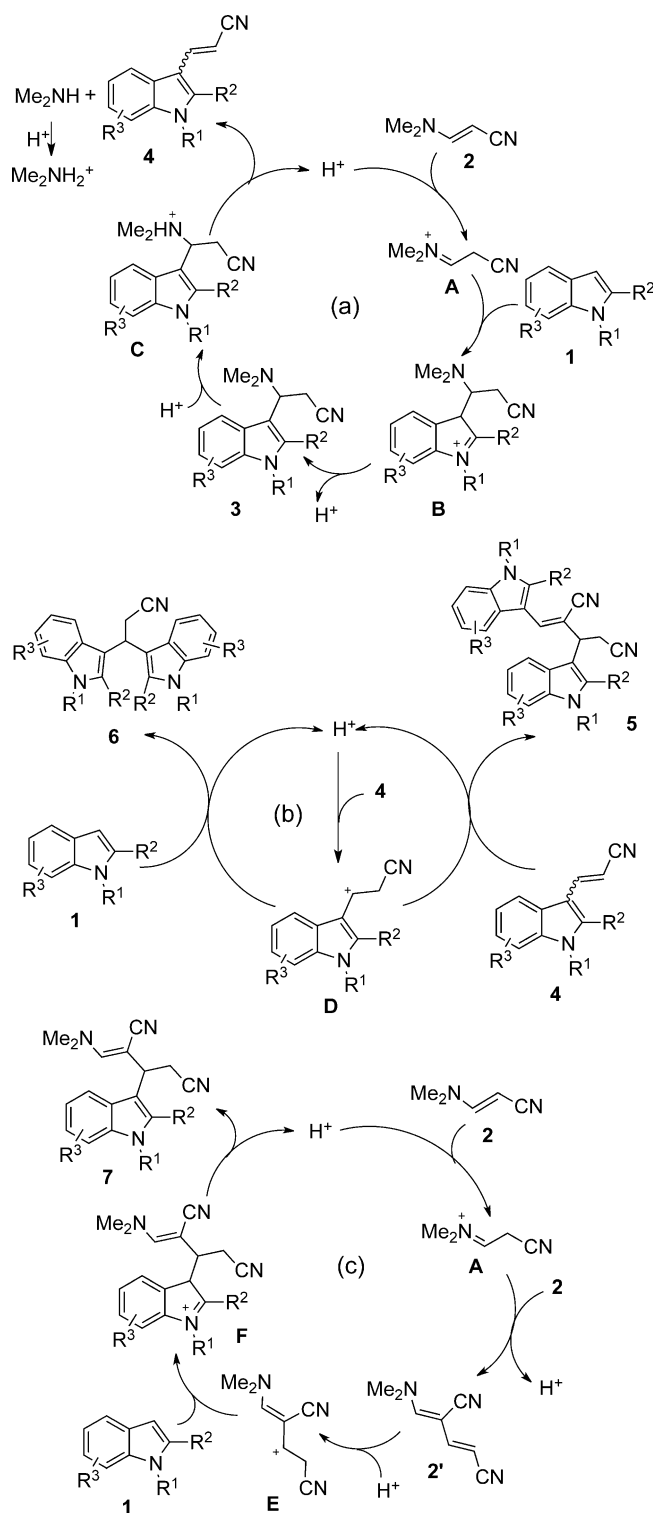
For the preparation of bisindoles **6**, two procedures were established [Eq. (4) and Eq. (5)], affording alkenylated homo- and heterobisindoles **6a–6d** (68–87%). Compounds of type **4** are reasonably considered as the intermediates to form **6** [Eq. (4)].

A plausible mechanism is proposed for the formation of **3–7** (Scheme 2). Protonation of the polarized alkene **2** by a Brønsted acid initiates the reaction sequence. The Friedel–Crafts reaction of the protonated



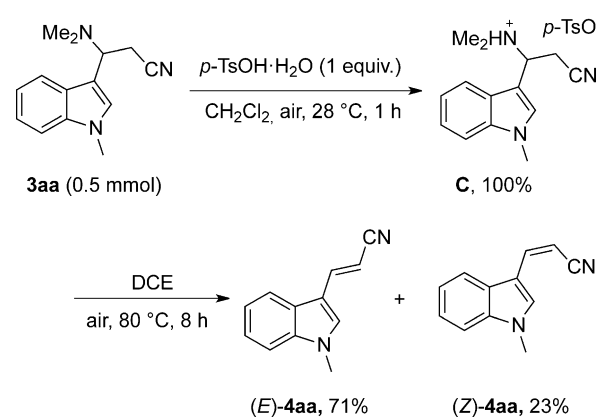
species of **2**, i.e., **A**, with indole **1** forms 3-alkenylated indole product **3** which undergoes acid-mediated deamination to give 3-alkenylated indole **4** and Me<sub>2</sub>NH<sub>2</sub><sup>+</sup> salt (Scheme 2, a). With a 2-substituent in





**Scheme 2.** Proposed mechanism.

**1**, species **B** may favour in being converted to **C** and directly form **4**. Acid-mediated self-condensation of **4** or condensation with **1** provides **5** or **6** (Scheme 2, b), respectively. Indole **1** reacts with *in-situ* generated **2'** to form the alkylation product **7** (Scheme 2, c) which can also be decomposed to **4** and **2'** under the acidic



**Scheme 3.** Synthesis and transformation of intermediate **C**.

conditions. In the overall reaction, the acidity of the medium determines the reaction pathways.

The intermediates **A**, **B**, **D**, **E**, and **F** shown in Scheme 2 are unstable and cannot be detected or isolated. Fortunately, we successfully prepared intermediate **C** by the reaction of **3aa** with an equivalent of *p*-TsOH·H<sub>2</sub>O at ambient temperature and tested its transformation. In DCE on heating **C** could be deaminated to form **4aa** (*E/Z* = 76/24 by <sup>1</sup>H NMR determination) without additional additives (Scheme 3). After work-up, (*E*)-**4aa** (71%) and (*Z*)-**4aa** (23%) were isolated, respectively, further revealing that ≥ 1.0 equivalent of *p*-TsOH·H<sub>2</sub>O should be involved in the reactions to achieve complete conversion of substrates **1** or **3**.

In summary, Brønsted acidity-dependent alkylation and alkenylation reactions of indoles were efficiently achieved. Regulating the acidity of the reaction medium led to diverse formation of the alkylation and alkenylation products from the reactions of indoles with 3-(dimethylamino)acrylonitrile. The 3-alkylated indoles were nearly quantitatively converted into the corresponding separable (*E*)/(*Z*)-alkenylated indoles. The present metal-free protocol provides an applicable route to 3-alkylated/alkenylated indoles. The more challenging direct olefination of heteroarenes with β-alkyl-β-(dimethylamino)acrylonitriles will be considered in our future work.

## Experimental Section

### Typical Procedure for the Synthesis of **3**: Synthesis of **3aa**

A mixture of **1aa** (98 mg, 0.75 mmol), **2** (48 mg, 0.50 mmol), and *p*-TsOH·H<sub>2</sub>O (190 mg, 1.00 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) was stirred at room temperature for 4 h. After the reaction was complete by TLC monitoring, 5 mL of saturated aqueous NaHCO<sub>3</sub> was added and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous

Na<sub>2</sub>SO<sub>4</sub>, and all the volatiles were evaporated under reduced pressure. Purification of the resulting residue by silica gel column chromatography (eluent CH<sub>2</sub>Cl<sub>2</sub>/EtOAc=5:1, v/v) afforded **3aa** as a yellow oil; yield: 107 mg (94%).

### Typical Procedure for the Synthesis of **4** from **3**: Synthesis of **4aa**

A mixture of **3aa** (113.6 mg, 0.5 mmol), HOAc (300.0 mg, 5.0 mmol) in DCE (2 mL) was stirred at 80 °C for 8 h. After the reaction was complete by TLC monitoring, saturated aqueous NaHCO<sub>3</sub> (5 mL) was added and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and all the volatiles were evaporated under reduced pressure. Purification of the resulting residue by silica gel column chromatography [eluent petroleum ether (60–90 °C)/EtOAc=10/1, v/v] afforded (*E*)- and (*Z*)-**4aa**.

### Typical Procedure for Mixed Acids-Mediated Alkenylation of 2-Substituted Indoles (**1b**) with **2**: Synthesis of **4bl**

A mixture of **1bl** (82.8 mg, 0.5 mmol), **2** (48.0 mg, 0.5 mmol), HOAc (300.0 mg, 5.0 mmol), and *p*-TsOH·H<sub>2</sub>O (95.1 mg, 0.5 mmol) in DCE (2 mL) was stirred at 80 °C for 8 h. After the reaction was complete by TLC monitoring, saturated aqueous NaHCO<sub>3</sub> (5 mL) was added and the resultant mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×10 mL). The combined organic phase was washed with brine (5 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and all the volatiles were evaporated under reduced pressure. Purification of the resulting residue by silica gel column chromatography [eluent petroleum ether (60–90 °C)/EtOAc=10/1, v/v] afforded **4bl** as a white solid; yield: 76.9 mg (71%).

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