

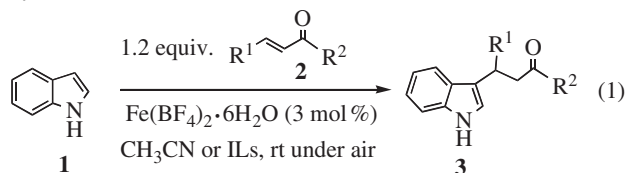
## Alkylation of N-Protecting Group-free Indole with Vinyl Ketones Using Iron Salt Catalyst

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Indole was reacted with vinyl ketones in the presence of 3 mol % of iron(II) tetrafluoroborate in acetonitrile or ionic liquids to give 3-alkylated product in an excellent yield. 2,3-Di-alkylated indole was also obtained when the reaction was carried out using an excess amount of methyl vinyl ketone with the same catalyst; the results were significantly dependent on the reaction medium and both methanol and ionic liquid were found to be good solvents for double alkylation of indole.

Iron is recognized as an economical and pollution free metal source.<sup>1</sup> We have developed several types of iron salt-catalyzed reactions: the intramolecular cyclization of cyclopropanone-dithioacetals,<sup>2</sup> [2 + 2]-cycloaddition of *trans*-anethol,<sup>3</sup> and [2 + 3]-type cycloaddition of styrene derivatives with 1,4-benzoquinone; it was then established that the reaction was greatly accelerated in an ionic liquids (ILs) solvent system.<sup>4,5</sup> We further discovered that the Michael-type addition of  $\beta$ -ketoesters with  $\alpha,\beta$ -unsaturated ketones was catalyzed by iron(II) tetrafluoroborate ( $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ ) under air conditions and demonstrated that recyclable use of catalyst was possible when the reaction was carried out in a 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide ([bmim][TFSI]) solvent system.<sup>6</sup> The Lewis acid-mediated Friedel–Crafts-type alkylation of indole with unsaturated carbonyl compounds has attracted growing interest over the past few years.<sup>7,8</sup> We anticipated that the same type of product might be obtained if indole **1** was subjected to the reaction with vinyl ketones **2** using  $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  as catalyst (Eq 1). To our delight, the desired product **3** was indeed obtained in good to excellent yield. Further, even the double-alkylated product **4** was produced when the reaction was carried out in the presence of excess amount of acceptor methyl vinyl ketone. Here, we wish to report the iron salt-catalyzed novel alkylation of indole.<sup>9</sup>



Typically, the reaction was carried out as follows: to a solution of indole (**1**) (59 mg, 0.5 mmol) and 3-buten-2-one (**2a**) (53 mg, 1.5 equiv.) in acetonitrile ( $\text{CH}_3\text{CN}$ ) (0.5 mL) was added  $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$  (5.0 mg, 3 mol %) and the mixture was stirred at room temperature (rt) under an air atmosphere for 2 h. The reaction mixture was extracted with ether and subsequent purification using silica gel thin layer (TLC) chromatography to afford the product **3a** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Me}$ )<sup>7b</sup> (66 mg, 0.35 mmol) in 71% yield (Entry 2, Table 1). Very simple alkylation of indole was thus accomplished. The reaction proceeded smoothly in  $\text{CH}_3\text{CN}$  or ionic liquids solvent and no reaction took place when

**Table 1.** Alkylation of indole (**1**) with vinyl ketones **2**<sup>a</sup>

Entry		Vinyl ketone <b>2</b> $\text{R}^1$ $\text{R}^2$	Solvent	Time/h	Yield of <b>3</b> <sup>c</sup> / %
1	a:	H $\text{CH}_3$	$\text{CH}_3\text{CN}$ <sup>b</sup>	2	75
2	a:	H $\text{CH}_3$	$\text{CH}_3\text{CN}$	2	71
3	a:	H $\text{CH}_3$	[bmim][TFSI]	2	86
4	b:	H $n\text{-C}_5\text{H}_{11}$	$\text{CH}_3\text{CN}$	4	66
5	b:	H $n\text{-C}_5\text{H}_{11}$	[bmim][PF <sub>6</sub> ]	2	76
6	b:	H $n\text{-C}_5\text{H}_{11}$	[bmim][TFSI]	2	62
7	c:	H $\text{PhCH}_2\text{CH}_2$	[bmim][PF <sub>6</sub> ]	1	78
8	c:	H $\text{PhCH}_2\text{CH}_2$	[bmim][TFSI]	3	92
9	d:	$-(\text{CH}_2)_2-$	$\text{CH}_3\text{CN}$	48	86
10 <sup>d</sup>	d:	$-(\text{CH}_2)_2-$	$\text{CH}_3\text{CN}$	24	94 (2% ee) <sup>f</sup>
11 <sup>e</sup>	d:	$-(\text{CH}_2)_2-$	$\text{CH}_3\text{CN}$	24	83 (3% ee) <sup>f</sup>

<sup>a</sup>1.5 equiv. vs substrate was used. <sup>b</sup>Dry air (5 mL/mmol vs substrate) was bubbled into the solvent prior to the reaction. <sup>c</sup>Isolated yield. <sup>d</sup>The reaction was carried out in the presence of 3 mol % of the Jacobsen ligand. <sup>e</sup>The reaction was carried out in the presence of 3 mol % of pybox ligand. <sup>f</sup>The enantiomeric excess was determined by HPLC analysis using Chiralcel OD (*i*-PrOH:*n*-Hexane = 9:1).

the reaction was conducted in  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{Cl}$ ,  $\text{Et}_2\text{O}$ , THF, toluene, or benzene. Unfortunately, however, there was also no reaction when ethyl acrylate, acrylonitrile, or nitroethene was used as acceptor. We initially performed the reaction using  $\text{CH}_3\text{CN}$  in which dry air was bubbled prior to the reaction,<sup>6</sup> but no significant modification of the reaction efficiency was recorded. Therefore, further reactions were carried out under only air atmospheric conditions. The results of reactions using various types of ketones in  $\text{CH}_3\text{CN}$  or ionic liquid solvent systems are summarized in Table 1.

The ionic liquid solvent system gave better results than those in  $\text{CH}_3\text{CN}$  solvent for these reactions, and **3a** was obtained in 86% yield in [bmim][TFSI] solvent, respectively (Entry 3). Excellent results were obtained when **2c** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{PhCH}_2\text{CH}_2$ ) was used as acceptor in [bmim][TFSI] solvent system and **5c** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{PhCH}_2\text{CH}_2$ ) was obtained in 92% yield (Entry 8). Indole also reacted with cyclopentenone **2d** ( $\text{R}^1, \text{R}^2 = -(\text{CH}_2)_2-$ ) and **3d** was obtained in 86% yield (Entry 9). Since chiral Lewis acid-mediated enantioselective alkylation was reported,<sup>8f</sup> we tested the reaction in the presence of two types of chiral ligands, the (*R,R*)-Jacobsen<sup>10</sup> or (*S,S*)-bis-(oxazoliny)pyridine (pybox) ligand.<sup>11</sup> However, no enantioselectivity was obtained even when these optically active ligands were employed for these reactions, though excellent chemical yields of **3d** were recorded (Entries 10 and 11). Further, the reaction was completely inhibited by addition of 1 equiv. of TEMPO. These results may suggest that the reaction takes place without influence of the ligand via the radical cation pathway, though TEMPO is reported to bind with the iron(III) cation and inactivate the catalytic property.<sup>12</sup>

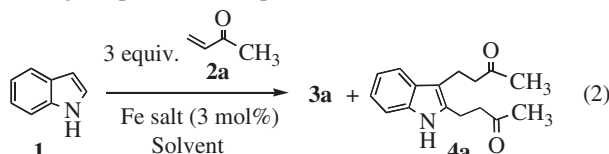
Interestingly, the reaction using  $\text{Fe}(\text{ClO}_4)_3\text{-Al}_2\text{O}_3$ <sup>3</sup> as catalyst gave 2,3-dialkylated product **4a** in low yield of 12%

**Table 2.** Iron salt-catalyzed double alkylation of indole (**1**)

Entry	Catalyst	Solvent	Temp	Time /h	Yield of <b>3a</b> <sup>a</sup> /%	Yield of <b>4a</b> <sup>a</sup> /%
1 <sup>b</sup>	Fe(ClO <sub>4</sub> ) <sub>3</sub> -Al <sub>2</sub> O <sub>3</sub>	CH <sub>3</sub> CN	rt	24	52	12
2	Fe(ClO <sub>4</sub> ) <sub>3</sub> -Al <sub>2</sub> O <sub>3</sub>	CH <sub>3</sub> CN	rt	24	43	44
3	Fe(NO <sub>3</sub> ) <sub>3</sub> ·9H <sub>2</sub> O	CH <sub>3</sub> CN	rt	24	45	14
4	FeCl <sub>3</sub>	CH <sub>3</sub> CN	rt	24	<34 <sup>c</sup>	<20 <sup>c</sup>
5	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>3</sub> CN	rt	24	73	0
6	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	CH <sub>3</sub> CN	60 °C	72	62	12
7	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	[bmim][TFSI]	60 °C	72	63	14
8	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	[emim][EtSO <sub>4</sub> ]	60 °C	72	36 <sup>d</sup>	62 <sup>d</sup>
9	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	[demem][BF <sub>4</sub> ]	60 °C	72	54 <sup>e</sup>	42 <sup>e</sup>
10	Fe(ClO <sub>4</sub> ) <sub>3</sub> -Al <sub>2</sub> O <sub>3</sub>	MeOH	rt	24	28	28
11	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	MeOH	rt	24	26	54
12	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	MeOH-H <sub>2</sub> O(1:1)	rt	24	57	33
13	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	H <sub>2</sub> O	rt	24	84	2
14 <sup>f</sup>	Fe(BF <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	MeOH	rt	24	30	0

<sup>a</sup>Isolated yield by silica gel TLC. <sup>b</sup>The reaction was carried out in the presence of 1.2 equiv. of methyl vinyl ketone **2a**. <sup>c</sup>Purification was difficult owing to the formation of polymeric products. <sup>d</sup>It was essential to use benzene to extract the products. <sup>e</sup>Extraction of the product was accomplished very easily by ethyl acetate. <sup>f</sup>The reaction was carried out in the presence of 1.0 equiv. of TEMPO under an argon atmosphere. Separation of **1** was difficult from the mixture with TEMPO or compound derived from TEMPO.

(Entry 1, Table 2), and the yield of **4a** was increased up to 44% when the reaction was carried out using an excess amount acceptor **2a** (Entry 2, Table 2). So we investigated further reaction using 3 equiv. of **2a** (Eq 2).



As expected, strong Lewis acids, Fe(NO<sub>3</sub>)<sub>3</sub> and FeCl<sub>3</sub>, catalyzed the alkylation of indole to afford the desired products, **3a** and **4a**, but the results were inferior to that of Fe(ClO<sub>4</sub>)<sub>3</sub>-Al<sub>2</sub>O<sub>3</sub>-catalyzed reaction because a significant amount of polymeric by-products were produced during the reaction (Entries 3 and 4). The catalytic activity was significantly dependent on the anionic part of the iron(III) salts; alkylation products **3a** were also obtained using K<sub>3</sub>Fe(CN)<sub>6</sub> as catalyst, though the yield was less than 10%, and no desired product was obtained for Fe<sub>2</sub>O<sub>3</sub> or FeO(OH).

As shown in Table 2, Fe(BF<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O again worked as a good catalyst for double alkylation of indole in the presence of 3 equiv. of **2a** in an ionic liquid solvent, 1-ethyl-3-methylimidazolium ethyl sulfate ([emim][EtSO<sub>4</sub>]) or *N,N*-diethyl-*N*-methyl-*N*-methoxyethylammonium tetrafluoroborate ([demem][BF<sub>4</sub>]) (Entries 8 and 9). On the contrary, the reaction proceeded very slowly in CH<sub>3</sub>CN solvent and **4a** was obtained in poor yield even under elevated temperature conditions (Entry 6). We tested five types of iron(II) salts and found that desired products **3a** and **4a** were produced using FeCl<sub>2</sub>, Fe(OTf)<sub>2</sub>, FeSO<sub>4</sub>, or Fe(OAc)<sub>2</sub> as catalyst without formation of polymeric by-products, but we were unsuccessful in increasing the chemical yield; **3a** was obtained in less than 30% with trace amount of **4a** and indole was recovered at over 70% yield for these iron(II) salt-catalyzed reactions.

Very interestingly, we further recognized that the present alkylation of indole with vinyl ketone **2a** took place in methanol or water as solvent. In particular, the second alkylation proceed-

ed faster in the protonic solvents than those in CH<sub>3</sub>CN; double-alkylated indole **4a** was obtained in 54% yield for 24 h reaction at rt in methanol (Entry 11). Since Fe(BF<sub>4</sub>)<sub>2</sub>-catalyzed [2 + 3]-type cycloaddition reaction of *trans*-anethol with benzoquinone had not proceeded at all in methanol,<sup>4</sup> this was quite an unexpectedly result for us. The reaction in the presence of TEMPO produces another unexpected result; it proceeded in methanol and **3a** was obtained in 30% yield after 24 h reaction at room temperature (Entry 14), while the reaction was completely inhibited by addition of 1.0 equiv. of TEMPO in CH<sub>3</sub>CN. It seems that the mechanism of the present reaction may depend on the reaction medium.

To the best of our knowledge, this is the first example that alkylation of *N*-protecting group free indole with vinyl ketones was accomplished using iron salt catalyst and, in particular, giving 2,3-dialkylated indole. Although the reaction mechanism is still unclear, the alkylation products were obtained in good to excellent yield under very mild reaction conditions: the reaction proceeds very smoothly at room temperature and requires no tedious argon atmospheric conditions. Further investigation of the scope and limitations of iron salt-catalyzed reaction will make it even more valuable.<sup>13</sup>

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This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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- We have also discovered an even more interesting iron salt-catalyzed reaction: alkylation of pyrrole or thiophene is also possible using our iron salt catalyst.<sup>9</sup> Optimization of the reaction conditions is now ongoing, and we will be able to report the results before long.
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.