Hafnium Trifluoromethanesulfonate [Hf(OTf)$_4$]-Catalyzed Conjugate Addition of Indoles to α,β-Enones

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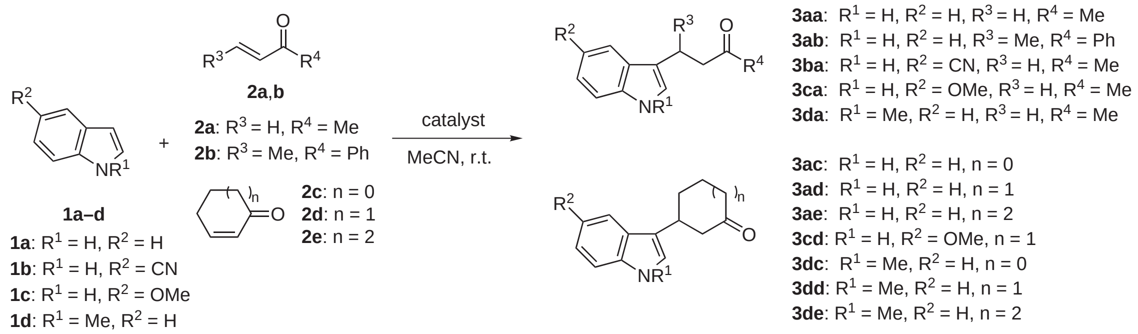
Abstract: Hafnium trifluoromethanesulfonate [Hf(OTf)$_4$]- and scandium trifluoromethanesulfonate [Sc(OTf)$_3$]-catalyzed conjugated addition of 3-position of indoles to several enones proceeded in acetonitrile as solvent. Especially, Hf(OTf)$_4$ exhibited high catalytic activity and gave the conjugate addition product in good yield.

Key words: hafnium trifluoromethanesulfonate, conjugate additions, Lewis acids, indoles, enones, catalysis

Indoles are the key components of many drugs and some biologically active compounds, and the development of new forming methods leading to indole derivatives has attracted much attention in organic synthesis.[1] Especially, 3-substituted indoles exhibit several biological activities, and are versatile intermediates for the synthesis of several indole derivatives.[2] Based on these reasons, there are several addition reactions of indoles to enones,[3] and recently the Lewis acid-catalyzed conjugate addition of the 3-position of indoles to enones had been reported by several groups. The reaction using a Lewis acid requires careful control to prevent side reactions such as the dimerization or polymerization of indoles. For example, Bi(NO)$_3$,[4] Bi(OTf)$_3$,[5] InBr$_3$,[6] InCl$_3$[7] and Yb(OTf)$_3$[8] have been reported as useful Lewis acid catalysts for this reaction. However, the reaction usually demands over a 10 mol% catalyst and requires several hours. Also, Kobayashi and co-worker reported Sc(DS)$_3$ (DS = dodecyl sulfate) catalyzed the conjugate addition of indoles to α,β-enones in water, however, they also reported Sc(OTf)$_3$ exhibited a low catalytic activity in water.[9] Herein, we report that the Sc(OTf)$_3$[10] catalyzed the indole addition to enones in MeCN solvent, and furthermore, Hf(OTf)$_4$[11] exhibited a high catalytic activity even at a lower catalyst loading for this reaction.

We examined the reaction of indole (**1a**) and methyl vinyl ketone (**2a**) using some Lewis acid catalysts in MeCN (Scheme 1, Table 1). The reaction with 10 mol% Sc(OTf)$_3$ proceeded smoothly and gave 90% of the conjugate addition product (entry 1). The reaction rate was faster than other reported catalysts, and the amount of Sc(OTf)$_3$ was reduced to 5 mol% without decreasing the yield (entry 2). On the other hand, Hf(OTf)$_4$ showed a really high reactivity for this reaction. The reaction using the 10 mol% catalyst was complete only in ten minutes. The reaction with Sc(DS)$_3$ also finished in ten minutes, although the reaction yield was lower than that with Hf(OTf)$_4$ (entries 3 and 4). Thus, Hf(OTf)$_4$ was a very effective catalyst for this conjugate addition of indoles to enones, and the reaction with 1 mol% of Hf(OTf)$_4$ proceeded efficiently to give the product in 90% yield (entry 5).

The results of the 5-substituted indoles (**1b** and **1c**) and 1-methyl indole (**1d**) addition to several enones catalyzed by Hf(OTf)$_4$ compared to Sc(OTf)$_3$ are summarized in Table 2. In all cases, the reation with Hf(OTf)$_4$ was faster than the reaction with Sc(OTf)$_3$. The reaction of the 5-substituted indoles to methyl vinyl ketone (**2a**) smoothly proceeded with Sc(OTf)$_3$ (entries 1 and 3), and the same reactions were catalyzed by Hf(OTf)$_4$ in a much shorter



Scheme 1

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reaction time and gave similar yields (entries 2 and 4). The reaction of 1-methyl indole was also catalyzed by Hf(OTf)$_4$ and gave the conjugate addition product in good yield (entry 6). The pheny 1-propenyl ketone (**2b**) was also usable for this reaction (entries 7–10). Cyclic enones (**2c**,**d**) were also good Michael acceptors under these catalytic conditions (entries 11–16). For the indoles (**1a**), 1-methyl indole (**1d**) and the 5-substituted indoles (**1b**,**c**) also react with cyclic enones (**2c**,**d**) and gave the corresponding products in good yield (entries 17–24). In some cases, the reaction with Hf(OTf)$_4$ gave a lower yield than when using of Sc(OTf)$_3$ due to the dimerization and/or polymerization of indoles, but the rate of the conversion was much faster than with Sc(OTf)$_3$.

Table 1 Catalytic 1,4-Addition of Indole **1a** to Methyl Vinyl Ketone (**2a**)[a]

Entry	Catalyst	Time	Yield (%)[b]
1	Sc(OTf)$_3$ (10 mol%)	2 h	90
2	Sc(OTf)$_3$ (5 mol%)	24 h	90
3	Sc(DS)[c] (10 mol%)	10 min	76
4	Hf(OTf)$_4$ (10 mol%)	10 min	85
5	Hf(OTf)$_4$ (1 mol%)	2 h	90

[a] All reactions were carried out in MeCN at r.t.

[b] Isolated yield by silica gel column chromatography.

[c] DS = dodecyl sulfate.

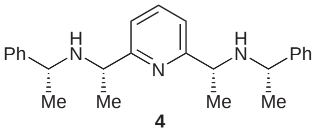
Table 2 Hf(OTf)$_4$- or Sc(OTf)$_3$-Catalyzed 1,4-Addition of Indoles **1a**–**d** to Enones **2a**–**e**[a]

Entry	1	2	Product 3	Catalyst	Time	Yield (%)[b]
1	**1b**	**2a**	**3ba**	Sc(OTf)$_3$	30 min	85
2	**1b**	**2a**	**3ba**	Hf(OTf)$_4$	10 min	83
3	**1c**	**2a**	**3ca**	Sc(OTf)$_3$	4 h	56
4	**1c**	**2a**	**3ca**	Hf(OTf)$_4$	10 min	50
5	**1d**	**2a**	**3da**	Sc(OTf)$_3$	2 h	88
6	**1d**	**2a**	**3da**	Hf(OTf)$_4$	10 min	82
7	**1a**	**2b**	**3ab**	Sc(OTf)$_3$	3 h	62
8	**1a**	**2b**	**3ab**	Hf(OTf)$_4$	15 min	80
9	**1d**	**2b**	**3db**	Sc(OTf)$_3$	30 min	50
10	**1d**	**2b**	**3db**	Hf(OTf)$_4$	15 min	90
11	**1a**	**2c**	**3ac**	Sc(OTf)$_3$	72 h	57
12	**1a**	**2c**	**3ac**	Hf(OTf)$_4$	9 h	57
13	**1a**	**2d**	**3ad**	Sc(OTf)$_3$	4 h	94
14	**1a**	**2d**	**3ad**	Hf(OTf)$_4$	30 min	70
15	**1a**	**2e**	**3ae**	Sc(OTf)$_3$	3 h	90
16	**1a**	**2e**	**3ae**	Hf(OTf)$_4$	10 min	99
17	**1b**	**2d**	**3bd**	Sc(OTf)$_3$	72 h	39
18	**1b**	**2d**	**3bd**	Hf(OTf)$_4$	2 h	70
19	**1c**	**2d**	**3cd**	Sc(OTf)$_3$	6 h	69
20	**1c**	**2d**	**3cd**	Hf(OTf)$_4$	20 min	68
21	**1d**	**2c**	**3dc**	Sc(OTf)$_3$	17 h	73
22	**1d**	**2c**	**3dc**	Hf(OTf)$_4$	1 h	85
23	**1d**	**2d**	**3dd**	Sc(OTf)$_3$	30 min	70
24	**1d**	**2d**	**3dd**	Hf(OTf)$_4$	15 min	66

[a] All reactions were carried out with 10 mol% of catalyst in MeCN at r.t., and were stopped when indoles were consumed.

[b] Isolated yield by silica gel column chromatography.

We have examined some amine ligands for this reaction and found tridentate amine ligands having a pyridine unit largely improved the chemical yield without a formation of bisindole. The reaction of **1a** with **2b** in the presence of 10 mol% of $Hf(OTf)_4$ and 12 mol% of ligand **4** (Figure 1) was complete within ten minutes and gave **3ab** in a quantitative yield. On the other hand, that in the presence of ligand **5** was complete in 30 minutes and **3ab** was obtained quantitatively. These tridentate amine ligands were also effective for reactions with cyclic enones (**2c** and **2d**). The reaction of **2c** and **2d** with **1a** using ligand **4** gave the conjugate addition product in 95% (1 h) and 98% isolated yield (0.5 h), respectively. However, an asymmetric induction was observed in less than 5% in all cases.



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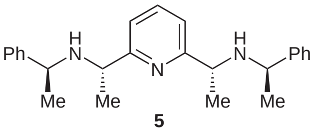

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Figure 1

In summary, we have demonstrated that $Hf(OTf)_4$ is an effective catalyst for the conjugate addition of indoles to α,β-enones. The reaction proceeded within several minutes and gave products in good yield. Also we discovered that tridentate amine ligands increase the yield of this catalytic reaction. The development of asymmetric variants for these reactions will be the subject of future work.[12]

General Procedure

A mixture of indole **1** (0.1 mmol), enone **2** (0.15 mmol), and $Hf(OTf)_4$ (10 mol%) in MeCN (0.5 mL) was stirred at r.t. for the appropriate time (see Table 1 and Table 2). After complete conversion, as indicated by TLC, the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by column chromatography on silica gel to afford the pure product **3** (see Table 1 and Table 2).

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