Copper (II)-or Iron (III)-Catalyzed Aldol Reactions and Michael Additions Using Silyl Enol Ethers or Silyl Ketene Acetals

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Copper(II)- or Iron(III)-Catalyzed Aldol Reactions and Michael Additions Using Silyl Enol Ethers or Silyl Ketene Acetals

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Copper(II) trifluoromethanesulfonate and iron(III) chloride, by use of a catalytic loading, accelerate both the aldol reactions and Michael additions using silyl enol ethers and silyl ketene acetals. The reactions proceed at -78 °C, but anti/syn- and enantioselectivities are low.

Lewis acid-catalyzed aldol reactions and Michael additions of silyloxy alkenes provide one of the most useful methodologies for the carbon-carbon bond formation. These reactions can be often accelerated by use of catalytic loadings of Lewis acid catalysts; the catalysts ever successfully employed include silyl cations, trityl cations, transition metal complexes, lanthanide complexes, and others. However, use of simple transition metal salts is rare for the activation of silyl enol ethers or ketene acetals. In this communication we would like to add two simple transition metal salts, copper(II) trifluoromethanesulfonate and iron(III) chloride, as effective catalysts for the aldol reactions and Michael additions of silyloxy alkenes.

Among a variety of transition metal salt catalysts examined in the aldol reactions of α-

\[
\begin{align*}
1a & \quad 1b,c & \quad 1d & \quad 1e & \quad E:Z = 85:15 \\
& \quad \text{b} & \quad R_1 = \text{Me}, R_2 = \text{SiMe}_3 (1b: E:Z = 86:14) \\
& \quad \text{c} & \quad R_1 = \text{t-Bu}, R_2 = \text{SiMe}_2(\text{t-Bu}) (1c: E:Z = 94:6)
\end{align*}
\]

Scheme 1

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Dedicated to Professor Hitoshi Takeshita on the occasion of his retirement

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\[ \text{1b} + \text{PhCHO} \]
\[ E:Z = 86:14 \]
\[ \text{Cat (10 mol\%)} \]
\[ \text{rt in CH}_2\text{C}_2\text{Cl}_2 \]

(Equation 1)

Table 1  Aldol reactions of silyl ketene acetals 1 to PhCHO at -78 °C in CH_2Cl_2

<table>
<thead>
<tr>
<th>Donor</th>
<th>Catalyst</th>
<th>Ratio^a</th>
<th>Mol%^b</th>
<th>Yield%^c</th>
<th>Isomer ratio d^{syn:anti}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Cu(OTf)_2/A</td>
<td>1/1</td>
<td>10</td>
<td>56</td>
<td>43:57</td>
</tr>
<tr>
<td></td>
<td>Cu(OTf)_2/B</td>
<td>1/1</td>
<td>10</td>
<td>89</td>
<td>46:54</td>
</tr>
<tr>
<td></td>
<td>FeCl_3/A</td>
<td>1/1</td>
<td>10</td>
<td>92</td>
<td>45:55</td>
</tr>
<tr>
<td></td>
<td>FeCl_3/B</td>
<td>1/1</td>
<td>10</td>
<td>90</td>
<td>45:55</td>
</tr>
<tr>
<td></td>
<td>FeCl_2/B+I_2^e</td>
<td>1/1</td>
<td>10</td>
<td>91</td>
<td>42:58</td>
</tr>
<tr>
<td></td>
<td>FeCl_2/B+I_2^e</td>
<td>1/1</td>
<td>100</td>
<td>65</td>
<td>47:53</td>
</tr>
<tr>
<td></td>
<td>FeCl_2/B+I_2^e,f</td>
<td>1/3</td>
<td>10</td>
<td>45</td>
<td>26:74</td>
</tr>
<tr>
<td>1c</td>
<td>FeCl_2/B+I_2^e</td>
<td>1/1</td>
<td>10</td>
<td>100</td>
<td>40:60</td>
</tr>
</tbody>
</table>

^aMetal salt/ligand. ^bMolar percentage of the metal salt used. ^cYields of isolated products. ^dDetermined by 1H NMR. ^eIodine was used in half an equivalent of FeCl_2. ^fSolvent: EtCN.

(trimethylsilyloxy)styrene (1a) with benzaldehyde, Cu(OTf)_2 and FeCl_3 were especially effective. In expectation of the improved solubility of the metal salt as well as the chirality control at the newly formed chiral centers in the product, the complexes of Cu(OTf)_2 and FeCl_3 with enantio-merically pure amine ligands such as (R,R)-N,N'-di(mesitylmethyl)-1,2-diphenylethanediamine (A), (S,S)-2,2'-bi(4-isopropyl-2-oxazoline) (B), and (R,R)-2,2'-methylenebis(4-phenyl-2-oxazoline) (C) were employed. The resulting complexes are highly soluble in dichloromethane so that they show higher catalytic activity than the salt without ligand. Thus, the reaction of 1-methoxy-1-(trimethylsilyloxy)propene (1b, E:Z = 86:14) with benzaldehyde took place at -78 °C in the presence of 10 mol% amount of Cu(OTf)_2/A or Cu(OTf)_2/B to give the corresponding aldol product (Equation 1, 56, 89% in each case); FeCl_3/A and FeCl_3/B were more effective (92, 90% in each case, Table 1). However, the syn:anti- and enantioselectivities were both not satisfactory.

Use of excess amounts of ligand B (B/FeCl_3 = 2 or 5) resulted in rather decreased chemical yields and no improvement of optical yields was recorded. Either when the iron(III) catalyst was in situ prepared by oxidation of FeCl_2 with iodine or when t-butyloxy-1-(t-butyldimethylsilyloxy)propane (1c) was used as a bulkier donor molecule, comparably low stereo- and enantioselectivities resulted. Use of propionitrile as reaction solvent led to a little higher anti selectivity and enantioselectivity. As a result, these chiral ligands A-C have served only to improve the solubility of the metal salt catalysts. These metal salt complexes were also highly effective in the Michael addition reactions of 1b with 2-cyclohexen-1-one (2a, Equation 2). Thus, at -78 °C, the reaction between 1b and 2a was promoted in the presence of 5 mol% of Cu(OTf)_2/A in dichloromethane to give a mixture of stereoisomers of Michael adduct (100%), while uncatalyzed reaction gave no adducts under various reaction conditions. The complex FeCl_3/A is also a reac-
Table 2  Michael additions of silyl ketene acetals or silyl enol ethers 1 to \( \alpha, \beta \)-unsaturated carbonyl compounds

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Catalyst</th>
<th>Ratio(^a)</th>
<th>Mol(^b)%</th>
<th>Yield(^c)%</th>
<th>Isomer ratio(^d) syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b + 2a</td>
<td>Cu(OTf)(_2)</td>
<td>–</td>
<td>5</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cu(OTf)(_2)/A</td>
<td>1/1</td>
<td>5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FeCl(_3)/A</td>
<td>1/1</td>
<td>5</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1d + 2a</td>
<td>Cu(OTf)(_2)/A</td>
<td>1/1</td>
<td>5</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>1d + 2a</td>
<td>FeCl(_3)/A</td>
<td>1/1</td>
<td>5</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>1e + 2b</td>
<td>Cu(OTf)(_2)/A</td>
<td>1/2</td>
<td>5</td>
<td>66</td>
<td>63:37</td>
</tr>
<tr>
<td></td>
<td>Cu(OTf)(_2)/B</td>
<td>1/1</td>
<td>5</td>
<td>73</td>
<td>66:34</td>
</tr>
<tr>
<td></td>
<td>Cu(OTf)(_2)/C</td>
<td>1/2</td>
<td>5</td>
<td>58</td>
<td>62:38</td>
</tr>
<tr>
<td>1b + 2c</td>
<td>Cu(OTf)(_2)/A</td>
<td>1/1</td>
<td>10</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FeCl(_3)/A</td>
<td>1/1</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1a + 2d</td>
<td>Cu(OTf)(_2)/A (^e)</td>
<td>1/1</td>
<td>10</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cu(OTf)(_2)/A</td>
<td>1/1</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Metal salt/ligand.  \(^b\)Molar percentage of the metal salt used.  \(^c\)Yields of isolated products.  \(^d\)Determined by \(^1\)H NMR.  \(^e\)In the presence of Me\(_3\)SiCl (1 equiv).

A reaction mechanism including Lewis acid-mediated electron transfer has been recently reported for the Lewis acid-catalyzed Michael addition reactions of ketene silyl acetics, in which the donor molecules bearing more substituents at the reaction site show much higher reactivity than the less substituted donors.\(^{14}\) However, the reversed substituent effect was recorded in the present reactions and the electron transfer-casused deactivation of the catalyst\(^{15}\) was not observed. Addition of radical inhibitors such as 2,6-di-tert-butyl-4-methylphenol and 1,4-benzoquinone did not inhibit the reaction. The low \( \text{anti/syn} \) selectivity observed here rules out the linear transition state in which the acceptor molecules are activated by the metal salt. Only in the reactions catalyzed by Cu(OTf)\(_2\) or complexes, there may be a possibility remained that HOTf produced by hydrolysis of Cu(OTf)\(_2\) has worked as a real catalyst. So far we can not propose a likely reaction mechanism. The work along this line is now in progress, and the details of results will be reported elsewhere.

References and Note

Lewis Acid-Catalyzed Aldol Reactions and Michael Additions of Silyloxy Alkenes


9. The metal salts examined are CrCl3 (10 mol%), MnBr2 (100 mol%), FeCl3 (10 mol%), CoCl2 (10 mol%), NiBr2 (100 mol%), Cu(OIT)2 (5 mol%), CuCl2 (10 mol%), AgBF4 (100 mol%), CoCl2/AgBF4 (1/1, 10 mol%), and NiBr2/AgBF4 (1/1, 10 mol%).

10. Desilylation of the silylated aldol product by treatment with CH3COOH/THF/H2O (8/8/1 v/v) at room temperature was followed by HPLC analysis using Daicel chiralcel OD with hexane/2-propanol (95:5 v/v).

11. Optical yields did not exceed 10% ee in each case.


