Catalytic Enantioselective Aldol Reactions of Unprotected Carboxylic Acids under Phosphine Oxide Catalysis

Shunsuke Kotani,* Yusaku Yoshiwara, Masanichi Ogasawara, Masaharu Sugiura, and Makoto Nakajima*

Abstract: The first catalytic enantioselective aldol reaction of various unprotected carboxylic acids is described. In the presence of a chiral bis(phosphine oxide) as a Lewis base catalyst, carboxylic acids were activated with silicon tetrachloride to form the corresponding bis(trichlorosilyl)enediolates in situ, which subsequently underwent an aldol reaction with an aldehyde or a ketone to produce β-hydroxycarboxylic acids in high enantioselectivities of up to 92% ee.

The carboxylic acid functional group is fundamentally important in the biochemistry of living systems as well as in a wide range of biologically significant substances, including amino acids, prostanooids, and nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Recently, much attention has been paid to the development of direct transformations of carboxylic acids to simplify synthetic sequences. However, owing to their inherent Brønsted acidity, the reactivity of carboxylic acids is markedly different from that of other carbonyl compounds.[2]

Generating enolates of carboxylic acids, known as enediolates, is rather difficult and usually requires more than two equivalents of a strong base.[3] Thus the direct application of carboxylic acids in aldol-type reactions is often problematic and difficult to control. Whereas “masked” derivatives of carboxylic acids, such as esters and amides, have been frequently employed in stereoselective aldol reactions, asymmetric variants employing unprotected carboxylic acids have been rare.[4–9] While the groups of Mulzer,[4] Zakarian,[5] and Fringuelli[6] developed asymmetric aldol reactions of carboxylic acids, their procedures required stoichiometric amounts of chiral reagents to realize enantioselectivity (Scheme 1a,b).

Our strategy for activating carboxylic acids is shown in Scheme 2. Carboxylic acid 1 reacts with silicon tetrachloride to form trichlorosilyl carboxylate 2. Subsequently, intermediate 2 reacts with another molecule of silicon tetrachloride to form the corresponding bis(trichlorosilyl)-enediolates, which subsequently underwent an aldol reaction with an aldehyde or ketone to give β-hydroxycarboxylic acids in up to 92% ee (Scheme 1c). [11]

We report the first catalytic enantioselective aldol reaction of unprotected carboxylic acids. In the presence of a chiral Lewis base organocatalyst, carboxylic acids were activated with silicon tetrachloride to form the corresponding bis(trichlorosilyl)-enediolates, which subsequently underwent an aldol reaction with an aldehyde or ketone to give β-hydroxycarboxylic acids in high enantioselectivities of up to 92% ee.
boxylate $\text{S}$ in an enantioselective fashion and to release the Lewis base, which is available to another catalytic cycle.\[^{[12,13]}\]

At the outset, the reaction of carboxylic acid $\text{S}$ with aldehyde $\text{S}$ was examined in the presence of silicon tetrachloride (2 equiv relative to $\text{S}$), excess triethylamine, and (S)-BINAPO (9a, 10 mol\% \text{ in dichloromethane at } -20^\circ\text{C} \text{ for } 6 \text{ hours} \text{ (Table 1, entry 1). As expected, the reaction proceeded smoothly to yield aldol adduct $\text{S}$ in } 51 \% \text{ yield, albeit in low stereoselectivity (syn:anti } 52:48, 18 \% \text{ ee for the syn isomer).}\[^{[14,15]}\] The presence of Lewis base 9a was essential; the reaction did not proceed without 9a under otherwise identical reaction conditions (entry 2). Among the amine bases surveyed, sterically demanding N,N-diisopropylisobutylamine showed the best result (entry 4).\[^{[16]}\] A longer reaction time (15 h) improved the yield to 93% with retention of the stereoselectivity (entry 5). The use of 1 equiv of silicon tetrachloride reduced the yield to 49% (entry 6). This result is consistent with our hypothesis, in which two equivalents of silicon tetrachloride are necessary to activate the carboxylic acid (Scheme 2).

Next, several chiral phosphine oxide catalysts were screened to enhance the enantioselectivity.\[^{[17]}\] Modifying the diarylsulfone moiety of chiral phosphine ligands is a common tactic to improve their performance in metal-catalyzed reactions; however, analogous modifications of BINAPOs did not improve the enantioselectivity in the present reaction; the 4-toly1 and 3,5-xyl1 BINAPO derivatives (9b and 9e) gave lower enantioselectivities than BINAPO (entries 7 and 8).\[^{[18]}\] Recently, we reported that modifications of BINAPO at the 4- and 4-positions of the binaphthyl skeleton enhanced the enantioselectivity of Lewis base catalyzed reactions.\[^{[19]}\] Whereas 4,4'-Br$_2$-BINAPO (9d) gave a lower enantioselectivity than 9a (entry 9), the 4,4'-bis(trialkylsilyl) derivatives 9e--g were more enantioselective than 9a (entries 10--12). Among the three 4,4'-bis(trialkylsilyl)-BINAPO derivatives, 4,4'-TIPS$_2$-BINAPO (9g), which contains the bulkiest silyl groups, showed the highest enantioselectivity of 56% ee (entry 12). Lowering the temperature to $-60^\circ\text{C}$ further increased the enantioselectivity to 72% ee (entry 13). The sodium salt of 7a could be used as the substrate of the aldol reaction, affording 10aa in nearly identical yield and selectivity as from free acid 7a (entry 14). It should be mentioned that catalyst 9g could be easily recovered from the reaction mixture and reused.

With optimized reaction conditions and a suitable Lewis base catalyst in hand, the scope of the present reaction was examined using various carboxylic acids (Table 2).\[^{[20]}\] Both the diastereo- and enantioselectivities were improved in the reaction with ortho-bromohydrocinnamic acid (7b; entry 2). The reactions with o-halogenated carboxylic acids $\text{S}$--$\text{S}$ afforded the aldol products in excellent enantioselectivities (entries 3--5); $\delta$-bromocarboxylic acid $\text{S}$ showed the highest enantioselectivity of 92% ee (entry 4). The aldol reaction was applicable to acids with an ether (7f), a sulfide (7g), or a nitro (7h) group, and the corresponding aldol adducts were obtained in 80--85% ee (entries 6--8). Carboxylic acid 7i, bearing a nitrile group, features two acidic methylene groups, one is adjacent to the carboxyl group, and the other one is next to the nitrile group. The present aldol reaction of 7i proceeded with excellent regioselectivity at the $\alpha$-position to the carboxylic acid to give 10ia exclusively in 92% ee (entry 9). As summarized in Table 2, the present protocol tolerates a wide range of carboxylic acids, affording aldol adducts bearing various functional groups in good enantiose-

**Scheme 2.** Strategy for the SiCl$_4$-assisted catalytic asymmetric aldol reaction of carboxylic acids.

**Table 1:** Optimization of the reaction conditions.\[^{[21]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>9</th>
<th>Time</th>
<th>Yield [%]^b</th>
<th>$d,%$^c</th>
<th>ee [%]$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et$_3$N</td>
<td>9a</td>
<td>6</td>
<td>51</td>
<td>52:48</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>Et$_3$N</td>
<td>9a</td>
<td>6</td>
<td>78</td>
<td>72:22</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Pr$_3$NEt</td>
<td>9a</td>
<td>6</td>
<td>67</td>
<td>78:22</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Pr$_3$NBu</td>
<td>9a</td>
<td>15</td>
<td>93</td>
<td>80:20</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>Pr$_3$NBu</td>
<td>9a</td>
<td>15</td>
<td>49</td>
<td>80:20</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>Pr$_3$NBu</td>
<td>9b</td>
<td>15</td>
<td>92</td>
<td>83:17</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>Pr$_3$NBu</td>
<td>9c</td>
<td>15</td>
<td>93</td>
<td>85:15</td>
<td>22</td>
</tr>
<tr>
<td>9</td>
<td>Pr$_3$NBu</td>
<td>9d</td>
<td>15</td>
<td>84</td>
<td>79:21</td>
<td>18</td>
</tr>
<tr>
<td>10</td>
<td>Pr$_3$NBu</td>
<td>9e</td>
<td>15</td>
<td>94</td>
<td>81:19</td>
<td>43</td>
</tr>
<tr>
<td>11</td>
<td>Pr$_3$NBu</td>
<td>9f</td>
<td>15</td>
<td>94</td>
<td>82:18</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>Pr$_3$NBu</td>
<td>9g</td>
<td>15</td>
<td>91</td>
<td>80:20</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>Pr$_3$NBu</td>
<td>9g</td>
<td>24</td>
<td>82</td>
<td>76:24</td>
<td>72</td>
</tr>
<tr>
<td>14</td>
<td>Pr$_3$NBu</td>
<td>9g</td>
<td>24</td>
<td>76</td>
<td>76:24</td>
<td>72</td>
</tr>
</tbody>
</table>

[a] Unless otherwise noted, reactions were carried out in the presence of $\text{S}$ ($0.5 \text{ mmol}$), 8a ($0.6 \text{ mmol}$), SiCl$_4$ ($1.0 \text{ mmol}$), an amine ($2.5 \text{ mmol}$), and ($0.05 \text{ mmol}$) in dichloromethane ($5.0 \text{ mL}$) at $-20^\circ\text{C}$. \[b\] Yield of the isolated diastereomeric mixture. \[c\] Determined by $^1$H NMR analysis. \[d\] For the syn isomer, determined by HPLC analysis on a chiral stationary phase. \[e\] With SiCl$_4$ (0.5 mmol). \[f\] At $-60^\circ\text{C}$. \[g\] Using the sodium salt of 7a instead of $\text{S}$. 

Table 2: Substrate scope: carboxylic acids.\(^\text{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield [%]</th>
<th>d.r. [%]</th>
<th>ee [%](^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a Ph</td>
<td>7a Ph</td>
<td>87</td>
<td>89:12</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>7b 2-BnC(_6)H(_4)</td>
<td>7b 2-BnC(_6)H(_4)</td>
<td>86</td>
<td>91:12</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>7c (CH(_2))(_4), Cl</td>
<td>7c (CH(_2))(_4), Cl</td>
<td>85</td>
<td>92:12</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>7d (CH(_2))(_4), Br</td>
<td>7d (CH(_2))(_4), Br</td>
<td>84</td>
<td>93:12</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>7e (CH(_2))(_4),I</td>
<td>7e (CH(_2))(_4),I</td>
<td>83</td>
<td>94:12</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>7f (CH(_2))(_4),OMe</td>
<td>7f (CH(_2))(_4),OMe</td>
<td>72</td>
<td>95:12</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>7g (CH(_2))(_4),SbN</td>
<td>7g (CH(_2))(_4),SbN</td>
<td>71</td>
<td>96:12</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>7h CH(_2)(_3)NO(_2)</td>
<td>7h CH(_2)(_3)NO(_2)</td>
<td>70</td>
<td>97:12</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>7i (CH(_2))(_4),CN</td>
<td>7i (CH(_2))(_4),CN</td>
<td>71</td>
<td>98:12</td>
<td>100</td>
</tr>
</tbody>
</table>

[a] Reactions were carried out in the presence of 7 (0.5 mmol), 8a (0.6 mmol), SiCl\(_4\) (1.0 mmol), Pr\(_3\)N\(_4\)Bu (2.5 mmol), and 9g (0.05 mmol) in dichloromethane (5.0 mL) at —60 °C for 24 h. Yields and selectivities were determined after conversion into the corresponding methyl esters. [b] Yield of the isolated diastereomeric mixture. [c] Determined by \(^1\)H NMR analysis.

Table 3: Substrate scope: aldehydes.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product</th>
<th>Yield [%](^{[b]})</th>
<th>d.r. [%]</th>
<th>ee [%](^{[c]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a Ph</td>
<td>7a Ph</td>
<td>88</td>
<td>83:12</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>8b 4-MeC(_6)H(_4)</td>
<td>7b 4-MeC(_6)H(_4)</td>
<td>82</td>
<td>84:12</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>8c 4-MeOC(_6)H(_4)</td>
<td>7c 4-MeOC(_6)H(_4)</td>
<td>81</td>
<td>85:12</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>8d 4-BrC(_6)H(_4)</td>
<td>7d 4-BrC(_6)H(_4)</td>
<td>80</td>
<td>86:12</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>8e 4-CF(_3)C(_6)H(_4)</td>
<td>7e 4-CF(_3)C(_6)H(_4)</td>
<td>79</td>
<td>87:12</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>8f 4-NO(_2)C(_6)H(_4)</td>
<td>7f 4-NO(_2)C(_6)H(_4)</td>
<td>78</td>
<td>88:12</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>8g 4-HOC(_6)H(_4)</td>
<td>7g 4-HOC(_6)H(_4)</td>
<td>77</td>
<td>89:12</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>8h 3-BrC(_6)H(_4)</td>
<td>7h 3-BrC(_6)H(_4)</td>
<td>76</td>
<td>90:12</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>8i 2-BrC(_6)H(_4)</td>
<td>7i 2-BrC(_6)H(_4)</td>
<td>75</td>
<td>91:12</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>8j 2-naphthyl</td>
<td>7j 2-naphthyl</td>
<td>74</td>
<td>92:12</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>8k 2-furyl</td>
<td>7k 2-furyl</td>
<td>73</td>
<td>93:12</td>
<td>95</td>
</tr>
<tr>
<td>12</td>
<td>8l CH(_2)-C(_6)H(_5)</td>
<td>7l CH(_2)-C(_6)H(_5)</td>
<td>72</td>
<td>94:12</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>8m cyclopropyl</td>
<td>7m cyclopropyl</td>
<td>71</td>
<td>95:12</td>
<td>97</td>
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<tr>
<td>14</td>
<td>8n Ph</td>
<td>7n Ph</td>
<td>70</td>
<td>96:12</td>
<td>98</td>
</tr>
</tbody>
</table>

[a] Unless otherwise noted, reactions were carried out in the presence of 7d (0.5 mmol), 8j (0.6 mmol), SiCl\(_4\) (1.0 mmol), Pr\(_3\)N\(_4\)Bu (2.5 mmol), and 9g (0.05 mmol) in dichloromethane (5.0 mL) at —60 °C for 24 h. Yields and selectivities were determined after conversion into the corresponding methyl esters. [b] Yield of the isolated diastereomeric mixture. [c] Determined by \(^1\)H NMR analysis.

Scheme 3. Deuterium isotope effect studies.
conformation of complex I might be the “pin-wheel” form, in which the steric repulsion between the bulky peripheral groups is minimized. Deprotonation by a base preferably takes place via II to afford “cisoid” Z-bis(trichlorosilyl)enediolate III,[23] which is associated with the chiral phosphine oxide. The Z-enediolate subsequently reacts with an aldehyde via a six-membered transition state IV to achieve the high diastereo- and enantioselectivities.

The present procedure could be extended to the reaction with an α-ketoester (Scheme 5). Carboxylic acid 7d reacted smoothly with methyl benzoylformate (12) in dichloromethane at −45 °C to furnish adduct 13 in 53% yield with good diastereoselectivity (93:7 d.r.). The enantiomeric purity of the major diastereomer was 88% ee.

Scheme 5. Asymmetric aldol reaction with α-ketoester 12.

In conclusion, we have developed the first catalytic asymmetric aldol reaction of unprotected carboxylic acids. Key to success was the use of inexpensive silicon tetrachloride as an activator. The carboxylic acids readily reacted with silicon tetrachloride in the presence of the catalytic chiral phosphine oxide to form the corresponding bis(trichlorosilyl)enediolates, which reacted with an aldehyde or ketone to give the corresponding β-hydroxycarboxylic acids in high diastereo- and enantioselectivities. We are undertaking studies to disclose the reaction mechanism in detail and to extend the protocol of activating carboxylic acids to other stereoselective reactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldol reaction · carboxylic acids · hypervalent silicon · organocatalysis · phosphine oxides

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[14] The stereochemistry of the carboxylic acids was determined after conversion into methyl esters 11.

[15] The enantiomeric excess of the anti isomer was low; see the Supporting Information for details.


[17] P(O)Ph (20 mol %) was an ineffective catalyst for the reaction.

For facile purification and analysis, the yields and the stereoselectivities correspond to those of methyl esters. 

CCDC 1848185 ((2R,3R)-11ba) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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