The in situ generation of chiral metal enolates and their integration into a catalytic, enantioselective aldol process has been a topic of sustained interest.1,2 Our research has focused on the development of catalytic enantioselective aldol reactions of carboxylic acid derivatives under silylating conditions (eq 1).3 We now report that complexes of the general structure [Ni(L2)](OTf)2 are effective catalysts for this reaction with imide 1.4 Specifically, the complex derived from Ni(OTf)2 and (S,S)-tert-butylbis(oxazoline), [Ni((S,S)-t-BuBox)][OTf]2 (2), in the presence of TMSOTf and 2,6-lutidine, efficiently catalyzes the addition of N-propionylthiazolidinethione (1) to aromatic, unsaturated, and even enolizable aliphatic aldehydes with high syn diastereoselectivity and enantioselectivity (eq 2).

Attempts to perform the magnesium halide-catalyzed anti aldol addition in the presence of chiral ligands resulted in low conversion, poor diastereoselectivity, and racemic products. In addition, metal triflate salts were unreactive under these conditions.5 We speculated that these metal triflates were deactivated by the chloride ion generated by the Et3 N–TMSCl system. Employment of 2,6-lutidine and TMSOTf,6 however, revealed Ni(II) to be a promising candidate for asymmetric catalysis.7 An evaluation of bidentate ligands was increased from 0.4 to 0.8 M, efficient reaction was observed for asymmetric catalysis. 7 An evaluation of bidentate ligands for the bis(aquo) complex revealed a square-pyramidal geometry, a gram scale. Commercially available NiCl2 and (S,S)-t-BuBox9 as a hygroscopic yellow powder.11 X-ray diffraction analysis of this complex with 2 equiv of AgOTf afforded \([Ni((S,S)-t-BuBox)](OTf)2\) (9) as a hygroscopic yellow powder.12 X-ray diffraction of the bis(aquo) complex revealed a square-pyramidal geometry, with one triflate coordinated to the metal center (Figure 1).

The preformed catalyst exhibited greater activity than the analogous catalyst prepared in situ.12 Reaction enantioselectivity was enhanced in nonpolar media such as toluene and EtO, although the diastereoselectivity and reaction rate suffered. Ultimately, a 4:1 (toluene:CH2Cl2) solvent mixture provided the optimal combination of rate and selectivity. When the concentration of thiazolidinethione was increased from 0.4 to 0.8 M, efficient reaction was observed at −20 °C. An excess of 2,6-lutidine (3.33 equiv) was found to be beneficial to both rate and enantioselectivity. A representative selection of aldehydes was evaluated under the reaction conditions. As expected, aromatic aldehydes were good substrates (Table 2).13 Diastereoselectivity was uniformly high, ranging from 88:12 to 94:6, and good yields and enantioselectivities were observed. In some cases, the catalyst loading could be decreased to 5 mol % with no erosion in yield or selectivity. X-ray analysis of several crystalline adducts proved the product stereochemistry to be as shown.

The most gratifying aspect of this study was the observation of the desired crossed aldol reaction with enolizable aldehydes. In these reactions, no aldehyde self-addition was observed. For example, the addition of thiazolidinethione 1 to acetaldehyde, propanal, and isobutyraldehyde proceeded under unmodified reaction conditions, no aldehyde self-addition was observed. For example, the catalyst loading could be decreased to 5 mol % with no erosion in yield or selectivity. X-ray analysis of several crystalline adducts proved the product stereochemistry to be as shown.

The scope of this catalytic aldol reaction includes the use of triethylsilyl triflate (TESOTF) as a silylating agent. For example, the reaction of thiazolidinethione 1 with benzaldehyde in the presence of TESOTF was carried out on a 10 mmol scale. After 36 h, the reaction reached full conversion, and the TES-protected aldol...
Table 2. Enantioselective Aldol Addition to Various Aldehydes

<table>
<thead>
<tr>
<th>entry</th>
<th>RCHO</th>
<th>adduct syn:ant</th>
<th>ee(%)</th>
<th>yield(%)</th>
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<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>3a</td>
<td>94.6</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>XeH</td>
<td>3b</td>
<td>93.7</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>XeMe</td>
<td>3c</td>
<td>90.10</td>
<td>91</td>
</tr>
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<td>4</td>
<td>α-naphthaldehyde</td>
<td>3d</td>
<td>93.7</td>
<td>92</td>
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<td>5</td>
<td>β-naphthaldehyde</td>
<td>3e</td>
<td>92.8</td>
<td>93</td>
</tr>
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<td>6</td>
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<td>3f</td>
<td>88.12</td>
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<tr>
<td>7</td>
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<td>3g</td>
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<td>97</td>
</tr>
<tr>
<td>8</td>
<td>XeMe</td>
<td>3h</td>
<td>88.12</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>acetaldehyde</td>
<td>3i</td>
<td>97.3</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>propanal</td>
<td>3j</td>
<td>97.3</td>
<td>90</td>
</tr>
<tr>
<td>11</td>
<td>isobutyraldehyde</td>
<td>3k</td>
<td>98.2</td>
<td>90</td>
</tr>
</tbody>
</table>

* 1. 10 mol % 2, 2,3,3-3 equiv 2,6-lutidine, 1 mol L, 1.2 equiv PhCHO, 1.25 equiv TMSOTf, 0.8 M in 4:1 toluene:CH2Cl2, –70 to –20 °C, 2.5:1 THF:1.0 N HCl. * Determined by 500 MHz 1H NMR or HPLC analysis. Determined by HPLC analysis. 4 Isolated yield of a single diastereomer after column chromatography. * 5 mol % catalyst was used. * Isolated as a mixture of diastereomers.

There is an inherent ambiguity in the mechanism of this process that is linked to the point at which the silylating agent enters the catalytic cycle. For example, if the metal enolate is silylated, a Mukaiyama aldol mechanism would follow.

There was no silylketene acetal derived from 1 is observed under the reaction conditions in the absence of aldehyde suggests that this mechanistic option is not operative. An alternative catalytic cycle is outlined in Scheme 1.15

![Scheme 1. Proposed Catalytic Cycle](image)

Catalyst—substrate complex A6 is deprotonated by 2,6-lutidine to yield enolate B. Subsequent aldehyde addition affords aldolate C, which is silylated by TMSOTf to give D. This event facilitates decomplexation of the aldol product and catalyst turnover. The observed enantioselectivity is consistent with reaction of a chelated (Z)-enolate through a chair-like transition state.17

We attribute the lack of aldehyde-based side reactions to the chelate effect designed into the latent enolate. It is presumed that the affinity of sulfur for nickel biases coordination of the metal in favor of the thione—nickel complex, explaining the ease of crossed aldol with enolizable aliphatic aldehydes. Extension of these catalysis principles to other enolate-based transformations is underway.

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Supporting Information Available: Experimental procedures, spectral data for all compounds, crystallographic data, and stereochemical proofs (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

References


(4) For a stoichiometric, Sn(OTf)2/chiral diamine-mediated aldol reaction with these substrates, see Iwasawa, N.; Mukaiyama, T. Chem. Lett. 1983, 297–300. Under our conditions, N-acyloxazolidinones were unreactive.

(5) E.g., Sn(OTf)2, Zn(OTf)2, In(OTf)3, La(OTf)3, Sm(OTf)3, Yb(OTf)3.

(6) No reaction occurred in the absence of TMSOTf or in the absence of MO(OTf)2. Conversion suffered greatly with < 2 equiv of 2,6-lutidine.


(8) Presumably, the stoichiometric OTf− produced during the reaction displaces the less-coordinating Sn(IV) counterion. The high turnover requires that the Ni(OTf)2 generated in situ be catalytically active.


(10) See Supporting Information for X-ray crystallographic data.

(11) The anhydrous catalyst was stored in a glovebox. Hydrated catalyst was less effective in aldol reactions. See Supporting Information for X-ray crystallographic data.

(12) With the preferred catalyst, conversion increased by 5% and enantioselectivity by 1–2%.

(13) Surprisingly, enantioselectivity for p-MeOPhCHO was moderate (62%).


(15) For a similar catalytic cycle, see ref 3b.

(16) Ancillary ligands are omitted for the sake of clarity. The aldol transition state likely involves a five- or six-coordinate nickel complex.


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