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Ni(II) Bis(oxazoline)-Catalyzed Enantioselective Syn Aldol Reactions of *N*-Propionylthiazolidinethiones in the Presence of Silyl Triflates

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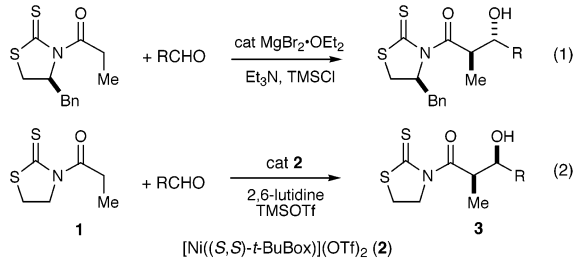
The in situ generation of chiral metal enolates and their integration into a catalytic, enantioselective aldol process has been a topic of sustained interest.[1,2] Our research has focused on the development of catalytic enantioselective aldol reactions of carboxylic acid derivatives under silylating conditions (eq 1).[3] We now report that complexes of the general structure $[Ni(L_2)](OTf)_2$ 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 enantioselection (eq 2).

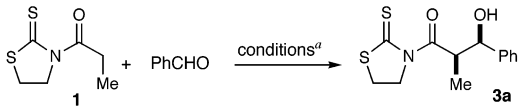


Attempts to perform the magnesium halide-catalyzed anti aldol addition in the presence of chiral ligands resulted in low conversion, poor diastereoselectivity, and racemic products. In addition, metal triflate salts were unreactive under these conditions.[5] We speculated that these metal triflates were deactivated by the chloride ion generated by the $Et_3N-TMSCl$ 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 determined the bis(oxazolines) to be superior in terms of rate and selectivity. Initial results with the (*S*,*S*)-*t*-BuBox ligand were encouraging, affording the aldol adduct in 83% ee as a 20:1 syn:anti mixture of diastereomers (1 h, CH_2Cl_2, 0 °C) (Table 1).

For optimization studies, the active catalyst[8] was synthesized on a gram scale. Commercially available $NiCl_2$ and (*S*,*S*)-*t*-BuBox[9] were heated at reflux in acetonitrile to provide the derived $NiCl_2-$Box complex as a bench-stable purple crystalline solid.[10] Treatment of this complex with 2 equiv of AgOTf afforded $[Ni((S,S)$-*t*-BuBox$)](OTf)_2$ (**2**) as a hygroscopic yellow powder.[11] 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 Et_2O, although the diastereoselectivity and reaction rate suffered. Ultimately, a 4:1 (toluene:CH_2Cl_2) 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.

Table 1. Bis(oxazoline) Ligands in Ni-Catalyzed Aldol Additions



entry	ligand	conv (%)[b]	syn:anti[b]	syn ee (%)[c]
1	*t*-BuBox	**92**	**23:1**	**83**
2	PhBox	80	2.3:1	60
3	*i*-PrBox	50	1.7:1	40
4	IndaBox	67	2.6:1	55

[a] 1. 10 mol % $Ni(SbF_6)_2$, 10 mol % ligand, 2.3 equiv 2,6-lutidine, 0.2 mmol **1**, 1.2 equiv PhCHO, 1.25 equiv TMSOTf, 0.4 M in CH_2Cl_2, −78 to 0 °C. 2. 5:1 THF/1.0 N HCl. [b] Determined by 500 MHz ^1H NMR spectroscopy. [c] Determined by HPLC analysis.

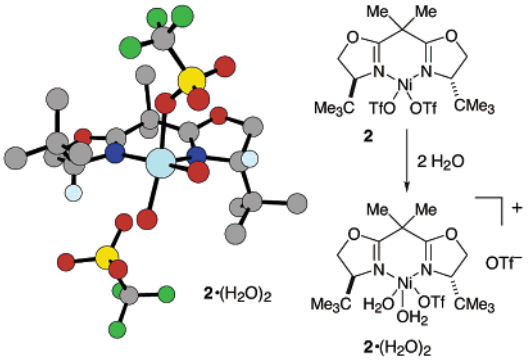


Figure 1. X-ray structure of $[Ni((S,S)$-*t*-BuBox$)](OTf)_2$ **2**•$(H_2O)_2$.

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 without competing side reactions of the aldehyde component (entries 9−11). Although longer reaction times were necessary to achieve full conversion, high ee's and yields were observed.

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

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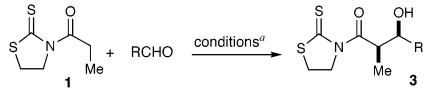
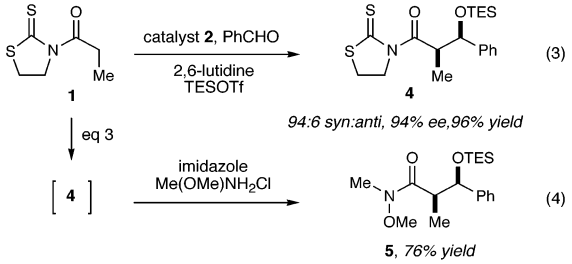
Table 2. Enantioselective Aldol Addition to Various Aldehydes



entry	RCHO		adduct	syn:anti[b]	syn ee(%)[c]	yield(%)[d]
1		X=H	**3a**	94:6	97	81[e]
2		X=Me	**3b**	93:7	95	80
3		X=Cl	**3c**	90:10	91	81
4	α-naphthaldehyde		**3d**	93:7	92	73
5	β-naphthaldehyde		**3e**	92:8	93	82[e]
6	furfural		**3f**	88:12	95	82[e]
7		X=Me	**3g**	93:7	97	46
8		X=Ph	**3h**	88:12	93	63
9	acetaldehyde		**3i**	97:3	93	86[f]
10	propanal		**3j**	97:3	90	84[f]
11	isobutyraldehyde		**3k**	98:2	90	70[f]

[a] 1. 10 mol % **2**, 3.33 equiv 2,6-lutidine, 1 mmol **1**, 1.2 equiv PhCHO, 1.25 equiv TMSOTf, 0.8 M in 4:1 toluene:CH_2Cl_2, −78 to −20 °C. 2. 5:1 THF:1.0 N HCl. [b] Determined by 500 MHz ^{1}H NMR or HPLC analysis. [c] Determined by HPLC analysis. [d] Isolated yield of a single diastereomer after column chromatography. [e] 5 mol % catalyst was used. [f] Isolated as a mixture of diastereomers.

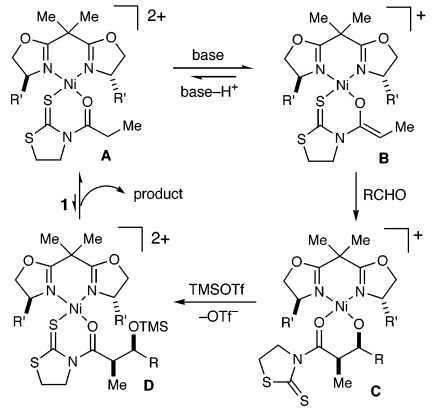
adduct was isolated as a 17:1 mixture of diastereomers in 96% yield (eq 3). In a related experiment, the unpurified reaction mixture of the TES-protected benzaldehyde adduct was treated with imidazole and Me(MeO)NH_2Cl to provide a 76% yield of the Weinreb amide (eq 4). This one-pot procedure typifies the documented versatility of the thiazolidinethiones as activated carboxylic acid equivalents.[14]



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. *The fact that 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] Catalyst−substrate complex **A**[16] 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 chairlike 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

Scheme 1. Proposed Catalytic Cycle



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.

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(4) For a stoichiometric, $Sn(OTf)_2$/chiral diamine-mediated aldol reaction with theses substrates, see Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297−300. Under our conditions, *N*-acyloxazolidinones were unreactive.
(5) E.g., $Sc(OTf)_3$, $Zn(OTf)_2$, $In(OTf)_3$, $Sn(OTf)_2$, $La(OTf)_3$, $Sm(OTf)_3$, $Yb(OTf)_3$.
(6) No reaction occurred in the absence of TMSOTf or in the absence of $M(OTf)_n$. Conversion suffered greatly with <2 equiv of 2,6-lutidine.
(7) For examples of Ni(II) complexes in chiral Lewis acid catalysis, see: (a) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (b) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355−12356.
(8) Presumably, the stoichiometric OTf^- produced during the reaction displaces the less-coordinating SbF_6^- counterion. The high turnover requires that the $Ni(OTf)_2$ thus generated in situ be catalytically active.
(9) Synthesis: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.
(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 preformed catalyst, conversion increased by 5% and enantioselectivity by 1−2%.
(13) Suprisingly, enantioselectivity for *p*-MeOPhCHO was moderate (62%).
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(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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