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Highly Diastereo- and Enantioselective Aldol Reaction of Methyl α-Isocyanoacetate: A Cooperative Catalysis Approach

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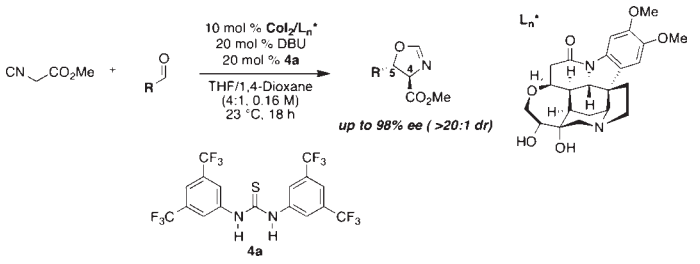
ABSTRACT



The cooperative catalyst activity between a chiral transition-metal catalyst and an achiral organocatalyst has been identified as one of the critical asymmetric reaction optimization components in the highly diastereo- and enantioselective aldol reaction of methyl α-isocyanoacetate.

The field of asymmetric catalysis continues to play a pivotal role in advancing the molecular-level understanding of chemical processes. While biocatalysts skillfully utilize multiple covalent (for metals) and noncovalent interactions (for H-bonding) *in concert* for the conformational stability and well-defined chiral environment,[1] the dominant asymmetric strategies in organic synthesis have relied on two divergent catalyses: (1) metal-centered Lewis acid catalysis (for electrophilic activation mode)[2] and (2) small-molecule organocatalysis (for H-bonding mode and Brønsted acid catalysis mode).[3] Although the concept of bifunctional asymmetric catalysts has been well established in transition-metal catalysis[4] and organocatalysis,[5] respectively, the recent emergence of cooperative catalysis between metals and small organic molecules has provided alternative ways of asymmetric reaction optimizations, where two distinctive catalysis modes are controlled by either one or two chiral (or achiral) components of the reaction.[6] Furthermore, such a combination of multiple catalyst systems has opened up new avenues for developing cooperative catalyst systems where the respective catalyst system alone fails to deliver sufficient catalyst reactivity and selectivity.

The recent discovery of anion-binding thiourea organocatalysts is beginning to gain momentum.[7] The laboratories of Jacobsen pioneered this field in halide-binding,[8]

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(2) *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008; Vols. 1−2.

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(4) For recent reviews, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (b) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (c) Shibasaki, M.; Matsunaga, S. *Chem. Soc. Rev.* **2006**, *35*, 269. (d) Shibasaki, M.; Matsunaga, M.; Kumagai, N. *Synlett* **2008**, 1583. (e) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

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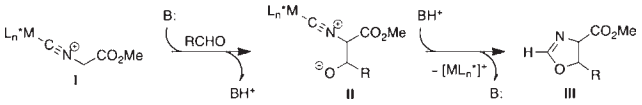
cyanide-binding,[9] and sulfonate-binding chiral thiourea organocatalysts.[10] The oxyanion-binding thiourea organocatalysts were explored by the laboratories of Schreiner in alcohol funtionalization strategies.[11] Most recently, the laboratories of Seidel disclosed the carboxylate-binding chiral thiourea organocatalyst systems for the kinetic resolution of various amine derivatives.[12] Given the facile synthetic variation of thiourea structures, it is of interest to exam if achiral thiourea derivatives exhibit the cooperative catalysis with chiral transition metal complexes.

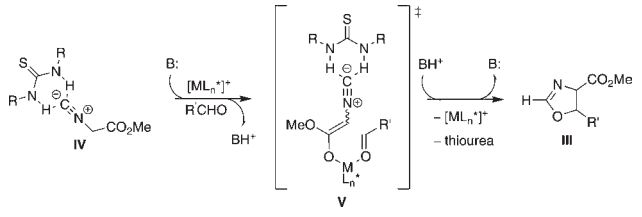
The idea of cooperative catalysis was explored in the context of direct catalytic asymmetric aldol reaction of α-isocyanoacetates. In the paradigm of transition-metal-catalyzed reactions of isocyanides, the ability of a metal ion to form a complex **I** with isocyano functionality dictates the chemical pathways of such complexes (Scheme 1).[13] Accordingly, the aldol reactions of α-isocyanoacetates are catalyzed by a number of metal complexes. While the highly diastereo- and enantioselective aldol reaction of methyl α-isocyanoacetate was demonstrated by Ito and Hayashi using chiral Au(I)− and Ag(I)−ferrocenylphosphine complexes,[14] the development of metal-catalyzed asymmetric aldol reactions of α-isocyanoacetates remains a significant challenge.[15] Given the strong complexing ability of isocyanides to metals, the low level of stereoinduction in oxazolines **III** likely stems from the fact that enolates derived from the linear metal−isocyanide

Scheme 1. Transition-Metal-Catalyzed Direct Aldol Reaction of α-Isocyanoacetate



complex **I** are far removed from the chiral pocket. In addition, a recent organocatalytic approach employing methyl α,α-arylisocyanoacetate by Gong et al. has resulted in modest diastereo- and enantioselectivities (2−6:1 dr's with 70−89% ee's) in the presence of cupreine-derived organocatalysts,[16a] while the related asymmetric aldol reactions of α-isothiocyanato esters and imides have been successful using chiral thiourea organocatalysts.[16b−e]

Scheme 2. Cooperative Catalysis of Lewis Acid and Thiourea for Aldol Reaction of α-Isocyanoacetates



Motivated by the historical evidence of strong H-bonding to carbon in isocyanides,[17] our initial experiments were directed to the establishment of anion-binding interactions **IV** between thiourea and methyl α-isocyanoacetate (Scheme 2). We envisioned that the thiourea-assisted enolates would be capable of coordinating to a chiral metal center in a more organized fashion **V**. From our preliminary spectroscopic investigation, the proposed anion-binding interaction between the carbon atom of isocyanides and N−H of thioureas was evident, where the downfield shift of thiourea proton in ^{1}H NMR as well as the lower N−H stretching frequency in IR were interpreted as that H-bonded complexes **IV** were being formed.[18]

Next, we focused on examining the cooperative catalysis that utilizes the anion-binding interactions of thioureas under chiral transition-metal catalysis for the aldol reaction of methyl α-isocyanoacetate (Table 1). The cooperative catalyst effect was clearly evident in the stereoselectivity of reactions employing the chiral Cu (I) complexes derived from brucine amino diol **L1** and copper(I) salts (entries 1−3).[19] While the use of copper(I) acetate eliminated use of an external base since acetate played a role of

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(13) For a recent review, see: Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

(14) For Au(I) catalysis, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. For a Ag(I) catalysis, see: (b) Hayashi, T.; Uozumi, Y.; Yamazaki, A. *Tetrahedron Lett.* **1991**, *32*, 2799. For a comprehensive review, see: ref 13.

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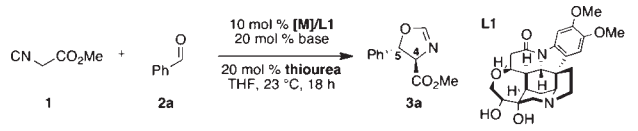
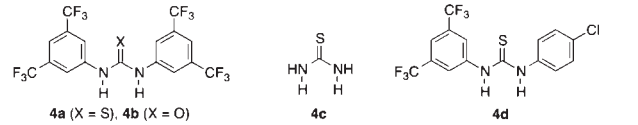
(18) See the Supporting Information for more details.

Table 1. Cooperative Catalysis in Asymmetric Aldol Reaction.[a]





entry	metal	base	thiourea	dr[b]	yield[c] (%)	ee[d] (%)
1	CuOAc			7:1	80	2
2	CuOAc		**4a**	4:1	85	26
3	CuOTf	NEt_3	**4a**	4:1	72	40
4	$CoCl_2$	NEt_3	-	5:1	50	8
5	$CoCl_2$	NEt_3	**4a**	5:1	50	70
6	CoF_2	NEt_3	**4a**	10:1	50	30
7	CoI_2	NEt_3	**4a**	12:1	88	2
8	CoF_2	DBU	**4a**	10:1	30	50
9	$CoCl_2$	DBU	**4a**	6:1	90	25
10	CoI_2	DBU	**4a**	15:1	50	75
11	CoI_2	DBN	**4a**	11:1	74	65
12	CoI_2	DMAP	**4a**	6:1	55	22
13	CoI_2	DABCO	**4a**	10:1	60	5
14[e]	*CoI_2*	*DBU*	***4a***	*17:1*	*70*	*97*
15[e]	CoI_2	DBU	**4b**	10:1	40	5
16[e]	CoI_2	DBU	**4c**	10:1	50	10
17[e]	CoI_2	DBU	**4d**	15:1	58	86
18[e]	CoI_2	DBU		10:1	40	10
19[e]	[f]	DBU	**4a**	14:1	84	12
20[e]	[f]		**4a**	5:1	10	12
21[e]	[f]			5:1	67	15

[a] Reaction with **1** (0.5 mmol) and **2** (0.5 mmol) in THF (0.16 M). [b] Determined by crude ^{1}H NMR. [c] Combined isolated yields of **3** after column chromatography. [d] Determined by chiral HPLC analysis (absolute configuration was determined by HPLC comparison with authentic samples). [e] Reaction in a mixture of THF/1,4-dioxane (4:1). [f] Use of 10 mol % of **L1** without metal.

base, the potential anion-binding property of acetate to thiourea was reasoned for the low enantioselectivity (entry 2). Thus, we employed an alternative approach to chiral Lewis acid formation using a catalytic amount of NEt_3. Among other copper salts screened,[20] only marginal improvement of enantioselectivity was observed with CuOTf (entry 3). Next, we opted for screening other metal salts that possess similar ionic radii and coordination numbers as those of copper(I) metal. To our delight, the more pronounced cooperative catalyst effect was observed upon using cobalt(II) salts (entries 4−7).[21] In particular, the use of cobalt(II) chloride improved the enantioselectivity up to 70% ee (entry 5), while the observed diastereoselectivity was superior in reactions using other cobalt(II) metals (entries 6−7). During our previous copper(I)-catalyzed asymmetric investigation, we observed the beneficial effect of DBU in the chiral copper catalysts derived from copper(I) iodide.[19a] Our speculation *at that time* was that a tight ion pair might be formed between the protonated DBU and iodide ions. Since halide ions are capable of H-bonding to thiourea, we further examined other bases in the cobalt(II)-catalyzed reactions (entries 8−13). The effect of amidine base, DBU, was detrimental to the outcomes of CoF_2- and $CoCl_2$-catalyzed reactions (entries 8−9); however, the beneficial effect of DBU was evident in the CoI_2-catalyzed reaction, providing chiral oxazoline **3a** in 75% ee with 15:1 dr (entry 10). The use of related amidine base, DBN, was slightly less efficient (entry 11), but delivered improved results compared to other bases (entries 7 and 12−13).[22] A further fine-tuning of reaction conditions was accomplished by employing a mixed solvent of THF/1,4-dioxane (4:1) to increase the solubility of chiral cobalt catalysts. With this final experimental modification, the exclusive formation of *trans*-(4*R*,5*S*)-**3a** was possible with 97% ee (entry 14). The importance of thiourea **4a** in the current catalytic system was further demonstrated in the structure−enantioselectivity studies (entries 15−17). Urea **4b** and thiourea **4c** rendered cooperative catalyst systems with enhanced diastereoselectivies, but they induced poor enantioselectivities (entry 15−16), whereas the unsymmetric thiourea **4d** restored the highly selective cooperative catalyst activity (entry 17). These results strongly suggest the cooperative role of thiourea and chiral Lewis acid in the enantioselectivity-determining transition state. Finally, we conducted a series of control experiments to establish the cooperative catalyst activity between the four catalyst components (entries 18−21).

The scope of the catalytic asymmetric aldol reaction of methyl α-isocyanoacetate was evaluated under the optimized cooperative catalysis conditions (Scheme 3). The reaction was applicable to a range of aromatic, heteroaromatic, and aliphatic aldehydes. In general, excellent diastereo- and enantioselectivities (>20:1 dr, 90−98% ee's) were obtained at ambient temperature within 18 h. Less satisfactory enantioselectivities were found in the reactions of 2-thiophenecarboxaldehyde (***trans*-3e**, 84% ee) and pivaldehyde (***trans*-3i**, 74% ee), while high diastereoselectivities were maintained (>20:1 dr). The limitation of the current cooperative catalysis lies in *ortho*- and *meta*-substituted benzaldeydes, where low levels of enantioselectivity were obtained in the range of 20−50% ee but with excellent diastereoselectivities (>20:1 dr). Our current efforts are directed to bring improvements with these substrates.[23]

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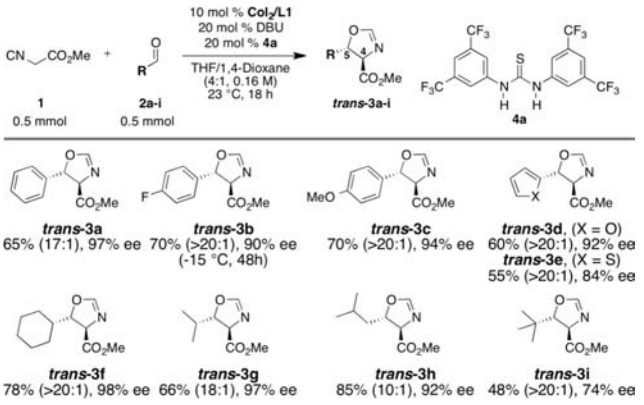
(20) Use of other copper salts (CuF, CuCl, CuBr, CuI, $Cu(CH_3CN)_4$-PF_6, $CuCl_2$) resulted in catalysts with low enantioselectivities.

(21) Typical ionic radius for Cu(I) with a coordination number of 4 is 0.60 Å, whereas that of Co(II) is around 0.56 Å; see: *Handbook of Chemistry and Physics*, 87th ed.; CRC: Boca Raton, FL, 2006; pp 12−11.

(22) Presently, we do not know the cause for the dramatic effect of amidine bases on enantioselectivity, but our **M/L1** catalyst systems provide trends: metal chlorides and bromides seem to tolerate tertiary amine bases (i.e., Et_3N, *i*-Pr_2NEt), but metal iodides require amidine bases (i.e., DBU); see: (a) Ref 19. A cooperative role of amidine bases in the asymmetric Co(II) catalysis has been recently reported; see: (b) Kalow, J. A.; Doyle, A. G. *J. Am. Chem. Soc.* **2010**, *132*, 3268.

(23) Use of other metal salts and modified thiourea derivatives is currently under investigation.

Scheme 3. Scope of the Catalytic Asymmetric Aldol Reaction.[a]



[a] Isolated yield of ***trans*-3** with dr values from crude ^{1}H NMR and ee values from chiral HPLC analysis.

To understand the observed stereochemical outcome of reactions, we monitored the asymmetric aldol reactions at frequent intervals for the possible formation of *cis*-oxazolines. The observed diastereoselectivities were consistently high for *trans*-oxazolines (> 20:1 dr) throughout the entire reaction period regardless of reaction conversions. Since the epimerization might be a facile process under the reaction conditions,[24] we also subjected a diastereomeric mixture of oxazolines (2.2:1 = *trans*/*cis*) to our optimized asymmetric reaction conditions, and found that there was a minimal change in the diastereomeric ratio of oxazolines (2.4:1 = *trans*/*cis*) after 8 h at ambient temperature, a clear indication that the experimentally observed diasteroselectivities are primarily derived from the action of catalytically active species.

A stereomodel for the cooperative catalysis, which is consistent with the observed stereoselectivities, is proposed in Figure 1. This transition-state model is consistent with our previous proposals for monometallic Cu(I)/**L1** catalysts,[19] where a *si*-face attack of enolates to aldehydes occurs through a chairlike conformation. While the nature of cooperative catalysis waits further studies,[25] the blue Co(II)−**L1** complexes support a possible involvement of tetrahedral cobalt complexes.[26] The (*Z*)-enolate configuration is proposed as the reactive species; however, use of *tert*-butyl α-isocyanoacetate resulted in markedly reduced reactivity and enantioselectivity,[27] implying the necessity of enolate coordination to the cobalt metal center. Furthermore, our preliminary studies into the potential role of the C_{21}-OH and C_{22}-OH in our ligand **L** revealed that both alcohol moieties are critical for the cooperative catalysis. Thus, upon using the modified ligands **L2**−**4** (having either the nitrogen atom or the C_{21}-OH/C_{22}-OH group protected), products with significantly lower enantioselectivities were observed.[28] These results suggest the possibilty of a secondary H-bond interaction between the enolate and the C_{22}-OH of chiral metal complexes.

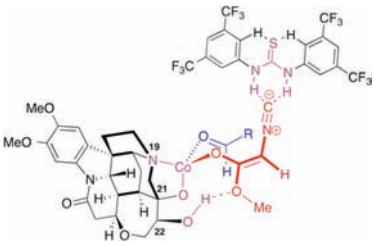


Figure 1. Proposed stereomodel for cooperative catalysis.

In summary, we have developed a cooperative catalyst system for the highly diastereo- and enantioselective catalytic aldol reaction of methyl α-isocyanoacetate. The key to our successful stereocontrol probably lies in the strong anion-binding interaction between isocyanides and thioureas, which potentially disturbs the intrinsic metal-isocyanide complexation. Additional studies to broaden this asymmetric approach are currently underway.

Acknowledgment. This research was supported by IUPUI. The Bruker 500 MHz NMR was purchased via an NSF-MRI award (CHE-0619254).

Supporting Information Available. Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(24) *cis*-Oxazolines were epimerized to *trans*-oxazolines with Et_3N in refluxing benzene, see: ref 14a. For the epimerization of *cis*-2-substituted oxazolines using Et_3N, see: Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884.

(25) The anion-binding of thioureas to isocyanides under our cooperative catalysis could not be confirmed by NMR or IR due to the line-broadening caused by the multifunctional nature of our chiral metal complexes. However, our control experiments (Table 1, entries 14−17) clearly indicate the cooperative role of thiourea derivatives on enantioselectivity.

(26) Tetrahedral Co(II) complexes are known to be blue, and octahedral Co(II) complexes are usually pink; see:(a) Norwood, V. M., III; Morse, K. W. *Inorg. Chem.* **1987**, *26*, 284. (b) Romerosa, A.; Saraiba-Bello, C.; Serrano-Ruiz, M.; Caneschi, A.; McKee, V.; Peruzzini, M.; Sorace, L.; Zanobini, F. *J. Chem. Soc., Dalton Trans.* **2003**, 3233.

(27) Oxazolines were isolated in < 10% yields after 48 h (> 20:1 dr and 5% ee).

(28) Use of modified ligand **L2** (C_{22}-OAc) gave ***anti*-3a** in 70% yield with 18:1 dr and 38% ee. Use of **L3** (C_{21}/C_{22}-OAc) was not successful, but **L4** (N_{19}-Bn,Br^-) provided racemic ***anti*-3a** in 71% yield and 10:1 dr.