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Anti-Selective Direct Catalytic Asymmetric Aldol Reaction of Thiolactams

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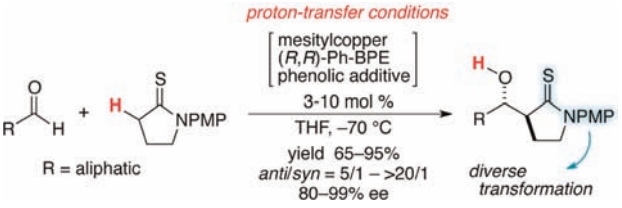
ABSTRACT



An *anti*-selective direct catalytic asymmetric aldol reaction of thiolactam is described. A soft Lewis acid/hard Brønsted base cooperative catalyst comprised of mesitylcopper/(*R*,*R*)-Ph-BPE exhibited high catalytic performance to produce an *anti*-aldol product with high stereoselectivity. The highly chemoselective nature of the present catalysis allows for the use of enolizable aldehydes as aldol acceptors. The diverse transformations of the thiolactam moiety highlight the synthetic utility of the present *anti*-aldol protocol.

Direct catalytic asymmetric aldol reactions have gained increasing popularity as the scope of the reaction has substantially expanded over the past decade.[1,2] The direct aldol methodology emerged as an atom-economical variant of the well-known catalytic asymmetric aldol reaction,[3] allowing for direct access to enantioenriched β-hydroxy carbonyl entities from unmodified aldol donors and acceptors. Elimination of the demanding preactivation/preformation process of active enolates in a separate operation is an obvious practical advantage. The scope of aldol donors amenable to in situ chemoselective enolization/aldol addition, however, was initially limited to mostly ketones and aldehydes.[1−3] Studies to enhance the synthetic utility of this methodology led to the implementation of other aldol donors in the carboxylic oxidation state that are generally reluctant to generate active enolates catalytically.[4,5] We have particularly focused on the soft Lewis basic character of the thiocarbonyl functionality to enable chemoselective activation via soft Lewis acid/hard Brønsted base

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(1) For reviews of direct catalytic asymmetric aldol reactions, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Berlin, 2004. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (e) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600.

(2) For selected early examples of direct catalytic asymmetric aldol reactions, see: (a) Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1871. (b) Yoshikawa, N.; Yamada, Y. M. A.; Das, J.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 4168. (c) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (d) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (e) Mahrwald, R.; Ziemer, B. *Tetrahedron Lett.* **2002**, *43*, 4459.

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(4) There are numerous examples of direct aldol reactions using aldol donors bearing electron-withdrawing α-substituents that are readily enolized under mild basic conditions.

(5) For direct catalytic asymmetric aldol (-type) reactions using aldol donors in the carboxylic acid oxidation state without electron-withdrawing α-substituents: Alkylnitriles: (a) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. Activated amides: (b) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704. β,γ-Unsaturated ester: (c) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 10842. 5*H*-Oxazol-4-ones: (d) Misaki, T.; Takimoto, G.; Sugimura, T. *J. Am. Chem. Soc.* **2010**, *132*, 6286. α-Hydroxyacylpyrroles: (h) Trost, B. M.; Seganish, W. M.; Chung, C. K.; Amans, D. *Chem.—Eur. J.* **2012**, *18*, 2948. (f) α-Phosphonoester via [1,2] phosphonate-phosphate rearrangement: Corbett, M. T.; Uraguchi, D.; Ooi, T.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 4685. (g) Direct catalytic asymmetric aldol reaction of thiazolidinethiones where the use of a stoichiometric amount of silylating reagent was essential: Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706.

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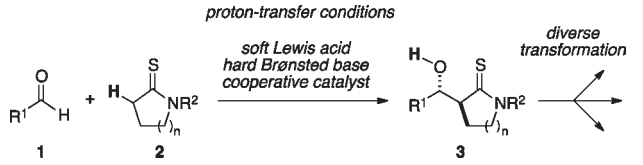
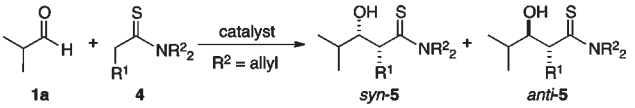
Scheme 1. *Anti*-Selective Direct Catalytic Asymmetric Aldol Reaction of Thiolactams



cooperative catalysis.[6,7] Herein, we report the direct catalytic asymmetric aldol reaction of thiolactam **2**, which preferentially affords *anti*-aldol products with high enantioselectivity (Scheme 1). Diverse functional group transformations of thiolactam highlight the synthetic utility of the product **3**.

We recently documented a *syn*-selective direct catalytic asymmetric aldol reaction of thioamides promoted by a chiral soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalyst (e.g., the reaction of isobutyraldehyde (**1a**) and *N*,*N*-diallylthiopropanamide (**4a**), Table 1, entry 3).[7b,8,9] The first-generation catalyst in this reaction required tedious catalyst preparation; a $[Cu(CH_3CN)_4]$-PF_6/(*R*,*R*)-Ph-BPE complex as a soft Lewis acid and a Li aryloxide as a Brønsted base need to be freshly prepared separately. We later disclosed the simplified catalytic system comprising mesitylcopper/(*R*,*R*)-Ph-BPE (second-generation catalyst), which allowed for a simple operation and comparable catalytic efficiency in the reaction using *N*,*N*-diallylthioacetamide (**4b**) (entries 1,2).[10,11] In our continuing studies of the direct aldol methodology in this line, we observed an unexpectedly drastic decrease in stereoselectivity when the second-generation catalyst was applied to a direct aldol reaction of *N*,*N*-diallylthiopropanamide (**4a**) (Table 1, entry 4). This striking result was likely due to the particularly high catalytic efficiency of the second-generation catalyst specifically for **4a**; the reaction proceeded remarkably faster than when using thioacetamide **4b**, and the initially formed product *syn*-**5** underwent a rapid retro-aldol/aldol reaction to give virtually racemic *syn*-**5** under otherwise identical conditions. The diastereoselectivity was also decreased, and *anti*-**5** was obtained with moderate enantioselectivity.[12] Indeed, when the reaction was run with a reduced catalyst loading (0.5 mol %) and quenched over a shorter period, the retro-aldol reaction was not prominent and *syn*-**5** was obtained with high stereoselectivity (entry 5). The absolute configuration of the *syn*- and *anti*-**5** suggested that both products were produced via the *Z*-enolate of **4a**, and prochiral-face selection of aldehyde **1a** was opposite (Figure 1a).[1c] The retro-aldol reaction of *anti*-**5** was much slower than that of *syn*-**5**, and a higher fraction of *anti*-**5** was produced by extending the reaction time. This finding led us to isolate *anti*-**5** as a thermodynamic product with high enantioselectivity, but none of the attempts succeeded, presumably due to inadequate stereocontrol via a disfavored cyclic transition state for *anti*-**5** (Figure 1a).[13] To develop a complementary *anti*-selective protocol for the

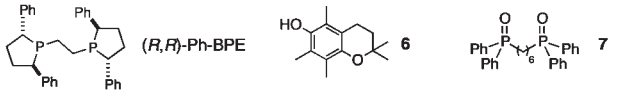
Table 1. Direct Catalytic Asymmetric Aldol Reaction Using the First and Second Generation Catalyst[a]



entry	catalyst	(mol %)	4	solvent	temp (°C)	time (h)	yield[b] (%)	*syn*/*anti*[b]	ee (%)[c]
1	1st gen	3	R¹ = H	DMF	−60	40	91	—	91
2	2nd gen	3	**4b**	DMF	−60	40	81	—	94
									syn/*anti*
3	1st gen	3	R¹ = Me	THF	−70	40	93	>20/1	95/–
4	2nd gen	3		THF	−70	40	99	2.5/1	−4[f]/59
5	2nd gen	0.5	**4a**	THF	−70	14	91	>20/1	95/–

1st generation[d]: $[Cu(CH_3CN)_4]PF_6$, (*R*,*R*)-Ph-BPE, Li salt of **6**

2nd generation[e]: mesitylcopper, (*R*,*R*)-Ph-BPE



[a] **1a**:**4** = 1:1.2. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. [d] 2 mol % of **6** and 1.5 mol % of **7** were used. [e] 1 mol % of **6** was used. [f] The opposite enantiomer was obtained in excess.

(6) For recent reviews on cooperative catalysis, see: Lewis acid/Brønsted base: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (b) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760. Lewis acid/Lewis base: (c) Kanai, M.; Kato, N.; Ichikawa, E.; Shibasaki, M. *Synlett* **2005**, 1491. (d) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. Lewis acid/Brønsted acid and Lewis acid/Lewis acid: (e) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (f) Yamamoto, H.; Futatsugi, K. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, 2008.

(7) (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026. (b) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244. (c) Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron: Asymmetry* **2010**, *21*, 1688. (d) Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554.

(8) For application of thioamides as pronucleophiles under stoichiometric conditions, see: (a) Tamaru, Y.; Harada, T.; Nishi, S.; Mizutani, M.; Hioki, T.; Yoshida, Z. *J. Am. Chem. Soc.* **1980**, *102*, 7806. (b) Tamaru, Y.; Hioki, T.; Yoshida, Z. *Tetrahedron Lett.* **1984**, *25*, 5793. (c) Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *Tetrahedron Lett.* **1983**, *24*, 4001. (d) Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *Tetrahedron Lett.* **1984**, *25*, 537. (e) Goasdoue, C.; Gaudemar, M. *Tetrahedron Lett.* **1985**, *26*, 1015.

(9) Use of thioamide as a pronucleophile in asymmetric aldol reaction under stoichiometric conditions, see: Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197.

(10) Kawato, Y.; Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2011**, *67*, 6539.

(11) For synthesis, characterization, and application of mesitylcopper, see: (a) Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192. (b) Tsuda, T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: New York, 1995; p 3271. (c) Eriksson, H.; Hakansson, M. *Organometallics* **1997**, *16*, 4243.

(12) The absolute configuration of *anti*-**5** was determined after converting to the reported compound. Details are summarized in the Supporting Information.

(13) The possibility of the production of *anti*-**5** through the *E*-enolate of thioamide **4a** cannot be ruled out. Although the formation of the *Z*-enolate is generally favored for thioamides, the production of the *anti*-product was observed at higher temperature and this result was ascribed to the reaction through the *E*-enolate in ref 8a. However, at −70 °C, the formation of the *E*-enolate is unlikely and we assume that *anti*-**5** was obtained through the transition state described in Figure 1.

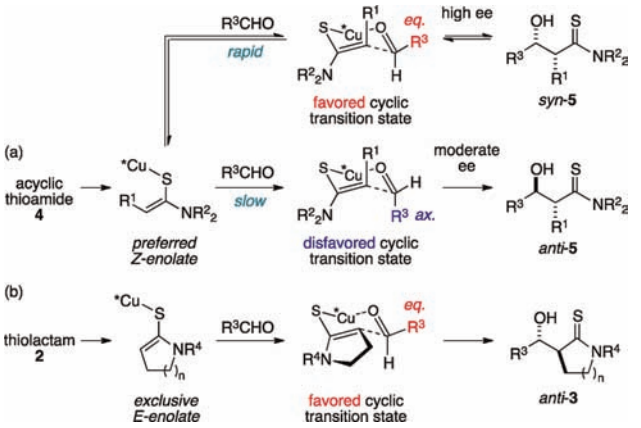
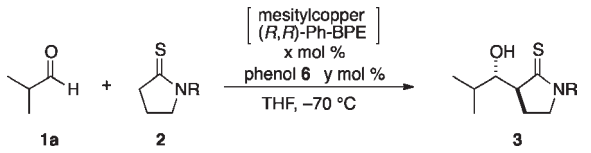


Figure 1. (a) Rapid aldol/retro-aldol reaction of acyclic thioamide **4** and *syn*-**5** through *Z*-enolate. *anti*-**5** was obtained likely through a disfavored cyclic transition state with moderate enantioselectivity. (b) Expected *anti*-aldol product from thiolactam **2** through *E*-enolate.

Table 2. *Anti*-Selective Direct Catalytic Asymmetric Aldol Reaction of Thiolactams[a]

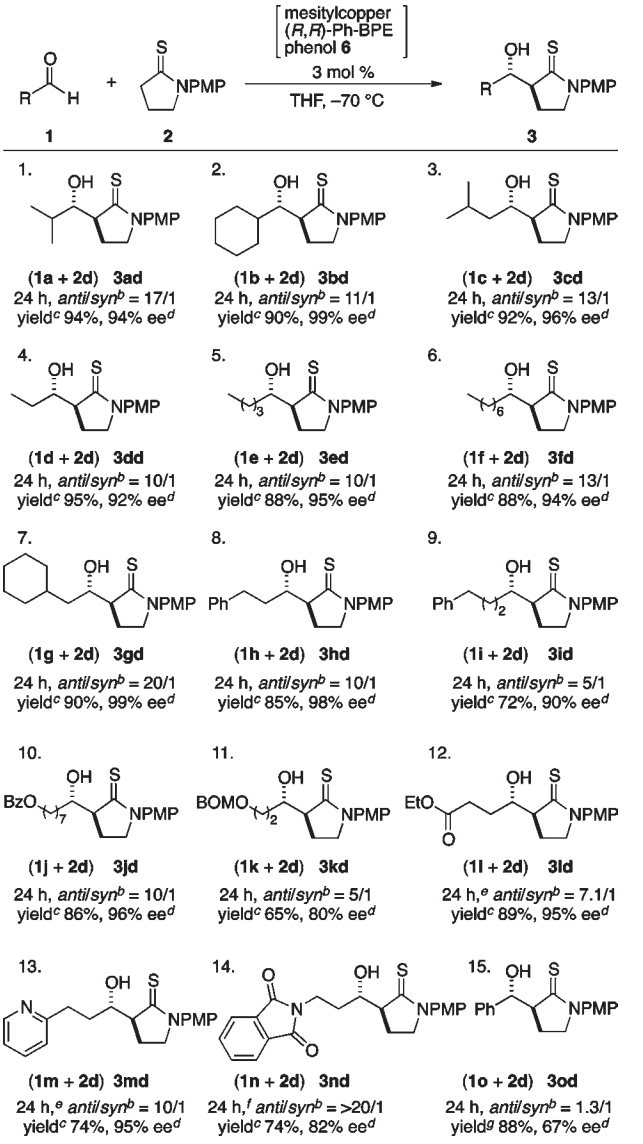


	thiolactam **2**								
entry	R		product	*x*	*y*	time(h)	yield[b](%)	*anti*/*syn*[b]	ee (%)[a]
1	allyl	**2a**	**3aa**	3	3	48	80	>20/1	82
2	Bn	**2b**	**3ab**	3	3	14	88	>20/1	82
3	Ph	**2c**	**3ac**	3	3	24	76	>20/1	95
4	PMP	**2d**	**3ad**	3	3	24	94	>20/1	94
5	PMP	**2d**	**3ad**	3	0	24	71	>20/1	95
6	PMP	**2d**	**3ad**	1	1	48	58	>20/1	95

[a] **1a**: 0.24 mmol. **2**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis. PMP = *p*-methoxyphenyl.

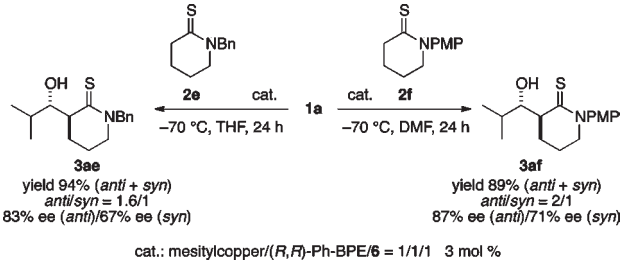
direct aldol reaction of thioamides, we turned our attention toward thiolactam as an aldol donor because; (1) it exclusively generates an *E*-enolate and the *anti*-product can be obtained via a favored cyclic transition state, and (2) various functional group transformations of the aldol product are anticipated (Figure 1b). Initial attempts using isobutyraldehyde (**1a**) and *N*-allylthiobutyrolactam (**2a**) with 3 mol % of the second-generation catalyst and a phenolic additive **6** afforded the desired *anti*-aldol product **3aa** predominantly in 82% ee (Table 2, entry 1). Although the *N*-Bn (**2b**) derivative produced a similar outcome (entry 2), the introduction of an aromatic substituent on the nitrogen led to a remarkable increase in enantioselectivity (entry 3). For the synthetic utility of the aldol product, thiolactam **2d** bearing an *N*-*p*-methoxyphenyl (PMP) group amenable to oxidative removal is more

Scheme 2. Substrate Generality[a]



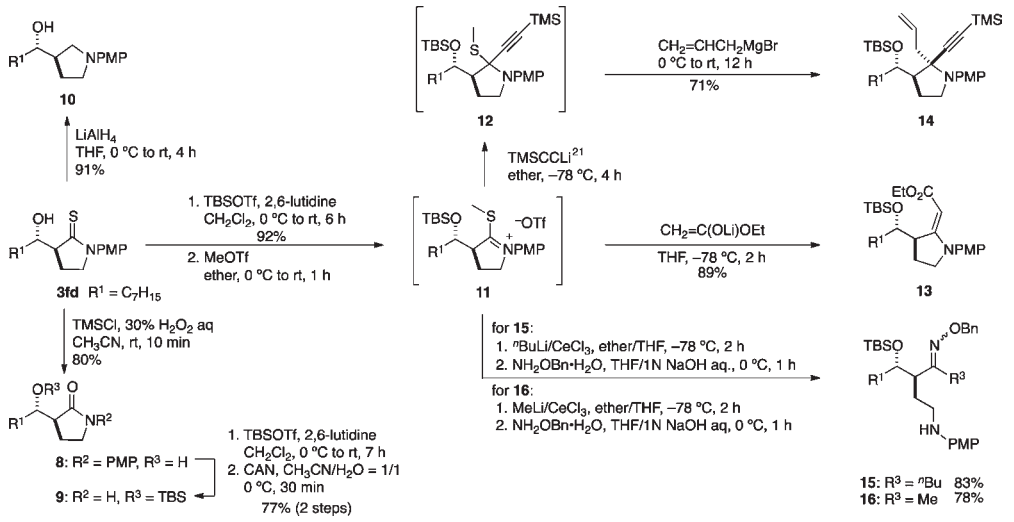
[a] **1a**: 0.24 mmol, **2**: 0.2 mmol. [b] Determined by ^{1}H NMR analysis. [c] Isolated yield of *anti*-diastereomer. [d] Determined by HPLC analysis. [e] 5 mol % of catalyst were used. [f] 10 mol % of catalyst were used. [g] Isolated yield of *anti* and *syn* products.

Scheme 3. Reaction with Six-Membered Thiolactams **2e** and **2f**



favorable, and product **3ad** was obtained in high stereoselectivity (entry 4).[14] Phenol **6** is particularly beneficial for

Scheme 4. Transformation of the Aldol Product



enhancing the catalytic efficiency, likely due to acceleration of the proton-transfer process (entry 4 vs 5).[15,16] High stereoselectivity was maintained with a 1 mol % catalyst loading, albeit with only a moderate yield (entry 6).

The present *anti*-selective direct aldol reaction is applicable to a wide range of aldehydes (Scheme 2). In addition to α-branched aldehydes (entries 1,2), the reaction with α-nonbranched aldehydes proceeded exclusively from the *E*-enolate derived from thiolactam **2d** to afford the desired *anti*-aldol products with high stereoselectivity (entries 3−9). A 1-g scale reaction using octanal (**1f**) and **2d** was performed with no detrimental effects. Ester, ether, pyridine, and imide functionalities were tolerated (entries 10−14), whereas BOM-protected aldehyde **1k** gave **3kd** in moderate yield and lower stereoselectivity (entry 11). Although the Lewis basic pyridyl group in aldehyde **1m** may coordinate to Cu^+, resulting in deteriorated catalytic efficiency, product **3md** was obtained with 5 mol % of the catalyst in reasonable yield with high enantioselectivity (entry 13). A much lower stereoselectivity was observed with aromatic aldehydes. The reaction with benzaldehyde (**1o**) exhibited a marginal *anti* preference with moderate enantioselectivity (entry 15). The retro-aldol pathway was not prominent,[17] and this lower stereoselectivity likely resulted from a less compatible transition state for aromatic aldehydes. The reaction with six-membered thiolactams **2e** and **2f** produced the aldol products with only a slight preference for *anti* diastereoselectivity, and the *N*-aryl substituent had no obvious beneficial effect on enantioselectivity (Scheme 3).[18]

Thiolactam in the aldol product can be transformed into various synthetically useful functionalities as shown in Scheme 4.[19,20]

In summary, we developed an *anti*-selective direct catalytic asymmetric aldol reaction of thiolactams. *N*-(*p*-Methoxyphenyl)thiobutyrolactam **2d** was a particularly suitable substrate to afford *anti*-aldol products with high enantioselectivity. The aldol product was transformed into various enantiomerically enriched pyrrolidino compounds and acyclic amino alcohols. Application of the present *anti*-aldol protocol to the enantioselective synthesis of biologically significant compounds is ongoing.

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Supporting Information Available. Characterization of new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) The absolute and relative configuration of **3ad** was confirmed by X-ray crystallographic analysis. See Supporting Information for details.

(15) 2,2,5,7,8-Pentamethylchromanol (**6**) is particularly effective in the direct aldol reaction. The reaction using *p*-methoxyphenol under otherwise identical conditions affords the inferior result: 70% yield of **3ad**, *anti*/*syn* = 20/1, 94% ee (*anti*).

(16) All the components of the catalyst are commercially available and used as received.

(17) The constant enantioselectivity was observed from the reaction samples quenched at different reaction times (4−24 h). In contrast, the aldol reaction of benzaldehyde (**1o**) and thioacetamide **4b** with the first-generation catalyst gave a different enantioselectivity and a retro-aldol reaction was highly anticipated (ref 7c).

(18) The use of DMF instead of THF as solvent gave better stereoselectivity in the reaction with thiolactam **2f** (THF: 70% yield of **3af**, *anti*/*syn* = 1.3/1, 81% ee (*anti*), 65% ee (*syn*)).

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(20) The details of transformation are described in Supporting Information.

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The authors declare no competing financial interest.