Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Catalytic Asymmetric Conjugate Addition of Saturated and Unsaturated Thioamides

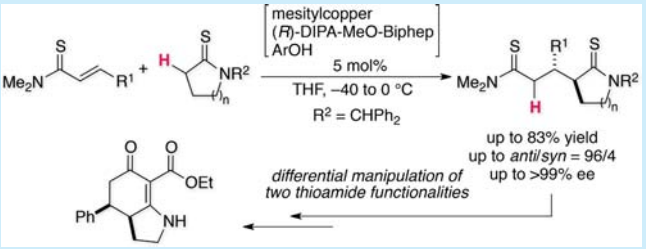
Nilanjana Majumdar,[†] Akira Saito,[†] Liang Yin,[†] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†,‡]

[†]Institute of Microbial Chemistry (BIKAKEN), Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

[‡]JST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

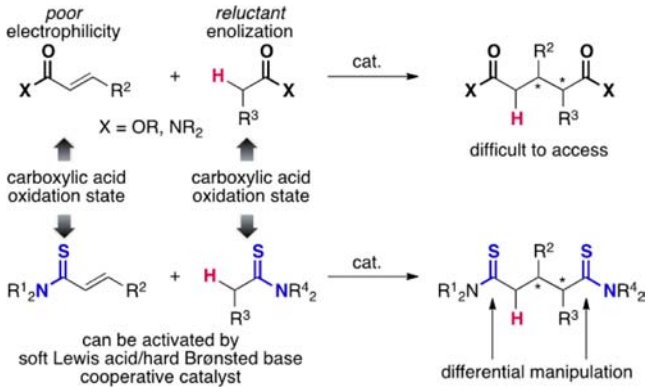
Supporting Information

ABSTRACT: Direct catalytic asymmetric conjugate addition of thiolactams to α,β-unsaturated thioamides was efficiently promoted by a soft Lewis acid/hard Brønsted base cooperative catalyst in a highly stereocontrolled manner. Thioamide functionality was crucial to promote both the efficient enolization of thiolactam pronucleophiles and the subsequent stereoselective conjugate addition to α,β-unsaturated thioamides. Differential manipulation of the two thioamide functionalities of the product highlights the synthetic utility of the present catalytic system.



Conjugate addition is a fundamental and reliable bond-forming process, and its enantioselective version has gained popularity in the field of asymmetric catalysis.[1] The substrate combination of a carbon-based pronucleophile and an electron-deficient olefin has been extensively studied to develop a number of enantioselective C−C bond-forming reactions. Among them, active methylene compounds bearing fairly acidic protons, e.g., malonates, β-ketoesters, and α-cyanoesters, etc., have frequently been employed as pronucleophiles because of their inherently facile enolization. Aldehydes and ketones constitute a growing class of potential nucleophiles in the flourishing field of organocatalysis.[2] In contrast, carbonyl compounds in the carboxylic acid oxidation state have been far less explored as pronucleophiles,[3] likely because they are less prone to enolization and the activation mode through an enamine is not applicable. Although the use of preformed enolate species as active nucleophiles is a viable option to afford the desired product, direct use of a pronucleophile is advantageous in terms of atom economy and synthetic efficiency.[4] For electrophiles, the reactivity is generally proportional to the electron-withdrawing ability of the substituents attached to olefins. Similarly, enals, enones, and nitroolefins exhibit sufficient electrophilicity in conjugate additions, whereas olefins conjugated with carboxylic acid derivatives are poor electrophiles and have been largely neglected as electrophilic partners.[5,6] In this context, the intermolecular conjugate addition of pronucleophiles and electrophiles that are both in the less reactive carboxylic acid oxidation state is clearly an undesirable substrate combination, and a catalytic enantioselective version of the reaction has remained virtually unexplored despite the synthetic utility of the corresponding conjugate adducts (Scheme 1). Quite recently, Kobayashi et al. reported an efficient catalytic system comprising KHMDS and chiral macro crown ether for highly diastereo- and enantioselective conjugate addition of simple amides.[7] In our

Scheme 1. Direct Catalytic Asymmetric Conjugate Addition of Carboxylic Acid Derivatives



previous studies on the potential utility of thioamides as pronucleophiles for catalytic asymmetric conjugate addition,[8−10] *intermolecular* reactions barely proceeded under typical enolization conditions for thioamides, and only *intramolecular* variants of the reaction with limited substrate scope were reported.[11] Herein, we report a direct catalytic asymmetric *intermolecular* conjugate addition of thiolactams to α,β-unsaturated thioamides as a demonstration of conjugate addition of substrates that are both in a carboxylic acid oxidation state. Differential manipulation of two thioamide functionalities embedded in the conjugate adduct validates the synthetic utility of the present catalysis.

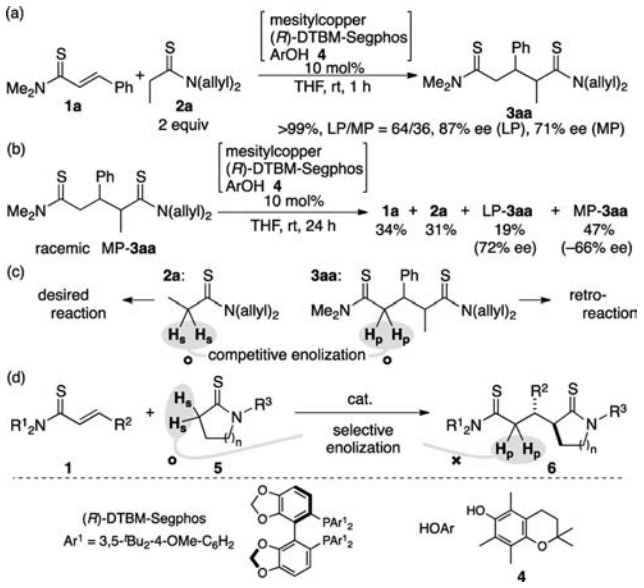
Although a soft Lewis acid/hard Brønsted base cooperative catalytic system comprising $[Cu(CH_3CN)_4]PF_6$, a bisphosphine

Received: June 5, 2015
Published: June 22, 2015

DOI: 10.1021/acs.orglett.5b01644
Org. Lett. 2015, 17, 3362−3365

ligand, and a Li phenoxide has proven to be effective for catalytic generation of a thioamide enolate,[12] no trace of intermolecular conjugate addition to electron-deficient olefins (e.g., enones, unsaturated esters, nitroolefins) was observed. We reasoned that simultaneous activation of the electrophilic reaction partner could enable intermolecular conjugate addition to take place in the asymmetric environment of the Cu catalyst. α,β-Unsaturated thioamides emerged as viable electrophiles that could be used to meet this demand; this class of compound is soft Lewis basic and can be electrophilically activated by a soft Lewis acid together with a saturated thioamide as a pronucleophile. We began our study with α,β-unsaturated thioamide **1a** and saturated thiopropionamide **2a** as an electrophile and a pronucleophile, respectively. The cooperative catalytic system comprising mesitylcopper,[13] (*R*)-DTBM-Segphos, and 2,2,5,7,8-pentamethyl-6-chromanol (HOAr **4**), in which the chirally decorated CuOAr was expected to function as a catalyst, promoted the desired reaction to afford the diastereomixture of **3aa** with promising enantioselectivity (Scheme 2a).[14] Although this result

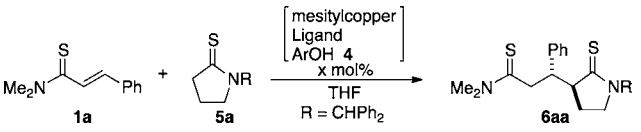
Scheme 2. Initial Observations



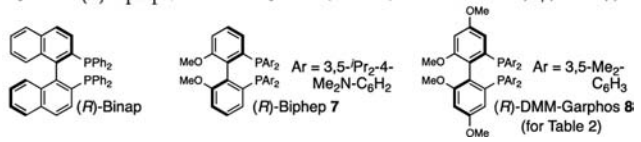
demonstrated that the simultaneous activation strategy was effective for intermolecular conjugate addition of substrates in the carboxylic acid oxidation state, **3aa** readily underwent retro-reaction under the catalytic conditions. Indeed, resubjecting racemic MP-**3aa** to the catalytic conditions gave a mixture of substrates **1a** and **2a** and nonracemic mixtures of **3aa** (Scheme 2b).[15] Due to the rapid retro-reaction, obtaining the product with high diastereo- and enantioselectivity turned out to be elusive despite extensive efforts. The retro-reaction was likely triggered by enolization at the α-nonbranched thioamide moiety of the product (deprotonation of H_p), which appeared to be difficult to suppress under the catalytic conditions used to generate the thioamide enolate of **2a** (deprotonation of H_s) (Scheme 2c). Hence, we directed our focus on the use of thiolactam **5** as a pronucleophile (Scheme 2d). With this substrate combination, the identification of reaction conditions that allowed for preferential enolization of **5** in the presence of the acyclic α-nonbranched thioamide fragment of product **6** (preferential deprotonation of H_s over H_p) was crucial to obtaining the conjugate adduct in a kinetically controlled manner.

For facile deprotection, *N*-benzhydrylpyrrolidine-2-thione (**5a**) was selected as a thiolactam pronucleophile, and direct catalytic conjugate addition was attempted with α,β-unsaturated thioamide **1a** under conditions identical to those used with thiopropionamide **2a** (Table 1). Thiolactam **5a** exhibited much

Table 1. Optimization of Reaction Conditions Using Thiolactam 5a as a Pronucleophile[a]



entry	ligand	x	temp (°C)	time (h)	yield[b] (%)	*anti*/*syn*[c]	ee[d] (%)
1	(*R*)-DTBM-Segphos	10	rt	<0.2	99	62/38	>99
2	(*R*)-DTBM-Segphos	10	−40	6	83	86/14	99
3	(*R*)-Binap	10	−40	6	71	69/31	99
4	(*R*)-Biphep **7**	10	−40	6	85	97/3	>99
5	(*R*)-Biphep **7**	5	−40	24	80	91/9	>99



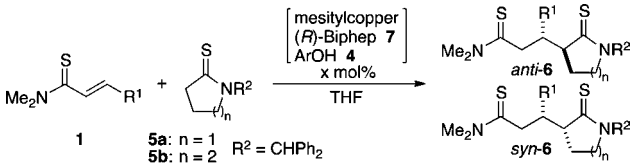
[a]**1a**: 0.1 mmol, **5a**: 0.2 mmol. [b]Determined by ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as internal standard. [c]Determined by ^{1}H NMR analysis of the crude product. [d]ee of the *anti*-adduct.

higher reactivity, and the reaction reached completion in approximately 10 min, affording the *anti*-adduct **6aa** preferentially with >99% ee, albeit with low diastereoselectivity (entry 1). The diasteremeric ratio was improved by lowering the reaction temperature to −40 °C without significant loss in reactivity (entry 2). Whereas the use of a less sterically demanding ligand such as (*R*)-Binap gave **6aa** with lower diastereoselectivity, (*R*)-Biphep **7**, bearing highly substituted aromatic groups, was identified as a optimal ligand to afford the desired product in high diastereo- and enantioselectivity (entries 3 and 4). Catalyst loading could be reduced to 5 mol% with marginal loss in diastereoselectivity (entry 5).

The substrate scope of the direct catalytic conjugate addition of thiolactams **5** to α,β-unsaturated thioamides **1** is summarized in Table 2. The reaction could be scaled up to 1.0 g of **1a** without any detrimental effect on stereoselectivity (entry 1). The reaction of **1**, bearing alkyl and alkoxy substituents at the *o*-, *m*-, and *p*-positions on the aromatic β-substituent, gave the desired product in high yield and stereoselectivity (entries 2−5). Ester functionality was tolerated under the mild basic conditions of the present catalytic system (entry 6). *p*-Cl-substituted substrate was less reactive in the present catalytic system, and product **6ga** was obtained after 6 h of stirring at −30 °C with moderate diastereoselectivity (entry 7). Unsaturated thioamides having heteroaromatic rings that could potentially coordinate to the Cu(I) catalyst were compatible, albeit with marginal loss in diastereoselectivity (entries 8 and 9). β-Methyl-substituted unsaturated thioamide exhibited much lower reactivity, and a higher reaction temperature (−20 °C) was required for the reaction to proceed, affording **6ja** with lower diastereo- and enantioselectivity (entry 10). Notably, only 1,4-conjugate addition proceeded with the $\alpha,\beta,\gamma,\delta$-unsaturated thioamide **1k** to afford the desired product **6ka** having a pendant 1-propenyl group on a 1,5-dithiocarbonyl framework (entry 11). Unexpectedly, the reaction using six-membered thiolactam **5b** gave *syn*-**6ab** predominantly with various biaryl-type chiral bi-

DOI: 10.1021/acs.orglett.5b01644
Org. Lett. 2015, 17, 3362−3365

Table 2. Direct Catalytic Asymmetric Conjugate Addition of Thiolactam 5 to α,β-Unsaturated Thioamide 1[a]



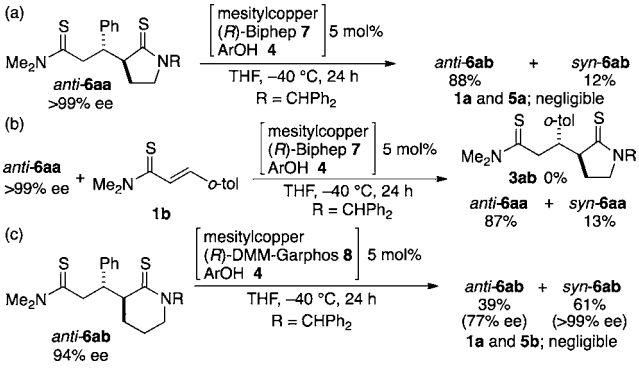
entry	1 R¹ =		5 n =		x	temp (°C)	time (h)	product	yield[b] (%)	anti/syn[c]	ee[d] (%)
1[e]	Ph	1a	1	5a	5	−40	24	6aa	83	92/8	>99
2	2-MeC$_6$H$_4$	1b	1	5a	5	−40	24	6ba	83	96/4	>99
3	4-MeC$_6$H$_4$	1c	1	5a	5	−40	20	6ca	71	92/8	>99
4	4-MeOC$_6$H$_4$	1d	1	5a	5	−40	24	6da	76	89/11	99
5	3-MeOC$_6$H$_4$	1e	1	5a	5	−40	24	6ea	82	92/8	>99
6	4-PivOC$_6$H$_4$	1f	1	5a	5	−20	2	6fa	78	84/16	>99
7	4-ClC$_6$H$_4$	1g	1	5a	5	−30	6	6ga	72	86/14	99
8	2-thienyl	1h	1	5a	5	−30	10	6ha	71	85/15	99
9	3-pyridyl	1i	1	5a	5	−30	6	6ia	60	84/16	>99
10	Me	1j	1	5a	15	−20	36	6ja	49	60/40	84
11	1-propenyl	1k	1	5a	10	−40	24	6ka	72	93/7	99
12[f]	Ph	1a	2	5b	5	−40	8	6ab	95	6/94	82

[a] **1**: 0.1 mmol, **5**: 0.2 mmol. [b] Isolated yields. [c] Determined by ^{1}H NMR analysis. [d] ee of major diastereomers. [e] 1.0 g of **1a** was used. [f] (*R*)-DMM-Garphos **8** (structure is shown in Table 1) was used instead of (*R*)-Biphep **7**.

sphosphine ligands including **7**. Among the ligands tested, (*R*)-DMM-Garphos **8** was optimal to produce *syn*-**6ab** with 82% ee (entry 12).[16]

The reactions summarized in Table 2 generally produced the corresponding products with high enantioselectivity, with the exception of α,β-unsaturated thioamide bearing an alkyl substituent at the β-position (entry 10). Some reactions displayed time-dependent erosion of diastereoselectivity, and this observation prompted us to examine the stability of the product under the catalytic conditions. When *anti*-**6aa** was subjected to the optimal catalytic conditions at −40 °C for 24 h, the *syn*-diastereomer was observed (Scheme 3a). Together with

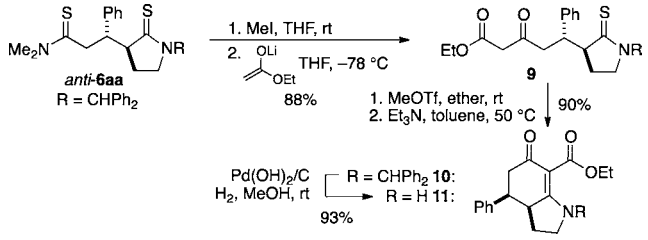
Scheme 3. Stability of the Product under the Catalytic Conditions



the observation that no crossover product was detected when the *anti*-**6aa** was resubjected to the catalytic conditions in the presence of α,β-unsaturated thioamide **1b** (Scheme 3b), epimerization would be a major pathway to produce the more thermodynamically stable *syn*-**6aa** in Scheme 3a.[17] Prolonged reaction times with 5-membered lactam **5a** tended to give lower diastereomeric ratios (higher mole fraction of *syn*-isomer), and undesired epimerization was partly associated even under the optimized conditions. Enolates of 5- and 6-membered lactam **5a** and **5b** likely reacted with **1a** via a similar transition state to give the *anti*-adducts predominantly, and unexpected reversal in diastereoselectivity for 6-membered lactam **5b** (Table 2, entry 12) could be explained by more prominent epimerization from *anti* to *syn* isomer. Indeed, the isolated minor diastereomer *anti*-**6ab** (94% ee) was resubjected to the catalytic conditions, and 61% of *syn*-**6ab** was obtained with >99% ee after 24 h (Scheme 3c).[18]

Differentiation of the two thioamide functionalities of the conjugate adduct is of prime importance for the synthetic utility of the methodology (Scheme 4). The α-nonsubstituted *N,N*-

Scheme 4. Transformation of the Product



dimethylthioamide moiety was more reactive toward alkylating agents, e.g., MeI, to give an iminium thioether intermediate with the thiolactam moiety intact, which was sufficiently reactive with Li-enolate prepared from ethyl acetate to give β-ketoester **9**. The electrophilic activation of the thiolactam could be attained by using the stronger alkylating agent MeOTf.[19] Cyclization proceeded upon heating to 50 °C in the presence of Et_3N to furnish bicyclic compound **10** having an azabicyclo[4.3.0] skeleton. A benzhydryl group on the nitrogen was readily removed by hydrogenolysis.

In conclusion, we have developed a direct catalytic asymmetric conjugate addition of thiolactams to α,β-unsaturated thiolamides. Simultaneous activation of both the pronucleophile and the electrophile was key to promoting the stereoselective C−C bond formation of substrates that had inherently low reactivity. Differential transformation of the two thioamide functionalities of the product allows for flexible elaboration of the optically active product and highlights the synthetic utility of the catalytic system.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01644.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: nkumagai@bikaken.or.jp.
*E-mail: mshibasa@bikaken.or.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported financially by JST, ACT-C, and JSPS KAKENHI Grant No. 25713002. N.M. and L.Y. thank JSPS for postdoctoral fellowships. Dr. Tomoyuki Kimura is gratefully acknowledged for technical assistance with the X-ray crystallographic analysis of *syn*-**6ab** and **10**.

DOI: 10.1021/acs.orglett.5b01644
Org. Lett. 2015, 17, 3362−3365

REFERENCES

(1) (a) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279. (c) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (d) Vicario, J. L.; Badia, D.; Carrillo, L. *Synthesis* **2007**, 2065. (e) Sulzer-Moseé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (f) Alexakis, A.; Bäckvall, J.-E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (g) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (h) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (i) Jautze, S.; Peters, R. *Synthesis* **2010**, 365.

(2) For selected recent reviews on organocatalysis, see: (a) Berkessel, A., Gröger, H., Eds. *Asymmetric Organocatalysis*; Wiley: Weinheim, 2006. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (c) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (e) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (f) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (g) Terada, M. *Curr. Org. Chem.* **2011**, *15*, 2227.

(3) For selected examples of catalytic enolization of pronucleophiles (or generation of carbanions) in the carboxylic acid oxidation state without any activating group at α-position, see: (a) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090. (b) Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, 745. (c) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706. (d) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632. (e) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (f) Saito, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 8704. (g) Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804. (h) Goto, A.; Endo, K.; Ukai, Y.; Irle, K.; Saito, S. *Chem. Commun.* **2008**, 2212. (i) Kobayashi, S.; Kiyohara, H.; Yamaguchi, M. *J. Am. Chem. Soc.* **2011**, *133*, 708. (j) Yamashita, Y.; Suzuki, H.; Kobayashi, S. *Org. Biomol. Chem.* **2012**, *10*, 5750. (k) Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7523. (l) Sureshkumar, D.; Venkataraman, G.; Kumagai, N.; Shibasaki, M. *Chem.—Eur. J.* **2014**, *20*, 15723.

(4) Trost, B. M. *Science* **1991**, *254*, 1471.

(5) For the use of doubly activated olefins with two carbonyl (carboxylic acid derivatives) groups in direct catalytic asymmetric C−C bond-forming conjugate additions, e.g., the use of alkylidene malonates and acyloxazolidinones, see ref 1f,i and references cited therein.

(6) For the intermolecular direct catalytic asymmetric conjugate addition of carbon-based pronucleophile to α,β-unsaturated thioamides (carboxylic acid derivatives), see: (a) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. (b) Yanagida, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7910. (c) Ogawa, T.; Mouri, S.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2012**, *14*, 110. (d) Yin, L.; Takada, H.; Lin, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5327.

(7) Suzuki, H.; Sato, I.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2015**, *137*, 4336.

(8) For the use of thioamide as a pronucleophile in C−C bond-forming reactions 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) Goasdoue, C.; Goasdoue, N.; Gaudemar, M.; Mladenova, M. *J. Organomet. Chem.* **1981**, *208*, 279. (c) Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *Tetrahedron Lett.* **1983**, *24*, 4001. (d) Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1984**, *263*, 273.

(9) For a pioneering work on the use of thioamide as a pronucleophile in asymmetric reactions under stoichiometric conditions, see: Iwasawa, N.; Yura, T.; Mukaiyama, T. *Tetrahedron* **1989**, *45*, 1197.

(10) For the use of thioamide as a pronucleophile in direct catalytic C−C bond-forming reactions, see: (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.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554. (d) Sureshkumar, D.; Kawato, Y.; Iwata, M.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2012**, *14*, 3108.

(11) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Chem.—Eur. J.* **2011**, *17*, 11998.

(12) For recent reviews on cooperative catalysis, see the following. 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.

(13) For pioneering work on mesitylcopper, see: Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192. For a comprehensive review on mesitylcopper, see: Stollenz, M.; Meyer, F. *Organometallics* **2012**, *31*, 7708.

(14) LP and MP represent less polar and more polar diastereomers on thin-layer chromatography with normal-phase silica gel.

(15) **1a** was recovered as a mixture of *E*/*Z* isomers. −66% ee of MP-**3aa** indicated that major enantiomer of MP-**3aa** obtained in Scheme 2a was more prone to retro-reaction.

(16) The absolute configuration of *anti*-**6aa** was determined after conversion to bicyclic compound **10** by X-ray crystallography. The configuration of *syn*-**6ab** was determined by X-ray crystallography.

(17) Treatment of *anti*-**6aa** with a simple base, e.g., NaO^{t}Bu (20 mol%, THF, rt, 2 h) gave a mixture of *anti*- and *syn*-**6aa** in a ratio 40/60.

(18) The higher mole fraction and lower ee of *syn*-**6ab** of entry 12 in Table 2 suggested that the epimerization was not an exclusive pathway to *syn*-**6ab** and diastereoselection of the conjugate addition of **5b** would be moderate.

(19) Mutoh, Y.; Murai, T. *Org. Lett.* **2003**, *5*, 1361.

DOI: 10.1021/acs.orglett.5b01644
Org. Lett. 2015, 17, 3362−3365