ORGANIC LETTERS

2012
Vol. 14, No. 1
110–113

Intermediate as Catalyst: Catalytic Asymmetric Conjugate Addition of Nitroalkanes to α,β-Unsaturated Thioamides

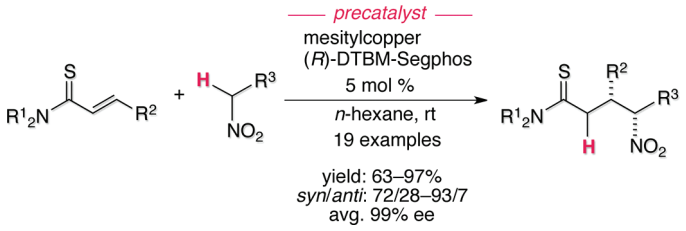
Takanori Ogawa,[†] Shinsuke Mouri,[†] Ryo Yazaki,[†,‡] Naoya Kumagai,*[,†] and Masakatsu Shibasaki*[,†]

Institute of Microbial Chemistry, Tokyo, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan, and Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

nkumagai@bikaken.or.jp; mshibasa@bikaken.or.jp

Received October 27, 2011

ABSTRACT



Catalytic asymmetric conjugate addition of nitroalkanes to α,β-unsaturated thioamides is promoted by a mesitylcopper/(*R*)-DTBM-Segphos precatalyst, affording γ-nitrothioamides in moderate to high *syn*-selectivity and excellent enantioselectivity. The intermediate Cu-thioamide enolate functions as a soft Lewis acid/hard Brønsted base cooperative catalyst to drive the catalytic cycle efficiently under proton transfer conditions.

Catalytic enantioselective conjugate addition of carbon nucleophiles offers a robust methodology for the production of optically active building blocks via C−C bond formation.[1] Nitroalkanes are widely used pronucleophiles in organic synthesis due to the facile formation of active nitronates and the masked amine nature of nitro functionality.[2] Although nitroalkanes **1** have been successfully applied in catalytic asymmetric 1,2-addition reactions,[3] their use in catalytic asymmetric conjugate addition is relatively less explored.[4] Both metallic catalysts and organocatalysts allow for enantioselective conjugate addition of nitroalkanes **1** to α,β-unsaturated ketones,[5]

[†] Institute of Microbial Chemistry.
[‡] The University of Tokyo.

(1) For general reviews of catalytic asymmetric conjugate addition, see: (a) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Hiedelberg, Germany, 2003; Suppl. 1, pp 151. (c) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (e) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(2) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

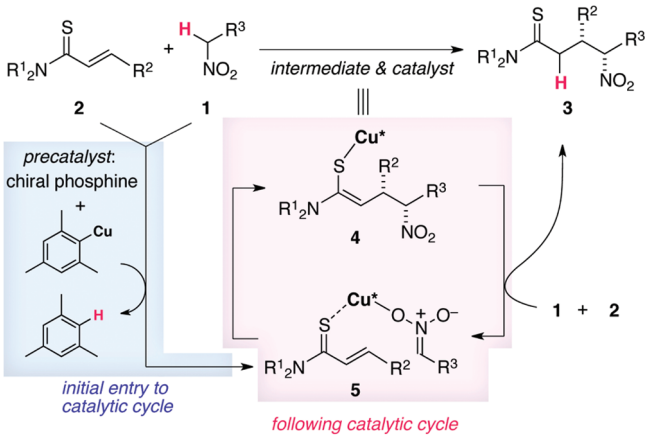
(3) For general review of catalytic asymmetric nitroaldol and nitro-Mannich reactions, see: (a) Boruwa, J.; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (b) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561. (c) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151. (d) Marqués-López, E.; Merino, P.; Tejero, T.; Herrera, R. P. *Eur. J. Org. Chem.* **2009**, 2401.

(4) For a review, see: Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(5) Recent selected examples: (a) Yamaguchi, M.; Shiraishi, T.; Igarashi, Y.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 8233. (b) Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557. (c) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257. (d) Hanessian, S.; Pharm, V. *Org. Lett.* **2000**, *2*, 2975. (e) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (f) Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4014. (g) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (h) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346. (i) Preito, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897. (j) Choudary, B. M.; Ranganath, K. V. S.; Pal, U.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2005**, *127*, 13167. (k) Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313. (l) Palomo, C.; Pazos, R.; Oiarbide, M.; García, J. M. *Adv. Synth. Catal.* **2006**, *348*, 1161. (m) Dijk, E. W.; Boersma, A. J.; Feringa, B. L.; Roelfes, G. *Org. Biomol. Chem.* **2010**, *8*, 3868. (n) Manzano, R.; Andrés, J. M.; Álvarez, R.; Muruzábal, M. D.; de Lera, Á. R.; Pedrosa, R. *Chem.—Eur. J.* **2011**, *17*, 5931. (o) Maltsev, O. V.; Chizhov, A. O.; Zlotin, S. G. *Chem.—Eur. J.* **2011**, *17*, 6109.

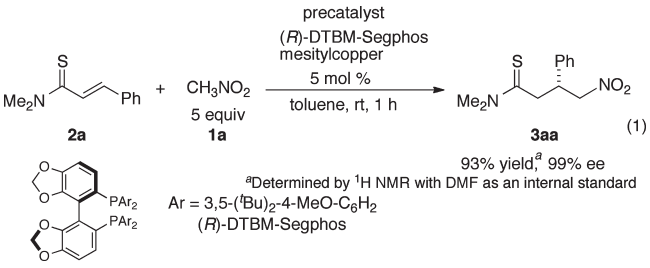
10.1021/ol202898e
Published on Web 11/23/2011

Scheme 1. Catalyst Design and Application to the Reaction of Nitroalkanes and α,β-Unsaturated Thioamides



aldehydes,[6] and nitroalkenes.[7] The analogous catalytic asymmetric addition to α,β-unsaturated carboxylic acid derivatives, however, is limited due to their low electrophilicity, and to date, only one successful example using α,β-unsaturated acylpyrazoles and nitromethane (**1a**) under Ni complex/2,2,6,6-tetramethylpiperidine catalyst has been reported.[8] Our recent research focused on the use of α,β-unsaturated thioamide **2** as a viable electrophile in the carboxylic acid oxidation state that is chemoselectively activated by a soft Lewis acid catalyst to overcome the intrinsic low reactivity.[9] In this context, we envisioned to develop a catalytic asymmetric conjugate addition of nitroalkanes **1** to α,β-unsaturated thioamides **2**, promoted by a soft Lewis acid/hard Brønsted base cooperative catalyst.[10] Divergent transformation of the thioamide functionality of the product **3** highlights the synthetic utility of the present protocol.

The soft Lewis acid/hard Brønsted base cooperative catalyst offers a particularly effective strategy for stereoselective C−C bond formation of soft Lewis basic substrates under proton transfer conditions.[11] A major drawback to this strategy, however, is the tedious catalyst preparation. A prototype catalyst required separate preparation of chiral bisphosphine ligand/$[Cu(CH_3CN)_4]PF_6$ (soft Lewis acid) and LiOAr (hard Brønsted base) just before use. Mechanistic studies revealed that {phosphine/Cu-OAr and $LiPF_6$}, generated in equilibrium with {phosphine/$CuPF_6$ and LiOAr}, also acts as a soft Lewis acid and a hard Brønsted base cooperative catalyst.[12] On the basis that a phosphine/Cu-base fragment can deprotonate the pronucleophile, which is an initial step to trigger proton transfer C−C bond formation, we focused on the use of the reaction intermediate as a catalyst to simplify the catalytic system (Scheme 1). In the reaction using nitroalkane **1** and thioamide **2**, the intermediate is a chiral phosphine/Cu-thioamide enolate **4**, in which the Cu and thioamide enolate would function as a soft Lewis acid and a hard Brønsted base, respectively. Nitroalkane **1** and the precatalyst comprising a chiral phosphine ligand/mesitylcopper[13] generated Cu-nitronate via irreversible deprotonation with concomitant generation of mesitylene, and the subsequent coordination of thioamide **2** delivered complex **5**. This is an entry point to the following catalytic cycle, in which enantioselective C−C bond formation through **5** generates the intermediate **4** that promotes proton exchange with nitroalkane **1** to regenerate **5**. By this catalytic cycle, the entry to **4**



initiates an efficient proton transfer C−C bond-forming catalysis, and this methodology would be applicable to other carbon pronucleophiles bearing an acidic proton. An (*R*)-DTBM-Segphos/mesitylcopper precatalyst quickly emerged as a suitable precatalyst for the reaction of nitromethane (**1a**) and *N*,*N*-dimethylthiocinnamide (**2a**), affording γ-nitrothioamide **3aa** in 93% yield and 99% ee after 1 h of stirring at room temperature in toluene (eq 1). Initially, mesitylcopper deprotonated **1a** with a concomitant

(6) Recent selected examples: (a) Hojabri, L.; Hartikka, A.; Moghaddam, F. M.; Arvidson, P. I. *Adv. Synth. Catal.* **2007**, *349*, 740. (b) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660. (c) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (d) Enders, D.; Wang, C.; Bats, J. W. *Synlett* **2009**, 1777. (e) Gotoh, H.; Okamura, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 4056. (f) Zhong, C.; Chen, Y.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279. (g) Anwar, S.; Chang, H.-J.; Chen, K. *Org. Lett.* **2011**, *13*, 2200. Examples using preformed silyl nitronate as active nucleophile: (h) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 9022.

(7) Rabalakos, C.; Wulff, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 13524.

(8) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.

(9) (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.

(10) Recent reviews on cooperative catalysis: (a) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (c) Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393. (d) Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res.* **2008**, *41*, 655. (e) Lee, J.-K.; Kung, M. C.; Kung, H. H. *Top. Catal.* **2008**, *49*, 136. (f) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222. (g) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760.

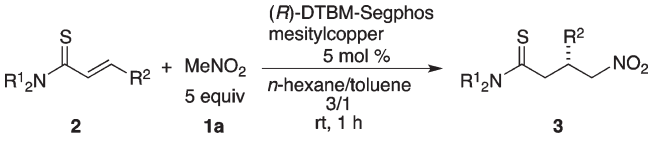
(11) (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 5522. (c) Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554.

(12) Yazaki, R.; Kumagai, N.; Shibasaki, M. *Chem.—Asian J.* **2011**, *6*, 1778.

(13) Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192.

(14) Experiments were conducted with mesitylcopper prepared from the reported procedure (ref 13). Mesitylcopper is commercially available from Strem Chemicals Inc., and purchased mesitylcopper exhibited comparable catalytic performance in the present reaction: the reaction of **1b** and **2a** (Table 2, entry 1) under otherwise identical conditions, **3ba** was obtained in 89% yield *syn*/*anti* = 80/20, 99% ee (*syn*).

Table 1. Catalytic Asymmetric Conjugate Addition of Nitromethane (**1a**) to α,β-Unsaturated Thioamides **2**[a]



	thioamide **2**					
entry	R^1	R^2		product	yield[b] (%)	ee (%)
1	Me	Ph	**2a**	**3aa**	95	99
2	Me	4-MeC_6H_4	**2b**	**3ab**	93	99
3	Me	4-ClC_6H_4	**2c**	**3ac**	92	99
4	Me	4-$MeOC_6H_4$	**2d**	**3ad**	82	99
5	Me	Me	**2e**	**3ae**	75	98
6	Bn	Ph	**2f**	**3af**	97	99

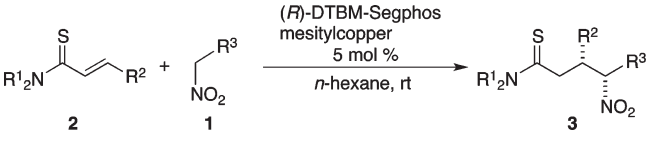
[a] **1a**: 2.0 mmol, **2**: 0.4 mmol. [b] Isolated yield.

liberation of mesitylene, and subsequent enantioselective addition to **2a** activated by the (*R*)-DTBM-Segphos/Cu complex through a soft−soft interaction gave **4**, which drove the following catalytic cycle. Both mesitylcopper and (*R*)-DTBM-Segphos are commercially available.[14] The scope of the catalytic asymmetric addition of nitromethane (**1a**) to α,β-unsaturated thioamides **2** is summarized in Table 1. A *n*-hexane/toluene binary solvent system proved best to produce maximum catalyst efficiency, completing the reaction in 1 h with 5 mol % of catalyst loading, and affording **3aa** in 95% yield and 99% ee (entry 1). The electronic nature of the β-substituent of thioamides had only a marginal impact on reactivity, and excellent enantioselectivity was observed (entries 2−4). Thioamide bearing a β-methyl substituent was also applicable, exhibiting high enantioselectivity (entry 5). The catalytic efficiency was not relevant to the substituent on the nitrogen, and *N*,*N*-dibenzylthioamide **2f** served as a suitable substrate to give the corresponding product **3af** with high enantioselectivity (entry 6), and the thioamide functionality can be regarded as a masked primary amine and is of synthetic value.

Our next focus was diastereoselectivity (Table 2), which remained a formidable challenge in this important transformation.[15] In the reaction using nitroethane (**1b**) and thioamide **2a**, the use of *n*-hexane as a solvent enhanced the catalytic efficiency, and high yield and enantioselectivity were observed, albeit with moderate *syn*-selectivity. An inverted configuration at the α-carbon of the nitro group in the minor *anti*-isomer, as well as the transition state model depicted in Figure 1, suggested that the steric bulk of nitroalkane is a dominant factor for diastereoselectivity in this catalytic system. Consistent with

(15) Examples with low diastereoselectivity (dr ≤3/1), see: refs 5d, 5e, 5h, 5i, 5k, 6a−6c, and 6f. Examples exhibiting moderate to high diastereoselectivity using silyl nitronate (ref 6h), nitroethanol (ref 6e), and homochiral nitroalkane (ref 6g) are reported; however, there is no example of general diastereo- and enantioselective addition of nitroalkanes to α,β-unsaturated carbonyl compounds.

Table 2. Catalytic Asymmetric Conjugate Addition of Nitroalkane **1** to α,β-Unsaturated Thioamides **2**[a]



	nitroalkane **1**		thioamide **2**						
entry	R^3		R^1	R^2		product	time (h)	yield[b] (%)	*syn*/*anti*[c]	ee (%) (*syn*)
1	Me	**1b**	Me	Ph	**2a**	**3ba**	1	95	81/19	99
2	Et	**1c**	Me	Ph	**2a**	**3ca**	1	96	93/7	99
3	allyl	**1d**	Me	Ph	**2a**	**3da**	2	95	89/11	99
4	allyl	**1d**	Me	4-MeC_6H_4	**2b**	**3db**	2	94	88/12	99
5	allyl	**1d**	Me	4-ClC_6H_4	**2c**	**3dc**	2	90	88/12	99
6[d]	allyl	**1d**	Me	4-ClC_6H_4	**2c**	**3dc**	6	81	84/16	99
7[e]	allyl	**1d**	Me	4-ClC_6H_4	**2c**	**3dc**	20	45	86/14	99
8	allyl	**1d**	Me	4-$MeOC_6H_4$	**2d**	**3dd**	6	63	84/16	99
9	allyl	**1d**	Me	2-furyl	**2g**	**3dg**	2	91	75/25	99
10	allyl	**1d**	Me	2-thienyl	**2h**	**3dh**	2	72	72/28	99
11	allyl	**1d**	Me	(*E*)-CH=$CHCH_3$	**2i**	**3di**	2	89	80/20	99
12	allyl	**1d**	Me	Me	**2e**	**3de**	1	91	81/19	99
13	allyl	**1d**	Bn	Ph	**2f**	**3df**	1	90	79/21	99
14	allyl	**1d**	Bn	4-ClC_6H_4	**2j**	**3dj**	1	86	80/20	99
15	allyl	**1d**	Bn	Me	**2k**	**3dk**	1	90	77/23	98

[a] **1**: 2.0 mmol, **2**: 0.4 mmol. [b] Isolated yield. [c] Determined by ^1H NMR of the crude mixture. [d] 2.0 equiv of **1d** was used. [e] 2 mol % of catalyst was used.

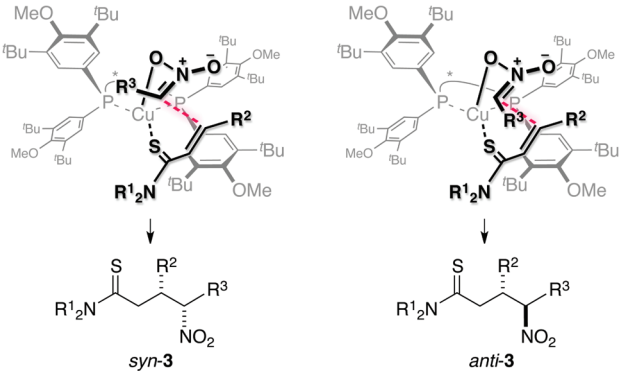


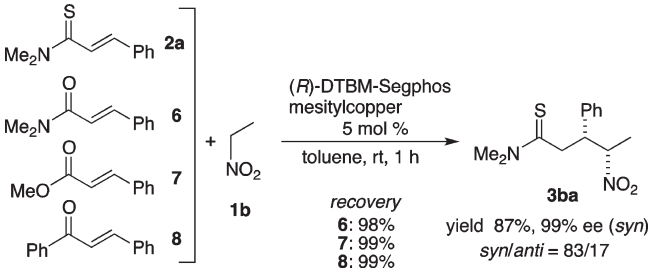
Figure 1. Proposed transition state model for diastereo- and enantioselectivity.

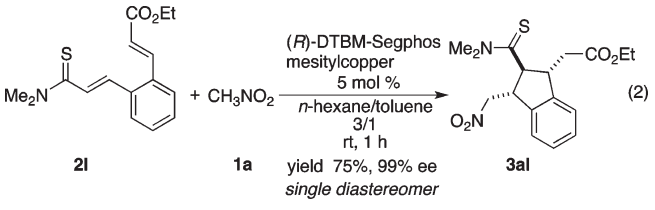
this assumption, bulkier nitroalkanes **1c** and **1d** exhibited higher diastereoselectivity (entries 2 and 3). The reaction with 4-nitro-1-butene (**1d**) and various α,β-unsaturated thioamides **2** provided a series of products bearing a pendant allyl group (entries 4−15). The amount of **1d**

could be reduced to 2.0 equiv with an extended reaction time (entry 6), whereas the reaction with 2 mol % of catalyst loading resulted in a significantly decreased reaction efficiency (entry 7). Thioamides bearing a heteroaromatic ring produced lower diastereoselectivity, albeit with excellent enantioselectivity (entries 9 and 10). Exclusive 1,4-addition was observed with the diene-conjugated thioamide **2i** (entry 11). The reaction with β-methyl-substituted α,β-unsaturated thioamide proceeded smoothly to afford a yield and stereoselectivity comparable to those obtained with β-aryl substrates (entry 12). The substituent on the thioamide nitrogen was not relevant to either the reactivity or stereoselectivity, and *N*,*N*-dibenzylthioamides also served as suitable substrates (entries 13–15).

The chemoselective nature of the present catalysis was evidenced by the following competition experiments (Scheme 2). In the reaction of nitroethane (**1b**) with thioamide **2a** in the presence of α,β-unsaturated amide **6**, ester **7**, and even α,β-unsaturated ketone **8**, which exhibits intrinsically higher electrophilicity than the corresponding thioamide **2a**, only **3ba** was produced and **6**–**8** were recovered unchanged. The high fidelity in chemoselectivity was exploited for the sequential conjugate addition using **2l**, where the enantioselective conjugate addition of **1a**, followed by the intramolecular conjugate addition of Cu-thioamide enolate **4** to unsaturated ester, furnished indane derivative **3al** having three consecutive stereogenic centers as a single diastereomer in 75% yield and 99% ee (eq 2).

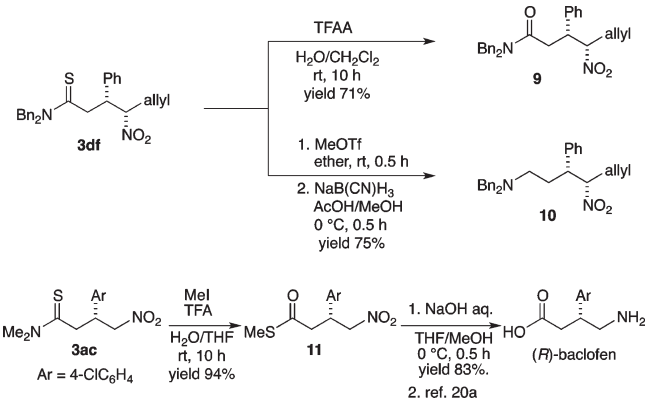
Scheme 2. Competitive Reaction: Highly Chemoselective Conjugate Addition to α,β-Unsaturated Thioamide **2a**





The divergent transformation of the thioamide functionality is useful for further synthetic manipulations (Scheme 3). The product **3df** was transformed into the corresponding amide **9** by treatment with TFAA.[16] S-Methylation with MeOTf followed by hydride reduction in acidic medium allowed desulfurization to give dibenzyl-protected amine **10**.[17] Thioamide moiety of the product **3ac** was converted to thioester **11** by MeI with TFA in wet THF.[18] The subsequent hydrolysis delivered the corresponding carboxylic acid, which can be transformed to (*R*)-baclofen in a single step, a therapeutically useful $GABA_B$ receptor agonist.[19,20]

Scheme 3. Transformation of the Products



In summary, we developed a catalytic asymmetric conjugate addition of nitroalkanes to α,β-unsaturated thioamides promoted by mesitylcopper/(*R*)-DTBM-Segphos precatalyst. The intermediate Cu-thioamide enolate functioned as a soft Lewis acid/hard Brønsted base cooperative catalyst to drive the catalytic cycle via efficient proton transfer between substrates. Divergent transformation of the thioamide functionality is advantageous for further manipulations. Studies of the application of the present mesitylcopper/chiral phosphine catalysis to other pronucleophiles are currently underway.

Acknowledgment. This work was financially supported by KAKENHI (20229001 and 23590038) from JSPS. N.K. thanks the Sumitomo Foundation for financial support. R.Y. thanks JSPS predoctral fellowship.

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.

(16) Masuda, R.; Hojo, M.; Ichi, T.; Sasano, S.; Kobayashi, T.; Kuroda, C. *Tetrahedron Lett*. **1991**, *32*, 1195.

(17) Sundberg, R. J.; Walters, C. P.; Bloom, J. D. *J. Org. Chem*. **1981**, *46*, 3730.

(18) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **1999**, *55*, 1187.

(19) (a) Olpe, H.-R.; Demiéville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol*. **1978**, *52*, 133. (b) Bowery, N. G. *Trends Pharmacol. Sci*. **1982**, *3*, 400.

(20) Recent selected examples of catalytic asymmetric synthesis of baclofen via atom-economical approach: (a) Camps, P.; Muñoz-Torrero, D.; Sánchez, L. *Tetrahedron: Asymmetry* **2004**, *15*, 2039. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119. (c) Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907. (d) Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett*. **2006**, *47*, 6577. See also refs 5c, 6a, and 6c.