Organic LETTERS

Letter

pubs.acs.org/OrgLett

Organocatalytic Enantioselective Addition of Thiols to Ketimines Derived from Isatins

Shuichi Nakamura,* Shun Takahashi, Daisuke Nakane, and Hideki Masuda

Department of Frontier Materials, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

Supporting Information

ABSTRACT: The first catalytic enantioselective addition of thiols to ketimines derived from isatins has been developed. Excellent yields and enantioselectivities were observed for the reaction of various ketimines and thiols using a cinchona alkaloid sulfonamide catalyst. Both enantiomers of products could be obtained by using pseudoenantiomeric chiral catalysts.

Chiral *N,S*-acetals are receiving considerable attention due to their wide applications in the synthesis of biologically active compounds, such as β-lactam antibiotics,[1] fusaperazine A,[2] and the fungal metabolite (+)-11,11′-dideoxyverticillin A (Figure 1).[3]

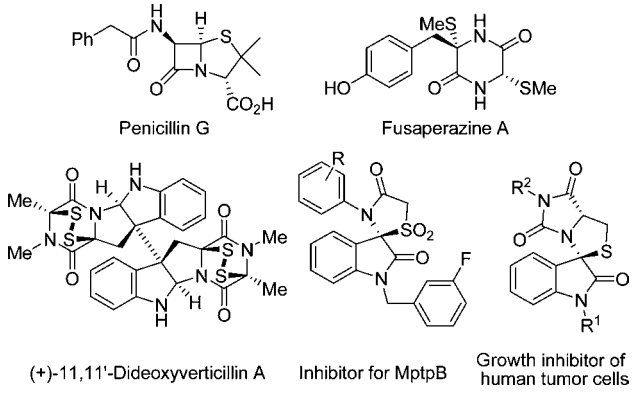


Figure 1. Biologically active compounds for *N,S*-acetals and related compounds.

Furthermore, their synthetic importance has prompted considerable interest to develop asymmetric methods for their preparation.[4] One of the most efficient methods for the preparation of chiral *N,S*-acetals is the enantioselective addition of thiols to imines. In particular, the utilization of ketimines derived from isatins has attracted much attention, because the reaction affords *N,S*-acetals having a 2-oxindole backbone, which is an important structural motif in biologically active compounds. For example, spirothiazolidinones[5] and spirothiazolidines[6] act as inhibitors of *Mycobacterium tuberculosis* protein tyrosine phosphatases B (MptpB) and the growth of human tumor cells. Therefore, the development of an asymmetric synthesis protocol for chiral *N,S*-acetals through the addition of thiols with ketimines derived from isatins is highly desired.[7]

To the best of our knowledge, there are only a few examples of the enantioselective addition of thiol to imines. The first enantioselective reaction of thiols with *N*-acylimines was reported by Antilla and co-workers using chiral phosphoric acids to give chiral *N,S*-acetals in excellent yields and enantioselectivities.[8] Wang and co-workers reported the highly enantioselective synthesis of *N,S*-acetals through the reaction of thiols with trifluoromethyl imines using chiral squaramide catalysts.[9] More recently, Zhao and co-workers[10] and Sun and Qian[11] also reported the enantioselective addition of thiols to imines derived from aldehydes by using amino acid based thiourea−ammonium salt catalysts or cinchona alkaloids.[12] Although such pioneering studies exist, there are no reports that challenge the difficulty involved in the enantioselective addition of thiols to ketimines.[13] Furthermore, only little attention has been paid to the enantioselective addition of heteroatoms to ketimines.[14] Therefore, the development of novel catalyst systems with acceptable catalytic activity for the addition of thiols to ketimines still remains a major challenge. We reported the first enantioselective reaction of ketimines with heteroatom nucleophiles, such as phosphites,[15] and we also recently developed novel catalysts derived from cinchona alkaloids.[16] Herein, our ongoing interest was extended to the enantioselective addition of thiols to various ketimines using our original chiral catalysts derived from cinchona alkaloids (Figure 2).

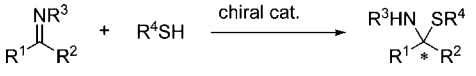


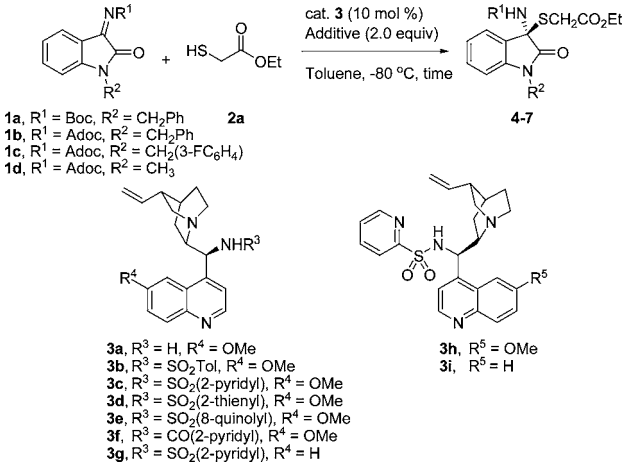
Figure 2. Enantioselective synthesis of *N,S*-acetals through the addition of thiols to ketimines.

Received: November 14, 2014
Published: December 19, 2014

dx.doi.org/10.1021/ol503309s | *Org. Lett.* 2015, 17, 106−109

First, we examined the reaction of ketimines derived from *N*-Boc-*N*′-benzyl isatin **1a** with ethyl thioglycolate **2a** in the presence of chiral organocatalysts **3a**–**i** derived from various cinchona alkaloids in toluene. The results are shown in Table 1.

Table 1. Enantioselective Addition of Ethyl Thioglycolate 2a to Ketimines 1a–d Derived from Isatins Using Various Chiral Organocatalysts 3a–i[a]



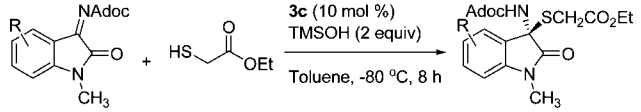
entry	1	cat.	additive	product	time (h)	yield (%)[b]	ee (%)
1	**1a**	**3a**	–	**4**	24	40	33
2	**1a**	**3b**	–	**4**	8	75	59
3	**1a**	**3c**	–	**4**	8	99	75
4	**1a**	**3d**	–	**4**	8	96	67
5	**1a**	**3e**	–	**4**	8	85	73
6	**1a**	**3f**	–	**4**	8	91	44
7	**1a**	**3g**	–	**4**	8	82	74
8	**1a**	**3h**	–	**4**	8	83	71[c]
9	**1a**	**3i**	–	**4**	8	68	68[c]
10	**1b**	**3c**	–	**5**	8	85	86
11	**1b**	**3c**	MeOH	**5**	8	92	86
12	**1b**	**3c**	*i*-PrOH	**5**	8	80	90
13	**1b**	**3c**	TMSOH	**5**	8	99	91
14	**1c**	**3c**	TMSOH	**6**	8	99	86
15	**1d**	**3c**	TMSOH	7	8	99	97
16	**1d**	**3h**	TMSOH	7	8	96	89[c]
17[d]	**1d**	**3c**	TMSOH	7	8	91	96

[a]Reaction conditions: ketimine **1** (0.03 mmol), **2a** (2.0 equiv), **3** (10 mol %), additive (2.0 equiv), and toluene (0.03 M) were used. Boc = *t*-BuOCO, Adoc = 1-AdamantylOCO. [b]Isolated yield. [c]Opposite enantiomer was obtained. [d]**3c** (5 mol %) was used.

The reaction using 9-amino-9-deoxy-*epi*-quinine **3a** afforded product **4** in moderate yield with low enantioselectivity (Table 1, entry 1).[17] In order to improve the reactivity and enantioselectivity, we attempted the reaction using *N*-substituted 9-amino-9-deoxy-*epi*-quinines **3b**–**f**. Although the reaction using *N*-tosylated 9-amino-9-deoxy-*epi*-quinine **3b** was completed within 8 h at −80 °C to give product **4** with moderate enantioselectivity, the reaction using *N*-heteroarene-sulfonylated catalysts **3c**–**e** afforded **4** with high enantioselectivity (Table 1, entries 2–5). The best enantioselectivity was obtained in the reaction using **3c** having a 2-pyridinesulfonyl group. The reaction using *N*-picolinyl catalyst **3f** afforded product **4** with lower enantioselectivity than that using catalyst **3c** (Table 1, entry 6). These results provide evidence of the clear superiority of the 2-pyridinesulfonyl group as a stereocontrolling group for chiral catalysts. We also examined the reaction using 2-pyridine-sulfonylated catalysts **3g**–**i**, prepared from cinchonidine, quinidine, and cinchonine (Table 1, entries 7–9). The reaction using **3h** and **3i** afforded product **4** with good enantioselectivity having the opposite stereochemistry than that using **3c**. Changing the substituent on the nitrogen in the imino group from the Boc group to the 1-adamantyloxycarbonyl group (Adoc) showed high enantioselectivity (Table 1, entry 10). Interestingly, the reaction using a protic additive could improve the yield and enantioselectivity of the product (Table 1, entries 11–13). Good enantioselectivity can be obtained by the reaction using TMSOH as a protonation reagent (Table 1, entry 13).[18] After optimizing the substituent on the nitrogen in **1**, the reaction of *N*-Boc-*N*′-methyl isatinimine **1d** showed the best enantioselectivity (Table 1, entries 13–15). Furthermore, the reaction using catalyst **3h** derived from quinidine with TMSOH instead of **3c** afforded an opposite enantiomer of product **7** with high enantioselectivity (Table 1, entry 16). The catalyst loading of **3c** was successfully reduced to 5 mol % without a loss of enantioselectivity (Table 1, entry 17).[19]

The scope and limitations of the addition of thioglycolate **2a** to various ketimines **1d**–**l** using **3c** were investigated. The results are summarized in Table 2. Both electron-rich and -deficient

Table 2. Enantioselective Addition of Ethyl Thioglycolate 2a to Various Ketimines 1d–l Using 3c



entry	1	R	product	yield (%)	ee (%)
1	**1d**	H	**7**	99	97
2	**1e**	5-Me	**8**	91	97
3	**1f**	5-MeO	**9**	96	97
4	**1g**	5-F	**10**	99	96
5	**1h**	5-Cl	**11**	96	96
6	**1i**	5-Br	**12**	93	96
7	**1j**	5-NO_2	**13**	94	93
8	**1k**	4-Br	**14**	96	96
9	**1l**	6-Br	**15**	99	94
10[a]	**1d**	H	**7**	96	89[b]
11[a]	**1f**	5-MeO	**9**	93	85[b]
12[a]	**1g**	5-F	**10**	92	88[b]
13[a]	**1i**	5-Br	**12**	93	86[b]
14[a]	**1k**	4-Br	**14**	91	94[b]
15[a]	**1l**	6-Br	**15**	95	82[b]

[a]**3h** (10 mol %) was used instead of **3c**. [b]Opposite enantiomer was obtained.

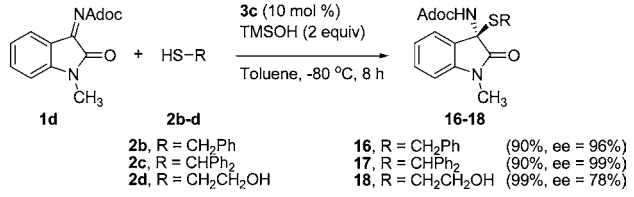
ketimines gave products **7**–**15** with 93–97% ee (Table 2, entries 1–9). A maximum of 97% ee was obtained in the case of the reaction of ketimines derived from 5-methyl or 5-methoxy substituted isatins (Table 2, entries 2 and 3). The chemical yield was excellent in most cases. The reaction using catalyst **3h** gave products with good enantioselectivity having the opposite stereochemistry than when **3c** was used (Table 2, entries 10–15).

We also examined the reaction of ketimines **1d** with other thiols, such as benzylthiol **2b**, diphenylmethanethiol **2c**, and 2-sulfanylethanol **2d**, using **3c** to give products **16**–**18** in high yield with high enantioselectivity (Scheme 1).[20] The absolute

dx.doi.org/10.1021/ol503309s | *Org. Lett.* 2015, 17, 106–109

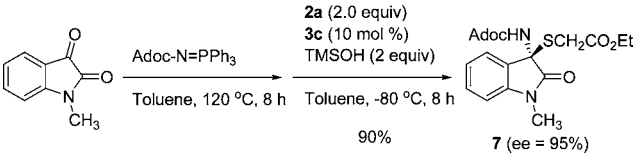
configuration of **17** was determined to be (*R*) by X-ray crystallographic analysis (see Supporting Information).

Scheme 1. Enantioselective addition of various thiols 2b−d with 1d



In order to improve the synthetic efficiency, we next examined the one-pot synthesis of aza-Wittig and the thiol addition reaction (Scheme 2). Although Ph_3PO remained in the reaction mixture, the thiol addition reaction afforded product **7** with almost the same enantioselectivity as the result in Table 1, entry 15.[21]

Scheme 2. One-Pot Synthesis of *N,S*-Acetal 7



The enantioselective reaction of **1** with thiols using organocatalysts **3c,e,g** having a heteroarenesulfonyl group gave products with good enantioselectivity, although the reaction using organocatalysts **3a,b** did not give good results (Table 1, entries 1−7). Therefore, the heteroarenesulfonyl groups play an important role in exerting enantioselectivity in the reaction. From these considerations and the absolute configurations of the products, the transition state for the reaction of a thiol **2a** to a ketimine **1d** using a chiral sulfonamide catalyst **3c** is proposed in Figure 3. The functionality of quinuclidine in the cinchona

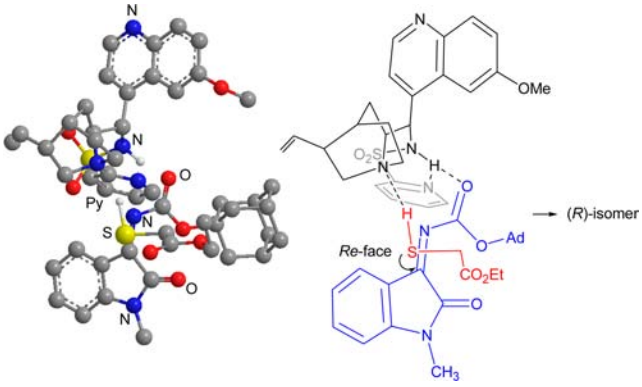


Figure 3. Assumed transition state for the reaction of *N*-Adoc-*N*′-methyl isatinimine **1d** with methyl thioglycolate **2a** using **3c**.

alkaloid could activate the thiol in thioglycolate by hydrogen bonding. Furthermore, the ketimine is activated by pyridinesulfonamide using hydrogen bonding to the N−H group including intramolecular hydrogen bonding to nitrogen in the pyridinesulfonyl group. The reaction of the thiol with the ketimine in the coordination sphere of the chiral catalyst **3c** led to a product with high enantioselectivity.[22] Further studies are required to fully elucidate the mechanistic details of the reaction.

In conclusion, we developed the asymmetric addition of thiols to ketimines derived from isatins using our original chiral catalysts. This approach not only is the first example of catalytic enantioselective formation of *N,S*-acetals from the reaction of ketimines but also provides direct access to both enantiomers of optically active *N,S*-acetals with satisfactory yield and enantioselectivity. The reaction of a broad range of ketimines derived from isatins afforded products with high enantioselectivity. Further studies focusing on the scope of the asymmetric reaction using novel organocatalysts are currently under investigation and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra and experimental procedures for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: snakamur@nitech.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partly supported by Grants-in-Aid for Scientific Research on Innovative Areas "Advanced Molecular Transformations by Organocatalysts" from MEXT (26105727).

■ REFERENCES

(1) (a) Sammes, P. G. *Chem. Rev.* **1976**, *76*, 113. (b) George, G. I., Ed. *The Organic Chemistry of β-Lactams*; VCH: New York, 1993.
(2) Usami, Y.; Aoki, S.; Hara, T.; Numata, A. *J. Antibiot.* **2002**, *55*, 655.
(3) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238.
(4) For enantioselective reactions of lithiated *N,S*-acetals as chiral formylating reagents, see; (a) Wang, L.; Nakamura, S.; Ito, Y.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 3059. (b) Wang, L.; Nakamura, S.; Toru, T. *Org. Biomol. Chem.* **2004**, *2*, 2168. For lithiated *N,S*-acetals with a chiral auxiliary, see: (c) Gawley, R. E.; Zhang, Q.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2093. (d) Gaul, C.; Seebach, D. *Org. Lett.* **2000**, *2*, 1501. (e) Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem.—Eur. J.* **2001**, *7*, 4117. (f) Gawley, R. E.; Campagna, S. A.; Santiago, M.; Ren, T. *Tetrahedron: Asymmetry* **2002**, *13*, 29. (g) Gaul, C.; Schärer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059. (h) Gaul, C.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 772.
(5) (a) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902. (b) Vintonyak, V. V.; Warburg, K.; Over, B.; Hübel, K.; Rauh, D.; Waldmann, H. *Tetrahedron* **2011**, *67*, 6713.
(6) (a) Gomez-Monterrey, I.; Bertamino, A.; Porta, A.; Carotenuto, A.; Musella, S.; Aquino, C.; Granata, I.; Sala, M.; Brancaccio, D.; Picone, D.; Ercole, C.; Stiuso, P.; Campiglia, P.; Grieco, P.; Ianelli, P.; Maresca, B.; Novellino, E. *J. Med. Chem.* **2010**, *53*, 8319. (b) Bertamino, A.; Soprano, M.; Musella, S.; Rusciano, M. R.; Sala, M.; Vernieri, E.; Sarno, V. D.; Limatola, A.; Carotenuto, A.; Cosconati, S.; Grieco, P.; Novellino, E.; Illario, M.; Campiglia, P.; Gomez-Monterrey, I. *J. Med. Chem.* **2013**, *56*, 5407.
(7) There are several reports on the enantioselective nucleophilic addition reaction to ketimines derived from isatins. For catalytic enantioselective Strecker-type reactions of ketimines derived from isatins, see: (a) Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847. (b) Wang, D.; Liang, J.; Feng, J.;

Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548. For catalytic enantioselective Pictet−Spengler reactions of isatins, see: (c) Badillo, J. J.; Silva-Garcia, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. *Tetrahedron Lett.* **2011**, *52*, 5550. (d) Duce, S.; Pesciaioli, F.; Gramigna, L.; Bernardi, L.; Mazzanti, A.; Ricci, A.; Bartoli, G.; Bencivenni, G. *Adv. Synth. Catal.* **2011**, *353*, 860. For catalytic enantioselective Mannich reactions of ketimines derived from isatins, see: (e) Guo, Q.-X.; Liu, Y. W.; Li, X.-C.; Zhong, L.-Z.; Peng, Y.-G. *J. Org. Chem.* **2012**, *77*, 3589. (f) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512. For enantioselective Friedel−Crafts reactions of indoles to ketimines derived from isatins, see: (g) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003. For catalytic enantioselective aminals formation of isatins, see: (h) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. For catalytic enantioselective spirocyclization of ketimines derived from isatins, see: (i) Zhang, B.; Feng, P.; Sun, L.-H.; Cui, Y.; Ye, S.; Jiao, N. *Chem.—Eur. J.* **2012**, *18*, 9198. (j) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 5412. For an enantioselective Povarov reaction, see: (k) Shi, F.; Xing, G.; Zhu, R.; Tan, W.; Tu, S. *Org. Lett.* **2013**, *15*, 128.

(8) Ingle, G. K.; Mormino, M. G.; Wojtas, L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 4822.

(9) Fang, X.; Li, Q.-H.; Tao, H.-Y.; Wang, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 327.

(10) Wang, H.-Y.; Zhang, J.-X.; Cao, D.-D.; Zhao, G. *ACS Catal.* **2013**, *3*, 2218.

(11) Qian, H.; Sun, J. *Asian J. Org. Chem.* **2014**, *3*, 387.

(12) For the enantioselective synthesis of *N,N*-acetals, see: (a) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (b) Liang, Y.; Rowland, E. B.; Rowland, G. B.; Perman, J. A.; Antilla, J. C. *Chem. Commun.* **2007**, 4477. (c) Cheng, X.; Vellalath, S.; Goddard, R.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 15786. (d) Liu, W.-J.; Chen, X.-H.; Gong, L.-Z. *Org. Lett.* **2008**, *10*, 5357. (e) Rueping, M.; Antonchick, A. P.; Sugiono, E.; Grenader, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 908. (f) Hatano, M.; Ozaki, T.; Sugiura, Y.; Ishihara, K. *Chem. Commun.* **2012**, 4986. (g) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389. (h) Jiang, Y.; Liu, Y.; Tu, S.-J.; Shi, F. *Tetrahedron: Asymmetry* **2013**, *24*, 1286. For the enantioselective synthesis of *N,O*-acetals, see: (i) Li, G.; Fronczek, F. R.; Antilla, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 12216. (j) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749. (k) Nimmagadda, S. K.; Zhang, Z.; Antilla, J. C. *Org. Lett.* **2014**, *16*, 4098.

(13) Sha and Wu's group reported the reaction of ketimines with alcohols to give chiral *N,O*-acetals with moderate enantioselectivity; see: Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *Tetrahedron* **2013**, *69*, 7314.

(14) For enantioselective additions of phosphites to ketimines, see: (a) Xie, H.; Song, A.; Zhang, X.; Chen, X.; Li, H.; Sheng, C.; Wang, W. *Chem. Commun.* **2013**, *49*, 928. (b) George, J.; Sridhar, B.; Reddy, B. V. S. *Org. Biomol. Chem.* **2014**, *12*, 1595.

(15) (a) Nakamura, S.; Hayashi, M.; Hiramatsu, Y.; Shibata, N.; Funahashi, Y.; Toru, T. *J. Am. Chem. Soc.* **2009**, *131*, 18240. For our related work on enantioselective reactions to ketimines, see: (b) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *Org. Lett.* **2011**, *13*, 1662. (c) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276. (d) Hayashi, M.; Sano, M.; Funahashi, Y.; Nakamura, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5557. (e) Nakamura, S.; Hyodo, K.; Nakamura, M.; Nakane, D.; Masuda, H. *Chem.—Eur. J.* **2013**, *19*, 7304. (f) Hayashi, M.; Iwanaga, M.; Shiomi, N.; Nakane, D.; Masuda, H.; Nakamura, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 8411.

(16) Hayashi, M.; Shiomi, N.; Funahashi, Y.; Nakamura, S. *J. Am. Chem. Soc.* **2012**, *134*, 19366. See also ref 15c,d,f.

(17) We also examined the reaction using various cinchona alkaloids, such as quinine, quinidine, cinchonine, and cinchonidine; however, the reaction afforded product **4** with lower enantioselectivity than when **3c** was used.

(18) The reaction using 10 mol % of TMSOH cannot improve the enantioselectivity of the product.

(19) The reaction of nonprotected isatin ketimine with **2a** using **3c** also afforded the product with high enantioselectivity but in low yield (27%, 86% ee).

(20) The reaction of **1d** with benzenethiol also gave the product, but it was not a stable compound.

(21) We also examined the transformation of products such as removal of the Adoc group or the cyclization reaction between ester groups with amides, but these compounds are not so stable.

(22) For a similar reaction mechanism in the enantioselective 1,4-addition reaction of thiols using cinchona alkaloid-thiourea catalysts, see: Duan, S.-W.; Li, Y.; Liu, Y.-Y.; Zou, Y.-Q.; Shi, D.-Q.; Xiao, W.-J. *Chem. Commun.* **2012**, *48*, 5160.