

Asymmetric Indoline Synthesis via Intramolecular Aza-Michael Addition Mediated by Bifunctional Organocatalysts

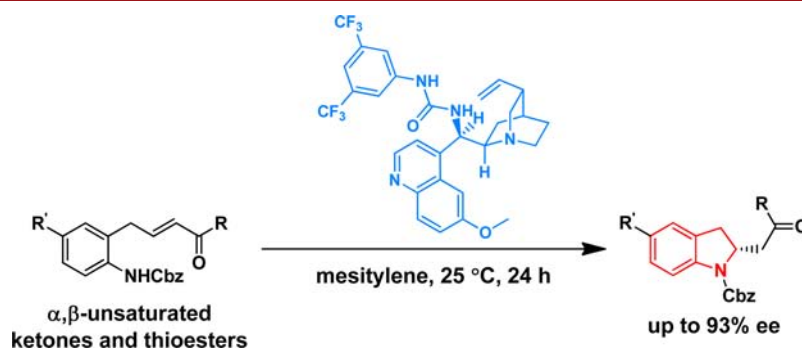
Ryota Miyaji, Keisuke Asano,* and Seijiro Matsubara*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University,
Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510, Japan

asano.keisuke.5w@kyoto-u.ac.jp; matsubara.seijiro.2e@kyoto-u.ac.jp

Received May 31, 2013

ABSTRACT



A novel method for the asymmetric synthesis of 2-substituted indolines, employing bifunctional amino(thio)urea catalysts, was developed. The reaction proceeded via an intramolecular aza-Michael addition mediated by activation through hydrogen bonding. The catalytic process was shown to be highly versatile and applicable to a wide range of substrates due to the flexible catalytic mechanism utilizing a noncovalent interaction.

Optically active indoline frameworks are found in many natural products and biologically active agents (Figure 1).¹ This has stimulated a great deal of research into the asymmetric synthesis of substituted indolines.^{2–5} Among the approaches that have been studied, one of the most powerful candidates for the synthesis of 2-substituted indolines is intramolecular aza-Michael addition^{6,7} from aniline derivatives that bear an α,β -unsaturated carbonyl

moiety. This is a straightforward route to the desired structures and leaves a carbonyl group available for further structural modifications. Previous approaches utilizing chiral secondary^{3a,b} and primary^{3c} amine catalysts have been shown to be useful for the reaction of α,β -unsaturated aldehydes and ketones, respectively. However, these methods are not applicable to substrates in a higher oxidation state because of the mechanistic necessity for iminium formation.⁸ To expand the utility of this synthetic reaction, the development of a novel catalytic process is required.

We have recently established a useful protocol for asymmetric heterocycle synthesis via an intramolecular

(1) For reviews, see: (a) *Modern Alkaloids*; Fattorusso, E., Tagliatella-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008. (b) *Anticancer Agents from Natural Products*; Cragg, G. M., Kingstom, D. G. I., Newman, D. J., Eds.; CRC: Boca Raton, FL, 2005. (c) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (d) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787.

(2) For reviews, see: (a) Anas, S.; Kagan, H. B. *Tetrahedron: Asymmetry* **2009**, *20*, 2193. (b) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975. (c) Kuwano, R. *Heterocycles* **2008**, *76*, 909. (d) Zhou, Y.-G. *Acc. Chem. Res.* **2007**, *40*, 1357. (e) Glorius, F. *Org. Biomol. Chem.* **2005**, *3*, 4171.

(3) For examples of organocatalytic asymmetric syntheses of 2-substituted indolines via intramolecular aza-Michael addition, see: (a) Fustero, S.; Moscardo, J.; Jiménez, D.; Pérez-Carrion, M. D.; Sánchez-Rosello, M.; del Pozo, C. *Chem.—Eur. J.* **2008**, *14*, 9868. (b) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155. (c) Fustero, S.; del Pozo, C.; Mulet, C.; Lazaro, R.; Sánchez-Rosello, M. *Chem.—Eur. J.* **2011**, *17*, 14267.

(4) For examples of other organocatalytic asymmetric syntheses of substituted indolines, see: (a) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525. (b) Austin, J. F.; Kim, S.-G.; Sinz, C. J.; Xiao, W.-J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (c) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10661. (d) Rueping, M.; Brinkmann, C.; Antonchick, A. P.; Atodiresei, I. *Org. Lett.* **2010**, *12*, 4604. (e) Maciver, E. E.; Thompson, S.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 9979. (f) Martínez, A.; Webber, M. J.; Müller, S.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, Early View (DOI: 10.1002/anie.201301618). (g) Yang, Q.-Q.; Wang, Q.; An, J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem.—Eur. J.* **2013**, *19*, 8401.

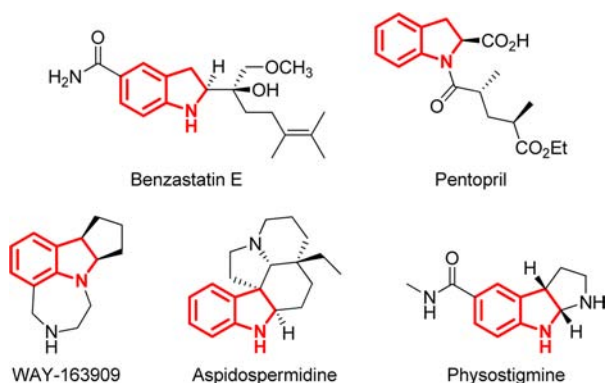


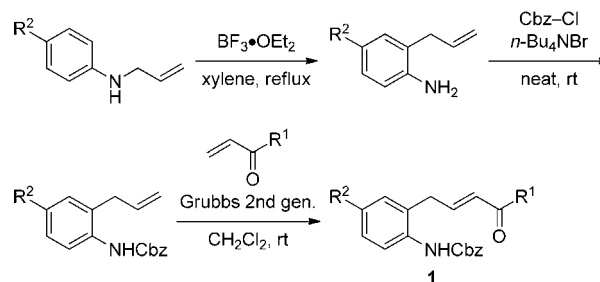
Figure 1. Representative indoline derivatives in natural products.

hetero-Michael addition.⁹ This methodology utilizes multipoint recognition by bifunctional aminothiourea catalysts through hydrogen bonding.^{10,11} Thus, we attempted to use this efficient cyclization approach in order to develop a novel asymmetric intramolecular aza-Michael addition reaction for generating a variety of 2-substituted indolines.¹² The potential versatility of this type of catalysis, utilizing noncovalent interactions, was demonstrated using a range of different substrates.

The starting materials **1** were prepared through the synthetic route indicated in Scheme 1.¹³ The investigation was initiated using substrate **1a** with 5 mol % quinidine-derived bifunctional thiourea catalyst **3a** in cyclopentyl methyl ether (CPME) at 25 °C, and indoline product **2a** was obtained enantioselectively (Table 1, entry 1).

(5) For other selected examples of asymmetric syntheses of substituted indolines, see: (a) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 9919. (b) Han, B.; Xiao, Y.-C.; Yao, Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 10189. (c) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163. (d) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614. (e) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213. (f) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653. (g) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K.; Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521. (h) Mršić, N.; Jerphagnon, T.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Tetrahedron: Asymmetry* **2010**, *21*, 7. (i) Maj, A. M.; Suisse, I.; Méliet, C.; Agbossou-Niedercorn, F. *Tetrahedron: Asymmetry* **2010**, *21*, 10. (j) Baeza, A.; Pfaltz, A. *Chem.—Eur. J.* **2010**, *16*, 2036. (k) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909. (l) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803. (m) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (n) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238. (o) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (p) Yamamoto, H.; Ho, E.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem.—Eur. J.* **2010**, *16*, 11271. (q) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron Lett.* **2010**, *51*, 5124. (r) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130. (s) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874. (t) Hyde, A. M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 177. (u) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (v) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (w) Orsat, B.; Alper, P. B.; Moree, W.; Mak, C.-P.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 712. (x) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (y) Hou, X. L.; Zheng, B. H. *Org. Lett.* **2009**, *11*, 1789. (z) Gil, G. S.; Groth, U. M. *J. Am. Chem. Soc.* **2000**, *122*, 6789. (aa) Zhu, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 10815. (ab) Zhou, F.; Guo, J.; Liu, J.; Ding, K.; Yu, S.; Cai, Q. *J. Am. Chem. Soc.* **2012**, *134*, 14326.

Scheme 1. Synthetic Route to Substrates **1**



Screening of various solvents revealed that less polar aromatic solvents were the most effective for giving **2a** with high enantioselectivity and an acceptable yield (Table 1, entries 6–9). The fact that the reaction in a protic solvent resulted in poor yield and enantioselectivity implies the crucial role of hydrogen bonding in the catalysis mode of this reaction (Table 1, entry 5). As a longer reaction time led to lower enantioselectivity, which was likely due to the competing noncatalytic reaction (Table 1, entry 10), 10 mol % **3a** was employed to improve the yield (Table 1, entry 11). On decreasing the reaction temperature to 0 °C, the yield was considerably reduced, albeit with a slight increase in the enantioselectivity (Table 1, entry 12). The use of urea catalyst **3b** instead of thiourea catalyst **3a** largely improved both the yield and enantioselectivity (Table 1, entry 13). Substrates with other protecting groups (**1b**, **1c**) gave poorer results (Table 1, entries 14 and 15). Furthermore, the screening of urea catalysts showed that quinine-derived **3d** was an efficient catalyst for obtaining the opposite enantiomer of **2a** with good enantioselectivity (Table 1, entry 17).¹⁴

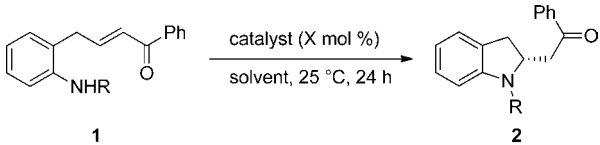
Subsequently, the scope of substrates that the reaction could be successfully applied to was explored using the optimized conditions (Table 2). Although urea catalyst **3b** exhibited low reactivity for an electron-rich enone, thiourea catalyst **3a** proved to be more suitable in this case for improving the yield while giving a similarly good enantiomeric

(6) For reviews on asymmetric aza-Michael addition reactions, see: (a) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (b) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657. (c) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. (d) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513.

(7) For examples of asymmetric intramolecular aza-Michael addition reactions, see ref 3 and the following: (a) Liu, X.; Lu, Y. *Org. Lett.* **2010**, *12*, 5592. (b) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519. (c) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666. (d) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283. (e) Liu, J.-D.; Chen, Y.-C.; Zhang, G.-B.; Li, Z.-Q.; Chen, P.; Du, J.-Y.; Tu, Y.-Q.; Fan, C.-A. *Adv. Synth. Catal.* **2011**, *353*, 2721. (f) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238. (g) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. *Chem.—Eur. J.* **2010**, *16*, 12462.

(8) For a review on redox economy in organic synthesis, see: Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.

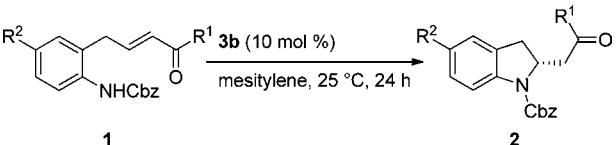
(9) (a) Fukata, Y.; Asano, K.; Matsubara, S. *Chem. Lett.* **2013**, 42, 355. (b) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711. (c) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620. (d) Okamura, T.; Asano, K.; Matsubara, S. *Chem. Commun.* **2012**, 48, 5076. (e) Fukata, Y.; Miyaji, R.; Okamura, T.; Asano, K.; Matsubara, S. *Synthesis* **2013**, 45, 1627.

Table 1. Optimization of Reaction Conditions^a


entry	R	catalyst (mol %)	solvent	yield (%) ^b	ee (%)
1	Cbz (1a)	3a (5)	CPME ^c	18	79
2	Cbz (1a)	3a (5)	Et ₂ O	10	76
3	Cbz (1a)	3a (5)	acetone	23	78
4	Cbz (1a)	3a (5)	CH ₂ Cl ₂	80	67
5	Cbz (1a)	3a (5)	CH ₃ OH	10	11
6	Cbz (1a)	3a (5)	benzene	99	75
7	Cbz (1a)	3a (5)	toluene	73	79
8	Cbz (1a)	3a (5)	xylene	57	81
9	Cbz (1a)	3a (5)	mesitylene	57	83
10 ^d	Cbz (1a)	3a (5)	mesitylene	70	79
11	Cbz (1a)	3a (10)	mesitylene	73	81
12 ^e	Cbz (1a)	3a (10)	mesitylene	14	84
13	Cbz (1a)	3b (10)	mesitylene	99	87
14	Boc (1b)	3b (10)	mesitylene	46	75
15	Bz (1c)	3b (10)	mesitylene	48	1
16	Cbz (1a)	3c (10)	mesitylene	59	76
17	Cbz (1a)	3d (10)	mesitylene	66	–84
18	Cbz (1a)	3e (10)	mesitylene	53	–78

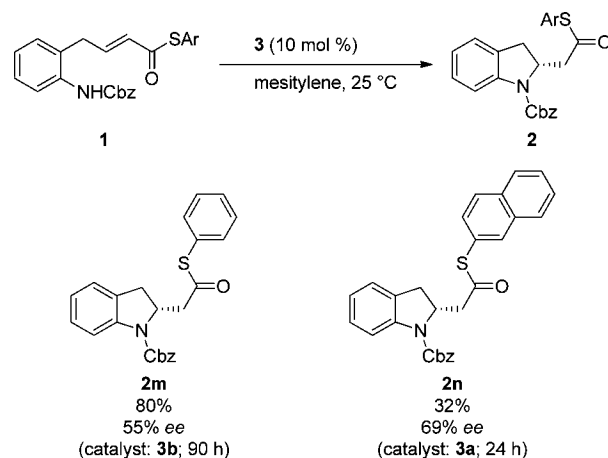
^a Reactions were run using **1** (0.1 mmol) and the catalyst in the solvent (0.8 mL). ^b Isolated yields. ^c CPME = cyclopentyl methyl ether. ^d Reaction was run for 48 h. ^e Reaction was run at 0 °C.

excess (Table 2, entry 2). In contrast, an electron-poor enone afforded the corresponding product in good yield with high enantioselectivity using **3b** as a catalyst (Table 2, entry 3). In addition, a substrate bearing a naphthyl group also underwent this reaction in the presence of **3b**, yielding the indoline product (Table 2, entry 4). Notably, particularly high enantioselectivity was obtained using a substrate bearing a *p*-bromo group, which may then be easily transformed into other organic groups (Table 2, entry 5). Substituents on the aniline moiety were also investigated, and again in this case, thiourea catalyst **3a** was found to be better for a substrate with a methoxy group (Table 2, entry 6). Electron-poor anilines were tolerated by using **3b** as a catalyst and gave the corresponding products in

Table 2. Scope of Substrates^a


entry	R ¹	R ²	2	yield (%) ^b	ee (%)
1	Ph	H	2a	99	87
2 ^c	4-CH ₃ OC ₆ H ₄	H	2d	73 (26) ^d	84 (86) ^d
3	4-CF ₃ C ₆ H ₄	H	2e	79	88
4	2-naphthyl	H	2f	83	88
5	4-BrC ₆ H ₄	H	2g	75	91
6 ^c	Ph	CH ₃ O	2h	82 (33) ^d	83 (86) ^d
7	Ph	F	2i	69	82
8	Ph	Cl	2j	82	84
9	4-BrC ₆ H ₄	CH ₃ O	2k	53	93
10 ^c	CH ₃	H	2l	18 (24) ^d	74 (65) ^d

^a Reactions were run using **1** (0.1 mmol) and **3b** (0.01 mmol) in mesitylene (0.8 mL). ^b Isolated yields. ^c Reactions were run using **3a** instead of **3b**. ^d Results of the reaction run using **3b**.

Scheme 2. Reactions from α,β -Unsaturated Thioesters

moderate to good yield with high enantioselectivity (Table 2, entries 7 and 8). A bromo group in the enone moiety again provided good enantioselectivity in the reaction of an electron-rich aniline (Table 2, entry 9). An aliphatic ketone substrate was much less reactive, but moderate enantioselectivity was obtained (Table 2, entry 10).

Moreover, higher oxidation state substrates, α,β -unsaturated thioesters **1m** and **1n**, were also applicable, although obtaining a further improvement in enantioselectivity requires additional investigation (Scheme 2).¹⁵ The

(15) It was also found that alkylthiol ester resulted in good enantioselectivity although the yield was low (benzylthiol ester: 19%, 76% ee). Results of further investigations on the reactions from α,β -unsaturated thioesters are described in the Supporting Information in detail.

(10) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (d) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. (e) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (f) Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813.

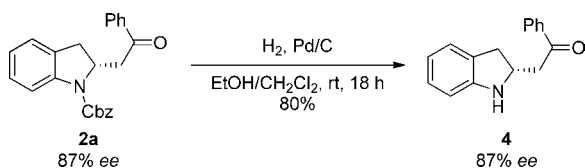
(11) For reviews on asymmetric catalysis based on hydrogen bonding, see: (a) *Hydrogen Bonding in Organic Synthesis*; Pihko, P. M., Ed.; Wiley-VCH: Weinheim, 2009. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

(12) For examples of asymmetric intramolecular aza-Michael addition reactions mediated by bifunctional aminothiourea catalysts, see refs 7a, 7b, and 9a.

(13) See Supporting Information for details.

(14) Results of further catalyst screening are described in the Supporting Information.

Scheme 3. Deprotection of **2a**



thioester functionality allows for a variety of subsequent transformations, thereby offering an efficient pathway to a range of pharmacological compounds.^{9d} This demonstrates the great potential of the reaction scheme described in this work for expanding the scope of compounds that can be successfully synthesized.

In addition, deprotection of **2a** could be carried out under hydrogenation conditions to afford **4** in high yield without any erosion of optical purity (Scheme 3). The absolute configuration of **2g** was determined using X-ray analysis (see Supporting Information for details), and the configurations of all other examples were assigned accordingly.

In summary, we have demonstrated a novel asymmetric synthesis of 2-substituted indolines via intramolecular aza-Michael addition by means of bifunctional organocatalysts. The reaction proceeded by activation via hydrogen bonding, enabling a flexible catalytic mechanism that was widely applicable to a range of substrates with α,β -unsaturated carboxylic acid derivatives. Further studies on the expansion of the substrate scope and the application of this methodology to other heterocycle syntheses are currently underway in our laboratory and will be reported in due course.

Acknowledgment. We thank Professor Takuya Kurahashi (Kyoto University) for X-ray crystallographic analysis. This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Supporting Information Available. Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.