doi:10.1246/cl.121245
Published on the web March 19, 2013

Asymmetric Synthesis of 1,3-Oxazolidines via Intramolecular Aza-Michael Addition by Bifunctional Organocatalysts

Yukihiro Fukata, Keisuke Asano,* and Seijiro Matsubara*
Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyotodaigaku-katsura, Nishikyo-ku, Kyoto 615-8510

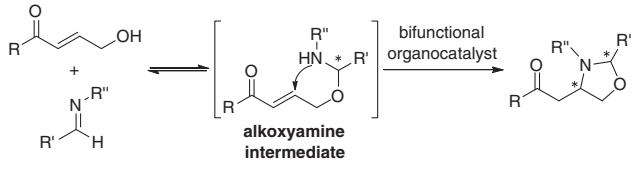
(Received December 14, 2012; CL-121245; E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp)

A novel synthetic route to optically active 1,3-oxazolidines via formal [3 + 2] cycloaddition in the presence of cinchona-alkaloid-thiourea-based bifunctional organocatalysts is reported. This protocol gives easy access to a wide range of chiral 1,3-oxazolidines. In addition, the results show that bifunctional organocatalysts can effect the intramolecular aza-Michael addition, leading to the asymmetric synthesis of nitrogen-containing heterocycles.

Asymmetric 1,3-oxazolidine frameworks are found in natural products and pharmaceutical compounds.[1] They are also utilized as versatile chiral intermediates leading to β-amino-carbonyl compounds as well as synthetic reagents such as chiral auxiliaries and ligands.[2] Therefore, the development of an efficient route to various asymmetric 1,3-oxazolidine derivatives is highly desirable. Nevertheless, their synthesis is based mainly on optically active starting materials, and there are very few examples of catalytic enantioselective synthesis methods.[3]

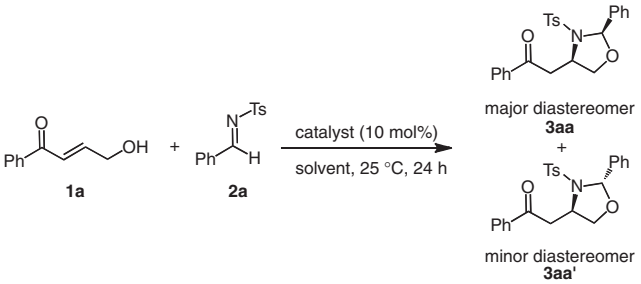
Recently, we developed several asymmetric cycloetherification reactions mediated by bifunctional organocatalysts, which can facilitate multipoint recognition utilizing hydrogen bonding in the intramolecular oxy-Michael addition step.[4,5] This methodology could also be extended to the formal [3 + 2] cycloaddition of γ-hydroxy-α,β-unsaturated carbonyls with aldehydes via hemiacetal intermediates.[4b,4c] Inspired by our previous results, we attempted to use this formal cycloaddition approach for the development of an efficient route to nitrogen-containing chiral heterocycles through the intramolecular aza-Michael addition (Scheme 1).[6] Herein, we present a novel asymmetric catalytic formal [3 + 2] cycloaddition method for the synthesis of 1,3-oxazolidines using cinchona-alkaloid-thiourea-based bifunctional organocatalysts.[7]

We initiated our investigations by carrying out the formal cycloaddition of (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**2a**) in the presence of the cinchonidine-derived bifunctional catalyst **4a** (10 mol %) in $CHCl_3$ at 25 °C. As expected, 1,3-oxazolidines were formed as a diastereomer mixture with modest enantioselectivity in 83% yield (Table 1, Entry 1). Screening of various solvents revealed that less polar solvents are more efficient for the stereoselectivity (Table 1, Entries 8–10).[8] When the reaction was carried out in toluene at 0 °C, the enantioselectivity was improved to 64% ee (Table 1, Entry 11). Notably, even when the catalyst loading was reduced to 1 mol %, the stereoselectivity



Scheme 1. Formal cycloaddition route to 1,3-oxazolidines using bifunctional organocatalyst.

Table 1. Optimization of conditions[a]



Entry	Catalyst	Solvent	Yield /%[b]	dr[c] (**3aa**:**3aa′**)	ee/% (**3aa**, **3aa′**)
1	**4a**	$CHCl_3$	83	2.4:1	43, 30
2	**4a**	Et_2O	78	3.0:1	59, 44
3	**4a**	THF	53	2.4:1	46, 46
4	**4a**	CPME[g]	77	2.6:1	51, 51
5	**4a**	DME[h]	63	2.4:1	55, 48
6	**4a**	CH_3CN	79	2.7:1	54, 19
7	**4a**	AcOEt	79	2.7:1	47, 22
8	**4a**	benzene	93	5.6:1	54, 22
9	**4a**	toluene	85	4.5:1	54, 32
10	**4a**	xylene	89	4.3:1	56, 37
11[d]	**4a**	toluene	95	2.4:1	64, 59
12[d,e]	**4a**	toluene	46	2.5:1	64, 60
13[f]	**4a**	toluene	62	2.4:1	67, 62
14[d]	**4b**	toluene	53	3.0:1	53, 48
15[d]	**4c**	toluene	84	9.1:1	−63, −40
16[d]	**4d**	toluene	59	10:1	−62, −24

[a]Reactions were run using **1a** (0.25 mmol), **2a** (0.25 mmol), and the catalyst (0.025 mmol) in the solvent (0.5 mL). [b]Isolated yields. [c]Diastereomeric ratios were determined by ^{1}H NMR. [d]Reactions were run at 0 °C. [e]Reaction was run using 1 mol % of **4a** (0.0025 mmol). [f]Reaction was run at −20 °C. [g]CPME: cyclopentyl methyl ether. [h]DME: 1,2-dimethoxyethane.

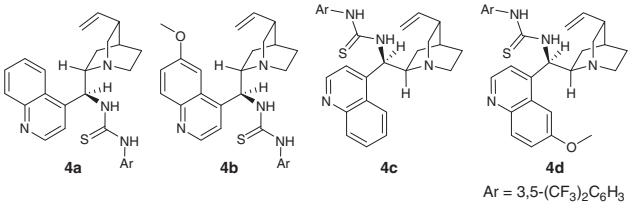
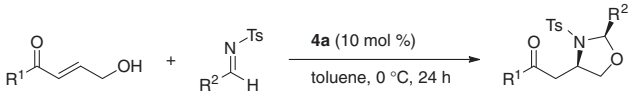


Table 2. Scope of substrates[a]



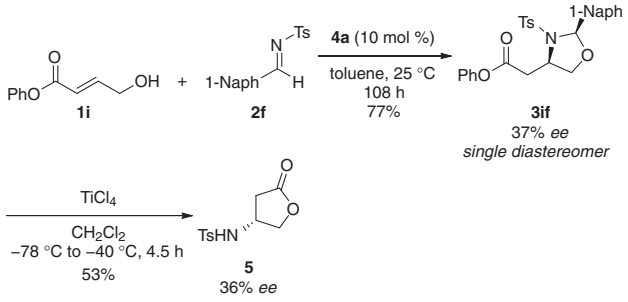
1 2 3

Entry	R^1	R^2	3	Yield /%[b]	dr[c]	ee /%[d]
1	Ph	Ph	**3aa**	95	2.4:1	64
2[e]	Ph	4-$CH_3OC_6H_4$	**3ab**	75	3.7:1	65
3	Ph	4-$CF_3C_6H_4$	**3ac**	70	4.3:1	66
4	Ph	4-BrC_6H_4	**3ad**	84	3.1:1	51
5	Ph	2-$CH_3C_6H_4$	**3ae**	74	5.3:1	57
6	Ph	1-naphthyl	**3af**	95	7.2:1	55
7	Ph	2-thienyl	**3ag**	55	9.3:1	53
8	Ph	cyclohexyl	**3ah**	99	1.9:1	74
9	Ph	*t*-Bu	**3ai**	62	2.6:1	87
10	4-$CH_3OC_6H_4$	Ph	**3ba**	58	2.2:1	63
11	4-$CH_3OC_6H_4$	1-naphthyl	**3bf**	88	5.3:1	55
12	4-$CF_3C_6H_4$	Ph	**3ca**	71	4.8:1	66
13	4-$CF_3C_6H_4$	1-naphthyl	**3cf**	95	11:1	60
14	4-BrC_6H_4	Ph	**3da**	84	4.0:1	68
15	4-BrC_6H_4	1-naphthyl	**3df**	87	11:1	60
16	2-$CH_3C_6H_4$	Ph	**3ea**	55	11:1	23
17	2-$CH_3C_6H_4$	1-naphthyl	**3ef**	90	11:1	19
18	1-naphthyl	Ph	**3fa**	93	11:1	24
19	1-naphthyl	1-naphthyl	**3ff**	87	11:1	20
20	2-thienyl	Ph	**3ga**	74	2.6:1	61
21	2-thienyl	1-naphthyl	**3gf**	91	7.2:1	49
22	$C_6H_5(CH_2)_2$	Ph	**3ha**	45	3.3:1	65
23[f]	$C_6H_5(CH_2)_2$	1-naphthyl	**3hf**	54	6.3:1	65

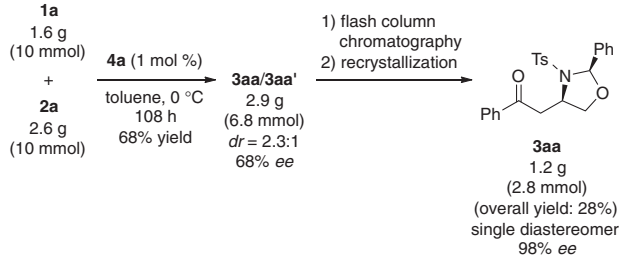
[a]Reactions were run using **1** (0.25 mmol), **2** (0.25 mmol), and **4a** (0.025 mmol) in toluene (0.5 mL). [b]Isolated yields. [c]Diastereomeric ratios were determined by ^{1}H NMR. [d]Values are for the major diastereomers of **3**. See Supporting Information for minor diastereomers.[16] [e]Reaction was run at 25 °C. [f]Reaction was run for 48 h.

remained unchanged (Table 1, Entry 12). No dramatic improvement in the stereoselectivity was observed when the reaction temperature was decreased to −20 °C, and the yield decreased considerably (Table 1, Entry 13). Catalyst screening identified that **4c** efficiently aided the formation of the opposite enantiomer of **3aa** in good yield and with high stereoselectivity (Table 1, Entry 15).[9]

With the optimized conditions and **4a** as the catalyst, we explored the substrate scope (Table 2). γ-Hydroxy-α,β-unsaturated ketones **1** could be prepared readily from commercially available materials through our reported procedure.[10] Using **1a** as the substrate, we examined the feasibility of extending the reaction to various imines **2** (Table 2, Entries 1–9).[11] The corresponding products were obtained with similar stereoselectivities regardless of the electronic nature of the imine (Table 2, Entries 2 and 3). An imine bearing a *p*-bromophenyl group also afforded the corresponding product (Table 2, Entry 4). In addition, imines with *o*-tolyl, 1-naphthyl, and 2-thienyl substituents gave the cycloadducts with high diastereoselectivity (Table 2, Entries 5–7). Notably, a high enantioselectivity of up



Scheme 2. Formal [3 + 2] cycloaddition of γ-hydroxy-α,β-unsaturated ester **1i** with **2f** and further transformation to β-amino-γ-butyrolactone **5**.

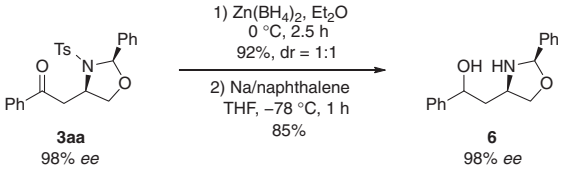


Scheme 3. Asymmetric synthesis of 1,3-oxazolidine **3aa** on a gram scale.

to 87% ee was achieved when using imines with alkyl substituents (Table 2, Entries 8 and 9). We next investigated the reactions of various enones with imines **2a** and **2f** (Table 2, Entries 10–23). In most cases, **2f** gave the corresponding 1,3-oxazolidines with high diastereoselectivity. Both electron-rich and electron-deficient enones afforded the desired cycloaddition products (Table 2, Entries 10–13). A substrate bearing a *p*-bromophenyl group was tolerated, but *o*-tolyl- and 1-naphthyl-substituted enones gave low enantioselectivities (Table 2, Entries 14–19). Further, heterocycle- or alkyl-substituted enones gave the corresponding 1,3-oxazolidines with acceptable stereoselectivities (Table 2, Entries 20–23). The absolute configuration of **3af** (the major diastereomer) was determined by X-ray analysis (see Supporting Information for details[16]),[12] and the configurations of all other examples were assigned analogously.

The γ-hydroxy-α,β-unsaturated ester **1i** could also be used with this protocol. The reaction of **1i** with the imine **2f** afforded **3if** as a single diastereomer, albeit with low enantioselectivity (Scheme 2). Subsequent treatment of **3if** with titanium tetrachloride gave β-tosylamino-γ-butyrolactone (**5**).[13] The absolute configuration of **5** was assigned as (*R*) by comparing the optical rotation with the literature value[13e] (see Supporting Information for details[16]).[14]

Although a major limitation of this reaction is its moderate stereoselectivity, we were able to establish the catalytic synthesis of enantioenriched **3aa** on a gram scale (Scheme 3). Formal [3 + 2] cycloaddition of **1a** (1.6 g, 10 mmol) with **2a** (2.6 g, 10 mmol) in the presence of 1 mol % **4a** afforded **3aa**/**3aa′** (2.9 g, 6.8 mmol, 68% yield) in a 2.3:1 diastereomeric ratio, with 68% ee for the major diastereomer **3aa**. Separation of the major diastereomer by flash silica gel column chromatography using toluene/EtOAc/hexane (v/v/v = 30/1/10) as an eluent and



Scheme 4. Deprotection of **3aa**.[15]

subsequent one-time recrystallization with 2-propanol gave 1.2 g of **3aa** (2.8 mmol, overall yield: 28%) with 98% ee. Besides, the tosyl group could be removed after reduction of the carbonyl group by treatment with sodium naphthalenide to afford **6** in high yield without any deterioration of the optical purity (Scheme 4).

In summary, we have developed a novel, efficient route to a wide range of optically active 1,3-oxazolidines via organocatalytic formal [3 + 2] cycloaddition. Despite its moderate stereoselectivity, this protocol is expected to contribute significantly to the construction of a 1,3-oxazolidine library. In addition, we have demonstrated that bifunctional organocatalysts can aid the asymmetric synthesis of nitrogen-containing heterocycles via the intramolecular aza-Michael addition. Further studies toward stereoselectivity improvement and the application of this methodology to the synthesis of other heterocycles are currently underway in our laboratory. The results of these studies will be reported in due course.

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.

References and Notes

1 For selected examples, see: a) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669. b) G. P. Moloney, D. J. Craik, M. N. Iskander, T. L. Nero, *J. Chem. Soc., Perkin Trans. 2* **1998**, 199. c) R. M. Williams, T. Glinka, M. E. Flanagan, R. Gallegos, H. Coffman, D. Pei, *J. Am. Chem. Soc.* **1992**, *114*, 733. d) F. Tomita, K. Takahashi, T. Tamaoki, *J. Antibiot.* **1984**, *37*, 1268.

2 For reviews, see: a) D. Seebach, A. R. Sting, M. Hoffmann, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. b) C. Agami, F. Couty, *Eur. J. Org. Chem.* **2004**, 677. c) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159.

3 a) K. S. Williamson, T. P. Yoon, *J. Am. Chem. Soc.* **2012**, *134*, 12370. b) M. B. Shaghafi, R. E. Grote, E. R. Jarvo, *Org. Lett.* **2011**, *13*, 5188. c) D. J. Michaelis, K. S. Williamson, T. P. Yoon, *Tetrahedron* **2009**, *65*, 5118. d) Z. Jin, X. Wang, H. Huang, X. Liang, J. Ye, *Org. Lett.* **2011**, *13*, 564.

4 a) K. Asano, S. Matsubara, *J. Am. Chem. Soc.* **2011**, *133*, 16711. b) K. Asano, S. Matsubara, *Org. Lett.* **2012**, *14*, 1620. c) T. Okamura, K. Asano, S. Matsubara, *Chem. Commun.* **2012**, *48*, 5076.

5 For reviews on asymmetric catalysis based on hydrogen bonding, see: a) *Hydrogen Bonding in Organic Synthesis*, ed. by P. M. Pihko, Wiley-VCH, Weinheim, **2009**. doi:10.1002/9783527627844. b) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713. c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem., Int. Ed.* **2006**, *45*, 1520.

6 For examples of aminocyclizations utilizing the interaction between a quinuclidine moiety in an organocatalyst and an acidic N–H group, see: a) L. Zhou, J. Chen, C. K. Tan, Y.-Y. Yeung, *J. Am. Chem. Soc.* **2011**, *133*, 9164. b) J. Chen, L. Zhou, Y.-Y. Yeung, *Org. Biomol. Chem.* **2012**, *10*, 3808.

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

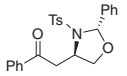
8 With an increase in the reaction time when using toluene as a solvent at 25 °C, the diastereomeric ratio improved, but the ee decreased slightly. See Supporting Information for more details, Table S1.[16]

9 Results of further catalyst screening were listed in Supporting Information (Table S2).[16]

10 M. Sada, S. Ueno, K. Asano, K. Nomura, S. Matsubara, *Synlett* **2009**, 724.

11 Reactions of imines with other protecting groups on the nitrogen atom were also investigated; sterically hindered imines such as *N*-mesitylsulfonylimine and *N*-(2-nosyl)-imine dramatically improved the diastereoselectivity but caused a slight decrease in the ee. See Supporting Information for more details, Table S3.[16]

12 The absolute configuration of **3aa′** (the minor diastereomer) was determined by X-ray analysis to be as follows (see Supporting Information for details).[16]



13 a) S. C. Bergmeier, W. K. Lee, H. Rapoport, *J. Org. Chem.* **1993**, *58*, 5019. b) C. W. Jefford, J. Wang, *Tetrahedron Lett.* **1993**, *34*, 1111. c) C. W. Jefford, B. Wang, Z.-H. Lu, *Tetrahedron Lett.* **1993**, *34*, 7557. d) C. W. Jefford, J. McNulty, *Helv. Chim. Acta* **1994**, *77*, 2142. e) C. W. Jefford, J. McNulty, Z.-H. Lu, *J. Chem. Soc., Chem. Commun.* **1995**, 123. f) C. W. Jefford, J. McNulty, Z.-H. Lu, J. B. Wang, *Helv. Chim. Acta* **1996**, *79*, 1203. g) C. Ensch, M. Hesse, *Helv. Chim. Acta* **2002**, *85*, 1659. h) R. Detterbeck, A. Guggisberg, K. Popaj, M. Hesse, *Helv. Chim. Acta* **2002**, *85*, 1742. i) G. Calvisi, N. Dell'Uomo, F. De Angelis, R. Dejas, F. Giannessi, M. O. Tinti, *Eur. J. Org. Chem.* **2003**, 4501.

14 The relative configuration of **3if** was determined by X-ray analysis. See Supporting Information for details.[16]

15 The reduction of **3aa** with $Zn(BH_4)_2$ gave a diastereomer mixture (1/1). One of the isolated diastereomers of the alcohol obtained by reduction was used for subsequent deprotection. See Supporting Information for more details.[16]

16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

