ORGANIC LETTERS

2009
Vol. 11, No. 9
2027−2029

Organocatalytic Approach to Enantioselective One-Pot Synthesis of Pyrrolidine, Hexahydropyrrolizine, and Octahydroindolizine Core Structures

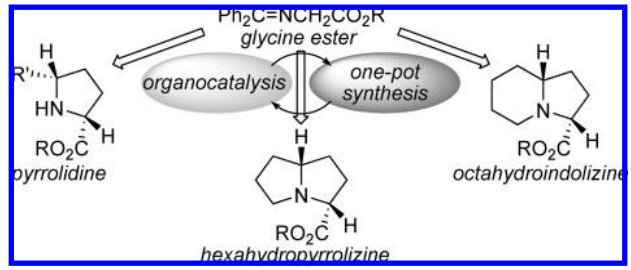
Yong-Gang Wang, Takeshi Kumano, Taichi Kano, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

maruoka@kuchem.kyoto-u.ac.jp

Received March 7, 2009

ABSTRACT



An enantioselective organocatalytic, one-pot synthesis of pyrrolidine, hexahydropyrrolizine, and octahydroindolizine core structures was realized starting from readily available glycine esters by combination with several different organocatalytic reactions.

Enantioselective organocatalysis has emerged as a powerful and promising synthetic field which is complementary to metal-catalyzed transformations and has accelerated the development of new methodologies to synthesize diverse chiral molecules.[1] The operational simplicity, ready availability of catalysts, and low toxicity associated with organocatalysis provide a highly attractive method to synthesize complex organic structures. In particular, the development of fully organocatalytic approaches to certain core structures for preparing natural products or physiologically active compounds is quite attractive and challenging in terms of the environmental consciousness. Here we wish to report our case study on this subject, targeting an enantioselective organocatalytic, one-pot synthesis of hexahydropyrrolizine and octahydroindolizine core structures[2] **1** starting from readily available glycine esters[3] **2** in combination with several different organocatalytic reactions (Scheme 1).

Our key strategy is based on the development of asymmetric conjugate addition of *N*-(diphenylmethylene)glycine ester **2** and α,β-enones **3** ($n = 1$ or 2) by using a chiral phase transfer catalyst of type (*S*)-**4** (Figure 1).[4,5] Organocatalytic intramolecular reductive amination of conjugate adduct **5** with Hantzsch ester[6,7] would proceed in a stereoselective manner to give pyrrolidine derivative **6** as an intermediate,

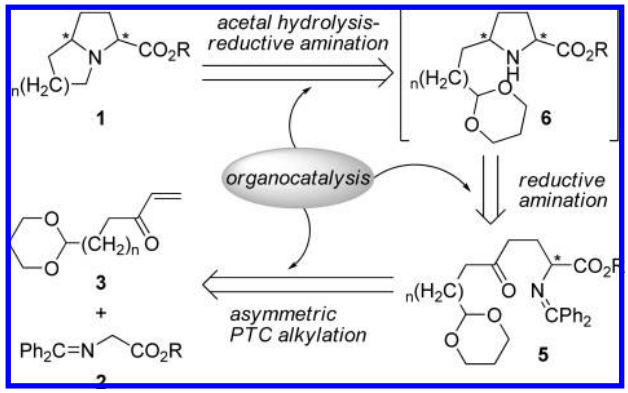
(1) Reviews: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Application in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (e) *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, Germany, 2007. (f) List, B. *Chem. Commun.* **2006**, 819. (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(2) (a) Rizk, A.-F. M., Ed. *Pyrrolizidine Alkaloids*; CRC Press: Boston, 1991; World Health Organization: Geneva, 1988. (b) Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Elsevier Science, Ltd.: Oxford, 1995; Vol. 9, Cahpter 4. (c) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (d) Michael, J. P. *Alkaloids* **2001**, *55*, 91. (e) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, *15*, 2670. (f) Cheng, Y.; Huang, Z.-T.; Wang, M.-X. *Curr. Org. Chem.* **2004**, *8*, 325. (g) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625.

(3) Maruoka, K.; Ooi, T.; Kano, T. *Chem. Commun.* **2007**, 1487.

10.1021/ol900477x CCC: $40.75 © 2009 American Chemical Society
Published on Web 04/06/2009

Scheme 1. Organocatalytic Approach to Alkaloid Core Structures



which is susceptible to the acetal hydrolysis and reductively aminated to furnish a hexahydropyrrolizine or octahydroindolizine core structure **1** (n = 1 or 2), respectively.

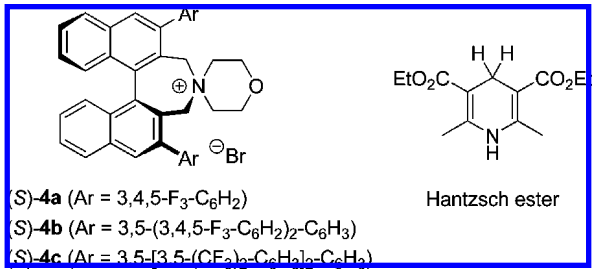


Figure 1. Chiral phase transfer catalysts and Hantzsch ester.

We first examined asymmetric conjugate addition of *N*-(diphenylmethylene)glycine di(*tert*-butyl)methyl ester **2a** and ethyl vinyl ketone under the influence of a chiral phase transfer catalyst of type (*S*)-**4** (Scheme 2 and Table 1).

Scheme 2. Synthesis of 2,5-Disubstituted *cis*-Pyrrolidine **8**

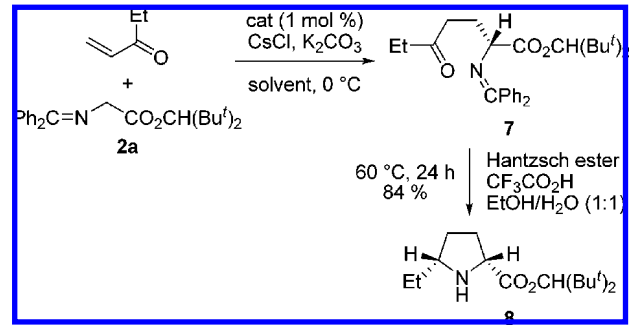


Table 1. Asymmetric Conjugate Addition of Glycine Ester **2a** with (*S*)-**4a**−**c** under Phase Transfer Conditions[a]

entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	(*S*)-**4a**	CPME	62	75
2	(*S*)-**4b**	CPME	71	94
3	(*S*)-**4c**	CPME	59	88
4	(*S*)-**4b**	THF	85	91
5	(*S*)-**4b**	Et_2O	84	94
6	(*S*)-**4b**	dioxane	55	88
7	(*S*)-**4b**	toluene	68	80

[a] Unless otherwise specified, the reaction was carried out at 0 °C for 6 h with glycine derivative **2a** and 2 equiv of ethyl vinyl ketone in the presence of 1 mol % of (*S*)-**4a**−**c**, 10 mol % of CsCl, and 5 equiv of K_2CO_3 under the given solvent and reaction conditions. [b] Isolated yield of **7**. [c] Enantiopurity of the conjugate adducts **7** was determined by HPLC analysis using a chiral column [DAICEL Chiralcel AD-H] with hexane/isopropanol as solvent.

Attempted reaction of glycine derivative **2a** and ethyl vinyl ketone with K_2CO_3 in the presence of 1 mol % of spiro-type catalyst (*S*)-**4a** and 10 mol % of CsCl[8] in cyclopentyl methyl ether (CPME) at 0 °C gave conjugate adduct **7** in 62% yield with 75% ee (entry 1). Switching (*S*)-**4a** to a sterically more hindered (*S*)-**4b** under similar conditions improved the enantioselectivity to 94% ee (entry 2).[9] On the other hand, another sterically hindered (*S*)-**4c**, which is found to be very effective in the asymmetric conjugate additions of α-substituted α-cyanoacetates to acetylenic esters,[4] was not as effective as (*S*)-**4b** in terms of both reactivity and selectivity (entry 3). Among other ethereal solvents (THF, Et_2O, and dioxane), Et_2O was found to be superior, giving 94% ee for **7** (entry 5). Use of toluene slightly decreased enantioselectivity (entry 7). With the optimal reaction condition for asymmetric conjugate addition at hand, we carried out intramolecular reductive amination of **7** with Hantzsch ester (2 equiv)[6] and CF_3CO_2H (1 equiv) in aqueous EtOH at 60 °C to furnish 2,5-disubstituted *cis*-pyrrolidine **8** stereospecifically in 84% yield (Scheme 2).

(4) (a) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (b) Lan, Q.; Wang, X.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 4675. See also: (c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656.

(5) Tandem asymmetric conjugate addition−cyclization sequence: Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Oshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.

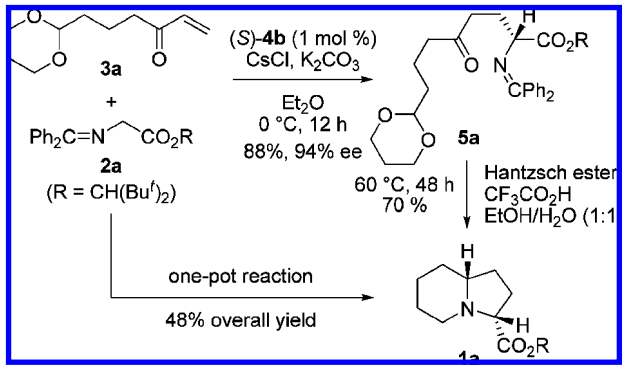
(6) Reviews: (a) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (b) You, S.-L. *Chem. Asian J.* **2007**, *2*, 820. See also (c) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036.

(7) (a) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. (b) Yang, J. W.; Hechavarria Fonseca, M. T.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108. (c) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (d) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (e) Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193. (f) Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662. (g) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368. (h) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (i) Hoffmann, S.; Nicoletti, N.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (j) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (k) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (l) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18.

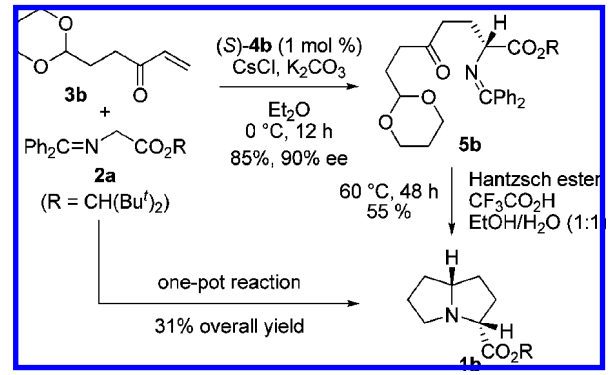
(8) Without CsCl, no reaction was observed. See also our preceding paper in this issue: Kano, T.; Kumano, T.; Maruoka, K. *Org. Lett.* **2009**, DOI: 10.1021/ol900476e.

(9) Replacement of a di(*tert*-butyl)methyl group of **2a** with a *tert*-butyl group, which is labile to CF_3CO_2H, resulted in a slight decrease in ee (from 94 to 92%).

Scheme 3. Synthesis of Octahydroindolizine **1a**



Scheme 4. Synthesis of Hexahydropyrrolizine **1b**



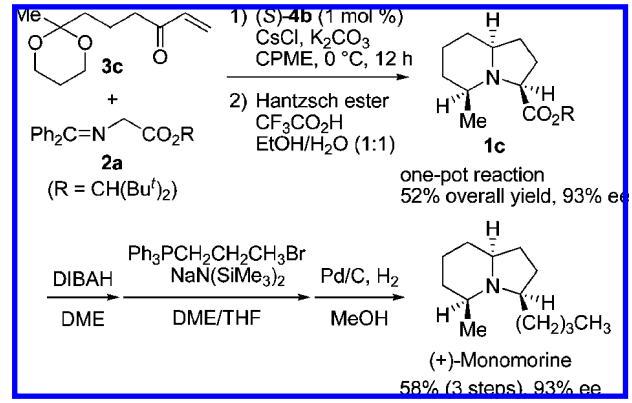
This information led us to develop a facile synthesis of octahydroindolizine core structure **1a** (Scheme 3). Accordingly, we carried out asymmetric conjugate addition of glycine ester **2a** with α,β-enone **3a** (2.0 equiv) and K_2CO_3 (5 equiv) under the influence of chiral phase transfer catalyst (*S*)-**4b** and CsCl in Et_2O at 0 °C for 15 h to give conjugate adduct **5a** in 88% yield with 94% ee. Intramolecular reductive amination of adduct **5a** and subsequent acetal hydrolysis followed by reductive amination was effected with Hantzsch ester (5 equiv) and CF_3CO_2H in aqueous EtOH at 60 °C for 48 h to furnish octahydroindolizine core structure **1a** in 70% yield without loss of enantioselectivity. The absolute configuration of **1a** was unambiguously confirmed by X-ray crystallographic analysis after reduction and subsequent *p*-bromobenzoate formation. The one-pot reaction of the whole reaction sequence was also realized without any difficulty by sequentially adding several different reagents to afford **1a** in 48% overall yield.

Asymmetric conjugate addition of glycine ester **2b** with α,β-enone **3b** (2.0 equiv) and K_2CO_3 (5 equiv) in the presence of chiral phase transfer catalyst (*S*)-**4b** and CsCl in Et_2O at 0 °C for 16 h afforded conjugate adduct **5b** in 85% yield with 90% ee (Scheme 4). It should be noted that the enantioselectivity was slightly decreased by switching the cyclic acetal moiety of **3b** to 1,3-dioxolane (78% yield, 86% ee). Treatment of the adduct **5b** with Hantzsch ester (5 equiv) and CF_3CO_2H in aqueous EtOH at 60 °C for 48 h produced hexahydropyrrolizine core structure **1b** in 55% yield. The one-pot reaction of the entire sequence was again realized to afford **1b** in 31% overall yield.

Our approach was highlighted by the short synthesis of physiologically active (+)-Monomorine in a highly stereoselective manner as shown in Scheme 5.[10,11]

In summary, we were successfully able to develop an enantioselective organocatalytic, one-pot synthesis of pyrrolidine, hexahydropyrrolizine, and octahydroindolizine core structures starting from readily available glycine esters by combination with several different organocatalytic reactions. This approach allows the facile synthesis of a natural alkaloid such as (+)-Monomorine.

Scheme 5. Synthesis of (+)-Monomorine



Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. Y.W. thanks to the Japan Society for the Promotion of Science for Postdoctoral Fellowship for Foreign Researchers.

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900477X

(10) (a) Ritter, F. J.; Rotgans, I. E. M.; Tulman, E.; Verwiel, P. E. J.; Stein, F. *Experientia* **1973**, *29*, 530. (b) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357.

(11) (a) Riesinger, S. W.; Löfstedt, J.; Petersson-Fasth, H.; Bäckvall, J.-E. *Eur. J. Org. Chem.* **1999**, 3277. (b) Momose, T.; Toshima, M.; Seki, S.; Koike, Y.; Toyooka, N.; Hirai, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1315. (c) Higashiyama, K.; Nakahata, K.; Takahashi, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 351. (d) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399, and references cited therein. (e) Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879.