ORGANIC LETTERS

2007
Vol. 9, No. 6
965−968

Chiral Diphenylprolinol TES Ether Promoted Conjugate Addition–Aldol-Dehydration Reactions between α,*β*-Unsaturated Aldehydes and 2-*N*-Protected Amino Benzaldehydes

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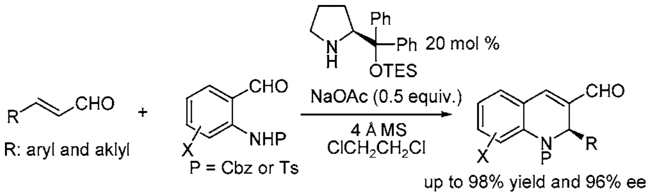
Received November 27, 2006

ABSTRACT



A conjugate addition–aldol-dehydration reaction of α,*β*-unsaturated aldehydes with 2-*N*-protected amino benzaldehydes has been developed. The process is promoted by (*S*)-diphenylprolinol TES ether to afford synthetically useful 1,2-dihydroquinolines in high enantioselectivities with good yields.

Hydroquinolines are an important class of scaffolds found in numerous naturally occurring and synthetic molecules possessing a broad spectrum of biological activities.[1,2] Accordingly, the development of efficient synthetic strategies for the construction of this molecular architecture is of considerable imporatance from the standpoint of the medicinal and organic chemistry. In addition to being an important motif in many biologically and pharmaceutically interesting compounds, functionalized 1,2-dihydroquinolines are versatile synthons for the preparation of structually complex alkaloids.[1−3] Although a number of strategies have been developed for the synthesis of the skeletons, methods for the formation of chiral 1,2-dihydroquinolines mainly rely on the use of chiral precursors and chiral auxiliaries for stereocontrol.[3] A catalytic asymmetric Reissert reaction, developed by Shibasaki et al., is a rare exception in this regard.[4]

Given the importance of this class of molecules and the fact of the lack of efficient methods for their asymmetric

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(1) For a review, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031.

(2) For examples of natural products, see: (a) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682. (b) Rakotoson, J. H.; Fabre, N.; Jacquemond-Collet, I.; Hannedouche, S.; Fouraste, I.; Moulis, C. *Planta Med.* **1998**, *64*, 762. (c) Kariba, R. M.; Houghton, P. J.; Yenesew, A. *J. Nat. Prod.* **2002**, *65*, 566.

(3) For recent examples, see: (a) Rezgui, F.; Mangeney, P.; Alexis, A. *Tetrahedron Lett.* **1999**, *40*, 6241. (b) Evans, P. A.; Robinson, J. E.; Moffett, K. K. *Org. Lett.* **2001**, *3*, 3269. (c) Pastine, S. J.; Youn, S.-W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859. (d) Pohlhaus, P. D.; Bowman, R. K.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2294. (e) Lu, G.-L.; Malinakova, H. C. *J. Org. Chem.* **2004**, *69*, 4701. (f) Cointeaus, L.; Alexakia, A. *Tetrahedron: Asymmetry* **2005**, *16*, 925.

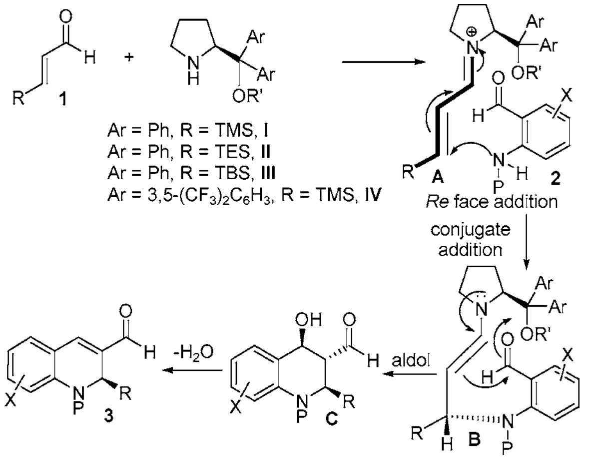
(4) (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327. Catalytic, asymmetric hydrogenation for synthesis of 1,2,3,4-tetrahydroquinolines, see: (b) Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2003**, *125*, 10536. (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. Example of catalytic, enantioselective synthesis of isoquinolines, see: (e) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700.

10.1021/ol062877u CCC: $37.00

preparation, recently we have initiated a program, aimed at the development of new organocatalytic, enantioselective cascade reactions for the facile assembly of complex structures.[5−7] Herein, we describe the first operationally simple, "one-pot" conjugate addition−aldol-dehydration protocol that enables facile access to enantioenriched 1,2-dihydroquinolines from achiral 2-*N*-protected benzaldehydes and α,*β*-unsaturated aldehydes.[8] The notable features of the process include (1) the cascade reaction efficiently catalyzed by a readily available, aerobically stable catalyst (*S*)-pyrrolidine silyl ether in the presence of a base (NaOAc) with high enantioselectivities (88−96% ee) and yields (83−98%) under very mild reaction conditions and (2) the generation of the chiral products possessing synthetically useful α,*β*-unsaturated aldehyde functionality for further structural elaboration.

Recently, we have developed an organocatalytic, enantioselective tandem thio-Michael−aldol-dehydration process.[7i] The development of conjugate addition of an amine to an electron-defficient α,*β*-unsaturated system presents a formidable synthetic challenge since, generally, an amine is a much weaker nucleophile than a thiol. Therefore, the activation of an Michael acceptor, α,*β*-unsaturated system for an amine attack by a strong Lewis acid is often required.[9,10] The first organocatalyzed enantioselective Michael addition of amines to α,*β*-unsaturated aldehydes only occurred recently, reported by MacMillan and co-workers.[11] In their case, more nucleophilic *N*-silyloxycarbamates were used as the Michael donors. The strategy we presented here is the utilization of an acyl-derived amine for a conjugate addition (Scheme 1). The conjugate addition could be enhanced by a subsequent intramolecular aldol reaction by trapping the in situ formed chiral enamine intermediate, thus significantly slowing down the retro-Michael process.[12] It is noted that Hamada and co-workers have described the tandem process.[8] However, they used a stoichiometric amount of base to activate the amine nucleophile (Michael donor), a strategy that is different from ours by activation of an Michael acceptor.

Scheme 1. Cascade Organocatalytic Enantioselective Conjugate Addition−Aldol-Dehydration Reactions



To test the feasibility of the tandem conjugate addition−aldol-dehydration process, we undertook an investigation of a variety of chiral pyrrolidine derived organocatalysts using reaction of *trans*-4-nitro cinnamaldehyde **1a** with 2-*N*-acyl-protected benzaldehydes **2a** as a model in CH_2Cl_2 at rt (Scheme 1 and Table 1). It was found that (*S*)-diarylprolinol silyl ethers **I**−**IV** were the most promising promoters among

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(5) For recent reviews of tandem reactions, see: (a) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354. (b) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (c) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143. (d) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (e) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (f) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(6) Recent reviews of organocatalystsis, see: (a) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (b) Taylor, M. S.; Jacobesn, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (c) List, B. *Chem. Commun.* **2006**, 819. (d) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5419. (e) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (f) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis−From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005. (g) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (h) Special Issue on Asymmetric Organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487.

(7) For selected examples of organocatalytic tandem reactions, see: (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199. (b) Dudding, T.; Hafez, A. M.; Taggi, A. E.; Wagerle, T. R.; Lectka, T. *Org. Lett.* **2002**, *4*, 387. (c) Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962. (d) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (e) Marigo, M.; Schulte, T.; Franzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (f) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (g) Wang, Y.; Liu, X.-F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (h) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (i) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354.

(8) Hamada and co-workers have developed the first non-asymmetric version of tandem Michael−aldol reactions, see: (a) Makino, K.; Hara, O.; Takiguchi, Y.; Katano, T.; Asakawa, Y.; Hatano, K.; Hamada, Y. *Tetrahedron Lett.* **2003**, *44*, 8925. (b) Hara, O.; Sugimoto, K.; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625.

(9) For recent reviews related to aza-Michael additions, see: (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991. (b) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.

(10) Some recent examples of enantioselective conjugate amination, see: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (c) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, 30. (d) Sibi, M. P.; Prabagaran, N.; Ghorpades, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (e) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; Garcia, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188. (f) Yamagiwa, N.; Qin, H.; Matunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419 and references cited therein.

(11) (a) Chen, Y. K.; Yishida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (b) Guerin, D. J.; Miller, S. J. *J. Am Chem. Soc.* **2002**, *124*, 2134.

(12) A reviewer proposed a plausible alternative mechanism for the tandem aza-Michael−aldol (Mannich)-dehydration reactions. In the pathway, the catalyst plays a dual role of activation of both substrates **1** and **2**.

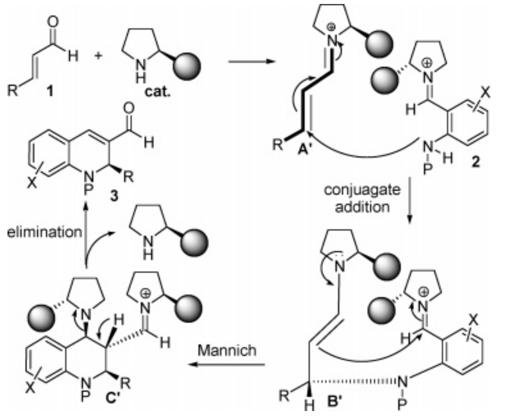
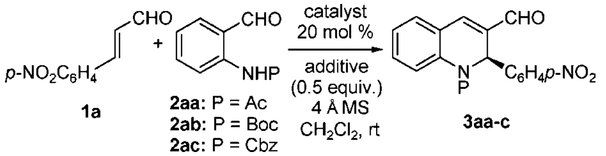


Table 1. Organocatalytic Enantioselective Cascade Conjugate Addition−Aldol-Dehydration Reaction of *trans*-4-Nitrocinnamaldehyde (**1a**) with 2-*N*-Protected Benzaldehyde (**2a**)[a]



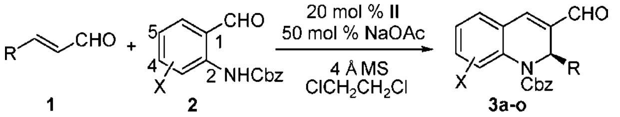
entry	cat.	P	additive	time (h)	% yield[b]	% ee[c]
1	**I**	Ac	none	84	45	92
2	**I**	Ac	$PhCO_2H$	36	41	91
3	**I**	Ac	NaOAc	84	45	92
4	**I**	Ac	PPh_3	84	45	92
5	**I**	Ac	TEA	84	44	92
6	**I**	Boc	$PhCO_2H$	84	<5	nd[d]
7	**I**	Cbz	$PhCO_2H$	24	27	93
8	**I**	Cbz	NaOAc	24	81	90
9	**II**	Cbz	NaOAc	24	71	94
10[e]	**II**	**Cbz**	**NaOAc**	**18**	**95**	**94**
11	**III**	Cbz	NaOAc	60	68	94
12	**IV**	Cbz	NaOAc	35	<5	nd[d]

[a] Reaction conditions: unless specified, catalyst (0.02 mmol) was added to a vial containing **1a** (18 mg, 0.1 mmol), **2a** (76 mg, 0.3 mmol), NaOAc (0.05 mmol), and 4 Å MS (50 mg) in CH_2Cl_2 (0.2 mL). [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Not determined. [e] $Cl(CH_2)_2Cl$ used as solvent.

organocatalysts probed (Scheme 1 and Table 1).[13] The studies revealed that the protection form of the amino group in **2** played an important role in governing the reactivity of the process. It appeared that the **I**-catalyzed reactions were not sensitive to an additive when an Ac group (**2aa**) in **2** was used (entries 1−5). High enantioselectivities (91−92% ee) but low yields (41−45%) were obtained. However, no reaction occurred for Boc-protected amino aldehyde (**2ab**) (entry 6). We found that the enantioselectivity and yield of the reaction was significantly affected by an additive when the Cbz-protected form (**2ac**) was employed (entries 7 and 8). In the presence of base NaOAc, the reaction yield was dramatically improved without sacrificing ee (81% yield, 90% ee, entry 8), presumably because NaOAc may enhance the nucleophilicity by deprotonation of the NH moiety. It was also realized that 4 Å MS significantly facilitated the elimination process. Under the same reaction conditions, a survey of other silyl ethers **II**−**IV** (entries 9−12) resulted in the best catalyst **II** for the process in terms of reaction yield (71%) and enantioselectivity (94% ee) (entry 9). Finally, screening reaction media revealed that the reaction performed in $Cl(CH_2)_2Cl$ afforded the best results in a shorter reaction time (18 h, 95% yield and 94% ee, entry 10).

The new methodology provides a facile access to a range of substituted 1,2-dihydroquinolines **3** in high enantiomeric excess (88−96% ee, Table 2). The **II**-promoted tandem aza-Michael−aldol-dehydration processes were tolerant of a variety of Michael acceptor α,β-unsaturated aldehydes **1**, which possess electron-withdrawing (entries 1−5), neutral (entries 6 and 7), donating (entries 8 and 9), a combination of withdrawing-donating (entries 10, 12, and 13), and heteroaromatic (entry 11) groups. It appeared that the steric effect imposed by these substituents (entries 2 and 9) in **1** on the process was also limited. Variation of the 2-*N*-Cbz-benzaldehydes (**2**) was also applicable for the process regardless of the nature of electronic characteristics (e.g., neutral (entries 1−2, 6, and 8−11), electron-withdrawing (entries 3 and 13) and donating (entries 4−5, 7, and 12) moieties. When alkyl α,β-unsaturated aldehydes were explored for the cascade reaction with 2-*N*-Cbz-benzaldehydes (**2**), the process proceeded very slowly (data not shown). However, the change of the protecting group from Cbz to Ts (tosyl) group in **2** led to significant enhancement of reactivity of the reaction with high enantioselectivities (91−92% ee) (entries 14 and 15). The absolute stereoconfiguration of **3n** is determined to be *R* (Figure 1).[14]

Table 2. Catalyst **II** Promoted Cascade Conjugate Addition−Aldol-Dehydration Reactions of α,β-Unsaturated Aldehydes (**1**) with 2-*N*-Cbz-benzaldehydes (**2**)[a]



entry	R	X	time (h)	% yield[b]	% ee[c]
1	4-$NO_2C_6H_4$	H	18	95	94
2	2-$NO_2C_6H_4$	H	60	98	91
3	4-$NO_2C_6H_4$	5-Cl	36	95	94
4	4-$NO_2C_6H_4$	3-MeO	12	98	93
5	4-$NO_2C_6H_4$	4,5-$(MeO)_2$	36	89	94
6	Ph	H	60	92	93
7	Ph	4,5-$(MeO)_2$	60	84	95
8	4-$MeOC_6H_4$	H	60	96	92
9	2-$MeOC_6H_4$	H	60	96	92
10	3-AcO-4-$MeOC_6H_3$	H	24	91	95
11[d]	2-furyl	H	120	83	88
12	3-AcO-4-$MeOC_6H_3$	4,5-$(MeO)_2$	120	86	96
13	3-AcO-4-$MeOC_6H_3$	5-Cl	60	96	94
14[d,e]	Me	H	12	86	92
15[e,f]	$BnOCH_2$	H	1	86	91

[a] Unless specified, for reactions conditions see footnote *a* in Table 1 and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC (Chiralpak AS-H or Chiralcel OD-H). [d] 3 equiv of **1** used. [e] Tosyl (Ts) instead of Cbz used. [f] CH_2Cl_2 instead of $Cl(CH_2)_2Cl$ used as solvent.

In conclusion, we have developed a new catalytic, highly enantioselective conjugate addition−aldol-dehydration process for the facile preparation of synthetically and biologically useful chiral 1,2-dihydroquinolines. The process, efficiently catalyzed by chiral diphenylprolinol TES ether **II**, is applicable for a wide range of readily available α,β-unsat-

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[13] For examples of (*S*)-diarylprolinol silyl ether promoted reactions, see: (a) A recent review: Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (c) Marigo, M. T.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (d) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804.

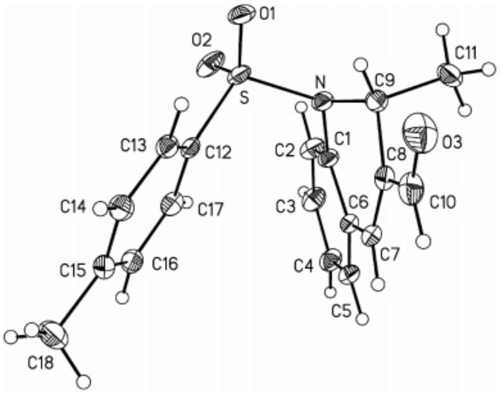

Figure 1. X-ray crystal structure of **3n**.

urated aldehydes **1** as Michael acceptors and 2-*N*-protected amino benzaldehydes **2** as donors. Our current efforts include further exploration of the reaction scope and its applications in alkaloid synthesis.

Acknowledgment. The financial support by the Department of Chemistry and the Research Allocation Committee, University of New Mexico and the American Chemical Society-PRF (G1 type) is gratefully acknowledged. The Bruker X8 X-ray diffractometer was purchased via an NSF CRIF:MU award to the University of New Mexico, CHE-0443580.

Supporting Information Available: Experimental procedures and spectra data for compounds **3a**−**o** and X-ray data (CIF file) for **3n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) See the Supporting Information for X-ray crystal data (CIF file); CCDC-619151 also contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.