J|A|C|S COMMUNICATIONS

Published on Web 06/30/2006

Enantioselective Organocatalytic Amine Conjugate Addition

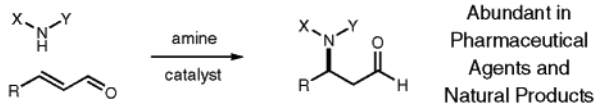
Young K. Chen, Masanori Yoshida, and David W. C. MacMillan*

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125

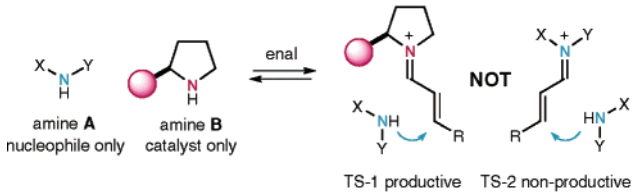
Received May 10, 2006; E-mail: dmacmill@caltech.edu

The prevalence of amines in pharmaceutical agents and natural products places C−N stereogenicity among the most important synthon targets for enantioselective reaction development.[1] While the 1,4-addition of stoichiometric chiral amines to electron-deficient olefins has long been established as a principal strategy for C−N bond construction,[2] it is surprising that corresponding catalytic variants have only recently been realized using Lewis acids with α,β-unsaturated ketones,[3a,b] imides,[3b,c] and amides.[3d] Moreover, the enantioselective conjugate amination of α,β-unsaturated aldehydes has remained elusive, a notable deficiency given the broad utility of β-amino aldehydes. Over the last six years, our laboratory has demonstrated that the reversible formation of iminium ions from chiral amine catalysts and α,β-unsaturated aldehydes is a useful platform for conjugate addition reactions involving carbon[4a−c] and hydrido[4d] nucleophiles. In this communication, we further advance this activation concept to describe the first enantioselective organocatalytic amine conjugate addition, a highly chemo- and stereoselective transform that is founded upon a rationally designed N-centered nucleophile. This operationally simple protocol allows rapid and predictable access to enantioenriched β-amino aldehydes and β-amino acids using an inexpensive amine catalyst.

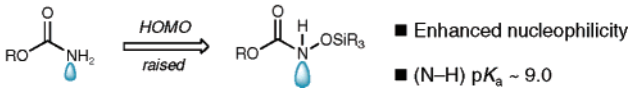
Enantioselective Organocatalytic β-Amino Aldehyde Synthesis



Iminium Catalyzed Amination Requires Selective Amine Partition

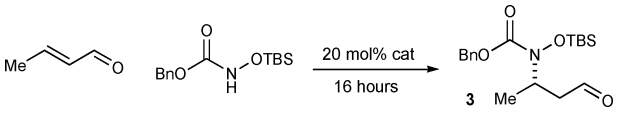


Amine A Design: Carbamate Nucleophilicity Enhanced by α-Effect



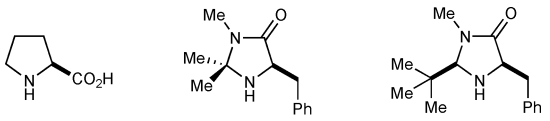
Design Plan. From the outset, we recognized that a number of chemoselectivity issues must be addressed if an enantioselective conjugate amination were to be realized using an iminium catalysis platform. First, an amine **A** must be identified that will selectively function as a 1,4-addition nucleophile (TS-1), yet will not participate in iminium activation (TS-2, a racemic pathway). Moreover, a second amine **B** must be found that will perform as an iminium catalyst (TS-1) while avoiding a nucleophilic role (a pathway that would lead to catalyst consumption). Third, to ensure that the reaction can proceed under asymmetric (kinetic) control, the stereodefining heteroatom addition step must be accompanied by *irreversible* loss of the nucleophile's proton. More specifically, this deprotonation step removes the possibility of an equilibrium-controlled process involving a reversible N-addition step (a thermodynamic pathway that would demand the formation of racemic products). In consideration of these requirements, we selected *N*-silyloxycarbamates as the nucleophilic component **A** on the basis that the N−O functionality would enhance nucleophilicity at the nitrogen center via the α-effect,[5,6] while the carbamate functionality would render the amino aldehyde product effectively nonbasic (silyloxycarbamate N−H, estimated $pK_a \sim 9.0$).[7] With respect to the catalyst component **B**, we focused upon the use of imidazolidinone amines given their established capacity[4] to participate in asymmetric iminium activation with enals and enones while selectively avoiding heteroconjugate addition.

Table 1. Effect of Catalyst and Solvent on the Conjugate Amination



entry	catalyst	solvent	temp (°C)	% conversion[a]	% ee[b]
1	L-proline	CH_2Cl_2	0	0	
2	**1**•TFA	CH_2Cl_2	−20	25	3
3	**2**•TFA	CH_2Cl_2	−20	29	81
4	**2**•HCl	CH_2Cl_2	−20	32	69
5	**2**•*p*TSA	CH_2Cl_2	−20	70	87
6	**2**•*p*TSA	EtOAc	−20	12	92
7	**2**•*p*TSA	THF	−20	45	92
8	**2**•*p*TSA	$CHCl_3$	−20	95	92

[a] Conversion determined by ^{1}H NMR analysis. [b] Enantiomeric excess determined by chiral HPLC analysis on the corresponding amino alcohol.

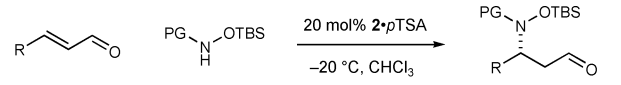


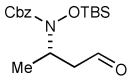
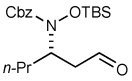
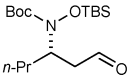
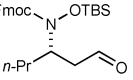
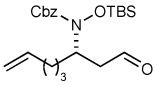
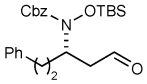
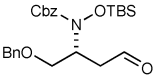
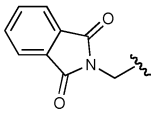
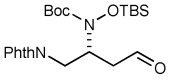
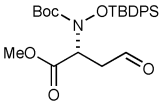
To our great delight, exposure of crotonaldehyde to benzyl *tert*-butyldimethylsilyloxycarbamate in the presence of imidazolidinone catalyst **2**•TFA did indeed provide the desired β-amino aldehyde product with good levels of enantiocontrol (Table 1, entry 3, 81% ee). Further evaluation of a variety of catalyst salts (entries 3−5) revealed that imidazolidinone **2**•*p*TSA exhibited superior conversion and selectivity. Last, a survey of reaction media (entries 5−8) demonstrated that $CHCl_3$ was the optimal solvent (entry 8, 92% ee). The superior levels of induction and reaction efficiency exhibited by catalyst **2**•*p*TSA in $CHCl_3$ to provide the amino aldehyde **3** in 92% ee and 92% yield prompted us to select these conditions for further reaction exploration (Table 2, entry 1).

The scope of the α,β-unsaturated aldehyde component in this enantioselective heteroconjugate addition has been examined. As

10.1021/ja063267s CCC: $33.50

Table 2. Scope of Enantioselective Organocatalytic Conjugate Amination



entry	R[a]	PG	product	% yield	% ee[b,c]
1	Me	Cbz		92	92
2	*n*-Pr	Cbz		77	95
3	*n*-Pr	Boc		85[d]	92
4	*n*-Pr	Fmoc		78	89
5		Cbz		87	96
6	$PhCH_2CH_2$–	Cbz		69	90
7	$BnOCH_2$–	Cbz		70	96
8		Boc		85[d]	87
9	CO_2Me	Boc		78[d]	97

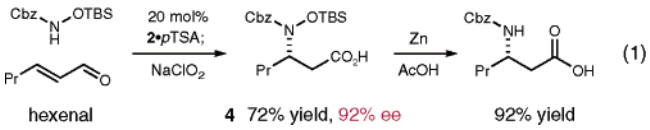
[a] Performed with 3 equiv of enal. [b] Enantioselectivity determined by HPLC or SFC analysis. [c] Stereochemistry assigned by chemical correlation or by analogy. [d] Performed with catalyst **2**·TFA.

highlighted in Table 2, enal substituents, including alkyl, alkenyl, aryl, ether, amine, and ester groups, are readily tolerated (Table 2, entries 2−9, 87−97% ee).[8] Moreover, variation of the carbamate protecting group from Cbz to Boc to Fmoc can be realized without loss in enantiocontrol (entries 2−4, 95, 92, and 89% ee). Variation of the silyloxy protecting group is also possible as illustrated by the TBDPS derivative (entry 9, 97% ee).[9] In accord with our design plan, it is important to note that β-amino aldehyde products arising from 1,4-catalyst incorporation were not detected in this study.

A demonstration of the utility of this organocatalytic amine addition and the accompanying products is presented in the one-pot (two-step) conversion of simple aldehydes to enantioenriched β-amino acids. As revealed in eq 1, exposure of 2-hexenal to our asymmetric amination conditions followed by in situ Pinnick oxidation provided the corresponding β-amino acid **4** with excellent enantioselectivity (92% ee). Notably, N−O bond removal can be accomplished under mildly reducing conditions (Zn/AcOH).[10]

Alternatively, the amino-oxy moiety can be strategically exploited to generate 1,3-amino alcohols with valuable levels of absolute and relative stereocontrol (Scheme 1). In this case, hexenal amination

Enantioselective Two-Step Synthesis of β-Amino Acids

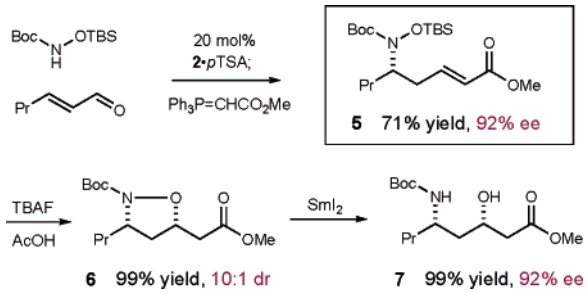


(1)

hexenal **4** 72% yield, 92% ee 92% yield

was followed by in situ Wittig homologation to afford the unsaturated ester **5** in a single operation (71% yield, 92% ee). Subsequent exposure of amino enoate **5** to fluoride ion then enabled both silyl group removal and intramolecular oxy-Michael addition to afford isoxazolidine **6** with excellent diastereocontrol (99% yield, 10:1 *syn*/*anti*). Reduction of the N−O bond was accomplished with SmI_2 to afford the 1,3-amino alcohol **7** in excellent yield (99% yield, 70% yield over three steps).[11]

Scheme 1. Enantioselective Synthesis of 1,3-Amino Alcohols



Acknowledgment. Financial support was provided by the NIHGMS (R01 GM66142-01) and kind gifts from Amgen and Merck. Y.K.C. thanks the National Cancer Institute for a postdoctoral fellowship (1 F32 CA108376-01).

Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided (9 pages, print/PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For recent reviews, see: (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367.
(2) For a review, see: Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
(3) Some recent examples of enantioselective conjugate amination: (a) Jin, X. L.; Sugihara, H.; Daika, K.; Takeishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321. (b) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (c) Guerin, D. J.; Miller, S. J. *J. Am Chem. Soc.* **2002**, *124*, 2134. (d) Yamagiwa, N.; Qin, H.; Matunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13419 and references therein. (e) Sibi, M. P.; Prabagaran, N.; Ghorpades, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796. (f) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (g) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240.
(4) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4243. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192. (d) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.
(5) This FMO description is one of several explanations for the α-effect: (a) Fleming, I. *Frontier Orbitals and Organic Reactions*. Wiley-Science: New York, 1977; p 77. (b) Heaton, M. M. *J. Am. Chem. Soc*. **1978**, *100*, 2004.
(6) An alternative explanation involving transition-state charge stablization by the adjacent heteroatom has also been described: (a) DePuy, C. H.; Della, E. W.; Filley, J.; Grabowski, J. J.; Bierbaum, V. M. *J. Am. Chem. Soc.* **1983**, *105*, 2481. (b) Buncel, E.; Um, I.-H. *Chem. Commun*. **1986**, 595.
(7) Calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (1994−2006 ACD/LABS).
(8) The catalysts shown are not successful with α-alkyl-substituted enals.
(9) The use of TBDPS-substituted systems does not generally provide an increase in selectivities in comparison to the TBS-substituted analogues.
(10) Aschwanden, P.; Kvaerno, L.; Geisser, R. W.; Kleinbeck, F.; Carreira, E. M. *Org. Lett*. **2005**, *7*, 5741.
(11) Keck, G. E.; Wagner, T. T.; McHardy, S. F. *Tetrahedron* **1999**, *55*, 11755.

JA063267S