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Enantio- and Diastereoselective Synthesis of Piperidines by Coupling of Four Components in a "One-Pot" Sequence Involving Diphenylprolinol Silyl Ether Mediated Michael Reaction

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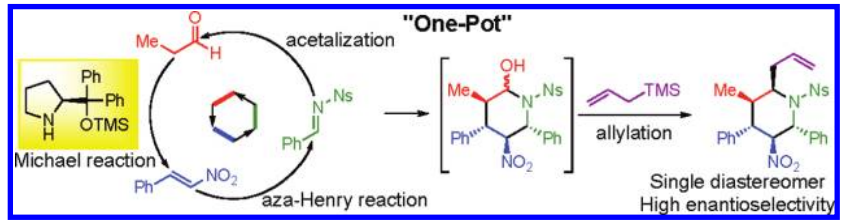
ABSTRACT



An efficient, asymmetric, four-component, one-pot synthesis of highly substituted piperidines with excellent diastereo- and enantioselectivity was established through the diphenylprolinol silyl ether mediated Michael reaction of aldehyde and nitroalkene, followed by the domino aza-Henry reaction/hemiaminalization reaction and a Lewis acid mediated allylation or cyanation reaction. All carbons of the piperidine ring are substituted with different groups, and its five contiguous stereocenters are completely controlled in both relative and absolute senses.

The "one-pot" synthesis is an effective method both for carrying out several transformations and forming several bonds in a single reaction vessel, and at the same time cutting out several purifications, minimizing chemical waste generation, and saving time.[1] Hence it is ideal for preparing complex structures by a sequence of reactions that assembles several components. Generally the number of possible diastereomers increases along with the number of components. Even though several successful examples have been reported,[2] it is difficult to develop a "one-pot" multicomponent coupling reaction sequence that proceeds with high diastereoselectivity in a catalytic, asymmetric manner.[3]

The piperidine ring is a key structural unit in organic chemistry, and there are many natural products and medicines that contain this feature. There are several methods for the preparation of the piperidine ring system.[4] The aza-Diels−Alder reaction[5] and aza [3 + 3] cycloaddition

(1) One-pot reaction covers the domino reaction and cascade reaction; see the review or book of these reactions: (a) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (b) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH, Weinheim, 2006. (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (d) Enders, D.; Grondal, C.; Huettl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (e) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167.

(2) For selected examples of the diastereoselective four-component coupling reaction, see: (a) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552. (b) Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776. (c) Smith, A. B., III; Kim, D.-S.; Xian, M. *Org. Lett.* **2007**, *9*, 3307.

(3) For selected examples of the catalytic, asymmetric four-component coupling reaction, see: (a) Ramachary, D. B.; Barbas, C. F., III *Chem.—Eur. J.* **2004**, *10*, 5323. (b) Selander, N.; Kipke, A.; Sebelius, S.; Szabo, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723. (c) Xu, X.; Zhou, J.; Yang, L.; Hu, W. *Chem. Commun.* **2008**, 6564. (d) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem.—Eur. J.* **2009**, *15*, 6815. (e) Evans, C. G.; Gestwicki, J. E. *Org. Lett.* **2009**, *11*, 2957.

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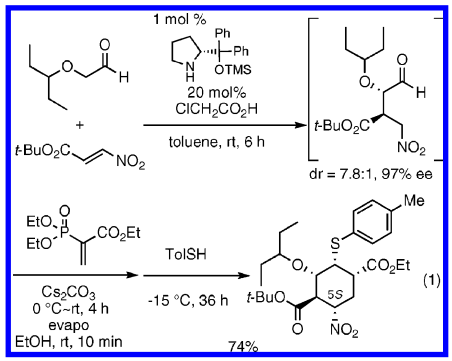
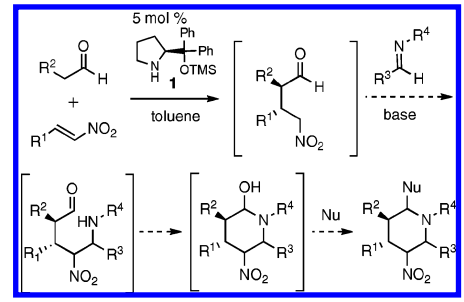
reaction[6] are straightforward methods, and we ourselves have reported an asymmetric aza [3 + 3] cycloaddition reaction of ene-carbamate and α,β-unsaturated aldehyde catalyzed by diphenylprolinol silyl ether[7] to afford substituted piperidines with excellent enantioselectivity.[8] In these preparations, not only making the piperidine framework itself but also controlling the relative and absolute configurations on the ring are key issue.

Recently we reported a synthesis of (−)-oseltamivir that involves two one-pot sequences, in which the asymmetric Michael reaction of aldehyde and nitroalkene[9] catalyzed by diphenylprolinol silyl ether,[7a] followed by a domino Michael and an intramolecular Horner−Wardsworth−Emmons reaction with a vinyl phosphonate, proceeded to afford a highly substituted cyclohexene carboxylate with excellent enantioselectivity (eq 1).[10]



In the above synthesis of (−)-oseltamivir, a γ-nitroaldehyde was reacted with a vinyl phosphonate. Were the γ-nitroaldehyde to react with an imine, an aza-Henry reaction would occur, and subsequent hemiaminalization would provide a 2-hydroxypiperidine derivative. As the generated piperidine possesses an *N*,*O*-acetal moiety, it is expected to react further with a nucleophile to afford more complex piperidine derivatives (Scheme 1). As diphenylprolinol silyl ether,[7] the catalyst in the first Michael reaction, would not interfere with the following reactions, the synthesis of highly substituted piperidine derivatives could then be performed in one pot. The realization of this hypothesis with control of the relative configuration will be described in this communication. While our work was in progress, Xu and co-workers reported a three-component coupling reaction for the formation of piperidine derivatives using two different chiral catalysts.[11]

Scheme 1. Proposed Reaction Sequence



We choose nitrostyrene and propanal as model substrates in the first Michael reaction. *N*-Benzylidene-*p*-nitrophenylsulfonylamine[12] was selected as the model imine in the second step. We choose the *p*-nitrophenylsulfonyl (Ns)[13] substituent as the protecting group on nitrogen, because it is easily removed under mildly basic conditions and is a good electron-withdrawing group. Allylsilane was chosen as the final nucleophile. The reaction sequence consists of several steps, each of which had to be optimized. The first operation is the Michael reaction of nitrostyrene and propanal, catalyzed by diphenylprolinol silyl ether, which has been developed in our group.[7a] The second is a domino aza-Henry reaction/hemiaminalization reaction, for which the effect of base was investigated. Base and imine were added to the Michael adduct reaction mixture, which was then stirred for several hours. As it is difficult to purify 2-hydroxypiperidine **2**, it was treated with Et_3SiH in the presence of CF_3CO_2H to afford piperidine derivative **3**, which was isolated (Table 1). While the reaction does not proceed in the presence of weak bases such as pyridine and $NaHCO_3$, a stronger base such as DBU gave a complex mixture. Et_3N gave the product **2** in 60% yield (entry 1), and a better yield was obtained when K_2CO_3 was employed (entry 5). Experiments to optimize the

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(5) For reviews, see: (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (c) Kobayashi, S. In *Cycloaddition Reaction in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002;, pp 187−209. For selected examples, see: (d) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999. (e) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646. (f) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (g) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075. (h) Sisti, N. J.; Motorina, I. A.; Dau, M. T. H.; Riche, C.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715.

(6) For reviews, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

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(8) Hayashi, Y.; Gotoh, H.; Masui, R.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 4012.

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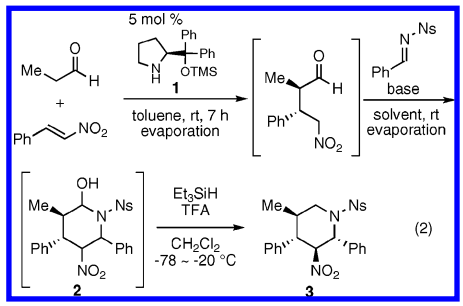
(11) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem.—Eur. J.* **2010**, *16*, 3922.

(12) (a) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber.* **1964**, *97*, 483. (b) Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2009**, *11*, 4660.

(13) For reviews, see: (a) Kan, T.; Fukuyama, T. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 779. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

Table 1. Effect of Base in the Michael/aza-Henry/Hemiaminalization Reaction[a]

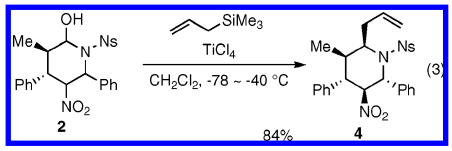


entry	base	equiv of base	solvent[b]	time[c] (h)	yield[d] (%)
1	Et_3N	1.0	toluene	6	60
2	pyridine	1.0	toluene	24	<10
3	DBU	1.0	toluene	0.5	*e*
4	$NaHCO_3$	1.0	toluene	24	<10
5	K_2CO_3	1.0	toluene	6	66
6	K_2CO_3	1.0	1,4-dioxane	6	74
7	K_2CO_3	0.2	1,4-dioxane	12	75[f]

[a] The reaction was performed using nitrostyrene (0.2 mmol), propanal (0.24 mmol), catalyst **1** (0.01 mmol), imine (0.24 mmol), and base (0.2 mmol). See Supporting Information for details. [b] Solvent in the second aza-Henry/hemiaminalization reaction. [c] Reaction time of the second aza-Henry/hemiaminalization reaction. [d] Yield of isolated product. [e] Complex mixture. [f] 97% ee.

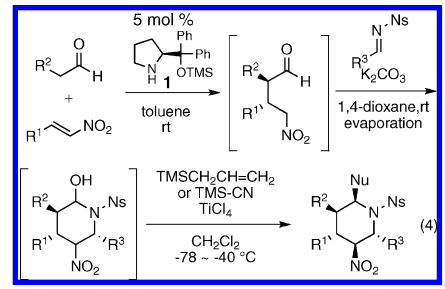
solvent led to 1,4-dioxane, use of which increased the yield of the aza-Henry reaction to 74% (entry 6). Catalyst loading (K_2CO_3) can be reduced to 20 mol % (entry 7). Piperidine derivative **3** was obtained as a single isomer, the relative configuration of which was determined from coupling constants, and the absolute configuration of which was deduced from the first enantioselective Michael reaction. The enantioselectivity of the sequence forming piperidine derivative **3** was found to be excellent (97% ee).

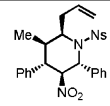
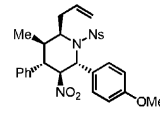
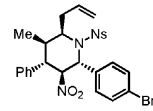
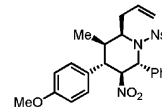
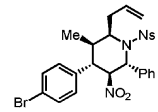
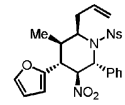
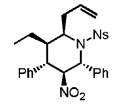
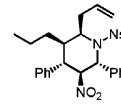
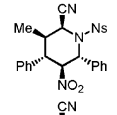
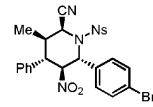
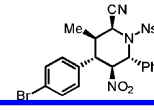
The next operation is the allylation reaction of 2-hydroxypiperidine derivative **2**. As Lewis acids are known to promote this kind of addition, their use was investigated. After several trials, $TiCl_4$ was found to be effective and to afford allylated product **4** in 84% yield as a single isomer (eq 3).



Now that each reaction had been optimized, a one-pot operation was investigated. The organocatalyst in the first Michael reaction and the base (K_2CO_3) in the second domino aza-Henry reaction/hemiaminalization are both catalytic. As bases are employed only as a catalytic amount, they should not interfere with the subsequent allylation if the proper quantity of Lewis acid is used. After adjusting the amount of Lewis acid, highly substituted piperidines can be prepared in good yield. The one-pot procedure follows: The first Michael reaction of nitrostyrene and propanal proceeded in

Table 2. One-Pot Synthesis of Chiral Piperidine Derivative Based on Michael/aza-Henry/Hemiaminalization/Allylation or Cyanation[a]



entry	product	yield[b]/%	ee[c]/%
1		79	99
2		81	99
3		79	95
4		72	98
5		78	95
6[d]		66	94
7		69	93
8		88	96
9		78	94
10		80	99
11		73	96
12		77	97

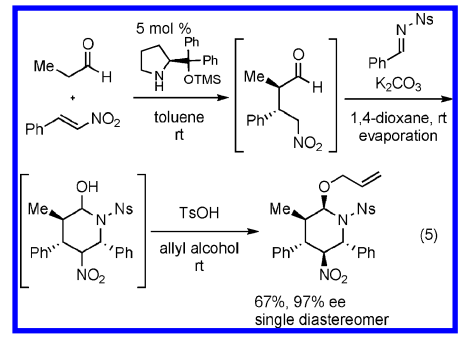
[a] The reaction was performed using nitroalkene (0.2 mmol), aldehyde (0.24 mmol), catalyst **1** (0.01 mmol), imine (0.24 mmol), and base (0.2 mmol). See Supporting Information for details. [b] Yield of isolated product. [c] For the determination of ee, see Supporting Information. [d] The reaction was performed using propanal (2.4 mmol) and nitroalkene (2.0 mmol). The purification was performed by recrystallization.

the presence of 5 mol % of diphenylprolinol silyl ether in toluene over 7 h. 1,4-Dioxane, imine, and K_2CO_3 (0.2 equiv.) were then added. After formation of the 2-hydroxypiperidine, the solvent was exchanged from a mixture of toluene and 1,4-dioxane to CH_2Cl_2, and allylsilane and $TiCl_4$ (2 equiv) were added at −78 °C. The allylated piperidine was obtained in 79% yield as a single isomer with excellent enantioselectivity (99% ee, Table 2, entry 1). The relative configuration was determined from coupling constants and a NOESY spectrum.

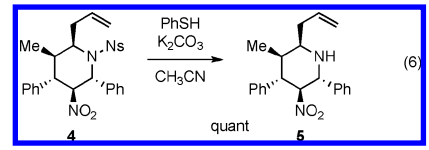
As highly diastereo- and enantioselective piperidine formation had been achieved for the model substrates, the generality of the reaction was investigated with the results summarized in Table 2. Imines derived from not only benzaldehyde (entry 1) but also benzaldehyde possessing either electron-donating or -withdrawing substituents on the phenyl ring can be successfully employed to afford piperidine derivatives in good yield (entries 2 and 3). As the β-substituent of the nitroethene, not only the phenyl group but also phenyl with either electron-donating or -withdrawing substituents, e.g., *p*-methoxyphenyl *p*-bromophenyl, can be employed (entries 4−6). 2-Furyl-1-nitroethene is also a good substrate, providing the desired piperidine in good yield with excellent enantioselectivity (entry 7). As the aldehyde in the first Michael reaction, not only propanal but also butanal and pentanal are suitable reagents (entries 8 and 9). In all of these reactions, a single isomer was obtained with excellent enantioselectivity. The reaction also proceeds efficiently in 2 mmol scale, to affrod the product in good yield after recrystallization (entry 6).

The reaction also proceeds efficiently when trimethylsilylcyanide is used as the nucleophile in place of allylsilane, affording the corresponding 2-cyano piperidine in good yield with excellent enantioselectivity (entries 10−12).

Not only allylsilane and silyl cyanide but also alcohol can be successfully employed as a nucleophile. Instead of allyltrimethylsilane and $TiCl_4$, allylalcohol and a catalytic amount of TsOH afforded 2-allyloxy piperidine as a β-isomer stereoselectively (eq 5).



As shown in eq 6, the Ns protecting group on the nitrogen is easily removed,[13] and piperidine derivative **5** was obtained quantitatively under mild conditions.



In summary, an asymmetric, one-pot reaction sequence for the synthesis of substituted piperidine derivatives has been developed via a diphenylprolinol silyl ether mediated Michael reaction of aldehyde and nitroalkene, followed by the aza-Henry reaction/hemiaminalization reaction and Lewis acid mediated allylation or cyanation. All carbons of the piperidine ring are substituted with different groups, and its five contiguous both relative and absolute configurations are completely controlled. As the allyl and cyano moieties are easily transformed into other useful functional groups, the 2-allyl and 2-cyano piperidines generated are useful optically active building blocks.

Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^1H and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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