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Organocatalytic Approach to Polysubstituted Piperidines and Tetrahydropyrans

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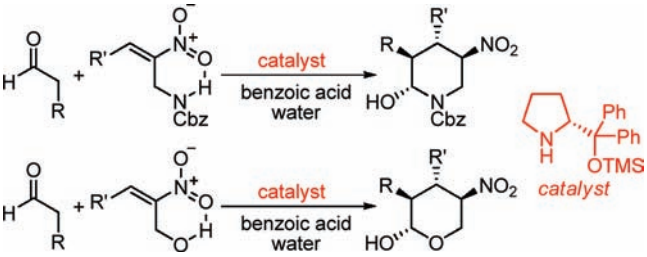

Polysubstituted piperidines and tetrahydropyrans are synthesized from aldehydes and two classes of trisubstituted nitroolefins via an *O*-TMS protected diphenylprolinol catalyzed domino Michael addition/aminalization (or acetalization) process. This approach allows formation of four contiguous stereocenters in the piperidine or tetrahydropyran ring in one step with excellent enantioselectivity.

In recent years, organocatalytic Michael addition of aldehydes to nitroolefins has received great attention.[1,2,4a,4b] However, attempts to extend the reaction scope to trisubstituted nitroolefins are rare.[3] Until now only two such substrates, 1-nitrocyclohexene and 1-nitrocyclopentene, were reported to be suitable Michael acceptors for this reaction.[3] This problem might result from these trisubstituted olefins being less reactive owing to their steric hindrance and electronic nature.

By employing functionalized electron-deficient olefins, we have explored the scope of organocatalytic Michael addition and found some synthetically useful reactions.[4] Recently, we discovered that Cbz-protected 1-aminomethyl nitroolefins **3** could react with aldehydes under the catalysis of *O*-TMS protected diphenylprolinol to give adducts **4** (Scheme 1), which spontaneously underwent aminalization to provide polysubstituted piperidines **5**.[5,6] Additionally, 1-hydroxymethyl nitroolefins were found to undergo a similar process to afford polysubstituted tetrahydropyrans. Herein, we wish to disclose our results.

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(1) For reviews, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065.

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(5) For reviews, see: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (c) Harrity, J. P. A.; Provoost, O. *Org. Biomol. Chem.* **2005**, *3*, 1349. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198.

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Scheme 1. Organocatalytic Michael Addition of Aldehydes to Cbz-Protected 1-Aminomethyl Nitroolefins **3** and Subsequent Aminalization

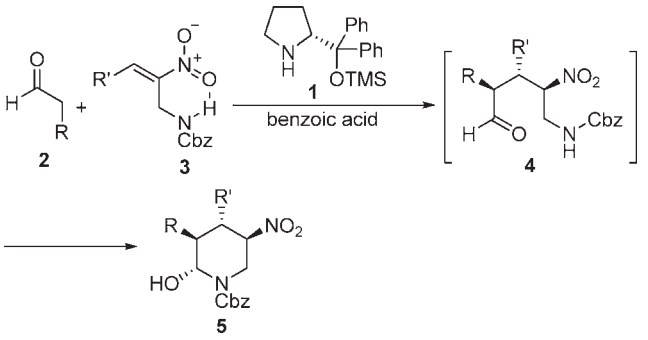
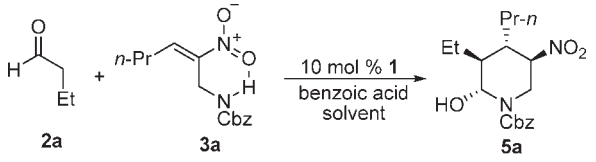


Table 1. Condition Screening for Formation of **5a** from *n*-Butanal and Nitroolefin **3a**[a]

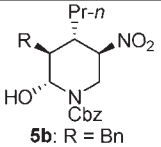
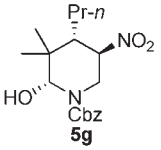
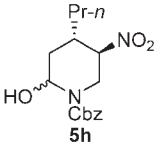
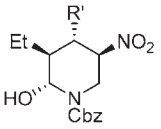
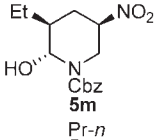
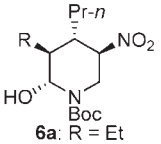
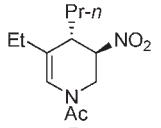


entry	solvent	BzOH (mol %)	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	H_2O	50	4	82	6:1	98
2	H_2O	30	4	85	6:1	98
3	$CHCl_3$	60[e]	24	24	5:1	99
4	MeOH	30	24	54	5:1	-
5	H_2O	30[f]	4	60	6:1	-

[a] Reaction conditions: **3a** (0.15 mmol), *n*-butanal (0.30 mmol), 10 mol % **1**, 30 mol % BzOH, water (0.3 mL), rt. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude product. [d] Determined by chiral-phase HPLC analysis of **5a**. [e] 20 mol % **1** was used. [f] HOAc was used to replace benzoic acid.

As indicated in Table 1, we chose the reaction of *n*-butanal with nitroolefin **3a** (prepared via condensation of Cbz protected 2-amino-1-nitroethane with *n*-butanal and subsequent elimination) as a model to explore optimized reaction conditions. It was found that this reaction worked under our previous conditions (10 mol % of **1** and 50 mol % of benzoic acid, in water) to afford hemiaminal **5a** in 82% yield (entry 1). Reducing the amount of benzoic acid gave a similar result (entry 2), and therefore this ratio was used in later studies. Using organic solvents (entries 3 and 4) or switching the additive to acetic acid (entry 5) reduced the

Table 2. Assembly of Polysubstituted Piperidines via Organocatalytic Reaction of Aldehydes and Functionalized Nitroolefins[a]

entry	product	yield (%)[b]	dr[c]	ee (%)[d]
1	 **5b**: R = Bn	87	9:1	>99[e]
2	**5c**: R = *i*-Pr	88	19:1	>99[e]
3	**5d**: R = $(CH_2)_7CH{=}CH_2$	86	7:1	>99[e]
4	**5e**: R = 3-butynyl	83	6:1	99
5	**5f**: R = $(CH_2)_3OBn$	91	9:1	>99
6	 **5g**	65	3:1	90 (92)[f,g]
7	 **5h**	68	ND	83[e]
8				86[e,h]
9	 **5i**: R' = Me	88	>20:1	98
10	**5j**: R' = Ph	82	>20:1	>99
11	**5k**: R' = 4-F-C_6H_4	84	>20:1	>99[i]
12	**5l**: R' = furyl	80	>20:1	>99
13	 **5m**	52	>20:1	79
14	 **6a**: R = Et	87	>20:1	>99
15	**6b**: R = $(CH_2)_3Br$	95	13:1	>99
16	 **7**	77	-	93

[a] Reaction conditions: nitroolefin (0.15 mmol), aldehyde (0.30 mmol), 10 mol % **1**, 30 mol % BzOH, water (0.3 mL), rt. [b] Isolated yield. [c] Determined by ^{1}H NMR of the crude products. [d] Determined by chiral-phase HPLC analysis of piperidines **5**−**7**. [e] Determined by chiral-phase HPLC analysis of reduced products (with $Et_3SiH/BF_3{\bullet}OEt_2$) of **5**. [f] 20 mol % **1** was used. [g] The data in parentheses is for the minor isomer. [h] The reaction was catalyzed by *O*-TMS protected dinaphthylprolinol in the absence of BzOH. [i] 15 mol % **1** was used.

(6) For recent examples on the synthesis of polysubstituted piperidines, see: (a) 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. (b) Urushima, T.; Sakamoto, D.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 4588. (c) Gnamm, C.; Krauter, C. M.; Brodner, K.; Helmchen, G. *Chem.—Eur. J.* **2009**, *15*, 2050. (d) Stephens, B. E.; Liu, F. *J. Org. Chem.* **2009**, *74*, 254. (e) Etayo, P.; Badorrey, R.; Diaz-de-Villegaas, M. D.; Galvez, J. A. *J. Org. Chem.* **2008**, *73*, 8594. (f) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (g) Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646. (h) Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.* **2006**, *128*, 4023. (i) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465. (j) Smith, A. B.; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. (k) Focken, T.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2985. (l) Legault, C. Y.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (m) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398. (n) Yu, S.; Zhu, W.; Ma, D. *J. Org. Chem.* **2005**, *70*, 7364.

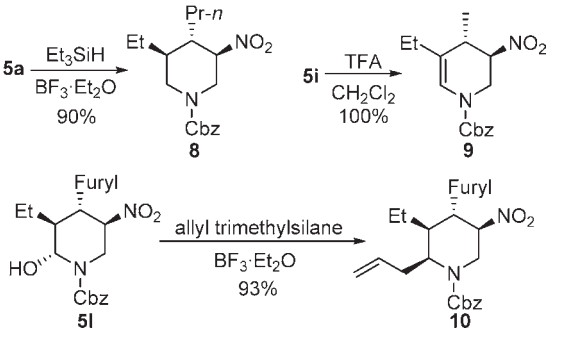
reaction yields. Thus, it seemed that a combination of benzoic acid and water is essential for this transformation.

We next examined the reaction scope by varying aldehydes and functionalized nitroolefins. As summarized in Table 2, two other simple aldehydes and three functionalized aldehydes worked well, affording substituted piperidines **5b**−**5f** with good to excellent yields and diastereoselectivity (entries 1−5). In these transformations greater than 99% ee were observed for major isomers. However, the reaction became sluggish when bulky isobutyraldehyde was employed. In this case only a moderate yield and diastereoselectivity were observed, although the enantioselectivity did not drop significantly (entry 6). We were pleased that acetaldehyde could be used successfully, delivering 3-unsubstituented piperidines with a good yield and satisfactory stereochemical outcome (entry 7). A better result was obtained by changing reaction conditions (entry 8, using *O*-TMS protected dinaphthylprolinol as a catalyst and without the addition of $PhCO_2H$).

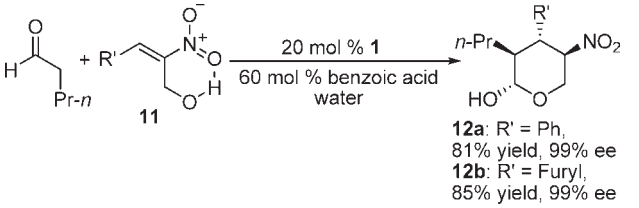
For functionalized nitroolefins, it was found that both alkyl substituted (entries 1−8) and aryl substituted olefins (entries 10−12) were compatible with this reaction. Additionally, an olefin without any substituents at the 2-position could be applied in this reaction, although both the yield and enantioselectivity were only moderate (entry 13). Furthermore, changing the N-protecting group to Boc was found possible, as evident from the fact substituted piperidines **6a** and **6b** could be elaborated from the corresponding olefins. In this case improved diastereoselectivity was obtained (compare entry 14 with entry 2 of Table 1). While an Ac-protected substrate was utilized, the resulting product was found not stable during column purification, and therefore these piperidines were converted into tetrahydropyridine **7** by treatment with TFA in order to obtain the pure product (entry 16).

Obviously, the present cyclic hemiaminals are valuable building blocks for elaborating other substituted piperidines. For example, the reduction of **5a** with Et_3SiH in the presence of $BF_3 \cdot OEt_2$ produced 1,3,4,5-tetrasubstituted piperidine **8** (Scheme 2) and the dehydration of **5i** with TFA afforded tetrahydropyridine **9**, while $BF_3 \cdot OEt_2$ mediated allylation of **4l** with allyl trimethylsilane delivered piperidine **10** as a single product. This fact, together with the knowledge that a wide range of cyclic hemiaminals could be assembled via the domino process, demonstrated that our approach provides a useful method for the diverse synthesis of substituted piperidines.[5,6] It is notable that nitro group-containing piperidines have been used as valuable intermediates for the synthesis of novel farnesyltransferase inhibitors[7] and selective dipeptidyl peptidase IV inhibitors that are promising for treatment of type 2 diabetes.[8]

Scheme 2. Transformation of Cyclic Hemiaminals into Other Substituted Piperidines



Scheme 3. Formation of Tetrahydropyrans via Reaction of Hydroxymethyl Substituted Nitroolefins with *n*-Pentanal



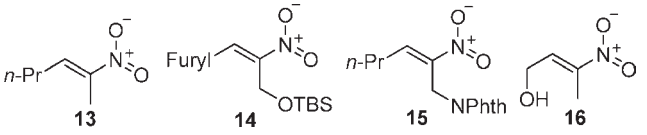


Figure 1. Structures of some trisubstituted nitroolefins.

In view of the above encouraging results, we next checked other trisubstituted nitroolefins. As outlined in Scheme 3, the reaction of hydroxymethyl substituted nitroolefins **11** and *n*-pentanal proceeded smoothly under the catalysis of **1** and benzoic acid, giving hemiacetals **12** with good yields and excellent enantioselectivity. However, nitroolefins **13**−**16** (Figure 1) were found inert under our typical reaction conditions. These results clearly demonstrated that a free NH or OH group at the 1-methylene position is essential for Michael addition of these two classes of trisubstituted nitroolefins. We speculated that two factors might be responsible for their special reactivity. One is that the intramolecular hydrogen bond might lead to a more active nitro group.[9] Another one is subsequent cyclization might facilitate the first Michael reaction. Noteworthy is that compounds **12**

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(8) Pei, Z.; Li, X.; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983.

(9) During the preparation of this manuscript, an example about the activation of a nitro group via an intramolecular hydrogen bond was reported; see: Zhang, F.; Wei, M.; Dong, J.; Zhou, Y.; Lu, D.; Gong, Y.; Yang, X. *Adv. Synth. Catal.* **2010**, *352*, 2875.

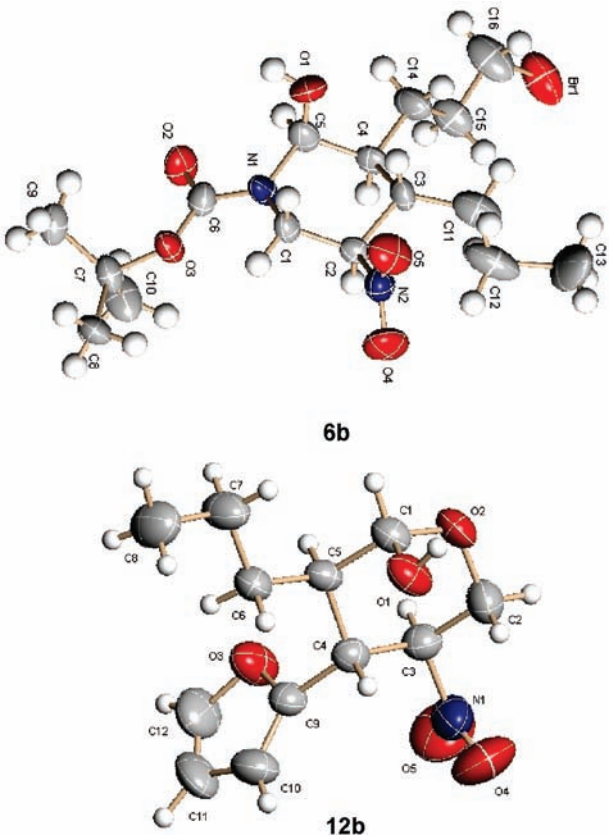

Figure 2. X-ray structures of **6b** and **12b**.

could be transformed into substituted glutamate derivatives that are useful building blocks for assembling biologically important compounds.[10] Unfortunately, only aryl substituted nitroolefins **11** were compatible with this process, while related alkyl substituted nitroolefins were found inactive. Further studies are required in order to solve this problem.

The structures of the present products were initially established by NMR analysis. Their stereochemistry was further confirmed by X-ray analysis of **6b** and **12b** as depicted in Figure 2. It is notable that in our case the stereochemistry of the nitro group was controlled excellently through enantioselective protonation (presumably in a thermodynamic manner).[11]

In conclusion, we have developed a highly efficient domino process for the assembly of polysubstituted piperidines and tetrahydropyrans. This process allows for the formation of four contiguous stereocenters in the piperidine or tetrahydropyran ring in one step with excellent enantioselectivity. The diverse functional groups in the products will permit further manipulation for synthesizing bioactive compounds. More importantly, our results demonstrated that some trisubstituted nitroolefins are suitable Michael acceptors for organocatalytic reactions, in which the intramolecular hydrogen bond might play an important role for activating the nitro group. Further investigations for extending the scope of Michael addition by using this concept are actively pursued in our laboratory, and the results will be reported in due course.

Acknowledgment. The authors are grateful to the Ministry of Science and Technology (Grant 2009ZX09501-00), Chinese Academy of Sciences, and National Natural Science Foundation of China (Grants 20632050 and 20921091) for their financial support.

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

(10) (a) Wermuth, C. G.; Mann, A.; Schoenfelder, A.; Wright, R. A.; Johnson, B. G.; Burnett, J. P.; Mayne, N. G.; Schoepp, D. D. *J. Med. Chem.* **1996**, *39*, 814. (b) Liang, B.; Carroll, P. J.; Joullié, M. M. *Org. Lett.* **2000**, *2*, 4157. (c) Okamotao, N.; Hara, O.; Makino, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1353. (d) Calimsiz, S.; Lipton, M. M. *J. Org. Chem.* **2005**, *70*, 6218. (e) Xie, W.; Ding, D.; Zi, W.; Li, G.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 2844.

(11) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359.