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One-Pot Asymmetric Synthesis of Substituted Piperidines by Exocyclic Chirality Induction

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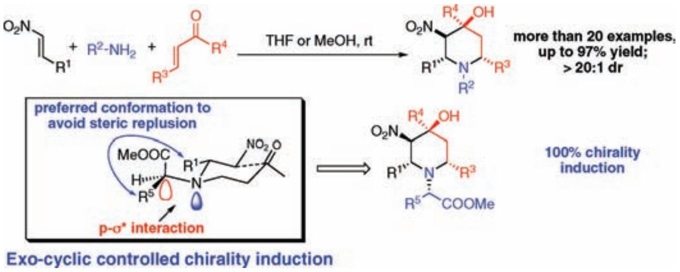
ABSTRACT



A highly efficient one-pot synthesis of substituted piperidines was developed through nitroalkene, amine, and enone condensation. The transformation was suitable for a large group of substrates, giving excellent yields and diastereoselectivity. Reactions using chiral amines revealed a chirality induction through the unusual exocyclic stereochemistry control, producing enantiomeric pure piperidines in simple steps.

Efficient new approaches for the preparation of chemically important and biologically active complex molecules are of great significance in chemical research, especially those with an intriguing mechanism and good chemo/stereoselectivity. One example is the recent fast-growing stereoselective cascade synthesis,[1] where complex building blocks are prepared from simple starting materials in “one pot”. This strategy is *particularly* important when active, unstable intermediates are involved and the desired products *cannot be achieved* through a stepwise approach.

Recently, we reported an intermolecular cross-conjugate addition between carbonyl- and nitro-activated alkenes, where primary and secondary amines served as Lewis base[2] (LB), conducting conjugate addition with nitroalkenes. The LB catalyst was sequentially released through an irreversible-β-elimination, giving the corresponding allylic nitro products (Scheme 1A). Applying this strategy, several attractive heterocycles, such as NH-1,2,3-triazoles and isoxazoline *N*-oxides, were prepared in one pot.[3] This new reaction mode, especially the amine conjugate addition to nitroalkene,[4] initiated our interest in extending the cascade process to these reactions and involved highly reactive intermediates to

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(1) For selected reviews, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Padwa, A.; Bur, S. K. *Tetrahedron.* **2007**, *63*, 5341.

(2) (a) Sun, X.; Sengupta, S.; Petersen, J. L.; Wang, H.; Lewis, J. P.; Shi, X. *Org. Lett.* **2007**, *9*, 4495. (b) Zhong, C.; Chen, Y.; Petersen, J. L.; Akhmedov, N. G.; Shi, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 1279.

(3) (a) Sengupta, S.; Duan, H.; Lu, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 1493. (b) Duan, H.; Sun, X.; Liao, W.; Petersen, J. L.; Shi, X. *Org. Lett.* **2008**, *10*, 4113.

(4) For selected examples, see: (a) Ziyaei-Halimehjani, A.; Saidi, A.; Saidi, M. R. *Tetrahedron Lett.* **2008**, *49*, 1244. (b) Ballini, R.; Araújo Baźan, N.; Bosica, G.; Palmieri, A. *Tetrahedron Lett.* **2008**, *49*, 3865. (c) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391. (d) Kamimura, A.; Kadowaki, A.; Nagato, Y.; Uno, H. *Tetrahedron Lett.* **2006**, *47*, 2471. (e) Deng, X.; Mani, N. S. *Org. Lett.* **2006**, *8*, 3505. (f) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887. (g) Barco, A.; Benetti, S.; Risi, C. D.; Pollini, G. P.; Romagnoli, R.; Zanirato, V. *Tetrahedron Lett.* **1994**, *35*, 9293. (h) Morris, M. L.; Sturgess, M. A. *Tetrahedron Lett.* **1993**, *34*, 43. (i) Worrall, D. E. *J. Am. Chem. Soc.* **1927**, *49*, 1598.

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Scheme 1. Amine Conjugate Addition to Nitroalkene as a New Reaction Mode in Promoting the Cascade Process

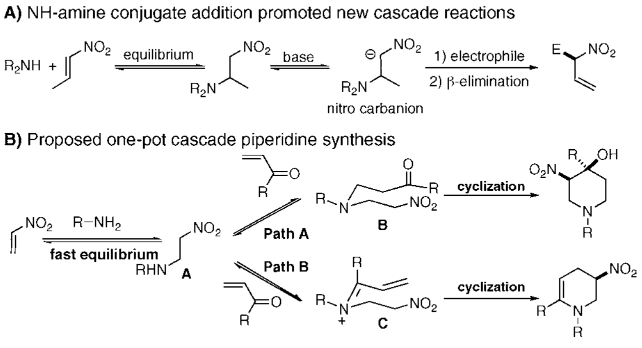
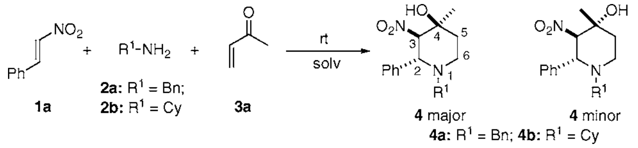


Table 1. One-Pot Condensation for the Synthesis of Piperidines[a]



	solvent	time (h)	yield[b] (%)	dr[c]	recovered **1a** (%)
4a	MeOH	12	65	5:1	30
	THF	36	97	7:1	trace
4b	MeOH	12	60	10:1	35
	THF	72	85	15:1	trace

[a] General reaction conditions: compounds **1a** (1.0 equiv), **2** (1.5 equiv), **3a** (2.0 equiv) were mixed in solvents ($c = 0.2$ M of **1a**). [b] Isolated yields of both major and minor isomers. **3a** was consumed at the end of the reaction in all cases. [c] dr determined by crude NMR.

produce complex products that are difficult to access through conventional stepwise approaches. Herein, we report the asymmetric synthesis of substituted piperidines with excellent diastereoselectivity through an unusual exocyclic stereoelectronic effect controlled complete chirality induction.

Substituted piperidines are an attractive group of heterocycles in chemical and biological research.[5] As a result, considerable interest is centered on the synthesis of these heterocycles with focus on high efficiency and good stereoselectivity.[6] This need is particularly emphasized by the fast growing call for enantiomeric pure, diverse piperidines in alkaloid[7] and aza-sugar[8] researches.

Revealed by our previous experimental and computational studies, the addition of amine to nitroalkene involves a fast equilibrium.[2a,9] We then postulated that the amine–nitroalkene adduct **A** may be suitable for sequential Michael addition and ring closure, providing the substituted piperidines through a one-pot cascade process (Scheme 1B). As rather complex reaction mixtures, different reaction pathways are possible (i.e., Baylis–Hillman reactions, Rauhut–Currier reaction). However, to our surprise, reactions between *β*-nitrostyrene **1a**, amine **2a**/**2b**, and methyl vinyl ketone (MVK) **3a** proceeded through one dominant pathway, giving the substituted piperidines **4a** and **4b** in excellent yields and good diastereoselectivity (Table 1).

The condensation products were generated through the proposed reaction path **A** shown in Scheme 1B. Notably, aza-Michael additions are known to be a challenging transformation.[10] However, through a cascade process, the aza-Michael adduct **B** was successfully trapped by the sequential Henry–aldol cyclization, giving the substituted piperidines that cannot be achieved by a stepwise synthesis.

Although three stereogenic centers were generated in piperidine **4**, only two C-4 isomers were observed.[11] The major products were the *cis* isomers of C-3 nitro and C-4 hydroxy groups. Even though other condensation products were possible, amazingly, the only side reaction observed was the polymerization of enone **3a**, when the reaction was conducted in MeOH. With THF as solvent, this side reaction was successfully minimized, giving the substituted piperidines in excellent yields (Table 1). The diastereoselectivity was also improved under this optimized condition.[12] Different nitroalkenes, amines, and enones were then applied to investigate the reaction substrate scope, and the results are summarized in Table 2.

Various kinds of substrates were suitable for this transformation, and only the C-4 isomers were obtained in all cases. Besides aryl (including heterocycles)-substituted nitroalkenes, alkyl-substituted nitroalkenes could also be applied in this transformation, providing variation on the C-2 position (i.e., **4h**, **4i**, **4k**, **4o**). In addition, both alkyl and aryl ketones were suitable for this cascade process, giving different choices of substituents on the C-4 position (i.e., **4a**, **4m**). The α-substituted enone, though giving a lower dr, could also be applied to introduce different functional groups on the C-5 position (**4t**). The *β*-substituted enone did not work well with alkyl amines due to possible steric hindrance in the aza-Michael addition. However, with NH_3 as the amine nucleophile, the desired piperidines were

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(5) For reviews, see: (a) Kallstrom, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601. (b) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875. For recent example, see: (c) Mochizuki, A.; Nakamoto, Y.; Naito, H.; Uoto, K.; Ohta, T. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 782.

(6) For review, see: (a) Buffat, M. G. P. *Tetrahedron.* **2004**, *60*, 1701. (b) For recent examples, see: Sarkar, N.; Banerjee, A.; Nelson, S. G. *J. Am. Chem. Soc.* **2008**, *130*, 9222. (c) Denmark, S. E.; Baiazitov, R. Y. *J. Org. Chem.* **2006**, *71*, 593. (d) Kobayashi, T.; Nakashima, M.; Hakogi, T.; Tanaka, K.; Katsumur, S. *Org. Lett.* **2006**, *8*, 3809.

(7) For review, see. (a) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, *19*, 3693. For recent examples, see: (b) Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126. (c) Nilsson, B. L.; Overman, L. E.; de Alaniz, J. R.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297.

(8) For selected reviews, see: (a) Cipolla, L.; La Ferla, B.; Nicotra, F. *Curr. Top. Med. Chem.* **2003**, *3*, 485. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809. (c) Pearson, M. S. M.; Mathe-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, *11*, 2159.

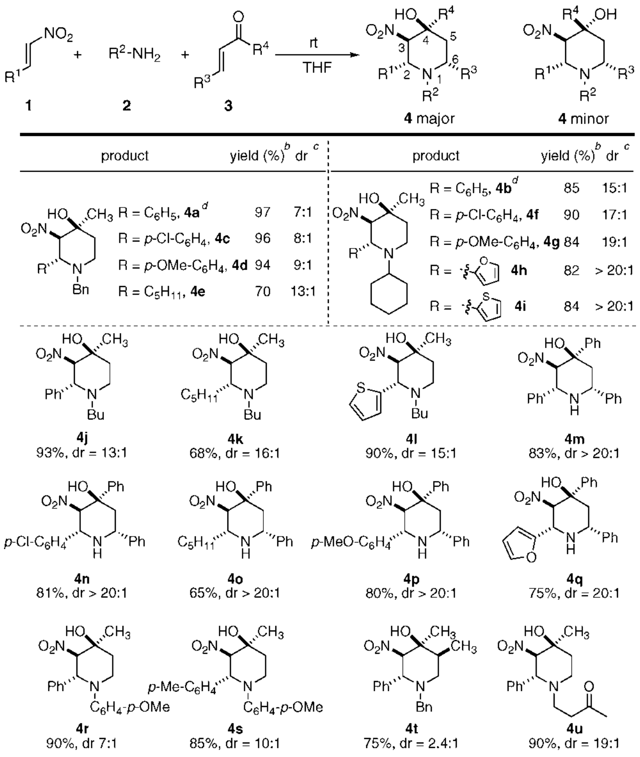
(9) At room temperature, the reaction reaches equilibrium within 1 h, and around 60% to 95% nitroalkene is converted to adduct **A** various by solvents and substrates.

(10) For selected examples, see: (a) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (b) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1246. (c) Sani, M.; Bruch, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060. (d) Fadini, L.; Togni, A. *Chem. Commun.* **2003**, *1*, 30. (e) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960.

(11) See detailed X-ray and 1D, 2D NMR information in the Supporting Information.

(12) See reaction conditions screening in the Supporting Information.

Table 2. Reaction Substrate Scope[a]

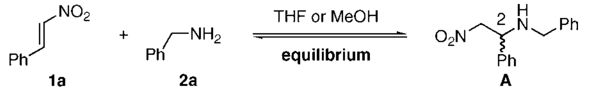


[a] General reaction conditions: compounds **1** (1.0 equiv), **2** (1.5 equiv), and **3** (2.0 equiv) were mixed in THF ($c = 0.2$ M of **1**). The reactions were monitored by TLC until compound **1** was totally consumed. [b] Isolated yields of both isomers. [c] dr determined by NMR of crude reaction mixtures. [d] Structure and relative stereochemistry were determined by X-ray crystallography.

obtained with excellent yields and diastereoselectivity (i.e., **4m−q**). Therefore, the C-6 position could also be modified by using different β-substituted enones.

Considering the great efficiency and good diastereoselectivity of this new cascade process, we then focused on investigating the stereochemistry with the hope of achieving enantiomeric pure piperidine derivatives. With the formation of C-2 stereogenic center in the amine conjugate addition to nitroalkene, it is possible that the stereochemistry of the final piperidine product is driven by this stereogenic center through the chair transition state. However, the reaction NMR studies revealed one important mechanistic insight: recharging pure adduct **A** into the reaction condition produced nitroalkene **1a** in 30 min (Scheme 2).

Scheme 2. Equilibrium in the Nitroalkene Conjugate Addition: Recharging Pure **A** into the Reaction Gave **1a** in 30 min

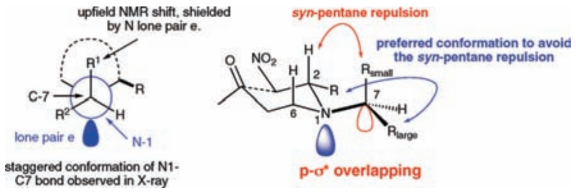


Moreover, the aza-Michael adduct **B** (Scheme 1) was never observed by reaction NMR, and piperidine products **4** were rather stable under strong basic conditions (no ring-opening products were observed even upon treating **4a** with NaOMe in MeOH for 24 h). All these results strongly suggested that the irreversible Henry−aldol cyclization was the rate-determining step, which accounts for the piperidine diastereoselectivity. We then wondered whether chiral amines could deliver the chirality into the piperidine ring by involving in the spatial arrangement in the chair transition state, through the dynamic kinetic resolution of intermediate **A**.

To investigate the chirality induction by chiral amines, arylethanamines **5a−c** were applied. As expected, piperidines **6a−c** were obtained in good yields. With the formation of two possible C-4 isomers, introduction of new stereogenic center on C-7 position could result in the formation of four diastereomers as indicated in Table 3. Excellent diastereoselectivity on C-4 position was obtained in **6a** and **6b** (comparing **P1** to **P3** and **P2** to **P4**), giving dr >10:1. For amine **5c**, MeOH was required for optimal outcome, due to the slow reaction rate in THF, which caused a slight decrease of dr on C-4 selectivity. However, to evaluate the chirality transfer by chiral amine, the relative stereochemistry of the exocyclic C-7 and the piperidine ring is the key (comparing the C-7 isomers: **P1** to **P2** or **P3** to **P4**). With possible free rotation of the exocyclic N−C bond, one may expect poor stereochemistry control. To our surprise, modest chirality induction was obtained in all three cases, giving dr on C-7 around 4:1.

Based on the X-ray crystallography and NMR spectroscopy, structures of all obtained isomers were identified. Interestingly, as shown in all crystal structures, the exocyclic C-7 adopted perfect a *staggered conformation* with the ring.[11] Moreover, the chemical shift of the C-8 and C-9 carbons were significantly shifted upfield when they were at the antiparallel position relative to nitrogen lone pair electrons (C-8 in **P1/P3** and C-9 in **P2**, Table 3)[13] Therefore, it suggested that the N1−C7 σ-bond rotation was restricted. Considering all these results, a Henry−aldol cyclization chair transition state is proposed in Scheme 3.

Scheme 3. Proposed Exocyclic Chirality Induction



As part of the six-membered ring, the N-1 nitrogen lone pair electrons adopted the axial position. Thus, with the preferred *staggered* N1−C7 conformation, three *syn*-pentane interactions would be generated in the transition state: [C-2-R to C-7-H] and [C-2/C-6-H to C-7-R_{small}]. This proposed transition-state model was consistent with the experimental observation in the synthesis of piperidine **6a−c**, where in the major stereoisomers

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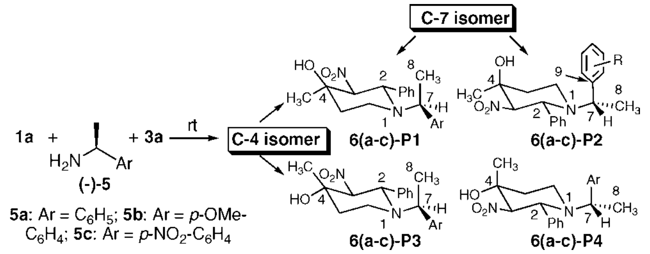
(13) See experimental details of gHMBC and HETCRO-LR NMR studies in the Supporting Information.

Table 3. Investigation of Chirality Induction by Chiral Amines[a]



5a: Ar = C_6H_5; 5b: Ar = p-OMe-C_6H_4; 5c: Ar = p-NO_2-C_6H_4

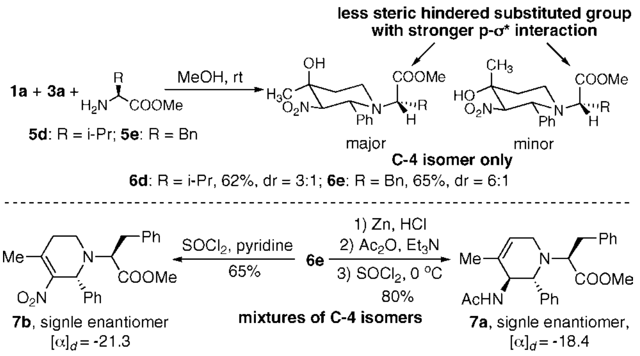
			dr (%)	^{13}C chemical shift of C-8				^{13}C chemical shift of C-9			
Ar	solvent	yield[b] (%)	**P1**:**P2**:**P3**:**P4**[c]	**P1**	**P2**	**P3**	**P4**	**P1**	**P2**	**P3**	**P4**
5a	THF	88	82:18:0:0	8.6	18.8			143.3	137.9		
5b	THF	84	78:15:7:0	8.7	19.1	8.3		135.3	130.0	135.0	
5c	MeOH	88	73:16:11:0	8.8	18.4	8.6		151.1	145.8	150.8	

[a] General reaction condition as described in Table 2. [b] Combined isolated yields of all isomers. Structures of all reported isomers were determined by either X-ray crystallography or comprehensive 1D and 2D NMR experiments. [c] dr determined by NMR of crude reaction mixtures.

the less bulky methyl group (relative to the aryl groups) was placed on the R^1 position to generate the energetically favored transition state by minimizing the *syn*-pentane steric repulsion. However, besides the steric interaction, the stability of the chair transition state could also be influenced by the p−σ* electronic interaction between nitrogen lone pair electrons and *exocyclic* axial R_{small} group. Compared to the methyl group, the more bulky phenyl group could form stronger p−σ* interactions if it were placed on the R^1 position. Therefore, we wondered whether this chirality induction could be further enhanced by application of the chiral amine with a *less bulky group that would produce stronger p−σ* interaction.* The readily available amino acid derivatives become ideal chiral amines for this application with the smaller COOMe group that provides stronger p−σ* interaction, giving energetically a more favored transition state than other different alternatives (Scheme 4). As expected, reactions among **1a**, **3a** and amino esters **5d** and **5e** generated the desired enantiomeric pure piperidine **6d** and **6e** with only C-4 isomers observed: *100% chirality induction was achieved through the chirality control by exocyclic asymmetry.*

Based on the reaction crude NMR, the C-4 isomers were the only piperidine products observed. Under the reaction conditions, 25% of unreacted **1a** was recovered in both cases, making the theoretical isolated yields of **6d** and **6e** to 83% and 87%. This result was exciting since it revealed a possible new strategy in transition state stereochemistry control, which could be applied into other amine-related heterocycle synthesis. No epimerization occurred under the reaction conditions and compounds **6d** and **6e** were indeed prepared with 100% enantiomeric purity.[14] Through some simple transformations, the two C-4 isomers were converted into single enantiomer **7a** and **7b** (Scheme 4).

Scheme 4. Enhanced Exocyclic Stereochemistry Control by Amino Esters: 100% Chirality Induction



In conclusion, applying the one-pot cascade strategy, substituted piperidines were prepared with excellent yields and great stereoselectivity. The transformation was suitable for a large group of substrates and selective functionalization on each position of the piperidine ring have been achieved. Moreover, based on an exocyclic stereochemistry control, 100% chirality induction was achieved with amino esters, giving enantiomeric pure substituted piperidines in less than three steps. It is our belief that this new stereochemistry control strategy may be further applied into similar systems for the synthesis of other chemical and biological important heterocycles.

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Supporting Information Available: Experimental details, spectrographic data, and XRD information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The functional group transformation confirmed that no epimerization occurred during the reaction.