

Stereoselective Synthesis of 2,6-*cis*- and 2,6-*trans*-Piperidines through Organocatalytic Aza-Michael Reactions: A Facile Synthesis of (+)-Myrtine and (–)-Epimyrtine

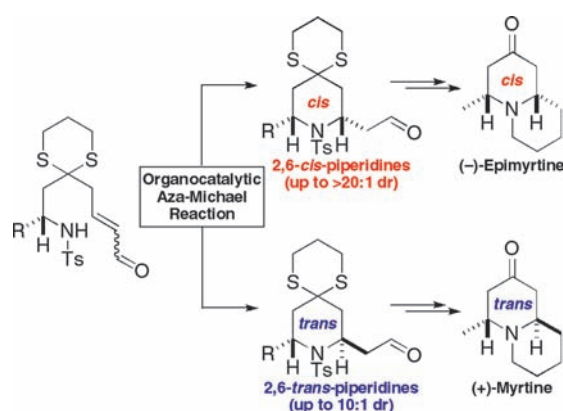
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ABSTRACT



Both 2,6-*cis*- and 2,6-*trans*-piperidines were prepared from common substrates through organocatalytic aza-Michael reactions promoted by the *gem*-disubstituent effect in conjunction with dithiane coupling reactions. The organocatalytic aza-Michael reaction enabled a facile synthesis of (+)-myrtine and (–)-epimyrtine from a common substrate.

Structurally complex piperidines are found in a wide range of biologically interesting natural products. In particular, 2,6-disubstituted piperidines have attracted considerable interest because of their therapeutic potential.¹ Although an increasing amount of interest has focused on the generation of 2,6-disubstituted piperidines,^{2,3} there are

few methods that enable the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from a common substrate. Moreover, it is surprising that the organocatalytic aza-Michael reaction has rarely been used for the stereoselective synthesis of piperidines.^{4,5}

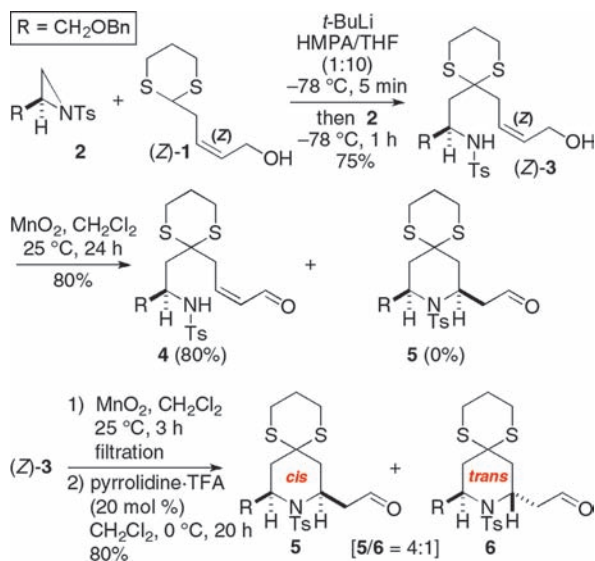
(1) (a) Struntz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 89–193. (b) Schneider, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S.W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155–299.

(2) For reviews on the synthesis of 2,6-disubstituted piperidines, see: (a) Weintraub, J. S.; Sabol, P. M.; Kane, J. M.; Borcharding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989. (b) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729. (c) Cossy, J. *Chem. Rec.* **2005**, *5*, 70–80.

(3) For recent examples of the synthesis of 2,6-disubstituted piperidines, see: (a) Gnamm, C.; Krauter, C. M.; Broedner, K.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 2050–2054. (b) Gnamm, C.; Broedner, K.; Krauter, C. M.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 10514–10532. (c) Kumar, R. S. C.; Sreedhar, E.; Reddy, V. G.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 1160–1163. (d) Kumar, R. S. C.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Chem. Lett.* **2009**, *38*, 564–565. (e) Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808–1811.

Herein, we report the stereoselective synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from common substrates through the organocatalytic aza-Michael reaction promoted by the *gem*-disubstituent effect and its application to a facile synthesis of (+)-myrtine and (–)-epimyrtine.

Scheme 1. Synthesis of 2,6-*cis*-Piperidine **5** through an Intra-molecular Aza-Michael Reaction

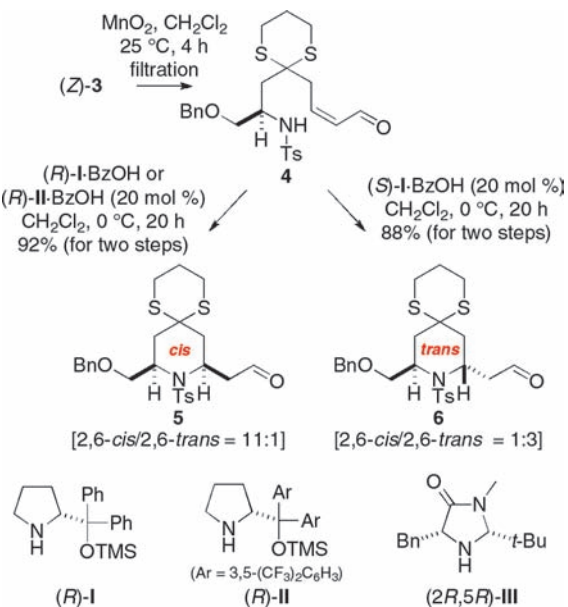


To test the feasibility of the tandem allylic oxidation/aza-Michael reaction⁶ in the synthesis of 2,6-disubstituted piperidines, we prepared substrate (Z)-3 by coupling⁷ allyl alcohol (Z)-1⁶ with the readily available Ts-protected chiral aziridine **2** and subjected it to MnO₂-oxidation conditions (Scheme 1). However, due to the poor nucleophilicity of sulfonamide **4**, the tandem allylic oxidation/aza-Michael reaction of (Z)-3 in the presence of MnO₂ failed to provide the desired 2,6-*cis*-piperidine **5**. Instead, it resulted in the exclusive formation of the intermediate (Z)-enal **4** (80%).

We hypothesized that the activation of the conjugate acceptor would help overcome the poor nucleophilicity of **4** in the aza-Michael reaction. To test this hypothesis, we converted **4** to the corresponding iminium ion by treatment

with pyrrolidine·TFA (Scheme 1). As expected, the iminium activation of **4** dramatically promoted the aza-Michael reaction to successfully provide the desired 2,6-*cis*-piperidine **5**.⁸ However, the stereoselectivity of the *substrate-controlled* aza-Michael reaction was modest (**5**:**6** = 4:1).

Scheme 2. Organocatalytic Aza-Michael Reactions for the Synthesis of 2,6-*cis*- and 2,6-*trans*-Piperidines



To further improve the stereoselectivity of the aza-Michael reaction, we decided to test chiral organocatalysts.^{4,5,9} When (R)-I¹⁰ or (R)-II^{10a} was employed (Scheme 2), the desired 2,6-*cis*-piperidine **5** was obtained with good stereoselectivity (dr = 11:1).¹¹ The catalyst (2R,5R)-III¹² also provided **5**, but in modest stereoselectivity (dr = 4:1). When (S)-I was used for the aza-Michael reaction of **4**, the 2,6-*trans*-piperidine **6** was obtained as the major diastereomer (dr = 3:1), demonstrating that the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines could be achieved from a common substrate through the organocatalytic aza-Michael reactions.¹³ To the best of our

(4) For a review on the organocatalytic aza-Michael reaction, see: Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058–11076.

(5) For examples of the synthesis of monosubstituted or benzofused piperidines by the organocatalytic aza-Michael reaction, see: (a) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51–55. (b) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–5286. (c) Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collett, N. D.; Carter, R. G. *J. Org. Chem.* **2008**, *73*, 5155–5158. (d) Fustero, S.; Moscardó, J.; Jimenez, D.; Perez-Carrion, M. D.; Sanchez-Rosello, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868–9872.

(6) For an analogous tandem allylic oxidation/oxa-Michael reaction, see: (a) Kim, H.; Park, Y.; Hong, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577–7581. (b) Kim, H.; Hong, J. *Org. Lett.* **2010**, *12*, 2880–2883.

(7) (a) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2004**, *6*, 1493–1495. (b) Smith, A. B., III; Kim, D.-S. *Org. Lett.* **2005**, *7*, 3247–3250. (c) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547–2557.

(8) The relative stereochemistry of the major diastereomer of the reaction was determined to be *cis* by 2D NMR spectroscopy (see the Supporting Information for details).

(9) For recent examples of organocatalytic aza-Michael reaction, see: (a) Uria, U.; Vicario, J. L.; Badia, D.; Carrillo, L. *Chem. Commun.* **2007**, 2509–2511. (b) Perdicchia, D.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3565–3568. (c) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636–5638. (d) Lin, Q.; Meloni, D.; Pan, Y.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999–2002. (e) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, 4119–4124. (f) Lv, J.; Wu, H.; Wang, Y. *Eur. J. Org. Chem.* **2010**, *11*, 2073–2083.

(10) (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794–797. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

(11) A variety of solvents were tested to further optimize the reaction conditions, and CH₂Cl₂ proved to be the most effective for the reaction (see the Supporting Information for details).

(12) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172–1173.

(13) To assess the effect of protecting groups on stereochemical outcome, we prepared the corresponding Boc- and Cbz-carbamates of **4** and subjected them to the organocatalytic aza-Michael reaction conditions. Both (R)-I and (S)-I provided 2,6-*cis*-piperidines as the major diastereomer (dr = 2–20:1; see the Supporting Information for details).

knowledge, the stereoselective synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from a common substrate has not been achieved for intramolecular organocatalytic aza-Michael reaction, although it has been appeared in a few other reactions such as Ir-catalyzed allylic substitutions.^{3a,b}

Table 1. Substrate Scope of the Organocatalytic Aza-Michael Reaction

entry	substrate	conditions ^a	major product (yield ^b)	dr ^c
1	(<i>Z</i>)- 8a	A	9a (91%)	11:1
		B	10a (82%)	1:3
	(<i>E</i>)- 8a	A	9a (93%)	15:1
		B	10a (86%)	1:5
2	(<i>Z</i>)- 8b	A	9b (90%)	>15:1
		B	10b (75%)	1:2
	(<i>E</i>)- 8b	A	9b (97%)	>20:1
		B	10b (80%)	1:4
3	(<i>Z</i>)- 8c	A	9c (78%)	10:1
		B	10c (78%)	1:8
	(<i>E</i>)- 8c	A	9c (87%)	12:1
		B	10c (79%)	1:10
4	(<i>Z</i>)- 8d	A	9d (90%)	15:1
		B	10d (86%)	1:1
5	(<i>Z</i>)- 8e	A	NR ^d	NA ^e
		B	NR ^d	NA ^e

^a **A**: (1) MnO₂, CH₂Cl₂, 25 °C, 3 h, filtration; (2) (*S*)-**I**·BzOH (20 mol %), CH₂Cl₂, 0 °C, 7–45 h. **B**: (1) MnO₂, CH₂Cl₂, 25 °C, 3 h, filtration; (2) (*R*)-**I**·BzOH (20 mol %), CH₂Cl₂, 0 °C, 9–67 h. ^b Combined yield of the isolated 2,6-*cis*- and 2,6-*trans*-piperidines. ^c The diastereomeric ratio (2,6-*cis*-piperidine:2,6-*trans*-piperidine) was determined by integration of the ¹H NMR spectrum of the crude product. ^d No reaction. ^e Not applicable.

To investigate the scope and stereochemical outcome of the organocatalytic aza-Michael reaction with respect to substituents at the C2 position, we prepared sulfonamides **8a–e** by coupling **1** with the commercially or readily available chiral aziridines **7a–e** and subjected them to the allylic oxidation/organocatalytic aza-Michael reaction (Table 1). We were pleased to find that the aza-Michael reaction of **8a–d** in the presence of (*S*)-**I** proceeded smoothly to provide the corresponding 2,6-*cis*-piperidines **9a–d** with good to excellent stereoselectivities (up to 20:1 dr, entries 1–4). In addition, when (*R*)-**I** was used for the aza-Michael reaction of **8a–d**, 2,6-*trans*-piperidines **10a–d** were obtained with

modest to good stereoselectivities (up to 10:1 dr, entries 1–4). However, sterically hindered tertiary amine **8e** did not afford the desired piperidines (Table 1, entry 5). It is noteworthy that higher stereoselectivities were observed with (*E*)-enals compared with the corresponding (*Z*)-enals.

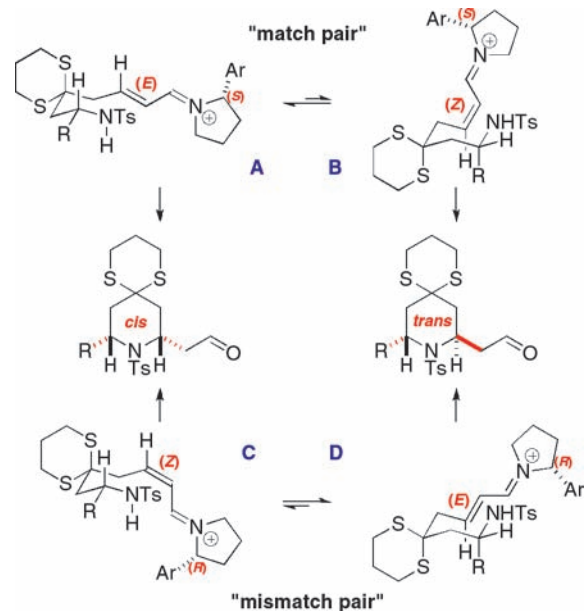


Figure 1. Proposed mechanism of cyclization of (*E*)- and (*Z*)-iminium ions.

The origin of the higher stereoselectivity with (*S*)-**I** relative to (*R*)-**I** can be explained as illustrated in Figure 1. The (*E*)-enal forms a “match pair”¹⁴ with (*S*)-**I** and proceeds through conformer **A** to provide the 2,6-*cis*-piperidine with excellent stereoselectivity. However, the combination of (*R*)-**I** and (*E*)-enal produces a “mismatch pair”, which leads to the formation of multiple competing transition states to give 2,6-*trans*-piperidine with lower stereoselectivity (conformer **D**). The reason for the higher stereoselectivity with (*E*)-enals relative to (*Z*)-enals can be rationalized on the basis that while the (*Z*)-iminium ion intermediates undergo a cyclization to provide the corresponding 2,6-*trans*-piperidine (through conformer **B** in “match pair”) and 2,6-*cis*-piperidine (through conformer **C** in “mismatch pair”), competitive and rapid isomerization to the corresponding (*E*)-iminium ion intermediates¹⁵ could occur to eventually provide the opposite diastereomers, which results in lower stereoselectivity relative to (*E*)-iminium ion intermediates.

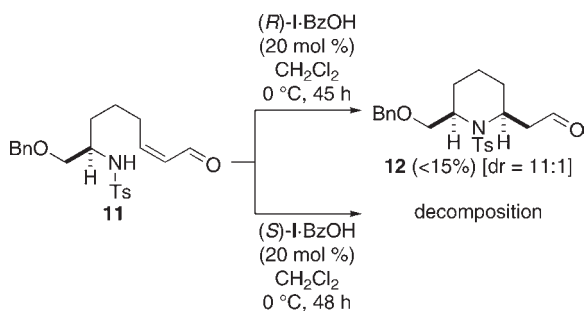
We hypothesized that the 1,3-dithiane group would be critical to overcome the low reactivity of sulfonamides by promoting an ideal conformation for cyclization through the *gem*-disubstituent effect.¹⁶ To test this hypothesis, we prepared substrate **11** with no *gem*-disubstituent effect and

(14) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1–30.

(15) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32–33.

(16) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

Scheme 3. *gem*-Disubstituent Effect on Stereoselectivity and Reaction Rate



subjected it to the reaction conditions (Scheme 3). Although the organocatalytic aza-Michael reaction of **11** in the presence of *(R)*-**I** provided 2,6-*cis*-piperidine **12** with good stereoselectivity (dr = 11:1), the yield was poor (<15%). The organocatalytic aza-Michael reaction of **11** in the presence of *(S)*-**I** failed to provide the corresponding 2,6-*trans*-piperidine; instead, decomposition of **11** was observed. These data clearly demonstrate that the *gem*-disubstituent effect by the 1,3-dithiane group is critical to overcoming the poor nucleophilicity of sulfonamides and improving the yield.

To demonstrate the versatility of the organocatalytic aza-Michael reactions for the stereoselective synthesis of 2,6-disubstituted piperidines, we embarked on the facile synthesis of (–)-epimyrntine (**16**) and (+)-myrntine (**18**) (Scheme 4).^{17,18} We envisioned that both 2,6-*cis*- and 2,6-*trans*-piperidines embedded in **16** and **18**, respectively, could be constructed from a common substrate using the organocatalytic aza-Michael reactions.

Wittig reaction of aldehyde **9b** with methyl (triphenylphosphoranylidene)acetate followed by dissolving metal reduction of the resulting (*E*)- α,β -unsaturated ester **13** afforded ester **14** with accompanying deprotection of the Ts group. LiAlH₄-reduction, mesylation, and subsequent intramolecular *N*-alkylation provided quinolizidine **15**.

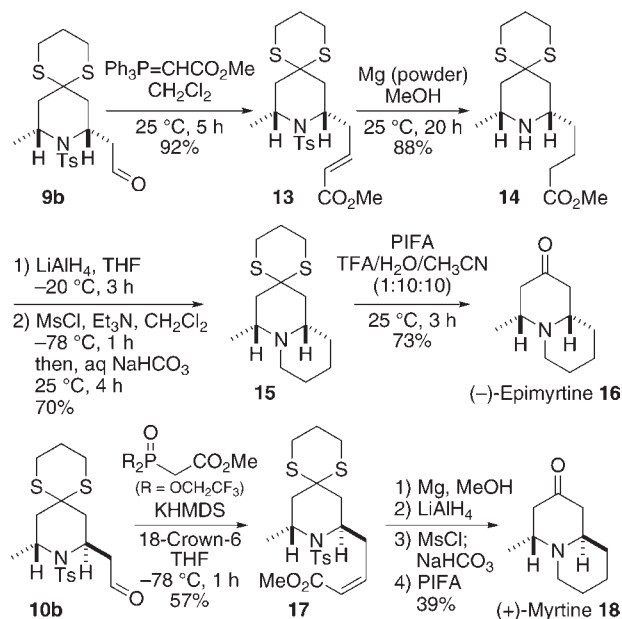
(17) For the isolation of (+)-myrntine and (–)-epimyrntine, see: (a) Slosse, P.; Hootete, C. *Tetrahedron Lett.* **1978**, 397–398. (b) Slosse, P.; Hootete, C. *Tetrahedron* **1981**, 37, 4287–4294.

(18) For the synthesis of myrntine and epimyrntine, see: (a) Slosse, P.; Hootete, C. *Tetrahedron Lett.* **1979**, 19, 4587–4588. (b) King, F. D. *J. Chem. Soc., Perkin Trans. 1* **1986**, 447–453. (c) Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, 27, 4549–4552. (d) Comins, D. L.; Weglarz, M. A.; O'Connor, S. *Tetrahedron Lett.* **1988**, 29, 1751–1754. (e) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, 30, 5053–5056. (f) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, 57, 5807–5809. (g) Gelas-Mialhe, Y.; Gramain, J.-C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, 33, 73–76. (h) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *Tetrahedron Lett.* **1993**, 34, 2729–2732. (i) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, 60, 717–722. (j) Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron: Asymmetry* **1998**, 9, 1823–1828. (k) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, 68, 8061–8064. (l) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, 70, 967–972. (m) Amorde, S. M.; Judd, A. S.; Martin, S. F. *Org. Lett.* **2005**, 7, 2031–2033. (n) Davis, F. A.; Xu, H.; Zhang, J. *J. Org. Chem.* **2007**, 72, 2046–2052. (o) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Org. Biomol. Chem.* **2008**, 6, 3464–3466. (p) Amorde, S. M.; Jewett, I. T.; Martin, S. F. *Tetrahedron* **2009**, 65, 3222–3231.

(19) (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, 30, 287–290. (b) Fleming, F. F.; Funk, L.; Altundas, R.; Tu, Y. *J. Org. Chem.* **2001**, 66, 6502–6504.

(20) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405–4408.

Scheme 4. Synthesis of (–)-Epimyrntine and (+)-Myrntine



Final deprotection of 1,3-dithiane group in **15** in the presence of bis(trifluoroacetoxy)iodo benzene¹⁹ completed the synthesis of (–)-epimyrntine (**16**).

Starting from an inseparable mixture of **10b** and **9b** (4:1), Still–Gennari olefination²⁰ followed by a separation of the resulting α,β -unsaturated esters provided (*Z*)- α,β -unsaturated ester **17**. Compound **17** was converted to (+)-myrntine (**18**) following the procedures described above.

In summary, the organocatalytic aza-Michael reaction was explored for the stereoselective synthesis of 2,6-disubstituted piperidines. The organocatalytic aza-Michael reactions allowed the synthesis of both 2,6-*cis*- and 2,6-*trans*-piperidines from the common substrates. The reaction proceeded with modest to excellent stereoselectivities (up to 20:1 dr) and yields. The 1,3-dithiane group allowed for rapid access to substrates and promoted the intramolecular aza-Michael reaction via the *gem*-disubstituent effect. We also demonstrated the utility of the combination of the organocatalytic aza-Michael reaction and the dithiane coupling reaction in the concise synthesis of (–)-epimyrntine (**16**) and (+)-myrntine (**18**) from the common intermediate. This synthetic method would be broadly applicable to the efficient synthesis of a diverse set of bioactive natural products with 2,6-disubstituted piperidines.

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Supporting Information Available. General experimental procedures including spectroscopic and analytical data along with copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.