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Formal Synthesis of (+)-Lasubine II and (−)-Subcosine II via Organocatalytic Michael Addition of a Ketone to an α-Nitrostyrene

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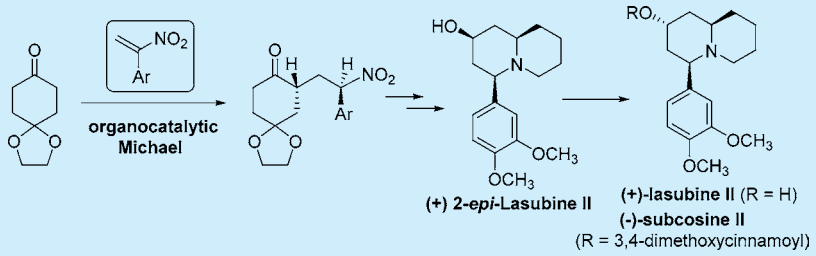
Supporting Information



ABSTRACT: The first examples of an organocatalytic Michael addition of a ketone to in situ generated α-nitrostyrenes are reported. A suitably functionalized γ-nitroketone obtained from the organocatalyzed Michael addition was converted into (+)-2-*epi*-lasubine II, the immediate synthetic precursor of (+)-lasubine II and (−)-subcosine II (enantiomers of the natural quinolizidine alkaloids). Two of the three stereocenters in (+)-2-*epi*-lasubine II are set by the Michael reaction.

The 4-arylquinolizidine motif is found in several Lythraceae alkaloids of which (−)-lasubine I and (−)-lasubine II are prominent examples (Figure 1).[1] From a structural perspective,

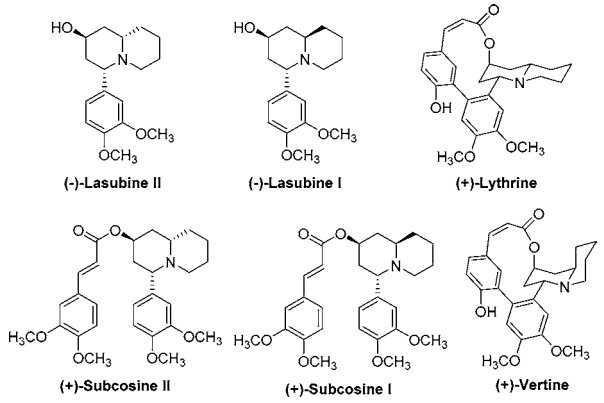


Figure 1. Selected alkaloids having the 4-arylquinolizidine motif.

the lasubine framework is incorporated in other members of the lythraceous alkaloids such as subcosines I and II[1] and the macrocyclic lactones (+)-lythrine[2] and (+)-vertine.[2] Hence, a synthetic strategy for the lasubines also provides a potential route to the macrocyclic members of the Lythraceae family. Several enantioselective syntheses of lasubine II have been investigated,[3] and only three enantioselective syntheses of subcosine II are documented.[3h,n,6e] Herein, we describe formal syntheses of (+)-lasubine II and (−)-subcosine II. Our strategy employs the previously unreported, enantioselective organocatalytic Michael addition of a ketone to an in situ generated α-nitrostyrene as the key step.

In developing a synthetic route to the quinolizidine framework in lasubine II (Figure 2), we noted that the relative

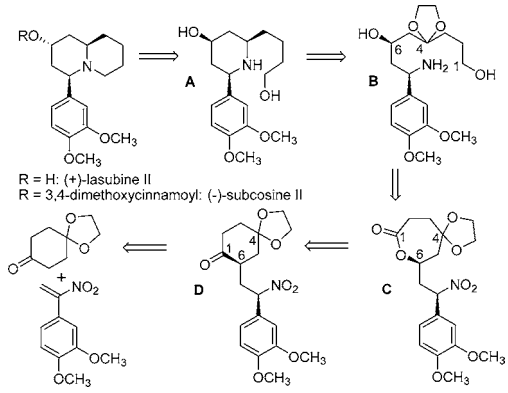


Figure 2. Strategy for the synthesis of (+)-lasubine II and (−)-subcosine II.

stereochemistry of the secondary alcohol and of the benzylic stereocenter could be established regardless of the stereochemistry in a bicyclic precursor, as either of these stereocenters can be inverted at a later stage if necessary.[4] The quinolizidine could be obtained by cyclization of a trisubstituted piperidine **A**. Construction of **A** was planned from a diastereomerically pure acyclic precursor **B** by homologation of the alcohol, deprotection of the acetal, and piperidine ring formation by intramolecular reductive amination. We anticipated that 1,3-induction during the formation of

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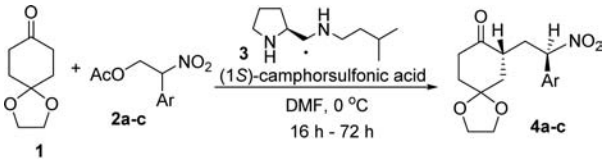
the piperidine ring[5] would assist in setting the new stereocenter in the product (diequatorial disposition of Ar and side chain in **A**). Compound **B** derives from the nitrolactone **C** by reductive ring opening of the lactone. The nitrolactone ultimately leads to the γ-aryl-γ-nitroketone **D** as the key starting material. From a methodology development perspective, γ-aryl-γ-nitroketones like **D** are appealing starting materials for 2,6-disubstituted 3-hydroxypiperidines such as **B**, many of which have interesting biological profiles and are also valuable synthetic intermediates.[6] We therefore chose to address the stereoselective synthesis of the γ-nitroketone **D** by employing the organocatalytic Michael addition of a monoprotected cyclohexanedione to an α-nitrostyrene as the pivotal step.

At the outset, since organocatalytic Michael additions of ketones to α-nitrostyrenes (1-aryl-1-nitroethylenes) are not reported,[7] the stereochemistry of **D** that could be obtained from such a reaction was not foreseeable. However, the approach was attractive since it had the potential to establish two of the three stereocenters in the product (Figure 2). Accordingly, we initiated studies on the Michael addition of ketone **1** to a suitable α-nitrostyrene. In anticipation of the high reactivity of the α-nitrostyrene, and the known tendency of such nitroalkenes to either polymerize[8a] or rearrange,[8b] we chose to generate the required α-nitrostyrene in situ[9] from the nitroacetate **2a**.[10] Initially, selected[11] primary and secondary amines were screened for their ability to induce the elimination of acetate from **2a** (Ar = 3,4-dimethoxyphenyl) as well as catalyze the Michael addition of ketone **1** to provide the nitroketone **4a**. From this study, the diamine **3**[12] (20 mol %) in the presence of (1*S*)-camphorsulfonic acid as the cocatalyst (20 mol %) in DMF emerged as the catalytic system of choice. The nitroacetates **2b**[10] (Ar = 4-bromophenyl) and **2c**[10] (Ar = phenyl) were also employed for the Michael addition, and these provided the corresponding nitroketones **4b** and **4c**, respectively. These results are summarized in Scheme 1.

Scheme 1. Diamine-Catalyzed Michael Addition of 1 to in Situ Generated α-Nitrostyrenes



	Ar	yield(%)[a]	dr	er[a]
4a	3,4-$(CH_3O)_2C_6H_4$	51	1.7:1	96:4
4b	4-BrC_6H_4	52	1.4:1	93:7
4c	Phenyl	51	1.4:1	91:9

[a]For major diastereomer.

The syntheses of nitroketones **4** constitute the first examples of the stereoselective Michael addition of a ketone to in situ generated α-nitrostyrenes. The diastereoselectivity of the process is low (~1.5:1 dr), but the diastereomers can be easily separated to provide the major diastereomer in synthetically useful yield (51−52%) and enantiomeric excess (82−92% ee).[13] Employing the optimized reaction conditions, gram quantities of **4a** could be synthesized routinely. The absolute configuration of **4a** (*R*,*R*) was established by X-ray crystallographic analysis (Figure 3).[14] The absolute configurations of **4b** and **4c** are based on the similarity in chemical shift and multiplicity of the benzylic proton as compared to **4a**.

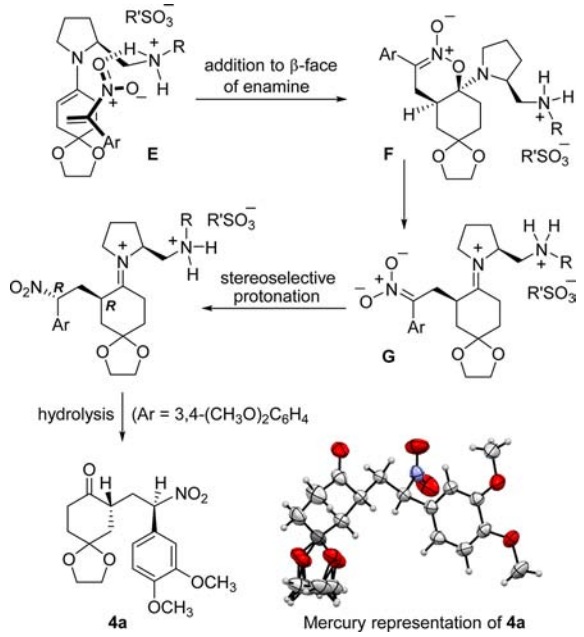


Figure 3. Formation of the major diastereomer **4** and X-ray crystal structure of nitroketone **4a**.

Although the mechanistic details for the formation of **4a−c** are not established, it is plausible that the Michael addition of **1** with the α-nitrostyrenes derived from **2a−c** proceeds via a hydrogen-bonded[15] intermediate **E** (Figure 3) in which the nitroalkene is delivered to the β face of the enamine derived from **1** and the catalyst **3**. This step establishes the ring stereocenter in the major diastereomers **4a−c**, and it could generate the 1,2-oxazine *N*-oxide intermediate **F**.[16] Subsequent opening of the oxazine produces the nitronate **G**, which is protonated stereoselectively to generate the benzylic stereocenter in **4**. The origin of stereoselectivity in the protonation step is not known at present. The low diastereoselectivity of the Michael addition may be due to the high reactivity of the α-nitrostyrene, which enables a competing, non-hydrogen-bonded addition to the α face of the enamine.

With **4a** in hand, a synthesis of the lasubine framework was initiated. Treatment of **4a** with *m*-CPBA provided the Baeyer−Villiger oxidation product **5**, which was reduced to the nitrodiol **6**. In order to prevent potentially competing reactions involving the primary alcohol in **6** (hemiacetal formation and its reduction to a tetrahydrofuran[17] in subsequent transformations), it was converted to the primary acetate prior to hydrolysis of the acetal. This provided the δ-nitroketone **7** (Scheme 2) which was examined as a precursor to the functionalized piperidine ring in lasubine.

Initial studies with **7** were focused on converting the nitroketone in **7** to the cyclic nitrone **9** (Scheme 3), which could potentially be reduced stereoselectively to establish the third stereocenter in the piperidine ring. However, only a trace of nitrone **9** could be detected in the complex mixture of products obtained from the attempted reduction of **7** (Zn/aq NH_4Cl). It is plausible that **9** is unstable and it undergoes unwanted side reactions such as dehydration and/or isomer-

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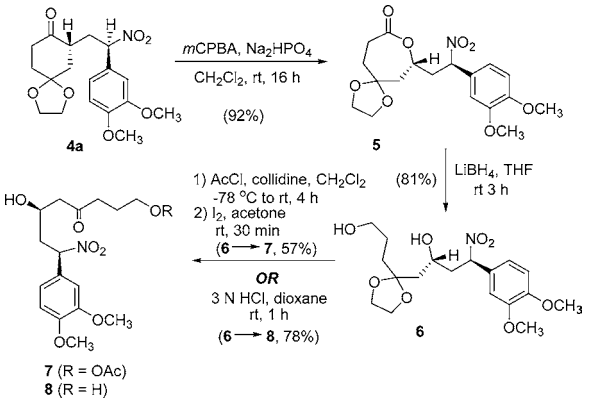
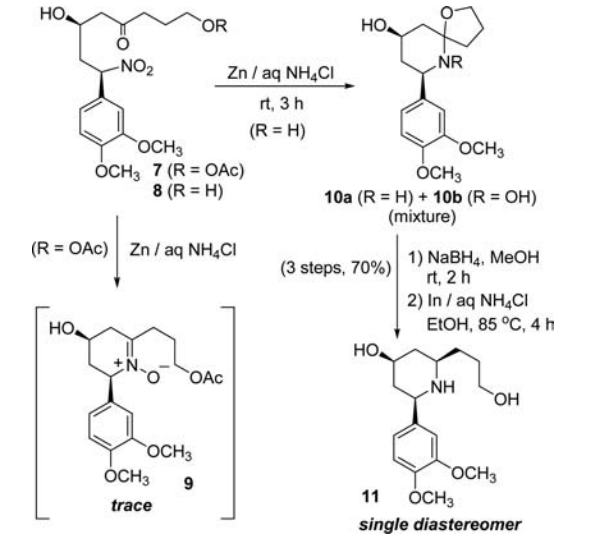
Scheme 2. Conversion of 4a into the γ-Nitroketones 7 and 8



Scheme 3. Synthesis of the Trisubstituted Piperidine 11

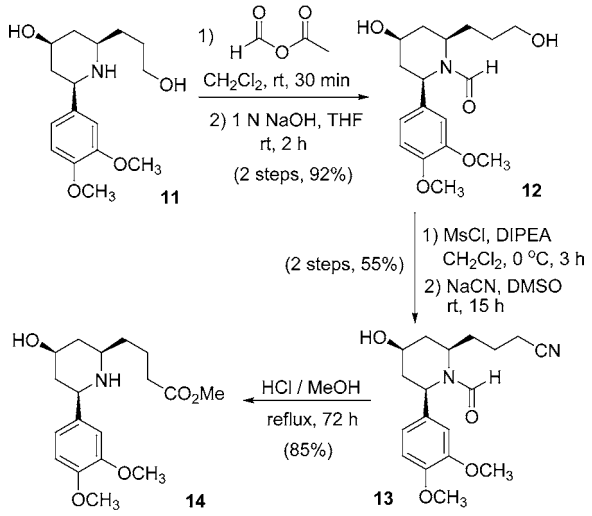


ization[18] to the conjugated nitrone. In contrast, reduction of the nitroketone **8** (obtained by deprotection of **6**, Scheme 2) with Zn/aq NH_4Cl provided an inseparable mixture of the spiropiperidine **10a** and its *N*-hydroxy analogue **10b**. This mixture was first reduced with $NaBH_4$ to provide a mixture of the trisubstituted piperidine **11** and the corresponding *N*-hydroxypiperidine. Subsequent reduction of this mixture with indium metal provided **11** as a single diastereomer. The newly formed stereocenter in **11** was assigned the *R* configuration on the assumption that the 2,6-*cis* (diequatorial) isomer would be favored[5] in the reduction of the imine or nitrone that is transiently formed from **10**.

The conversion of **11** into the quinolizidine framework required a homologation of the hydroxypropyl side chain at C6. This was achieved by transitory protection of the nitrogen by formylation (treatment with excess formic acetic anhydride, followed basic hydrolysis of the concurrently formed formate esters) to provide **12** (Scheme 4) followed by activation of the primary alcohol as the mesylate and subsequent cyanation to provide **13**. Simultaneous methanolysis of the nitrile as well as the formamide in **13** provided the amino ester **14**.

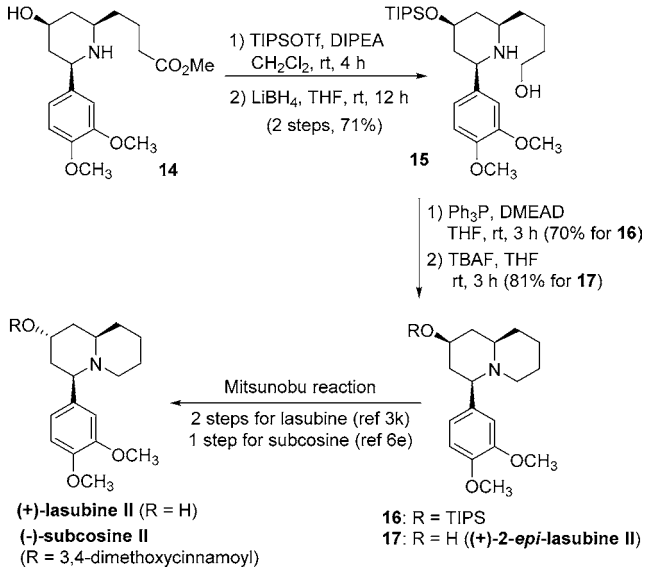
Reduction of the ester in **14** and cyclization of the resulting amino diol could potentially provide 2-*epi*-lasubine II. However, the observation[3a] that this amino diol, prepared by an unrelated approach, has poor solubility in conventional solvents suggested the need for an alternative strategy. Hence, the

Scheme 4. Homologation of 11 to 14



secondary alcohol in **14** was first protected as a TIPS ether. Subsequent reduction of the ester provided **15** (Scheme 5),

Scheme 5. Formal Synthesis of (+)-Lasubine II and (−)-Subcosine II



which was cyclized to **16** employing a Mitsunobu-type reaction (Ph_3P, di-2-methoxyethyl azodicarboxylate (DMEAD)[19]). Deprotection of **16** provided (+)-2-*epi*-lasubine II **17**. The enantiomer of **17** has previously been converted into (−)-lasubine II by Mitsunobu inversion of the secondary alcohol,[3k] and a Mitsunobu reaction of *ent*-**17** with 3,4-dimethoxycinnamic acid provides (+)-subcosine II.[6e] Thus, the present synthesis of **17** constitutes a formal synthesis of (+)-lasubine II and (−)-subcosine II.

In conclusion, the first examples of organocatalytic enantioselective Michael additions of a ketone to in situ generated α-nitrostyrenes have been developed. The methodology has been applied to a formal synthesis of (+)-lasubine II and (−)-subcosine II. We are currently investigating the scope of the Michael addition reaction and the application of this methodology in the stereoselective synthesis of various trisubstituted piperidines.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02677.

Experimental methods and spectroscopic data for all compounds (PDF)

X-ray data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Isolation and structure determination: Fuji, K.; Yamada, T.; Fujita, E.; Murota, H. *Chem. Pharm. Bull.* **1978**, *26*, 2515.

(2) (a) Rumalla, C. S.; Jadhav, A. N.; Smillie, T.; Fronczek, F. R.; Khan, I. A. *Phytochemistry* **2008**, *69*, 1756. (b) Ferris, J. P.; Boyce, C. B.; Briner, R. C. *J. Am. Chem. Soc.* **1971**, *93*, 2942.

(3) (a) Saha, N.; Biswas, T.; Chattopadhyay, S. K. *Org. Lett.* **2011**, *13*, 5128. (b) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (c) Cheng, G.; Wang, X.; Su, D.; Liu, H.; Liu, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 1911. (d) Chandrasekhar, S.; Murali, R. V. N. S.; Reddy, Ch. R. *Tetrahedron Lett.* **2009**, *50*, 5686. (e) Verkade, J. M. M.; van der Pijl, F.; Willems, M. M. J. H. P.; Quaedflieg, P. J. L. M.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2009**, *74*, 3207. (f) Weymann, M.; Kunz, H. *Zeit. Naturforschung B. Chem. Sci.* **2008**, *63*, 425. (g) Lim, J.; Kim, G. *Tetrahedron Lett.* **2008**, *49*, 88. (h) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967. (i) Zaja, M.; Blechert, S. *Tetrahedron* **2004**, *60*, 9629. (j) Gracias, V.; Zeng, Y.; Desai, P.; Aube, J. *Org. Lett.* **2003**, *5*, 4999. (k) Ma, D.; Zhu, W. *Org. Lett.* **2001**, *3*, 3927. (l) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623. (m) Ukaji, Y.; Imai, M.; Yamada, T.; Inomata, K. *Heterocycles* **2000**, *52*, 563. (n) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361. Formal enantioselective syntheses of lasubine II: (o) Shi, S.-L.; Wei, X.-F. *J. Am. Chem. Soc.* **2012**, *134*, 17019. (p) Beng, T. K.; Gawley, R. E. *J. Am. Chem. Soc.* **2010**, *132*, 12216. (q) Coldham, I.; Leonori, D. *J. Org. Chem.* **2010**, *75*, 4069.

(4) Epimerization of the C4 stereocenter: Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717. For inversion of the C2 stereocenter, see ref 3k.

(5) For the stereoselective reduction of 2,6-disubstituted, 2,3,4,5-tetrahydropyridines to *cis* 2,6-disubstituted piperidines, see: Ryckman, D. M.; Stevens, R. V. *J. Org. Chem.* **1987**, *52*, 4274.

(6) Selected recent reports: (a) Martin, T. J.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 5368. (b) Shi, S.-L.; Wei, X.-F.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2012**, *134*, 17019. (c) Daly, M.; Cant, A. A.; Fowler, L. S.; Simpson, G. L.; Senn, H. M.; Sutherland, A. *J. Org. Chem.* **2012**, *77*, 10001. (d) Marca, E.; Delso, I.; Tejero, T.; Merino, P. *Tetrahedron* **2012**, *68*, 6674. (e) Cui, L.; Li, C.; Zhang, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9178. (f) Leflemme, N.; Freret, T.; Boulouard, M.; Dallemagne, P.; Rault, S. *J. Enzym. Inhib. Med. Chem.* **2005**, *20*, 551.

(7) Only three reports of enantioselective organocatalytic Michael additions to *α-alkyl* nitroalkenes are available (a) Han, Y.; Zheng, B.; Peng, Y. *Adv. Synth. Catal.* **2015**, *357*, 1136. (b) Kimmel, K. L.; Weaver, J. D.; Lee, M.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 9058. (c) Zheng, B.; Wang, H.; Han, Y.; Liu, C.; Peng, Y. *Chem. Commun.* **2013**, *49*, 4561. For stoichiometric reactions of preformed *α*-nitrostyrene with achiral enamines, see: (d) Bradamante, P.; Pitacco, G.; Risaliti, A.; Valentin, E. *Tetrahedron Lett.* **1982**, *23*, 2683. (e) Benedetti, F.; Drioli, S.; Nitti, P.; Pitacco, G.; Valentin, E. *ARKIVOC* **2001**, *v*, 140.

(8) (a) Kunetsky, R. A.; Dilman, A. D.; Struchkova, M. I.; Tartakovsky, V. A.; Ioff, S. L. *Tetrahedron Lett.* **2005**, *46*, 5203. (b) Lešetický, L.; Fidler, V.; Procházka, M. *Collect. Czech. Chem. Commun.* **1973**, *38*, 459.

(9) For application in the conjugate additions of thiols, see: Baricordi, N.; Benetti, S.; Bertolasi, V.; De Risi, C.; Pollini, G. P.; Zamberlan, F.; Zanirato, V. *Tetrahedron* **2012**, *68*, 208.

(10) Nitroacetate **2a** was prepared by acetylation of the nitro alcohol, which was obtained by reaction of the corresponding epoxide with $NaNO_2$ employing a modification of the reported method, see: Borah, J. C.; Gogoi, S.; Boruwa, J.; Barua, N. C. *Synth. Commun.* **2005**, *35*, 873. Nitroacetates **2b** and **2c** were prepared by acetylation of the corresponding nitro alcohols. These were obtained by hydroxymethylation of the respective aryl nitromethanes. See the Supporting Information for details

(11) (*S*)-Proline, (1*R*,2*R*)-1,2-diphenylethylenediamine, and (*S*)-3-methyl-*N*-(pyrrolidin-2-ylmethyl)butan-1-amine also provided **4a** but in lower yield and with lower ee as compared to **3**. (1*R*,2*S*)-Ephedrine was not effective as a catalyst. See the Supporting Information for a summary of the optimization studies.

(12) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624.

(13) The enantiomeric excess of the minor diastereomers is typically low (50−55% ee). Treatment of pure **4a** (92% ee) with catalyst **3** (20 mol %) in the presence of ketone **1** (5 equiv) did not result in any loss of enantiomeric excess of **4a** under the conditions employed for the Michael addition. The minor diastereomer could not be detected in this reaction mixture. These observations suggest that the Michael adduct **4a** does not revert back to **1** and the nitroalkene and also that the minor diastereomer is not obtained by epimerization of the major diastereomer under the reaction conditions.

(14) The crystallographic data has been deposited with the Cambridge Crystallographic Data Centre, reference no. CCDC 1423549.

(15) For a theoretical study of the role of hydrogen bonding in the Michael addition of enamines to nitroalkenes, see: Arnó, M.; Zaragozá, R. J.; Domingo, L. R. *Tetrahedron: Asymmetry* **2007**, *18*, 157.

(16) Similar intermediates have previously been proposed in stoichiometric reactions of 4-*tert*-butylcyclohexanone-derived enamines with *α*-nitrostyrene. Two of the 1,2-oxazine *N*-oxide intermediates were isolated and characterized. See ref 7d.

(17) Gellert, B. A.; Kahlke, N.; Feurer, M.; Roth, S. *Chem. - Eur. J.* **2011**, *17*, 12203.

(18) Ali, S. A.; Hashmi, S. M. A.; Siddiqui, M. N.; Wazeer, M. I. M. *Tetrahedron* **1996**, *52*, 14917.

(19) DMEAD is reduced to a water-soluble hydrazine dicarboxylate, thereby simplifying the purification of **16**. (a) Sugimura, T.; Hagiya, K. *Chem. Lett.* **2007**, *36*, 566. (b) Hagiya, K.; Muramoto, N.; Misaki, T.; Sugimura, T. *Tetrahedron* **2009**, *65*, 6109. DMEAD is commercially available.

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