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Selective Access to Both Diastereoisomers in an Enantioselective Intramolecular Michael Reaction by Using a Single Chiral Organocatalyst and Application in the Formal Total Synthesis of (−)-Epibatidine

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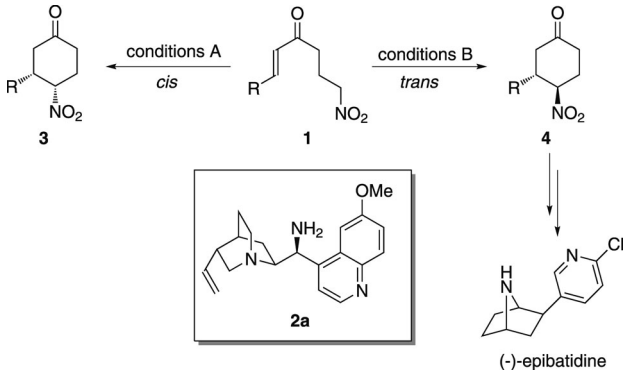
The development of enantioselective and diastereoselective reactions, utilizing simple prochiral precursors and generating multiple stereocenters in one step, plays a major role in synthesis.[1] One significant limitation of asymmetric catalysis is the lack of access to the full array of stereoisomers of a complex chiral molecule. While complementary enantioselectivity can be obtained by using the enantiomeric pair of the catalyst, modulation of the enforced sense of diastereoselectivity is a challenge.

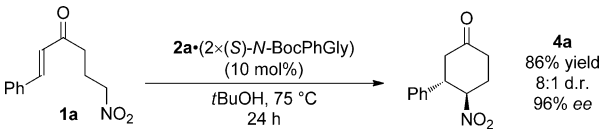
Controlling the diastereoselectivity by applying a single catalyst is an interesting but largely unmet challenge. In terms of transition-metal catalysis, a change in diastereoselectivity can be obtained by substrate modifications,[2] changing the Lewis acid[3] or tuning the electronic properties of the ligand.[4] Organocatalysis[5] has made a significant impact on asymmetric catalysis and is an attractive and complementary approach to transition-metal catalysis. While several examples in which different organocatalytic systems induce opposite diastereoselectivity exist,[6] examples relying on a single catalyst to provide complementary diastereoisomers remain scarce. Recently, it was demonstrated that a cinchona-based primary amine is able to catalyze a highly diastereoselective addition of alkyl thiols to a range of α-branched enones.[7] Through the use of different combinations of additives[8] and solvents, the diastereoselectivity could be switched to favor either the *syn*- or the *anti*-stereoisomer.

Herein, we present our efforts in the development of an enantio- and diastereoselective reaction toward the formation of both the *cis*- and *trans*-diastereoisomers in an intramolecular Michael reaction by using a single chiral organocatalyst (Scheme 1). Initial results indicated that either the *cis*- or *trans*-diastereoisomer could be obtained selectively depending on the reaction conditions. This led us to investigate the mechanism of the reaction. ^{1}H NMR spectroscopy showed that the reaction is selective for the *cis*-diastereoisomer and DFT calculations suggested that the selectivity arises from a favorable electrostatic interaction between the iminium ion and the nucleophile. The results of these investigations also indicated that the *trans*-isomer is generated through catalyst-induced epimerization of the labile nitro stereocenter.[9] The mechanistic studies enabled the rational development of reaction conditions that allowed for the isolation of either the *cis*- or *trans*-diastereoisomer in high yields and stereoselectivities for a broad range of substrates. The concept was used in the enantioselective synthesis of all stereoisomers of 4-nitro-3-phenylcyclohexanone. Finally, the synthetic utility of the reaction was demonstrated by the formal total synthesis of (−)-epibatidine in only seven steps from a commercially available aldehyde.



Scheme 1. Enantio- and diastereoselective formation of *cis*- and *trans*-stereoisomers by an intramolecular Michael reaction.

We started our study by examining the asymmetric intramolecular Michael addition[10] of (*E*)-6-nitro-1-phenylhex-1-en-3-one (**1a**) by using the cinchona-alkaloid-based primary aminocatalyst **2a** (Scheme 2).[11] Despite numerous reports



Scheme 2. Optimized conditions for the selective formation of the *trans*-diastereoisomer.

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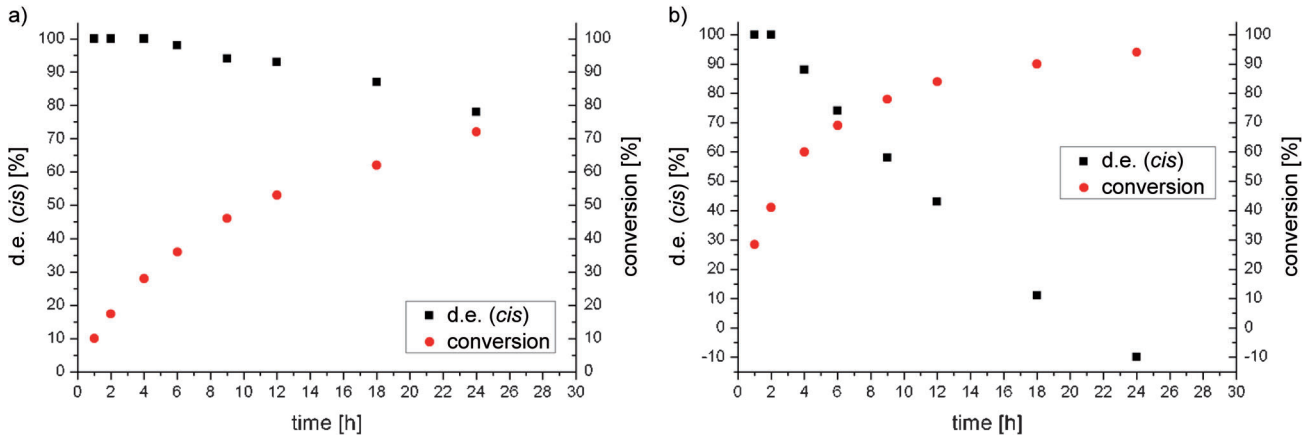


Figure 1. Conversion and diastereomeric excess (d.e.) as a function of time for the intramolecular Michael reaction of **1a** in a) $CH_3OH/CHCl_3$ (4:1) and b) *t*BuOH at 40 °C (see the Supporting Information for details).

on organocatalyzed Michael additions of nitronates to enones,[12] this catalytic, enantioselective, intramolecular variant has not been described previously.[13] Preliminary reactions indicated that the *trans*-diastereoisomer **4a** was favored upon cyclization. A screening of reaction conditions showed that the best result was obtained with the (*S*)-*N*-Boc-phenylglycine salt of catalyst **2a** (see the Supporting Information for details). Accordingly, by employing this catalyst in *t*BuOH at 75 °C, the product was obtained in 86 % yield, 96 % *ee*, and a 8:1 d.r. in favor of the *trans*-isomer.

However, it is worth noting that the diastereoselectivity dropped to a 4:1 and 1.2:1 ratio in favor of **4a** when the temperature was lowered to 50 and 40 °C, respectively. Interestingly, a dramatic change was observed when CH_3OH was applied as the solvent; after 24 h, *cis*-4-nitro-3-phenylcyclohexanone (**3a**) was formed in 67 % conversion and a 7:1 d.r. with 90 % *ee*.

To further understand the change in diastereoselectivity, we monitored the reaction ($CH_3OH/CHCl_3$ at 40 °C) by ^{1}H NMR spectroscopy (Figure 1 a).[14] The conversion slowly increased to 36 and 72 % at 6 and 24 h, respectively. Interestingly, the diastereoselectivity was excellent in favor of the *cis*-diastereosiomer **3a** (>20:1 d.r., >99 % d.e.)[15] after 6 h and then slowly reduced to 7:1 d.r. (78 % d.e.) after 24 h.

The same study was performed for the reaction in *t*BuOH at 40 °C. In this solvent the reaction proceeded faster, giving 69 and 94 % conversion after 6 and 24 h, respectively (Figure 1 b). Interestingly, the reaction was also selective in *t*BuOH, affording the *cis*-diastereoisomer **3a** exclusively at 41 % conversion in 2 h, after which the d.e. was reduced to 74 (6.7:1 d.r.) and −10 % (1:1.2 d.r.) at 6 and 24 h, respectively. These experiments suggest that the organocatalyzed intramolecular Michael reaction is *cis*-diastereoselective independent of the solvent. The corresponding *trans*-diastereoisomer **4a** is then likely to arise from catalyst-promoted epimerization of the labile nitro stereocenter.[16] It is worth noting that heating of the *cis*-diastereoisomer **3a** to 75 °C in *t*BuOH and in the absence of catalyst **2a** did not provide the *trans*-diastereoisomer **4a**.

Theoretical calculations (M06-2x/6-31+G(d,p))[17] provide an explanation for the observed diastereoselectivity in the reaction. A simplified model system (Figure 2) was used to

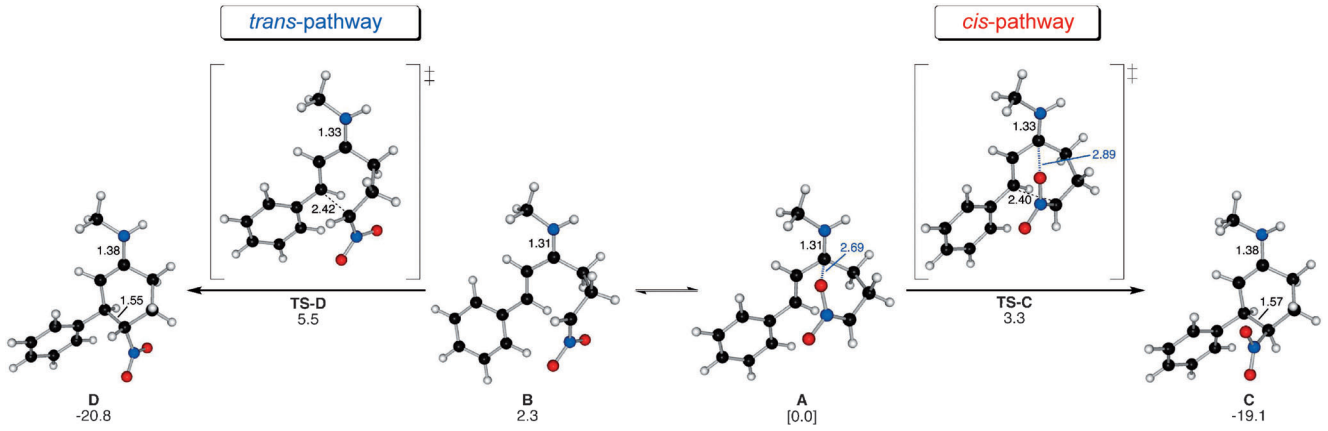


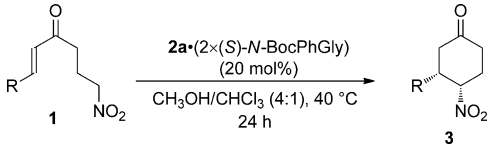
Figure 2. Optimized structures and relative energies (kcal mol^{-1}) for the two cyclization pathways leading to the *cis*- and *trans*-diastereoisomers. Distances are in Ångstrøm. Reported values are free energies at 40 °C.

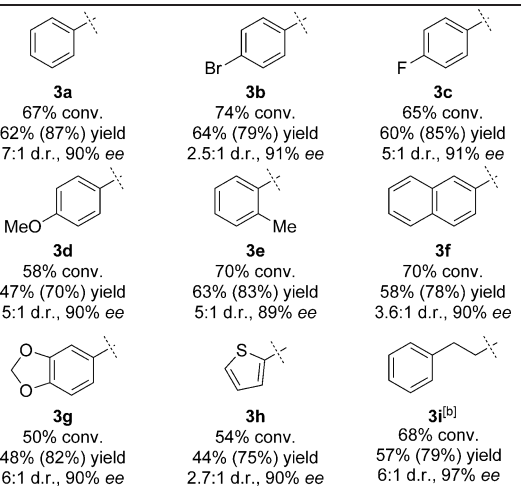
study the cyclization pathways for both the *cis*- and *trans*-diastereoisomers.[18,19] The lowest energy productive conformer of the zwitterionic intermediate **A** was found to have a weak interaction between the lone pair of the electron-rich oxygen atom (lp_O) of the nitro group and the anti-bonding orbital of the electron-deficient carbon atom of the iminium ion (π^*_C). This interaction preorganizes the substrate into a conformation that, upon cyclization, leads to the *cis*-diastereoisomer **C**. This nitro–iminium-ion interaction is not present in **B**, the conformer which leads to the *trans*-diastereoisomer **D**, and, as a result, this conformer is 2.3 kcal mol^{-1} higher in energy. As the cyclization of **A** progresses, the lp_O–π^*_C interaction diminishes. This can be seen by a change in the distance between the oxygen atom of the nitro group and the iminium-ion carbon atom when going from **A** to **TS-C**. Comparison of the transition-state energies for both the *cis*- and *trans*-selective pathways shows that the transition-state structure on the pathway leading to the *cis*-diastereoisomer **TS-C** is favored over the transition-state structure on the *trans*-selective pathway **TS-D** by 2.2 kcal mol^{-1}. Inspection of the products of both pathways reveals that the *trans*-product **D** is favored over the *cis*-diastereoisomer **C** by 1.7 kcal mol^{-1}. This data suggests that the *cis*-diastereoisomer is kinetically favored, while the *trans*-diastereoisomer is thermodynamically favored. In both pathways the cyclization is highly exergonic, suggesting that the cycloreversion reaction is much slower and unlikely to occur to a significant degree. This lends further support to our hypothesis that the *trans*-diastereoisomer is formed by epimerization.

The fact that the reaction is *cis*-selective and the product only slowly epimerizes over time makes it possible to access the kinetically favored isomer if the reaction is stopped at a time when conversion and selectivity are both high. Initially, owing to the higher enantioselectivity observed (98% *ee*), *t*BuOH was employed as the solvent for the enantioselective formation of the *cis*-diastereoisomer. However, an inseparable byproduct, presumably arising from the intermolecular dimerization of the starting material, was also formed. Interestingly, this byproduct was not observed at elevated temperatures, suggesting that it forms reversibly at high temperatures.

Owing to the abovementioned issues, the asymmetric synthesis of the *cis*-diastereoisomers **3** was conducted in a 4:1 mixture of $CH_3OH/CHCl_3$[14] (Table 1). Because it was not possible to achieve full conversion without eroding the *cis*-diastereoselectivity, the reactions were stopped after 24 h, ensuring a good yield and selectivity. The developed reaction concept showed good tolerance toward a series of substrates, affording the products in good yields and stereoselectivities. In general, the substituent and the electronic nature of the aromatic ring had little effect on the outcome of the reaction, as demonstrated for the products **3a–g**. Heterocycles were also tolerated, as shown by thiophene-substituted product **3h**. Initial attempts to expand the substrate scope to aliphatic substituents were not successful, owing to acetal formation of the starting material. However, changing the solvent to *t*BuOH solved this problem, and product **3i** was formed in 62% yield, 6:1 d.r., and 97% *ee*. In all cases, the unreacted starting material could be recovered.

Table 1. Scope of the intramolecular Michael reaction for the *cis*-diastereoisomers **3**.[a]



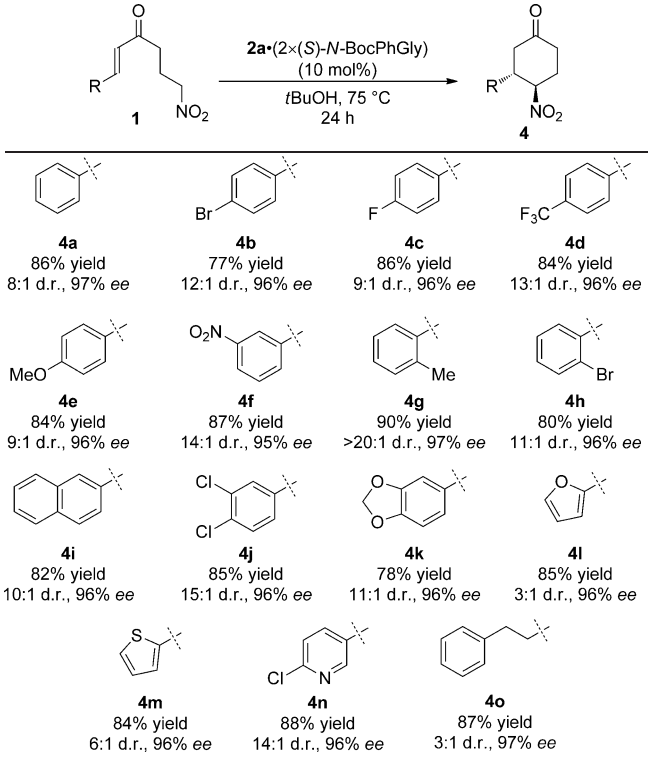


[a] All reactions were performed on a 0.2 mmol scale (see the Supporting Information). Yield after isolation by flash chromatography is given, and yield based on recovered starting material is provided in parentheses. The d.r. was determined by ^{1}H NMR spectroscopy. The *ee* was determined by chiral stationary phase (CSP)-HPLC. [b] The reaction was performed in *t*BuOH.

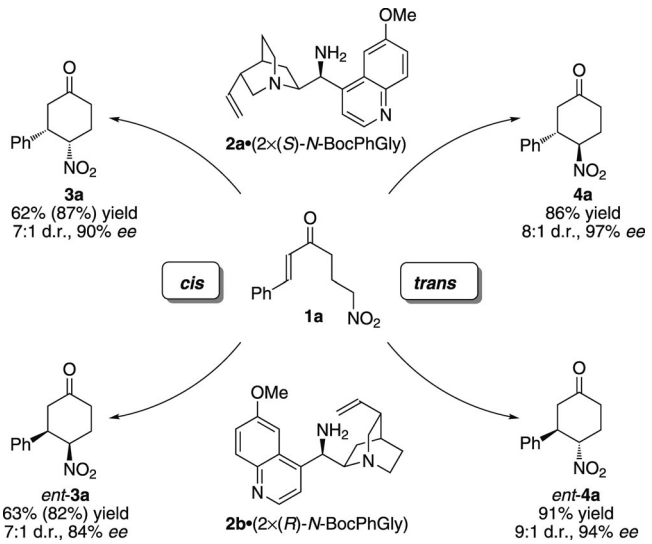
Having successfully demonstrated that the developed reaction conditions could be applied for the synthesis of the kinetically favored *cis*-diastereoisomer, we wanted to expand the methodology to include the formation of the *trans*-diastereoisomer. As observed in the initial screening and the kinetic studies, *trans*-diastereoisomer **4** is formed at prolonged reaction times. Accordingly, by increasing the reaction temperature and performing the reaction in *t*BuOH, the *trans*-diastereoisomers **4** were afforded in excellent yields, diastereo-, and enantioselectivities (Table 2). As with the scope of the *cis*-diastereoisomer **3**, a series of aromatic substrates with different substitution patterns and electronic properties performed well, affording the products **4a–k**. Heterocycles were also tolerated, which was illustrated by the furan, thiophene, and chloropyridine substrates that underwent cyclization to afford products **4l–n** with very good results. An aliphatic substrate could also be applied, as shown by the formation of homobenzyl product **4o**. Finally, it was demonstrated that the catalyst loading could be reduced to 5 mol%, giving product **4a** in 80% yield, 8:1 d.r., and 96% *ee* after 48 h (not shown).

The absolute and relative stereochemistry of the products was determined by X-ray crystallographic analysis of compounds **3b** and **4b**.[20]

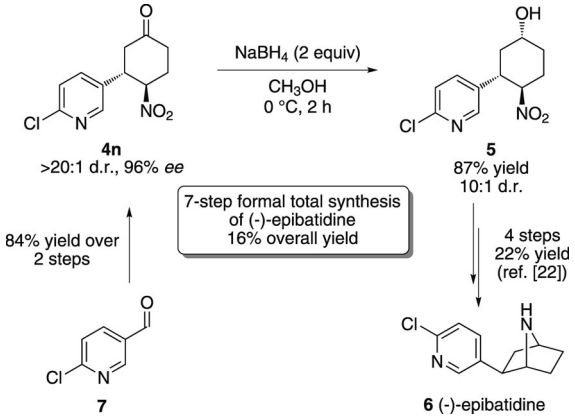
Table 2. Scope of the intramolecular Michael reaction for the *trans*-diastereoisomer **4**.[a]



[a] All reactions were performed on a 0.2 mmol scale (see the Supporting Information). Yield after isolation by flash chromatography is given. The d.r. was determined by ^{1}H NMR spectroscopy. The *ee* was determined by CSP-HPLC.



Scheme 3. Accessing the full array of stereoisomers of 4-nitro-3-phenylcyclohexanone.



Scheme 4. Stereoselective reduction of ketone **4n** and its application in the formal total synthesis of (−)-epibatidine **6**.

After having demonstrated that both diastereoisomers can be accessed by the application of a single chiral organocatalyst, we wanted to demonstrate that the full array of stereoisomers, derived from **1a**, can be obtained (Scheme 3). By reacting **1a** with the *pseudo*-enantiomeric catalyst **2b**, derived from quinidine, in $CH_3OH/CHCl_3$ (4:1) at 40 °C, product *ent*-**3a** was isolated in 63% yield with a d.r. of 7:1 and 84% *ee*. Likewise, treating the substrate with the catalyst in *t*BuOH at 75 °C afforded product *ent*-**4a** in a higher yield (91%), higher d.r. (9:1), and slightly lower enantioselectivity (94% *ee*) compared to **4a**.

To demonstrate the synthetic utility of the reaction, product **4n** was applied in the formal total synthesis of the natural alkaloid (−)-epibatidine **6**, an analgesic approximately 200 times more potent than morphine and a highly potent agonist of the nicotinic acetylcholine receptor.[21] To achieve this synthesis, a stereoselective reduction of the ketone functionality of product **4n** was performed (Scheme 4).

Treating the pure *trans*-isomer with two equivalents of $NaBH_4$ in CH_3OH at 0 °C afforded the corresponding alcohol **5** in 87% yield and 10:1 d.r. From alcohol **5**, only four additional synthetic steps (mesylation, reduction/cyclization, and epimerization) are needed to reach the target **6**.[22] Starting from chloropyridine aldehyde **7**, this is, to the best of our knowledge, the shortest (seven steps) and most selective, organocatalytic, formal total synthesis of (−)-epibatidine.[23]

In summary, we have demonstrated that both diastereoisomers of 4-nitro-3-substituted cyclohexanones can be accessed selectively by an intramolecular Michael reaction using a single chiral aminocatalyst. Mechanistic studies based on ^{1}H NMR spectroscopy showed that the reaction is selective for the *cis*-diastereoisomer and that the *trans*-diastereoisomer arises over time. DFT calculations suggest that the high selectivity toward the formation of the *cis*-diastereoisomer is due to a favorable electrostatic interaction between the iminium ion and the nucleophile. These combined mechanistic studies enabled the rational development of reaction conditions that allow for the isolation of either the *cis*- or *trans*-diastereoisomer in high yields and stereoselectivities for a broad range of substrates. Furthermore, the strategy was used for the enantioselective synthesis of all four stereoisomers of 4-nitro-3-phenylcyclohexanone. Final-

ly, the synthetic utility of the reaction has been demonstrated by the formal total synthesis of (−)-epibatidine.

Acknowledgements

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Keywords: asymmetric synthesis · total synthesis · reaction mechanisms · organocatalysis

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[14] Owing to solubility issues, the addition of $CHCl_3$ was necessary for some substrates.

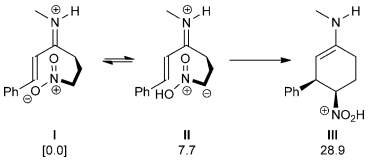
[15] While these numbers do not directly correlate, they refer to the fact that no *trans*-diastereoisomer was observed in the ^{1}H NMR spectrum at that time.

[16] Retro-Michael/Michael seems unlikely, because treatment of the product **4a** with *pseudo*-enantiomeric catalyst **2b** did not deteriorate the enantiopurity of the product. Other bases led to decomposition of the *cis*-product.

[17] Calculations were performed with Gaussian 09 (Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**). Geometries were optimized with the M06–2x/6-31+G(d,p) level of theory and basis set (Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.) by using a Polarizable Continuum Model with a dielectric for CH_3OH ($\varepsilon = 32.613$). See the Supporting Information for full details and complete references on theoretical methods.

[18] For coordinates and energies of all intermediates and transition state structures, see the Supporting Information.

[19] Cyclization through a tautomerization pathway was also considered. However, tautomerization of **I** to reactive intermediate **II** was found to be energetically unfavorable, with **II** being 7.7 kcal mol^{-1} higher in energy than **I**. Cyclization of **II** to **III** was also found to be energetically unfavorable. Thus, it seems unlikely that the reaction proceeds through this cyclization pathway..



I [0.0] II 7.7 III 28.9

[20] CCDC 878386 (**3b**) and 878387 (*ent*-**4b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[21] For a comprehensive review, see: H. F. Olivo, M. S. Hemenway, *Org. Prep. Proced. Int.* **2002**, *34*, 1.

[22] C. Szántay, Z. Kardos-Balogh, I. Moldvai, C. Szántay Jr., E. Temesvári-Major, G. Blaskó, *Tetrahedron* **1996**, *52*, 11053.

[23] For another epibatidine synthesis (10 steps) by using hydrogen-bonding catalysis (75% *ee*), see: Y. Hoashi, T. Yabuta, Y. Takemoto, *Tetrahedron Lett.* **2004**, *45*, 9185.

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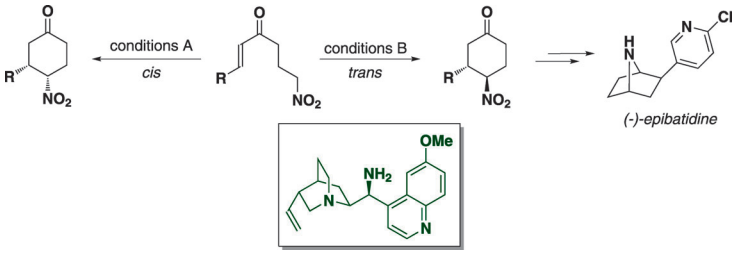

Two in one: Both diastereoisomers of 4-nitro-3-substituted cyclohexanones are accessed selectively by an intramolecular Michael reaction using a single chiral aminocatalyst (see scheme). Mechanistic studies show that the reaction is selective for the *cis*-diastereoisomer and that the *trans*-diastereoisomer arises over time. DFT calculations suggest that the *cis*-selectivity is due to a favorable electrostatic interaction between the iminium ion and the nucleophile.

Organocatalysis

*K. L. Jensen, C. F. Weise, G. Dickmeiss, F. Morana, R. L. Davis, K. A. Jørgensen** ..... ▮▮▮▮–▮▮▮▮

Selective Access to Both Diastereoisomers in an Enantioselective Intramolecular Michael Reaction by Using a Single Chiral Organocatalyst and Application in the Formal Total Synthesis of (−)-Epibatidine