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Sequential Organocatalyzed Michael Addition/[3 + 2]-Heterocyclization for the Stereoselective Synthesis of Fused-Isoxazoline Precursors of Enantiopure Cyclopentanoids

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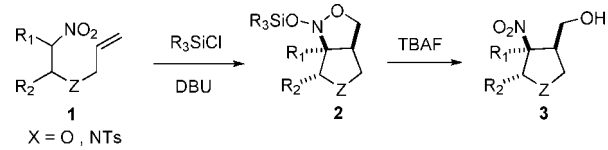
ABSTRACT

We propose an asymmetric synthesis of functionalized cyclopentanoids bearing up to four stereogenic centers from easily accessible nitroalkenes and unsaturated aldehydes. The overall sequence includes an enantioselective organocatalytic Michael addition and a [3 + 2]-heterocyclization between an in situ generated silylnitronate and the unactivated double bond. Finally, the fused isoxazoline can be further transformed to various cyclopentanoids.

The development of enantioselective methods to access functionalized cyclopentanoids is a challenging problem since these valuable building blocks have found many applications in organic chemistry and are precursors of a plethora of natural products.[1] Very recently, elegant asymmetric and organocatalyzed cascade reactions[2] have been described for the synthesis of cyclopentanes, demonstrating the growing interest for this type of structure.[3] Although these methods are very efficient because many stereogenic centers are controlled in one single operation, the variety and diversity of the substitution of the final cyclopentane ring is rather limited. We have a long-standing and continuing interest in the field of nitroolefins.[4] Recently, we reported an efficient diastereoselective synthesis of tetrahydrofurans and pyrrolidines based on a 1,3-dipolar cycloaddition between a silylnitronate[5] and an unactivated double bond (Scheme 1).[6] The unsaturated β-heteronitroalkane **1** was obtained through

Scheme 1. Diastereoselective Synthesis of Tetrahydrofurans and Pyrrolidines



(1) For reviews on the synthesis and applications of cyclopentanes, see: (a) Silva, L. F. *Tetrahedron* **2002**, *58*, 9137–9161. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831. (c) Trost, B. M. *Angew. Chem., Int. Ed.* **1986**, *25*, 1–20.

(2) For a review on enantioselective cascade reactions, see: Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037–2046.

(3) (a) Tan, B.; Chua, P. J.; Zeng, X.; Lu, M.; Zhong, G. *Org. Lett.* **2008**, *10*, 3489–3492. (b) Tan, B.; Shi, Z.; Chua, P. J.; Zhong, G. *Org. Lett.* **2008**, *10*, 3425–3428. (c) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732–3734.

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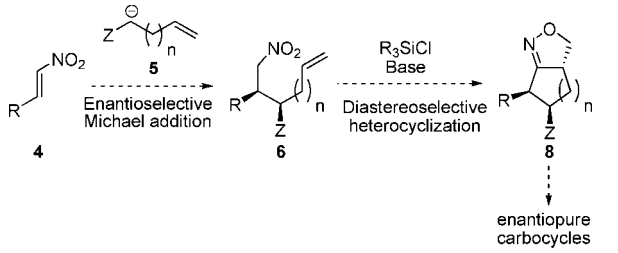
a hetero-Michael reaction between the corresponding nitroolefin and an allylic alcohol or amine.

Because the cyclization step proceeds with total diastereoselectivity,[7] we reasoned that this useful methodology could be in principle translated to a versatile enantioselective carbocyclization version providing the control of the Michael addition of a properly functionalized carbonucleophile **5** to a simple nitroolefin **4** (Scheme 2). The resulting enantiomerically enriched unsaturated nitoalkanes **6** could be easily cyclized stereoselectively to the corresponding fused-isoxazoline precursor of the expected functionalized carbocycles.

Scheme 2



Over recent years, very important developments of asymmetric Michael addition of aldehydes to nitroolefins have emerged.[8,9] Chiral amines such as pyrrolidine analogues constitute a broadly applicable class of organocatalysts for asymmetric conjugate addition via enamine activation (Figure 1).[10]

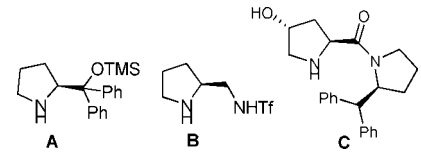
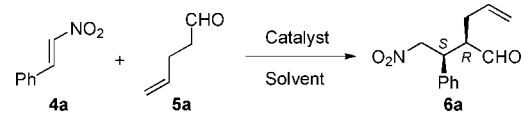


Figure 1. Pyrrolidine-type organocatalysts.

Therefore, in order to validate our strategy, we selected nitrosyrene (**4a**) and 4-pentenal (**5a**) as test substrates to study this reaction with different organocatalysts. The results are summarized in Table 1. Various reaction conditions were tested, and it clearly appeared that catalyst **A** in combination with benzoic acid as the additive in water[9a] (entries 1 and 2) and catalyst **C** in DCM[9g] (entry 4) were the best way to achieve high levels of diastereoselectivity and enantioselectivity along with excellent yields. Catalyst **B**[9k] was efficient (yield = 95%, entry 3) but showed only moderate enantioselectivity. The best conditions for this enantioselective transformation (entry 2) having been identified, they were applied to diversely substituted nitroalkenes and different unsaturated aldehydes. The resulting γ-nitroaldehydes (**6b**−**g**) are represented in Figure 2. The aromatic-substituted nitroolefins worked well in this reaction with high yields and very good levels of diastereoselectivity and enantioselectivity, except when 2-(2-nitrovinyl)furan **4d** was engaged, which resulted in the formation of **6d** with slightly lower yield and enantioselectivity. Aliphatic-substituted nitroolefin **4e** and β-nitroacrylate **4f** are also suitable substrates for this transformation, leading to **6e** and **6f**, respectively. Finally, the variation in the aldehyde structure either by increasing

Table 1. Catalyst and Solvent Optimization for the Enantioselective Michael Addition[a]



entry	catalyst		solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**A**	2 mol %	water	97[e]	92:8	99
2	**A**	2 mol %	water	98[f]	91:9	99
3	**B**	20 mol %	*i*PrOH	95	10:1	40
4	**C**	20 mol %	DCM	92	98:2	95

[a] Reaction conditions: 1 mmol of **4a**, 2 mmol of **5a** and catalyst **A**, **B**, or **C** in 2 mL of solvent at 0 °C. [b] Isolated yield by flash chromatography. [c] Determined by proton NMR of the crude reaction product. [d] Determined by HPLC on a chiral stationary phase. [e] 10 mol % of $PhCO_2H$ was used. [f] 20 mol % of $PhCO_2H$ was used.

(4) (a) Guillaume, M.; Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Synlett* **2002**, *n/a*, 1183–1185. (b) Dulcère, J.-P.; Dumez, E. *Chem. Commun.* **1997**, 971–972. (c) Dumez, E.; Rodriguez, J.; Dulcère, J.-P. *Chem. Commun.* **1997**, *n/a*, 1831–1832. (d) Dumez, E.; Faure, R.; Dulcère, J.-P. *Eur. J. Org. Chem.* **2001**, *257*, 7–2588.

(5) For examples of the use of silylnitronate in synthesis, see: (a) Torssell, K.; Zeuthen, O. *Acta Chem. Scand.* **1978**, *B33*, 379. (b) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2227–2230. (c) Torsell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569. (d) Uno, H.; Watanabe, N.; Fujiki, S.; Suzuki, H. *Synthesis* **1987**, *n/a*, 471–474. (e) Ishikawa, T.; Shimizu, Y.; Kudoh, T.; Saito, S. *Org. Lett.* **2003**, *5*, 3879–3882. (f) Kudoh, T.; Ishikawa, T.; Shimizu, Y.; Saito, S. *Org. Lett.* **2003**, *5*, 3875–3878.

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(7) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(8) For recent reviews on asymmetric organocatalyzed conjugate additions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716. (b) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, *n/a*, 3123–3135. (c) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092. (d) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299–365.

(9) For recent examples of conjugate additions between aldehydes and nitroolefins with organocatalysts, see: (a) Zhu, S. L.; Yu, S. Y.; Ma, D. W. *Angew. Chem., Int. Ed.* **2008**, *3*, 545–548. (b) Wiesner, M.; Revell, J. D.; Wennemers, H. *Angew. Chem., Int. Ed.* **2008**, *10*, 1871–1874. (c) Barros, M. T.; Phillips, A. M. F. *Eur. J. Org. Chem.* **2007**, *17*, 8–185. (d) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599–602. (e) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *27*, 4212–4215. (f) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *38*, 6366–6370. (g) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *36*, 5984–5987. (h) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559–2562. (i) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966. (j) Wang, J.; Li, J.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem. Eur. J.* **2006**, *12*, 4321. (k) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (l) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (m) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527. (n) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (o) Betancourt, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737.

(10) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569.

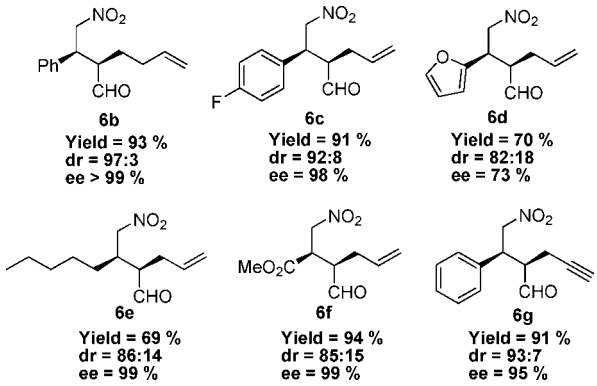
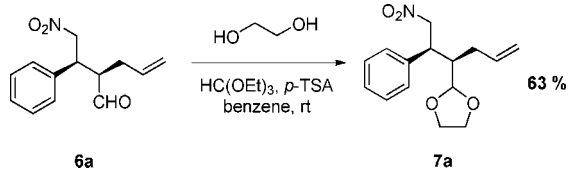


Figure 2. Synthesis of γ-nitroaldehydes.

the length of the chain (**6b**) or by introducing a triple bond (**6g**) had no apparent impact on the reaction outcome.

Having in hand a versatile enantioselective preparation of a variety of functionalized unsaturated nitroalkanes (**6a**−**g**), we next examined the feasibility of the cyclization step[11] starting with **6a**, which required prior protection of the aldehyde function as cyclic acetal[12] to afford compound **7a** (Scheme 3).[13]

Scheme 3. Protection of γ-Nitroaldehydes **6a**

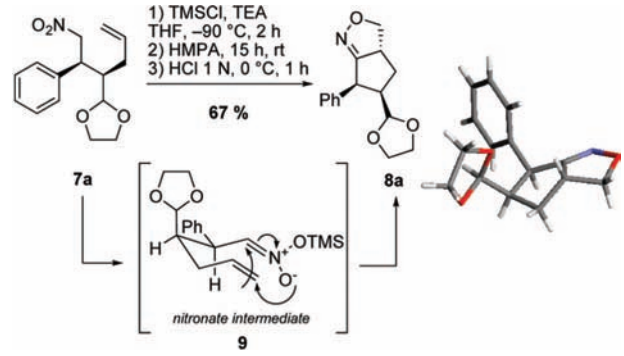


When the protected adduct **7a** was engaged in the cyclization step with the conditions recently used by our team (DBU, Me_2NTMS),[4] we unfortunately did not observe the formation of the expected isoxazoline **8a**.

Nevertheless, when **7a** was treated using conditions developed by Hassner,[14] the desired product **8a** was formed in 67% isolated yield (Scheme 4). As shown here, only one stereoisomer could be detected, demonstrating the very high diastereoselectivity of the cyclization step most probably resulting from the 1,3-allylic strain allowing only one conformation for the nitronate intermediate **9**.[7,4d] The absolute stereochemistry of **8a** was unambiguously established by analysis of the X-ray crystal structure.[15]

The present sequence (Michael addition, protection, cyclization) allows the rapid construction of bicyclic hetero-

Scheme 4. [3 + 2]-Heterocyclization to Fused Isoxazoline **8a**



cycles bearing three controlled stereogenic centers starting from simple achiral acyclic substrates. After protection,[16] the previous γ-nitroaldehydes **6b**-**6g** were submitted to the same cyclization conditions allowing the synthesis of diversely substituted five- and six-membered ring isoxazolines **8b**−**8f** in good yields (Figure 3). With protected aldehyde

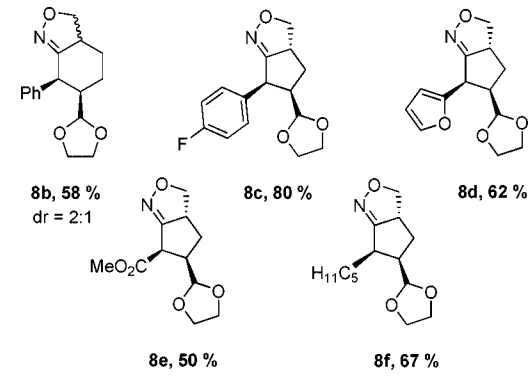


Figure 3. Synthesis of isoxazolines **8b**−**8f**.

7b, the cyclization to the six-membered ring **8b** proved to be more difficult and less stereoselective, a mixture of two diastereomers (2:1) being obtained.[17] Nevertheless, in all other cases, the cyclization proceeded with very high diastereoselectivity as only one diasteromer was detected.

Interestingly, when compound **7g** was engaged in the cyclization reaction, we did not observe the formation of the expected isoxazole **9**, but rather the unsaturated aldehyde **10** was isolated in 28% yield (Scheme 5).[18] This reactivity of silylnitronates with alkynes has indeed already been

(11) For a review, see: Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988.

(12) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122–2124.

(13) Running the cyclization step without protection of the aldehyde function led to lower yields and partial epimerization of the product; see Supporting Information for details.

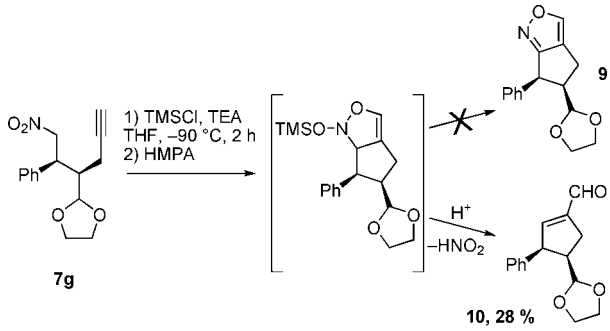
(14) Namboothiri, I. N.; Hassner, A.; Gottlieb, H. E. *J. Org. Chem.* **1997**, *62*, 485–492.

(15) CCDC 704278 contains 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.

(16) Yields of protected compounds **7a**−**f** refers to pure single diastereomers as they are separable by chromatography on silica gel. In all cases, the minor diastereomer (3−7%) did not engage in the cyclization step.

(17) The major diastereomer can be obtained in pure form after recristallization in EtOAc/PE; see Supporting Information.

Scheme 5. Formation of Unsaturated Aldehyde **10**



observed and exploited by Kurth et al. for the synthesis of dihydrofuraldehydes and dihydropyranaldehydes.[19]

The isoxazolines are versatile masked structural entities and allow easy access to γ-amino alcohols,[20] β-hydroxy ketones,[21] or isoxazolidines,[22] opening up a convenient and useful entry into natural product synthesis. This behavior was exploited, and several transformations were accomplished with the possibility to introduce a fourth controlled stereogenic center (Scheme 6). For exemple, selective hydride reduction of **8a** can lead to 1,3-aminoalcohol **11** or bicyclic isoxazolidine **12** in very good yields. Alternatively, direct catalytic hydrogenation of **8c** afforded trisubstituted cyclopentanone **13** with 60% yield.

In conclusion, we have developed a new enantioselective and diastereoselective sequence including a Michael addition

(18) For exemples of intramolecular INOC reaction affording isoxazoles, see: (a) Akritopoulou-Zanze, I.; Gracias, V.; Moore, J. D.; Djuric, S. W. *Tetrahedron Lett.* **2004**, *45*, 3421–3423. (b) Hassner, A.; Dehaen, W. *Chem. Ber.* **1991**, *124*, 1181–1186.

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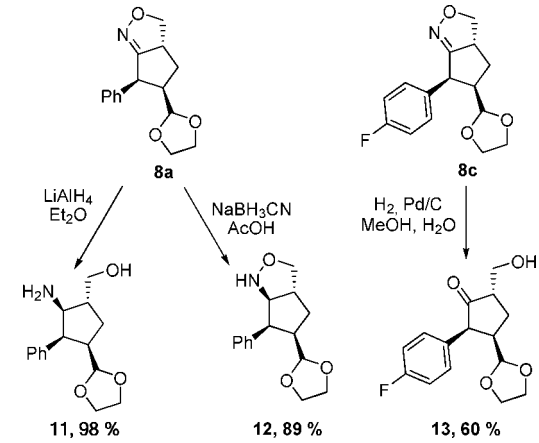
(21) (a) Tsantali, G. G.; Dimtsas, J.; Tsoleridis, C. A.; Takakis, I. M. *Eur. J. Org. Chem.* **2007**, *n/a*, 258–265. (b) Fernández-Mateos, A.; Coca, G. P.; González, R. R. *Tetrahedron* **2005**, *61*, 8699–8704. (c) Tranmer, G. K.; Tam, W. *Org. Lett.* **2002**, *4*, 4101–4104.

(22) (a) Itoh, T.; Watanabe, M.; Fukuyama, T. *Synlett* **2002**, 1323–1325. (b) Cerri, A.; Micheli, D.; Gandolfi, R. *Synthesis* **1974**, 710–712.

Scheme 6. Transformations of Fused Isoxazolines **8a** and **8c**



followed by [3 + 2]-heterocyclization allowing the rapid access to diversely substituted fused isoxazolines with the control of three stereogenic centers. These products were further transformed in various cyclopentanoids bearing up to four stereogenic centers, opening up a convenient, useful, and complementary way to access a five-membered ring system with a high level of complexity.

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Supporting Information Available: Available Experimental procedures, spectroscopic data for all new compounds, and crystallographic data of **8a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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