ORGANIC LETTERS

2001
Vol. 3, No. 16
2423−2425

Efficient Proline-Catalyzed Michael Additions of Unmodified Ketones to Nitro Olefins

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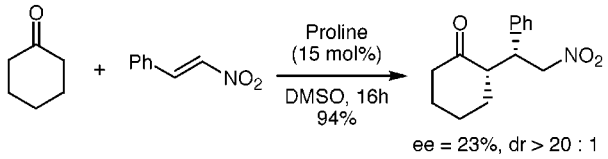
Received March 6, 2001

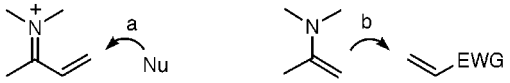
ABSTRACT



Here we describe the proline-catalyzed Michael addition of unmodified ketones to nitro olefins. This novel reaction provides γ-nitro ketones in modest enantioselectivity yet excellent yields.

Aminocatalysis has recently gained considerable attention, particularly in asymmetric synthesis.[1] There are two aminocatalytic pathways. Iminium catalysis proceeds via conversion of a carbonyl compound into an iminium ion, facilitating Knoevenagel-type condensations, cyclo- and nucleophilic additions, and cleavage of σ-bonds adjacent to the α-carbon.[2] Enamine catalysis on the other hand involves catalytically generated enamine intermediates, which react with various electrophiles or engage in pericyclic transformations.[3] Analysis of the Michael reaction reveals potential for both forms of aminocatalysis (Scheme 1).[4]

Scheme 1. Iminium- and Enamine-Catalytic Michael Reactions



While asymmetric iminium-catalytic Michael reactions (path a) have been described,[5] the intermolecular enamine-catalytic Michael reaction (path b) is unknown.[6] Moreover, the use of unmodified and nonactivated ketones in catalytic Michael reactions is extremely rare.[7] Herein, we disclose the proline-catalyzed Michael addition of unmodified ketones

(1) (a) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529−532 and references therein. (b) Albus, S. *Nachr. Chem., Tech. Lab.* **2000**, 48, 1459. (c) Bahmanyar, S.; Houk, K. N. *Chemtracts* **2000**, *13*, 904−911. (d) Diez, E.; Ley, S. *Chemtracts* **2000**, *13*, 592−595. (e) Doye, S. *Chem. Unserer Zeit* **2001**, *35*, 62−63.

(2) For examples, see: (a) Knoevenagel reaction, review: Tietze, L. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.11, p 341−394. (b) Diels−Alder reaction: Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244. (c) 1,3-Dipolar cycloaddtion: Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875. (d) Decarboxylation: Guthrie, J. P.; Jordan, F. *J. Am. Chem. Soc.* **1972**, *94*, 9136.

(3) For examples, see: (a) Intramolecular aldol reaction: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. (b) Cycloaddition−annulation: Boger, D. L.; Panek, J. S.; Meier, M. M. *J. Org. Chem.* **1982**, *47*, 895−897. (c) Intermolecular aldol reaction: List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386−7387. List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573−575. (d) Three-component Mannich reaction: List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.

(4) For a recent review on the asymmetric Michael reaction, see: Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196.

(5) (a) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Orlova, S. A.; Kuz'mina, N. A.; Bodrov, D. E *Russ. Chem. Bull.* **1993**, *42*, 1525−1529. (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176−1178. (c) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520−3530. (d) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *47*, 8805−8808. (e) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371.

10.1021/ol015799d CCC: $20.00
Published on Web 07/14/2001

to nitro olefines. This new reaction is only modestly enantioselective, yet highly efficient. It furthermore serves as proof of principle for enamine catalysis of the Michael reaction, a strategy that may ultimately lead to novel highly enantioselective catalysts.

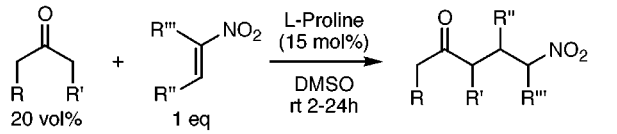
Previous aminocatalytic Michael reactions include the asymmetric conjugate addition of nitroacetate, malonates, nitroalkanes, and recently pyrroles to α,β-unsaturated carbonyl compounds.[5] It is likely that these reactions involve iminium ion intermediates according to path a in Scheme 1, although definite conclusions have to await further mechanistic studies.

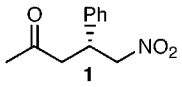
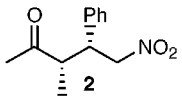
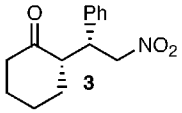
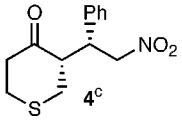
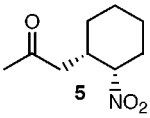
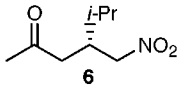
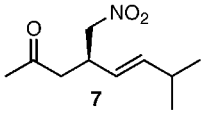
The stoichiometric use of enamines as nucleophiles in the Michael reaction has been pioneered by Stork et al.,[8] and several examples, including asymmetric variants,[9] have been described in the literature since then. Michael reactions of preformed enamines with nitro olefins have been thoroughly studied by Seebach et al.[10] Enamine *catalysis*, however, has been rarely used so far, and no intermolecular examples are known.[6]

We have recently described proline-catalyzed intermolecular aldol and Mannich reactions and postulated the involvement of nucleophilic ketone enamines.[3c,d] It became an apparent question if Michael acceptors may be used as electrophile. We found α,β-unsaturated ketones, esters, and amides to give the Michael products in only low yields and enantioselectivities upon reacting with acetone and a catalytic amount of proline under our standard reaction conditions.[3c,d] However, if the more reactive β-nitrostyrene was subjected to the same conditions, crystalline nitro ketone **1** was obtained in excellent yield (Table 1). Although the enantioselectivity of this process was low (7% ee), the high yield and exceptional simplicity of the process prompted us to investigate the scope of this novel aminocatalytic reaction.

We studied the Michael reaction of four different nitro olefins with four different ketones (Table 1). All reactions gave the products in very good yields but low enantioselectivities (≤23%). However, excellent regio- and diastereoselectivities were observed (entries 2−4). Furthermore, both aromatic (entries 1−4) and aliphatic nitro olefins, either saturated (entries 5 and 6) or conjugated (entry 7), may be used with similar efficiencies. γ-Nitroketones such as **1**−**7** serve as useful precursors for various functionalized organic compounds,[11] including pyrrolidines.[12] As an illustration, nitroketone **1** was hydrogenated to give pyrrolidine **8** in 87% yield as a mixture of diastereomers (Scheme 2). Pyrrolidines such as **8** are pharmacologically active and selectively block presynaptic dopamine receptors.[12]

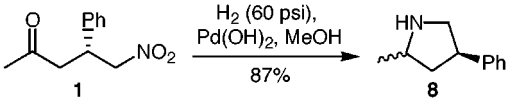
Table 1. Proline-Catalyzed Michael Addition of Unmodified Ketones to Nitroolefins



entry	product	yield	selectivity[a]
1	 **1**	97%	*ee* = 7%
2	 **2**	85%	*rr* > 20 : 1 *dr* = 3 : 1 *ee* = 10%[b]
3	 **3**	94%	*dr* > 20 : 1 *ee* = 23%
4	 **4**[c]	92%	*dr* > 20 : 1 *ee* = 10%
5	 **5**	95%	*dr* = 10 : 1 *ee* = 19%
6	 **6**	87%	not determined
7	 **7**	85%	not determined

[a] For ee, dr, and rr determination, see Supporting Information; rr = regioisomeric ratio. [b] ee of major *syn*-diastereomer. [c] Ten equivalents of the crystalline ketone tetrahydro-thiopyran-4-one was used.

Scheme 2



(6) For intramolecular enamine-catalytic Michael reactions, see: (a) Kozikowski, A. P.; Mugrage, B. B. *J. Org. Chem.* **1989**, *54*, 2275−2277. (b) Hirai, Y.; Takashi, T.; Yamazaki, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509−516.

(7) For a recent catalytic asymmetric example, see: Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097−1100.

(8) Stork, G.; Brizzolara, A.; Landesman, H.; Smuszkovicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

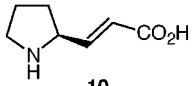
(9) (a) Yamada, S.; Hiroi, K.; Aiwa, K. *Tetrahedron Lett.* **1969**, *48*, 4233−4236. (b) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637−1654. (c) Martens, J.; Luebben, S. *Tetrahedron* **1991**, *47*, 1205−1214. (d) Using imine precursors: Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273−274. Review: d'Angelo, J.; Desmaele, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459−505.

(10) See, for example: Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413−1423.

(11) Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1−18.

(12) Svensson, K. A. I. et al. PCT Int. Appl. WO 9218475, 1992.

(13) Guided by the concept of considering the Michael reaction as a vinylogous aldol reaction, we have used "vinylogous" proline (**10**) (Grison, C.; Geneve, S.; Halbin, E.; Coutrot, P. *Tetrahedron* **2001**, *57*, 4903−4923) as the catalyst.



10

Remarkably, if **10** was used in the reaction of β-nitrostyrene with acetone, product **1** was obtained in 40% ee (68% yield).

In summary, we have developed a novel enamine-catalytic transformation, the proline-catalyzed Michael reaction of unmodified ketones to nitro olefins. Important features of this reaction are the following: (1) Yields are typically excellent. (2) Enantioselectivities are poor, but good diastereoselectivities and regioselectivities can be achieved. (3) The reactions are operationally simple and do not require inert atmosphere, temperature manipulations, metal salts, or preformed enolate equivalents.

Currently we study other chiral aminocatalysts to improve the enantioselectivity of this new reaction.[13]

Acknowledgment. We are most grateful to Richard A. Lerner and The Scripps Research Institute for generous support and encouragement and to Chris Castello and William Biller for technical assistance.

Supporting Information Available: Experimental procedures, characterizations, chiral-phase HPLC data, and stereochemistry. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015799D