ORGANIC LETTERS

2001
Vol. 3, No. 23
3737−3740

Catalytic Direct Asymmetric Michael Reactions: Taming Naked Aldehyde Donors

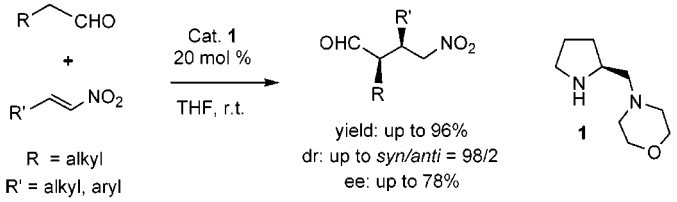
Juan M. Betancort and Carlos F. Barbas III*

The Skaggs Institute for Chemical Biology and the Department of Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

carlos@scripps.edu

Received September 5, 2001

ABSTRACT



Direct catalytic enantio- and diastereoselective Michael addition reactions of unmodified aldehydes to nitro olefins using (*S*)-2-(morpholinomethyl)-pyrrolidine as a catalyst are described. The reactions proceed in good yield (up to 96%) in a highly *syn*-selective manner (up to 98:2) with enantioselectivities approaching 80%. The resulting γ-formyl nitro compounds are readily converted to chiral, nonracemic 3,4-disubstituted pyrrolidines.

The Michael reaction is generally regarded as one of the most efficient carbon−carbon bond forming reactions, and studies concerning this reaction have played an important role in the development of modern synthetic organic chemistry.[1] As the demand for optically active compounds has soared in recent years, much progress has been made in the development of asymmetric variants of this reaction, providing for the preparation of Michael adducts with high enantiomeric purity.[2] Though remarkable advances have been made in the development of asymmetric catalysts containing metals,[3] relatively few asymmetric transformations have been reported which employ small organic molecules as catalysts.[4]

Typically, carbon nucleophiles that contain an active methylene center such as malonic acid esters, β-keto esters, nitroalkanes, etc. have been studied in the Michael reaction. Carbonyl compounds, and ketones in particular, have generally only been used as donors following their preactivation by conversion into a more reactive species such as enol or enamine equivalents.[5,6] In these cases, additional synthetic

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(2) For general reviews on the asymmetric Michael reaction, see: (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171−196. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (c) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1105−1120. (d) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. III, pp 1121−1139. (e) Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, *10*, 2051−2061.

(3) (a) Chataigner, I.; Gennari, C.; Ongeri, S.; Piarulli, U.; Ceccarelli, S. *Chem. Eur. J.* **2001**, *7*, 2628−2634. (b) Alexakis, A.; Benhaim, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1151−1157. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142. (d) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506−6507. (e) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878. (f) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215−10216. (g) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568−570. (h) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (i) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520−3530.

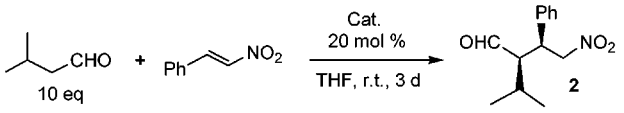
(4) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371. (b) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975−2978. (c) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hebrault, D. *Org. Lett.* **2000**, *2*, 2959−2962. (d) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 1097−1100.

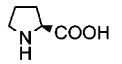
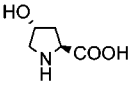
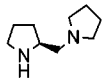
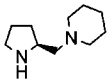
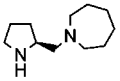
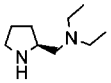
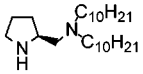
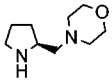
10.1021/ol0167006 CCC: $20.00
Published on Web 10/23/2001

step(s), stoichiometric amounts of base, additional reagents, or chiral ligands are required. A potentially advantageous strategy in terms of atom economy would involve direct additions of unmodified carbonyl compounds to Michael-type acceptors.[7] Following our initial disclosure of L-proline as a functional catalyst for the Michael reaction,[8] we reported our success in carrying out direct catalytic asymmetric Michael additions of unmodified ketones to alkylidene malonates and nitro olefins using (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine as a catalyst.[9] We envisioned at that time the possibility of employing unmodified aldehydes as donors. Due to the difficulty in controlling reactions of enolates or enols of aldehydes, there had been no examples of catalytic asymmetric conjugate additions of naked aldehydes.[10] Herein we report our results concerning enantioselective Michael additions of unmodified aldehyde donors catalyzed by chiral amines that operate using an enamine mechanism.[11]

The reaction of isovaleraldehyde with diethyl benzalmalonate was explored as a model transformation. Initial experiments were performed using (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine as catalyst. Under these conditions, no product formation was observed. However, when the more reactive *trans*-β-nitrostyrene acceptor was employed, the reaction proceeded smoothly to furnish the Michael adducts in 80% yield, with a dr of 80:20 in favor of the *syn* stereochemistry and 75% ee (Table 1, entry 3).[12] The *syn* selectivity of this reaction is in accord with our studies concerning ketone donors.[9] To search for more optimal catalysts, we synthesized and screened a number of structurally related amines (Table 1).[13] We found that (*S*)-2-(morpholinomethyl)pyrrolidine **1** (entry 9) was the most effective catalyst in terms of stereochemical control, providing a high level of diastereoselection and good enantioselection. In contrast to results obtained with diamine catalysts, reactions with L-proline and its analogues provided only trace amounts of the Michael adducts (entries 1 and 2).

Table 1. Catalyst Screening for the Michael Reaction



entry	cat	yield[a] (%)	dr[b] (*syn*/*anti*)	ee[c] (*syn*)
1		< 5	93 : 7	25
2		< 5	--	--
3		80	80 : 20	75
4		89	83 : 17	73
5		80	82 : 18	64
7		70	82 : 18	70
8		88	80 : 20	47
9		78	92 : 8	72

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of crude mixture. [c] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material.

Additional studies indicated a temperature profile with ascending selectivity with descending temperature. Upon cooling the reaction, the addition product was obtained with higher diastereo- and enantioselectivity but lower yield.

With the optimal catalyst, we examined a series of aldehydes and nitro olefins in order to establish the scope of the reaction (Table 2).[14] Higher enantioselection was achieved with increasing bulkiness of the substituents on the aldehyde donor in the order Me < Et < ^{n}Bu < ^{i}Pr (entries 1−4).[15] On the basis of our previous results,[9] we anticipated that ortho-substitution on the aromatic ring should affect both diastereoselectivity and enantioselectivity. Gratifyingly, excellent dr (up to 98:2) and good ee values were obtained,

(5) (a) Yasuda, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1996**, *37*, 6343−6346. (b) Enders, D.; Demir, A. S.; Rendenbach, B. E. M. *Chem. Ber.* **1987**, *120*, 1731−1735. (c) Martens, J.; Lubben, S. *Tetrahedron* **1991**, *47*, 1205−1214. (d) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2250−2260.

(6) For a seminal reference, see: Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222.

(7) For a general discussion of atom economy in organic synthesis, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

(8) (a) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267. (b) For a later communication on the same topic, see: List, B.; Pojarliev, P.; Martin, H. *Org. Lett.* **2001**, *3*, 2423−2425.

(9) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441−4444.

(10) For a recent example of addition of naked aldehydes to electron-deficient olefins in a nonenantioselective manner, see: (a) Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V. P.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* **2001**, *42*, 2705−2707. (b) Hagiwara, H.; Komatsubara, N.; Ono, H.; Okabe, T.; Hoshi, T.; Suzuki, T.; Ando, M.; Kato, M. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 316−322.

(11) For previous work from our laboratories in the asymmetric aldol reaction, Mannich reaction, and Robinson annulations through an enamine-type mechanism, see ref 8a and the following. (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III .*Tetrahedron Lett.* **2001**, *42*, 199−201. (b) Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951−6954. (c) List, B.; Lerner, R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396.

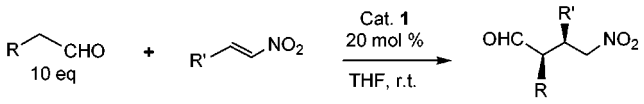
(12) For a review on stereoselective additions to nitroalkenes, see: Pyne, S. G. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*, E21 ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart NewYork, 1996; Vol. IV, pp 2161−2176.

(13) Diamines were prepared according to the method of Asami. Asami, M. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 721−727.

(14) In the case of the more reactive substrates such as hexanal, the reaction still proceeded smoothly when the amount of aldehyde was reduced to 5 or 2 equiv or when the catalyst loading was reduced to 10 or 5 mol % to provide the Michael adducts in over 85% yield, though a decrease in dr and ee values associated with longer reaction times was noted.

(15) No substantial change of ee and dr in time was observed when employing isovaleraldehyde as donor, but both decreased with longer reaction times when using the smaller homologues such as propionaldehyde.

Table 2. Michael Addition of Unmodified Aldehydes to Nitro Olefins



entry	aldehyde	R'	time	yield[a] (%)	dr[b] (*syn/anti*)	ee[c] (*syn*)	product
1	CHO	Ph	3 h	85	90/10	56[d]	**3**
2	CHO	Ph	27 h	94	86/14	65	**4**
3	CHO	Ph	27 h	87	85/15	69	**5**
4	CHO	Ph	3 d	78	92/8	72	**2**
5	CHO	Ph	3 d	No reaction			
6	CHO		3 d	67	96/4	75[e]	**6**
7	CHO		3 d	96	89/11	69	**7**
8	CHO	CF_3	3 d	77	98/2	78[e]	**8**
9	CHO	S	2 d	82	86/14	71	**9**
10	CHO		3 d	42	89/11	N. d.[f]	**10**
11	CHO		3 d	No reaction			

[a] Isolated yield after column chromatography. [b] Determined by ^{1}H NMR of crude mixture. [c] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material. [d] Determined after conversion to pyrrolidine **11**. [e] Determined after conversion to the corresponding primary alcohol by treatment with $NaBH_4$. [f] Not determined.

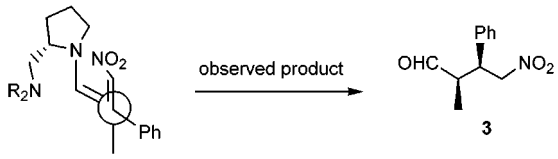
albeit with a slight decrease in yield (entries 6 and 8). Alkyl nitro olefins also provided Michael adducts but in low yield (entry 10).[16] Steric factors play an important role in this reaction. While isovaleraldehyde was a suitable aldehyde for the reaction, the more sterically demanding 3,3-dimethylbutyraldehyde was ineffective (entry 5). In the same way, introduction of an isopropyl substituent on the nitro olefin precluded the reaction from taking place (entry 11).

As is evident from the results shown in Table 2, the method is quite effective in a number of instances and produces the desired products in moderate to good yields, stereoselectivities, and enantioselectivities. The relative and absolute configurations of the Michael adducts were determined via NMR studies and chemical correlation to known compounds.[17]

(16) New compounds have been fully characterized spectroscopically, and elemental composition has been established by high-resolution mass spectrometry or combustion analysis.

Though further studies are needed to firmly elucidate the mechanism of this Michael addition, it very likely proceeds via an enamine mechanism.[18] The high *syn* selectivity we observe is in accord with results obtained in conjugate additions of preformed enamines to nitro olefins.[19] The *syn* selectivity is explained by an acyclic synclinal model, in which there are favorable electrostatic interactions between the partially positive nitrogen of the enamine and the partially negative nitro group in the transition state (Scheme 1).[20]

Scheme 1. Proposed Transition State



Approach of the nitro olefin from the less hindered *si* face of the enamine would produce the observed stereochemistry.

The methodology presented herein provides an easy and convenient way of synthesizing novel optically active 2,3-disubstituted γ-formyl nitro compounds in one step.[21] These useful synthons can be further converted into a wide array of interesting building blocks such as 1,4-amino alcohols or amino acids in a straightforward manner. A particular transformation that attracted our interest was the application of this approach to the synthesis of pyrrolidines. Substituted chiral, nonracemic pyrrolidines are common structural motifs found in many natural and unnatural products that possess interesting and important biological activities, and a great deal of effort has been devoted toward the development of asymmetric methods for their synthesis.[22,23] As an example of this application, we studied the hydrogenation of γ-formyl nitro compounds **2** and **3** with $Pd(OH)_2$. The reductive

(17) For further details, see the Supporting Information.

(18) When (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine and 2,4-pentanedione are mixed in equimolar amounts in DMSO, enamine formation is detected through UV spectroscopy. Furthermore, while pyrrolidine itself promotes the Michael reaction, the *N*-methyl derivative which lacks the secondary amine is ineffective as catalyst. An enamine mechanism is also in accord with our other studies concerning aldol, Mannich, and Michael reactions; see refs 8, 9, and 11.

(19) (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413−1423. (b) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1637−1654. (c) Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, *116*, 3086−3096. (d) Haner, R.; Laube, T.; Seebach, D. *Chimia* **1984**, *38*, 255−257. (e) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162−172. (f) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319−324.

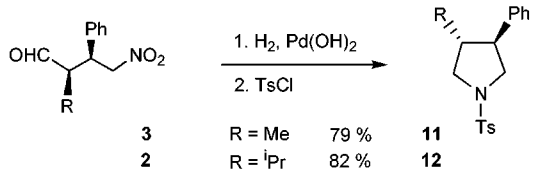
(20) See refs 5d, 12, 19a, 19b, and 19e. For theoretical studies of the reaction of chiral enamines to electrophilic olefins, see: (a) Sevin, A.; Masure, D.; Giessner-Prettre, C.; Pfau, M. *Helv. Chim. Acta* **1990**, *73*, 552−573. (b) Lucero, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 826−827 and references therein.

(21) Search of the Scifinder database resulted in no hits for the reported γ-formyl nitro compounds.

(22) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446. (b) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31, Chapter 6. (c) Massiot, G.; Delaude, C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 27, Chapter 3.

(23) (a) Ling, R.; Ekhato, I. V.; Rubin, J. R.; Wustrow, D. J. *Tetrahedron* **2001**, *57*, 6579−6588. (b) Karlsson, S.; Han, F.; Hogberg, H.-E.; Caldirola, P. *Tetrahedron: Asymmetry* **1999**, *10*, 2605−2616. (c) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221−3235 and references therein.

Scheme 2. Synthesis of 3,4-Disubstituted Pyrrolidines



3 R = Me 79 % **11**
2 R = ^{i}Pr 82 % **12**

amination proceeded smoothly to afford the desired pyrrolidines that were isolated as their *N*-tosyl derivatives **11** and **12** in good overall yields (Scheme 2).

In conclusion, we have developed a highly diastereoselective direct catalytic Michael reaction involving the addition of naked aldehydes to nitro olefins. These reactions afford a variety of γ-formyl nitro products in good yields with moderate to good enantioselectivity. To the best of our knowledge, this is the first report of the utilization of unmodified aldehydes as donors in the catalytic asymmetric Michael reaction. The simplicity and mildness of the reaction protocol, in combination with options for further efficient transformations of the resulting Michael adducts into synthetically interesting enantiomerically enriched 3,4-disubstituted pyrrolidines among others, makes this process useful. Further elaboration and application of this methodology is currently underway in our laboratories.

Acknowledgment. This work was supported by the NIH (CA27489) and The Skaggs Institute for Chemical Biology. We thank Kandasamy Sakthivel for helpful discussions, Laura Pasternack for NMR assistance, and Ghofu Zhong for UV studies.

Supporting Information Available: Experimental procedures, characterization data of Michael adducts, chiral phase HPLC data, and determination of configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0167006