Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 693–696

Amine-catalyzed Michael reactions of an aminoaldehyde derivative to nitroolefins

Klaus Albertshofer, Rajeswari Thayumanavan, Naoto Utsumi, Fujie Tanaka* and Carlos F. Barbas, III*

The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, United States

Received 12 October 2006; accepted 15 November 2006
Available online 11 December 2006

Abstract—Catalytic enantioselective Michael addition reactions of α-amino functionalized aldehydes to nitroolefins have been developed. The Michael product was obtained in up to 98% ee, but the enantiomeric purity of the Michael product was decreased during isolation of the product.

Michael addition reactions of carbonyl compounds to nitroolefins constitute important carbon–carbon bond-forming reactions. In recent years, direct catalytic asymmetric versions of the Michael reactions have been developed.[1,2] For example, pyrrolidine derivatives have been used as catalysts for asymmetric Michael reactions of in situ-formed enamines of carbonyl compounds.[1] Reactions catalyzed by these enamine-based catalysts typically proceed under mild, environmentally benign conditions. Enamine-based Michael reactions of α-amino functionalized carbonyl compounds should allow access to amino group-containing functionalized compounds; however, in most of the reported enamine-based Michael reactions, only simple ketones (such as cyclohexanone and acetone) and alkylaldehydes have been used as nucleophile sources. We have recently reported amino acid-catalyzed asymmetric aldol reactions of α-nitrogen-functionalized aldehyde **1**.[3] Use of **1** as the nucleophile source for enamine-based reactions provides concise routes to enantiomerically enriched amino acids and their derivatives. Here, in continuation of these efforts, we report amine-catalyzed Michael addition reactions of α-aminoaldehyde **1** to nitroolefins.

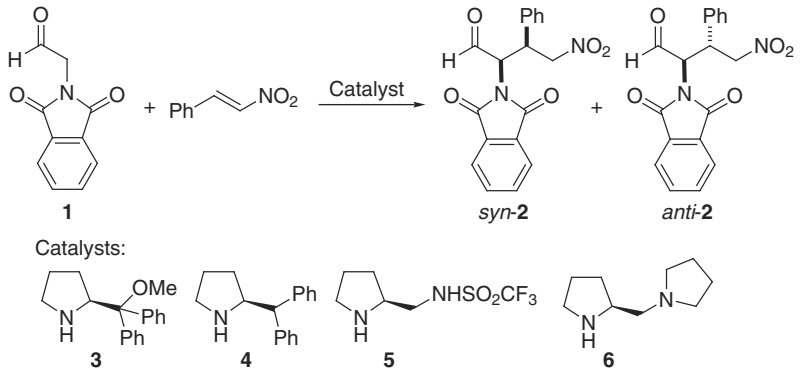
First, the reaction between aldehyde **1** and β-nitrostyrene to afford **2**[4] was performed in the presence of possible catalysts **3**–**6** (Table 1) in order to identify catalysts that afforded products with high enantioselectivity for this reaction. Since aldehyde **1** was soluble in $CHCl_3$, this solvent was used. Diastereomeric ratio (dr) was determined by ^1H NMR of the crude extract; then the crude reaction mixture was transformed to the oxime with *O*-benzylhydroxylamine,[5] either directly from the crude extract or after quick purification of **2**, and the enantiomeric excess (ee) was determined by HPLC analysis.

Although sulfonamide **5**[11] and diamine **6**-CF_3CO_2H[1f] are excellent asymmetric catalysts for Michael reactions between simple alkylaldehydes and β-nitrostyrenes, these catalysts were less optimal for the Michael reaction of **1** with respect to the yield of the desired product and enantioselectivity (entries 4–6). Some of the reactions formed polymer-like byproducts. Since use of brine has been demonstrated to suppress polymerization of nitrostyrene,[1o] the reaction with catalyst **3** was also tested in $CHCl_3$–brine. Catalyst **3** contains hydrophobic phenyl groups and was expected to be present in $CHCl_3$ phase with aldehyde **1** and nitrostyrene when the reaction is performed in $CHCl_3$–brine. The **3**-catalyzed reaction in $CHCl_3$–brine was slightly faster than the same reaction in $CHCl_3$. This screening showed that the best results were obtained when the Michael reaction of **1** was performed using pyrrolidine derivative **3** in $CHCl_3$–brine (entry 2). The enantioselectivity of the major diastereomer of this reaction was 94% ee.

Keywords: Michael reaction; Aminoaldehyde; Nitroolefin; Asymmetric reactions; Amine; Enamine.
* Corresponding authors. Tel.: +1 858 784 2559; fax: +1 858 784 2583 (F.T.); tel.: +1 858 784 9098; fax: +1 858 784 2583 (C.F.B.); e-mail addresses: ftanaka@scripps.edu; carlos@scripps.edu

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.11.096

Table 1. Evaluation of catalysts for the Michael addition reaction of aldehyde **1** to nitrostyrene[a]



Entry	Catalyst	Solvent	dr[b] *syn*:*anti*	ee[c] (%) *syn*/*anti*
1	**3**	$CHCl_3$	2:1	86/66
2	**3**	$CHCl_3$–brine	3:1	94/76
3	**4**	$CHCl_3$	2:1	72/30
4[d]	**5**	$CHCl_3$	4:1	—[e]
5	**6**	$CHCl_3$	2:1	67/<5
6	**6**-CF_3CO_2H (1:1)	$CHCl_3$	1:1	50/<5

[a] Conditions: A mixture of aldehyde **1** (0.2 mmol), β-nitrostyrene (0.4 mmol), and catalyst (0.04 mmol, 20 mol % to **1**) in $CHCl_3$ (1.0 mL) or in $CHCl_3$ (1.0 mL)–brine (1 mL) was stirred at room temperature for 24–72 h. Conversion of **1** was >70% in all cases, except for the reaction shown in entry 4.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral phase HPLC of oxime of **2** with *O*-benzylhydroxylamine. Absolute configurations were not determined.
[d] The reaction afforded significant amount of precipitation, possibly polymerized products of nitrostyrene.
[e] Not determined.

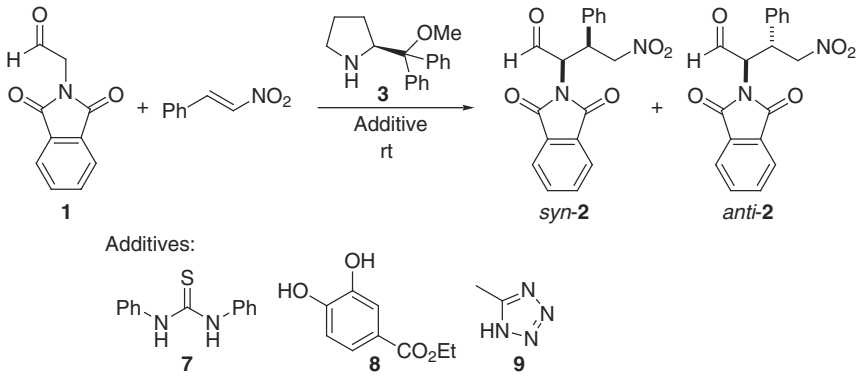
Since catalyst **3** was best among those tested for the Michael reaction of **1**, reactions using **3** were investigated further (Table 2). The **3**-catalyzed reaction was repeated numerous times and the dr and ee were slightly different each time (the range of the ee of the *syn*-isomer: 85–94% ee). When product **2** was carefully purified by silica gel column chromatography and then converted to the oxime for the determination of the ee, the ee of the major isomer *syn*-**2** was lower than when the ee was determined without isolation of **2** (entries 1 and 2). When **2** was directly converted to the oxime using the reaction mixture or a crude extract of the reaction mixture, the ee of the *syn*-**2** was higher than when **2** was purified. These differences may originate from enolization of the aldehyde of the product.[5] The α-position of the aldehyde in product **2** should be readily epimerized because of the phthalimide group.[5] The enantiomeric purity of the *anti*-isomer was lower than that of the *syn*-product; therefore interconversion between the *syn*- and *anti*-isomers decreases the ee of the *syn*-product.

Catalyst **3** should form an enamine with aldehyde **1** for catalysis. This catalyst, however, does not have a functional group for activation of nitrostyrene. Nitrostyrenes are more reactive with the enamine intermediate when hydrogen bonds are formed with the nitro group.[1,2] These hydrogen bonds should accelerate the rate of the reaction and might increase the dr and ee of the products.[1,2] Therefore, potential hydrogen bond-forming compounds, thiourea **7**, catechol **8**, and methyltetrazol **9**, were added to the **3**-catalyzed reaction (Table 2, entries 2–5) and reaction rate, diastereo- and enantioselectivities were analyzed. As a control, the **3**-catalyzed reaction with CF_3CO_2H was also performed (entry 6). In order to minimize epimerization during purification, conversion yield and dr were determined by ^{1}H NMR of a crude extract of the reaction mixture. The mixture was then directly, or after quick purification, transformed to the oxime with *O*-benzylhydroxylamine and the ee values were determined by HPLC analysis of the oxime,[4] except as noted. The **3**-catalyzed reaction with thiourea **7** afforded higher ee of the major isomer (98% ee without purification) and had a slightly faster reaction rate (~1.2-fold) than that of the reaction in the absence of **7** (entry 2 vs entry 1). But the actual function of **7** was not clear compared to the reactions with other additives (entries 4–6).

The reaction using catalyst **3** and thiourea **7** in $CHCl_3$–brine under conditions of Table 2, entry 2 afforded the best results of those tested with respect to the reaction rate, extent of byproduct formation, and enantiomeric excess of the major isomer *syn*-product. Although the ee of **2** slightly decreased when product **2** was purified because of possible enolization, this problem should be overcome by direct transformation of the aldehyde group of the Michael product to other functional groups prior to workup.[6]

The conditions that afforded the highest enantioselectivity for the major isomer of the Michael product, that is, use of catalyst **3** with thiourea **7** in $CHCl_3$–brine, were applied to Michael reactions of a series of nitroolefins (Table 3). The Michael products were purified and characterized in order to confirm that the reactions afforded desired Michael products under these conditions, though it is likely that erosion in enantiomeric purity occurred due to the purification. The desired Michael

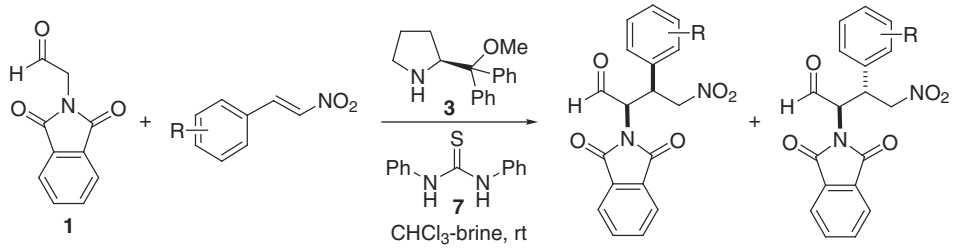
Table 2. Evaluation of additives for the **3**-catalyzed Michael addition reaction of aldehyde **1** to nitrostyrene[a]



Entry	Additive	Solvent	Time (h)	Conversion and yield[b] (%)	dr[c] *syn*:*anti*	ee[d] (%) *syn*/*anti*
1[e]	—	$CHCl_3$–brine	24	60	3:1	94/76
			48	100 (72)	(1.5:1)[f]	(88/72)[f]
2	**7**	$CHCl_3$–brine	24	70	2:1	98/68
			48	100 (95)	(2:1)[f]	(85/68)[f]
3[g]	**7**	$CHCl_3$–brine	24	50	5:1	90/76
4	**8**	$CHCl_3$–brine	24	57	2:1	94/90
			48	100	2:1	90/68
5	**9**	$CHCl_3$–brine	24	100	4:1	90/61
6	CF_3COOH	$CHCl_3$–brine	24	58	2:1	88/74
7	**7**	$CHCl_3$	24	87	1:1	86/41

[a] Conditions: A mixture of aldehyde **1** (0.2 mmol), β-nitrostyrene (0.4 mmol), catalyst **3** (0.04 mmol, 20 mol % to **1**), and additive (0.04 mmol) in indicated organic solvent (1.0 mL) or in $CHCl_3$ (1.0 mL)–brine (1 mL) was stirred at room temperature.
[b] Conversion yield was determined based on the ratio of **1** and **2** determined by ^{1}H NMR. Isolated yield was indicated in parenthesis.
[c] Determined by ^{1}H NMR of the crude reaction mixture, except noted.
[d] Determined by chiral phase HPLC of oxime of **2** with *O*-benzylhydroxylamine.
[e] See Table 1, entry 2.
[f] Determined on purified **2**. The *syn*- and *anti*-isomers were not discriminated on TLC.
[g] The reaction was performed with doubled concentration for each reactant, catalyst **3**, and additive **7**.

Table 3. Michael addition reactions of aldehyde **1** to nitroolefins catalyzed by pyrrolidine derivative **3** with thiourea **7**[a]



Entry	R	Time (d)	Yield[b] (%)	dr[c] *syn*:*anti*
1	4-Me	7	99	2:1
2	4-Br	4	70	2:1
3	3,4-di-Cl	3	92[d]	2:1
4	2,4-di-Cl	4	97	2:1
5	2-CF_3	1	45	1:1

[a] A mixture of aldehyde **1** (0.2 mmol), nitroolefin (0.4 mmol), catalyst **3** (0.04 mmol, 20 mol % to **1**), and **7** (0.04 mmol) in $CHCl_3$ (1.0 mL)–brine (1 mL) was stirred at room temperature. Typical work-up and purification afforded the Michael products (*syn*/*anti* mixture).
[b] Isolated yield.
[c] Determined by ^{1}H NMR of the purified products.
[d] Enantiomeric excesses of the isolated product: *syn* 86% ee, *anti* 86% ee (determined by chiral phase HPLC of the oxime with *O*-benzylhydroxylamine).

products were obtained in good yields in a few to 7 days. Because of the possible epimerization of the products, in the further development of the Michael reactions of aldehyde **1**, the product aldehyde group should be transformed directly, without isolation of the Michael products, to other groups that do not promote epimerization.

In summary, catalytic enantioselective Michael reactions of α-amino aldehyde **1** to nitroolefins have been performed using catalyst **3** and thiourea **7**. When the Michael product was transformed to its oxime without purification, the enantiomeric purity of the major isomer was excellent. Further development of the Michael reactions of α-amino aldehyde **1** and their applications to the synthesis of enantiomerically enriched functionalized compounds should take into account the lability of these compounds: The Michael reactions of aldehyde **1** should be directly coupled with other reactions that modify the aldehyde functionality of these products.

Acknowledgement

This study was supported in part by the Skaggs Institute for Chemical Biology.

References and notes

1. (a) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441; (b) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423; (c) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737; (d) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611; (e) Enders, D.; Seki, A. *Synlett* **2002**, 26; (f) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. , III. *Org. Lett.* **2004**, *6*, 2527; (g) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558; (h) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Synthesis* **2004**, 1509; (i) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808; (j) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611; (k) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147; (l) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369; (m) Terakado, D.; Takano, M.; Oriyama, T. *Chem. Lett.* **2005**, *34*, 962; (n) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212; (o) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966; (p) Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491; (q) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901; (r) Tsogoeva, S.; Wei, S. *Chem. Commun.* **2006**, 1451; (s) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826; (t) Huang, H.; Jacobsen, E. *J. Am. Chem. Soc.* **2006**, *128*, 7170; (u) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624; (v) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984; (w) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366; (x) Xu, D.; Luo, S.; Yue, H.; Wang, L.; Liu, Y.; Xu, Z. *Synlett* **2006**, 2569.
2. (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (b) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148; (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906; (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119; (e) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958; (f) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481; (g) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713; (h) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367; (i) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454.
3. Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541.
4. Compound **2**. ^{1}H NMR (300 MHz, $CDCl_3$): *syn*-isomer, δ 4.75 (ddd, $J = 4.8$ Hz, 9.3 Hz, 9.9 Hz, 1H), 4.94 (dd, $J = 9.9$ Hz, 13.2 Hz, 1H), 4.95 (d, $J = 9.3$ Hz, 1H), 5.24 (dd, $J = 4.8$ Hz, 1H), 7.08–7.18 (m, 5H), 7.67–7,76 (m, 4H), 9.72 (s, 1H); *anti*-isomer, δ 4.63–4.70 (m, 1H), 4.73–4.78 (m, 2H), 5.05 (d, $J = 9.6$ Hz, 1H), 7.35–7.42 (m, 5H), 7.79–7.92 (m, 4H), 9.47 (s, 1H). HPLC of the oxime of **2** with *O*-benzylhydroxylamine: Daicel Chiralpak AD, hexane/2-PrOH = 10:90, 1.0 mL/min, retention times: *syn*-**2** major enantiomer 69.8 min; *syn*-**2** minor enantiomer 25.9 min; *anti*-**2** major enantiomer 57.9 min; *anti*-**2** minor enantiomer 29.4 min.
5. Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanuvan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624.
6. Watanabe, S.; Cordova, A.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2002**, *4*, 4519.