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Organocatalytic Asymmetric Michael Addition of Aldehydes to β-Nitroacroleine Dimethyl Acetal

Efraim Reyes, Jose L. Vicario,* Dolores Badía, and Luisa Carrillo

Department of Organic Chemistry II, Faculty of Science and Technology, University of the Basque Country, P.O. Box 644, 48080 Bilbao, Spain

joseluis.vicario@ehu.es

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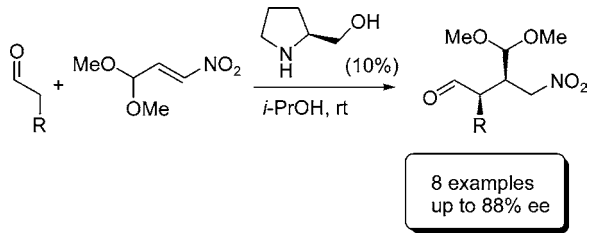
ABSTRACT



The organocatalytic asymmetric Michael addition of aldehydes to β-nitroacroleine dimethyl acetal has been studied in detail. The reaction took place with excellent yields and high stereoselectivities when a chiral β-amino alcohol such as L-prolinol was employed as the catalyst, leaving a formation of highly functionalized enantioenriched compounds containing two differentiated formyl groups together with a nitro moiety.

In the past few years, organocatalysis has emerged as a very powerful tool for the preparation of enantiomerically pure compounds.[1] Interest in this field has increased as a result both of the novelty of the concept and of the high efficiencies and selectivities attained by many organocatalytic transformations. Further advantages of this methodology are connected to the operational simplicity and availability of the organic catalysts, especially compared to the corresponding transition-metal species typically employed to promote the same reactions. Moreover, the fact that the use of toxic metals is precluded makes this methodology even more interesting from the environmental point of view. In this context, proline and other chiral secondary amines have been shown to be extremely useful catalysts in many C−C and C−heteroatom bond-forming reactions, being that the formation of an intermediate enamine or iminium species is a common feature in all these cases.[1,2]

Among all the organocatalytic asymmetric transformations reported so far that have been carried out using secondary amine catalysts, the asymmetric Michael addition of carbonyl compounds to nitroalkenes[3] has attracted much attention by several research groups worldwide.[4,5] This transformation has a huge potential in organic synthesis, not only because of the generation of a new C−C bond together with the potential for the formation of up to three contiguous stereocenters but also because of the high synthetic versatility of the nitro group present at the final adduct which opens the way for the preparation of many valuable compounds.[6]

(1) For some recent reviews on asymmetric organocatalysis, see: (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Special issue on organocatalysis: *Acc. Chem. Res.* **2004**, *37*, 487. See also: (d) Berkessel, A.; Groger, H. In *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.

(2) (a) List, B. *Chem. Commun.* **2006**, 819. (b) Jarvo, E. R.; Miller, S. D. *Tetrahedron* **2002**, *58*, 2481. (c) List, B. *Tetrahedron* **2002**, *58*, 5573.

(3) For a general review on Michael additions to nitroalkenes, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877.

(4) (a) Wang, J.; Li, H.; Lou, B.; Zu, L.; Guo, H.; Wang, W. *Chem.−Eur. J.* **2006**, *12*, 4321. (b) Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491. (c) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (d) Xu, Y.; Cordova, A. *Chem. Commun.* **2006**, 460. (e) Mitchell, C. E. T.; Cobb, A. J. A.; Ley, S. V. *Synlett* **2005**, 611. (f) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (g) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (h) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (i) Enders, D.; Seki, A. *Synlett* **2002**, 26. (j) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

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In relation to this topic, although many successful methodologies are known for performing the reaction using ketones as nucleophiles,[4] the organocatalytic asymmetric Michael reaction between aldehydes and nitroalkenes is significantly less developed and still several issues remain unsolved.[5] In fact, most papers reported are mainly focused on the use of nitrostyrenes as Michael acceptors, showing that, in most cases, changing to the corresponding β-alkyl-substituted nitroalkenes leads to a significant decrease in chemical yield and/or enantioselectivity. Moreover, as far as we know, there is only one single example that can be found in the literature in which a functionalized nitroalkene acceptor is employed.[7] Another drawback typically associated with the procedures reported is the high catalyst loading required (typically 20−30%) and the need for a large excess of aldehyde, which can turn into a serious limitation when scaling-up the reactions, especially if the catalyst or the aldehyde is not commercially available.

With all these precedents in mind, we turned our attention to β-nitroacroleine dimethylacetal **1**, which is a functionalized nitroalkene that has been employed in several metal-catalyzed conjugate addition reactions.[8] We wish to report herein our recently performed studies focused on the organocatalytic Michael reaction of aldehydes and this particular functionalized nitroalkene acceptor. This transformation has opened the way to the preparation of highly enantioenriched polyfunctionalized γ-nitroaldehydes containing a second chemically differentiated formyl group, which are anticipated to be extremely useful chiral building blocks in organic synthesis.

We began our experiments with the identification of the best amine catalyst, limiting our study to commercially available chiral pyrrolidines (Figure 1).[9]

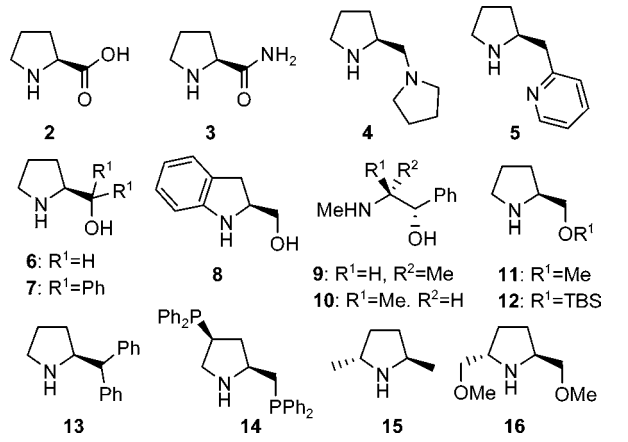


Figure 1. Chiral amine catalysts tested.

For the catalyst screening, we employed the reaction between propionaldehyde and nitroalkene **1** in THF at room temperature as a model reaction (Scheme 1), which led to the formation of γ-nitroaldehyde **17a**.[10] It has to be pointed out that, in all cases, the reaction was performed using a 1:1 aldehyde/nitroalkene ratio. The results obtained are summarized in Table 1.

Scheme 1

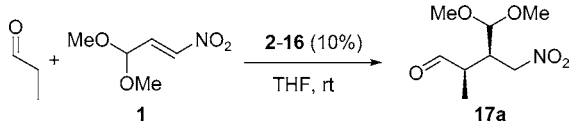


Table 1. Optimization of the Catalyst Structure[a]

entry	catalyst	time (h)	yield (%)	syn/anti[b]	ee (%)[b]
1	**2**	48	83	1:1	37
2	**3**	96	55	1.1:1	66
3	**4**	48	43	1:1.5	40
4	**5**	120	48	1.1:1	22
5	**6**	72	93	1.1:1	70
6	**7**	240	16	2.1:1	92
7	**8**	312	21	3.3:1	−88
8	**9**	288	49	>20:1	20
9	**10**	168	99	3.1:1	−34
10	**11**	24	81	1.2:1	68
11	**12**	30	75	1:1.4	64
12	**13**	24	60	1.1:1	−65
13	**14**	168	18	2.1:1	42
14	**15**	24	99	1.1:1	−30
15	**16**	72	70	1:1	30

[a] All reactions were carried out on a 1.00 mmol scale with 1 equiv of **1** and 1 equiv of propionaldehyde in the presence of 10 mol % of the catalyst at room temperature in 2 mL of solvent. [b] Determined by chiral GC on the corresponding propylene acetal (see Supporting Information for details).

As can be seen in this table, L-proline did not perform well in the reaction (entry 1). Amide **3** and diamines **4** and **5**, which have been successfully employed in the Michael

(5) (a) Enders, D.; Huttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Palomo, C.; Vera, S.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984. (c) Mosse, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, *8*, 2559. (d) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (e) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (f) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (g) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2527. (h) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (i) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737.

(6) Ono, N. In *The Nitro Group in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.

(7) Andrey, O.; Vidonne, A.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 7901. See also ref 8f.

(8) (a) Polet, D.; Alexakis, A. *Tetrahedron Lett.* **2005**, *46*, 1529. (b) Choi, H.; Hua, Z.; Ojima, I. *Org. Lett.* **2004**, *6*, 2689. (c) Mampreian, D. M.; Hoveyda, A. H. *Org. Lett.* **2004**, *6*, 2829. (d) Rimkus, A.; Sewald, N. *Synthesis* **2004**, 135. (e) Duursma, A.; Minaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 3700. We also found one example of the use of this nitroalkene in an organocatalytic reaction: (f) Andrey, O.; Alexakis, A.; Tomasini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147.

(9) MacMillan imidazolidinone catalysts were also tested in the reaction, but they did not show any catalytic activity.

(10) The absolute configuration of **17a** has been assigned by assuming a reaction pathway identical to that reported in the literature (ref 5). The relative configuration was established by comparison of NMR data.

addition of ketones to nitroalkenes, also delivered poor results (entries 2−4). However, when we changed to L-prolinol **6**, we obtained a good yield of the adduct **17a** in a moderate enantioselectivity (entry 5). We surveyed other more sterically demanding prolinol derivatives **7** and **8** observing that, although the enantioselectivity of the reaction was significantly increased, reaching 92% ee in the case of diphenylprolinol **7**, low yields of the final product were obtained (entries 6 and 7) even after prolonged reaction times.

We also tried other acyclic amino alcohols such as ephedrine (entry 8) and pseudoephedrine (entry 9) observing that, interestingly, the latter was an active and efficient catalyst leading to the formation of **17a** in a quantitative yield, although with low enantioselectivity. Prolinol ethers **11** and **12** also showed good catalytic activity with moderate levels of enantioselection (entries 10 and 11). We turned our attention to other commercially available potential catalysts such as chiral pyrrolidine **13**, aminodiphosphine **14**, and the C_2-symmetric derivatives **15** and **16**, observing no improvement in the degree of enantioselection of the transformation. The fact that a β-amino alcohol such as prolinol[11] is not only active but also a very effective catalyst in this transformation also has to be emphasized because of the well-known tendency of β-amino alcohols to react with aldehydes forming oxazolidines which leads to an unproductive intermediate.[12]

After these experiments, we accepted that L-prolinol **6** was the best catalyst for this transformation considering, in average, both the yield and enantioselectivity of the reaction.[13] Consequently, we proceeded to optimize the reaction, especially with regard to the solvent used (Table 2), although

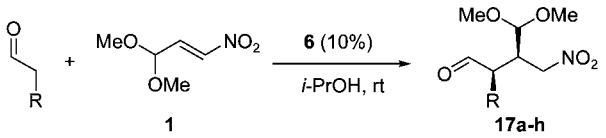
Table 2. Optimization of the Reaction Solvent

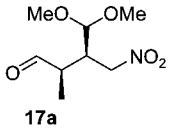
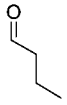
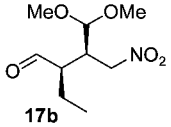
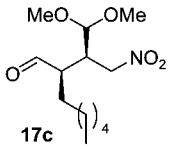
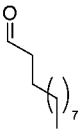
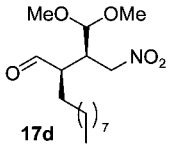
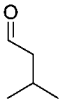
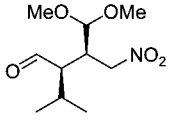
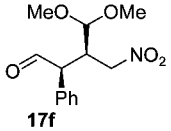
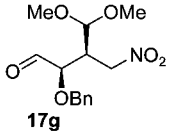
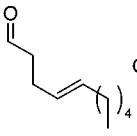
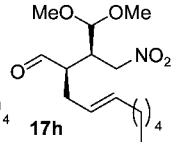
entry	solvent	time (h)	yield (%)	syn/anti[a]	ee (%)[a]
1	hexane	120	<5	–	–
2	$CHCl_3$	12	75	2:1	72
3	AcOEt	24	99	1:1	78
4	Et_2O	12	90	1.1:1	68
5	THF	72	93	1.1:1	70
6	DME	48	80	1:1.9	64
7	dioxane	48	56	1.1:1	64
8	MeCN	16	95	1:1	79
9	DMF	12	99	2.5:1	74
10	DMSO	24	68	1.6:1	74
11	MeOH	96	57	1.3:1	70
12	*i*-PrOH	12	74	1.7:1	80
13	*i*-PrOH[b]	72	55	1.7:1	80
14	*i*-PrOH[c]	24	67	1.7:1	80

[a] Determined by chiral GC on the corresponding propylene acetal (see Supporting Information for details). [b] Reaction run at −25 °C. [c] Reaction run with 1% catalyst.

the temperature of the reaction and the amount of catalyst employed were also examined. Regarding the nature of the solvent, we observed that, in general, increasing the polarity resulted in better yields of the Michael product, but the enantioselectivity of the reaction did not appear to be strongly affected by the solvent employed. The best enantioselection

Table 3. Organocatalytic Asymmetric Michael Reaction Using Several Aldehydes and Nitroalkene **1**[a]



entry	aldehyde	product	time (h)	yield (%)	*syn/anti*[b]	ee (%)[b]
1		 **17a**	12	74	1.7/1	80
2		 **17b**	48	75	3.7/1 (5/1)[c]	80
3		 **17c**	72	65	1.7/1	80
4		 **17d**	72	63	2/1 (9/1)[c]	83
5		 **17e**	70	46	9/1	88
6		 **17f**	36	99	1.3/1	40
7		 **17g**	48	99	1.5/1	n.d.[d]
8		 **17h**	72	63	1.3/1 (3/1)[c]	82

[a] All reactions were carried out on a 1.00 mmol scale with 1 equiv of **1** and 1 equiv of propionaldehyde in the presence of 10 mol % of the catalyst at room temperature in 2 mL of solvent. [b] Determined by chiral GC or HPLC analysis of the crude reaction mixture. [c] After flash column chromatography. [d] n.d. = not determined. We were not able to get baseline separation of enantiomers in all conditions tried.

was observed using *i*-PrOH as solvent leading to the formation of the adduct **17a** in good yields and in an acceptable reaction time (entry 12). In this case, we also performed the reaction at lower temperatures (entry 13); however, we could only observe that the reaction slowed down, and the enantioselectivity remained unchanged. Remarkably, we have also observed that a much lower catalyst

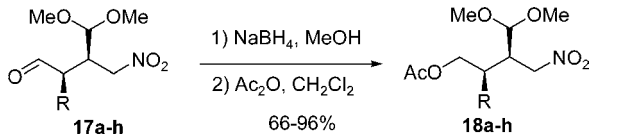
loading (1%) was possible without significantly affecting the yield and the enantioselectivity of the reaction (entry 14). Disappointingly, the syn/anti ratio of the reaction still remained in moderate values under the optimized conditions.

Having established an optimal protocol for the reaction, we proceeded next to examine the scope and limitations of the method with regard to the aldehyde substrate. We therefore proceeded to perform the reaction using a variety of aldehydes with different structures (Table 3).

As can be seen in Table 3, the reaction proceeded well with most aldehydes employed, furnishing comparable levels of enantioinduction in all cases, with the only exception being phenylacetaldehyde (entry 6). Concerning the yield of the reaction, we observed that longer reaction times were needed to reach synthetically useful yields of the product when increasing the length of the alkyl chain of the aldehyde (see, for example, entries 1−3). Finally, it also has to be pointed out that the syn/anti selectivity was also affected by the nature of the aldehyde, reaching the highest ratio with the bulky 3-methylbutanal (entry 5). In all cases, the reaction was carried out using 1 equiv of aldehyde with respect to nitroalkene **1**.

γ-Nitro aldehydes **17a**−**h** appeared to be somewhat unstable compounds, and therefore, for better characterization purposes, we proceeded to carry out the reduction of the formyl group ($NaBH_4$) followed by esterification with acetic anhydride (Scheme 2). The obtained esters **18a**−**h** were

Scheme 2



stable compounds that could be stored for several weeks without decomposition, and moreover, the minor anti diastereoisomer could be partially removed at this point in some cases by column chromatography purification.

In conclusion, we have shown that even though prolinol has not given good results in all the previous examples reported in the literature it works as a very efficient organocatalyst for the asymmetric Michael reaction of aldehydes to β-nitroacroleine dimethyl acetal, leading to the formation of highly functionalized enantioenriched chiral compounds in which two differentiated formyl groups are present together with a nitro moiety. The methodology reported herein has additional advantages, such as the fact that the reaction can be carried out using equimolar amounts of aldehyde donor and nitroalkene acceptor, the low catalyst loading required compared to other methods reported, and finally, those derived from the nature of the catalyst, which is a cheap reagent and commercially available in both enantiomeric forms.

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Supporting Information Available: Characterization of all new compounds and copies of their ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) To the best of our knowledge, this is the highest enantioselectivity reported for an organocatalytic reaction mediated by prolinol. For other prolinol-mediated reactions, see the following. Aldol reaction: (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (b) Mase, N.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. Fluorination: (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706. Knoevenagel: (d) Ramachary, D.; Chowdary, N. S.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. Diels−Alder: (e) Juhl, K.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1498. Michael: (f) Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966. (g) Melchiorre, P.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151. Epoxidation: (h) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579.

(12) The high catalyst loading required in many proline-catalyzed reactions is reported to be needed due to the formation of an unproductive oxazolidinone intermediate: List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839.

(13) Although the use of L-prolinol ethers **11** and **12** furnished a promising result in the initial experiments (Table 1), when we surveyed other solvents, we did not observe a significant inprovement in the enantio- and/or diastereoselectivity of the reaction.