Organocatalysis

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Highly Efficient Asymmetric Michael Addition of Aldehydes to Nitroalkenes Catalyzed by a Simple *trans*-4-Hydroxyprolylamide**

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Methods based exclusively on organocatalysts have become of major significance in synthetic chemistry.[1] The Michael addition of carbonyl compounds to nitroalkenes[2] is a challenging benchmark for such a development owing to its potential for the construction of a C–C bond with simultaneous generation of up to three adjacent stereogenic centers and because of the pivotal importance of the nitro group as a precursor to many functionalities.[3] While bifunctional thioureas[4] and chiral Brønsted bases[5] have been developed to control the stereochemistry of the process with malonate esters and related methylene-active substrates,[6] stereocontrol during the reaction involving aldehydes and ketones is most often effected from chiral cyclic secondary amines via enamine formation.[7] However, despite the recent efforts in the area, unmet challenges remain with regard to substrate generality and reaction selectivity, including both diastereo- and enantioselectivity.[8] For example, proline[8a–c] and several diamine/protonic acid catalysts[8d–h] are capable of promoting the reactions with ketones, but with aldehydes poor chemical and stereochemical results are produced (*syn*/*anti* 80:20 to 90:10; 70–75% *ee*). The groups of Kotsuki and Ley have described a pyrrolidine–pyridine/protonic acid system[8i] and a homoprolinetetrazole catalyst,[8j,k] which also provide excellent results for ketones. However, very poor enantioselectivities (22–37% *ee*) are observed when an aldehyde is used as the substrate. Highly diastereo- and enantioselective conjugate additions involving aldehydes were reported by the groups of Hayashi and Wang using a diphenylprolinol silyl ether[8l] and a pyrrolidine–sulfonamide,[8m] respectively. Nonetheless, one drawback is the need for a large excess of the aldehyde substrate, generally 10 equivalents, which becomes a serious limitation in the case of aldehydes that are not commercially available. Most importantly, the catalysts are effective in reactions with nitrostyrenes, but with β-alkyl-substituted nitroalkenes moderate yields (50%)[8l] or essentially no enantioselectivity (22% *ee*)[8m] is produced. The need for high catalyst loading, typically 15–20 mol%, is another important inconvenience related to most of the above approaches,[8] specially when the reactions have to be scaled up. Most recently, an attractive organocatalytic Michael reaction in brine was disclosed.[8n] Again, low diastereo- and enantioselectivities (*syn*/*anti* 60:40, 38–74% *ee*) are observed when aldehydes are employed. Herein we report a new catalyst design (**B**, Figure 1) which provides a highly efficient solution to these problems.

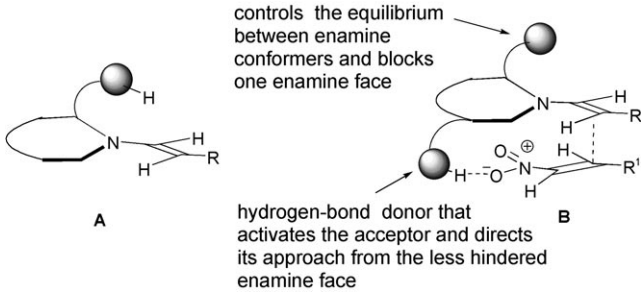

Figure 1. Features of the catalyst design.

The basis of our proposal stems from the observation that in the majority of the above catalyst systems a hydrogen-bond donor at the α-position of the pyrrolidine nitrogen atoms (**A**, Figure 1) is introduced to help the catalytic reaction to proceed.[9] This observation can be correlated to the amine-catalyzed aldol additions wherein a hydrogen-bond motif arising from the same position is involved in a half-chair, six-membered transition state during the catalytic cycle,[10] thus suggesting that the self-aldol reaction[11] in competition with the Michael addition could be the reason for most of the observed problems of the latter. Our hypothesis was that if the design outlined for **B** in Figure 1, wherein the α-hydrogen-bond donor is omitted, could be operative, the aldol reaction might be kept at a minimum whilst the Michael addition should proceed with a high degree of diastereo- and enantiocontrol. To evaluate this hypothesis, *trans*-4-hydroxyprolylamides were selected as potential candidates, as they meet the proposed structural requirements and, in turn, are readily available from commercial sources.

To get initial information on the above assumptions, catalysts **14**–**20** (Scheme 1) were prepared and screened for the reaction of *trans*-nitrostyrene with two representative aldehydes, butyraldehyde **1a** and isovaleraldehyde **1d**. With catalysts **14** and **15**, which lack hydrogen-bond donors, the reaction proceeded to give adducts **8a** and **8d** with good diastereoselectivity, albeit with poor enantioselectivity (Table 1, entries 1 and 2). To our delight, when the same reactions were carried out in the presence of *trans*-4-hydroxyprolylamides **16**, **17**, and **18**, adducts **8a** and **8d** were produced with similar diastereoselectivity levels but, most significantly, with much better enantioselectivities

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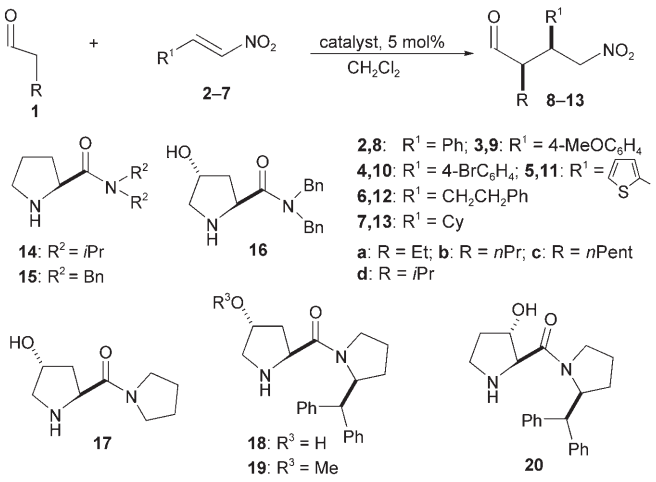
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 1. Catalytic asymmetric conjugate additions of aldehydes to nitroalkenes. Bn = benzyl; Cy = cyclohexyl.

Table 1: Catalyst screening for reaction of **1a** and **1d** with *trans*-β-nitrostyrene (**2**).[a]

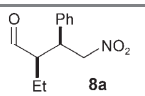
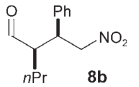
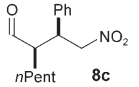
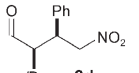
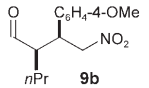
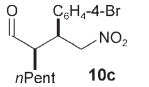
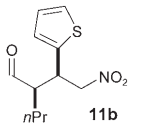
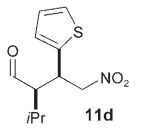
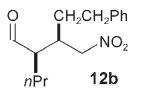
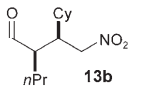
Entry	Cat.	Product **8a** (R = Et, R^1 = Ph) Conv. [%][b]	d.r.[c] (*syn*/*anti*)	*ee* [%][c]	Product **8d** (R = *i*Pr, R^1 = Ph) Conv. [%][b]	d.r.[c] (*syn*/*anti*)	*ee* [%][c]
1	**14**	>99	92:8	60	>99	98:2	40
2	**15**	>99	92:8	60	99[d]	98:2	60
3	**16**	>99	98:2	86	50	96:4	90
4	**17**	>99[e]	98:2	92	75	98:2	90
5	**18**	>99[e]	98:2	94	>99	95:5	91
6	**19**	n.r.[f]	–	–	n.r.	–	–
7	**20**	>99[e]	96:4	40	>99	90:10	70

[a] Reactions conducted on a 0.25-mmol scale with a tenfold excess of aldehyde and Cl_2CH_2 as solvent. [b] Determined by ^{1}H NMR spectroscopy (500 MHz) after 20–24 h at room temperature. [c] Determined by HPLC. See the Supporting Information for further details. [d] After 60 h at room temperature. [e] After 2 h at room temperature. [f] n.r. = no reaction.

(Table 1, entries 3–5). Interestingly, in no case was the corresponding aldol adduct observed despite the excess of aldehyde employed.[12] On the other hand, the fact that no reactions were observed with methyl ether **19** (Table 1, entry 6) further establishes the importance of the hydroxy group not only for reaction stereocontrol, but also for catalyst activity. Furthermore, the position of the hydroxy group in the catalyst seems also to be important as the 3-hydroxyproylamide derivative **20** led to lower enantio- and diastereoselectivities (Table 1, entry 7).

Results from the reaction of several aldehydes and nitroalkenes promoted by catalysts **16** and **18** are summarized in Table 2. While both catalysts provided comparable *syn*/*anti* selectivity ratios, the latter was most effective in terms of reaction enantioselectivity (Table 2, entries 7/8, 10/11, and 14/15). The optimum results were achieved when the reactions were carried out in CH_2Cl_2 at room temperature in the presence of 10 mol% of catalyst **18** for β-branched aldehydes (Table 2, entries 8 and 13) and 5 mol% for linear-chain aldehydes at 0°C. To the best of our knowledge, this finding

Table 2: Michael addition reactions of aldehydes to nitroalkenes catalyzed by **16** and/or **18**.[a]

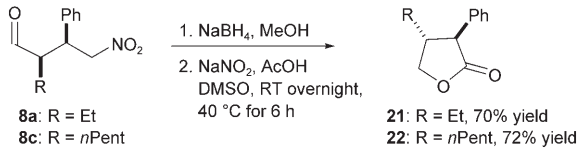
Entry	Cat.[b]	Product **8–13**	*T* [°C]	*t* [h]	Yield[c] [%]	d.r.[d] (*syn*/*anti*)	*ee* [%]
1	**18**(10)	 **8a**	RT	2	75	98:2	94
2	**18**(5)		0	20	90[e]	99:1	>99
3	**18**(10)	 **8b**	RT	2.5	67	90:10	94
4	**18**(10)		0	20	72	95:5	96
5	**18**(5)	 **8c**	0	20	70[e]	99:1	96
6	**18**(5)		0	20	87[f]	90:10	99
7	**16**(10)	 **8d**	RT	20	66[g]	97:3	93
8	**18**(10)		RT	20	75	95:5	91
9	**18**(5)	 **9b**	0	20	72[e]	96:4	>99
10	**16**(10)	 **10c**	0	20	90[g]	92:8	76
11	**18**(5)		0	20	70	97:3	98
12	**18**(5)	 **11b**	0	20	70	>99:1	94
13	**18**(10)	 **11d**	RT	14	76	94:6	92
14	**16**(10)	 **12b**	0	20	90[g]	97:3	86
15	**18**(5)		0	20	72	>99:1	>99
16	**18**(5)	 **13b**	0	20	75	>99:1	>99

[a] Reactions conducted on a 1-mmol scale in CH_2Cl_2 (1 mL) when 10 mol% is used and CH_2Cl_2 (0.5 mL) when 5 mol% of catalyst is used. [b] Number in parenthesis refers to the catalyst loading in mol%. [c] Yield of isolated product after column chromatography. [d] Determined by chiral high-performance liquid chromatography. [e] Reaction conducted on a 3-mmol scale using 1.2 equivalents of aldehyde. [f] Reaction conducted on a 20-mmol scale. [g] Conversion determined by ^{1}H NMR spectroscopy.

represents the lowest catalyst/substrate ratio employed in enamine-based Michael additions. Under these conditions, the enantioselectivities obtained were above 90% for essentially all substrates that were explored, including β-alkyl-substituted nitroalkenes, which gave adducts with diastereomeric ratios greater than 99:1 and enantioselectivities of up to 99% (Table 2, entries 15, 16).[13] Furthermore, in these reactions only a slight excess of the aldehyde substrate (1.5–2.0 equiv) is employed, but nearly equimolar amounts are also tolerated with equal efficiency (Table 2, entries 2, 5, and 9). The utility of this approach is illustrated in the reaction of heptanal with nitrostyrene performed on a 20-mmol scale (Table 2, entry 6), which provided **8c** with no significant detrimental effect on yield or stereoselectivity. Moreover, the

catalyst can be easily recovered in 70–80% yield after the reaction by simple aqueous acid/base work up, which is an additional aspect of the approach that is of practical importance.

The excellent chemical and stereochemical efficiency observed in these Michael reactions is also of particular interest in that it may provide a simple route to 3,4-disubstituted pyrrolidines[8d] or, as shown in Scheme 2, to γ-butyrolactones, which are common structural units of natural products.[14]



Scheme 2. Elaboration of the Michael adducts.

To better understand the efficiency of the present model the reaction between propionaldehyde and 1-nitropropene catalyzed by *N*,*N*-dimethyl-*trans*-4-hydroxyprolylamide was studied by DFT calculations at the B3LYP/6-31G* level. Concordant with our initial hypothesis, the results show that the OH group helps to discriminate between the two possible transition-state (TS) models **C** and **D** by 2.1 kcal mol^{-1} (Figure 2) and that in the absence of a hydrogen-bond donor, the reactions promoted by the naked prolylamide derivative or the OMe derivative are 10^3 times slower.[15]

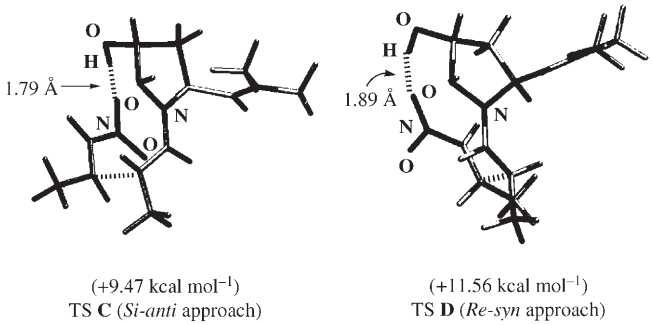


Figure 2. Models for the TS in the catalytic addition of propionaldehyde to 1-nitropropene.

In conclusion, we have documented a new model for the catalytic asymmetric Michael addition of aldehydes to nitroalkenes which holds several interesting features: a) Michael adducts with very high diastereo- and enantioselectivity and a broad range of β-substitution patterns are accessible; b) the catalyst, which in most cases is used in only 5 mol%, is readily available and recoverable; and c) almost equimolar amounts of the aldehyde donor can be employed.

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[12] Control experiments conducted without nitroalkene revealed the complete absence of self-aldol reaction. Concurrent with this research, a related design which works for the *anti*-Mannich reaction has been reported: S. Mitsumori, H. Zhang, P. H.-Y. Cheong, K. N. Houk, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2006**, *128*, 1040 – 1041.

[13] This catalytic system seems to be less effective for ketones; for instance, using catalyst **18** (10 mol%) and cyclohexanone (3 equiv) at room temperature gave d.r. 83:17 and 20% *ee*; using tetrahydrothiopyran-4-one (10 equiv) at 0°C gave d.r. >99:1 and 60% *ee*. For recent catalysts for ketone additions, see: homoproline: a) D. Terakado, M. Takano, T. Oriyama, *Chem. Lett.* **2005**, *34*, 962 – 963; chiral ionic liquids: b) S. Luo, X. Mi, L. Zhang, S. Liu, H. Xu, J.-P. Cheng, *Angew. Chem.* **2006**, *118*, 3237 – 3241; *Angew. Chem. Int. Ed.* **2006**, *45*, 3093 – 3097; amine–thiourea catalysts: c) H. Huang, E. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170 – 7171; d) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451 – 1453; primary amines: e) Y. Xei, A. Córdova, *Chem. Commun.* **2006**, 460 – 462; triamines: f) M.-K. Zhu, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Tetrahedron: Asymmetry* **2006**, *17*, 491 – 493.

[14] For a review, see: a) S. S. C. Koch, A. R. Chamberlin, *Studies in Natural Products Chemistry*, *Vol. 16* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1995**, pp. 687 – 725; for leading references, see: b) R. B. Chhor, B. Nosse, S. Sörgel, C. Böhm, M. Seitz, O. Reiser, *Chem. Eur. J.* **2003**, *9*, 260 – 270.

[15] For details, see the Supporting Information.

