Organocatalysis

DOI: 10.1002/anie.201101835

Dual Hydrogen-Bond/Enamine Catalysis Enables a Direct Enantioselective Three-Component Domino Reaction**

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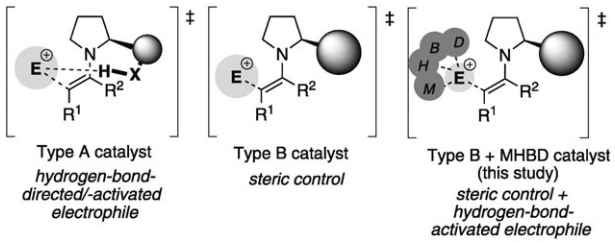
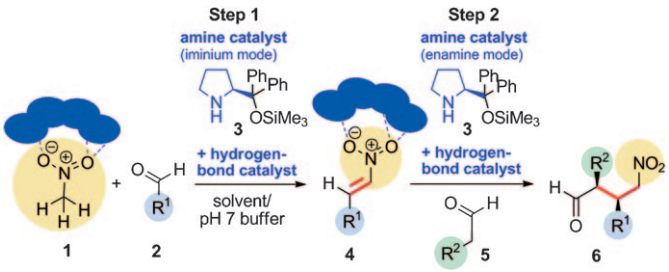
The nitro group enjoys a privileged position among the functional groups that can be activated through hydrogen-bond catalysis.[1] However, the hydrogen-bond-acceptor capacity of the nitro group is lower than that of the carbonyl or the imine group.[2] To increase reactivity, the use of catalysts bearing multiple-hydrogen-bond donor (MHBD) groups to increase the catalytic activity through possible formation of several hydrogen bonds represents an attractive option for enantioselective catalysis.[3,4] Although this approach has been successfully used in multifunctional catalysts where all the necessary functionalities are incorporated in the same catalyst molecule, the use of separate catalysts for electrophile and nucleophile activation might allow more opportunities for catalyst and reaction screening because both catalysts could be optimized separately. As an example, enantioselective enamine catalysts typically incorporate a hydrogen-bond-donor site (Scheme 1, Type A) or rely on steric control alone (Type B).[5]

Herein we demonstrate that the use of a dual catalyst system[6] can lead to significant rate enhancements in enamine catalysis and describe the successful use of a dual MHBD/enamine catalyst system for a highly enantioselective domino three-component reaction sequence (Scheme 2).[7] Both steps are catalyzed by the MHBD catalyst as well as the amine catalyst, and two different aldehydes can also be used in a cross-domino sequence, thus providing the products in excellent enantioselectivity, diastereoselectivity, and high yield.[8]



Scheme 1. Activation modes in enamine catalysis.



Scheme 2. A domino three-component sequence with activation of the nitro group by the hydrogen-bond catalyst.

Step 1, the condensation of aliphatic aldehydes with nitromethane to yield nitroolefins (**4**; Scheme 2), is not as trivial as it first appears because aliphatic aldehydes readily undergo self-aldolization and self-condensation reactions with secondary amine catalysts.[9] Although the preparation of β-aryl-substituted nitroolefins is relatively straightforward,[10] the more challenging β-alkyl-substituted nitroolefins are typically prepared through a two-step sequence.[11] Step 2 of the sequence, the conjugate addition of aldehydes to nitroolefins, has been intensively studied.[12] The most active catalyst systems typically include either extra hydrogen-bond donors in the enamine catalyst[13] or employ acids,[14] phenols,[15] or water[16] as additives, thus allowing lower catalyst concentrations and/or better aldehyde/nitroolefin stoichiometry. Nevertheless, an excess of the donor aldehyde, up to 10 equivalents, is typically used to boost the reaction rates, and long reaction times (12–48 h) are often required with aliphatic aldehydes.

We reasoned that significant improvement could be achieved in one stroke if the most enantioselective enamine catalyst of Step 2 reported to date, the diphenylprolinol derivative **3** disclosed by Hayashi et al. in 2005,[12c] would be boosted with a MHBD co-catalyst. In Step 1, **3** would function as an iminium catalyst, thus promoting a one-pot condensation process between aldehyde **2** and nitromethane **1**.[17] This step would require assistance of a MHBD co-catalyst because **3** does not promote the condensation process alone.[8] The MHBD catalyst would then activate the newly generated β-substituted nitroolefin **4** towards conjugate addition with the second aldehyde **5**, activated by **3** that now functions as an

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[**] We thank Reijo Kauppinen and Mirja Lahtiperä for assistance with the NMR and HRMS measurements, respectively. This work was supported by the Academy of Finland (projects 217221 and 217224), and OTKA (Hungary, grant no. NN-82955).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101835.

enamine catalyst. If the catalyst is successful in activating the nitro component in both steps, the entire sequence from **1** to **6** could be completed in a domino fashion, while avoiding aldehyde–aldehyde condensations or the conjugate addition of nitromethane to **4**.

We initiated our screen with a domino reaction of propionaldehyde **2a** with nitromethane. A biphasic mixture of $CHCl_3$ and aqueous buffer at pH 7 generally offered the fastest rates, but the reactions could also be performed without added buffer.[18] As summarized in Table 1, most catalysts bearing two or three hydrogen-bond-donor sites afforded very slow conversions and relatively high amounts of self-aldol product **18** (Table 1, entries 2, 5, and 7). However, with more lipophilic hybrid BINOL-(thio)urea catalysts **15** and **17**, a rapid and highly selective conversion to the desired domino product was observed (Table 1, entries 10 and 12).

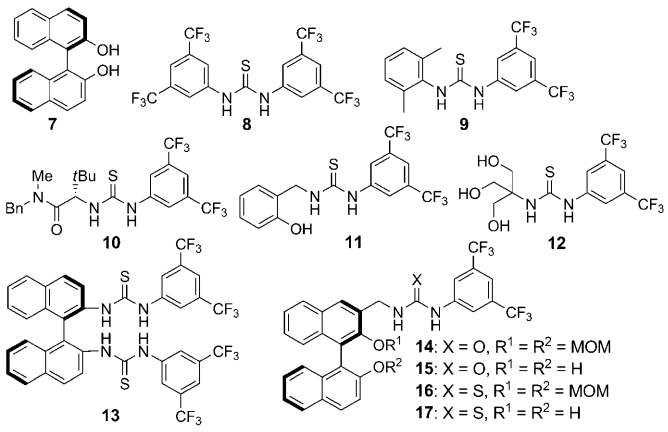
Notably, the double thiourea catalyst **13** or the triol catalyst **12** were not significantly more active than the standard thiourea catalysts **8** or **9**. In addition, the importance of neutral conditions is illustrated by the fact that undistilled propionaldehyde (containing propionic acid) afforded significant amounts of side products **18** and **19**, even with the best catalyst system. These side reactions could be completely suppressed when freshly distilled propionaldehyde was used. The presence of a buffer solution boosted the rates somewhat but the chemoselectivity and enantioselectivity were also maintained without buffer solution (Table 1, entry 13).

A range of aldehydes with different polarities and functionalities was then subjected to the reaction sequence. To preserve the stereochemical integrity of the products and to facilitate the reliable analysis of the enantiomeric purity, the aldehydes were further processed with phosphorane **20** to afford the enoates **21**. As summarized in Table 2, several different aliphatic aldehydes readily participated in the reaction sequence, without limitations in the size or hydrophobicity of the aldehyde partner. In all cases, the products were obtained in excellent yields, diastereoselectivities, and near-perfect enantioselectivities.[19]

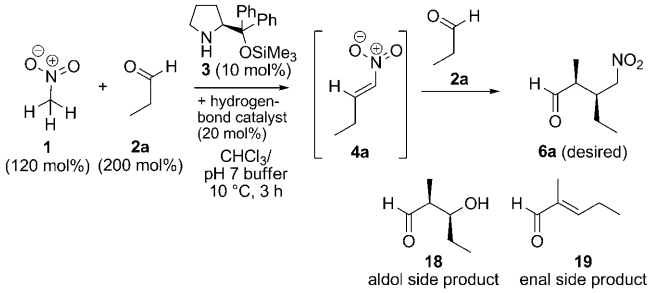
To demonstrate that the MHBD catalyst **17** does indeed promote Step 2 (conjugate addition, Scheme 2), control

Table 1: Screening of hydrogen-bond-donor co-catalyst.

Hydrogen-bond catalysts



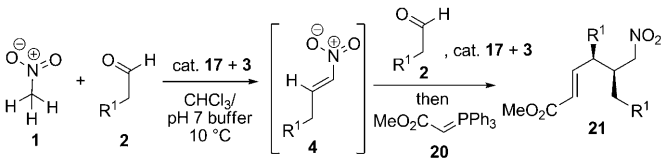
Reaction screened



Entry	Hydrogen-bond donor	Conv. into **6a** [%][a]	Conv. into **18** [%][a]	Conv. into **19** [%][a]	d.r.[b]	e.r.[c]
1	none	<1	<1	<1	–	–
2	**7**	<1	10	<1	–	–
3	**8**	<1	9	<1	–	–
4	**9**	<1	5	<1	–	–
5	**10**	<1	3	<1	–	–
6	**11**	4	8	<1	–	–
7	**12**	<1	4	<1	–	–
8	**13**	<1	9	<1	–	–
9	**14**	<1	<1	<1	–	–
10	**15**	67	8	1	95:5	>99.5:<0.5
11	**16**	<1	<1	4	–	–
12	**17**	91	6	3	94:6	>99.5:<0.5
13[d]	**17**	70	6	5	93:7	>99.5:<0.5

[a] Conversion into **6a**, **18**, and **19** was determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Diastereoselectivity was determined by ^{1}H NMR analysis. [c] Enantioselectivity was determined by HPLC on a chiral stationary phase after conversion into the corresponding enoate **21a** (see Table 2). [d] Without buffer. Bn = benzyl, MOM = methoxymethyl.

Table 2: Domino sequence catalyzed by MHBD and enamine starting with a range of aliphatic and arylaliphatic aldehydes.[a]



Entry	R^1	*t* [h]	Yield of **21** [%][b]	d.r.[c]	e.r.[d]
1	CH_3	3.0	89 (**21a**)	93:07	>99.5:<0.5
2[e]	CH_3	3.8	78 (**21a**)	93:07	>99.5:<0.5
3[f]	CH_3	3.0	88 (**21a**)	94:06	<0.5:>99.5
4	*n*Pr	3.3	96 (**21b**)	95:05	>99.5:<0.5
5	*n*Bu	3.7	91 (**21c**)	98:02	>99.5:<0.5
6	$(CH_2)_4CH_3$	3.3	89 (**21d**)	98:02	>99.5:<0.5
7	$(CH_2)_5CH_3$	3.8	95 (**21e**)	96:04	>99.5:<0.5
8	$(CH_2)_7CH_3$	4.3	85 (**21f**)	98:02	>99.5:<0.5
9	$(CH_2)_9CH_3$	4.2	95 (**21g**)	97:03	>99.5:<0.5
10	Bn	7.0	81 (**21h**)	95:05	>99.5:<0.5
11	3-ClBn	10.0	72 (**21i**)	94:06	>99.5:<0.5
12	PMB	6.5	78 (**21j**)	96:04	>99.5:<0.5
13	$(CH_2)_2$OTBDPS	5.5	94 (**21k**)	97:03	>99.5:<0.5

[a] Conditions: **3** + **17** (10 mol% + 20 mol%), **1** (120 mol%) and aldehyde **2** (200 mol%), $CHCl_3$,/pH 7 buffer, 10°C; then add **20** (200 mol%). [b] Yield of isolated product. [c] Diastereoselectivity was determined by ^{1}H NMR analysis. [d] Enantioselectivity was determined by HPLC on a chiral stationary phase (see the Supporting Information for details). [e] With urea catalyst **15**. [f] With enantiomeric (*R*)-**3**. PMB = *para*-methoxybenzyl, TBDPS = *tert*-butyldiphenylsilyl.

experiments were carried out with separately formed nitroolefins. Both aliphatic and aromatic nitroolefins afforded the products at a rapid rate and with excellent enantio- and diastereoselectivity (Table 3). Importantly, the amount of catalyst could be lowered to 1 mol% (for the enamine catalyst **3**) and 2 mol% (for the MHBD catalyst) while maintaining useful levels of reaction rate, diastereoselectivity, and enantioselectivity. We also tested the activity of simpler MHBD catalysts **22a** and **22b** because **22a** is known to bind very strongly to carboxylate anions,[20] but these catalysts were inactive (Table 3, entries 7 and 8).

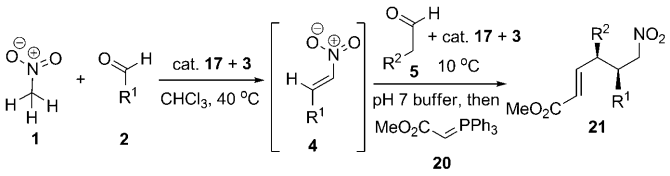
Finally, two different aldehydes can readily be used in the domino reaction sequence. In this case, the aldehyde **2** is first added to generate the nitroolefin at slightly higher temperature, followed by the addition of the second aldehyde **5** at 10 °C.[21] In this manner, crossed reaction products can be readily accessed (Table 4). Importantly, the sequence can also be carried out without aqueous buffer (Table 4, entry 7), with only a slight decrease in yield, thus demonstrating that the dual catalyst system operates also under truly homogenous conditions, without the need of phase separation of different catalyst or reaction components.

Mechanistically, we believe that in the first step, the role of catalyst **17** is to activate nitromethane **1** as a hydrogen-bonded nitromethane anion towards a Knoevenagel-type condensation with iminium ion derived from aldehyde **2** and catalyst **3**.[22] Support for the proposed role of **17** is provided by the chemoselectivity of the reaction sequence: in the absence of **17** but in the presence of the amine catalyst **3**, the reaction affords mainly aldol and aldol-type products, thereby bypassing nitromethane altogether.

In Step 2, catalyst **17** would then activate the newly formed nitro olefin **4** as an electrophile towards the enamine derived from aldehyde **5**. Evidence for the role of **17** in the second step is provided by the experiments in Table 3, where Step 2 is studied separately. Importantly, without **17**, the reaction is either very sluggish (Table 3, entry 2) or does not proceed at all (Table 3, entry 10). In addition, kinetic experiments performed without buffer revealed that Step 2 is first order in **3** and 0.4th order in **17**,[23,24] thus demonstrating that both catalyst components contribute to the activation of reaction components in the same phase. Although several dual catalyst systems are known,[6] the kinetic contributions of the two catalysts has not usually been verified. The simplest explanation for these results, assuming that the C–C bond formation is rate limiting, is that **17** activates selectively the nitro olefin **4** and **3** activates the aldehyde component (**2**).

To explain the activity of **17**, the complexation of 1-nitropropene **4t** and **17** was studied by computational methods. The structures of hydrogen-bonded complexes were generated with a Monte Carlo simulation using various force

Table 4: Crossed three-component sequence catalyzed by MHBD catalyst **17** and chiral amine catalyst **3**.[a]

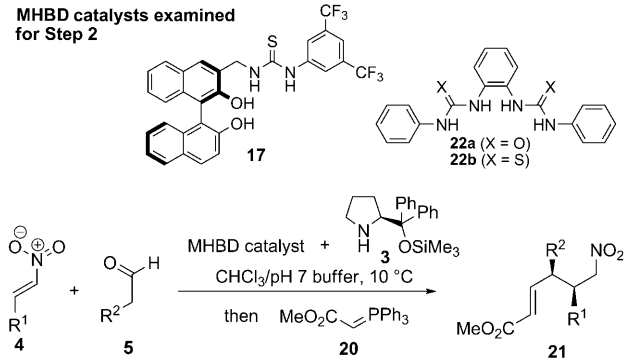


1 2 4 5 20 21

Entry	R^1	R^2	t [h][b]	Yield of **21** [%][c]	d.r.[d]	e.r.[e]
1	Ph	CH_3	0.5	91 (**21o**)	95:5	>99.5:<0.5
2	Ph	*n*Bu	0.5	87 (**21n**)	99:1	>99.5:<0.5
3	Ph	$(CH_2)_2$OTBDPS	0.5	92 (**21p**)	99:1	>99.5:<0.5
4	3-FC_6H_4	*n*Bu	1.3	63 (**21q**)	97:3	>99.5:<0.5
5	Cy	*n*Bu	9	71 (**21r**)	96:4	>99.5:<0.5
6	Cy	$(CH_2)_2$OTBDPS	12	76 (**21s**)	97:3	>99.5:<0.5
7[f]	Ph	*n*Bu	0.8	78 (**21n**)	99:1	>99.5:<0.5

[a] Conditions: Step 1: **3** + **17** (10 mol% + 20 mol% +), **1** (120 mol%) and aldehyde **2** (200 mol%), $CHCl_3$, 40 °C, 12 h. Step 2: **5** (100 mol%) + (optional) buffer (pH 7), 10 °C, then add **20** (300 mol%). [b] Time of Step 2. [c] Yield of isolated product. [d] Diastereoselectivity was determined by ^{1}H NMR analysis. [e] Enantioselectivity was determined by HPLC on a chiral stationary phase (see the Supporting Information for details). [f] Without added buffer. Cy = cyclohexyl.

Table 3: Demonstration of the catalytic efficiency of the MHBD catalyst **17** in the conjugate addition step.[a]



4 5 20 21

Entry	Cat. [mol%][b]	R^1	R^2	t [min]	Yield of **21** [%][c]	d.r.[d]	e.r.[e]
1	20:10	$C_{11}H_{23}$	*n*Bu	40	92 (**21l**)	99:1	>99.5:<0.5
2	0:10	$C_{11}H_{23}$	*n*Bu	40	19 (**21l**) [h]	–	–
3	20:10	$C_{11}H_{23}$	$(CH_2)_2$OTBDPS	30	90 (**21m**)	99:1	>99.5:<0.5
4	20:10	Ph	*n*Bu	7	95 (**21n**)	99:1	>99.5:<0.5
5	10:5	Ph	*n*Bu	20	91 (**21n**)	99:1	>99.5:<0.5
6	2:1	Ph	*n*Bu	90	95 (**21n**)	98:2	>98.5:<1.5
7	20:10[f]	Ph	CH_3	90	<3 (**21o**) [h]	–	–
8	20:10[g]	Ph	CH_3	90	<6 (**21o**) [h]	–	–
9	2:1	Ph	CH_3	390	86 (**21o**)	98:2	>99.5:<0.5
10	0:1	Ph	CH_3	90	<1 (**21o**)	–	–
11[i]	2:1	Ph	CH_3	240	90 (**21o**)	98:2	>99.5:<0.5

[a] Conditions: See the Supporting Information for details. [b] Catalyst loading in the order **17**/**3**. [c] Yield of isolated product. [d] Diastereoselectivity was determined by ^{1}H NMR analysis. [e] Enantioselectivity was determined by HPLC on a chiral stationary phase (see the Supporting Information for details). [f] Urea catalyst **22a** instead of **17** (catalyst ratio for **22a**/**3**). [g] Thiourea catalyst **22b** instead of **17** (catalyst ratio for **22b**/**17**). [h] Conversion (determined by ^{1}H NMR analysis). [i] Without added buffer.

fields, and the lowest energy structures thus obtained were further refined by accurate quantum chemical calculations.[23] The most stable structure of the **17**···**4t** complex is characterized by multiple hydrogen bonds formed between the NO_2 group of the substrate and the catalyst, but involving only two hydrogen-bond-donor functionalities (see Figure 1). However, other types of secondary interactions were found to contribute to the binding as well. Namely, π-stacking with the naphthyl ring and anion-π interaction with the electron-deficient aromatic ring provide notable stabilization for complex formation, which is borne out by the relatively large binding energy ($\Delta E = -15.7$ kcal mol^{-1}).[25] These results lend further support to our hypothesis of the role of **17** as the activator of the nitroolefin **4**.[26]

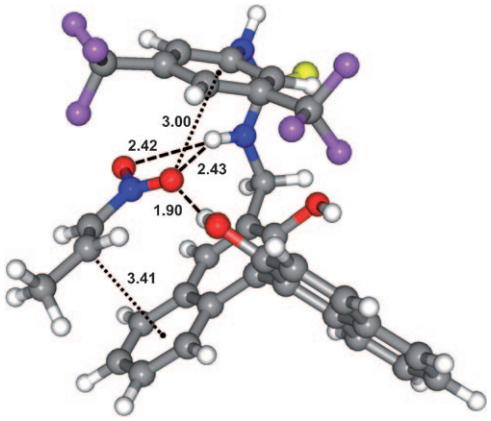


Figure 1. Optimized structure of the most stable form of the **17**···**4t** complex; F purple, N blue, O red, S yellow. Selected distances characterizing the key hydrogen bonds (dashed) and secondary interactions (dotted) are given in Å.

In summary, we have identified a dual catalyst combination that achieves the three-component enantioselective aldehyde–nitroalkene–aldehyde domino reaction with excellent enantio- and diastereoselectivities using either two similar or two different aldehydes. The separate activation of the nitro reaction component with a multiple-hydrogen-bond catalyst allows the chemoselective union of the components with a minimal competition from the side reactions such as aldol additions and aldol condensations. The obtained enantioselectivities are generally superior (or at least equal) to those reported previously for separately prepared nitroolefins, and the overall reaction times are short due to the dual activation of the reaction components with two chemoselective catalysts. We believe the dual catalysis concept using the MHBD catalyst could readily be extended to other dual catalysis modes.

Received: March 15, 2011
Published online: May 23, 2011

Keywords: domino reactions · enamine catalysis · hydrogen-bond catalysis · nitroolefins · organocatalysis

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[9] a) A. Erkkilä, P. M. Pihko, *J. Org. Chem.* **2006**, *71*, 2538 – 2541; b) A. Erkkilä, P. M. Pihko, *Eur. J. Org. Chem.* **2007**, 4205 – 4216; c) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798 – 6799.

[10] For examples, see: a) B. S. Furniss, A. J. Hannaford, P. W. G. Smith, A. R. Tatchell *Vogel's Textbook of Practical Organic Chemistry*, 5th ed., Longman, **1989**, pp. 1035 – 1036; b) X.-F. Xia, X.-Z. Shu, K.-G. Ji, Y.-F. Yang, A. Shaukat, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2010**, *75*, 2893 – 2902.

[11] a) H. Ishikawa, T. Suzuki, Y. Hayashi, *Angew. Chem.* **2009**, *121*, 1330 – 1333; *Angew. Chem. Int. Ed.* **2009**, *48*, 1304 – 1307; b) H. Ohta, K. Ozaki, G.-i. Tshuchihashi, *Chem. Lett.* **1987**, 191 – 192; c) N. J. A. Martin, L. Ozores, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 8976 – 8977.

[12] For selected examples, see: a) R. Husmann, M. Jörres, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 12549 – 12552; b) M. Wiesner, M. Neuburger, H. Wennemers, *Chem. Eur. J.* **2009**, *15*, 10103 – 10109, and references therein; c) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284 – 4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212 – 4215; for a pioneering study, see: d) J. M. Betancort, C. F. Barbas III, *Org. Lett.* **2001**, *3*, 3737 – 3740; for a full list of references, see the Supporting Information; for the discovery of the catalyst family **3**, see also: e) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804 – 807; *Angew. Chem. Int. Ed.* **2005**, *44*, 794 – 797.

[13] a) C. Palomo, S. Vera, A. Mielgo, E. G. Bengoa, *Angew. Chem.* **2006**, *118*, 6130 – 6133; *Angew. Chem. Int. Ed.* **2006**, *45*, 5984 – 5987; b) M. Wiesner, G. Upert, G. Angelici, H. Wennemers, *J. Am. Chem. Soc.* **2010**, *132*, 6 – 7; c) Y.-Q. Cheng, Z. Bian, Y.-B. He, F.-S. Han, C.-Q. Kang, Z.-L. Ning, L.-X. Gao, *Tetrahedron: Asymmetry* **2009**, *20*, 1753 – 1758; see also: d) Y.-F. Ting, C. Chang, R. J. Reddy, D. R. Magar, K. Chen, *Chem. Eur. J.* **2010**, *16*, 7030 – 7038.

[14] Acids: a) Z. Zheng, B. L. Perkins, B. Ni, *J. Am. Chem. Soc.* **2010**, *132*, 50 – 51; b) S. K. Ghosh, Z. Zheng, B. Ni, *Adv. Synth. Catal.* **2010**, *352*, 2378 – 2382; c) M. Lombardo, M. Chiarucci, A. Quintavalla, C. Trombini, *Adv. Synth. Catal.* **2009**, *351*, 2801 – 2806.

[15] Phenols: a) see Ref. [13c].; b) See also: K. Patora-Komisarska, M. Benohoud, H. Ishikawa, D. Seebach, Y. Hayashi, *Helv. Chim. Acta* **2011**, *94*, 719 – 745.

[16] For recent examples, see: a) J. Wu, B. Ni, A. D. Headley, *Org. Lett.* **2009**, *11*, 3354 – 3356; see also Ref. [14].

[17] For kinetic evidence of the involvement of iminium intermediates in pyrrolidine-catalyzed aldehyde condensation reactions, see Ref. [9b].

[18] For a full description of the solvents and alternative amine catalysts screened, see the Supporting Information.

[19] As the enantiomeric ratios have not been calibrated, ratios higher than 200:1 are reported as $>99.5:<0.5$. The actual observed ratios were: for Table 2, entry 1 (with (*S*)-**3**): 99.90:0.10, and for Table 2, entry 3 (with (*R*)-**3**): 0.02:99.98. In addition, we have also prepared *ent*-**17** ((*S*)-**17**), which gives 99.98:0.02 e.r. with (*S*)-**3**). These are, to the best of our knowledge, the highest enantioselectivities reported for these conjugate addition processes. These results also indicate that catalyst **3** appears to be almost solely responsible for the sense of enantioinduction. Although **17** is chiral, the results indicate that achiral versions of **17** could also be conceived.

[20] S. J. Brooks, P. A. Gale, M. E. Light, *Chem. Commun.* **2005**, 4696 – 4698.

[21] Step 1 (formation of **4**) proceeds faster with unbranched aliphatic aldehydes than with branched aliphatic or aromatic aldehydes, thus precluding the addition of all three components at once.

[22] For a review of iminium catalysis, including a discussion of the mechanism of iminium-catalyzed Knoevenagel condensations, see: A. Erkkilä, I. Majander, P. M. Pihko, *Chem. Rev.* **2007**, *107*, 5416 – 5470.

[23] For details, see the Supporting Information.

[24] Wennemers and co-workers determined an order of 0.4 for the nitro olefin component for this reaction. See Ref. [13b].

[25] Several other structures with binding energies ranging between -14 and -10 kcal mol^{-1} have also been identified and they are presented in the Supporting Information. The reported binding energies were obtained from the gas-phase electronic energies.

[26] In preliminary binding studies, the complexation of nitroolefin **4g** ((*E*)-*n*C_9H_{19}-CH=$CHNO_2$) and **17** was also studied by ^{1}H NMR analysis. A slight upfield shift for the vinylic protons of **4g** ($\Delta\delta = -0.017$ ppm for the α and -0.020 ppm for the β proton) was observed in presence of **17** (see the Supporting Information). Further binding studies are in progress.

