Water-Compatible Iminium Activation: Organocatalytic Michael Reactions of Carbon-Centered Nucleophiles with Enals**

Claudio Palomo,* Aitor Landa, Antonia Mielgo, Mikel Oiarbide, Ángel Puente, and Silvia Vera

Water offers unique characteristics as a solvent. It displays unparalleled physical properties, is cheap, available in bulk, and hazardless in handling, and overall it sustains life and therefore most biosynthetic reactions. In the practice of chemical synthesis, however, water had been considered a contaminant for a while. Over the last few decades, chemists have started to investigate the possibility of using water as solvent for organic reactions^[1] because of potential benefits with respect to industrial^[2] and biological implications. As for the field of asymmetric synthesis, the development of watercompatible catalytic methods still remains challenging, essentially because most metal catalysts are unstable toward hydrolysis.^[3] Water can also interfere with organocatalysis^[4] given its capacity for disrupting hydrogen bonds and other polar interactions. Interestingly, however, chiral secondary amines have been shown to be viable organocatalysts in varying degrees of an aqueous environment^[5] for several C-C bond-forming processes known to proceed through activation of the substrate carbonyl through enamine formation.^[6,7] A second major category of amine catalysis relies on activation of carbonyl Michael acceptors through formation of iminium species.^[8] However, little success has been met in aqueous systems.^[9] Experimental data suggest that iminium activation is less compatible with the presence of water, and to date no general catalytic system has been reported fully watercompatible.^[10] Here, we present evidence of the suitability of organocatalytic asymmetric iminium activation in watercontaining systems by describing highly selective conjugate additions of several carbon-centered nucleophiles to α,β unsaturated aldehydes catalyzed by secondary amines using water as the only solvent.

As candidates for water-compatible iminium catalysis, compounds **1–8** were prepared starting from proline (or *trans*-4-hydroxyproline).^[11] These molecules were conceived according to two main design elements: a) the favorable

[*] Prof. Dr. C. Palomo, Dr. A. Landa, Dr. A. Mielgo,
Prof. Dr. M. Oiarbide, Á. Puente, S. Vera
Departamento de Química Orgánica I
Universidad del País Vasco
Manuel Lardizabal 3. 20018-San Sebastián (Spain)
Fax: (+34) 943-015-270
E-mail: claudio.palomo@ehu.es
Homepage: http://www.sc.ehu.es/qpwaiipj/organica.html

^[**] This work was supported by The University of the Basque Country (UPV/EHU), the Ministerio de Educación y Ciencia (MEC, Spain), and Gobierno Vasco (GV)-Programa Saiotek. A Ramón y Cajal contract to A.L. from the MEC, and predoctoral grants to S.V. and A.P. from the MEC and GV, respectively, are acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author. role played by hydrophobic alkyl chains in water-compatible enamine-mediated catalysis,^[5e,h,j] and b) the assumption that for effective control of iminium geometry and face shielding, a bulky group should be located near the nitrogen atom of the catalyst (Figure 1).^[12]



Figure 1. Key design elements of a new family of pyrrolidine catalysts for water-compatible iminium catalysis.

At the outset, the conjugate addition of nitromethane to enals was selected to study the catalysts.^[13] Despite the interest of the resulting adducts as intermediates in synthesis,^[14] enantioselective versions of this reaction have been hardly developed,^[15] presumably because of the undesired competing 1,2-addition process. In particular, by this approach an atom-economic route to α -unsubstituted γ amino acids, which exhibit potent activity on the central nervous system,^[16] would be made feasible in a concise and practical fashion.

To evaluate the catalysts, the reaction of nitromethane and cinnamaldehyde in the presence of 5 mol% of the corresponding pyrrolidine 1-8 using water as the only solvent was carried out at room temperature (Scheme 1 and Table 1). All tested catalysts were able to promote the reaction, but the performance varied as a function of the length of the alkyl side chain (Table 1, entries 1–7). Dimethyl and dipropyl prolynol derivatives 1 and 2 catalyzed the reaction but led to only moderate yields and insufficient selectivity. The dihexyl derivative 3 gave satisfactory reactivity and enantioselectivity of 91%. An increase in length of the side chain to nonyl and dodecyl derivatives 4 and 5, respectively, had a detrimental effect on both the reaction speed and selectivity (Table 1, entries 4–7). With the optimal side chain hexyl, the effect of the silvl group was examined. Thus, the triphenylsilyl ether 6 gave improved yields and selectivities (Table 1, entry 8) as compared to the parent trimethylsilyl catalyst. On the other hand, the *trans*-4-hydroxypyrrolidine derivative



Communications



Scheme 1. Enantioselective conjugate addition of nitromethane to enals catalyzed by pyrrolidines **1–7**, and elaboration of the adducts to the corresponding alcohols and carboxylic esters.

Table 1: Catalyst screening for the reaction of nitromethane with enal 9a to give 10a.^[a]

Entry	Cat.	<i>t</i> [h]	Conv. [%] ^[b]	Yield [%] ^[c]	ee [%] ^[d]
1	1	3	> 99	41	50
2	2	6	>99	43	70
3	3	16	>99	65	91
4	4	16	60	_	-
5	4	32	>99	65	85
6	5	16	50	_	-
7	5	32	80	30	73
8	6	16	>99	70	96
9 ^[e]	6	32	>99	66	94
10	7	16	>99	59	83
11	8	16	_	40	-40
12 ^[f]	8	16	-	55	-87

[a] Reactions performed on 1 mmol scale at room temperature using catalyst **1–8** (5 mol%), benzoic acid (5 mol%), nitromethane (2 equiv, 110 μ L), and water (1 mL). [b] Measured by ¹H NMR spectroscopy on crude material. [c] Yield of product (after chromatography) after reduction to alcohol. [d] Determined by HPLC (Daicel-Chiralpak IB; eluent 90:10 hexane/2-propanol). [e] In the absence of benzoic acid. [f] Neat reaction using 10 mol% catalyst without benzoic acid.

7 (Table 1, entry 10) exhibited an inferior performance. Interestingly, the amino alcohol **8**, which contains a free hydroxy group, is also able to catalyze the reaction either in neat conditions or with water as solvent and gives rise to a product of reversed configuration. The stereochemical reversal may be rationalized by assuming that hydrogen bonding is established between the OH group of the catalyst and the NO₂ group in the transition state.^[17] While the above reactions were generally carried out in the presence of 5 mol% of benzoic acid, reactions without such an additive were accompanied with similar levels of enantioselection, although elapsed reaction times were required (Table 1, compare entries 8 and 9).

A representative selection of enals was evaluated under the best conditions, and the results are summarized in Table 2. Good yields, corresponding to two or three synthetic steps to the final alcohol or ester product,^[18] and regularly high selectivity are attained with neutral, electron-poor, or electron-rich substituted cinnamaldehydes (Table 2, entries 1–6 and 9–12). With crotonaldehyde (Table 2, entry 7) slightly lower selectivity was observed, but by running the reaction at 0°C in this case above 90% *ee* was attained (Table 2, entry 8). Of practical importance, lowering the catalyst loading from 5 mol% to only 2 mol% was well tolerated, while the reaction starting from 5 mmol of substrate enal displayed no significant loss in reactivity and stereoselectivity (Table 2, entry 3).

Adduct **12h**, which was produced in very high enantioselectivity, was subsequently transformed into the *S* isomer of Rolipram (Scheme 2), a type IV phosphodiesterase inhibitor.^[16] Thus, the configuration of the product is consistent with the expected preferential attack of nitromethane across the rear π face of the activated iminium species depicted in Figure 1. The

Table 2: Reaction of nitromethane with α,β -unsaturated aldehydes catalyzed by **6** (see Scheme 1).^[a]

Entry	R	Product	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	10a	70	96
2 ^[d]			65	96
3 ^[e]			61	95
4	4-MeOC ₆ H ₄	10Ь	71	96
5 ^[d]			68	94
6 ^[f]	4-MeC ₆ H ₄	10c	66	97
7 ^[g]	Me	10 d	60	87
8			42	91 ^[g,h]
9	3-MeOC ₆ H₄	12 e	57	95
10 ^[f]	$4-NO_2C_6H_4$	12 f	60	98
11	4-ClC ₆ H ₄	12g	69	95
12	3-cPentO-4-MeOC ₆ H ₃	12 h	62	98

[a] Reactions carried out overnight on a 1 mmol scale using nitromethane (2 mmol), **6** (5 mol%), benzoic acid (5 mol%), and H_2O (1 mL) unless otherwise stated. [b] Yield after chromatography of the corresponding alcohol or ester compound. [c] Determined by HPLC. [d] Using 1 mL of EtOH/ H_2O (1:1) as solvent. [e] Reaction carried out on 5 mmol scale using 2 mol% catalyst. [f] Full conversion after 6 h. [g] 5 mmol of nitromethane was used. [h] Reaction performed at 0°C.

configuration of the remaining adducts was assigned assuming a uniform reaction mechanism.

Further proof of the capacity of the present catalyst system can be inferred from its remarkable performance in the conjugate addition of malonates, a category of Michael donors previously shown to react poorly in aqueous systems.^[10a] As the results in Table 3 show, the reaction of dibenzyl malonate with cinnamaldehyde and *p*-methoxycinnamaldehyde under similar catalytic conditions, with water as the sole solvent, led to the corresponding adducts **13** in good yields and with up to 99% *ee.* The triphenylsilyl catalyst **6** afforded again slightly improved results as compared with the TMS derivative **3**, even in reactions run at room temperature.



Scheme 2. Synthesis of (S)-Rolipram from adduct **12h**. $[\alpha]_{D}^{25} = +26.2$ (c=0.6, MeOH) (c.f. $[\alpha]_{D}^{25} = +24.7 (c=0.23, \text{MeOH})^{[19]}$).

Table 3: Reaction of benzyl malonate and enals in water catalyzed by 3 or 6.^[a]

CO ₂ Bn CHO		3 or 6 (5 mol%) PhCO ₂ H (5 mol%)		BnO ₂ C CO ₂ Bn		
CO ₂ Br	R R	9	25 0	H₂O ⁰C/36 h or ⁰C/72 h	R 13	3
Entry	R	Product	Cat.	T [°C]	Yield [%] ^[b]	ee [%] ^[c]
1	Н	13 a	3	25	83	82
2	Н	13 a	3	0	74	88
3	н	13 a	6	25	77	96
4	MeO	13 b	3	0	69	92
5	MeO	13 b	6	25	74	99

[a] Reaction conditions: enal (1 mmol), 3 or 6 (5 mol%), benzoic acid (5 mol%), dibenzyl malonate (0.8 mmol), and water (1 mL). Bn = benzyl. [b] Yield of adduct 13 after chromatography. [c] Determined by HPLC after transformation into the corresponding methyl ester.

Finally, the potential of this family of catalysts in an aqueous environment was tested for the yet unprecedented enantioselective amine-catalyzed intermolecular Michael addition of aldehydes to enals.^[20] This reaction bears additional mechanistical interest, as it likely involves a double enamine/iminium activation process. As the results in Table 4 show, reactions of propanal and pentanal with cinnamaldehyde and 4-methoxycinnamaldehyde took place effectively at

Table 4: Amine-catalyzed Michael additions of aldehydes to enals.^[a]

HO R²

Ű	+	SCI	HO Cat. (20	mol%)		NaBH₄	HO R ²	
R^1	R²	Ý	PhCO ₂ H (2 H ₂ O,	!0 mol%) RT) E	EtOH, 0 °C	R^1	ОН 4
Entry	14	R ¹	R ²	Cat.	t [h]	Yield [%] ^[b]	d.r. [%] ^[c] anti/syn	ee [%] ^[d] (anti)
1	14 a	Me	Ph	3 ^[e]	20	50	85:15	74
2	14 a	Me	Ph	6	20	62	81:19	98
3 ^[f]	14 a	Me	Ph	6	20	52	85:15	93
4	14b	Pr	Ph	3	48	68	\geq 98:2	85
5	14 b	Pr	Ph	4	72	45	\geq 98:2	73
6	14b	Pr	Ph	6	72	55	\geq 98:2	97
7	14 c	Pr	$4-MeOC_6H_4$	6	72	42 ^[g]	\geq 98:2	98

[a] Reactions performed on 2 mmol scale at room temperature in the presence of catalyst (20 mol%), benzoic acid (20 mol%), enal (3 equiv), and water (2 mL). [b] Yield referred to isolated 14. [c] Measured by NMR spectroscopy and HPLC. [d] Determined by HPLC. [e] 10 mol% catalyst used. [f] Using 1 mL of 1:1 EtOH/H₂O mixture as solvent. [g] Reaction conversion 85%.

room temperature in the presence of 20 mol% of the corresponding catalyst. In all cases, very high diastereoselectivity in favor of the anti adduct and very high enantioselectivities were obtained with catalyst 6. The resulting adducts could be oxidized to the corresponding glutarates or alternatively reduced to 1,5-diols 14, which in turn may be transformed into cis-3,4-disubstituted tetrahydropyrans by standard protocols.^[21]

The physical appearance of the reaction mixture in the above developments was in general an easy to stir emulsion. As a consequence, the yet unanswered question about where the reaction actually occurs (either in the aqueous or organic phase, or on the boundary) arises. In this connection, what seems to be apparent is the tolerance of the present iminium activation model with a homogeneous aqueous environment and its robustness, as the same level of catalytic effectiveness is maintained even in the reactions carried out in water/ ethanol homogeneous solutions (Table 2, entries 2 and 5; Table 4, entry 3).

In summary, a new family of prolinol-based catalysts have been developed that enable iminium-type catalysis of enals in aqueous systems to provide high enantioselectivies under practical conditions. With this addition, the emerging pool of water-compatible organocatalysts is reinforced and the range of chemical transformations amenable for asymmetric catalysis in water-containing systems is extended.

Experimental Section

General procedure for the reaction of nitromethane and α,β unsaturated aldehydes. Nitromethane (2 mmol, 110 µL) and benzoic acid (0.05 mmol, 6.1 mg) were added to a mixture of catalyst 3 or 6 (0.05 mmol, 5 mol%) and the corresponding α , β -unsaturated aldehyde 9 (1 mmol) in water (1 mL). The resulting emulsion was stirred for 18 h at room temperature. The mixture was elaborated according to two alternative procedures. Method A (derivatization to alcohols): A solution of the above reaction mixture in EtOH (25 mL) was added dropwise to a cooled solution $(-5^{\circ}C)$ of NaBH₄ (47.25 mg, 2.5 mmol) in EtOH (50 mL). The reaction was stirred at -5 °C for 20 min (TLC, 1:1 EtOAc/hexane) and afterwards quenched with H₂O (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine and dried (MgSO₄). The solvent was evaporated, and the crude product was purified by chromatography (eluent, 1:2 EtOAc/hexane) to obtain 10. Method B (derivatization to carboxylic acid methyl esters): The crude material was dissolved in a mixture of MeOH (1.0 mL), CH₃CN (1.0 mL), and water (1.0 mL). The resulting solution was cooled to 0°C, and KH₂PO₄ (63 mg, 0.46 mmol) and $NaClO_2$ (46 mg, 0.43 mmol) were added. After the injection of H_2O_2 (35% solution, 0.5 mL), the mixture was warmed to room temperature and stirred for an additional 2 h. The pH was adjusted to pH 3 with 1M HCl, and saturated Na₂SO₃ (5 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were washed with 10 mL water and dried over MgSO4. The organic layer was concentrated in vacuum, and the residue was dissolved in a toluene/methanol mixture (2.0:5.0 mL). Trimethylsilyl diazomethane (2.0 M in n-hexane) was added dropwise, and the solution was stirred for an additional 10 min and then guenched with a drop of concentrated AcOH. The solvents were evaporated under vacuum. The crude product was subjected to flash chromatography on silica gel (1:9 EtOAc/n-pentane) to give 12.

Received: July 20, 2007 Published online: September 27, 2007

Communications

Keywords: aldehydes · amines · asymmetric catalysis · iminium activation · organocatalysis

- General reviews: a) Organic Synthesis in Water (Ed.: P. A. Grieco), Blackie Academic & Profesional, London, **1998**;
 b) U. M. Lindström, Chem. Rev. **2002**, 102, 2751–2772; c) C.-J. Li, Chem. Rev. **2005**, 105, 3095–3165; d) C.-J. Li, L. Cheng, Chem. Soc. Rev. **2006**, 35, 68–82.
- [2] For a critical recent essay, see: D. G. Blackmond, A. Armstrong,
 V. Coombe, A. Wells, *Angew. Chem.* 2007, *119*, 3872–3874;
 Angew. Chem. Int. Ed. 2007, *46*, 3798–3800.
- [3] For successful metal catalysis in aqueous systems, see: a) Aqueous-Phase Organometallic Catalysis (Eds.: B. Cornils, W. A. Herrman), Wiley-VCH, Weinheim, 1998; b) S. Kobayashi, C. Ogawa, Chem. Eur. J. 2006, 12, 5954–5960; c) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W. L. Lam, Chem. Rev. 2002, 102, 2227–2302; d) D. Sinou, Adv. Synth. Catal. 2002, 344, 221–237.
- [4] Reviews on organocatalysis: a) P. I. Dalko, L. Moisan, Angew. Chem. 2001, 113, 3840-3864; Angew. Chem. Int. Ed. 2001, 40, 3726-3748; b) E. R. Jarvo, S. J. Miller, Tetrahedron 2002, 58, 2481-2495; c) P. I. Dalko, L. Moisan, Angew. Chem. 2004, 116, 5248-5286; Angew. Chem. Int. Ed. 2004, 43, 5138-5175; d) J. Seayad, B. List, Org. Biomol. Chem. 2005, 3, 719-724; e) A. Berkessel, H. Gröger, Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis, Wiley-VCH, 2005. See also special issues on organocatalysis: f) Acc. Chem. Res. 2004, 37(8); g) Adv. Synth. Cat. 2004, 346(9-10).
- [5] Aldol reactions: a) T. J. Dickerson, K. D. Janda, J. Am. Chem. Soc. 2002, 124, 3220-3221; b) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, Angew. Chem. 2004, 116, 2017-2020; Angew. Chem. Int. Ed. 2004, 43, 1983-1986; c) P. Dziedzic, W. Zou, J. Hafren, A. Cordova, Org. Biomol. Chem. 2006, 4, 38-40; d) P. M. Pihko, K. M. Laurikainen; A. Usano, A. I. Nyberg, J. A. Kaavi, Tetrahedron 2006, 62, 317-328; A. Usano, A. I. Nyberg, J. A. Kaavi, Tetrahedron 2006, 62, 317-328; e) Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya, M. Shoji, Angew. Chem. 2006, 118, 5653-5655; Angew. Chem. Int. Ed. 2006, 45, 5527-5529; f) D. Font, C. Jimeno, M. A. Pericàs, Org. Lett. 2006, 8, 4653-4655; g) Y. Wu, Y. Zhang, M. Yu, G. Zhao, S. Wang, Org. Lett. 2006, 8, 4417-4420; h) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas, J. Am. Chem. Soc. 2006, 128, 734-735; Mannich reaction: i) L. Cheng, X. Wu, Y. Lu, Org. Biomol. Chem. 2007, 5, 1018-1020; Michael reactions: j) N. Mase, K. Watanabe, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas III, J. Am. Chem. Soc. 2006, 128, 4966-4967; k) L. Zu, J. Wang, H. Li, W. Wang, Org. Lett. 2006, 8, 3077-3079; 1) Z.-Y. Yan, Y.-N. Niu, H.-L. Wei, L.-Y. Wu, Y.-B. Zhao, Y.-M. Liang, Tetrahedron: Asymmetry 2006, 17, 3288-3293; m) S. Luo, X. Mi, S. Liu, H. Xu, J.-P. Cheng, Chem. Commun. 2006, 3687-3689; n) Y.-J. Cao, Y.-Y. Lai, X. Wang, Y.-J. Li, W.-J. Xiao, Tetrahedron Lett. 2007, 48, 21-24; o) V. Singh, V. K. Singh, Org. Lett. 2007, 9, 1117 - 1119
- [6] Reviews on enamine catalysis: a) B. List, *Tetrahedron* 2002, 58, 5573-5590; b) B. List, *Acc. Chem. Res.* 2004, 37, 548-557; c) B. List, *Chem. Commun.* 2006, 819-824; d) M. Marigo, K. A. Jørgensen, *Chem. Commun.* 2006, 2001-2011; e) G. Guillena, D. J. Ramón, *Tetrahedron: Asymmetry* 2006, 17, 1465-1492.
- [7] For a recent exchange on the enamine-based organocatalysis carried out in systems containing water, see: a) A. P. Brogan, T. J. Dickerson, K. D. Janda, Angew. Chem. 2006, 118, 8278–8280; Angew. Chem. Int. Ed. 2006, 45, 8100-8102; b) Y. Hayashi, Angew. Chem. 2006, 118, 8281-8282; Angew. Chem. Int. Ed. 2006, 45, 8103-8104; c) see also Ref. [2].
- [8] For the uncovering of the iminium activation concept in asymmetric catalysis, see: a) K. A. Ahrendt, C. J. Borths,

D. W. C. MacMillan, J. Am. Chem. Soc. 2000, 122, 9874–9875. For a review, see: b) G. Lelais, D. W. C. MacMillan, Aldrichimica Acta 2006, 39, 79–87. For recent advances in asymmetric organocatalytic 1,4-additions, see: c) S. B. Tsogoeva, Eur. J. Org. Chem. 2007, 1701–1716; d) D. Almasi, D. A. Alonso, C. Nájera, Tetrahedron: Asymmetry 2007, 18, 299–365; e) J. L. Vicario, D. Badía, L. Carrillo, Synthesis 2007, 2065–2092.

- [9] Epoxidations: a) W. Zhuang, M. Marigo, K. A. Jørgensen, Org. Biomol. Chem. 2005, 3, 3883–3885; b) M. Marigo, J. Franzén, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, J. Am. Chem. Soc. 2005, 127, 6964–6965. Conjugate 1,4-additions of ketoesters: c) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, Chem. Commun. 2006, 4928–4930. Conjugate additions of thiols: d) T. Ishino, T. Oriyama, Chem. Lett. 2007, 36, 550–551.
- [10] For instance, while the conjugate addition of β-keto esters to enals catalyzed by a diarylprolinol silyl ether has been reported to occur in aqueous solutions (Ref. [9c]), the parent addition of malonates and malononitriles appears to work sluggishly if at all: a) S. Brandau, A. Landa, J. Franzén, M. Marigo, K. A. Jørgensen, *Angew. Chem.* 2006, *118*, 4411–4415; *Angew. Chem. Int. Ed.* 2006, *45*, 4305–4309; b) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* 2007, *119*, 1119–1122; *Angew. Chem. Int. Ed.* 2007, *46*, 1101–1104.
- [11] For details, see the Supporting Information.
- [12] For pertinent information on this subject, see: a) Ref. [8b]; b) C.
 Palomo, A. Mielgo, Angew. Chem. 2006, 118, 8042-8046;
 Angew. Chem. Int. Ed. 2006, 45, 7876-7880.
- [13] For a review on conjugate additions of nitroalkanes, see: R. Ballini, G. Bosica, D. Fiorini, A. Palmieri, M. Petrini, *Chem. Rev.* 2005, 105, 933–971.
- [14] For the chemistry and transformations of the nitro group, see: a) R. Ballini, M. Petrini, *Tetrahedron* 2004, 60, 1017–1047; b) N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001, pp. 103–125.
- [15] a) T. Ooi, K. Doda, K. Maruoka, J. Am. Chem. Soc. 2003, 125, 9022-9023; b) D. Enders, M. R. M. Hütll, C. Grondal, G. Raabe, Nature 2006, 441, 861-863; c) L. Hojabri, A. Hartikka, F. M. Moghaddam, P. I. Arvidsson, Adv. Synth. Catal. 2007, 349, 740-748. For conjugate additions to enones involving iminium activation, see: d) S. Hanessian, V. Pham, Org. Lett. 2000, 2, 2975-2978; e) S. Hanessian, Z. Shao, J. S. Warrier, Org. Lett. 2006, 8, 4787-4790; f) S. Hanessian, S. Govindan, J. S. Warrier, Chirality 2005, 17, 540-543; g) C. E. T. Mitchell, S. E. Brenner, J. García-Fortanet, S. V. Ley, Org. Biomol. Chem. 2006, 4, 2039-2049; h) S. B. Tsogoeva, S. B. Jagtap, Z. A. Ardemasova, Tetrahedron: Asymmetry 2006, 17, 989-992.
- [16] For pertinent information on this subject, see: A. L. L. García, M. J. S. Carpes, A. C. B. M. de Oca, M. A. G. dos Santos, C. C. Santana, C. R. D. Correia, J. Org. Chem. 2005, 70, 1050–1053.
- [17] This hypothesis correlates well with the observed variation in enantioselectivity from the neat reaction to the aqueous reaction, as water may disrupt any well-organized hydrogenbond network. For computational models supporting hydrogen bonding between the catalyst OH group and the substrate NO₂ group in a related system, see: C. Palomo, S. Vera, A. Mielgo, E. Gómez-Bengoa, Angew. Chem. 2006, 118, 6130–6133; Angew. Chem. Int. Ed. 2006, 45, 5984–5987.
- [18] Transformation into the alcohols or ester derivatives was required to avoid partial decomposition of the aldehyde products during chromatographic isolation.
- [19] J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, F. Fernández-Marí, A. Salinas, B. Olano, *Chem. Eur. J.* 2001, 7, 3533–3544.
- [20] For amine-catalyzed intramolecular Michael reactions of aldehydes, see: a) M. T. E. Fonseca, B. List, Angew. Chem. 2004, 116, 4048-4050; Angew. Chem. Int. Ed. 2004, 43, 3958-3960; b) J. W. Yang, M. T. E. Fonseca, B. List, J. Am. Chem. Soc. 2005, 127,

8434 www.angewandte.org



15036–15037. For intermolecular versions, see: (to enones) c) Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, *7*, 4253–4256; d) T. J. Peelen, Y. Chi, S. H. Gellman, *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599; e) P. Melchiorre, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 4151–4157; (to vinyl sulfones) f) S. Mossé, A. Alexakis, *Org. Lett.* **2005**, *7*, 4361–4364; (to maleimides) g) G.-L. Zhao, Y.

Xu, H. Sundén, L. Eriksson, M. Sayah, A. Córdova, *Chem. Commun.* **2007**, 734–735. Amine-catalyzed Michael addition of ketones to chalcones: h) J. Wang, H. Li, L. Zu, W. Wang, *Adv. Synth. Catal.* **2006**, *348*, 425–428.

[21] A. Bernardi, P. Dotti, G. Poli, C. Scolastico, *Tetrahedron* 1992, 48, 5597-5606, and references therein.