DOI: 10.1002/adsc.200800340

Enantioselective Organocatalytic Reactions of 4-Hydroxycoumarin and 4-Hydroxypyrone with α,β-Unsaturated Aldehydes – An Efficient Michael Addition-Acetalization Cascade to Chromenones, Quinolinones and Pyranones

Magnus Rueping,[a,*] Estíbaliz Merino,[a] and Erli Sugiono[a]

[a] Institute of Organic Chemistry and Chemical Biology, University of Frankfurt, Max-von-Laue Strasse 7, 60438 Frankfurt, Germany
Fax: (+49)-69-798-29248; e-mail: M.Rueping@chemie.uni-frankfurt.de

Received: June 2, 2008; Published online: August 25, 2008

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200800340.

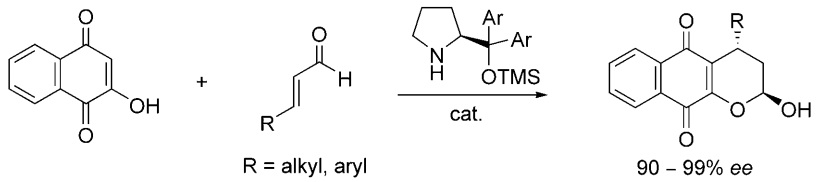
Abstract: An efficient, organocatalytic enantioselective addition-cyclization reaction of cyclic 1,3-dicarbonyl compounds with different α,β-unsaturated aldehydes has been developed. The diarylprolinol ether-catalyzed reaction cascade provides a variety of chromenones, quinolinones and pyranones in good yields and with excellent enantioselectivities.

Keywords: Brønsted acids; diarylprolinol ethers; domino reaction; iminium catalysis; pyranocoumarins

Coumarin derivatives are widely distributed in nature. Especially pyranocoumarins, whose principal core, the pyrano[3.3-*c*]coumarin system, is a common motif found in a variety of natural products, and is used as a versatile intermediate in organic and natural product synthesis. Moreover, this class of compound is reported to have various biological activities, such as antimalarial, antibacterial, anticoagulant and anti-HIV activities.[1] Consequently, the development of an efficient synthesis to obtain these valuable compounds has attracted our interest. Here we report the development of a new asymmetric, organocatalytic procedure for the synthesis of pyranocoumarins, chromenones, quinolinones and pyranones starting from readily available cyclic 1,3-dicarbonyl compounds and α,β-unsaturated aldehydes.

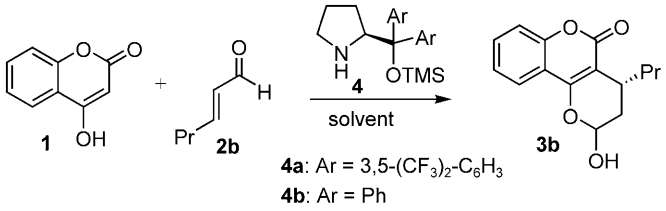
Recently, we described for the first time the development of a general and practical organocatalytic enantioselective addition-cyclization cascade of 2-hydroxynaphthoquinone with α,β-unsaturated aldehydes (Scheme 1). This efficient diarylprolinol ether-catalyzed reaction provided pyranonaphthoquinones in good yields and with excellent enantioselectivities.[2] Additionally, we were able to extend this procedure to the catalytic enantioselective synthesis of benzopyrans and chromenes employing different 1,3-diketones.[3]

Based on this strategy and our interest in the development of organocatalytic domino and cascade reactions,[4] our initial studies toward the synthesis of pyranocoumarins started with the diarylprolinol ether-catalyzed reaction of 4-hydroxycoumarin **1** with *trans*-2-hexenal **2b**.[5] The effects of catalyst loading, solvent, and temperature on the enantioselectivity of these reactions are summarized in Table 1. As shown in Table 1, lower catalyst loadings resulted in slightly reduced enantioselectivities (Table 1, entries 3–5). Further reaction optimization focused on the choice of reaction media. The reactions proceeded smoothly in



Scheme 1. Diarylprolinol ether-catalyzed enantioselective addition cyclization cascade reaction.

Table 1. Influence of the solvent, catalyst loading and temperature on the enantioselectivity.



Entry[a]	4	mol% of 4	Solvent	Temperature [°C]	*ee* [%][b]
1	**4a**	20	CH_2Cl_2	10	92
2	**4b**	20	CH_2Cl_2	0	84
3	**4b**	20	CH_2Cl_2	−20	90
4	**4b**	10	CH_2Cl_2	−20	88
5	**4b**	5	CH_2Cl_2	−20	85
6	**4b**	20	toluene	−20	95
7	**4b**	20	DMSO	−20	87
8	**4b**	20	Et_2O	−20	94
9	**4b**	20	Bu_2O	−20	90

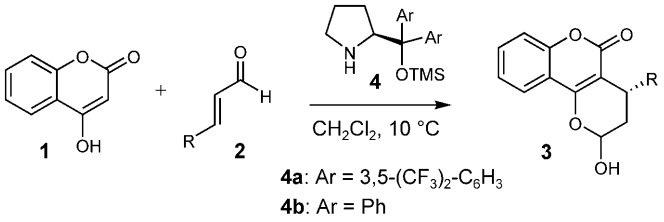
[a] Reactions were performed with 4-hydroxycoumarin **1** (1.0 equiv.) and aldehyde **2b** (1.3 equiv.).
[b] Determined by HPLC analysis.

various solvents in the presence of diarylprolinol ether **4**.[6,7] While the polarity of the solvent appeared to have only a minimum effect on the enantioselectivity (Table 1, entries 3, 6–9), the reaction temperature showed a noticeable impact on the enantiomeric excess observed (Table 1, entry 2 *vs.* entry 3). With catalyst **4b** the highest enantioselectivity was achieved when the reaction was carried out in toluene at −20 °C (Table 1, entry 6). However, comparable results could also be obtained with catalyst **4a** in dichloromethane at 10 °C (Table 1, entry 1).

Having established the optimal reaction conditions for the reaction of 4-hydroxycoumarin **1** with α,β-unsaturated aldehydes **2**, we decided to explore the scope of substrates by employing a range of aliphatic and aromatic α,β-unsaturated aldehydes. The results are summarized in Table 2. In general, the addition-cyclization reaction proceeded well affording the pyranocoumarins **3** in moderate to good isolated yields and with high enantioselectivities (89–95% *ee*).

To explore further the potential of this addition-cyclization cascade[8] we decided to use other cyclic 1,3-dicarbonyl compounds, such as the 4-hydroxy-6-methyl-2-pyrone **5**. Table 3 shows the optimization of the diarylprolinol ether-catalyzed reaction of pyrone **5** with *trans*-2-hexenal **2b**. Again dichloromethane was found to be the solvent of choice and product **6b** was isolated with high enantioselectivities (Table 3, entries 2–5). A slight loss of enantiomeric excess was observed when the catalyst loading was decreased (Table 3, entry 3 *vs.* entry 2). However, lowering the reaction temperature from 10 °C to 0 °C improved the

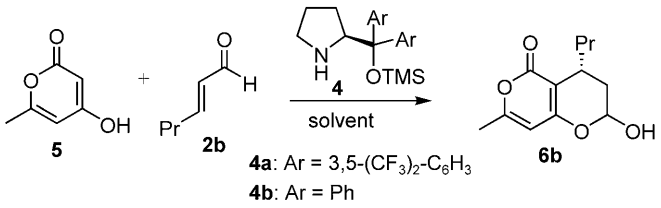
Table 2. Substrate scope of the new addition-cyclization cascade.



Entry[a]	Catalyst 4	R	Product 3	Yield [%][d]	*ee* [%][e]
1	**4a**	C_2H_5	**3a**	83	93
2	**4a**	C_3H_7	**3b**	85	92
3[b]	**4b**	C_3H_7	**3b**	83	95
4	**4a**	C_4H_9	**3c**	81	93
5[b]	**4b**	C_4H_9	**3c**	63	94
6	**4a**	C_7H_{15}	**3d**	89	91
7	**4a**	$C_{10}H_{21}$	**3e**	80	95
8[b]	**4b**	$C_{10}H_{21}$	**3e**	76	92
9[c]	**4a**	Ph	**3f**	41	89
10	**4a**	2-Br-C_6H_4	**3g**	82	92
11[c]	**4a**	4-Br-C_6H_4	**3h**	45	94
12[c]	**4a**	4-MeO-C_6H_4	**3i**	57	94

[a] Reactions were performed with 4-hydroxycoumarin **1** (1.0 equiv.), aldehyde **2** (1.5 equiv.) and catalyst **4** (20 mol%).
[b] Performed in toluene at −20 °C for 50 h.
[c] In MeCN.
[d] Yield of isolated products after column chromatography.
[e] Enantiomeric excess was determined by chiral HPLC.

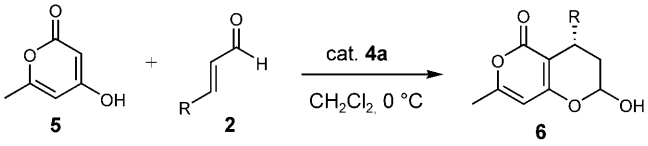
Table 3. Influence of the solvent, catalyst loading, and temperature on the enantioselectivity of the diphenyl prolinol ether catalyzed reaction cascade.



Entry[a]	4	mol% of 4	Solvent	Temperature [°C]	*ee* [%][b]
1	**4b**	20	CH_2Cl_2	10	64
2	**4a**	20	CH_2Cl_2	10	92
3	**4a**	10	CH_2Cl_2	10	88
4	**4a**	10	CH_2Cl_2	0	91
5	**4a**	20	CH_2Cl_2	r.t.	90
6	**4a**	20	Toluene	r.t.	88
7	**4a**	20	DMSO	r.t.	65
8	**4a**	20	DMF	r.t.	78
9	**4a**	20	CH_3CN	r.t.	80

[a] Reactions were performed with pyrone **5** (1.0 equiv.), aldehyde **2b** (1.3 equiv.) and catalyst **4**.
[b] Determined by HPLC analysis.

Table 4. Substrate scope of the organocatalytic enantioselective addition-cyclization cascade.



Entry[a]	6	R	Yield [%][d]	*ee* [%][e]
1	**6a**	C_2H_5	82	92
2	**6b**	C_3H_7	86	91
3	**6c**	C_4H_9	74	91
4	**6d**	C_7H_{15}	96	90
5	**6e**	$C_{10}H_{21}$	59	91
6[b]	**6f**	Ph	56	83
7[c]	**6g**	4-MeO-C_6H_4	43	85
8[c]	**6h**	2-Cl-C_6H_4	48	80 (95)[f]
9[c]	**6i**	4-Br-C_6H_4	55	84

[a] Reactions were performed with pyrone **5** (1.0 equiv.), aldehyde **2** (1.5 equiv.), 60 h.
[b] 96 h at room temperature.
[c] 48 h at room temperature.
[d] Yield of isolated product after column chromatography.
[e] Enantiomeric excess was determined by HPLC.
[f] After one recrystallization from CH_2Cl_2.

enantioselectivity considerably (Table 3, entry 3 *vs.* entry 4). Further evaluation of the reaction parameters revealed that the best results with regard to both selectivity and reactivity were achieved when the reaction was conducted with 10 mol% of diarylprolinol ether **4a** in dichloromethane at 0 °C (Table 3, entry 4).

With this optimized reaction protocol in hand, we explored the scope of our methodology using 4-hydroxy-6-methyl-2-pyrone **5** and a variety of α,β-unsaturated aldehydes **2**. As shown in Table 4, the reaction generally proceeds with both aliphatic and aromatic α,β-unsaturated aldehydes yielding various pyranones **6** in moderate to good yields and with good to excellent enantioselectivities (Table 4).

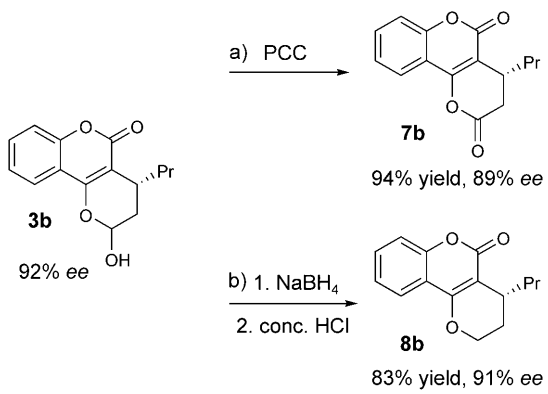
Pyranocoumarins **3** are not only important, biologically interesting substrates but can also easily be used as valuable intermediates for the synthesis of pharmacologically active compounds. For instance, the oxidation of **3b** with PCC in dichloromethane at ambient temperature afforded the lactone **7b** without a considerable loss of enantiomeric excess (Scheme 2). Additionally, employing reductive conditions the pyranocoumarin **3b** can be directly transformed to the cyclic ether **8b** in good yields. Again, no significant loss of enantiomeric excess was observed.

The new addition-acetalization reaction can also be utilized for the reaction of 4-hydroxy-1-methyl-1,2-dihydroquinolin-2-one **9** with *trans*-2-heptenal **2c**. Again, the reaction proceeded smoothly with 20 mol% catalyst **4a** in dichloromethane at ambient temperature to give the corresponding product which after subsequent oxidation with PCC resulted in the desired quinolinone **10** with an acceptable enantiomeric excess of 89% (Scheme 3).

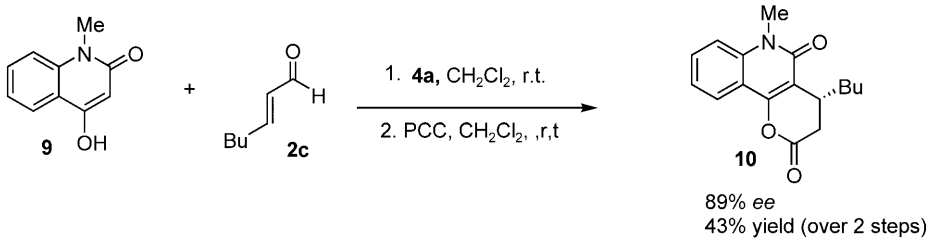
The carbazole-containing pyranocoumarin **11** has been shown to have excellent anticoagulant properties.[9] Therefore, we decided to prepare **11** using our newly developed procedure. Hence, the diarylprolinol ether **4a** catalyzed reaction of cinnamaldehyde with 4-hydroxycoumarin **1** afforded the desired pyranocoumarin **3f** which after subsequent reaction with carbazole resulted in the first enantioselective synthesis of **11** (Scheme 4).

The constitution and absolute configuration of the pyranocoumarins **3** was determined by single X-ray crystal structure analysis of **3g**. On the basis of this structure compound **3** was assigned to have (*R*)-configuration (Figure 1).

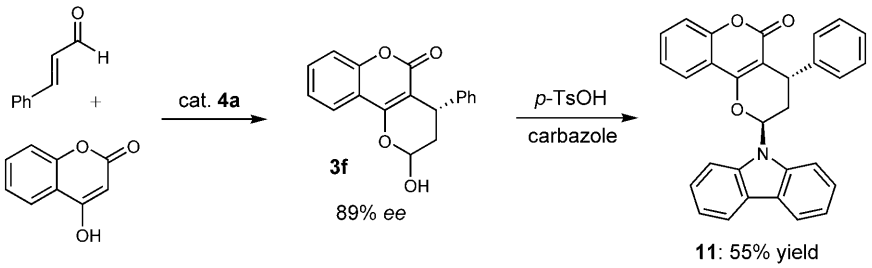
In summary, we have developed an efficient and highly enantioselective addition-cyclization cascade in



Scheme 2. Transformation of pyranocoumarin **3b** in the corresponding lactone **7b** or cyclic ether **8b**.



Scheme 3. Enantioselective synthesis of quinolinone **10**.



Scheme 4. Enantioselective synthesis of carbazole substituted pyranocoumarin **11**.

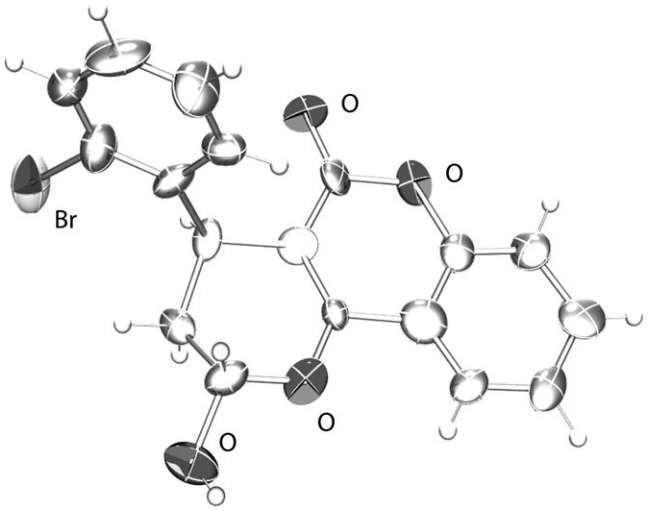


Figure 1. X-ray crystal structure of pyranocoumarin **3g**.

which various different cyclic dicarbonyl compounds and α,β-unsaturated aldehydes can successfully be employed. The attractive features of this new diarylprolinol-catalyzed transformation are the practicability and operational simplicity, as well as the mild reaction conditions which provide a series of coumarin, chromenone, quinolinone and pyranone derivatives in good yields and with high enantioselectivities starting from readily available starting materials.

Experimental Section

General Remarks

Unless otherwise stated, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was carried out using silica gel Merck 60 (particle size 0.040–0.063 mm).

General Procedure

A screw-capped test tube equipped with a stir bar was charged with aldehyde (1.30 equiv.), catalyst (0.02 equiv.) and solvent (0.20 M) at the temperature indicated. The cyclic 1,3-dicarbonyl compound (1.00 equiv.) was then added. The mixture was allowed to stir at the temperature indicated for 48–96 h. The crude reaction mixture was directly subjected to column chromatography (hexane:ethyl acetate, 5:1 → hexane:ethyl acetate, 1:1) on silica gel to afford the corresponding product.

The characterization data for the compounds made is available in the Supporting Information.

Acknowledgements

We gratefully acknowledge Evonik Degussa and the DFG (Priority Programme Organocatalysis) for generous support and the Ministerio de Educación y Ciencia, Spain, for a stipend given to E.M.

References

[1] For biological and pharmaceutical activities, see, e.g.: a) R. D. H. Murray, J. Medez, S. A. Brown, *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*, Wiley, New York, **1982**; b) G. Cravotto, G. M. Nano, G. Palmisano, S. Tagliapietra, *Tetrahedron*: *Asymmetry* **2001**, *12*, 707–709; c) P. Druzgala, X. Zhang, J. R. Pfister, *PCT Pat. Appl.* WO 02/085882; d) D. M. X. Donnelly; D. J. Molloy, J. P. Reilly, J.-P. Finet, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2531–2534; e) E. Melliou, P. Magiatis, S. Mitaku, A.-L. Skaltsounis, E. Chinou, I. Chinou, *J. Nat. Prod.* **2005**, *68*, 78–82; f) L. Xie, Y. Takeuchi, L. M. Cosentino, K.-H. Lee, *J. Med. Chem.* **1999**, *42*, 2662–2672; g) T. Ishikawa, *Heterocycles* **2000**, *53*, 453–474; h) L. Xie, Y. Takeuchi, L. M. Cosentino, A. T. McPhail, K.-H. Lee, *J. Med. Chem.* **2001**, *44*, 664–671.

[2] M. Rueping, E. Sugiono, E. Merino, *Angew. Chem.* **2008**, *120*, 3089–3092; *Angew. Chem. Int. Ed.* **2008**, *47*, 3046–3049.

[3] a) M. Rueping, E. Sugiono, E. Merino, *Chem. Eur. J.* **2008**, *14*, 6329–6332; b) P. T. Franke, B. Richter, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 6317–6321.

[4] a) M. Rueping, T. Theissmann, A. P. Antonchick, *Synlett* **2006**, 1071–1074; b) M. Rueping, A. P. Antonchick, T. Theissmann, *Angew. Chem.* **2006**, *118*, 3765–3768;

Angew. Chem. Int. Ed. **2006**, *45*, 3683–3686; c) M. Rueping, C. Azap, *Angew. Chem.* **2006**, *118*, 7996–7999; *Angew. Chem. Int. Ed.* **2006**, *45*, 7832–7835; d) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2007**, *119*, 4646–4649; *Angew. Chem. Int. Ed.* **2007**, *46*, 4562–4565; e) M. Rueping, A. P. Antonchick, *Angew. Chem.* **2008**, *120*, 5920–5922, *Angew. Chem. Int. Ed.* **2008**, *47*, 5836-5838.

[5] For the organocatalytic asymmetric Michael reaction of 1,3-dicarbonyl compounds with α,β-unsaturated enones see: N. Halland, T. Hansen, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 5105–5107; *Angew. Chem. Int. Ed.* **2003**, *42*, 4955–4957.

[6] Recent examples of the successful application of diarylprolinol silyl ethers in asymmetric catalysis: a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804–807; *Angew. Chem. Int. Ed.* 2005, 44, 794–797; b) M. Marigo, D. Fielenbach, A. Braunton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 3769–3772; *Angew. Chem. Int. Ed.* **2005**, *44*, 3703–3706; c) J. Franzen, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304; d) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284–4287; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212–4215; e) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964–6965; f) Y. Chi, S. H. Gellman, *Org. Lett.* **2005**, 7, 4253–4256; g) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; h) W. Wang, H. Li, J. Wang, L. Zu, *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355; i) A. Carlone, M. Marigo, C. North, A. Landa, K. A. Jørgensen, *Chem. Commun.* **2006**, 4928–4930; j) I. Ibrahem, A. Córdova, *Chem. Commun.* **2006**, 1760–1762; k) S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536–1537; l) J. Vesely, I. Ibrahem, G. L. Zhao, R. Rios, A. Córdova, *Angew. Chem.* **2007**, *119*, 792–795; *Angew. Chem. Int. Ed.* **2007**, *46*, 778–781; m) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471–473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467–469; n) L. Zu, H. Li, H. Xie, J. Wang, W. Jiang, Y. Tang, W. Wang, *Angew. Chem.* **2007**, *119*, 3806–3808; *Angew. Chem. Int. Ed.* **2007**, *46*, 3732–3734; o) A. Carlone, S. Cabrera, M. Marigo, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 1119–1121; *Angew. Chem. Int. Ed.* **2007**, *46*, 1101–1104; p) Y. Hayashi, T. Okano, S. Aratake, D. Hazelard, *Angew. Chem.* **2007**, *119*, 5010–5013; *Angew. Chem. Int. Ed.* **2007**, *46*, 4922–4925; q) J. Alemán, S. Cabrera, E. Maerten, J. Overgaard, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 5616–5619; *Angew. Chem. Int. Ed.* **2007**, *46*, 5520–5523; r) C. Palomo, S. Vera, I. Velilla, A Mielgo, E. Gómez-Bengoa, *Angew. Chem.* **2007**, *119*, 8200–8202; *Angew. Chem. Int. Ed.* **2007**, *46*, 8054–8056; s) P. Dinér, A. Kjærsgaard, M. A. Lie, K. A. Jørgensen, *Chem. Eur. J.* **2008**, *14*, 122–127; t) S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen, K. A. Jørgensen, *Angew. Chem.* **2008**, *120*, 127–131; *Angew. Chem. Int. Ed.* **2008**, *47*, 121–125; u) S. Zhu, S. Yu, D. Ma, *Angew. Chem.* **2008**, *120*, 555–558; *Angew. Chem. Int. Ed.* **2008**, *47*, 545–548; v) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405; w) Y. Wang, P Li, X. Liang, T. Y. Zhang, J. Ye, *Chem. Commun.* **2008**, 1232–1234; x) R. M. de Figueiredo, R. Fröhlich, M. Christmann, *Angew. Chem.* **2008**, *120*, 1472–1475; *Angew. Chem. Int. Ed.* **2008**, *47*, 1450–1453; y) O. Penon, A. Carlone, A. Mazzanti, M. Locatelli, L. Sambri, G. Bartoli, P. Melchiorre, *Chem. Eur. J.* **2008**, *14*, 4788–4791.

[7] Reviews on the use of diarylprolinol ethers: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, 118, 8042–8046; *Angew. Chem. Int. Ed.* **2006**, 45, 7876–7880; b) A. Mielgo, C. Palomo, *Chem. Asian J.* **2008**, *3*, 922–948; c) for an interesting review on the application of organocatalysis in natural products synthesis, see: R. M. de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575–2600.

[8] For an excellent review on organocatalytic cascade reactions, see: D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, 119, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

[9] G. Cravotto, G. M. Nano, G. Palmisano, S. Tagliapietre, *J. Heterocycl. Chem.* **2001**, *38*, 965–971.

