Asymmetric Synthesis

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Core-Structure-Motivated Design of Iminium–Enolate Organocascade Reactions: Enantioselective Syntheses of 5,6-Dihydroindolizines**

*Xianxing Jiang, Bin Tan, and Carlos F. Barbas III**

Bioactive natural products are a key source of inspiration for syntheses of biological tools and potential therapeutic compounds.[1] The indolizine core is a privileged heterocyclic ring system found in a large number of bioactive natural alkaloids and clinically useful pharmaceuticals.[2] The 5,6,7,8-tetra- and 5,6-dihydroindolizine frameworks (Figure 1) have recently

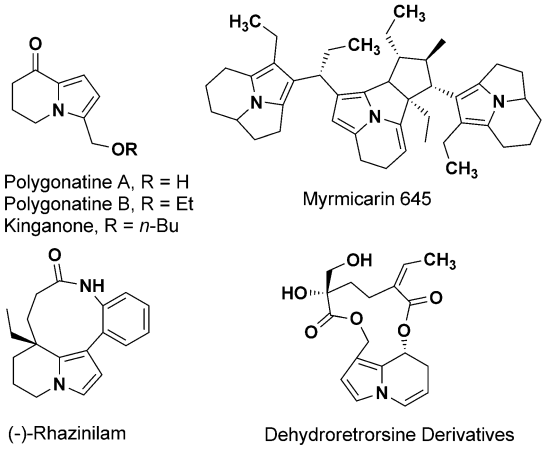
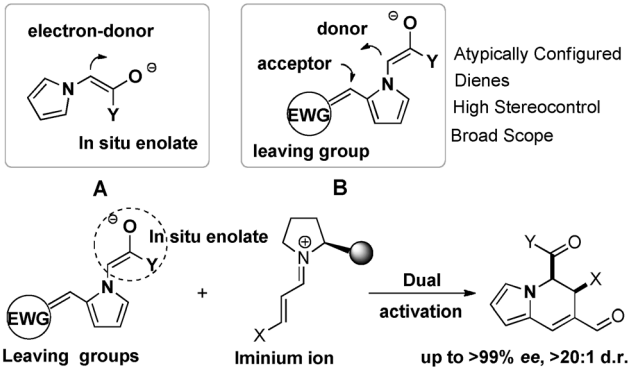


Figure 1. Hydroindolizine-containing natural products and biologically active molecules.

drawn tremendous interest from both synthetic and medicinal chemists because of their properties as anti-tumor,[3a,g] anti-leukemia,[3b] anti-cholinergic agents,[2a] and other important biological activities.[3] In addition, 5,6,7,8-tetra- and 5,6-dihydroindolizine alkaloids are common secondary metabolites in plants, invertebrates, fungi, and bacteria.[4] Thus, the design of new synthetic methods to provide molecules in this class of compounds is of interest, and intramolecular cyclization of intermediates using metal-catalyzed,[5c–g] radical,[5h–i] and base-induced processes have been reported.[5]

Current synthetic methods to access these motifs require multi-steps and are largely racemic. Recently, there has been considerable progress in the field of organocatalytic asymmetric synthesis of other important nitrogen-containing heterocycles based on the (ox)indole skeleton,[6,7] but the enantioselective synthesis of pyrrole derivatives has been less studied because of the difficulties in stereocontrol and mode of activation. To date, there have been few or no reports concerning catalytic asymmetric methodologies that systematically address the construction of privileged indolizine core scaffolds of this type.

In view of the operational and economical advantages associated with organocatalysis, our laboratory has been engaged in the design of broadly useful new strategies for enantioselective oxindole syntheses using enamine, iminium, hydrogen-bonding, alkaloid, and phosphine catalysis.[7] Inspired by the utility of in situ generated enolates,[8] we hypothesized that a pyrrole enolate intermediate formed in situ (**A**, Scheme 1) could serve as an electron donor for the



Scheme 1. Dual iminium–enolate activated catalytic strategy (EWG = leaving group).

synthesis of a 5,6-dihydroindolizine framework. We also reasoned that the α position of a pyrrole enolate functionalized with a terminal electron-withdrawing leaving group at the ethene substituent would act as an effective electron-donor/acceptor intermediate (**B**, Scheme 1). Such an atypically configured diene **B** could then be employed in an asymmetric domino reaction[9] with the iminium species derived from α,β-unsaturated carbonyl compounds and chiral amines (Scheme 1). Here we report a dual iminium–enolate generation/activation strategy as a new platform for organocatalytic intermolecular cycloaddition processes. This catalytic asymmetric methodology provides for the synthesis

[*] Dr. X. Jiang, B. Tan, Prof. Dr. C. F. Barbas III
The Skaggs Institute for Chemical Biology and
the Departments of Chemistry and Cell and Molecular Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: carlos@scripps.edu

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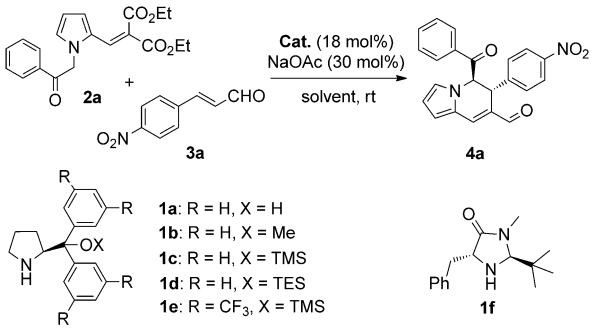
of a diverse range of functionalized 5,6-dihydroindolizine architectures in a single step.

To begin our initial investigation, several chiral amine organocatalysts were screened to evaluate their ability to promote the model reaction of pyrrole substrate **2a** with α,β-unsaturated aldehyde **3a** in the presence of 18 mol% of catalyst[10] and 30 mol% NaOAc as an additive at room temperature in CH_2Cl_2 (Table 1, entries 1–6). These results

Table 1: Studies and optimization of the reaction parameters.[a]



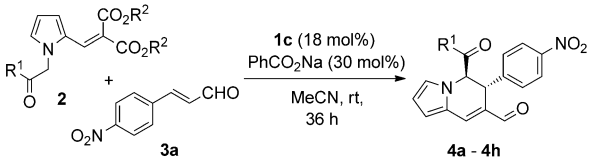
entry	catalyst	solvent	yield [%][b]	*ee* [%][c]	d.r.[d]
1	**1a**	CH_2Cl_2	<10	n.d.	n.d.
2	**1b**	CH_2Cl_2	12	6	8:1
3	**1c**	CH_2Cl_2	82	81	6:1
4	**1d**	CH_2Cl_2	45	78	6:1
5	**1e**	CH_2Cl_2	80	35	12:1
6	**1f**	CH_2Cl_2	20	23	5:1
7	**1c**	toluene	61	60	3:1
8	**1c**	$CHCl_3$	81	63	4;1
9	**1c**	MeCN	88	97	>20:1
10	**1c**	DMF	71	24	18:1
11	**1c**	MeOH	45	42	>20:1
12[e]	**1c**	MeCN	<10	n.d.	n.d.
13[f]	**1c**	MeCN	91	>99	>20:1
14[g]	**1c**	MeCN	84	92	8:1

[a] Unless noted, the reaction was conducted with **2a** (0.2 mmol) and **3a** (0.2 mmol) for 36 h at room temperature. [b] Isolated yield. [c] The *ee* values were determined by HPLC, and the configuration was assigned based on the X-ray crystal structure of **4c**. [d] The d.r. values were determined by ^{1}H NMR spectroscopy and HPLC. [e] 30 mol% $Mg(OAc)_2$ base additive. [f] 30 mol% $PhCO_2Na$ base additive. [g] 30 mol% Na_2CO_3 base additive.

indicated that the α,α-diphenylprolinol *O*-TMS ether **1c**[11] provided the highest chemical yield and enantioselectivity of the catalysts tested, furnishing the desired product **4a** in 82% yield and 81% *ee* (entry 3). Subsequently, a survey of solvents was carried out (entries 7–11). We found that the solvent had a significant effect on the reaction. Among the solvents tested, acetonitrile was optimal, giving the product with 88% yield in high stereoselectivity (97% *ee* and >20:1 diastereomeric ratio (d.r.), entry 9). A high yield and enantioselectivity (91% yield, and >99% *ee*) were observed in the presence of 30 mol% of sodium benzoate (entry 13).

The catalytic domino reaction of α,β-unsaturated aldehyde **3a** with *N*-protected dialkyl 2-((1*H*-pyrrol-2-yl)methylene)malonates in the presence of 18 mol% **1c** proceeded smoothly under optimized conditions. A variety of *N*-protected dialkyl 2-((1*H*-pyrrol-2-yl)methylene)malonates, including those bearing electron-withdrawing and electron-donating substituents on the aryl ring and with different ester-substituted terminal leaving groups, were examined (Table 2). All products were obtained in excellent diastereoselectivities and in excellent enantioselectivities (94%–>99% *ee*) with high yields (85–95% yields, entries 1–10). As expected, an aliphatic substrate was also suitable for this asymmetric process and the corresponding product was obtained with excellent diastereo- and enantioselectivity albeit with lower yield (entry 11).

Table 2: Scope of substrates for asymmetric reaction of *N*-protected dialkyl 2-((1*H*-pyrrol-2-yl)methylene)malonates.[a]

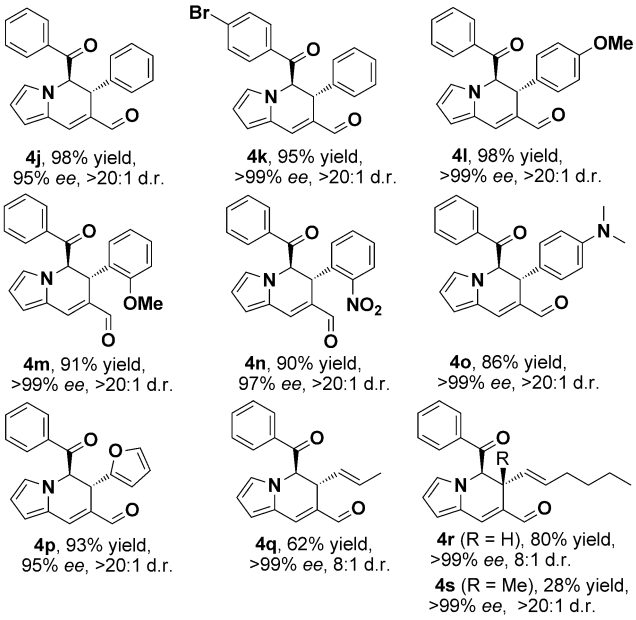


entry	R^1	R^2	yield [%][b]	*ee* [%][c]	d.r.[d]
1	Ph	Et	91 (**4a**)	>99	>20:1
2	Ph	Me	92 (**4a**)	98	>20:1
3	Ph	Bn	86 (**4a**)	>99	>20:1
4	2-naphthyl	Et	85 (**4b**)	>99	>20:1
5	4-ClPh	Et	89 (**4c**)	>99	>20:1
6	4-BrPh	Et	92 (**4d**)	>99	>20:1
7	3-ClPh	Et	92 (**4e**)	97	>20:1
8	2-ClPh	Et	94 (**4f**)	94	>20:1
9	4-MeOPh	Et	95 (**4g**)	>99	>20:1
10	4-MePh	Et	90 (**4h**)	>99	>20:1
11	Et	Et	55 (**4i**)	99	>20:1

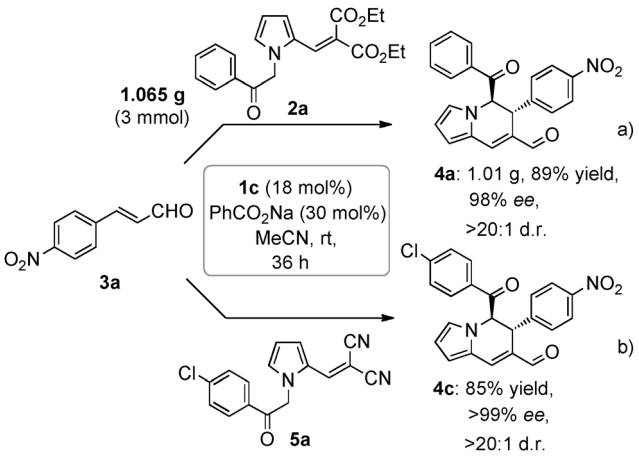
[a] Unless noted, the reaction was conducted with **2** (0.2 mmol) and **3a** (0.2 mmol) for 36 h at room temperature. [b] Isolated yield. [c] The *ee* values were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **4c**. [d] The d.r. values were determined by ^{1}H NMR spectroscopy and HPLC. When R^1 = OBn, no reaction.

We then sought to expand the reaction to various α,β-unsaturated aldehydes. Diverse, structured chiral 5,6-dihydroindolizines were synthesized (Scheme 2). Variation of the electronic properties of the substituents at different positions on the aromatic ring of α,β-unsaturated aldehydes and on the heterocyclic group were tolerated, affording **4j**–**4p** with excellent enantioselectivities (95–>99% *ee*) and diastereoselectivities (>20:1 d.r.) in yields ranging from 86% to 98%. The catalytic system also proved to be efficient with aliphatic unsaturated aldehydes, furnishing the chiral 5,6-dihydroindolizines (**4q** and **4r**) in excellent enantioselectivity (>99% *ee*) and high diastereoselectivity (8:1 d.r.) with good to high yields (62 and 80%). In addition, the reaction of an unsaturated aldehyde bearing an aliphatic β-substituent was successful and provided the virtually optically pure product (**4s**), albeit in reduced yield. The relative and absolute configurations of **4c** were unambiguously determined by X-ray crystallography, and all other products were assigned by analogy (see the Supporting Information).[12]

The excellent small-scale performance of our stereocontrolled catalytic system encouraged us to attempt gram-scale synthesis. When the reaction of **3a** and **2a** was carried out on

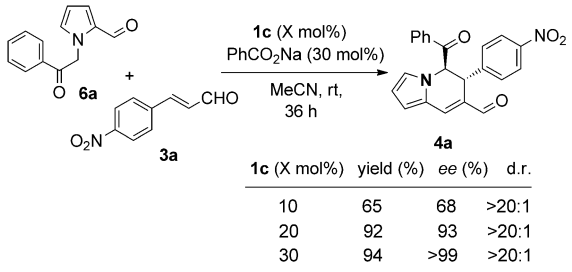


Scheme 2. Synthesis of diverse chiral 5,6-dihydroindolizines under established reaction conditions.



Scheme 3. Preparative-scale experiments and asymmetric reactions of *N*-protected 2-((1*H*-pyrrol-2-yl)methylene)malononitrile.

a gram scale (Scheme 3a), there was no significant loss of yield or stereoselectivity relative to the small-scale synthesis. The catalytic reaction of *N*-protected 2-((1*H*-pyrrol-2-yl)methylene)malononitrile **5a** with **3a** was also conducted under the optimized conditions (Scheme 3b). The reaction afforded the optically pure product in 85% yield. To gain a better understanding of the roles of the terminal electron-withdrawing leaving groups in our atypically configured diene precursors, *N*-protected pyrrole aldehydes were investigated in the same catalytic system. As shown in Scheme 4, a reaction of *N*-protected pyrrole aldehyde **6a** with α,β-unsaturated aldehyde provided the desired product, albeit a higher catalyst loading (30 mol%) was required to reach the high enantioselectivity (>99% *ee*) achieved in the malonate system. In comparison, the reaction of diene **2a** gave



1c (X mol%)	yield (%)	*ee* (%)	d.r.
10	65	68	>20:1
20	92	93	>20:1
30	94	>99	>20:1

Scheme 4. Control reaction of *N*-protected pyrrole aldehyde.

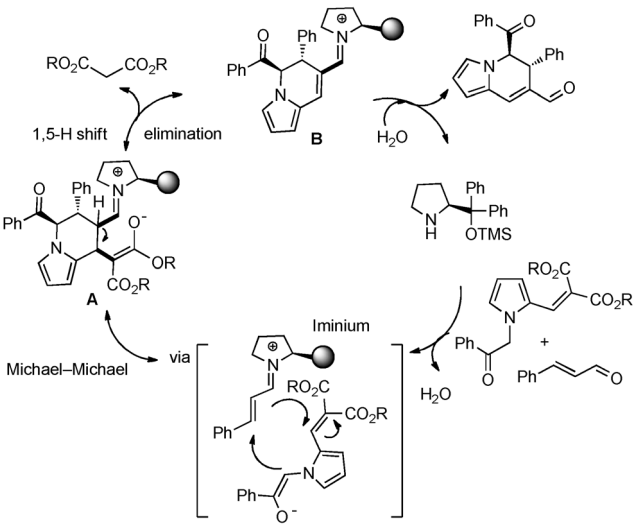
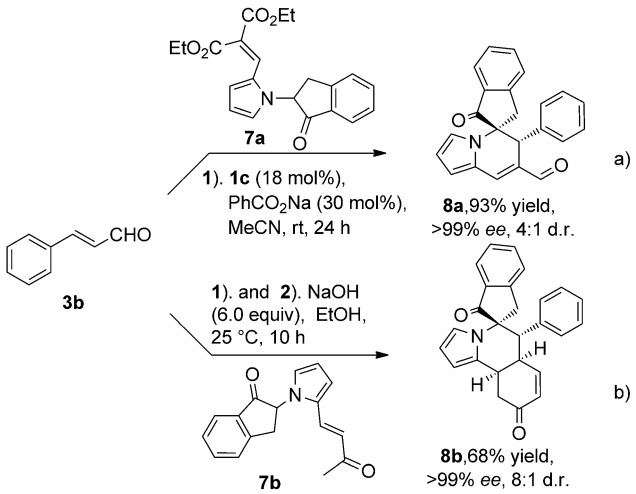


Figure 2. Proposed catalytic cycle.

>99% *ee* with only 18 mol% of catalyst (Table 2, entry 1). These results indicate a role of the terminal electron-withdrawing leaving group in the reaction.

A possible mechanism is shown in Figure 2. The reaction likely occurs through dual iminium–enolate generation/activation mode. We propose that the pyrrole enolate serves as an electron-donor/acceptor intermediate and reacts with the iminium species derived from the α,β-unsaturated aldehyde and a chiral amine, thus triggering a cascade asymmetric Michael–Michael process[13] to afford intermediate **A**. The subsequent 1,5-proton transfer provides for the release of malonates[14] to generate a transient intermediate **B**, which finally provides the chiral 5,6-dihydroindolizine. Stereocontrol directed by catalyst **1c** is consistent with the literature on this versatile catalyst.[9d,11]

Finally, we investigated the synthetic versatility of the multifunctional pyrrole derivatives, with the goal of enhancing scaffold diversity. Ring-fused chiral spiro-5,6-dihydroindolizines were successfully synthesized using the optimized protocol (Scheme 5). The reaction of pyrrole substrate **7a** efficiently proceeded to yield the (2*R*,6′*R*) sprio-5,6-dihydroindolizine **8a** in excellent yield and enantioselectivity (93% yield and >99% *ee*), which is in accordance with the experimental results. Notably, a fused polycyclic spiro-5,6-dihydroindolizine, *endo*(*trans*)-isomer **8b** was also produced preferentially with high stereoselectivity (>99% *ee* and 8:1



Scheme 5. Synthesis of chiral spiro-5,6-dihydroindolizines.

d.r.) in 68% yield in two steps. These representative examples demonstrated the inherent synthetic potential of this protocol to yield compounds with complex pyrrolizidine skeletons.

In summary, we have developed a highly efficient dual iminium–enolate generation/activation process that enabled organocatalytic intermolecular domino reactions for the direct construction of 5,6-dihydroindolizines derivatives. This asymmetric method can be readily extended to the synthesis of ring-fused pyrrolizidine skeletons. This straightforward process provided complex products in high optically purity (up to 99% *ee*, >20:1 d.r.) from simple starting materials. This unique reaction was made possible by design of an atypically configured diene with broad potential in organocatalysis. Additional studies and applications of this unique diene system to other organocatalytic systems are ongoing.

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[1] a) K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46; *Angew. Chem. Int. Ed.* **2000**, *39*, 44; b) K. C. Nicolaou, S. A. Snyder, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 11929; c) D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461; d) A. Ganesan, *Curr. Opin. Chem. Biol.* **2008**, *12*, 306; e) J. W. H. Li, J. C. Vederas, *Science* **2009**, *325*, 161; f) A. L. Harvey, *Drug Discovery Today* **2008**, *13*, 894.

[2] For selected reviews, see: a) L. B. Bull, C. C. J. Culvenor, A. T. Dick, *The Pyrrolizidine Alkaloids*, North-Holland Publishing Co., Amsterdam, **1968**; b) G. W. Gribble in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. S. V. Scriven), Pergamon, New York, **1996**; c) P. W. Le Quesne, Y. Dong, T. A. Blythe, *Alkaloids Chem. Biol. Perspect.* **1999**, *13*, 237–287; d) T. Janosik, J. Bergman in *Progress in Heterocyclic Chemistry*, *Vol. 15* (Eds.: G. W. Gribble, J. A. Joule), Pergamon, Amsterdam, **2003**, pp. 140–166.

[3] For selected examples, see: a) D. J. Abraham, R. D. Rosenstein, R. L. Lyon, H. H. S. Fong, *Tetrahedron Lett.* **1972**, *13*, 909; b) W. K. Anderson, P. F. Corey, *J. Med. Chem.* **1977**, *20*, 812; c) M. F. Weidner, S. T. Sigurdsson, P. B. Hopkins, *Biochemistry* **1990**, *29*, 9225; d) A. R. Katritzky, C. N. Fali, J. Li, *J. Org. Chem.* **1997**, *62*, 4148; e) F. Schröder, V. Sinnwell, H. Baumann, M. Kaib, W. Francke, *Angew. Chem.* **1997**, *109*, 161; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 77; f) B. Sayah, N. Pelloux-Léon, Y. Vallée, *J. Org. Chem.* **2000**, *65*, 2824; g) O. Baudoin, D. Guénard, F. Guéritte, *Mini-Rev. Org. Chem.* **2004**, *1*, 333.

[4] A. Gossauer, *Prog. Chem. Org. Nat. Prod.* **2003**, *86*, 1–188.

[5] a) K. Orito, R. Harada, S. Uchiito, M. Tokuda, *Org. Lett.* **2000**, *2*, 1799; b) R. Settambolo, G. Guazzellib, R. Lazzaronib, *Tetrahedron: Asymmetry* **2003**, *14*, 1447; c) A. Fiumana, K. Jones, *Tetrahedron Lett.* **2000**, *41*, 4209; d) S. M. Allin, W. R. Bowman, M. R. J. Elsegood, V. McKee, R. Karim, S. S. Rahman, *Tetrahedron* **2005**, *61*, 2689; e) S. Rocchiccioli, R. Settambolo, R. Lazzaroni, *J. Organomet. Chem.* **2005**, *690*, 1866; f) C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico, M. Lautens, *Org. Lett.* **2006**, *8*, 2043; g) R. Settambolo, *Synthesis* **2010**, 2915; h) H.-J. Knölker, S. Agarwal, *Tetrahedron Lett.* **2005**, *46*, 1173; i) C. A. Olsen, N. Parera, F. Albericio, M. Alvarez, *Tetrahedron Lett.* **2005**, *46*, 2041.

[6] For selected recent examples, see: a) P. Chauhan, S. S. Chimni, *Tetrahedron: Asymmetry* **2013**, *24*, 343; b) Y. M. Cao, F. F. Shen, F. T. Zhang, R. Wang, *Chem. Eur. J.* **2013**, *19*, 1184; c) R. Dalpozzo, G. Bartoli, G. Bencivenni, *Chem. Soc. Rev.* **2012**, *41*, 7247; d) X. Yang, C. Wang, Q. Ni, D. Enders, *Synthesis* **2012**, 2601; e) X. X. Jiang, Y. L. Sun, J. Yao, Y. M. Cao, M. Kai, N. He, X. Y. Zhang, Y. Q. Wang, R. Wang, *Adv. Synth. Catal.* **2012**, *354*, 917; f) G. Bergonzini, P. Melchiorre, *Angew. Chem.* **2012**, *124*, 995; *Angew. Chem. Int. Ed.* **2012**, *51*, 971; g) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212; h) Y. M. Cao, X. X. Jiang, L. P. Liu, F. F. Shen, F. T. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 9290; *Angew. Chem. Int. Ed.* **2011**, *50*, 9124; i) F. Zhong, X. Han, Y. Wang, Y. Lu, *Angew. Chem.* **2011**, *123*, 7983; *Angew. Chem. Int. Ed.* **2011**, *50*, 7837; j) X. X. Jiang, Y. M. Cao, Y. Q. Wang, L. P. Liu, F. F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328; k) G. Bencivenni, L. Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. P. Song, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200; l) R. He, S. Shirakawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 16620; m) X. H. Chen, Q. Wei, S. W. Luo, H. Xiao, L.-Z. Gong, *J. Am. Chem. Soc.* **2009**, *131*, 13819.

[7] Our recent work, see: a) K. Albertshofer, B. Tan, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 1834; b) K. Albertshofer, K. E. Anderson, C. F. Barbas III, *Org. Lett.* **2012**, *14*, 5968; c) B. Tan, X. Zeng, W. W. Y. Leong, Z. Shi, C. F. Barbas III, G. Zhong, *Chem. Eur. J.* **2012**, *18*, 63; d) B. Tan, N. R. Candeias, C. F. Barbas III, *Nat. Chem.* **2011**, *3*, 473; e) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672; f) B. Tan, G. Hernández-Torres, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 12354; g) T. Bui, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2010**, *132*, 5574; h) T. Bui, G. Hernández-Torres, C. Milite, C. F. Barbas III, *Org. Lett.* **2010**, *12*, 5696; i) T. Bui, S. Syed, C. F. Barbas III, *J. Am. Chem. Soc.* **2009**, *131*, 8758; j) T. Bui, M. Borregan, C. F. Barbas III, *J. Org. Chem.* **2009**, *74*, 8935.

[8] For recent review see: T. D. Sheppard, *Synlett* **2011**, 1340; For selected examples from our recent studies, see: a) B. Tan, G. Hernández-Torres, C. F. Barbas III, *Angew. Chem.* **2012**, *124*, 5477; *Angew. Chem. Int. Ed.* **2012**, *51*, 5381; b) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 4664; *Angew. Chem. Int. Ed.* **2008**, *47*, 4588.

[9] For reviews concerning domino reactions, see: a) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006**; b) K. C. Nico-

laou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; d) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44; *Angew. Chem. Int. Ed.* **2008**, *47*, 42; e) B. Westermann, A. Muhammad, van S. S. Berkel, *Angew. Chem.* **2010**, *122*, 858; *Angew. Chem. Int. Ed.* **2010**, *49*, 846; f) H. Pellissier, *Adv. Synth. Catal.* **2012**, *354*, 237.

[10] Details of catalyst loading analyses can be found in the Supporting Information.

[11] For reviews on organocatalytic reactions based on prolinols and their ethers, see: a) C. Palomo, A. Mielgo, *Angew. Chem.* **2006**, *118*, 8042; *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; b) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; c) L.-W. Xu, L. Li, Z.-H. Shi, *Adv. Synth. Catal.* **2010**, *352*, 243; d) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht, K. A. Jørgensen, *Acc. Chem. Res.* **2012**, *45*, 248. For selected examples, see: e) T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951; f) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749; g) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 804; *Angew. Chem. Int. Ed.* **2005**, *44*, 794; h) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem.* **2005**, *117*, 4284; *Angew. Chem. Int. Ed.* **2005**, *44*, 4212; i) M. Marigo, J. Franzen, T. B. Poulsen, W. Zhuang, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 6964; j) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861; k) J. Li, T. Kang, S. Zhou, R. Li, L. Wu, Y.-C. Chen, *Angew. Chem.* **2010**, *122*, 6562; *Angew. Chem. Int. Ed.* **2010**, *49*, 6418.

[12] CCDC 931266 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] For selected recent examples of organocatalytic asymmetric double Michael reactions, see: a) W. Yang, Y. Yang, D.-M. Du, *Org. Lett.* **2013**, *15*, 1190; b) C. Wang, X. Yang, G. Raabe, D. Enders, *Adv. Synth. Catal.* **2012**, *354*, 2629; c) P. G. McGarraugh, J. H. Jones, S. E. Brenner-Moyer, *J. Org. Chem.* **2011**, *76*, 6309; d) C. Yu, C. Y. Zhang, A. Song, Y. Ji, W. Wang, *Chem. Eur. J.* **2011**, *17*, 770; also see references [9] and [11].

[14] For examples concerning elimination of malonates, see: a) S. Bokotey, M. Kövári-Rádkai, B. Podányi, I. Ritz, M. Hanusz, S. Bátori, *Synth. Commun.* **2002**, *32*, 2325; b) C.-K. Sha, C.-P. Tsou, Y.-C. Li, R.-S. Lee, F.-Y. Tsai, R.-H. Yeh, *J. Chem. Soc. Chem. Commun.* **1988**, 1081.

