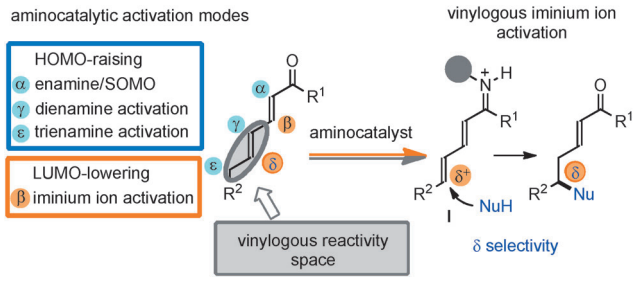
Asymmetric Organocatalysis

DOI: 10.1002/anie.201202392

Aminocatalytic Enantioselective 1,6 Additions of Alkyl Thiols to Cyclic Dienones: Vinylogous Iminium Ion Activation **

*Xu Tian, Yankai Liu, and Paolo Melchiorre**

The field of asymmetric aminocatalysis[1] has developed from two pioneering studies,[2,3] wherein it was recognized that chiral amines could activate carbonyl compounds according to fundamental concepts on reactivity (Scheme 1).[4] The LUMO-lowering effect is the underlying principle that governs activation in iminium ion catalysis.[1,2] This type of



Scheme 1. Established activation modes in aminocatalysis and the vinylogous iminium ion strategy; the gray circle represents the primary aminocatalyst scaffold.

aminocatalysis is based on the ability of an amine to reversibly condense with α,β-unsaturated carbonyl substrates to form the corresponding α,β-unsaturated iminium ion, the β-carbon atoms of which are more susceptible to nucleophilic attack than those of the substrate because of the lower energy of their LUMO. Conversely, enamine catalysis[1,3] induces a nucleophilic character at the α-carbon atom of the covalent enamine intermediate, which is generated from enolizable carbonyl substrates, by means of a HOMO-raising effect. Enamine catalysis has shown unique versatility and its successful combination with the principle of vinylogy[5] has led to the development of novel aminocatalytic activation modes. Indeed, propagation of the HOMO-raising electronic effect through the conjugated π system of polyunsaturated carbonyl compounds has been recently used to induce vinylogous nucleophilicity in extended enamines. Dienamine-[6] and trienamine-based[7] activation has been used for the direct, stereoselective, and site-selective functionalization of unsaturated carbonyl compounds at remote positions, such as the γ and ε positions.

However, the mergence of iminium ion catalysis with the concept of vinylogy has not yet been reported.[8] This is surprising, because the transmission of the LUMO-lowering effect within the extended π system of 2,4-unsaturated carbonyl compounds, upon iminium ion formation, could be used to effect direct and stereoselective functionalization at the remote δ position, a transformation for which few catalytic methods are available.[9,10]

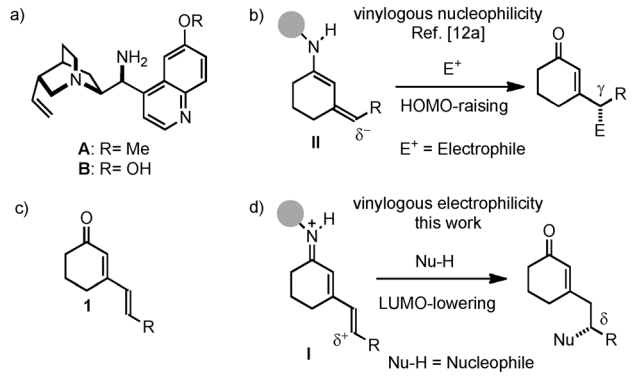
Herein, we report on the realization of this idea. When a cinchona-based primary amine[11] condenses with β-substituted cyclic dienones, an iminium ion intermediate of extended conjugation is formed (species **I** in Scheme 1 and 2); the electrophilicity of the δ-carbon atom of this intermediate is higher than that of the cyclic dieneone substrate. This aminocatalytic activation mode, termed "vinylogous iminium ion catalysis", accounts for a highly stereo- and δ-position-selective addition of alkyl thiols to cyclic α,β,γ,δ-unsaturated dienones.

From the outset, we recognized two critical issues. We needed a chiral aminocatalyst that, i) condenses easily with a dienone substrate to form the desired electrophilic iminium ion intermediate of extended conjugation **I**, and ii) ensures configurational control and π-facial discrimination of intermediate **I**, which are essential factors in enforcing high levels of enantioselectivity. The choice of the catalyst and the suitable polyunsaturated enone substrate was motivated by our previous studies on vinylogous reactivity.[12] In these previous studies, we found that cinchona-based primary amines **A** and **B** (Scheme 2a) activate β-substituted cyclohexenones toward reaction with electrophiles at the γ-carbon atom.[12a] The relatively high-energy HOMO of the transiently generated cyclic dienamine intermediate **II** allowed for intermolecular vinylogous Michael additions to take place exclusively at the γ position with high levels of enantioselectivity (Scheme 2b). To be successful, the cinchona aminocatalyst needed to communicate its inherent stereochemical information while forging the new stereocenter at the remote γ position, several atoms apart from the catalyst binding point within the cyclic dienamine **II**.

This previous work allowed us to recognize the unique ability of cinchona-based amines to stereochemically bias

[*] Prof. Dr. P. Melchiorre
ICREA—Institució Catalana de Recerca i Estudis Avançats
Passeig Lluís Companys 23, 08010 Barcelona (Spain)
X. Tian, Dr. Y. Liu, Prof. Dr. P. Melchiorre
ICIQ—Institute of Chemical Research of Catalonia
Avenida Països Catalans 16, 43007 Tarragona (Spain)
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.es/portal/862/default.aspx

[**] Research support from the ICIQ Foundation, MICINN (grant CTQ2010-15513), and the European Research Council (ERC Starting grant agreement no. 278541—ORGA-NAUT) is gratefully acknowledged. Y.L. is grateful to the European Union for a Marie Curie fellowship (grant FP7-PEOPLE-2010-IIF no. 273088). The authors thank Eduardo Escudero-Adán for X-ray crystallographic analysis.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201202392.

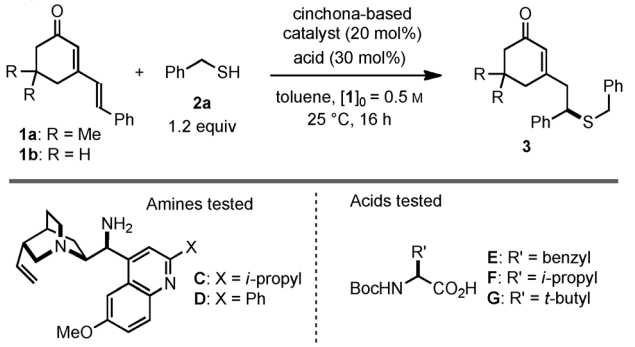


Scheme 2. Outline for the vinylogous iminium ion strategy. Central to the study is the structural analogy of species **I** and **II**, and the idea that the ability of cinchona-based primary amines to effectively control the molecular topology of the cyclic dienamine **II** can be translated to the cyclic vinylogous iminium ion **I**.

intermediary cyclic species thus ensuring highly predictable reaction outcomes. We envisioned that we could further exploit this ability to address the challenge of developing a method for a stereoselective 1,6 addition reaction involving cyclic dienones **1** (Scheme 2c and d). In addition, we reasoned that the β substituent of **1** would represent an additional control element for securing selective reaction at the δ position because, through steric hindrance, 1,4-addition reaction would be disfavored.

To test the feasibility of the vinylogous iminium ion based strategy, we investigated the potential of the quinine-derived primary amine **A** (20 mol%)[13] to activate cyclic dienone **1a** toward a 1,6-addition reaction (Table 1; more extensive documentation of the optimization studies can be found in the Supporting Information, Tables S1-8). Among the different nucleophiles investigated (see the Supporting Information, Table S1 for details), benzylthiol (**2a**)[13d–e] afforded promising reaction conversion to the 1,6-addition adduct **3** with promising optical purity (Table 1, entry 1; 81% *ee*). When the reaction was conducted in the absence of benzoic acid as a co-catalyst, no conversion to **3** was observed (Table 1, entry 2); this result suggests that a reaction pathway involving general-base activation of **2a** is unlikely. These results further establish cinchona-based primary amines as highly versatile catalysts for the covalent activation of keto compounds and demonstrate their potential as catalysts in vinylogous iminium ion catalysis. To achieve improved levels of stereocontrol, we tested other cinchona-based amines as catalysts. The use of the bifunctional catalyst **B** gave a poorer result (Table 1, entry 3). Gratifyingly, the stereoselectivity of the reaction was sensitive to structural modification of the catalyst at the 2′ position of the quinoline ring. This observation is in agreement with a recent report by List and coworkers, wherein this type of modification of a cinchona amine was used for fine tuning the stereoselectivity of an aminocatalyzed reaction.[14] Among the catalysts investigated (more details can be found in the Supporting Information, Table S5), amine **D** provided the best result (Table 1, entry 5) and was therefore selected as the catalyst for further reaction optimization.

Table 1: Optimization studies for the asymmetric 1,6-addition reaction of cyclic dienones **1**.[a]



Entry	Amine	Acid	2	1	Conv. [%] [b]	*ee* [%][c]
1	**A**	$PhCO_2H$	**2a**	**1a**	58	81
2	**A**	–	**2a**	**1a**	< 5	–
3	**B**	$PhCO_2H$	**2a**	**1a**	32	69
4	**C**	$PhCO_2H$	**2a**	**1a**	56	78
5	**D**	$PhCO_2H$	**2a**	**1a**	67	83
6	**D**	D-**E**	**2a**	**1a**	55	85
7	**D**	D-**F**	**2a**	**1a**	63	87
8	**D**	L-**F**	**2a**	**1a**	55	89
9	**D**	L-**G**	**2a**	**1a**	65	85
10[d]	**D**	L-**F**	**2a**	**1a**	84	79
11[d,e]	**D**	L-**F**	**2a**	**1a**	90	86
12[e,f]	**D**	L-**F**	**2a**	**1b**	91	91

[a] Reactions were performed on a 0.05 mmol scale using 1.2 equiv of thiol with $[\mathbf{1}]_0 = 0.5$ M in toluene, without any precaution for excluding air. [b] Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. A product derived from sequential 1,6 and 1,4-addition reactions leading to products of type **4** (see Table 3) were sometimes observed. Products derived from a selective 1,4-addition reaction were not detected. Further details can be found in the footnotes of Table 2 and in the Supporting Information. [c] Determined by HPLC analysis using a chiral stationary phase. [d] Reaction time: 60 h. [e] Reaction performed using a 10:1 toluene/H_2O mixture as the solvent with $[\mathbf{1}]_0 = 0.25$ M and 3 equiv of **2a**. [f] 5 mol% of amine **D** and 7.5 mol% of acid L-**F** were used; reaction time: 36 h.

An extensive screening of acid co-catalysts (more details given in the Supporting Information, Tables S4 and S6) revealed that chiral acids could be used as an additional handle for modulating reaction efficiency (Table 1, entries 5–9).[11,13b–d] In particular, the use of inexpensive *N*-Boc protected L-valine (L-**F**) gave increased levels of stereoselectivity (89% *ee*; Table 1, entry 8); the use of the other enantiomer (D-**F**) resulted in slightly poorer results (Table 1, entry 7). We were satisfied with the level of enantioselectivity of the reaction catalyzed by the amine **D**/acid **F** combination (1:1.5 ratio) and we then focused on improving the yield of the 1,6 addition. When the reaction was allowed to proceed for a longer time, a higher reaction conversion was obtained but the optical purity of the product **3** was lower (Table 1, entry 10). Experimental observations that have been detailed in the Supporting Information, Figure S1 and Table S8, reveal that the erosion of the enantiomeric excess was mainly due to the presence of a retroaddition pathway. When the reaction was conducted in a toluene/water mixture (10:1) and under more dilute reaction conditions, the use of longer reaction times gave increased reaction conversion without any erosion

in *ee* value over time (Table 1, entry 11). When the sterically less encumbered substrate, (*E*)-3-styryl-2-cyclohexenone (**1b**), was used, the catalyst loading could be reduced (5 mol% of amine **D** together with 7.5 mol% of L-**F**) while maintaining synthetically useful results (91% *ee*; Table 1, entry 12); **1b** was more reactive than **1a** presumably because of a more facile condensation reaction with the aminocatalyst. The optimized conditions were then used for examining the scope of the 1,6-addition reaction.

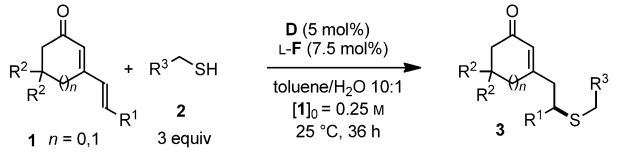
As highlighted in Table 2, the presence of a wide range of dienone δ substituents are compatible with the reaction. Substrates containing a variety of substitution patterns at the aromatic moiety were well tolerated, regardless of their electronic properties, and the corresponding adducts **3** were obtained in good yields and with high *ee* values (Table 2, entries 1–10). The reaction was compatible with heteroaryl frameworks, as shown in the synthesis of the thiophenyl-substituted adduct **3j** (Table 2, entry 11). Remarkably, the scope of the reaction was successfully extended to include substrates containing an aliphatic substituent at the δ position ($R^1 = Me$; Table 2, entry 12). The use of a cyclopentenone-based dienone resulted in lower conversion and enantioselectivity (Table 2, entry 13), thus highlighting how strongly the cyclic geometry is connected with the propagation of the LUMO-lowering effect and with an effective control over the molecular topology of the vinylogous iminium ion intermediate. Consistent with this hypothesis, an acyclic 2,4-dienone did not react under the optimized reaction conditions (Supporting Information, Figure S2). The pseudoenantiomeric catalyst of amine **D**, derived from quinidine (structure given in the Supporting Information, Figure S3), showed a similar reactivity profile and gave the other enantiomer of the product **3b** with a similar *ee* value (Table 2, entry 3). The absolute configuration of the stereogenic center of compounds **3c** and **3f** was unambiguously determined by anomalous-dispersion X-ray crystallographic analysis.[15,16]

The scope of the 1,6-addition reaction with respect to the nucleophilic component was also explored. Remarkably, a broad range of alkyl thiols, containing either aromatic or vinyl moieties, can also be used in the reaction (Table 2, entries 14–16).

The products **3** contain functional groups that are amenable toward further transformations. In particular, the presence of the α,β-unsaturated carbonyl moiety can be used for rapidly increasing the stereochemical and structural complexity of adducts **3** by means of an organocascade reaction.[17] We explored the potential of amine **D** to activate cyclic dienones **1** toward a cascade reaction involving both 1,6 and 1,4 additions of thiols. The cascade reaction was successfully implemented by using a large excess of thiol **2b** and a relatively long reaction time (Table 3), thus providing adducts **4** with moderate diastereoselectivity but with high *ee* value. X-ray crystallographic analysis of suitable crystals of compound **4a** established the stereochemical outcome of the cascade reaction.[16]

In summary, we have discovered that the LUMO-lowering activating effect can be transmitted through the conjugated π system of 2,4-dienones upon selective condensation with a cinchona primary amine catalyst. The resulting

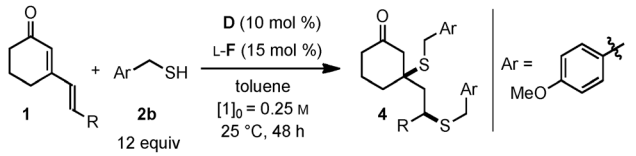
Table 2: Generality of the 1,6-addition reactions.[a]



Entry	R^1	*n*	R^2	R^3	**3**	Yield [%][b]	*ee* [%][c]
1[d]	Ph	1	Me	Ph	**3a**	68	86
2	Ph	1	H	Ph	**3b**	66	91
3[e]	Ph	1	H	Ph	**3b**	56	89[e]
4	4-$NO_2C_6H_4$	1	H	Ph	**3c**	63	91
5	4-$MeOC_6H_4$	1	H	Ph	**3d**	65	88
6	4-MeC_6H_4	1	H	Ph	**3e**	70	91
7	4-BrC_6H_4	1	H	Ph	**3f**	58	91
8	4-FC_6H_4	1	H	Ph	**3g**	56	87
9	4-ClC_6H_4	1	H	Ph	**3h**	63	92
10	3-ClC_6H_4	1	H	Ph	**3i**	60	93
11	3-thiophenyl	1	H	Ph	**3j**	60	87
12[f]	Me	1	H	Ph	**3k**	54	89
13[f]	Me	0	H	Ph	**3l**	35	55
14	Ph	1	H	4-$MeOC_6H_4$	**3m**	65	93
15	Ph	1	H	4-ClC_6H_4	**3n**	62	90
16	Ph	1	H	CH=CH_2	**3o**	60	91

[a] Reactions performed on a 0.2 mmol scale. Results represent the average of two runs per substrate. For all the dienones **1** used, the *E*/*Z* ratio was >95:5. See also Ref. [15]. [b] Yield of the isolated compound **3** after purification by column chromatography on silica gel. The yields are partially affected by a difficulty in separating the product from the starting material, dienone **1** in the case when reactions did not reach completion, and/or by the presence of products, **4**, derived from the competing reaction that involves sequential 1,6 and 1,4-addition reactions, products, which were sometimes formed in a low amounts (generally approximately 15% yield, see the Supporting Information for details). Products derived from a selective 1,4-addition reaction were not detected. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 20 mol% of **D** and 30 mol% of **F** was used; reaction time: 60 h. [e] The use of pseudoenantiomeric quinidine-derived catalyst in combination with *N*-Boc L-valine (L-**F**) gave the other enantiomer of **3b**. [f] Toluene was used as the reaction solvent.

Table 3: Cascade reactions involving sequential 1,6 and 1,4-addition reactions.[a]



Entry	R	**4**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	**a**	50	4:1	97
2	4-MeC_6H_4	**b**	45	4:1	97
3	3-ClC_6H_4	**c**	54	3.5:1	95
4	4-BrC_6H_4	**d**	50	4:1	95
5	4-FC_6H_4	**e**	48	5:1	97

[a] Reactions performed on a 0.1 mmol scale using 12 equiv of (4-methoxyphenyl)methanethiol (**2b**). [b] Yield of isolated product **4.** The yields are partially affected by a difficult separation of adducts **4** from the 1,6-addition adducts **3**, which were generally formed in approximately 15% yield. [c] Determined by ^1H NMR analysis and confirmed by HPLC analysis. [d] The *ee* value refers to the major diastereoisomer of **4** and was determined HPLC analysis using a chiral stationary phase.

vinylogous iminium ion activation was used to develop a rare example of asymmetric organocatalytic 1,6-addition proceeding with high stereocontrol and good selectivity. We believe this reactivity will rapidly find application in the design of other asymmetric δ functionalizations of unmodified carbonyl compounds and the implementation of more sophisticated cascade sequences.

Received: March 27, 2012
Published online: May 22, 2012

Keywords: asymmetric synthesis · iminium ions · nucleophilic addition · organocatalysis · vinylogous reactivity

[1] For insightful perspectives on the historical origins of aminocatalysis, see: a) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44 – 50; *Angew. Chem. Int. Ed.* **2008**, *47*, 42 – 47; b) B. List, *Angew. Chem.* **2010**, *122*, 1774 – 1779; *Angew. Chem. Int. Ed.* **2010**, *49*, 1730 – 1734; c) G. Lelais, D. W. C. MacMillan, *Aldrichimica Acta* **2006**, *39*, 79 – 87; for an overview: d) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232 – 6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138 – 6171.

[2] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243 – 4244.

[3] B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395 – 2396.

[4] HOMO- and LUMO-activations are general catalytic concepts, which permeate the whole area of asymmetric catalysis (e.g. LUMO activation is the principle behind the classical Lewis acid activation of a carbonyl compound by a metal salt).

[5] R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1 – 27.

[6] For the seminal study, see: S. Bertelsen, M. Marigo, S. Brandes, P. Dinér, K. A. Jørgensen, *J. Am. Chem. Soc.* **2006**, *128*, 12973 – 12980.

[7] For landmark reports, see: a) Z. J. Jia, H. Jiang, J.-L. Li, B. Gschwend, Q.-Z. Li, X. Yin, J. Grouleff, Y.-C. Chen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2011**, *133*, 5053 – 5061; b) X.-F. Xiong, Q. Zhou, J. Gu, L. Dong, T.-Y. Liu, Y.-C. Chen, *Angew. Chem.* **2012**, *124*, 4477 – 4480; *Angew. Chem. Int. Ed.* **2012**, *51*, 4401 – 4404; for a contribution from our research group, see: c) Y. Liu, M. Nappi, E. Arceo, S. Vera, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 15212 – 15218.

[8] We note that iminium ion catalysis (Refs. [1c] and [2]) is inherently connected with the vinylogy concept. Indeed, it was conceived through mechanistic analogy with the reductive amination of a saturated aldehyde, where the formation of the positively charged iminium ion effectively lowers the LUMO of the isolated π system. Extension to the conjugated π system of an enal conceptualized the iminium ion activation strategy.

[9] The most versatile method for achieving catalytic stereoselective δ functionalizations of carbonyl compounds is the stereoselective 1,6 addition to α,β,γ,δ-unsaturated carbonyl compounds. In addition to the challenge of stereoselectivity, this approach has the additional challenge of site selectivity. For reviews, see: a) A. C. Csákÿ, G. de La Herrán, M. C. Murcia, *Chem. Soc. Rev.* **2010**, *39*, 4080 – 4102; b) A. T. Biju, *ChemCatChem* **2011**, *3*, 1847 – 1849; for metal-catalyzed processes involving cyclic unsaturated carbonyl compounds, see: c) T. Hayashi, S. Yamamoto, N. Tokunaga, *Angew. Chem.* **2005**, *117*, 4296 – 4299; *Angew. Chem. Int. Ed.* **2005**, *44*, 4224 – 4227; d) E. Fillion, A. Wilsily, E.-T. Liao, *Tetrahedron: Asymmetry* **2006**, *17*, 2957 – 2959; e) H. Hénon, M. Mauduit, A. Alexakis, *Angew. Chem.* **2008**, *120*, 9262 – 9264; *Angew. Chem. Int. Ed.* **2008**, *47*, 9122 – 9124; f) K. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898 – 2900; for metal-catalyzed processes involving acyclic unsaturated carbonyl compounds, see: g) T. den Hartog, S. R. Harutyunyan, D. Font, A. J. Minnaard, B. L. Feringa, *Angew. Chem.* **2008**, *120*, 404 – 407; *Angew. Chem. Int. Ed.* **2008**, *47*, 398 – 401; h) T. Nishimura, Y. Yasuhara, T. Sawano, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7872 – 7873; for an intriguing umpolung strategy, in which the δ position has nucleophilic character, see: i) C. C. Ventocilla, K. A. Woerpel, *J. Am. Chem. Soc.* **2011**, *133*, 406 – 408.

[10] The only two precedents dealing with enantioselective organocatalytic 1,6 additions are based on the selective activation of the nucleophiles, see: a) L. Bernardi, J. López-Cantarero, B. Niess, K. A. Jørgensen, *J. Am. Chem. Soc.* **2007**, *129*, 5772 – 5778; b) J. J. Murphy, A. Quintard, P. McArdle, A. Alexakis, J. C. Stephens, *Angew. Chem.* **2011**, *123*, 5201 – 5204; *Angew. Chem. Int. Ed.* **2011**, *50*, 5095 – 5098.

[11] a) L. Jiang, Y.-C. Chen, *Catal. Sci. Technol.* **2011**, *1*, 354 – 365; b) G. Bartoli, P. Melchiorre, *Synlett* **2008**, 1759 – 1771.

[12] a) G. Bencivenni, P. Galzerano, A. Mazzanti, G. Bartoli, P. Melchiorre, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20642 – 20647; b) G. Bergonzini, S. Vera, P. Melchiorre, *Angew. Chem.* **2010**, *122*, 9879 – 9882; *Angew. Chem. Int. Ed.* **2010**, *49*, 9685 – 9688.

[13] For selected examples, see: a) W. Chen, W. Du, L. Yue, R. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Org. Biomol. Chem.* **2007**, *5*, 816 – 821; b) G. Bartoli, A. Carlone, F. Pesciaioli, L. Sambri, P. Melchiorre, *Org. Lett.* **2007**, *9*, 1403 – 1405; c) X. Wang, C. M. Reisinger, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 6070 – 6071; d) X. Tian, C. Cassani, Y. Liu, A. Moran, A. Urakawa, P. Galzerano, E. Arceo, P. Melchiorre, *J. Am. Chem. Soc.* **2011**, *133*, 17934 – 17941; for a review on the sulfa-Michael reaction, see: e) D. Enders, K. Lüttgen, A. Narine, *Synthesis* **2007**, 959 – 980.

[14] a) A. Lee, A. Michrowska, S. Sulzer-Mosse, B. List, *Angew. Chem.* **2011**, *123*, 1745 – 1748; *Angew. Chem. Int. Ed.* **2011**, *50*, 1707 – 1710; for the first report that described how to modify the cinchona scaffold at the 2′ quinoline position, see: b) L. Hintermann, M. Schmitz, U. Englert, *Angew. Chem.* **2007**, *119*, 5256 – 5259; *Angew. Chem. Int. Ed.* **2007**, *46*, 5164 – 5167.

[15] NMR spectroscopic analysis showed that the substrate bearing a nitro group at the 4 position of the R^1 aryl moiety has the *Z* geometry (Table 2, entry 4). This is in agreement with: S. Luo, X. Mi, H. Xu, P. G. Wang, J.-P. Cheng, *J. Org. Chem.* **2004**, *69*, 8413 – 8422. We established that adducts **3c** and **3f** have the same absolute configuration (see Ref.[15]), thus suggesting that an enantioconvergent 1,6-addition pathway is operating. We excluded the possibility that the geometry of the γ,δ double bond of the substrate undergoes scrambling under the reaction conditions (see the Supporting Information, Figure S4); the origin of the enantioconvergence thus remains unclear. Further studies, based on computational investigations, are underway.

[16] CCDC 868862 (**3c**), 868863 (**3f**), and 872092 (**4a**) contain 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..

[17] a) C. Grondal, M. Jeanty, D. Enders, *Nat. Chem.* **2010**, *2*, 167 – 178; for the use of cinchona-based primary amines in cascade reactions that combine iminium ion and enamine activation, see: b) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332 – 7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196 – 7199; c) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 8032 – 8034; *Angew. Chem. Int. Ed.* **2009**, *48*, 7892 – 7894.

