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Organocatalytic Asymmetric 1,6-Additions of β-Ketoesters and Glycine Imine

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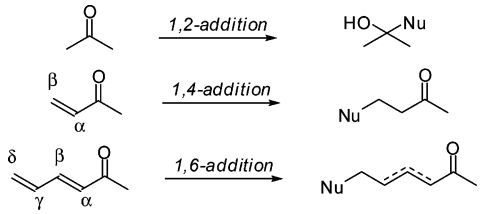
Abstract: The first organocatalytic enantioselective 1,6-addition of β-ketoesters and benzophenone imine to electron-poor δ-unsubstituted dienes using cinchona alkaloids under phase-transfer conditions is demonstrated. The scope of the reaction for the β-ketoesters is outlined for reactions with different δ-unsubstituted dienes having ketones, esters, and sulfones as electron-withdrawing substituents giving the corresponding optically active products in good yields and enantioselectivities in the range of 90−99% ee. The 1,6-addition also proceeds with a number of cyclic β-ketoesters having different ring sizes, ring systems and substituents in high yields and enantioselectivities. The potential of this new organocatalytic 1,6-addition for β-ketoesters is demonstrated by a two-step synthesis of the bicyclo[3.2.1]octan-8-one structure, a bicyclic bridged skeleton occurring in a variety of natural compounds. Benzophenone imines also undergo the organocatalytic asymmetric 1,6-addition to the activated dienes in high yields and with enantioselectivities from 92% to 98% ee, except in one case. The synthetic utility of this asymmetric reaction is demonstrated by the two-step transformation of the allylated α-amino acid derivative to highly attractive optically active pyrrolidines.

Introduction

Vinylogy is generally referred to as the propagation of the electronic effects exerted by a functional group through a conjugated system, typically a double bond.[1] In general terms, this principle accounts for the possibility of extending the reactivity of a functional group in a π-system, moving the reactive site of a molecule through the conjugation. Several polar reactions can be rationalized according to this principle, outstanding examples being vinylogous aldol transformations,[2] by which a nucleophilic enolate reacts at its γ-position, and Michael reactions,[3] wherein the addition of a nucleophile to an α,β-unsaturated electron-withdrawing group is shifted to its β-position, giving a conjugated 1,4-addition, instead of the direct 1,2-addition to the functional group (Scheme 1). Nevertheless, the propagation of the electronic effects of a distinct functional group is not limited to a single unsaturation, as it can be further transmitted to additional conjugated bonds which could then turn into the reactive site of the molecule (higher vinylogy).[4] In the particular case of a Michael acceptor, the presence of a second unsaturation extending the π-system gives at the δ-position another possible site for the nucleophilic attack, resulting in a 1,6-addition (Scheme 1).

Scheme 1. Principle of Vinylogy in Nucleophilic Additions



The 1,4-addition of nucleophiles to electron-deficient unsaturated bonds is an important and useful transformation in organic chemistry and has accordingly been studied in great detail. Concerning the use of carbon-centered nucleophiles, several methods have been developed, including catalytic asymmetric versions,[5] which in many cases have been used successfully in the synthesis of target compounds, clearly demonstrating the high utility of this transformation.[6] The corresponding vinylogous 1,6-addition to electron-deficient dienes has received comparably less attention, partly due to the regioselectivity

(1) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.
(2) (a) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (d) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43.
(3) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapters 1.1−1.6, pp 1−268.
(4) (a) Ralls, J. W. *Chem. Rev.* **1959**, *59*, 329. (b) Fredrick, M. A.; Hulce, M. *Tetrahedron* **1997**, *53*, 10197. (c) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 186. (d) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1.
(5) For reviews, see: (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 3, Chapter 31, pp 1105−1142. (d) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 569. (e) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
(6) See, for example: (a) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546. (b) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (c) Van Summeren, R. P.; Moody, D. B.; Feringa, B. L.; Minnaard, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 4546. (d) Cesati, R. R., III; de Armas, J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 96. (e) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635. (f) Brandau, S.; Landa, A.; Franzén, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305.

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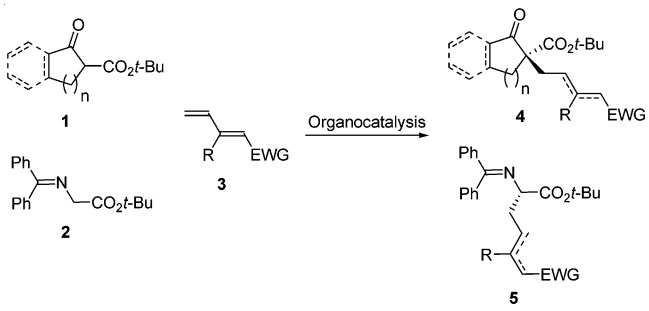
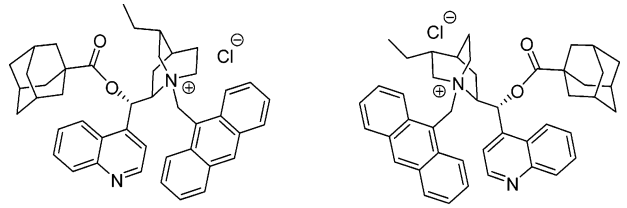
issues arising during the attack of a nucleophile.[4] However, a few methods based on stoichiometric, as well as catalytic, transition metals have been developed, allowing the regioselective,[7] and in some cases enantioselective,[8] addition of organometallic reagents in a 1,6-fashion. Besides the coordination of a transition metal to the doubly unsaturated π-system directing the attack to a certain position in the molecule, the regioselectivity of the addition can also be governed by steric factors, as it is known that δ-unsubstituted dienes tend to react with stabilized carbanions, such as metal enolates, at their terminal double bond.[4,a,b,9]

Scheme 2. Organocatalytic Asymmetric 1,6-Additions



The development of new asymmetric transformations giving rapid access to chiral building blocks for synthetic applications is undoubtedly of great importance in modern organic chemistry. In this context, asymmetric organocatalysis[10] and in particular phase-transfer catalysis (PTC)[11] play a fundamental role, due to the typical operational simplicity of their procedures and the relatively easy scalability. On these grounds, we thought it would be of interest to investigate the possibility of an organocatalytic, asymmetric 1,6-addition of stabilized enolates to activated dienes. Herein, we present our efforts toward this goal which culminated in the development of an enantioselective, phase-transfer-catalyzed 1,6-addition of cyclic β-ketoesters **1**[12] and the benzophenone imine **2**[13] derived from glycine to electron-poor δ-unsubstituted dienes **3** (Scheme 2). This reaction, besides expanding the applications of the principle of vinylogy in asymmetric catalytic synthesis, gives an easy access to optically active β-ketoesters **4** and α-amino acid derivatives **5** bearing a double bond and an electron-withdrawing group in the side chain (Scheme 2), offering opportunities for further synthetic elaborations leading to, e.g., carbocycles or substituted pyrrolidines.

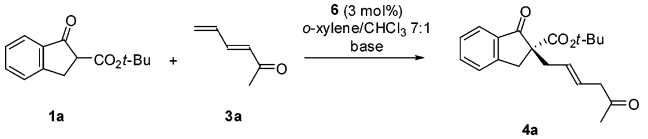
Chart 1. Structures of Catalysts **6** Derived from Dihydrocinchonine and **6′** Derived from Dihydrocinchonidine



Results and Discussion

***β*-Ketoesters as Nucleophiles.** We recently disclosed the new phase-transfer catalysts **6** and **6′**, derived from dihydrocinchonine and dihydrocinchonidine (Chart 1), bearing a 9-anthracenylmethyl substituent at the quinuclidine nitrogen atom[14] and a 1-adamantoyl group at the oxygen atom, enabling different asymmetric transformations using cyclic *tert*-butyl β-ketoesters.[12g,h] Their easy preparation (two steps without chromatography), their high catalytic efficiency under mild reaction conditions, and the synthetic versatility of the β-ketoester moiety render this system a promising tool for the development of new routes leading to optically active structures of use for further synthetic elaborations.

Scheme 3. Representative Results for the Reaction between the *tert*-Butyl β-Ketoester **1a** and Diene **3a**



Accordingly, to test the feasibility of an asymmetric 1,6-addition of β-ketoesters, we tried the reaction between 1-indanone-derived *tert*-butyl β-ketoester **1a** and the activated diene **3a** as a single *E*-isomer,[15] using **6** as the catalyst (Scheme 3). At first instance, we tried the reaction under liquid−liquid phase-transfer conditions at a temperature between +4 and −20 °C, using different mild aqueous inorganic bases.[12g,h] Under these conditions the reaction proceeded with complete regioselectivity,

(7) (a) Ganem, B. *Tetrahedron Lett.* **1974**, *15*, 4467. (b) Corey, E. J.; Kim, C. U.; Chen, R. H. K.; Takeda, M. *J. Am. Chem. Soc.* **1972**, *94*, 4395. (c) Canisius, J.; Mobley, T. A.; Berger, S.; Krause, N. *Chem.—Eur. J.* **2001**, *7*, 2671. (d) Uerdingen, M.; Krause, N. *Tetrahedron* **2000**, *56*, 2799. (e) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 5164. (f) de la Herrán, G.; Murcia, C.; Csáky, A. G. *Org. Lett.* **2005**, *7*, 5629. (g) Fukuhara, K.; Urabe, H. *Tetrahedron Lett.* **2005**, *46*, 603 and references therein.

(8) (a) Hayashi, T.; Yamamoto, S.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4224. (b) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305. (c) Fillon, E.; Wilsily, A.; Liao, E.-T. *Tetrahedron: Asymmetry* **2006**, *17*, 2957.

(9) See, for example: (a) Kohler, E. P.; Butler, F. R. *J. Am. Chem. Soc.* **1926**, *48*, 1036. (b) Danishefsky, S.; Koppel, G.; Levine, R. *Tetrahedron Lett.* **1968**, *9*, 2257. (c) Danishefsky, S.; Hatch, W. E.; Sax, M.; Abola, E.; Pletcher, J. *J. Am. Chem. Soc.* **1973**, *95*, 2410. (d) Pettig, D.; Schöllkopf, U. *Synthesis* **1988**, 173. (e) Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* **2001**, *42*, 8471. (f) Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.

(10) See, e.g.: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) *Asymmetric Organocatalysis*; Berkessel, A., Gröger, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005.

(11) (a) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 727. (b) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddard, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; p 123.

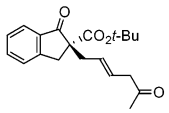
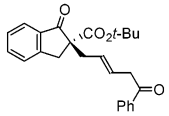
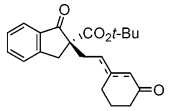
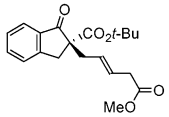
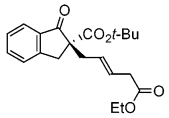
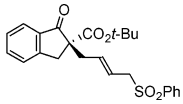
(12) For asymmetric PTC transformations of β-ketoesters, see: (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807. (b) Manabe, K. *Tetrahedron* **1988**, *54*, 14465. (c) Dehmlov, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Eur. J. Org. Chem.* **2002**, 2087. (d) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (e) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897. (f) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (g) Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980. (g) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551. (h) Poulsen, T. B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441.

(13) For reviews on the use of **2** for asymmetric transformations under PTC, see: (a) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (d) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

(14) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Corey, E. J.; Noe, M. C. *Org. Synth.* **2003**, *80*, 38.

(15) Compound **3a** was prepared in 39% yield by the aldol reaction between acetone and acrolein, followed by Ac_2O-promoted dehydration (see the Supporting Information).

Table 1. Catalytic Asymmetric 1,6-Addition of β-Ketoesters: Variation of the Diene[a]

entry	diene	base T (°C)	reac. time (h)	product	yield (%)[b]	ee (%)[c]
1	**3a**	K_2HPO_4 50% -20	17		**4a** – 99	96
2	**3b**	K_2HPO_4 50% -20	18		**4b** – 79	99[d]
3	**3c**	K_2HPO_4 50% -20	40		**4c**,**4c'**– 83[e]	90[f]
4	**3d**	Cs_2CO_3 40% +4	40		**4d** – 96 (81)	97 (80)
5	**3e**	Cs_2CO_3 40% +4	43		**4e** – 80	97
6	**3f**[g]	K_2HPO_4 50% -20	17		**4f** – 94	95

[a] Reactions carried out using 0.15 mmol of β-ketoester **1a** (0.15 M in *o*-xylene/$CHCl_3$, 7:1), 0.30 mmol of diene **3**, and 3 mol % **6**. Values in parentheses refer to the opposite enantiomer, obtained using **6′** as the catalyst. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Absolute configuration determined as *R* by X-ray analysis. [e] Yield: 66% α,β-unsaturated **4c**; 17% β,γ-unsaturated **4c′**. [f] Determined on **4c**. [g] A 0.22 mmol (1.5 equiv) portion of **3f** was used.

furnishing the allylated 1,6-addition product **4a** as a single *E*-isomer at the newly formed double bond. The position of the double bond in **4a** at the nonconjugated position and its *E*-stereochemistry can be rationalized through the kinetic protonation of the extended enolate deriving from the 1,6-addition of the β-ketoester **1a** to the diene **3a**.[16] After a short optimization (Scheme 3; see also the Supporting Information), it was found that very good levels of conversion and enantioselectivity could be achieved at −20 °C, using aqueous K_2HPO_4 as the inorganic base with only 3 mol % catalyst.

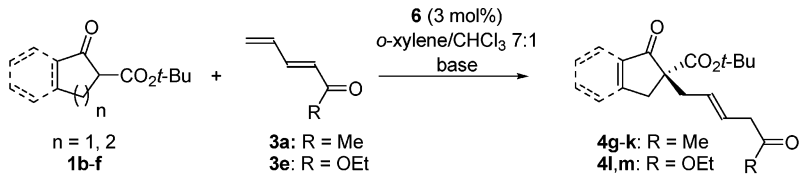
Having established an efficient protocol for the catalytic enantioselective 1,6-addition, we tested different activated dienes **3a**−**f** using the 1-indanone-derived β-ketoester **1a** as the model substrate employing 3 mol % catalyst **6**. As shown in Table 1, besides the methyl ketone derivative **3a** (entry 1), its phenyl counterpart **3b** furnished the corresponding adduct **4b** in good yield and with an excellent enantioselectivity of 99% ee, as did the 3-vinyl-2-cyclohexenone (**3c**) (entries 2 and 3). In the latter case, although the reaction gave almost exclusively the β,γ-unsaturated product, partial double bond isomerization was observed during the purification on silica gel, affording a separable mixture of the α,β- and β,γ-unsaturated adducts **4c** and **4c′**. Different activating groups in the diene were also well tolerated, as the ester derivatives **3d** and **3e**, as well as the sulfone **3f**, could be used in the 1,6-addition reaction with good results in terms of yields and with enantioselectivities from 95% to 97% ee (entries 4−6). In the case of the less reactive esters **3d** and **3e**, a stronger base (aqueous Cs_2CO_3) and higher temperature (4 °C) had to be used to obtain the corresponding adducts **4d** and **4e** in good yields (entries 4 and 5).

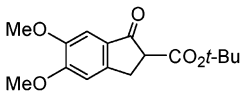
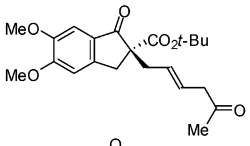
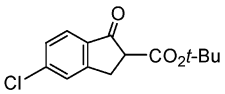
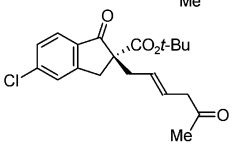
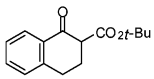
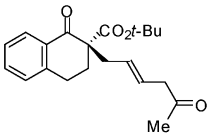
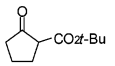
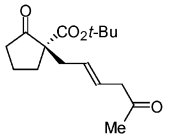
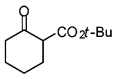
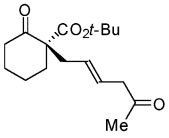
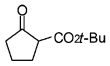
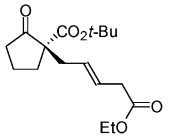
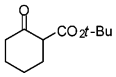
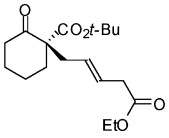
We then explored the possible variation in the β-ketoester partner applying this catalytic system. As shown in Table 2 (entries 1−5), different cyclic β-ketoesters **1b**−**f** could be used successfully in the reaction with diene **3a**, providing the 1,6-adducts **4g**−**k** as single *E*-isomers in generally good yields and enantioselectivities. In particular, the two β-ketoesters **1b** and **1c**, derived from 1-indanones bearing electron-withdrawing as well as electron-donating groups at the aromatic ring, reacted well under the same conditions used for their parent 1-indanone derivative **1a**, affording the corresponding allylated compounds **4g** and **4h** with excellent enantioselectivities. The 1-tetralone derivative **1d** and the two non-ring-fused β-ketoesters **1e** and **1f** were instead found to be relatively less reactive, as only the use of stronger bases allowed the obtainment of the adducts **4i**−**k** in satisfactory yields and enantioselectivities (entries 3−5). Under these reaction conditions the optically active products were formed in good yields and enantioselectivities from 79% to 94% ee.

Unfortunately, noncyclic β-ketoesters were found to undergo the 1,6-addition reaction with **3a**, using catalyst **6**, with poor enantioselectivity, thus showing the lack of efficiency of this catalytic system in the transmission of the chiral information

(16) (a) Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, *3*, 669. (b) Malhotra, S. K.; Ringold, H. J. *J. Am. Chem. Soc.* **1963**, *85*, 1538.

Table 2. Catalytic Asymmetric 1,6-Addition of β-Ketoesters: Variation of the β-Ketoester[a]



entry	β-ketoester		base T (°C)	product	yield (%)[b]	ee (%)[c]
1		**1b**	K_2HPO_4 50% -20		**4g** – 98 (98)	92 (89)
2		**1c**	K_2HPO_4 50% -20		**4h** – 89	93
3		**1d**	Cs_2CO_3 66% -25 (+4)		**4i** – 78 (65)	94 (79)
4		**1e**	K_3PO_4 50% -30		**4j** – 95	79
5		**1f**	K_3PO_4 50% -20		**4k** – 84	91
6[d]		**1e**	K_3PO_4 50% -20		**4l** – 92	80
7[d,e]		**1f**	Cs_2CO_3 -20		**4m** – 66	95

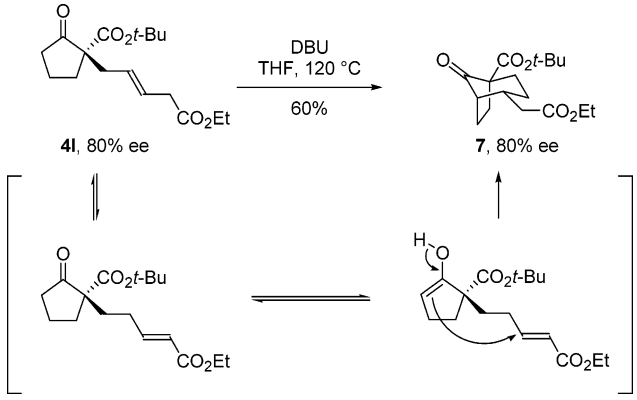
[a] Reactions carried out using 0.15 mmol of β-ketoester **1** (0.15 M in *o*-xylene/$CHCl_3$, 7:1), 0.30 mmol of diene **3a**, and 3 mol % **6**. Reaction time 18−24 h. Values in parentheses refer to the opposite enantiomer, obtained using **6′** as the catalyst. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Diene **3e** (0.30 mmol) was used in the reaction. Reaction time 60 h. [e] A 6 mol % amount of **6** was used.

to this class of substrates. However, it is important to note that this asymmetric transformation could be performed successfully even combining the least reactive β-ketoesters **1e** and **1f** and the least reactive diene **3e**, bearing an ethyl ester as the electron-withdrawing group, simply prolonging the reaction time (Table 2, entries 6 and 7). In the latter case, solid−liquid phase-transfer conditions (Cs_2CO_3, 1 equiv) were found to be necessary for promoting the catalytic reaction to a satisfactory extent (entry 7).

The absolute configuration of compound **4b** was determined as *R* by means of X-ray crystallographic analysis (see the Supporting Information). The observed absolute configuration is accounted for by the shielding of the *Re*-face of the deprotonated β-ketoesters **1** by catalyst **6**, in line with our proposed model of a defined tight ion pair between the chiral quaternary ammonium salt **6** and the enolates derived from *tert*-butyl β-ketoesters **1**.[17] This model also provides a plausible explanation for the high enantioselectivities observed in compounds **4**, in the particular case of the asymmetric 1,6-addition. The use of the quasienantiomeric catalyst **6′** derived from dihydrocinchonidine (Chart 1) gave access to the enantiomeric products *ent*-**4** (Tables 1 and 2, values in parentheses). This latter catalyst was found to be less efficient than catalyst **6** in terms of enantioinduction, though providing the corresponding adducts *ent*-**4** still with useful levels of enantioselectivity.

(17) This model was developed on the basis of an X-ray crystallographic analysis of catalyst **6** bearing *p*-nitrophenolate as the counterion. See ref 12h.

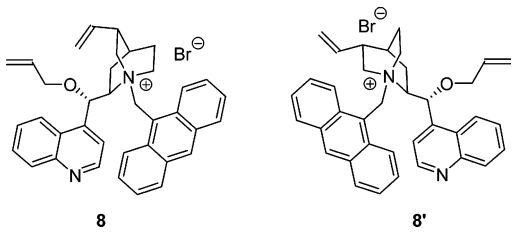
Scheme 4. DBU-Promoted Synthesis of the Bicyclo[3.2.1]octan-8-one **7**



The optically active products **4** resulting from the 1,6-addition of β-ketoesters **1** to electron-deficient dienes **3** possess different functionalities, which can in principle be exploited for further synthetic transformations. For instance, the presence of an enolizable ketone in the cyclopentanone derivative **4l** allowed the expeditious synthesis of a bicyclo[3.2.1]octan-8-one structure, a bicyclic bridged skeleton occurring in a variety of natural compounds.[18] Simple treatment of **4l** with 1,8-diazabicyclo-[5,4.0]undec-7-ene (DBU) promoted isomerization of the double bond followed by an intramolecular Michael addition,[9b] furnishing the corresponding bicyclo[3.2.1]octan-8-one **7** in acceptable yield and as a single diastereoisomer via the mechanism outlined in Scheme 4. The absolute configuration of the newly formed stereogenic center, tentatively determined as *S* and *R* by ^{1}H NMR analysis, can be rationalized considering the possible reversibility of the intramolecular Michael reaction under the reaction conditions, thus favoring the exclusive formation of the stereoisomer **7** bearing the acetyl substituent in the more stable equatorial position.

Benzophenone Imine as the Nucleophile. Since the seminal report by O'Donnell et al. on the use of the benzophenone imine **2** as a glycine enolate equivalent,[19] this substrate represents one of the most reliable starting materials for the synthesis of optically active α-amino acids, especially in combination with PTC.[13] Due to the importance of chiral α-amino acid derivatives, a large number of different catalytic systems have been developed through the years, offering an array of available structures, mostly based on quaternary ammonium salts, capable of performing different asymmetric transformations using **2** with very high efficiency. With the aim of performing an asymmetric 1,6-addition of benzophenone imine **2**, we first focused on the use of quaternary ammonium salts derived from cinchona alkaloids[20] as PTC due to their ready availability and our experience in the use of cinchona alkaloids in asymmetric synthesis. The *O*-allyl *N*-(9-anthracenylmethyl) catalysts **8** and **8′** (Chart 2),[14b,c] derived from cinchonine and cinchonidine, respectively, are certainly efficient systems for asymmetric

Chart 2. Structures of Catalysts **8** Derived from Cinchonine and **8′** Derived from Cinchonidine



transformations using glycine imines such as **2**.[21] Considering also the commercial availability of **8′**, we decided to investigate the possibility of an asymmetric 1,6-addition of the glycine-derived Schiff base **2** using **8** and **8′** as catalysts.[22]

An initial matter of concern was the possible instability of the dienes **3** under the strongly basic conditions which are usually required in the PTC reactions of the benzophenone imine **2**, due to its lower acidity compared to that of the β-ketoesters **1**. However, preliminary experiments between **2** and the methyl ketone-derived diene **3a** using **8′** as the catalyst showed that an asymmetric catalytic addition reaction was indeed possible, giving the corresponding allylated compound **5a** as a single *E*-isomer and with good enantioselectivity, although in moderate yield. After different bases, solvents, and temperatures were tested (see the Supporting Information), it was finally found that the catalytic reaction performed at −40 °C, using aqueous KOH as the inorganic base for a short reaction time, afforded **5a** in moderate yield and with excellent enantioselectivity of 98% ee (Table 3, entry 1). Alternatively, the same product could be obtained in higher yield under milder conditions, still keeping a good level of enantioselectivity, using aqueous Cs_2CO_3 as the base at −20 °C for prolonged reaction time (entry 2).

The phenyl ketone derivative **3b** was found to be too unstable to be used in the reaction, although different conditions were tested; however, 3-vinyl-2-cyclohexenone (**3c**) afforded product **5b** in moderate yield and enantioselectivity, even at −40 °C (Table 3, entry 3). Presumably due to the strongly basic conditions used, only the α,β-unsaturated compound **5b**, and not its γ,δ-unsaturated counterpart, was detected by ^{1}H NMR spectroscopy in the crude mixture. Better results were obtained with the less activated dienes **3d**−**f**, probably for their higher stability. As a matter of fact, both ester-activated dienes **3d** and **3e**, as well as the sulfone derivative **3f**, afforded at −40 °C the corresponding adducts **5c**−**e** with excellent results, in terms of both yields and enantioselectivities (entries 4−6).[23] For the latter products the enantiomeric excess was in the range 92−95%.

(18) For a review on the synthesis and applications of bicyclo[3.2.1]octanes, see: (a) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27. For recent approaches, see, for example: (b) Kim, J. N.; Kim, J. M.; Lee, K. Y. *Synlett* **2003**, 821. (c) Ghera, E.; Ramesh, N. G.; Laxer, A.; Hassner, A. *Tetrahedron Lett.* **1995**, *36*, 1333. (d) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 389. (e) Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Catal.* **2005**, *347*, 1576. See also ref 9b.

(19) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, *19*, 4625.

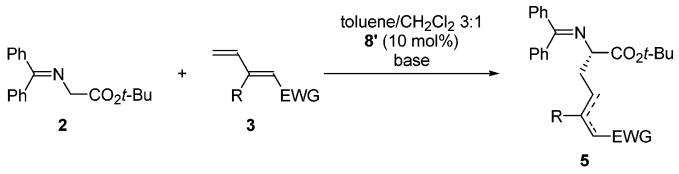
(20) For a comprehensive review on the use of cinchona alkaloids in asymmetric synthesis, see: Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961.

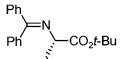
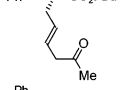
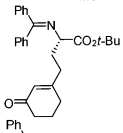
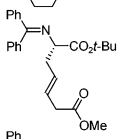
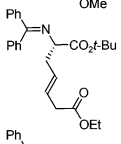
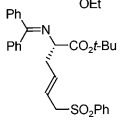
(21) See, e.g.: (a) Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Reddy, M. V. R.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450. (b) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (c) O'Donnell, M. J.; Delgado, F.; Domínguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821. (d) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (e) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.

(22) It should be noted that **6** and **6′** are less effective catalysts compared to **8** and **8′**, giving the catalytic product in very low yield. This observation could be justified considering the bulkiness of the adamantoyl group, which might prevent an efficient interaction between the sterically demanding enolate derived from **2** and the quaternary nitrogen. In fact, in the solid state a *p*-nitrophenolate counterion in catalyst **6** was found to be in a different position with respect to the quaternary nitrogen, compared to the same counterion in catalyst **8′**, presumably due to the steric effects exerted by the adamantoyl group. For a discussion see ref 12h.

(23) In the case of **5a** and **5c**, a small amount (<10%) of the corresponding α,β-unsaturated compounds was detected in the crude mixture, when 50% KOH was used as the base, which could be separated by chromatography from the major γ,δ-unsaturated compounds in both cases.

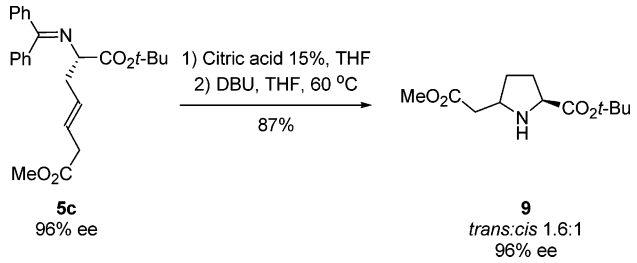
Table 3. Catalytic Asymmetric 1,6-Addition of Benzophenone Imine **2** to Activated Dienes **3**[a]



entry	diene	base T (°C)	t (h)	product	yield (%)[b]	ee (%)[c]
1	**3a**	KOH 50% -40	1		**5a** – 63	98
2		Cs_2CO_3 66% -20	60		**5a** – 73	96
3	**3c**	KOH 50% -40	1.5		**5b** – 49	60
4	**3d**	KOH 50% -40	1		**5c** – 84 (90)	95 (96)
5	**3e**	KOH 50% -40	1		**5d** – 98	92[d]
6	**3f**[e]	KOH 50% -40	18		**5e** – 89	93

[a] Reactions carried out using 0.15 mmol of benzophenone imine **2** (0.15 M in toluene/CH_2Cl_2, 3:1), 0.30 mmol of diene **3**, and 10 mol % **8′**. Values in parentheses refer to the opposite enantiomer, obtained using **8** as the catalyst. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Absolute configuration determined as *S* by chemical correlation (see below). [e] A 0.22 mmol (1.5 equiv) portion of **3f** was used.

Scheme 5. Synthesis of the Disubstituted Pyrrolidine **9**



The synthetic utility of the present transformation was briefly outlined by the two-step transformation of the allylated adduct **5c** into the corresponding pyrrolidine **9**, via mild hydrolysis of the benzophenone imine followed by DBU-promoted double bond isomerization and cyclization (Scheme 5). The importance of these compounds, usually obtained in several steps from glutamic acid derivatives, stems from their widespread application as synthetic intermediates for carbapenam-3-carboxylic acid,[24] the simplest member of the carbapenem β-lactam family of antibiotics,[25] as well as for bicyclic, rigid peptide mimics.[26]

The obtainment of the 2,5-*cis*-pyrrolidine **9** in diastereomerically pure form (96% ee) by chromatography on silica gel allowed the determination of its absolute configuration after Cbz protection as 2*S*,5*R* by comparison of its optical rotation with a literature value (see the Supporting Information). The observed *S* configuration at C-2, established during the catalytic asymmetric reaction, can be explained considering the previously described ion pair between the enolate derived from **2** and catalyst **8′** which provides a very efficient shielding of the *Re*-face of the enolate, allowing approach of an electrophile almost exclusively from the *Si*-face.[14b] Considering this model, the same absolute configuration at the stereogenic center might also be inferred for the other catalytic products **5**. Using the quasienantiomeric catalyst **8** derived from cinchonidine (Chart 2), the enantiomeric adducts *ent*-**5** can be obtained with the same efficiency (Table 3, values in parentheses).

Conclusion

We have presented the first example of an organocatalytic asymmetric 1,6-addition of β-ketoesters and a benzophenone imine to electron-deficient δ-unsubstituted dienes having ketones, esters, and sulfones as substituents to give the corresponding optically active addition products in good yields and excellent enantioselectivities, using readily accessible chiral

(24) See, e.g.: (a) Stapon, A.; Li, R.; Townsend, C. A. *J. Am. Chem. Soc.* **2003**, *125*, 15746. (b) Bycroft, B. W.; Chhabra, S. R.; Kellam, B.; Smith, P. *Tetrahedron Lett.* **2003**, *44*, 973. (c) Bycroft, B. W.; Chhabra, S. R. *J. Chem. Soc., Chem. Commun.* **1989**, 423.

(25) Bradley, J. S.; Garau, J.; Lode, H.; Rolston, K. V. I.; Wilson, S. E.; Quinn, J. P. *Int. J. Antimicrob. Agents* **1999**, *11*, 93.

(26) See, e.g.: (a) Campbell, J. A.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6313. (b) Mulzer, J.; Schülzchen, F.; Bats, J.-W. *Tetrahedron* **2000**, *56*, 4289.

phase-transfer catalysts. The catalytic enantioselective 1,6-addtion was performed for various cyclic β-ketoesters having different ring sizes, ring systems, and substituents in generally high yields and enantioselectivities. The usefulness of the organocatalytic 1,6-addition of β-ketoesters was demonstrated by the asymmetric synthesis of a bicyclic bridged skeleton occurring in a variety of natural compounds. For the benzophenone imine, the organocatalytic asymmetric 1,6-addition to the activated dienes proceeds also in high yields and with enantioselectivities from 92% to 98% ee, except in one case. The synthetic utility of this asymmetric reaction was documented by the formation of an attractive optically active pyrrolidine easily synthesized from the enantioenriched allylated α-amino acid derivatives obtained from the catalytic reaction.

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Supporting Information Available: Complete experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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