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Organocatalytic Asymmetric Conjugate Addition to Allenic Esters and Ketones

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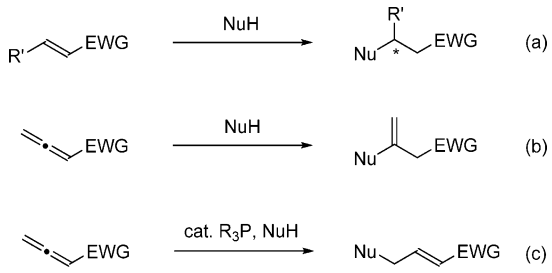
Abstract: The first example of an organocatalytic enantioselective conjugate addition of cyclic β-ketoesters and glycine imine derivatives to electron-deficient allenes is described. We disclose that the corresponding chiral β,γ-unsaturated carbonyl compounds are formed exclusively under phase-transfer conditions using either cinchona-alkaloid-derived or biphenyl-based chiral quaternary ammonium salts as catalysts. The scope of the reaction for β-ketoesters is outlined for allenes having a ketone or ester motif as electron-withdrawing group as well as different substituents in the 3-position, giving the optically active products in high yields and excellent diastereo- and enantioselectivities (90−96% ee). The conjugate addition also proceeds for a number of cyclic β-ketoesters having different ring sizes, ring systems, and substituents in high yields and enantioselectivities. Glycine imine derivatives also undergo the asymmetric conjugate addition to electron-deficient allenes in high yields and with enantioselectivities in the range of 60−88% ee, thus providing a rapid entry to optically active α-vinyl-substituted α-amino acid derivatives. It is shown that the enantioselectivity is strongly dependent on the size of the ester moiety of the nucleophile in combination with the catalytic system used. The high synthetic value of the chiral products arising from these new catalytic processes is demonstrated by two straightforward transformations leading in one case to optically active hexahydrobenzopyranones and in the other to substituted pyroglutamates (γ-lactames).

Introduction

Regarding the significance of carbon−carbon bond formation, the vinylogous addition to unsaturated carbonyl compounds displays one of the cornerstones in synthetic organic chemistry. As a consequence, in the past decades, much attention has been drawn to the development of asymmetric versions of this type of reaction. Next to the vinylogous aldol reaction,[1] conjugate additions[2] to α,β-unsaturated carbonyl compounds cover a large part of the tremendous effort in this research area (Scheme 1, equation a). In these reactions highly functionalized compounds with up to two chiral centers can be formed, which provides an excellent opportunity to access complex and valuable intermediates for asymmetric synthesis. In this context, acroleins, acrylates, vinyl ketones, and α-nitroalkenes have been studied extensively as electrophiles for the 1,4-addition of carbon-centered nucleophiles. Numerous methods have been developed, especially catalytic asymmetric versions,[3] which in many cases have been successfully applied for the synthesis of biologically significant molecules, clearly demonstrating the utility of this transformation.[4]

Scheme 1. Products Arising from Conjugate Addition to Electron-Deficient Alkenes, Allenes, and Electron-Deficient Allenes in Presence of a Tertiary Phosphine



In recent years, allenes, in particular electron-deficient allenes, have emerged as attractive electrophiles in organic synthesis.[5] This growing interest is to a large extent due to the development

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(4) 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.

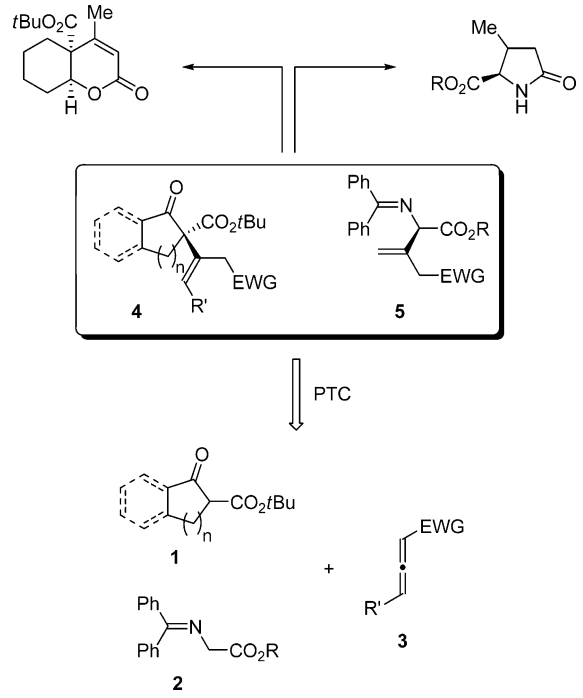
(5) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

of efficient methods for the preparation of allenes based on either classical organic chemistry or organometallic reagents.[6] The conjugate addition to electron-deficient allenes gives rise to β,γ-unsaturated carbonyl compounds (Scheme 1, eq b) bearing a nonconjugated double bond as a further functionality available compared to the 1,4-addition to enoates and enones. This makes them even more versatile as structural motives and chiral building blocks for further elaborations. However, since allenes possess no prochiral center at the β-carbon atom, the chirality must be induced by their reaction partner(s), which leads as a consequence to new developments in asymmetric methodology. This was just recently very effectively underlined by the group of Shibasaki, who demonstrated that the β,γ-double bond of allenoates, in situ activated by the addition of dialkylzinc reagents, can be used within a catalytic asymmetric multicomponent process, serving as a nucleophile to form quaternary stereocenters via vinylogous aldol addition.[7] The same group and the group of Riant also reported a catalytic asymmetric reductive aldol reaction of allenic esters to ketones.[8]

In contrast, if a catalytic amount of a tertiary phosphine is present, attack of the nucleophile to the electron-deficient allene occurs at the γ-carbon atom, resulting in an inverse addition (Scheme 1, eq c). It was shown by Zhang et al. that this umpolung addition reaction, first described by the group of Trost[9] for alkynoates and by the group of Lu[10] for allenoates, can be performed in a stereoselective fashion with chiral phosphines and β-ketoesters as nucleophiles.[11] The zwitterionic dipole resulting from addition of a tertiary phosphine to allenoates can also be used for [3 + 2]-cycloadditions with electron-deficient alkenes. This reaction was also pioneered by Lu et al.,[12] and progress toward a catalytic asymmetric version of this kind of annulation was made by the groups of Zhang,[13] Fu,[14] Wallace,[15] and Miller.[16] The group of Miller also noted that the course of this reaction can be changed to give a conjugate addition product if the phosphine catalyst is exchanged for an amine catalyst.[17]

Since formation of all-carbon quaternary stereocenters is a significant challenge in organic chemistry[18] and examples of stereoselective conjugate additions to electron-deficient allenes remain scarce,[19] we wondered if we could apply asymmetric organocatalysis to get direct access to enantioenriched β,γ-unsaturated carbonyl compounds with a vinyl-substituted quaternary carbon center. In this context, asymmetric phase-transfer catalysis (PTC)[20] with, e.g., β-ketoesters as nucleophiles is a powerful tool, as demonstrated by several highly efficient transformations developed by our group and others.[21] We now wish to report our efforts in the development of the first enantioselective, phase-transfer-catalyzed conjugate addition of cyclic β-ketoesters **1** to electron-deficient allenes **3** (Scheme 2). Furthermore, the utility of the use of allenes for the synthesis of vinyl-substituted chiral carbon centers prompted us to the realization of an asymmetric addition of benzophenone imines **2**[22] derived from glycine leading to a very simple and direct access to pharmaceutically interesting optically active α-vinyl-substituted α-amino acids **5**. Finally, the products **4** and **5** arising from this catalytic process are shown to be suitable for subsequent transformations yielding valuable optically active building blocks, e.g., cis-fused bicyclic lactones and γ-lactames.

Scheme 2. Phase-Transfer-Catalyzed Asymmetric Conjugate Addition to Electron-Deficient Allenes



(6) For reviews, see: (a) Miesch, M. *Synthesis* **2004**, 746. (b) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 2933. (c) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671.
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(15) Wallace, D. J.; Sidda, R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, *72*, 1051.
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(17) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394.
(18) For reviews, see, e.g.: (a) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388.
(19) For achiral examples, see: (a) Lucas, S.; Kazmaier, U. *Synlett* **2006**, 255. (b) Silvestri, M. A.; Bromfield, D. C.; Lepore, S. D. *J. Org. Chem.* **2005**, *70*, 8239. (c) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2000**, *65*, 8715. (d) Dieter, R. K.; Lu, K. *Tetrahedron Lett.* **1999**, *40*, 4011. (e) Sugita, T.; Eida, M.; Ito, H.; Komatsu, N.; Abe, K.; Suama, M. *J. Org. Chem.* **1987**, *52*, 3789. For a chiral example, see: El Achqar, A.; Boumzebra, M.; Roumestant, M. L.; Viallefont, P. *Tetrahedron* **1988**, *44*, 5319.
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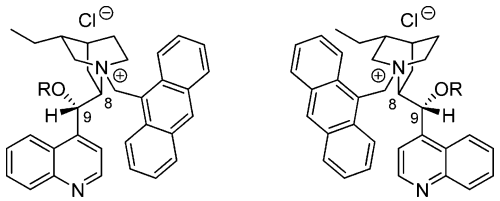
Results and Discussion

β-Ketoesters as Nucleophiles. Recently, phase-transfer catalysts **6** and **6′**, based on the structural motif of dihydrocinchonine and dihydrocinchonidine, respectively, were identified to be effective in a number of different asymmetric transformations applying cyclic *tert*-butyl β-ketoesters.[21h−k] While it was known that the sterically demanding 9-anthracenylmethyl substituent at the quinuclidine nitrogen atom amplifies enantioselectivities in PTC reactions,[23] for our system an additional bulky substituent at the C9-hydroxyl group was crucial to obtain high enantioselectivities (Chart 1).

Chart 1

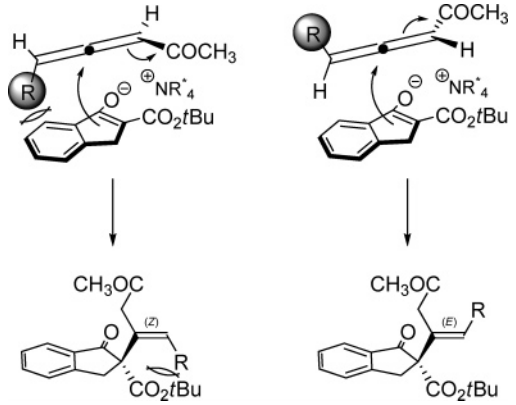


The generality of this catalytic system and mild reaction conditions encouraged us to determine whether an asymmetric conjugate addition to electron-deficient allenes could be achieved. In preliminary attempts the interplay of base strength and reaction temperature were identified as crucial parameters in order to obtain significant conversion (see Supporting Information for measurements of base strengths and further discussions), since strong basic conditions led to competing polymerization of the allene, leaving the β-ketoester nearly unreacted. In addition, the formed product was considered to be prone to isomerize to the thermodynamically favored α,β-unsaturated carbonyl compound. Apart from one example (vide infra), double-bond isomerization was never observed. Accordingly, in our initial experiments with 1-indanone-derived β-ketoester **1a** as nucleophile and allenic ester **3a** as electrophile, several mild inorganic bases gave high conversion to the desired β,γ-unsaturated carbonyl compound at −20 °C. After optimization, it turned out that K_2CO_3 was the base of choice in terms of conversion and enantioselectivity (see Supporting Information). Using liquid−liquid phase-transfer conditions with aq K_2CO_3 as the base at −20 °C afforded the conjugate addition product **4a** after 18 h reaction time with full conversion and a high enantioselectivity using only 1.3 equiv of allene **3a** and 3 mol % of catalyst.

After identification of the best conditions for the catalytic enantioselective conjugate addition to activated allenes, we tested different allenes **3a**−**e** using 1-indanone-derived β-ketoester **1a** as a model substrate employing 3 mol % of catalyst **6**. As summarized in Table 1, allenes with an ester or a ketone moiety as activating group afforded the corresponding β,γ-unsaturated carbonyl compounds in comparable high yields and enantioselectivities of 93% and 94% ee, respectively (entries 1 and 2). Applying the diastereomeric catalyst **6′** allows the preparation of the opposite enantiomer of the products with nearly similar results, as exemplified for compound **4a** (entry 1). Substitution at the 4-position of the allene was also investigated. Using the racemic allenes **3c**−**e** gave the corresponding products with a high preference for one diastereomer (entries 3−5). The phenyl-substituted allenes **3c** and **3d** thereby showed slightly better enantioselectivities (93% and 96% ee, respectively) than the *n*-butyl-substituted allene **3e** (90% ee) with K_2CO_3 as the base. This is probably due to the fact that the reaction with **3e** is much faster under identical reaction conditions, thus suggesting a significant noncatalyzed background reaction eroding slightly the enantioselectivity. Consequently, the reaction with allene **3e** was conducted using K_2HPO_4 as the base, which resulted in an elevated reaction time (4.5 h instead of 3 h) and an increase in enantioselectivity (94% ee, entry 5).

The double-bond geometry of the major diastereomers of compounds **4c**−**e** was determined to be *E* by analogy with the X-ray analysis of the *N*-tosylhydrazone of 5-chloroindanone-derived β,γ-unsaturated carbonyl compound **4h** (see Supporting Information). This can be rationalized by assuming that the substituted allene is approaching from the less hindered side to the *Si*-face of the enolate formed from the β-ketoester and the chiral phase-transfer catalyst (Chart 2, right). Additionally, enhanced 1,3-allylic strain in the formed (*Z*)-product should favor formation of the (*E*)-product (Chart 2). Although the 4-substituted allenes **3c**−**e** were applied as their racemates, there is only one enantiomer shown in Chart 2 since the axial chirality of the allene has no impact on the diastereoselectivity.

Chart 2. Steric Interactions Favoring Formation of (*E*)-Products with 4-Substituted Activated Allenes



Having in hand a general and efficient protocol for the asymmetric conjugate addition to activated allenes, we next explored to which extent this catalytic system could be applied to various other cyclic β-ketoesters. As can be seen from Table 2, different cyclic β-ketoesters **1b**−**h** were found to be suitable for this catalytic transformation, providing addition products **4f**−**o** generally in good to excellent yields (59−95%) and enantioselectivities (67−95% ee).

As expected, the catalytic system had to be fine tuned for some β-ketoesters through variation of the inorganic base. While the 1-indanone-derived β-ketoester **1b** bearing electron-donating

(22) For reviews on the use of **2** for asymmetric transformations under PTC, see: (a) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (e) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (f) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569.

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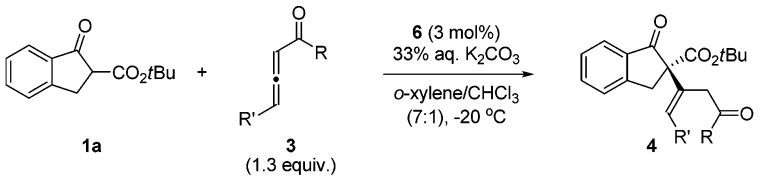
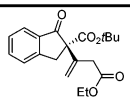
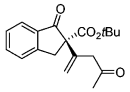
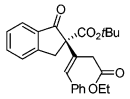
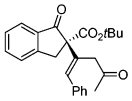
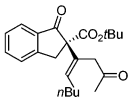
Table 1. Catalytic Asymmetric Conjugate Addition of β-Ketoesters—Variation of the Allene[a]



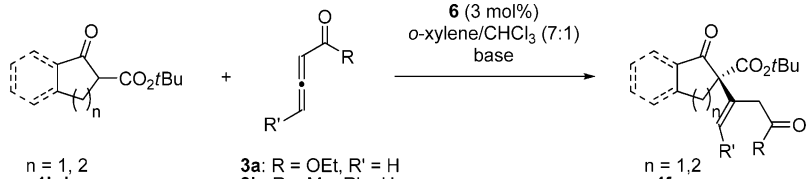
1a 3 (1.3 equiv.) 4

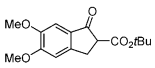
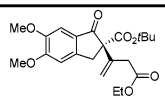
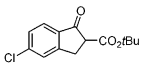
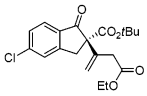
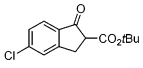
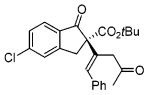
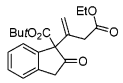
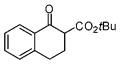
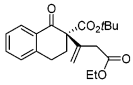
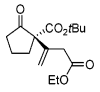
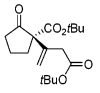
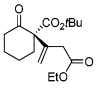
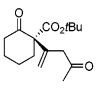
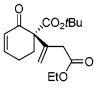
entry	allene	reac. time (h)	product	yield (%)[b]	d.r.	ee (%)[c]
1	 **3a**	18	 **4a**	93 (91)	-	93 (91)
2	 **3b**	18	 **4b**	94	-	94
3	 **3c**	18	 **4c**	93	9:1[d]	96
4	 **3d**	18	 **4d**	97	9:1[d]	93
5[e]	 **3e**	4.5	 **4e**	89	9:1[d]	94

[a] Reaction performed with 0.20 mmol of **1a** (0.16 M), 0.6 mL of aq base, 0.26 mmol of allene **3**, and 3 mol % of catalyst **6**. Values in parentheses refer to the opposite enantiomer, obtained using catalyst **6′**. [b] Isolated yield after column chromatography. [c] The enantiomeric excess was determined by HPLC using an amylose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralpak AD) or a cellulose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralcel OD). [d] Major diastereomer determined as *E*-isomer in analogy to compound **4h**. [e] 50 wt % aq K_2HPO_4 was used as the base.

groups at the aromatic ring worked well with the initially established conditions (entry 1), the β-ketoester **1c** with a 5-chloro-substituent gave only 58% ee with K_2CO_3 as a base. However, changing to the milder base K_2HPO_4 gave adduct **4g** with an increased enantioselectivity of 90% ee (entry 2). Recrystallization from hexane afforded the product in enantiomerically pure form. The lowest enantioselectivy was obtained with 2-indanone-derived β-ketoester **1d** (entry 4). It turned out that the substrate **1d** underwent decarboxylation during the course of the reaction, giving 2-indanone as a byproduct. In order to lower the reaction times, stronger inorganic bases were tested which resulted in higher yields of the desired adduct **4i** but unfortunately also in decreased enantioselectivity (see Supporting Information). Finally, we used an increased catalyst loading of 6 mol % and 3 equiv of allene in combination with an aqueous saturated $NaHCO_3$ solution as basic media to obtain the best combination of chemical yield and enantioselectivity. In contrast, the least reactive β-ketoesters **1e**,**g**,**h** based on the cyclohexanone core gave very good results when stronger bases were applied. The most reactive among these, β-ketoester **1e**, afforded the corresponding adduct **4j** even with aq Cs_2CO_3 as a base and 3 mol % of catalyst **6** in excellent yield and enantioselectivity (entry 5). This reaction was additionally scaled up to 8.1 mmol of substrate, and full conversion and product **4j** was obtained in 85% yield (2.48 g) after column chromatography with an enantiomeric excess of 96% ee. In the case of β-ketoesters **1g** and **1h** it turned out that the addition products could be formed with satisfactory yields switching to aq K_3PO_4 as a base in combination with a slightly increased temperature and catalyst loading (entries 8 and 10). When scaling up the reaction with β-ketoester **1g** and allene **3a** to 7.5 mmol of substrate it turned out that the conversion stopped at 70% after 96 h. However, **4m** was isolated in 53% yield (1.23 g) after column chromatography, and the high enantiomeric excess of 91% ee was retained. When conducting the reaction of β-ketoester **1g** with acetylallene **3b** as electrophile it was necessary to switch to solid−liquid phase-transfer conditions (Cs_2CO_3, 1.2 equiv) and lower the temperature in order to suppress partial olefin isomerization of the formed product (entry 9, for details see Supporting Information). Finally, for cyclopentane-derived β-ketoester **1f** we investigated whether an increase of the bulk at the ester moiety of the allene had an impact on the enantioselectivity, since the reaction with ethyl allenoate **3a** furnished the product **4k** in only moderate

Table 2. Catalytic Asymmetric Conjugate Addition of β-Ketoesters—Variation of the β-Ketoester[a]



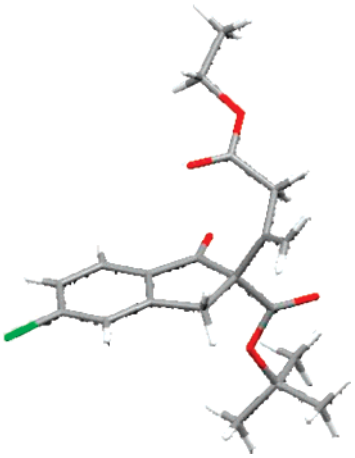
Entry	β-ketoester **1**	allene **3**	base, T (°C)	product **4**	yield (%)[b]	ee (%)[c]
1	 **1b**	**3a**	aq K_2CO_3 33%, -20	 **4f**	95	94
2	 **1c**	**3a**	aq K_2HPO_4 50%, -20	 **4g**	91	90 (> 99)[d]
3[e]	 **1c**	**3d**	aq K_2CO_3 33%, -20	 **4h**	90[h]	84
4[f,g]	 **1d**	**3a**	aq $NaHCO_3$ sat., +4	 **4i**	60	67
5	 **1e**	**3a**	aq Cs_2CO_3 40%, -20	 **4j**	91	95
6	 **1f**	**3a**	aq K_3PO_4 50%, -30	 **4k**	89	76
7	 **1f**	**3f**	aq K_3PO_4 50%, -30	 **4l**	81	79
8[f]	 **1g**	**3a**	aq K_3PO_4 50%, +4	 **4m**	81	91
9[f]	 **1g**	**3b**	Cs_2CO_3,[i] -20	 **4n**	59	90
10[f]	 **1h**	**3a**	aq K_3PO_4 50%, +4	 **4o**	87	95

[a] Reactions performed with 0.20 mmol of **1** (0.16 M in *o*-xylene/$CHCl_3$ 7:1), 0.6 mL of aqueous base (concentrations are given in wt%), 0.26 mmol of allene **3**, and 3 mol % of **6**. [b] Isolated yields after column chromatography. [c] The enantiomeric excess was determined by HPLC using an amylose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralpak AD), a cellulose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralcel OD), a cellulose-tris-(4-methylbenzoate) column (Daicel Chiralcel OJ) or GC. [d] After recrystallization from hexane. [e] Reaction performed on a 1.13 mmol scale. [f] 6 mol % of catalyst **6** was used. [g] 0.60 mmol of allene **3** was used. [h] The *E*/*Z* ratio was determined as 9:1 by ^{1}H NMR. [i] 0.24 mmol of solid base was used.

enantioselectivity (entry 6). As can be seen from entry 7, a switch to *tert*-butyl allenoate **3f** as electrophile gave no significant improvement in enantioselectivity.

The absolute configuration of compound **4g** was determined to be *S* by X-ray crystallography (Chart 3).[24] The observed absolute configuration is accounted for by shielding of the *Re* face of the enolate formed from *β*-ketoesters **1** via deprotonation by catalyst **6**, which is in agreement 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**.[25]

Chart 3. X-ray Crystal Structure of Compound **4g**[a]

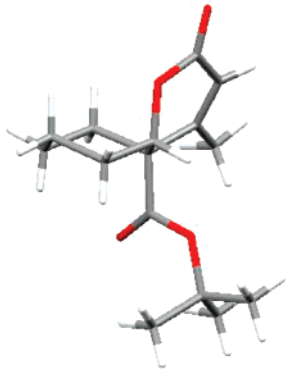


[a] C, gray; H, white; O, red; Cl, green.

The products arising from this catalytic process bearing a quaternary chiral center, an exo-double bond, and various carbonyl functionalities possess, in general, a high potential for further synthetic transformations. For example, in light of several classes of natural compounds comprising the hexahydrobenzopyranone core[26] as well as total synthesis based on that motif,[27] cyclohexanone derivative **4m** seemed to be for us a promising starting point to gain rapid access to this kind of chiral bicyclic building block. After a short investigation, it turned out that we were able to meet our objectives by treatment of **4m** with $NaBH_4$ in the presence of stoichiometric amounts of anhydrous $CaCl_2$. Under these reaction conditions, the keto group was reduced chemoselectively and the resulting alcohol underwent subsequent lactonization followed by isomerization of the double bond to furnish the two diastereomeric lactones **10a** and **10b** in a ratio of 2:1 separable by column chromatography (Scheme 3). The use of $LiClO_4$ or $CeCl_3 \cdot 7H_2O$ as additive gave only minor results in terms of yield and diastereoselectivity. In the latter case a complex mixture was obtained containing also the diastereomeric diols formed by reduction of both the keto and the ethyl ester group.

On the basis of NMR and X-ray analysis, the relative configurations were assigned as cis for lactone **10a** and trans for lactone **10b**. Comparison of the ^1H NMR spectra of lactones **10a** and **10b** showed a significant downfield shift for the proton at the ring junction in lactone **10a**, indicating enhanced shielding of this proton by the ester group. This is in good agreement with former observations for very similar bicyclic lactones with an ester group at the ring junction.[28] This assignment was finally confirmed by the X-ray structure of lactone **10a** (Chart 4), which

Chart 4. X-ray Crystal Structure of Compound **10a**[a]

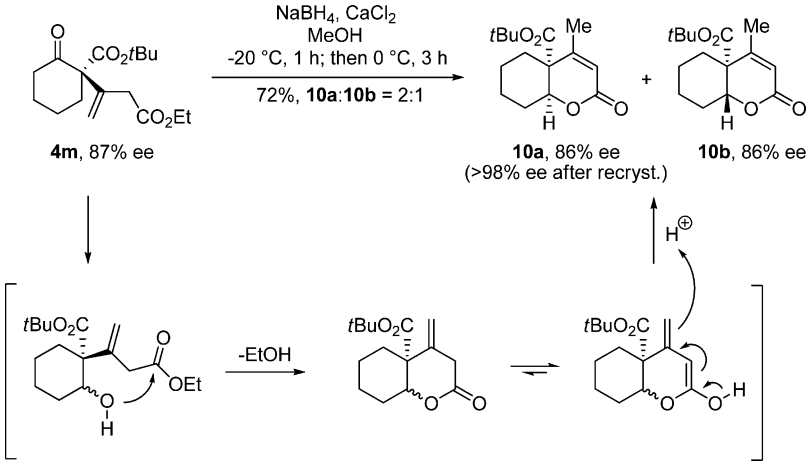


[a] C, gray; H, white; O, red.

was obtained with an enhanced enantiomeric excess of >98% ee after recrystallization from pentane.[24]

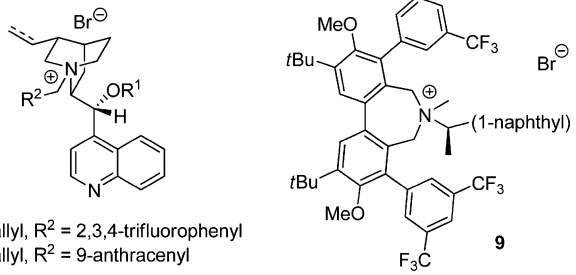
Schiff Bases Derived from α-Amino Acids as Nucleophiles. Despite the many and, in principle, general methods available for synthetic access of chiral α-branched amino acids,[22f,29] there is ongoing interest and research in this field considering the development of general and efficient strategies. In the late 1970s O'Donnell and co-workers introduced the stable Schiff bases **2** derived from glycine esters and benzophenone as suitable nucleophiles for the synthesis of optically active α-alkylated amino acids under phase-transfer conditions.[30] Since then

Scheme 3. Synthesis of Hexahydrobenzopyranone Derivatives **10a** and **10b**



application of chiral phase-transfer catalysts has had a major impact on the synthesis of optically active natural and unnatural α-amino acids. In particular, the use of quaternary ammonium salts derived from cinchona alkaloids has been studied thoroughly, culminating in the development of *N*-(9-anthracenylmethyl)ammonium salts of cinchonine and cinchonidine showing high enantioselectivities for alkylation of imine **2a**.[22] Moreover, it was shown that the scope of this catalytic system could be extended to 1,4-addition reactions with α,*β*-unsaturated carbonyl compounds[31] and 1,6-addition reactions with activated dienes,[21j] respectively. Another highly suitable catalyst (**9**, Chart 5) based on a biphenyl backbone was introduced by Lygo et al. to perform conjugate addition reactions of **2b** to methyl vinyl ketones.[32] However, preparation of this catalyst requires six synthetic steps. Considering the commercial availability of catalyst **8** and easy access of catalyst **7** which was shown to be as effective as catalyst **8** for the asymmetric alkylation of **2a**,[33] we decided to focus first on these cinchona alkaloid-based catalysts in order to promote an asymmetric conjugate addition of benzophenone imine **2a** to allene **3a** (Table 3).[34] In contrast to the countless methods able to provide enantioenriched α-alkyl-substituted α-amino acid derivatives with high fidelity through alkylation of **2a**, addition of the same imine to allenes has, to our knowledge, never been reported in an asymmetric fashion, although this transformation certainly represents direct access to optically active α-vinyl-substituted α-amino acid derivatives.

Chart 5



7: R^1 = allyl, R^2 = 2,3,4-trifluorophenyl
8: R^1 = allyl, R^2 = 9-anthracenyl

9

At the outset we had to consider both the fragility of the electrophile as well as the formed product toward basic conditions, so we first tried to evade the strongly basic conditions usually required to obtain reasonable conversion with benzophenone imine **2a**. After testing several bases, temperatures, and solvents (see Supporting Information) it turned out that full conversion to the desired product **5a** could only be obtained using solid $CsOH{\cdot}H_2O$ as a base. Performing the reaction at −40 °C in CH_2Cl_2 with 3.0 equiv of allenoate **3a** seemed to be the optimum conditions to get a high turnover rate and full conversion to the desired product **5a**. A high turnover rate was found to be crucial to obtain the best enantioselectivities, since elevated reaction times lead to a decrease in the enantioselectivity. This supported the initial consideration of product **5a** being prone to undergo racemization under these reaction conditions.

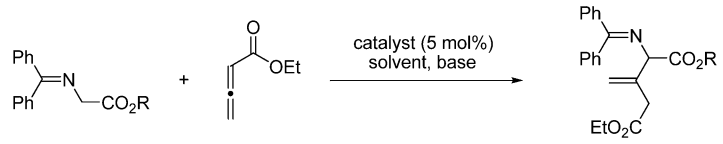
Having set the parameters in terms of conversion, we compared the cinchonidine-derived catalysts **7** and **8** under these reactions conditions. As can be seen from Table 3, catalyst **7** furnished compound **5a** in almost racemic form (entry 1) and catalyst **8** showed a moderate enantioselectivity of 60% ee (entry 2). Lowering the temperature (entry 3) had no influence on the enantioselectivity, and using toluene as a cosolvent (entry 4) gave only a slight increase in enantioselectivity. In order to test if another catalyst was able to improve the enantioselectivity, we applied chiral ammonium salt **9** to the before optimized conditions. Performing the reaction with only 1 mol % of catalyst **9** gave full conversion to the product **5a** after 2 h; however, the enantioselectivity dropped to 15% ee (entry 5). Inspired by the work of Lygo et al.,[32] we next tried Et_2O as a solvent together with a higher dilution of the reaction mixture due to solubility reasons. In this case, longer reaction times were needed to reach full conversion to the desired product **5a**. To our delight, the enantioselectivity increased to 58% ee using $CsOH{\cdot}H_2O$ as the base at −40 °C and to 63% ee using Cs_2CO_3 as the base at 4 °C. Being able to reach full conversion with the use of a mild base such as Cs_2CO_3 encouraged us to apply this catalytic system for optimization. Finally, by increasing the catalyst loading to 4 mol % and using the sterically more demanding benzophenone imine **2b** we were able to obtain the corresponding imino ester **5b** after 4 h at 4 °C with full conversion and a high enantioselectivity of 86% ee (entry 8).[35]

The two optimized systems for application of catalysts **8** and **9** in the addition of glycine imines **2a** and **2b** to allenic ester **3a** were subsequently scaled up to give products **5a** and **5b** in high yields and reproducibly moderate enantioselectivity for **5a** (Table 4, entry 1) and high enantioselectivity for **5b** (Table 4, entry 2). This reaction was also scaled up, and compound **5b** was obtained in 80% yield (1.26 g) after 5.5 h of reaction time and an enantiomeric excess of 85% ee when performing the reaction on a 3.0 mmol scale with respect to substrate **2b**. Glycine imine **2b** was also successfully added to allenic ketone **3b**. The corresponding product **5c** was isolated in 62% yield and showed a high enantioselectivity of 88% ee (Table 4, entry 3).

The general synthetic utility of the α-vinylated imino esters **5** was demonstrated by their straightforward transformation into

(24) The crystallographic coordinates of **4g** (CCDC 654132) as well as **10a** (CCDC 664412) have been deposited with the Cambridge Crystallographic Data Centre. These data can be obtained free of charge from the the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(25) This model was developed on the basis of an X-ray analysis of catalyst **6** bearing *p*-nitrophenolate as the counterion. See ref 21i.
(26) (a) Shing, T. K. M.; Yeung, Y.-Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981. (b) Murakami, N.; Sugimoto, M.; Kawanishi, M.; Tamura, S.; Kim, H.-S.; Begum, K.; Wataya, Y.; Kobayashi, M. *J. Med. Chem.* **2003**, *46*, 638.
(27) Ahmad, Z.; Ray, U. K.; Venkateswaran, R. V. *Tetrahedron* **1990**, *46*, 957.
(28) (a) Krawczyk, H.; Śliwiński, M. *Tetrahedron* **2003**, *59*, 9199. (b) Śliwiński, M.; Wojciech, M. W.; Bodalski, R. *Synlett* **2004**, *11*, 1995.
(29) For a recent reviews on catalytic asymmetric synthesis of α-amino acids, see: Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.
(30) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, *19*, 2641.
(31) (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (b) Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J.; Yus, M. *Arkivoc* **2005**, *vi*, 222.
(32) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461.
(33) Jew, S.-S.; Yoo, M.-S.; Jeong, B.-S.; Park, H.-G. *Org. Lett.* **2002**, *4*, 4245.
(34) It should be noted that **6** and **6′** are less effective catalysts compared to **8**, giving the catalytic product in very low yield. 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 atom, compared to the same counterion in catalyst **8**, presumably due to the steric effects exerted by the 1-adamantoyl substituent. For a discussion, see ref 21i.
(35) It has to be noted that the more bulky glycine imine **2b** has an opposite effect on the enantioselectivity with catalyst **8** giving the product **5b** with only 35% ee.

Table 3. Catalytic Asymmetric Conjugate Addition of Glycine Imines **2**—Optimization of Reaction Conditions[a]



2a: R = *t*Bu
2b: R = $CHPh_2$

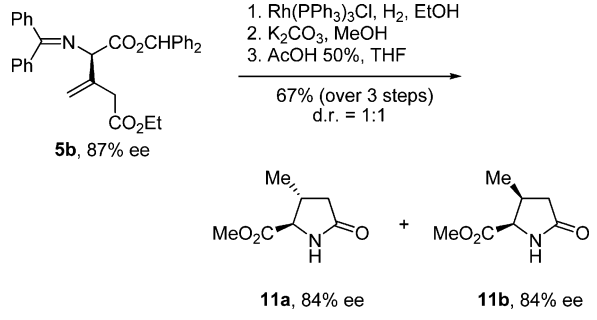
3a, 3.0 equiv

5a: R = *t*Bu
5b: R = $CHPh_2$

Entry	nucleophile	solvent	catalyst	base	temp. (°C)	reac. time (h)	conversion (%)[b]	ee (%)[c]
1	**2a**	CH_2Cl_2	**7**	$CsOH·H_2O$ (5 equiv)	-40	3	>95	13
2	**2a**	CH_2Cl_2	**8**	$CsOH·H_2O$ (5 equiv)	-40	3	>95	60
3	**2a**	CH_2Cl_2	**8**	$CsOH·H_2O$ (5 equiv)	-78	4	>95	60
4	**2a**	toluene/CH_2Cl_2 2:1	**8**	$CsOH·H_2O$ (5 equiv)	-40	2	>95	65
5[d]	**2a**	toluene/CH_2Cl_2 2:1	**9**	$CsOH·H_2O$ (5 equiv)	-40	2	>95	–15[g]
6[d,f]	**2a**	Et_2O	**9**	$CsOH·H_2O$ (5 equiv)	-40	18	>95	–58[g]
7[d,f]	**2a**	Et_2O	**9**	Cs_2CO_3 (5 equiv)	4	24	>95	–63[g]
8[e,f]	**2b**	Et_2O	**9**	Cs_2CO_3 (5 equiv)	4	4	>95	86

[a] Reaction performed with 0.05 mmol of **2a** or **2b** (0.16 M), 0.25 mmol of solid base, 0.15 mmol of allene **3a**, and 5 mol % of catalyst. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC using an amylose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralpak AD). Compound **5a** was transformed into the corresponding Cbz-protected amino ester before HPLC analysis (see Supporting Information). [d] 1 mol % of catalyst **9** was used. [e] 4 mol % of catalyst **9** was used. [f] Concentration was 0.05 M. [g] The opposite enantiomer was enriched.

Scheme 4. Synthesis of 2,3-Disubstituted γ-Lactames **11**



5b, 87% ee

11a, 84% ee **11b**, 84% ee

the corresponding 2,3-disubstituted γ-lactames **11**. This consecutive three-step transformation outlined in Scheme 4 included homogeneous hydrogenation of the double bond with Wilkinson's catalyst followed by transesterification of the two ester groups and subsequent hydrolysis/cyclization with aq AcOH. It should be noted that attempts to cyclize imino ester **5b** directly with aq AcOH led to considerable racemization, and the corresponding unsaturated lactam was obtained with an enantioselectivity of 18% ee. The assignment of relative stereochemistry of lactames **11a** and **11b** was made by comparison of their NMR data with literature data (see Supporting Information).

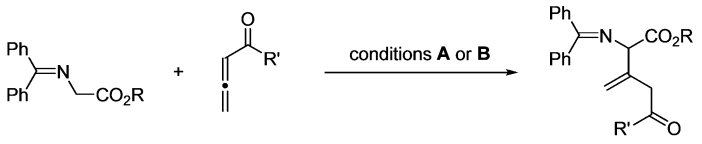
This transformation exemplifies that direct access to optically active substituted γ-lactames from the α-vinylated imino ester **5b** is in general possible. The γ-lactam core displays a unique structural motif for a variety of biologically active molecules. Among these, Lactacystin and Salinosporamide A have currently attracted a lot of attention due to their potent biological properties and synthetically challenging structure.[36] Furthermore, 2,3-disubstituted γ-lactames are useful scaffolds for the synthesis of halipeptins[37] as well as peptide mimetics.[38]

Conclusion

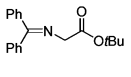
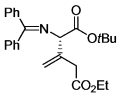
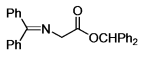
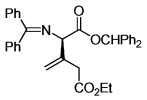
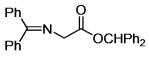
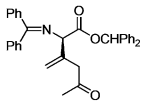
In this article the first example of a catalytic asymmetric conjugate addition to electron-deficient allenes to form tertiary and quaternary stereogenic centers has been described. The reaction enables the α-vinylation of cyclic β-ketoesters using a readily accessible cinchona-alkaloid-derived chiral phase-transfer catalyst under experimentally simple conditions. The products are isolated generally in high yields and with excellent diastereo-

(36) For a review, see: Shibasaki, M.; Kanai, M.; Fukuda, N. *Chem. Asian J.* **2007**, *2*, 20.
(37) Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 8031.
(38) (a) Hannessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomely, M. *J. Org. Chem.* **2005**, *70*, 6746. (b) Zhang, J.; Ying, J.; Wang, W.; Hruby, V. J. *Org. Lett.* **2003**, *5*, 3115. (c) Bentz, E. L.; Goswami, R.; Moloney, M. G.; Westaway, S. M. *Org. Biomol. Chem.* **2005**, *3*, 2872.

Table 4. Catalytic Asymmetric Conjugate Addition of Glycine Imines **2**[a]



2a-b **3a-b** **5a-c**

Entry	glycine imine **2**	conditions	product	yield (%)[b]	ee (%)[c]
1	 **2a**	**A**	 **5a**	85	60[d]
2	 **2b**	**B**	 **5b**	84	87
3	 **2b**	**B**	 **5c**	62	88

[a] Conditions A: Reaction performed with 0.2 mmol of **2a** (0.16 M), 1.0 mmol of $CsOH{\cdot}H_2O$, 0.6 mmol of allene **3a**, and 5 mol % of catalyst **8** at −40 °C in toluene/CH_2Cl_2 (2:1). Conditions B: Reaction performed with 0.2 mmol of **2b** (0.05 M), 1.0 mmol of Cs_2CO_3, 0.6 mmol of allene **3a** or **3b**, and 4 mol % of catalyst **9** at 4 °C in Et_2O. [b] Isolated yield after column chromatography. [c] Determined by chiral stationary phase HPLC using an amylose-tris-(3,5-dimethylphenylcarbamate) column (Daicel Chiralpak AD). [d] Enantiomeric excess determined after transformation of **5a** into the corresponding Cbz-protected amino ester **5d** (see Supporting Information).

and enantioselectivities. The reaction exhibits broad substrate scope in both the cyclic β-ketoester as well as the allenic moiety. Furthermore, it was shown that α-vinylation of glycine imine derivatives can be achieved with high enantioselectivities, changing to chiral phase-transfer catalyst based on a substituted biphenyl backbone. Finally, the synthetic value of the chiral products arising from this catalytic process was exemplified by their straightforward transformation into optically active hexahydrobenzopyranones and γ-lactames, respectively.

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Supporting Information Available: Complete experimental procedures and characterizations (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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