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One-Pot Organocatalytic Domino Michael-Aldol and Intramolecular S_N2 Reactions. Asymmetric Synthesis of Highly Functionalized Epoxycyclohexanone Derivatives

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Abstract: The development of the organocatalytic asymmetric one-pot Michael−Darzens condensation giving highly functionalized complex epoxycyclohexanone derivatives with up to four chiral centers is presented. Depending on the reaction conditions, either the polysubstituted 7-oxa-bicyclo[4.1.0]heptan-2-one ring system or 2-chloro-cyclohex-2-enone derivatives can be formed. For the former class of compounds a high diversity in substitution pattern is demonstrated, and the optically active products are obtained in excellent diastereo- and enantioselectivities. The potential synthetic applications of the products have been demonstrated by performing a series of highly diastereoselective transformations leading to optically active products useful for the life-science industry. Furthermore, mechanistic investigations on the formation of the chiral centers in the optically active epoxycyclohexanone are presented.

Introduction

Organocatalysis has in the past few years proved to be a powerful approach to the preparation of important optically active building blocks.[1] However, the quest for efficient methods for the preparation of complex chiral molecules is just at the beginning. Enantioselective domino, multicomponent and one-pot reactions try to meet these more challenging requirements because with these strategies, it will be possible to obtain optically active products with more than one stereocenter minimizing the number of manual operations and purifications.[2]

Here we wish to report the diastereo- and enantioselective one-pot synthesis of highly functionalized epoxycyclohexanone derivatives with up to four new stereocenters, as well as optically active 2-chlorocyclohex-2-enone derivatives (Scheme 1). The chosen strategy, based on organocatalysis,[3] also benefits from the use of benign catalysts and reagents.

The polysubstituted 7-oxa-bicyclo[4.1.0]heptan-2-one ring (epoxycyclohexanones) is a ubiquitous motif in natural products synthesis,[4] and it is present in many biologically active compounds.[5] At the same time, substituted 2-chlorocyclohex-2-enone derivatives show, for example, antifungal activity,[6] while the α-chloro-α,β-unsaturated carbonyl compounds are useful intermediates in organic synthesis.[7] Attracted by these important synthetic target molecules we elaborated a strategy that also takes atom economic principles into account. Along this line, we thought it highly preferable to develop two processes that consider a common intermediate (Scheme 1). The organocatalytic reaction is based on the full stereochemical control of first a Michael reaction, followed by an aldol reaction, and finally, depending on the product of choice, a S_N2 or an E1cB reaction.

Results and Discussion

Scope of the Reaction. The one-pot organocatalytic domino reactions between γ-chloro-β-ketoesters **2a**−**d** and α,β-unsaturated aldehyde **1a**−**i** occurs in the presence of 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine[8] **7a** and AcONa as additive in CH_2Cl_2. The product is then converted

(1) For recent reviews on organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2004. (c) Seayed, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (d) List, B. *Chem. Commun.* 2006, 8119. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, Advance Article.

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(6) See e.g.: Wild, H. *J. Org. Chem.* **1994**, *59*, 2748.

(7) For Diels−Alder reactions, see e.g.: Stork, G.; Brorowitz, I. J. *J. Am. Chem. Soc.* **1960**, *82*, 4307.

Scheme 1. One-Pot Organocatalytic Domino Reactions Leading to Optically Active Epoxycyclohexanone and 2-Chlorocyclohex-2-enone Derivatives

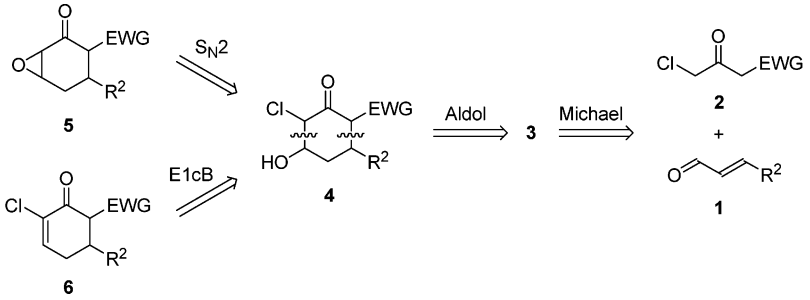
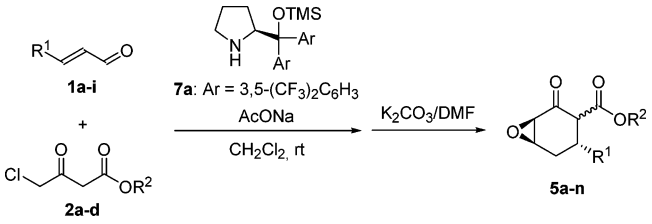


Table 1. Scope of the Organocatalyzed One-Pot Michael Addition/Aldol/S_N2 Reaction of α,β-Unsaturated Aldehydes and γ-Chloro-β-ketoesters[a]



entry	R^1	R^2	yield[b] (%)	de[c] (%)	ee[d] (%)
1	Me − **1a**	Et − **2a**	**5a** − 57	−	86
2		allyl − **2b**	**5b** − 56	99	85
3	Et − **1b**	Et − **2a**	**5c** − 53	−	92
4		allyl − **2b**	**5d** − 46	>99	92
5		Bn − **2c**	**5e** − 47	−	84
6	*n*-Pr − **1c**	allyl − **2b**	**5f** − 48	>99	91
7	*i*-Pr − **1d**	allyl − **2b**	**5g** − 44	>99	97
8		Me − **2d**	**5h** − 50	−	97
9	CH_2OBn − **1e**	allyl − **2b**	**5i** − 47	>99	88
10		Me − **2d**	**5j** − 56	−	88
11	CH_2OTIPS − **1f**	allyl − **2b**	**5k** − 51	>99	86
12	hex-3-ene-yl − **1g**	allyl − **2b**	**5l** − 42	>99	88
13[e]	Ph − **1h**	Et − **2d**	**5m** − 47	−	90
14	CH_2Ph − **1i**	allyl − **2d**	**5n** − 40	>99	92

[a] Conditions: 0.375 mmol of **1**, catalyst **7a** (10 mol %) and AcONa (50 mol %) were stirred in CH_2Cl_2 (0.5 mL) for 15 min before the addition of 0.25 mmol of **2**. After 16 h, K_2CO_3 (0.5 mmol) and DMF (0.5 mL) were added and the crude mixture was stirred for other 2−6 h. [b] Isolated after extraction and flash chromatography. [c] de after decarboxylation; dr before decarboxylation 4:1−7:1 (see text). [d] ee determined by GC after decarboxylation or α-chlorination (see Supporting Information). [e] In the presence of AcONa (50 mol %), AcOH (10 mol %) and at 5 °C.

into the optically active epoxy cyclohexanone in the presence of K_2CO_3 and DMF as cosolvent. The reaction is very general and γ-chloro-β-ketoesters **2a**−**d** bearing different ester groups, all react with similar yields and enantioselectivities (Table 1, entries 3−5, 8). The nature of the β-substituent in the Michael acceptor **1** has a minor effect on this one-pot reaction and the three reaction steps proceed in high overall yield. At the same time, the enantiomeric excess is consistently in the range of 84−97% ee. It is worth noticing that more complex products with differently protected hydroxy groups **5i**−**k** (entries 9−11), with an additional double bond **5l** (entry 12), or aromatic substituents **5m**,**n** (entries 13, 14) can be obtained under similar reaction conditions.

The stereocenter between the two electron-withdrawing groups (ketone and ester) is not configurationally stable, and the products are present in equilibrium in a 4:1 to 7:1 diastereomeric ratio in $CDCl_3$. Nevertheless, after decarboxylation only one diastereoisomer can be detected (>99% diastereomeric purity by NMR spectroscopy and GC).

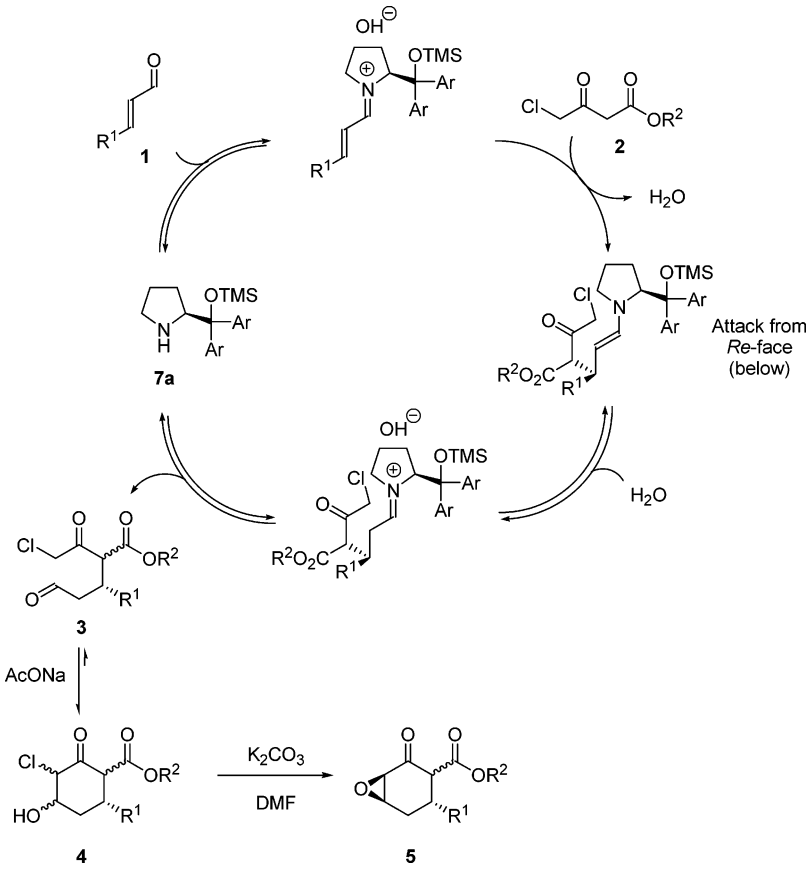
Mechanistic Insight. The proposed mechanism for the chain of transformations is summarized in Scheme 2. The Michael addition follows the common path of related organocatalytic transformations[7h,i,8a,b] and the TMS-protected prolinol derivative **7a** forms with the α,β-unsaturated aldehyde **1** the reactive intermediate. The β-ketoester **2** approach the planar iminium-ion from the Re-face due to the steric hindrance of the bulky substituents (Ar and OTMS groups) at the chiral substituent in the pyrrolidine ring of catalyst **7a**. Hydrolysis of the enamine intermediate leads to the formation of the Michael adducts **3** in a 1:1 diastereomeric mixture and to the release of **7a** that can reenter in the catalytic cycle. The rate of the conjugate addition is generally decreasing with the conversion due to the competition for the catalyst to react with the aliphatic aldehyde **3** and the α,β-unsaturated aldehyde **1**. The role of AcONa is therefore to promote the aldol reaction and the consequent consumption of the optically active product **3**. Finally, the stronger base (K_2CO_3) deprotonates the alcohol and enables the intramolecular S_N2 reaction that lead to the one-pot formation of the highly functionalized products **5**.

The most important feature of this reaction for the formation of the polysubstituted 7-oxa-bicyclo[4.1.0]heptan-2-one ring **5** is the perfect control of the relative configuration of the three stable chiral centers. The aldol intermediate **4** has four stereocenters, and each of the eight possible diastereoisomers is characterized by different conformations. However, only those having both the chlorine and the hydroxy group in axial positions (antiperiplanar) can lead to the formation of the desired bicyclic product **5** (Scheme 3). There is a relatively large energy difference between the intermediate **4d(I)** and the alternative **4d(II)**, in which the R^1-substituent is also in the axial position. A model based on DFT-calculations for the optimized intermediates using a B3LYP/6-31G(d) basis set[9] gave a difference of 2.7 kcal/mol in favor of **4d(I)** when R^1 = Et and R^2 = allyl. We postulate that, under the optimized reaction conditions, the aldol reaction is reversible and the diastereoisomers are in equilibrium with the reactive intermediate **3** being irreversibly

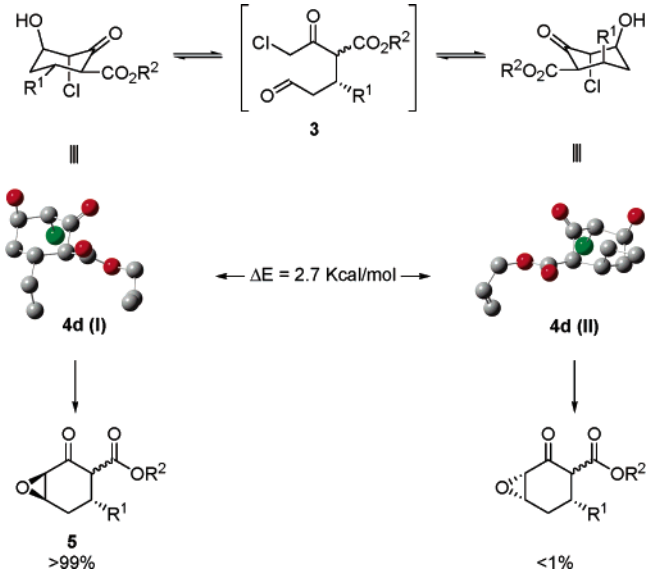
(8) For application of **7a** in enantioselective reactions, see: (a) Marigo, M.; Fránzen, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 4790. (b) Marigo, M.; Schulte, T.; Fránzen, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (c) Zhuang, W.; Marigo, M.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *21*, 3383. (d) Fránzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, 18296. (e) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703. (f) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. See also: (g) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (h) Chi, Y.; Gellman, S. H. *Org. Lett.* **2005**, *7*, 4253.

(9) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Pittsburgh, PA, 2003.

Scheme 2. Mechanism of the Diastereo- and Enantioselective One-Pot Michael Addition/Darzens Condensation Reaction



Scheme 3. Proposed Explanation for the Highly Diastereoselective Aldol-S_N2 Reaction (Darzens Condensation)[10]



transformed to product **5** via intermediate **4d(I)**. In Scheme 3 are reported the optimized structures of the aldol intermediates with both the chlorine and the hydroxy group in axial positions.

Solvent and Additive Screening for the Michael Addition and Aldol Reaction. The Michael addition reaction is very important in this multistep reaction, since it will determine the enantiomeric excess of the product formed at the end of the reaction sequence. We therefore tested the effect of different solvents on the enantioselectivity of the process and on the overall yield. Spectroscopic experiments revealed that the conjugated addition of the γ-chloro-β-ketoester **2a** to crotonaldehyde **1a** took place smoothly at room temperature in CH_2Cl_2 and the final product **5a** was isolated in good yield over the three steps and with 86% ee (Table 2, entry 1). More polar solvents seem to suppress the reactivity of the system, and the reaction essentially did not occur in MeCN (entry 6) while in hexane, toluene, and dichloroethane both yields and enantioselectivities were just slightly lower than in CH_2Cl_2 (entries 2−4).

Table 2. Solvent Screening for the Michael Addition Reaction between **1a** and **2a**[a]

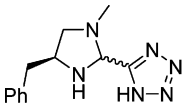
entry	solvent	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	57	86
2	DCE[d]	38	80
3	toluene	45	85
4	hexane	40	81
5	TBME[e]	37	69
6	MeCN	<10	n.d.

[a] Conditions: 0.375 mmol of **1a**, catalyst **7a** (10 mol %), and AcONa (50 mol %) were stirred in the indicated solvent (0.5 mL) for 15 min before the addition of 0.25 mmol of **2a**. After 16 h, K_2CO_3 (0.5 mmol) and DMF (0.5 mL) were added and the crude mixture was stirred for other 2−6 h. [b] Isolated after extraction and flash chromatography. [c] ee determined by GC after α-chlorination of the product **5a** (see Supporting Information). [d] DCE = dichloroethane. [e] TBME = *tert*-butyl methyl ether.

The role of AcONa in the mechanism in Scheme 1 has already been elucidated in the previous paragraph. We initially decided to restrict the search of the suitable additive among the heterogeneous inorganic bases because these are generally cheap and easy to remove from the crude reaction mixture. AcONa turned out to be superior to, for example, $KHCO_3$ and K_2HPO_4

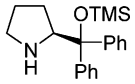
since the latter reagents did not convert **3a** into the aldol product **4a** due to their scarce basicity or poor solubility. On the other hand, K_2CO_3 turned out to be too strong catalyzing also the Michael addition step with consequent detriment of the enantiomeric excess. Under the optimized reaction conditions, the main reason for the loss in chemical yield is the partial decomposition of the γ-chloro-β-ketoesters **2a**−**d**.

Catalyst Investigations. For the first important Michael addition step we relied on 2-[bis(3,5-bistrifluoromethylphenyl)-trimethylsilanyloxymethyl]pyrrolidine **7a** as the organocatalyst. This choice was based on the fact that we recently demonstrated the efficiency of this chiral amine for the iminium-ion activation of α,β-unsaturated aldehydes.[8a,b] Nevertheless, to evaluate the properties of catalyst **7a**, other common chiral organocatalysts have been tested in the one-pot reaction between the γ-chloro-β-ketoester **2a** and 2-pentenal **1b**. L-Proline and L-prolinamide turned out not to be catalytically active under the same reaction conditions. On the other hand, in the presence of the C_2-symmetric (*R*,*R*)-2,5-diphenylpyrrolidine or L-2-methoxymethyl-pyrrolidine, the epoxycyclohexanones **5b** was obtained in good yield, but as a racemate. The organocatalyst **7b**, which has been successfully applied to the enantioselective conjugate addition of nitroalkenes to α,β-unsaturated ketones[11] also lead to the formation of almost racemic product (**5b**: 5% ee), while the organocatalyst **7c**, closely related to **7a**, showed good enantioselectivity, but gave lower yield (**5b**: 34% yield, 74% ee) compared to catalyst **7a**. This last result also highlights the importance of the trifluoromethyl substituents on the aromatic rings of the catalyst **7a**.[12]



7b

40% yield
5% ee



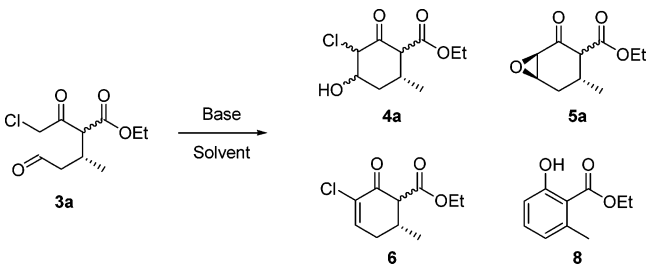
7c

36% yield
74% ee

Optimization of the S_N2 Reaction. The destiny of the enantioselective organocatalytic domino reaction is dependent on small variations in the cyclization reaction conditions (Table 3). When 2 equiv of Et_3N were added to a CH_2Cl_2 solution containing the Michael adduct **3a**, a complex mixture of products could be detected. After 72 h, we observed, along with the aldol intermediate **4a**, also the expected products **5a** and **6**, but the aromatized derivative **8** appeared to be the main component in the crude mixture (Table 3, entry 1). On the contrary, when K_2CO_3 was chosen as base, the product of the Darzens condensation was the most abundant is solution (entry 2). To favor the formation of the 7-oxa-bicyclo[4.1.0]heptan-2-one ring, we increased the polarity of the reaction media by adding MeCN or DMF. In the latter solvent the desired compound **5a** was the only product formed (entry 4).

The interesting optically active compound **6**, under the described reaction conditions (Table 3), could be isolated only as minor product. On the basis of the mechanism in Scheme 2,

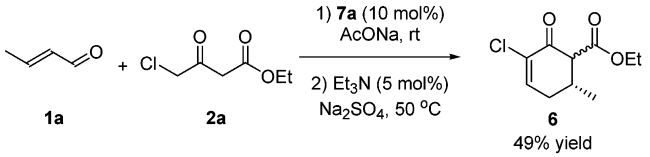
Table 3. Solvent and Base Screening for the S_N2 Reaction[a]



entry	base (2 equiv)	solvent	time (h)	**4a**[b] (%)	**5a**[b] (%)	**6**[b] (%)	**8**[b] (%)
1	Et_3N	CH_2Cl_2	72	15	15	25	45
2	K_2CO_3	CH_2Cl_2	24	5	70	25	−
3	K_2CO_3	CH_2Cl_2/CH_3CN (1/1)	3	−	85	15	−
4	K_2CO_3	CH_2Cl_2/DMF (1/1)	1	5	>90	<5	−

[a] To a solution containing 0.25 mmol of **3a** in CH_2Cl_2 (0.5 mL) were added the indicated base (0.5 mmol) and solvent (0.5 mL), and the crude mixture was stirred for the indicated time. [b] Relative distribution of the four possible products estimated by ^1H NMR spectroscopy on the crude reaction mixture.

Scheme 4. One-Pot Domino Organocatalytic Michael-Aldol and Elimination Reaction[a]



49% yield
4:1 dr ($CDCl_3$), 85% ee

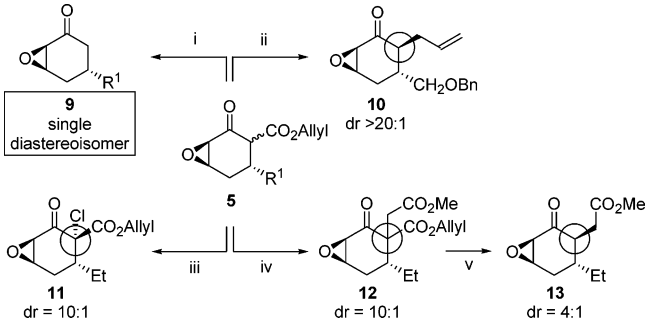
[a] Conditions: 0.375 mmol of **1a**, catalyst **7a** (10 mol %), and AcONa (50 mol %) were stirred in toluene (0.5 mL) for 15 min before the addition of 0.25 mmol of **2a**. After 16 h, Et_3N (5 mol %) and Na_2SO_4 (150 mg) were added to the crude mixture and stirred at 50 °C for 48 h.

we reasoned that a catalytic amount of Et_3N, the presence of a dehydrating agent (Na_2SO_4), and a slightly higher temperature (50 °C, in toluene) could enhances the rate of the E1cB reaction over the S_N2 reaction. In fact, after full conversion of the intermediate **4**, the 3-chloro-6-methyl-2-oxo-cyclohex-3-enecarboxylic acid ethyl ester **6** was isolated in good yield and enantiomeric excess after three steps and only traces of **5a** and of the aromatic product **8** where detected in the crude mixture (Scheme 4).

Products Elaboration. It is important to highlight the fact that all the carbon atoms of epoxycyclohexanone ring **5a**−**n** are chemically different and therefore prompt for being chemoselectively further elaborated (Scheme 5). Our attention has been focused on the versatile products bearing the allyl ester group. The diastereomerically pure products **9** were obtained quantitatively by decarboxylation (see Table 1).[13] Allylic β-ketoesters can undergo stereoselective decarboxylative allylation[14] as also recently demostrated by the groups of Stoltz[14b] and Nakamura.[14c] We were pleased to find that the product **10**, with four

(10) For stereoselective Darzen condensations see: (a) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Tetrahedron* **1999**, *55*, 6375. (b) Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J. *J. Am. Chem. Soc.* **2002**, *124*, 9964.
(11) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897.
(12) For a rationalization of the effect on the enantioselectivity of the substituents of the aromatic ring of TMS-protected diaryl prolinol see ref 8d.
(13) Rouillard, A.; Bonin, M.-A.; Deslongchamps, P. *Helv. Chem. Acta* **2003**, *86*, 3730.
(14) (a) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6384. For recent developments, see: (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (c) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248.

Scheme 5. Product Elaboration (the dr refers to diastereoisomers that are epimeric at C6. No other diastereoisomers are observed)[a]



[a] Conditions: (i) $Pd(PPh_3)_4$, morpholine, THF, rt, 1 h, quant. (ii) $Pd(PPh_3)_4$, DMF, rt, 1 h, 53%. (iii) NCS, $Cu(OTf)_2$, CH_2Cl_2, rt, 6 h, 85%. (iv), TBAI, K_2CO_3, $BrCH_2CO_2Me$, acetone, rt, 14 h, 69%, (v) $Pd(PPh_3)_4$, morpholine, THF, rt, 1 h, quant.

stereocenters, was obtained as a single diastereoisomer, following simple literature procedures (Scheme 5).

On the other hand, the presence of the ester functionality adjacent to the ketone is a superb handle for a variety of transformation since the β-ketoester motif can react with different electrophiles. The rigid bicyclic structure guarantees excellent stereocontrol in the formation of a new quaternary stereocenter, e.g. α-halogenation leading to **11** with high diastereomeric ratio (Scheme 5). The use of $Cu(OTf)_2$ was essential for this reaction since the use of a base such as Et_3N as catalyst leads to poor conversion and lower diastereoselectivity. The product **11m** bearing an aromatic substituent (R^1 = Ph) was obtained diastereomerically pure with 93% ee after recrystallization and was subjected to X-ray crystallographic analysis (Figure 1).

The α-alkylation reaction proceeds in a diastereoselective manner and in high yields under the formation of a new quaternary stereocenter in **12** (Scheme 5). The presence of TBAI as phase transfer catalyst is important to increase both diastereoselectivity and the C/O selectivity. The decarboxylation of **12** proceeds also in high yield to give the most thermodynamically stable product (**13**). It should be noted that the two diastereoisomers in the last reaction can be separated by flash chromatography.

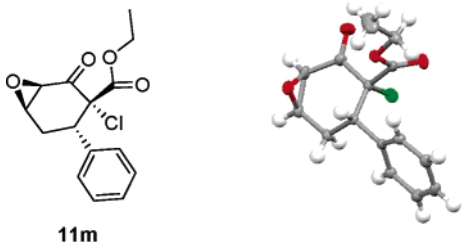


Figure 1. X-ray structure of 3-chloro-2-oxo-4-phenyl-7-oxa-bicyclo[4.1.0]-heptane-3-carboxylic acid ethyl ester **11m**.

Conclusions

In summary, we have developed a simple and versatile organocatalytic strategy for the preparation of structurally complex molecules having up to four stereocenters. The products, epoxycyclohexanone or 2-chlorocyclohex-2-enone derivatives, were isolated in good yields with very good enantiomeric excess and high diastereomeric ratio using a chiral amine as the catalyst and AcONa and K_2CO_3 as the bases. Furthermore, the potential synthetic applications of the products have been demonstrated by performing a series of highly diastereoselective transformations.

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Supporting Information Available: Complete experimental procedures and characterization. Complete ref 9. This material is free of charge via the Internet at http://pubs.acs.org.

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