A simple asymmetric organocatalytic approach to optically active cyclohexenones†

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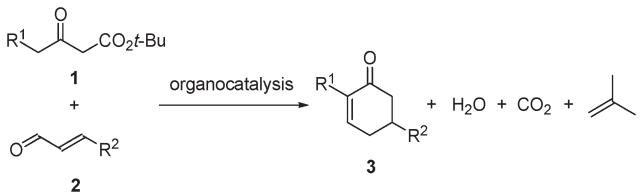
Optically active 2,5-disubstituted-cyclohexen-2-one derivatives have been prepared in a one-pot process consisting of five reaction steps: an organocatalytic asymmetric conjugated addition of β-ketoesters to α,β-unsaturated aldehydes that proceeds in aqueous solutions or under solvent-free conditions has been implemented in a multi-step process.

Organocatalysis[1] has in the last few years gained considerable attention in chemistry, because the use of metal-free catalysts rather than organometallic complexes for the formation of optically active molecules has several potential advantages. For instance, the organocatalytic approach might become valuable in the preparation of life science products such as pharmaceutical compounds which do not tolerate metal contamination. Furthermore, organocatalysis is often associated with mild and simple reaction conditions that are appealing because of the easy handling, cost and safety issues. Unfortunately, the advantages have sometimes been tempered by the use of large excesses of solvent and/or reagent and catalyst, and by long reaction times. To overcome these limitations, recently serious efforts have been dedicated, not only to develop new organocatalytic transformations, but also to select more appealing reaction conditions. For example, the use of water/aqueous solutions[2] as an environmentally friendly solvent has naturally received special attention.[3]

Here we wish to report a new series of asymmetric organocatalytic transformations that focus on the preparation of important optically active molecules and on the green chemistry principles.[4] We thought it would be important to design a new catalytic process that could be easily incorporated into the synthesis of complex chiral structures in "one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in high yield".[5]

In this context, we have developed a one-pot (5 step) asymmetric synthesis of the important optically active cyclohex-2-enone derivatives, based on organocatalysis and which gives H_2O and CO_2 as major by-products, along with isobutene (Scheme 1).

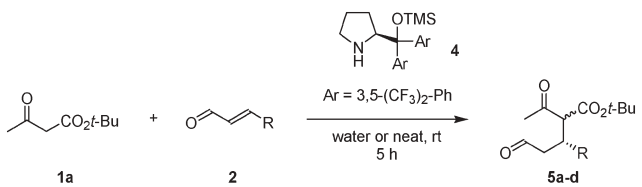
Chiral cyclohex-2-enones are versatile building blocks for the synthesis of a large number of natural occurring products and other important compounds for the life science industry.[6] They can be prepared by kinetic resolution,[7] or by more articulated multi-step synthesis,[8] but a well exploited approach is based on the functionalization of readily available compounds from the chiral pool, such as carvone, pulegone or piperitone. Optical purity and low cost starting materials are advantages of the latter strategy; however, this has as the obvious limitation, the lack of flexibility deriving from the necessity of planning the synthesis of any desired product using only a limited number of different starting materials.



Scheme 1 One-pot organocatalytic asymmetric synthesis of cyclohex-2-enone derivatives.

Our goal is to develop a practical, efficient and flexible method to access a broad range of optically active cyclohex-2-enone derivatives. The optimization of our synthesis started with the extension of the asymmetric Michael reactions of α,β-unsaturated aldehydes to different β-ketoesters as nucleophiles[9,10] but focusing the screening process only on environmentally friendly reaction conditions (Table 1).

Table 1 Organocatalytic Michael addition of *tert*-butyl-3-oxo-butyric ester **1a** with α,β-unsaturated aldehydes **2**[a]



Entry	Solvent	R	Yield (%)[b,c]	Ee (%)[d]
1	H_2O	Ph – **5a**	97	94
2[e]	AcOH (0.5 M)	Ph – **5a**	89	95
3[e]	$NaHCO_3$ (0.5 M)	Ph – **5a**	<10	68
4	aq. NaCl (sea water)	Ph – **5a**	88	93
5	5% EtOH (beer)[f]	Ph – **5a**	98	96
6	—[g]	Ph – **5a**	90	94
7	H_2O	Me – **5b**	82	84
8	H_2O	Et – **5c**	95	90
9	H_2O	*n*-Bu – **5d**	71	93

[a] All reactions were performed on a 0.25 mmol scale using 0.5 mL of solvent. [b] Product isolated by flash chromatography. [c] 1 : 1–6 : 1 *dr* were obtained. [d] Determined by chiral HPLC or GC after derivatization (see ESI). [e] Reaction time: 16 h. [f] Carlsberg Hof. [g] Neat reaction conditions.

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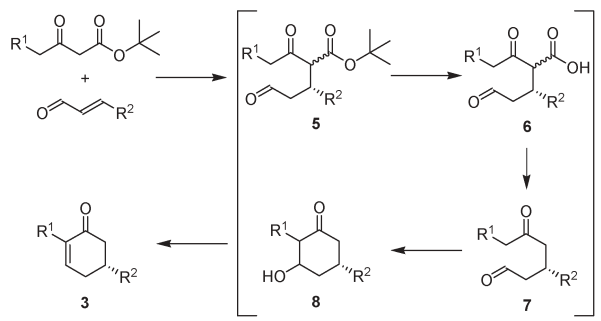
The *tert*-butyl-3-oxo-butyric ester **1a** reacted smoothly with cinnamaldehyde **2a** in distilled H_2O using 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyl-oxymethyl]pyrrolidine **4** as the catalyst[3d,9a,b,9d,11] (Table 1, entry 1). In solvents, such as AcOH(aq), sea water and ca. 5% EtOH (beer) (entries 2, 4, 5) high yields and enantioselectivities were also obtained, while somewhat surprisingly, the reaction gave low yield when performed using a basic water solution (entry 3). This iminium-ion catalyzed Michael reaction is very effective and good yields (71–97%) and enantioselectivities, 84–94% ee of the Michael adducts **5a–d** can generally be obtained using H_2O as solvent at room temperature (entries 1, 7–9). It is important to highlight that the use of H_2O as solvent in processes catalyzed by secondary amines often imposes the use of a large excess of the organic reagents to force the reaction to completion[3a] but in this transformation, using **4** as the catalyst, only a slight excess of cinnamaldehyde **2a** is required to achieve very high yields. A closer look at the reaction reveals that the chosen reagents and the catalyst "cluster together" in H_2O and the reaction probably occurs in the organic phase constituted by the α,β-unsaturated aldehyde, the β-ketoester and the newly formed product.[3b,c] In fact, under solvent-free conditions product **5a** was also obtained with 90% yield and 94% ee (Table 1, entry 6). The same results can also obtained with 5 mol% of catalyst.

The *tert*-butyl ester group was essential for the integration of the Michael reaction into our synthetic strategy. Under the chosen conditions, the addition of *p*-TSA[12] as the second organocatalyst leads directly to the formation of the chiral cyclohex-2-enones **3**. The Brønsted acid is capable of catalyzing the hydrolysis of the *tert*-butyl ester, the decarboxylation of the newly formed β-ketoacid **6**, and finally *p*-TSA also catalyzes the aldol reaction of **7**, and the elimination reaction of **8**. The combination of organocatalysts 2-[bis(3,5-bistrifluoromethyl-phenyl)trimethylsilanyloxymethyl]pyrrolidine **4** and *p*-TSA constitutes a catalytic system which leads to the one-pot five reaction step synthesis of the optically active cyclohex-2-enones **3** (Scheme 2).

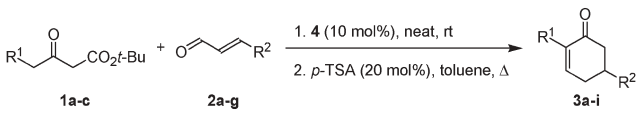
The carefully designed five step and one-pot reaction for the formation of the optically active cyclohex-2-enones derivatives proceed in excellent yield and with remarkable enantioselectivities (Table 2).

Our model substrate *tert*-butyl-3-oxo-butyric ester **1a** works perfectly well with different β-alkyl substituted α,β-unsaturated aldehydes, and with the exception of 2-butenal, the enantioselectivity of the products are in the range of 92–96% ee (Table 2, entries 1–4). It should be noted that the reaction works well for



Scheme 2 Mechanism of the one-pot organocatalytic asymmetric synthesis of optically active cyclohex-2-enone derivatives.[13]

Table 2 One-pot organocatalytic asymmetric synthesis of **3a–i**[a]



Entry	R^1	R^2	Product	Yield (%)[b]	Ee (%)[c]
1	H	Me	**3a**	93	80
2	H	Et	**3b**	98	94
3	H	*i*-Pr	**3c**	56	96
4	H	*n*-Bu	**3d**	69	92
5	H	Ph	**3e**	63 (81)[d]	94
6	H	*p*-F-Ph	**3f**	65	95
7	H	*m*-Me-Ph	**3g**	72	94
8	Me	Et	**3h**	82	91
9	Et	Et	**3i**	(74)[d]	89

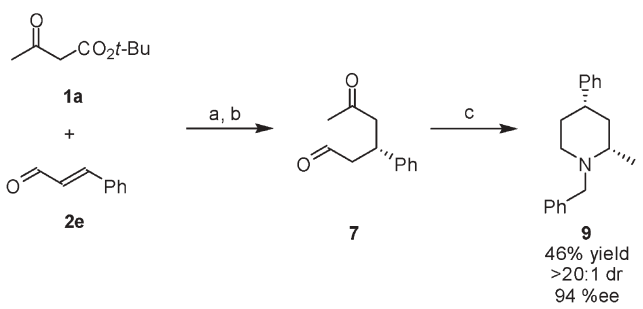
[a] The β-ketoester **1** (0.25 mmol) was added to a mixture of catalyst **4** (0.025 mmol, 10 mol%) and α,β-unsaturated aldehyde **2** (0.37 mmol) and after 5–16 h toluene (1 mL) and *p*-TSA (0.05 mmol, 20 mol%) were added. The product was isolated after 16 h at 80 °C. [b] Product isolated by flash chromatography. [c] Determined by chiral HPLC or GC. [d] The yield in brackets refers to the two-pot process involving the isolation of the Michael adduct.

α,β-unsaturated aldehydes with aromatic substituents and both electronic withdrawing and donating groups are tolerated leading to products with excellent stereoselectivity (entries 5–7). The one-pot organocatalytic asymmetric reaction can also be used for the formation of more complex products by modifying the structure of the β-ketoester. The very interesting 2,5-disubstituted cyclohex-2-enones **3h** and **3i** were synthesized in 74–82% yield and 89–91% ee with the same simple procedure (entries 8, 9).

The optically active products obtained from this solvent-free Michael reaction are also excellent starting materials for the preparation of other biologically active compounds such as optically active piperidines (Scheme 3).[14]

The five step synthesis of the benzyl protected piperidine **9** was achieved with a limited number of manual operations. In this case, the Michael addition between *tert*-butyl-3-oxo-butyric ester and cinnamaldehyde was followed by the addition of TFA and CH_2Cl_2. The crude mixture of **7**, obtained after aqueous workup, was directly subjected to double reductive amination and the *cis*-2-methyl-4-phenyl-piperidine[15] derivative **9** was isolated as one diastereomer with 94% ee and in 46% overall yield.

In summary, we have reported the first organocatalytic asymmetric conjugated addition of β-ketoesters to α,β-unsaturated aldehydes that proceeds in aqueous solutions or under solvent-free



Scheme 3 Synthesis of (2*S*,4*S*)-1-benzyl-2-methyl-4-phenylpiperidine. Reagents: (a) **4** (10 mol%), neat, rt; (b) 50% TFA in CH_2Cl_2, rt, 1 h; (c) benzyl amine (1.5 equiv.), $NaBH_3CN$, MeOH, rt, 20 h.

conditions. The potential of this reaction has been demonstrated by its easy and efficient incorporation in the synthesis of important optically active molecules and by the great substrate generality. In particular, the preparation of optically active 2,5-disubstituted-cyclohex-2-enone derivatives was achieved in very high yield and enantiomeric excess, in a simple one-pot procedure. The value of this "green" process is further enhanced by having isobutene, H_2O and CO_2 as the sole by-products.‡

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‡ General procedure for the Michael addition: 15.0 mg (0.025 mmol, 0.1 equiv.) of **4** was added to the α,β-unsaturated aldehyde (0.37 mmol, 1.5 equiv.) **2** followed by the addition of the β-ketoester (0.25 mmol, 1.0 equiv.) **1** under neat conditions or using water as solvent. The product can be isolated by flash chromatography. General procedure for the preparation of the cyclohex-2-enone derivatives **3**: 15.0 mg (0.025 mmol, 0.1 equiv.) of **4** was added to the α,β-unsaturated aldehyde (0.37 mmol, 1.5 equiv.) **2** followed by the addition of the β-ketoester (0.25 mmol, 1.0 equiv.) **1**. After 5–16 h toluene (1 mL) and *p*-TSA (0.05 mmol, 0.2 equiv.) were added and the reaction mixture was kept at 80 °C for 16 h. The product can be isolated by flash chromatography.

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