Organocatalytic asymmetric "*anti*-Michael" reaction of β-ketoesters†

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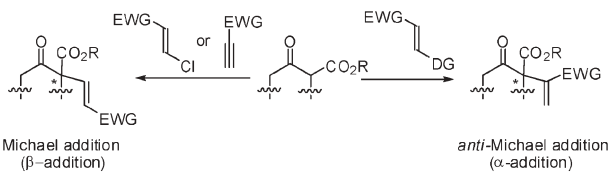
The first organocatalytic "*anti*-Michael" reaction of cyclic-β-ketoesters to unsaturated double bonds is described in a highly asymmetric version leading to the synthesis of α,α′-di-substituted branched double bonds as optically active Baylis–Hillman-like adducts.

The conjugate addition of nucleophilic species to α,β-unsaturated systems is a fundamental reaction in organic chemistry.[1] One of the most important carbon-carbon bond forming reactions in this field is the Michael reaction[2] – the 1,4-addition. For the performance of a Michael reaction leading to optically active products having an unsaturated functionality several strategies can be applied (left equation, Scheme 1). Two main strategies are the addition of β-ketoesters to triple bonds, leading to products as a mixture of *Z*/*E* Michael-addition products[3] or the addition/elimination of β-ketoesters to β-haloacrylate esters, where complete control of the double-bond geometry and good enantioselectivies are found.[4a]

In some cases, the addition to the carbonyl compound can take place as an *anti*- or contra-Michael reaction (right equation, Scheme 1).[5] This reaction can be achieved by different methodologies, such as alkynoates redirected by phosphine base modification, addition at the α-position of Michael acceptors catalyzed by palladium complexes, or by controlling the selectivity of the Michael reaction with organometallic reagents.

We considered the possibility of developing an organocatalytic asymmetric version of the *anti*-Michael reaction by using β-ketoesters as nucleophiles and as the electrophiles, alkenes having both an electron-withdrawing substituent and a directing group (DG in Scheme 1). For the latter reagent, we decided to use a sulfone, which also acts as a leaving group[6] in a one-pot reaction (intermediate not isolated). Thus, it will allow the synthesis of optically active *anti*-Michael- or α-addition-Baylis–Hillman-like adducts (Scheme 2).



Scheme 1 Two different approaches for the synthesis of α- and β-Michael addition products.

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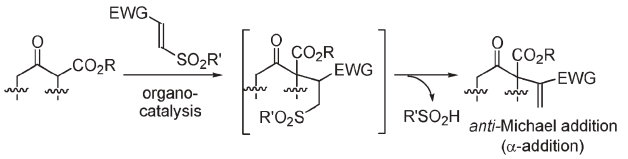
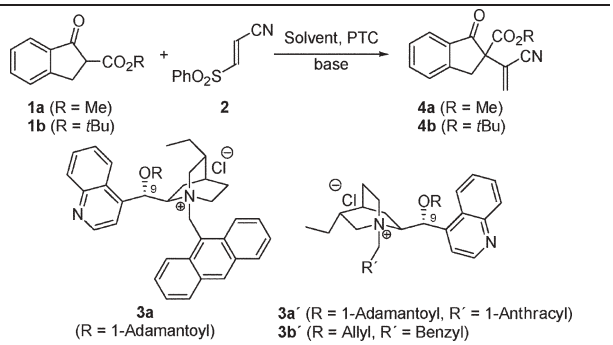


Scheme 2 The sulfone moiety as a directing and leaving group for the *anti*-Michael product or α-addition.

We started our investigation by the addition of the indanone β-ketoester derivative **1a** to the sulfone **2**,[6c] using cinchona alkaloids[7] as the catalysts under various reaction conditions. It turned out, that the application of the cinchona alkaloids as quaternary ammonium salts **3a**, **3a′** and **3b′** under phase-transfer catalytic (PTC) conditions, in the presence of aq. NaOH (10 wt%) as the base provided the desired *anti*-Michael reaction. In Table 1 some representative results are shown.

Table 1 Screening and optimization conditions for the addition of indanones **1a**,**b** to sulfone **2**[a]



Entry	Catalyst (mol%)	Solvent	Base (wt%)[b]	*T*/°C	ee[c] (%)
1[d]	**3a** (6)	Tol–$CHCl_3$ (7 : 1)	Cs_2CO_3 (33%)	−20	76
2[d]	**3b′** (6)	Tol–$CHCl_3$ (7 : 1)	Cs_2CO_3 (33%)	−20	−44
3[e]	**3a** (6)	Tol–$CHCl_3$ (7 : 1)	Cs_2CO_3 (66%)	−20	86
4[e]	**3a** (6)	Tol–$CHCl_3$ (7 : 1)	NaOH (10%)	−20	20
5[e]	**3a** (6)	Tol–$CHCl_3$ (7 : 1)	K_3PO_4 (50%)	4	28
6[e]	**3a** (3)	Tol–$CHCl_3$ (7 : 1)	Cs_2CO_3 (33%)	−20	70
7[e]	**3a** (6)	Tol–$CHCl_3$ (7 : 1)	K_2CO_3 (33%)	−20	70
8[e]	**3a** (6)	*o*-Xylene–$CHCl_3$[f]	Cs_2CO_3 (66%)	−20	55
9[e]	**3a** (6)	$CHCl_3$	Cs_2CO_3 (66%)	−20	86
10[e]	**3a** (6)	CH_2Cl_2	Cs_2CO_3 (66%)	−20	72
11[e]	**3a** (6)	Toluene	Cs_2CO_3 (66%)	−20	83
12[e]	**3a** (6)	*o*-Xylene	Cs_2CO_3 (66%)	−20	75

[a] All the reactions were performed in 0.10 mmol scale (0.15 M). [b] In all the cases after the consumption of the starting material 0.1 mL of NaOH was added for 1 h to eliminate the sulfone anion (except in entries 4 and 5). [c] The enantiomeric excess was determined by HPLC using a chiral stationary phase. [d] Indanone **1a** was used for this entry. [e] Indanone **1b** was used for this entry. [f] 7 : 1.

We found that the use of the indanone **1a** and catalyst **3a** gave good results after few hours, obtaining the *anti*-Michael product **4a** with 76% ee (Table 1, entry 1). Changing the catalyst from **3a** to **3b′** led to a decrease in enantioselectivity of **4a** to 44% ee (entry 2). When the ester moiety in the β-ketoester was changed from Me (**1a**) to *t*-Bu (**1b**), it was observed that the elimination of the sulfone from the intermediate to give the final product was more sluggish compared to the methyl β-ketoester. In this case, it was necessary to add aq. NaOH (10%) to eliminate the sulfone counterpart after the enantioselective addition step performed with Cs_2CO_3 as an external base. Thus, the reaction of indanone **1b** led to an improvement of the enantiomeric excess of the *anti*-Michael product **4b** to be 86% ee (entry 3). Using aq. NaOH (10%) as sole base gave **4b** directly; however, due to the background reaction poor enantioselectivity was obtained (entry 4). Weaker bases, such as K_3PO_4, allowed also the isolation of **4b** with better enantioselectivity even at room temperature (entry 5). It was also noted that lowering the concentrations of the catalyst, as well as changing the base to K_2CO_3, decreased the enantioselectivity when the reaction was performed at −20 °C (entries 6, 7). In addition, performing the reaction in solvents such as *o*-xylene–$CHCl_3$ (7 : 1), CH_2Cl_2 or *o*-xylene gave enantioselectivities in the range of 55–83% ee (entries 8, 10, 11), whereas in $CHCl_3$ and toluene the enantioselectivity was 83–86% ee (see entries 3, 9, 11).

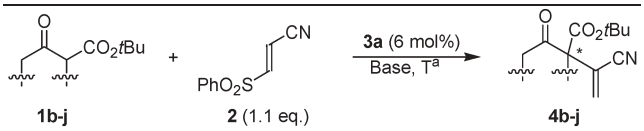
With the reaction conditions developed, a number of different nucleophiles were tested with (*E*)-3-(phenylsulfonyl)acrylonitrile **2** in the presence of catalyst **3a** (6 mol%) (Table 2). The reaction of the indanone derivatives **1b–e** proceeded in all the cases with good yields and enantioselectivies of up to 94% ee (entries 1–4). The dimethoxy indanone derivative **1c** (entry 2) gave the highest enantioselectivity, 94% ee, while for the chloro indanone **1d** the enantioselectivity was 79% ee (entry 3). Alternatively, by using the indanone derivative with only one methoxy group an enantioselectivity of 88% ee was observed (entry 4).

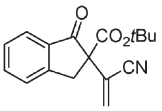
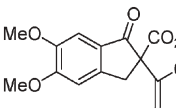
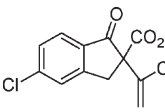
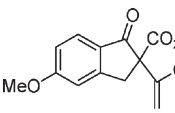
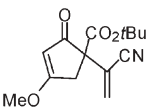
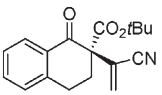
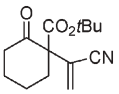
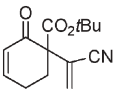
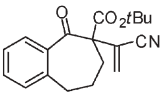
A decrease in the asymmetric induction was noted when the adjacent aromatic group was removed. Thus, for the *tert*-butyl derivative **1f**, the enantioselectivity was reduced to be 66% ee; however, the good yield was maintained (entry 5). The reaction of the functionalized tetralone **1g** leads to an enantiomeric excess of 68% ee, which was increased to >99% ee by recrystallization (entry 6). Remarkably, the *anti*-Michael reaction also proceeded well for other non-phenyl-fused β-ketoesters **1h** and **1i** (entries 7, 8) observing moderate enantioselectivities (63 and 60% ee, respectively). In addition, this reaction could be achieved with the seven-membered ring β-ketoester derivative **1j** giving similar enantioselectivity and moderate yield (entry 9), demonstrating in this manner, that the *anti*-Michael reaction could be performed with five-, six- and seven-membered rings.

The absolute configuration was determined by X-ray crystal structure analysis of compound **4g** to be *S* of the new created chiral center (Fig. 1).[8] The observed configuration was in agreement with previous results that we have observed in reactions of cyclic-β-ketoesters with the same catalyst **3a**.[4]

In order to show the potential of this new *anti*-Michael reaction, we have performed some chemoselective transformations of the optically active product **4c**. Thus, acrylonitrile **4c** could be reduced under $NaBH_4$ creating a mixture of diastereoisomers with two new chiral centers, due to the non-chemoselective reaction,[9] however, this problem could be solved by $CaCl_2/NaBH_4$ reduction,[10]

Table 2 Scope of the addition of β-ketoesters **1b–f** to the sulfone **2a**[a]



Entry	1	Base, *T*/°C	Product 4	Yield[b] (%)	ee[c] (%)
1	**1b**	Cs_2CO_3 66%, −20		**4b** – 90	86
2	**1c**	Cs_2CO_3 66%, −20		**4c** – 89 *ent*-**4c** – 88[c]	94 66[d]
3	**1d**	Cs_2CO_3 66%, −20		**4d** – 85	79
4	**1e**	Cs_2CO_3 66%, −20		**4e** – 80	88
5	**1f**	K_3PO_4 50%, +4		**4f** – 76	66
6	**1g**	Cs_2CO_3 66%, +4		**4g** – 80	68[e] (>99)[f]
7	**1h**	K_3PO_4 50%, −20		**4h** – 52	63
8	**1i**	K_3PO_4 50%, +4		**4i** – 60	60
9	**1j**	K_3PO_4 50%, +4		**4j** – 42	63

[a] In all the cases after the consumption of the starting material 0.2 mL of NaOH was added for 1 h at rt to eliminate the sulfone anion. [b] Isolated yield. [c] The enantiomeric excess was determined by HPLC using a chiral stationary phase or by GC (see ESI). [d] Reaction performed with the quasi-enantiomeric catalyst **3a′** derived from dihydrocinchonidine. [e] Absolute configuration determined by X-ray analysis (see Fig. 1). [f] After recrystallization from hexane–AcOEt (95 : 5).

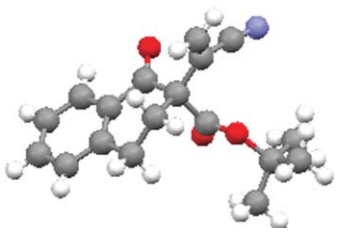
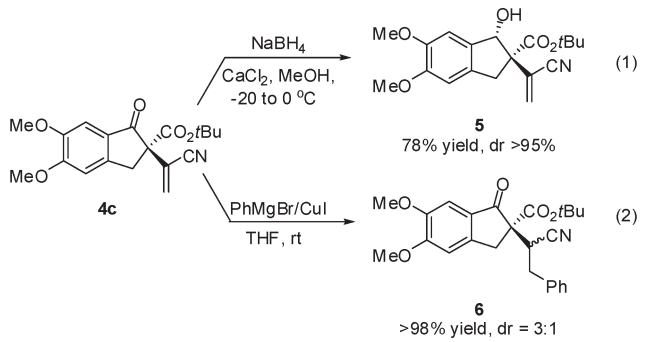


Fig. 1 X-Ray crystal structure of compound **4g**. Carbon: grey, hydrogen: white, oxygen: red, nitrogen: blue.



Scheme 3 Chemoselective transformations of acrylonitrile **4c**.

obtaining a complete diastereo- and chemo-selective reaction (Scheme 3, eqn (1)).

The alkene functionality undergoes conjugate addition of cuprate reagents;[11] thus, when acrylonitrile **4c** was treated with PhMgBr/CuI, the β-functionalization of the double bond proceeds with excellent yield and in a 3 : 1 diastereomeric ratio (Scheme 3, eqn (2)).

In conclusion, the first organocatalytic enantioselective *anti*-Michael reaction has been presented by using a sulfone as directing group of the regioselectivity and as a leaving group in the same reaction. These special properties of the sulfone have allowed the creation of a α,α′-branched terminal double bond joined to a quaternary center. Consequently, this very reactive double bond could be functionalized by different nucleophiles creating in this way new chiral centers with good diastereoselectivities.

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Notes and references

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8 *Crystal data* for [**4g**]: $C_{18}H_{19}NO_3$, M = 297.34, monoclinic, space group $P2_1$ (no. 4), a = 6.2084(2), b = 10.3461(3), c = 12.6475(3) Å, V = 805.76(4) Å^3, T = 150 K, Z = 2, μ(Cu-Kα) = 0.674 mm^{-1}, 9544 reflections collected, 1687 unique (R_{int} = 0.0329) which were used in all calculations. Refinement on F^2, final $R(F)$ = 0.0313, $R_w(F^2)$ = 0.0778. CCDC 651317. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b710393j. For more details about the absolute configuration see ESI†.

9 Reduction of the double bond and the ketone was observed in a diastereoisomeric mixture (60 : 40). These compounds were most likely epimers at the α nitrile position.

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