Highly Enantio- and Diastereoselective Organocatalytic Domino Michael-Aldol Reactions of β-Diketone and β-Ketosulfone Nucleophiles with α,β-Unsaturated Ketones

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Abstract: A chiral imidazolidine catalyst was shown to catalyze the highly enantio- and diastereoselective domino Michael-aldol reaction of β-diketone and β-ketosulfone derivatives with α,β-unsaturated ketones to form optically active cyclohexanones having three or four contiguous chiral centers. The Michael-aldol adducts were formed as single diastereomers in up 99% ee.

Keywords: asymmetric catalysis; C–C bond formation; cyclization; cyclohexanone; domino reactions; Michael-aldol; organic catalysis

A great challenge in organic synthesis is the catalytic asymmetric synthesis of optically active building blocks containing multiple chiral centers from simple and easily-available starting materials.[1] Towards this goal a number of catalytic asymmetric reactions has been developed and especially the direct organocatalytic asymmetric processes are of particular interest due to ease of purification and environmentally benign reaction conditions. Furthermore, a major advantage over traditional Lewis-acid catalysis is that tedious removal of toxic heavy metal residues from the products can be omitted. Among the various organocatalytic asymmetric reactions developed lately,[2,3] conjugate addition reactions to α,β-unsaturated carbonyl compounds have proven to be particularly challenging and only a limited number of examples exist where excellent enantioselectivities have been obtained.[4,5]

We have recently reported the organocatalytic asymmetric Michael[6] reaction of α,β-unsaturated ketones with various nucleophiles such as nitroalkanes, malonates and cyclic 1,3-dicarbonyl compounds in the presence of a chiral imidazolidine catalyst. During our attempts to develop novel organocatalytic asymmetric Michael reactions of α,β-unsaturated ketones using this chiral catalyst, we discovered that in the reaction of β-ketoesters, optically active cyclohexanones with up to three or four chiral carbon centers were formed through a domino Michael-aldol reaction.[7]

In this communication we disclose the further development of the organocatalytic asymmetric domino Michael-aldol reaction catalyzed by the chiral imidazolidine (*S*)-**1** to the application of β-diketone **3** and β-ketosulfone **4** as the nucleophiles. The mechanism for the domino Michael-aldol reaction is proposed in Scheme 1, and the adducts formed in the reaction, possessing three or four contiguous chiral carbon atoms, are obtained as single diastereomers in up to 99% ee.

The reason for our decision to extend our previously developed domino Michael-aldol reaction of acyclic β-ketoesters[7] to β-diketones as Michael donors is that these substrates have only very rarely been employed in catalytic enantioselective Michael reactions.[8] The present approach thus offers a simple procedure for the formation of optically active cyclohexanones having ketone and sulfone functionalities in high diastereomeric and enantiomeric excesses. An initial screening of the reaction conditions using dibenzoylmethane **3** as the β-diketone at ambient temperature revealed $CHCl_3$ to be the solvent which provided the highest yields and enantioselectivities. Using 10 mol % of phenylalanine-derived catalyst (*S*)-**1**, a number α,β-unsaturated ketones **2a–g** were reacted with **3** to afford optically active cyclohexanones **5** as single diastereomers having up to four chiral carbon centers (Table 1).

The results in Table 1 show that the domino Michael-aldol reaction of dibenzoylmethane **3** proceeded in moderate to good isolated yields (41–87%) and in up to 91% ee using various α,β-unsaturated ketones **2a–g**, and in all cases only a single diastereomer of the Michael-aldol adduct **5a–g** was observed. The reactions proceeded well for α,β-unsaturated ketones having both aromatic and heteroaromatic substituents and for the former class of compounds, both electron-withdrawing and electron-donating substituents, are tolerated. Un-

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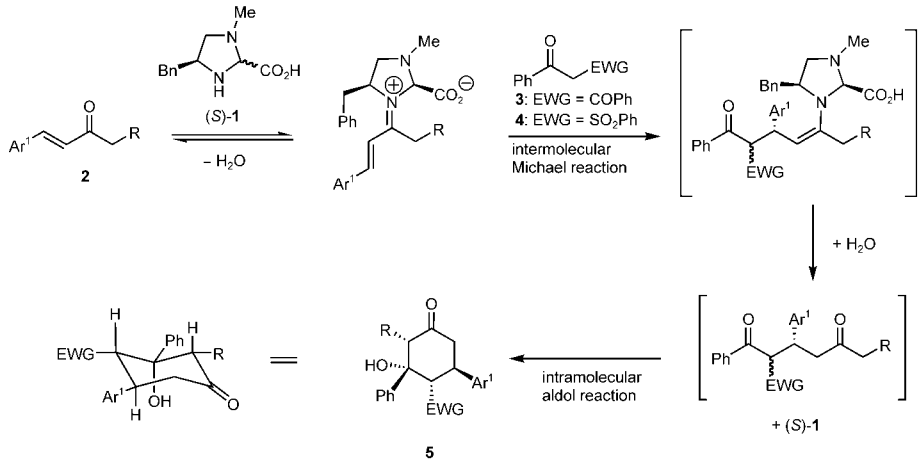
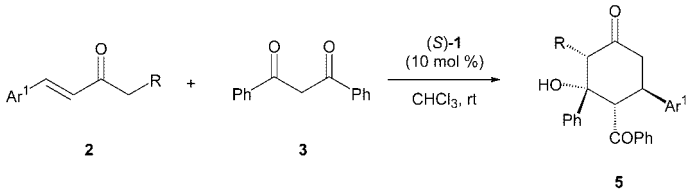


Scheme 1. Domino Michael-aldol reaction of α,β-unsaturated ketones **2** with β-carbonyl compounds catalyzed by (*S*)-**1**.

Table 1. Domino Michael-aldol reaction of α,β-unsaturated ketones **2** with dibenzoylmethane **3** catalyzed by (*S*)-**1**.



Entry	**2**	Ar^1	R	Time [h]	**5**	Yield [%][a]	de [%][b]	ee [%][c]
1	**a**	Ph	H	160	**a**	56	>95	91
2	**b**	2-Np	H	160	**b**	67	>95	81
3	**c**	4-Cl-C_6H_4	H	135	**c**	87	>95	80
4	**d**	4-NO_2-C_6H_4	H	150	**d**	47	>95	87
5	**e**	2-furyl	H	150	**e**	59	>95	85
6	**f**	Ph	Me	160	**f**	41	>95	67
7	**g**	4-MeO-C_6H_4	H	120	**g**	50	>95	64

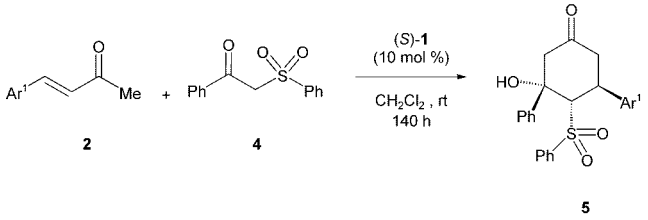
Experimental conditions: To a solution of α,β-unsaturated ketone **2** (0.5 mmol) in 1.0 mL $CHCl_3$ was added dibenzoylmethane **3** (1.0 mmol, 2.0 equiv.) and catalyst (*S*)-**1** (10 mol %) and the reaction mixture was stirred for the time indicated in the table.
[a] Yield of isolated products.
[b] Measured by ^{1}H NMR spectroscopy and confirmed by HPLC.
[c] Determined by CSP-HPLC.

fortunately, the reaction was found not to proceed when using alkyl-substituted diketones such as 2,4-pentanedione as Michael donors and only traces (<5%) of product was observed.

It should be noted that in order to isolate the analytically pure, optically active Michael-aldol adducts no chromatography is required as the optically active cyclohexanones precipitate from the reaction mixture and were recovered by simple filtration, washing with Et_2O to remove unreacted starting materials and drying under vacuum. Due to this very simple work-up procedure it might be expected that a continuous recrystallization takes place during the reaction, but in order to omit this possibility, several reactions purified by flash chromatography afforded the domino Michael-aldol adducts having the same optical purity as those recovered by filtration.

We then turned our attention to β-ketosulfones, another classical Michael donor, as substrates for the imidazolidine-catalyzed domino Michael-aldol reaction to form optically active sulfone-substituted cyclohexanones **5**. An initial screening of reaction conditions, using 2-phenylsulfonylacetophenone **4** as the Michael donor, revealed that excellent diastereo- and enantioselectivities were obtained in most solvents such as MeOH, toluene and Et_2O, however, the highest yields were obtained when the reactions were performed in CH_2Cl_2 and $CHCl_3$. Subsequently, the aromatic and heteroaromatic α,β-unsaturated ketones **2a**–**e**, **h**–**j** were reacted with 2-phenylsulfonylacetophenone **4** to show the scope

Table 2. Domino Michael-aldol reaction of α,β-unsaturated ketones **2** with phenylsulfonylacetophenone **4** catalyzed by (*S*)-**1**.



2 **4** **5**

Entry	**2**	Ar^1	**5**	Yield [%][a]	de [%][b]	ee [%][c]
1	**a**	Ph	**h**	93	>95	96
2	**b**	2-Np	**i**	31[d]	>95	99
3	**b**	2-Np	**i**	93	>95	86
4	**c**	4-Cl-Ph	**j**	95	>95	94
5	**d**	4-NO_2-Ph	**k**	59	>95	90
6	**e**	2-furyl	**l**	77	>95	94
7	**h**	2-thienyl	**m**	48	>95	99
8	**i**	4-HO-Ph	**n**	87	>95	98
9	**j**	1-Np	**o**	52[d]	>95	97
10	**j**	1-Np	**o**	73	>95	90

Experimental conditions: To a solution of α,β-unsaturated ketone **2** (1.0 mmol) in 1.0 mL CH_2Cl_2 was added 2-phenylsulfonylacetophenone **4** (0.5 mmol) and catalyst (*S*)-**1** (10 mol %) and the reaction mixture was stirred for 140 h.
[a] Yield of isolated products.
[b] Measured by ^{1}H NMR spectroscopy and confirmed by HPLC.
[c] Determined by CSP-HPLC.
[d] Performed using one equivalent of α,β-unsaturated ketone **2b**.

of the domino Michael-aldol reaction and the results are presented in Table 2.

As demonstrated by the results in Table 2, all the aromatic α,β-unsaturated ketones employed in the reaction with 2-phenylsulfonylacetophenone **4** afforded the cyclohexanones **5 h–o** in excellent enantioselectivities. In all cases only a single diastereomer was formed in the reaction, and analogously to the domino Michael-aldol reaction of β-diketone **3**, the product was isolated by a simple filtration procedure, thus avoiding tedious chromatographic steps. As was the case when using β-ketoesters[7] or β-diketones as Michael donors, alkyl-substituted β-ketosulfones only provided trace amounts (<5%) of products.

It should be noted that catalyst (*S*)-**1** is believed to have three roles during the reaction (1) activation of the Michael acceptor by iminium ion formation, (2) deprotonation of the Michael donor, and (3) acting as a base catalyst for the intramolecular aldol step (Scheme 1). The structure of the iminium ion intermediate is presumably identical to previously proposed structures[6a, c] and consequently the absolute stereochemistry of the Michael-aldol adducts **5** is assigned by analogy to the β-ketoester Michael-aldol adducts.[7] The relative stereochemistry was determined on the basis of ^{1}H NMR studies and by comparison with NMR spectra of similar cyclohexanones formed using acyclic β-ketoesters as Michael-aldol donors.[7]

The synthetic value of the cyclohexanone Michael-aldol adducts as optically active building blocks has previously been proved by their facile transformation into ε-lactones, cyclohexenones, and cyclohexanediols.[7]

In summary, we have developed an organocatalytic highly diastereo- and enantioselective domino Michael-aldol reaction of β-diketone and β-ketosulfone derivatives with α,β-unsaturated ketones. The very mild reaction conditions, inexpensive catalyst, and chromatography-free process make this Michael-aldol reaction an attractive approach to optically active cyclohexanone building blocks.

Experimental Section

General Procedure for the Organocatalytic Asymmetric Domino Michael-Aldol Reaction of Dibenzoylmethane 3 with α,β-Unsaturated Ketones

To a solution of 0.5 mmol of α,β-unsaturated ketone **2** in 1.0 mL of $CHCl_3$ in a disposable glass test tube equipped with a magnetic stirring bar, were added 1.0 mmol of dibenzoylmethane **3**, 0.05 mmol of catalyst and the mixture was stirred at ambient temperature for the time indicated in Table 1. The reaction mixture was diluted with Et_2O (2 mL), filtered by suction and the precipitate washed with 2 mL of Et_2O and dried under vacuum. The enantiomeric excess and purity of the products were determined by HPLC (see Supporting Information).

General Procedure for the Organocatalytic Asymmetric Domino Michael-Aldol Reaction of Phenylsulfonylacetophenone 4 with α,β-Unsaturated Ketones

To a solution of 0.5 mmol phenylsulfonylacetophenone **4** in 1.0 mL of CH_2Cl_2 in a disposable glass test tube equipped with a magnetic stirring bar, were added 1.0 mmol of α,β-unsaturated ketone **2**, 0.05 mmol of catalyst and the mixture was stirred at ambient temperature for the time indicated in Table 2. The CH_2Cl_2 was evaporated and Et_2O (2 mL) was added and the precipitate was isolated by suction filtration, washed with Et_2O and dried under vacuum. The enantiomeric excess and purity of the products was determined by HPLC (see Supporting Information).

Supporting Information

Experimental procedures and spectral data for all novel compounds are available.

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