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Highly Enantioselective Organocatalytic Michael Addition Reactions of Ketones with Chalcones

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Abstract: A highly enantioselective, organocatalytic Michael addition reaction of unmodified ketones with chalcones has been developed for the first time. The process, catalyzed by (*S*)-*N*-(pyrrolidin-2-ylmethyl)-trifluoromethanesulfonamide, affords 1,5-diketones in high yields (73–89%) and with high degrees of enantio- and diastereoselectivity (86–97% ee, >30:1 dr).

Keywords: asymmetric catalysis; enones; ketones; Michael addition; organic catalysis; pyrrolidine-sulfonamides

Michael addition reactions are powerful tools for the generation of new C–C bonds as part of synthetic routes for the preparation of complex organic targets.[1,2] The importance of this methodology has stimulated significant interest in the development of catalytic, asymmetric versions of the process. Lewis acid-based catalytic[1,2] and organocatalytic[3,4] systems have been reported. Most organocatalyzed Michael addition reactions that have been described to date employ either highly active, stabilized carbanions (e.g., 1,3-dicarbonyls,[5] nitroalkanes[6] or preformed silyl enol ethers[7]) as Michael donors or highly activated Michael acceptors (e.g., nitroalkenes[8] and sulfones[9]). Organocatalyst-promoted Michael additions of aldehdyes to enones also have been investigated and a direct version of this process catalyzed by a chiral pyrrolidine has been reported by Jørgensen and co-workers.[10] List and Gellman have independently used MacMillan's imidazolidinones as organocatalysts for intramolecular and intermolecular Michael reactions of aldehydes with enones.[11] Despite this moderately large effort, enantioselective catalytic conjugate addition reactions of ketones with enones remain challenging and studies probing this issue have not yet been reported. In this communication, we describe the results of an investigation which has led to the development of the first method for carrying out highly enantioselective, organocatalytic Michael addition reactions of ketones with α,β-unsaturated ketones by using a chiral pyrrolidinylmethylsulfonamide.

This investigation began with screening several chiral amine-based organocatalysts for their ability to promote asymmetric Michael addition reactions of cyclohexanone **1a** with 4-chlorochalcone **2a** (Figure 1). The initial reactions were performed by using 20 mol % of the catalysts at room temperature in *i*-PrOH. Examination of the results from this survey revealed that their catalytic activities varied significantly (Table 1). For example, processes promoted by L-proline **I** and pyrrolidine diamine **III** proceeded slowly in very low yields (14% and 8%, respectively) and with only moderate enantioselectivities (41% and 75% ee, respectively) (entries 1 and 5). Diphenylprolinol silyl ether **IV** and MacMillan's imidazolidinone **V** were not effective catalysts for this process (entries 6 and 7). The most promising results came from studies with (*S*)-*N*-(pyrrolidin-2-ylmethyl)-trifluoromethanesulfonamide **II**, a catalyst first developed in our laboratory.[8a] By using **II**, reaction of cyclohexanone **1a** with 4-chlorochalcone **2a** took place to form adduct **3a** more rapidly (2 d), in high yield (85%), and with a remarkably high level of stereocontrol (90% ee and 50:1 dr, Table 1, entry 2). Reducing the catalyst loading to 10 mol % did not significantly affect the enantioselectivity and reaction rate of this reaction (entry 3). Finally, lowering the reaction temperature to 0 °C resulted in a much longer reaction time and the enantioselectivity was improved only marginally (entry 4).[12]

The conditions that proved optimal for the reaction of cyclohexanone **1a** with 4-chlorochalcone **2a**, catalyzed by **II** (10 mol %) were general for Michael additions of other cyclic ketones (Table 2).[13] Reactions with 6-membered ring ketones took place efficiently (73–89%) with high to excellent levels of enantioselectivity (86–97% ee) and exceptionally high diastereoselectivity (>40:1 dr) (entries 1–5). Reaction of cyclopenta-

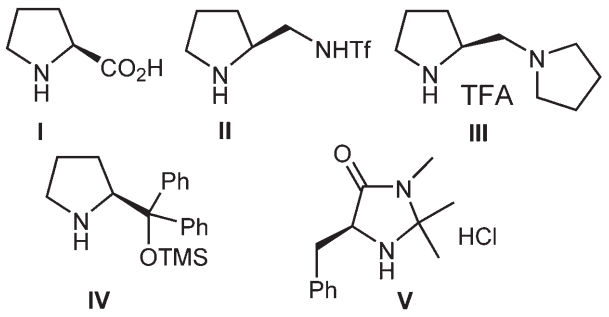
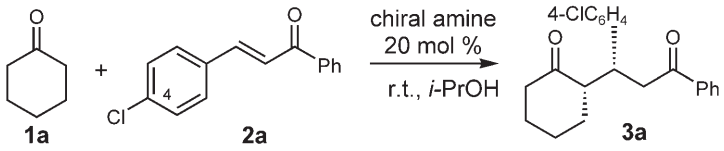


Figure 1. Chiral amine organocatalysts.

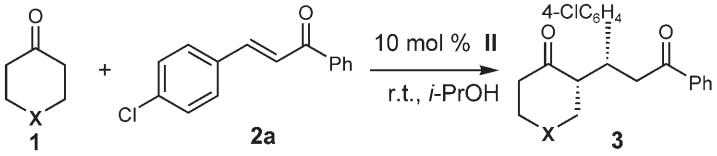
Table 1. Results of exploratory studies of catalytic asymmetric Michael addition reactions of cyclohexanone **1a** with 4-chlorochalcone **2a**.[a]



Entry	Catalyst	*t* [days]	Yield [%][b]	dr[c]	% ee[d]
1	**I**	6	14	50:1	41
2	**II**	2	85	50:1	90
3[e]	**II**	4	80	50:1	90
4[f]	**II**	7	48 (88)[g]	50:1	92
5	**III**	6	8	30:1	75
6	**IV**	6	<5	–[h]	–[h]
7	**V**	6	<5	–[h]	–[h]

[a] *Reaction conditions:* see Experimental Section and Supporting Information.
[b] Yields of isolated products.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis (Chiralpak AS-H).
[e] 10 mol % used.
[f] 0 °C and 10 mol% used.
[g] Yield based on recovered starting material.
[h] Not determined.

Table 2. Catalytic asymmetric Michael addition reactions of cyclic ketones with 4-chlorochalcone **2a**.[a]



Entry	X	t [days]	Yield [%][b]	dr[c]	% ee[d]
1	CH_2	4	80	50:1	90
2	NMe	4	89	40:1	97
3	O	5	73	50:1	87
4	$C[O(CH_2)_2O]$	5	73	50:1	89
5	S	6	77	50:1	86
6	none	2	87	3:1	73 (91)[e]

[a] *Reaction conditions:* see Experimental Section and Supporting Information.
[b] Yields of isolated products.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC analysis (Chiralpak AS-H).
[e] Major isomer: 73% ee, minor isomer: 91% ee.

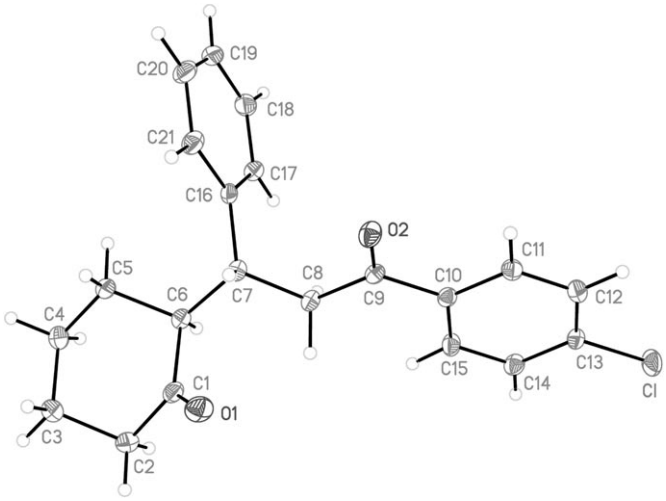


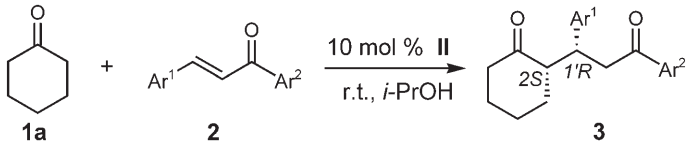
Figure 2. X-Ray crystal structure of **3b**.

none occurred at a higher rate (2 d) and in high yield (87%, entry 6), but the product diastereomeric ratio was low (3:1 dr). The minor diastereomer generated in this process has a high enantiomeric excess (91%) and the major isomer has a comparably lower ee (73%). Interestingly, cycloheptanone reacted under these conditions to afford a Michael adduct with an excellent dr (30:1) but almost no enantioselectivity (data not shown).

Structural variation in the α,β-unsaturated ketones was found to be tolerated in Michael addition reactions catalyzed by **II** (Table 3).[14] Excellent levels ($\geq$90% ee) of enantioselectivity and diastereomeric ratios (>50:1 in all cases) were observed for reactions of α,β-unsaturated ketones containing different aromatic substituents (Ar^1), including carbocyclic (entries 1–7) and hetereocyclic groups (entry 8). The organocatalyst **II**-promoted processes were successful with aromatic systems (Ar^2) possessing electron-withdrawing (entries 5 and 7), electron-donating (entry 6) and hetereocyclic functionalities (entry 8). The absolute configuration of **3b** (entry 5) was determined by using X-ray crystallography to be 2*S*, 1′*R* (Figure 2).[15]

A possible model **A** to rationalize the high levels of enantio- and diastereoselectivity of Michael addition reactions of cyclic ketones with unsaturated ketone is shown in Figure 3. As is the case for L-proline catalyzed processes,[8g,15] the NH proton in **II** can provide transi-

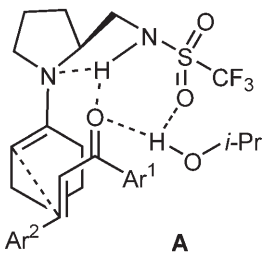
Table 3. Catalytic asymmetric Michael addition reactions of cyclohexanone **1a** with chalcone **2**.[a]



1a **2** **3**

Entry	Ar^1	Ar^2	t [days])	Yield [%][b]	dr[c]	% ee[d]
1	4-ClC_6H_4	Ph	4	80	>50:1	90
2	2-ClC_6H_4	Ph	4	78	>50:1	91
3	4-$NO_2C_6H_4$	Ph	4	87	>50:1	92
4	Ph	Ph	5	79	>50:1	92
5	Ph (**3b**)	4-ClC_6H_4	3.5	82	>50:1	94
6	Ph	4-$MeOC_6H_4$	6	63 (88)[e]	>50:1	90
7	4-FC_6H_4	4-FC_6H_4	4	84	>50:1	92
8	2-thiophene	2-thiophene	6	65 (93)[e]	>50:1	90

[a] *Reaction conditions:* see Experimental Section and Supporting Information.
[b] Yields of isolated products.
[c] Determined by ^1H NMR.
[d] Determined by chiral HPLC analysis (Chiralpak AS-H).
[e] Yields based on recovered starting material.



A

Figure 3. Proposed transition state **A**.

tion state stabilization through a hydrogen bonding interaction with the chalcone carbonyl group. In addition, the CF_3SO_2 group in **II** might participate in an additional H-bonding interaction with the carbonyl group by solvent *i*-PrOH, thus synergistically bringing about a tighter transition state and higher stereoselectivities. Moreover, in a manner similar to the more bulky prolinediamine **III** (Table 1, entry 5) and pyrrolidinetetrazole,[16] the higher levels of enantioselectivity associated with the reactions catalyzed by **II** are likely caused by the big CF_3SO_2 group, which leads to a higher facial preference for the approaching enone.

In summary, we have developed a new organocatalytic, direct Michael addition reaction of ketones with chalcones. This process, catalyzed by (*S*)-pyrrolidinesulfonamide **II**, is carried out under mild reaction conditions to afford synthetically useful 1,5-dicarbonyl compounds in high yields and with high to excellent levels of enantio- and diastereoselectivity. Further investigations of the mechanistic features, scope and synthetic applications of this valuable reaction are underway.

Experimental Section

Typical Procedure

Catalyst **II** (1.0 mg, 0.0017 mmol) was added to a vial containing cyclohexanone (**1a**; 0.23 mL, 2.19 mmol) and (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**2a**; 53 mg, 0.22 mmol) in *i*-PrOH (1 mL) at room temperature. After 4 days of stirring, the reaction mixture was concentrated under vacuum. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane, 1:20 to 1:10) to afford the adduct as a white solid; yield: 60 mg (80%; 50:1 dr (determined by ^1H NMR) and 90% ee; Chiralpak AS-H column (*i*-PrOH/hexane = 10/90, flow rate 0.7 mL/min, $\lambda = 254$ nm): $t_R =$ 19.5 min (minor) and 31.1 min (major); $[\alpha]_D$ (major): -48.3 (*c* 1.7, $CHCl_3$).

Acknowledgements

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[12] Other solvents were also screened: DMSO: 2 days (reaction time), 25% yield, 88% ee, 50:1 dr; in 1,4-dioxane, CH_3CN, THF or Et_2O, no reactions were observed.

[13] Acyclic ketones were also evaluated including acetone, 3-pentanone, and acetophenone, unfortunately no reaction occurred. Isovaleraldehyde (1 equiv.) was also tested in an initial study with 4′-chlorochalcone (3 equivs.) and afforded an adduct in 22% yield, 50:1 dr, 52% ee using 20 mol % **II** in DMSO/*i*-PrOH (1/1) at room temperature for 4 d.

[14] No reaction was observed for benzylideneacetone probably due to its less reactivity than chalcones.

[15] CCDC-281557 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk.

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