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Catalytic enantioselective direct Michael additions of ketones to alkylidene malonates†

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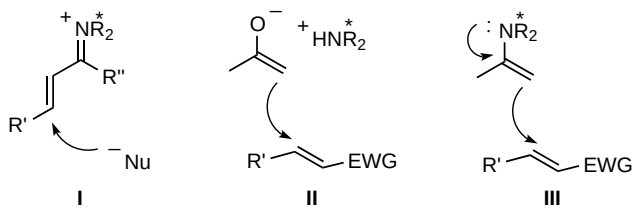
Abstract—Enantioselective direct Michael additions of ketones using (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as a catalyst are described. Michael adducts with up to 91% e.e. were obtained by the reaction of alkylidene malonates with simple unactivated ketones under mild reaction conditions.

An increasing demand for optically active compounds has stimulated the development of catalytic asymmetric bond-forming reactions.[1] Of the carbon–carbon bond forming reactions, the enantioselective Michael reaction has been one of the most studied in synthetic organic chemistry.[2] Typically, carbon nucleophiles that contain an active methylene center such as malonic acid esters, β-keto esters, nitroalkanes, etc. have been studied.[3] Ketones, however, while they are versatile carbon nucleophiles, have generally been used as donors only following their pre-activation by conversion into highly reactive enol or enamine equivalents.[4] In these cases, additional synthetic step(s), stoichiometric amounts of base, additional reagents (silylating agents to form the enol silyl ether or chiral amines to form the enamine derivative) or chiral ligands are required. A potentially more promising strategy would involve catalysis of direct additions of unmodified ketones to Michael-type acceptors. The development of catalytic asymmetric variants of this process would provide access to optically enriched 1,5-dicarbonyl synthons.

As part of our ongoing program directed towards identifying small organic molecules as catalysts of asymmetric reactions, we explore here the direct addition of ketones through an enamine-type mechanism to Michael-type acceptors. Chiral amines have been used previously in catalytic asymmetric Michael additions,[5] serving either to activate the Michael donor via formation of an iminium species (I, Scheme 1),[3c,3d] or as bases where a complex formed between the amine and the enolate react with the acceptor (II, Scheme 1).[6] A third mechanism could involve transient activation ketone donors through formation of an enamine intermediate (III, Scheme 1). Herein we wish to report our preliminary studies concerning enantioselective direct Michael additions of ketone donors catalyzed by chiral amines that operate using an enamine mechanism.

Our previous studies had identified L-proline as a catalyst of direct asymmetric aldol reactions, Mannich reactions, and Robinson annulations.[7] As a model transformation we studied the proline-catalyzed Michael addition of acetone to diethyl benzalmalonate in DMSO. The Michael adduct was isolated albeit in racemic form and together with (*E*)-$PhCHCHCOCH_3$ as a byproduct. In order to achieve enantioselectivity, we screened a variety of chiral amines as catalysts of the reaction.[8] When (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine was studied as a catalyst of the same reaction we found that the addition product was formed exclusively



Scheme 1. Mechanisms for amine-catalyzed Michael reactions.

Keywords: asymmetric catalyst; asymmetric synthesis; Michael reaction.

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† Dedicated to Professor K. Barry Sharpless, a pioneer in asymmetric catalysis, on the occasion of his 60th birthday.

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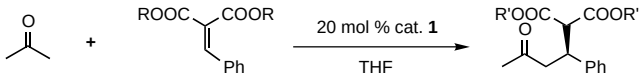
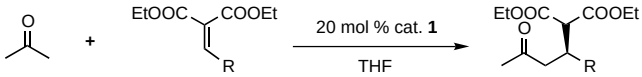
Table 1. Ester substituent effect on the Michael reaction



Entry	R	Yield[a]	E.e.[b]	Configuration
1	Me	55 (84)	56	*S*
2	Et	47 (89)	59	*S*
3	^{i}Pr	22 (87)	61	*S*

[a] Isolated yield after column chromatography, values in brackets refer to yields based on conversion.
[b] Enantioselectivities were determined by chiral-phase HPLC analysis in comparison with authentic racemic material using a Chiralcel AD column (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents.

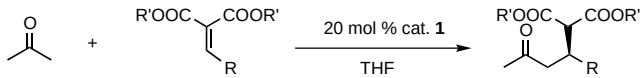
Table 2. Effect of temperature on the Michael reaction



Entry	R	E.e. % (yield %)[a,b]		
		25°C	4°C	−25°C
1	Ph	59 (47)	69 (16)	72 (5)
2	1-Naphthyl	64 (31)	76 (21)	84 (5)
3	2-CF_3Ph	70 (46)	80 (46)	91 (14)

[a] Enantioselectivities were determined by chiral-phase HPLC analysis in comparison with authentic racemic material using a Chiralcel AD column (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents.
[b] Isolated yield after column chromatography.

Table 3. Effect of the β-substituents on the malonates



Entry	R	R′	Yield[a]	E.e.[b]
1	Ph	Et	47 (89)	59
2	1-Naphthyl	Et	31 (72)	64
3	2-Naphthyl	Et	60 (84)	55
4	2-Tolyl	Et	17 (86)	70
5	2-CF_3Ph	Et	46 (94)	70
6	2-Furyl	Et	84 (91)	33
7	*n*-Pentyl	Bn	16 (23)	24
8	Cyclohexyl	Bn	27 (42)	14
9	^{i}Pr	Bn	16 (28)	17

[a] Isolated yield after column chromatography; values in brackets refer to yields based on conversion.
[b] Enantioselectivities were determined by chiral-phase HPLC analysis in comparison with authentic racemic material using a Chiralcel AD column (Daicel Chemical Industries, Ltd.) with hexane/2-propanol mixtures as eluents.

in 41% yield and 47% e.e. Screening of diverse solvents allowed us to further improve both yield and enantioselectivity. Use of THF as the solvent provided the product in 47% yield with 59% e.e.[9] Even though the yield and enantioselectivity of this reaction is moderate, the result is encouraging since the catalytic direct addition of unfunctionalized unactivated ketones to Michael acceptors has not, to the best of our knowledge, been reported in the literature.

With optimal catalyst and solvent conditions established, we studied other factors that might effect selectivities. To study the influence of the ester moiety of the Michael acceptors, a number of benzylidene malonates were synthesized. When these substrates were reacted with acetone under optimal conditions, the corresponding addition products were isolated (Table 1). Configurations of the products were determined following their conversion into mono-methyl esters.[10] Increasing the size of the alkyl group provided only a modest enhancement of the enantioselectivity.

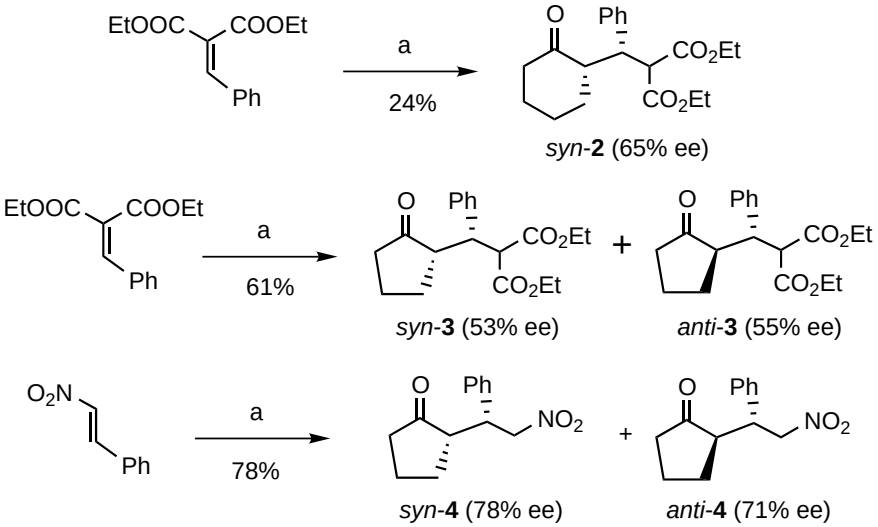
A temperature dependence study of the reaction revealed ascending selectivity with descending temperature (Table 2). However, lower temperatures compromised the yield of the reaction.

A variety of alkylidene malonates were then evaluated as substrates.[11] Aromatic substituents such as phenyl, 1-naphthyl, 2-naphthyl, 2-tolyl and 2-trifluoromethylphenyl provided good selectivities with *ortho* substitution on the aromatic ring giving better results (entries 1–5, Table 3). 2-Furyl substitution gave a higher yield of the addition product, but with low selectivity (entry 6, Table 3). Alkyl substrates also gave Michael adducts but in low yield and enantioselectivities (entries 7–9, Table 3).[12] This particular type of Michael acceptor turned out to be unstable in the reaction conditions yielding significant amounts of the malonate and the corresponding aldehyde (retro-Knoevenagel).

Cyclic ketones can also be used as nucleophiles (Scheme 2). Cyclohexanone reacts with diethylbenzalmalonate to furnish *syn*-**2** with a dr >20:1 and 65% e.e. in 24% yield.[13] Cyclopentanone provided two readily separable diastereomers, *syn*-**3** and *anti*-**3** in 55% and 6% yield with 53% and 55% e.e., respectively. This ketone also reacts smoothly with *trans*-β-nitrostyrene, as a Michael acceptor, to furnish a 4:1 mixture of *syn* and *anti* diastereomers in 78% yield. The major isomer, *syn*-**4**, was formed in 78% e.e. and the minor isomer, *anti*-**4**, in 71% e.e.[14,15]

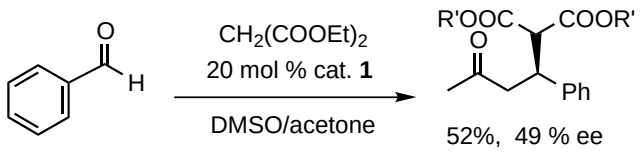
Though further studies are needed to firmly elucidate the mechanism of this Michael addition, we currently speculate that it follows an enamine mechanism analogous to our amine-catalyzed aldol and Mannich reactions.[7] Consistent with the observed stereochemistries, the preferred reaction pathway involves attack of the *re*-face of the acetone enamine on the *re*-face of the malonate derivative.

The potential of this methodology can be further extended if we consider that the (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine can also catalyze the Knoevenagel reaction used to synthesize the alkylidene malonates. Following this proposal, we have carried out the one-



[a] Cat. 1 (20 mol%), cyclopentanone (cyclohexanone)/THF (1:4), r.t.

Scheme 2. Michael reactions of cyclic ketones.



Scheme 3. One-pot Knoevenagel and Michael additions.

pot sequence that directly converts an aldehyde into the final Michael adduct (Scheme 3) via amine catalysis of both steps.

In summary, we have presented enantioselective Michael reactions catalyzed by a small organic molecule ((*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine) as an alternative to metal-based catalysts that operate via pre-activated ketone equivalents. In our approach, ketones (acting as donors) can be used without prior modification. Though both yields and enantioselectivities are moderate, further studies should improve these results and extend this novel methodology to a wider range of substrates.

Acknowledgements

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8. (*S*)-2-(Anilinomethyl)pyrrolidine: <10% yield, 51% e.e.; (2*S*,4*S*)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine: <10% yield, 42% e.e.. L-5,5-Dimethylthiazolidine-4-carboxylic acid: no reaction.
9. Dioxane, 1,2-dichloroethane <5% yield; DMF, AcOEt, $CHCl_3$, 15–25% yield. Acetone, DMSO, THF >40%.

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11. Typical procedure for the Michael addition: To a solution of diethyl benzalmalonate (62 mg, 0.25 mmol) in a mixture of THF (2 mL) and acetone (0.5 mL) was added (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine (8.5 μL, 20% mol). The reaction was stirred at room temperature for 4 days. Then, the solution was diluted with CH_2Cl_2 (5 mL) and treated with 1N HCl (4 mL) with vigorous stirring. The layers were separated and the aqueous phase was extracted thoroughly with CH_2Cl_2 (3×2 mL). The combined organic phases were dried ($MgSO_4$), concentrated and purified by flash column chromatography on silica gel affording the Michael adduct in 47% yield (36 mg, 0.12 mmol).
12. In this case we opted for the preparation of the dibenzyl derivatives since the aryl group provided a better chromophore for chiral-phase HPLC determination of the enantiomeric excess.
13. For the configuration assignments, see: Ref. 4d.
14. The relative and absolute configuration of compounds **3** and **4** has been assigned by assumption of an identical reaction pathway to that followed with cyclohexanone and from common characteristic NMR patterns with related known compounds, see: Ref. 4d and: Seebach, D.; Lyapkalo; Dahinden, R. *Helv. Chim. Acta* **1999**, *82*, 1829–1842.
15. L-Proline as catalyst furnished **4** in 88% yield as a 5:1 *syn*/*anti* mixture in 29 and 52% e.e., respectively.