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Enantioselective Michael Reaction of α-Alkyl-β-keto Esters and Enones under Multifunctional Catalysis

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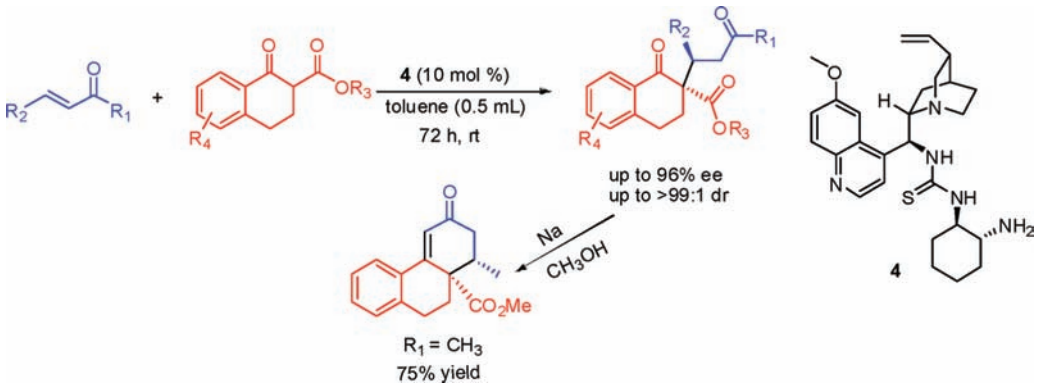
ABSTRACT



An efficient approach for the enantioselective Michael additions of β-alkyl-β-keto esters to β-substituted α,β-unsaturated ketones has been developed. The Michael products could be obtained in good to excellent yields (75−98%) with excellent diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to 96% ee) and could easily be transformed into a synthetically useful hexahydrophenanthrene structure under mild conditions in good yield.

Of those common methods for construction of valuable compounds in modern organic synthesis, the Michael addition has been the most fascinating and powerful one,[1] whose product might also be a key intermediate for further transformations such as the Robinson annulation reaction affording a variety of substituted cyclohexenones.[2] Therefore, the asymmetric version has been increasingly attractive to most scientists either in natural product preparations or in enantioselective organic synthetic methodologies.[3] The past few decades have witnessed a tremendous development of various efficient methodologies for asymmetric synthesis involving enzyme catalysis, organometallic catalysis, and more recently, organic catalysis.[4] Among those powerful approaches for enantioselective catalysis, the asymmetric organocatalytic synthesis has been one of the most outstanding methods mainly due to its high efficiency, low toxicity, and ready availability.[5] Up until now, great efforts have been made in this field, and remarkable progress has been achieved in both aldehyde and ketone activations through certain catalytic modes such as iminium, enamine, and SOMO activation.[6] Nevertheless, compared with the magnificent achievements in asymmetric aldehyde activation,[7] the organo-catalytic Michael addition involving α,β-unsaturated ketone, whose reactivity is generally weak, remains a

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challenging task, and the control of stereoselectivity is another formidable issue for this transformation. Moreover, the formation of an all-carbon chiral center and a simultaneous construction of a vicinal chiral tertiary carbon center with complete stereocontrol would certainly add to those difficulties greatly.[8] During the past couple of years, α-alkyl-β-keto esters have been applied frequently in such transformations with a variety of conjugate electrophilic Michael acceptors to conquer those difficulties involving both organic and organometallic catalysts,[9] and of course, a number of investigations of the Michael addition of β-keto esters with different vinyl ketones had also been implemented.

For example, Hermann and Wynberg reported a seminal work on the enantioselective conjugate additions of β-keto esters to methyl vinyl ketone using natural cinchona alkaloid as catalyst,[10] and the highly enantioselective conjugate addition reaction of β-keto esters with methyl vinyl ketone had been disclosed by Sasai and Shibasaki.[11] Moreover, there were also excellent reports employing chiral organometallic catalysts such as scandium(III) catalysts,[12] palladium catalysts,[13] and ruthenium catalysts,[14] as well as the phase transfer catalysis reported by Maruoka and co-workers.[15] More recently, an efficient cinchona alkaloid catalyst which has been developed by Deng and co-workers also represented an outstanding work in this transformation.[16]

Although the asymmetric conjugate addition of β-keto esters to methyl vinyl ketone catalyzed by a variety of chiral Lewis base, Lewis acid, Brønsted base, and Brønsted acid has been reported, asymmetric conjugate addition of α-alkyl-β-keto esters to β-substituted α,β-unsaturated ketones still remains a challenge due to the above-mentioned difficulties and is definitely worthy

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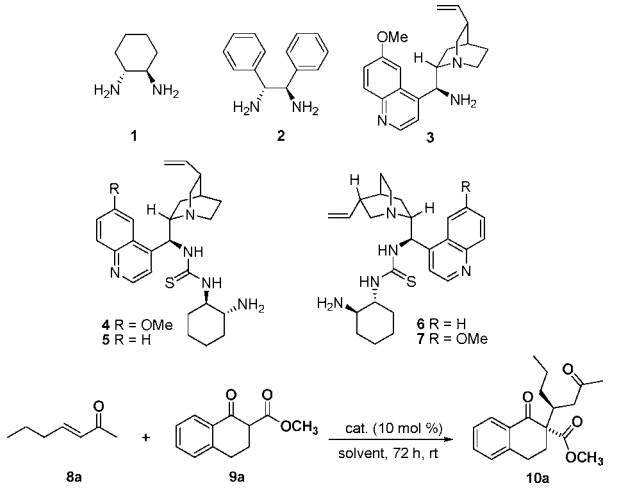
of our best effort to overcome those barriers. Herein, we report our new development of the enantioselective Michael addition of α-alkyl-*β*-keto esters to *β*-substituted α,*β*-unsaturated ketones under multifunctional catalysis with excellent diastereo- and enantioselectivities, and the products could also be easily transformed into synthetically useful chiral cyclohexenones through the Robinson annulation.

The reaction of **8a** and **9a** was first investigated as the model reaction, and optimizations of catalyst and solvent were carried out, whose representative results were shown in Table 1. A variety of chiral primary amine catalysts were tested in this transformation, and a high diastereoselectivity of 90/10 was obtained when (1*R*,2*R*)-diaminocyclohexane **1** was used as catalyst, but with very low enantioselectivity of 22% (Table 1, entry 1). However, moderate enantioselectivity of 47% and diastereoselectivity of 68/32 were obtained using (1*R*,2*R*)-diphenylethylene-1,2-diamine **2** as catalyst (entry 2). Increasingly, when 9-amino (9-deoxy) epiquinine **3** was used as catalyst, 87/13 dr and 77% ee were achieved (entry 3). Acidic additives, such as trifluoroacetic acid, decreased both diastereo- and enantioselectivity (entry 4). To our great delight, when multifunctional catalysts were used, both the diastereo- and enantioselectivity improved (entries 5−8). After a series of attempts, catalyst **4** was found to be the best one. Examination of solvent effects found that toluene, ethyl acetate, acetonitrile, and THF were all good solvents for this Michael reaction (entries 9−18). Finally, the result proved best when using catalyst 4 in toluene with a concentration of 1.0 M based on **8a** at ambient temperature (entry 19).

Under the optimized conditions, we next explored the scope of the asymmetric Michael addition of α-alkyl-*β*-keto esters to *β*-substituted α,*β*-unsaturated ketones. Experimental data showed that the reaction proceeded very well with a variety of alkyl vinyl ketones, and the substituents on the α-alkyl-*β*-keto esters had little effect on the results. All these Michael products were obtained in good to excellent yields and high diastereoselectivities with excellent ee values (Table

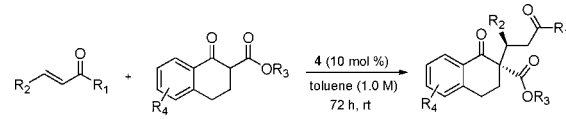
Table 1. Primary Screening Results[a]



entry	cat.	solvent	conv %[b]	dr[c]	ee %[d]
1	**1**	DCM	65	90:10	22
2	**2**	DCM	6	68:32	47
3	**3**	DCM	5	87:13	−77
4[e]	**3**	DCM	15	77:33	51
5	**4**	DCM	88	99:1	90
6	**5**	DCM	76	97:3	92
7	**6**	DCM	41	95:5	86
8	**7**	DCM	38	84:16	90
9	**4**	toluene	93	97:3	91
10	**4**	EtOAc	97	94:6	91
11	**4**	CH_3CN	90	84:16	90
12	**4**	DMF	60	86:14	86
13	**4**	DMSO	52	37:63	75
14	**4**	$CHCl_3$	92	96:4	85
15	**4**	MTBE	96	96:4	86
16	**4**	THF	85	94:6	94
17	**4**	Et_2O	97	97:3	85
18	**4**	MeOH	73	92:8	51
19[f]	**4**	toluene	95[g]	98:2	93

[a] All reactions were carried out using 1.0 equiv of **8a** (0.10 mmol, 0.5 M), 2.0 equiv of **9a**, and 0.10 equiv of catalyst. [b] Conversion was determined by GC. [c] Diastereoselectivity was determined by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC. [e] With 10 mol % of CF_3CO_2H as additive. [f] The reaction was carried out using 1.0 M of **8a**. [g] Isolated yield of the final product.

Table 2. Expanding the Scope of the Asymmetric Michael Additions of α-Alkyl-*β*-keto Esters to *β*-Substituted α,*β*-Unsaturated Ketones[a]



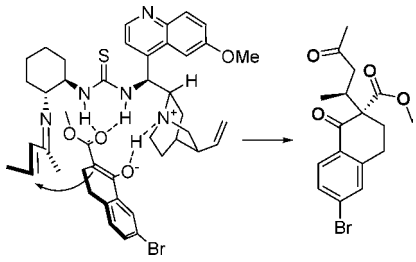
entry	R_1	R_2	R_3	R_4	yield %[b]	dr[c]	ee %[d,e]
1	Me	*n*-Pr	Me	H	95, **10a**	98:2	94
2	Me	Me	Me	H	82, **10b**	99:1	95
3	Me	*n*-Bu	Me	H	86, **10c**	98:2	96
4	Me	*n*-Pen	Me	H	97, **10d**	98:2	91
5	Me	*n*-Hex	Me	H	97, **10e**	98:2	96
6	Me	Me	Et	H	95, **10f**	99:1	95
7	Me	*n*-Hex	Et	H	93, **10g**	98:2	93
8	Et	Me	Me	H	95, **10h**	99:1	96
9	*n*-Bu	Me	Me	H	80, **10i**	98:2	95
10	Me	*n*-Pen	Me	7-OMe	92, **10j**	98:2	92
11	Me	*n*-Bu	Me	7-OMe	82, **10k**	98:2	97
12	Me	Me	Me	6-OMe	92, **10l**	97:3	93
13	Me	*n*-Hex	Me	6-OMe	90, **10m**	98:2	93
14	Me	*n*-Bu	Me	6-Br	85, **10n**	97:3	93
15	Me	*n*-Pr	Me	6-Br	87, **10o**	98:2	92
16	Me	*n*-Pen	Me	6-Cl	92, **10p**	98:2	87
17	Et	Me	Me	6-Cl	93, **10q**	>99:1	95
18	Me	*i*-Bu	Me	H	75, **10r**	>99:1	86
19	Me	$(CH_2)_2Ph$	Me	H	95, **10s**	>99:1	91
20	Et	Me	Me	6-Br	89, **10t**	>99:1	93
21	*n*-Bu	Me	Me	6-Cl	75, **10u**	>99:1	92
22[f]	Ph	Me	Me	H	85, **10v**	77:23	15 (82)
23	$-(CH_2)_3-$		Me	Me	98, **10w**	57:43	65 (82)
24	$-(CH_2)_4-$		Me	Me	90, **10x**	60:40	94 (92)

[a] All reactions were carried out using 1.0 equiv of **8** (0.50 mmol, 1.0 M), 2.0 equiv of **9**, and 0.10 equiv of **4**. [b] Isolated yield of both diastereoisomers. [c] Diastereoselectivity was determined by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess of the major diastereoisomer, determined by chiral HPLC. [e] The value in parentheses was enantiomeric excess of the minor diastereoisomer, determined by chiral HPLC. [f] 30 mol % of **4** was used.

2, entries 1−21). Notably, several cyclic vinyl ketones also participate well in this reaction, and the products could be gathered as a mixture of two diastereoisomers in excellent yields with moderate to excellent enantiomeric excesses, albeit with generally moderate diastereoselectivities (entries 23−24). However, only a moderate ee value could be observed when benzylideneacetone was employed as the electrophilic reagent, and the corresponding product was collected as a mixture of two diastereoismers with a 77:23 ratio in 85% yield (entry 22). What's more, no reactions occurred when the more bulky Michael acceptors such as chalcones were used as the electrophilic reactant.

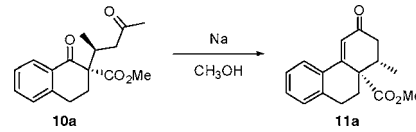
The absolute configuration of the Michael product **10t** was determined by single-crystal X-ray analysis.[17] This result prompted us to assume a possible process for the asymmetric Michael addition based on our previous works,[18] as summarized in Scheme 1.

Scheme 1. Assuming Process of the Asymmetric Michael Addition



Having successfully extended the scope of the Michael addition with a wide range of substrates, we also were eager to apply this approach in some useful synthetic transformations. As shown in Scheme 2, a Robinson annulation could easily be promoted by use of sodium in methanol,[19] and the corresponding hexahydrophenanthrene derivative could be obtained in 75% yield as a white solid.

Scheme 2. Robinson Annulation of **10a**



In conclusion, we have developed an efficient approach for the enantioselective Michael additions of α-alkyl-β-keto esters to β-substituted α,β-unsaturated ketones with excellent diastereo- and enantioselectivities, and the product could easily be transformed into synthetically useful hexahydrophenanthrene structure under mild conditions in good yield. Further applications of this methodology are currently well under way and will be published soon.

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Supporting Information Available: Experimental procedures, structural proofs, NMR spectra, and HPLC chromatograms of the products and cif file of enantiopure **10t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For more details, see Supporting Information.

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