Organocatalytic Enantioselective Michael Additions of Malonates to 2-Cyclopentenone

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Abstract: The Michael reaction of a dialkyl malonate to a cyclic enone using a chiral diamine/acid combination catalyst gave the desired Michael adduct in high yield with excellent enantiomeric excess in a protic solvent such as methanol and ethanol. The methanol molecule participates in a proton relay system in which the dialkyl malonate is activated through hydrogen bonding to afford the Michael adduct with excellent enantioselectivity.

Key words: enone, malonate, Michael addition, organocatalysis, proton relay

The organocatalytic asymmetric Michael reaction via an iminium intermediate is a key transformation in organic synthesis. In recent years, many chiral organocatalysts have been developed that exhibit high reactivities and stereoselectivities for this fundamental transformation.[1] β-Chiral cyclic alkanones are common structures in natural products. One of the best ways to construct this skeleton is through the asymmetric Michael addition of a nucleophile to α,β-unsaturated cycloalkanones. In particular, iminium catalysis has been intensively studied due to its high versatility, adaptability, and stereoselectivity.[2,3] Although malonate nucleophiles are valuable in modern organic synthesis, the Michael addition of a malonate nucleophile to cyclic enones via iminium catalysis is considered a worthwhile subject in asymmetric synthesis[4,5,6] and its addition to 2-cyclopentenone is an especially challenging topic in organocatalysis.[7] There are two likely reasons for this difficulty. The first is that the conformational control of an iminium intermediate **2** derived from 2-cyclopentenone is more difficult than that from acyclic enone **1**. Calculations of the energy difference between acyclic iminium intermediate **1A** and **1B** optimized at the HF/6-31G(d) level of theory using the GAMESS program package[8] showed that the intermediate **1A** is relatively preferred over **1B** due to steric repulsion (R^1 = *t*Bu, R^2 = H, ΔE = 2.6 kcal/mol).[9] On the other hand, in a cyclic system, no clear energy difference between **2A** and **2B** is observed (R^1 = *t*Bu, ΔE = 0.8 kcal/mol, Figure 1). The second reason is that the activation of a less reactive malonate is required for the Michael reaction with the iminium intermediate. Since an activating interaction between the catalyst and the malonate donor through acid or base functionality should be formed, the reactive site of the acyclic iminium intermediate **3** is three-dimensionally different from that of the cyclic iminium intermediate **4**. Thus, it is difficult to achieve excellent stereoselectivity in both acyclic *trans*-acceptors and cyclic *cis*-acceptors. As detailed in this communication, we investigated the direct Michael reaction of malonate donors with 2-cyclopentenone acceptor using a chiral diamine/acid combination catalyst in a protic solvent in which the malonate was activated through hydrogen bonding to afford the Michael adduct with excellent enantioselectivity.

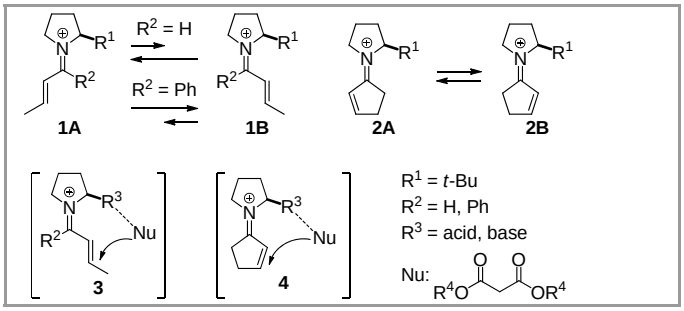


Figure 1. Michael addition of malonates to cyclic and acyclic enones

First we examined amine catalysts **5**-**13** (Figure 2) for the Michael reaction of dibenzyl malonate (**15a**) and 2-cyclopentenone (**14a**) to afford the Michael product **16a**. The results are shown in Table 1. When pyrrolidine (**5**) was used as the catalyst, the desired product **16a** was obtained in 46% isolated yield (Entry 1). The reaction with L-proline (**6**) or (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**7**) did not proceed (Entries 2 and 3). Diarylprolinol silyl ether **8** and imidazolidinone **9** have been successfully used as iminium catalysts,[10] however, these catalysts did not yield the Michael adduct **16a** at all (Entries 4 and 5). L-Prolinol (**10**) was a good catalyst providing the desired product **16a** in quantitative yield but with no enantioselectivity (entry 6). Similarly, (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine (**11**) afforded the adduct **16a** in 87% yield in racemic form (Entry 7).[11] In contrast, the diamine/TFA combination catalyst **12**[12,13] improved the enantioselectivity up to 58% ee (Entry 7 vs. Entry 8). The tetrazole catalyst **13** also gave the adduct **16a** with 49% ee, but the reaction was slow and the yield was low (Entry 9).

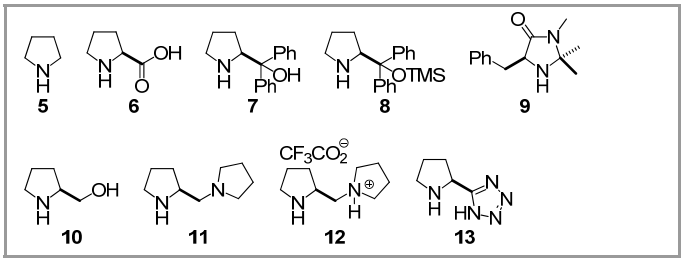
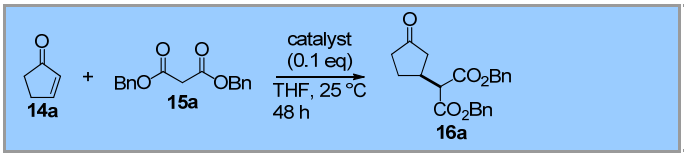


Figure 2. Various amine catalysts

Table 1 Michael addition of **15a** to **14a**[a]

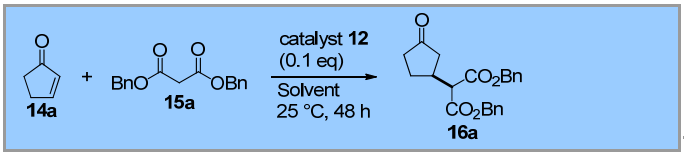


Entry	Catalyst	Conv. (%)[b]	Yield (%)[c]	Ee (%)[d]
1	**5**	67	46	-
2	**6**	NR[e]	-	-
3	**7**	NR[e]	-	-
4	**8**	NR[e]	-	-
5	**9**	NR[e]	-	-
6	**10**	99	98	0
7	**11**	95	87	0
8	**12**	39	30	58
9	**13**	10	8	49

[a] Reactions were carried out using **14a** (0.5 mmol), **15a** (0.6 mmol, 1.2 eq), and catalyst (0.05 mmol, 0.1 eq) in THF (0.5 mL) at 25 °C for 48 h.
[b] Determined by GC analysis.
[c] Isolated yield.
[d] Determined by chiral-phase HPLC analysis.
[e] NR = no reaction.

Using catalyst **12**, a series of different solvent systems was evaluated as shown in Table 2. Non-polar solvents, such as toluene and $CHCl_3$, were inferior in terms of their product yield (Entries 2 and 3). Aprotic polar solvents such as DMSO and DMF showed better yield with moderate enantioselectivities (Entries 4 and 5). The Michael addition was prevented in protic polar acetic acid (Entry 6). Interestingly, protic polar alcoholic solvents improved the chemical yield as well as the enantioselectivity (Entries 7-10); in particular, methanol gave the highest chemical yield and enantiomeric excess of the solvents tested (Entry 10). Excellent enantioselectivity in the Michael reaction of less reactive malonate to 2-cyclopentenone (**14a**) was achieved by simple diamine catalyst **12**.

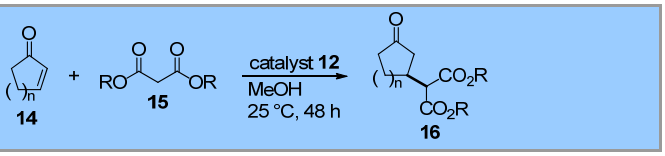
Table 2 Screening of various solvents in Michael addition of **15a** to **14a**[a]



Entry	Solvent	Conv. (%)[b]	Yield (%)[c]	Ee (%)[d]
1	THF	39	30	58
2	toluene	30	30	64
3	$CHCl_3$	19	18	64
4	DMSO	66	56	67
5	DMF	75	70	46
6	AcOH	NR[e]	-	-
7	*t*-BuOH	29	27	76
8	2-PrOH	70	69	81
9	EtOH	75	74	85
10	MeOH	99	98	94

[a, b, c, d, e] See footnotes in Table 1.

Table 3 Michael addition of various donors **15** to cyclic enones **14**[a]



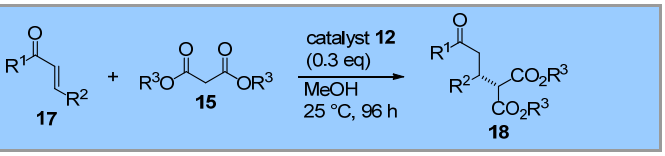
Entry	n	R	Conv. (%)[b]	Yield (%)[c]	Ee (%)[d]	Product
1	1	Bn	99	98	94	**16a**
2[e]	1	Me	80	75	>95[g]	**16b**
3[e]	1	Et	51	46	>95[g]	**16c**
4[e]	1	*i*-Pr	40	36	>95[g]	**16d**
5[e]	1	*t*-Bu	28	23	>95[g]	**16e**
6	2	Bn	99	95	87	**16f**
7[e,f]	3	Bn	40	35	69	**16g**

[a, b, c, d] See footnotes in Table 1.
[e] Donor (2 eq) and catalyst (0.3 eq) were used.
[f] Reaction was carried out for 96 h.
[g] Determined by ^{13}C NMR after transformation to chiral aminals.

Encouraged by these results, we further examined the scope of this class of Michael reaction with a series of malonate donors **15** and cycloalkenone acceptors **14** using catalyst **12** under the same reaction conditions (Table 3).[14] High enantioselectivities were observed in the Michael addition to cyclopentenone acceptor **14a**. Substituents on malonate donor did not affect the enantioselectivity (>95% ee), but decreasing reactivity as a bulkier substituent was used (Entries 1-5). 2-Cyclohexenone (**14b**) was also a good acceptor: the reaction provided the Michael product **16f** in excellent yield in 48 hours with 87% ee (Entry 6), while the reaction of 2-cycloheptanone (**14c**) afforded the adduct **16g** in 35% yield with 69% ee after 96 hours of stirring (Entry 7).

Next, we probed the scope of the reaction with a variety of acyclic *trans*-acceptors **17** and malonates **15** (Table 4). Benzalacetone (**17a**) was suitable as a Michael acceptor, providing high yield and enantioselectivity (Table 4, Entry 1). Chalcone (**17b**) was a poor acceptor to give the adduct **18b** in low yield with 80% ee (Entry 2). Aliphatic 3-nonen-2-one (**17c**) was a moderate acceptor, furnishing the product **18c** with good enantioselectivity (Entry 3).

Table 4 Michael addition of **15** to acyclic acceptors **17**[a]



Entry	R^1	R^2	R^3	Conv. (%)[b]	Yield (%)[c]	Ee (%)[d]	Product
1	Me	Ph	Me	98	97	71	**18a**
2	Ph	Ph	Me	10	9	80	**18b**
3	Me	C_5H_{11}	Bn	60	40	80	**18c**

[a] Reactions were carried out using **17** (0.5 mmol), **15** (1.0 mmol, 2.0 eq), and catalyst **12** (0.15 mmol, 0.3 eq) in MeOH (0.5 mL) at 25 °C for 96 h.
[b] Determined by GC and/or HPLC analysis.
[c] Isolated yield.
[d] Determined by chiral-phase HPLC analysis.

The major cyclic Michael product **16a** was determined to have an (*S*)-configuration by comparison with the reported optical rotation value of **16a** ($[\alpha]^{26}_D$ = -49.4° (*c* 1.00, $CHCl_3$), lit.) $[\alpha]^{24}_D$ = -35.1° (*c* 1.33, $CHCl_3$, 92% ee)).[6a] This result shows a *si*-facial attack of a malonate nucleophile on the iminium intermediate derived from the cyclic enone **14a** (Figure 3). On the other hand, the major acyclic Michael product **18** has (*R*)-configuration by comparison with the reported HPLC data,[7] thus, *re*-facial attack is preferred with acyclic *trans*-acceptors **17**.

For a better understanding of the mechanism of this Michael addition, the transition state was computationally calculated. The methanol molecule plays an important role in reactivity as well as in enantioselectivity, as described above. We proposed the following set of transition states: (1) direct addition of the nucleophile (**TS-1**), (2) direct activation of the nucleophile by the catalyst (**TS-2**), and (3) proton relay activation system (**TS-3**).[15] These transition states were initially optimized at the PM3 level of theory and further optimized at the HF/6-31G(d) level of theory using the GAMESS program package. Results are shown in Figure 3. The difference in the relative energies of the transition states shows that **TS-3** is preferred to **TS-1** and **TS-2**. Two intermolecular bondings and one intramolecular hydrogen bonding in **TS-3** form a proton relay system to activate the malonate nucleophile. It is noted that catalyst **12** could not activate the nucleophile well in a direct way, but, with the aid of the methanol molecule, it could indirectly catalyze the Michael reaction. This flexible catalysis system probably gives rise to good-to-excellent enantioselectivities in the Michael addition to both cyclic cis-acceptors and acyclic trans-acceptors.

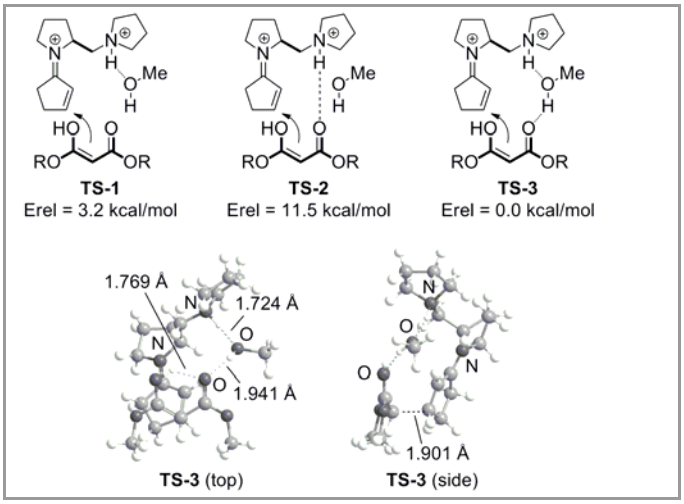
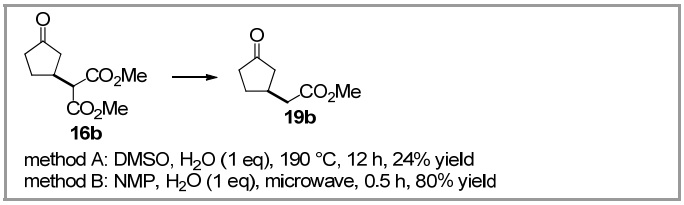


Figure 3. Proposed transition state through a proton relay system

Finally, we examined the decarboxylation of the Michael product **16b** as shown in Scheme 1. The usual heating condition[16] was not effective, giving the decarboxylated product **19b** in low yield (Method A). Currans's procedure using microwave irradiation was employed for the decarboxylation of our compound **16b**.[17] N-Methylpyrrolidone was the most effective solvent, affording the ketone **19b** in good yield after 30 min with no loss of enantioselectivity (Method B).[18] This β-chiral cyclopentanone derivative **19b** are useful intermediates in methyl jasmonate syntheses.[19]



Scheme 1. Decarboxylation of the Michael product **16b**

In summary, we have developed direct access to β-chiral cyclopentanone possessing malonate functionality. The diamine bifunctional catalyst **12** demonstrated excellent reactivity and enantioselectivity in this class of Michael reactions. Further studies focusing on the full scope of this unique catalyst system are currently under investigation and will be reported in due course.

Acknowledgments

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