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Rate Acceleration of Triethylamine-Mediated Guanidine-Catalyzed Enantioselective Michael Reaction

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Abstract: A chiral bicyclic guanidine was found to be an excellent catalyst for enantioselective Michael reactions. It was observed that additives such as non-chiral amines could accelerate the rate of reaction. When triethylamine (Et_3N) was as used as the solvent, the reaction rate can be increased up to 1000 times without compromising the enantioselectivity. Michael acceptors such as 2-cyclopenten-1-one **2** and *N*-alkylmaleimides were investigated, with various commercially available Michael donors such as dialkyl malonates and benzoylactetates. Michael adducts were obtained in excellent enantiomeric excesses (up to 96%) and yields (up to 99%).

Keywords: asymmetric catalysis; chiral bicyclic guanidines; Michael addition; organic catalysis; triethylamine (Et_3N)

Introduction

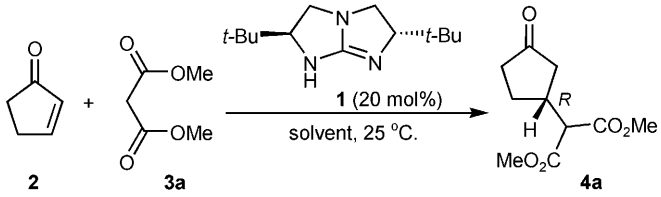
It is well known that the efficiency of asymmetric organometallic catalysts can often be improved through the use of additives or co-catalysts.[1] As such, catalyst loading, turnover number, yield and enantioselectivity can be tuned and optimized. They can be employed to alter the reaction pathway leading to less side products or different products. Nitrogen bases are among the most common additives.[1] Although organocatalysis has made tremendous progress in recent years,[2] the use of additives and co-catalysts in organocatalysis has yet to be systematically investigated. A good example is the use of Brønsted acids as additives in amine-catalyzed aldol reactions to promote the formation of enamines and iminiums.[3] Another example would be the use of peptides with proline as co-catalyst in the Baylis–Hilman reaction of alkyl vinyl ketones.[4]

Brønsted bases are usually utilized to remove acids generated *in situ*, but sometimes their role is not as well defined. It has been demonstrated that the addition of 5 equivalents of Hunig's base greatly accelerated the reaction between allyltrichlorosilane and aldehydes catalyzed by axially chiral *N,N′*-dioxides. It was postulated that the base might have promoted dissociation of the catalyst from the silicon atom.[5] In another example, tertiary amines such as tributylamine and Et_3N were utilized as co-solvents, and led to improvement in the diastereoselectivities upon the addition of *n*-BuLi to chiral aldehydes.[6] It was also demonstrated that a higher rate of ketone enolization was achieved with Et_3N as solvent and LHMDS (lithium hexamethyldisilazide) as a strong base.[7] Et_3N was suggested to have promoted the formation of dimer-based transition states.

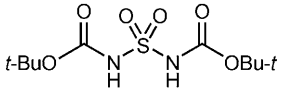
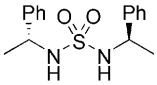
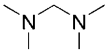
We have recently shown that chiral bicyclic guanidines, such as **1** (Table 1), are efficient catalysts for Diels–Alder, Michael, phospha-Michael and protonation reactions.[8] We have observed that Michael reactions using commercially available dialkyl malonates gave very low reactivities and the Michael adducts obtained had moderate enantioselectivities. Therefore, dialkyl dithiomalonates were introduced in our previous work to overcome the problem.[8b] These donors have much lower pK_a values and thus higher acidities and higher activities. We are still very keen to develop methodology for the commercially available dialkyl malonates and therefore we continue to optimize the reaction.

A particularly useful but slow reaction was the addition of 1,3-dicarbonyl compounds to 2-cyclopenten-1-one **2**. This reaction provides a direct approach to chiral cyclopentanones, allowing access to a variety of

Table 1. Michael addition of dimethyl malonate **3a** to 2-cyclopenten-1-one **2** using different solvents and additives.



2 3a 4a

Entry	Solvent	Additive	Time [h]	Yield [%][a]	*ee* [%][b]
1	toluene	none	96	92	78
2	THF	none	144	91	73
3	CH_2Cl_2	none	96	82	58
4	$PhCF_3$	none	96	80	70
5	toluene	*t*-BuOH (1 equiv.)	108	73	70
6	toluene	 (1 equiv.)	72	99	49
7	toluene	 (1 equiv.)	12	95	67
8	toluene	 (1 equiv.)	72	88	24
9	toluene	pyridine (1 equiv.)	72	80	78
10	toluene	$(i\text{-Pr})_2$EtN (1 equiv.)	72	99	80
11	toluene	Et_3N (1 equiv)	72	99	81
12	toluene	toluene:Et_3N (9:1)	12	86	82
13	Et_3N	none	9	92	82

[a] Isolated yield.
[b] Chiral HPLC.

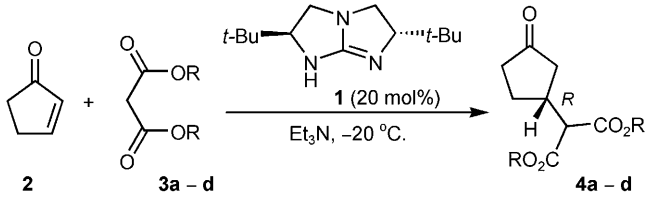
natural products.[9] Examples using organometallic catalysts such as Al-Li-BINOL,[10] Al-Li-aminodiols,[11] La-linked-BINOL[12] and Ru-amido complexs had been reported.[13] Organocatalytic methods include the use of (2-pyrrolidyl)alkylammonium hydroxide derivatives[14] and *Cinchona* alkaloid derivatives.[15] Herein, we report a highly enantioselective version using chiral bicyclic guanidine **1** as catalyst and mediated by Et_3N.

Results and Discussion

In the presence of 20 mol% of guanidine **1**, the addition of dimethyl malonate **3a** to 2-cyclopenten-1-one **2** was found to give a good yield using toluene as solvent at room temperature (Table 1, entry 1). The adduct **4a** was obtained with an *ee* of 78% but the reaction was slow (96 h). Solvents such as THF, CH_2Cl_2 and *p*-CF_3Ph (Table 1, entries 2–4) were found to give lower *ee*s than toluene (Table 1, entry 1). Next, we screened several additives (Table 1, entries 5–8). Addition of *t*-BuOH[16] decreased the *ee* and yield slightly (Table 1, entry 5). It was known that sulfonamides or thioureas could activate the Michael acceptor through hydrogen bonding.[17] Hence, two sulfonamides were examined as additive (Table 1, entries 6 and 7). The reaction rate was increased as expected but the *ee* decreased.

As amidines and guanidines are known to absorb carbon dioxide to form zwitterions,[18] the addition of non-chiral bases like amines may speed up the reaction by assisting the regeneration of the guanidine catalyst. One equivalent of a series of amines such as *N,N,N′,N′*-tetramethyldiaminomethane, pyridine, Et(*i*-Pr)$_2$N, and Et_3N was used as additive (Table 1, entries 8–11). All the reactions were completed within three days, much faster than without the additives. The *ee*s were maintained with the exception of *N,N,N′,N′*-tetramethyldiaminomethane (entry 8). Considering that Et_3N has a low boiling point and subsequent removal from the reaction mixture may not be much of a problem, the amount used was increased. The reaction rate improved tremendously when Et_3N was used as a 1:9 co-solvent with toluene (Table 1, entry 12) and reaction rate was fastest when Et_3N was

Table 2. Chiral bicyclic guanidine **1**-catalyzed Michael addition of malonates **3a–d** to 2-cyclopenten-1-one **2**.



2 **3a – d** **4a – d**

Entry	**3**	Time [h]	Product	Yield [%][a]	*ee* [%][b]
1	**3a** [R = Me]	120	**4a**	94	91
2	**3b** [R = Et]	120	**4b**	93	92
3	**3c** [R = Bn]	120	**4c**	99	92
4	**3d** [R = *i*-Pr]	192	**4d**	84	96

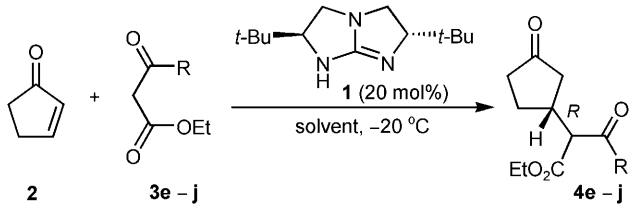
[a] Isolated yield.
[b] Chiral HPLC.

used as solvent (Table 1, entry 13). More importantly, the increase in reaction rate was achieved without compromising the enantioselectivity.

We conducted further experiments at a lower temperature of −20 °C using Et_3N as solvent and found that *ee* was increased to 91% (Table 2, entry 1). Other commercially available dialkyl malonates **3b–d** were investigated and similar level of enantioselectivities were observed. The reactions of diethyl malonate **3b** and dibenzyl malonate **3c** were completed within 120 h (Table 2, entries 2 and 3). The reaction of the more hindered substrate, diisopropyl malonate **3d** gave the highest level of *ee* at 96% (Table 2, entry 4).

The pK_a values[19] of dialkyl malonates **3a–d** fall within the range 11.6–13.8 and the pK_a of the conjugate acid of guanidine **1** should be in the range of 13.3–14.4.[20] With lower pK_a values ranging from 8.7 to 10.0, benzoylacetates **3e–j** should be more reactive due to their increased acidities. The possibility of side reaction catalyzed by Et_3N (pK_a value of its conjugate acid is 10.6) should also be considered as it might compromise the enantioselectivity. Therefore, with ethyl benzoylacetates as donor, a comparison of enantioselectivity in both toluene and Et_3N was necessary. As evident from Table 3, the reaction rate was about 2–3 times faster in Et_3N than in toluene, and for **3e–i**

Table 3. Michael addition of various ethyl benzoylacetates **3e–j** to 2-cyclopenten-1-one **2**.

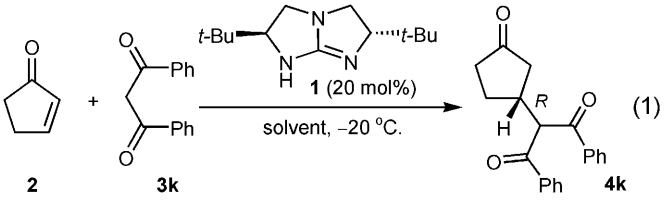


2 **3e – j** **4e – j**

Entry	**4**	Solvent	Time [h]	Product	Yield [%][a]	*ee* [%][b,c]
1	**3e** [R = Ph]	Et_3N	72	**4e**	98	90, 93
2	**3e** [R = Ph]	toluene	120	**4e**	25[d]	88, 92
3	**3f** [R = *m*-MeC_6H_4]	Et_3N	60	**4f**	89	86, 87
4	**3f** [R = *m*-MeC_6H_4]	toluene	192	**4f**	85	91, 90
5	**3g** [R = *p*-$CF_3C_6H_4$]	Et_3N	72	**4g**	91	91, 92
6	**3g** [R = *p*-$CF_3C_6H_4$]	toluene	144	**4g**	90	92, 96
7	**3h** [R = *p*-ClC_6H_4]	Et_3N	48	**4h**	99	94, 95
8	**3h** [R = *p*-ClC_6H_4]	toluene	144	**4h**	99	92, 93
9	**3i** [R = *m*-ClC_6H_4]	Et_3N	48	**4i**	99	93, 93
10	**3i** [R = *m*-ClC_6H_4]	toluene	144	**4i**	99	90, 90
11	**3j** [R = *p*-$NO_2C_6H_4$]	Et_3N	72	**4j**	99	78, 80
12	**3j** [R = *p*-$NO_2C_6H_4$]	toluene	120	**4j**	91	93, 94

[a] Isolated yield.
[b] Chiral HPLC.
[c] *dr* 1:1, determined by ^1H NMR and chiral HPLC.
[d] 30 mol% of catalyst **1** was used.

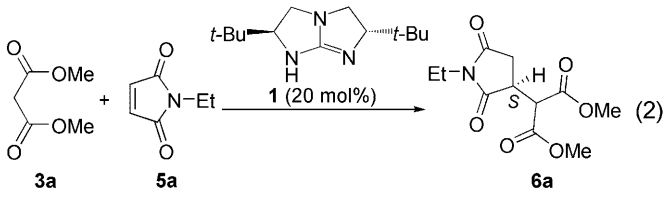
(Table 3, entries 1–10) the *ee*s were similar in both solvents. A slight decrease in *ee* was observed for the reaction of ethyl *p*-nitrobenzoylacetates **3j** (pK_a: 8.7; Table 3, entries 11 and 12) with Et_3N as solvent. An important and common donor, 1,3-diphenylpropane-1,3-dione **3k** (pK_a: 8.95), was also investigated. The reaction rate was increased using Et_3N as solvent with a slight decrease in *ee* was observed [Eq. (1)].



(1)

tol., 120 h, yield 61%, 91% *ee*
Et_3N, 48 h, yield 99%, 87% *ee*

This strategy was expanded to include other classes of Michael acceptors. As important cyclic Michael acceptors, maleimides can provide a practical route to biologically important chiral α-substituted succinimides.[8b,21,22] *Cinchona* alkaloids were found to be suitable catalysts for the conjugate addition of 1,3-dicarbonyl compounds to *N*-benzylmaleimide.[21a] We had also previously reported the addition of dimethyl malonate **3a** to *N*-ethylmaleimide **5a** using chiral bicyclic guanidine **1** as catalyst with toluene as solvent. Low yield and poor enantioselectivity were obtained.[8b] Employing the new reaction conditions, using Et_3N as solvent, the reaction could be completed at −50 °C



(2)

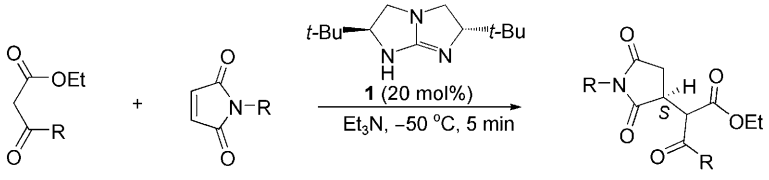
tol., r.t., 96 h, yield 20%, 47% *ee*
Et_3N, –50 °C, 96 h, yield 90%, 71% *ee*

and the *ee* increased to 71% [Eq. (2)]. This promising result prompted us to continue this investigation.

Ethyl benzoylacetate **3e**, a more active donor, was found to react with *N*-ethylmaleimide **5a** using Et_3N as solvent at −50 °C and in the presence of 20 mol% **1** (Table 4, entry 1). The reaction was completed in just 5 min with 99% yield and 93% *ee*. Different *N*-alkylmaleimides **5b–d** were also tested under these reaction conditions (Table 4, entries 2–4). All reactions were completed within 5 min, providing the corresponding adducts in high yields and *ee*s. Several substituted ethyl benzoylacetates **3f**, **h**, **k** and ethyl 2-furoylacetate **3l** also gave excellent results (Table 4, entries 5–8).

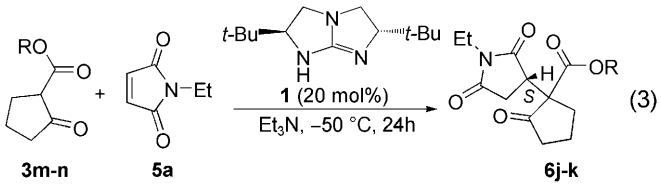
The bulkier and more hindered substituted cyclic β-keto esters **3m** and **n** were examined. No Michael adducts were found when chiral bicyclic guanidine **1** was used with toluene as solvent. However, the corresponding 1,4-adducts were obtained with good yields and enantioselectivities were obtained when Et_3N was used as the solvent [Eq. (3)]. β-Keto ester **3n** with an ethyl group gave adduct **6k** with higher enantioselectivity than adduct **6j**.

Table 4. Michael additions of ethyl benzoylacetates **3e–f**, **h**, **k**, **l** to *N*-alkylmaleimides **5a–d**.



Entry	3	5	Product	Yield [%][a]	*ee* [%][b,c]
1	**3e** [R = Ph]	**5a** [R = ethyl]	**6b**	99	93, 93
2	**3e** [R = Ph]	**5b** [R = methyl]	**6c**	93	93, 93
3	**3e** [R = Ph]	**5c** [R = cyclohexyl]	**6d**	99	93, 93
4	**3e** [R = Ph]	**5d** [R = *n*-hexyl]	**6e**	90	90, 91
5	**3f** [R = *m*-MeC_6H_4]	**5a** [R = ethyl]	**6f**	88	92, 93
6	**3h** [R = *p*-ClC_6H_4]	**5a** [R = ethyl]	**6g**	99	90, 91
7	**3k** [R = *p*-$MeOC_6H_4$]	**5a** [R = ethyl]	**6h**	91	89, 89
8	**3l** [R = 2-furanyl]	**5a** [R = ethyl]	**6i**	99	86, 86

[a] Isolated yield.
[b] Chiral HPLC.
[c] *dr* 1:1, determined by ^1H NMR and chiral HPLC.



R = methyl **3m**, yield 85%; 66, 82% *ee*; *dr* 1:1
R = ethyl **3n**, yield 80%; 83, 90% *ee*; *dr* 1:1

We studied the reaction between ethyl benzoylacetate **3e** and *N*-ethylmaleimide **5a** in more detail (Figure 1). The reaction temperatures were varied from ambient to −50 °C; the *ee* increased from 41% to 93%. As the temperature was lowered to below −50 °C, the *ee* decreased dramatically. In the absence of the catalyst **1**, at −50 °C, the reaction was completed in 5 min with >80% yield. This shows that significant background reaction can be achieved by Et_3N. It is crucial for the catalyzed reaction to be much faster than the non-catalyzed reaction for high enantioselectivity to be obtained. The selectivity of the guanidine improved as the temperature was lowered. As the temperature decreased beyond −50 °C, however, the catalyzed reaction became too slow as compared to the non-catalyzed reaction that was promoted by Et_3N. The guanidine-catalyzed reaction mediated by Et_3N was about 1000 times faster than the guanidine-catalyzed reaction in toluene (<5 min *vs.* 60 h). We postulate that Et_3N may be involved in the stabilization of the enolate-guanidinium complex; allowing the catalyzed reaction in Et_3N to proceed at a much faster rate. The initial speculation that guanidine may have absorbed atmospheric carbon dioxide and the formation of a guanidinium carbonate may result in the catalyst being quenched was ruled out.[19] Subsequent experiments were conducted under stringent conditions such as under inert nitrogen atmosphere but reactions with toluene as solvent still remained slow and products still were obtained with poor yield and *ee*. This is thus an unlikely reason for the rate enhancement. The catalyst was prepared as the guanidinium iodide salt and in the final step of its preparation AcOH was used. The possibility of acid impurities in the catalyst was also ruled out as the catalyst was purified using flash chromatography and was freshly basified using K_2CO_3 just before each experiment.

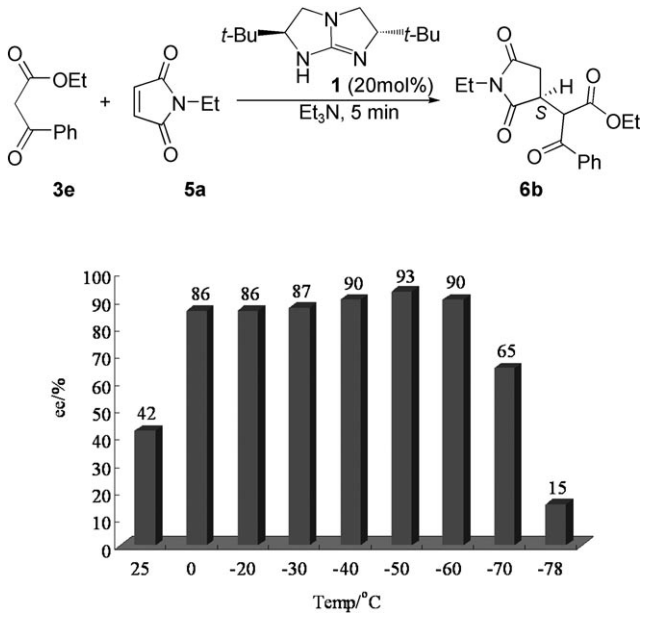


Figure 1. Michael addition of ethyl benzoylacetate **3e** to *N*-ethylmaleimide **5a** at different reaction temperatures.

Conclusions

In summary, the guanidine-catalyzed reaction mediated by Et_3N resulted in a huge acceleration in reaction rate. Using this new methodology, high enantioselectivities and yields can be obtained for Michael reactions which were previously unattainable due to slow reaction rates. This includes reactions between 2-cyclopenten-1-one or *N*-alkylmaleimides with various commercially available Michael donors such as dialkyl malonates and benzoylactetates. This approach expands the range of Michael donors and acceptors that are compatible with the bicyclic guanidine catalyst. The role of Et_3N in the guanidine-catalyzed Michael reaction will be investigated in more detail using both kinetic and computational studies.

Experimental Section

General Procedure for the Michael Addition of 1,3-Dicarbonyl Compounds (3a–k) to 2-Cyclopenten-1-one 2 Catalyzed by Bicyclic Guanidine 1

(a) Toluene as solvent: Toluene (0.2 mL) was added to 1,3-dicarbonyl compounds (**3a–k**) (0.06 mmol) and catalyst **1** (2.24 mg, 0.01 mmol). After cooling the mixture at −20 °C for about 30 min, 2-cyclopenten-1-one **2** (4.2 μL, 4.2 mg, 0.05 mmol) was added. The reaction mixture was monitored by TLC and upon complete consumption of **2**, the solvent was removed under vacuum. The crude product was directly loaded onto a short silica gel column, followed by gradient elution with hexane:ethyl acetate = 10/1 to 4/1 to provide products **4a–k**.

(b) Et_3N as solvent: Et_3N (0.2 mL) was added to 1,3-dicarbonyl compounds (**3a–k**) (0.06 mmol) and catalyst **1** (2.24 mg, 0.01 mmol). After cooling the mixture at −20 °C for about 30 min, 2-cyclopenten-1-one **2** (4.2 μL, 4.2 mg, 0.05 mmol) was added. The reaction mixture was monitored by TLC and upon complete consumption of **2**, the solvent was removed under vacuum. The crude product was directly loaded onto a short silica gel column, followed by gradient

elution with hexane:ethyl acetate = 10/1 to 4/1 to provide products **4a–k**.

Reactions were conveniently performed in capped round-bottom flasks without special precautions. Catalyst can be recovered from the column using MeOH:CH_2Cl_2 (1:4) and reused without lost of *ee*.

(*R*)-(+)-Dimethyl 2-(3-oxocyclopentyl)malonate (4a): Colorless oil; yield: 94% (Et_3N as solvent); 91% *ee* (Et_3N as solvent); $[\alpha]_D^{26}$: +132.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 3.67 (s, 3H), 3.33 (d, J = 9.2 Hz), 2.87–2.72 (m, 1H), 2.43 (dd, J = 18.1, 8.0 Hz, 1H), 2.33–2.03 (m, 3H), 1.94 (dd, J = 18.1, 10.8 Hz, 2H), 1.62–1.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.7, 168.4, 168.3, 55.9, 52.4, 42.7, 38.0, 36.2, 27.3; LRMS (ESI) *m/z* 231.9 (M+ NH_4^+); HR-MS (ESI): *m/z* = 213.0762 (M−H), calcd. for $C_{10}H_{13}O_5$: 213.0763; The *ee* was determined by HPLC analyses after conversion to the ethylene ketal.[23] CHIRALCEL OD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol = 97/3; flow rate: 0.5 mL min^{-1}; 25 °C; 210 nm; retention time: 24.6 min (major) and 25.9 min (minor).

(*R*)-Ethyl 3-oxo-2-(3-oxocyclopentyl)-3-phenylpropanoate (4e): Colorless oil; yield: 98% (Et_3N as solvent); 1:1 mixture of diastereomers. 90% and 93% *ee* (Et_3N as solvent); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04–7.99 (m, 4H), 7.62–7.58 (m, 2H), 7.52–7.46 (m, 4H), 4.29 (d, J = 6.3 Hz, 1H), 4.26 (d, J = 6.6 Hz, 1H), 4.20–4.10 (m, 4H), 3.15–3.06 (m, 2H), 2.58–2.50 (m, 2H), 2.38–2.04 (m, 7H), 1.86–1.71 (m, 2H), 1.54–1.42 (m, 1H), 1.20–1.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.3, 193.6, 193.4, 168.5, 168.4, 136.3, 136.1, 133.8, 128.8, 128.6, 61.7 (two peaks), 59.4, 59.1, 43.3, 42.8, 38.3, 38.1, 36.6, 36.4, 28.0, 27.4, 14.0; LR-MS (EI): *m/z* = 274.1 (M^+); HR-MS (EI): *m/z* = 274.1207 (M^+), calcd. for $C_{16}H_{18}O_4$: 274.1205. The *ee* was determined by HPLC analyses of the Michael adduct. Double columns, CHIRALPAK (AD-H)-(AD-H) (4.6 mm i.d. × 250 mm); hexane/2-propanol 80/20; flow rate: 0.5 mL min^{-1}; 25 °C; 254 nm; retention time: 28.3 min (minor) and 45.3 min (major), 90% *ee*; 32.7 min (minor) and 33.6 min (major), 93% *ee*.

(*R*)-Ethyl 3-(4-nitrophenyl)-3-oxo-2-(3-oxocyclopentyl)-propanoate (4j): Colorless oil; yield: 91% (toluene as solvent); 1:1 mixture of diastereomers. 93% and 94% *ee* (toluene as solvent); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.32 (m, 4H), 8.20–8.15 (m, 4H), 4.26 (dd, J = 9.4, 7.7 Hz, 2H), 4.21–4.12 (m, 4H), 3.16–3.05 (m, 2H), 2.56 (dd, J = 18.1, 7.7 Hz, 2H), 2.41–2.20 (m, 6H), 2.09 (dd, J = 18.8, 11.2 Hz, 1H), 1.87–1.71 (m, 2H), 1.51 (m, 1H), 1.21–1.15 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.7, 216.6, 192.2, 192.0, 167.8, 167.7, 150.6, 140.5, 140.3, 129.6, 124.1, 62.2, 62.1, 60.1, 59.8, 43.3, 42.5, 38.2, 38.0, 36.3, 36.1, 28.0, 27.2, 14.0 (two peaks); IR (film): ν = 1735, 1688, 1648, 1528, 1405, 1351, 1153, 999 cm^{-1}; LR-MS (EI): *m/z* = 318.9 (M^+); HR-MS (EI): *m/z* = 319.1062 (M^+), calcd. for $C_{16}H_{17}NO_6$: 319.1056. The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol 90/10; flow rate: 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 21.6 min (minor), 23.6 min (major), 93% *ee*; 32.6 min (major), 36.5 min (minor), 94% *ee*.

(*R*)-(+)-3-(1,3-Dioxo-1,3-diphenylpropan-2-yl)cyclopentanone (4k): Colorless oil; yield: 99% (Et_3N as solvent), 91% *ee* (toluene as solvent); $[\alpha]_D^{26}$: +47.1 (*c* 0.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–7.95 (m, 4H), 7.61–7.56 (m, 2H), 7.49–7.41 (m, 4H), 5.19 (d, J = 9.4 Hz, 1H), 3.37–3.22 (m, 1H), 2.49 (dd, J = 18.5, 7.3 Hz, 1H), 2.37–2.12 (m, 3H), 1.96 (dd, J = 18.5, 11.5 Hz, 1H), 1.73–1.63 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 217.1, 195.0, 194.8, 136.6, 136.5, 134.0 (two peaks), 129.2, 128.9, 63.2, 43.5, 38.4, 37.9, 28.3; IR (film): ν = 3019, 1740, 1697, 1217 cm^{-1}; LR-MS (ESI): *m/z* = 305.1172 (M−H); HR-MS (ESI): *m/z* = 305.3472 (M−H), calcd. for $C_{20}H_{17}O_3$: 305.3475. The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK AD-H (4.6 mm i.d. × 250 mm); hexane/2-propanol 90/10; flow rate: 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 22.0 min (minor), 24.5 min (major).

General Procedure for the Michael Addition of 1,3-Dicarbonyl Compounds (3a, e–f, h and k–n) to *N*-Alkylmaleimides 5a–d Catalyzed by Bicyclic Guanidine 1

Et_3N (0.2 mL) was added to 1,3-dicarbonyl compounds (**3a**, **e–f**, **h** and **k–n**) (0.06 mmol) and catalyst **1** (2.24 mg, 0.01 mmol). After cooling the mixture at −50 °C for about 30 min, the *N*-alkylmaleimide **5a–d** (0.05 mmol) was added. The reaction mixture was monitored by TLC and upon complete consumption of **5a–d**, the solvent was removed under vacuum. The crude product was directly loaded onto a short silica gel column, followed by gradient elution with hexane:ethyl acetate = 10/1 to 2/1 to provide product **6a–k**.

Ethyl 2-(1-methyl-2,5-dioxopyrrolidin-3-yl)-3-oxo-3-phenylpropanoate (6c): Colorless oil; yield: 93%; 1:1 mixture of diastereomers. 93% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.97–7.88 (m, 2H), 7.63–7.41 (m, 3H), 5.11–4.86 (m, 1H), 4.20–4.08 (m, 2H), 3.49–3.28 (m, 1H), 2.99–2.81 (m, 5H), 1.16–1.09 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.8, 193.1, 177.8, 177.6, 176.1, 176.0, 167.9, 167.7, 135.6, 135.4, 134.0, 133.9, 128.8, 128.6 (two peaks), 128.4, 62.1, 61.9, 53.3, 51.9, 39.6, 39.4, 32.4, 32.1, 24.8, 13.7 (two peaks); IR (film): ν = 2982, 2940, 1734, 1701, 1439, 1387, 1284, 1122 cm^{-1}; LR-MS (ESI): *m/z* = 302.3 (M^-); HR-MS (ESI): *m/z* = 326.0999 (M + Na^+), calcd. for $C_{16}H_{17}NO_5Na$: 326.0999. The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 85/15; flow rate: 1.0 mL min^{-1}; 25 °C; 254 nm; retention time: 11.3 min (major), 18.9 min (minor); 13.9 min (minor), 43.5 min (major).

Ethyl 1-[(*S*)-1-ethyl-2,5-dioxopyrrolidin-3-yl]-2-oxocyclopentanecarboxylate (6k): Colorless oil; yield: 80%; 1:1 mixture of diastereomers. 90% *ee* and 83% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24–4.04 (m, 2H), 3.55–3.32 (m, 3H), 2.91–1.96 (m, 8H), 1.28–1.07 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.6, 212.6, 177.2, 176.9, 175.6, 175.3, 169.9, 169.7, 62.1, 62.0, 60.8, 60.67, 43.3, 42.0, 37.9, 37.8, 33.7, 32.7, 32.5, 31.9, 31.8, 19.6, 19.2, 14.0, 13.9, 12.7; IR (film): ν = 2978, 1751, 1720, 1699, 1445, 1406, 1350, 1227 cm^{-1}; LR-MS (EI): *m/z* = 281.1 (M^+); HR-MS (FAB): *m/z* = 281.1272 (M^+), calcd. for $C_{14}H_{19}NO_5$: 281.1263. The *ee* was determined by HPLC analyses of the Michael adduct. CHIRALPAK IA (4.6 mm i.d. × 250 mm); hexane/2-propanol 92/08; flow rate: 0.8 mL min^{-1}; 25 °C; 210 nm; retention time: 13.9 min (minor), 16.4 min (major), 90% *ee*; 18.5 min (major), 22.2 min (minor), 83% *ee*.

Supporting Information

Experimental procedures, characterization and spectroscopic data (PDF) are available as Supporting Information.

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