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Enantio- and Diastereoselective Michael Reaction of 1,3-Dicarbonyl Compounds to Nitroolefins Catalyzed by a Bifunctional Thiourea

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Abstract: We synthesized a new class of bifunctional catalysts bearing a thiourea moiety and an amino group on a chiral scaffold. Among them, thiourea **1e** bearing 3,5-bis(trifluoromethyl)benzene and dimethylamino groups was revealed to be highly efficient for the asymmetric Michael reaction of 1,3-dicarbonyl compounds to nitroolefins. Furthermore, we have developed a new synthetic route for (*R*)-(−)-baclofen and a chiral quaternary carbon center with high enantioselectivity by Michael reaction. In these reactions, we assumed that a thiourea moiety and an amino group of the catalyst activates a nitroolefin and a 1,3-dicarbonyl compound, respectively, to afford the Michael adduct with high enantio- and diastereoselectivity.

Introduction

Urea and thiourea derivatives have been intensively investigated in the area of molecular recognition because of their strong hydrogen bonding activity.[1] They can be used to recognize carboxylic acid,[1a] sulfonic acid,[1b] nitrate,[1c] etc., through multihydrogen bondings. Recently, several groups reported that urea and thiourea not only recognized organic compounds but also activated them as an acid catalyst.[2−4] Curran et al. reported that addition of a urea derivative improved diastereoselectivity of allylation of α-bromosulfoxide with allyltributylstannane.[2b] Schreiner investigated the effect of urea derivatives on reactivity and selectivity of Diels−Alder reaction of enones with cyclopentadiene.[2d,e] Concerning enantioselective reactions,[3,4] Jacobsen et al. found that chiral urea derivatives catalyzed the Strecker reaction, Mannich reaction, hydrophosphonylation of imines, and Pictet−Spengler reaction, affording the products with high enantiomeric excess.[4a−i] Nagasawa et al. reported that their chiral urea derivatives promoted Michael reaction of pyrrolidine to α,β-unsaturated γ-lactone with low to moderate ee.[4j] They also found that bis-thiourea catalyzed the Baylis−Hillman reaction with up to 90% ee.[4k] Although both research groups used urea derivatives as a simple acid, the activity of ureas as acids is rather weaker than that of metallic Lewis acids. Therefore, application of urea derivatives to enantioselective reactions seems to be limited.[2g]

Michael reaction of nitroolefins represents a convenient access to nitroalkanes that are versatile intermediates in organic synthesis.[5] The nitro functionality can be easily transformed into amine,[6] nitrile oxide,[7] ketone or carboxylic acid,[8] hydrogen,[9] etc., providing a wide range of synthetically interesting compounds. Although the catalytic asymmetric versions of this reaction were achieved, most required metal catalysts or strict reaction conditions.[10−14] Recently, L-proline derivatives have been reported to afford enantiomerically enriched Michael adducts in good yield.[15] To achieve catalytic enantioselective Michael reaction into nitroolefins with thioureas, we designed

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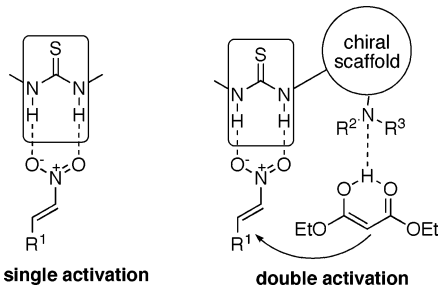


Figure 1. Multifunctional organocatalysts.

new chiral bifunctional organocatalysts[2f,16] (Figure 1) that have both a thiourea moiety and an amino group on a chiral scaffold. These bifunctional catalysts would be able to activate both nitroolefins and nucleophiles simultaneously and could control the approach of nucleophiles to nitroolefins. On the basis of this concept, we have recently reported that novel bifunctional catalysts realized Michael reaction of 1,3-dicarbonyl compounds to nitroolefins with high enantioselectivity up to 93% ee.[3a] In this article, we investigated the structure−activity relationship of thiourea catalysts in the Michael reaction and also the adaptation of α-substituted β-ketoesters to the reaction to construct contiguous stereogenetic centers containing an asymmetric quaternary carbon. In addition, a plausible reaction mechanism is proposed from these results.

Results and Discussion

Synthesis and Activity of Catalysts. We first synthesized various thiourea derivatives **1a**−**n** to examine the effects of (1) the diamine moiety (cyclic or acyclic, n, R^1), (2) a functional group of the aromatic ring (Y), and (3) substituents on the amino group (R^2, R^3) on the reactivity and selectivity of the reaction (Figure 2). These catalysts could be prepared simply by condensation of isocyanates/isothiocyanates with 1 equiv of amines. Furthermore, we synthesized urea **1o**, whose pK_a would be larger than that of the corresponding thiourea **1e**.[17] We then carried out Michael reaction of β-nitrostyrene **2a** with 2 equiv of diethyl malonate **3a** in toluene with 10 mol % of catalysts (Table 1 and Figure 3). The reaction in the presence of TEA

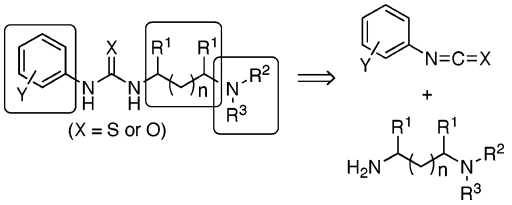
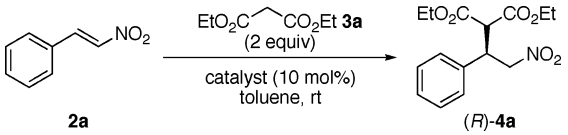


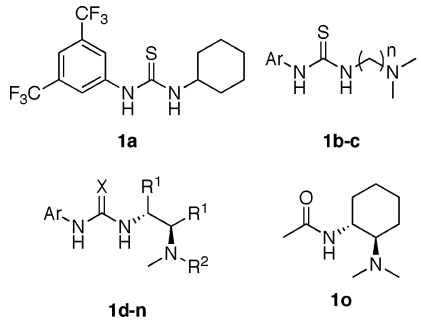
Figure 2. Synthesis of thiourea catalysts.

Table 1. Michael Reaction of **2a** with Various Catalysts[a]



entry	additive	time (h)	% yield[b]	% ee[c,d]
1	TEA	24	17	−
2	DBU	3	13	−
3	TEA + **1a**	24	57	−
4	**1b**	48	38	−
5	**1c**	48	43	−
6	**1d**	48	52	64
7	**1e**	24	86	93
8	**1f**	48	69	74
9	**1g**	48	88	83
10	**1h**	48	78	84
11	**1i**	48	58	80
12	**1j**	24	72	72
13	**1k**	48	88	77
14	**1l**	48	76	87
15	**1m**	48	38	89
16	**1n**	24	87	91
17	**1o**	24	14	35

[a] The reaction was conducted with **2a** (1 equiv), **3a** (2 equiv), and toluene in the presence of various additives (10 mol %) at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4a** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4a** with that of literature data.[12b]



1b; Ar = 3-$CF_3C_6H_4$, n = 2
1c; Ar = 3-$CF_3C_6H_4$, n = 3
1d; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = Ph, Ph, R^2 = Me
1e; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me
1f; X = S, Ar = 3-$MeOC_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
1g; X = S, Ar = 3-CNC_6H_4, R^1 = $(CH_2)_4$, R^2 = Me
1h; X = S, Ar = 3-$CF_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
1i; X = S, Ar = Ph, R^1 = $(CH_2)_4$, R^2 = Me
1j; X = S, Ar = 2-$CF_3C_6H_4$ R^1 = $(CH_2)_4$, R^2 = Me
1k; X = S, Ar = 4-$CF_3C_6H_4$, R^1 = $(CH_2)_4$, R^2 = Me
1l; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = ^{i}Pr
1m; X = S, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Bn
1n; X = O, Ar = 3,5-$(CF_3)_2C_6H_3$, R^1 = $(CH_2)_4$, R^2 = Me

Figure 3. Structure of catalysts.

(10 mol %) provided the desired Michael adduct **4a** in only 17% yield (entry 1). Replacement of the base with a strong base DBU did not improve the chemical yield (13%, entry 2). The

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low yield of **4a** was attributed to decomposition of β-nitrostyrene **2a** by these bases. To activate β-nitrostyrene with something other than a base, thiourea **1a** was added to the reaction mixture. When **1a** and TEA coexist in the reaction mixture, Michael reaction was accelerated and **4a** was obtained in 57% yield (entry 3). In contrast to our expectation of higher activity, achiral bifunctional organocatalysts **1b** and **1c** gave almost the same results as that of entry 3 (entries 4 and 5). In these cases, the two functional groups might not be fixed in proper positions because of the conformational flexibility. Indeed, although chiral catalyst **1d**, bearing 1,2-diphenylethylenediamine as the scaffold, gave **4a** with 64% ee, catalyst **1e**, bearing a rigid chair-form structure, afforded **4a** in good yield with 93% ee (entries 6 and 7). The absolute configuration of **4a** was determined to be *R* by comparing the specific rotation of **4a** with that of literature data.[12] We next examined the catalytic activity of several catalysts **1f**−**i**, which had differernt substituents (Y = CF_3, CN, OMe, H in Figure 2) on the meta position of the aromatic rings. Although these catalysts showed lower catalytic activity than **1e**, similar results in terms of chemical yield and ee were obtained except in the case of **1f** possessing an electron-donating group (entries 8−11). Similarly, the position of CF_3 groups on the aromatic ring had a marginal effect on the chemical yield and enantioselectivity of **4a** (entries 10, 12, and 13). Concerning the number of trifluoromethyl groups on the aromatic ring of the catalyst (entries 7, 10, and 11, **1e**, **1h**, and **1i**), the catalyst **1e**, bearing two CF_3 groups, showed the highest catalytic activity due to enhancement of the acidity of thiourea N−H groups. When a bulkier alkyl group (R^2) was introduced to the catalyst, the chemical yield of **4a** decreased without affecting the ee of **4a** (entries 14 and 15). It implied that steric hindrance of the catalyst did not relate to the facial selectivity of nitroolefin **2a**, but disturbed the approach of the nucleophile to **2a**. In general, the pK_a of the N−H groups of urea derivatives is smaller than that of the corresponding thiourea. Though we speculated that urea **1n** would show lower activity than **1e**, the catalytic activity of **1n** was almost the same as that of **1e** (entry 16). The unsatisfactory result with amide **1o**[18] indicated the importance of cooperative effect of two N−H groups in the catalyst (entry 17).

Although it is known that the solubility of ureas and thioureas in nonpolar solvents is low because of strong intermolecular hydrogen bonding, introduction of an amino group in the thiourea would induce formation of intramolecular hydrogen bonding between the amino group (NR_2) and the N−H groups of the thiourea, leading to increasing solubility to nonpolar solvents.[1d] Indeed, bifunctional thioureas **1d**−**n** became soluble in toluene. Analysis of the X-ray crystallographic structure of racemic thiourea **1e** would support the intramolecular hydrogen bonding between the amino group and the thiourea N−H group (H−N = 2.70 Å, Figure 4). In addition, the X-ray crystallography of **1e** would indicate that amino groups and thiourea N−H orient to the same direction. If thiourea and the amino group interact with nitroolefins and nucleophiles, respectively, nucleophiles can approach nitroolefins in an ideal way. This hypothesis agrees with the experimental result in Table 1, and it encouraged us to employ the catalyst **1e** to Michael reaction of various nucleophiles **3b**−**o** to nitroolefin **2a**.

Michael Reaction with Symmetric 1,3-Dicarbonyl Compounds. We next examined the scope of this class of Michael reactions with a series of malonates **3b**−**o** using the best catalyst **1e** (Table 2). The size of ester groups of malonates had a marginal effect on the selectivity of Michael adducts, but the large ester groups such as *tert*-butyl ester decreased reactivity of the malonates (entries 1−3). Acetylacetone **3e**, whose α-proton was more acidic than that of malonates, reacted with β-nitrostyrene for 1 h to afford 80% yield of Michael adduct **4e** with 89% ee (entry 4). In contrast, malononitrile **3f** and Meldrum's acid **3g** gave the corresponding adducts **4f** and **4g** in 85% yield and 88% yield, respectively, but the selectivity of both adducts was low (entries 5 and 6). The results suggest that the six-membered cyclic enol form of 1,3-dicarbonyl compounds might be important for the good enantioselectivity. If α-substituted malonates can be employed as a nucleophile in the Michael reaction, various products bearing a quaternary carbon

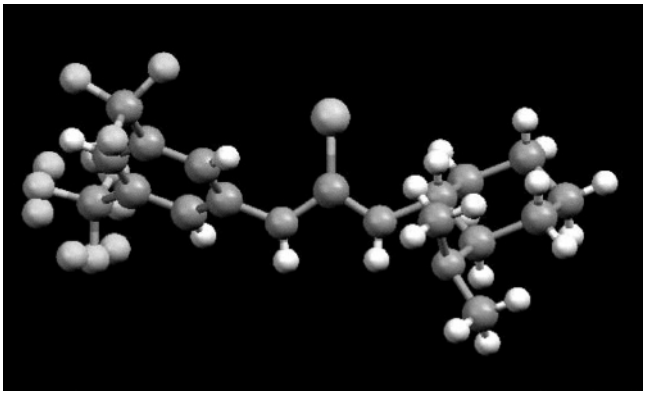
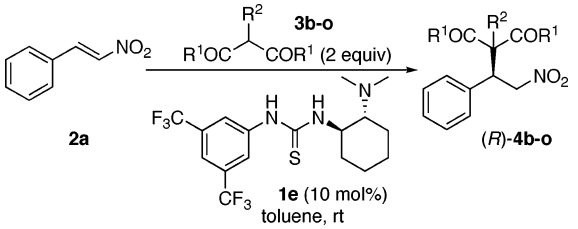


Figure 4. X-ray analysis of *rac*-**1e**.

Table 2. Enantioselective Michael Reaction of **2a** with Malonates **3b**−**o** in the Presence of **1e**[a]



entry	3	R^1	R^2	time (h)	yield[b] (%)	ee[c,d] (%)
1	**3b**	OMe	H	9	89	86
2	**3c**	O^{i}Pr	H	48	70	88
3	**3d**	O^{t}Bu	H	48	trace	−
4	**3e**	Me	H	1	80	89[e]
5	**3f**	$NCCH_2CN$	0.25	85	25[e]	
6	**3g**	$OCMe_2O$	H	24	88	46[f]
7	**3h**	OMe	Me	36	82	93[e]
8	**3i**	OMe	OMe	28	89	94
9	**3j**	OMe	OMs	1	86	79[e]
10	**3k**	OEt	NHBoc	48	81	82[e]
11	**3l**	OEt	NHAc	24	72	33
12	**3m**	OMe	Cl	1	>99	89[e]
13	**3n**	OEt	Br	48	nr	−
14	**3o**	OMe	Ph	48	trace	−

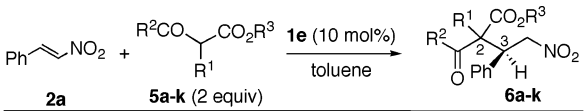
[a] The reaction was conducted with **2a** (1 equiv), nucleophiles (2 equiv), and toluene in the presence of **1e** (10 mol %) at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4** with that of literature data.[12b] [e] Absolute configuration was not determined. [f] Enantiomeric excess was determined after conversion to **4a** (see Supporting Information).

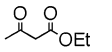
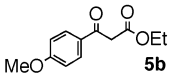
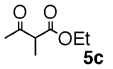
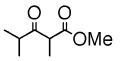
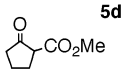
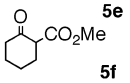
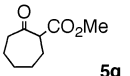
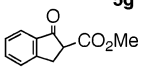
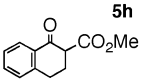
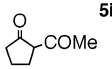
(18) Bordwell, F. G.; Ji, G. *J. Am. Chem. Soc.* **1991**, *113*, 8398−8401.

center would be obtained. Barnes et al. had already carried out such reactions with magnesium catalysts, but the products were obtained only in low to moderate selectivity.[12b] However, α-methyl malonate **3h** smoothly reacted with β-nitrostyrene in the presence of **1e** to provide Michael adduct **4h** in 82% yield with 93% ee (entry 7). The α-hydroxymalonate derivatives **3i** and **3j** also gave Michael adducts **4i** and **4j** in high yield with good to excellent selectivity (entries 8 and 9). In the reactions with malonates bearing nitrogen substituents on the α-position, the selectivity of the products depended on the protecting groups of the nitrogen (entries 10 and 11). In the case of *N*-Boc α-aminomalonate **3k**, the reaction afforded the product **4k** in 81% yield with 82% ee. Similarly, the reactivity of the halogenated malonates **3m** and **3n** depended on acidity of the malonates. Although α-chloromalonate **3m** provided the desired product **4m** quantitatively with 89% ee, the same reaction with α-bromomalonate **3n** did not proceed (entries 12 and 13). Unfortunately, the reaction with α-phenylmalonate **3o** gave only a trace amount of **4o**. The absolute configurations of **4b**, **4c**, **4i**, and **4l** were determined by comparing their specific rotations with those of literature data[12b] to reveal that all products had the same *R* configuration. These results would indicate that the reactions listed in Table 2 proceed through the same mechanism and also that adequate acidity of malonate is crucial for good chemical yield but not high enantioselectivity. We succeeded in highly enantioselective Michael reaction of β-nitrostyrene **2a** with several malonates to construct a quaternary carbon center.

Application to Enantio-/Diastereoselective Michael Reaction. Having succeeded in the Michael reaction of β-nitrostyrene with symmetric 1,3-dicarbonyl compounds such as malonate, we next carried out the Michael reaction of **2a** with prochiral 1,3-dicarbonyl compounds (Table 3). We first investigated the addition of α-unsubstituted β-ketoester **5a**,**b** to β-nitrostyrene **2a**. When ethyl aceoacetate **5a** (2 equiv) and β-nitrostyrene were combined in toluene in the presence of 10 mol % of catalyst **1e** at room temperature, the Michael addition completed within 30 min, giving the desired product **6a** in 91% yield. Although the dr of **6a** was low (55/45), the enantioselectivity was high (entry 1). The absolute configuration of the C3 position of **6a** was determined to be *R* by comparing the retention time of chiral HPLC analysis of **6a** with that of literature data.[12b] This result indicated that the reaction of ketoester **5a** with nitroolefin **2a** would proceed in the same way as that of malonates. The β-ketoester **5b** bearing aryl groups could be used as a nucleophile to afford the adduct **6b** in good yield with high enantioselectivity (entry 2). We next investigated the diastereo- and enantioselective Michael addition by using α-substituted β-ketoester **5c**−**j**, which generates a configurationally stable quaternary stereocenter. To the best of our knowledge, there is no report of Michael reaction of ketoesters to nitroolefins constructing a stereogenic quaternary carbon center with high diastereo- and enantioselectivity. We screened a variety of nucleophiles, and the representative results are listed in Table 3, entries 3−10. The same reaction of ethyl 2-methylacetoacetate **5c** with **2a** in the presence of 10 mol % of **1e** completed within 6 h to provide the desired product **6c** in 89% yield (entry 3). Although the enantioselectivity of major product **6c** was still high (91% ee), the ratio of two diastereomers was moderate (78/22). The use of **5d** bearing a bulky alkyl group led to a decrease of the

Table 3. Enantio- and Diastereoselective Michael Reaction of **2a** with Ketoesters **5a**−**k** in the Presence of **1e**



entry	5	temp. (°C)	time (h)	yield[a] (%)	dr[b] (2*R*/2*S*)[c]	ee (%)[d] major
1	 **5a**	rt	0.5	91	-[d]	89[e]
2	 **5b**	rt	2	99	-[d]	89
3	 **5c**	rt	6	89	22/78	91
4	 **5d**	rt	48	87	36/64	95
5	 **5e**	-50	24	96	93/7	93
6	 **5f**	-20	36	93	96/4	85
7	 **5g**	-40	24	76	83/17	89
8	 **5h**	-50	3	96	57/43	93
9	 **5i**	rt	2	97	95/5	90
10	 **5j**	-60	24	94	7/93	81

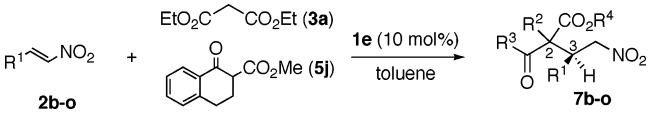
[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Relative configuration was determined by ^{1}H NMR(NOE) or X-ray analysis. [d] Enantiomeric excess was determined by HPLC analysis of **6** using a chiral column. [e] Absolute configuration was determined by comparing the retention time of HPLC of **6** with that of literature data.[12b]

diastereoselectivity, but the enantioselectivity was maintained at a high level (entry 4). Therefore, we turned our attention to cyclic ketoester **5e**−**j** as a reacting partner (entries 5−10). It was revealed that 2-methoxycarbonycyclopentanone **5e** added to **2a** to provide adduct **6e** with 93/7 diastereoselectivity and 93% ee at −50 °C. The scope of the reaction proved to be quite broad with respect to ring size of the nucleophile: five- to seven-membered substrates as well as bicyclic compounds could be employed to give the Michael adducts **6e**−**i** with good to high stereoselectivity with the exception of entry 8.

Furthermore, the reaction was applied to cyclic 1,3-diketone **5j** to give **6j** in 94% yield with good stereoselectivity (93/7 dr, 81% ee). The relative configurations of **6e** and **6j** were determined by comparing the ^{1}H NMR spectrum with that of literature data,[19] and those of **6f** and **6i** were determined by X-ray analysis. The relative configurations of **6c** and **6g** were determined by their NOE analysis of cyclic nitrones, which were transformed from **6c** and **6g**. The configuration of the remaining adducts was presumed from these results. It should be noted that acyclic 1,3-ketoesters **5c**,**d** afforded the major isomers **6c**,**d**

(19) Deutsch, J.; Niclas, H.-J.; Ramm, M. *J. Prakt. Chem.* **1995**, *337*, 23−28.

Table 4. Enantio- and Diastereoselective Michael Reaction of Nitroolefins **2b**−**o** in the Presence of **1e**



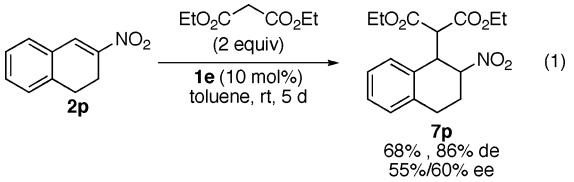
entry	R^1 (**2**)	**3**	yield (%, **7**)[a]	dr[b] (2*R*/2*S*)	ee[d,e] (%)
1	4-$MeOC_6H_4$ (**2b**)	**3a**	85 (**7b**)	−	91[f]
2	2,6-$(MeO)_2C_6H_3$ (**2c**)	**3a**	87 (**7c**)	−	93
3	3,4-$(OCH_2O)C_6H_3$ (**2d**)	**3a**	71 (**7d**)	−	86
4	4-FC_6H_4 (**2e**)	**3a**	87 (**7e**)	−	92
5	2-BrC_6H_4 (**2f**)	**3a**	96 (**7f**)	−	94[f]
6	1-naphthyl (**2g**)	**3a**	95 (**7g**)	−	92[f]
7	^{i}Bu (**2h**)	**3a**	88 (**7h**)	−	81
8	pentyl (**2i**)	**3a**	78 (**7i**)	−	81
9	2-thienyl (**2j**)	**3a**	74 (**7j**)	−	90[f]
10	*N*-Ts-3-indolyl (**2k**)	**3a**	64 (**7k**)	−	88[f]
11	4-FC_6H_4 (**2l**)	**5j**	93 (**7l**)	96/4	90[f]
12	4-BrC_6H_4 (**2m**)	**5j**	99 (**7m**)	97/3[c]	92[f]
13[g]	2-BrC_6H_4 (**2n**)	**5j**	94 (**7n**)	92/8	95[c]
14[h]	2-thienyl (**2o**)	**5j**	98 (**7o**)	99/1	90[f]

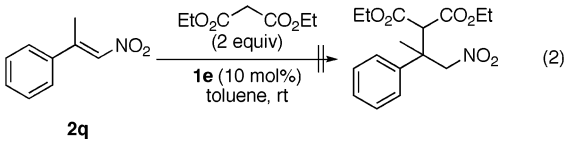
[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Absolute and relative configuration was determined by X-ray analysis. [d] Enantiomeric excess was determined by HPCL analysis of **7** using a chiral column. [e] Absolute configuration was determined by comparing the specific rotation of **7** with that of literature data.[12b] [f] Absolute configuration was not determined. [g] The reaction was carried out at −40 °C. [h] The reaction was carried out at −20 °C.

bearing 2*S* configuration, while cyclic 1,3-ketoesters **5e**−**j** provided the opposite diastereoisomers. (The reaction mechanism of these reactions is discussed later.) This is the first report of such highly diastereo- and enantioselective Michael addition of ketoesters to nitroolefins.

Michael Reaction with Various Nitroolefins. We screened various nitroolefins **2b**−**o** to reveal the scope and limitations of this reaction (Table 4). The Michael reaction of the aryl-substituted nitroolefins **2b**−**g** with malonate **3a** proceeded with excellent enantioselectivities (86−94% ee, entries 1−6). Electron-donating groups on the aryl group of **2b**−**d** prolonged reaction time, but did not affect the yield and selectivity (entries 1−3). Although the enantioselectivity of the reaction with the alkyl-substituted nitroolefins **2h**,**i** slightly decreased (81% ee, entries 7 and 8), nitroolefins **2j**,**k** bearing heteroaryl groups reacted with **3a** to afford the desired adduct **7j**,**k** in moderate to good yield with high enantioselectivity (entries 9 and 10). Similarly, we found that nitroolefins bearing aryl and heteroaryl groups were effective reacting partners in the Michael addition with cyclic β-ketoester **5j** (entries 11−14). The absolute configurations of **7c**−**e**, **h**, and **i** were determined by comparing the specific rotation of adducts with that of literature data.[12] The absolute and relative configuration of **7n** was determined by X-ray crystallographic analysis. In this way, it was revealed that all Michael adducts with various nitroolefins have the same absolute configuration 3*R* as that of the adducts listed in Tables 2 and 3.

We next examined the Michael reaction of α-substituted or β-disubstituted nitroolefins. Although 3-nitro-1,2-dihydronaphthalene **2p** reacted with malonate **3a** slowly to afford the corresponding adduct **7p** with moderate selectivity (86% de, 55% ee, eq 1), α-methyl-β-nitrostyrene **2q** did not provide the Michael adduct (eq 2). These results indicated that steric hindrance of the β-position of nitroolefins drastically reduced the reactivity.



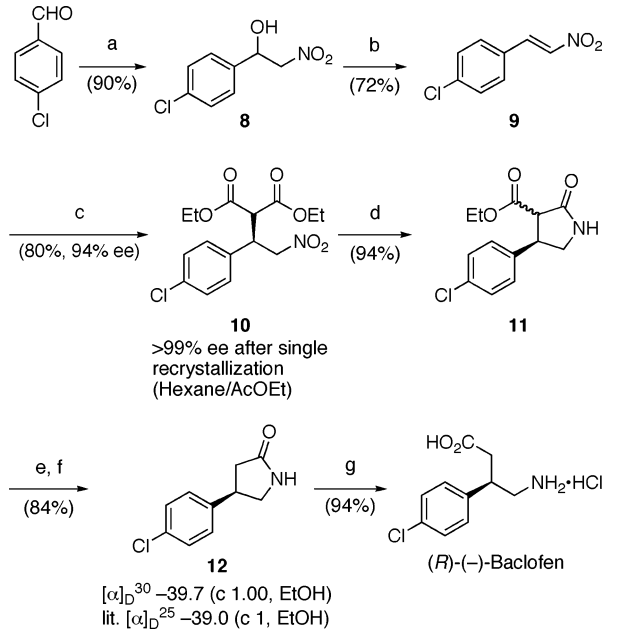


Synthesis of (*R*)-(−)-Baclofen. γ-Amino butylic acid (GABA) plays an important role as an inhibitory neurotransmitter in the central nervous system (CNS) of mammalians,[20,21] and the deficiency of GABA is associated with diseases that exhibit neuromuscular dysfunctions such as epilespy, Huntington's and Parkinson's diseases, etc.[22] Baclofen is a lipophilic analogue of GABA, and it is widely used as an antispastic agent. Although baclofen is commercialized in its racemic form, it has been reported that its biological activity resides exlusively in the (*R*)-enantiomer.[23] We next applied our enantioselective Michael reaction for the synthesis of (*R*)-(−)-baclofen (Scheme 1). The reaction of 4-chlorobenzaldehyde with nitromethane and subsequent dehydration of the resultant alcohol **8** provided nitroolefin **9**, which was reacted with diethyl malonate **3a** in the presence of 10 mol % of **1e** to afford the adduct **10** in 80% yield with 94% ee. Furthermore, enantiomerically pure **10** (>99% ee) was obtained after single recrystallization from Hexane/EtOAc. Reduction of the nitro group with nickel borite and in situ lactonization gave lactone **11** in 94%. The ester group of **11** was hydrolyzed and decarboxylated to afford **12**. The specific rotation of **12** was compared with that of literature data[24] ($[\alpha]^{30}_D$ −39.7° (*c* 1.00, EtOH), lit. $[\alpha]^{25}_D$ −39.0° (*c* 1, EtOH)), and, as expected, the absolute configuration of **12** was determined to be *R*. Lactam **12** was finally hydrolyzed with 6N HCl, affording enantiomerically pure (*R*)-(−)-baclofen as its hydrochloric salt with 38% overall yield in six steps from 4-chlorobenzaldehyde. Consequently, we succeeded in the synthesis of (*R*)-(−)-baclofen by the simple procedure with high enantioselctivity.

Reaction Mechanism. We finally evaluated the effects of the solvent and catalytic amount to elucidate the reaction mechanism (Table 5). In nonpolar solvents (toluene, CH_2Cl_2), **1e** efficiently promoted the reaction with **3a** to afford the adduct **4a** in moderate yield with high enantioselectivity (entries 1 and 2). In contrast, enantioselectivity of **4a** was low in methanol as a reaction solvent, since solvation of methanol to the nitro group of **2a** might disturb the hydrogen bonding of **1e** with **2a** (entry 3). Solvents such as THF and MeCN, which could form hydrogen bonding with **1e**, reduced the activity of **1e** and resulted in poor yields of **4a** (entries 4 and 5). When benzoyl

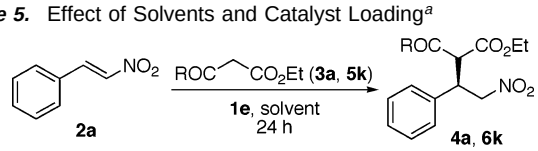
(20) (a) Bowery N. G.; Hill, D. R.; Hudson, A. L.; Doble, A.; Middemiss, N. D.; Shaw, J.; Turnbull, M. *Nature* **1980**, *283*, 92−94. (b) Silverman, R. B.; Levy, M. A. *J. Biol. Chem.* **1981**, *256*, 11565−11568.
(21) Mann, A.; Boulanger, T.; Brandau, B.; Durant, F.; Evrard, G.; Heaulme, M.; Desaulles, E.; Wermuth C. G. *J. Med. Chem.* **1991**, *34*, 1307−1313.
(22) Goka, V. N.; Schlewer, G.; Linget, J. M.; Chambon, J. P.; Wermuth, C. G. *J. Med. Chem.* **1991**, *34*, 2547−2557.
(23) Olpe, H. R.; Demiéville, H.; Baltzer, V.; Bencze, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133−136.
(24) Schoenfelder, A.; Mann, A.; Coz, S. L. *Synlett* **1993**, 63−64.

Scheme 1. Total Synthesis of (*R*)-(−)-Baclofen[a]



[a] Conditions: (a) $MeNO_2$, NaOMe, MeOH, room temperature, 15 h; (b) MsCl, TEA, THF, room temperature, 1 h; (c) diethyl malonate, **1e**, toluene, room temperature, 24 h; (d) $NiCl_2 \cdot 6H_2O$, $NaBH_4$, MeOH, room temperature, 7.5 h; (e) NaOH, EtOH, room temperature, 45 h; (f) toluene, reflux, 6.5 h; (g) 6N HCl, reflux, 24 h.

Table 5. Effect of Solvents and Catalyst Loading[a]



entry	R	solvent	temp (°C)	**1e** (mol %)	yield[b] (%)	ee[c,d] (%)
1	OEt	toluene	rt	10	60	92
2	OEt	CH_2Cl_2	rt	10	53	90
3	OEt	MeOH	rt	10	33	29
4	OEt	MeCN	rt	10	47	75
5	OEt	THF	rt	10	29	88
6	Ph	toluene	−40	10	93	94
7	Ph	toluene	−40	5	95	94
8	Ph	toluene	−40	2	96	94

[a] The reaction was conducted with **2a** (1 equiv), **3a**, or **5k** and various solvents in the presence of **1e** at room temperature. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis of **4a** and **6k** using a chiral column. [d] Absolute configuration was determined by comparing the specific rotation of **4a** and **6k** with that of literature data.[12b]

acetate **5k** was employed as a nucleophile, the reaction completed shortly, providing adduct **7k** in 93% yield with 94% ee (entry 6). It should be emphasized that Michael reaction could be carried out with only 5−2 mol % of **1e** without decreasing chemical yield and enantioselectivity (entries 7 and 8).

To identify the hydrogen bonding between nitroolefin **2a** and thiourea, we took the ^{1}H NMR spectra of **2a** in the presence of several thioureas. Although there was little change in the ^{1}H NMR spectrum of **1e** by mixing with **2a**, the ^{1}H NMR spectrum of a mixture of the bis-arylthiourea **1p** and nitroolefin **2a** revealed some information about the interaction of **2a** with **1p** through hydrogen bonding (Figure 5). The chemical shifts of H^a and H^b of **1p** were gradually shifted to downfield with increasing the ratio of **3a** to **1p**. When **1p** was mixed with **3a** (**1p**/**3a** = 1/3), the chemical shift of H^a was shifted from 6.63 to 6.70 ppm, and the chemical shift of H^b

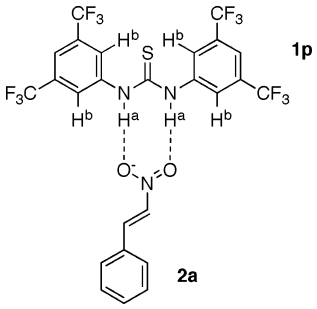


Figure 5. Recognition of nitroolefin with thiourea.

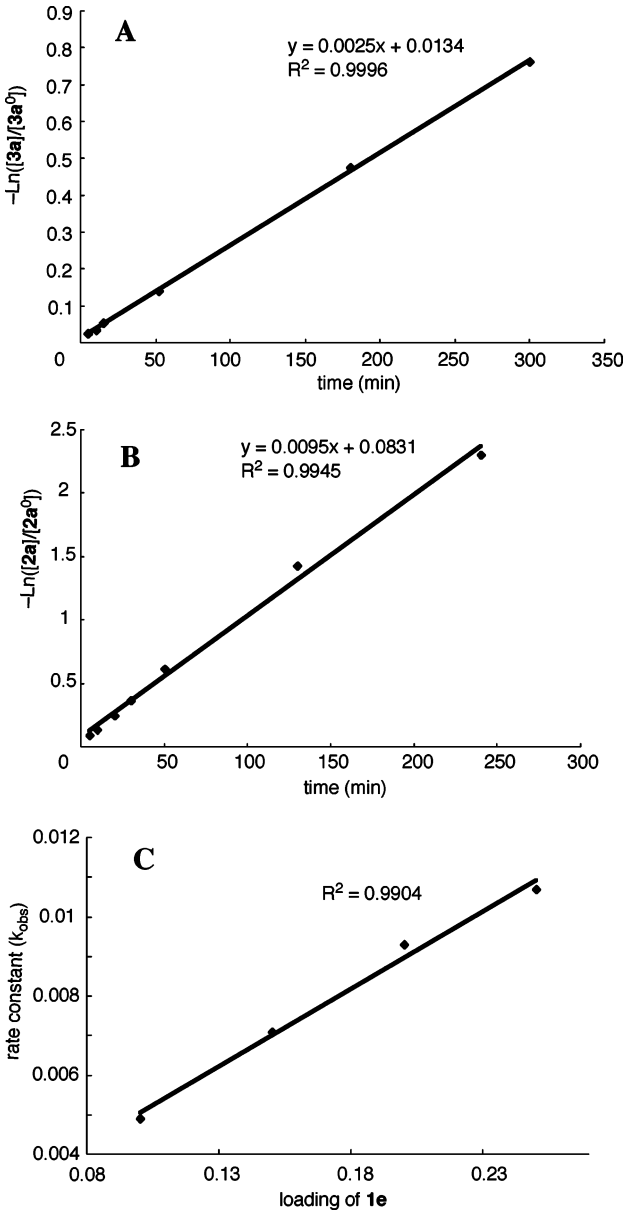


Figure 6. Kinetic studies on the Michael reaction of **2a** with **3a**.

was shifted from 7.31 to 7.35 ppm. It implied that the acidic protons (H^a) of **1p** interacted with two oxygens of the nitro group in **2a**.

To obtain further information about the reaction mechanism, we carried out kinetic studies on the Michael reaction. When the reaction was carried out with a large excess of **3a**, plotting in ln([**2a**]/[**2a**^{0}]) versus time gave a straight line (R^2 = 0.9959,

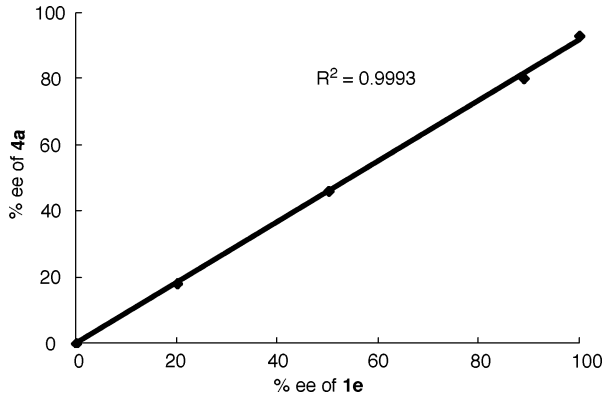


Figure 7. Observation of nonlinear effect of **1e** with **4a**.

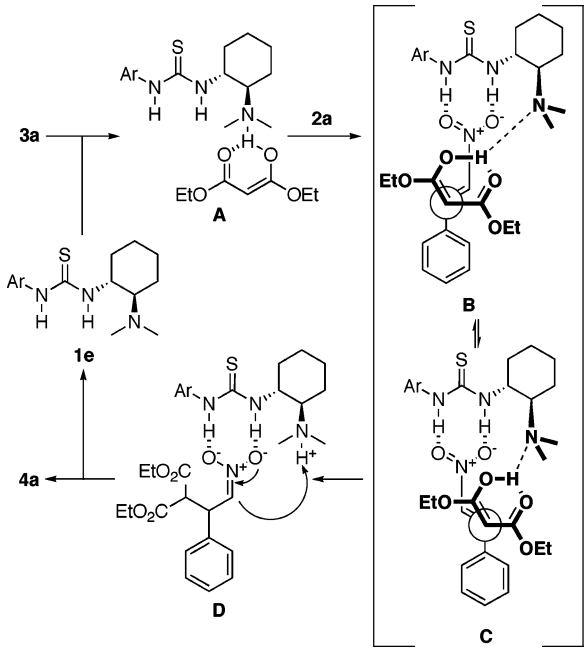


Figure 8. Transition-state models of Michael reactions of malonate.

Figure 6A), which indicates the reaction is first-order in **2a**. By the same procedure, it was determined that the reaction was first-order in **3a** (Figure 6B). The order in catalyst was also examined by plotting the kinetic rate constant (k_{obs}) against the loading of **1e** (Figure 6C), which indicates that the reaction is first-order in **1e**.

Figure 7 indicated the relationship between the ee value of catalyst **1e** used in the Michael reaction and the ee value of the Michael adduct. If the linear relationship is not followed, that implies association of the chiral catalysts, which give a diastereomeric active species. But the relationship obtained was linear, suggesting that the active catalyst is a monomeric species.[25]

A plausible reaction cascade is shown in Figure 8. The amino group of a monomeric catalyst **1e** first deprotonates an acidic proton of malonate **3a**, generating the complex **A** of **3a** and **1e**. Then nitroolefin **2a** interacts with the complex **A** through the hydrogen bonding, forming a new ternary complex (**B** or **C**). On the basis of the product configuration, the reaction would proceed through complex **B** to give the nitronate complex **D**,

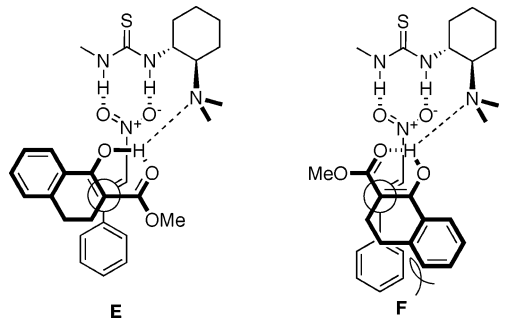


Figure 9. Transition-state models of Michael reactions of ketoester.

bearing *R* configuration, with high selectivity. Although the reason for the high enantioselectivity is not clarified at this stage, we assumed that the cyclohexyl scaffold of the catalyst would restrict the approach of **3a** to **2a** (Figure 8). Since the generated nitronate has two negatively charged oxygens on the nitrogen atom, the thiourea could stabilize the nitronate more effectively in complex **D**. Finally, the nitronate takes the proton from the amino group of the catalyst to provide the product **4a** along with the catalyst.

In the reactions of ketoesters **5a**−**j** with nitroolefin **2a**, the absolute configurations of the C2 position of the products are determined by the size of the alkyl groups adjacent to each carbonyl group of ketoesters, which restrict approach of ketoester to nitroolefin (Figure 9). In the case of cyclic ketoester **5i** with **2a**, to avoid steric repulsion between the phenyl group of **2a** and the cyclohexane ring of **5i**, the Michael reaction would proceed via transition state **E**, giving the (2*R*,3*S*) adduct **6i**. The proposed mechanism is compatible with the experimental results.

Conclusion

In conclusion, we have prepared a variety of novel bifunctional organocatalysts that possess a thiourea moiety and an amino group. We investigated the structure−activity relationship of these catalysts in the Michael reaction of 1,3-dicarbonyl compounds to various nitroolefins to find that the catalyst **1e** is the best for the Michael reaction among these catalysts. Using **1e**, we succeeded in the total synthesis of (*R*)-(−)-baclofen with a simple and mild procedure. In addition, we examined the Michael reaction of α-substituted *β*-ketoesters to *β*-nitrostyrene with **1e** to construct contiguous stereogenetic centers containing an asymmetric quaternary carbon. In many cases, the Michael adducts were obtained with high enantio- and diastereoselectivity. Finally, kinetic studies were investigated to propose the reaction mechanism.

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Supporting Information Available: Experimental procedures, characterization of the catalysts and products, and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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