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Michael Reaction

Diphenylprolinol Silyl Ether Catalyzed Asymmetric Michael Reaction of Nitroalkanes and β,β-Disubstituted α,β-Unsaturated Aldehydes for the Construction of All-Carbon Quaternary Stereogenic Centers

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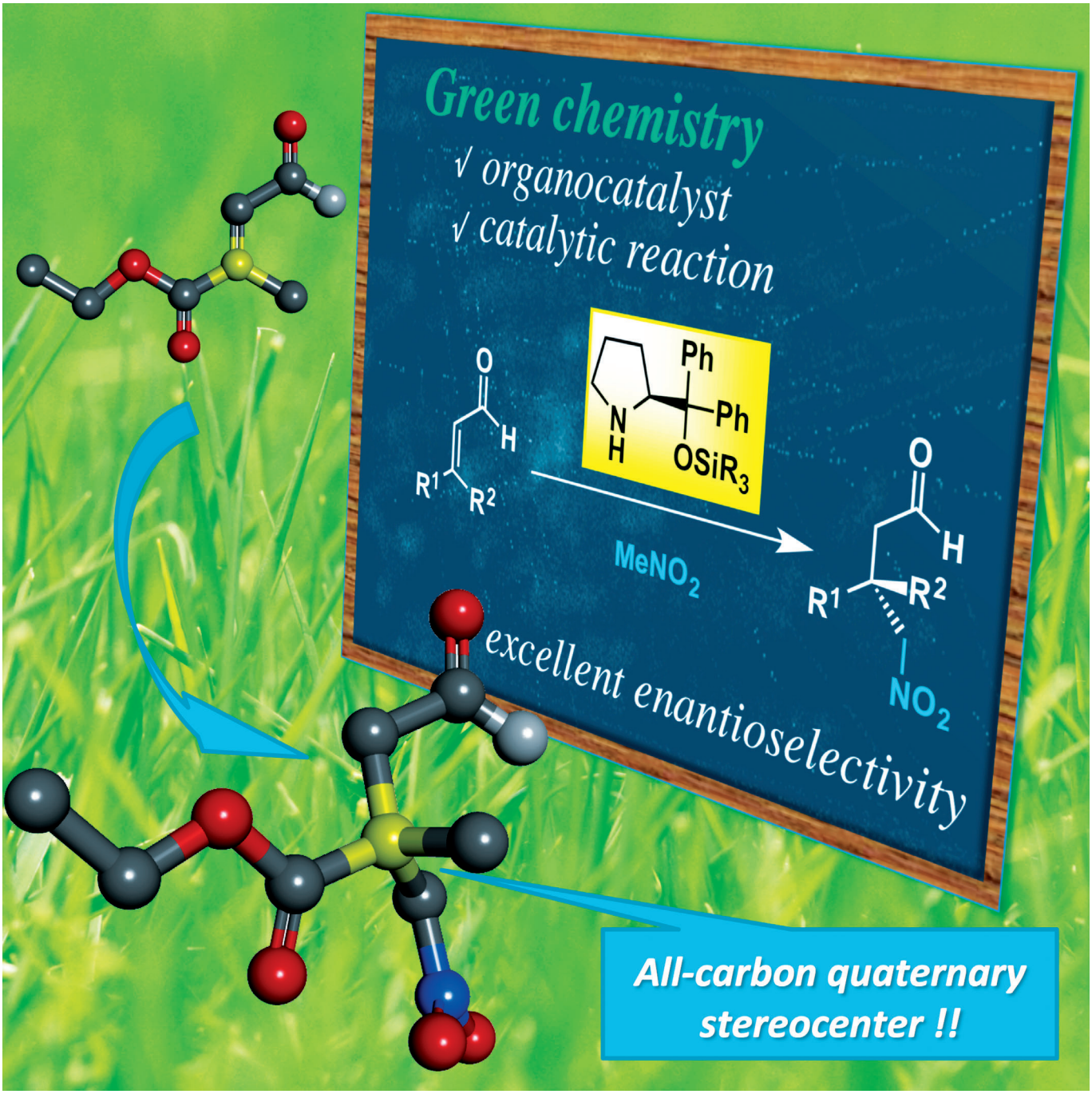
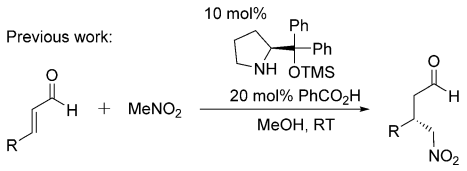


Abstract: The asymmetric Michael reaction of nitroalkanes and β,β-disubstituted α,β-unsaturated aldehydes was catalyzed by diphenylprolinol silyl ether to afford 1,4-addition products with an all-carbon quaternary stereogenic center with excellent enantioselectivity. The reaction is general for β-substituents such as β-aryl and β-alkyl groups, and both nitromethane and nitroethane can be employed. The addition of nitroethane is considered a synthetic equivalent of the asymmetric Michael reaction of ethyl and acetyl substituents by means of radical denitration and Nef reaction, respectively. The short asymmetric synthesis of (*S*)-ethosuximide with a quaternary carbon center was accomplished by using the present asymmetric Michael reaction as the key step. The reaction mechanism that involves the *E*/*Z* isomerization of α,β-unsaturated aldehydes, the retro-Michael reaction, and the different reactivity between nitromethane and nitroethane is discussed.

Introduction

The Michael reaction of carbon nucleophiles is one of the synthetically useful carbon–carbon bond-forming reactions. Recently, organocatalysts[1] have been employed in various asymmetric catalytic Michael reactions with great success.[2] Construction of an all-carbon quaternary stereogenic center is a synthetically important topic in current synthetic organic chemistry.[3] Even though there are several successful asymmetric Michael reactions that use α,α-disubstituted aldehydes[4] and 2-substituted-1,3-dicarbonyl compounds[5] as nucleophiles, several challenges remain for the asymmetric Michael reaction to construct an all-carbon quaternary stereogenic center using an organocatalyst. The Michael reaction of carbon nucleophiles onto β,β-disubstituted α,β-unsaturated carbonyl compounds is another method for the construction of all-carbon quaternary stereogenic centers. As a carbon nucleophile, nitroalkanes are useful nucleophiles because they can be converted into several functional groups.[6] Yet the asymmetric Michael reaction of β,β-disubstituted α,β-unsaturated carbonyl compounds with nitroalkanes using organocatalysts is still rare. Ley and co-workers reported one example of the Michael reaction of 3-methylcyclohexenone and nitromethane catalyzed by 5-pyrrolidin-2-yltetrazole.[7] Kudo and Akagawa reported the peptide-mediated asymmetric Michael reaction of nitromethane and β,β-disubstituted α,β-unsaturated aldehydes with excellent enantioselectivity.[8,9] Kwiatkowski and co-workers also reported the asymmetric Michael reaction of β,β-disubstituted enones with nitromethane catalyzed by a cinchonine-derived organocatalyst under high pressure.[10] In the peptide-mediated reaction, the catalyst with a high molecular weight was employed to obtain excellent enantioselectivity, and high pressure was necessary for completion of the reaction. Only nitromethane was employed in these reactions, and there is no successful report of nitroethane.

In 2007, we reported the asymmetric Michael reaction of nitroalkanes with β-monosubstituted α,β-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether [Eq. (1)],[11] an organocatalyst developed independently by our group[12] and Jørgensen's group.[13] The obtained γ-nitro aldehyde can be transformed into a γ-amino carboxylic acid, and we synthesized pregabalin and bachlofen by using this asymmetric Michael reaction of nitromethane and β-monosubstituted α,β-unsaturated aldehyde as the key step.[11a] In the present paper, we further applied this reaction to β,β-disubstituted α,β-unsaturated aldehydes and describe in full the asymmetric Michael reaction of nitroalkanes to construct all-carbon quaternary stereogenic centers with high enantioselectivity [Eq. (2)].



Results

We chose the reaction of ethyl 2-methyl-4-oxobut-2-enoate (*E*/*Z* = 95:5) and nitromethane as a model and examined the reaction conditions [Table 1, Eq. (3)]. In the previous reaction of β-monosubstituted α,β-unsaturated aldehydes, the reaction proceeded in MeOH catalyzed by diphenylprolinol trimethylsilyl ether **1** (Figure 1) to afford the Michael product in good yield with excellent enantioselectivity [Eq. (1)].[11a] When we employed the same catalyst **1** and MeOH as a solvent, the Henry reaction proceeded to afford β-hydroxynitro compound **5** in 72% yield with no desired Michael product (Table 1, entry 1). In toluene, the reaction barely proceeded (Table 1, entry 2), and both Michael and Henry reaction products were obtained in CH_3CN (Table 1, entry 3). The Michael product was obtained in good yield with good enantioselectivity in hexane, in which two-phases formed owing to the low solubility of nitrome-

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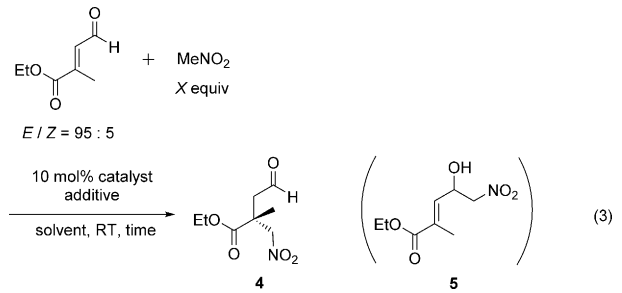
Table 1. Effect of solvent, acid additive, and stoichiometry of CH_3NO_2 on the organocatalytic Michael reaction of ethyl 2-methyl-4-oxobut-2-enoate.[a]

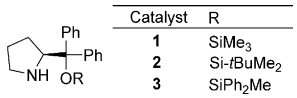


(3)

4 5

Entry	Catalyst	*X* [equiv][b]	Solvent	Additive	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**1**	10	MeOH	–	16	<5[e]	–
2	**1**	10	toluene	–	24	<5	–
3	**1**	10	MeCN	–	120	32[f]	–
4	**1**	10	hexane	–	24	77	83
5	**1**	10	neat	–	22	77	86
6	**1**	10	neat	$PhCO_2H$	24	27	84
7	**1**	10	neat	p-$NO_2C_6H_4OH$	24	22	91
8	**1**	10	neat	$ClCH_2CO_2H$	24	7	82
9	**1**	5	neat	–	24	87	91
10	**1**	28	neat	–	19	90	88
11	**2**	5	neat	–	24	82	90
12	**3**	5	neat	–	19	91	90

[a] Unless noted otherwise, reactions were performed by employing ethyl 2-methyl-4-oxobut-2-enoate (0.5 mmol), nitromethane (2.5, 5, 14 mmol), organocatalyst (0.05 mmol, 10 mol%) and additive (0.1 mmol) in solvent (1.0 mL) or neat at room temperature for the indicated time. [b] Equivalents of nitromethane. [c] Yield of purified Michael product. [d] Enantiomeric excess of the Michael product, which was determined by HPLC analysis on a chiral phase. [e] Henry product **5** was obtained in 72% yield. [f] Henry product **5** was obtained in 12% yield.



Catalyst	R
1	$SiMe_3$
2	Si-*t*$BuMe_2$
3	$SiPh_2Me$

Figure 1. Catalysts examined in this study.

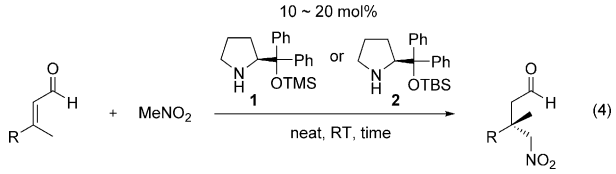
thane in hexane (Table 1, entry 4). When the reaction was performed neat (10 equiv of CH_3NO_2), the product was obtained in 77% yield with 86%*ee* (Table 1, entry 5). Next, we investigated the potential effects of acid as described previously.[11a] Acids such as benzoic acid, *p*-nitrobenzoic acid, chloroacetic acid, and trifluoroacetic acid were found to be unsuitable, as they provided several side products, and the desired product was obtained in low yield (Table 1, entries 6–8). The amount of nitromethane could be reduced to five equivalents (Table 1, entry 9). The effect of the bulky silyl ether substituents on enantioselectivity of the catalyst was also investigated. Not only trimethylsilyl ether **1**, but also *tert*-butyldimethylsilyl ether **2** and diphenylmethylsilyl ether **3**[14] were found to be efficient catalysts; they afforded the Michael product in similarly high enantioselectivities (Table 1, entries 11, 12). Thus, trimethylsilyl ether **1** and *tert*-butyldimethylsilyl ether **2** were selected for further study.

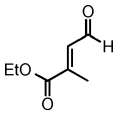
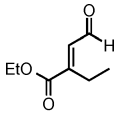
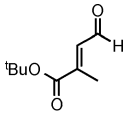
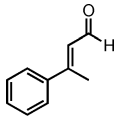
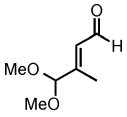
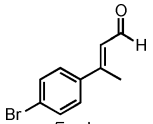
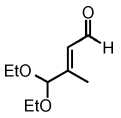
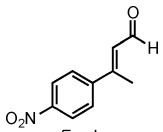
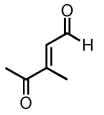
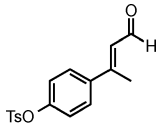
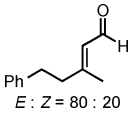
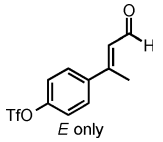
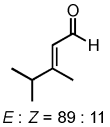
Having optimized the Michael reaction conditions for ethyl 2-methyl-4-oxobut-2-enoate, the generality of the reaction with the other β,β-disubstituted α,β-unsaturated aldehydes was investigated [Table 2, Eq. (4)]. As the reaction was slow with *tert*-butyl 2-methyl-4-oxobut-2-enoate on account of the bulkiness of the *tert*-butyl ester, 10 equivalents of nitromethane were employed to afford the product in good yield with 89%*ee* (Table 2, entry 2). Although an *E*/*Z* mixture of Michael acceptors with low isomeric ratios was employed in the reaction with dimethoxy and diethoxy butenal derivatives, excellent enantioselectivities resulted (see below; Table 2, entries 3 and 4). 3-Methyl-4-oxopent-2-enal can be employed as a Michael acceptor, and the desired product was generated in good yield and enantioselectivity (Table 2, entry 5). The enantioselectivity of the reaction of 3-methyl-5-phenylpent-2-enal, which bears two different alkyl β-substituents, was 72%. Although lower than other substrates, similar steric effects appear to exist between the two substituents at the β-position, such as the methyl and 2-phenylethyl substituents (Table 2, entry 6). For the reaction of 3,4-dimethylpent-2-enal, which bears the sterically distinct β-substituents isopropyl and methyl, good enantioselectivity resulted (Table 2, entry 7). When the methyl β-substituent was extended to ethyl, such as in ethyl 2-ethyl-4-oxobut-2-enoate, the enantioselectivity dropped to 80%*ee* (Table 2, entry 8).

Next, the Michael reaction of β-aryl-substituted substrate was examined. Akagawa and Kudo reported the resin-supported peptide catalyst Pro-D-Pro-Aib-$(Trp)_2$-$(Leu)_6$-resin as an efficient catalyst for the Michael addition of nitromethane to 3-phenylbut-2-enal.[8] In their investigation, they used diphenylprolinol silyl ether **1** as a control catalyst under nonoptimized conditions and found that the product was obtained in 12% yield with 88%*ee*. They used 20 mol% of catalyst with five equivalents of nitromethane in water in the presence of 20 mol% of benzoic acid at room temperature. Using our best reaction conditions for catalyst **1** (see above) under neat conditions using five equivalents of nitromethane, several byproducts were obtained with the desired product in low yield. After some optimization, the reaction of 3-phenyl-2-butenal and nitromethane (28 equiv) proceeded well when catalyzed by TBS-ether **2** (TBS = *tert*-butyldimethylsilyl). This provided the Michael product in 49% yield with 88%*ee* (Table 2, entry 9). The generality of the reaction of β-aryl, β-alkyl α,β-unsaturated aldehydes was investigated under these reaction conditions. Not only phenyl but also *p*-bromophenyl, *p*-nitrophenyl, *p*-toluenesulfonyloxylphenyl, and trifluoromethanesulfonyloxyphenyl were found to be suitable aryl substituents, and the reaction proceeded efficiently to afford the Michael products with excellent enantioselectivity (Table 2, entries 10–13).

Next, we examined the reaction using nitroethane instead of nitromethane. Under reaction conditions with five equivalents of nitroalkane, the Michael product was obtained in low yield with moderate enantioselectivity owing to side products such as **7** [Eq. (5); Table 3, entry 1]. Cyclohexadiene derivative **7** would be generated by the Michael reaction of dienamine[15] and α,β-enal followed by intramolecular aldol reaction and dehydration (Scheme 1). When the amount of nitroethane was in-

Table 2. Michael reaction of nitromethane and β,β-disubstituted α,β-unsaturated aldehydes.[a]



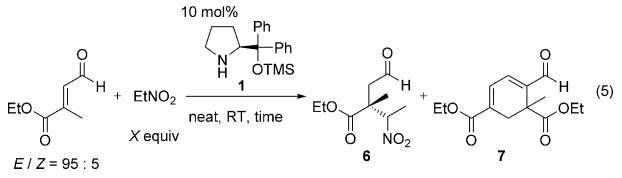
Entry	Starting material	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]	Entry	Starting material	Catalyst	*t* [h]	Yield [%][b]	*ee* [%][c]
1	 *E* : *Z* = 95 : 5	**1**	24	87	91	8[g]	 *E* only	**1**	18	67	80
2[d]	 *E* : *Z* = 90 : 10	**1**	24	76	89	9[h]	 *E* only	**2**	69	49	88
3	 *E* : *Z* = 78 : 22	**1**	28	78	91	10[h]	 *E* only	**2**	82	81	88
4	 *E* : *Z* = 68 : 32	**1**	16	76	91	11[h]	 *E* only	**2**	49	69	89
5	 *E* : *Z* = 90 : 10	**1**	7	88	90	12[h]	 *E* only	**2**	52	89	90
6[e]	 *E* : *Z* = 80 : 20	**1**	2	74	72	13[h]	 *E* only	**2**	54	38	87
7[f]	 *E* : *Z* = 89 : 11	**1**	10	62	86						

[a] Unless noted otherwise, reactions were performed by employing Michael acceptor (0.5 mmol), nitromethane (2.5 mmol), and organocatalyst **1** (0.05 mmol, 10 mol%) or **2** (0.10 mmol, 20 mol%) at room temperature for the indicated time. [b] Isolated yield of Michael product. [c] Enantiomeric excess of the Michael product, which was determined by HPLC analysis on a chiral phase. [d] Nitromethane (5 mmol) was employed. [e] Catalyst (0.1 mmol) was employed. [f] Nitromethane (14 mmol) and H_2O (1 mmol) were employed. [g] Catalyst (0.1 mmol) and nitromethane (7.5 mmol) were employed and the reaction was performed at 0 °C. [h] Nitromethane (14 mmol) was employed and the reaction was performed at 0 °C to RT.

creased from five to ten equivalents, a good yield of the desired Michael product **6** resulted. Even though the diastereoselectivity was not high, and the relative stereochemistry was not determined, the two diastereomers possessed similarly good enantioselectivity (Table 3, entry 4).

The generality of the reaction of nitroethane with β,β-disubstituted α,β-unsaturated aldehydes is summarized in Table 4 [Eq. (6)]. When one of the β-substituents is an electron-withdrawing group—for example, ethoxycarbonyl, methoxycarbonyl, or diethoxymethyl—excellent enantioselectivity was obtained (Table 4, entries 1–3). When both β-substituents are alkyl groups, such as in 3-methyl-5-phenylpent-2-enal, moderate enantioselectivity was obtained (Table 4, entry 4). When the *trans*-β-substituent was an aryl group, phenyl, *p*-bromophenyl, *p*-nitrophenyl, *p*-toluenesulfonyloxyphenyl, and trifluoromethanesulfonyloxyphenyl were all found to be suitable aryl substituents, and the reaction proceeded efficiently to afford the Michael products with excellent enantioselectivity (Table 4, entries 5–10). However, diastereoselectivity of the reaction of nitroethane is low. It should be noted that the reaction of nitro-

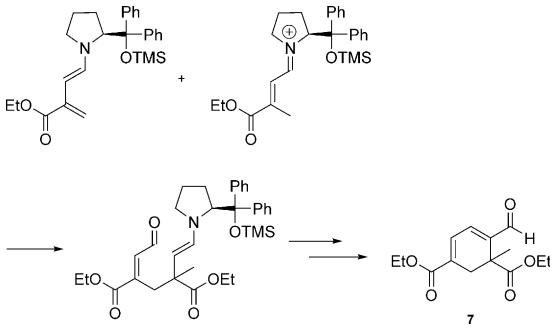
Table 3. Effect of nitroethane stoichiometry on the organocatalytic Michael reaction of ethyl 2-methyl-4-oxobut-2-enoate.[a]



E / *Z* = 95 : 5

Entry	*X* [equiv][b]	*t* [h]	Yield **6** [%][c]	Yield **7** [%][c]	d.r.[d]	*ee* [%][e]
1	5	50	45	34	1.3:1	54, 59
2	10	17	85	< 5	1.6:1	85, 88
3	28	7	78	< 5	1.4:1	85, 88
4[f]	28	22	77	< 5	1.5:1	91, 91

[a] Unless noted otherwise, reactions were performed with ethyl 2-methyl-4-oxobut-2-enoate (0.5 mmol), nitroethane (2.5, 5 or 14 mmol), and organocatalyst **1** (0.05 mmol, 10 mol%) at room temperature for the indicated time. [b] Equivalents of nitroethane. [c] Isolated yield. [d] Diastereomer ratio, as determined by ^{1}H NMR spectroscopy. [e] Enantiomeric excess of the Michael product, as determined by HPLC analysis on a chiral phase. [f] Reaction was performed at 0 °C.



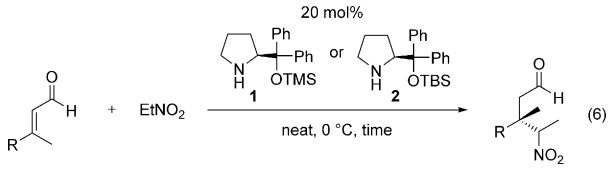
Scheme 1. Michael–aldol–dehydrative sequence to generate **7**.

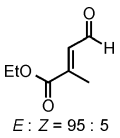
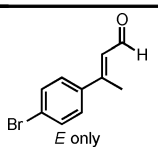
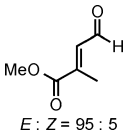
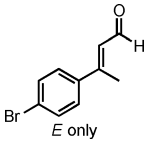
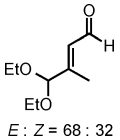
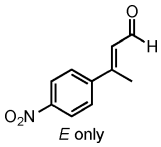
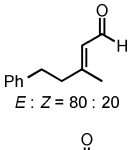
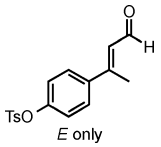
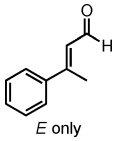
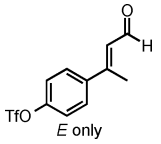
ethane is much faster than that of nitromethane in most of the cases (see below).

Synthetic utility and determination of the absolute configuration

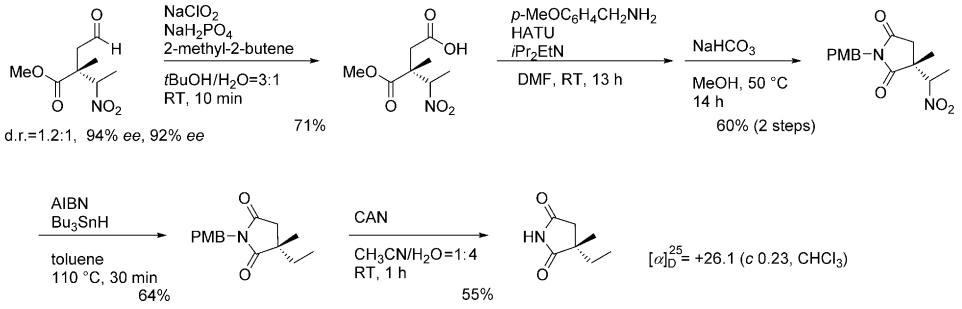
As the Michael product possesses a γ-nitro aldehyde moiety, it can be converted into a γ-amino carboxylic acid with β,β-di-

Table 4. Michael reaction of nitroethane and β,β-disubstituted α,β-unsaturated aldehyde.[a]



Entry	Starting material	Catalyst	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]	Entry	Starting material	Catalyst	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	 *E* : *Z* = 95 : 5	**1**	22	77	1.5:1	91, 91	6	 *E* only	**2**	27	77	1:1	85, 89
2	 *E* : *Z* = 95 : 5	**1**	24	75	1.2:1	94, 92	7	 *E* only	**1**	27	72	1:1	83, 88
3	 *E* : *Z* = 68 : 32	**1**	23	72	2:1	96, 93	8	 *E* only	**2**	25	77	1:1	92, 93
4	 *E* : *Z* = 80 : 20	**1**	17	94	1:1	75, 68	9	 *E* only	**2**	25	94	1:1	88, 90
5	 *E* only	**2**	8	60	1:1	88, 93	10	 *E* only	**2**	24	62	1:1	86, 91

[a] Unless noted otherwise, reactions were performed by employing Michael acceptor (0.5 mmol), nitroethane (14 mmol), and organocatalyst **1** or **2** (0.1 mmol, 20 mol%) at 0 °C for the indicated time. [b] Yield of purified compound. [c] Diastereomer ratio, as determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excess of the Michael product, as determined by HPLC analysis on a chiral phase.



Scheme 2. Asymmetric synthesis of (*S*)-ethosuximide.

substituents. Akagawa and Kudo already demonstrated this transformation and also described the importance of these compounds.[8] The reaction of nitroethane afforded the Michael product with low diastereoselectivity. Both diastereomers can be transformed into the same synthetically useful compounds. As the nitro moiety can be converted into hydrogen by means of radical denitration,[6,16] the asymmetric Michael reaction of nitroethane is a synthetic equivalent of an asymmetric Michael reaction of an ethyl group.

To illustrate this utility, we synthesized (*S*)-ethosuximide, which is used to treat petit mal epilepsy,[17] by means of our diphenylprolinol silyl ether mediated Michael reaction of nitroethane as the key step (Scheme 2). The Michael product of methyl 2-methyl-4-oxobut-2-enoate and nitroethane catalyzed by TMS ether **1** (1.2:1 diastereomer mixture, 94 and 92% *ee*; Table 4, entry 2) was oxidized to its carboxylic acid by means of Kraus oxidation[18] in 71% yield. Amide coupling with *p*-methoxybenzylamine (PMB-NH_2) using 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) and *i*Pr_2EtN afforded its amide, which was directly treated with $NaHCO_3$ to provide its imide in 60% yield in two steps. Radical denitration with Bu_3SnH in the presence of catalytic azobisisobutyronitrile (AIBN) provided the denitrated compound in 64% yield. Subsequent treatment of the imide with ammonium hexanitratocerate(IV) (CAN)[19] afforded (*S*)-(+)-ethosuximide in 55% yield. All spectroscopic and optical properties were found to be in good agreement with the literature.[17c]

The absolute configuration of the Michael adduct between methyl 2-methyl-4-oxobut-2-enoate and nitroethane was also confirmed after conversion to a known dimethyl 2-ethyl-2-methylsuccinate (Scheme 3). The Michael adduct (Table 4, entry 2) was converted into its carboxylic acid by Kraus oxidation, which was treated with $TMSCHN_2$ to afford the bis-methyl ester. Radical denitration afforded dimethyl 2-ethyl-2-methylsuccinate. Comparison of the optical rotation of the literature data[20] indicated that the Michael product had an *S* configuration.

The nitro group can be converted into the carbonyl group using the Nef reaction.[6] After the Michael product was reduced to alcohol, it was protected as its benzyl ether. When the nitro compound was treated with $KMnO_4$ supported on SiO_2,[21] the ketone was obtained in 52% yield [Eq. (7)]. Thus, the asymmetric Michael reaction of nitroethane was shown to be the synthetic equivalent (umpolung) for a nucleophilic acetyl group.

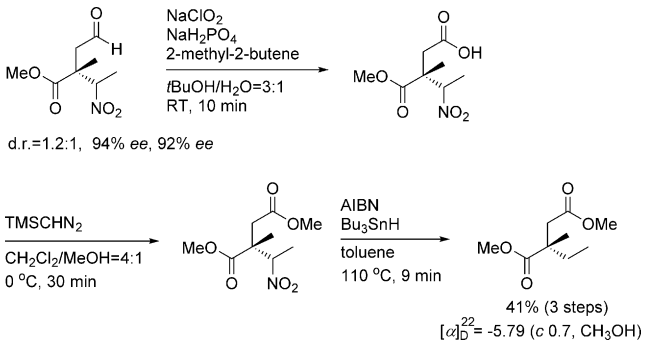
Even though the diastereoselectivity of the Michael reaction of nitroethane is relatively low, the conversion of nitroethyl group into ethyl group or acetyl group can be achieved readily, in which both diastereomers can be converted into the same synthetically useful compound.

Discussion

Isomerization between *E* and *Z* isomers of α,β-unsaturated aldehyde

A mixture of *E* and *Z* isomers of the α,β-unsaturated aldehyde was employed in the previous reactions. Even though the *E*/*Z* ratio of the starting α,β-unsaturated aldehyde was rather low in some cases, excellent enantioselectivity was obtained. As opposite enantiomers would be generated between the *E* and *Z* isomers, we began to investigate the effect of the *E*/*Z* ratio of the α,β-unsaturated aldehyde toward the enantioselectivity of the Michael product. MacMillan et al.[22] and List et al.[23] independently reported similar phenomena in the organo-catalyzed Hantzsch ester reduction of β,β-disubstituted α,β-unsaturated aldehydes, in which a facile *E*/*Z* isomerization of the α,β-unsaturated aldehyde was demonstrated. Kudo et al. also observed the same phenomena in the peptide-catalyzed Michael reaction of β,β-disubstituted α,β-unsaturated aldehyde and nitromethane.[8] We prepared 3-(4-toluenesulfonyloxyphenyl)but-2-enal with different *E*/*Z* ratios: $Z/E => 95:<5$ or $Z/E = 56:44$. These α,β-unsaturated aldehydes were treated with diphenylprolinol silyl ether **2** in *i*$PrNO_2$ as a solvent because it does not react with α,β-unsaturated aldehydes owing to steric reasons, and the reaction was monitored for changes in the *E*/*Z* ratio over time. The results are shown in Figure 2 [Eq. (8)]. Starting from pure *E* isomer, the *Z* isomer was generated gradually. After 8 h, the reaction reached equilibrium, in which the *E*/*Z* ratio was 72:28. The same ratio was reached after 8 h when starting from an *E* and *Z* mixture of $E/Z = 56:44$. These results indicate that there is equilibration between the *E* and *Z* isomers, and a steady-state *E*/*Z* equilibration was reached within 8 h.

We also investigated the progress of the reaction of nitromethane and 3-(4-toluenesulfonyloxyphenyl)but-2-enal starting from the α,β-unsaturated aldehyde with different *E*/*Z* ratios. The results are summarized in Figure 3 [Eq. (9)]. The profile of the *E*/*Z* ratio of the α,β-unsaturated aldehyde according to time was found to be different between the reactions with nitromethane with α,β-unsaturated aldehyde using a pure *E* isomer relative to a starting mixture of *E* and *Z* isomers ($E/Z = 56:44$). In the reaction starting with pure *E* isomer, the *E*/*Z* ratio gradually decreased to 80:20 after 55 h. In comparison, the *E*/*Z* ratio initially decreases and then increases to reach 40:60 after



Scheme 3. Determination of the absolute configuration.

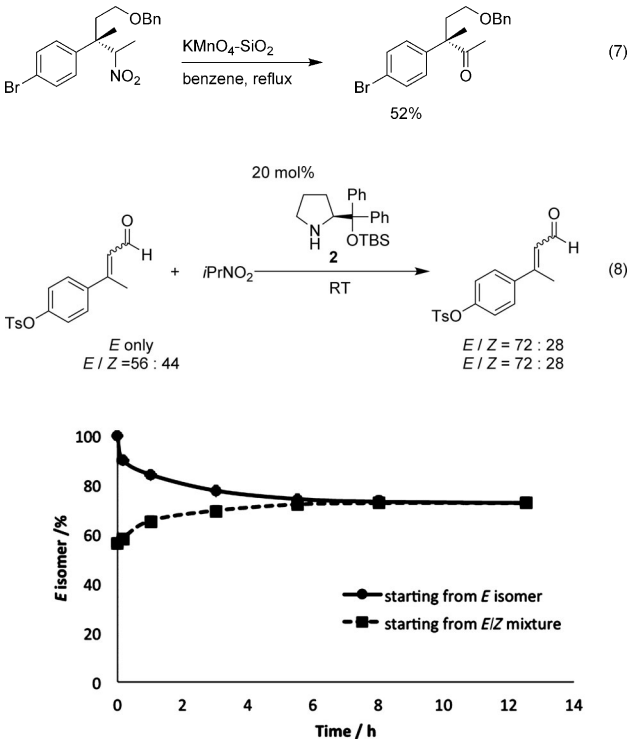


Figure 2. Relationship between the *E*/*Z* ratio of the Michael acceptor and the reaction time in the presence of catalyst **2** and *i*PrNO$_2$.

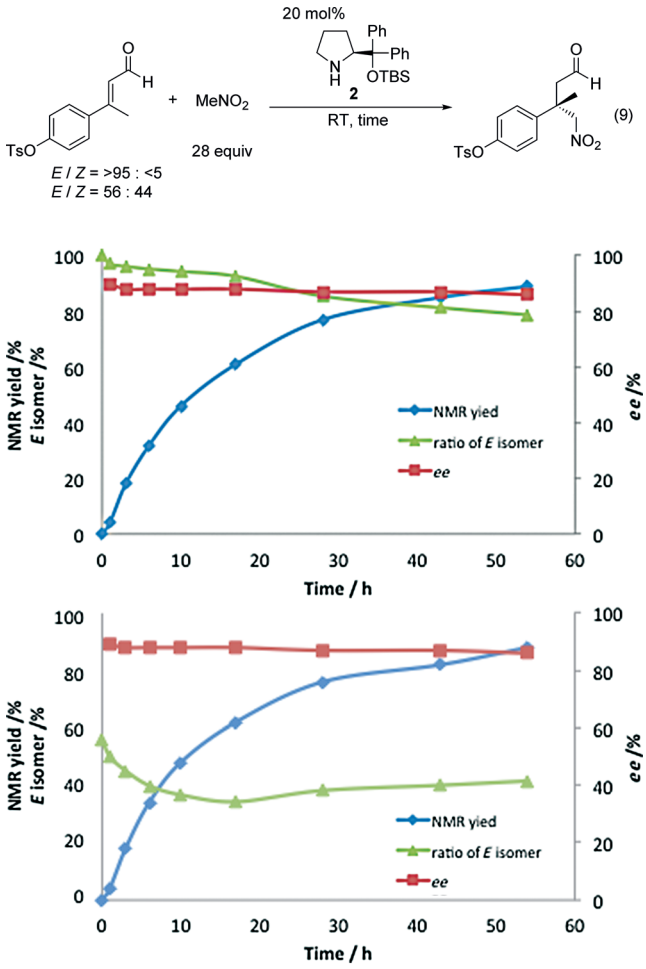


Figure 3. Reaction profiles of Michael reaction starting from α,β-unsaturated aldehydes with different *E*/*Z* ratios. Top: Starting from only the *E* isomer. Bottom: Starting from the *E*/*Z* mixture (*E*/*Z* = 56:44).

time, and profile of enantioselectivity according to time, are identical between the two reactions, whether by using α,β-unsaturated aldehyde as a pure *E* isomer or as a mixture of *E* and *Z* isomers (*E*/*Z* = 56:44). Notably, the resultant yield and enantioselectivity are identical for both reactions, despite the start-

55 h when starting from a mixture of *E* and *Z* isomers (*E*/*Z* = 56:44). These results indicate that the *E* isomer reacts preferentially with nitromethane over the *Z* isomer and there is a slower process of isomerization between the *E* and *Z* isomers. Isomerization between *Z* and *E* isomers would proceed through a dienamine intermediate or through the addition–elimination of water to the iminium ion (Figure 4). The reaction profile of yields according to reaction

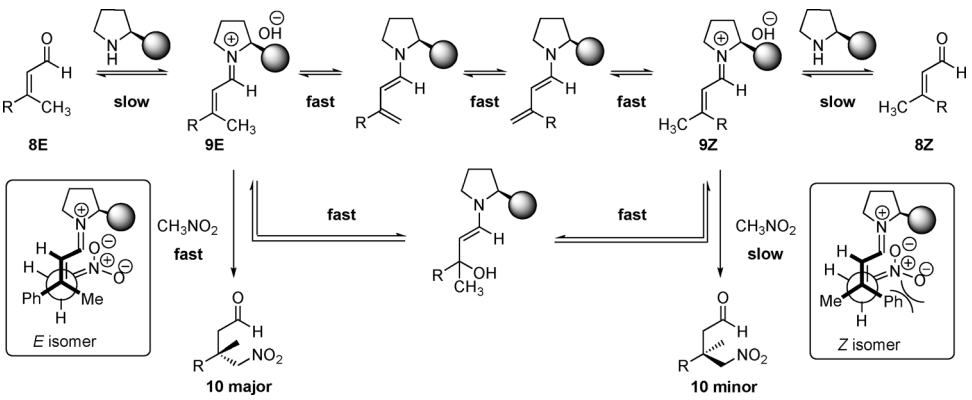


Figure 4. Relative reaction rates between the interconversion of *E*- and *Z*-α,β-unsaturated aldehydes and proline-catalyst derivatives, and eventual addition of nitromethane.

ing *E*/*Z* ratio of the α,β-unsaturated aldehyde and the apparently slow isomerization rate between the *E* and *Z* isomers. This can be reasonably explained by considering the following three conditions (Figure 4): 1) the condensation reactions of the α,β-unsaturated aldehydes **8E** and **8Z** with the catalyst **2** to afford iminium salts **9E** and **9Z** are the slowest processes; 2) the isomerization processes between **9E** and **9Z** are relatively fast; and 3) the nitronate anion reacts with the iminium salts **9E** and **9Z** by means of an acyclic synclinical transition state as proposed by Seebach et al.[24] Figure 4 shows the transition-state model for the reaction of *E* and *Z* isomers of 3-phenylbut-2-enal. In this model, electrostatic interactions between the nitro group and iminium ion are proposed to operate. There are larger steric repulsions between the phenyl and nitro groups at the synclinical position in the *Z* isomer relative to the repulsions between the methyl and nitro groups in the *E* isomer. Thus, the reaction of the *E* isomer (**9E**) is rationalized to be much faster. Under these considerations, the reaction profiles of Figures 2 and 3 would thus be observed.

Importantly, these reactivity profiles mean that it is not necessary to prepare pure *E* or *Z* α,β-unsaturated aldehydes, which is a practical advantage. It is also noteworthy that the enantioselectivity remained constant during the course of these reactions with nitromethane (see below).

Michael reaction and retro-Michael reaction

When we investigated the reaction of nitroethane and β-aryl-substituted α,β-unsaturated aldehydes, we observed a decrease in enantioselectivity during the reaction. Although the enantioselectivity of the Michael product of the reaction of nitromethane is constant during the reaction, as shown in Figure 3 (see above), the reaction of nitroethane and β-aryl-substituted α,β-unsaturated aldehyde was found to change [Figure 5, Eq. (10)]. When the reaction was conducted at 0 °C for the first

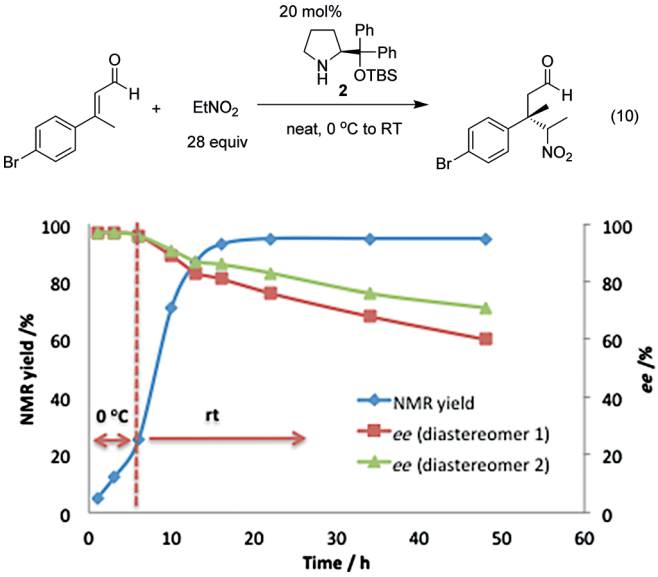


Figure 5. Relationship between enantioselectivity and reaction time in the Michael reaction of nitroethane and 3-(4-bromophenyl)but-2-enal.

8 h, the reaction proceeded slowly but the enantioselectivity was excellent and constant. When the reaction temperature was increased to room temperature, the enantioselectivity began to decrease. These results suggest a retro-Michael reaction that occurs at room temperature for the present substrate.

To confirm the retro-Michael reaction, we monitored the following reaction [Figure 6, Eq. (11)]. We thus treated the Michael product of nitroethane and 3-(4-bromophenyl)but-2-enal with nitromethane in the presence of diphenylprolinol silyl

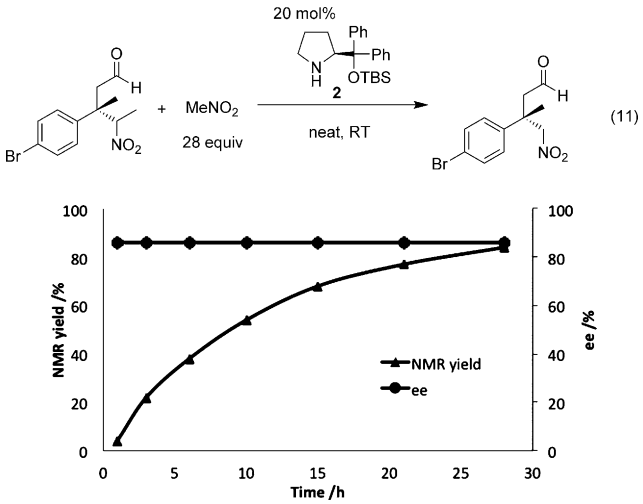


Figure 6. Generation of the Michael adduct of nitromethane from the Michael product of nitroethane.

ether **2**. The starting Michael product with nitroethane was gradually converted into a new Michael adduct with nitromethane, which at all time points gave excellent enantioselectivity throughout the reaction time.

However, when the Michael product of 3-(4-bromophenyl)-but-2-enal and nitromethane was treated with nitroethane in the presence of catalyst **2**, the reaction did not proceed. These results indicate that a retro-Michael reaction proceeded from the Michael product of nitroethane at room temperature, and that this retro reaction was slower at 0 °C. For nitromethane, the retro-Michael reaction did not proceed during the reaction of the Michael product at room temperature. We also investigated other β,β-disubstituted α,β-unsaturated aldehydes and found that no retro-Michael reaction occurred in the β,β-dialkyl-substituted α,β-unsaturated aldehyde, even at room temperature. Thus, the retro-Michael reaction was found to be dependent on the substrate and temperature. The steric hindrance in the Michael product of nitroethane and β-aryl-substituted α,β-unsaturated aldehyde would facilitate the retro-Michael reaction. Thus, it was found essential to carry out the Michael reaction of these substrates at 0 °C to obtain high enantioselectivity.

The reactivity of nitromethane and nitroethane

When we were investigating the generality of the reaction using nitromethane and nitroethane, we noticed that in most

cases the reaction of nitroethane was faster than the reaction of nitromethane. These results are counterintuitive to the idea that nitromethane should be more nucleophilic and react faster than nitroethane under pure steric grounds. We therefore decided to investigate the reactivity between nitromethane and nitroethane systematically.

We chose four representative Michael acceptors such as 3-methyl-5-pent-2-enal, 3,4-dimethylpent-2-enal, ethyl 2-methyl-4-oxobut-2-enoate, and 3-(4-bromophenyl)but-2-enal. The reactions were performed as follows: A mixture of Michael acceptor, nitromethane (14 equiv), and nitroethane (14 equiv) was treated with diphenylprolinol silyl ether (10 or 20 mol%) and the progress of the reaction was monitored over time by ^{1}H NMR spectroscopy (Figures 7–10).

In the reaction of 3-(4-bromophenyl)but-2-enal, the reaction was first carried out at 0 °C for 116 h. After this time, the reaction temperature was increased to room temperature [Figure 7, Eq. (12)]. The reactivity of nitroethane was found to be higher than that of nitromethane at 0 °C. The reaction profile dramatically changed at 116 h. The yield of Michael adduct of nitroethane decreased, whereas that of nitromethane increased rapidly. At 212 h, the yield of nitromethane adducts overtook that of nitroethane. This is because a retro-Michael reaction of the Michael adduct of nitroethane occurs at room temperature, whereas retro-Michael reactions for nitromethane do not proceed, as illustrated in the previous section. Even though the reaction profile is complicated after 116 h, the resultant reactivity of nitroethane was clearly found to be higher than that of nitromethane in these cases.

In other reactions of 3-methyl-5-phenylpent-2-enal and ethyl 2-methyl-4-oxobut-2-enoate, nitroethane was also more reactive than nitromethane [Figures 8 and 9; Eqs. (13) and (14)]. Only in the reaction of 3,4-dimethylpent-2-enal was nitromethane found to be more reactive than nitroethane [Figure 10, Eq. (15)]. This can be explained by the reaction mechanism given in Scheme 4. The reaction begins by formation of an iminium ion and hydroxy ion from the α,β-unsaturated aldehyde and catalyst. The hydroxide anion acts as a base to transform

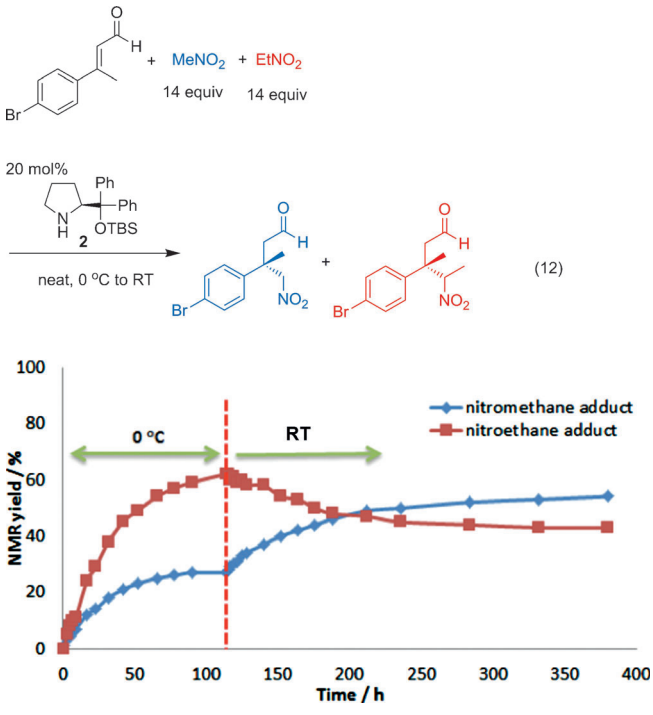


Figure 7. Competitive reaction of 3-(4-bromophenyl)but-2-enal with nitromethane and nitroethane.

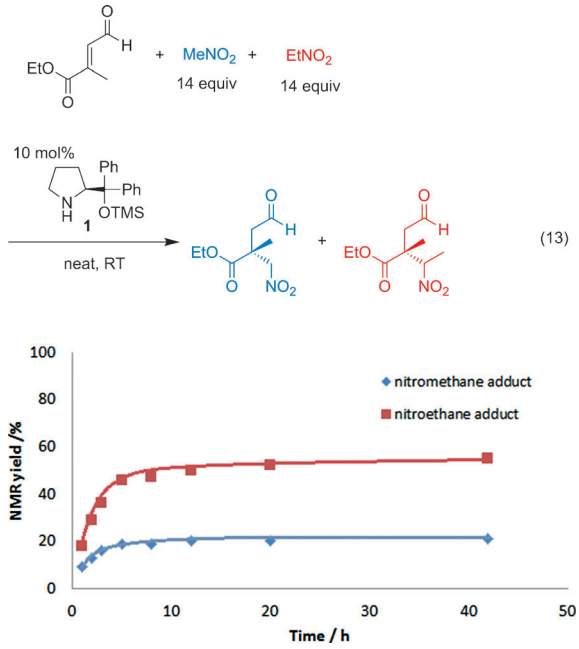


Figure 8. Competitive reaction of ethyl 2-methyl-4-oxobut-2-enoate with nitromethane and nitroethane.

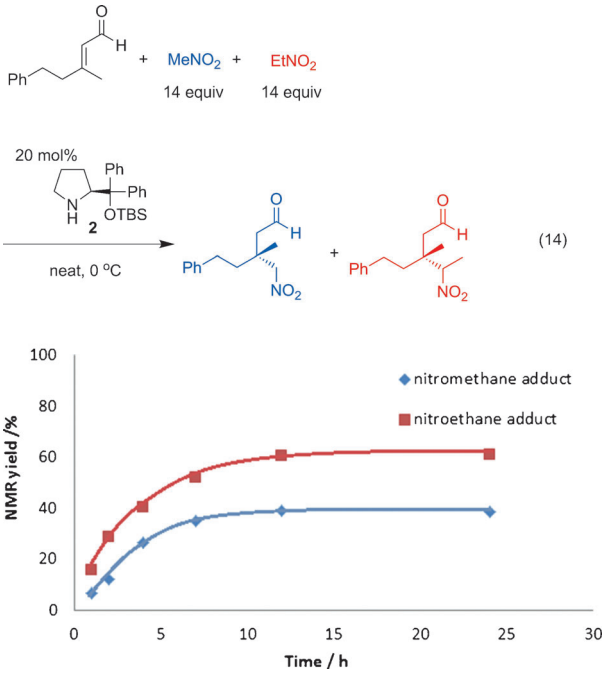


Figure 9. Competitive reaction of 3-methyl-5-phenylpent-2-enal with nitromethane and nitroethane.

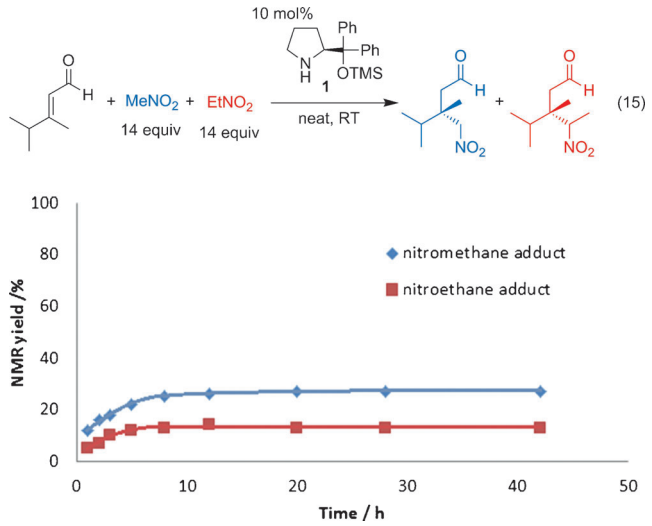
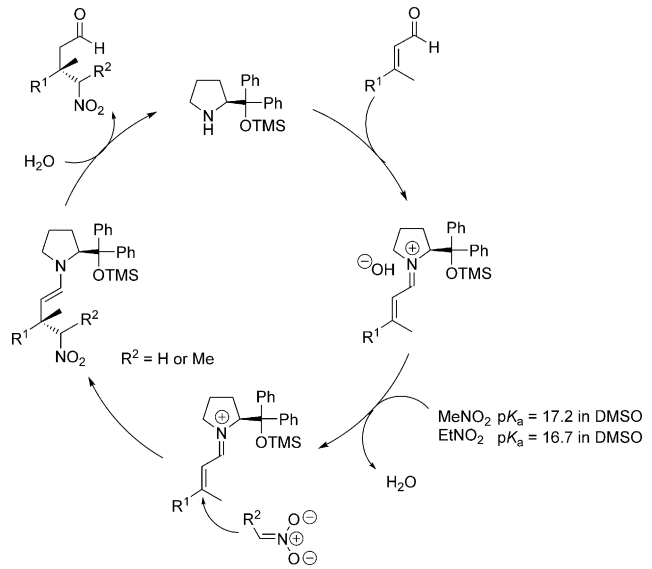


Figure 10. Competitive reaction of 3,4-dimethylpent-2-enal with nitromethane and nitroethane.

the nitroalkane to its aci-nitronate ion, which then reacts with the iminium ion in a 1,4-addition manner to generate an enamine. During this addition reaction, the nucleophile attacks from the *Si* face of the iminium salt preferentially because the opposite *Re* face is covered by the bulky diphenyltrimethylsiloxymethyl moiety of the catalyst. This is one reason why excellent enantioselectivity was obtained. The enamine reacts with water to afford the Michael product with recovery of the catalyst. The pK_a of nitromethane is 17.2 in DMSO, whereas that of nitroethane is 16.7.[25] As nitroethane is more acidic than nitromethane, the anion of nitroethane would generate more readily, thereby reacting with the iminium ion faster than the anion of nitromethane. Thus, the reaction of nitroethane is faster than that of nitromethane in general. This said, the reactivity of nitromethane is higher than that of nitroethane in the reaction of 3,4-dimethylpent-2-enal, which is much more sterically hindered than other Michael acceptors. In the reaction of 3,4-dimethylpent-2-enal, which possesses a bulky isopropyl group and a methyl group at the β-position of the α,β-unsaturated aldehyde, the anion of nitroethane can not react on account of steric repulsions, whereas the anion of nitromethane, the smaller nucleophile, reacts more readily.



Scheme 4. Prolinol silyl ether catalytic reaction mechanism.

Conclusion

We have developed the asymmetric Michael reaction of nitroalkanes and β,β-disubstituted α,β-unsaturated aldehydes catalyzed by diphenylprolinol silyl ether to afford Michael adducts with all-carbon quaternary stereogenic centers in excellent enantioselectivity. There are several noteworthy features in this reaction: 1) As there is a facile *E*/*Z* isomerization between the *E* and *Z* isomers of the β,β-disubstituted α,β-unsaturated aldehyde under the reaction conditions, it is not necessary to separate the *E* and *Z* isomers, which is a practical advantage. 2) Not only nitromethane but also nitroethane can be employed as the nucleophile. 3) Although the diastereoselectivity of the reaction using nitroethane is low, the addition of nitroethane is regarded as a Michael reaction of an ethyl group or an acetyl group by successive radical denitration or Nef reactions, respectively. 4) The Michael products are known to be readily converted into medicinally useful β,β-disubstituted γ-amino acids. 5) Temperature-dependent retro-Michael reactions can decrease the enantioselectivity during the course of the reaction, as observed during the reaction of nitroethane and β-aryl-β-alkyl-substituted α,β-unsaturated aldehydes, and a careful selection of reaction conditions needs to be considered for some substrates. 6) Generally the reactivity of nitroethane is higher than that of nitromethane owing largely to the acidity of the α-proton of the nitro group, but the order of reactivity may be reversed in some cases on account of overriding steric effects.

Acknowledgements

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Keywords: asymmetric synthesis · enantioselectivity · isomerization · Michael addition · organocatalysis

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