Asymmetric Michael addition of aldehydes to nitroalkenes using a primary amino acid lithium salt†

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Received 9th March 2010, Accepted 16th April 2010
First published as an Advance Article on the web 12th May 2010
DOI: 10.1039/c003940c

Enantioselective Michael addition of aldehydes to nitroalkenes was successfully carried out by asymmetric catalysis with L-phenylalanine lithium salt, giving γ-nitroaldehydes in good yields with high enantioselectivity.

Introduction

Asymmetric carbon–carbon bond formation is an extremely important technology in modern organic synthesis. An exhaustive investigation of transition metal catalysts and asymmetric ligands by chemists has made various organic syntheses with high enantioselectivity possible. Compared with the history of transition metal catalysis, asymmetric organocatalysis is still in a developing period; however, organocatalysis has achieved explosive growth in the past decade.[1] In organocatalysis based on the formation of an imine–enamine intermediate from carbonyl compounds, secondary amines, especially L-proline and its derivatives, have generally been employed as catalysts. Within common natural amino acids, however, only a few secondary amino acids are available, while more than 20 types of primary amino acids are readily obtainable from commercial sources. Although the use of primary amines as asymmetric catalysts is behind compared with that of secondary amines, results of successful works have been published in recent years.[2]

The Michael addition of aldehydes to nitroalkenes is a useful method to obtain γ-nitroaldehydes, and various enantioselective organocatalyses have been published.[3–5] Most of them are enamine-based catalyses using a secondary amine catalyst,[4] since secondary amines can generate enamines from carbonyl compounds more readily than can primary amines. However, in the case of using sterically hindered carbonyl compounds, such as α-branched aldehydes, as substrates, primary amines can generate enamines more readily than can secondary amines. Indeed, primary amine catalysts are generally effective for the Michael addition of α-branched aldehydes with nitroalkenes.[5] Recently, we found that the Michael addition of isobutyraldehyde with nitrostyrene was effectively promoted by a primary amino acid lithium salt, and we reported the results in a short communication.[6,7] In this paper, we disclose the details of primary amino acid lithium salt-catalyzed Michael addition reactions of various aldehydes with nitroalkenes.

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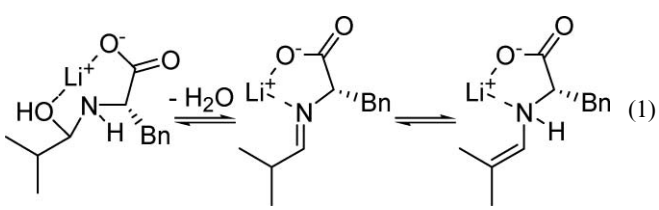
† Electronic supplementary information (ESI) available: Compound characterization data of the Michael adducts **3**. See DOI: 10.1039/c003940c

Results and discussion

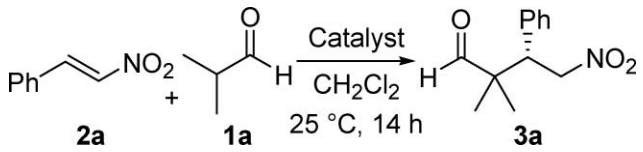
First, we examined the Michael addition of isobutyraldehyde (**1a**) to (*E*)-β-nitrostyrene (**2a**) by using a primary amino acid, L-phenylalanine, as a catalyst; however, the catalyst did not dissolve in the reaction media and no reaction was observed (Table 1, entry 1). We assumed that the addition of L-phenylalanine to **1a** did not occur well, since the amino acid firmly forms a zwitterion, $R(NH_3^+)COO^-$, in the reaction conditions. Therefore, in order to increase the basicity, L-phenylalanine was treated with a base to prepare an amino acid salt, Phe–OM.[7] To our delight, we found that L-phenylalanine lithium salt, which can be readily prepared from L-phenylalanine and lithium hydroxide, promoted the reaction of **1a** with **2a** effectively to give the Michael adduct **3a** in 92% yield with 94% ee (Table 1, entry 2). Other alkaline metal salts and a magnesium salt of L-phenylalanine also promoted the Michael addition to afford **3a** with high enantioselectivity; however, the reaction rate was reduced compared to that of the lithium salt (Table 1, entries 3–7). Methyl L-phenylalaninate was also used as a catalyst; however, the starting material **2a** was recovered (Table 1, entry 8). From these results, it was found that an amino acid lithium salt is necessary to progress the Michael addition of **1a** to **2a** effectively. The lithium cation probably behaves as a Lewis acid to aid the formation of enamine between the catalyst and **1a**, as shown in eqn (1).[8] Although an attack of an enolate of **1a** can produce **3a**, the enamine mechanism seems to be preferable, since the use of a stronger base than the lithium salt resulted in a slow reaction rate.[2,5,9]



(1)

Then, other readily obtainable amino acid lithium salts were evaluated for the Michael addition reaction. Relatively bulky amino acids, L-phenylalanine, L-valine, D-phenylglycine and L-*tert*-leucine, gave **3a** with over 90% ee (Table 1, entries 9–11). A secondary amino acid, L-proline, and its lithium salt did not show catalytic activity under the reaction conditions (Table 1, entries 18 and 19). *O*-*tert*-Butyldimethylsilyl tyrosine lithium salt, Tyr(*O*-TBS)-OLi, was very soluble in dichloromethane; however,

Table 1 Catalyst screen for the Michael addition of **1a** to **2a**[a]



2a **1a** **3a**

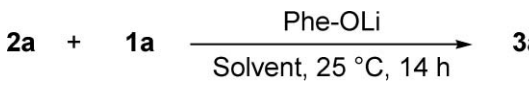
Entry	Catalyst[b]	Yield [c](%)	ee[d] (%)
1	Phe-OH	n.r.	—
2	Phe-OLi	92	94
3	Phe-ONa	84	83
4	Phe-OK	73	88
5	Phe-ORb	60	84
6	Phe-OCs	22	92
7	Phe-OMgBr	11	92
8	Phe-OCH_3	n.r.	—
9	Val-OLi	89	94
10	D-PhenylGly-OLi	92	94[e]
11	*tert*-Leu-OLi	80	93
12	Leu-OLi	93	80
13	Ile-OLi	95	88
14	Ala-OLi	70	87
15	Trp-OLi	90	84
16	Met-OLi	91	78
17	Ser-OLi	32	67
18	Pro-OLi	Trace	—
19	Pro-OH	n.r.	—
20	Tyr(*O*-TBS)-OLi	80	94

[a] The reaction was carried out with **1a** (1 mmol), **2a** (0.5 mmol) and a catalyst (0.1 mmol) in dichloromethane (1 mL) at 25 °C for 14 h. [b] Phe: L-phenylalanine; Val: L-valine; D-PhenylGly: D-2-phenylglycine; Leu: L-leucine; Ile: L-isoleucine; Ala: L-alanine; Trp: L-tryptophane; Met: L-methionine; Ser: L-serine; Pro: L-proline; Tyr: L-tyrosine. [c] Isolated yield based on **2a**. [d] Determined by chiral HPLC analysis. The absolute configuration of the major enantiomer was determined as *S* by comparison of the optical rotation with that of the literature.[11] [e] (*R*)-**3a** was obtained as a major enantiomer.

no enhancement of the reaction rate and enantioselectivity was observed (Table 1, entry 20).[10]

Next, we examined a solvent screen with Phe–OLi (Table 2). The Michael addition of **1a** with **2a** in a high-polarity solvent, DMSO or DMF, gave the Michael adduct **3a** in low yields with low enantioselectivity with many minor products, although nitroalkene **2a** was consumed very rapidly (Table 2, entries 1 and 2). In CH_3CN, acetone, AcOEt, THF and Et_2O, the Michael adduct **3a** was afforded in high yields with moderate enantioselectivity (Table 2, entries 3–7). When low-polarity solvents, $CHCl_3$, CH_2Cl_2, 1,2-dichloroethane and toluene, were used, better enantioselectivity was observed than that with high-polarity solvents (over 90% ee) (Table 2, entries 8–11). Hexane gave relatively poor results due to the low solubility of **2a** and the catalyst in the solvent (Table 2, entry 12). Thus, CH_2Cl_2 was chosen as a solvent for further investigations.

Table 2 Solvent screen for the Michael addition of **1a** to **2a**[a]

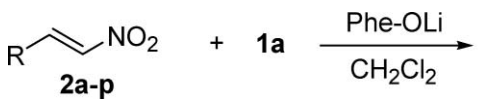


Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	DMSO	14	43
2	DMF	18	58
3	CH_3CN	90	90
4	Acetone	82	85
5	AcOEt	96	86
6	THF	95	83
7	Et_2O	86	86
8	$CHCl_3$	93	92
9	CH_2Cl_2	92	94
10	$(CH_2Cl)_2$	88	94
11	Toluene	82	93
12	Hexane	76	86

[a] The reaction was carried out with **1a** (1 mmol), **2a** (0.5 mmol) and Phe-OLi (0.1 mmol) in a solvent (1 mL) at 25 °C for 14 h. [b] Isolated yield based on **2a**. [c] Determined by chiral HPLC analysis.

Next, we examined further optimization of the reaction conditions for Michael addition of **1a** to **2a** with Phe–OLi in CH_2Cl_2 and found that the reaction was completed within 5 h at 25 °C (Table 3, entry 1). Although a longer reaction time was required, the amount of **1a** could be reduced to 1.2 equivalents to **2a** without considerable loss of yield and enantioselectivity of the product **3a** (Table 3, entry 2). By carrying out the reaction at 0 °C, the enantioselectivity was improved to 98% ee (Table 3, entry 3). We then investigated the substrate scope of the reaction

Table 3 Michael addition of **1a** with nitroalkenes **2a–p** using L-phenylalanine lithium salt as a catalyst[a]

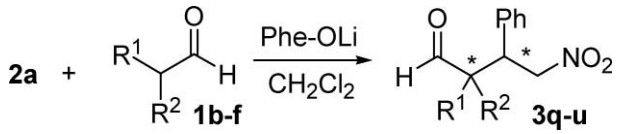


2a-p

Entry	*R*	*T*/°C	*t*/h	Yield[b] (%)	ee[c] (%)
1	Ph, **2a**	25	5	92, **3a**	94
2[d]	Ph, **2a**	25	10	85, **3a**	93
3	Ph, **2a**	0	72	82, **3a**	98
4	4-$CH_3OC_6H_4$, **2b**	25	6	88, **3b**	93
5	4-$CH_3OC_6H_4$, **2b**	0	72	92, **3b**	96
6	4-BrC_6H_4, **2c**	25	4	86, **3c**	94
7	4-BrC_6H_4, **2c**	0	72	81, **3c**	99
8	3-BrC_6H_4, **2d**	25	5	89, **3d**	86
9	3-BrC_6H_4, **2d**	0	72	86, **3d**	92
10	2-BrC_6H_4, **2e**	25	5	82, **3e**	86
11	2-BrC_6H_4, **2e**	0	72	83, **3e**	92
12	4-FC_6H_4, **2f**	25	5	87, **3f**	95
13	4-FC_6H_4, **2f**	0	72	72, **3f**	99
14	4-$(CO_2CH_3)C_6H_4$, **2g**	25	5	94, **3g**	89
15	4-$(CO_2CH_3)C_6H_4$, **2g**	0	72	94, **3g**	96
16	4-$NO_2C_6H_4$, **2h**	25	5	91, **3h**	90
17	4-$NO_2C_6H_4$, **2h**	0	72	87, **3h**	97
18	Furan-2-yl, **2i**	25	5	91, **3i**	87
19	Furan-2-yl, **2i**	0	72	71, **3i**	96
20	Thiophen-2-yl, **2j**	25	5	95, **3j**	86
21	Thiophen-2-yl, **2j**	0	72	96, **3j**	95
22	3-Pyridyl, **2k**	25	7	76, **3k**	89
23	3-Pyridyl, **2k**	0	72	78, **3k**	93
24	(*E*)-PhCH=CH, **2l**	25	8	89, **3l**	91
25	(*E*)-PhCH=CH, **2l**	0	72	57,[e] **3l**	96
26	(*E*)-C_3H_7CH=CH, **2m**	25	16	91, **3m**	94
27	Cyclohexyl, **2n**	25	120	8,[f] **3n**	88
28	$PhCH_2CH_2$, **2o**	25	120	41,[g] **3o**	88
29	CH_3, **2p**	25	24	60, **3p**	91

[a] Unless otherwise mentioned, the reaction was carried out with **1a** (1 mmol), **2** (0.5 mmol) and Phe-OLi (0.1 mmol) in CH_2Cl_2 (1 mL). [b] Isolated yield based on **2**. [c] Determined by chiral HPLC analysis. [d] The amount of **1a** was reduced to 1.2 equiv. [e] Conversion: 64%. [f] Conversion: 41%. [g] Conversion: 82%.

Table 4 Michael addition of aldehydes **1b–f** with **2a** using L-phenylalanine lithium salt as a catalyst[a]



Entry	R^1	R^2	Yield[b] (%)	conv. (%)	dr[c]	ee[d] (%)
1	CH_3	Ph, **1b**	84, **3q**	100	2 : 1	10
2	CH_3	C_3H_7, **1c**	60, **3r**	92	3.5 : 1	22
3	H	C_3H_7, **1d**	59, **3s**	71	2 : 1	78
4	H	$PhCH_2$, **1e**	61, **3t**	72	2 : 1	89
5	H	$(CH_3)_2CH$, **1f**	41, **3u**	65	6.1 : 1	89[e]

[a] Unless otherwise mentioned, the reaction was carried out with **1** (1 mmol), **2a** (0.5 mmol) and Phe-OLi (0.1 mmol) in CH_2Cl_2 (1 mL) at 25 °C for 48 h. [b] Isolated yield based on **2a**. [c] *Syn* product was obtained as a major diastereomer. The relative configuration was determined by ^{1}H NMR spectra. [d] Ee of the major diastereomer. Determined by chiral HPLC analysis. [e] The absolute configuration of the major enantiomer was determined as 2*S*,3*R* by comparison of the optical rotation with that of the literature.5*c*,14

with **1a**. Michael addition reactions with various β-nitrostyrene derivatives, having an electron-donating group or an electron-withdrawing group on the phenyl group, were completed within 4–6 h at 25 °C to provide the corresponding Michael adducts **3b–h** in 82–94% yields with 86–95% ee (Table 3, entries 4–17). A lowering of the reaction temperature to 0 °C increased the enantioselectivity up to 99% ee. Heteroaromatic nitroalkenes, (*E*)-2-(furan-2-yl)nitroethene (**2i**), (*E*)-2-(thiophen-2-yl)nitroethene (**2j**) and (*E*)-2-(3-pyridyl)nitroethene (**2k**), also gave Michael adducts in good yields (71–96%) with high enantioselectivity (86–96% ee) (Table 3, entries 18–23). The Michael addition with conjugated nitroalkadienes such as (*E*,*E*)-4-phenyl-1-nitrobuta-1,3-diene (**2l**) and (*E*,*E*)-1-nitrohepta-1,3-diene (**2m**) afforded 1,4-adducts selectively without the generation of 1,6-adducts (Table 3, entries 24–26).[4g,5a,13] Unfortunately, Michael addition reactions using aliphatic nitroalkenes such as (*E*)-2-cyclohexyl-1-nitroethene (**2n**) and (*E*)-4-phenyl-1-nitrobut-1-ene (**2o**) were very slow, even at 25 °C, and gave the corresponding Michael adducts with many minor by-products, although the enantioselectivity was high (Table 3, entries 27 and 28). Since the reaction of a sterically small substrate, (*E*)-1-nitroprop-1-ene (**2p**), was completed within 24 h to give the Michael adduct **3p** in a good yield with high enantioselectivity, it was found that the bulkiness of nitroalkenes greatly affects the reaction rate (Table 3, entry 29).

Next, various α-branched and unbranched aldehydes **1b–f** were employed as Michael donors for the reaction with **2a** (Table 4). Since Michael addition reactions were very slow at 0 °C, the reactions were carried out at 25 °C. The use of asymmetric α-branched aldehydes such as 2-phenylpropionaldehyde (**1b**) and 2-methylvaleraldehyde (**1c**) led to low enantioselectivity, although the corresponding Michael adducts, **3q** and **3r**, were obtained in good yields with moderate *syn*-diastereoselectivity (Table 4, entries 1 and 2). The Michael addition of α-unbranched aldehydes, *n*-valeraldehyde (**1d**), hydrocinnamaldehyde (**1e**) and isovaleraldehyde (**1f**), proceeded slowly to give the Michael adducts **3s–u** *syn*-selectively with high enantioselectivity (Table 4, entries 3–5).

Mechanism

Plausible transition states for the Michael addition of **1a** to **2a** are shown in Fig. 1. As shown in eqn (1), it is likely that Michael addition proceeds *via* formation of an enamine from **1a** and Phe–OLi.[2,5,9] The benzyl group of the enamine occupies the opposite side of the isobutenyl group to avoid a steric hindrance; therefore, the carboxylate group is fixed on one side of the enamine. Since the absolute configuration of the C-3 stereocenter in the Michael adduct **3a** was determined as *S*, it is thought that the enamine attacks the *Re* face of nitrostyrene **2a**.[4,5] According to the Seebach and Goliński's model for Michael addition of an enamine to a nitroalkene,[15] there is an electrostatic interaction between the nitrogen atom of enamine and the nitro group; therefore, the transition state of the reaction can be presented as TS-1 or TS-2. If direction of the approach of the enamine to nitrostyrene **2a** is controlled by chelation of the nitro group with the lithium cation, the Michael addition will proceed *via* TS-2. On the other hand, if the enamine approaches nitrostyrene **2a** to avoid a steric hindrance and/or an electrostatic repulsion between the carboxylate group and the nitro group, the Michael addition will proceed *via* TS-1. In this model, the steric hindrance between the two methyl groups of the enamine and the phenyl group of nitrostyrene **2a** is smaller than that of TS-2. Therefore, it is likely that the Michael addition of **1a** to **2a** proceeds *via* TS-1.

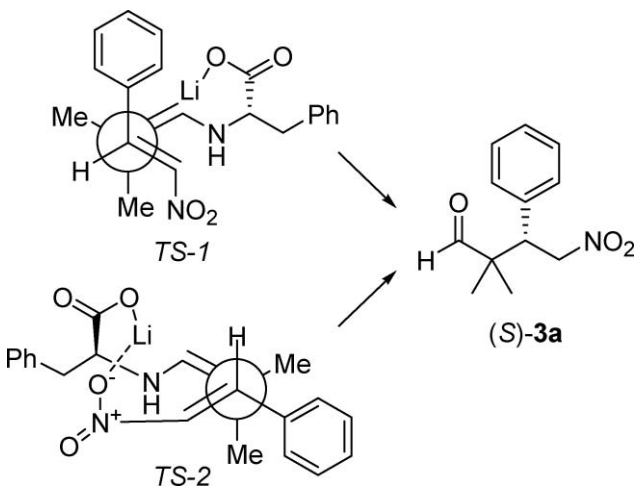


Fig. 1 Plausible transition state for the Michael addition of **1a** to **2a**.

As for a transition state for the Michael addition of α-unbranched aldehydes to nitroalkenes, TS-3 and TS-4 can be chosen as candidates, since the absolute configuration of a major enantiomer of the Michael adduct **3u**, which was synthesized by the reaction of **1f** with **2a**, was determined as 2*S*,3*R* (Fig. 2). Generally, enamine-based Michael addition with nitroalkenes gives a *syn*-diastereomer *via* the reaction of the thermodynamically stable (*E*)-enamine with an (*E*)-nitroalkene, which can be explained by an acyclic synclinal transition model proposed by Seebach and Goliński (Scheme 1, a).[4,5,15] Recently, Barbas's group succeeded in *anti*-selective Michael addition of aldehydes with nitroalkenes by forming a (*Z*)-enamine using a primary amine catalyst.[16] They used a silyloxyacetaldehyde as a Michael donor

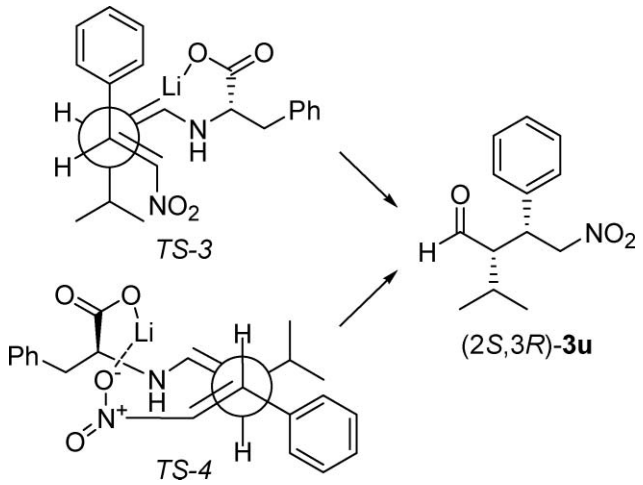
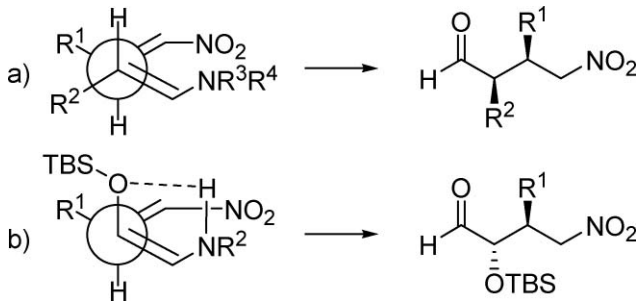


Fig. 2 Plausible transition state for the Michael addition of **1f** to **2a**.



Scheme 1 (a) Seebach and Goliński model; (b) Barbas's *anti*-selective synthesis.

to promote generation of the thermodynamically unstable (*Z*)-enamine by forming a hydrogen-bond between the oxygen atom of the siloxy group and the hydrogen atom of the amino group (Scheme 1, b). These studies suggest that the Michael addition of **1f** to **2a** proceeds *via* the transition state TS-4, since we obtained a *syn* Michael product; however, we cannot rule out the possibility that the reaction proceeds *via* the transition state TS-3 in the case of considering a steric and/or an electrostatic repulsion of the carboxylate group with the nitro group and a steric hindrance between the isopropyl group of the enamine and the phenyl group of nitrostyrene.

Conclusions

In conclusion, we revealed that an alkaline metal salt of a primary amino acid, especially L-phenylalanine lithium salt, catalyzes the Michael addition of aldehydes with nitroalkenes to produce γ-nitroaldehydes. The use of isobutyraldehyde as a Michael donor led to good yields and high enantioselectivity of γ-nitroaldehydes. From asymmetric α-branched and unbranched aldehydes, the corresponding Michael adducts were obtained *syn*-selectively. Various functionalized-aromatic and heteroaromatic nitroalkenes were found to be good Michael acceptors for this reaction. Conjugated nitroalkadienes also gave the corresponding Michael adducts in good yields with high enantioselectivity without generation of 1,6-adducts.

Experimental

General

IR spectra were recorded using a JASCO FT/IR-410 spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a JEOL JNM-A400II or ECX-400P FT NMR. Chemical shifts, δ are referred to TMS. ESI high-resolution mass spectra were measured on a JEOL JMS-T100GC or JMS-T100LC spectrometer. Optical rotation was measured by a JASCO P-2200. Melting points are measured by Yanagimoto micro melting point apparatus and are uncorrected. HPLC was carried out using a JASCO PU-2089 Plus intelligent pump and a UV-2075 Plus UV detector.

Materials

Aldehydes were used after distillation. Nitroalkenes **2g**,[17a] **2h**,[17a] **2i**,[17b] **2l**,[17c] **2n**,[17d] **2o**[17d] and **2p**[17a,e] were prepared according to the literatures. (*E*,*E*)-1-Nitrohepta-1,3-diene (**2m**) was prepared according to the following procedure.[17a,f] (*E*)-4-Methoxy-β-nitrostyrene (**2b**) was used after recrystallization. (*E*)-2-(3-Pyridyl)nitroethene (**2k**) was used after purification by column chromatography. Amino acid salts were prepared according to the literatures.[6,7] Other materials were purchased from commercial suppliers and were used without purification.

Synthesis of (*E*,*E*)-1-nitrohepta-1,3-diene (2m)[17a,f]

In a round-bottomed flask, a mixture of nitromethane (40 mL) and triethylamine (4.2 mL, 30 mmol) was added dropwise to a solution of 2-hexenal (2.9 g, 30 mmol) in nitromethane (20 mL) at 0 °C. The reaction mixture was stirred for 10 h at 0 °C, then 20 h at room temperature. Volatile organics were removed by evaporation to give a crude product. (*E*)-1-Nitrohept-3-en-2-ol was isolated by column chromatography (silica gel, hexane–EtOAc) in 47% yield (2.23 g, 14 mmol). To a solution of (*E*)-1-nitro-3-hept-3-en-2-ol (2.23 g, 14 mmol) and *N*,*N*-dimethylaminopyridine (51 mg, 0.42 mmol) in CH_2Cl_2 (50 mL), trifluoroacetic anhydride (2.1 mL, 15 mmol) was added at 0 °C. After the reaction mixture was stirred for 5 h at room temperature, saturated aqueous $NaHCO_3$ was added and extracted with CH_2Cl_2. The combined organic phase was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained crude (*E*)-1-nitro-2-trifluoroacetoxyhept-3-ene was dissolved in CH_2Cl_2 (50 mL), and *N*,*N*-dimethylaminopyridine (51 mg, 0.42 mmol) was added to the solution at room temperature. After the reaction mixture was stirred for over night at room temperature, saturated aqueous $NaHCO_3$ was added and extracted with CH_2Cl_2. The combined organic phase was washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. (*E*,*E*)-1-Nitrohepta-1,3-diene (**2m**) was isolated by column chromatography (silica gel, hexane–EtOAc) in 50% yield (1.12 g, 7.02 mmol). $\delta_H(CDCl_3)$ 0.94 (3H, t, *J* 7.2 Hz), 1.46–1.55 (2H, m), 2.21–2.26 (2H, m), 6.20 (1H, dd, *J* 11.8, 14.9 Hz), 6.44 (1H, dt, *J* 7.2, 14.9 Hz), 7.07 (1H, d, *J* 13.1 Hz), 7.59 (1H, dd, *J* 11.8, 13.1 Hz); $\delta_C(CDCl_3)$ 13.5, 21.5, 35.3, 123.2, 137.3, 139.4, 151.2; ν(neat)/cm^{-1} 3104, 3031, 2962, 2930, 2873, 1723, 1697, 1641, 1609, 1512, 1464, 1339, 1229, 1202, 1167, 1042, 994, 961, 840, 739; [HR ESI-MS: Calc. for $C_7H_{11}NO_2$ (*M*): 141.0790. Found: M^+, 141.0788].

General procedure for the Michael addition of aldehydes to nitroalkenes

In a 7 mL vial, isobutyraldehyde (**1a**) (72 mg, 1 mmol) was added to a slurry of L-phenylalanine lithium salt (17.1 mg, 0.1 mmol), CH_2Cl_2 (1 mL) and methyl 4-[(*E*)-2-nitrovinyl]benzoate (**2g**) (103.6 mg, 0.5 mmol) at 0 °C. After the reaction mixture was stirred for 72 h at 0 °C, saturated aqueous NaCl (1.5 mL) was added to the vial and extracted with Et_2O (3 mL × 3). The combined organic phase was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The Michael adduct, methyl 4-(3,3-dimethyl-1-nitro-4-oxobutan-2-yl)benzoate (**3g**), was isolated by column chromatography (silica gel, hexane–Et_2O) in 94% yield (131.3 mg) as white solid. The enantioselectivity was determined by HPLC analysis [96% ee, DAICEL CHIRALPAK AD-H, 20% isopropanol–hexanes, 1.0 mL min^{-1}, 209 nm; t_r(major enantiomer) = 13.5 min, t_r(minor enantiomer) = 11.5 min]. $[\alpha]_D^{26}$ = +7.9° (*c* = 1.0, $CHCl_3$), white solid, Mp. 88–89 °C, $\delta_H(CDCl_3)$ 1.01 (3H, s), 1.14 (3H, s), 3.86 (1H, dd, *J* 4.1, 11.4 Hz), 3.92 (3H, s), 4.73 (1H, dd, *J* 4.1, 13.2 Hz), 4.89 (1H, dd, *J* 11.4, 13.2 Hz), 7.30 (2H, d, *J* 8.2 Hz), 8.01 (2H, d, *J* 8.2 Hz), 9.52 (1H, s); $\delta_C(CDCl_3)$ 18.9, 21.8, 48.1, 48.2, 52.2, 75.9, 129.2, 129.9, 130.1, 140.7, 166.5, 203.6; ν(neat)/cm^{-1} 3101, 3060, 3031, 2975, 2952, 2816, 2723, 1723, 1611, 1553, 1436, 1378, 1284, 1192, 1112, 1020, 962, 900, 862, 797, 762, 710, 630; [HR ESI-MS: Calc. for $C_{14}H_{17}NNaO_5$ (*M*+Na): 302.1004. Found: M^++Na, 302.1007].

Spectroscopic data of **3a–f**,**h–j**,**l**,**n**,**o**,**q–u** are in agreement with the published data and are presented in the Electronic Supplementary Information.†

2,2-Dimethyl-4-nitro-3-(3-pyridyl)butanal (3k)

The enantioselectivity was determined by HPLC analysis [93% ee, DAICEL CHIRALPAK AD-H, 20% isopropanol–hexane, 1.0 mL min^{-1}, 209 nm; t_r(major enantiomer) = 11.1 min, t_r(minor enantiomer) = 13.0 min]. $[\alpha]_D^{23}$ = +9.9° (*c* = 1.0, $CHCl_3$), orange oil, $\delta_H(CDCl_3)$ 1.05 (3H, s), 1.15 (3H, s), 3.82 (1H, dd, *J* 4.1, 11.4 Hz), 4.75 (1H, dd, *J* 4.1, 13.7 Hz), 4.88 (1H, dd, *J* 11.4, 13.7 Hz), 7.27–7.31 (1H, m), 7.57–7.60 (1H, m), 8.51–8.52 (1H, m), 8.56–8.58 (1H, m), 9.51 (1H, s); $\delta_C(CDCl_3)$ 18.9, 21.8, 46.0, 48.2, 75.7, 123.5, 131.4, 136.1, 149.6, 150.6, 203.4; ν(neat)/cm^{-1} 3420, 2975, 2934, 2872, 2822, 2722, 1725, 1555, 1469, 1430, 1379, 1186, 1027, 883, 822, 718; [HR ESI-MS: Calc. for $C_{11}H_{15}N_2O_3$ (*M*+H): 223.1083. Found: M^++H, 223.1081].

(*E*)-2,2-Dimethyl-3-(nitromethyl)oct-4-enal (3m)

The enantioselectivity was determined by HPLC analysis [94% ee, DAICEL CHIRALCEL OD-H, 20% isopropanol–hexane, 1.0 mL min^{-1}, 209 nm; t_r(major enantiomer) = 10.0 min, t_r(minor enantiomer) = 6.1 min]. $[\alpha]_D^{28}$ = –20.3° (*c* = 1.0, $CHCl_3$), colorless oil, $\delta_H(CDCl_3)$ 0.86 (3H, t, *J* 7.3 Hz), 1.09 (6H, s), 1.31–1.41 (2H, m), 1.98 (2H, dt, *J* 6.8, 7.3 Hz), 3.05 (1H, ddd, *J* 3.9, 9.8, 10.7 Hz), 4.30 (1H, dd, *J* 10.7, 11.7 Hz), 4.42 (1H, dd, *J* 3.9, 11.7 Hz), 5.26 (1H, dd, *J* 9.8, 15.1 Hz), 5.59 (1H, dt, *J* 6.8, 15.1 Hz), 9.47 (1H, s); $\delta_C(CDCl_3)$ 13.4, 18.8, 20.5, 22.1, 34.5, 46.9, 47.3, 76.9, 123.2, 138.1, 204.0; ν(neat)/cm^{-1} 2963, 2931, 2873, 2714, 1728, 1556, 1466, 1436, 1380, 1339, 1202, 1056, 934, 887, 780, 718, 634.

2,2,3-Trimethyl-4-nitrobutanal (3p)

The enantioselectivity was determined by HPLC analysis [91% ee, DAICEL CHIRALCEL OD-H, 20% isopropanol–hexane, 1.0 mL min^{-1}, 209 nm; t_r(major enantiomer) = 10.5 min, t_r(minor enantiomer) = 8.4 min]. $[\alpha]_D^{26}$ = –20.0° (*c* = 1.0, $CHCl_3$), colorless oil, $\delta_H(CDCl_3)$ 1.03 (3H, d, *J* 6.8 Hz), 1.09 (3H, s), 1.10 (3H, s), 2.65–2.71 (1H, m), 4.17 (1H, dd, *J* 10.2, 12.2 Hz), 4.44 (1H, dd, *J* 3.9, 12.2 Hz), 9.47 (1H, s); $\delta_C(CDCl_3)$ 12.9, 18.7, 19.1, 36.5, 47.6, 78.3, 203.9; ν(neat)/cm^{-1} 2977, 2942, 2883, 2820, 2716, 1725, 1556, 1469, 1436, 1380, 1241, 1128, 1050, 885, 847, 778, 717.

Acknowledgements

This work was partly supported by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) from the Ministry of Education, Culture, Sports, Science and technology, Japan.

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