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Highly Enantioselective Michael Addition of Nitroalkanes to Enones and Its Application in Syntheses of (*R*)-Baclofen and (*R*)-Phenibut

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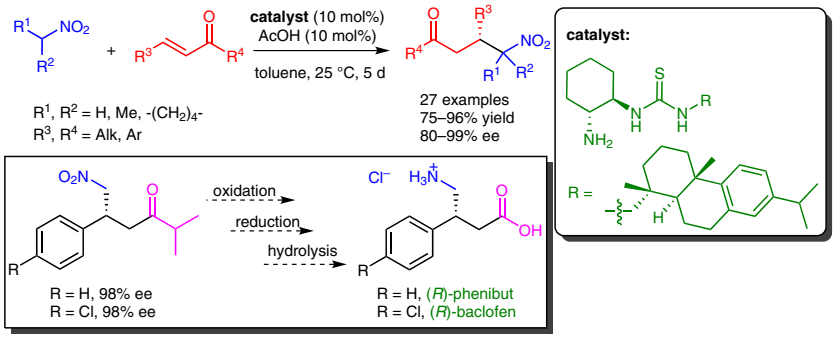

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Abstract A highly enantioselective Michael addition of nitroalkanes to α,β-unsaturated ketones was developed. In the presence of a chiral primary amine–thiourea catalyst based on dehydroabietic amine, γ-nitro ketones were obtained with excellent enantioselectivities (up to 99% ee) and in up to 96% yield. This protocol was successfully applied in asymmetric syntheses of (*R*)-baclofen and (*R*)-phenibut with high yields and excellent enantioselectivities.

Key words chiral primary amine–thiourea, dehydroabietic amine, enantioselective Michael addition, nitroalkanes, α,β-unsaturated ketones

As versatile building blocks for natural and synthetic biologically active molecules, γ-nitro ketones are of significant interest in organic chemistry.[1] The Michael addition of nitroalkanes to α,β-unsaturated ketones is a useful way of obtaining γ-nitro ketones.[2] In recent decades, many chiral organocatalysts have been used in asymmetric conjugate additions of nitroalkanes to chalcones[3] or cyclic enones.[4] However, fewer studies on alkyl cinnamyl ketones have been reported,[4f,j,l,m,5] and only a few organocatalytic systems provided high enantioselectivities (≥90% ee) for these Michael acceptors.[5d,5f–h] For example, in 2009, Wang and co-workers[5d] reported a Michael addition of nitroalkanes to alkyl cinnamyl ketones catalyzed by a chiral diaminocyclohexane-derived primary amine–thiourea bearing a 3,5-bis(trifluoromethyl)phenyl group; this reaction gave the desired products in 92–99% ee. Later, chiral primary and secondary diamines derived from camphor and phenylalanine were shown to have a high efficiency (90–96% ee) in the reactions of acetocinnamones.[5f] The intramolecular Michael reactions of (1*E*)-1-aryl-6-nitrohex-1-en-3-ones in the presence of a quinine-derived primary amine as a chiral organocatalyst gave the corresponding adducts in 95–97% ee.[5g] Recently, a quinine-derived primary amine has been shown to be an efficient catalyst for the conjugate addition of nitroalkanes to benzalacetones (91–99% ee).[5h] There is still, therefore, a need to develop a highly effective organocatalytic Michael reaction for alkyl cinnamyl ketones.

Dehydroabietic amine (abieta-8,11,13-trien-18-amine), a readily available rosin derivative with a well-defined chiral structure, is a privileged scaffold for chiral bifunctional organocatalysts.[6–9] Although considerable progress has been made in the application of dehydroabietic amine-based bifunctional organocatalysts, the corresponding primary amine–thioureas have only been successfully employed in Michael addition with ketones as donors[6a] and in a Diels–Alder reaction.[6b] We surmised that these primary amine–thioureas might serve as efficient catalysts for the Michael reactions of nitroalkanes. Here we report an enantioselective conjugate catalytic addition of nitroalkanes to enones.[10]

Initially, we selected the addition of nitromethane (**2a**) to (3*E*)-4-(4-chlorophenyl)but-3-en-2-one (**3a**) as a model reaction. To our delight, the desired product was obtained in high yield when the reaction was catalyzed by thioureas **1a–c** (Figure 1), synthesized from diaminocyclohexane (DACH) and dehydroabietic amine (Table 1, entries 1–3). Among these catalysts, the (*1R,2R*)-DACH-derived thiourea **1a** gave the highest enantioselectivity (entry 1), whereas catalyst **1c**, containing a racemic DACH backbone, gave only a 4% ee (entry 3). These results showed that dehydroabietic amine had a slight effect on the stereocontrol of the reaction and that it matched well with the (*1R,2R*)-DACH scaffold. This observation were unlike those made by Wang and co-workers[6a] with respect to the Michael reaction of ketones with nitroolefins. For comparison, catalysts **1d–g** (Figure 1) lacking a rosin scaffold were examined. All the (*1R,2R*)-DACH-derived catalysts gave product **4aa**[11] in excellent enantioselectivity (96% ee; entries 1 and 4–7). Cata-

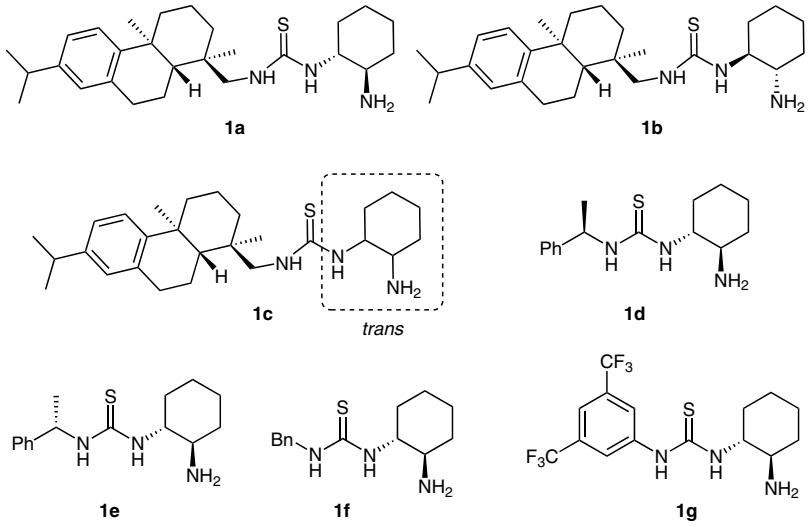


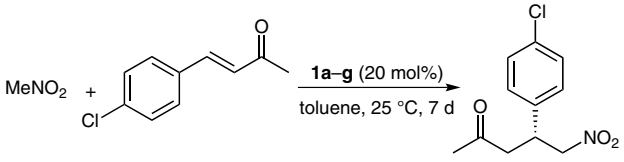
Figure 1 Structures of chiral bifunctional organocatalysts **1a–g**

lysts **1d** and **1e**, bearing different chiral phenylethyl groups, gave the product in good yields (74% and 70%, respectively), showing that a chiral phenylethyl moiety adjacent to the thiourea has a limited effect on the reactivity and that the enantioselectivity is depended on the chiral DACH backbone. When thiourea **1f** containing a benzyl group was used as the organocatalyst, the Michael reaction gave only a 69% yield. Catalyst **1g** gave the product in 82% yield, which was lower than that obtained with catalyst **1a** (entries 7 and 1). We therefore selected organocatalyst **1a** for our subsequent investigations.

Next, we examined the effects of various solvents (Table 2). When toluene, a xylene, or mesitylene was used as the solvent, the Michael product was obtained in a good yield (81–88%) and an excellent ee (95–96%). In contrast, other solvents such as dichloromethane, ethyl acetate, tetrahydrofuran, acetonitrile, nitromethane, and dimethyl sulfoxide gave slow conversions and yields of 13–72%; however, high enantioselectivities were observed in these solvents (other than dimethyl sulfoxide). Toluene was therefore selected as the optimal solvent for the Michael reaction.

We then examined various additives in an attempt to accelerate the reaction (Table 3). Additives had various effects on the rate and yield of the reaction, but had no observable effects on its enantioselectivity. The reaction gave a lower conversion when formic acid or phenylacetic acid was used (Table 3, entries 2 and 5). Encouragingly, the addition of acetic acid led to a shorter reaction time and a higher yield (entry 3). It appeared that propionic acid or the basic additive triethylamine had a limited effect on the reaction (entries 4 and 8). With benzoic acid, the chemical yield was maintained but the reaction was completed in a shorter time (entry 6). Moreover, the stronger acid 4-toluenesulfonic acid had a markedly detrimental effect on the transformation, and no product was obtained (entry 7). The use of the correct additive is therefore critical for both the rate and yield of the reaction, and acetic acid was selected as the additive for subsequent screening studies.

Table 1 Screening of Catalysts for a Michael Reaction of Nitromethane[a]



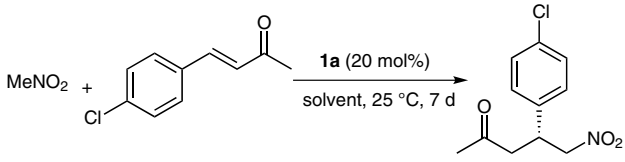
2a **3a** **4aa**

Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1a**	88	96
2	**1b**	86	–88
3	**1c**	86	4
4	**1d**	74	96
5	**1e**	70	96
6	**1f**	69	96
7	**1g**	82	96

[a] *Reaction conditions*: $MeNO_2$ (**2a**; 3.0 mmol), enone **3a** (0.3 mmol), catalyst (0.06 mmol), toluene (2 mL), 25 °C, 7 d.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Other aspects of the reaction conditions, including the substrate concentration, temperature, catalyst loading, and amount of nitromethane were then investigated (Table 4). When the concentration of **3a** was increased to 0.3 M, the reaction was completed in a shorter time but with a re-

Table 2 Solvent Screening for a Michael Reaction of Nitromethane[a]

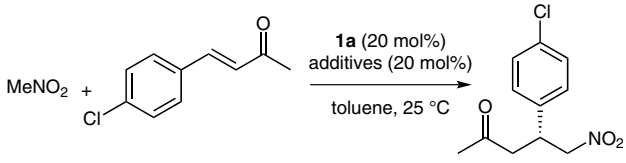


2a **3a** **4aa**

Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	toluene	88	96
2	*o*-xylene	81	95
3	*m*-xylene	86	95
4	*p*-xylene	86	95
5	mesitylene	88	95
6	CH_2Cl_2	72	97
7	EtOAc	65	96
8	THF	46	95
9	MeCN	32	93
10	$MeNO_2$	45	90
11	DMSO	13	6

[a] *Reaction conditions*: $MeNO_2$ (**2a**; 3.0 mmol), enone **3a** (0.3 mmol), catalyst **1a** (0.06 mmol), solvent (2 mL), 25 °C, 7 d.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

Table 3 The Effect of Various Additives on the Michael Reaction[a]



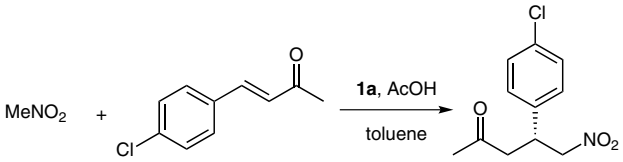
2a **3a** **4aa**

Entry	Additive	Time (d)	Yield[b] (%)	ee[c] (%)
1	–	7	88	96
2	HCO_2H	7	70	96
3	AcOH	5	94	96
4	$EtCO_2H$	7	89	96
5	$BnCO_2H$	7	72	96
6	$PhCO_2H$	4.5	86	96
7	TsOH	7	trace	n.d.[d]
8	Et_3N	7	89	96

[a] *Reaction conditions*: $MeNO_2$ (**2a**; 3.0 mmol), enone **3a** (0.3 mmol), catalyst **1a** (0.06 mmol), additive (0.06 mmol), toluene (2 mL), 25 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Not determined.

duced yield (Table 4, entries 1 and 2). Conversely, a lower substrate concentration (0.1 M) gave an obviously increase in reaction time (entry 3). Although the shortest reaction time was observed when the reaction was carried out at 40 °C, the yield dropped markedly and byproducts were obtained (entry 4). At 0 °C, on the other hand, the reaction became sluggish and required a longer time to give a high yield (entry 5). Reducing the catalyst loading resulted in a lower reaction rate (entries 6 and 7). The desired product was obtained in excellent yield when the amount of nitromethane relative to that of the enone **3a** was increased to 15 equivalents, but a further increase in the amount of nitromethane did not improve the yield any further (entries 8 and 9). In terms of the yield and enantioselectivity, the optimal reaction conditions were selected as a substrate concentration of 0.15 M, a temperature of 25 °C, a catalyst loading of 10 mol%, and 15 equivalents of nitromethane.

Table 4 Further Optimization of the Reaction Conditions for the Michael Reaction[a]



2a **3a** **4aa**

Entry	**1a** (mol%)	Time (d)	Yield[b] (%)	ee[c] (%)
1	20	5	94	96
2[d]	20	3	90	96
3[e]	20	6.5	93	95
4[f]	20	1	88	96
5[g]	20	9	90	96
6	15	6	92	97
7	10	8	88	97
8[h]	10	5	94	97
9[i]	10	4	92	97

[a] *Reaction conditions*: $MeNO_2$ (**2a**; 3.0 mmol), enone **3a** (0.3 mmol, 0.15 M), catalyst **1a**, AcOH (0.06 mmol), toluene (2 mL), 25 °C (unless otherwise stated).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] The concentration of **3a** was 0.3 M.
[e] The concentration of **3a** was 0.1 M.
[f] The temperature was 40 °C.
[g] The temperature was 0 °C.
[h] $MeNO_2$ (15 equiv) relative to enone **3a** was used.
[i] $MeNO_2$ (20 equiv) relative to enone **3a** was used.

By using the optimal reaction conditions, the substrate scope with regard to the α,β-unsaturated ketone was then investigated with nitromethane as the donor (Table 5, entries 1–17). The reaction was only slightly sensitive to electronic effects of the substituents on the phenyl group of the α,β-unsaturated ketones, and the desired products were ob-

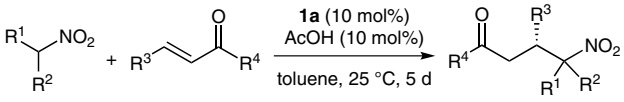
tained in excellent yields and enantioselectivities (entries 1–9). Substrate **3** bearing a 2-furyl heteroaromatic group also performed well, giving product **4aj** in 86% yield and 98% ee (entry 10). Other alkyl cinnamyl ketones and aliphatic acyclic enones also provided excellent stereoselectivities, despite requiring longer reaction time or higher reaction temperature as a result of steric hindrance or low reactivity (entries 11–15). Moreover, cyclohex-2-en-1-one was well tolerated, giving the desired product in 75% yield and 95% ee (entry 17). However, chalcone gave the corresponding product **4ap** with only 80% ee, even when the catalyst loading was increased to 20 mol%; this was probably due to an electronic effect of the phenyl group attached to the ketone (entry 16).

Our further explorations of the scope of the reaction focused on changing the structure of the nitroalkane. When nitroethane was used as the Michael donor, the *syn*-diastereomer of the product was obtained in 94% ee, whereas the *anti*-diastereomer was obtained with 84% ee; the reaction therefore gave a high yield but a poor diastereoselectivity (Table 5, entry 18). Other, more sterically hindered, nitroalkanes, such as 2-nitropropane or nitrocyclopentane, were still well tolerated and gave the desired products with high yields and excellent enantioselectivities (entries 19–27). On the basis of the optical rotations reported in the literature,[3d,4f,j,5d,f,h,12] all the products other than **4aj–al**, **4aq**, **4bh**, and **4bi** were assigned as having an (*R*)-absolute configuration.

The reactions of several enones were examined under the optimal reaction conditions, but with catalyst **1g**. Catalyst **1a** gave higher yields than catalyst **1g** when (1*E*)-1-phenylpent-1-en-3-one or (1*E*)-4-methyl-1-phenylpent-1-en-3-one was used as the Michael acceptor (Table 5; entries 13 and 14 versus 28 and 29). When the reaction time was reduced to 1.5 days, both **1a** and **1g** gave products **4aa**, **4ag**, and **4ap** in similar yields and enantioselectivities, but catalyst **1a** gave the cyclic γ-nitro ketone **4aq** in a higher yield than did catalyst **1g**.[13] These results show that catalyst **1a** is a better catalyst than **1g** for the Michael reactions of nitroalkanes with enones.

An important synthetic application of this method is the transformation of the γ-nitro ketones **4** into the corresponding optically active γ-aminobutyric acids, such as (*R*)-baclofen and (*R*)-phenibut. Baclofen and phenibut are therapeutically useful as agonists of γ-aminobutyric acid type-B receptors, and their (*R*)-enantiomers are the biological active forms.[14,15] In recent decades, syntheses of (*R*)-baclofen and (*R*)-phenibut by using asymmetric catalysts have been reported by several groups,[16,17] and organocatalysis is among the most powerful methods for generating the stereocenters of the two drugs.[16] However, few highly enantioselective syntheses (≥95% ee) of chiral intermediates of (*R*)-baclofen and (*R*)-phenibut by using organocatalysts have been reported.[16c,h] Although Wang and co-workers[16c]

Table 5 Substrate Scope of the Michael Addition of Nitroalkanes and Enones[a]



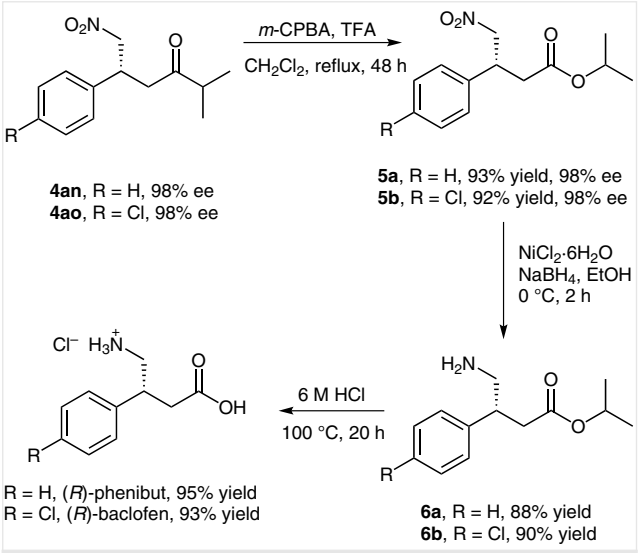
2 **3** **4**

Entry	R^1	R^2	R^3	R^4	Yield[b] (%)	ee[c] (%)
1	H	H	4-ClC_6H_4	Me	94 (**4aa**)	97
2	H	H	2-ClC_6H_4	Me	92 (**4ab**)	97
3	H	H	3-ClC_6H_4	Me	90 (**4ac**)	97
4	H	H	4-$NO_2C_6H_4$	Me	87 (**4ad**)	96
5	H	H	4-FC_6H_4	Me	94 (**4ae**)	97
6	H	H	4-BrC_6H_4	Me	95 (**4af**)	97
7	H	H	C_6H_5	Me	96 (**4ag**)	97
8	H	H	4-MeC_6H_4	Me	93 (**4ah**)	97
9	H	H	4-$MeOC_6H_4$	Me	90 (**4ai**)	97
10	H	H	2-furyl	Me	86 (**4aj**)	98
11[d]	H	H	*n*-C_5H_{11}	Me	86 (**4ak**)	97
12[d]	H	H	$(CH_2)_2Ph$	Me	92 (**4al**)	97
13[e]	H	H	Ph	Et	91 (**4am**)	99
14[d]	H	H	Ph	*i*-Pr	83 (**4an**)	98
15[d]	H	H	4-ClC_6H_4	*i*-Pr	85 (**4ao**)	98
16[f]	H	H	Ph	Ph	75 (**4ap**)	80
17[g]	H	H	$(CH_2)_3$		75 (**4aq**)	95
18[h]	H	Me	Ph	Me	96 (**4ba**)	94 (84)
19	Me	Me	4-FC_6H_4	Me	89 (**4bb**)	92
20	Me	Me	4-ClC_6H_4	Me	89 (**4bc**)	94
21	Me	Me	4-BrC_6H_4	Me	90 (**4bd**)	91
22	Me	Me	Ph	Me	92 (**4be**)	95
23	Me	Me	4-MeC_6H_4	Me	87 (**4bf**)	95
24	Me	Me	4-$MeOC_6H_4$	Me	85 (**4bg**)	95
25[d]	Me	Me	*n*-C_5H_{11}	Me	82 (**4bh**)	95
26[d]	Me	Me	$(CH_2)_2Ph$	Me	88 (**4bi**)	95
27	$(CH_2)_4$		Ph	Me	93 (**4bj**)	92
28[e,i]	H	H	Ph	Et	54 (**4am**)	99
29[d,i]	H	H	Ph	*i*-Pr	45 (**4an**)	98

[a] *Reaction conditions*: nitroalkane **2** (4.5 mmol), enone **3** (0.3 mmol), catalyst **1a** (0.03 mmol), AcOH (0.03 mmol), toluene (2 mL), 25 °C, 5 d (unless otherwise stated).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Temperature 40 °C.
[e] Reaction time 9 d.
[f] **1a** (20 mol%) and AcOH (20 mol%) were used, and the reaction time was 10 d.
[g] Reaction time 3 d.
[h] Total yield for both diastereomers. The dr (*syn*/*anti*) was 4:3, and the ee of the *anti*-diastereomer is shown in parentheses.
[i] Catalyst **1g** (10 mol%).

approached (*R*)-baclofen by a three-step approach involving an enantioselective Michael addition of nitromethane to (2*E*)-3-(4-chlorophenyl)acrylaldehyde (96% ee), their overall yield was unsatisfactory (50%). Kokotos and co-workers[16h] completed a synthesis of (*R*)-baclofen beginning with a highly stereoselective (>99% ee) conjugate addition of acetophenone to 1-chloro-4-[(*E*)-2-nitrovinyl]benzene, but they obtained only a 55% overall yield for the initial two steps. To the best of our knowledge, a synthesis of γ-aminobutyric acids from a 1-alkyl-3-aryl-4-nitrobutan-1-one as a key precursor has not previously been described.

We began our synthesis with a Bayer–Villiger oxidation of products **4an** and **4ao** to give the corresponding γ-nitro esters **5** in 93% and 92% yield, respectively, with retained enantioselectivity (Scheme 1). Reduction of the nitro group of compounds **5** gave the corresponding γ-amino esters **6** in 88% and 90% yield, respectively. Subsequent hydrolysis of **6** gave (*R*)-baclofen and (*R*)-phenibut in 95% and 93% yield, respectively. Thus, the four-step synthesis starting from nitromethane gave (*R*)-baclofen and (*R*)-phenibut in high yields (65% overall) and excellent enantioselectivities.



Scheme 1 Asymmetric syntheses of (*R*)-baclofen and (*R*)-phenibut

In summary, a highly enantioselective Michael addition of nitroalkanes to α,β-unsaturated ketones was achieved by using a chiral primary amine–thiourea catalyst **1a** based on dehydroabietic amine. The reaction has a wide substrate scope, providing chiral γ-nitro ketones in excellent enantioselectivities (≤99% ee) and high yields (≤96%). Moreover, this synthetic method was successfully applied in asymmetric syntheses of (*R*)-baclofen and (*R*)-phenibut.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 or a Bruker 400 spectrometer with $CDCl_3$ or D_2O as solvent. Chemical shifts are reported relative to TMS (δ = 0.00 ppm). IR spectra were recorded on a Nicolet Magna-I 550 spectrometer. High-resolution mass spectra were recorded on a Waters Micromass GCT Premier spectrometer with an EI resource. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm). TLC was performed on 10–40 µm silica gel plates. Column chromatography was carried out on silica gel (300–400 mesh) with EtOAc–PE as eluent. HPLC analysis was performed on Waters equipment using a Daicel Chiralcel OD-H column, a Daicel Chiralpak AS-H column, or a Daicel Chiralpak AD-H column. CH_2Cl_2, EtOAc, MeCN, and DMSO were freshly distilled from CaH_2. THF, toluene, *o*-xylene, *m*-xylene, *p*-xylene, and mesitylene were freshly distilled from sodium–benzophenone. Nitroalkanes were commercial products of analytical grade and were used without purification. The α,β-unsaturated ketones were prepared by the reported methods.[18]

Nitro Ketones 4aa–aq and 4ba–bj; General Procedure

Nitroalkane **2** (4.5 mmol) was added to a solution of catalyst **1a** (0.03 mmol), AcOH (0.03 mmol), and enone **3** (0.3 mmol) in toluene (2 mL) at 25 °C, and the mixture was stirred at 25 °C until the reaction was complete (TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography.

(R)-4-(4-Chlorophenyl)-5-nitropentan-2-one (4aa)[12]

White solid; yield: 68.1 mg (94%; 97% ee); $[\alpha]_D^{25}$ –10.2 (*c* 0.68, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (15:85), flow rate: 0.9 mL/min]; t_R = 11.0 min (minor), 12.5 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.4 Hz, 2 H), 4.68 (dd, *J* = 6.6, 12.6 Hz, 1 H), 4.57 (dd, *J* = 7.8, 12.6 Hz, 1 H), 4.03–3.95 (m, 1 H), 2.89 (dd, *J* = 2.4, 7.2 Hz, 2 H), 2.13 (s, 3 H).

(4*R*)-4-(2-Chlorophenyl)-5-nitropentan-2-one (4ab)[12]

Colorless oil; yield: 66.8 mg (92%; 97% ee); $[\alpha]_D^{25}$ –18.2 (*c* 0.67, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 20.7 min (minor), 23.0 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 1 H), 7.27–7.19 (m, 3 H), 4.78–4.66 (m, 2 H), 4.48–4.44 (m, 1 H), 3.09–2.93 (m, 2 H), 2.16 (s, 3 H).

(4*R*)-4-(3-Chlorophenyl)-5-nitropentan-2-one (4ac)[12]

Colorless oil; yield: 65.2 mg (90%; 97% ee); $[\alpha]_D^{25}$ –7.8 (*c* 0.65, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 31.2 min (minor), 47.9 min (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 3 H), 7.13–7.10 (m, 1 H), 4.68 (dd, *J* = 6.3, 12.6 Hz, 1 H), 4.55 (dd, *J* = 6.3, 12.6 Hz, 1 H), 4.03–3.93 (m, 1 H), 2.90 (d, *J* = 7.2 Hz, 2 H), 2.12 (s, 3 H).

(4*R*)-5-Nitro-4-(4-nitrophenyl)pentan-2-one (4ad)[5d]

Pale-yellow solid; yield: 65.4 mg (87%; 96% ee); $[\alpha]_D^{25}$ –10.7 (*c* 0.65, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 254 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 43.8 min (minor), 60.0 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.4 Hz, 2 H), 7.45 (d, *J* = 8.4 Hz, 2 H), 4.77 (dd, *J* = 6.3, 12.6 Hz, 1 H), 4.66 (dd, *J* = 8.1, 12.6 Hz, 1 H), 4.19–4.12 (m, 1 H), 3.04–2.93 (m, 2 H), 2.17 (s, 3 H).

(4*R*)-4-(4-Fluorophenyl)-5-nitropentan-2-one (4ae)[5d]

Pale-yellow oil; yield: 63.6 mg (94%; 97% ee); $[\alpha]_D^{25}$ –9.1 (*c* 0.64, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 14.5 min (minor), 16.2 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 7.06–7.02 (m, 2 H), 4.70 (dd, *J* = 6.6, 12.3 Hz, 1 H), 4.59 (dd, *J* = 7.8, 12.3 Hz, 1 H), 4.06–3.98 (m, 1 H), 2.91 (d, *J* = 7.2 Hz, 2 H), 2.15 (s, 3 H).

(4*R*)-4-(4-Bromophenyl)-5-nitropentan-2-one (4af)[5d]

Pale-yellow solid; yield: 81.5 mg (95%; 97% ee); $[\alpha]_D^{25}$ +8.9 (*c* 0.81, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 16.2 min (minor), 18.6 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.0 Hz, 2 H), 7.12 (d, *J* = 8.4 Hz, 2 H), 4.70 (dd, *J* = 6.6, 12.6 Hz, 1 H), 4.59 (dd, *J* = 8.1, 12.6 Hz, 1 H), 4.03–3.96 (m, 1 H), 2.91 (d, *J* = 7.2 Hz, 2 H), 2.15 (s, 3 H).

(4*R*)-5-Nitro-4-phenylpentan-2-one (4ag)[5d]

White solid; yield: 59.3 mg (96%; 97% ee); $[\alpha]_D^{25}$ –5.3 (*c* 0.59, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 12.7 min (minor), 13.6 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H), 4.69 (dd, *J* = 6.9, 12.3 Hz, 1 H), 4.59 (dd, *J* = 7.8, 12.3 Hz, 1 H), 4.04–3.97 (m, 1 H), 2.91 (d, *J* = 6.9 Hz, 2 H), 2.12 (s, 3 H).

(4*R*)-5-Nitro-4-(4-tolyl)pentan-2-one (4ah)[5d]

White solid; yield: 61.7 mg (93%), 97% ee; $[\alpha]_D^{25}$ –3.8 (*c* 0.62, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 11.5 min (minor), 12.7 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, *J* = 8.0, 14.8 Hz, 4 H), 4.69 (dd, *J* = 6.9, 12.3 Hz, 1 H), 4.59 (dd, *J* = 7.8, 12.3 Hz, 1 H), 4.03–3.95 (m, 1 H), 2.91 (d, *J* = 7.2 Hz, 2 H), 2.34 (s, 3 H), 2.14 (s, 3 H).

(4*R*)-4-(4-Methoxyphenyl)-5-nitropentan-2-one (4ai)[5d]

White solid; yield: 64.0 mg (90%; 97% ee); $[\alpha]_D^{25}$ +7.7 (*c* 0.64, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 17.9 min (minor), 19.9 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 4.68 (dd, *J* = 6.9, 12.3 Hz, 1 H), 4.57 (dd, *J* = 7.8, 12.3 Hz, 1 H), 4.01–3.94 (m, 1 H), 3.80 (s, 3 H), 2.90 (d, *J* = 7.2 Hz, 2 H), 2.13 (s, 3 H).

(4*S*)-4-(2-Furyl)-5-nitropentan-2-one (4aj)[5d]

Pale-yellow oil; yield: 50.7 mg (86%; 98% ee); $[\alpha]_D^{25}$ +9.0 (*c* 0.51, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 12.4 min (minor), 14.1 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 1 H), 6.32–6.30 (m, 1 H), 6.17–6.15 (m, 1 H), 4.71–4.68 (m, 2 H), 4.15–4.09 (m, 1 H), 3.03–2.89 (m, 2 H), 2.20 (s, 3 H).

(4*S*)-4-(Nitromethyl)nonan-2-one (4ak)[5d]

Colorless oil; yield: 52.0 mg (86%; 97% ee); $[\alpha]_D^{25}$ +2.3 (*c* 0.52, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 12.2 min (minor), 13.8 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.37 (d, *J* = 5.2 Hz, 2 H), 2.58–2.44 (m, 3 H), 2.10 (s, 3 H), 1.29–1.18 (m, 8 H), 0.81 (t, *J* = 6.8 Hz, 3 H).

(4*S*)-4-(Nitromethyl)-6-phenylhexan-2-one (4al)[5d]

Pale-yellow oil; yield: 64.9 mg (92%; 97% ee); $[\alpha]_D^{25}$ –6.2 (*c* 0.64, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 16.0 min (minor), 17.8 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.21–7.14 (m, 3 H), 4.49–4.47 (m, 2 H), 2.73–2.52 (m, 5 H), 2.14 (s, 3 H), 1.75–1.68 (m, 2 H).

(5*R*)-6-Nitro-5-phenylhexan-3-one (4am)[5d]

Colorless oil; yield: 60.5 mg (91%; 99% ee); $[\alpha]_D^{25}$ –10.2 (*c* 0.60, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 15.7 min (minor), 19.1 min (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 3 H), 7.26–7.20 (m, 2 H), 4.70 (dd, *J* = 6.9, 12.3 Hz, 1 H), 4.60 (dd, *J* = 7.8, 12.3 Hz, 1 H), 4.08–3.98 (m, 1 H), 2.88 (d, *J* = 7.2 Hz, 2 H), 2.46–2.29 (m, 2 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

(5*R*)-2-Methyl-6-nitro-5-phenylhexan-3-one (4an)[5d]

Pale-yellow oil; yield: 88.0 mg (83%; 98% ee); $[\alpha]_D^{25}$ –18.2 (*c* 0.88, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 9.4 min (minor), 12.2 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 4.69 (dd, *J* = 7.2, 12.4 Hz, 1 H), 4.60 (dd, *J* = 8.4, 12.4 Hz, 1 H), 4.05–3.98 (m, 1 H), 2.97–2.85 (m, 2 H), 2.57–2.46 (m, 1 H), 1.04 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H).

(5*R*)-5-(4-Chlorophenyl)-2-methyl-6-nitrohexan-3-one (4ao)

Pale-yellow oil; yield: 103.1 mg (85%; 98% ee); $[\alpha]_D^{25}$ –21.7 (*c* 1.03, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 11.0 min (minor), 18.1 min (major).

IR (KBr, film): 2972, 2933, 1712, 1552, 1492, 1379, 1093, 1014, 829, 542 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 2 H), 7.18–7.15 (m, 2 H), 4.68 (dd, *J* = 6.8, 12.4 Hz, 1 H), 4.58 (dd, *J* = 8.0, 12.4 Hz, 1 H), 4.04–3.97 (m, 1 H), 2.89 (dd, *J* = 2.0, 6.8 Hz, 2 H), 2.55–2.49 (m, 1 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 1.00 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.2, 137.6, 133.6, 129.2, 128.8, 79.2, 42.9, 41.2, 38.4, 17.9.

HRMS (EI): *m/z* calcd for $C_{13}H_{16}ClNO_3$: 269.0819; found: 269.0816.

(3*R*)-4-Nitro-1,3-diphenylbutan-1-one (4ap)[3d]

White solid; yield: 76.8 mg (75%; 80% ee); $[\alpha]_D^{25}$ +5.2 (*c* 0.76, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 254 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 20.5 min (minor), 26.6 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.8 Hz, 2 H), 7.58 (t, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 7.8 Hz, 2 H), 7.34 (t, *J* = 7.2 Hz, 2 H), 7.30–7.27 (m, 3 H), 4.84 (dd, *J* = 6.4, 12.8 Hz, 1 H), 4.70 (dd, *J* = 4.0, 12.4 Hz, 1 H), 4.29–4.19 (m, 1 H), 3.52–3.40 (m, 2 H).

(3*S*)-3-(Nitromethyl)cyclohexanone (4aq)[5h]

Colorless oil; yield: 35.2 mg (75%; 95% ee); $[\alpha]_D^{25}$ +8.2 (*c* 0.35, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 21.2 min (minor), 23.3 min (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.40–4.35 (m, 2 H), 2.69–2.63 (m, 1 H), 2.55–2.46 (m, 2 H), 2.35–2.27 (m, 1 H), 2.22–2.13 (m, 2 H), 2.03–1.98 (m, 1 H), 1.82–1.72 (m, 1 H), 1.59–1.49 (m, 1 H).

(4*R*)-5-Nitro-4-phenylhexan-2-one (4ba)[5h]

syn-Diastereomers

Colorless oil; yield: 36.4 mg (55%; 94% ee); $[\alpha]_D^{25}$ –7.2 (*c* 0.36, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 30.4 min (major), 34.8 min (minor).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 3 H), 7.21–7.18 (m, 2 H), 4.81–4.71 (m, 1 H), 3.75–3.67 (m, 1 H), 2.97 (dd, *J* = 9.6, 17.1 Hz, 1 H), 2.73 (dd, *J* = 4.5, 17.4 Hz, 1 H), 2.00 (s, 3 H), 1.31 (d, *J* = 6.6 Hz, 3 H).

anti-Diastereomers

Colorless oil; yield: 27.2 mg (41%; 84% ee); $[\alpha]_D^{25}$ –6.8 (*c* 0.27, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 30.9 min (minor), 35.8 min (major).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 3 H), 7.16–7.13 (m, 2 H), 4.92–4.83 (m, 1 H), 3.73 (q, *J* = 6.9, 13.8 Hz, 1 H), 3.05 (dd, *J* = 6.6, 17.7 Hz, 1 H), 2.90 (dd, *J* = 7.5, 17.4 Hz, 1 H), 2.12 (s, 3 H), 1.48 (d, *J* = 6.6 Hz, 3 H).

(4*R*)-4-(4-Fluorophenyl)-5-methyl-5-nitrohexan-2-one (4bb)[5f]

Colorless oil; yield: 67.6 mg (89%; 92% ee); $[\alpha]_D^{25}$ +29.2 (*c* 0.67, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 13.6 min (major), 21.4 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.15 (m, 2 H), 7.02–6.97 (m, 2 H), 3.92 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.05 (dd, *J* = 10.8, 17.2 Hz, 1 H), 2.73 (dd, *J* = 3.2, 17.2 Hz, 1 H), 2.04 (s, 3 H), 1.55 (s, 3 H), 1.48 (s, 3 H).

(4*R*)-4-(4-Chlorophenyl)-5-methyl-5-nitrohexan-2-one (4bc)[5f]

Colorless oil; yield: 72.1 mg (89%; 94% ee); $[\alpha]_D^{25}$ +30.2 (*c* 0.72, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 13.2 min (major), 16.3 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (dd, *J* = 2.0, 7.2 Hz, 2 H), 7.12 (d, *J* = 8.8 Hz, 2 H), 3.90 (dd, *J* = 3.6, 10.8 Hz, 1 H), 3.04 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.73 (dd, *J* = 3.6, 17.6 Hz, 1 H), 2.05 (s, 3 H), 1.54 (s, 3 H), 1.48 (s, 3 H).

(4*R*)-4-(4-Bromophenyl)-5-methyl-5-nitrohexan-2-one(4bd)[5h]

Pale-yellow solid; yield: 84.8 mg (90%; 91% ee); $[\alpha]_D^{25}$ +27.2 (*c* 0.84, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.6 mL/min]; t_R = 23.1 min (major), 25.9 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 8.4 Hz, 2 H), 7.00 (d, *J* = 8.4 Hz, 2 H), 3.81 (dd, *J* = 3.6, 10.8 Hz, 1 H), 2.97 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.65 (dd, *J* = 3.6, 17.6 Hz, 1 H), 1.96 (s, 3 H), 1.46 (s, 3 H), 1.40 (s, 3 H).

(4*R*)-5-Methyl-5-nitro-4-phenylhexan-2-one (4be)[5h]

Colorless oil; yield: 65.1 mg (92%; 95% ee); $[\alpha]_D^{25}$ +35.2 (*c* 0.65, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 12.0 min (major), 16.9 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 3 H), 7.20–7.18 (m, 2 H), 3.94 (dd, *J* = 3.6, 10.4 Hz, 1 H), 3.10 (dd, *J* = 10.4, 16.8 Hz, 1 H), 2.70 (dd, *J* = 3.6, 16.8 Hz, 1 H), 2.01 (s, 3 H), 1.55 (s, 3 H), 1.47 (s, 3 H).

(4*R*)-5-Methyl-5-nitro-4-(4-tolyl)hexan-2-one (4bf)[5f]

Colorless oil; yield: 65.1 mg (87%; 95% ee); $[\alpha]_D^{25}$ +30.1 (*c* 0.65, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: EtOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 27.5 min (major), 31.7 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03–6.98 (m, 4 H), 3.82 (dd, *J* = 3.2, 10.8 Hz, 1 H), 3.00 (dd, *J* = 10.8, 17.2 Hz, 1 H), 2.60 (dd, *J* = 3.2, 17.2 Hz, 1 H), 2.22 (s, 3 H), 1.93 (s, 3 H), 1.46 (s, 3 H), 1.38 (s, 3 H).

(4*R*)-4-(4-Methoxyphenyl)-5-methyl-5-nitrohexan-2-one (4bg)[5f]

Pale-yellow oil; yield: 67.7 mg (85%; 95% ee); $[\alpha]_D^{25}$ +33.7 (*c* 0.67, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 15.5 min (minor), 18.2 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.8 Hz, 2 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 3.80 (dd, *J* = 3.6, 10.8 Hz, 1 H), 3.69 (s, 3 H), 2.96 (dd, *J* = 10.8, 17.6 Hz, 1 H), 2.60 (dd, *J* = 3.6, 17.6 Hz, 1 H), 1.94 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H).

(4*S*)-4-(1-Methyl-1-nitroethyl)nonan-2-one (4bh)[4f]

Colorless oil; yield: 56.4 mg (82%; 95% ee); $[\alpha]_D^{25}$ +13.3 (*c* 0.56, $CHCl_3$).

HPLC: [Daciel Chiralpak AD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (1:99), flow rate: 0.9 mL/min]; t_R = 15.6 min (major), 16.8 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72–2.66 (m, 1 H), 2.45 (dd, *J* = 4.4, 17.6 Hz, 1 H), 2.28 (dd, *J* = 6.0, 18.0 Hz, 1 H), 2.10 (s, 3 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.34–1.26 (m, 1 H), 1.21–1.08 (m, 6 H), 1.04–0.98 (m, 1 H), 0.79 (t, *J* = 6.8 Hz, 3 H).

(4*S*)-5-Methyl-5-nitro-4-(2-phenylethyl)hexan-2-one (4bi)[5f]

Colorless oil; yield: 69.6 mg (88%; 95% ee); $[\alpha]_D^{25}$ +20.1 (*c* 0.69, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.5 mL/min]; t_R = 16.0 min (minor), 17.8 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.2 Hz, 2 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 7.12 (t, *J* = 7.2 Hz, 2 H), 2.87–2.82 (m, 1 H), 2.62–2.51 (m, 3 H), 2.42 (dd, *J* = 6.4, 18.0 Hz, 1 H), 2.16 (s, 3 H), 1.77–1.68 (m, 1 H), 1.52 (s, 3 H), 1.50 (s, 3 H), 1.45–1.37 (m, 1 H).

(4*R*)-4-(1-Nitrocyclopentyl)-4-phenylbutan-2-one (4bj)[5h]

Colorless oil; yield: 72.7 mg (93%; 92% ee); $[\alpha]_D^{25}$ +3.5 (*c* 0.72, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 10.0 min (major), 14.0 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 3 H), 7.15–7.13 (m, 2 H), 3.88 (dd, *J* = 3.6, 10.0 Hz, 1 H), 3.13 (dd, *J* = 10.0, 17.2 Hz, 1 H), 2.90 (dd, *J* = 4.0, 17.2 Hz, 1 H), 2.57–2.44 (m, 2 H), 2.01 (s, 3 H), 1.87–1.78 (m, 2 H), 1.68–1.56 (m, 4 H).

γ-Nitro Esters 5; General Procedure

m-CPBA (0.9 mmol) was added to a solution of γ-nitro ketone **4** (0.3 mmol) and TFA (0.3 mmol) in CH_2Cl_2 (3 mL), and the mixture was refluxed until the reaction was complete (TLC). The solvent was removed under reduced pressure and the residue was purified by column chromatography.

Isopropyl (3*R*)-4-Nitro-3-phenylbutanoate (5a)

Pale-yellow oil; yield: 70.1 mg (93%; 98% ee); $[\alpha]_D^{25}$ +21.8 (*c* 0.56, $CHCl_3$).

HPLC: [Daciel Chiralpak AS-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 14.6 min (major), 19.4 min (minor).

IR (KBr, film): 2981, 2935, 1720, 1550, 1375, 1107, 964, 763, 700, 530 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.18 (m, 5 H), 4.94–4.85 (m, 1 H), 4.72–4.55 (m, 2 H), 3.99–3.89 (m, 1 H), 2.71–2.63 (m, 2 H), 1.10 (t, *J* = 6.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 138.5, 129.2, 128.2, 127.6, 79.7, 68.6, 40.5, 38.2, 21.9.

HRMS (EI): *m/z* calcd for $C_{13}H_{17}NO_4$: 251.1158; found: 251.1160

Isopropyl (3*R*)-3-(4-Chlorophenyl)-4-nitrobutanoate (5b)

Pale-yellow oil; yield: 78.8 mg (92%; 98% ee); $[\alpha]_D^{25}$ +28.1 (*c* 0.55, $CHCl_3$).

HPLC: [Daciel Chiralcel OD-H, λ = 220 nm, eluent: *i*-PrOH–hexane (10:90), flow rate: 0.9 mL/min]; t_R = 15.9 min (major), 20.9 min (minor).

IR (KBr, film): 2981, 2935, 1728, 1556, 1494, 1377, 1107, 833, 542 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 9.6 Hz, 2 H), 7.13 (d, *J* = 8.1 Hz, 2 H), 4.93–4.85 (m, 1 H), 4.66 (dd, *J* = 6.6, 12.9 Hz, 1 H), 4.55 (dd, *J* = 8.1, 12.3 Hz, 1 H), 3.97–3.86 (m, 1 H), 2.68–2.63 (m, 2 H), 1.10 (t, *J* = 6.3 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 137.0, 134.0, 129.3, 129.0, 79.4, 68.8, 39.9, 38.0, 21.8.

HRMS (EI): *m/z* calcd for $C_{13}H_{16}ClNO_4$: 285.0768; found: 285.0767.

γ-Aminobutyrates 6; General Procedure

$NaBH_4$ (3.6 mmol) was added in a portionwise manner to a solution of compound **5** (0.3 mmol) and $NiCl_2{\cdot}6\,H_2O$ (0.3 mmol) in EtOH (3 mL) at 0 °C, and the mixture was then stirred at 0 °C until the reaction was complete (TLC). The reaction was quenched with sat. aq NH_4Cl (3 mL) and the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography.

Isopropyl (3*R*)-4-Amino-3-phenylbutanoate (6a)[19]

Pale-yellow oil; yield: 58.4 mg (88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.26 (m, 2 H), 7.22–7.17 (m, 3 H), 4.92–4.84 (m, 1 H), 3.17–3.07 (m, 1 H), 2.96–2.81 (m, 2 H), 2.68 (dd, *J* = 7.2, 15.0 Hz, 1 H), 2.55 (dd, *J* = 8.1, 15.0 Hz, 1 H), 1.91 (s, 2 H), 1.11 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 141.9, 128.8, 128.0, 127.1, 67.9, 47.6, 45.9, 39.3, 21.9 (d).

Isopropyl (3*R*)-4-Amino-3-(4-chlorophenyl)butanoate (6b)[20]

Pale-yellow oil; yield: 69.1 mg (90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.1 Hz, 2 H), 7.12 (d, *J* = 6.6 Hz, 2 H), 4.91–4.82 (m, 1 H), 3.15–3.05 (m, 1 H), 2.93–2.78 (m, 2 H), 2.64 (dd, *J* = 6.9, 15.0 Hz, 1 H), 2.47 (dd, *J* = 8.1, 15.0 Hz, 1 H), 1.90 (s, 2 H), 1.10 (d, *J* = 6.3 Hz, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 140.5, 132.8, 129.4, 129.0, 68.0, 47.5, 45.2, 39.1, 21.9 (d).

γ-Aminobutyric Acids; General Procedure

γ-Amino butyrate **6** (0.25 mmol) was added to 6 M aq HCl (5 mL), and the suspension was heated at 100 °C until the reaction was complete (TLC). The mixture was cooled to r.t., diluted with deionized H_2O (10 mL), and washed with Et_2O (2 × 10 mL). Finally, the aqueous layer was concentrated in vacuo.

(*R*)-Phenibut Hydrochloride [(3*R*)-4-Amino-3-phenylbutanoic Acid Hydrochloride][16f]

White solid; yield: 51.4 mg (95%).

^{1}H NMR (300 MHz, D_2O): δ = 7.31–7.16 (m, 5 H), 3.29–3.17 (m, 2 H), 3.13–3.02 (m, 1 H), 2.74–2.53 (m, 2 H).

^{13}C NMR (75 MHz, D_2O): δ = 175.6, 138.5, 129.5, 128.4, 128.0, 43.9, 40.0, 38.4.

(*R*)-Baclofen Hydrochloride [(3*R*)-4-Amino-3-(4-chlorophenyl)butanoic Acid Hydrochloride][17o]

Pale-yellow solid; yield: 58.3 mg (93%).

^{1}H NMR (300 MHz, D_2O): δ = 7.29–7.23 (m, 2 H), 7.18–7.12 (m, 2 H), 3.29–3.16 (m, 2 H), 3.10–3.01 (m, 1 H), 2.72–2.51 (m, 2 H).

^{13}C NMR (75 MHz, D_2O): δ = 175.5, 137.1, 133.5, 129.5, 129.4, 43.8, 39.6, 38.4.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380203.

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