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Enantioselective Michael reaction of nitroalkanes and chalcones by phase-transfer catalysis using chiral quaternary ammonium salts

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Abstract—The catalytic enantioselective Michael reaction promoted by quaternary ammonium salt from cinchonidine as a phase transfer catalyst is described. Treatment of nitroalkanes with chalcone derivatives under mild reaction conditions afforded the corresponding Michael adducts in good yields with good to moderate enantiomeric excesses.

The Michael reaction of carbanionic reagents to α,β-unsaturated carbonyl compounds is one of the most fundamental C–C bond-forming reactions.[1] The products of conjugated addition of nitroalkanes to enones are useful as precursors to aminoalkanes[2] through reduction and to other functionality that can be derived from the nitro group.[3] Catalytic asymmetric conjugate additions of nitroalkenes to enones in the presence of chiral catalysts have been studied. The reactions of nitroalkenes with chalcone catalyzed by chiral ammonium salts,[4] quinine,[5] azacrown ethers,[6] proline–Rb complex,[7] Ni(II) complexes,[8] and Al complex of aminoalcohol[10] have been reported. Especially, Shibasaki[9] and Hanessian[7d] reported excellent Michael reaction of nitroalkanes with up to 95 and 93% ee using La–BINOL complex and L-proline, respectively. Recently, Corey and co-workers reported enantioselective Michael reaction of nitromethane to 4-chlorobenzylidineacetophenone catalyzed by chiral cinchoninium salt as the phase-transfer catalyst.[11] This report prompts us to disclose our results with new chiral cinchonidinium salts for the enantioselective Michael addition of nitroalkanes to chalcones.

Phase-transfer catalysis is clean and efficient processes in organic synthesis.[12] Recently, there have been successful applications to catalytic asymmetric synthesis using cinchona alkaloid-derived quaternary ammonium salts.[13] The attachment of the bulky group to a bridgehead nitrogen leads to a quaternary ammonium structure of well-defined geometry in which the tetrahedral face about ammonium nitrogen is blocked by the bulky subunit.[14] The introduction of the bulky subunit at the bridgehead nitrogen of cinchona alkaloids leads to enhancement of the stereoselectivity in catalytic phase-transfer reactions. As part of our research program toward the development of a more effective cinchona-alkaloid-derived phase-transfer catalyst, we introduced bulky environment at the bridgehead nitrogen by (3,5-di-*tert*-butyl-4-methoxy)benzyl group.[15] In this paper, we wish to report the catalytic asymmetric conjugate addition of nitroalkanes to chalcones **1** using the new cinchona alkaloid-derived quaternary ammonium salts **4** and **5** containing the 9-(3,5-di-*tert*-butyl-4-methoxy)benzyl group.

The new catalysts **4** and **5** are derived in two steps from the cinchona alkaloids and (3,5-di-*tert*-butyl-4-methoxy)benzyl

Table 1. Catalytic asymmetric Michael reaction of nitromethane to chalcone **1a** with phase-transfer catalysts

Entry	Catalyts	Temperature (°C)	Yields (%)	ee[a] (%) (config)[b]
1	**4a**	20	85	15(*S*)
2	**4b**	20	90	35(*S*)
3	**4c**	20	0	–
4	**5a**	20	71	6(*R*)
5	**5b**	20	73	7(*R*)
6	**5c**	20	68	13(*R*)
7	**4b**	0	0	–
8	**4b**	−15	0	–
9[c]	**4b**	100	70	11(*S*)
10[d]	**4b**	20	87	9(*S*)
11	**6**	20	59	3(*S*)
12	**7**	20	74	6(*S*)

[a] Enantiopurity of **2a** was determined by HPLC analysis with a Chiralcel AS column, 2-propanol/hexane (1:9), 1.2 mL min^{-1}, λ_{max}=254 nm, retention times: major 12.7 min, minor 16.3 min. It was established by analysis of racemic **2a** that the enantiomers were fully resolved.
[b] For absolute configulation see: Ref. 9.
[c] KOH was employed as base.
[d] CH_2Cl_2 was employed as solvent.

Keywords: phase-transfer; Michael reactions; ammonium salt; asymmetric reactions.

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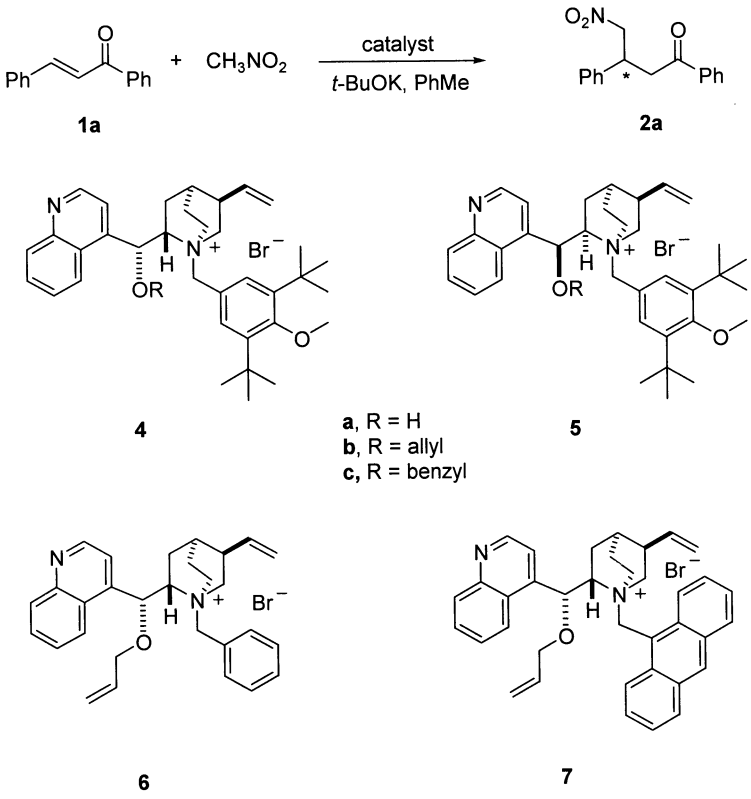


Scheme 1.

bromide which is easily obtained from cheap 2,6-di-*tert*-butyl-4-methylphenol (BHT). In order to determine suitable reaction conditions for the catalytic asymmetric conjugate addition of nitroalkanes to chalcones **1**, we initially investigated the reaction system using 7 mol% of catalyst, with nitromethane as the Michael donor and chalcone **1a** as the Michael acceptor (Table 1, Scheme 1).

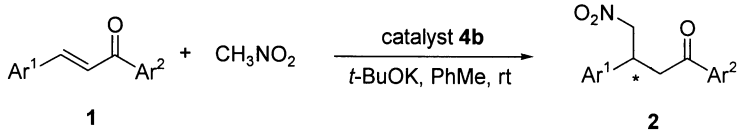
Nitromethane reacted with chalcone in the presence of *t*-BuOK and catalyst **4b** (7 mol%), at room temperature, to afford the Michael adduct **2a** in 90% yield and 35% ee (Table 1, entry 2). The absolute configuration of the major enantiomer of **2a** was determined to be *S* from the optical rotation and chiral HPLC analysis.[8,9] Catalyst **4b** was more effective than the other catalysts (Table 1, entries 1–6). The absolute configuration of the major Michael adduct **2a** differed between the cinchonidinium salts (**4**) and the cinchoninium salts (**5**). The reaction did not proceed at 0°C below (entries 7 and 8). In the presence of KOH as the base, **2a** was obtained in 70% yield and low enantioselectivity (entry 9). The enantioselectivity was low, when methylene chloride was used as the solvent (entry 10). Known cinchona-type phase-transfer catalysts **6** and **7**[14] were less effective than catalyst **4b** in this reaction (entries 11 and 12). The stirring rate does not appear to influence the enantioselectivity of this reaction, however, it does affect the rate of reaction and substantially decreased reaction times can be achieved with high stirring rate.

Table 2. Catalytic asymmetric Michael reaction of nitromethane to chalcones **1** with phase-transfer catalyst **4b**

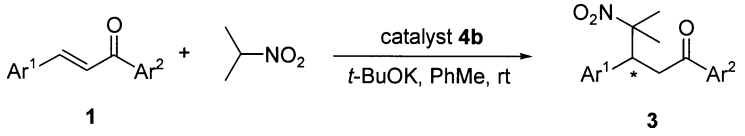
Ar^1	Ar^2	Time (h)	Yields (%)	ee[a] (%) (config)[b]
Ph	Ph	16	**2a**, 90	35(*S*)
p-Cl, Ph	Ph	20	**2b**, 85	42(*S*)
2-Naphthyl	Ph	24	**2c**, 57	31

[a] Enantiopurity of **2** was determined by HPLC analysis with chiral column (Chiralcel AS for **2a**, AD for **2b** and **2c**), 2-propanol/hexane (1:9), 1.2 mL min^{-1}, λ_{max}=254 nm. In each case, it was established by analysis of racemic **2** that the enantiomers were fully resolved.
[b] For absolute configuration see: Ref. 9.

Under the optimized reaction conditions described above (7 mol% of catalyst **4b**, *t*-BuOK, toluene, rt), we investigated the catalytic asymmetric Michael reaction of nitroalkanes to chalcone derivatives **1**. The reaction proceeded smoothly to afford the corresponding adducts **2** with good enantioselectivities. Reaction of 2.3 equiv. of nitromethane with chalcone derivatives **1**, cinchonidinium salt **4b** (7 mol%), and *t*-BuOK (0.34 equiv.) in toluene at room



Scheme 2.



1 3

Scheme 3.

Table 3. Catalytic asymmetric Michael reaction of 2-nitropropane to chalcones **1** with phase-transfer catalyst **4b**

Ar^1	Ar^2	Time (h)	Yields (%)	ee%[a]
Ph	Ph	16	**3a**, 94	31
Ph	*p*-CF_3, Ph	15	**3b**, 61	39(94)
Ph	*p*-Br, Ph	15	**3c**, 92	59(87)
Ph	2-Thienyl	14	**3d**, 62	57
Ph	2-Furanyl	14	**3e**, 63	61
Ph	*m*-Br, Ph	15	**3f**, 62	71
p-CF_3, Ph	Ph	15	**3g**, 63	60
3-Cl, 4-F, Ph	Ph	15	**3h**, 87	53(>99)
2-Naphthyl	*m*-Br, Ph	20	**3i**, 75	69(>99)
2-Naphthyl	*p*-Br, Ph	20	**3j**, 82	51(>99)
1-Naphthyl	*m*-Br, Ph	20	**3k**, 64	57
1-Naphthyl	*p*-Br, Ph	20	**3l**, 68	57

Parenthesis indicate ee% after recrystallization of each product from ethanol.

[a] Enantiopurity of **3** was determined by HPLC analysis with chiral column (Chiralcel OJ for **3a**, **3g**, and **3h**, OD-H for **3b**, **3c**, **3f**, **3k**, and **3l**, AS for **3i** and **3j**, Regis Whelk-O1 for **3d** and **3e**), 2-propanol/hexane (1:9), 1.2 mL min^{-1}, λ_{max}=254 nm. In each case, it was established by analysis of racemic **3** that the enantiomers were fully resolved.

temperature with stirring for 16–24 h afforded the Michael adducts **2** with good yields and moderate enantioselectivities (31–42% ee) (Table 2, Scheme 2).

As shown in Table 3, the addition of 2-nitropropane to chalcone derivatives **1** produced the Michael adduct **3** with 61–94% of yields and 31–71% ee optical purity of the products. Recrystallization of some of the Michael adducts from ethanol furnished of 87–99% ee with good recovery (Table 3, entries 2–6). In all cases the enantiomeric excesses were determined by HPLC analysis (Scheme 3).

In conclusion, we have developed a new class of asymmetric phase-transfer catalysts, which show moderate enantioselectivity in the Michael reaction of nitroalkane to chalcones. We are currently involved in the further development of these catalyst systems and are investigating their applicability to other asymmetric phase-transfer processes.

1. Experimental

1.1. General

^{1}H NMR spectra were recorded on Bruker AC 300 and AC 200F spectrometers. ^{13}C NMR spectra were recorded at 50 MHz on a Bruker AC 200F spectrometer. Optical rotations were measured with a JASCO-DIP-1000 digital polarimeter. Melting points were determined using an electrothermal apparatus and are uncorrected. Mass spectra were recorded on Shimadzu QP 5050A and Jeol HX 100/110 instruments. Chiral HPLC analyses were carried out using Daicel Chiralcel AS, AD, OJ, OD-H, and Regis Whelk-O1 columns (250, 4.6 mm, eluent: hexane/2-propanol).

1.1.1. *N*-(4-Methoxy-3,5-di-*tert*-butylbenzyl)cinchonidinium bromide (4a). To a suspension of cinchonidine (2.94 g, 10 mmol) in toluene (70 mL) was added 3,5-di-*tert*-butyl-4-methoxybenzyl bromide (4.38 g, 14 mmol), and the mixture was stirred at reflux for 4 h. The reaction mixture was cooled at room temperature, evaporated, and the residue was recrystallized from diethyl ether/CH_2Cl_2 to give the product as a dark brown solid. Purification of the residue by flash chromatography (93:7, dichloromethane/methanol) afforded the desired product **4a** (91%, 5.57 g) as a brown solid: $[\alpha]^{25}_D$=−77.8 (*c*=2, $CHCl_3$); mp 210–212°C; IR(film, cm^{-1}) 3504, 3040, 3000, 2950, 1700, 1585, 1500, 1460, 1450, 1410, 1389, 1352, 1262, 1225, 1210, 1115, 1010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 18H), 1.69 (m, 1H), 2.05 (s, 1H), 2.14–2.20 (m, 2H), 2.66 (m, 1H), 3.30 (m, 1H), 3.45 (m, 1H), 3.64 (d, *J*=11.4 Hz, 1H), 3.68 (s, 3H), 3.79 (t, *J*=8.5 Hz, 1H), 4.86 (t, *J*=11.0 Hz, 1H), 5.01 (d, *J*=10.3 Hz, 1H), 5.08 (s, 1H), 5.13 (d, *J*=5.9 Hz, 1H), 5.50–5.62 (m, 1H), 5.74 (d, *J*=11.0 Hz, 1H), 6.56 (d, *J*=6.5 Hz, 1H), 6.74 (d, *J*=6.2 Hz, 1H), 7.58–7.61 (m, 2H), 7.69 (s, 2H), 7.74(d, *J*=4.4 Hz, 1H), 8.01–8.07 (m, 2H), 8.85 (d, *J*=4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.54, 24.85, 26.68, 32.01, 35.98, 37.88, 51.33, 60.37, 61.12, 63.59, 64.14, 64.33, 68.53, 117.87, 120.14, 121.06, 122.78, 124.70, 127.61, 129.15, 130.42, 132.37, 136.47, 144.84, 144.95, 148.02, 150.08, 161.19; MS (EI) *m/z* 527, 472, 456, 210, 165; HRMS: calcd for $C_{35}H_{46}N_2O_2^+$ 526.3559, found 526.3563.

1.1.2. *O*-Allyl-*N*-(4-methoxy-3,5-di-*tert*-butylbenzyl)cinchonidinium bromide (4b). To a suspension of *N*-(3,5-di-*tert*-butyl-4-methoxybenzyl)cinchonidinium bromide **4a** (3.03 g, 5.0 mmol) in 40 mL of CH_2Cl_2 was added allyl bromide (0.64 mL, 7.5 mmol) and 2.8 mL of 50% of aq. KOH (25.0 mmol). The resulting mixture was stirred for 5 h. The mixture was diluted with 40 mL of water and extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by chromatography on silica gel (93:7, dichloromethane/methanol) to give product **4b** (92%, 2.98 g) as a yellow solid: $[\alpha]^{25}_D$=−142.5 (*c*=2, $CHCl_3$); mp 220–221°C; IR(film, cm^{-1}) 3407, 3000, 2949, 1704, 1625, 1596, 1567, 1510, 1502, 1491, 1470, 1454, 1400, 1350, 1210. 1115, 1070, 1010; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47–1.50 (s, 19H), 2.09–2.17 (m, 3H), 2.63 (s, 1H), 3.34–3.47 (m, 3H), 3.75 (s, 3H), 4.01 (m, 1H), 4.28 (m, 2H), 4.64 (d, *J*=11.5 Hz, 2H), 5.01 (d, *J*=8.4 Hz, 1H), 5.05 (d, *J*=10.5 Hz, 1H), 5.32–5.43 (m, 3H), 5.77 (m, 1H), 6.18 (m, 1H), 6.23 (s, 1H), 6.31 (d, *J*=11.5 Hz, 1H), 7.70 (s, 3H), 7.80 (t, *J*=7.4 Hz, 1H), 7.93 (m, 1H), 8.14 (d, *J*=8.39 Hz, 1H), 8.71 (d, *J*=8.48 Hz, 1H), 8.97 (d, *J*=4.39 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.99, 22.54,

25.28, 27.02, 31.99, 35.92, 37.77, 42.30, 51.04, 59.39, 60.31, 62.72, 64.34, 65.73, 70.30, 115.55, 118.40, 119.17, 120.04, 121.14, 124.40, 125.10, 129.10, 129.85, 130.28, 132.37, 132.47, 136.29, 139.88, 144.82, 148.40, 149.40, 161.18; MS (EI) *m/z* 567, 470, 394, 268, 167; HRMS: calcd for $C_{38}H_{50}N_2O_2^+$ 566.3872, found 566.3869.

1.2. General procedure for the Michael addition of nitroalkanes to chalcones

A mixture of nitroalkane (1.16 mmol), *t*-BuOK (19.6 mg, 0.17 mmol), chiral cinchonidinium salt **4b** (22.6 mg, 0.035 mmol), and chalcone (0.5 mmol) in toluene (2 mL) was stirred at room temperature for 14–20 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (silica gel, ethyl acetate/hexane=1:8) to afford the Michael adduct.

1.2.1. (*S*)-4-Nitro-1,3-diphenyl-butane-1-one (2a). R_f 0.41 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-9.3$ (*c*=1.0, $CHCl_3$, 35% ee); mp 101–103°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.46 (d, *J*=5.2 Hz, 1H), 3.48 (s, 1H), 4.13–4.30 (m, 1H), 4.69 (dd, *J*=8.0 and 7.8 Hz, 1H), 4.85 (dd, *J*=6.6 and 6.6 Hz, 1H), 7.25–7.94 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.4, 133.5, 129.0, 128.7, 128.0, 127.8, 127.4, 124.8, 79.5, 41.5, 39.2; MS (EI) *m/z* 228, 165, 105, 77; HRMS: calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1048; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel AS column, t_R=12.7 min (major), t_R=16.3 min (minor).

1.2.2. (*S*)-3-(4-Chlorophenyl)-4-nitro-1-phenylbutane-1-one (2b). R_f 0.42 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-10.8$ (*c*=1.0, $CHCl_3$, 42% ee), lit.[11] $[\alpha]^{23}_D=+17.9$ (*c*=1.0, CH_2Cl_2, 70% ee, major (*R*)); mp 108–110°C [lit.[11] 110–112°C]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.43 (d, *J*=7.0 Hz, 2H), 4.14–4.30 (m, 1H), 4.65 (dd, *J*=8.0 and 8.0 Hz, 1H), 4.82 (dd, *J*=6.4 and 6.0 Hz, 1H), 7.21–7.91 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.4, 137.5, 136.1, 133.6, 129.2, 128.8, 128.7, 127.9, 79.3, 41.3, 38.6; MS (EI) *m/z* 258, 207, 105, 77; HRMS: calcd for $C_{16}H_{14}ClNO_3$ 303.0662, found 303.0669; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel AD column, t_R=16.7 min (major), t_R=25.3 min (minor).

1.2.3. 3-Naphthalen-2-yl-4-nitro-1-phenylbutane-1-one (2c). R_f 0.38 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-7.4$ (*c*=1.0, $CHCl_3$, 31% ee); mp 129–133°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.56 (dd, *J*=3.7 and 2.8 Hz, 1H), 3.67 (t, *J*=3.3 Hz, 1H), 4.30–4.45 (m, 1H), 4.79 (dd, *J*=8.0 and 8.1 Hz, 1H), 4.91 (dd, *J*=6.7 and 6.7 Hz, 1H), 7.39–7.96 (m, 12H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.7, 136.4, 133.5, 133.3, 132.7, 130.8, 128.9, 128.7, 128.0, 127.7, 127.6, 127.3, 126.5, 126.4, 126.1, 125.8, 125.0, 79.5, 62.7, 41.5, 39.3; MS (EI) *m/z* 272, 244, 153, 105, 77; HRMS: calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1212; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel AD column, t_R=15.7 min (major), t_R=19.3 min (minor).

1.2.4. 4-Methyl-4-nitro-1,3-diphenylpentan-1-one (3a). R_f 0.46 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-30.5$ (*c*=1.0, $CHCl_3$, 31% ee); mp 147–149°C [lit.6 146–148°C]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.63 (s, 3H), 3.27 (dd, *J*=3.2 and 3.6 Hz, 1H), 3.67 (dd, *J*=10.4 and 10.3 Hz, 1H), 4.15 (dd, *J*=3.4 and 3.4 Hz, 1H), 7.25–7.85 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.8, 133.2, 129.2, 128.6, 128.4, 127.9, 127.7, 92.1, 48.9, 39.1, 26.1, 22.5; MS (EI) *m/z* 250, 207, 105, 77; HRMS: calcd for $C_{18}H_{19}NO_3$ 297.1365, found 297.1369; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OJ column, t_R=25.8 min (major), t_R=35.4 min (minor).

1.2.5. 4-Methyl-4-nitro-3-phenyl-1-(4-trifluoromethylphenyl)pentan-1-one (3b). R_f 0.46 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-19.4$ (*c*=1.0, $CHCl_3$, 39% ee); mp 89–92°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.63 (s, 3H), 3.28 (dd, *J*=3.5 and 3.2 Hz, 1H), 3.68 (dd, *J*=10.3 and 10.3 Hz, 1H), 4.13 (dd, *J*=2.8 and 3.2 Hz, 1H), 7.26–7.97 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.4, 129.1, 128.5, 128.3, 127.9, 125.7, 91.0, 48.9, 39.4, 26.3, 22.6; MS (EI) *m/z* 320, 173, 145, 131, 91, 77; HRMS: calcd for $C_{19}H_{18}F_3NO_3$ 365.1239, found 365.1247; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OD-H column, t_R=6.6 min (minor), t_R=7.8 min (major). One recrystallization from ethanol gave colorless crystals: $[\alpha]^{25}_D=-37.4$ (*c*=1.0, $CHCl_3$), ee 94%.

1.2.6. 1-(4-Bromophenyl)-4-methyl-4-nitro-3-phenylpentan-1-one (3c). R_f 0.47 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-35.2$ (*c*=1.0, $CHCl_3$, 59% ee); mp 124–126°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.63 (s, 3H), 3.22 (dd, *J*=3.4 and 3.1 Hz, 1H), 3.65 (dd, *J*=10.3 and 10.3 Hz, 1H), 4.13 (dd, *J*=3.3 and 3.4 Hz, 1H), 7.20–7.97 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.4, 137.6, 136.1, 131.0 130.2, 129.1, 128.5, 127.8, 126.4, 91.0, 48.8, 39.1, 26.2, 22.4; MS (EI) *m/z* 330, 183, 131, 91, 76; HRMS: calcd for $C_{18}H_{18}BrNO_3$ 375.0470, found 375.0477; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OD-H column, t_R=7.4 min (major), t_R=8.4 min (minor). One recrystallization from ethanol gave colorless crystals: $[\alpha]^{25}_D=-47.9$ (*c*=1.0, $CHCl_3$), ee 87%.

1.2.7. 4-Methyl-4-nitro-3-phenyl-1-thiophen-2-ylpentan-1-one (3d). R_f 0.48 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-27.5$ (*c*=1.0, $CHCl_3$, 57% ee); mp 122–125°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 3H), 1.61 (s, 3H), 3.21 (dd, *J*=3.6 and 3.2 Hz, 1H), 3.59 (dd, *J*=10.4 and 10.4 Hz, 1H), 4.12 (dd, *J*=3.6 and 3.2 Hz, 1H), 7.11 (dd, *J*=4.0 and 4.4 Hz, 1H), 7.22–7.30 (m, 5H), 7.60 (dd, *J*=0.4 and 1.2 Hz, 1H), 7.72 (dd, *J*=0.8 and 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 189.5, 133.9, 131.9, 129.1, 128.4, 128.0, 127.8, 91.1, 49.1, 39.7, 26.0, 22.5; MS(EI) *m/z* 257, 165, 111, 77; HRMS: calcd for $C_{16}H_{17}NO_3S$ 303.0929, found 303.0933; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Regis Whelk-O1 column, t_R=16.1 min (major), t_R=27.2 min (minor).

1.2.8. 1-Furan-2-yl-4-methyl-4-nitro-3-phenylpentan-1-one (3e). R_f 0.48 (EtOAc/hexane=1:8); $[\alpha]^{25}_D=-32.1$ (*c*=1.0, $CHCl_3$, 61% ee); mp 121–123°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (s, 3H), 1.62 (s, 3H), 3.08 (dd, *J*=3.6 and 3.6 Hz, 1H), 3.59 (dd, *J*=10.4 and 10.8 Hz, 1H), 4.12 (dd, *J*=3.6 and 3.2 Hz, 1H), 6.50 (dd, *J*=1.2 and 2.0 Hz, 1H), 7.13 (d, *J*=3.6 Hz, 1H), 7.20–7.29 (m, 5H), 7.55 (d, *J*=1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 190.2, 146.3,

129.2, 128.4, 127.8, 117.1, 112.3, 91.3, 48.6, 38.7, 25.8, 22.6; MS(EI) *m/z* 240, 198, 131, 95, 77; HRMS: calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1158; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Regis Whelk-O1 column, t_R=16.5 min (major), t_R=28.2 min (minor).

1.2.9. 1-(3-Bromophenyl)-4-methyl-4-nitro-3-phenylpentan-1-one (3f). R_f 0.47 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−42.3 (*c*=1.0, $CHCl_3$, 71% ee); mp 122–125°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.53 (s, 3H), 1.62 (s, 3H), 3.22 (dd, *J*=3.6 and 1.4 Hz, 1H), 3.65 (dd, *J*=10.4 and 10.3 Hz, 1H), 4.13 (dd, *J*=3.0 and 3.4 Hz, 1H), 7.24–7.98 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.3, 136.1, 130.9, 129.1, 128.7, 128.5, 127.8, 126.4, 91.0, 48.8, 39.1, 26.2, 22.4; MS (EI) *m/z* 330, 183, 131, 91, 76; HRMS: calcd for $C_{18}H_{18}BrNO_3$ 375.0470, found 375.0478; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OD-H column, t_R=7.4 min (major), t_R=8.4 min (minor).

1.2.10. 4-Methyl-4-nitro-1-phenyl-3-(4-trifluoromethylphenyl)pentan-1-one (3g). R_f 0.46 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−20.5 (*c*=1.0, $CHCl_3$, 60% ee); mp 105–107°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (s, 3H), 1.63 (s, 3H), 3.32 (dd, *J*=3.2 and 3.4 Hz, 1H), 3.69 (dd, *J*=10.2 and 10.2 Hz, 1H), 4.21 (dd, *J*=3.2 and 3.2 Hz, 1H), 7.34–7.95 (m, 9H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.2, 136.2, 133.5, 129.5, 128.7, 127.9, 125.4, 125, 90.7, 48.6, 38.8, 25.9, 22.8; MS(EI) *m/z* 320, 199, 105,77; HRMS: calcd for $C_{19}H_{18}NO_3$ 365.1239, found 365.1244; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OJ column, t_R=11.3 min (major), t_R=15.6 min (minor).

1.2.11. 3-(3-Chloro-4-fluorophenyl)-4-methyl-4-nitro-1-phenylpentan-1-one (3h). R_f 0.48 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−36.8 (*c*=1.0, $CHCl_3$, 53% ee); mp 123–126°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.63 (s, 3H), 3.29 (dd, *J*=3.4 and 3.5 Hz, 1H), 3.60 (dd, *J*=10.4 and 10.7 Hz, 1H), 4.11 (dd, *J*=3.3 and 3.3 Hz, 1H), 7.09–7.90 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.1, 136.2, 135.1, 133.5, 131.0, 129.0, 128.8, 128.7, 127.9, 116.8, 116.3, 90.7, 47.9, 38.9, 25.8, 22.9; MS (EI) *m/z* 302, 207, 105, 77; HRMS: calcd for $C_{18}H_{17}ClFNO_3$ 349.0881, found 349.0891; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OJ column, t_R=26.1 min (major), t_R=35.3 min (minor). One recrystallization from ethanol gave colorless crystals: $[\alpha]^{25}_D$=−59.4 (*c*=1.0, $CHCl_3$), ee>99%.

1.2.12. 1-(3-Bromophenyl)-4-methyl-3-naphthalen-2-yl-4-nitropentan-1-one (3i). R_f 0.40 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−55.6 (*c*=1.0, $CHCl_3$, 69% ee); mp 117–119°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 1.68 (s, 3H), 3.31(dd, *J*=3.0 and 2.9 Hz, 1H), 3.78 (dd, *J*=10.4 and 10.5 Hz, 1H), 4.31 (dd, *J*=3.1 and 3.1 Hz, 1H), 7.26–7.98 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.2, 136.1, 131.0, 130.2, 128.2, 127.9, 127.5, 127.0, 126.5, 126.3, 126.2, 122.9, 91.2, 48.9, 39.3, 26.4, 22.5; MS (EI) *m/z* 378, 337, 257, 181, 152; HRMS: calcd for $C_{22}H_{20}BrNO_3$ 425.0627, found 425.0633; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 0.8 mL min^{-1}) Chiralcel AS column, t_R=8.4 min (major), t_R=9.1 min (minor). One recrystallization from ethanol gave colorless crystals: $[\alpha]^{25}_D$=−78.2 (*c*=1.0, $CHCl_3$), ee>99%.

1.2.13. 1-(4-Bromophenyl)-4-methyl-3-naphthalen-2-yl-4-nitropentan-1-one (3j). R_f 0.40 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−47.2 (*c*=1.0, $CHCl_3$, 51% ee); mp 120–122°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.57 (s, 3H), 1.67 (s, 3H), 3.31 (dd, *J*=3.1 and 3.2 Hz, 1H), 3.75 (dd, *J*=10.4 and 10.4 Hz, 1H), 4.30 (dd, *J*=3.3 and 3.3 Hz, 1H), 7.29–7.95 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 199.0, 131.9, 130.0, 129.5, 128.6, 128.3, 128.2, 127.9, 127.5, 127.0, 126.3, 126.2, 91.2, 49.1, 39.2, 26.5, 22.5; MS (EI) *m/z* 378, 337, 257, 181, 152; HRMS: calcd for $C_{22}H_{20}BrNO_3$ 425.0627, found 425.0631; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 0.8 mL min^{-1}) Chiralcel AS column, t_R=7.9 min (major), t_R=8.8 min (minor). One recrystallization from ethanol gave colorless crystals: $[\alpha]^{25}_D$=−90.3 (*c*=1.0, $CHCl_3$), ee>99%.

1.2.14. 1-(3-Bromophenyl)-4-methyl-3-naphthalen-1-yl-4-nitropentan-1-one (3k). R_f 0.40 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−52.5 (*c*=1.0, $CHCl_3$, 57% ee); mp 120–123°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 1.68 (s, 3H), 3.35 (dd, *J*=3.2 and 3.2 Hz, 1H), 3.80 (dd, *J*=10.4 and 10.5 Hz, 1H), 4.33 (dd, *J*=3.1 and 3.2 Hz, 1H), 7.25–7.95 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.8, 131.8, 129.4, 128.9, 128.5, 126.6, 125.8, 124.8, 124.5, 123.6, 122.7, 120.3, 92.1, 48.9, 39.3, 27.0, 22.0; MS (EI) *m/z* 378, 337, 257, 181, 152; HRMS: calcd for $C_{22}H_{20}BrNO_3$ 425.0627, found 425.0631; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OD-H column, t_R=8.5 min (minor), t_R=9.2 min (major).

1.2.15. 1-(4-Bromophenyl)-4-methyl-3-naphthalen-1-yl-4-nitropentan-1-one (3l). R_f 0.40 (EtOAc/hexane=1:8); $[\alpha]^{25}_D$=−44.8 (*c*=1.0, $CHCl_3$, 57% ee); mp 119–121°C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.58 (s, 3H), 1.68 (s, 3H), 3.30 (dd, *J*=3.0 and 3.4 Hz, 1H), 3.79 (dd, *J*=10.4 and 10.4 Hz, 1H), 4.31 (dd, *J*=3.3 and 3.0 Hz, 1H), 7.26–7.98 (m, 11H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 195.2, 136.1, 133.0, 132.7, 131.0, 130.2, 128.2, 127.8, 127.5, 127.0, 126.5, 126.3, 126.2, 91.2, 48.8, 39.3, 26.4, 22.4; MS (EI) *m/z* 378, 337, 257, 181, 152; HRMS: calcd for $C_{22}H_{20}BrNO_3$ 425.0627, found 425.0633; HPLC (90:10, hexane/*iso*-PrOH, 254 nm, 1.2 mL min^{-1}) Chiralcel OD-H column, t_R=7.6 min (minor), t_R=9.3 min (major).

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