A One-Pot Amidation of Primary Nitroalkanes

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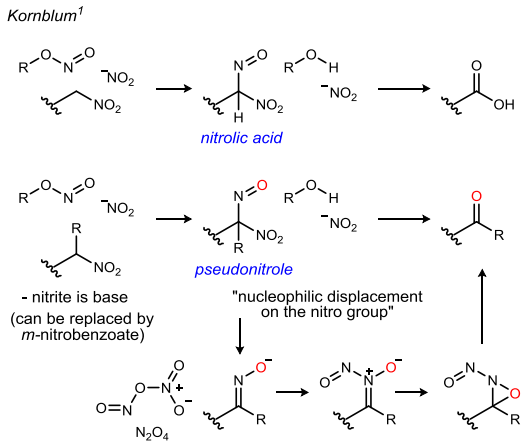
SI-1-X

Experimental Section

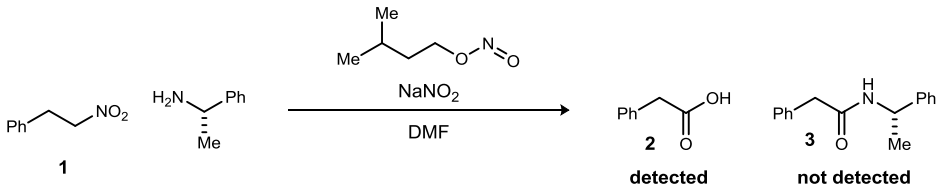
All reagents and solvents were commercial grade and purified prior to use when necessary. Nitroalkanes were prepared according to literature procedures.[1,2,3,4,5] NIS was recrystallized from dioxane/CCl_4. Flash column chromatography was performed using Sorbent Technologies 40-63 mm, pore size 60 Å silica gel with solvent systems indicated. Analytical thin layer column chromatography was performed using Sorbent Technologies 250 mm glass-backed UV254 silica gel plates, and were visualized by fluorescence upon 250 nm radiation and/or the by use of ceric ammonium molybdate or potassium permanganate. Solvent removal was effected by rotary evaporation under vacuum (~ 25-40 mm Hg). All extracts were dried with $MgSO_4$ unless otherwise noted.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker AV-400 (400 MHz) or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.16 ($CDCl_3$), unless otherwise specified. Mass spectra were recorded on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of the ionization method noted by the Indiana University Mass Spectrometry Facility. IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}) as neat films on a NaCl plate (transmission). Optical rotations were measured on a Perkin Elmer-341 polarimeter.

Proposed mechanism (Kornblum) for conversion of primary nitroalkanes to carboxylic acids

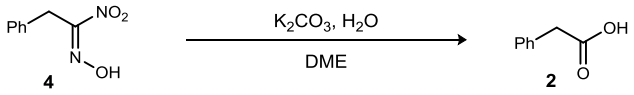


Adaptation of Kornblum's Protocol for Acid Formation to Amide Formation (Unsuccessful)

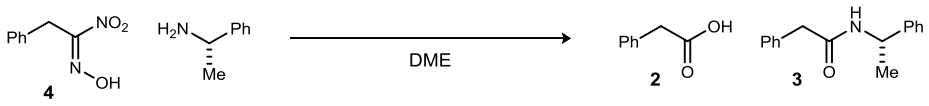


[1] Erickson, A. S.; Kornblum, N. *J. Org. Chem.* **1977**, *42*, 3764-3765.
[2] Shen, B.; Makley, D. M.; Johnston, J. N. *Nature*. **2010**, *465*, 1027-1032
[3] Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622-17623.
[4] Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976-8977.
[5] Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, Á.; Vera, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 8431-8435.

Adapting from the literature procedure,[6] nitroalkane **1** (1 equiv.), isopentyl nitrite (1 equiv.), sodium nitrite (1.5 equiv.) and (*S*)-1-phenylethan-1-amine (1 equiv.) were stirred in DMF for 48 h. The mixture was quenched with cold 3 M HCl and extracted with DCM. The organic layer was dried and concentrated. Formation of **2** was observed by ^{1}H NMR (confirmed by spiking the crude reaction mixture with phenyl acetic acid).



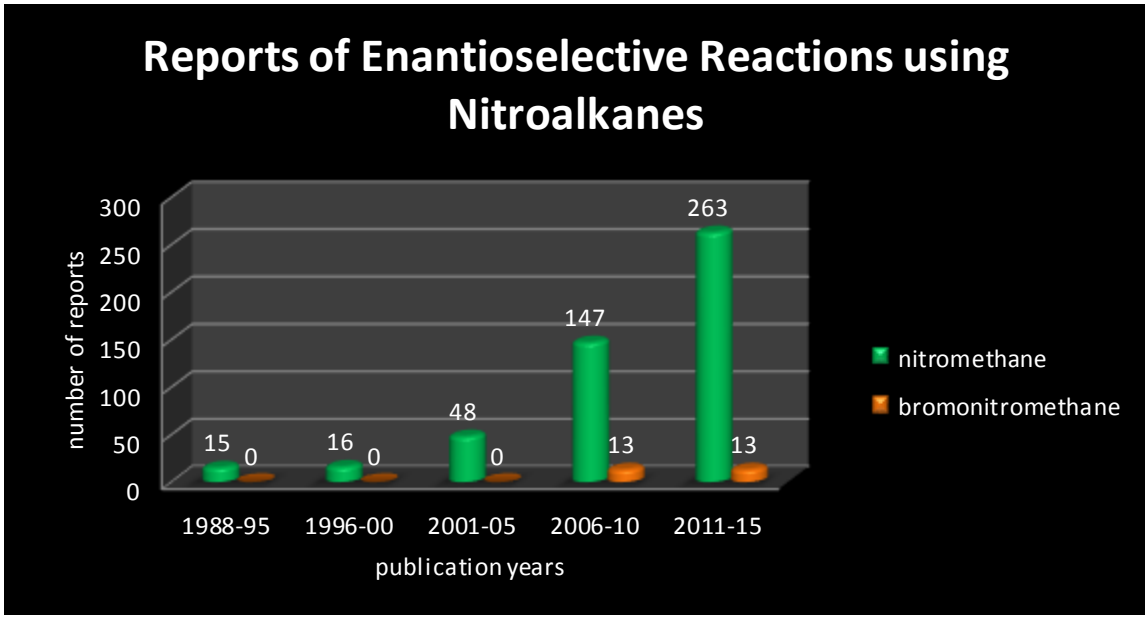
Nitrolic acid **4** was prepared according to the literature procedure.[7] Nitrolic acid **4** (1 equiv.), K_2CO_3 (2 equiv.) and H_2O (5 equiv.) were stirred in DME at 25 °C for 16 h. The mixture was quenched with 1 M HCl and extracted with DCM. The organic layer was dried and concentrated to afford full conversion to acid **2**.



Nitrolic acid **4** (1 equiv.) and (*S*)-1-phenylethan-1-amine (1 equiv.) were stirred in DME at 25 °C for 16 h. The mixture was quenched with 1 M HCl and extracted with DCM. The organic layer was dried and concentrated. Trace amounts of acid **2** and amide **3** were observed in conjunction with unreacted nitrolic acid **4** (major).

Nitromethane vs. bromonitromethane in enantioselective synthesis

A literature search (SciFinder) was performed using the search terms "bromonitromethane" and "enantioselective" as well as "nitromethane" and "enantioselective."



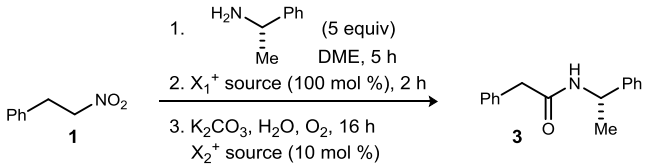
[6] Kornblum, N.; Wade, P. A. *J. Org. Chem.* **1973**, *38*, 1418-1420.
[7] Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234-235.

Bromination of nitroalkanes

Method A: According to the literature procedure[1], the nitroalkane (1 equiv.) was stirred with KOH (1 equiv.) in THF:H_2O (3:1, 0.4 M). After the mixture became homogenous (~5 h), the mixture was cooled to 0 °C and added to a separatory funnel containing the bromonium source (1 equiv.) and DCM (0.2 M) at -78 °C. The funnel was shaken vigorously and the layers separated. The aqueous layer was extracted with DCM. The combined organic layers were dried and concentrated. The residue was purified by flash column chromatography.

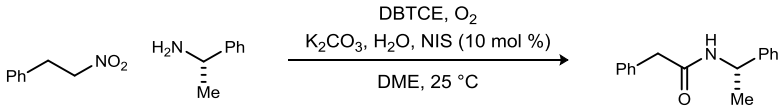
Method B: Nitroalkane (1 equiv.), triethylamine (3 equiv.), and the bromonium source were stirred in DME (0.4 M) for 20 h at 25 °C. The mixture was quenched with 1 M HCl and extracted with DCM. The organic layer was dried and concentrated. The residue was purified by flash column chromatography.

Procedure for step-wise protocol for one-pot halogenation of primary nitroalkanes

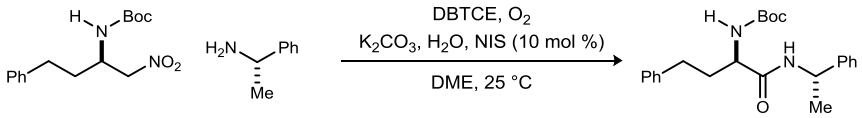


Nitroalkane **1** (1 equiv.) and (*S*)-1-phenylethan-1-amine (5 equiv.) were stirred at 25 °C in DME for 5 h. Halonium source X_1^+ (1 equiv.) was added and the mixture was allowed to stir for 2 h. Halonium source X_2^+ (0.1 equiv.), K_2CO_3 (2 equiv.), and H_2O (5 equiv.) were added to the reaction. The reaction setup was affixed with an O_2 balloon and allowed to stir for 16 h. The mixture was quenched with 1 M HCl and extracted with DCM. The organic layers were washed with satd aq $Na_2S_2O_3$, dried and concentrated. The resulting residue was purified by flash column chromatography.

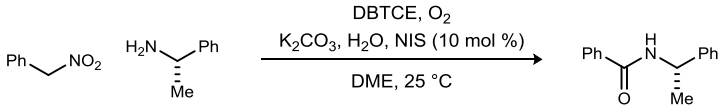
General procedure for one-pot amidation: To a round-bottomed flask equipped with a stir bar was added nitroalkane (1 equiv.), amine (2 equiv.), H_2O (5 equiv.) and DME (0.2 M). DBTCE (1 equiv.), K_2CO_3 (2 equiv.), and NIS (0.1 equiv.) were added. The reaction setup was equipped with an O_2 balloon and stirred at 25 °C for 24 h. The mixture was treated with 1 M HCl and extracted with DCM. The organics were washed with satd aq $Na_2S_2O_3$, dried and concentrated. The resulting residue was purified by flash column chromatography.



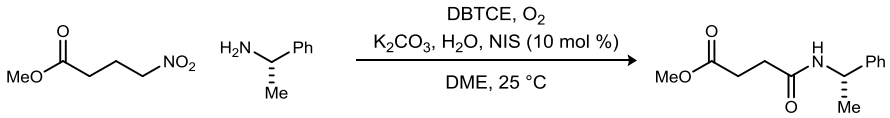
2-Phenyl-*N*-(1-phenylethyl)acetamide (3). Prepared according to the general procedure using (2-nitroethyl)benzene (30.2 mg, 200 µmol) and (*S*)-1-phenylethan-1-amine (51 µL, 400 µmol). Flash column chromatography (SiO_2, 20-30% ethyl acetate in hexanes) yielded the amide as a white solid (34 mg, 70%). Characterization data matched the literature.[2]



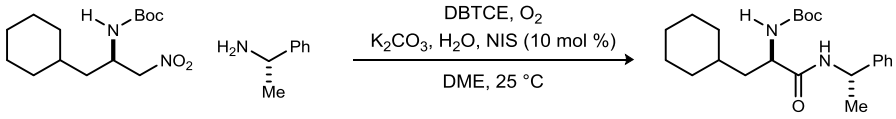
***tert*-Butyl ((*R*)-1-oxo-4-phenyl-1-(((*S*)-1-phenylethyl)amino)butan-2-yl)carbamate (6).** Prepared according to the general procedure using *tert*-butyl (*R*)-(1-nitro-4-phenylbutan-2-yl)carbamate (29.4 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 10-40% ethyl acetate in hexanes) yielded the amide as a white solid (26 mg, 67%) in >20:1 dr (^{1}H NMR). Characterization data matched the literature.[8]



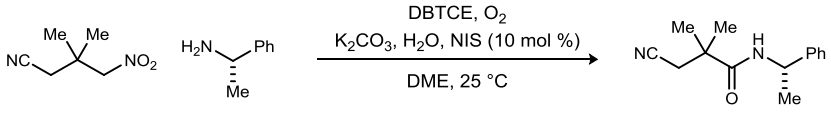
***N*-(1-Phenylethyl)benzamide (9a).** Prepared according to the general procedure using (nitromethyl)benzene (13.7 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) yielded the amide as a white solid (20 mg, 87%). Characterization data matched the literature.[2]



Methyl (S)-4-oxo-4-((1-phenylethyl)amino)butanoate (9b). Prepared according to the general procedure using methyl 4-nitrobutanoate (14.7 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 20-40% ethyl acetate in hexanes) yielded the amide as a white solid (16 mg, 68%). Characterization data matched the literature.[2]

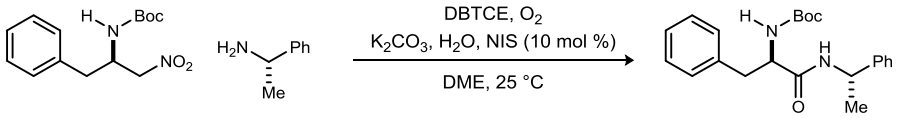


***tert*-Butyl ((*R*)-3-cyclohexyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)carbamate (9c).** Prepared according to the general procedure using *tert*-butyl (*R*)-(1-cyclohexyl-3-nitropropan-2-yl)carbamate (14.3 mg, 50 µmol) and (*S*)-1-phenylethan-1-amine (13 µL, 100 µmol). Flash column chromatography (SiO_2, 10-40% ethyl acetate in hexanes) yielded the amide as a white solid (11 mg, 59%) in >20:1 dr (^{1}H NMR). Characterization data matched the literature.[8]

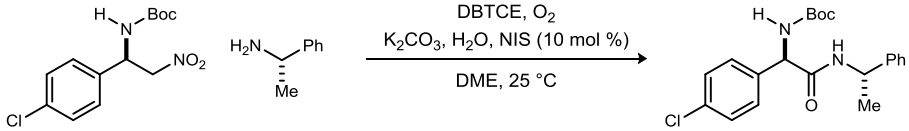


(*S*)-3-Cyano-2,2-dimethyl-*N*-(1-phenylethyl)propanamide (9d). Prepared according to the general procedure using 3,3-dimethyl-4-nitrobutanenitrile (14.2 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) yielded the amide as a white solid (15 mg, 65%). Characterization data matched the literature.[2]

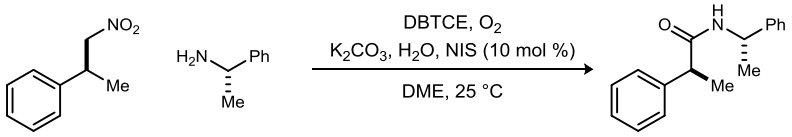
[8] Schwieter, K. E.; Johnston, J. N. *Chem. Sci.* **2015**, *6*, 2590-2595



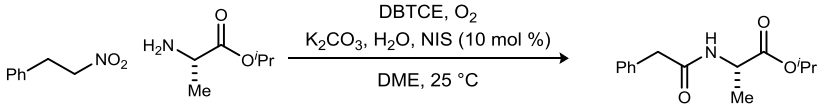
***tert*-Butyl ((*R*)-1-oxo-3-phenyl-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)carbamate (9e).** Prepared according to the general procedure using *tert*-butyl (*R*)-(1-nitro-3-phenylpropan-2-yl)carbamate (28.0 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) yielded the amide as a white solid (28 mg, 76%) in >20:1 dr (^{1}H NMR). Characterization data matched the literature.[8]



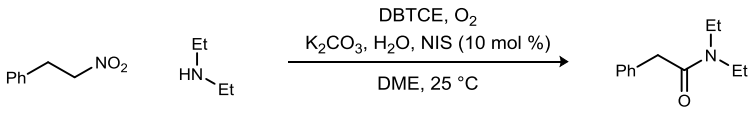
***tert*-Butyl ((*R*)-1-(4-chlorophenyl)-2-oxo-2-(((*S*)-1-phenylethyl)amino)ethyl)carbamate (9f).** Prepared according to the general procedure using *tert*-butyl (*R*)-(1-(4-chlorophenyl)-2-nitroethyl)carbamate (60.1 mg, 200 µmol) and (*S*)-1-phenylethan-1-amine (51 µL, 400 µmol). Flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) yielded the amide as a white solid (52 mg, 67%) in >20:1 dr (^{1}H NMR). Characterization data matched the literature.[2]



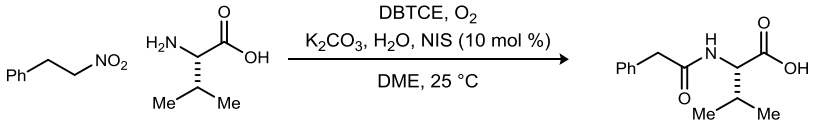
(*S*)-2-Phenyl-N-((*S*)-1-phenylethyl)propanamide (9g). Prepared according to the general procedure using (*S*)-(1-nitropropan-2-yl)benzene (16.5 mg, 100 µmol) and (*S*)-1-phenylethan-1-amine (26 µL, 200 µmol). Flash column chromatography (SiO_2, 10-30% ethyl acetate in hexanes) yielded the amide as a white solid (15 mg, 60%) in >20:1 dr (^{1}H NMR). R_f = 0.35 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ +4.1 (*c* 0.46, $CHCl_3$); mp 96-100 °C; IR (film) 3288, 2928, 1645, 1541 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.31-7.27 (m, 5H), 7.24-7.21 (m, 1H), 7.11 (d, *J* = 7.2 Hz, 2H), 5.56 (d, *J* = 6.3 Hz, 1H), 5.12 (m, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 1.54 (d, *J* = 7.2 Hz, 3H), 1.42 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.3, 143.4, 141.5, 129.0, 128.6, 127.8, 127.4, 127.2, 125.9, 48.8, 47.3, 22.0, 18.6; HRMS (ESI) Exact mass calcd for $C_{17}H_{19}NaNO$ $[M+Na]^+$ 276.1364, found 276.1357.



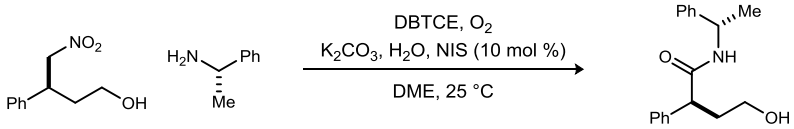
Isopropyl (2-phenylacetyl)-*L*-alaninate (9h). Prepared according to the general procedure using (2-nitroethyl)benzene (15.1 mg, 100 µmol) and isopropyl *L*-alaninate (26.2 mg, 200 µmol). Flash column chromatography (SiO_2, 20-30% ethyl acetate in hexanes) yielded the amide as a white solid (18 mg, 72%). R_f = 0.25 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ +9.7 (*c* .35, $CHCl_3$); mp 56-60 °C; IR (film) 3297, 2981, 2926, 1735, 1650, 1546 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2H), 7.31-7.27 (m, 3H), 6.03 (br s, 1H), 5.01 (m, 1H), 4.53 (m, 1H), 3.60 (s, 2H), 1.34 (d, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) ppm 172.3, 170.3, 134.6, 129.4, 129.0, 127.3, 69.1, 48.3, 43.6, 21.62, 21.57, 18.4; HRMS (ESI) Exact mass calcd for $C_{14}H_{19}NaNO_3$ $[M+Na]^+$ 272.1263, found 272.1258.



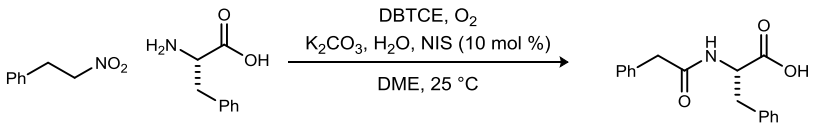
***N*,*N*-Diethyl-2-phenylacetamide (9i).** Prepared according to the general procedure using (2-nitroethyl)benzene (15.1 mg, 100 µmol) and diethylamine (21 µL, 200 µmol). Flash column chromatography (SiO_2, 20-30% ethyl acetate in hexanes) yielded the amide as a clear oil (12 mg, 63%). Characterization data matched the literature.[2]



(2-Phenylacetyl)-*L*-valine (9j). Prepared according to the general procedure using (2-nitroethyl)benzene (30.2 mg, 200 µmol) and *L*-valine (46.8 mg, 400 µmol). Flash column chromatography (SiO_2, 20-30% ethyl acetate in dichloromethane with 1% AcOH) yielded the amide as a white solid (27 mg, 57%). R_f = 0.15 (30% EtOAc/DCM, 1% AcOH); $[\alpha]_D^{20}$ -5.6 (*c* 0.13, DMSO); mp 126-130 °C; IR (film) 3316, 2922, 1710, 1597, 1551 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 8.21 (d, *J* = 8.6 Hz, 1H), 7.32-7.26 (m, 4H), 7.22-7.20 (m, 1H), 4.15 (dd, *J* = 8.6, 5.8 Hz, 1H), 3.56 (d, *J* = 13.8 Hz, 1H), 3.48 (d, *J* = 13.8 Hz, 1H), 2.05 (dqq, *J* = 13.6, 6.8, 6.8 Hz, 1H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H)[9]; ^{13}C NMR (100 MHz, d_6-DMSO) ppm 173.1, 170.4, 136.6, 129.0, 128.1, 126.3, 57.2, 41.9, 29.9, 19.1, 18.0; HRMS (ESI) Exact mass calcd for $C_{13}H_{17}NaNO_3$ $[M+Na]^+$ 258.1095, found 258.1106.



(*S*)-4-Hydroxy-2-phenyl-*N*-((*S*)-1-phenylethyl)butanamide (9k). Prepared according to the general procedure using (*S*)-4-nitro-3-phenylbutan-1-ol (78.1 mg, 400 µmol) and (*S*)-1-phenylethan-1-amine (102 µL, 800 µmol). Flash column chromatography (SiO_2, 1-5% methanol in dichloromethane) yielded the amide as a clear oil (59 mg, 52%) in >20:1 dr (^1H NMR). R_f = 0.36 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ +7.2 (*c* 0.25, $CHCl_3$); IR (film) 3287, 2931, 1648, 1544 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.35-7.32 (m, 2H), 7.29-7.19 (m, 6H), 7.08 (d, *J* = 7.2 Hz, 2H), 5.80 (d, *J* = 7.4 Hz, 1H), 5.08 (m, 1H), 3.71-3.67 (m, 2H), 3.63-3.59 (m, 1H), 2.42-2.36 (m, 1H), 2.02-1.97 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H)[10]; ^{13}C NMR (150 MHz, $CDCl_3$) ppm 173.0, 142.9, 139.7, 128.9, 128.5, 128.0, 127.4, 127.1, 125.7, 60.7, 50.3, 48.9, 35.9, 21.9; HRMS (ESI) Exact mass calcd for $C_{18}H_{22}NO_2$ $[M+H]^+$ 284.1651, found 284.1659.



(2-Phenylacetyl)-*L*-phenylalanine (9l). Prepared according to the general procedure using (2-nitroethyl)benzene (30.2 mg, 200 µmol) and *L*-phenylalanine (66.0 mg, 400 µmol). Flash column chromatography (SiO_2, 20-30% ethyl acetate in dichloromethane with 1% AcOH) yielded the amide as a yellow

[9] Carboxylic acid ^1H not observed.
[10] Alcohol ^1H not observed.

oil (30 mg, 53%). R_f = 0.23 (30% EtOAc/DCM, 1% AcOH); $[\alpha]_D^{20}$ +5.8 (*c* 0.38, DMSO); IR (film) 3286, 3062, 3030, 2927, 2522, 2362, 1727, 1655, 1540 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ 8.39 (d, *J* = 8.0 Hz, 1H), 7.27-7.16 (m, 8H), 7.13-7.11 (m, 2H), 4.44 (m, 1H), 3.44 (d, *J* = 14.0 Hz, 1H), 3.39 (d, *J* = 14.0 Hz, 1H), 3.07 (dd, *J* = 13.8, 4.8 Hz, 1H), 2.87 (dd, *J* = 13.8, 9.6 Hz, 1H)[9]; ^{13}C NMR (100 MHz, d_6-DMSO) ppm 173.0, 170.0, 137.5, 136.2, 129.1, 129.0, 128.2 , 128.1, 126.4, 126.2, 53.5, 42.0, 36.8; HRMS (ESI) Exact mass calcd for $C_{17}H_{17}NO_3$ $[M]^+$ 284.1287, found 284.1280.