

Use of polymer-supported amines in the catalytic nitro-aldol reaction of nitroalkanes with aldehydes

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Dedicated to Professors José Elguero and Pedro Molina on the occasion of their 70th and 60th anniversaries, respectively

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Abstract

An efficient catalytic synthesis of 2-nitroalcohols has been achieved through a catalytic nitro-aldol (Henry) reaction promoted by polymer-supported amines. These achiral and chiral polymer-bound amines show general utility in their reactions with a variety of aromatic and functionalized aldehyde acceptors. Moreover, the catalyst can be reused without loss of activity.

Keywords: Achiral and chiral polymer-bound amines, catalytic nitro-aldol, 2-nitroalcohols, polymer-supported catalysts

Introduction

The capability for high-throughput screening of potential drug substances is placing ever-increasing demands on the methods for the fast and efficient generation of new pharmacological targets. In general, chemical libraries or arrays containing a large number of compounds may be prepared either on polymer supports or in solution.^{1a} While most of the published work on small molecule library synthesis has been performed using solid supports, solution-phase strategies have been applied successfully by a number of researchers. The advantages of polymer-supported reactions (*e.g.*, that the reaction is accelerated by using an excess of the soluble reaction partner without the need for additional purification steps) and the benefits of solution-phase chemistry (*e.g.*, the ease of monitoring the process of the reactions by applying TLC, LC-MS or NMR techniques) can be combined by using polymer-supported reagents. Polymer-bound reagents have been utilized widely for many chemical transformations in organic chemistry.^{1b} Two of the most significant advantages of these reagents over their soluble counterparts are their ability to drive the reaction to completion by using an excess, and the ease of their separation

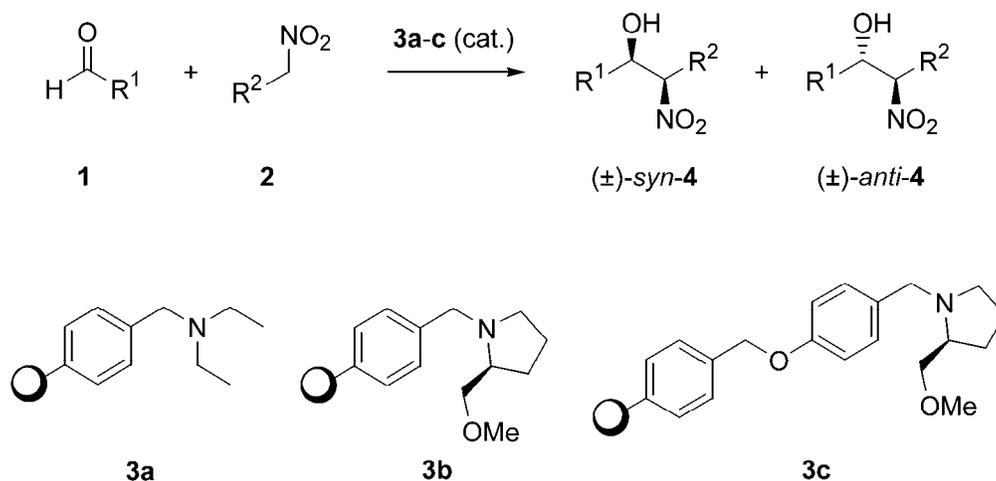
from the desired product by filtration. Furthermore, there is a constant need for new methodologies which can be applied to the preparation of heterocycles and small organic molecules.^{2,3} For this reason the development of new polymer-supported reagents has attracted growing interest in recent years. Recent work by our group has focused on the development of new bases^{4,5} and of new polymer-supported catalysts for the preparation of enantiomerically enriched 2H-azirines derived from phosphine oxides^{5a} and phosphonates.^{5b} We now report a further example using achiral- and chiral- polymer-supported amines for the construction of carbon-carbon bonds by nitroalkanes through the nitro-aldol (Henry) reaction.

The Henry- or nitro-aldol- reaction is a classical yet powerful carbon-carbon bond-forming process in organic chemistry,⁶ by which 2-nitroalcohols are formed by treating primary or secondary nitroalkanes with a base and carbonyl compounds, providing efficient access to valuable synthetic building blocks such as β -aminoalcohols and α -hydroxycarboxylic acids.⁷ Nitroalcohols are useful intermediates in the elaboration of pharmacologically important derivatives, including hepatotoxin, 7-epicyclindrospermopsin,^{8a} Taxotere[®]^{8b,c} side-chain and (-)-bestatin,^{8b,c} the β -receptor agonists (-)-denopamine^{8d} and (-)-arbutamine,^{8d,e} the β -blocker (S)-propranolol,^{8f} and antibiotics such as chloroamphenicol, ephedrine, nor-ephedrine and anthracycline.^{8g,h} The most commonly applied protocols for performing the above reaction require the use of basic catalysts under homogeneous or heterogeneous conditions.⁹

Bases such as phosphorus ylides,⁴ cyclic guanidines,^{10a} and ammonium salts,^{10b} have been applied in the nitro-aldol reaction¹⁰ and an asymmetric version of this reaction which uses an optically active metal catalyst has recently been developed.^{11,12} However, to our knowledge, there are no literature reports on the nitro-aldol reaction of nitroalkanes with aldehydes promoted by achiral or chiral polymer-supported amines as catalysts. Herein we explore the applicability of these resins in catalytic asymmetric nitro-aldol reactions.

Results and Discussion

To evaluate the catalytic efficiency of the polymer-supported amines **3**, the reaction of p-nitrobenzaldehyde **1a** with nitroethane, **2a**, was examined. Thus, treatment of **1a** with nitroethane **2a** in the presence of commercially available polymer-supported amine derived from diethylamine, **3a**, (50 mol. %) at room temperature for 3h, resulted in clean formation of the corresponding nitroalcohol **4a** as a diastereomeric mixture [(±)-syn/anti, 1:1] in 84% yield (Scheme 1, Table 1, entry 1). Further, the catalyst-loading can be reduced to 10 mol. % without significant loss of reactivity, to afford a mixture of (±)-syn- and (±)-anti-nitroalcohols with low diastereoselectivity (Table 1, entry 2).



Scheme 1

Table 1. Nitroaldol reaction of aldehydes with nitroalkanes catalyzed by polymer-supported amines **3a–c**

Entry	Product	R ¹	R ²	Catalyst (% mol.)	τ (%) ^a	(%) Yield ^b (syn / anti) ^c
1	4a	p-NO ₂ -C ₆ H ₄ -	Me	3a (50)	>99	84 (50:50)
2	4a	p-NO ₂ -C ₆ H ₄ -	Me	3a (10)	97	95 (50:50)
3	4a	p-NO ₂ -C ₆ H ₄ -	Me	3b (15)	95	66 (50:50)
4	4a	p-NO ₂ -C ₆ H ₄ -	Me	3c (20)	>99	81 (56:44)
5	4b	p-NO ₂ -C ₆ H ₄ -	H	3c (10)	92	60
6	4c	p-Me-C ₆ H ₄ -	Me	3c (20)	83	26 (64:36)
7	4d	p-Cl-C ₆ H ₄ -	Me	3c (20)	72	49 (57:43)
8	4e	p-F-C ₆ H ₄ -	Me	3c (20)	n.d.	38 (n.d.)
9	4f	CO ₂ Et	Me	3c (20)	>99	87 (n.d.)
10	4f	CO ₂ Et	Me	3c (20) ^d	>99	80 (n.d.)
11	4g	CO ₂ Et	H	3a (20)	>99	69

^a The conversion (τ) was calculated by ¹H- NMR analysis of the crude reaction mixture. ^b Values are isolated yields after chromatographic purification. ^c The syn / anti ratio was determined by ¹H- NMR analysis of the crude reaction mixture. ^d Recovered catalyst used once in Entry 9.

The spectroscopic data were in agreement with the assigned structure of compound **4a**.¹³ The ¹H- NMR spectrum showed an absorption at δ_H 5.21 ppm as a doublet with coupling constant ³J_{HH} = 8.5 Hz for the methylene proton directly bonded to the hydroxyl group of compound (±)-*syn*-**4a**, while the methylene proton directly bonded to the hydroxyl group of diastereoisomer (±)-*anti*-**4a** resonates at δ_H 5.58 ppm (³J_{HH} = 3.3 Hz).

In order to extend this process to the asymmetric synthesis of nitroalcohols **4**, the chiral polymer-supported amine **3b**^{5a} derived from Merrifield resin and (*S*)-(+)-2-(methoxymethyl)pyrrolidine was used. This chiral **3b** was used as the chiral base in the nitro-aldol reaction of aldehydes with nitroalkanes, in a similar way to that reported before for the achiral resin amine **3a**, to give the nitroalcohol **4a** in moderate yield (no appreciable diastereoselectivity was observed) (Scheme 1, Table 1, entry 3). The enantiopurity of nitroalcohol **4a** was examined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) with hexane/2-propanol as solvent, but showed no enantioselectivity.

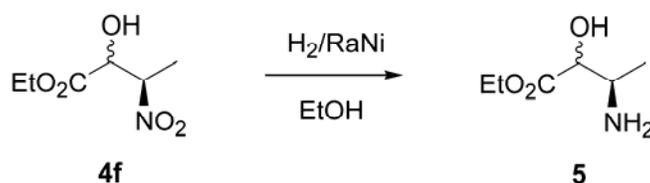
Finally, to improve both the diastereo- and enantio-selectivities, the chiral supported base **3c** derived from (*S*)-(+)-2-(methoxymethyl)pyrrolidine was synthesized. The preparation of this polystyrene chiral resin **3c** can be achieved by attachment of the chiral secondary amine to the solid support using Wang resin. Wang resin was reacted with (*S*)-(+)-2-(methoxymethyl)pyrrolidine at 65 °C in DMF to afford the new chiral resin **3c**.¹⁴ This chiral polymer-supported amine **3c** was then used as chiral base in the nitro-aldol reaction using aromatic- and functionalized aldehydes. Thus, treatment of aromatic (Scheme 1, Table 1, entries 4–8) and functionalized aldehydes (entries 9–10) with nitromethane or nitroethane in the presence of polymer-supported chiral amine **3c** (10–20 mol. %), afforded the corresponding nitroalcohols **4** with low diastereoselectivities and no enantiomeric excess.

Combination of polymer-supported reactions and solution-phase chemistry allows the preparation of 2-nitroalcohols **4** after filtration of the corresponding polymer-supported amines **3**. These polymer-supported amines **3**, after activation, were efficiently recycled for further cycles without loss of activity (Table 1, entry 10).

The high synthetic potential of the Henry reaction has been demonstrated previously for β -nitroalcohols¹⁵ and for β -nitro- α -amino acid derivatives,¹⁶ as well as for the easy conversion of the β -nitro- α -hydroxy acid derivatives into a variety of important functionalities—for example, β -amino- α -hydroxy esters.¹⁷ During the last several years, enantioselective synthesis of β -amino- α -hydroxy acids has attracted much attention not only because of the synthetic interest to put the right functional moieties in the right positions in a stereospecific manner but also because of their presence in various medicinally important molecules.¹⁸ Paclitaxel, one of the most promising anticancer agents so far discovered, has 2-(*N*-benzoylamino)-2-hydroxy-3-phenylpropionic acid as a side chain for the essential structural element for the activity.^{19a} Another member of this class of compounds bearing 3-amino-2-hydroxy-5-methyl hexanoate as a key component is amastatin, with immunoregulatory, antitumor, and antibacterial activity.^{19b} The β -amino- α -hydroxy acid is also found in renin inhibitor for antihypertensive agent, as the transition state mimic including KRI 1314,^{19c} bestatin,^{19d} — a dipeptide with antitumor and antibacterial activities — and microginin^{19e} — a linear pentapeptide natural product which showed angiotensin-converting enzyme inhibitory activity.

A straightforward synthetic route to β -amino- α -hydroxy acid derivatives can be designed by hydrogenolysis of starting β -nitro- α -hydroxy esters as shown in Scheme 2. Thus, for the β -nitro-

α -hydroxy ester **4f** (catalyst **3c** used) the reduction of the nitro group was performed using Raney-Ni to give the amino ester **5** in 68 % yield (Scheme 2).



Scheme 2

In summary, we have demonstrated the ability of achiral and chiral polymer-supported amines **3a–c** as highly active promoters of the addition of nitroalkanes to aldehydes. Nitroalcohols are valuable synthetic building blocks in the elaboration of pharmacologically important derivatives.^{7,8} Furthermore, it was shown that the β -nitro- α -hydroxy esters can be converted into synthetically valuable β -amino- α -hydroxy esters. This methodology combine the advantages of polymer-supported reactions and the benefits of solution-phase chemistry, allowing automated implementation of these processes in a way similar to that reported for the synthesis of other small molecule libraries.

Experimental Section

General Procedures. Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica-gel 60 F₂₅₄ plates. Spot visualization was accomplished by using UV light or KMnO_4 solution. Flash chromatography was carried out using silica gel 60 (230–400 mesh). Melting points were determined with an Electrothermal IA9100 digital apparatus and are uncorrected. ^1H - (400 MHz) and ^{13}C - (100 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer, with tetramethylsilane (TMS) (0.00 ppm) or chloroform (7.24 ppm) as internal reference in CDCl_3 solutions for ^1H - NMR spectra, or chloroform (77.0 ppm) as internal reference in CDCl_3 solutions for ^{13}C - NMR spectra. Chemical shifts (δ) are given in ppm; multiplicities are indicated by s (singlet), brs (broad singlet), d (doublet), dd (double-doublet), t (triplet), q (quadruplet) or m (multiplet); coupling constants (J) are in Hz. Low-resolution mass spectra (MS) were obtained on a Hewlett Packard 5971 MSD Series spectrometer at 50–70 eV by electron impact (EI), or a Hewlett Packard 1100 MSD Series spectrometer by chemical ionization (CI). Data are reported in the form m/z (intensity relative to base peak = 100). Infrared spectra (IR) (in cm^{-1}) were taken on a Nicolet FTIR Magna 550 spectrometer, and were obtained for solids in KBr or for neat oils (NaCl plates). Elemental analyses were performed in a Perkin

Elmer Model 240 instrument. (*S*)-(+)-2-(methoxymethyl)pyrrolidinomethyl polystyrene resin **3b**^{5a} was synthesized according to literature procedures. RT denotes room temperature

Synthesis of (*S*)-(+)-2-(methoxymethyl)pyrrolidine Wang resin (3c**).** A suspension of Wang chlorinated resin (4 mmol, 0.5–1.0 mmol of Cl/g resin, 5.34 g) in DMF (40 ml) was treated with (*S*)-(+)-2-(methoxymethyl)pyrrolidine (16 mmol, 2 ml). The resulting mixture was shaken at 65 °C for 18 h under N₂ and then allowed to stand at RT for 24 h. After this time, the resin was filtered and washed successively with MeOH, DMF, MeOH, CH₂Cl₂, MeOH, CH₂Cl₂, MeOH, AcOEt, and pentane. The resulting polymer-supported amine was dried at 20 °C under vacuum for 12 h and stored in tightly sealed bottles. Data for **3c**: IR (KBr) 2806 (OMe st.), 1096 (C-O-C st.) cm⁻¹; Anal. Found: C, 85.42; H, 8.07; N, 1.54.

General procedure for the synthesis of 2-nitroalcohols **4**

To a suspension of resin-supported amine **3a–c** (*ca.* 0.2 mmol, 0.2 equiv.) in nitroalkane (5.0 ml) was added the corresponding aldehyde **1** (1 mmol, 1 equiv.). The mixture was shaken at RT or 60 °C under N₂ atmosphere, after which the resin was filtered off, and washed with CH₂Cl₂ (5 ml), Et₂O (5 ml), CH₂Cl₂ (5 ml) and Et₂O (5 ml). The filtrate was evaporated under vacuum and the crude product purified by flash-chromatography (silica gel, Et₂O–hexanes, 1:20) to yield compounds **4**. Resin-supported amines **3a–c** were recovered by washing successively with MeOH (3x), CH₂Cl₂ (3x), TEA (3x), TEA/CH₂Cl₂ (1:1) (3x), CH₂Cl₂ (3x), MeOH (3x). The resulting polymer-supported amine **3a–c** was dried at 20 °C under vacuum for 12 h and stored in tightly sealed bottles.

(±)-*anti*- and *syn*-2-Nitro-1-*p*-nitrophenylpropan-1-ol (**4a**).¹³ (A) Prepared as described in the general procedure, 190 mg (84%) was obtained as a white solid from *p*-nitrobenzaldehyde **1a**, nitroethane **2a** and resin-supported amine **3a** (0.5 equiv.) at RT for 3h. (B) By the general procedure, 215 mg (95%) was obtained as a white solid from *p*-nitrobenzaldehyde **1a**, nitroethane **2a** and resin-supported amine **3a** (0.1 equiv.) at RT for 17h. (C) By the general procedure, (149 mg, 66%) was obtained as a white solid from *p*-nitrobenzaldehyde **1a**, nitroethane **2a** and resin-supported amine **3b** (0.15 equiv.) at RT for 23h. (D) As described in the general procedure, 183 mg (81%) was obtained as a white solid from *p*-nitrobenzaldehyde **1a**, nitroethane **2a** and resin-supported amine **3c** (0.2 equiv.) at RT for 17h. Data for **4a**: mp 91–93 °C; ¹H-NMR (CDCl₃) δ 8.28 (d, ³J_{HH} = 8.8 Hz, 2H), 8.27 (d, ³J_{HH} = 8.8 Hz, 2H), 7.62 (d, ³J_{HH} = 8.8 Hz, 2H), 7.62 (d, ³J_{HH} = 8.8 Hz, 2H), 5.58 (d, ³J_{HH} = 3.3 Hz, 1H), 5.21 (d, ³J_{HH} = 8.5 Hz, 1H), 4.82–4.76 (m, 1H), 4.76–4.70 (m, 1H), 2.98 (brs, 1H), 2.98 (brs, 1H), 1.51 (d, ³J_{HH} = 6.7 Hz, 3H), 1.40 (d, ³J_{HH} = 6.7 Hz, 3H) ppm; ¹³C-NMR (CDCl₃) δ 148.3, 147.9, 145.5, 145.3, 127.9, 127.0, 124.1, 124.0, 87.8, 86.8, 75.1, 72.9, 16.3 11.9 ppm; IR (KBr) 3562, 3523, 1561, 1523, 1346 cm⁻¹; MS (EI) *m/z* 151 (100), 150 (90), 77 (70). Anal. Calcd. for C₉H₁₀N₂O₅: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.84; H, 4.40; N, 12.09%.

(±)-2-Nitro-1-*p*-nitrophenylethan-1-ol (**4b**).²⁰ By the general procedure, 127 mg (60%) was obtained as a white solid from *p*-nitrobenzaldehyde **1a**, nitromethane **2b** and resin-supported

amine **3c** (0.1 equiv.) at 60 °C for 48h. Data for **4b**: mp 85–86 °C; $^1\text{H-NMR}$ (CDCl_3) δ 8.22 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 7.63 (d, $^3J_{\text{HH}} = 8.8$ Hz, 2H), 5.64–5.60 (m, 1H), 4.65–4.58 (m, 2H), 3.70 (brs, 1H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 148.2, 145.0, 126.9, 124.2, 80.6, 69.9 ppm; IR (KBr) 3443, 1540, 1513, 1341 cm^{-1} ; MS (EI) m/z 151 (100), 150 (87), 77 (66). Anal. Calcd. for $\text{C}_8\text{H}_8\text{N}_2\text{O}_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 44.90; H, 3.82; N, 13.11%.

(\pm)-*anti*- and *syn*-2-Nitro-1-*p*-tolylpropan-1-ol (**4c**).^{10b} By the general procedure, 51 mg (26%) was obtained as a pale yellow oil from *p*-tolualdehyde **1b**, nitroethane **2a** and resin-supported amine **3c** (0.2 equiv.) at reflux for 48h. Data for **4c**: $^1\text{H-NMR}$ (CDCl_3) δ 7.28–7.20 (m, 8H), 5.34–5.32 (m, 1H), 4.99 (d, $^3J_{\text{HH}} = 9.1$ Hz, 1H), 4.81–4.73 (m, 1H), 4.72–4.66 (m, 1H), 2.82 (brs, 1H), 2.71 (brs, 1H), 2.38 (s, 3H), 2.37 (s, 3H), 1.51 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H), 1.31 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 139.1, 138.4, 135.5, 135.4, 129.7, 129.4, 126.9, 125.9, 88.5, 87.5, 76.2, 74.0, 21.2, 21.2, 16.5, 12.3 ppm; IR (NaCl) 3463, 2919, 1686, 1554, 1461, 1381, 1355 cm^{-1} ; MS (EI) m/z 120 (88), 119 (100), 91 (96), 65 (25). Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{NO}_3$: C, 61.53; H, 6.71; N, 7.18. Found: C, 61.49; H, 6.59; N, 7.14%.

(\pm)-*anti*- and *syn*-1-*p*-Chlorophenyl-2-nitropropan-1-ol (**4d**).²¹ By the general procedure, 106 mg (49%) was obtained as a pale yellow oil from *p*-chlorobenzaldehyde **1c**, nitroethane **2a** and resin-supported amine **3c** (0.2 equiv.) at RT for 72h. Data for **4d**: $^1\text{H-NMR}$ (CDCl_3) δ 7.36–7.24 (m, 8H), 5.33 (t, $^3J_{\text{HH}} = 3.6$ Hz, 1H), 4.97 (dd, $^3J_{\text{HH}} = 3.9$ Hz, $^3J_{\text{HH}} = 8.9$ Hz, 1H), 4.72–4.67 (m, 1H), 4.66–4.61 (m, 1H), 2.95 (d, $^3J_{\text{HH}} = 3.8$ Hz, 1H), 2.91 (d, $^3J_{\text{HH}} = 4.1$ Hz, 1H), 1.44 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H), 1.28 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 136.9, 136.7, 135.0, 134.3, 129.1, 128.9, 128.2, 127.3, 88.1, 87.2, 75.4, 73.2, 16.3, 11.9 ppm; IR (NaCl) 3516, 1554, 1387, 1096 cm^{-1} ; MS (EI) m/z 140 (73), 139 (100), 111 (46), 75 (31). Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{ClNO}_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.01; H, 4.50; N, 6.39%.

(\pm)-*anti*- and *syn*-1-*p*-Fluorophenyl-2-nitropropan-1-ol (**4e**). As described in the general procedure, **4e** (76 mg, 38%) was obtained as a pale yellow oil from *p*-fluorobenzaldehyde **1d**, nitroethane **2a** and resin-supported amine **3c** (0.2 equiv.) at reflux for 96h. Data for **4e**: $^1\text{H-NMR}$ (CDCl_3) δ 7.40–7.08 (m, 8H), 5.32 (d, $^3J_{\text{HH}} = 3.5$ Hz, 1H), 4.98 (d, $^3J_{\text{HH}} = 8.8$ Hz, 1H), 4.73–4.66 (m, 1H), 4.65–4.60 (m, 1H), 2.80 (d, $^3J_{\text{HH}} = 3.5$ Hz, 1H), 2.69 (d, $^3J_{\text{HH}} = 4.1$ Hz, 1H), 1.52 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H), 1.34 (d, $^3J_{\text{HH}} = 7.0$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 162.9 (d, $^1J_{\text{CF}} = 249.4$ Hz), 162.8 (d, $^1J_{\text{CF}} = 248.6$ Hz), 129.9 (d, $^4J_{\text{CF}} = 3.7$ Hz), 129.8 (d, $^4J_{\text{CF}} = 3.8$ Hz), 129.2 (d, $^2J_{\text{CF}} = 8.8$ Hz), 129.0 (d, $^2J_{\text{CF}} = 8.4$ Hz), 116.7 (d, $^3J_{\text{CF}} = 22.0$ Hz), 116.5 (d, $^3J_{\text{CF}} = 22.4$ Hz), 88.3, 87.4, 75.6, 73.3, 16.4, 12.2 ppm; IR (NaCl) 3476, 1550, 1509, 1226 cm^{-1} ; MS (EI) m/z 152 (6), 124 (91), 123 (100), 95 (79), 75 (25). Anal. Calcd. For $\text{C}_9\text{H}_{10}\text{FNO}_3$: C, 54.27; H, 5.06; N, 7.03. Found: C, 53.89; H, 4.98; N, 6.96%.

(\pm)-*anti*- and *syn*-2-Hydroxy-3-nitrobutyric acid ethyl ester (**4f**). By the general procedure, 150 mg (85%) was obtained as a pale yellow oil from ethyl glyoxalate **1d**, nitroethane **2a**, and resin-supported amine **3c** (0.2 equiv.) at RT during 1.5h. Data for **4f**: $^1\text{H-NMR}$ (CDCl_3) δ 4.91–4.88 (m, 1H), 4.81–4.78 (m, 2H), 4.34–4.23 (m, 5H), 3.40 (brs, 1H), 3.40 (brs, 1H), 1.64 (d, $^3J_{\text{HH}} = 6.9$ Hz, 3H), 1.50 (d, $^3J_{\text{HH}} = 6.9$ Hz, 3H), 1.28 (t, $^3J_{\text{HH}} = 7.1$ Hz, 6H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 171.0, 170.7, 83.3, 83.0, 71.8, 71.4, 62.9, 62.8, 14.9, 13.9, 13.9, 12.3 ppm; IR (NaCl) 3489,

2992, 1746, 1554, 1394, 1368, 1268 cm^{-1} ; MS (EI) m/z 130 ($M^+ - \text{HNO}_2$, 7), 104 (17), 85 (78), 76 (39), 57 (100). Anal. Calcd. for $\text{C}_6\text{H}_{11}\text{NO}_5$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.51; H, 6.17; N, 7.87%.

(±)-2-Hydroxy-3-nitropropionic acid ethyl ester (4g).²² As in the general procedure, 112 mg (69%) was obtained as a white solid from ethyl glyoxalate **1d**, nitromethane **2b** and resin-supported amine **3a** (0.2 equiv.) at RT for 6h. Data for **4g**: mp 47–48 °C; $^1\text{H-NMR}$ (CDCl_3) δ 4.71 (dd, $^3J_{\text{HH}} = 4.4$ Hz, $^2J_{\text{HH}} = 1.8$ Hz, 2H), 4.61 (d, $^3J_{\text{HH}} = 4.4$ Hz, 1H), 4.29–4.20 (m, 2H), 3.79 (d, $^3J_{\text{HH}} = 4.4$ Hz, 1H), 1.24 (t, $^3J_{\text{HH}} = 7.0$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 170.7, 76.8, 67.5, 62.8, 13.8 ppm; IR (KBr) 3397, 2992, 2939, 1739, 1560, 1388 cm^{-1} . Anal. Calcd. for $\text{C}_5\text{H}_9\text{NO}_5$: C, 36.81; H, 5.56; N, 8.59. Found: C, 37.12; H, 5.48; N, 8.47%.

anti- and syn-3-Amino-2-hydroxybutyric acid ethyl ester (5). Compound **4f** (88.5 mg, 0.50 mmol) was dissolved in EtOH (7 ml) and Raney nickel (200 mg) was added. The reaction was treated with H_2 at 1 atm. and left for 48h. The catalyst was filtered off and the crude product purified by flash-chromatography (silica gel, AcOEt–hexanes, 2:1) to yield the title compound **5**, 50 mg (68 %) yield as a pale yellow oil. $^1\text{H-NMR}$ (CDCl_3) δ 4.22–4.15 (m, 4H), 4.09 (d, $^3J_{\text{HH}} = 3.5$ Hz, 1H), 3.91 (d, $^3J_{\text{HH}} = 3.5$ Hz, 1H), 3.26–3.17 (m, 2H), 2.77 (brs, 6H), 1.25 (t, $^3J_{\text{HH}} = 7.0$ Hz, 6H), 1.14 (d, $^3J_{\text{HH}} = 6.8$ Hz, 3H), 1.00 (d, $^3J_{\text{HH}} = 6.5$ Hz, 3H) ppm; $^{13}\text{C-NMR}$ (CDCl_3) δ 173.8, 173.0, 74.8, 74.3, 61.5, 61.4, 49.5, 49.3, 20.1, 17.1, 14.1 ppm; IR (NaCl) 3443, 2991, 1743, 1553 cm^{-1} ; MS (CI) m/z 148 ($M^+ + 1$, 100). Anal. Calcd. for $\text{C}_6\text{H}_{13}\text{NO}_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.88; H, 8.93; N, 9.47%.

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References and Footnotes

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