EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201201682

Henry Reaction in Aqueous Media at Neutral pH

Pranjal P. Bora[a] and Ghanashyam Bez*[a]

Keywords: Henry reaction / C–C coupling / β-Nitro alcohols / Asymmetric synthesis / Diastereoselectivity

An efficient method for the synthesis of β-nitro alcohols from nitro alkanes and aldehydes in aqueous phosphate buffer under neutral pH conditions at room temperature is reported. In the case of higher nitro alkanes, the reaction showed very good diastereoselectivity to give *syn* β-nitro alcohols in preference to their *anti* products.

Introduction

Among carbon–carbon bond-forming reactions, the synthesis of β-nitro alcohols[1] by the nitro aldol (Henry) reaction is one of the most extensively studied reactions in organic synthesis and has been the subject of continuous effort to develop better synthetic protocols over the years. Because of the presence of two versatile functionalities in the form of nitro and hydroxy groups, nitro alcohols can be the synthetic precursors to many important organic bifunctional derivatives, including 2-hydroxycarboxylic acids, 2-nitro ketones, 2-amino alcohols, and nitro alkenes, which in turn are precursors to a diverse range of pharmaceutically important compounds.[2] The majority of the procedures for the synthesis of β-nitro alcohols focus on the use of organic and inorganic bases as catalysts for the reaction of aldehydes with nitro alkanes, which leads to the generation of many undesired side products resulting from competitive base-catalyzed transformations,[3] such as the aldol reaction, the Michael reaction, the Cannizaro reaction, and dehydration reactions (Figure 1). Therefore, control of the reaction conditions is important in nitro aldol reactions, and this point needs attention so that these competitive side reactions can be avoided. Recently, nitro aldol reactions catalyzed by organocatalysts[4] and enzymes[5] have gained tremendous attention, and these reactions are considered to work under mild reaction conditions.

Given the current emphasis on the development of green synthetic protocols, organic reactions in water have become highly desirable for process development in both industry and academia.[6] Water is cheap, harmless, and very easy to handle; organic reactions performed in water are important in many acid- and base-catalyzed reactions. As water is an essential ingredient in biological processes,[7] study of any organic reaction in aqueous media is considered to be helpful in understanding the mechanism of biological processes. Although there are a large number of methods[8] available to synthesize β-nitro alcohols through the nitro aldol reaction in organic media, only a few reports exist for the nitro aldol reaction in aqueous media. The most notable method is the NaOH-catalyzed nitro aldol reaction reported by Ballini et al.,[9] which is effective for both aliphatic and aromatic aldehydes. However, the yields for the Henry reactions of aromatic aldehydes were comparatively low, probably owing to the formation of side products. Additionally, the use of the strong base NaOH may not be compatible with base-sensitive functionalities in multistep syntheses. Wang et al.[10] reported the use of Et_3N as a catalyst for the same transformation in aqueous media, but the reaction was not effective for aromatic aldehydes having electron-donating substituents on the phenyl ring. A few biocatalysts, such as DNA[11] and hydroxynitrile lyase,[5b,5c] were also used as catalysts, but these enzymes are costly. Recently, Lai et al.[12] reported the use of Cu^{II} complexes for nitro aldol reactions in water, in which the preparation of the catalyst is required before use. In other interesting work, Pitchumani et al.[13] reported a highly stereoselective nitro aldol reaction in water/acetonitrile by using per-6-amino-β-cyclodextrin.

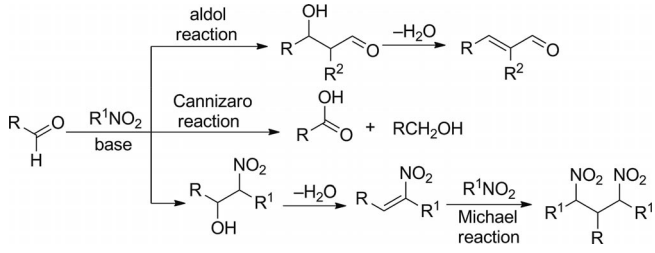


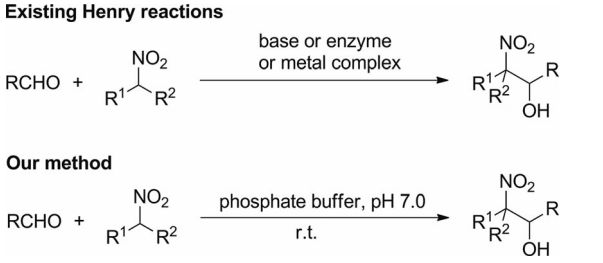
Figure 1. Side products in the base-catalyzed Henry reaction.

Given that the role of a base is to generate the nitronate anion to enable nucleophilic attack on the carbonyl moiety to generate β-nitro alcohols in the Henry reaction, careful

[a] Department of Chemistry, North Eastern Hill University, Shillong 793022, India
Fax: +91-3642558014
E-mail: ghanashyambez@yahoo.com
Homepage: http://www.nehu.ac.in/Schools/Physical%20Sciences/Chemistry/GB.php

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201201682.

control of the experimental conditions is necessary to avoid competitive side reactions. We were intrigued by the possibility of carrying out the reaction without the addition of any base catalyst or enzyme, in which case the formation of the side products could be avoided. Therefore, we wanted to carry out the Henry reaction under neutral conditions by maintaining the pH at 7.0 with an aqueous phosphate buffer. Carrying out this reaction in the laboratory under physiological pH in aqueous media would be advantageous in terms of procedural simplification, and it would potentially provide higher functional group compatibility in multistep syntheses, in addition to reducing the cost and environmental impact. To the best of our knowledge, the nitro aldol (Henry) reaction in aqueous media under neutral pH conditions has not been reported. Herein, we wish to report our findings that resulted in the development of a very efficient method for the synthesis of β-nitro alcohols in aqueous phosphate buffer at pH 7.0 (Scheme 1).



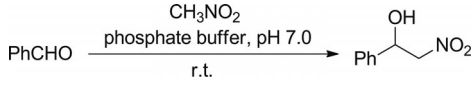
Scheme 1. Synthesis of β-nitro alcohols.

Results and Discussion

Efficient methods for the synthesis of β-nitro alcohols starting from aromatic aldehydes through the base-catalyzed nitro aldol reaction are very few because of the instantaneous formation of β-nitro alkenes.[9] We presumed that if the nitro aldol reaction of aromatic aldehydes could be carried out at neutral pH, subsequent formation of the nitro alkenes may be minimized. Notably, in many enzymatic[14] and enamine-based asymmetric organocatalytic reactions,[15] aqueous buffer solution (pH 7–8) is used to avoid general base catalysis[16] that is possible in nonbuffered solution. However, no effort has been made to understand whether (1) the buffer itself can perform any catalytic role in those reactions and (2) the buffer can contribute to the overall stereochemical outcome of the products. To address these issues, we planned to carry out the Henry reaction in aqueous phosphate buffer at pH 7.0. To that effect, a mixture of benzaldehyde (1 mmol) and nitromethane (3 mmol) in water at neutral pH, which was maintained by using a pH 7.0 phosphate buffer solution (2 mL), was stirred vigorously at room temperature. After 24 h, complete conversion of the starting benzaldehyde was observed, and the corresponding β-nitro alcohol was obtained in 78% yield. Optimization of the reaction conditions revealed that the reaction was complete within 18 h at room temperature. The fact that pure water is also pH neutral inevitably led to the question as to whether the reaction could be simply accomplished in water. To that end, we vigorously stirred the same reaction mixture in water (2 mL) for 24 h at room temperature, but the formation of the product was not detected.

To optimize the volume of the buffer solution, we carried out the model reaction with different volumes of the phosphate buffer at pH 7.0 (Table 1). As is evident from Table 1, the optimal reaction conditions included the use of 1.0 mL of phosphate buffer solution (Table 1, entry 2). Reduction of the volume of the buffer to 0.5 mL (Table 1, entry 1) affected the overall reaction time, and this suggests that the amount of phosphate affected the overall yield and time. Likewise, an increase in the volume of the buffer (Table 1, entries 3 and 4) reduced the reaction time, although this had very little effect on the reaction yield. The amount of phosphate present in solution changes with the volume of buffer added, and thus, the amount of phosphate ions in solution may affect the reaction time and yield. As the rate of a catalytic reaction depends on the catalyst loading, we concluded that phosphate ions in the buffer might be involved as a catalyst in the reaction.

Table 1. Effect of the volume of the buffer on the Henry reaction.[a]



Entry	Buffer volume [mL]	*t* [h]	% Yield[b]
1	0.5	36	56
2	1.0	18	78
3	1.5	16	80
4	2.0	14	78

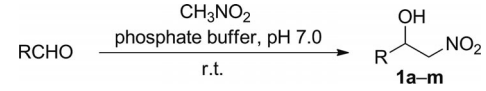
[a] Reaction conditions: aldehyde (0.25 mmol)/nitromethane = 1:3, r.t. [b] Yield of isolated product.

We wanted to explore the general applicability of our method for the nitro aldol reactions of various aromatic aldehydes with nitromethane (Table 2). Aryl aldehydes with a large negative inductive effect or a small positive resonance effect (Table 2, entries 1–5) underwent the reaction more quickly than aryl aldehydes with a large positive resonance effect (Table 2, entries 6–12). The position of the electron-withdrawing group, for example, the nitro group on the phenyl ring, hardly affected the rate and the yield of the reaction.

We also employed this protocol in the nitro aldol (Henry) reaction of nitromethane with ketones. The reaction of acetophenone (Scheme 2) with nitromethane in phosphate buffer at pH 7.0 did not take place at room temperature even after 120 h. When a more electrophilic ketone such as *p*-nitro acetophenone was treated under similar reaction conditions, the reaction failed to show any conversion after the same reaction time.

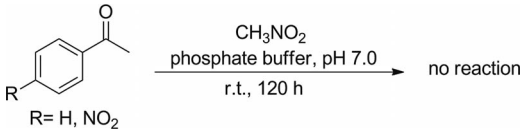
When we tried to extend the same protocol to the nitro aldol reaction of aliphatic aldehydes, we observed that the reaction of hexanal (Table 3, entry 3) with nitromethane did not give any yield upon stirring at room temperature even after 96 h. We suspected that the hydrophobicity of the hy-

Table 2. Reaction of aromatic aldehydes with nitromethane.[a]



Entry	R	Product	*t* [h]	% Yield[b]
1	4-$NO_2C_6H_4$	**1a**	14	95
2	3-$NO_2C_6H_4$	**1b**	15	92
3	2-$NO_2C_6H_4$	**1c**	14	96
4	4-ClC_6H_4	**1d**	18	87
5	4-BrC_6H_4	**1e**	16	90
6	C_6H_5	**1f**	18	78
7	4-$CH_3OC_6H_4$	**1g**	19	85
8	3,4-$(CH_3O)_2C_6H_3$	**1h**	22	87
9	3,4-$(OCH_2O)C_6H_3$	**1i**	24	68
10	4-HOC_6H_4	**1j**	28	78
11	4-OH,3-$MeOC_6H_3$	**1k**	30	80
12	4-$(NMe_2)C_6H_4$	**1l**	40	61
13	2-pyridyl	**1m**	12	90

[a] Reaction conditions: aldehyde/nitromethane = 1:3, r.t. [b] Yield of isolated product.

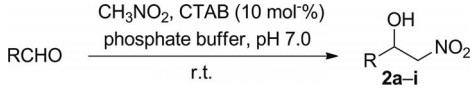


Scheme 2. Henry reaction with ketone.

drocarbon chain might have caused solubility problems in the aqueous solution, so that it could not react with nitromethane, and it could be that under our reaction conditions, the nitro aldol reaction takes place only in the aqueous phase. To test our assumption, the phase transfer reagent *N*,*N*,*N*,*N*-cetyltrimethylammonium bromide (CTAB) was added to a mixture of hexanal and nitromethane in aqueous phosphate buffer at pH 7.0, and the mixture was allowed to stir. The reaction proceeded and was complete within 40 h to give the desired product in 82% isolated yield. When other aliphatic aldehydes (Table 3, entries 1, 2, and 5–10) and nitromethane were treated under similar reaction conditions, good to excellent yields of the desired products were obtained.

Then we turned our attention to the reaction of aldehydes with nitroethane at room temperature. Under similar reaction conditions, the reactions with nitroethane gave excellent yields of the β-nitro alcohols, although longer reaction times were required for completion. The longer reaction time with higher nitro alkanes suggested that the reaction rate might be controlled by the solubility of the nitro alkanes in the water (buffer) solution. Given that the solubility of nitromethane[17] (10 g/100 mL) in water is higher than that of nitroethane[17] (4.6 g/100 mL), the reaction of aldehydes with nitromethane is comparatively fast. This finding led us to define this Henry reaction in phosphate buffer at pH 7.0 as a reaction in water.[18] Interestingly, the reaction of aromatic aldehydes with nitroethane in phosphate buffer at pH 7.0 resulted in moderate to excellent diastereoselectivity in favor of the *syn* product. To the best of

Table 3. Nitro aldol reaction of nitromethane with aliphatic aldehyde at room temperature.[a]

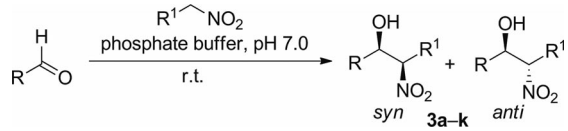


Entry	R	*t* [h]	Product	% Yield[b]
1	*n*-C_3H_7	40	**2a**	70
2	*n*-C_5H_{11}	40	**2b**	82
3	*n*-C_6H_{13}	96	**2c**	0[c]
4	*n*-C_6H_{13}	40	**2c**	82
5	*n*-C_7H_{15}	40	**2d**	85
6	*n*-C_8H_{17}	40	**2e**	65
7	*n*-C_9H_{19}	40	**2f**	75
8	*n*-$C_{11}H_{23}$	40	**2g**	72
9	$PhCH_2CH_2$	40	**2h**	60
10	EtO_2C	20	**2i**	90

[a] Reaction conditions: aldehyde/nitromethane/CTAB = 1:3:0.1, r.t. [b] Yield of isolated product. [c] Without CTAB.

our knowledge, this is the first report on the diastereoselective synthesis of β-nitro alcohols under catalyst-free conditions. Upon generalization, it was observed that the *syn* product was formed preferentially to the *anti* nitro aldol product (Table 4) in all cases. In general, aromatic aldehydes having electron-donating substituents (Table 4, entries 1–4) showed higher diastereoselectivity relative to more electrophilic aromatic aldehydes (Table 4, entries 6–8). For example, the reaction of nitroethane with *p*-anisaldehyde gave extremely good diastereoselectivity (*syn*/*anti* = 94:6). Likewise, very good selectivities were observed for less electrophilic aldehydes (Table 4, entries 2 and 3) such as 3,4-methylenedioxybenzaldehyde (*dr* = 91:9) and 3,4,5-trimethoxybenzaldehyde (*dr* = 86:14). Given the diastereoselectivity pattern and the reaction time for completion, we were led to believe that a slower reaction rate might yield

Table 4. Diastereoselective synthesis of β-nitro alcohols.[a]



Entry	R	R^1	*t* [h]	Product	% Yield[b]	*syn*/*anti*[c]
1	4-$MeOC_6H_4$	Me	30	**3a**	94	94:6
2	3,4-$(OCH_2O)C_6H_3$	Me	30	**3b**	94	91:9
3	3,4,5-$(OMe)_3C_6H_2$	Me	60	**3c**	72	86:14
4	4-MeC_6H_4	Me	30	**3d**	87	74:26
5	C_6H_5	Me	50	**3e**	86	73:27
6	4-$NO_2C_6H_4$	Me	30	**3f**	85	67:33
7	3-$NO_2C_6H_4$	Me	30	**3g**	92	78:22
8	4-BrC_6H_4	Me	30	**3h**	90	62:38
9	4-ClC_6H_4	Me	30	**3i**	81	75:25
10	4-$NO_2C_6H_4$	Et	50	**3j**	87	88:12
11	4-ClC_6H_4	Et	72	**3k**	82	94:6
12	4-MeC_6H_4	Et	72	**3l**	70	67:33

[a] Reactions were carried out at r.t. with aldehyde/nitro alkane (1:3) in aqueous phosphate buffer. [b] Calculated on the basis of isolated pure product. [c] Diastereoselectivity determined by HPLC by using Chiralcel OD-H and Chiralpak AD-H columns.

better selectivity. Keeping that in mind, we chose 1-nitropropane, which was expected to be less reactive than its lower homologue, nitroethane, because of the high pK_a of the α-hydrogen atoms of 1-nitropropane. Interestingly, the selectivities of more electrophilic aldehydes were found to be comparatively higher with 1-nitropropane (Table 4, entries 10 and 11). The diastereoselectivity for the reaction of *p*-chlorobenzaldehyde with 1-nitropropane was significantly higher (*syn*/*anti* = 94:6; Table 4, entry 11) than that for the reaction of *p*-chlorobenzaldehyde with nitroethane (*syn*/*anti* = 75:25; Table 4, entry 9). These observations confirmed our assumption that the overall diastereoselectivity is dependent on the reactivity of the aldehydes and nitro alkanes.

A plausible mechanism for buffer catalysis at pH 7.0 may be due to the presence of an equilibrium mixture of the Brønsted acid (dihydrogen phosphate anion) and its conjugate base (phosphate dianion) in the phosphate buffer at pH 7.0. Likely, these species would form a complex with the nitro alkane, in which the required tautomerization occurs. The phosphate ions might accelerate the initial formation of the nitronic acid (aci–nitro tautomer) through abstraction of the acidic α_{CH} proton by the phosphate dianion to generate the resonance-stabilized nitronate dianion species followed by proton transfer to the oxygen ion (Figure 2). The resulting nitronic acid[19] might react with the aldehydes to afford the corresponding β-nitro alcohols.

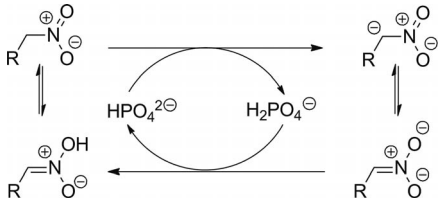


Figure 2. Plausible catalytic role of the phosphate buffer at pH 7.0 with nitro alkane species (likely as phosphate complexes).

Mechanistically, the preferential formation of the *syn*-nitro aldol product for the aromatic aldehydes might be attributed to the formation of water-assisted cyclic transition states TS-**I** and TS-**II**, which are formed by H-bonding between the oxygen atom of the aldehyde and the hydrogen atom of the nitronic acid, that is, the aci–nitro tautomer of nitroethane (Figure 3). The orientation of the aryl group in the equatorial position of TS-**I** might be preferred to the axial position of the aryl group in TS-**II**, which results in the preferential formation of the *syn* diastereomer. In contrast, aliphatic aldehydes cannot form the water-assisted transition state with the nitronic acid because of the possible micellar nature of the solvent after the addition of CTAB, and hence, no diastereoselectivity was observed.

As for aliphatic aldehydes, the reaction of butanal with nitroethane (Table 5, entry 1) in aqueous phosphate buffer at pH 7.0 did not give any product upon stirring at room temperature for 50 h. However, the addition of CTAB to the reaction mixture resulted in almost complete conversion after 72 h. Under these conditions, we investigated the scope of the reaction with a variety of aldehydes (Table 5).

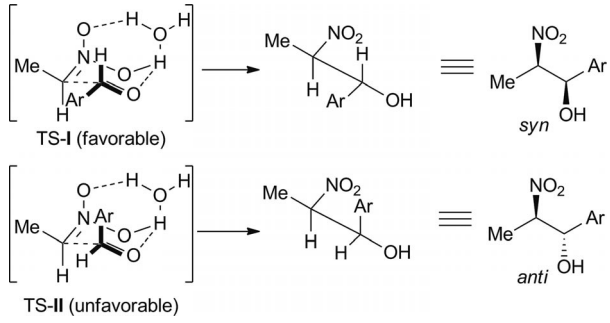
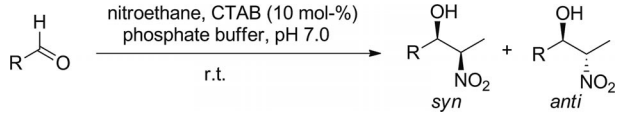


Figure 3. Preferential formation of the *syn* diastereomer.

Butanal, heptanal, nonanal, and dodecanal also gave excellent yields of the corresponding β-nitro alcohols under these conditions, but lower diastereoselectivities were obtained for these aldehydes.

Table 5. Synthesis of β-nitro alcohols of aliphatic aldehydes with nitroethane.[a]



Entry	R	Product	% Yield[b]	*syn*/*anti*[c]
1	butanal	**4a**	70	57:43
2	3-methylbutanal	**4b**	72	61:39
3	heptanal	**4c**	78	51:49
4	nonanal	**4d**	75	54:46
5	dodecanal	**4e**	68	59:41

[a] The reactions were carried out at r.t. for 60 h. [b] Isolated yield. [c] Diastereoselectivity determined by HPLC by using Chiralcel OD-H and Chiralpak AD-H columns.

Conclusions

In conclusion, the nitro aldol (Henry) reaction of aldehydes with nitro alkanes in aqueous phosphate buffer at neutral pH is reported for the first time. The reaction works excellently at room temperature without the formation of side products. Unlike base-catalyzed Henry reactions, no instantaneous formation of the olefin was observed for the Henry reaction with aromatic aldehydes. For higher nitro alkanes, the reaction was diastereoselective and gave *syn*-β-nitro alcohols in preference to *anti*-β-nitro alcohols. With nitroethane, the *syn* selectivity was excellent for less electrophilic aromatic aldehydes, but more electrophilic aromatic aldehydes and aliphatic aldehydes showed marginal diastereoselectivity. Interestingly, a slight increase in the selectivity was observed in the reaction of aldehydes with 1-nitropropane. No added base catalyst or hazardous solvents, the use of an aqueous reaction medium, easy workup, the simplicity of the method, excellent yields of the products, and excellent diastereoselectivities are some of the highlights of this method.

Experimental Section

General Information: All chemicals and reagents are commercially available and were used without further purification. All the products were characterized by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ by using tetramethylsilane as an internal standard. LRMS and HRMS data were recorded by using the electrospray ionization (ESI) method. HPLC analyses were carried out with the help of Diacel chiral columns (Chiralcel OD-H and Chiralpak AD-H) by using mixtures of *n*-hexane/2-propanol as mobile phase at 25 °C.

Preparation of Phosphate Buffer: One buffer tablet (pH 7.0) containing chlorides, potassium phosphates, and sodium phosphates (product no. 43155, batch no. 0198/Mfg/6385/81), purchased from s.d. Fine Chemicals, Ltd., India, was dissolved in Millipore water in a 100 mL volumetric flask. The pH of the solution was ascertained by using a digital pH meter and was used for the nitro aldol (Henry) reaction.

Synthesis of 2-Nitro-1-phenylethanol (1f) as a Representative Procedure: The aqueous phosphate buffer solution (pH 7.0, 1.0 mL) was added to a round-bottomed flask containing a mixture of benzaldehyde (0.027 g, 0.25 mmol) and nitromethane (0.046 g, 0.75 mmol). [For aliphatic aldehydes, CTAB (10 mol-%) was also added]. Upon vigorous stirring at room temperature for the specified time, the reaction was complete. The reaction mixture was extracted with ethyl acetate (3× 15 mL), and the combined organic layer was dried with anhydrous sodium sulfate, concentrated under vacuum, and purified by column chromatography (ethyl acetate/hexane) to obtain the pure product (0.033 g, 00197 mmol, 78%).

2-Nitro-1-(4-nitrophenyl)ethanol (1a):[13] Pale yellow solid: 53.3 mg, 95% yield; m.p. 38–39 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (s, 1 H), 4.56–4.65 (m, 2 H), 5.60–5.64 (m, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 8.24 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.98, 80.63, 124.17, 126.99, 145.15, 148.04 ppm. MS (ESI): m/z = 235.2 $[M + Na]^+$. $C_8H_8N_2O_5$ (212.16): calcd. C 45.29, H 3.80, N 13.20; found C 45.27, H 3.78, N 13.22.

2-Nitro-1-(3-nitrophenyl)ethanol (1b):[13] Pale yellow solid: 48.7 mg, 92% yield; m.p. 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (d, J = 4 Hz, 1 H), 4.55–4.67 (m, 2 H), 5.60–5.64 (m, 1 H), 7.62 (t, J = 8 Hz, 1 H), 7.78 (d, J = 7.2 Hz, 1 H), 8.23 (d, J = 8 Hz, 1 H), 8.33 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.83, 80.68, 121.14, 124.22, 130.14, 132.03, 140.22, 148.53 ppm. $C_8H_8N_2O_5$ (212.16): calcd. C 45.29, H 3.80, N 13.20; found C 45.25, H 3.76, N 13.21.

2-Nitro-1-(2-nitrophenyl)ethanol (1c):[13] Yellow solid: 51 mg, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.07 (s, 1 H), 4.37 (dd, J = 9.2, 13.6 Hz, 1 H), 4.67 (dd, J = 2, 13.6 Hz, 1 H), 5.85 (dd, J = 1.6, 9.2 Hz, 1 H), 7.37 (t, J = 8 Hz, 1 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.76 (d, J = 8 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 66.78, 80.13, 124.99, 128.72, 129.68, 134.15, 134.45, 147.11 ppm. $C_8H_8N_2O_5$ (212.16): calcd. C 45.29, H 3.80, N 13.20; found C 45.26, H 3.77, N 13.23.

1-(4-Chlorophenyl)-2-nitroethanol (1d):[13] White solid: 43.7 mg, 87% yield; m.p. 34–35 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79 (s, 1 H), 4.39–4.52 (m, 1 H), 5.36 (d, J = 9.2 Hz, 2 H), 7.19–7.31 (m, 5 H) ppm. ^{13}C NMR (100 Hz, $CDCl_3$): δ = 70.29, 81.03, 127.35, 129.21, 134.78, 136.61 ppm. $C_8H_8ClNO_3$ (201.61): calcd. C 47.66, H 4.00, N 6.95; found C 47.64, H 4.01, N 6.96.

1-(4-Bromophenyl)-2-nitroethanol (1e):[13] White solid: 55 mg, 90% yield; m.p. 64–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99 (s, 1 H), 4.47–4.60 (m, 2 H), 5.44 (dd, J = 2.8, 9.2 Hz, 1 H), 7.24–7.30 (m, 2 H), 7.54 (d, J = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.34, 80.90, 122.99, 127.62, 132.20, 137.00 ppm. MS (ESI): m/z = 269 $[M + Na]^+$.

2-Nitro-1-phenylethanol (1f):[13] Colorless oil: 32.5 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 (s, 1 H), 4.48 (dd, J = 2.8, 13.2 Hz, 1 H), 4.58 (dd, J = 9.6, 13.2 Hz, 1 H), 5.42 (dd, J = 2.8, 9.6 Hz, 1 H), 7.33–7.41 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.98, 81.35, 125.96, 128.90, 129.00, 129.18, 129.41, 132.19 ppm.

1-(4-Methoxyphenyl)-2-nitroethanol (1g):[13] Yellow oil: 42 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.81 (s, 1 H), 3.74 (s, 3 H), 4.40 (dd, J = 2.8, 13.2 Hz, 1 H), 4.53 (dd, J = 10, 13.2 Hz, 1 H), 5.33 (dd, J = 2.4, 9.6 Hz, 1 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.55, 70.67, 81.27, 114.39, 127.29, 130.19, 160.03 ppm.

1-(3,4-Dimethoxyphenyl)-2-nitroethanol (1h):[20] Yellow solid: 49 mg, 87% yield; m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H), 3.90 (s, 3 H), 4.50 (dd, J = 3.2, 13.2 Hz, 1 H), 4.62 (dd, J = 9.6, 13.2 Hz, 1 H), 5.42 (dd, J = 2.8, 9.6 Hz, 1 H), 6.86–6.94 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.95, 55.97, 70.88, 81.33, 108.73, 111.23, 118.34, 130.61, 149.40 ppm. $C_{10}H_{13}NO_5$ (227.22): calcd. C 52.86, H 5.77, N 6.16; found C 52.81, H 5.68, N 6.21.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroethanol (1i): White solid: 38 mg, 72% yield; m.p. 90–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (s, 1 H), 4.47 (dd, J = 2.8, 13.2 Hz, 1 H), 4.58 (dd, J = 9.6, 13.2 Hz, 1 H), 5.37 (d, J = 8.8 Hz, 1 H), 5.99 (s, 2 H), 6.85 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 70.82, 81.23, 101.39, 106.35, 108.62, 119.61, 131.97, 148.08, 148.24 ppm. MS (ESI): m/z = 234.1 $[M + Na]^+$. $C_9H_9NO_5$ (211.17): calcd. C 51.19, H 4.30, N 6.63; found C 51.22, H 4.33, N 6.43.

4-(1-Hydroxy-2-nitroethyl)phenol (1j):[13] Colorless oil: 35.7 mg, 78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (s, 1 H), 4.48 (dd, J = 3.3, 13.5 Hz, 1 H), 4.61 (dd, J = 8.7, 12.6 Hz, 1 H), 5.12 (s, 1 H), 5.41 (d, J = 9.9 Hz, 1 H), 6.87 (d, J = 7.2 Hz, 2 H), 7.28 (d, J = 9.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 70.65, 81.23, 115.86, 127.54, 130.31, 156.13 ppm.

4-(1-Hydroxy-2-nitroethyl)-2-methoxyphenol (1k):[13] Colorless oil: 42.6 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.82 (s, 1 H), 3.92 (s, 3 H), 4.49 (dd, J = 2.8, 12.8 Hz, 1 H), 4.61 (dd, J = 9.6, 13.2 Hz, 1 H), 5.70 (s, 1 H), 6.87 (dd, J = 1.2, 8 Hz, 1 H), 6.93 (d, J = 8.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.01, 70.94, 81.37, 108.22, 114.69, 119.03, 130.06, 146.11, 146.93 ppm. MS (ESI): m/z = 214 $[M + 1]^+$.

1-[4-(Dimethylamino)phenyl]-2-nitroethanol (1l):[13] Yellowish oil: 32 mg, 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2. 97 (s, 6 H), 4.46 (dd, J = 1.2, 9.9 Hz, 1 H), 4.63 (dd, J = 10.5, 13.8 Hz, 1 H), 5.36 (dd, J = 3, 10.5 Hz, 1 H), 6.72 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.46, 70.98, 81.33, 112.51, 125.46, 127.01, 150.92 ppm.

2-Nitro-1-(pyridin-2-yl)ethanol (1m):[13] Yellow gum: 37.8 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$/[D_6]DMSO): δ = 4.52–4.55 (m, 1 H), 4.88 (dd, J = 2, 12.8 Hz, 1 H), 5.37 (d, J = 8.8 Hz, 1 H), 7.18 (d, J = 4.8 Hz, 1 H), 7.55 (d, J = 7.6 Hz, 1 H), 7.70 (d, J = 6 Hz, 1 H), 8.43 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/[D_6]DMSO): δ = 70.60, 80.65, 120.77, 122.82, 137.23, 148.15, 158.69 ppm.

1-Nitropentan-2-ol (2a):[21] Colorless oil: 23.3 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, J = 6.8 Hz, 3 H), 1.38–1.57

(m, 4 H), 2.68 (br., 1 H), 4.33–4.45 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.04, 18.43, 35.73, 68.41, 80.70 ppm. MS (ESI): *m*/*z* = 156 [M + Na]$^+$.

1-Nitroheptan-2-ol (2b):[21] Colorless oil: 33 mg, 82% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.3 Hz, 3 H), 1.31–149 (m, 8 H), 2.95 (br., 1 H), 4.32–4.45 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.91, 22.44, 24.83, 31.44, 33.71, 68.73, 80.73 ppm.

1-Nitrooctan-2-ol (2c):[22] Colorless oil: 35.9 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.82 (t, *J* = 6.8 Hz, 3 H), 1.19–1.32 (m, 8 H), 1.41–1.5 (m, 2 H), 2.51 (br., 1 H), 4.22–4.39 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.01, 22.51, 25.12, 28.96, 31.60, 33.72, 68.68, 80.66 ppm. MS (ESI): *m*/*z* = 198 [M + Na]$^+$.

1-Nitrononan-2-ol (2d):[22] Colorless oil: 40 mg, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H), 1.22–1.29 (m, 10 H), 1.45–1.55 (m, 2 H) 2.91 (br., 1 H), 4.24–4.45 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 22.58, 25.16, 29.08, 29.25, 31.70, 33.75, 68.72, 80.72 ppm.

1-Nitrodecan-2-ol (2e):[21,22] Colorless oil: 33 mg, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64 (t, *J* = 6.8 Hz, 3 H), 1.05–1.08 (m, 12 H), 1.19–1.35 (m, 2 H), 2.00 (br., 1 H), 4.05–4.22 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.07, 22.63, 25.16, 29.16, 29.30, 29.38, 31.80, 33.72, 68.66, 80.64 ppm. MS (ESI): *m*/*z* = 204 [M + H]$^+$.

1-Nitroundecan-2-ol (2f):[23] Colorless liquid: 40.7 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3 H), 1.25 (m, 14 H), 1.45–1.56 (m, 2 H) 2.92 (br., 1 H), 4.27–4.45 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.08, 22.65, 25.17, 29.26, 29.30, 29.43, 29.47, 31.84, 33.75, 68.72, 80.72 ppm.

1-Nitrotridecan-2-ol (2g): White solid: 44.1 mg, 72% yield; m.p. 45–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.4 Hz, 3 H), 1.17–1.36 (m, 18 H), 1.47–152 (m, 2 H), 2.69 (d, *J* = 2.8 Hz, 1 H), 4.31–4.33 (m, 1 H), 4.35–4.46 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.13, 22.69, 25.17, 29.31, 29.33, 29.44, 29.51, 29.61, 31.90, 33.70, 68.66, 80.63 ppm. MS (ESI): *m*/*z* = 245.1 [M]$^+$. $C_{13}H_{27}NO_3$ (245.36): calcd. C 63.64, H 11.09, N 5.71; found C 63.68, H 11.12, N 5.57.

1-Nitro-4-phenylbutan-2-ol (2h):[22,23] Colorless gummy liquid: 42.4 mg, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.78–192 (m, 2 H), 2.7–2.92 (m, 2 H), 4.27–4.41 (m, 3 H), 7.20–7.27 (m, 3 H), 7.3–7.35 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.33, 35.14, 67.79, 80.60, 126.34, 128.44, 128.66, 140.65 ppm. MS (ESI): *m*/*z* = 196 [M + H]$^+$.

Ethyl 2-Hydroxy-3-nitropropanoate (2i):[24] Colorless gummy liquid: 36.7 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 4.27 (m, 2 H), 4.58 (t, *J* = 4 Hz, 1 H), 4.71 (d, *J* = 4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.01, 62.08, 66.54, 75.73, 169.73 ppm.

1-(4-Methoxyphenyl)-2-nitropropan-1-ol (3a):[13] Yellow gummy liquid: 49.6 mg, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 6.8 Hz, 3 H), 1.52 (d, *J* = 6.8 Hz, 3 H), 2.51 (br., 1 H), 3.82 (s, 3 H), 3.89 (s, 3 H), 4.62–4.67 (m, 1 H), 4.71–4.78 (m, 1 H), 4.98 (d, *J* = 9.2 Hz, 1 H), 5.27 (d, *J* = 4 Hz, 1 H) 6.92 (d, *J* = 8.4 Hz, 2 H), 7.29 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.47 (12.47), 55.34 (55.31), 75.89 (73.79), 88.53 (87.57), 114.35 (114.09), 128.19 (127.27), 130.41 (130.57), 160.11 (159.64) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 21.4, 23.6 min (*anti*); 29, 33.1 min (*syn*); *syn*/*anti* = 94:6.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitropropan-1-ol (3b): Colorless gummy liquid: 52.9 mg, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.4 Hz, 3 H), 1.45 (d, *J* = 6.8 Hz, 3 H), 2.09 (br. s, 1 H), 4.55–4.67 (m, 1 H), 4.87 (d, *J* = 8.8 Hz, 1 H), 5.20 (d, *J* = 4.0 Hz, 1 H), 5.94 (s, 2 H), 6.7–6.8 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.50 (12.47), 76.10 (73.82), 88.42 (87.55), 101.42 (101.29), 106.88 (106.46), 108.53 (108.37), 120.83 (119.58), 132.10 (132.34), 148.27 ppm. HRMS (ESI): calcd. for $C_{10}H_{11}NO_5$ [M – H]$^-$ 224.0559; found 224.0550. HPLC (Chiralpak OD-H, 2-propanol/*n*-hexane = 6:94, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 46.2, 47.4 min (*anti*), 50.3, 54.8 min (*syn*); *syn*/*anti* = 90:10.

2-Nitro-1-(3,4,5-trimethoxyphenyl)propan-1-ol (3c): White solid: 65 mg, 96% yield; m.p. 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H), 1.44 (d, *J* = 6.4 Hz, 3 H), 2.50 (br. s, 1 H), 3.73 (s, 3 H), 3.74 (s, 6 H), 3.77 (s, 3 H), 3.78 (s, 6 H), 4.60 (m, 1 H), 4.67 (m, 1 H), 4.86 (d, *J* = 9.6 Hz, 1 H), 5.23 (d, *J* = 3.6 Hz, 1 H), 6.49 (d, *J* = 3.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.30 (15.50), 55.12, 59.83, 72.94 (75.47), 86.47 (87.37), 101.81, 102.69, 133.09, 133.38, 152.34, 152.47 ppm. MS (ESI): *m*/*z* = 294.1 [M + Na]$^+$. $C_{12}H_{17}NO_6$ (271.27): calcd. C 53.13, H 6.32, N 5.16; found C 53.28, H 6.40, N 5.07. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 14:86, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 12.0, 19.9 min (*anti*); 22.0, 23.5 min (*syn*); *syn*/*anti* = 86:14.

2-Nitro-1-(*p*-tolyl)propan-1-ol (3d):[21] Colorless gummy liquid: 42.4 mg, 87% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.30 (d, *J* = 7.2 Hz, 3 H), 1.48 (d, *J* = 6.6 Hz, 3 H), 2.35 (s, 3 H), 2.36 (s, 3 H), 2.72 (br., 1 H), 2.82 (br., 1 H), 4.66–4.80 (m, 2 H), 4.97 (d, *J* = 9.2 Hz, 1 H), 5.33 (s, 1 H), 7.17–7.27 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.47 (21.14), 21.20 (23.39), 76.14 (73.92), 88.48 (87.53), 126.84 (125.89), 129.68 (129.40), 135.53 (135.37), 139.13 (138.36) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 21.7, 23.5 min (*anti*); 28.7, 32.5 min (*syn*); *syn*/*anti* = 74:26.

2-Nitro-1-phenylpropan-1-ol (3e):[13] Colorless oil: 38.9 mg, 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 6.8 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 2.95 (br., 1 H), 4.62–4.67 (m, 1 H), 4.68–4.76 (m, 1 H), 4.95 (d, *J* = 9.2 Hz, 1 H), 5.31 (d, *J* = 4 Hz, 1 H) 7.28–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.41 (12.10), 76.22 (73.98), 88.49 (87.47), 127.00 (126.01), 128.71 (128.47), 128.98 (129.05), 138.39 (138.64) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 12:88, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 21.8, 23.8 min (*anti*); 29, 33 min (*syn*); *syn*/*anti* = 73:27.

2-Nitro-1-(4-nitrophenyl)propan-1-ol (3f):[13] Yellow gummy liquid: 48 mg, 85% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.6 Hz, 3 H), 1.48 (d, *J* = 6.6 Hz, 3 H), 2.74 (s, 1 H), 4.70–4.82 (m, 2 H), 5.19 (d, *J* = 8.4 Hz, 1 H), 5.56 (d, *J* = 4.4 Hz, 1 H), 7.56–7.61 (m, 2 H), 8.22–8.24 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.24 (11.84), 75.04 (72.87), 87.78 (86.78), 124.11 (123.96), 127.93 (127.02), 145.26 (145.51), 148.26 (147.87) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 14:86, flow rate = 0.5 mL min^{-1}, λ = 254 nm): t_R = 23.4 (*anti*); 32.9, 38.8 min (*syn*); *syn*/*anti* = 67:33.

2-Nitro-1-(3-nitrophenyl)propan-1-ol (3g):[13] Yellow gummy liquid: 52 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 7.2 Hz, 3 H), 1.45 (d, *J* = 6.8 Hz, 3 H), 2.87 (d, *J* = 3.6 Hz, 1 H), 2.94 (d, *J* = 4 Hz, 1 H), 4.63–4.76 (m, 2 H), 5.13 (dd, *J* = 3.6, 8.4 Hz, 1 H), 5.48 (s, 1 H), 7.54 (q, *J* = 8, 16 Hz, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 8.14–8.24 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.26 (10.94), 73.99 (71.70), 86.78 (85.84), 120.95 (120.16), 123.03 (122.49), 128.97 (128.85), 131.91 (131.07), 139.43 (139.59), 147.47 ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hex-

ane = 6:74, flow rate = 0.8 mL min^{-1}, λ = 254 nm): t_R = 21.8, 23.5 min (*anti*); 26, 40 min (*syn*); *syn*/*anti* = 78:22.

1-(4-Bromophenyl)-2-nitropropan-1-ol (3h):[25] Colorless oil: 58.5 mg, 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.4 Hz, 3 H), 1.47 (d, J = 6.8 Hz, 3 H), 3.01 (br., 1 H), 4.62–4.66 (m, 1 H), 4.67–4.75 (m, 1 H), 4.99 (d, J = 9.2 Hz, 1 H), 5.35 (d, J = 3.2 Hz, 1 H), 7.25 (t, J = 5.2 Hz, 2 H), 7.52 (t, J = 8 Hz, 2 H) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL min^{-1}, λ = 220 nm): t_R = 16.8, 17.8 min (*anti*); 22.4, 25.3 min (*syn*); *syn*/*anti* = 62:38.

1-(4-Chlorophenyl)-2-nitropropan-1-ol (3i):[23] Colorless liquid: 43.5 mg, 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.8 Hz, 3 H), 1.48 (d, J = 7.2 Hz, 3 H), 2.87 (br., 1 H), 4.65–4.76 (m, 2 H), 5.01 (d, J = 9.2 Hz, 1 H), 5.38 (d, J = 3.6 Hz, 1 H), 7.27–7.33 (m, 2 H), 7.35–7.4 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.38, 75.52, 88.20, 128.34 (127.38), 129.21 (128.94), 135.03, 136.78 ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL min^{-1}, λ = 230 nm): t_R = 17.5, 18.5 min (*anti*); 23.1, 24.8 min (*syn*); *syn*/*anti* = 75:25.

2-Nitro-1-(4-nitrophenyl)butan-1-ol (3j):[23] White solid: 52.2 mg, 87% yield; m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68–0.89 (m, 6 H), 1.37–1.47 (m, 1 H), 1.72–1.81 (m, 1 H), 1.82–1.91 (m, 1 H), 2.07–2.16 (m, 1 H), 2.84 (d, J = 4.4 Hz, 1 H), 2.99 (d, J = 2.4 Hz, 1 H), 4.48–4.58 (m, 2 H), 5.11 (dd, J = 4.8, 8 Hz, 1 H), 5.27 (t, J = 3.2 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 2 H), 8.20 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.11 (10.36), 23.88 (21.12), 74.30 (73.20), 94.51, 124.17 (123.97), 127.81 (127.24), 145.55 (148.27) ppm. HPLC (Chiralpak OD-H, 2-propanol/*n*-hexane = 10:90, flow rate = 0.5 mL min^{-1}, λ = 215 nm): t_R = 24.9, 27.7 min (*anti*); 33.9 min (*syn*); *syn*/*anti* = 88:12.

1-(4-Chlorophenyl)-2-nitrobutan-1-ol (3k):[22,23] Colorless oil: 46.9 mg, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.6 Hz, 3 H), 0.91 (t, J = 7.6 Hz, 3 H), 1.20–1.29 (m, 1 H), 1.32–1.39 (m, 1 H), 1.75–1.91 (m, 1 H), 2.03–2.13 (m, 1 H), 3.22 (s, 1 H), 4.49–4.57 (m, 2 H), 4.97 (d, J = 9.2 Hz, 1 H), 5.0 (d, J = 5.2 Hz, 1 H), 7.26–7.37 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.75 (9.47), 25.19 (23.88), 75.55 (74.07), 95.95 (94.42), 128.14 (127.62), 128.36 (128.13), 129.78 (129.23), 130.07 (130.02), 134.92 (134.51), 137.26 ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 6:94, flow rate = 0.5 mL min^{-1}, λ = 200 nm): t_R = 18.6, 20.7 min (*anti*); 27.2, 32.3 min (*syn*); *syn*/*anti* = 94:6.

2-Nitro-1-(*p*-tolyl)butan-1-ol (3l):[22] Colorless oil, 36.6 mg, 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.8 Hz, 3 H), 0.93 (t, J = 7.8 Hz, 3 H), 1.28–1.43 (m, 1 H), 1.79–1.96 (m, 2 H), 2.12–2.16 (m, 1 H), 2.34 (s, 3 H), 2.36 (s, 3 H), 2.72 (br., 1 H), 2.85 (br., 1 H), 4.55–4.63 (m, 2 H), 4.97 (d, J = 9.9 Hz, 1 H), 5.09 (d, J = 4.8 Hz, 1 H), 7.16–7.25 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.08 (10.39), 21.16 (21.57), 23.93 (23.39), 75.39 (74.19), 95.33 (94.81), 126.84 (126.19), 129.71 (129.40), 135.75 (135.64), 139.11 (138.60) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 4:96, flow rate = 0.5 mL min^{-1}, λ = 215 nm): t_R = 28.4, 30.6 min (*anti*); 47.0 min (*syn*); *syn*/*anti* = 67:33.

2-Nitrohexan-3-ol (4a):[21] Colorless oil: 25.7 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88–1.05 (m, 6 H), 1.35–1.47 (m, 8 H), 1.51 (d, J = 1.2 Hz, 3 H), 1.53 (d, J = 1.5 Hz, 3 H), 1.99 (br., 1 H), 2.62 (br., 1 H), 3.90 (br., 1 H), 4.17 (br., 1 H), 4.47–4.57 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.75 (12.26), 13.78 (16.15), 18.37 (18.95), 34.96 (35.07), 72.66 (71.85), 87.86 (86.41) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 6:94, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_R = 17.0, 17.9 min (*anti*); 20.0, 23.1 min (*syn*); *syn*/*anti* = 57:43.

5-Methyl-2-nitrohexan-3-ol (4b):[21] Colorless oil: 29 mg, 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.79–0.96 (m, 12 H), 1.08–1.26 (m, 2 H), 1.37–1.41 (m, 2 H), 1.46–152 (m, 6 H), 1.69–2.01 (m, 2 H), 2.85 (br., s, 1 H), 3.85–3.94 (m, 1 H), 4.21 (m, 1 H), 4.38–4.50 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.09 (16.02), 21.58 (21.24), 23.56 (23.25) 24.47 (24.16), 41.83 (41.75), 72.43 (71.24), 86.75 (88.37) ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 2:98, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_R = 30.6, 33.3 min (*anti*); 39.7, 44.3 min (*syn*); *syn*/*anti* = 61:39.

2-Nitrononan-3-ol (4c): Colorless oil, 36.8 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, J = 6.4 Hz, 6 H), 1.29–1.61 (m, 26 H), 2.21 (d, J = 7.2 Hz, 1 H), 2.31 (d, J = 4.4 Hz, 1 H), 3.90 (d, J = 5.6 Hz, 1 H), 4.19 (t, J = 4 Hz, 1 H), 4.48–4.56 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.37, 14.04, 16.27, 22.54, 25.11, 25.69, 29.03, 29.66, 31.64, 31.65, 33.01, 33.04, 72.04, 72.90, 86.34, 87.68 ppm. HRMS (ESI): calcd. for $C_9H_{19}NO_3$ [M – H]$^-$ 188.1287; found 188.1280. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 2:98, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_R = 30.5 min (*anti*); 40.4, 43.1 min (*syn*); *syn*/*anti* = 50:50.

2-Nitroundecan-3-ol (4d):[25] Colorless oil: 40.7 mg, 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.2 Hz, 6 H), 1.25–1.52 (m, 34 H), 2.71 (br., 1 H), 3.83–3.90 (m, 1 H), 4.12–4.17 (m, 1 H), 4.44–4.56 (2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.22, 14.05, 16.11, 22.62, 25.09, 25.72, 29.19, 29.32, 29.37, 29.55, 31.80, 32.88, 33.07, 72.16, 72.91, 86.39, 87.83 ppm. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 2:98, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_R = 25.1 min (*anti*); 34.9, 36.4 min (*syn*); *syn*/*anti* = 46:54.

2-Nitrotetradecan-3-ol (4e): White solid: 44 mg, 68% yield; m.p. 40–41 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.4 Hz, 6 H), 1.16–1.58 (m, 46 H), 2.18 (d, J = 7.2 Hz, 1 H), 2.28 (d, J = 4.8 Hz, 1 H), 3.90 (d, J = 5.6 Hz, 1 H), 4.18 (q, J = 3.6 Hz, 1 H), 4.48–4.56 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.36, 14.14, 16.29, 22.70, 25.15, 25.75, 29.34, 29.37, 29.46, 29.48, 29.53, 29.58, 29.61, 31.91, 33.01, 33.03, 72.04, 72.91, 86.34, 87.70 ppm. MS (ESI): m/z = 259.2 [M]$^+$. $C_{14}H_{29}NO_3$ (259.39): calcd. C 64.83, H 11.27, N 5.40; found C 64.90, H 11.18, N 5.17. HPLC (Chiralpak AD-H, 2-propanol/*n*-hexane = 2:98, flow rate = 0.5 mL min^{-1}, λ = 210 nm): t_R = 19.9 min (*anti*); 27.3, 29.6 min (*syn*); *syn*/*anti* = 59:41.

Supporting Information (see footnote on the first page of this article): Copies of the NMR spectra for all compounds and HPLC data for compounds **3a**–**l** and **4a**–**4e**.

Acknowledgments

The authors are grateful to the Department of Science and Technology (DST), New Delhi (Ref. No. SR/S1/OC-25/2007) for providing financial support to carry out this work. Analytical support from Sophisticated Analytical Instrumentation Facility (SAIF), NEHU, is gratefully acknowledged. Central Instrumentation Facility, Indian Institute of Technology, Guwahati, is acknowledged for providing HRMS data. Finally, the authors acknowledge the valuable input of the reviewers to revise the manuscript.

[1] a) A. Cwik, A. Fuchs, Z. Hell, J. M. Clacens, *Tetrahedron* **2005**, *61*, 4015–4021; b) I. Kudyba, J. Raczko, Z. Urbanczyk-Lipkowska, J. Jurczak, *Tetrahedron* **2004**, *60*, 4807–4820; c) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; d) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574.

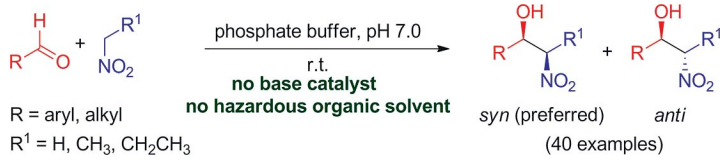
[2] a) P. A. Wade, R. M. Giuliano, in: *Nitro Compounds: Recent Advances in Synthesis and Chemistry* (Eds.: H. Feuer, A. T. Nielsen), VCH, Weinheim, Germany, **1990**, pp. 137–265; b) N.

Ono, *The Nitro Group in Organic Synthesis*, Wiley, New York, **2001**, pp. 30–69.
[3] a) G. Rosini, R. Ballini, *Synthesis* **1988**, 833–847; b) G. Rosini, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, UK, **1991**, vol. 2, pp. 321–340; c) M. A. Shvekhgeimer, *Russ. Chem. Rev.* **1998**, *67*, 35–68.
[4] a) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326; b) C. Christensen, K. Juhl, K. A. Jørgensen, *Chem. Commun.* **2001**, 2222–2223; c) M. Gaab, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Eur. J.* **2009**, *15*, 5450–5462; d) W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, *Chem. Eur. J.* **2010**, *16*, 8259–8261.
[5] a) E. Busto, V. G. Fernández, V. Gotor, *Org. Process Res. Dev.* **2011**, *15*, 236–240; b) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, *Adv. Synth. Catal.* **2007**, *349*, 1445–1450; c) T. Purkarthofer, K. Gruber, M. Gruber-Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew. Chem.* **2006**, *118*, 3532; *Angew. Chem. Int. Ed.* **2006**, *45*, 3454–3456.
[6] a) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751–2772; b) S. Kobayashi, K. Manabe, *Acc. Chem. Res.* **2002**, *35*, 209–217; c) C. J. Li, *Chem. Rev.* **1993**, *93*, 2023–2035; d) C. J. Li, *Chem. Rev.* **2005**, *105*, 3095–3165; e) C. J. Li, T. H. Chan, *Organic Reactions in Aqueous Media*, John Wiley & Sons, New York, **1997**; f) P. A. Grieco, *Organic Synthesis in Water*, Thompson Science, Glasgow, Scotland, **1998**.
[7] a) F. Franks, *Water: A Matrix of Life*, 2nd ed., Royal Society of Chemistry, Cambridge, UK, **2000**; b) G. W. Robinson, *Water in Biology, Chemistry, and Physics*: *Experimental Overviews and Computational Methodologies*, World Scientific, Singapore, **1996**; c) P. Ball, *Life Matrix: A Biography of Water*, 1st ed., Farrar, Straus, and Giroux, New York, **2000**.
[8] a) T. Jiang, H. X. Gao, B. X. Han, G. Y. Zhao, Y. H. Chang, W. Z. Wu, L. Gao, G. Y. Yang, *Tetrahedron Lett.* **2004**, *45*, 2699–2701; b) F. A. Khan, J. Dash, R. Satapathy, S. K. Upadhyay, *Tetrahedron Lett.* **2004**, *45*, 3055–3058; c) S. Huh, H.-T. Chen, J. W. Wiench, M. Pruski, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2004**, *126*, 1010–1011; d) K. Akutu, H. Kabashima, T. Seki, H. Hattori, *Appl. Catal. A* **2003**, *247*, 65–74; e) R. Ballini, G. Bosica, D. Livi, A. Palmieri, R. Maggi, G. Sartori, *Tetrahedron Lett.* **2003**, *44*, 2271–2273; f) P. B. Kisanga, J. G. Verkade, *J. Org. Chem.* **1999**, *64*, 4298–4303; g) J. G. Verkade, P. B. Kisanga, *Tetrahedron* **2003**, *59*, 7819–7858; h) D. Simoni, F. P. Invidiata, S. Manfredini, R. Ferroni, I. Lampronti, M. Roberti, G. P. Pollini, *Tetrahedron Lett.* **1997**, *38*, 2749–2752; i) D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.* **2000**, *41*, 1607–1610; j) D. W. Ma, Q. B. Pan, F. S. Han, *Tetrahedron Lett.* **2002**, *43*, 9401–9403.
[9] R. Ballini, G. Bosica, *J. Org. Chem.* **1997**, *62*, 425–427.
[10] C. L. Zhou, Y. Q. Zhou, Z. Y. Wang, *Chinese Chem. Lett.* **2003**, *14*, 355–358.
[11] J. Fan, G. Sun, C. Wan, Z. Wang, Y. Li, *Chem. Commun.* **2008**, 3792–3794.
[12] G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2011**, *17*, 1114–1117.
[13] K. Kanagaraj, P. Suresh, K. Pitsumani, *Org. Lett.* **2010**, *12*, 4070–4073.
[14] a) D.-H. Leng, D.-X. Wang, J. Pan, Z.-T. Huang, M.-X. Wang, *J. Org. Chem.* **2009**, *74*, 6077–6082; b) Z.-B. Xie, N. Wang, G.-F. Jiang, X.-Q. Yu, *Tetrahedron Lett.* **2013**, *54*, 945–948; c) T. C. Bhalla, A. Miura, A. Wakamoto, Y. Ohba, K. Furuhashi, *Appl. Microbiol. Biotechnol.* **1992**, *37*, 184–190; d) A. Kinnell, T. Harman, M. Bingham, A. Berry, A. Nelson, *Tetrahedron* **2012**, *68*, 7719–7722; e) F. Tanaka, R. Fuller, C. F. Barbas III, *Biochemistry* **2005**, *44*, 7583–7592.
[15] a) C. J. Rogers, T. J. Dickerson, A. P. Brogan, K. D. Janda, *J. Org. Chem.* **2005**, *70*, 3705–3708; b) T. J. Dickerson, K. D. Janda, *J. Am. Chem. Soc.* **2002**, *124*, 3220–3221; c) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024–3025.
[16] X. Zhang, K. N. Hauk, *J. Org. Chem.* **2005**, *70*, 9712–9716.
[17] R. M. Stephenson, *J. Chem. Eng. Data* **1992**, *37*, 80–95.
[18] a) Y. Hayashi, *Angew. Chem.* **2006**, *118*, 8281; *Angew. Chem. Int. Ed.* **2006**, *45*, 8103–8104; b) A. P. Brogan, T. J. Dickerson, K. M. Janda, *Angew. Chem.* **2006**, *118*, 8278; *Angew. Chem. Int. Ed.* **2006**, *45*, 8100–8102.
[19] M. Sato, Y. Kitamura, N. Yushimura, H. Yamataka, *J. Org. Chem.* **2009**, *74*, 1268–1274.
[20] C. V.-L. Bray, F. Jiang, X.-F. Wu, J.-B. Sortais, C. Darcel, *Tetrahedron Lett.* **2010**, *51*, 4555–4557.
[21] Y. Q. Ji, G. Qi, Z. M. A. Judeh, *Eur. J. Org. Chem.* **2011**, 4892–4898.
[22] Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588–600.
[23] G. Blay, L. R. Domingo, V. Hernández-Olmos, J. R. Pedro, *Chem. Eur. J.* **2008**, *14*, 4725–4730.
[24] G. Blay, F. Palacios, J. M. De Los Santos, D. Aparicio, *ARKIVOC* **2005**, *9*, 405–414.
[25] L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761–6765.

Received: December 13, 2012
Published Online: ■

EurJOC European Journal of Organic Chemistry

Henry Reaction



Base-free Henry reaction! The synthesis of a variety of β-nitro alcohols is achieved by the reaction of aldehydes with nitro alkanes in aqueous phosphate buffer at pH 7.0. Good to excellent diastereoselectivities are achieved in the reactions of aromatic aldehydes with higher nitro alkanes.

Keywords: Henry reaction / C–C coupling / β-Nitro alcohols / Asymmetric synthesis / Diastereoselectivity

