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Protein-Mediated Nitroaldol Addition in Aqueous Media. Catalytic Promiscuity or Unspecific Catalysis?

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Abstract:

A high efficient and environmentally friendly procedure for the production of aromatic and heteroaromatic β-nitroalcohols has been developed. This synthetic approach involves the condensation of an appropriate aldehyde with 1-nitroalkanes in aqueous media using as catalyst the inexpensive carrier protein Bovine serum albumin (BSA). According to the experimental data, the Henry reaction between aromatic aldehydes and nitroalkanes in aqueous media proceeds by unspecific protein catalysis rather than catalytic promiscuity. By proper choice of the reaction conditions, the corresponding nitroalcohols were obtained in yields up to 91% at 30 °C. Catalyst recycling and scale-up of the reactions have been considered as important factors, in order to show this methodology as a valuable synthetic approach.

Introduction

The Henry or nitroaldol reaction is a widely used reaction in organic synthesis, being essentially a coupling between a carbonyl compound and an alkyl nitrocompound, leading to the formation of a β-nitroalcohol.[1] From a synthetic point of view, β-nitroalcohols are very interesting difunctional compounds since they are versatile precursors for the preparation of a great variety of manufactures such as pharmaceutically active β-aminoalcohols, 2-nitroketones, α-hydroxycarboxylic acids or nitroalkenes.[2] Traditional syntheses of nitroalcohols involve the base catalyzed condensation between aldehydes and nitroalkanes in organic solvents. For these processes, commonly strong bases such as sodium methoxide, sodium hydroxide, LDA, butyl lithium, barium hydroxide or sodium carbonate are used as catalysts, however the formation of undesired side products is often observed due to their ability to catalyze competitive reactions such as aldol addition, Cannizzaro reaction and water elimination.[3] In recent years, different research groups found that the nitroaldol reaction can be performed efficiently in aqueous media[4] or under free solvent conditions[5] using very mild reaction conditions where the formation of unwanted products is prevented. In addition sensitive functionalities such as tetrahydropyranes, ketals, and furanes are maintained unaltered.

On the other hand, the importance of nonchemical methods have increasingly grown in recent years, and for example enzymatic sources have presented themselves as chemo-, regio-, and stereoselective catalysts,[6] creating a wealth of opportunities for the production of very different chemical structures, facts that have not gone unnoticed by a great number of organic chemists. One of the emerging areas in biocatalysis is catalytic promiscuity, based on the ability of a single enzyme active site to catalyze different transformations.[7] For instance, the hydroxynitrile lyase from *Hevea brasilensis* has been used by Griengl and co-workers as a promiscuous catalyst for the asymmetric Henry reaction between aromatic aldehydes and nitromethane in a water/TBME biphasic system.[8] More recently, He and co-workers have reported the ability of the protein−glutamine γ-glutamyltransferase (TGase) to promote the Henry reaction also in a biphasic system composed of water and CH_2Cl_2.[9] On the other hand, the research group of Lin have reported the D-aminoacylase-catalyzed Henry reaction between nitroethane and a variety of aldehydes in DMSO as organic solvent.[10] However, to the best of our knowledge the nonchemical catalyzed Henry reaction using water as a unique solvent has not been described yet.

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Scheme 1. **Protein-catalyzed Henry reaction between *p*-nitrobenzaldehyde and nitromethane**

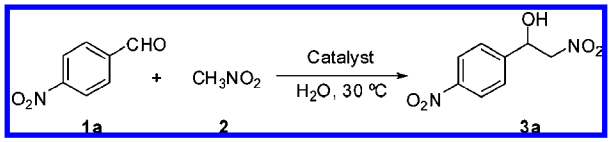

Table 1. **Catalytic activities of different proteins in the nitroaldol addition between nitromethane and *p*-nitrobenzaldehyde**

entry	protein	*c* (%)[a]
1	no protein	<3
2	CAL-B	<3
3	PSL-C	6
4	PPL	65
5	PPL (denatured)[b]	31
6	BSA	91

[a] Determined by ^{1}H NMR of the reaction crude. [b] Pretreated with urea at 140 °C for 48 h.

In this contribution, we describe an environmentally friendly methodology for the production of β-nitroalcohols under very mild reaction conditions. Different nonchemical catalysts have been considered to promote the Henry reaction between a series of nitroalkanes and a wide family of aromatic aldehydes in aqueous medium.

Results and Discussion

First of all, we decided to examine the condensation between *p*-nitrobenzaldehyde (**1a**) and nitromethane (**2**) as a model reaction. With this aim we selected a nitromethane/water, 8:2 (v/v), biphasic system as the reaction medium and several lipases operating at 30 °C (Scheme 1).

Just as we expected, no adduct formation was observed in the absence of catalyst (Table 1, entry 1). On the other hand, low conversion values were observed for *Candida antarctica* lipase B (CAL-B, entry 2) and *Pseudomonas cepacia* lipase supported on a ceramic support (PSL-C, entry 3); meanwhile, 65% yield was attained using porcine pancreas lipase (PPL, entry 4). In order to exclude protein catalysis, we decided to perform some control experiments where denaturalized PPL or a carrier transport protein [bovine serum albumin (BSA)] was used to mediate the desired transformation (entries 5−6). Surprisingly, 31% conversion was reached with denatured PPL (entry 5), and more interestingly, a very high conversion value (91%) was achieved when the reaction was performed using the carrier protein BSA (entry 6).

With these results in hand we found a clear contradiction between our observations and the results previously reported by He and co-workers, where the possibility of protein catalysis is excluded.[9] With the aim of validating the hypothesis of unspecific protein catalysis, we decided to carry out two experiments employing the initial (cyclohexane/water, 10:1) and the optimized (CH_2Cl_2/water, 5:3) conditions reported by He and co-workers using the nonenzyme protein BSA as biocatalyst. In agreement with the previously reported results, low conversion (21%) was detected under the initial reaction conditions; however, when the Henry reaction was performed under the optimized conditions, we observed that, after the workup of the reaction, 83% conversion was detected by ^{1}H NMR analysis of the reaction crude after 48 h. This fact provides a strong evidence that the reaction could proceed *via* unspecific protein catalysis rather than specific promiscuous catalysis as observed for the Henry reaction in DMSO by Lin and co-workers.[10] A plausible explanation for this observation could be performed on the basis of the basic character of the amino group present in the side chain of the lysine residue as occurs in other processes catalyzed by BSA[11] such as the decomposition of Meisenheimer complexes,[12] hydrolysis of *p*-nitrophenyl acyl esters and *p*-nitrophenylcarbonates,[13] Kemp elimination,[14] tandem Kemp elimination/β-elimination,[15] β-elimination of umbelliferone,[16] Morita−Baylis−Hillman reaction,[17] or Michael addition between methyl nitroacetate and 3-buten-2-one.[18] First of all, the basic amino group could remove the acidic hydrogen of the nitrocompound obtaining the corresponding nitronate. Next, the nucleophilic attack of the nitronate towards the aldehydes would lead to the formation of the C−C bond leading to the corresponding β-nitroalcohol.

Table 2. **Effect of the water/nitromethane ratio in the conversion of the BSA-catalyzed Henry reaction between *p*-nitrobenzaldehyde and nitromethane[a]**

entry	H_2O (%)	$MeNO_2$ (equiv)[a]	*c* (%)[b]
1	−	97	<3
2	5	92	80
3	20	78	93
4	40	58	97
5	70	29	>97
6	80	19	>97
7	90	10	>97 (91)
8	95	5	97
9	98	2	84

[a] All reactions were performed using *p*-nitrobenzaldehyde (45 mg, 0.30 mmol), BSA (50 mg), and a water/nitromethane system (1.56 mL total volume). [b] Determined by ^{1}H NMR of the reaction crude. Isolated yields in brackets of **3a**.

Once we had demonstrated the ability of BSA to promote the Henry reaction in aqueous media, we decided to look for the optimal amount of nitromethane in order to raise the conversion of the transformation. In this manner the reaction was performed by employing different water/nitromethane ratios (Table 2). No conversion was observed when the reaction was performed in anhydrous nitromethane (entry 1), which means that the presence of water is essential for the protein-mediated Henry reaction. Interestingly, an acceleration of the reaction rate was observed by increasing the amount of water (entries 2−8), achieving a complete conversion using water content

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Scheme 2. **Catalytic nitroaldol addition between different aromatic aldehydes and nitromethane**

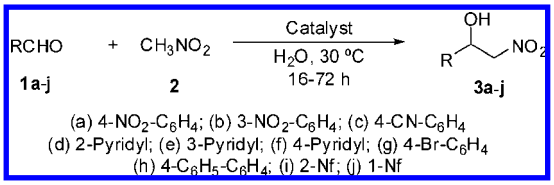
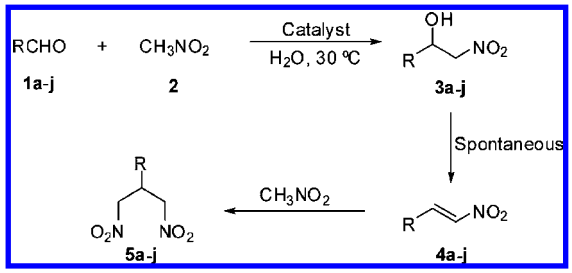


Table 3. **Catalytic Henry reaction between nitromethane and a series of aromatic aldehydes 1a−j including spontaneous formation of Michael adducts 5a−j[a]**

entry	R	catalyst	*t* (h)	*c* (%)[b]	3a−j (%)[c]	5a−j (%)[b]
1	4-NO_2−C_6H_4 (**1a**)	BSA	16	>97	91	<3
2	4-NO_2−C_6H_4 (**1a**)	BSA (denatured)	16	>97	83	5
3	4-NO_2−C_6H_4 (**1a**)	L-lysine	16	>97	70	25
4	3-NO_2−C_6H_4 (**1b**)	BSA	16	>97	91	5
5	4-CN-C_6H_4 (**1c**)	BSA	16	>97	74	10
6	2-Pyridyl (**1d**)	BSA	16	>97	75	5
7	3-Pyridyl (**1e**)	BSA	16	>97	54	21
8	4-Pyridyl (**1f**)	BSA	16	>97	68	5
9	4−Br-C_6H_4 (**1g**)	BSA	48	>97	79	13
10	4-Ph−C_6H_4 (**1h**)	BSA	72	55	46	<3
11	2-Nf (**1i**)	BSA	72	77	59	14
12	1-Nf (**1j**)	BSA	72	30	--	<3
13[d]	4-NO_2−C_6H_4 (**1a**)	BSA	26	>97	82	<3

[a] Entries 1−12: Reactions were performed using the corresponding aldehyde (0.30 mmol), BSA, or L-lysine (50 mg), water (1.44 mL), and nitromethane (160 μL, 2.98 mmol). [b] Determined by ^{1}H NMR of the reaction crude. [c] Isolated yields after flash chromatography. [d] Reaction was performed using **1a** (1.00 g, 6.60 mmol), BSA (1.10 g), water (31.68 mL), and nitromethane (3.52 mL, 65.56 mmol).

Scheme 3. **Tandem Henry reaction/Michael addition between aromatic aldehydes 1a−j and nitromethane (2)**



solutions between 70 and 90%, which means that only a 10-fold excess of nitromethane is necessary to obtain complete conversion (entries 5−7). A slight decrease of the conversion was observed for water contents higher than 95%, probably due to the insolubility of the starting material in the reaction medium (entries 8−9).

Once that we had in hand the optimized reaction conditions, we decided to perform the nitroaldol addition between **1a** and **2** using denatured BSA (Scheme 2, Table 3, entry 2) or L-lysine (entry 3) as catalysts with the aim of excluding the possibility that a specific residue in a certain region of the protein was responsible for the catalytic activity.

As expected, quantitative conversions were observed for both processes which mean that nitroaldol addition proceeds *via* nonspecific catalysis rather than catalytic promiscuity. Interestingly, higher isolated yields were recovered with BSA (entry 1) in comparison with L-lysine (entry 3), where an appreciable amount of the dinitrocompound **5a** was observed through a tandem Henry/Michael reaction depicted in Scheme 3.

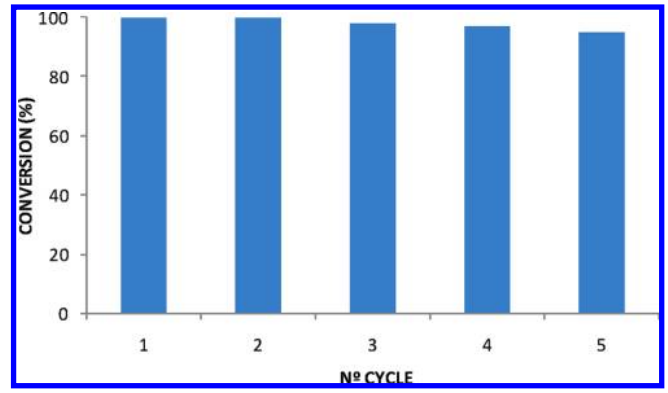


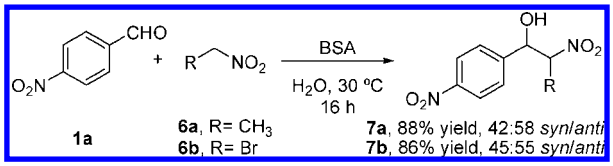
Figure 1. **Catalyst recycling experiments for the Henry reaction between *p*-nitrobenzaldehyde and nitromethane. The reaction was performed using 0.3 mmol of 1a, 2.97 mmol of 2, 50 mg of BSA, and 1.44 mL of water. Conversion values were determined by ^{1}H NMR of the reaction crude after 16 h.**

On the other hand, different aromatic aldehydes were tested in order to generalize the scope of the BSA-catalyzed Henry reaction (entries 1 and 4−12). Complete conversion was achieved for aldehydes bearing strong electron-withdrawing groups (entries 1 and 4−8), especially for **1a**,**b** yielding the final products with excellent yields (entry 1 and 4), meanwhile nitrocompounds **3c**,**d**,**f**,**g** (entries 5, 6, 8, and 9) were recovered in good isolated yields (68−79%). However, the 3-pyridyl nitroalcohol **3e** was obtained in moderate yield as an appreciable amount of the dinitrocompound **5e** (entry 7). As expected, moderate yields were found for *β*-nitroalcohols with neutral or electron-donating groups (entries 10−12) as the poor electrophilic character of the carbonyl groups made the nucleophilic attack of nitromethane less probable. Disappointingly, we could not find any enantioselectivity grade in any of the BSA-mediated experiments. It must be also mentioned that the BSA-catalyzed nitroaldol addition between nitromethane and aliphatic aldehydes such as *n*-hexanal and *n*-butanal led to very low conversions (<5%) (data not shown).

In order to take advantage of this approach we have also explored two important factors in the application of this methodology in the industrial scale: scale up of the reaction catalyst and catalyst recycling. The reaction between 4-nitrobenzaldehyde (**1a**) and nitromethane (**2**) was scaled up using 1 g of starting material (6.6 mmol), obtaining the nitroalcohol **3a** in complete conversion and 82% isolated yield (entry 13). Compared to the small-scale experiment (entry 1) additional 10 h were required to achieve complete conversion which could be due to the fact that the orbital shaking is less efficient when the reaction is performed with a higher volume of solvent; additionally, a slight decrease on the reaction yield was observed.

At the same time we have also investigated the possibility of reusing the catalytic BSA. Figure 1 shows the efficiency of the catalyst employed during five consecutive cycles to promote the reaction between *p*-nitrobenzaldehyde (**1a**) and nitromethane (**2**) under the previous optimized reaction conditions. Complete conversion was observed up to third reaction cycle, and interestingly only a very slight loss of activity was observed for the fourth (97% conversion) and fifth (95% conversion) catalytic cycles.

Scheme 4. **BSA catalyzed nitroaldol addition between 4-nitrobenzaldehyde and nitrocompounds 6a-b**



Furthermore, the scope of the procedure has been guaranteed, performing the reaction between 4-nitrobenzaldehyde (**1a**) and different nitrocompounds such as bromonitromethane (**6a**) or nitroethane (**6b**) at 30 °C during 16 h (Scheme 4). In both cases, the final adducts were isolated with high yields (86−88%); furthermore, a slight diastereomeric induction was observed in favor of the *anti*-diastereomer.

Conclusions

In summary, we have developed a simple, mild, inexpensive and green synthetic methodology to produce β-nitroalcohols that are useful intermediates in organic synthesis. After an exhaustive analysis of the reaction parameters we have found that Bovine serum albumin (BSA) efficiently promotes the nitroaldol addition between aromatic aldehydes and 1-nitroalkanes in aqueous medium in contradiction with previous observations reported.[9] According to our observations, the Henry reaction between aromatic aldehydes and nitroalkanes is possible by unspecific protein catalysis rather than catalytic promiscuity. Isolated yields of the final products were very dependent on structural limitations, obtaining most of them with good to excellent isolated yields (68−91%). More interestingly, the reaction between 4-nitrobenzaldehyde and nitromethane has been extensively studied, finding that BSA can be recycled and reused for several times without a significant loss of activity. Additionally we were able to scale up the reaction on a gram scale, yielding the desired 2-nitro-1-(4-nitrophenyl)ethanol in high yield.

Experimental Section

Bovine serum albumine (BSA, 41 U/mg for the transformation of **1a** in **3a**) was purchased from Sigma-Aldrich (see Supporting Information for the determination of the specific activity). Chemical reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230−240 mesh). ^{1}H and ^{13}C NMR experiments were obtained using a Brüker AV-300 spectrometer (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz).

General Procedure for the Preparation of Nitroalcohols. A typical experiment procedure is as follows: Over a suspension of the corresponding aldehyde (0.30 mmol) in water (1.40 mL) were added nitromethane (160 μL, 2.98 mmol) and BSA (50 mg). The mixture was shaken at 30 °C and 250 rpm for the corresponding time (see Table 3). After that time the reaction was quenched by adding H_2O (5 mL) and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The organic phases were combined, dried over Na_2SO_4 and filtered, and the solvent was removed by distillation under reduced pressure. The reaction crude was purified by flash chromatography (EtOAc/hexane mixtures), yielding the corresponding nitroalcohols **3a-j**.

2-Nitro-1-(4-nitrophenyl)ethanol (3a):[19] R_f (20% EtOAc/hexane) 0.25; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.25 (brs, 1H), 4.58−4.61 (m, 2H), 5.63−5.68 (m, 1H), 7.64 (d, $^3J_{HH}$ = 6.5 Hz, 2H), 8.26 (d, $^3J_{HH}$ = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.4 (CH_2), 81.0 (CH), 125.5 (2CH), 127.4 (2CH), 145.5 (C), 148.5 (C).

2-Nitro-1-(3-nitrophenyl)ethanol (3b):[20] R_f (30% EtOAc/hexane) 0.25; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 4.55−4.89 (m, 2H), 5.51−5.57 (m, 1H), 7.81−7.89 (m, 1H), 7.75−7.83 (m, 1H), 8.15−8.23 (m, 1H), 8.41 (s, 1H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 69.8 (CH_2), 81.2 (CH), 121.1 (CH), 123.1 (CH), 130.0 (CH), 132.5 (CH) 142.9 (C), 148.8 (C).

4-(1-Hydroxy-2-nitroethyl)benzonitrile (3c):[21] R_f (40% EtOAc/hexane) 0.20; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.21 (brs, 1H), 4.50−4.59 (m, 2H), 5.50−5.56 (m, 1H), 7.81−7.89 (m, 1H), 7.53 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.71 (d, $^3J_{HH}$ = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.6 (CH_2), 81.3 (CH), 113.4 (2CH), 118.9 (2CH), 127.5 (C), 133.5 (C), 143.8 (C).

2-Nitro-1-(pyridin-2-yl)ethanol (3d):[4e] R_f (100% EtOAc) 0.32; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.41 (brs, 1H), 4.61−4.83 (m, 2H), 5.41−5.55 (m, 1H), 7.17−7.47 (m, 2H), 7.71−7.83 (m, 1H), 8.49−8.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.7 (CH_2), 81.2 (CH), 121.4 (CH), 124.1 (CH), 138.0 (CH), 149.3 (CH), 157.0 (C).

2-Nitro-1-(pyridin-3-yl)ethanol (3e):[20] R_f (100% EtOAc) 0.22; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 4.52−4.67 (m, 2H), 5.41−5.55 (m, 1H), 6.03 (brs, 1H), 7.30−7.36 (m, 1H), 7.53 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 8.40 (s, 1H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 68.4 (CH_2), 81.3 (CH), 124.1 (CH), 134.7 (CH), 135.6 (CH), 147.1 (CH), 149.1 (C).

2-Nitro-1-(pyridin-4-yl)ethanol (3f):[20] R_f (20% EtOAc/hexane) 0.27; ^{1}H NMR (CD_3OD, 300.13 MHz): δ 4.63−4.95 (m, 2H), 7.65 (d, $^3J_{HH}$ = 5.7 Hz, 2H), 8.65 (brs, 2H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 67.5 (CH_2), 78.9 (CH), 119.9 (2CH), 147.3 (2CH), 149.9 (C).

2-Nitro-1-(4-bromophenyl)ethanol (3g):[22] R_f (20% EtOAc/hexane) 0.27; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.15 (brs, 1H), 4.41−4.55 (m, 2H), 5.39−5.48 (m, 1H), 7.61 (m, 1H), 7.23 (d, $^3J_{HH}$ = 6.5 Hz, 2H), 7.52 (d, $^3J_{HH}$ = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 70.7 (CH_2), 81.3 (CH), 123.3 (C), 128.0 (2CH), 132.6 (2CH), 137.5 (C).

1-(Biphenyl-4-yl)-2-nitroethanol (3h):[22] R_f (20% EtOAc/hexane) 0.19; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 2.85 (brs, 1H), 4.52−4.65 (m, 2H), 5.40−5.52 (m, 1H), 7.32−7.37 (m, 1H), 7.42−7.47 (m, 4H), 7.55−7.60 (m, 2H), 7.61 (d, $^3J_{HH}$ = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 71.2 (CH_2), 81.6 (CH), 126.8 (2CH), 127.5 (2CH), 128.1 (2CH), 128.2 (CH) 129.3 (2CH), 137.0 (C), 140.3 (C), 141.8 (C).

1-(Naphthalen-2-yl)-2-nitroethanol (3i):[21] R_f (20% EtOAc/hexane) 0.23; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.15 (brs, 1H), 4.41−4.55 (m, 2H), 5.39−5.48 (m, 1H), 7.48−7.55 (m, 3H),

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7.81−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 71.6 (CH_2), 81.6 (CH), 123.6 (CH), 125.8 (CH), 127.1 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 129.4 (CH), 133.6 (C), 133.8 (C), 135.8 (C).

1-(Naphthalen-1-yl)-2-nitroethanol (3j):[22] R_f (10% EtOAc/hexane) 0.21; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.55 (brs, 1H), 4.41−4.55 (m, 2H), 6.11−6.23 (m, 1H), 7.45−7.65 (m, 3H), 7.75 (d, $^3J_{HH}$ = 7.9 Hz, 1H), 7.85 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 7.91 (d, $^3J_{HH}$ = 8.0 Hz, 1H), 8.06 (d, $^3J_{HH}$ = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 68.3 (CH_2), 80.8 (CH), 121.8 (CH), 123.9 (CH), 125.5 (CH), 126.1 (CH), 127.1 (CH), 129.3 (CH), 129.6 (C), 133.5 (C), 133.6 (C).

2-Nitro-1-(4-nitrophenyl)propan-1-ol (7a):[23] R_f (20% EtOAc/hexane) 0.29; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 1.35 (d, $^3J_{HH}$ = 7.1 Hz, 3H_{syn}), 1.52 (d, $^3J_{HH}$ = 7.1 Hz, 3H_{anti}), 3.20 (brs, 1H_{syn}+1H_{anti}), 4.59−4.72 (m, 1H_{syn}+1H_{anti}), 5.20 (d, $^3J_{HH}$ = 9.3 Hz, 1H_{syn}), 5.55 (d, $^3J_{HH}$ = 3.5 Hz, 1H_{anti}), 7.58−7.63 (m, 1H_{syn}+1H_{anti}), 8.21−8.35 (m, 1H_{syn}+1H_{anti}); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ *anti* 11.7 (CH_3), 72.3 (CH), 86.6 (CH), 123.8 (2CH), 126.9 (2CH), 145.2 (C), 148.1 (C). δ *syn* 16.1 (CH_3), 74.9 (CH), 87.7 (CH), 124.0 (2CH), 127.8 (2CH), 145.5 (C), 148.1 (C).

2-Bromo-1-(4-nitrophenyl)propan-1-ol (7b):[24] R_f (20% EtOAc/hexane) 0.21; ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ 3.45 (brs, 1H_{syn}+1H_{anti}), 5.50 (d, $^3J_{HH}$ = 9.3 Hz, 1H_{anti}), 5.55 (d, $^3J_{HH}$ = 3.5 Hz, 1H_{syn}), 5.93 (d, $^3J_{HH}$ = 9.3 Hz, 1H_{anti}), 6.15 (d, $^3J_{HH}$ = 3.7 Hz, 1H_{syn}), 7.61−7.73 (m, 2H_{syn}+2H_{anti}), 8.22−8.29 (m, 2H_{syn}+2H_{anti}); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ *anti* 75.1 (CH), 80.3 (CH), 123.9 (2CH), 128.6 (2CH), 142.8 (C), 148.5 (C). δ *syn* 73.4 (CH), 85.0 (CH), 124.0 (2CH), 127.6 (2CH), 143.0 (C), 148.3 (C).

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Supporting Information Available

Determination of BSA specific activity is described. This material is available free of charge via the Internet at http://pubs.acs.org.

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