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Synthesis of enantiomerically pure γ-azidoalcohols by lipase-catalyzed transesterification

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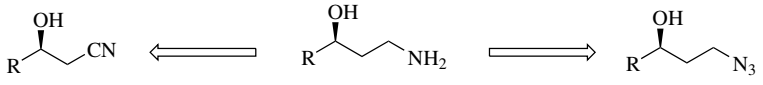
Abstract—An enantioselective synthesis of chiral γ-azidoalcohols via lipase-catalyzed resolution is described. The efficiency of various lipases and the effect of different solvents have been studied. *Pseudomonas cepacia* immobilized on diatomaceous earth (PS-D) in *n*-hexane catalyzed the transesterification process in an efficient manner providing γ-azidoalcohols in high enantiomeric excess.

1. Introduction

Enantiomerically pure chiral aminoalcohols are of great interest, owing to their presence in biologically active natural products and their application as chiral catalysts in asymmetric synthesis.[1] Amongst these, β-aminoalcohols are more popular than γ-aminoalcohols and some other higher aminoalcohols. Nevertheless, the interest in chiral γ-aminoalcohols has increased, as they are also important structural units in many natural products, pharmacologically useful drugs and chiral ligands or auxillaries, which are useful in stereoselective synthesis.[2] Notably, the γ-aminoalcohol unit is present in many selective serotonin/norepinephrine reuptake inhibitors such as fluoxetine, tomoxetine, nisoxetine and duloxetine, which are being used in the clinic as antidepressant drugs for the treatment of impulse control disorders.[3] Chiral γ-azidoalcohols are the immediate precursors of γ-aminoalcohols, in addition to β-hydroxynitriles, which are not particularly safe as their preparation involves the use of cyanide salts (Scheme 1). However, some methods utilizing milder reagents for the synthesis of β-hydroxynitriles have recently been developed.[4] Furthermore, chiral γ-azidoalcohols have been found to be useful in the ring expansion of symmetrical cyclohexanones in the asymmetric Schmidt reaction.[5] Chiral γ-azidoalcohols can be obtained from a lipase-catalyzed kinetic resolution, which is considered as a powerful technique for providing access to new chiral synthons with high enantiopurity.[6] A number of chiral β-azidoalcohols have been prepared by kinetic resolution using hydrolytic enzymes;[7] however, there is one report on the resolution of γ-azidoalcohol relating to the evaluation of the active site's size of lipase from *Candida rugosa* and *Pseudomonas cepacia*.[8] Moreover, γ-azidoalcohols possess a somewhat challenging structural unit for carrying out a lipase-catalyzed resolution process. This is because of the increase in the flexibility of the side chain as an additional methylene unit is present in comparison to β-azidoalcohols. In view of the aforementioned importance of γ-azidoalcohols as well as in continuation of our interest for the development of new chemoenzymatic routes towards biologically active compounds and chiral intermediates,[9] we herein report the synthesis of optically active γ-azidoalcohols by employing a lipase-mediated kinetic resolution protocol.



Scheme 1.

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2. Results and discussion

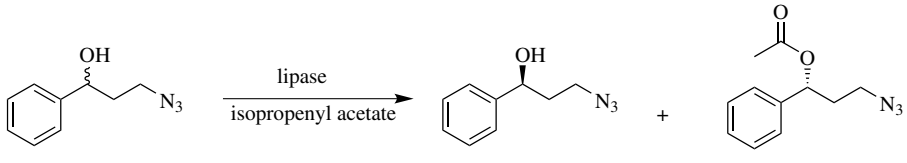
Some approaches based on non-enzymatic methods have already been reported in the literature that provide an access to chiral γ-aminoalcohols.[2f] However, a few biocatalytic procedures such as the kinetic resolution of β-hydroxynitriles and microbial reductions of β-keto acid derivatives involving chemical transformation are also known for the preparation of chiral γ-aminoalcohols.[10] Herein, γ-azidoalcohols (useful precursors of chiral γ-aminoalcohols) have been synthesized by lipase-catalyzed enantioselective acylation of racemic 3-azido-1-arylpropanols. In this investigation, in order to optimize the enantioselectivity of the process, 3-azido-1-phenyl propanol **1a** was chosen as the model substrate for the lipase-mediated kinetic resolution process. The selection of lipase is an important aspect in the development of an efficient resolution protocol. Hence, twelve commercially available lipases obtained from different sources have been screened for the transesterification of γ-azidoalcohol **1a** employing isopropenyl acetate and diisopropyl ether as an acyl donor and solvent, respectively. The preliminary results obtained for some selected potential lipases are summarized in Table 1.

It has been observed that the transesterification of γ-azidoalcohol **1a** by employing lipases from sources such as *Candida antartica*, *Rhizopus arrhizus*, *Mucor miehei* (lipozyme) and papain (latex from *Carica papaya*) did not show significant conversions even after prolonged reaction time. However, the lipases from *C. rugosa* (CRL), *Pseudomonas fluorescens* (AK-20), *Candida cyclindracea* (CCL) and *P. cepacia* (immobilized on ceramic particles, PS-C) provide moderate to good enantioselectivity for the acetate. The results are significant when employing *P. cepacia* lipase (immobilized on diatomaceous earth, PS-D), which gives 48% ee and 77% ee of the alcohol and acetate, respectively.

In order to improve the enantioselectivity of this transesterification process, the effect of various solvents was investigated by employing lipase PS-D with isopropenyl acetate as the acyl donor. Moreover, these reactions have been performed at slightly higher temperatures (42 °C) with a view to improve the rate of conversion; the results obtained are shown in Table 2. It was observed that the rate of lipase-mediated resolution and enantioselectivity varied with the type of solvents used. The selectivity as well as the conversion was poor when solvents such as dioxane and THF were used, whereas the use of toluene or *tert*-butyl methyl ether (TBME) provided good selectivity and conversion. Moreover, when using a more hydrophobic solvent such as *n*-hexane, the lipase PS-D has showed very high enantioselectivity providing alcohol (*S*)-**1a** with 99% ee and acetate (*R*)-**2a** with 92% ee. However, changing the acyl donor from isopropenyl acetate to vinyl acetate lowered the enantioselectivity.

Based on the above investigations, various racemic 3-azido-1-arylpropanols **1a–f** have been examined for the lipase-catalyzed transesterification process employing lipases from *P. cepacia* (PS-D) in *n*-hexane with isopropenyl acetate as the acyl donor. The effect of substituents on the aryl ring has also been studied (Table 3). It is found that the kinetic resolution of 3-azido-1-phenylpropanol and its derivatives **1a–d** has proceeded efficiently to provide the resolved alcohols (*S*)-**1a–d** with 99% ee and acetates (*R*)-**2a-d** with 92–99% ee, whereas the *p*-methoxy substituted phenyl derivative **1e** showed very little conversion even after prolonged reaction time in *n*-hexane. However, the use of diisopropyl ether as a solvent afforded the resolved alcohol (*S*)-**1e** and acetate (*R*)-**2e** with >99% ee and 96% ee, respectively. The results also indicate that in the presence of different substituents at the *para*-position of the aromatic ring, comparatively higher conversion rates and enantiopurities were observed. Using this protocol, the

Table 1. Lipase-mediated transesterification of γ-azidoalcohol (±)-**1a**[a]



(*RS*)-**1a** (*S*)-**1a** (*R*)-**2a**

Entry	Lipase	Time (h)[b]	% ee[c]		c[d] (%)	E[e]
			Alcohol (*S*)-**1a**	Acetate (*R*)-**2a**		
1	PS-C	48	10	63	14	<5
2	PS-D	48	48	77	38	12
3	CRL	48	15	70	18	<10
4	AK-20	58	15	44	25	<5
5	CCL	48	10	55	16	<5

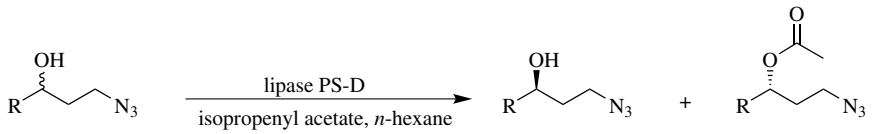
[a] Conditions: 30 mg of (±)-**1a**, 30 mg of lipase (1 equiv w/w), isopropenyl acetate (6 equiv), 3 mL of diisopropyl ether (DIPE).
[b] Time taken for transesterification at 35 °C.
[c] Determined by chiral HPLC analysis employing Daicel Chiralcel OD-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.
[d] Conversion (c) is calculated from the enantiomeric excess of substrate alcohol **1a**, (ee_s) and product acetate **2a** (ee_p) using the formula: $c = ee_s/(ee_s + ee_p)$.
[e] Enantiomeric ratio calculated with the formula $E = \{\ln[1 - c(1 + ee_p)]\}/\{\ln[1 - c(1 - ee_p)]\}$.

Table 2. Effect of solvents on enantioselectivity of γ-azidoalcohol **1a** using lipase PS-D

Entry	Lipase	Time (h)[a]	% ee		c[b] (%)	E[c]
			Alcohol (*S*)-**1a**	Acetate (*R*)-**2a**		
1	*n*-Hexane	48	99	92	52	153
2	TBME	42	88	69	56	15
3	Toluene	42	35	82	30	14
4	Dioxane	42	10	34	23	<5
5	*n*-Hexane[d]	48	94	85	53	<100
6	DIPE[d]	48	10	55	15	<5

[a] Time taken for transesterification at 42 °C.
[b] Conversion.
[c] Enantiomeric ratio.
[d] Vinyl acetate used as acyl donor.

Table 3. Lipase-catalyzed kinetic resolution of racemic γ-azidoalcohols **1**[a]



(*rac*)-**1a-f** **1a-f** **2a-f**

Entry	Substrate	R	Time (h)	% ee		c[b] (%)	E[c]
				Alcohol-**1**	Acetate-**2**		
1	**1a**	Ph	48	99[d]	92[d]	52	153
2	**1b**	*p*-Me–C_6H_4	40	>99[e]	94[e]	51	147
3	**1c**	*p*-Cl–C_6H_4	20	99[d]	93[d]	51	115
4	**1d**	*p*-Br–C_6H_4	23	99[e]	99[e]	50	>200
5	**1e**	*p*-MeO–C_6H_4	42[f]	>99[e]	96[e]	51	>200
6	**1f**	2-Thienyl	16	96[g]	76[g]	56	26

[a] Conditions: 30 mg of *rac*-**1**, 30 mg of lipase (1 equiv w/w), isopropenyl acetate (6 equiv), 3 mL of *n*-hexane, 40–42 °C.
[b] Conversion.
[c] Enantiomeric ratio.
[d] Determined by chiral HPLC analysis employing Daicel Chiralcel OD-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.
[e] Determined by chiral HPLC analysis employing Daicel Chiralcel AD-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.
[f] Diisopropyl ether used as solvent.
[g] Determined by chiral HPLC analysis employing Daicel Chiralcel OB-H column (0.46 × 25 cm); eluent: hexane/2-propanol = 90:10; flow rate: 0.5 mL/min; detector: 230 nm.

heteroaromatic γ-azidoalcohol **1f** has also been resolved efficiently but with lower enantiomeric ratios in comparison to the aryl substituted ones. Attempts to improve the enantioselectivity in this case by employing diisopropyl ether instead of *n*-hexane did not provide any significant enhancement in the selectivity.

Finally, the absolute configuration of the enantiomerically pure unreacted γ-azidoalcohol **1a** obtained by the enzymatic reaction was assigned an (*S*)-configuration on the basis of the comparison of the specific rotation of γ-aminoalcohol (prepared by the reduction of **1a)** reported in the literature.[11a] Similarly, the configuration of the resolved substituted phenyl azidoalcohols **1b–e** has been assigned based on the comparison of the sign of the specific rotation with that of the parent azidoalcohol **1a**. Azidoalcohol **1f** was assigned an (*S*)-configuration by comparing the specific rotation of its ethyl carbamate derivative (prepared from aminoalcohol, which was obtained by the reduction of **1f**) with that reported in the literature.[11b]

3. Conclusion

In conclusion, we have developed a simple and efficient enantioselective method for the synthesis of enantiomerically enriched γ-azidoalcohols by employing a lipase-mediated kinetic resolution process. The present method could find extensive applications for the preparation of various biologically active γ-aminoalcohols.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on an 'Innova-4080 incubator-shaker' at 200 rpm. Infrared spectra of neat samples are reported in wave numbers (cm^{-1}). ^1H NMR was recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (PPM, δ) on a 300 MHz instrument. Coupling constants are reported in Hertz (Hz). ESI

spectra were recorded on Micro mass, Quattro LC using ESI^+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Elemental analyses were performed on an elemental analyzer, Model: VARIO EL, Elementar, Germany. HPLC analysis was performed on an instrument that consisted of a Shimadzu SCL-10A system controller, SPA-M10A Diode array detector. Specific rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Chemicals and solvents were obtained commercially and used without purification. *P. cepacia* lipase immobilized on diatomaceous earth (PS-D) was purchased from Amano (Nagoya, Japan).

4.3. General procedure for the synthesis of racemic azidoalcohols 1a–f

The racemic azidoalcohols were prepared by Friedel–Crafts acylation on aryl/thienyl compounds using chloropropionyl chloride and anhydrous aluminium chloride to provide the corresponding ketochlorides in quantitative yields. These substituted ketochlorides were transformed into ketoazides using sodium azide in the presence of catalytic 18-crown-6. The crude substituted ketoazides were reduced to racemic azidoalcohols **1a**–**f** employing sodium borohydride in methanol in quantitative yields.

4.3.1. General procedure for Friedel–Crafts acylation. To a solution of aluminium chloride (12 mmol) in dry CH_2Cl_2, 3-chloropropionyl chloride (11 mmol) was added dropwise at 0 °C. To the resulting mixture, aryl or thienyl compound (10 mmol) was added and allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched by slowly adding crushed ice pieces at 0 °C and the aqueous layer was extracted with CH_2Cl_2. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, evaporated under reduced pressure and purified by column chromatography. Yield: 87–92%.

4.3.2. General procedure for the synthesis of racemic azidoalcohols. To a stirred solution of substituted ketochlorides (10 mmol) in dry CH_2Cl_2 was added sodium azide (15 mmol) followed by 18-crown-6 (1 mmol) and stirred for 8–10 h. To the reaction mixture, cold water was added and the aqueous layer extracted with CH_2Cl_2. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, evaporated under reduced pressure to give crude substituted ketoazides, which were dissolved in methanol. Sodium borohydride (10 mmol) was added in portions at 0 °C and stirred at room temperature for 2 h. The solvent was evaporated, water was added followed by extraction with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure and purified by column chromatography to give racemic azidoalcohols **1a**–**f**. Yield: 75–82%.

4.4. General procedure for the synthesis of chiral azidoalcohols 1a–f and azidoacetates 2a–f

To a solution of racemic γ-azidoalcohol **1** (1 mmol) dissolved in *n*-hexane (15 mL) under ultrasonication were added lipase (1 equiv w/w) and isopropenyl acetate (6 mmol) and the reaction mixture was shaken at 40–42 °C in an orbital shaker. The progress of the reaction was monitored by chiral HPLC and after about 50% conversion, the reaction mixture was filtered and the residue washed with ethyl acetate. The organic solvent was evaporated under reduced pressure and purified by column chromatography. The enantiopure products **1** and **2** obtained were analyzed by chiral HPLC and compared with the corresponding racemic products.

4.4.1. (*S*)-3-Azido-1-phenyl-1-propanol 1a. Yield: 46%; 99% ee ($t_{major} = 14.87$, $t_{minor} = 16.01$ min); $[\alpha]_D^{30} = -33.5$ (*c* 6.0, $CHCl_3$); IR (neat): 3408, 2097, 1261, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (1H, s), 1.83–2.07 (2H, m), 3.31–3.55 (2H, m), 4.77–4.84 (1H, m), 7.22–7.38 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.61, 48.15, 71.46, 125.60, 127.71, 128.50, 143.90; ESIMS *m*/*z*: 200 $(M+Na)^+$; Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26. Found: C, 61.03; H, 6.23.

4.4.2. (*R*)-3-Azido-1-phenylpropyl acetate 2a. Yield: 45%; 92% ee ($t_{major} = 10.65$, $t_{minor} = 12.03$ min); $[\alpha]_D^{30} = +56.4$ (*c* 3.0, $CHCl_3$); IR (neat): 2096, 1737, 1231, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.93–2.24 (2H, m), 2.06 (3H, s), 3.17–3.36 (2H, m), 5.77–5.83 (1H, m), 7.23–7.36 (5H, m); ESIMS *m*/*z*: 242 $(M+Na)^+$; Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98. Found: C, 60.22; H, 5.94.

4.4.3. (*S*)-3-Azido-1-*p*-tolylpropan-1-ol 1b. Yield: 45%; >99% ee ($t_{minor} = 14.31$, $t_{major} = 15.90$ min); $[\alpha]_D^{30} = -26.9$ (*c* 0.5, $CHCl_3$); IR (neat): 3397, 2096, 1260, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (1H, s), 1.82–2.05 (2H, m), 2.35 (3H, s), 3.28–3.52 (2H, m), 4.75 (1H, dd, $J = 4.5$, $J = 8.3$ Hz), 7.12 (2H, d, $J = 7.5$ Hz), 7.20 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.06, 37.52, 48.16, 71.30, 125.57, 129.18, 137.51, 140.60; ESIMS *m*/*z*: 214 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85. Found: C, 62.79; H, 6.81.

4.4.4. (*R*)-3-Azido-1-*p*-tolylpropyl acetate 2b. Yield: 46%; 94% ee ($t_{major} = 8.86$, $t_{minor} = 9.82$ min); $[\alpha]_D^{30} = +62.1$ (*c* 0.6, $CHCl_3$); IR (neat): 2097, 1740, 1233, 813 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.92–2.24 (2H, m), 2.06 (3H, s), 2.34 (3H, s), 3.17–3.36 (2H, m), 5.73–5.79 (1H, m), 7.12 (2H, d, $J = 7.5$ Hz), 7.19 (2H, d, $J = 7.5$ Hz); ESIMS *m*/*z*: 256 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48. Found: C, 61.75; H, 6.45.

4.4.5. (*S*)-3-Azido-1-(4-chlorophenyl)propan-1-ol 1c. Yield: 44%; 99% ee ($t_{major} = 13.28$, $t_{minor} = 14.75$ min); $[\alpha]_D^{30} = -20.3$ (*c* 0.7, $CHCl_3$); IR (neat): 3400, 2099, 1086, 827 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (1H, s), 1.80–2.00 (2H, m), 3.31–3.57 (2H, m), 4.77–4.84 (1H, m), 7.27 (2H, d, $J = 9.0$ Hz), 7.31 (2H, d, $J = 9.0$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.58, 48.04, 70.82, 126.96, 128.62, 133.25, 142.08; ESIMS *m*/*z*: 234 $(M+Na)^+$; Anal.

Calcd for $C_9H_{10}ClN_3O$: C, 51.07; H, 4.76. Found: C, 51.08; H, 4.75.

4.4.6. (*R*)-3-Azido-1-(4-chlorophenyl)propyl acetate 2c. Yield: 46%; 93% ee ($t_{minor} = 10.43$, $t_{major} = 11.10$ min); $[\alpha]_D^{30} = +55.4$ (*c* 1.0, $CHCl_3$); IR (neat): 2098, 1739, 1232, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.86–2.26 (2H, m), 2.06 (3H, s), 3.16–3.41 (2H, m), 5.76 (1H, dd, $J = 5.4$, $J = 6.2$ Hz), 7.20–7.36 (4H, m); ESIMS *m*/*z*: 276 $(M+Na)^+$; Anal. Calcd for $C_{11}H_{12}ClN_3O_2$: C, 52.08; H, 4.77. Found: C, 52.09; H, 4.77.

4.4.7. (*S*)-3-Azido-1-(4-bromophenyl)propan-1-ol 1d. Yield: 46%; 99% ee ($t_{minor} = 15.88$, $t_{major} = 16.56$ min); $[\alpha]_D^{30} = -23.1$ (*c* 1.0, $CHCl_3$); IR (neat): 3408, 2095, 1072, 821 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.42 (1H, s), 1.81–1.98 (2H, m), 3.27–3.59 (2H, m), 4.72–4.84 (1H, m), 7.15–7.28 (2H, m), 7.41–7.51 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.58, 48.05, 70.81, 122.72, 127.80, 128.95, 141.20; ESIMS *m*/*z*: 279 $(M+Na)^+$; Anal. Calcd for $C_9H_{10}BrN_3O$: C, 42.21; H, 3.94. Found: C, 42.20; H, 3.93.

4.4.8. (*R*)-3-Azido-1-(4-bromophenyl)propyl acetate 2d. Yield: 47%; 99% ee ($t_{minor} = 7.91$, $t_{major} = 10.05$ min); $[\alpha]_D^{30} = +40.8$ (*c* 1.2, $CHCl_3$); IR (neat): 2099, 1739, 1232, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–2.18 (2H, m), 2.05 (3H, s), 4.05–4.32 (2H, m), 5.52–5.59 (1H, m), 7.17 (2H, d, $J = 8.3$ Hz), 7.44 (2H, d, $J = 8.3$ Hz); ESIMS *m*/*z*: 321 $(M+Na)^+$; Anal. Calcd for $C_{11}H_{12}BrN_3O_2$: C, 44.32; H, 4.06. Found: C, 44.31; H, 4.04.

4.4.9. (*S*)-3-Azido-1-(4-methoxyphenyl)propan-1-ol 1e. Yield: 45%; >99% ee ($t_{minor} = 19.94$, $t_{major} = 21.89$ min); $[\alpha]_D^{30} = -18.4$ (*c* 0.6, $CHCl_3$); IR (neat): 3410, 2097, 1513, 1247, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (1H, s), 1.81–2.10 (2H, m), 3.25–3.55 (2H, m), 3.79 (3H, s), 4.69–4.79 (1H, m), 6.78–6.88 (2H, m), 7.18–7.27 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 37.58, 48.24, 55.19, 71.12, 113.76, 126.93, 135.70, 158.95; ESIMS *m*/*z*: 230 $(M+Na)^+$; Anal. Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32. Found: C, 57.95; H, 6.30.

4.4.10. (*R*)-3-Azido-1-(4-methoxyphenyl)propyl acetate 2e. Yield: 46%; 96% ee ($t_{major} = 11.26$, $t_{minor} = 12.93$ min); $[\alpha]_D^{30} = +77.4$ (*c* 1.0, $CHCl_3$); IR (neat): 2097, 1737, 1513, 1234, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.91–2.26 (2H, m), 2.04 (3H, s), 3.16–3.36 (2H, m), 3.79 (3H, s), 5.71–5.79 (1H, m), 6.83 (2H, d, $J = 9.0$ Hz), 7.22 (2H, d, $J = 9.0$ Hz); ESIMS *m*/*z*: 272 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07. Found: C, 57.81; H, 6.06.

4.4.11. (*S*)-3-Azido-1-(2-thienyl)-1-propanol 1f. Yield: 42%; 96% ee ($t_{major} = 21.58$, $t_{minor} = 22.81$ min); $[\alpha]_D^{30} = -17.8$ (*c* 1.7, $CHCl_3$); IR (neat): 3407, 2098, 1263, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.96–2.15 (2H, m), 3.32–3.58 (2H, m), 5.01–5.12 (1H, m), 6.91–6.99 (2H, m), 7.19–7.24 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.84, 48.00, 67.26, 123.85, 124.75, 126.64, 147.82; ESIMS *m*/*z*: 206 $(M+Na)^+$; Anal. Calcd for $C_7H_9N_3OS$: C, 45.89; H, 4.95. Found: C, 45.85; H, 4.96.

4.4.12. (*R*)-3-Azido-1-(2-thienyl)propyl acetate 2f. Yield: 46%; 76% ee ($t_{major} = 16.75$, $t_{minor} = 18.10$ min); $[\alpha]_D^{30} = +67.3$ (*c* 1.1, $CHCl_3$); IR (neat): 2929, 2099, 1739, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.06 (3H, s), 2.07–2.33 (2H, m), 3.24–3.42 (2H, m), 6.09–6.15 (1H, m), 6.93–6.97 (1H, m), 7.04 (1H, d, $J = 3.0$ Hz), 7.25 (1H, d, $J = 3.0$ Hz); ESIMS *m*/*z*: 248 $(M+Na)^+$; Anal. Calcd for $C_9H_{11}N_3O_2S$: C, 47.99; H, 4.92. Found: C, 47.95; H, 4.90.

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