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Synthesis of enantiopure β-azidoalcohols from their ketoazides by reduction with $NaBH_4$ in the presence of alumina and in situ lipase resolution

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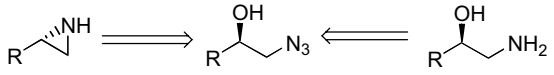
Abstract—An enantioselective synthesis of chiral β-azidoalcohols via the reduction of the corresponding ketoazides with $NaBH_4$ in the presence of moist aluminium oxide followed by an in situ lipase-mediated resolution is described. The efficiency of various lipases and the effect of solvents have also been studied for this method. The excellent results obtained under mild reaction conditions, indicates its applicability and importance over classical methods previously reported.

1. Introduction

Enantiopure β-azidoalcohols are of great significance as potential precursors for optically active aziridines[1] and β-amino alcohols[2] (Scheme 1). Chiral 1,2-amino alcohols have become of great significance because of their presence in biologically active natural products, such as ephedrine and pharmacologically active bronchodilators, salmeterol and albuterol.[3a,b]

They are also useful chiral building blocks for the synthesis of the HIV protease inhibitor, indinavir[4a] and some chiral auxiliaries[4b,c] in asymmetric synthesis. In particular, chiral 2-amino-1-aryl ethanones are important structural elements for α- or β-adrenergic blockers and agonists in the treatment of cardiovascular disease, cardiac failure, asthma and glucoma.[5] There has been a great demand for the regio- and enantioselective synthesis of chiral 2-azido-1-arylethanols. The known approaches to these synthetically valuable compounds include nucleophilic epoxide ring openings,[6] catalytic asymmetric hydrogenation,[7a] biocatalytic[7b,c] microbial reduction using baker's yeast[8a] and β-cyclodextrin assisted oxirane ring opening.[8b] Enantioselective preparation of both the enantiomers is achieved by the well-known lipase-mediated kinetic resolution of racemic azidoalcohols,[9a–d] whereas a dynamic kinetic resolution with a ruthenium catalyst enables preparation of only one enantiomer exclusively.[9e] Some of these methods have disadvantages such as poor enantioselectivity, lower yields and expensive chiral metal catalysts. Recently we have developed a new one-pot reduction followed by a resolution protocol employing $NaBH_4$–alumina and lipase for the preparation of chiral alcohols, allylic alcohols, 1,2-diols and chiral lactones.[10] The results encouraged us to develop a convenient method for the synthesis of optically active β-azidoalcohols from their ketone precursors.



Scheme 1.

2. Results and discussion

Herein, chiral β-azidoalcohols have been synthesized from the corresponding ketones in high enantioselectivity by $NaBH_4$–alumina reduction followed by lipase-catalyzed resolution of the corresponding racemic azidoalcohols in a one-pot reaction (Scheme 2). The azidoketone **1** was reduced quantitatively to the corresponding racemic β-azidoalcohol **2** by employing sodium borohydride and activated moist alumina in diisopropyl ether. This reaction mixture was then subjected to lipase-catalyzed transesterification in the same pot using isopropenyl acetate as an acyl donor.

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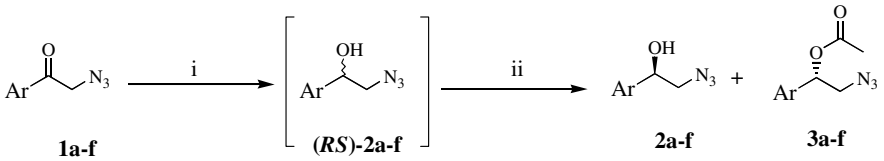


Scheme 2. Reagents and conditions: (i) $NaBH_4$, activated alumina, diisopropyl ether; (ii) PS-C lipase, isopropenyl acetate.

2.1. Screening of lipases

The primary requirement for a successful kinetic resolution is the selection of suitable lipases and solvents. Initially nine different commercially available lipases were screened for the $NaBH_4$–alumina reduction of 2-azido-1-phenyl ethanone **1a** followed by the resolution of the corresponding 2-azido-1-phenyl ethanol in diisopropyl ether with the results summarized in Table 1. Amongst the lipases screened,[11] lipase from *Pseudomonas cepacia*, that is, PS-C and PS-D gave good results for **3a**. PS-C, lipase immobilized on ceramic particles, not only gave good conversions but also high enantioselectivity for both the enantiomers in 24 h in diisopropyl ether. PS-D lipase, which was immobilized on diatomaceous earth, also provided high enantioselectivity (>99%) but took 72 h for the transesterification process. These results are in concurrence with the earlier observations reported for the resolution of secondary and allylic alcohols.[10a,b]

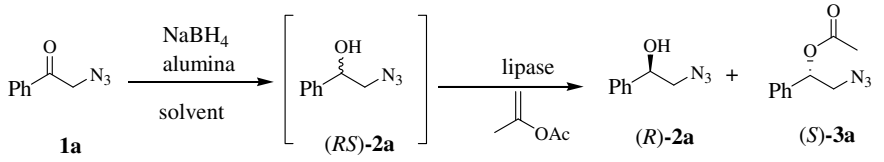
2.2. Effect of solvents

In order to investigate the effect of solvent on the one-pot reduction followed by transesterification reaction process, different solvents were studied by PS-C lipase. It was observed that the rate of lipase-mediated resolution, as well as enantioselectivity, had some correlation with the type of solvent used. The in situ transesterification of racemic alcohol **2a** by PS-C lipase in hexane and diisopropyl ether gave similar results for (*R*)-**2a** and (*S*)-**3a**. However the transesterification process in toluene and MTBE (methyl *tert*-butyl ether) provided >99% enantiomeric excess for (*R*)-**2a** and for (*S*)-**3a**, respectively (Table 1).

2.3. Synthesis and resolution of chiral azidoalcohols

Various 2-azido-1-aryl ethanones have been examined for this one-pot process and the effect of substituents in the aryl ring have also been studied. β-Ketoazide reduction with $NaBH_4$–alumina in diisopropyl ether proved facile and gave the corresponding racemic azidoalcohol in 3 h, which was then kinetically resolved in the same pot by PS-C lipase and isopropenyl acetate (Table 2). The resolved products (*R*)-**2** and (*S*)-**3** were obtained in high enantiopurity for almost all the substrates investigated. Acetate (*S*)-**3** was obtained in >99% enantiomeric excess for halosubstituted ketoazides. Interestingly *p*-bromo substituted ketoazide **1e** afforded the corresponding alcohol and acetate in high enantiomeric ratio ($E = 645$). In an earlier report,[8a] β-azidoalcohols **2a–e** were synthesized in high enantiomeric excess employing baker's yeast to only give the

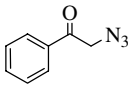
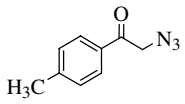
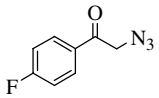
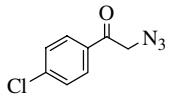
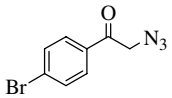
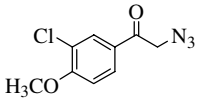
Table 1. Effect of solvent on enantioselectivity in one-pot reduction of **1a** and in situ resolution of azidoalcohol with various lipases[a]



Lipase	Solvent	Time[b] (h)	Ee[c] (%)		(%) Conv.[d]	E[d]
			(*R*)-**2a**	(*S*)-**3a**		
PS-C	DIPE	24	98	94	51	146
PS-C	Hexane	36	98	94	51	146
PS-C	Toluene	48	>99	95	51	201
PS-C	MTBE	48	27	>99	21	257
PS-D	DIPE	72	40	>99	29	296
PS	DIPE	96	6	58	8	4
AK-20	DIPE	96	8	82	9	11

[a] Conditions: 0.25 mmol of **1a**, 2.5 mL of solvent, 0.25 g activated alumina, 0.5 mmol $NaBH_4$; after 3 h lipase (1 equiv w/w), 1.5 mmol isopropenyl acetate at 40 °C; DIPE = diisopropyl ether, MTBE = methyl *tert*-butyl ether; PS = *P. cepacia* lipase.
[b] Time taken for transesterification.
[c] Determined by chiral HPLC analysis (Chiralcel OD column) 90:10; hexane/2-propanol, 0.5 mL/min flow rate.
[d] Conversion $c = ee_2/ee_2 + ee_3$, enantiomeric ratio $E = \{\ln[1 - c(1 + ee_3)]\}/\{\ln[1 - c(1 - ee_3)]\}$.[12]

Table 2. Lipase-mediated one-pot resolution of azidoalcohol obtained by in situ reduction of corresponding ketoazides[a]

Substrate **1a–f**	Time[b] (h)	(*R*)-**2**			(*S*)-**3**			(%) Conv.[h]	*E*[h]
		(%) Yield[c]	(%) Ee[d]	$[\alpha]_D^{25}$[g] (concn)	(%) Yield[c]	(%) Ee[d]	$[\alpha]_D^{25}$ (concn)[g]		
	24	46	98	−89.2 (1.0)	49	94	+89.7 (1.0)	51	146
	20	45	>99	−82.7 (1.0)	47	97	+100.8 (1.0)	50	278
	24	47	88	−70.8 (1.0)	43	>99	+78.2 (1.3)	47	581
	28	48	90	−82.5 (1.0)	38	>99[e]	+104.9 (1.0)	47	581
	28	42	92	−77.0 (1.1)[i]	44	>99[e]	+93.8 (1.1)[i]	48	645
	28	43	75[f]	−66.5 (1.2)[i,j]	37	>99[f]	+108.2 (1.1)[i]	43	4492

[a] Conditions: 1 mmol of **1**, 10 mL of diisopropyl ether, 1 g activated alumina, 2 mmol $NaBH_4$; after 3 h lipase PS-C (1 equiv w/w), 6 mmol isopropenyl acetate at 40 °C.

[b] Same as Table 1.

[c] Isolated yield from column chromatography.

[d] Determined by chiral HPLC analysis (Chiralcel OD column) 90:10; hexane/2-propanol, 0.5 mL/min flow rate.

[e] Determined by chiral HPLC analysis (Chiralcel OJ column) 80:20; hexane/2-propanol, 0.5 mL/min flow rate.

[f] % Ee of **2f** was calculated by converting it into its acetyl derivative and determined by chiral HPLC analysis (Chiralcel OD-H column) 90:10; hexane/2-propanol, 0.5 mL/min flow rate.

[g] Rotation recorded in chloroform.

[h] Conversion $c = ee_2/ee_2 + ee_3$, enantiomeric ratio $E = \{\ln[1 - c(1 + ee_3)]\}/\{\ln[1 - c(1 - ee_3)]\}$.[12]

[i] The absolute configuration is unknown, but has been assigned based on comparison of the order of elution in HPLC analysis and comparison of sign of the optical rotation with their analogues.

[j] The configuration has been assigned based on the analogy of azidoalcohol **2f**, with structurally related substrate (*R*)-(−)-2-azido-1-(3′,4′-dichlorophenyl)ethanol, **8h** reported earlier.[14]

(*R*)-enantiomer of β-azidoalcohol. However the present method describes the synthesis of both the (*S*)- and (*R*)-enantiomers of β-azidoalcohol in high enantiomeric excess. Brenelli and Fernandes[9c] have resolved β-azidoalcohol **2a** using *P. cepacia* lipase under ultrasonic conditions but in low enantioselectivity (74% ee in **2a** and 85% ee in **3a**) and longer reaction time (62 h), while in the present report azidoalcohol **2a** was resolved using PS-C lipase in high enantioselectivity (98% ee in **2a** and 94% ee in **3a**) in 24 h. Moreover, reduction of ketoazide with sodium borohydride in β-cyclodextrin[13] offered only (*S*)-azidoalcohols **2a**,**b**,**c**,**e** in very low enantioselectivity (4–80% ee).

3. Conclusion

In summary, we have described a new and highly efficient method for the synthesis of optically active β-azidoalcohols from ketoazides, employing a one-pot reduction followed by lipase-mediated resolution protocol. Both the enantiomers of various substituted azidoalcohols have been prepared in high enantioselectivity and in shorter reaction times. The present method is an attractive alternative to the existing ones for obtaining homochiral azidoalcohols.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on a 'Lab-line environ-shaker' at 150 rpm. Infrared spectra of neat sample are reported in wave numbers (cm^{-1}). ^1H NMR were recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (ppm, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). LSIMS mass spectra were recorded on Autospec M with 7 kV acceleration voltage and 25 kV gun voltage. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-10AT system controller,

SPD-10 Å fixed wavelength UV monitor as 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

Sodium borohydride, neutral alumina and solvents were obtained commercially and used without purification. Activated neutral alumina was prepared by the homogeneous addition of 1.1 mL water to 10 g of neutral alumina (preheated in oven at 200 °C). Lipase from *P. cepacia* (PS), *Pseudomonas fluorescens* (AK), *P. cepacia* immobilized on ceramic particles (PS-C), *P. cepacia* immobilized on diatomaceous earth (PS-D) were purchased from Amano (Nagoya, Japan).

4.3. General procedure for the one-pot synthesis of enantiopure azidoalcohols 2a–f and acetates 3a–f

To a solution of β-azidoketone (1 mmol) in diisopropyl ether (10 mL) was added activated alumina (1.0 g) and $NaBH_4$ (2 mmol). The suspension was shaken at 150 rpm at 40 °C for 3–4 h and monitored by TLC for the complete reduction to racemic azidoalcohol. Then lipase PS-C (1 equiv w/w), isopropenyl acetate (6 mmol) were added to the reaction mixture and monitored on chiral HPLC analysis until it reached 50% conversion. The reaction was filtered and the filtrate washed with water, followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography. The enantiopure products **2** and **3**, were analyzed by chiral HPLC and compared with the corresponding racemic products.

4.3.1. (*R*)-2-Azido-1-phenyl-1-ethanol[9c] 2a. Yield: 46%; 98% ee ($t_R = 18.87$ min); $[\alpha]_D^{25}$ −89.2 (*c* 1, $CHCl_3$) [lit.[8a] −80.1 (*c* 0.78, $CHCl_3$), ee 100%]; IR (neat): 3414, 2095 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.4 (1H, br s), 3.3–3.5 (2H, m), 4.8 (1H, m), 7.33 (5H, s); LSIMS (*m*/*z*): 165 (M^++2). Anal. Calcd for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.28; H, 5.13; N, 25.36.

4.3.2. (*S*)-2-Azido-1-phenyl-1-ethyl acetate[8a] 3a. Yield: 49%; 94% ee ($t_R = 12.32$ min); $[\alpha]_D^{25}$ +89.7 (*c* 1, $CHCl_3$) [lit.[8a] +62.9 (*c* 0.98, $CHCl_3$), ee 82%]; IR (neat): 2105, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.14 (3H, s), 3.45–3.33 (1H, dd, $J = 12.63$, 4.45 Hz), 3.53–3.67 (1H, dd, $J = 12.63$, 8.17 Hz), 5.88 (1H, dd, $J = 8.17$, 4.45 Hz), 7.33 (5H, s); LSIMS (*m*/*z*): 206 (M^++1). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.25; H, 5.20; N, 20.23.

4.3.3. (*R*)-2-Azido-1-(4-methylphenyl)-1-ethanol[8a] 2b. Yield: 45%; >99% ee ($t_R = 16.74$ min); $[\alpha]_D^{25}$ −82.7 (*c* 1, $CHCl_3$) [lit.[8a] $[\alpha]_D^{25}$ −28.2 (*c* 1.2, $CHCl_3$), ee 95%]; IR (neat): 3425, 2100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (3H, s), 3.3 (1H, dd, $J = 12.63$, 4.45 Hz), 3.5 (1H, dd, $J = 12.63$, 8.17 Hz), 4.8 (1H, dd, $J = 8.17$, 4.45 Hz), 7.1–7.3 (4H, m); LSIMS (*m*/*z*): 121 (M^+−57). Anal. Calcd for $C_9H_{11}N_3O$: C, 61; H, 6.26; N, 23.71. Found: C, 60.89; H, 6.11; N, 23.59.

4.3.4. (*S*)-2-Azido-1-(4-methylphenyl) ethyl acetate 3b. Yield: 47%; 97% ee ($t_R = 10.44$ min); $[\alpha]_D^{25}$ +100.8 (*c* 1, $CHCl_3$); IR (neat): 2100, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.12 (3H, s), 2.34 (3H, s), 3.33–3.40 (1H, dd, $J = 13.21$, 4.15 Hz), 3.5–3.62 (1H, dd, $J = 13.21$, 8.30 Hz), 5.84 (1H, dd, $J = 8.30$, 4.15 Hz), 7.1–7.25 (4H, m); LSIMS (*m*/*z*): 163 (M^+−57). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.08; H, 5.76; N, 19.03.

4.3.5. (*R*)-2-Azido-1-(4-fluorophenyl)-1-ethanol[8a] 2c. Yield: 47%; 88% ee ($t_R = 14.82$ min); $[\alpha]_D^{25}$ −70.8 (*c* 1, $CHCl_3$) [lit.[8a] −14.7 (*c* 2, $CHCl_3$), ee 98%]; IR (neat): 3417, 2105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.36 (1H, br s), 3.33–3.45 (2H, m), 4.75–4.88 (1H, m), 7.04 (2H, t, $J = 8.17$ Hz), 7.24–7.4 (2H, m). Anal. Calcd for $C_8H_8FN_3O$: C, 53.04; H, 4.45; F, 10.48; N, 23.9. Found: C, 52.94; H, 4.26; F, 10.19; N, 23.68.

4.3.6. (*S*)-2-Azido-1-(4-fluorophenyl) ethyl acetate 3c. Yield: 43%; >99% ee ($t_R = 11.25$ min); $[\alpha]_D^{25}$ +78.2 (*c* 1.3 $CHCl_3$); IR (neat): 2095, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.13 (3H, s), 3.35–3.43 (1H, dd, $J = 13.22$, 4.15 Hz), 3.54–3.63 (1H, dd, $J = 13.22$, 7.93 Hz), 5.85 (1H, dd, $J = 7.93$, 4.15 Hz), 7.1 (2H, t, $J = 8.68$ Hz), 7.24–7.35 (2H, m); LSIMS (*m*/*z*): 167 (M^+−56). Anal. Calcd for $C_{10}H_{10}FN_3O_2$: C, 53.81; H, 4.52; F, 8.51; N, 18.83. Found: C, 53.65; H, 4.39; F, 8.43; N, 18.63.

4.3.7. (*R*)-2-Azido-1-(4-chlorophenyl)-1-ethanol[8a] 2d. Yield: 48%; 90% ee ($t_R = 16.38$ min); $[\alpha]_D^{25}$ −82.5 (*c* 1, $CHCl_3$) [lit.[8a] −79.1 (*c* 1.25, $CHCl_3$), ee 100%]; IR (neat): 3417, 2099 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.33 (1H, d, $J = 2.97$ Hz), 3.4 (2H, d, $J = 5.94$ Hz), 4.82 (1H, m), 7.24–7.37 (4H, m); LSIMS (*m*/*z*): 154 (M^+−43). Anal. Calcd for $C_8H_8ClN_3O$: C, 48.62; H, 4.08; Cl, 17.94; N, 21.26. Found: C, 48.53; H, 4.02; Cl, 17.78; N, 21.12.

4.3.8. (*S*)-2-Azido-1-(4-chlorophenyl) ethyl acetate 3d. Yield: 38%; >99% ee ($t_R = 18.61$ min); $[\alpha]_D^{25}$ +104.9 (*c* 1, $CHCl_3$); IR (neat): 2100, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.13 (3H, s), 3.33–3.45 (1H, dd, $J = 13.37$, 4.45 Hz), 3.51–3.65 (1H, dd, $J = 13.37$, 8.17 Hz), 5.8–5.88 (1H, dd, $J = 8.17$, 4.45 Hz), 7.22–7.38 (4H, m); LSIMS (*m*/*z*): 183 (M^+−56). Anal. Calcd for $C_{10}H_{10}ClN_3O_2$: C, 50.12; H, 4.21; Cl, 14.79; N, 17.53. Found: C, 50.05; H, 4.11; Cl, 14.66; N, 17.50.

4.3.9. (*R*)-2-Azido-1-(4-bromophenyl)-1-ethanol 2e. Yield: 42%; 92% ee ($t_R = 17.98$ min); $[\alpha]_D^{25}$ −77 (*c* 1.1, $CHCl_3$); IR (KBr): 3420, 2100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (1H, br s), 3.4 (2H, d, $J = 5.94$ Hz), 4.81 (1H, t, $J = 5.94$ Hz), 7.24 (2H, d, $J = 8.17$ Hz), 7.5 (2H, d, $J = 8.17$ Hz); LSIMS (*m*/*z*): 185 (M^+-57). Anal. Calcd for $C_8H_8BrN_3O$: C, 39.69; H, 3.33; Br, 33.01; N, 17.36. Found: C, 39.52; H, 3.21; Br, 32.96; N, 17.12.

4.3.10. (*S*)-2-Azido-1-(4-bromophenyl) ethyl acetate 3e. Yield: 44%; >99% ee ($t_R = 18.52$ min); $[\alpha]_D^{25}$ +93.8 (*c* 1.1, $CHCl_3$); IR (neat): 2085, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.13 (3H, s), 3.35–3.43 (1H, dd, $J = 13.21$, 4.15 Hz), 3.53–3.62 (1H, dd, $J = 13.21$, 7.93 Hz), 5.82 (1H, dd, $J = 7.93$, 4.15 Hz), 7.2 (2H, d, $J = 8.30$ Hz), 7.5 (2H, d, $J = 8.30$ Hz); LSIMS (*m*/*z*): 227 (M^+-57). Anal. Calcd for $C_{10}H_{10}BrN_3O_2$: C, 42.28; H, 3.55; Br, 28.12; N, 14.79. Found: C, 42.13; H, 3.45; Br, 28.03; N, 14.65.

4.3.11. (*R*)-2-Azido-1-(3-chloro-4-methoxyphenyl)-1-ethanol 2f. Yield: 43%; 75% ee [based on acetylated **2f** ($t_R = 14.99$ min)]; $[\alpha]_D^{25}$ −66.5 (*c* 1.2, $CHCl_3$); IR (neat): 3420, 2100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.3 (1H, br s), 3.36–3.44 (2H, m), 3.9 (3H, s), 4.76 (1H, t, $J = 5.94$ Hz), 6.88 (1H, d, $J = 8.17$ Hz), 7.2 (1H, dd, $J = 8.17$, 2.23 Hz), 7.36 (1H, d, $J = 2.23$ Hz); LSIMS (*m*/*z*): 171 (M^+-56). Anal. Calcd for $C_9H_{10}ClN_3O_2$: C, 47.48; H, 4.43; Cl, 15.57; N, 18.46. Found: C, 47.29; H, 4.38; Cl, 15.32; N, 18.28.

4.3.12. (*S*)-2-Azido-1-(3-chloro-4-methoxyphenyl) ethyl acetate 3f. Yield: 37%; >99% ee ($t_R = 14.71$ min); $[\alpha]_D^{25}$ +108.2 (*c* 1.1, $CHCl_3$); IR (neat): 2085, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.13 (3H, s), 3.21–3.3 (1H, dd, $J = 12.84$, 4.15 Hz), 3.53–3.63 (1H, dd, $J = 12.84$, 7.93 Hz), 3.9 (3H, s), 5.79 (1H, dd, $J = 7.93$, 4.15 Hz), 6.87 (1H, d, $J = 8.68$ Hz), 7.15–7.21 (1H, dd, $J = 8.68$, 2.26 Hz), 7.34 (1H, d, $J = 2.26$ Hz); LSIMS (*m*/*z*): 269 (M^+). Anal. Calcd for $C_{11}H_{12}ClN_3O_3$: C, 48.99; H, 4.48; Cl, 13.15; N, 15.58. Found: C, 48.50; H, 4.35; Cl, 13.05; N, 15.31.

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