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Synthesis of Optically Pure 2-Azido-1-arylethanols with Isolated Enzymes and Conversion to Triazole-Containing β-Blocker Analogues Employing Click Chemistry

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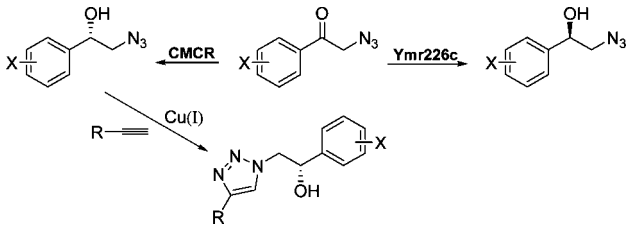
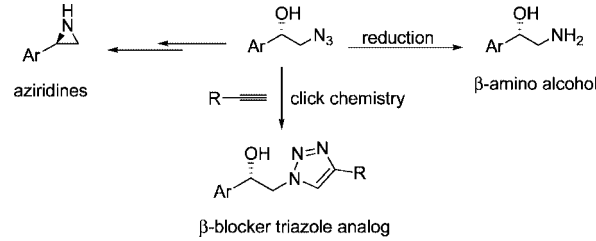


Both antipodes of 2-azido-1-arylethanols were synthesized with excellent optical purity via enzymatic reduction of the corresponding α-azidoacetophenone derivatives catalyzed by a recombinant carbonyl reductase from *Candida magnoliae* (**CMCR**) or an alcohol dehydrogenase from *Saccharomyces cerevisiae* (**Ymr226c**). This provides an effective route to this class of important compounds in optically pure form. (*S*)-2-Azido-1-(*p*-chlorophenyl)ethanols reacted with alkynes employing click chemistry to afford high yields of optically pure triazole-containing β-adrenergic receptor blocker analogues with potential biological activity.

Optically active 2-azido-1-arylethanols are precursors of chiral aziridines and vicinal amino alcohols as shown in Scheme 1. Chiral aziridines are important building blocks in organic synthesis[1] and key components in bioactive molecules (e.g., aziridine-based cysteine protease inhibitors).[2–4] Optically pure β-amino alcohols are widely used as chiral ligands for asymmetric catalysis and in the construction of biologically active compounds such as β-adrenergic receptor blockers. In addition, employing click chemistry, i.e., copper(I)-catalyzed azide−alkyne [3 + 2] cycloaddition, 2-azido-1-arylethanols can be converted to β-adrenergic receptor blocker analogues with 1,2,3-triazole moiety.[5] The triazole ring is a potential pharmacophore that has gained attention over the past few years.[6,7] For example, the 1,2,3-triazole moiety has be used as an effective peptide surrogate in HIV-1 protease inhibitors.[8]

SCHEME 1. 2-Azido-1-arylethanols as Important Intermediates



Given the importance of optically active 2-azido-1-arylethanols, various methods have been sought for their preparation in optically pure form. For example, the azidolysis of optically pure epoxides[9–11] and diol derivatives[12] with azide anion led to the formation of optically active azido alcohols. Resolutions of racemic 2-azido-1-arylethanols catalyzed by lipases[13–15] and racemic epoxides catalyzed by halohydrin dehalogenase with azide anion as nucleophile[16] have also been utilized to obtain enantiomerically pure 2-azido-1-arylethanols. Since α-azidoacetophenone derivatives are readily available from the azidolysis of α-haloacetophenes with sodium azide, the enantioselective reduction of α-azidoacetophenones to chiral 2-azido-1-arylethanols should be an attractive approach. However, only a few reports have appeared to deal with enantioselective chemical reduction of α-azidoacetophenones.[17–21] Watanabe et al. have examined the transfer hydrogenation of α-azidoacetophenone in a study on the asymmetric transfer hydrogenation of functionalized acetophenones.[17] Reddy et al. have reported that

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the reduction of α-azidoacetophenones with sodium borohydride in the presence of β-cyclodextrin gave (*S*)-2-azido-1-arylethanols with 4−81% ee.[18,21] Yadav, Rao, and their co-workers have used oxazaborolidine-borane as the reducing agent in the enantioselective reduction of α-azidoketones.[19,20] This scarcity may be due to the chemoselectivity required over the reduction of the azido group.

In this context, biocatalytic reduction of α-azidoacetophenone derivatives has attracted attention. Enantioselective bioreduction of α-azidoacetophenones to (*R*)-2-azido-1-arylethanols has been investigated with whole cell biocatalysts such as baker's yeast (*Saccharomyces cerevisiae*), [22,23] *Daucus carota* root,[24,25] and *Rhodotorula glutinis*,[26,27] while (*S*)-2-azido-1-arylethanols have been obtained with *Geotrichum candidum* as biocatalyst.[27] Stewart et al. have reported an approach to paclitaxel C13 side chain via Baker's yeast mediated reduction of methyl 3-azido-2-oxo-3-phenylpropionate, although its application was limited by low diastereoselectivity.[28] Recently, Edegger et al. have employed lyophilized cells of *E. coli* containing an overexpressed alcohol dehydrogenase (ADH-'A') from *Rhodococcus rubber* DSM 44541 as a biocatalyst in the reduction of α-azidoacetophenone and α-azido-*p*-hydroxyacetophenone.[29] Most of the above biocatalysts follow Prelog's rule for the reduction of α-azidoacetophenones, and only one shows anti-Prelog enantiopreference.

The use of isolated enzymes offers several advantages including the elimination of undesirable enantiomer formation mediated by contaminating enzymes in the whole cell biocatalytic system, the possibility of achieving high substrate load, easy downstream product separation, and easy handling by organic chemists without microbiological knowledge. In recent years, isolated carbonyl reductase enzymes have been demonstrated to be highly effective catalysts for the enantioselective reduction of a wide range of ketones.[30] Given the advantages of isolated enzyme catalysts and the importance of optically pure 2-azido-1-arylethanols, herein we report the synthesis of both antipodes of 2-azido-1-arylethanols via enantioselective reduction of α-azido aromatic ketones catalyzed by isolated carbony reductases. The obtained azido alcohols reacted with alkynes through click chemistry to give the triazole analogues of β-adrenergic receptor blockers, a class of compounds with potential biological activity.

We have recently cloned and overexpressed several carbonyl reductase/alcohol dehydrogenase genes from various sources in *E. coli*. The recombinant proteins have been purified and their substrate profiles have been studied. These isolated enzyme catalysts catalyze the reduction of a series of ketones, β-ketonitriles, and α- and β-ketoesters to furnish both antipodes of the corresponding chiral alcohols in excellent optical purity.[31–35] Therefore, we have screened these isolated enzymes toward the reduction of α-azidoacetophenone (**1a**). α-Azidoacetophenone (**1a**) was treated with a catalytic amount of carbonyl reductase and cofactor NADPH, which was regenerated with D-glucose and D-glucose dehydrogenase (GDH) systems (Scheme 2), in potassium phosphate buffer. The reaction mixture was extracted with methyl *tert*-butyl ether, and the extract was subjected to chiral HPLC analysis to determine the conversion and ee value. The results are summarized in Table 1. It can be seen from the data that **CMCR**, **SSCR**, **Ymr226c**, and **Ygl039w** effectively catalyzed the reduction of α-azidoacetophenone (**1a**) with 100% conversion. The reduction with **CMCR** and **SSCR** gave (*S*)-2-azido-1-phenylethanol in essentially optically pure form, while (*R*)-2-azido-1-phenylethanol was obtained with **Ymr226c** as the catalyst. For **Ygl039w**, the enantioselectivity was poor with 27% ee. Other enzymes, PFADH, GRE2, and 7-HSDH, showed almost no activity.

The reductions of α-azidoacetophenone (**1a**) and other α-azidoacetophenone derivatives bearing various substituents on the phenyl ring were carried out with **CMCR** or **Ymr226c** as biocatalyst at about 1 mmol scale. α-Azidoacetophenones (**1a**−**k**) were treated with a catalytic amount of **CMCR** or **Ymr226c** and cofactor NADPH, which was regenerated with D-glucose and D-glucose dehydrogenase (GDH) systems (Scheme 2), in potassium phosphate buffer. The reaction mixtures were worked up as described in the Experimental Section. The products (*S*)- or (*R*)-2-azido-1-arylethanols were isolated and

SCHEME 2. Enzymatic Reduction of α-Azidoacetophenone with the D-Glucose Dehydrogenase/D-Glucose NADPH Regeneration System

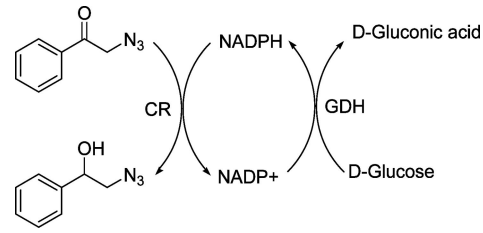

TABLE 1. Screening of Carbonyl Reductases toward the Reduction of α-Azidoacetophenone

entry	enzym[a]	conversion (%)[b]	ee (%)[c]	absolute configuration
1	**CMCR**	100	>99	*S*
2	**SSCR**	100	>99	*S*
3	**Ymr226c**	100	>99	*R*
4	**Ygl039w**	100	27	*S*
5	**PFADH**	3		
6	**GRE2**	<1		
7	**7-HSDH**	0		

[a] See the Experimental Section for the sources of these enzymes. [b] The conversions were measured by HPLC analysis. [c] ee values were measured by chiral HPLC analysis.

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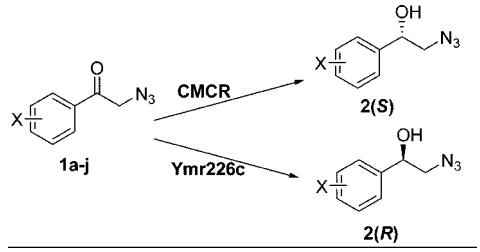
TABLE 2. Enzymatic Reduction of α-Azidoacetophenones Catalyzed by Carbonyl Reductases



	CMCR			Ymr226c		
X	time (h)	yield (%)	ee[a] (%)	time (h)	yield (%)	ee[a] (%)
1a (H)	24	92	99 (*S*)	24	89	>99 (*R*)
1b (4-F)	24	93	>99 (*S*)	24	84	>99 (*R*)
1c (2,4-F_2)	24	90	>99 (*S*)	24	82	>99 (*R*)
1d (4-Cl)	24	92	>99 (*S*)	32	85	>99 (*R*)
1e (4-Br)	24	88	98 (*S*)	24	84	>99 (*R*)
1f (4-CH_3)	24	85	99 (*S*)	96	87	>99 (*R*)
1g (4-OCH_3)	24	88	99 (*S*)	240	5[b]	-
1h (3-OCH_3)	24	95	99 (*S*)	240	19[b]	>99 (*R*)
1i (4-NO_2)	24	84	99 (*S*)	216	10[b]	63 (*R*)
1j (3-NO_2)	24	82	99 (*S*)	120	85	>99 (*R*)
1k (4-CN)	24	80	99 (*S*)	240	0	-

[a] The ee value was determined by chiral HPLC analysis. [b] The yield was determined by HPLC. The product was not isolated.

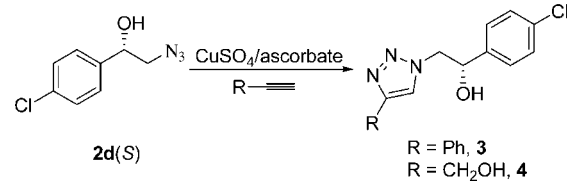
characterized by IR and NMR analysis. The ee values were measured by chiral HPLC analysis. The results are presented in Table 2.

From Table 2 it can be seen that the carbonyl reductase (**CMCR**) efficiently catalyzed the reduction of various α-azidoacetophenone derivatives bearing an electron-withdrawing or electron-donating group on the phenyl ring to furnish the (*S*)-enantiomer of the corresponding 2-azido-1-arylethanols in essentially optically pure form. In some cases, (*R*)-2-azido-1-arylethanols were obtained with **Ymr226c**. The activity of **Ymr226c** toward the reduction of these α-azidoacetophenone derivatives was greatly affected by the substituents on the phenyl ring. For unsubstituted and para-halo-substituted α-azidoacetophenones, the reduction was completed in about 1 day, while the reaction was much slower for the substrate with 4-methyl, 3- or 4-nitro, and 3- or 4-methoxy groups on the phenyl ring. No reduction was observed for α-azido-4′-cyanoacetophenone. The naphthalene analogue was not reduced by both enzymes.

It has be known that copper(I) catalyzed the [3 + 2] Huisgen's cycloaddition reaction between azides and terminal alkynes to form 1,2,3-triazoles.[36] (S)-2-Azido-1-(*p*-chlorophenyl)ethanol reacted with phenylacetylene or propargyl alcohol under the action of Cu(I) catalyst, which was in situ generated from the stable copper(II) sulfate/sodium ascorbate redox system, to afford (*S*)-1-(4-chlorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (**3**) and (*S*)-1-(4-chlorophenyl)-2-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)ethanol (**4**) in 90% and 83% yield, respectively (Scheme 3). Since the triazole functional group showed similar properties as the amide functionality,[8] this class of compounds should be expected to possess potential biological activity of β-adrenergic receptor blockers.

In conclusion, enantioselective reductions of α-azidoacetophenone derivatives catalyzed by a recombinant carbonyl reductase from *Candida magnoliae* (**CMCR**) or an alcohol dehydrogenase from *Saccharomyces cerevisiae* (**Ymr226c**) afforded the corresponding (*S*)- or (*R*)-2-azido-1-arylethanols with excellent optical purity. This demonstrated that these enzymes were valuable biocatalysts for the synthesis of this class of important compounds in optically pure form. The obtained 2-azido-1-arylethanols reacted with alkynes via copper(I)-catalyzed [3 + 2] Huisgen's cycloaddition to give enatiomerically pure triazole-containing β-blocker analogues, a type of compounds with potential biological activity, in high yields.

SCHEME 3. Synthesis of β-Blocker Analogues Containing 1,2,3-Triazole Moiety



Experimental Section

Typical Procedure for the Enzymatic Reduction of α-Azidoacetophenones. A typical procedure for the reduction of α-azidoacetophenones was as follows (using α-azidoacetophenone **1a** as an example): Into a solution of carbonyl reductase **CMCR** (20 U, 1 U was defined as the enzyme converting 1 μmol of NADPH to $NADP^+$ per minute with ethyl 4-chloro-3-oxobutyrate as substrate), D-glucose dehydrogenase (5 U), NADPH (5 mg), and D-glucose (400 mg) in potassium phosphate buffer (100 mM, pH 7.0, 100 mL) was added a solution of α-azidoacetophenone (**1a**, 170 mg, 1.07 mmol) in DMSO (5 mL). The mixture was stirred at room temperature with TLC monitoring from time to time. After complete consumption of substrate, the reaction mixture was extracted with methyl *tert*-butyl ether. Removal of solvents gave the crude product, which was purified by preparative TLC (hexane/ethyl acetate = 90/10) to give (*S*)-2-azido-1-phenylethanol (**2a**).[27] The characterization data are presented in the Supporting Information, except for two new compounds.

(*S*)-2-Azido-1-(2′,4′-difluorophenyl)ethanol 2c(*S*). Colorless liquid, 120 mg, 90% yield (ketone: 130 mg, 0.67 mmol); ^{1}H NMR ($CDCl_3$) δ (ppm) 2.41 (br, 1H,), 3.44 (dd, J = 12.5, 7.8 Hz, 1H), 3.53 (dd, J = 12.5, 3.4 Hz, 1H), 5.16 (dd, J = 7.8, 3.4 Hz, 1H), 6.81 (m, 1H,), 6.95 (m, 1H), 7.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 57.2, 67.6, 104.2 (t, $^2J_{C-F}$ = 25.4 Hz,), 112.1 (dd, $^2J_{C-F}$ = 21.0 Hz, $^4J_{C-F}$ = 3.5 Hz), 123.9 (d, $^2J_{C-F}$ = 17.3 Hz), 128.9 (dd, $^3J_{C-F}$ = 9.6 Hz, $^3J_{C-F}$ = 5.7 Hz), 160.1 (dd, $^1J_{C-F}$ = 246.9 Hz, $^3J_{C-F}$ = 12.2 Hz), 163.2 (dd, $^1J_{C-F}$ = 247.9 Hz, $^3J_{C-F}$ = 12.1 Hz); IR (cm^{-1}) 3427.4, 2106.7, 1624.6, 1503.1, 1429.2, 1270.3, 1173.7, 1100.1, 964.4, 850.8; $[\alpha]_D^{22}$ +73.9 (*c* 0.5, CH_3OH). Anal. Calcd for $C_8H_7F_2N_3O$: C 48.25, H 3.54, N 21.10. Found: C 48.60, H 3.97, N 20.99.

(*S*)-2-Azido-1-(4′-cyanophenyl)ethanol 2k(*S*). Light yellow solid, 81 mg, 80% yield (ketone: 100 mg, 0.54 mmol); ^{1}H NMR ($CDCl_3$) δ (ppm) 2.70 (br, 1H), 3.48−3.53 (m, 2H), 4.99−5.03 (m, 1H), 7.57 (d, J = 8.8 Hz, 2H), 8.23 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 57.8, 72.6, 112.0, 118.5, 126.7, 132.4, 145.7; IR (cm^{-1}) 3422.2, 2230.3, 2103.7, 1642.4, 1260.7, 1079.9, 880.2, 815.02; $[\alpha]_D^{22}$ +139.9 (*c* 0.17, CH_3OH). Anal. Calcd for $C_9H_8N_4O$: C 57.45, H 4.29, N 29.76. Found: C 57.63, H 4.57, N 29.44.

Synthesis of β-Blocker Analogues Containing 1,2,3-Triazole Moiety. (*S*)-2-Azido-1-(4′-chlorophenyl)ethanol, **2d(S)**, was converted to β-blocker analogues containing 1,2,3-triazole moiety by following the literature procedures.[36] To a suspension of phenylacetylene (204.0 mg, 2.0 mmol) and (*S*)-2-azido-1-(4′-chlorophenyl)ethanol (395.1 mg, 2.0 mmol) in a 1:1 mixture of water and *tert*-butyl alcohol (8 mL) were added sodium ascorbate (0.2 mmol,

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200 μL of a freshly prepared 1 M solution in water), followed by coppe (II) sulfate pentahydrate (0.02 mmol, 200 μL of a 0.1 M solution). The resulting mixture was stirred vigorously at 45 °C for 5−8 h until TLC showed the disappearance of **2d**. The mixture was cooled to 0 °C and diluted with water (30 mL). White precipitate formed and was filtered. The solid was washed with water three times (3 × 20 mL) and dried under vacuum to afford product.

(*S*)-1-(4-Chlorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethanol (3). Colorless crystal, mp 218−219 °C; 341 mg, 90%; ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) 4.45 (dd, J = 13.8, 8.0 Hz, 1H), 4.55 (dd, J = 13.8, 4.0 Hz, 1H), 5.02 (d, J = 4.40, 1H), 5.11 (m, 1H), 7.17−7.32 (m, 5H), 7.36 (d, J = 8.36, 2H), 7.75 (d, J = 8.17, 2H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) 57.3, 72.0, 121.9, 125.7, 128.0, 128.3, 128.8, 129.1, 131.9, 133.3, 141.2, 147.0; IR (cm^{-1}) 3413.4, 3134.7, 1631.1, 1483.9, 1224.9, 1081.5, 828.6, 762.7; $[\alpha]_D^{22}$ +48.93 (*c* 1.0, acetone). Anal. Calcd for $C_{16}H_{14}ClN_3O$: C 64.11, H 4.71, N 14.02. Found: C 63.84, H 4.88, N 14.14.

(*S*)-1-(4-Chlorophenyl)-2-(4-(hydroxymethyl)-1*H*-1,2,3-triazol-1-yl)ethanol (4). White powder, mp 140−141 °C; 422 mg, 83%; ^{1}H NMR (400 MHz, acetone-d_6) δ (ppm) 4.05 (t, J = 5.4, 1H), 4.36−4.52 (m, 4H), 4.96 (d, J = 4.3, 1H), 5.03−5.06 (m, 1H), 7.25 (d, J = 8.1, 2H), 7.32 (d, J = 8.2, 2H), 7.69 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ (ppm) 56.3, 57. 1, 72.1, 123.4, 128.2, 128.7, 133.3, 141.3; IR (cm^{-1}) 3288.2, 3094.18, 2951.3, 2879.4, 1485.9, 1413.9, 1339.9, 1145.4, 1083.1, 1014.3, 825.4, 783.4; $[\alpha]_D^{22}$ +32.27 (*c* 1.0, CH_3OH). Anal. Calcd for $C_{11}H_{12}ClN_3O_2$: C 52.08, H 4.77, N 16.56. Found: C 51.69, H 4.86, N 16.27.

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Supporting Information Available: The procedure for the preparation of α-azidoacetophenones, HPLC retention times and characterization data of 2-azido-1-arylethanols, ^{1}H NMR spectra of new compounds, and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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