

Note

Pd-catalyzed oxidative kinetic resolution of 2-azido-1-arylethanols

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(-)-Sparteine/ Pd (II) complex in combination with oxygen as a stoichiometric oxidant, catalyses the oxidative kinetic resolution of β -azido alcohols to afford the corresponding chiral 2-azido-1-arylethanols.

Keywords: β -Azidoalcohol, chiral 2-azido-1-arylethanol, (-)-Sparteine-Pd (II) complex, kinetic resolution

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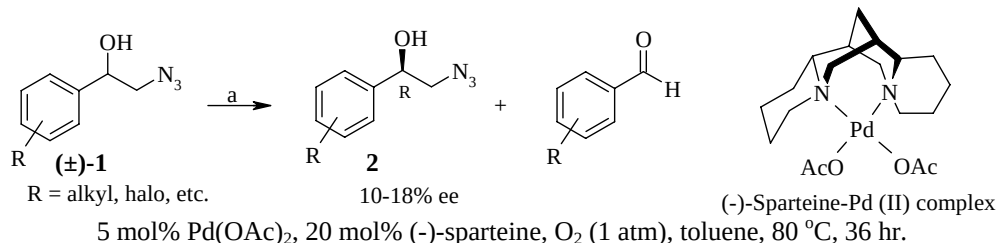
Traditionally, oxidations of alcohols are performed with stoichiometric amounts of inorganic oxidants, notably Cr (VI) reagents that are relatively expensive and generate copious amounts of heavy metal wastes in environmentally undesirable solvents. Hence, there is a need for catalytic oxidations that use dioxygen (O_2) or hydrogen peroxide as the oxidant. These oxidants are atom efficient and produce water as the only by-product¹. Optically active β -azido alcohols are of great significance as they are direct precursors of chiral aziridines² and vicinal aminoalcohols³. During recent years, there has been a growing interest in chiral aziridines due to the increasing importance of functionalized aziridines in organic synthesis and their presence in bioactive molecules. Moreover, chiral 1, 2-amino alcohols are important structural elements present in chiral ligands for asymmetric

catalysis as well as in biologically active compounds. In contrast to chiral 2-amino-1-arylethanols, which are readily available by reduction of α -amino acids⁴, the corresponding regioisomeric chiral 1-amino-2-ols are not as easy to access.

Although there are many methods reported in the literature for regio- and enantio-selective synthesis of 2-azido-1-arylethanols⁵ **2**, these methods suffer from the following drawbacks: (i) the azidolysis of aryloxiranes is commonly accompanied by the formation of undesired regio isomers having the azido group at the benzylic position; (ii) other methods involve multi-step synthesis employing optically active cyanohydrins as starting materials; (iii) enzymatic methods involve the use of costly enzymes. In order to overcome these difficulties, there is a definite need to develop a convenient method for the synthesis of enantio-pure 2-azido-1-arylethanols **2**.

Recently, Sigmann *et al.*^{6a,b} have independently discovered that a combination of Pd (II) salts with (-)-sparteine effectively catalyses the aerobic oxidative kinetic resolution of secondary benzylic alcohols. Inspired by the above result, we became interested to apply this methodology for the synthesis of chiral 2-azido-1-arylethanols **2** from the corresponding racemic 2-azido-1-arylethanols **1** (**Scheme I**), the results of which are presented in this note.

Racemic 2-azido-1-arylethanols **1** were readily obtained from the corresponding styrenes in two steps. Thus, styrene on treatment with NBS in the presence of acetonitrile-water mixture at room temperature gave 2-bromo-1-phenylethanol in almost quantitative yield followed by displacement of bromide with azide was achieved in DMF at 100 °C to produce the racemic 2-azido-1-phenylethanol **1**. When racemic 2-azido-1-arylethanols **1** were subjected to oxidative kinetic resolution with



Scheme I

$\text{Pd}(\text{OAc})_2$ as catalyst and (-)-sparteine as chiral auxiliary at 80 °C, (*R*)-2-azido-1-arylethanols **2** were obtained in high yields with low enantio-selectivity (10-18% ee) along with its over-oxidized product aldehydes in < 20% yield (**Scheme I**).

It was observed that, a variety of racemic aromatic azido alcohols **1** underwent oxidative kinetic resolution to afford the corresponding enantiopure (*R*)-2-azido-1-arylethanols **2** although in low enantiomeric excess. In order to improve the enantio-selectivity of the process change of various parameters was studied. First, we increased the time of the reaction up to 72 hr, but this did not show any appreciable increase in enantio-selectivity. Secondly, increase of concentration of (-)-sparteine also did not show the desired result. Variety of solvents like benzene, acetonitrile, methanol, acetone, toluene and THF were tested for this reaction, but toluene proved to be the best among all other solvents used. Other Pd-catalysts like PdCl_2 , $\text{Pd}(\text{acac})_2$ and $(\text{C}_6\text{H}_5\text{CN})_2\text{PdCl}_2$ were also screened for the above reaction, but this also did not show any appreciable increase in enantio-selectivity. The low enantio-selectivity observed may be due to the presence of azido alcohol moiety, which might prohibit the (-)-sparteine- $\text{Pd}(\text{OAc})_2$ complex formations. To investigate this we prepared an orange coloured complex of (-)-sparteine and $\text{Pd}(\text{OAc})_2$ separately and used for this reaction. We observed that the isolated $\text{Pd}[(\text{-})\text{sparteine}](\text{OAc})_2$ complex was also incompetent to increase the enantio-selectivity of the reaction. Further, when the azido alcohols, prepared from disubstituted olefins like stilbene and β -methylstyrene, were subjected to oxidative kinetic resolution, they gave the mixtures of products.

In conclusion, we have developed a new method for the synthesis of chiral 2-azido-1-arylethanols **2** by following the oxidative kinetic resolution of racemic 2-azido-1-arylethanols **1** with (-)-sparteine/ $\text{Pd}(\text{II})$ catalyst system. The reaction makes use of easily available and cheap chiral reagents. Molecular oxygen is used as terminal oxidant. The present method provides a new route to optically active (*R*)-2-azido-1-arylethanols **2**, although enantio-selectivity observed is not very high (10-18% ee).

General procedure for kinetic resolution of racemic azido alcohols

To a 50 mL side arm flask, $\text{Pd}(\text{OAc})_2$ (0.140 mg, 0.59 mmole) was added followed by dry toluene (20

mL), 3Å MS (50 mg) and (-)-sparteine (0.033 g, 0.14 mmole). A condenser and balloon filled with O_2 were then attached to the flask. The whole system was evacuated and refilled with O_2 from the balloon three to four times. The flask was warmed to 80 °C in an oil-bath. After 30 min of reflux azido alcohol **1** (3 mmole) in toluene (10 mL) was added dropwise and refluxed for 36 hr, then it was cooled to RT. The reaction was quenched with 2% TFA / methanol (15 mL). The solvent was removed under reduced pressure and the residue was taken up in minimal amount of dichloromethane. The crude residue was then purified by column chromatography to give (*R*)-azido alcohol **2**.

(*R*)-2-Azido-1-phenylethanol 2a: Yield 80%; gum; $[\alpha]_{\text{D}}^{25}$ -8.5 (c 0.8, CHCl_3); [lit. $[\alpha]_{\text{D}}^{25}$ -80.1 (c 0.78, CHCl_3)], ee: 10.6%; IR (CHCl_3 , cm^{-1}): 3421, 3015, 2107, 1493, 1216, 761, 701; ^1H NMR (200 MHz, CDCl_3): δ 2.42 (brs, 1H), 3.35-3.55 (dd, J = 4.0 and 6.0 Hz, 2H), 4.82-4.90 (m, 1H), 7.25-7.45 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): δ 57.81, 73.18, 125.81, 128.17, 128.53, 140.55; MS (m/z , % RI): 164 (M^+ , 2), 146 (3), 135 (4), 107 (100), 91 (6), 79 (70), 77 (68), 63 (10), 51 (50); Anal. $\text{C}_8\text{H}_9\text{N}_3\text{O}$ requires C, 58.88; H, 5.55; N, 25.75. Found: C, 58.82; H, 5.56; N, 25.79%.

(*R*)-2-Azido-1-(4-methylphenyl)ethanol 2b: Yield 72%; gum; $[\alpha]_{\text{D}}^{25}$ -4.5 (c 1.2, CHCl_3); [lit. $[\alpha]_{\text{D}}^{25}$ -28.2 (c 1.0, CHCl_3)], ee: 17.8%; IR (CHCl_3 , cm^{-1}): 3449, 3020, 2950, 2095, 1710, 1495, 1363, 1222, 750; ^1H NMR (200 MHz, CDCl_3): δ 2.25 (brs, 1H), 2.35 (s, 3H), 3.43 (t, J = 4.0 and 6.0 Hz, 2H), 4.80-4.86 (dd, J = 4.0 Hz, 1H), 7.10-7.30 (m, 5H); ^{13}C NMR (50 MHz, CDCl_3): δ 20.87, 57.59, 72.92, 125.70, 129.09, 137.58, 137.80; MS (m/z , % RI): 177 (M^+ , 5), 122 (55), 120 (15), 105 (100), 92 (15), 65 (50), 64 (20); Anal. $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$ requires C, 61.00; H, 6.25; N, 23.7. Found: C, 61.09; H, 6.32; N, 23.7%.

(*R*)-2-Azido-1-(4-methoxyphenyl)ethanol 2c: Yield 75%; gum; $[\alpha]_{\text{D}}^{25}$ -8.1 (c 0.9, CHCl_3); [lit. $[\alpha]_{\text{D}}^{25}$ -39.0 (c 1.0, CHCl_3)], ee: 16.0%; IR (CHCl_3 , cm^{-1}): 3256, 3019, 2676, 2107, 1215, 750, 669; ^1H NMR (200 MHz, CDCl_3): δ 2.20 (brs, 1H), 3.42 (m, 2H), 3.79 (s, 3H), 4.80 (dd, J = 7.5 and 4.0 Hz, 1H), 6.90 (d, J = 6.5 Hz, 1H), 7.29 (d, J = 6.5 Hz, 1H); ^{13}C NMR (50 MHz, CDCl_3): δ 55.5, 58.3, 73.2, 114.3, 127.4, 132.5, 159.8; Anal. $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$ requires C, 55.95; H, 5.73; N, 21.75. Found: C, 55.86; H, 5.77; N, 21.79%.

(*R*)-2-Azido-1-(4-chlorophenyl)ethanol 2d: Yield 85%; m.p. 46-48°C; $[\alpha]_{\text{D}}^{25}$ -9.1 (c 1.2, CHCl_3); [lit.

$[\alpha]_D^{25}$ -79.1 (c 1.2, CHCl₃), ee: 11.5%; IR (CHCl₃, cm⁻¹): 3418, 3017, 2923, 2106, 1493, 1215, 1091, 1014, 754; ¹H NMR (200 MHz, CDCl₃): δ 2.81 (brs, 1H), 3.37 (d, J = 6.0 Hz, 2H), 4.78 (t, J = 2.0 and 6.0 Hz, 1H), 7.25-7.35 (m, 5H); ¹³C NMR (50 MHz, CDCl₃): δ 57.70, 72.52, 127.17, 128.68, 133.90, 138.94; Anal. C₈H₈N₃ClO requires C, 48.62; H, 4.07; N, 21.26, Cl, 17.94. Found: C, 48.55; H, 4.16; N, 21.21, Cl, 17.93%.

(R)-2-Azido-1-(4-bromophenyl)ethanol 2e: Yield 75%; m.p. 65-66°C; $[\alpha]_D^{25}$ -6.5 (c 0.9, CHCl₃); [lit. $[\alpha]_D^{25}$ -36.4 (c 0.95, CHCl₃)], ee: 18.0%; IR (CHCl₃, cm⁻¹): 3430, 3153, 3018, 2724, 2108, 1215, 1012, 980, 761; ¹H NMR (200 MHz, CDCl₃): δ 2.55 (d, J = 2.5 Hz, 1H), 3.50 (m, 2H), 4.82 (m, 1H), 7.24 (d, J = 6.5 Hz, 2H), 7.50 (d, J = 6.5 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃): δ 39.5, 73.3, 122.4, 127.5, 131.5, 139.8; MS (m/z, % RI): 275 (M⁺, 10), 273 (10), 223 (25), 221 (25), 144 (65), 143 (10), 128 (18), 65 (100); Anal. C₈H₈BrN₃O₃ requires C, 39.69; H, 3.32; N, 17.35; Br, 33.00. Found: C, 39.69; H, 3.33; N, 17.42; Br, 33.10%.

(R)-2-Azido-1-(3,4-methylenedioxyphenyl)ethanol 2f: Yield 82%; gum; $[\alpha]_D^{25}$ -3.5 (c 2.6, CHCl₃); IR (CHCl₃, cm⁻¹): 3437, 3015, 2899, 2359, 2104, 1489, 1444, 1249, 1039, 658; ¹H NMR (200 MHz, CDCl₃): δ 2.70 (brs, 1H), 3.35-3.45 (dd, J = 2.0 and 6.0 Hz, 2H), 4.70-4.80 (dd, J = 2.5 Hz, 1H), 5.96 (s, 2H), 6.75-6.90 (m, 3H); ¹³C NMR (50 MHz, CDCl₃): δ 57.70, 72.92, 100.97, 106.26, 108.10, 119.27, 134.60, 147.28, 147.69; MS (m/z, % RI): 207 (M⁺, 8), 151 (80), 150 (24), 123 (20), 122 (12), 93 (100), 75 (8), 65 (68), 64 (28); Anal. C₉H₉N₃O₃ requires C, 52.17; H, 4.37; N, 23.16. Found: C, 52.19; H, 4.33; N, 23.19%.

(R)-2-Azido-1-(1-naphthyl)ethanol 2g: Yield 76%; gum; $[\alpha]_D^{25}$ -7.2 (c 2.0, CHCl₃); IR (CHCl₃, cm⁻¹): 3460, 3018, 2926, 2105, 1215, 756, 669; ¹H NMR (200 MHz, CDCl₃): 2.80 (brs, 1H), 3.50 (m, 2H), 5.50 (m, 1H); ¹³C NMR (50 MHz, CDCl₃): δ 57.22, 70.24, 122.25, 123.43, 125.30, 125.59, 126.33, 128.57, 128.94, 129.97, 133.61, 136.00; MS (m/z, % RI): 233 (M⁺, 5), 171 (10), 165 (3), 149 (100), 121 (30), 91 (10), 65 (15); Anal. C₁₂H₁₁N₃O requires C, 67.59; H, 5.19; N, 19.70. Found: C, 67.63; H, 5.21; N, 19.78%.

(R)-3-Azido-1-(4-chloromethylphenyl)ethanol 2h: Yield 73%; gum; $[\alpha]_D^{25}$ -4.7 (c 2.0, CHCl₃); IR (CHCl₃, cm⁻¹): 3500, 3019, 2400, 2104, 1215, 756;

¹H NMR (200 MHz, CDCl₃): δ 2.53 (d, J = 4.0 Hz, 1H), 3.35-4.46 (dd, J = 4.0 and 6.0 Hz, 2H), 4.32 (s, 2H), 4.85 (brs, 1H), 7.25-7.45 (m, 4H); ¹³C NMR (50 MHz, CDCl₃): δ 54.17, 57.70, 72.81, 126.26, 128.31, 135.26, 140.70; MS (m/z, % RI): 175 (4), 161 (15), 132 (100), 119 (55), 104 (20), 91 (25), 77 (80), 63 (10), 51 (5); Anal. C₉H₁₀ClN₃O requires C, 51.07; H, 4.75; N, 19.85; Cl, 16.75. Found: C, 51.16; H, 4.75; N, 19.81; Cl, 16.79%.

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