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Catalytic asymmetric synthesis of β -triazolyl amino alcohols by asymmetric transfer hydrogenation of α -triazolyl amino alkanones

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ABSTRACT

The synthesis of optically active β -triazolyl amino alcohols was carried out via ruthenium catalyzed asymmetric transfer hydrogenation of α -triazolyl amino alkanones. This reaction proceeds under mild reaction conditions with up to 99% yield and 99.9% enantiomeric excess (ee). This protocol was applied to the synthesis of an enantiopure antitubercular agent and its arylated product with retention in enantiomeric purity. The absolute configuration at the stereogenic center of the chiral product as found to be (*S*).

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Tetrahedron

1. Introduction

In medicinal chemistry, 1,2,3 and 1,2,4-triazole nuclei have immense importance as far as their application is concerned in drug discovery.¹ Due to its pharmacologically important structural unit, the triazole nucleus can be found in many biologically active compounds and have shown anti-HIV,^{2a} anti-cancer,^{2b} anti-viral^{2c} and anti-bacterial^{2d} activities. The β -triazolyl alcohols core structure has been found to be an important structural motif and a potent pharmacophore in medicinal chemistry and is widely known for its antifungal and antimalarial properties (Fig. 1). Moreover, in recent years this core structure has exhibited antitubercular activity (Fig. 1). Kim et al. synthesized various non-chiral β-triazolyl amino alcohols derivatives⁴ and compared their antitubercular activities with the known antitubercular agent econazole.⁵ It is evident from this work that by altering the substituent on the triazole nucleus, the pharmacological activity of the antitubercular drug can be tuned. In their work, they synthesized a range of β-triazolyl amino alcohols, including the corresponding ether functionalized triazoles, and their activities were evaluated against mycobacterium tuberculosis. This study revealed some structural units to be as good as or even better than econazole. By considering the potential of non-chiral β-triazolyl amino alcohols as a potent pharmacophore, the synthesis and evaluation of its enantiopure version is required in order to facilitate its biological screening.

Efforts have been made to construct optically active β -triazolyl amino alcohols by Hua et al. via the lipase catalyzed asymmetric

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http://dx.doi.org/10.1016/j.tetasy.2017.05.012 0957-4166/© 2017 Elsevier Ltd. All rights reserved. reduction of azido alkanones followed by copper(I)-catalyzed azide-alkyne [3+2] click cycloaddition to produce optically active triazolyl alcohols (Scheme 1Aa).⁶ In this work the authors concentrated on the asymmetric reduction of α -azidoalkanones; one of the derivatives of the product was subjected to click cycloaddition to produce *β*-triazolyl amino alcohols. However, there is no account with regards to the retention of the enantiomeric purity in the cycloaddition product. Feringa et al. reported a one pot enzymatic cycloaddition to produce β-triazolyl amino alcohols with excellent enantioselectivity, however, the conversion of the starting material into the desired product was poor (Scheme 1Ab).⁷ Recently, we reported the diastereo- and enantioselective asymmetric transfer hydrogenation of α -heteroaryl amino cycloalkanones catalyzed by tethered ruthenium complexes driven by dynamic kinetic resolution (Scheme 1B).⁸ In continuation of our interests in asymmetric transfer hydrogenation, we herein have focused our attention on the enantioselective synthesis of β-triazolyl amino alcohols through asymmetric transfer hydrogenation.

2. Results and discussions

We started our optimization studies with 1-phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-one **1a** as a model substrate. The tethered Ru-TsDPEN complex⁹ was applied under the optimized reaction conditions to the reduction of α -heteroaryl amino cycloalkanones⁸ and then used for the asymmetric transfer hydrogenation of **1a**. The results were not as promising as reported in the earlier work, as the reaction proceeded with only 96% ee (Table 1, entry 1). This led us to use *N*-sulfonylated-1,2-diamines ligands¹⁰ with various ruthenium complexes in the presence of formic acid/triethylamine as a hydrogen source. Moderate conversion

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Figure 1. Examples of β -1,2,3 and 1,2,4-triazoaryl amino alkanols and β -triazoaryl amino ether as an active pharmacophore.

was obtained by (R,R)-**B** with similar enantiomeric excess as (R,R)-**A** (Table 1, entry 2). Much better conversion was observed with (R, R)-**C** and (R,R)-**D** with excellent ee in the case of (R,R)-**D** (Table 1, entries 3 and 4). Superior results were observed with catalyst (R, R)-**E** in terms of conversion (99%) and ee (99%) (Table 1, entry 5). Hence (R,R)-**E** complex was used for further optimization studies. Overall solvent studies revealed that nonpolar and polar aprotic solvents were able to furnish good to excellent conversion and enantioselectivities (Table 1, entries 6–11), whereas polar protic solvents gave only poor to moderate conversion and enantioselectivities (Table 1, entries 12–14). A significant loss in conversion was observed when the catalyst loading was reduced to 0.5 mol %, whereas 2 mol % of catalyst loading did not produce better results compared to 1 mol % (Table 1, entries 15 and 16). Increasing

the temperature with 0.5 mol % of catalyst resulted in lower conversion and enantiopurity (Table 1, entries 17 and 18). A detailed time study revealed that 12 h was the optimum reaction time and gave the best conversion and enantioselectivities (Table 1, entries 19–22).

With the optimized reaction conditions in hand, a range of α -triazolyl alkanones were hydrogenated with (*R*,*R*)-E Ru-FsDPEN complex (Table 2). The substrate class was divided in two sets depending on the substitution patterns. The first set includes substituent variation on the parent benzene ring. Next, we studied the effect of electron donating and withdrawing groups on the enantiopurity of the products obtained. Substrates **1a**, **1b** and **1c** with an electron donating group on the parent nucleus were able to furnish the corresponding products 2a, 2b and 2c with almost similar levels of enantiopurity, but a minor decrease in conversion in the case of **2c**. Excellent conversions with only a slight decrease in enantioselectivities were observed in the case of 1d. 1e and 1h with weak electron withdrawing substituents on the parent nucleus at the para- and meta-positions. However, a considerable decrease in enantioselectivity was observed with strongly electron withdrawing substituents, such as nitro group, at the para- and meta-positions. Biaryl substrates 1i and 1j were converted into the corresponding products 2i and 2j with 95.7% and 95.1% ee respectively. Heteroaryl substrates 1k and 1l furnished the products 2k and 2l with best results in set I, producing 99.9% and 98.6% ee respectively. From the literature, it is evident that by altering the substituent on triazole nucleus, the pharmacological activity of the drug molecule can be tuned. Set II includes substrates with various substituents on the triazole nucleus. Substrates 1m and 1n with a substituted phenyl group on the triazole nucleus gave products **2m** and **2n** with 97.8% and 97.2% ee respectively. When the phenyl substituent was replaced by non-aromatic cyclic substrate, 10 and 1q, and with aliphatic side chain, substrate 1p, the corresponding products 2o, 2p and 2q were obtained with excellent yield and enantioselectivity. The next



Scheme 1. Enzymatic hydrogenation and asymmetric transfer hydrogenation of α-triazoaryl amino ketones.

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Table 1

Optimization of the reaction conditions^a



Entry	Catalyst	Solvent	Catalyst (mol %)	Temp. (°C)	Time (h)	Conv. (%) ^b	ee (%) ^b
1	(<i>R</i> , <i>R</i>)- A	DCM	1	27	24	>99	96
2	(R,R)- B	DCM	1	27	24	54	96
3	(R,R)- C	DCM	1	27	24	82	95
4	(R,R)- D	DCM	1	27	24	84	99
5	(R,R)-E	DCM	1	27	24	99	99
6	(R,R)- E	DCE	1	27	24	99	94
7	(R,R)- E	Toluene	1	27	24	75	88
8	(R,R)-E	CH₃CN	1	27	24	99	92
9	(R,R)-E	1,4-Dioxane	1	27	24	80	91
10	(R,R)-E	THF	1	27	24	90	90
11	(R,R)-E	DMF	1	27	24	99	82
12	(R,R)-E	CH₃OH	1	27	24	30	79
13	(R,R)-E	C ₂ H ₅ OH	1	27	24	35	74
14	(R,R)- E	(CH ₃) ₂ CHOH	1	27	24	50	81
15	(R,R)-E	DCM	0.5	27	24	60	99
16	(R,R)-E	DCM	2	27	18	>99	99
17	(R,R)-E	DCM	0.5	40	24	85	92
18	(R,R)-E	DCM	0.5	60	24	85	87
19	(R,R)- E	DCM	1	27	02	30	97
20	(R,R)- E	DCM	1	27	06	75	99
21	(R,R)-E	DCM	1	27	12	99	99.2
22	(<i>R</i> , <i>R</i>)- E	DCM	1	27	24	99	99

^a Conditions: 0.5 mmol of **1a**, 1 mol % of (*R*,*R*)-A-E and 0.5 mL HCOOH/Et₃N (5:2) were added into solvent (3.0 mL) and the mixture was stirred at given temperature for given time.

^b The conversions and ee's were for the chiral product determined by chiral HPLC.

class of substrates, **1r**, **1s**, **1t** and **1u** replaced the 1,2,3-triazole nucleus with a 1,2,4-triazole nucleus. All four substrates were converted into the corresponding products **2r**, **2s**, **2t** and **2u** with comparable enantioselectivities in all the cases.

We demonstrated the applicability of this method to the synthesis of enantiopure hydroxyl triazole **4** based drug molecule, which is two-fold better in terms of activity when compared to the known drug molecule econazole by asymmetric transfer hydrogenation of structure **3** with 97.3% enantioselectivity. This hydroxy triazole **4** was further arylated by 4-chlorobenzyl bromide to give the ether derivative **5** of compound **4** with excellent enantiopurity (97.5%) and 62% yield (Scheme 2).

In order to determine the absolute configuration at the stereogenic center, compound **2s** was recrystallized from *n*-hexane/ IPA to give needle shaped crystals. These crystals were subjected to single crystal XRD analysis and the absolute configuration at the stereogenic centre was found to be (*S*) (See ESI) (Fig. 2). The absolute configurations of the other compounds were assigned by comparing their specific rotations with that of **2s**.

3. Conclusion

In conclusion, we have devised a route to synthesize optically active β -triazolyl amino alcohols by the ruthenium catalyzed asymmetric transfer hydrogenation of β -triazolyl amino alcohols. The optically active compounds with varying substitution pattern on triazole nucleus were obtained with high enantiomeric excess and isolated yields. This method provides access to the synthesis of optically active β -triazolyl amino alcohols and their corresponding aryl ether compounds with retention in the enantiomeric purity in the latter case. The absolute configurations of the compounds were found to be (*S*).

4. Experimental

4.1. General

All reactions were carried out in oven-dried glassware. All derivatives of acetophenone and ruthenium complexes were purchased from commercial sources. Analytical TLC was performed with silica gel plates (0.25 mm thickness). Column chromatography was performed with silica gel (40–200 mesh). NMR spectra were recorded with an (¹H NMR at 400 MHz, ¹³C NMR at 125 MHz) spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane as the internal standard and the coupling constants *J* in Hz. The reaction was monitored by GC and the products were analyzed by GC–MS and IR. HRMS were recorded on a micro-mass ESI TOF (time of flight) mass spectrometer.

4.2. General procedure for the synthesis of α-bromo alkanones

A solution of substituted alkanone (10 mmol) in CH_2Cl_2 (4 mL) was added dropwise to a solution of *n*-bromosuccinimide (2.14 g, 12 mmol, 1.2 equiv) and *p*-TsOH (0.2 g, 1 mmol, 0.1 equiv) in

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Table 2 Substrate study^a



^a Conditions: 0.5 mmol of **1a**, 1 mol % of (*R*,*R*)-**E** and 0.5 mL HCOOH/Et₃N (5:2) were added into CH₂Cl₂ (3.0 mL) and the mixture was stirred at 27 °C for 12 h. The yields were for the product isolated by preparative chromatography. The ee values were determined by chiral HPLC. The absolute configurations of all compounds were assigned by comparing the specific rotation values with the specific rotation of **2s**.



(a) RuCl[(R,R)-FsDPEN]-(p-cymene), formic acid/triethylamine, DCM, 27 °C, 12 h

(b) NaH, DMF, 0 °C, 4-chloro benzyl bromide

Scheme 2. O-arylation of optically active β-triazoaryl amino alkanols.

CH₂Cl₂ (10 mL) at 0 °C. The reaction mixture was then heated at reflux for 4 h. After the addition of H₂O (10 mL), the organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (2 × 15 mL). The combined organic layers were washed with

saturated aqueous NaHCO₃ (10 mL) and brine (10 mL), dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. Column chromatography on silica gel provided substituted- α -bromoalkanone (80–94% yield).¹²

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Figure 2. Single crystal XRD of 2s (CCDC 1548034).

4.3. Experimental procedure for the synthesis of α -triazoaryl amino alkanone

4.3.1. Typical procedure for α -triazoaryl amino alkanone synthesis via click reactions (1a–1q)

To a slurry of substituted α -bromo alkanones (1.0 mmol), substituted alkynes (1.0 mmol), sodium azide (1.5 mmol) in water/ PEG-400 (1:1, 10 mL) was added cuprous iodide (0.05 mmol) and stirred for 2 h at 25–30 °C. The water was then extracted into ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and the volatiles evaporated. The crude compound was purified by column chromatography (EtOAc/hexanes: 25/:75) (88–99% yield).^{4d}

4.3.2. Procedure for the synthesis of triazoaryl amino cycloalkanols 1r–1u, 3

To a mixture of potassium carbonate (1.5 mmol), 1,2,3- and 1,2,4-triazole (1 mmol) and 5 mL of acetonitrile at 40 °C was added a solution of α -bromo alkanones (1.0 mmol) in 5 ml of acetonitrile. The mixture was allowed to react for 5 h at 40 °C and then at reflux temperature (80 °C) for 16 h. The solid was removed by filtration and the filtrate was concentrated to dryness leaving a residue. This was dissolved in dichloromethane and washed twice with water. The organic extract was dried over sodium sulfate and purified by column chromatography (60–75% yield).¹³

4.3.2.1. 1-Phenyl-2-(4-phenyl-1*H***-1,2,3-triazol-1-yl)ethan-1-one 1a**^{4d}. White solid, mp = 140–142 °C, 247 mg, 94% yield. MS (EI, 70 eV) *m*/*z* (%): 263 (M⁺ 16.59), 206 (40.75), 130 (94.43), 103 (98.65), 77 (100) IR (ATR) \tilde{v} (cm⁻¹): 2995, 1770, 1520, 1246. ¹H NMR (400 MHz, CDCl₃) δ 8.05–7.77 (m, 5H), 7.64–7.30 (m, 6H), 5.86 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 190.3, 134.6, 133.9, 130.5, 129.1, 128.8, 128.2, 128.1, 125.9, 125.8, 121.5, 55.4.

4.3.2.2. 2-(4-Phenyl-1*H***-1,2,3-triazol-1-yl)-1-(***p***-tolyl)ethan-1one 1b^{4d}. White solid, mp = 157–159 °C, 263 mg, 95% yield. MS (EI, 70 eV)** *m/z* **(%): 277 (M⁺ 22.54), 227 (48.87), 119 (100), 77 (67.05). IR (ATR) \tilde{\nu} (cm⁻¹): 2995, 1768, 1532, 1250. ¹H NMR (400 MHz, CDCl₃) \delta 7.95–7.82 (m, 5H), 7.45–7.39 (m, 2H), 7.35– 7.29 (m, 3H), 5.84 (s, 2H), 2.43 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) \delta 189.8, 148.1, 145.8, 131.4, 130.5, 129.8, 128.8, 128.26, 128.1, 125.8, 121.2, 55.3, 21.8.**

4.3.2.3. 1-(3-Methoxyphenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) ethan-1-one 1c. Yellow solid, mp = $125-127 \,^{\circ}$ C, 291 mg, 99% yield. MS (EI, 70 eV) m/z (%):293 (M⁺ 33.47), 263 (18.67), 130 (89.21), 77 (100). IR (ATR) \tilde{v} (cm⁻¹): 3095, 1770, 1246, 1026. ¹H NMR (400 MHz, DMSO) δ 8.52–8.47 (m, 1H), 7.87–7.81 (m, 2H), 7.69–7.63 (m, 1H), 7.56–7.41 (m, 4H), 7.35–7.26 (m, 2H), 6.23 (s, 2H), 3.82 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 192.9, 159.9, 146.7, 135.8, 131.2, 130.6, 129.4, 128.3, 125.6, 123.5, 121.0, 120.7, 113.2, 56.6, 55.9. HRMS Calculated for $C_{17}H_{16}N_3O_2 \ \left[M+H\right]^+$ 294.1237, found 294.1243.

4.3.2.4. 1-(4-Fluorophenyl)-2-(4-phenyl-1*H***-1,2,3-triazol-1-yl) ethan-1-one 1d¹¹. White solid, mp = 160–162 °C, 255 mg, 91% yield. MS (EI, 70 eV) m/z (%): 281 (M+17.20), 224 (39.00), 137 (69.60), 103 (72.10), 77 (100). IR (ATR) \tilde{v} (cm⁻¹): 2982, 1770, 1531, 1234. ¹H NMR (400 MHz, CDCl₃) \delta 8.09–8.02 (m, 2H), 7.94–7.89 (m, 1H), 7.88–7.80 (m, 2H), 7.45–7.38 (m, 2H), 7.36–7.30 (m, 1H), 7.25–7.16 (m, 2H), 5.85 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) \delta 188.7, 166.5 (d,** *J* **= 257.7 Hz), 148.2, 131.0, 130.9, 130.3, 128.8, 128.2, 125.8, 121.3, 116.5 (d,** *J* **= 22.2 Hz), 55.3.**

4.3.2.5. 1-(4-Chlorophenyl)-2-(4-phenyl-1*H***-1,2,3-triazol-1-yl) ethan-1-one 1e**^{4d}. White solid, mp = 133–135 °C, 267 mg, 90% yield. MS (EI, 70 eV) *m/z* (%):297 (M⁺ 15.99), 261 (14.23), 186 (41.44), 153 (56.11), 111 (100). IR (ATR) \tilde{v} (cm⁻¹): 2933, 1770, 1528, 1239. ¹H NMR (400 MHz, CDCl₃) δ 7.98–7.79 (m, 5H), 7.54–7.37 (m, 4H), 7.37–7.28 (m, 1H), 5.83 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 189.2, 141.3, 132.2, 130.3, 129.6, 129.5, 128.8, 128.8, 128.2, 125.8, 121.3, 55.3.

4.3.2.6. 1-(Naphthalen-1-yl)-2-(4-phenyl-1*H***-1,2,3-triazol-1-yl) ethan-1-one 1j.** Pale brown solid, mp = 190–192 °C, 300 mg, 96% yield. MS (EI, 70 eV) m/z (%):313 (M⁺ 8.96), 236 (20.11), 155 (100), 144 (66.78), 105 (48.22). IR (ATR) \tilde{v} (cm⁻¹): 2995, 1759, 1526, 1246. ¹H NMR (400 MHz, DMSO) δ 8.66–8.57 (m, 2H), 8.44 –8.37 (m, 1H), 8.27–8.20 (m, 1H), 8.07–8.00 (m, 1H), 7.92–7.86 (m, 2H), 7.72–7.60 (m, 3H), 7.50–7.41 (m, 2H), 7.38–7.30 (m, 1H), 6.29 (s, 2H). ¹³C NMR (101 MHz, DMSO) δ 195.5, 146.8, 134.5, 134.0, 131.8, 131.2, 130.0, 130.0, 129.4, 129.1, 128.8, 128.3, 127.2, 125.6, 125.3, 123.6, 57.9, 55.3. HRMS Calculated for C₂₀H₁₆N₃O [M+H]⁺ 314.1288, found 314.1291.

4.3.2.7. 2-(4-Cyclohexyl-1H-1,2,3-triazol-1-yl)-1-phenylethan-1one 10. White solid, mp = 90–92 °C, 244 mg, 91% yield. MS (EI, 70 eV) m/z (%):269 (M⁺ 3.68), 213 (17.55), 136 (100), 105 (61.35). IR (ATR) \tilde{v} (cm⁻¹): 2933, 1770, 1448, 1246. ¹H NMR (400 MHz, DMSO) δ 8.09–8.00 (m, 2H), 7.81–7.65 (m, 2H), 7.62– 7.53 (m, 2H), 6.09 (s, 2H), 3.40–3.30 (m, 1H), 2.74–2.63 (m, 1H), 2.01–1.87 (m, 2H), 1.77–1.59 (m, 3H), 1.45–1.27 (m, 4H). ¹³C NMR (101 MHz, DMSO) δ 192.7, 134.6, 134.6, 129.4, 128.6, 128.6, 122.6, 56.1, 55.3, 35.1, 33.0, 26.1. HRMS Calculated for C₁₆H₂₀N₃O [M+H]⁺ 270.1601, found 270.1605.

4.3.2.8. 2-(4-Cyclopropyl-1H-1,2,3-triazol-1-yl)-1-phenylethan-1-one 1q. White solid, mp = 88–90 °C, 199 mg, 88% yield. MS (EI, 70 eV) *m/z* (%):227 (M⁺ 5.59), 170 (4.57), 120 (13.47), 105 (100), 94 (39.01). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3268, 2995, 1759, 1246. ¹H NMR (400 MHz, DMSO) δ 8.07–7.99 (m, 2H), 7.79–7.74 (m, 1H), 7.74–7.66 (m, 1H), 7.61–7.53 (m, 2H), 6.07 (s, 2H), 2.02–1.90 (m, 1H), 0.94–0.84 (m, 2H), 0.76–0.65 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 192.7, 134.6, 134.5, 129.4, 129.3, 128.6, 122.9, 56.1, 8.1, 6.9. HRMS Calculated for C₁₃H₁₄N₃O [M+H]⁺ 228.1131, found 228.1136.

4.3.2.9. 1-(2,4-Dichlorophenyl)-2-(1*H***-1,2,3-triazol-1-yl)ethan-1-one 3.** White solid, mp = 101–103 °C, 166 mg, 65% yield. MS (EI, 70 eV) m/z (%): 256 (M⁺ 23.43), 186 (69.00), 172 (37.09), 144 (31.90), 110 (100). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 2995, 1759, 1240, 861. ¹H NMR (400 MHz, CDCl₃) δ 8.21 (s, 1H), 7.95 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.39–7.33 (m, 1H), 5.60 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 192.0, 152.1, 144.8, 139.5, 133.5, 132.7, 131.6, 130.8, 127.9, 57.8. HRMS Calculated for C₁₀H₈Cl₂N₃O [M+H]⁺ 256.0039, found 256.0042.

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4.3.3. General procedure for the asymmetric transfer hydrogenation of *rac*-α-heteroaryl amino cycloalkanones 2a–2u

The α -triazoaryl amino alkanone (0.5 mmol), catalyst (2 mg, 3.2×10^{-3} mmol), DCM (5 mL) and formic acid/triethylamine (0.5 ml) azeotrope were added sequentially to the reaction tube and stirred at 27 °C. The reaction was monitored by TLC. After completion of the reaction, it was quenched by water (20 mL) and extracted with ethyl acetate (2 × 20 mL). The organic layer was dried over Na₂SO₄ and concentrated to give a residue. The residue was purified by a silica gel column eluted with pet ether and ethyl acetate to give the pure desired product (yield 82–99%).⁹

4.3.3.1. (*S*)-1-Phenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1ol 2a^{7b}. White solid, mp = 150–152 °C, 124 mg, 94% yield, 99.2% ee, $[\alpha]_D^{25}$ = +86.3 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%):265 (M⁺, 11.47), 207 (29.05), 119 (47.61), 105 (83.57), 77 (100). IR (ATR) \tilde{v} (cm⁻¹): 3251 (br), 2930, 1462, 1057. ¹H NMR (400 MHz, DMSO) δ 8.48 (s, 1H), 7.86–7.75 (m, 2H), 7.45–7.22 (m, 8H), 5.85 (d, *J* = 4.7 Hz, 1H), 5.01 (dt, *J* = 8.6, 4.4 Hz, 1H), 4.58–4.42 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 146.3, 142.5, 131.3, 129.3, 128.7, 128.1, 128.0, 126.5, 125.5, 122.5, 71.8, 57.2. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), *t*_{major} = 33.9 min, *t*_{minor} = 37.2 min.

4.3.3.2. (*S*)-2-(4-Phenyl-1*H*-1,2,3-triazol-1-yl)-1-(*p*-tolyl)ethan-**1-ol 2b**^{4d}. White solid, mp = 160–162 °C, 136 mg, 98% yield, 99.1% ee, $[\alpha]_D^{25}$ = +54.1 (*c* 0.1. CHCl₃). MS (EI, 70 eV) *m*/*z* (%):279 (M⁺, 12.16), 207 (31.20), 130 (43.59), 103 (86.14), 77 (100). IR (ATR) \tilde{v} (cm⁻¹): 3305 (br), 2920, 1440, 1080. ¹H NMR (400 MHz, CDCl₃) δ 7.82–7.69 (m, 3H), 7.41–7.14 (m, 7H), 5.17 (d, *J* = 8.7 Hz, 1H), 4.61 (dd, *J* = 14.0, 3.2 Hz, 1H), 4.42 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.37 (s, 1H), 2.34 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.4, 138.3, 137.1, 130.4, 129.5, 128.8, 128.1, 125.8, 125.6, 121.1, 72.8, 57.4, 21.1. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), *t*_{major} = 26.3 min, *t*_{minor} = 31.6 min.

4.3.3.3. (*S*)-1-(3-Methoxyphenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol 2c. White solid, mp = 140–142 °C, 121 mg, 82% yield, 94.3% ee, $[\alpha]_D^{25}$ = +63.7 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m*/ *z* (%): 295 (M⁺, 8.30), 264 (13.12), 158 (40.01), 137 (100), 107 (88.28). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3317 (br), 2955, 1370, 1078. ¹H NMR (400 MHz, DMSO) δ 8.47 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.34–7.18 (m, 2H), 6.95 (d, *J* = 5.6 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.85 (s, 1H), 4.99 (t, *J* = 5.9 Hz, 1H), 4.59–4.38 (m, 2H), 3.70 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 159.6, 146.3, 144.1, 131.3, 129.7, 129.3, 128.1, 125.5, 122.5, 118.6, 113.6, 111.9, 71.8, 57.2, 55.4. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), *t*_{major} = 9.5 min, *t*_{minor} = 10.9 min. HRMS Calculated for C₁₇H₁₈N₃O₂ [M+H]⁺ 296.1394, found 296.1400.

4.3.3.4. (*s*)-1-(4-Fluorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1yl)ethan-1-ol 2d. White solid, mp = 180–182 °C, 127 mg, 96% yield, 96.3% ee, $[\alpha]_D^{25}$ = +31.8 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m*/ *z* (%): 283 (M⁺, 15.25), 226 (17.61), 159 (24.57), 117 (100), 103 (79.78). IR (ATR) $\bar{\nu}$ (cm⁻¹): 3288 (broad), 2922, 1220, 1078, 763. ¹H NMR (400 MHz, DMSO) δ 8.46 (s, 1H), 7.85–7.74 (m, 2H), 7.42 – 7.07 (m, 7H), 5.89 (d, *J* = 4.7 Hz, 1H), 5.04 (dd, *J* = 8.1, 4.3 Hz, 1H), 4.59–4.40 (m, 2H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 159.77 (d, *J* = 201.8 Hz), 146.35, 138.64, 131.29, 129.31, 128.49 (d, *J* = 8.4 Hz), 128.16, 125.50, 122.51, 115.40 (d, *J* = 21.4 Hz), 71.14, 57.09. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 85:15, detector: 210 nm, flow rate: 0.7 mL/min), *t*_{major} = 27.5 min, *t*_{minor} = 29.9 min. HRMS Calculated for C₁₆H₁₅FN₃O [M+H]+ 284.1194, found 284.1200. **4.3.3.5.** (*S*)-1-(4-Chlorophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol 2e^{4d}. White solid, mp = 148–150 °C, 143 mg, 96% yield, 95.3% ee, $[\alpha]_D^{25} = +96.3$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 299 (M⁺, 3.12), 227 (12.21), 159 (25.25), 141 (100), 95 (20.27). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3270 (broad), 2922, 1078, 761. ¹H NMR (400 MHz, DMSO) δ 8.47 (s, 1H), 7.85–7.77 (m, 2H), 7.44–7.26 (m, 7H), 5.94 (d, *J* = 4.8 Hz, 1H), 5.04 (dt, *J* = 8.7, 4.5 Hz, 1H), 4.59 – 4.42 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 146.4, 141.4, 132.5, 131.3, 129.3, 128.6, 128.4, 128.2, 125.5, 122.5, 71.1, 56.9. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), t_{major} = 30.0 min, t_{minor} = 33.2 min.

4.3.3.6. (*S*)-1-(4-Nitrophenyl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl) ethan-1-ol $2f^{7b}$. White solid, mp = 192–194 °C, 140 mg, 91% yield, 80.0% ee, $[\alpha]_D^{25}$ = +24.3 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 310 (M⁺, 2.06), 264 (18.97), 158 (31.55), 152 (100), 77 (87.08). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3153 (br), 2917, 1517, 1354, 1084. ¹H NMR (400 MHz, DMSO) δ 8.48 (s, 1H), 8.21–8.15 (m, 2H), 7.84–7.76 (m, 2H), 7.67–7.61 (m, 2H), 7.44–7.37 (m, 2H), 7.33–7.25 (m, 1H), 6.17 (d, *J* = 4.8 Hz, 1H), 5.20 (dt, *J* = 8.5, 4.5 Hz, 1H), 4.66–4.49 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 150.0, 147.4, 146.4, 131.2, 129.3, 128.2, 127.8, 125.5, 123.8, 122.6, 71.0, 56.6. HPLC (OD-H elute: Hexanes/*i*-PrOH = 85:15, detector: 210 nm, flow rate: 0.7 mL/min), t_{minor} = 58.6 min, t_{major} = 76.0 min.

4.3.3.7. (S)-1-(3-Nitrophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) White solid, mp = 142–144 °C, 139 mg, 90% ethan-1-ol 2g. yield, 88.0% ee, $[\alpha]_D^{25}$ = +40.5 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m*/*z* (%): 310 (M⁺, 1.59), 264 (11.66), 158 (30.11), 152 (39.40), 77 (100). IR (ATR) \tilde{v} (cm⁻¹): 3148 (br), 2923, 1524, 1349, 1085. ¹H NMR (400 MHz, DMSO) δ 8.48 (s, 1H), 8.24 (d, J = 3.9 Hz, 1H), 8.16 – 8.08 (m, 1H), 7.83-7.76 (m, 3H), 7.67-7.57 (m, 1H), 7.45-7.36 (m, 2H), 7.32 – 7.26 (m, 1H), 6.18 (d, J = 4.9 Hz, 1H), 5.22 (dt, J = 8.6, 4.5 Hz, 1H), 4.69–4.51 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 148.2, 146.4, 144.7, 133.3, 131.2, 130.2, 129.3, 128.2, 125.5, 122.9, 122.6, 121.2, 70.8, 56.7. HPLC (OD-H elute: Hexanes/ *i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), $t_{\text{major}} = 51.1 \text{ min}, \quad t_{\text{minor}} = 73.2 \text{ min}.$ HRMS Calculated for $C_{16}H_{15}N_4O_3$ [M+H]⁺ 311.1139, found 311.1145.

4.3.3.8. 1-(3-Chlorophenyl)-2-(4-phenyl-1*H***-1,2,3-triazol-1-yl) ethan-1-ol 2h. White solid, mp = 176–178 °C, 140 mg, 94% yield, 96.7% ee, [\alpha]_D^{25} = +96.3 (***c* **0.1, CHCl₃). MS (EI, 70 eV)** *m/z* **(%): 299 (M⁺, 5.06), 227 (17.25), 159 (52.77), 141 (82.59), 77 (100) IR (ATR) \tilde{v} (cm⁻¹): 3271 (br), 2922, 1079, 761. ¹H NMR (400 MHz, DMSO) \delta 8.48 (s, 1H), 7.86–7.79 (m, 2H), 7.46–7.30 (m, 7H), 6.01 (d,** *J* **= 4.8 Hz, 1H), 5.06 (dt,** *J* **= 8.6, 4.4 Hz, 1H), 4.64–4.45 (m, 2H). ¹³C NMR (101 MHz, DMSO) \delta 146.4, 145.0, 133.4, 131.3, 130.6, 129.3, 128.2, 127.9, 126.4, 125.5, 125.2, 122.6, 71.2, 56.9. HPLC (OD-H elute: Hexanes/***i***-PrOH = 80:20, detector: 250 nm, flow rate: 0.7 mL/min),** *t***_{major} = 35.5 min,** *t***_{minor} = 45.8 min. HRMS Calculated for C₁₆H₁₅ClN₃O [M+H]⁺ 300.0898, found 300.0903.**

4.3.3.9. (*S*)-1-(Naphthalen-2-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol 2i. White solid, mp = 170–172 °C, 157 mg, 99% yield, 95.7% ee, $[\alpha]_D^{25} = +102.1$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 315 (M⁺, 10.66), 238 (50.03), 171 (36.44), 157 (100), 77 (92.47). IR (ATR) \tilde{v} (cm⁻¹): 3389 (br), 2922, 1233, 1059. ¹H NMR (400 MHz, DMSO) δ 8.53 (s, 1H), 7.89 (dd, *J* = 9.4, 3.4 Hz, 4H), 7.84–7.78 (m, 2H), 7.58–7.40 (m, 5H), 7.34–7.28 (m, 1H), 6.01 (d, *J* = 4.6 Hz, 1H), 5.21 (dt, *J* = 8.5, 4.4 Hz, 1H), 4.71–4.50 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 146.4, 140.0, 133.2, 133.0, 131.3, 129.3, 128.3, 128.2, 128.0, 126.6, 126.4, 125.5, 125.2, 124.8, 122.6, 77.0, 57.1. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 75:25, detector: 250 nm, flow rate: 1.0 mL/min), t_{major} = 49.1 min, t_{minor} = 57.6 min. HRMS Calculated for C₂₀H₁₈N₃O [M+H]⁺ 316.1444, found 316.1448.

4.3.3.10. (*S*)-1-(Naphthalen-1-yl)-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)ethan-1-ol 2j. White solid, mp = 195–197 °C, 152 mg, 97% yield, 95.1% ee, $[\alpha]_D^{25} = +92.3$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m*/*z* (%): 315 (M⁺, 4.75), 237 (64.09), 170 (26.51), 157 (100), 77 (83.33). IR (ATR) $\bar{\nu}$ (cm⁻¹): 3331 (br), 2922, 1246, 1077. ¹H NMR (400 MHz, DMSO) δ 8.54 (s, 1H), 7.94–7.81 (m, 6H), 7.62–7.53 (m, 1H), 7.50–7.40 (m, 4H), 7.35–7.26 (m, 1H), 6.03 (d, *J* = 4.7 Hz, 1H), 5.23 (dt, *J* = 8.5, 4.4 Hz, 1H), 4.72–4.55 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 146.4, 140.0, 133.2, 133.0, 131.3, 129.3, 128.3, 128.2, 128.0, 126.6, 126.4, 125.5, 125.2, 124.8, 122.6, 72.0, 57.1. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 250 nm, flow rate: 0.7 mL/min), *t*_{major} = 49.1 min, *t*_{minor} = 57.7 min. HRMS Calculated for C₂₀H₁₈N₃O [M+H]⁺ 316.1444, found 316.1450.

4.3.3.11. (S)-2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-1-(thiophen-2vl)ethan-1-ol 2k. White solid, $mp = 132-134 \circ C$, 124 mg, 92% yield, 99.9% ee, $[\alpha]_D^{25}$ = +48.6 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m*/ z (%): 271 (M⁺, 28.43), 145 (55.12), 117 (100), 77 (70.91). IR (ATR) \tilde{v} (cm⁻¹): 3335 (broad), 3128, 1237, 766. ¹H NMR (400 MHz, CDCl₃) δ 7.77 (s, 1H), 7.71–7.62 (m, 2H), 7.38–7.22 (m, 4H), 7.07 – 6.98 (m, 2H), 5.52 (dt, J = 7.9, 3.4 Hz, 1H), 4.72 (dd, *I* = 13.9, 3.4 Hz, 1H), 4.52 (dd, *I* = 13.9, 8.7 Hz, 1H), 4.10 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 147.3, 143.5, 130.1, 128.8, 128.1, 127.1, 125.5, 125.4, 124.6, 121.2, 69.1, 57.4. HPLC (OJ-H elute: Hexanes/i-PrOH = 75:25, detector: 250 nm, flow rate: 1.0 mL/min), $t_{\text{major}} = 40.7 \text{ min}, \quad t_{\text{minor}} = 45.8 \text{ min}.$ HRMS Calculated for $C_{14}H_{14}N_3OS [M+H]^+ 272.0852$, found 272.0862.

4.3.3.12. (S)-1-(Furan-2-yl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl) White solid, mp = 122–124 °C, 121 mg, 95% ethan-1-ol 2l. yield, 98.6% ee, $[\alpha]_{D}^{25}$ = +50.0 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 255 (M⁺, 32.68), 190 (70.18), 146 (57.08), 117 (78.31), 102 (100). IR (ATR) \tilde{v} (cm⁻¹): 3309 (br), 2922, 1240, 1081. ¹H NMR (400 MHz, CDCl₃) δ 7.71 (s, 1H), 7.63–7.54 (m, 2H), 7.42–7.36 (m, 1H), 7.34–7.22 (m, 3H), 6.36–6.27 (m, 2H), 5.27 (t, J = 4.5 Hz, 1H), 4.82 - 4.69 (m, 2H), 4.57 (dd, I = 13.9, 8.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) & 152.7, 147.2, 142.6, 130.0, 128.7, 128.1, 125.4, 121.3, 110.5, 107.6, 66.6, 54.7. HPLC (OD-H elute: Hexanes/i-PrOH = 80/20, detector: 250 nm, flow rate: 0.7 mL/min), $t_{\text{major}} = 27.6 \text{ min}, \quad t_{\text{minor}} = 33.2 \text{ min}.$ HRMS Calculated for C₁₄H₁₄N₃O₂ [M+H]⁺ 256.1081, found 256.1089.

4.3.3.13. (*S*)-1-Phenyl-2-(4-(*p*-tolyl)-1*H*-1,2,3-triazol-1-yl)ethan-**1-ol 2m**^{4a}. White solid, mp = 156–158 °C, 133 mg, 96% yield, 97.8% ee, $[\alpha]_D^{25}$ = +57.8 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 279 (M⁺, 10.61), 251 (24.59), 206 (58.83), 115 (100), 104 (49.06). IR (ATR) \tilde{v} (cm⁻¹): 3272 (br), 2920, 1455, 1079. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.43–7.29 (m, 5H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.21 (dd, *J* = 8.8, 3.1 Hz, 1H), 4.62 (dd, *J* = 14.0, 3.2 Hz, 1H), 4.42 (dd, *J* = 14.0, 8.8 Hz, 1H), 3.49 (s, 1H), 2.35 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.5, 140.1, 137.9, 129.4, 128.8, 128.5, 127.5, 125.9, 125.5, 120.8, 72.9, 57.4, 21.3. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 250 nm, flow rate: 0.7 mL/min), *t*_{major} = 29.3 min, *t*_{minor} = 37.7 min.

4.3.3.14. (*S*)-2-(4-(4-Methoxyphenyl)-1*H*-1,2,3-triazol-1-yl)-1-phenylethan-1-ol 2n^{4a}. White solid, mp = 110–112 °C, 125 mg, 85% yield, 97.2% ee, $[\alpha]_D^{25} = +96.3$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 295 (M⁺, 9.61), 236 (32.09), 187 (55.42), 107 (100), 77 (51.30). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3212 (br), 2927, 1455, 1072, 1081. ¹H NMR (400 MHz, DMSO) δ 8.47 (s, 1H), 7.80 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.29 (dd, *J* = 8.1, 3.7 Hz, 3H), 6.88 (d, *J* = 8.2 Hz, 2H), 5.75 (d, *J* = 4.6 Hz, 1H), 4.96 (dt, *J* = 8.9, 4.6 Hz, 1H), 4.51 – 4.38 (m, 2H), 3.70 (s, 3H). ¹³C NMR (101 MHz, DMSO) δ 159.1, 146.3, 134.4, 131.3, 129.3, 128.1, 127.7, 125.5, 122.5, 114.0, 71.4, 57.2, 55.5. HPLC (OJ-H elute:

Hexanes/*i*-PrOH = 80:20, detector: 250 nm, flow rate: 0.7 mL/ min), $t_{major} = 51.4$ min, $t_{minor} = 57.3$ min.

4.3.3.15. (S)-2-(4-Cyclohexyl-1H-1,2,3-triazol-1-yl)-1-phenylethan-1-ol 2o. White solid, mp = 103–105 °C, 134 mg, 99% yield, 97.5% ee, $[\alpha]_D^{25}$ = +48.7 (*c* 0.1, CHCl₃). MS (EI, 70 eV) m/z (%): 271 (M⁺, 14.44), 189 (53.65), 164 (19.41), 107 (100), 77 (65.09). IR (ATR) \tilde{v} (cm⁻¹): 3221 (br), 2850, 1448, 1064, 1034. ¹H NMR (400 MHz, DMSO) δ 7.66 (s, 1H), 7.36-7.16 (m, 5H), 5.75 (s, 1H), 4.93 (s, 1H), 4.37 (t, J = 7.4 Hz, 2H), 2.60 (dt, J = 15.3, 8.4 Hz, 1H), 1.97 – 1.80 (m, 2H), 1.74 – 1.56 (m, 3H), 1.39 – 1.13 (m, 5H). $^{13}\mathrm{C}$ NMR (101 MHz, DMSO) & 152.0, 142.6, 128.6, 127.9, 126.4, 121.6, 71.9, 56.9, 35.0, 33.0, 26.1, 26.0. HPLC (OJ-H elute: Hexanes/ *i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), $t_{\rm minor}$ = 13.0 min, $t_{\rm major}$ = 14.5 min. HRMS Calculated for C₁₆H₂₂N₃O [M+H]⁺ 272.1757, found 272.1766.

4.3.3.16. (S)-2-(4-Hexyl-1H-1,2,3-triazol-1-yl)-1-phenylethan-1-Yellow oil, 132 mg, 97% yield, 98.0% ee, $[\alpha]_{D}^{25} = +39.1$ ol 2p. (c 0.1, CHCl₃). MS (EI, 70 eV) m/z (%): 273 (M⁺, 3.71), 229 (55.70), 167 (64.10), 110 (86.02), 79 (100). IR (ATR) \tilde{v} (cm⁻¹): 3340 (br), 2921, 1459, 1074. ¹H NMR (400 MHz, DMSO) δ 7.68 (s, 1H), 7.33 -7.22 (m, 4H), 5.76 (d, J = 4.7 Hz, 1H), 4.93 (dt, J = 7.6, 4.7 Hz, 1H), 4.44–4.33 (m, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.52 (t, *J* = 7.3 Hz, 2H), 1.29-1.17 (m, 6H), 0.86-0.79 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.9, 140.4, 128.6, 128.2, 125.8, 122.2, 72.7, 57.2, 31.5, 29.3, 28.8, 25.4, 22.5, 14.0. HPLC (OJ-H elute: Hexanes/i-PrOH = 85:15, detector: 210 nm, flow rate: 0.7 mL/min), $t_{\rm minor} = 11.2 \text{ min}, \quad t_{\rm major} = 12.3 \text{ min}.$ HRMS Calculated for C₁₆H₂₄N₃O [M+H]⁺ 274.1919, found 274.1924.

4.3.3.17. (*S*)-2-(4-Cyclopropyl-1*H*-1,2,3-triazol-1-yl)-1-phenylethan-1-ol 2q. White solid, mp = 105–107 °C, 124 mg, 99% yield, 98.6% ee, $[\alpha]_D^{25}$ = +55.2 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 229 (M⁺, 19.72), 185 (11.63), 107 (67.71), 94 (100), 77 (47.41). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3272 (br), 3000, 1246, 1069. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.12 (m, 6H), 5.16 – 5.07 (m, 1H), 4.49 (d, *J* = 14.0 Hz, 1H), 4.32 (dd, *J* = 13.9, 8.6 Hz, 1H), 3.63 (s, 1H), 2.01–1.66 (m, 1H), 0.82 (dd, *J* = 56.8, 6.8 Hz, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 149.9, 140.3, 128.7, 128.3, 125.8, 121.2, 72.8, 57.3, 7.6, 6.5. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), t_{minor} = 11.9 min, t_{major} = 12.9 min. HRMS Calculated for C₁₃H₁₆N₃O [M+H]⁺ 230.1288, found 230.1293.

4.3.3.18. (*S*)-1-Phenyl-2-(1*H*-1,2,4-triazol-1-yl)ethan-1-ol **2r**^{3a}. White solid, mp = 122–124 °C, 89 mg, 95% yield, 95.2% ee, $[\alpha]_D^{25} = +69.7$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 189 (M⁺, 11.43), 161 (21.53), 107 (100), 77 (43.05). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3202 (br), 2951, 1469, 1071. ¹H NMR (400 MHz, CDCl₃) δ 7.94 (s, 1H), 7.79 (s, 1H), 7.39–7.21 (m, 5H), 5.04 (dd, *J* = 8.6, 3.5 Hz, 1H), 4.41–4.28 (m, 2H), 4.24 (d, *J* = 8.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 151.6, 143.9, 140.3, 128.7, 128.3, 125.8, 72.2, 56.8. HPLC (OD-H elute: Hexanes/*i*-PrOH = 80:20, detector: 210 nm, flow rate: 0.7 mL/min), *t*_{minor} = 12.6 min, *t*_{major} = 13.4 min.

4.3.3.19. (*S*)-1-(4-Chlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethan-**1-ol 2s**^{3a}. White solid, mp = 120–122 °C, 109 mg, 98% yield, 96.4% ee, $[\alpha]_D^{25}$ = +83.4 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 223 (M⁺, 17.08), 140 (42.87), 111 (100), 68 (53.31). IR (ATR) $\bar{\nu}$ (cm⁻¹): 3200 (br), 2922, 1464, 1075, 760. ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.85 (s, 1H), 7.34 – 7.23 (m, 4H), 5.06 (dd, *J* = 8.6, 3.3 Hz, 1H), 4.32 (dd, *J* = 13.9, 3.2 Hz, 1H), 4.21 (dd, *J* = 14.0, 8.4 Hz, 1H), 4.14 (s, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 151.8, 143.9, 138.6, 134.2, 128.9, 127.1, 71.7, 56.6. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 85:15, detector: 210 nm, flow rate: 0.7 mL/min), t_{minor} = 10.7 min, t_{major} = 11.5 min. 8

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4.3.3.20. (*S*)-1-(Naphthalen-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethan- **1-ol 2t**^{3b}. White solid, mp = 134–136 °C, 112 mg, 94% yield, 96.8% ee, $[\alpha]_D^{25}$ = +64.6 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 239 (M⁺, 8.41), 157 (100), 127 (71.65), 68 (54.10). IR (ATR) $\tilde{\nu}$ (cm⁻¹): 3202 (br), 2923, 1442, 1071. ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 7.84 – 7.74 (m, 4H), 7.51 – 7.36 (m, 3H), 5.19 (dd, *J* = 8.6, 3.3 Hz, 1H), 4.56 (s, 1H), 4.38 (dd, *J* = 14.0, 3.4 Hz, 1H), 4.28 (dd, *J* = 14.0, 8.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 151.6, 143.9, 137.6, 133.2, 128.6, 128.0, 127.7, 126.4, 126.3, 124.9, 123.4, 72.3, 56.8. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 80/20, detector: 250 nm, flow rate: 0.7 mL/min), *t_{minor}* = 14.5 min, *t_{major}* = 15.9 min.

4.3.3.21. (*S*)-1-(Thiophen-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)ethan-1ol 2u. White solid, mp = 138–140 °C, 90 mg, 93% yield, 96.0% ee, $[\alpha]_D^{25} = +44.2$ (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 195 (M⁺, 9.19), 127 (50.98), 113 (100), 83 (46.75). IR (ATR) \tilde{v} (cm⁻¹): 3267 (br), 2921, 1481, 1081. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (*s*, 1H), 7.86 (*s*, 1H), 7.31–7.23 (m, 1H), 7.01–6.92 (m, 2H), 5.36 (dd, *J* = 8.0, 3.7 Hz, 1H), 4.45 (d, *J* = 17.5 Hz, 1H), 4.41–4.31 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 151.8, 144.0, 143.6, 127.0, 125.4, 124.4, 68.6, 56.7. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 90:10, detector: 210 nm, flow rate: 0.7 mL/min), $t_{minor} = 8.7 min$, $t_{major} = 9.1$ min. HRMS Calculated for C₈H₁₀N₃OS [M+H]⁺ 196.0539, found 196.0543.

4.3.3.22. (S)-1-(2,4-Dichlorophenyl)-2-(1*H***-1,2,3-triazol-1-yl) ethan-1-ol 4⁵. White solid, mp = 130–132 °C, 126 mg, 98% yield, 97.3% ee, [\alpha]_D^{25} = +51.0 (***c* **0.1, CHCl₃). MS (EI, 70 eV)** *m/z* **(%): 258 (M⁺, 31.42), 174 (49.22), 144 (100), 68 (48.21). IR (ATR) \tilde{\nu} (cm⁻¹): 3302 (br), 2918, 1462, 1079, 759. ¹H NMR (400 MHz, CDCl₃) \delta 8.04 (s, 1H), 7.97 (s, 1H), 7.46 (d,** *J* **= 8.4 Hz, 1H), 7.39 (d,** *J* **= 2.1 Hz, 1H), 7.26 (dd,** *J* **= 8.4, 2.1 Hz, 1H), 5.41 (d,** *J* **= 7.3 Hz, 1H), 4.52 (dd,** *J* **= 14.0, 2.4 Hz, 1H), 4.21 (dd,** *J* **= 14.1, 7.7 Hz, 1H), 3.80 (d,** *J* **= 3.7 Hz, 1H). ¹³C NMR (101 MHz, DMSO) \delta 146.8, 139.1, 131.5, 129.8, 127.3, 124.5, 123.6, 122.9, 64.0, 50.1. HPLC (0]-H elute: Hexanes/***i***-PrOH = 90:10, detector: 210 nm, flow rate: 0.7 mL/min),** *t***_{minor} = 30.1 min,** *t***_{major} = 31.9 min.**

4.4. O-Arylation of optically active $\beta\text{-triazoaryl}$ amino alkanols

To a stirred solution of 1-(2,4-dichlorophenyl)-2-(1*H*-1,2,3-triazol-1-yl)ethan-1-ol **4** (0.2 mmol) in dimethylformamide (DMF) (0.5 mL) at 0–5 °C was added sodium hydride (60% oil, 0.3 mmol) in small portions over 10 min. After stirring for 30 min, 4-chloro benzyl bromide (0.3 mmol) was added and then stirring was continued at 27 °C for 4 h. The reaction mixture was quenched with ice cold water (1 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to obtain the crude product, which was purified by preparative chromatography to produce 1-(2-((4-chlorobenzyl)oxy)-2-(2,4-dichlorophenyl) ethyl)-1*H*-1,2,3-triazole (5) in 50% yield (38 mg).

4.4.1. (S)-1-(2-((4-Chlorobenzyl)oxy)-2-(2,4-dichlorophenyl) ethyl)-1H-1,2,3-triazole $\mathbf{5}^5$

Pale yellow solid, mp = 120–122 °C, 47 mg, 62% yield, 97.5% ee, $[\alpha]_{2}^{D^5}$ = +44.6 (*c* 0.1, CHCl₃). MS (EI, 70 eV) *m/z* (%): 382 (M⁺, 1.24), 257 (26.08), 173 (100), 144 (94.78), 125 (45.91). IR (ATR) $\bar{\nu}$ (cm⁻¹): 3260 (br), 2926, 1467, 1085, 765. ¹H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 7.73 (d, *J* = 7.6 Hz, 2H), 7.44–7.24 (m, 6H), 5.56 (s, 2H), 5.01 (dt, *J* = 7.4, 4.6 Hz, 1H), 4.55–4.43 (m, 2H). ¹³C NMR (101 MHz, DMSO) δ 146.5, 140.8, 139.6, 133.1, 132.6, 130.7, 129.4, 128.6, 128.4, 128.3, 125.5, 122.5, 71.0, 56.7, 54.9. HPLC (OJ-H elute: Hexanes/*i*-PrOH = 87/13, detector: 250 nm, flow rate: 0.7 mL/min), *t*_{minor} = 45.3 min, *t*_{major} = 48.0 min.

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A. Supplementary data

Copies of ¹H, ¹³C NMR, HRMS and HPLC spectra of substrate and products. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10. 1016/j.tetasy.2017.05.012.

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