An Enantiospecific Approach to Triazolylalanine Derivatives

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Abstract: An efficient and practical route to an enantiomerically pure aziridinylmethyl azide is described that can be transformed to the corresponding triazole by a copper-catalysed [3+2] alkyne cycloaddition reaction. The transformation of these intermediates into triazolylalanine-type derivatives by aziridine ring-opening reactions is also described.

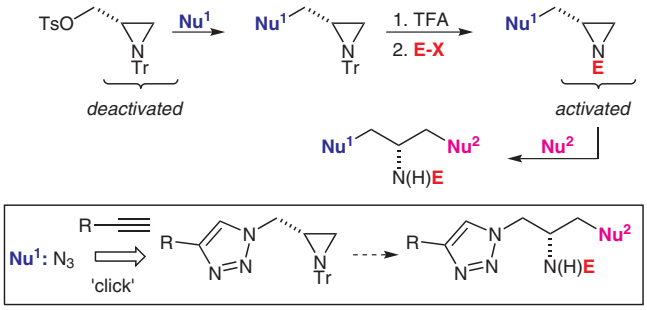
Key words: copper catalyst, 1,2,3-triazole, aziridine, cycloaddition, ring-opening reaction, alanine

The ability of aziridines to function as reactive electrophiles has made this a popular class of synthetic intermediates in organic synthesis.[1] Recent studies in our laboratories have uncovered an efficient and enantiospecific route to aziridines via the homologation of an aziridinylmethyl tosylate by a variety of Grignard reagents in the presence of a copper catalyst.[2] Notably, the aziridine is protected with a non-activating trityl group that allows chemoselective substitution of the primary alkyl tosylate, whilst subsequently providing the opportunity to activate the ring towards nucleophilic addition via a one-pot deprotection–sulfonylation/acylation protocol (Scheme 1). Among the potential substitution processes envisaged in step 1 of Scheme 1, the use of azide was particularly appealing because the intermediate aziridine could be converted into a range of enantiomerically pure triazole derivatives by sequential [3+2]-cycloaddition–ring activation/opening processes. This strategy would represent a convenient method for the synthesis of arrays of 1,2,3-triazoles, an increasingly popular class of pharmacophores in drug discovery research,[3] and would provide a useful alternative to existing approaches to amino acid based derivatives of these heterocycles.[4] We report herein our studies towards this end.

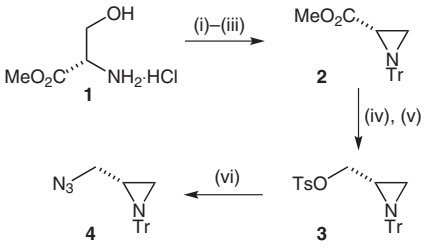
As outlined in Scheme 2, we developed a simple and practical method for the synthesis of the key tosylate intermediate **3**,[5] this route provided the compound on ~50-gram scale from (*S*)-serine methyl ester hydrochloride (**1**), and could be carried out without recourse to chromatographic purification. Finally, azide substitution of **3** took place in high yield to provide compound **4**.[2]

With enantiopure azide **4** in hand, we turned out attention to the cycloaddition reactions. 1,3-Dipolar cycloadditions of azides was studied in detail by Huisgen,[6] but the thermally promoted reaction with terminal alkynes generally provides a mixture of 1,4- and 1,5-substituted triazole products. The emergence of the 'click' chemistry[7] concept has however resulted in significant advances in this field and mild, efficient metal-catalyzed variants for both terminal and internal alkyne substrates are now available.[8] We decided to employ copper-catalysed cycloaddition methodology to carry out the reaction of **4** with a series of commercially available alkynes. As highlighted in Table 1, we were pleased to find that the cycloaddition of **4** proceeded smoothly with alkynes bearing a selection of alkyl and aryl substituents. A single regioisomer was provided in good to high yield in each case.

Our next goal was to perform the protecting group switch on the aziridine to activate the three-membered ring to nucleophilic addition. Our preliminary studies on this process had used a large excess of trifluoroacetic acid to remove the trityl group.[2] We wanted to reduce the loading of Brønsted acid and were attracted to the conditions reported by Vedejs and co-workers, who employed a small excess of trifluoroacetic acid in the presence of triethylsi-



Scheme 1 Enantiospecific approach to triazolylalanine derivatives



Scheme 2 Synthesis of key azide intermediate **4**. *Reagents and conditions*: (i) TrCl, Et_3N, CH_2Cl_2, r.t., 16 h, 83%; (ii) TsCl, pyridine, 0 °C, 8 h, 74%; (iii) Et_3N, THF, reflux, 16 h, 73%; (iv) $LiAlH_4$, Et_2O, r.t., 4 h, 91%; (v) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, r.t., 16 h, 82%; (vi) NaN_3 (5 equiv), DMF, 60 °C, 16 h, 96%.

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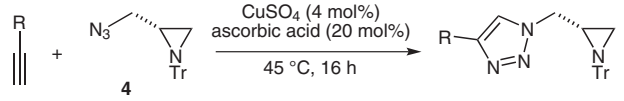
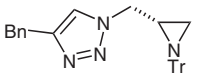
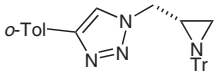
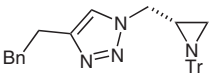
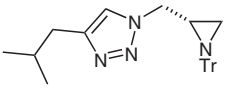
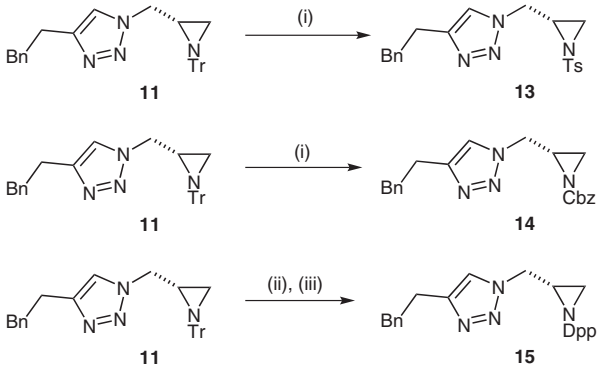
Table 1 [3+2] Cycloadditions of Azide **4** and Terminal Alkynes



5–8 9–12

Entry	Substrate	R	Product		Yield (%)
1	**5**	Bn	**9**		71
2	**6**	*o*-Tol	**10**		61
3	**7**	$(CH_2)_2Ph$	**11**		75
4	**8**	*i*-Bu	**12**		86

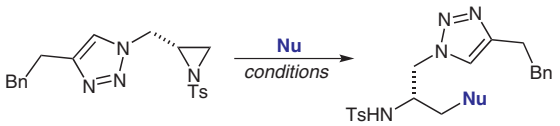
lane to trap the trityl cation.[9] In the event, we were able to successfully apply this technique to convert triazole **11** into tosyl-protected aziridine **13** after addition of triethylamine and tosyl chloride. Moreover, we were able to extend these conditions for the one-pot protecting group switch to prepare the benzyloxycarbonyl-protected aziridine **14**, however, attempts to generate a diphenylphosphoryl (Dpp)-protected aziridine **15** using the one-pot method proved to be unsatisfactory. Nonetheless, **15** could be generated by simply isolating the crude free aziridine and converting it into **15** under standard conditions (Scheme 3).



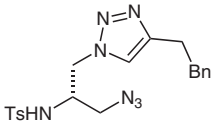
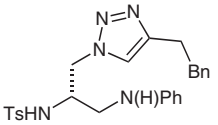
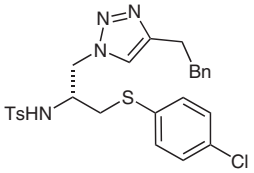
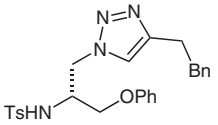
Scheme 3 Deprotection–protection of aziridine **11**. *Reagents and conditions*: (i) (a) TFA (4 equiv), Et_3SiH (4 equiv), CH_2Cl_2, 0 °C, 0.5 h, (b) Et_3N (7 equiv), RCl, (1.1 equiv), r.t., 4 h; R = Ts, 73%; R = Cbz, 85%; (ii) (a) TFA (4 equiv), Et_3SiH (4 equiv), CH_2Cl_2, 0 °C, 0.5 h, (b) Et_3N (5 equiv); (iii) Et_3N (1 equiv), $Ph_2P(O)Cl$, (1.1 equiv), CH_2Cl_2, r.t., 16 h, 46%.

Our final goal was to demonstrate that this approach could be employed to generate new enantiomerically pure scaffolds after nucleophilic aziridine ring cleavage. Accordingly, we opted to carry out ring-opening reactions of aziridine **13** with a selection of nucleophiles. As outlined in Table 2, a series of efficient ring-opening reactions were achieved that allowed the incorporation of N-, S-, or O-centred nucleophiles in good to excellent yield.[10]

Table 2 Ring-Opening Reactions of Aziridine **13**



13 16–19

Entry	Reagents and conditions	Product		Yield (%)
1	$TMSN_3$, DMSO, 40 °C, 4 h	**16**		70
2	$PhNH_2$, DMSO, 60 °C, 4 h	**17**		95
3	4-ClC_6H_4SH, DMSO, 60 °C, 4 h	**18**		95
4	PhOH, Cs_2CO_3, DMSO, 70 °C, 16 h	**19**		73

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In conclusion, we have developed a flexible enantiospecific strategy to triazolylalanine derivatives by a copper-catalysed [3+2] cycloaddition of alkynes with an enantiomerically pure aziridinylmethyl azide. Activation of the aziridine by a protecting group switch allows a series of nucleophiles to be introduced via aziridine ring-opening reactions.

Flash chromatography was performed on silica gel (BDH Silica Gel 60 43–60, or Fluorochem Davisil silica gel 43–60). The solvent system used was a gradient of petroleum ether–EtOAc (90:10) increasing in polarity to EtOAc. TLC was performed on aluminium-backed plates pre-coated with silica gel (0.2 mm, Merck DC-alufolien Kieselgel 60 F254), which were developed using standard visualizing agents: UV light or $KMnO_4$. $^1H/^{13}C$ NMR spectra were recorded on Bruker AC-250 or Av1-250 instruments or AMX-400 or AV1-400 instruments. ^1H: solvent resonance as the internal standard ($CHCl_3$:δ = 7.27). ^{13}C: complete proton decoupling, solvent resonance as the internal standard ($CDCl_3$: δ = 77.0). FT-IR spectra were recorded on a Perkin-Elmer Paragon 100 FT-IR spectrophotometer; samples were recorded as thin films using NaCl plates, as a CH_2Cl_2 soln or as a KBr disc. LR-MS were recorded on Micromass Autospec, operating in EI, CI, or FAB mode; or a Perkin-Elmer Turbomass Bench top GC-MS operating in either EI or CI mode. HRMS recorded for accurate mass analysis, were performed on either a MicroMass LCT (TOF ESI+ mode) or a MicroMass Prospec (FAB+, EI+, or CI+ mode). Optical rotation values were recorded on a Perkin-Elmer 241 automatic polarimeter at 589 nm (Na D-line) with a path length of either 1 dm or 0.1 dm, and are given in 10^{-1} deg·cm^2·g^{-1} with concentrations (*c*) quoted in g/100 mL. Melting points were performed on recrystallized solids and recorded on a Gallenkamp melting point apparatus and are uncorrected. Compounds **1**, **2**,[5] and **3**, **4**[2] were prepared according to literature procedures.

4-Benzyl-1-{[(*S*)-1-tritylaziridin-2-yl]methyl}-1*H*-1,2,3-triazole (9); Typical Procedure

To a soln of **4** (0.2 g, 0.59 mmol) and 1-(prop-2-ynyl)benzene (73 μL, 0.59 mmol) in *t*-BuOH–H_2O (1:1, 2.26 mL) was added 1 M ascorbic acid in H_2O (120 μL, 0.118 mmol, 20 mol%), followed by 0.3 M $CuSO_4$ in H_2O (80 μL, 0.024 mmol). The mixture was heated to 45 °C overnight. Upon cooling, the mixture was extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to provide crude **9**. Purification by flash chromatography provided **9** (192 mg, 71%) as a clear oil.

$[\alpha]_D^{22}$ –15.3 (*c* 1.3, $CHCl_3$).

FT-IR (film): 3057 (w), 2932 (w), 1450 (m), 1448 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.0 Hz, 1 H), 1.66–1.73 (m, 1 H), 1.75 (d, *J* = 3.0 Hz, 1 H), 4.05 (s, 2 H), 4.35 (dd, *J* = 14.0, 5.5 Hz, 1 H), 4.76 (dd, *J* = 14.0, 5.5 Hz, 1 H), 7.16–7.44 (m, 21 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.8, 32.0, 32.3, 52.8, 74.0, 121.5, 126.4, 126.8, 127.6, 128.6, 128.7, 129.2, 139.1, 143.9, 147.8.

HRMS (TOF ESI): *m*/*z* [M + H$^+$] calcd for $C_{31}H_{29}N_4$: 457.2392; found: 457.2378.

4-(2-Tolyl)-1-{[(*S*)-1-tritylaziridin-2-yl]methyl}-1*H*-1,2,3-triazole (10)

Following the typical procedure, **4** (1.5 g, 4.41 mmol), 2-tolylacetylene (0.52 mL, 4.41 mmol), 1 M ascorbic acid in H_2O (0.88 mL, 0.88 mmol, 20 mol%), and 0.3 M $CuSO_4$ in H_2O (0.59 mL, 0.18 mmol,) in *t*-BuOH–H_2O (1:1, 17 mL) were heated overnight. Purification provided **10** (1.22 g, 61%) as a colourless solid; mp 81–84 °C.

$[\alpha]_D^{22}$ –8.3 (*c* 1.2, $CHCl_3$).

FT-IR (film): 3027 (w), 2928 (w), 2360 (w), 1487 (m), 1448 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.0 Hz, 1 H), 1.83–1.88 (m, 2 H), 2.43 (s, 3 H), 4.54 (dd, *J* = 14.0, 5.5 Hz, 1 H), 4.88 (dd, *J* = 14.0, 5.0 Hz, 1 H), 7.21–7.73 (m, 20 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.3, 25.8, 31.9, 52.7, 74.1, 121.9, 126.0, 126.9, 127.6, 128.1, 128.9, 129.2, 129.9, 130.8, 135.4, 143.9, 147.1.

HRMS (TOF ESI): *m*/*z* [M + H$^+$] calcd for $C_{31}H_{29}N_4$: 457.2392; found: 457.2396.

4-Phenethyl-1-{[(*S*)-1-tritylaziridin-2-yl]methyl}-1*H*-1,2,3-triazole (11)

Following the typical procedure, **4** (1.85 g, 5.44 mmol), 4-phenylbut-1-yne (0.76 mL, 5.44 mmol), 1 M ascorbic acid in H_2O (1.08 mL, 1.09 mmol, 20 mol%), and 0.3 M $CuSO_4$ in H_2O (0.73 mL, 0.22 mmol,) in *t*-BuOH–H_2O (1:1, 20 mL) was heated overnight. Purification provided **11** (1.95 g, 76%) as a colourless solid; mp 78–81 °C.

$[\alpha]_D^{22}$ –23.8 (*c* 2.5, $CHCl_3$).

FT-IR (film): 3059 (m), 2930 (m), 1596 (m), 1490 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.0 Hz, 1 H), 1.71–1.77 (m, 2 H), 2.94–3.05 (m, 4 H), 4.34 (dd, *J* = 14.0, 5.5 Hz, 1 H), 4.78 (dd, *J* = 14.0, 4.0 Hz, 1 H), 7.16–7.48 (m, 21 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.9, 27.4, 31.8, 35.5, 52.7, 74.0, 121.0, 126.0, 126.9, 127.6, 128.3, 128.4, 129.2, 141.2, 143.9, 144.0.

HRMS (TOF ESI): *m*/*z* [M + H$^+$] calcd for $C_{32}H_{31}N_4$: 471.2571; found: 471.2549.

4-Isobutyl-1-{[(*S*)-1-tritylaziridin-2-yl]methyl}-1*H*-1,2,3-triazole (12)

Following the typical procedure, **4** (1.5 g, 4.41 mmol), 4-methylpent-1-yne (0.52 mL, 4.41 mmol), 1 M ascorbic acid in H_2O (0.88 mL, 0.88 mmol, 20 mol%), and 0.3 M $CuSO_4$ in H_2O (0.59 mL, 0.18 mmol) in *t*-BuOH–H_2O (1:1, 17 mL) was heated overnight. Purification provided **12** (1.59 g, 86%) as a colourless solid; mp 72–75 °C.

$[\alpha]_D^{22}$ –17.0 (*c* 1.1, $CHCl_3$).

FT-IR (film): 3029 (w), 2955 (m), 1594 (w), 1486 (m) 1447 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 4.0 Hz, 3 H), 0.94 (d, *J* = 4.0 Hz, 3 H), 1.21 (d, *J* = 4.0 Hz, 1 H), 1.73 (d, *J* = 6.0 Hz, 1 H), 1.74–1.79 (m, 1 H), 1.89–1.99 (m, 1 H), 2.56 (dd, *J* = 14.5, 2.0 Hz, 1 H), 2.58 (dd, *J* = 14.5, 2.0 Hz, 1 H), 4.41 (dd, *J* = 14.0, 5.5 Hz, 1 H), 4.83 (dd, *J* = 14.0, 5.0 Hz, 1 H), 7.21–7.48 (m, 16 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.2, 22.3, 25.7, 28.6, 31.9, 34.7, 52.4, 74.0, 121.4, 126.9, 127.6, 129.2, 144.0, 147.2.

HRMS (TOF ESI): *m*/*z* [M + H$^+$] calcd for $C_{28}H_{31}N_4$: 423.2549; found: 423.2531.

4-Phenethyl-1-{[(*R*)-1-tosylaziridin-2-yl]methyl}-1*H*-1,2,3-triazole (13); Typical Procedure

To a soln of **11** (0.2 g, 0.42 mmol) in CH_2Cl_2 (8.8 mL) at 0 °C was added Et_3SiH (0.272 mL, 1.7 mmol, 4 equiv) and TFA (0.126 mL, 1.7 mmol, 4 equiv). After 30 min, Et_3N (0.415 mL, 2.98 mmol, 7 equiv) was added and the mixture was stirred for a further 10 min upon which TsCl (85 mg, 0.45 mmol, 1.05 equiv) was added. The mixture was stirred at 0 °C for 4 h and $NaHCO_3$ soln was added. The soln was extracted with CH_2Cl_2 and the combined organic extracts

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were dried ($MgSO_4$) and concentrated in vacuo to provide crude **13**. Purification by flash chromatography provided **13** (0.12 g, 73%) as a colourless solid; mp 82–85 °C.

$[\alpha]_D^{22}$ –20.7 (*c* 1.4, $CHCl_3$).

FT-IR (film): 3027 (w), 2859 (w), 1597 (m), 1495 (m), 1454 (m), 1326 (s), 1226 (m), 1162 cm^{-1} (s).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.16 (d, *J* = 4.0 Hz, 1 H), 2.44 (s, 3 H), 2.75 (d, *J* = 7.0 Hz, 1 H), 2.87–2.98 (m, 4 H), 3.12–3.21 (m, 1 H), 4.09 (dd, *J* = 15.0, 7.0 Hz, 1 H), 4.67 (dd, *J* = 15.0, 4.0 Hz, 1 H), 7.16–7.74 (m, 10 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.7, 27.3, 31.2, 35.5, 38.0, 50.4, 121.3, 126.1, 128.0, 128.3, 128.4, 129.8, 134.0, 141.0, 145.0, 147.5.

HRMS (TOF ESI): *m*/*z* [M + H^+] calcd for $C_{20}H_{23}N_4O_2S$: 383.1542; found: 383.1526.

Benzyl (*S*)-2-[(4-Phenethyl-1*H*-1,2,3-triazol-1-yl)methyl]aziridine-1-carboxylate (14)

Following the typical procedure, Et_3SiH (0.068 mL, 0.42 mmol, 4 equiv) and TFA (0.032 mL, 0.42 mmol, 4 equiv) were added to a soln of **11** (0.05 g, 0.11 mmol) in CH_2Cl_2 (2.2 mL). After 30 min, Et_3N (0.10 mL, 0.74 mmol, 7 equiv) and CbzCl (18 μL, 0.13 mmol, 1.2 equiv) were added. Purification provided **14** (34 mg, 85%) as a yellow oil.

$[\alpha]_D^{22}$ –16.6 (*c* 1.2, $CHCl_3$).

FT-IR (film): 3029 (w), 2961 (m), 2851 (w), 1720 (s), 1597 (m), 1497 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.10 (d, *J* = 3.5 Hz, 1 H), 2.51 (d, *J* = 6.5 Hz, 1 H), 2.87–2.92 (m, 1 H), 2.94–3.05 (m, 4 H), 4.23 (dd, *J* = 14.5, 7.0 Hz, 1 H), 4.67 (dd, *J* = 14.5, 4.0 Hz, 1 H) 5.11 (d, *J* = 12.0 Hz, 1 H), 5.15 (d, *J* = 12.0 Hz, 1 H), 7.18–7.43 (m, 11 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.4, 29.8, 35.4, 36.0, 51.4, 68.6, 121.5, 126.0, 128.2, 128.3, 128.4, 128.6, 128.7, 135.2, 141.1, 147.6, 162.3.

HRMS (TOF ESI): *m*/*z* [M + H^+] calcd for $C_{21}H_{23}N_4O_2$: 363.1821; found: 363.1831.

1-{[(*R*)-1-(Diphenylphosphoryl)aziridin-2-yl]methyl}-4-phenethyl-1*H*-1,2,3-triazole (15)

To a soln of **11** (0.2 g, 0.42 mmol) in CH_2Cl_2 (8.8 mL) at 0 °C was added Et_3SiH (0.272 mL, 1.7 mmol, 4 equiv) and TFA (0.126 mL, 1.7 mmol, 4 equiv). After 30 min, Et_3N (0.370 mL, 2.13 mmol, 5 equiv) was added and the mixture stirred for a further 10 min upon which $NaHCO_3$ soln was added. The soln was extracted with Et_2O and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide crude free aziridine. The crude residue was dissolved in CH_2Cl_2 (2.1 mL) and cooled to 0 °C. Et_3N (0.058 mL, 0.42 mmol, 1 equiv) and $Ph_2P(O)Cl$ (0.080 mL, 0.42 mmol, 1 equiv) were added to the mixture. The mixture was left to warm to r.t. overnight upon which $NaHCO_3$ soln was added. The soln was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide crude **15**. Purification by flash chromatography provided **15** (0.08 g, 46%) as a yellow oil.

$[\alpha]_D^{22}$ +10.0 (*c* 1.0, $CHCl_3$).

FT-IR (film): 3060 (m), 3027 (m), 2859 (m), 2228 (s), 1603 (m), 1591 (m), 1552 (m), 1496 (m), 1438 (s), 1334 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.06 (dd, *J* = 12.5, 3.0 Hz, 1 H), 2.64 (dd, *J* = 17.0, 6.0 Hz, 1 H), 2.84–2.87 (m, 4 H), 3.11–3.19 (m, 1 H), 4.27 (dd, *J* = 14.0, 7.0 Hz, 1 H), 4.55 (dd, *J* = 14.0, 3.0 Hz, 1 H), 7.13–7.92 (m, 16 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.8, 28.2, 34.2, 35.7, 52.3, 121.1, 126.5, 128.7–129.1 (m, 2 C), 131.7–131.9 (m, 2 C), 132.5 (d, *J* = 145 Hz), 131.5, 132.5, 141.5, 147.8.

HRMS (TOF ESI): *m*/*z* [M + H^+] calcd for $C_{25}H_{26}N_4OP$: 429.1844; found: 429.1857.

1-[(*R*)-3-Azido-2-(tosylamino)propyl]-4-phenethyl-1*H*-1,2,3-triazole (16); Typical Procedure

To a soln of **13** (0.1 g, 0.26 mmol) in DMSO (2.1 mL) was added $TMSN_3$ (35 μL, 0.26 mmol); the mixture was heated to 40 °C for 4 h. Upon cooling, H_2O was added, the soln was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide crude **16**. Purification by flash chromatography provided **16** (0.078 g, 70%) as a clear oil.

$[\alpha]_D^{22}$ –24.9 (*c* 1.2, $CHCl_3$).

FT-IR (film): 3027 (w), 2916 (w), 2106 (s), 1599 (w), 1453 (w), 1329 (m), 1219 cm^{-1} (m).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.91–3.03 (m, 4 H), 3.23–3.38 (m, 2 H), 3.64–3.76 (m, 1 H), 4.29–4.44 (m, 2 H), 5.97 (br, 1 H), 7.14–7.75 (m, 10 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5, 27.1, 35.4, 50.5, 51.5, 52.5, 122.9, 126.2, 126.9, 128.4, 128.5, 129.9, 136.9, 140.8, 144.0, 147.2.

HRMS (TOF ESI): *m*/*z* [M + H^+] calcd for $C_{20}H_{24}N_7O_2S$: 426.1712; found: 426.1695.

4-Phenethyl-1-[(*S*)-3-(phenylamino)-2-(tosylamino)propyl]-1*H*-1,2,3-triazole (17)

Following the typical procedure, **13** (0.1 g, 0.26 mmol) and aniline (24 μL, 0.26 mmol) in DMSO (2.1 mL) were heated to 60 °C for 4 h. Purification provided **17** (0.12 g, 95%) as a yellow solid; mp 84–88 °C.

$[\alpha]_D^{22}$ –13.0 (*c* 1.5, $CHCl_3$).

FT-IR (film): 3027 (w), 2917 (w), 1919 (w), 1603 (s), 1497 (m), 1453 (m), 1327 cm^{-1} (s).

^1H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.99–3.01, (m, 6 H), 3.67–3.78 (m, 1 H), 4.00 (br, 1 H), 4.41 (dd, *J* = 14.5, 4.5 Hz, 1 H), 4.54 (dd, *J* = 14.5, 4.0 Hz, 1 H), 5.46 (br, 1 H), 6.29–7.73 (m, 15 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5, 27.2, 35.4, 44.4, 51.1, 51.6, 112.7, 118.1, 123.2, 126.1, 127.1, 128.4, 128.5, 129.3, 129.8, 136.5, 141.0, 143.9, 146.6, 147.2.

HRMS (TOF ESI): *m*/*z* [M + H^+] calcd for $C_{26}H_{30}N_5O_2S$: 476.2120; found: 476.2137.

1-[(*R*)-3-(4-Chlorophenylsulfanyl)-2-(tosylamino)propyl]-4-phenethyl-1*H*-1,2,3-triazole (18)

Following the typical procedure, **13** (0.05 g, 0.13 mmol) and 4-chlorothiophenol (18 mg, 0.13 mmol) in DMSO (2.1 mL) were heated at 60 °C for 4 h. Purification provided **18** (65 mg, 95%) as a clear oil.

$[\delta]_D^{22}$ –18.0 (*c* 1.3, $CHCl_3$).

FT-IR (film): 3026 (w), 2091 (w), 1497 (m), 1477 (m), 1329 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 2.91–3.05 (m, 6 H), 3.51–3.59 (m, 1 H), 4.47 (dd, *J* = 14.0, 4.5 Hz, 1 H), 4.61 (dd, *J* = 14.0, 3.5 Hz, 1 H), 6.17 (br, 1 H), 7.03 (d, *J* = 8.5 Hz, 2 H), 7.17–7.31 (m, 10 H), 7.64 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5, 27.2, 35.4, 35.6, 51.3, 51.9, 123.2, 126.1, 127.1, 128.4, 128.5, 129.3, 129.7, 130.9, 132.3, 132.9, 136.6, 140.9, 143.8, 147.0.

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HRMS (TOF ESI): *m/z* [M + Na^+] calcd for $C_{26}H_{28}{}^{35}ClN_4O_2S_2$: 527.1342; found: 527.1323.

4-Phenethyl-1-[(*R*)-3-phenoxy-2-(tosylamino)propyl]-1*H*-1,2,3-triazole (19)

To a soln of **13** (48 mg, 0.13 mmol) in DMSO (1.0 mL) was added phenol (12 mg, 0.13 mmol) and Cs_2CO_3 (40 mg, 0.13 mmol); the mixture was heated to 70 °C overnight. Upon cooling H_2O was added, the soln was extracted with EtOAc, and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to provide crude **19**. Purification by flash chromatography provided **19** (44 mg, 73%) as a clear oil.

$[\alpha]_D{}^{22}$ –19.0 (*c* 1.4, $CHCl_3$).

FT-IR (film): 3141 (w), 3063 (w), 2924 (s), 2854 (m), 1496 (s), 1454 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.91–3.01 (m, 4 H), 3.68 (dd, *J* = 10.0, 6.0 Hz, 1 H), 3.83 (dd, *J* = 10.0, 5.0 Hz, 1 H), 3.93–4.00 (m, 1 H), 4.47 (dd, *J* = 14.0, 5.0 Hz, 1 H), 4.55 (dd, *J* = 14.0, 5.0 Hz, 1 H), 5.46 (br, 1 H), 6.74 (d, *J* = 8.0 Hz, 2 H), 6.98–7.31 (m, 11 H), 7.75 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.5, 27.2, 35.3, 50.2, 52.4, 66.2, 114.3, 121.8, 122.6, 126.1, 127.0, 128.4 (2 C), 129.6, 129.8, 136.8, 140.9, 143.9, 147.3, 157.4.

HRMS (TOF ESI): *m/z* [M + Na^+] calcd for $C_{26}H_{29}N_4O_3S$: 477.1960; found: 477.1971.

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(10) Whilst the product ee values were not determined, we have previously shown that nucleophilic additions to **3** and subsequent manipulations preserve stereochemical integrity and hence assume that these processes are enantiospecific.

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