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Articles

Entry to Highly Hindered Chiral β-Amino Triazoles Bearing a *gem*-Diaryl Group by Azide-alkyne Click Chemistry

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Copper(I)-catalyzed Huisgen cycloaddition of terminal alkynes with unmasked azidoamines derived from amino acids is described. The reported strategy provides a new entry to highly hindered β-amino 1,2,3-triazole derivatives bearing a *gem*-diaryl group, which are potentially valuable entities as molecular catalysts for asymmetric transformations.

Key Words : Amino triazole, *gem*-Diaryl group, Azide-alkyne cycloaddition, Amino acid

Introduction

'Click chemistry' is a powerful technique to generate substances quickly and reliably by joining small units together as earlier described by K. Barry Sharpless in 2001.[1] Certainly, the key requirements could be highly efficient and wide in scope, stereospecific, and the process is to be environmentally benign and economically attractive. After the independent discovery by Meldal and Sharpless that copper(I) catalyzes Huisgen azide-alkyne cycloaddition,[2] this became one of the most popular prototype click reactions to date, leading to a plethora of triazole chemistry with an exploding diversity. The exceptional stability and the ready accessibility of 1,2,3-triazoles have enabled multilateral manipulation of this unique class of heterocycles in medicinal chemistry, chemical biology, and material science.[3] Interestingly, chiral triazoles have been recently exploited as useful surrogates such as triazole-modified amino acids[4] and glycosyl triazoles,[5] and triazole-incorporated heterocycles.[6]

On the other hand, asymmetric organocatalytic reaction mediated by small organic molecules is definitely one of the most powerful and versatile tool for the rapid construction of valuable chiral molecules. Since the seminal work of List and MacMillan, a variety of chiral α-amino acid derivatives have been successfully developed as efficient and versatile catalysts for various kinds of asymmetric transformations (Fig. 1(a)).[7] They are proven to be excellent organocatalyst pools for a variety of asymmetric transformations resulting in exceptionally high enantioselectivities.[8] Indeed, the structural motif of amino acids facilitates a highly pre-organized transition state during the reaction pathway. Chiral amino acids available in both enantiomeric forms have played the key roles in the development of organocatalysis because of their cost-effectiveness and ready availability. The strategies used for the modification of amino acids mainly focused on varying the electronic and/or steric properties of the amino and carboxylic groups. Recently disclosed proline-based molecules such as pyrrolidine-tetrazole,[9] -pyridine,[10] -imidazole,[11] and -triazole conjugates,[12] are also proven to be useful as asymmetric catalysts for Michael additions and aldol reactions (Fig. 1(b)).

In the light of the above, we designed a new class of β-amino triazole conjugates by the incorporation of a *gem*-diaryl moiety adjacent to a stereogenic center. Remarkably, quaternary carbon centers containing a geminal diaryl group have attracted particular interest when they are incorporated

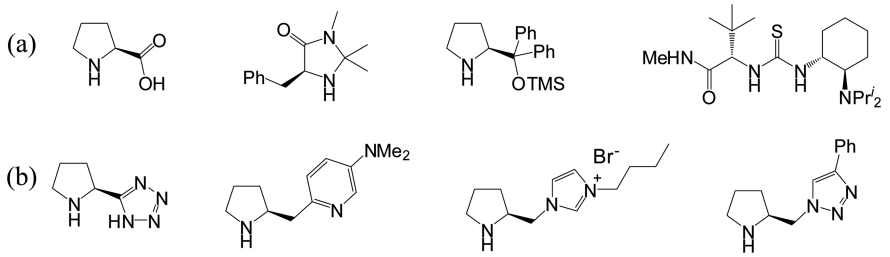
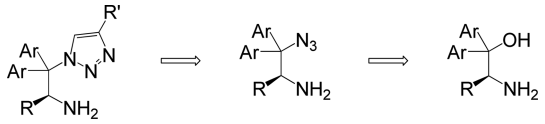


Figure 1. Representative examples of (a) amino acid-based organocatalysts and (b) proline-conjugates.



Scheme 1. Entry to sterically hindered β-amino triazoles derived from 1,1-diaryl-2-aminoethanols.

into a chiral 1,2-aminoalcohol functionality, and they serve as important structural motifs in the asymmetric transformations.[13] For example, diarylprolinol derivatives are of great importance as the privileged structures in asymmetric catalysis, such as Corey's oxazaborolidines[13a] and Jørgensen/Hayashi catalyst.[13e] We thus envisaged that highly hindered β-amino triazoles would provide a viable strategy for asymmetric transformations because they are more efficient for space shielding against an incoming substrate. In addition, two aryl groups are diastereotopic and might exert a great contribution to an enhanced facial selectivity due to their stereoelectronic effects. Until now there have been no significant reports on the synthesis of highly hindered β-amino triazoles derived from natural amino acids. Herein we would like to report a new entry to β-amino triazole derivatives bearing a *gem*-diaryl group using copper-catalyzed cycloaddition of terminal alkynes and 2,2-diaryl-2-azidoamines, as illustrated in Scheme 1.

Experimental Section

General Procedure for the Synthesis of β-Amino Triazoles. To a stirred solution of azide (1 mmol), $CuSO_4 \cdot 5H_2O$ (10 mol %) and sodium ascorbate (20 mol %) in a 1/1 mixture of water and acetonitrile (5 mL), acetylene (1.2 equiv.) was added under argon atmosphere. The reaction went to completion after stirring at room temperature for 4 h. The reaction mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The crude was purified by column chromatography on a silica gel (3% MeOH/CH_2Cl_2) to give a β-amino triazole.

(*S*)-1,1-Diphenyl-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)propan-2-amine (2a). Yield: 294.2 mg (83%); Pale yellow oil; $[\alpha]_D^{25}$ = 75.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.74 (m, 2H), 7.49 (s, 1H), 7.40-7.18 (m, 13H), 4.94 (q, 1H, *J* = 6.5 Hz), 1.76 (brs, 1H), 1.13 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.6, 141.0, 138.8, 130.4, 129.0, 128.7, 128.6, 128.3, 128.2, 128.2, 128.1, 125.6, 121.9, 78.8, 52.5, 19.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{23}N_4$: 355.1923; found 355.1925.

(*S*)-Ethyl-1-(2-amino-1,1-diphenylpropyl)-1*H*-1,2,3-triazole-4-carboxylate (2b). Yield: 262.8 mg (75%); Pale yellow oil; $[\alpha]_D^{25}$ = 19.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.40-7.28 (m, 8H), 7.17-7.14 (m, 2H), 4.92-4.90 (m, 1H), 4.38 (q, 2H, *J* = 7.1 Hz), 1.73 (brs, 2H), 1.37 (t, 3H, *J* = 7.1 Hz), 1.12 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8, 140.6, 139.1, 138.5, 129.8, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 79.3, 61.2, 52.1, 19.7, 14.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}N_4O_2$: 351.1794; found 351.1816.

(*S*)-2-(1-(2-Amino-1,1-diphenylpropyl)-1*H*-1,2,3-triazol-4-yl)ethanol (2c). Yield: 280.5 mg (87%); Pale brown oil; $[\alpha]_D^{25}$ = 9.3 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.29 (m, 8H), 7.14-7.11 (m, 3H), 4.87-4.85 (m, 1H), 3.86 (t, 2H, *J* = 6.2 Hz), 2.86 (t, 2H, *J* = 6.1 Hz), 2.31 (brs, 3H), 1.07 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 141.1, 138.8, 128.9, 128.5, 128.2, 128.19, 128.16, 128.08, 127.8, 123.8, 77.8, 61.3, 52.3, 28.7, 19.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{23}N_4O$: 323.1872; found 323.1872.

(*S*)-1,1-Diphenyl-1-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-amine (2d). Yield: 275.0 mg (83%); Pale brown oil; $[\alpha]_D^{25}$ = 79.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50-8.49 (m, 1H), 8.21 (d, 1H, *J* = 7.9 Hz), 7.94 (s, 1H), 7.79-7.73 (m, 1H), 7.41-7.29 (m, 8H), 7.23-7.16 (m, 3H), 4.96-4.94 (m, 1H), 1.67 (brs, 2H), 1.14 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 149.3, 147.1, 140.9, 138.7, 136.9, 129.0, 128.5, 128.3, 128.2, 128.1, 124.3, 122.8, 120.2, 78.9, 52.3, 19.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{22}N_5$: 356.1875; found 356.1869.

(*S*)-3-Methyl-1,1-diphenyl-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)butan-2-amine (2e). Yield: 313.4 mg (82%); Transparent oil; $[\alpha]_D^{25}$ = 77.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 7.3 Hz), 7.62 (s, 1H), 7.39-7.31 (m, 13H), 4.76 (s, 1H), 2.15-2.11 (m, 1H), 1.4 (brs, 2H), 1.24 (d, 3H, *J* = 6.8 Hz), -0.04 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 146.7, 140.6, 140.0, 130.5, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 125.6, 121.5, 78.8, 59.3, 28.4, 23.7, 15.2; LC/MS (ESI): *m/z* = 405 $[M+Na]^+$.

(*S*)-Ethyl-1-(2-amino-3-methyl-1,1-diphenylbutyl)-1*H*-1,2,3-triazole-4-carboxylate (2f). Yield: 336.6 mg (89%); Pale brown oil; $[\alpha]_D^{25}$ = –24.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.44-7.34 (m, 10H), 4.82 (s, 1H), 4.45 (q, 2H, *J* = 7.1 Hz), 2.16-2.11 (m, 1H), 1.55 (brs, 2H),1.50 (t, 3H, *J* = 7.1 Hz), 1.30 (d, 3H, *J* = 6.7 Hz), –0.02 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 140.2, 139.4, 129.5, 129.0, 128.6, 128.5, 128.5, 128.1, 128.0, 79.4, 61.3, 59.0, 28.4, 23.6, 15.1, 14.3; LC/MS (ESI): *m/z* = 401 $[M+Na]^+$.

(*S*)-2-(1-(2-Amino-3-methyl-1,1-diphenylbutyl)-1*H*-1,2,3-triazol-4-yl)ethanol (2g). Yield: 259.3 mg (74%); Transparent liquid; $[\alpha]_D^{25}$ = 23.4 (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.34 (m, 11H), 4.67 (s, 1H), 3.97 (t, 2H, *J* = 5.7 Hz), 2.95 (t, 2H, *J* = 5.7 Hz), 2.18-2.11 (m, 1H), 1.30 (d, 3H, *J* = 6.7 Hz), –0.02 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6, 140.8, 139.9, 129.0, 128.4, 128.2, 128.0, 127.8, 123.5, 78.6, 61.5, 59.3, 28.7, 28.3, 23.7, 15.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{27}N_4O$: 351.2185: found 351.2180.

(*S*)-3-Methyl-1,1-diphenyl-1-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)butan-2-amine (2h). Yield: 333.6 mg (87%); Pale yellow oil; $[\alpha]_D^{25}$ = 153.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59-8.57 (m,1H), 8.27 (d, 1H, *J* = 7.9 Hz), 8.16 (s, 1H), 7.85-7.80 (m, 1H), 7.45-7.37 (m, 10H), 7.28-7.24 (m, 1H), 4.84 (s, 1H), 2.22-2.16 (m, 1H), 1.53 (brs,

2H), 1.33 (d, 3H, J = 6.8 Hz), –0.01(d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.3, 147.3, 140.7, 139.8, 136.9, 129.0, 128.5, 128.4, 128.2, 128.1, 127.8, 123.9, 122.8, 120.2, 78.9, 59.2, 28.4, 23.7, 15.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{26}N_5$: 384.2188; found 384.2178.

(*S*)-1,2,2-Triphenyl-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-ethanamine (2i). Yield: 291.6 mg (70%); Transparent oil; $[\alpha]_D^{25}$ = 0.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78-7.70 (m, 2H), 7.58 (s, 1H), 7.40-7.08 (m, 14H), 7.18-7.00 (m, 3H), 6.92-6.90 (m, 2H), 5.79 (s, 1H), 2.17 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 140.1, 138.9, 130.5, 130.2, 128.9, 128.9, 128.6, 128.3, 128.1, 127.8, 127.7, 125.7, 122.8, 79.4, 62.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{25}N_4$: 417.2079; found 417.2076.

(*S*)-Ethyl-1-(2-amino-1,1,2-triphenylethyl)-1*H*-1,2,3-triazole-4-carboxylate (2j). Yield: 292.9 mg (71%); Pale yellow oil; $[\alpha]_D^{25}$ = 7.8 (c 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.37-7.20 (m, 9H), 7.15 (m, 2H), 6.90-6.85 (m, 4H), 5.83 (brs, 1H), 4.38 (q, 2H, J = 7.1 Hz), 1.92 (brs, 2H), 1.38 (t, 3H, J = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.8, 139.5, 139.0, 138.5, 130.5, 129.9, 129.8, 129.7, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 79.7, 62.25, 61.3, 14.2; LCMS (ESI): *m/z* = 413 $[M+H]^+$, 412, 411, 409.

(*S*)-2-(1-(2-Amino-1,1,2-triphenylethyl)-1*H*-1,2,3-triazol-4-yl)ethanol (2k). Yield: 280.7 mg (73%); Transparent oil; $[\alpha]_D^{25}$ = –9.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 7H), 7.19-7.13 (m, 4H), 6.99-6.93 (m, 2H), 6.86-6.84 (m, 2H), 5.73 (s, 1H), 3.89 (t, 2H, J = 6.0 Hz), 2.88 (t, 2H, J = 6.0 Hz), 2.4 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 140.1, 139.0, 138.8, 130.1, 130.0, 128.7, 128.4, 128.1, 127.9, 127.6, 127.6, 124.6, 78.9, 62.7, 61.6, 28.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{25}N_4O$: 385.2028; found 385.2018.

(*S*)-1,2,2-Triphenyl-2-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)ethanamine (2l). Yield: 354.9 mg (85%); Pale yellow oil; $[\alpha]_D^{25}$ = –7.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49-8.49 (m, 1H), 8.23-8.20 (m, 1H), 8.01 (s, 1H), 7.79-7.74 (m, 1H), 7.33-7.00 (m, 14H), 6.92-6.89 (m, 2H), 5.82 (brs, 1H), 2.12 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.3, 147.0, 140.0, 139.7, 138.8, 136.9, 130.0, 128.9, 128.4, 128.2, 127.8, 127.7, 127.6, 127.6, 125.1, 122.8, 120.3, 79.4, 62.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{24}N_5$: 418.2032; found 418.2035.

(*S*)-1,1,3-Triphenyl-1-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-propan-2-amine (2m). Yield: 361.7 mg (84%); Transparent oil; $[\alpha]_D^{25}$ = 53.2 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80-7.75 (m, 2H), 7.50 (s, 1H), 7.42-7.19 (m, 18H), 5.02 (d, 1H, J = 10.2 Hz), 3.36 (d, 1H, J = 13.2 Hz), 2.32 (brs, 2H), 2.16-2.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 139.8, 130.5, 129.3, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 126.5, 125.7, 122.0, 78.1, 59.1, 40.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{27}N_4$: 431.2236; found 431.2232.

(*S*)-Ethyl 1-(2-amino-1,1,3-triphenylpropyl)-1*H*-1,2,3-triazole-4-carboxylate (2n). Yield: 379.6 mg (89%); Transparent oil; $[\alpha]_D^{25}$ = 44.0 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.43-7.33 (m, 8H), 7.28-7.27 (m, 6H), 7.22-7.18 (m, 1H), 4.94 (d, 1H, J = 10.1 Hz), 4.38 (q, 2H, J = 7.1 Hz), 3.29 (d, 1H, J = 13.5 Hz), 1.94 (t, 1H, J = 11.5 Hz), 1.40 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 139.5, 139.3, 130.0, 129.2, 128.6, 128.6, 128.5, 128.4, 126.6, 78.6, 61.3, 58.8, 40.3, 14.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{27}N_4O_2$: 427.2134; found 427.2133.

(*S*)-2-(1-(2-Amino-1,1,3-triphenylpropyl)-1*H*-1,2,3-triazol-4-yl)ethanol (2o). Yield: 322.8 mg (81%); Transparent liquid; $[\alpha]_D^{25}$ = 19.3 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 15 H), 7.15 (s, 1H), 4.92 (d, 1H, J = 10.2 Hz), 3.90 (t, 2H, J = 6.0 Hz), 3.29 (d, 1H, J = 13.5 Hz), 2.88 (t, 2H, J = 6.0 Hz), 1.96-1.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 139.7, 129.2, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 126.5, 123.9, 77.8, 61.5, 59.0, 40.2, 28.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{27}N_4O$: 399.2185; found 399.2176.

(*S*)-1,1,3-Triphenyl-1-(4-(pyridin-2-yl)-1*H*-1,2,3-triazol-1-yl)propan-2-amine (2p). Yield: 349.5 mg (81%); Oily liquid; $[\alpha]_D^{25}$ = 45.8 (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51-8.49 (m, 1H), 8.22-8.19 (m, 1H), 7.98 (s, 1H), 7.95-7.73 (m, 1H), 7.44-7.28 (m, 14H), 7.22-7.17 (m, 2H), 5.03 (d, 1H, J = 10.1 Hz), 3.34 (d, 1H, J = 13.5 Hz), 2.07-1.99 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 149.4, 147.2, 139.8, 136.9, 129.3, 128.8, 128.5, 128.5, 128.4, 128.3, 128.3, 126.5, 124.5, 122.8, 120.3, 78.3, 58.9, 40.3; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{28}H_{26}N_5$: 432.2188; found 432.2189.

(*S*)-1-(Diphenyl(pyrrolidin-2-yl)methyl)-4-phenyl-1*H*-1,2,3-triazole (2q). Yield: 304.4 mg (80%); Pale yellow oil; $[\alpha]_D^{25}$ = 39.1 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.76 (m, 2H), 7.55 (s, 1H), 7.30-7.29 (m, 11H), 7.21-7.18 (m, 2H), 5.00 (q, 1H, J = 6.8 Hz), 2.98-2.88 (m, 2H), 2.30-2.21 (m, 1H), 1.75-1.57 (m, 2H), 1.35-1.32 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.1, 130.6, 129.3, 128.9, 128.7, 128.5, 128.2, 128.1, 127.9, 127.8, 125.7, 125.5, 125.3, 122.1, 64.83, 46.4, 31.54, 29.1, 25.7, 22.6, 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{25}H_{25}N_4$: 381.2079; found 381.2076.

(*S*)-2-(1-(Diphenyl(pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)ethanol (2r). Yield: 313.6 mg (90%); Transparent oil; $[\alpha]_D^{25}$ = 7.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.30 (m, 9H), 7.14-7.10 (m, 2H), 4.95-4.90 (q, 1H, J = 6.5 Hz), 3.91 (t, 2H, J = 5.8 Hz), 2.88 (t, 2H, J = 5.8 Hz), 2.84-2.80 (m, 2H) 2.41 (brs, 2H), 2.2-2.14 (m, 1H), 1.72-1.57 (m, 2H), 1.29-1.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 141.6, 141.0, 129.4, 128.2, 128.1, 128.0, 127.8, 123.9, 64.9, 61.6, 46.4, 29.1, 28.6, 25.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{21}H_{25}N_4O$: 349.2028; found 349.2026.

(*S*)-2-(1-(Diphenyl(pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazol-4-yl)pyridine (2s). Yield: 354.8 mg (93%); Transparent liquid; $[\alpha]_D^{25}$ = 55.6 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51-8.49 (m, 1H), 8.22-8.19 (m, 1H), 7.96 (s, 1H), 7.78-7.73 (m, 1H), 7.40-7.29 (m, 9H), 7.23-7.16 (m, 2H), 5.01 (t, J = 6.5 Hz, 1H), 2.86-2.81 (m, 2H), 2.25-2.15 (m, 2H), 2.12 (bs, 1H), 1.75-1.59 (m, 2H), 1.28-1.20 (m,

1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.3, 146.8, 141.4, 140.9, 136.9, 129.5, 128.3, 128.2, 128.1, 128.0, 127.9, 124.5, 122.7, 120.3, 77.2, 64.8, 46.5, 29.2, 25.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{24}N_5$: 382.2032; found 382.2032.

(*S*)-1-(Diphenyl(pyrrolidin-2-yl)methyl)-4-(6-methoxynaphthalen-2-yl)-1*H*-1,2,3-triazole (2t). Yield: 373.1 mg (81%); Pale brown oil; $[\alpha]_D^{25}$ = 121.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.86-7.83 (d, 1H, *J* = 8.5 Hz), 7.75-7.72 (d, 2H, *J* = 9.8 Hz), 7.62 (s, 1H), 7.42-7.33 (m, 8H), 7.24-7.20 (m, 2H), 7.15-7.12 (m, 2H), 5.04 (t, 1H, *J* = 7.1 Hz), 3.92 (s, 3H), 2.99-2.87 (m, 2H), 2.32-2.19 (m, 1H), 1.79-1.67 (m, 2H), 1.40-1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 146.4, 134.3, 129.6, 129.5, 128.9, 128.3, 128.2, 128.1, 127.9, 127.3, 125.9, 124.4, 124.3, 124.2, 122.0, 119.2, 105.8, 65.0, 55.3, 46.5, 29.1, 25.7, 22.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{30}H_{29}N_4O$: 461.2341; found 461.2339.

(*S*)-4-(2,5-Dimethylphenyl)-1-(diphenyl(pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole (2u). Yield: 310.5 mg (76%); Pale brown oil; $[\alpha]_D^{25}$ = 54.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.44 (s, 1H), 7.40-7.31 (m, 8H), 7.23-7.18 (m, 2H), 7.12 (d, 1H, *J* = 7.7 Hz), 7.05 (d, 1H, *J* = 7.7), 5.06 (q, 1H, *J* = 6.4 Hz), 2.95-2.83 (m, 2H), 2.33 (s, 3H), 2.31 (s, 3H), 2.28-2.21 (m, 1H), 1.77-1.64 (m, 2H), 1.34-1.28 (m, 1H), 1.26 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 135.5, 132.3, 130.8, 129.5, 129.3, 129.2, 128.8, 128.4, 128.3, 128.2, 128.1, 128.0, 124.5, 65.0, 46.5, 28.9, 25.6, 20.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{29}N_4$: 409.2392; found 409.2392.

(*S*)-4-(*tert*-Butyl)-1-(diphenyl(pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole (2v). Yield: 273.9 mg (76%); Pale brown oil; $[\alpha]_D^{25}$ = 7.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.28 (m, 8H), 7.13-7.09 (m, 2H), 7.0 (s, 1H), 5.04-4.98 (t, 1H, *J* = 7.7 Hz), 3.06-2.90 (m, 2H), 2.28-2.19 (m, 1H), 1.83-1.62 (m, 2H), 1.49-1.37 (m, 1H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 129.0, 128.5, 128.2, 127.8, 121.6, 75.8, 65.8, 46.48, 30.8, 30.3, 28.7, 25.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{29}N_4$: 361.2392; found 361.2388.

Preparation of (*S*)-1-[Diphenyl(pyrrolidin-2-yl)methyl]-1*H*-1,2,3-triazole (3). To a stirred solution of **1e** (250 mg, 0.9 mmol), potassium carbonate (149 mg, 1.08 mmol), $CuSO_4{\cdot}5H_2O$ (44.8 mg, 0.18 mmol), and sodium ascorbate (71.2 mg, 0.36 mmol) in a 1/1 mixture of water and methanol (5 mL), trimethylsilylacetylene (132.32 mg, 1.35 mmol) was added under argon atmosphere. The reaction went to completion after stirring at room temperature for 24 h. The reaction mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The residue was dissolved in anhydrous THF (5 mL), TBAF (1 M in THF, 0.45 mL, 0.45 mmol) was added drop wise under argon atmosphere and stirred for 6 h at room temperature. The reaction mixture was evaporated under reduced pressure. The crude was purified by column chromatography (3% MeOH/CH_2Cl_2) to afford **3** (237 mg, 78%) as a pale brown oil. $[\alpha]_D^{25}$ = 4.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.33-7.29 (m, 9H), 7.14-7.12 (m, 2H), 4.95 (t, 1H, *J* = 7.7 Hz), 2.84-2.80 (m, 2H), 2.23-2.13 (m, 1H), 1.94 (brs, 2H) 1.72-1.59 (m, 2H), 1.29-1.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 141.0, 132.4, 129.4, 128.3, 128.2, 128.1, 128.0, 127.8, 126.0, 64.9, 46.4, 29.0, 25.6; LC/MS (ESI): *m/z* = 305 $[M+H]^+$, 304, 236.

CuAAC of 1e with Ethyl Propiolate (Table 2, entry 1). To a stirred solution of **1e** (250.0 mg, 0.9 mmol), $CuSO_4{\cdot}5H_2O$ (22.43 mg, 0.09 mmol) and sodium ascorbate (35.58 mg, 0.18 mmol) in a 1/1 mixture of water and acetonitrile (5 mL), ethyl propiolate (105.78 mg, 1.08 mmol) was added under argon atmosphere. The reaction went to completion after stirring at room temperature for 4 h. The reaction mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and then evaporated under reduced pressure. The crude product was purified by column chromatography (15-30% EtOAc/hexanes) to afford **4a**, **4b**, and **4c**.

(*E*)-(*S*)-Ethyl 3-(2-(azidodiphenylmethyl)pyrrolidin-1-yl)acrylate (4a). Transparent oil; $[\alpha]_D^{25}$ = −178.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 13.0 Hz), 7.45-7.29 (m, 10H), 4.64-4.61 (m, 1H), 4.5 (d, 1H, *J* = 13.0 Hz), 4.11 (q, 2H, *J* = 7.1 Hz), 2.96-2.87 (m, 1H), 2.69-2.62 (m, 1H), 2.24-2.13 (m, 1H), 2.04-1.96 (m, 1H) 1.62-1.54 (m, 1H), 1.24 (t, 3H, *J* = 7.1 Hz), 0.84-0.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 150.2, 139.3, 138.6, 128.9, 128.5, 128.3, 128.2, 128.1, 87.0, 75.9, 68.2, 58.9, 48.6, 28.1, 22.3, 14.5; LC/MS (ESI): *m/z* = 377 $[M+H]^+$, 334, 236, 158.

(*S*)-Ethyl-1-(diphenyl(pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (4b). Transparent oil; $[\alpha]_D^{25}$ = 20.7 (c 1.0, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.34-7.31 (m, 8H), 7.14-7.13 (m, 2H), 5.0 (t, 1H, *J* = 7.1 Hz), 4.41 (q, 2H, *J* = 7.1 Hz), 2.86-2.79 (m, 2H), 2.22-2.12 (m, 1H), 2.0 (brs, 2H), 1.65-1.63 (m, 2H), 1.36 (t, 3H, *J* = 7.1 Hz), 1.21-1.17(m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 141.1, 140.1, 138.6, 130.0, 129.4, 128.8, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 77.7, 64.4, 61.2, 46.45, 29.0, 25.7, 14.3; LC/MS (ESI): *m/z* = 377 $[M+H]^+$, 237, 236, 275.

(*E*)-(*S*)-Ethyl-1-((1-(3-ethoxy-3-oxoprop-1-en-1-yl)pyrrolidine-2-yl)diphenylmethyl)-1*H*-1,2,3-triazole (4c). Off white solid, mp 134-137 °C; $[\alpha]_D^{25}$ = 122.8 (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.46-7.31 (m, 9H), 7.19-7.16 (m, 2H), 5.82 (d, 1H, *J* = 8.5 Hz), 4.45 (d, 1H, *J* = 13.0 Hz), 4.37 (q, 2H, *J* = 7.1 Hz), 4.08-3.93 (m, 2H) 2.95-2.86 (m, 1H), 2.79-2.72 (m, 1H), 2.55-2.41 (m, 1H), 2.16-2.09 (m, 1H) 1.53-1.42 (m, 1H), 1.37 (t, 3H, *J* = 7.1 Hz), 1.21-1.16 (t, 3H, *J* = 7.1 Hz), 0.15-0.04 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 160.6, 149.1, 139.6, 138.0, 137.8, 129.4, 129.3, 129.2, 128.7, 128.5, 128.4, 128.3, 89.2, 77.4, 67.3, 61.3, 58.8, 49.6, 29.8, 21.6, 14.4, 14.1; LC/MS (ESI): *m/z* = 475 $[M+H]^+$, 334, 246.

Crystallographic Data for 4c. Atomic coordinates and crystallographic parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 969619).

These data can be obtained free of charge *via* http://www. ccdc.cam.ac.uk/conts/retrieving.html or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, E-mail: deposit@ccdc.cam.ac.uk.

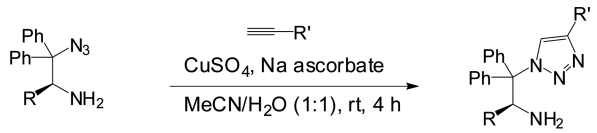
Results and Discussion

In order to address the problems associated with the installation of *gem*-diaryl moiety, we are particularly interested in the utilization of 1,1-diaryl-2-aminoethanols. We previously developed for an efficient and practical method for a direct azidation of tertiary alcohols including 1,1-diaryl-2-aminoethanols using sodium azide-sulfuric acid in toluene.[14] This prompted us to examine a facile entry to sterically hindered β-amino triazoles *via* Cu-catalyzed alkyne-azide cycloaddition (CuAAC).

While Cu(I) catalysis provides a reliable means for the assembly of 1,4-disubstituted 1,2,3-triazoles, often is requiring anhydrous conditions, and at least an amine base or high temperature to form the Cu-acetylide complexes.[15] On the contrary, *in situ* generation of Cu(I) species by the reduction of Cu(II) salts such as $CuSO_4$ with ascorbate allows the formation of 1,4-triazoles at room temperature and even under aqueous conditions. We first examined the reaction of **1a** with phenylacetylene in CH_3CN/H_2O (1:1) at room temperature. In fact, the 1,3-dipolar cycloaddition was completed within 4 h to give the desired 4-isomer **2a** in 83% isolated yield (Table 1, entry 1), in which $CuSO_4{\cdot}5H_2O$ (10 mol %) was used as a cheap copper source and sodium ascorbate (20 mol %) as a reducing agent.

After a successful installation, we next examined the efficacy and scope of the reaction with respect to both azides and alkyne components using the protocol described above. The reaction of alanine derivative **1a** with several alkynes afforded the corresponding triazoles in good yields (entries 2-4). After that, the most extensively studied 1,1-diaryl-2-aminoethanol substrates, derived from valine, phenylglycine, phenylalanine, and proline, were included and surveyed within the same protocol. The 2-azidoamine derivatives **1b-1e** also smoothly reacted with several kinds of terminal acetylenes to afford β-amino triazoles in good yield, without *N*-protection of the amino group. So far, the presence of sterically enforced functional groups in the azide partner did not have any significant effect on the product formation. The synthetic procedure was quite straightforward and all reactions afforded single isomers as summarized in Table 1. The structures of new triazoles are fully consistent with their ^1H, ^{13}C, and MS data. In ^1H NMR spectrum, the C(5)-proton of the triazole ring appears as a singlet in the range of δ 7.4-8.2 ppm. The C(4)-carbon resonates between δ 128-148 depending on the substituent present and the C(5)-carbon resonated around δ 128 in ^{13}C NMR spectrum. It is interesting to note that a series of sterically demanding pyrrolidine-triazole conjugates **2q-2v** were conveniently prepared from routine Cu-catalyzed cycloaddition reactions, which are potentially valuable entities for organocatalytic transformations. In addition, a monosubstituted triazole **3** was also prepared in 78%

Table 1. CuAAC of amino acid-derived tertiary azides with terminal alkynes[a]



1 **2**

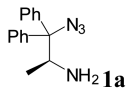
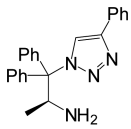
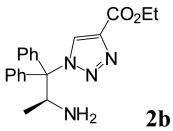
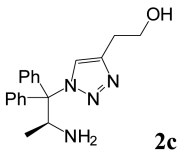
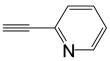
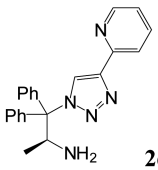
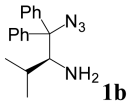
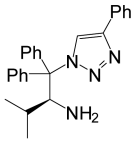
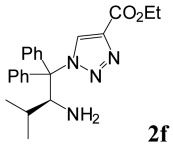
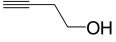
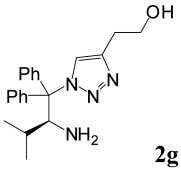
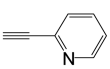
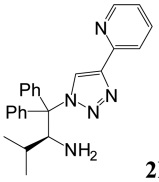
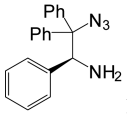
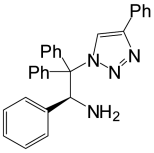
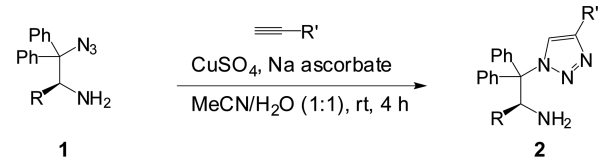
Entry	Azide **1**	Acetylene	Triazole **2**	Yield (%)
1	 **1a**		 **2a**	83
2			 **2b**	75
3			 **2c**	87
4			 **2d**	83
5	 **1b**		 **2e**	82
6			 **2f**	89
7			 **2g**	74
8			 **2h**	87
9	 **1c**		 **2i**	70

Table 1. Continued



1 2

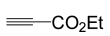
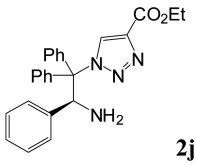
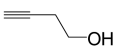
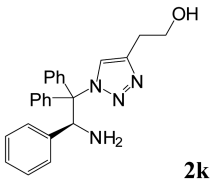
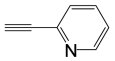
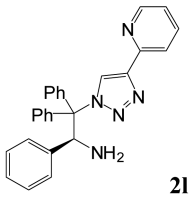
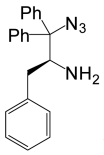
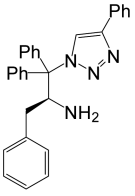
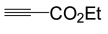
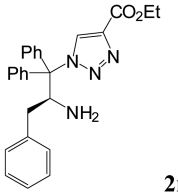
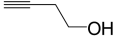
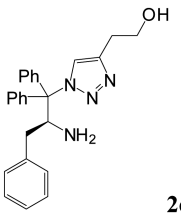
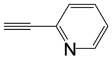
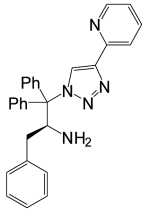
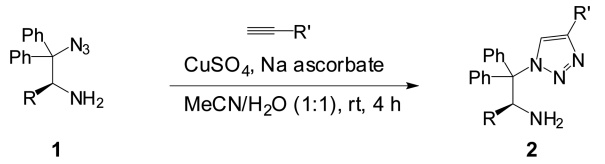
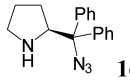
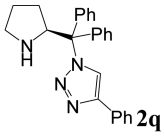
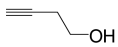
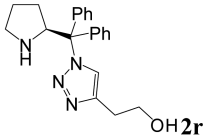
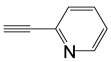
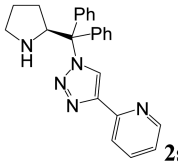
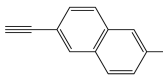
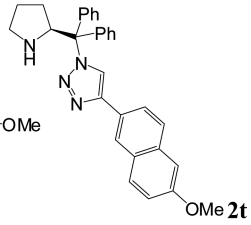
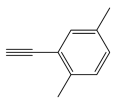
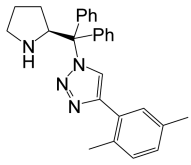
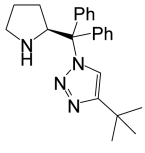
Entry	Azide **1**	Acetylene	Triazole **2**	Yield (%)
10			 **2j**	71
11			 **2k**	73
12			 **2l**	85
13	 **1d**		 **2m**	84
14			 **2n**	89
15			 **2o**	81
16			 **2p**	81

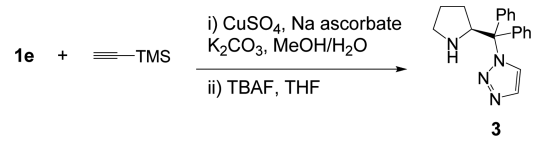
Table 1. Continued



1 2

Entry	Azide **1**	Acetylene	Triazole **2**	Yield (%)
17	 **1e**		 **2q**	80
18			 **2r**	90
19			 **2s**	93
20			 **2t**	81
21			 **2u**	76
22			 **2v**	76

[a]Reaction conditions: **1** (1 mmol), alkyne (1.2 equiv), $CuSO_4 \cdot 5H_2O$ (10 mol %), Na ascorbate (20 mol %), MeCN/H_2O (1/1, 5 mL)

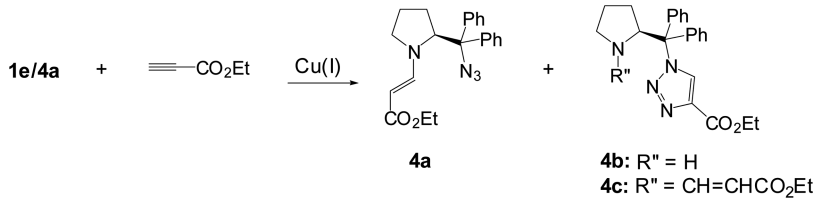


Scheme 2. CuAAC of **1e** with TMS-acetylene to give **3**.

yield by the reaction of **1e** with (trimethylsilyl)acetylene under the previous reported conditions, followed by a TMS-deprotection (Scheme 2).[16]

An interesting event has been observed during the reaction

Table 2. CuAAC of **1e** with ethyl propiolate



Entry	Azide	Equiv of alkyne	Temperature (°C)	Time (h)	Product distribution (yield, %)
1	**1e**	1.2	rt	4	**4a** (29), **4b** (4), **4c** (39)
2	**4a**	1.2	50	4	**4c** (78)
3	**1e**	3.0	50	16	**4c** (85)

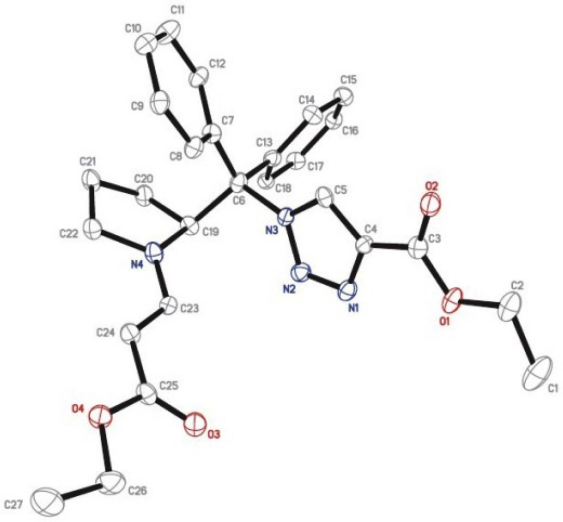


Figure 2. X-ray crystal structure of **4c**.

of **1e** with ethyl propiolate featuring a competition between Michael addition and Huisgen cycloaddition. When the reaction was subjected to our standard conditions, it afforded mixtures of products while Michael adducts are predominant (Table 2, entry 1). Meanwhile, the triazole geometry has not changed during the sequential steps, and has been confirmed later by the conversion of **4a** to **4c** (entry 2). Thus, the reaction pathway seems likely that an initially formed Michael adduct **4a** may undergo cycloaddition to afford the product **4c**. In order to complete this transformation, the addition of an extra ethyl propiolate and high reaction temperature were necessary (entry 3). In addition, X-ray crystal structure of **4c** has been solved and shown again that it is a 1,4-disubstituted triazole. Thus, the results clearly show strong 1,4-triazole formation preference even employed with sterically-demanding azides.

Conclusion

In summary, this investigation has identified a new entry leading to highly hindered chiral β-amino triazoles by azide-alkyne click chemistry. We probed the Cu(II)/sodium ascorbate is preferable and all cycloaddition reactions were performed under aqueous media at room temperature, and using stereo-demanding β-azidoamines as the starting materials. It is interesting to note that almost all reported methods utilized *N*-protected amino acid precursors for the synthesis of triazole-based amino acids and β-amino triazoles. This protocol provides an economically viable procedure to deliver new chiral triazoles from unmasked 1,1-diaryl-2-amino-ethanols, therefore, and renders as it fulfills many of the prerequisite for green and sustainable chemistry. The highly hindered β-amino triazoles are currently being investigated as potential molecular catalysts.

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