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C−H Bonds as Ubiquitous Functionality: Preparation of Multiple Regioisomers of Arylated 1,2,4-Triazoles via C−H Arylation

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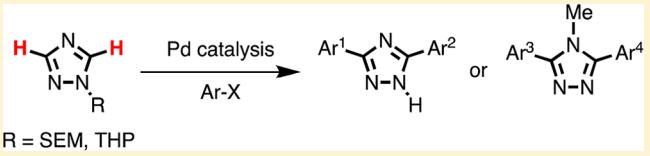
Supporting Information

ABSTRACT: We describe a general approach for the synthesis of complex aryl 1,2,4-triazoles. The electronic character of the C−H bonds and the triazole ring allows for the regioselective C−H arylation of 1-alkyl- and 4-alkyltriazoles under catalytic conditions. We have also developed the SEM and THP switch as well as trans-*N*-alkylation, which enable sequential arylation of the triazole ring to prepare 3,5-diaryltriazoles. This new strategy provides rapid access to a variety of arylated 1,2,4-triazoles and well complements existing cyclization methods.



1,2,4-Triazoles have emerged as an important heterocyclic class with a growing number of applications in medicinal chemistry and materials science.[1] In particular, C-arylated triazoles display a broad range of biological activities, including anticancer and antipsychotic activities.[2] In addition, conjugated triazoles and polymeric forms have been widely studied for the development of functional materials owing to interesting fluorescence and light emitting properties.[3]

In the context of a broad C−H functionalization program,[4] we have been developing new catalytic methods, based on transition-metal carboxylate systems, for regioselective C−H arylation of heteroarenes such as indoles, pyrroles, pyrazoles, imidazoles, and pyridines.[5−7] We herein report a general approach for the selective and sequential arylation of 1,2,4-triazoles. The synthesis of aryltriazoles typically relies on multistep cyclocondensation reactions, which require direct handling of hazardous hydrazines.[1,8] Much less common are cross-coupling reactions of halogenated 1,2,4-triazoles, which achieved limited success in terms of efficiency and selectivity.[2d,9]

During our study on the Pd-catalyzed C−H arylation of imidazoles, we observed that in the presence of a strong base (NaO-*t*-Bu), the C-2 position of imidazoles is preferred over the C-5 (Figure 1A).[5g] We also observed that in the arylation of pyridines, the presence of electron-withdrawing groups markedly increases the reactivity of the heteroarene ring (Figure 1B).[5h] These results together suggest that 1,2,4-triazoles, electron-deficient due to the presence of an additional nitrogen atom (in comparison to imidazoles), should be arylated at the C-5 position of 1*H*-triazoles and both C-3 and C-5 of 4*H*-triazoles, *even possibly in the presence of a weak base* (Figure 1C). Presumably, the deprotonation is facilitated by complexation of the palladium complex to the N-4 nitrogen of 1*H*-triazoles and the N-1 (or N-2) of 4*H*-triazoles. In contrast, a palladation at the C-3 of 1*H*-triazoles is disfavored due to electronic repulsion between the C−Pd bond and nitrogen lone pairs.[5g,h] Although catalytic C−H arylations of 1,2,4-triazoles have been reported, these protocols are mostly limited to 1-methyltriazole.[10−13]

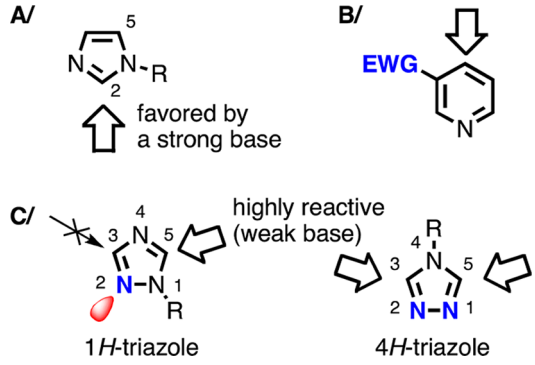


Figure 1. Regioselectivity of the direct catalytic C−H arylation governed by the electronic character of the C−H bonds and heteroarene rings.

First, we examined a direct C−H arylation of 1-substituted triazoles to develop a benchtop procedure using air-stable phosphonium salts (Table 1). Screening experiments found that DMA, typically employed for C−H arylation of azoles, was not suitable for the reaction of 1,2,4-triazole in the presence of air-stable phosphonium salts (entry 1). In toluene, however, a weak base, such as pivalate, generated in situ by the addition of a catalytic amount of pivalic acid and a stoichiometric amount of potassium carbonate, was sufficient for the C-5 arylation of 1,2,4-triazoles (entry 2). The presence of the carboxylic acid cocatalyst was essential to achieve efficiency (entry 3).[5a,c,14] As a ligand, $[P(n\text{-}Bu)Ad_2H]BF_4$ was superior to the corresponding tricyclohexylphosphonium salt (entry 4). Consistent with our previous report showing the importance of the steric bulk of carboxylate base,[5h] bulkier and more soluble carboxylic acid cocatalysts proved to be more efficient than pivalic acid

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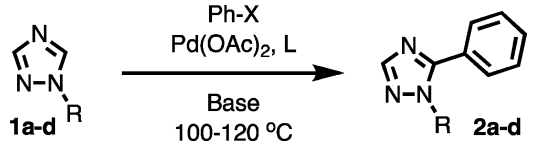
Table 1. C−H Arylation of 1-Alkyl-1,2,4-triazoles[a−c]



entry	R	X	ligand	base	solvent	2 (%)
1	SEM	Br	$[PCy_3H]BF_4$	K_2CO_3/Me_3CCO_2H	DMA	**2a**, 10
2	SEM	Br	$[PCy_3H]BF_4$	K_2CO_3/Me_3CCO_2H	toluene	**2a**, 74
3	SEM	Br	$[PCy_3H]BF_4$	K_2CO_3	toluene	**2a**, 20
4	SEM	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	K_2CO_3/Me_3CCO_2H	toluene	**2a**, 90
5	SEM	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/EtMe_2CCO_2H$	toluene	**2a**, 92
6	SEM	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/n\text{-}BuMe_2CCO_2H$	toluene	**2a**, 96
7	Me	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/EtMe_2CCO_2H$	toluene	**2b**, 92
8	Me	Cl	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/EtMe_2CCO_2H$	toluene	**2b**, 83
9[d]	Me	I	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	DMA	**2b**, 70
10	Ph	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/EtMe_2CCO_2H$	toluene	**2c**, 82
11	THP	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	$K_2CO_3/EtMe_2CCO_2H$	toluene	**2d**, 40
12[e]	THP	Br	$P(n\text{-Bu})Ad_2$	NaO*t*-Bu	toluene	**2d**, 90
13[e]	THP	Br	$[P(n\text{-Bu})Ad_2H]BF_4$	NaO*t*-Bu	toluene	**2d**, 9
14	SEM	Br	none	K_2CO_3/Me_3CCO_2H	DMA	**2a**, 0
15	THP	Br	none	K_2CO_3/Me_3CCO_2H	DMA	**2d**, 0
16	SEM	Br	none	K_2CO_3/Me_3CCO_2H	toluene	**2a**, 0
17	THP	Br	none	K_2CO_3/Me_3CCO_2H	toluene	**2d**, 0

[a]All reactions were performed on a 0.5 mmol scale. [b]Yield was determined by ^1H NMR analysis of the crude product using $(CHCl_2)_2$ as internal standard except entries 5, 7, 10, and 12 where yields of isolated products are reported. [c]Reaction conditions unless otherwise noted: 1.5 equiv of PhX, 5 mol % of $Pd(OAc)_2$, 10 mol % of ligand, 3.0 equiv of K_2CO_3, 0.3 equiv of carboxylic acid, solvent (1.0 M), 120 °C, 16−20 h. [d]Reaction conditions: 1.5 equiv of PhI, 5 mol % of $Pd(PPh_3)_2Cl_2$, 2.0 equiv of Ag_2CO_3, DMA (1.0 M), 120 °C, 18 h. [e]Reaction conditions: 1.5 equiv of PhBr, 5 mol % of $Pd(OAc)_2$, 7.5 mol % of $P(n\text{-Bu})Ad_2$, 2.0 equiv of NaO*t*-Bu, toluene (1.0 M), 100 °C, 2 h.

although the benefit was modest (entries 5 and 6). Hence, readily available, inexpensive pivalic acid was used for the examination of the substrate scope. Both bromobenzene and chlorobenzene were competent haloarene donors for the coupling of 1-methyltriazole (entries 7 and 8). While iodobenzene did not perform well under the standard conditions, a less activated catalytic system derived from $Pd(PPh_3)_2Cl_2$ and Ag_2CO_3 furnished the arylated product in 70% yield (entry 9). Not only 1-methyltriazole but also 1-phenyltriazole can be transformed to the arylated product in high yield (entry 10). We also investigated the bulkier, and thus less reactive tetrahydropyranyl protecting group (THP), which offers advantages over the SEM group in terms of cost and deprotection strategy. The benchtop procedure gave the desired product in moderate yield (entry 11), whereas the conditions developed for the C2-arylation of imidazoles[5g] were very efficient, leading to the formation of **2d** in 90% yield after heating at 100 °C for only 2 h (entry 12). In this protocol based on NaO-*t*-Bu, the generation of the active Pd catalyst from phosphonium salts was not practical (entry 13). It is also notable that phosphine-free conditions were not effective for this process, illustrating the importance of the generation of a phosphine-ligated palladium complex in the arylation of electron-deficient heterocycles (entries 14−17).[5h]

The scope of haloarene donors was tested, revealing that both electron-rich and electron-deficient aryl bromides can be coupled with 1-SEM-1,2,4-triazoles (Figure 2). A variety of functional groups, including methoxy, dimethylamino, ester, and pyridyl groups, were tolerated.

However, the C-3 position of 1,2,4-triazoles shows very low reactivity in the Pd-catalyzed reaction conditions,[15] which is consistent with the electronic argument we proposed for other

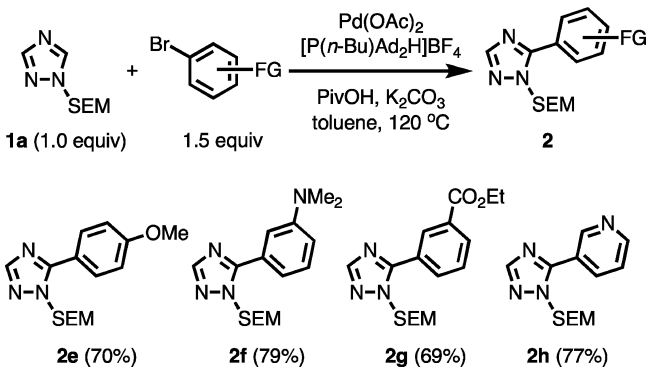


Figure 2. Bromoarene scope.

azoles and pyridines[5f−h] (see Figure 1). This regioselectivity rationale for C−H arylation of azoles and azines, based on the stability of the developing C−Pd bond, was recently supported by an independent theoretical study.[16] In order to address the low reactivity of the C-3 position, we examined the SEM switch in the context of 1,2,4-triazoles (Scheme 1). Similar to the SEM switch of diazoles,[5f,g] the SEM group can be transposed from N-1 to N-2 nitrogen in the presence of a catalytic amount of SEM-Cl. While N-4 nitrogen is more nucleophilic than N-2, the formation of a series of triazolium intermediates ultimately leads to the isolation of the least sterically hindered 3-aryltriazole **3a** as a consequence of thermodynamic control (for kinetic alkylation, vide infra). The alkylation at N-2, if it occurs, also results in the formation of **3a** via a 1,2-dialkyltriazolium salt. Through this process, the unreactive C-3 position is converted to the reactive C-5 position, where the second arylation can take place to provide diaryltriazole **4a**. Note that

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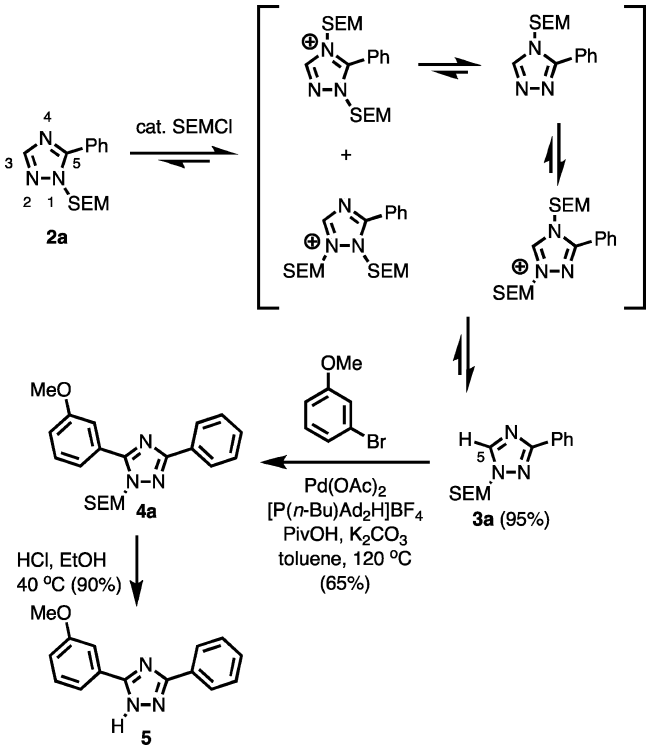
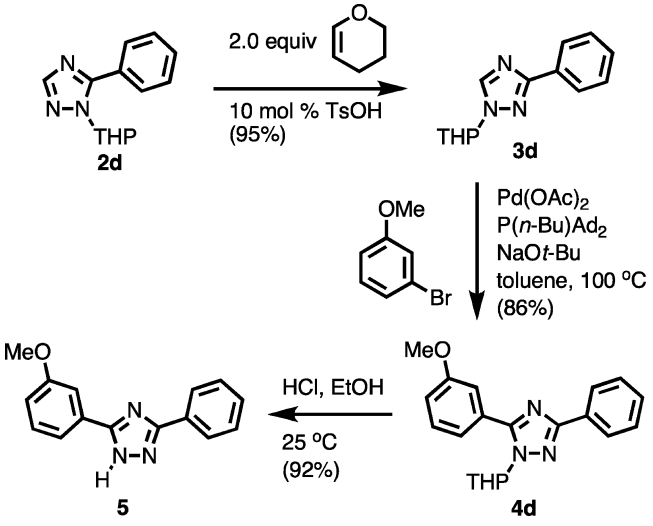
Scheme 1. SEM Switch



the SEM group of the triazole can be easily removed under mild acidic conditions.

Importantly, it was also found that the THP counterpart **2d** underwent a THP-switch to shift the THP group in a highly efficient and regioselective manner (Scheme 2).[17] The loss of

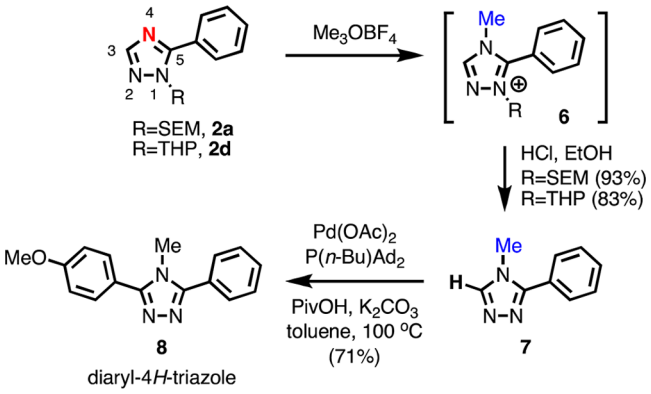
Scheme 2. THP Switch



the THP group and reinstallation at the least hindered N-2 position produced 3-aryltriazole **3d**. A subsequent C-5 arylation and removal of the THP group at ambient temperature provided (NH)-free triazole **5** in high yield.

Furthermore, the resulting 1-SEM- and 1-THP-5-aryltriazoles, **2a** and **2d**, can be employed for trans-*N*-alkylation to furnish regioisomeric 4-methyl-4*H*-triazole **7** (Scheme 3). Under kinetic control, the alkylation occurs selectively at the

Scheme 3. trans-*N*-Alkylation and Arylation of a 4*H*-Triazole



more nucleophilic N-4 nitrogen to give the corresponding triazolium salts **6**, from which 4-alkyl-4*H*-triazole **7** can be obtained by cleavage of the protecting groups.

The arylation of 4-alkyltriazoles presents a serious challenge.[18,19] Nonetheless, our protocol can be used for the arylation of 4*H*-triazoles, giving diaryltriazole **8** in 71% yield. This result represents the first catalytic C−H arylation of 4-alkyl-4*H*-triazoles.

In conclusion, we have developed a new approach for the synthesis of complex aryl 1,2,4-triazoles. Complementary to cyclization methods and catalytic *N*-arylation reactions, the direct C−H arylation of the 1,2,4-triazole ring provides rapid access to a variety of arylated products. It is the electronic character of the C−H bonds and triazole ring that allows for the regioselective C-5 arylation under practical laboratory conditions. It is also demonstrated that the protocol is quite general and applicable to not only 1-alkyltriazoles but also regioisomeric 4-alkyltriazoles. While the trans-*N*-alkylation was limited to the preparation of 4-methyl-triazoles, our approach based on direct C−H arylation enables the preparation of both isomeric series of mono- and diarylated 1,2,4-triazoles.

EXPERIMENTAL SECTION

The arylation reaction was carried out in a capped glass vial (4 mL) equipped with a magnetic stir bar and a Teflon-lined cap and heated in a 34-well reaction block. All reagents were used as received unless otherwise noted. Flash column chromatography was performed on silica gel (40−63 μm) using the indicated solvent system. Nuclear magnetic resonance spectra were recorded at 300 K on 300 or 400 Fourier transform NMR spectrometers in $CDCl_3$ or DMSO. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26; DMSO, δ 2.50). Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad), coupling constant (J) in Hertz, and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$, δ 77.0; DMSO, δ 40.0). Infrared (IR) spectra were reported in frequency of the absorption (cm^{-1}). High-resolution mass spectra (HRMS) were acquired on a high-resolution sector-type double-focusing mass spectrometer (ionization mode: FAB or EI).

1-Phenyl-1*H*-1,2,4-triazole (**1c**),[20] 1-methyl-5-phenyl-1*H*-1,2,4-triazole (**2b**),[10c] 1-phenyl-5-phenyl-1*H*-1,2,4-triazole (**2c**),[21] and 4-methyl-3-phenyl-4*H*-1,2,4-triazole (**7**)[22] are known compounds.

C−H Arylation of 1,2,4-Triazoles Using K_2CO_3 and Carboxylic Acid on the Benchtop (Table 1, Figure 2, and Scheme 1). To a 4 mL glass vial equipped with a magnetic stir bar were sequentially added carboxylic acid (0.15 mmol), K_2CO_3 (207 mg, 1.5 mmol), triazole substrate (0.5 mmol), aryl halide (0.75 mmol), toluene

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(0.5 mL, 1 M), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and [P(*n*-Bu)Ad_2H]BF_4[5g] (22.3 mg, 0.05 mmol). The reaction mixture was purged with argon through a Teflon-lined cap. Then the cap was replaced with a new Teflon-lined solid cap. The reaction vial was moved to a preheated reaction block (120 °C). After being stirred for 18 h at 120 °C, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography to provide the desired arylated product.

C−H Arylation of 1-THP-1*H*-1,2,4-triazoles Using NaO-*t*-Bu in the Glovebox (Table 1, Entry 12, and Scheme 2). To a 4 mL glass vial equipped with a magnetic stir bar were sequentially added triazole substrate (0.5 mmol), aryl halide (0.75 mmol), and toluene (0.5 mL, 1 M). The reaction mixture was purged with argon through a Teflon-lined cap. Then the reaction vial was moved to a glovebox. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), P(*n*-Bu)Ad_2 (13.4 mg, 0.038 mmol), and NaO-*t*-Bu (96 mg, 1.0 mmol), which were stored under argon in the glovebox, were added to the reaction mixture. The cap was replaced with a new Teflon-lined solid cap. The reaction vial was removed from the glovebox and then moved to a preheated reaction block (100 °C). After being stirred for 2 h at 100 °C, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography to provide the desired arylated product.

C−H Arylation of 4-Alkyl-4*H*-1,2,4-triazole Using K_2CO_3 and Pivalic Acid in the Glovebox (Scheme 3). To a 4 mL glass vial equipped with a magnetic stir bar were sequentially added pivalic acid (15.3 mg, 0.15 mmol), K_2CO_3 (207 mg, 1.5 mmol), triazole substrate (0.5 mmol), aryl halide (0.75 mmol), and toluene (0.5 mL, 1 M). The reaction mixture was purged with argon through a Teflon-lined cap. Then the reaction vial was moved to a glovebox. $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) and P(*n*-Bu)Ad_2 (13.4 mg, 0.038 mmol), which were stored under argon in the glovebox, were added to the reaction mixture. The cap was replaced with a new Teflon-lined solid cap. The reaction vial was removed from the glovebox and then moved to a preheated reaction block (100 °C). After being stirred for 18 h at 100 °C, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography to provide the desired arylated product.

trans-*N*-Alkylation (Scheme 3). To a stirred solution of **2a** or **2d** (1.0 mmol) in CH_2Cl_2 (2 mL) at 25 °C was added trimethyloxonium tetrafluoroborate (1.5 mmol). Then the reaction mixture was stirred at 25 °C until the starting material was completely consumed (~2 h). Then HCl in EtOH (1 N, 2 mL) was added to the reaction mixture. After being stirred for 3 h at 25 °C, the reaction mixture was neutralized with saturated aqueous Na_2CO_3 solution (10 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography to provide the product **7**.

*1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**1a**).*[23] To a stirred solution of 1,2,4-triazole (1.39 g, 20.0 mmol) in THF (20.0 mL, 1.0 M) at 25 °C under argon atmosphere were sequentially added NaH (60% in mineral oil, 800 mg, 20.0 mmol) and SEMCl (3.54 mL, 20.0 mmol). After being stirred for 16 h at 25 °C, the reaction mixture was quenched with water (5 mL) and transferred to a 125 mL separatory funnel that contained water (10 mL) and brine (10 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (25 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 1:1) to provide **1a** as a colorless oil (2.74 g, 68% yield): IR (film) 2954, 1508, 1272, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.95 (s, 1H), 5.49 (s, 2H), 3.65−3.55 (m, 2H), 0.94−0.85 (m, 2H), −0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 143.6, 77.7, 67.5, 17.7, −1.5; HRMS (FAB) calcd for $C_8H_{18}N_3OSi$ $[M + H]^+$ 200.1219, found 200.1209.

*1-(Tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (**1d**).* To a stirred solution of 1,2,4-triazole (3.45 g, 50.0 mmol) in THF (25.0 mL, 2.0 M) at 25 °C were sequentially added 3,4-dihydro-2*H*-pyran (9.0 mL, 100.0 mmol) and *p*-toluenesulfonic acid (951 mg, 5.0 mmol). Then the reaction mixture was heated to 70 °C. After being stirred for 2 h at 70 °C, the reaction mixture was cooled to 25 °C and then washed with saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (20 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (EtOAc) to provide **1d** as a colorless oil (6.89 g, 90% yield): IR (film) 2947, 1506, 1276, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.93 (s, 1H), 5.45 (dd, J = 8.5, 3.5 Hz, 1H), 4.07−4.01 (m, 1H), 3.76−3.60 (m, 1H), 2.16−1.89 (m, 3H), 1.77−1.52 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 141.9, 85.9, 67.5, 30.4, 24.7, 21.7; HRMS (FAB) calcd for $C_7H_{12}N_3O$ $[M + H]^+$ 154.0980, found 154.0982.

*5-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**2a**).* Purification by flash column chromatography (hexanes/EtOAc = 8:2) provided **2a** as a yellow oil (127 mg, 92% yield): IR (film) 2952, 1461, 1249, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.94−7.90 (m, 2H), 7.54−7.48 (m, 3H), 5.51 (s, 2H), 3.84−3.74 (m, 2H), 1.02−0.92 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 150.7, 130.4, 129.0, 128.9, 127.5, 77.2, 67.4, 17.9, −1.5; HRMS (FAB) calcd for $C_{14}H_{22}N_3OSi$ $[M + H]^+$ 276.1532, found 276.1522.

*5-Phenyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (**2d**).* Purification by flash column chromatography (hexanes/EtOAc = 7:3) provided **2d** as a colorless oil (103 mg, 90% yield): IR (film) 2943, 1455, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.76 (dd, J = 6.5, 2.8 Hz, 2H), 7.55−7.48 (m, 3H), 5.34 (dd, J = 9.8, 2.4 Hz, 1H), 4.21−4.11 (m, 1H), 3.67 (td, J = 11.4, 2.1 Hz, 1H), 2.50 (qd, J = 13.6, 4.2 Hz, 1H), 2.17−2.05 (m, 1H), 1.93−1.83 (m, 1H), 1.82−1.72 (m, 1H), 1.66−1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 150.9, 130.3, 129.0, 128.8, 127.9, 83.9, 67.6, 29.6, 24.7, 22.4; HRMS (EI) calcd for $C_{13}H_{16}N_3O$ $[M + H]^+$ 230.1293, found 230.1304.

*5-(4-Methoxyphenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**2e**).* Purification by flash column chromatography (hexanes/EtOAc=6:4) provided **2e** as a colorless oil (107 mg, 70% yield): IR (film) 2953, 1613, 1492, 1252 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 5.48 (s, 2H), 3.85 (s, 3H), 3.79 (t, J = 8.3 Hz, 2H), 0.97 (t, J = 8.3 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 155.7, 150.6, 130.5, 120.0, 114.3, 77.2, 67.3, 55.3, 17.9, −1.5; HRMS (EI) calcd for $C_{15}H_{24}N_3O_2Si$ $[M + H]^+$ 306.1638, found 306.1648.

*N,N-Dimethyl-3-(1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)aniline (**2f**).* Purification by flash column chromatography (hexanes/EtOAc = 6:4) provided **2f** as a colorless oil (126 mg, 79% yield): IR (film) 2952, 1606, 1492, 1278 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.41−7.32 (m, 1H), 7.30−7.26 (m, 1H), 7.25−7.22 (m, 1H), 6.87 (dd, J = 8.3, 2.5 Hz, 1H), 5.54 (s, 2H), 3.82 (t, J = 8.3 Hz, 2H), 3.02 (s, 6H), 0.99 (t, J = 8.3 Hz, 2H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 150.6, 129.5, 128.1, 116.7, 114.2, 112.8, 77.2, 67.2, 40.4, 17.9, −1.5; HRMS (FAB) calcd for $C_{16}H_{26}N_4OSi$ $[M]^+$ 318.1876, found 318.1874.

*Ethyl 3-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)benzoate (**2g**).* Purification by flash column chromatography (hexanes/EtOAc = 6:4) provided **2g** as a colorless oil (120 mg, 69% yield): IR (film) 2953, 1722, 1247, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.19 (d, J = 7.1 Hz, 1H), 8.12 (d, J = 7.0 Hz, 1H), 7.98 (s, 1H), 7.63−7.57 (m, 1H), 5.51 (s, 2H), 4.41 (q, J = 7.2 Hz, 2H), 3.80 (t, J = 8.0 Hz, 2H), 1.40 (t, J = 7.4 Hz, 3H), 0.99 (t, J = 8.0 Hz, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 155.0, 150.8, 133.0, 131.4, 130.1, 129.0, 127.9, 77.3, 67.5, 61.3, 17.9, 14.3, −1.5; HRMS (EI) calcd for $C_{17}H_{26}N_3O_3Si$ $[M + H]^+$ 348.1743, found 348.1736.

*3-(1-((2-(Trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazol-5-yl)-pyridine (**2h**).* Purification by flash column chromatography (DCM) provided **2h** as a colorless oil (106 mg, 77% yield): IR (film) 2953, 1413, 1249, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.72 (d, J = 4.7 Hz, 1H), 8.27−8.21 (m, 1H), 7.97 (s, 1H), 7.43 (dd, J = 7.9, 4.9 Hz, 1H), 5.50 (s, 2H), 3.77 (t, J = 8.2 Hz, 2H), 0.95 (t, J = 8.2 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1,

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151.2, 151.0, 149.6, 136.1, 123.8, 123.5, 77.3, 67.6, 17.8, −1.5; HRMS (FAB) calcd for $C_{13}H_{21}N_4OSi$ $[M + H]^+$ 277.1485, found 277.1474.

*3-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-1,2,4-triazole (**3a**).* To a 4 mL glass vial equipped with a magnetic stir bar were sequentially added **2a** (414 mg, 1.5 mmol), SEMCl (0.075 mmol), and CH_3CN (1.5 mL). Then the reaction mixture was heated to 80 °C. After being stirred for 20 h at 80 °C, the reaction mixture was cooled to 25 °C and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc = 8:2) to provide **3a** as an amorphous white solid (394 mg, 95% yield): IR (film) 2953, 1496, 1249, 1103 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.13 (dd, J = 8.2, 1.5 Hz, 2H), 7.47−7.38 (m, 3H), 5.52 (s, 2H), 3.69 (t, J = 8.2 Hz, 2H), 0.95 (t, J = 8.2 Hz, 2H), −0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 144.4, 130.7, 129.4, 128.6, 126.4, 77.8, 67.5, 17.7, −1.5; HRMS (FAB) calcd for $C_{14}H_{22}N_3OSi$ $[M + H]^+$ 276.1532, found 276.1525.

*3-Phenyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (**3d**).* To a 4 mL glass vial equipped with a magnetic stir bar were sequentially added **2d** (345 mg, 1.5 mmol), 3,4-dihydro-2*H*-pyran (3.0 mmol), *p*-toluenesulfonic acid (0.15 mmol), and THF (1.5 mL). Then the reaction mixture was heated to 70 °C. After being stirred for 2 h at 70 °C, the reaction mixture was cooled to 25 °C, diluted with THF (10 mL), and then washed with saturated aqueous $NaHCO_3$ solution (10 mL). The organic layer was collected, and the aqueous layer was extracted with EtOAc (10 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 6:4) to provide **3d** as a white solid (327 mg, 95% yield): mp 52−56 °C; IR (film) 2944, 1494, 1441, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 3.3 Hz, 1H), 8.16−8.08 (m, 2H), 7.47−7.34 (m, 3H), 5.52−5.45 (m, 1H), 4.14−4.05 (m, 1H), 3.78−3.67 (m, 1H), 2.20−2.10 (m, 2H), 2.09−1.95 (m, 1H), 1.77−1.58 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 142.7, 130.9, 129.2, 128.5, 126.4, 86.0, 67.6, 30.5, 24.7, 21.8; HRMS (EI) calcd for $C_{13}H_{16}N_3O$ $[M + H]^+$ 230.1293, found 230.1295.

*5-(3-Methoxyphenyl)-3-phenyl-1-((2-(trimethylsilyl)ethoxy)-methyl)-1H-1,2,4-triazole (**4a**).* Purification by flash column chromatography (DCM) provided **4a** as a white solid (124 mg, 65% yield): mp 79−82 °C; IR (film) 2953, 1609, 1516, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23−8.16 (m, 2H), 7.57−7.52 (m, 2H), 7.50−7.38 (m, 4H), 7.09−7.04 (m, 1H), 5.54 (s, 2H), 3.91−3.84 (m, 2H), 3.89 (s, 3H), 1.01 (t, J = 8.2 Hz, 2H), 0.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 159.8, 156.6, 130.9, 129.9, 129.3, 128.9, 128.5, 126.5, 121.3, 116.7, 114.0, 77.2, 67.3, 55.4, 17.9, −1.4; HRMS (FAB) calcd for $C_{21}H_{28}N_3O_2Si$ $[M + H]^+$ 382.1951, found 382.1966.

*5-(3-Methoxyphenyl)-3-phenyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (**4d**).* Purification by flash column chromatography (hexanes/EtOAc = 8:2) provided **4d** as an amorphous white solid (144 mg, 86% yield): IR (film) 2941, 1605, 1485, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.25−8.18 (m, 2H), 7.48−7.34 (m, 6H), 7.07 (ddd, J = 7.7, 2.5, 1.8 Hz, 1H), 5.38 (dd, J = 9.7, 2.7 Hz, 1H), 4.27−4.15 (m, 1H), 3.87 (s, 3H), 3.70 (td, J = 11.3, 2.4 Hz, 1H), 2.68−2.56 (m, 1H), 2.19−2.10 (m, 1H), 1.95−1.87 (m, 1H), 1.85−1.75 (m, 1H), 1.69−1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.8, 156.2, 131.0, 129.9, 129.1, 128.3, 126.6, 121.3, 116.6, 114.0, 84.0, 67.6, 55.3, 29.6, 24.7, 22.4; HRMS (FAB) calcd for $C_{20}H_{22}N_3O_2$ $[M + H]^+$ 336.1712, found 336.1712.

*5-(3-Methoxyphenyl)-3-phenyl-1H-1,2,4-triazole (**5**).* To a stirred solution of **4a** (1.0 mmol) in EtOH (0.5 mL) at 25 °C was added HCl in EtOH (1 N, 2 mL). After being stirred at 40 °C for 3 h, the reaction mixture was neutralized with saturated aqueous Na_2CO_3 solution (10 mL) and extracted with EtOAc (10 mL × 3). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexanes/EtOAc = 7:3) to provide **5** as an amorphous white solid (225 mg, 90% yield). In solution, **5** is present as three tautomeric forms, 1*H*-, 2*H*-, and 4*H*-triazoles: IR (film) 2526, 2074, 1462, 1117 cm^{-1}; ^1H NMR (400 MHz, DMSO) δ 8.10 (d, J = 6.0 Hz, 2H), 7.74−7.66 (m, 1H), 7.65 (s, 1H), 7.62−7.39 (m, 4H), 7.13−6.96 (m, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 160.1, 130.6, 130.1, 129.4, 126.5, 118.9, 115.9, 111.6, 55.7; HRMS (FAB) calcd for $C_{15}H_{14}N_3O$ $[M + H]^+$ 252.1137, found 252.1143.

*3-(4-Methoxyphenyl)-4-methyl-5-phenyl-4H-1,2,4-triazole (**8**).*[24] Purification by flash column chromatography (EtOAc/MeOH = 97:3) provided **8** as a white solid (94 mg, 71% yield): mp 205−208 °C; IR (film) 1614, 1482, 1255, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 4.6 Hz, 2H), 7.65 (d, J = 8.2 Hz, 2H), 7.52−7.46 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 3.85 (s, 3H), 3.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 155.6, 155.6, 130.4, 130.0, 128.8, 127.0, 119.0, 114.3, 55.4, 33.3; HRMS (FAB) calcd for $C_{16}H_{16}N_3O$ $[M + H]^+$ 266.1293, found 266.1290.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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