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Catalytic Deprotonative Functionalization of Propargyl Silyl Ethers with Imines

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Abstract: A metal-free, catalytic C–H functionalization of propargyl silyl ethers with imines using the phosphazene base (*t*-Bu-P_4 base) provides structurally defined multisubstituted pyrroles in modest to excellent yields under mild conditions. A one-pot, three-component reaction using silylated acetylenes, aldehydes, and imines is also presented.

Keywords: anionic reactions; C–C bond formation; heterocycles; metal-free conditions; phosphazene bases

Introduction

Direct C–C bond-forming reactions through propargylic C–H deprotonation are among the most powerful methods in modern organic synthesis, since they provide variously substituted allenes or propargylic compounds that serve as versatile building blocks in many synthetic scenarios.[1–3] Traditionally, strong organometallic bases such as organolithium reagents have been used for such deprotonations.[1,2] However, reactions using these reactive reagents often suffer from undesirable side reactions such as addition to electrophilic functional groups, and halogen-metal exchange reactions to organic halide functionalities. Furthermore, these reactions require stoichiometric use of the organometallic reagents, and need to be carried out at very low temperatures (−78 °C to −100 °C), both of which are undesirable for large-scale applications. Thus, a chemoselective, catalytic direct functionalization of propargylic compounds under mild conditions remains an attractive challenge.

We have recently focused on the potential applicability of phosphazene base (*t*-Bu-P_4 base)[4] as a chemoselective catalytic substitute for strong organometallic bases.[5] Herein, we report the first catalytic deprotonative C–C bond-forming functionalization of propargyl silyl ethers with imines. The reaction directly afforded a variety of highly substituted pyrroles under mild and metal-free conditions.

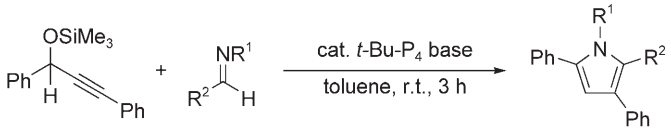
Results and Discussion

As a part of our survey on nucleophilic C–H and C–Si functionalization using catalytic *t*-Bu-P_4 base,[5,6] we found that reaction of propargyl silyl ether **1a** with imine **2a** in the presence of 10 mol% of *t*-Bu-P_4 base provides a tetraphenylated pyrrole **3aa** in 94% yield (Table 1, entry 1).[7]

Because the pyrrole ring architecture is one of the most ubiquitous functionalities found in natural products, bioactive chemicals, and functional molecules,[8,9] we expected that the present catalysis would be a powerful tool for the facile synthesis of multisubstituted pyrroles using propargyl silyl ethers **1** and imines **2**, both of which are easily prepared from aldehydes and alkynes, and from aldehydes and amines respectively. Thus, the reaction of **1a** with various imines **2a–n** using *t*-Bu-P_4 base was examined (Table 1). The reaction can be performed using 5 mol% of *t*-Bu-P_4 base to give pyrrole **3aa** in 92% yield (entry 2). Functional groups such as halogens (Cl, Br, and I), ester (COOMe), CF_3, methyl, and ether (OMe) on aromatic rings were tolerated to give variously substituted pyrroles in good to excellent yields (entries 3–12; 61–99%). The reaction of naphthyl- or heteroaromatic-substituted imines also proceeded efficiently to give the corresponding pyrroles **3al–an** (entries 13–15; 71–96%).

Reactions of other propargyl silyl ethers **1b–h** with imines were similarly carried out (Table 2). Formation of **3ba–da** was observed in the reaction of **1b–d** with **2a** (entries 1–3; 68–91%).[10] Bis-thienylated pyrrole

Table 1. Phosphazene-catalyzed direct functionalization of **1a** with imines **2a–n**.[a]



1a **2a – 2n** **3aa – 3an**

Entry	R^1, R^2 (Imine)	Product	Yield [%][b]
1	Ph, Ph (**2a**)	**3aa**	94
2[c]	Ph, Ph (**2a**)	**3aa**	92
3	*p*-C_6H_4Cl, Ph (**2b**)	**3ab**	97
4	*p*-C_6H_4Br, Ph (**2c**)	**3ac**	84
5	*p*-C_6H_4I, Ph (**2d**)	**3ad**	74
6	*p*-C_6H_4OMe, Ph (**2e**)	**3ae**	74
7	Ph, *p*-C_6H_4Cl (**2f**)	**3af**	99
8	Ph, *p*-C_6H_4Br (**2g**)	**3ag**	93
9	Ph, *p*-C_6H_4COOMe (**2h**)	**3ah**	86
10	Ph, *p*-$C_6H_4CF_3$ (**2i**)	**3ai**	83
11	Ph, *p*-C_6H_4Me (**2j**)	**3aj**	61
12	Ph, *p*-C_6H_4OMe (**2k**)	**3ak**	85
13	Ph, 2-naphthyl (**2*l***)	**3al**	96
14	Ph, 2-furyl (**2m**)	**3am**	71
15	Ph, 2-thienyl (**2n**)	**3an**	84

[a] The reactions were carried out using **1a** (0.375 mmol.), **2** (0.25 mmol), *t*-Bu-P_4 base (10 mol%) in hexane (25 μL), and toluene (1.0 mL).
[b] Isolated yield.
[c] 5 mol% of *t*-Bu-P_4 base were used.

3en and alkenyl-substituted pyrrole **3fa** were also successfully prepared in 80% and 73% yield, respectively (entries 4 and 5). Although the reaction of 1-alkyl-substituted silyl ether **1g** did not proceed at all (entry 6), the 3-alkyl-substituted silyl ether **1h** furnished the product **3ha** in 23% yield (entry 7). Assembly of various aromatic rings was easily accomplished, giving a multifunctionalized pyrrole **3ch** in 77% yield (entry 8).

Moreover, the one-pot, three-component reaction of alkynylsilane **4**, aldehyde **5**, and imine **2f** was carried out using *t*-Bu-P_4 base as a dual catalyst for Si–C and C–H functionalization [Eq. (1)].[6] The reaction was found to proceed smoothly to give the corresponding pyrrole **3df** in 84% yield.

To obtain mechanistic information, a preliminary deuterium labeling study using 1-[D]-**1a** was conducted. It was found that hydrogen at the 4-position on the pyrrole **3aa** originates exclusively from the propargylic hydrogen in the silyl ether, and that the eliminated Me_3SiOH does not act as a proton source [Eq. (2)].

A cross-over experiment using a mixture of 1-[D]-**1a** and 1-[H]-**1d** gave a mixture of partially deuterated pyrroles (4-[H]-**3aa**:4-[D]-**3aa** = 35:65, 4-[H]-**3da**:4-[D]-**3da** = 47:53), suggesting that the intermediate anions do not form strong ion pairs with the phosphazenium cations.[11] With these observations in hand, a mechanistic hypothesis involving *t*-Bu-P_4 base-mediated deprotonation of **1** at the propargylic position was developed (Scheme 1). We consider that the intermediate siloxylallenyl anion **A** reacts with imine **2** through a phosphazenium-activated imine **B** to form allenylated intermediate **C**. Protonative ring closure with another **1** gives the cyclized intermediate **D** and siloxyallenyl anion **A**. The elimination of $SiMe_3OH$ from **D** yields the pyrrole **3**.

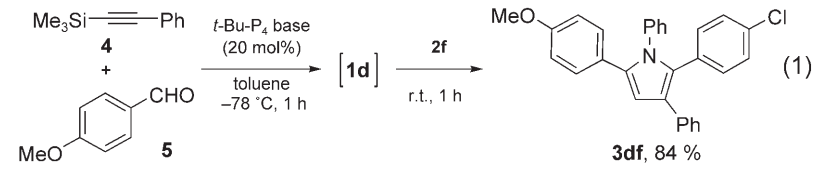
Conclusions

In summary, we found a novel direct C–C bond-forming functionalization of propargyl silyl ethers with imines catalyzed by *t*-Bu-P_4 base, providing multi-substituted pyrroles in good to excellent yields under metal-free mild conditions. The present method provides a convenient entry for the facile synthesis of variously functionalized pyrroles using easily accessible starting materials. Further studies to elucidate in detail the reaction mechanism, as well as the scope and limitations of this catalytic direct generation-functionalization of siloxyallenyl anions, are in progress.

Experimental Section

General Comments

Reactions were carried out under an argon atmosphere using dry solvents. Melting points (mp) were determined



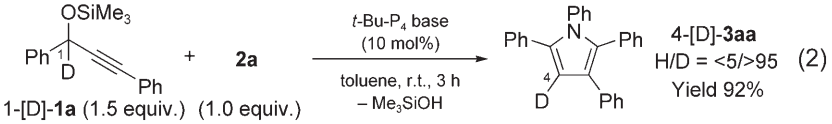
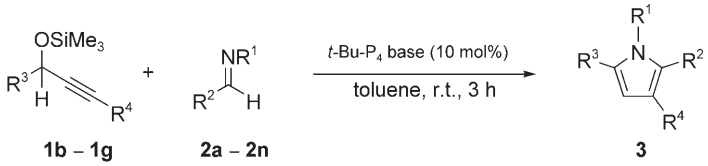
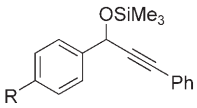
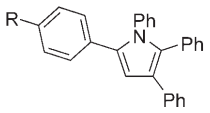
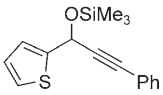
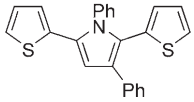
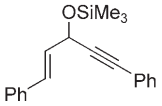
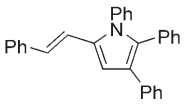
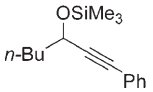
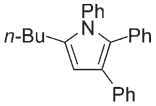
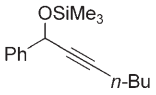
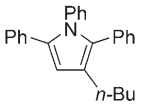
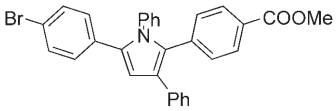


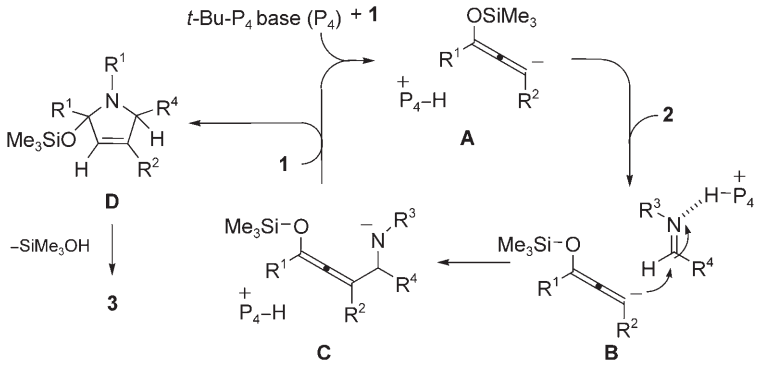
Table 2. Phosphazene-catalyzed direct functionalization of propargyl silyl ether with imines.[a]



1b – 1g **2a – 2n** **3**

Entry	Silyl ether		Imine	Product, Yield[b]	
1	**1b**: R = Cl		**2a**	**3ba**: R = Cl, 91%	
2	**1c**: R = Br		**2a**	**3ca**: R = Br, 76%	
3	**1d**: R = OMe		**2a**	**3da**: R = OMe, 68%	
4	**1e**		**2n**	**3en**, 80%	
5[c]	**1f**		**2a**	**3fa**, 73%	
6	**1g**		**2a**	**3ga**, 0%	
7	**1h**		**2a**	**3ha**, 23%	
8	**1c**		**2h**	**3ch**, 77%	

[a] The reactions were carried out using **1a** (0.375 mmol.), **5** (0.25 mmol), *t*-Bu-P_4 base (10 mol%) in hexane (25 μL), and toluene (1.0 mL) at room temperature for 3 h.
[b] Isolated yield.
[c] Reaction performed at −40 °C.



Scheme 1. A plausible mechanism for the phosphazene-catalyzed direct functionalization of propargyl silyl ether **1** with imine **2**.

with a Yazawa micro melting point apparatus and are uncorrected. Infrared (IR) data were recorded on a SensIR ATR (Attenuated Total Reflectance) FT-IR spectrometer. The spectra were acquired in 32 scans per spectrum at a resolution of four using system ReactIR™ 2.20 software. Absorbance frequencies are reported in reciprocal centimeters (cm^{-1}). NMR data were recorded on a JEOL AL400 spectrometer (395.75 MHz for ^1H, 99.50 MHz for ^{13}C). Chemical shifts are expressed in δ (parts per million, ppm) values, and coupling constants are expressed in hertz (Hz). ^1H NMR spectra were referenced to tetramethylsilane as an internal standard. ^{13}C NMR spectra were referenced to a tetrame-

thylsilane as an internal standard or to a solvent signal ($CDCl_3$: 77.0 ppm). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet, td = triple doublet, dq = double quartet, br = broad singlet. Low- and high-resolution mass spectra (LR-MS and HR-MS) were obtained from the Mass Spectrometry Resource, Graduate School of Pharmaceutical Sciences, Tohoku University, on JEOL JMS-DX303 and JMS-700 spectrometera, respectively.

Materials

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification (distillation or recrystallization). *t*-Bu-P_4 base (*tert*-butyl P_4 base, 1.0 M solution in *n*-hexane) was purchased from Fluka Chemie and used as supplied. Flash column chromatographies were performed with Kanto silica gel 60 N (spherical, neutral, 70–230 mesh).

Typical Procedure for the Preparation of Propargyl Silyl Ether 1a

To a solution of phenylacetylene (1.47 g, 15.0 mmol) in THF (100 mL) was added dropwise *n*-BuLi (1.6 M solution in *n*-hexane, 9.8 mL, 15.7 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 1 h, then benzaldehyde (1.02 g, 10.0 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h, then quenched with saturated NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated using a rotary evaporator to afford the crude product. Purification by column chromatography on silica gel (gradient elution; 5–15% AcOEt in hexane) afforded 1,3-diphenyl-prop-2-yn-1-ol. This product was used without further purification.

To a mixture of 1,3-diphenyl-prop-2-yn-1-ol and triethylamine (2.0 mL, 14 mmol) in CH_2Cl_2 (10 mL) was added trimethylsilylchloride (1.5 mL, 12.5 mmol) at 0 °C. The reaction mixture was stirred for 1 h, then hexane added and the mixture filtered to remove triethylammonium chloride. The filtrate was concentrated using a rotary evaporator to afford the crude product. Purification by distillation (4 torr, 140–145 °C) afforded trimethyl-(1,3-diphenylprop-2-ynyloxy)silane (**1a**); yield; 2.03 g (72% in 2 steps). Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.25$ (s, 9H), 5.71 (s, 1H), 7.28–7.33 (m, 4H), 7.38 (t, $J = 7.6$ Hz, 2H), 7.42–7.61 (m, 2H), 7.56 (d, $J = 7.6$ Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 0.34$, 65.14, 85.96, 89.73, 122.84, 126.50, 127.86, 128.23, 128.34, 128.40, 131.62, 141.44; LR-MS (EI): $m/z =$ 280 (M^+). HR-MS: $m/z = 280.1259$, calcd. for $C_{18}H_{20}NSi$: 280.1283; IR (neat): $\nu = 3062$, 2956, 1490, 1250, 1061, 872, 839, 752, 717, 688 cm^{-1}.

Typical Procedure for the Preparation of Imine 2a

Benzaldehyde (2.65 g, 25 mmol) and aniline (2.33 g, 25 mmol) were dissolved in ethanol (30 mL). The reaction mixture was stirred for 3 h at room temperature. The solvent was removed using a rotary evaporator. Purification of the residue by recrystallization gave *N*-benzylideneaniline (**2a**); yield: 3.36 g (83%) Recrystallization from Et_2O/hexane gave colorless needles; mp 51–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 7.18$–7.25 (m, 3H), 7.38 (t, $J = 8.0$ Hz, 2H), 7.44–7.48 (m, 3H), 7.87–7.92 (m, 2H), 8.44 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 120.83$, 125.89, 128.73, 128.77, 129.11, 131.33, 136.19, 152.05, 160.33; LR-MS (EI) $m/z = 181$ (M^+); HR-MS: $m/z = 181.0883$, calcd. for $C_{13}H_{11}N$: 181.0891; IR (neat): $\nu = 3058$, 2889, 2360, 1625, 1576, 1449, 1366, 1192, 1162, 754, 690 cm^{-1}.

Typical Procedure for the Synthesis of Pyrrole 3aa[12]

To a mixture of imine (0.25 mmol) and propargyl silyl ether (0.375 mmol) in toluene (1.0 mL) was added dropwise *t*-Bu-P_4 base (1.0 M solution in *n*-hexane, 25 μL, 0.025 mmol) at room temperature under an argon atmosphere. The reaction mixture was stirred for 3 h, then quenched with saturated NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated using a rotary evaporator to afford the crude product. Purification by column chromatography on silica gel afforded 1,2,3,5-tetraphenyl-1-*H*-pyrrole (**3aa**).Recrystallization from acetone/hexane gave colorless needles; mp 202–204 °C; anal. calcd. for $C_{28}H_{21}N$: C 90.53, H 5.70, N 3.77; found: C 90.58, H 5.90, N 3.74; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 6.70$ (s, 1H), 6.95–7.27 (m, 20H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 109.92$, 123.40, 125.39, 126.26, 126.87, 127.02, 127.75, 127.87, 128.04, 128.10, 128.38, 128.49, 129.02, 131.41, 132.11, 132.59, 132.82, 134.73, 136.04, 138.72; LR-MS (EI): $m/z = 371$ (M^+); HR-MS: $m/z = 371.1656$, calcd. for $C_{28}H_{21}N$: 371.1674; IR (neat): $\nu = 3058$, 1598, 1493, 1370, 1077, 1027, 914, 758, 694 cm^{-1}.

One-Pot Synthesis of Pyrrole 3df using Aldehyde, Alkynylsilane and Imine

To a mixture of 4-methoxybenzaldehyde (102.1 mg, 0.75 mmol) and phenylethynyltrimethylsilane (139.4 mg, 0.8 mmol) in toluene (1.0 mL) was dropwised *t*-Bu-P_4 base (1.0 M solution in n-hexane, 100 μL, 0.1 mmol) at −78 °C under an argon atmosphere. The reaction mixture was stirred for 1 h, then a solution of 4-chlorobenzylideneaniline (107.9 mg, 0.5 mmol) in toluene (0.5 mL) was added and the mixture warmed up to room temperature. The reaction mixture was stirred for 1 h, then quenched with saturated NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated using a rotary evaporator to afford the crude product. Purification by column chromatography on silica gel (gradient elution; 20–30% toluene in hexane) afforded 2-(4-chlorophenyl)-5-(methoxyphenyl)-1,3-diphenyl- 1-*H*-pyrrole (**3df**); yield: 182.4 mg (84%). Recrystallization from acetone/hexane gave colorless needles; mp 203–204 °C; anal. xalcd. for $C_{29}H_{22}ClNO$: C 79.90, H 5.09, Cl, 8.13, N 3.21, O 3.67; found: C 79.92, H 5.24, N 3.31; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.75$ (s, 3H), 6.61 (s, 1H), 6.73 (d, $J = 8.8$ Hz, 2H), 6.91–6.99 (m, 4H), 7.03 (d, $J = 8.8$ Hz, 2H), 7.09 (d, $J =$ 8.4 Hz, 2H), 7.13–7.26 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 55.11$, 109.43, 113.46, 123.78, 125.30, 125.66, 127.25, 128.12, 128.22, 128.28, 128.64, 129.09, 129.89, 130.05, 131.20, 132.59, 132.75, 135.07, 135.95, 138.61, 158.33; LR-MS (EI): $m/z = 435$ (M^+); HR-MS: $m/z = 435.1391$, calcd. for. $C_{29}H_{22}ClNO$: 435.1390; IR (neat): $\nu = 3074$, 2834, 2358, 1603,

1488, 1374, 1245, 1175, 1090, 1030, 1011, 829, 798, 760, 739 cm^{-1}.

X-Ray Analysis of 3ba

5-(4-Chlorophenyl)-1,2,3-triphenyl-1-*H*-pyrrole **3ba** was recrystallized from acetone/*n*-hexane at room temperature. X-ray data were collected on a Rigaku RAXIS-RAPID diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71075 Å). The data were corrected for Lorentz and polarization effects. The structures were solved by direct methods and refined by full-matrix least squares against F^2 using SHELXL-97 program.[13] Crystal data for the structure of **3ba** have been deposited in the Cambridge Crystallographic Data Center with number CCDC 671214. Crystal data of 5-(4-chlorophenyl)-1,2,3-triphenyl-1-*H*-pyrrole **3ba**: $C_{28}H_{20}NCl$, M = 405.93, triclinic, space group *P*-1 (No.2), a = 9.8755(4) Å, b = 10.2622(4) Å, c = 11.4287(6) Å, α = 83.9049(18)°, β = 86.0386(16)°, γ = 67.04551(12)°, V = 1060.01(8) $Å^3$, T = 173.3 K, Z = 2, μ(MoKα) = 1.945 cm^{-1}, 10457 reflections measured, 4798 unique (R_{int} = 0.027). The final R1 and wR2 were 0.0410 [$I > 2\sigma(I)$] and 0.1113 (for all data), respectively. {R1 = Σ||Fo| − |Fc||/Σ|Fo|, wR2 = [Σ(w($Fo^2 - Fc^2$)^2)/Σ w(Fo^2)^2]$^{1/2}$}.

Supporting Information

Full experimental details and characterization data for all compounds are given in the electronic Supporting Information.

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