JOC Note

Nickel- and Rhodium-Catalyzed Addition of Terminal Silylacetylenes to Propargyl Amines: Catalyst-Dependent Complementary Regioselectivity

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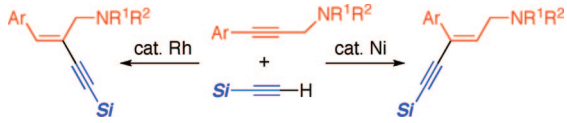

The cross-addition of terminal silylacetylenes to γ-arylated propargyl amines occurs efficiently via C−H cleavage by using either a nickel or rhodium catalyst. Taking advantage of the catalyst-controlled switching of regioselectivity in the reaction, both the 2- and 3-alkynylallylamines are readily accessible from the same starting materials.

The transition metal-catalyzed addition of terminal alkyne C−H bonds to carbon−carbon triple bonds ranks as the most simple and straightforward access to π-conjugated enynes, which are versatile building blocks in organic synthesis.[1] In particular, the catalytic homodimerization of terminal alkynes directed toward the selective synthesis of one of the three possible (*E*)-,[2] (*Z*)-,[3] and *gem*-[4]enyne isomers have been extensively studied. On the other hand, the selective cross-dimerization between terminal alkynes and internal ones is much more challenging since the terminal alkynes are prone to undergo the rapid homodimerization and oligomerization in the presence of transition metal catalysts. In 1987, Trost reported the highly selective palladium-catalyzed cross-dimerization with terminal and internal alkynes.[5] Subsequently, ruthenium,[6] rhodium,[7] iridium,[8] titanium,[9] and uranium[10] complexes were found to catalyze similar reactions. In most of these processes, however, the internal alkynes were limited to the activated ones bearing an electron-withdrawing group such as a carbonyl or sulfonyl moiety. Recently, some successful examples of the catalytic cross-addition of terminal silylacetylenes to unactivated terminal and internal alkynes or weakly activated ones such as propargyl ethers have been described.[11] Our groups also focused on the catalytic activities of nickel[12] and rhodium complexes and succeeded in the same type of transformation.[13] In the course of our study of this chemistry, we anticipated that our catalyst systems could be applied to the addition of terminal silylacetylenes to propargyl amines. The reaction is, to the best of our knowledge, unprecedented, while the expected products, 2- or 3-alkynylallylamines, are not only synthetically useful intermediates but also of pharmaceutical interest, especially the arylated derivatives for treating neurological disorders including Alzheimer's disease.[14] Herein, we report the nickel- and rhodium-catalyzed regio- and stereoselective addition of terminal silylacetylenes to γ-arylated propargyl amines, the regioselectivity being highly catalyst-dependent.

Treatment of *tert*-butyldimethylsilylacetylene (**1a**) with dimethyl(3-phenyl-2-propynyl)amine (**2a**) in the presence of $Ni(cod)_2$ (5 mol %) and an excess (to Ni) of 2,6-lutidine in toluene, which was an effective catalyst system in our previous work,[13a] gave the desired adduct **3aa** and its regioisomer **4aa** in a ratio of 94:6 with a good combined yield (Table 1, entry 1). The stereochemistry of each product was unambiguously determined by NOE analysis (see the Supporting Information). Notably, the corresponding stereoisomers were not detected. In

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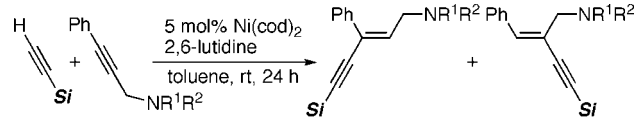
TABLE 1. Nickel-Catalyzed Addition of Terminal Silylacetylenes 1 to Propargylamines 2a−e[a]

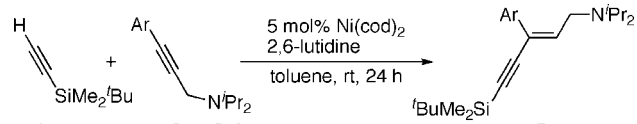


1 2 3 4

entry	Si in **1**	R^1, R^2 in **2**	% yield[b] **3**	% yield[b] **4**	**3**:**4**[c]
1	^{t}BuMe$_2$Si (**1a**)	Me, Me (**2a**)	**3aa**, 72	**4aa**, 6	94:6
2	**1a**	Et, Et (**2b**)	**3ab**, 82	**4ab**, 4	96:4
3	**1a**	^{i}Pr, ^{i}Pr (**2c**)	**3ac**, 90	**4ac**, trace	>99:1
4	**1a**	$(CH_2)_5$ (**2d**)	**3ad**, 82	**4ad**, 8	90:10
5	**1a**	$(CH_2)_2O(CH_2)_2$ (**2e**)	**3ae**, 80	**4ae**, 9	90:10
6	Me$_3$Si (**1b**)	**2a**	**3ba**, 54	**4ba**, 6	92:8
7	^{i}Pr$_3$Si (**1c**)	**2a**	**3ca**, 75	**4ca**, 7	92:8

[a] Reaction conditions: [**1**]:[**2**]:[Ni(cod)$_2$] = 0.75:0.25:0.0125 (in mmol), in toluene/2,6-lutidine (2.4:0.1 mL) under N_2 at rt for 24 h. [b] Isolated yield. The corresponding stereoisomers were not observed. [c] Determined by GC analysis in the crude mixture.

TABLE 2. Nickel-Catalyzed Addition of *tert*-Butyldimethylsilylacetylene (1a) to Propargylamines 2ca−cf[a]



1a 2ca−2cf 5

entry	Ar in **2**	**5**, % yield[b]
1	4-MeC$_6$H$_4$ (**2ca**)	**5aa**, 92
2	4-MeOC$_6$H$_4$ (**2cb**)	**5ab**, 87
3	4-CF$_3$C$_6$H$_4$ (**2cc**)	**5ac**, 98
4	4-ClC$_6$H$_4$ (**2cd**)	**5ad**, 75
5	4-MeO$_2$C (**2ce**)	**5ae**, 97
6	4-NCC$_6$H$_4$ (**2cf**)	**5af**, 82

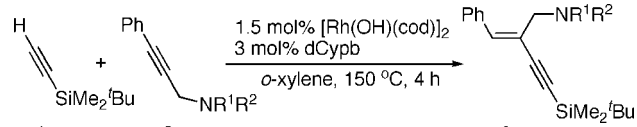
[a] Reaction conditions: [**1a**]:[**2**]:[Ni(cod)$_2$] = 0.75:0.25:0.0125 (in mmol), in toluene/2,6-lutidine (2.4:0.1 mL) under N_2 at rt for 24 h. [b] Isolated yield. No corresponding regio- and stereoisomer was detected.

addition, the reaction proceeded smoothly at room temperature, whereas the addition to propargyl ethers required elevated temperatures.[13a] Thus, the result may indicate that the propargyl amine has higher reactivity under nickel catalysis, compared to the corresponding ethers. The regioisomeric ratio of **3**:**4** increased from 94:6 to over 99:1 with increasing the size of substituents on nitrogen (entries 2 and 3). Piperidine and morpholine derivatives **2d** and **2e** also participated in the reaction without any difficulties (entries 4 and 5). Other terminal silylacetylenes were available for use. Both smaller trimethylsilylacetylene (**1b**) and bulkier triisopropylsilylacetylene (**1c**) reacted with **2a** to furnish **3ba** and **3ca**, respectively, with compatible regioselectivities (entries 6 and 7).

With *tert*-butyldimethylsilylacetylene (**1a**) as the terminal silylacetylene, we also examined the substituent effect on the phenyl moiety of **2c** (Table 2). Electron-rich **2cb** and electron-deficient **2cc** as well as electron-neutral **2ca** were converted to the corresponding enynes **5aa**−**ac** in high yields with excellent regioselectivities (entries 1−3). The reaction with **2cd** produced **5ad** in a good yield, leaving the sp^2 C−Cl moiety untouched (entry 4). Ester and nitrile functionalities were also tolerated under the reaction conditions (entries 5 and 6).[15]

(15) Unfortunately, the reaction with alkyl-substituted substrates such as diethyl(2-heptynyl)amine was unsuccessful. A large amount of the starting material was recovered intact.

TABLE 3. Rhodium-Catalyzed Addition of *tert*-Butyldimethylsilylacetylene (1a) to Propargylamines 2a−c[a]

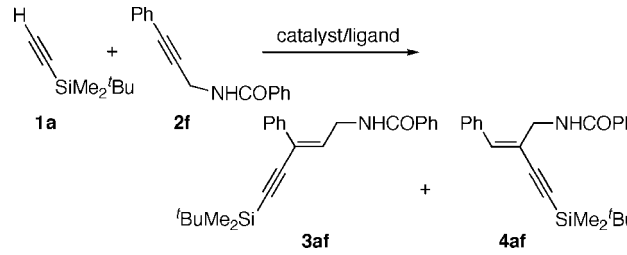


1a 2 4

entry	R^1, R^2 in **2**	**4**, % yield[b]	*E*/*Z*[c]
1	Me, Me (**2a**)	**4aa**, 92	91:9
2	Et, Et (**2b**)	**4ab**, 99	97:3
3	^{i}Pr, ^{i}Pr (**2c**)	**4ac**, 99	>99:1

[a] Reaction conditions: [**1a**]:[**2**]:[{Rh(OH)(cod)}$_2$]:[dCypb] = 0.75:0.25:0.0038:0.0075 (in mmol), in *o*-xylene (2.5 mL) at 150 °C under N_2 for 4 h. [b] Isolated yield. No corresponding regioisomer was detected. [c] Determined by ^{1}H NMR.

TABLE 4. Catalytic Addition of *tert*-Butyldimethylsilylacetylene (1a) to Propargylamide 2f[a]



1a 2f 3af 4af

entry	catalyst/ligand	conditions	% yield[b] (**3af**/**4af**)[c]
1	5 mol % of Ni(cod)$_2$/0.1 mL of 2,6-lutidine	toluene, rt, 24 h	21 (81:19)
2	5 mol % of Ni(cod)$_2$/5 mol % of xantphos	toluene, 120 °C, 3 h	75 (28:72)
3	1.5 mol % of [Rh(OH)(cod)]$_2$/3 mol % of dCypb	*o*-xylene, 150 °C, 4 h	79 (0:100[d])

[a] Reaction conditions: a mixture of **1a** (0.75 mmol), **2f** (0.25 mmol), and catalyst/ligand was stirred under the indicated conditions. [b] Isolated yield. [c] The ratio was determined by ^{1}H NMR. [d] *E*/*Z* = 90:10.

Next, in order to explore an efficient route to 2-alkynylallylamine **4**, we attempted to switch the regioselectivity in the reaction by ligand control. However, the approach was unsuccessful as far as we examined. According to our previous observation,[13b,c] we then turned our attention to rhodium-based processes (Table 3). Gratifyingly, upon treatment of **1a** with **2a** in the presence of [Rh(OH)(cod)]$_2$/dCypb (dCypb = 1,4-bis(dicyclohexylphosphino)butane) catalyst in *o*-xylene at 150 °C (bath temperature), the corresponding 2-alkynylated product **4aa** was obtained as the sole regioisomer in 92% yield with good stereoselectivity (entry 1). Bulkier substitutions on nitrogen improved the stereoselectivity (entries 2 and 3).

The catalytic addition to amide **2f** containing an acidic proton on nitrogen was also performed (Table 4). The reaction of **2f** using the Ni(cod)$_2$/2,6-lutidine system resulted in the formation of an 81:19 mixture of **3af** and **4af** with only 21% combined yield (entry 1). After some additional ligand investigation, the use of 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (xantphos) instead of 2,6-lutidine at 120 °C was found to lead to the corresponding adducts in 75% combined yield. However, to our surprise, a different regioselectivity was observed, and thus, the major regioisomer was enyne **4af** (entry 2). Although the exact

reason is not clear at this stage, the uniquely large bite angle of xantphos would cause the unusual regioselectivity. It is noteworthy that the amide **2f** was converted successfully to **4af** by using the $[Rh(OH)(cod)]_2$/dCypb system (entry 3).

In summary, we have found the nickel- and rhodium-catalyzed regio- and stereoselective addition of terminal silylacetylenes to propargyl amines and developed the facile methods for the preparation of allylamine-moiety-containing π-conjugated enynes of synthetic value. Notably, both regioisomers bearing a versatile silyl function can be selectively synthesized from the same starting materials by the proper choice of catalysts.

Experimental Section

Typical Procedure for Nickel-Catalyzed Addition of Terminal Silylacetylenes to Propargyl Amines. The reaction of *tert*-butyldimethylsilylacetylene (**1a**) with dimethyl(3-phenyl-2-propynyl)amine (**2a**) is representative (Table 1, entry 1). In a glovebox filled with nitrogen, $Ni(cod)_2$ (0.050 M toluene solution, 0.25 mL, 0.013 mmol), **1a** (105 mg, 0.75 mmol), **2a** (40 mg, 0.25 mmol), 2,6-lutidine (0.10 mL), toluene (2.4 mL), and dibenzyl (ca. 50 mg, internal standard) were placed in a Schlenk tube. The tube was then taken outside the glovebox, and the mixture was stirred at room temperature for 24 h. After the consumption of the starting materials was checked by GC analysis, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (80:20, v/v) as an eluent to furnish a mixture of (*E*)-[5-(*tert*-butyldimethylsilyl)-3-phenyl-2-penten-4-ynyl]dimethylamine (**3aa**) and (*E*)-[2-benzylidene-4-(*tert*-butyldimethylsilyl)-3-butynyl]dimethylamine [(*E*)-**4aa**]. Further purification by preparative TLC (PTLC) afforded analytically pure **3aa** (54 mg, 0.18 mmol) and (*E*)-**4aa** (4.5 mg, 0.011 mmol) in 72% and 6% yields, respectively. **3aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.95 (s, 9H), 2.20 (s, 6H), 3.09 (d, $J = 7.0$ Hz, 2H), 6.31 (t, $J = 7.0$ Hz, 1H), 7.25−7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, 16.7, 26.1, 45.7, 57.8, 91.1, 107.0, 125.8, 127.6, 128.0, 128.8, 136.9, 137.7; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{29}NSi$, 299.2069. Found 299.2075. (*E*)-**4aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.98 (s, 9H), 2.33 (s, 6H), 3.09 (s, 2H), 7.09 (s, 1H), 7.23−7.30 (m, 1H), 7.34 (t, $J = 7.3$ Hz, 2H), 7.45 (d, $J = 7.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, 16.8, 26.2, 45.4, 59.7, 92.2, 109.7, 127.7, 128.0, 128.2, 129.6, 136.3, 140.6; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{29}NSi$, 299.2069. Found 299.2073.

Typical Procedure for Rhodium-Catalyzed Addition of Terminal Silylacetylenes to Propargyl Amines. The reaction of *tert*-butyldimethylsilylacetylene (**1a**) with dimethyl(3-phenyl-2-propynyl)amine (**2a**) is representative (Table 3, entry 1). In a glovebox filled with nitrogen, $[Rh(OH)(cod)]_2$ (1.7 mg, 0.0038 mmol), dCypb (3.4 mg, 0.0075 mmol), **1a** (105 mg, 0.75 mmol), **2a** (40 mg, 0.25 mmol), *o*-xylene (2.5 mL), and dibenzyl (ca. 50 mg, internal standard) were placed in a Schlenk tube, and the tube was then taken outside the glovebox. After being heated at 150 °C for 4 h, the consumption of the starting materials was confirmed by GC analysis. The solvent was evaporated and purification of the residue by column chromatography on silica gel produced **4aa** (69 mg, 0.23 mmol, *E*/*Z* = 91:9) in 92% yield.

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Supporting Information Available: Characterization data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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