Synthetic Methods

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Highly Chemoselective Nickel-Catalyzed Three-Component Cross-Trimerization of Three Distinct Alkynes Leading to 1,3-Dien-5-ynes

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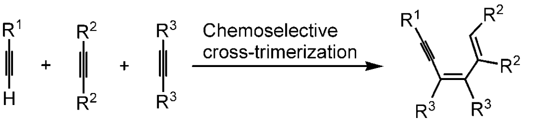
The transition-metal-catalyzed coupling reaction of alkynes is a highly attractive synthetic method for π-conjugated compounds because of its atom economy. Among its various applications in the field of dimerization of alkynes, the cross-dimerization of two different alkynes has been recognized as a versatile method in the formation of 1,3-enynes.[1] Recently, investigations of this reaction have been extended to involve bulky silyl-substituted terminal alkynes.[2] In contrast, the selective linear cross-trimerization of alkynes leading to 1,3-dien-5-ynes has yet to be studied in detail[3] even though much research on the two-component cross-cyclotrimerization reaction, which has been recognized as a versatile method for the synthesis of multisubstituted benzene rings, has been reported.[4] Moreover, such reactions have been limited to a two-component reaction involving two different alkynes, that is, 1:2 or 2:1 cross-trimerization between terminal and internal alkynes. The three-component linear cross-trimerization of three distinct alkynes has yet to be developed [Eq. (1)]. The three-component reaction is challenging because of the need to control the chemoselectivity of each alkyne.[5]

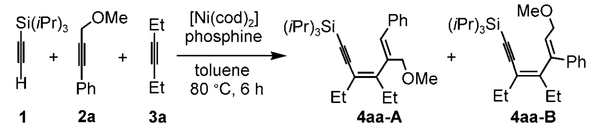


(1)

We have previously achieved the effective and highly regio- and stereoselective 1:2 cross-trimerization involving triisopropylsilylacetylene and two internal alkynes using $[Ni(cod)_2]/P(nPr)_3$ (cod = 1,5-cyclooctadiene) as the catalyst.[3d] In this report, we demonstrate the first highly chemo-, regio-, and stereoselective 1:1:1 three-component cross-trimerization leading to 1,3-dien-5-ynes by the combination of triisopropylsilylacetylene, an ether-functionalized unsymmetrical internal alkyne, and a symmetrical internal alkyl alkyne in the presence of $[Ni(cod)_2]/PPh_3$ as a catalyst.

First, the effect of phosphine was investigated for the three-component cross-trimerization reaction involving triisopropylsilylacetylene (**1**), the ether-functionalized internal alkyne **2a**, and 3-hexyne (**3a**), as shown in Table 1. In the presence of the $[Ni(cod)_2]/2\,PPh_3$ catalyst (10 mol%), the three-component cross-trimerization reaction proceeded smoothly at 80 °C to afford **4aa** in high yield with complete chemoselectivity (Table 1, entry 1); the ratio between the major (**4aa-A**) and minor (**4aa-B**) isomers was determined to be **A**/**B** = 93:7 by integrating the ^{1}H NMR signals for the alkene proton of each isomer.[6] In comparison, **4aa** was obtained in a lower yield using the $[Ni(cod)_2]/P(nPr)_3$ catalyst, which was previously shown to be effective for the two-component 1:2 cross-trimerization between **1** and two molecules containing an internal alkyne (Table 1, entry 2).[3d] A homodimer of **1** and the 1:2 cross-trimer between **1** and **2a** were also detected as byproducts by using GC-MS methods. In the case of a bulky arylphosphine, $P(o\text{-tolyl})_3$, the cross-trimerization reaction was not observed (Table 1, entry 3).[7] Other alkylphosphines such as $P(nBu)_3$, $P(iPr)_3$, and PCy_3 were not effective (Table 1, entries 4–6) in the reaction, and the $[Ni(cod)_2]$/dppe-catalyzed reaction resulted in a moderate product yield (Table 1, entry 7). On the basis of a screen of phosphine ligands, the highest yield and regioselectivity for the formation of the three-component cross-trimer **4aa** was achieved using PPh_3. For reactions using other bulky silylacetylene such as *tert*-butyldimethylsilylacetylene under these conditions, the corresponding three-component cross-trimer was obtained in lower yield and regioselectivity.[8]

Table 1: Screening of phosphine ligands for the three-component cross-trimerization between **1**, **2a**, and **3a**.[a]



Entry	Phosphine	Yield [%][b]	A/B[c]
1	PPh_3	92	93:7
2	$P(nPr)_3$	61	83:17
3	$P(o\text{-tolyl})_3$	0[d]	–
4	$P(nBu)_3$	51	81:19
5	$P(iPr)_3$	16	85:15
6	PCy_3	22	89:11
7	dppe	65	87:13

[a] Reaction conditions: $[Ni(cod)_2]$ (0.10 mmol), phosphine (0.20 mmol), **1** (1.0 mmol), **2a** (1.0 mmol), **3a** (2.0 mmol), and toluene (3 mL) were employed. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis. [d] Homodimer of **1** was formed; see reference [7]. Cy = cyclohexyl, dppe = bis(1,2-diphenylphosphinoethane).

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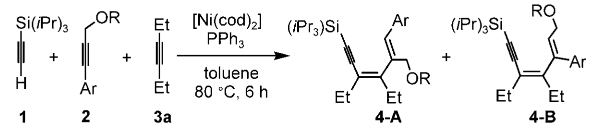
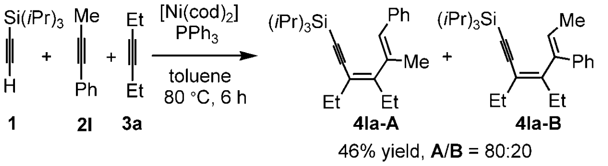
Table 2: Nickel-catalyzed three-component cross-trimerization between **1**, **2a–k**, and **3a**.[a]



Entry	**2**	R	Ar	**4** (yield [%])[b]	**A**/**B**[c]
1	**2a**	Me	Ph	**4aa** (92)	93:7
2	**2b**	Et	Ph	**4ba** (87)	91:9
3	**2c**	MOM	Ph	**4ca** (85)	91:9
4	**2d**	Me	p-MeC$_6$H$_4$	**4da** (88)	94:6
5	**2e**	Me	m-MeC$_6$H$_4$	**4ea** (75)	88:12
6	**2f**	Me	o-MeC$_6$H$_4$	**4fa** (74)	85:15
7	**2g**	Me	p-MeOC$_6$H$_4$	**4ga** (90)	96:4
8	**2h**	Me	p-CF$_3$C$_6$H$_4$	**4ha** (65)	82:18
9	**2i**	Me	p-ClC$_6$H$_4$	**4ia** (92)	89:11
10	**2j**	Me	3-pyridyl	**4ja** (90)	91:9
11	**2k**	Me	2-thiophenyl	**4ka** (89)	80:20

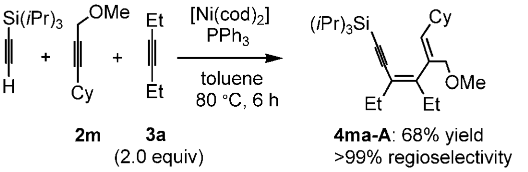
[a] Reaction conditions: [Ni(cod)$_2$] (0.10 mmol), PPh$_3$ (0.20 mmol), **1** (1.0 mmol), **2** (1.0 mmol), **3a** (2.0 mmol), and toluene (3 mL) were employed. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis.

Next, the [Ni(cod)$_2$]/2 PPh$_3$-catalyzed three-component cross-trimerization was examined using various ether-functionalized internal alkynes **2**, as shown in Table 2. Ethoxy- and methoxymethyl (MOM)-substituted alkynes (**2b** and **2c**, respectively) furnished the corresponding products, **4ba** and **4ca**, respectively, in good yields with high regioselectivities (Table 2, entries 2 and 3). In contrast, replacement of ether-functionalized alkyne **2** with 1-phenyl-1-propyne (**2l**) resulted in a lower yield and regioselectivity of the corresponding cross-trimer **4la** [Eq. (2)], whereas substitution with a bis(ether)-functionalized symmetrical internal alkyne, bis(ethoxymethyl)acetylene, resulted in a low yield of the cross-trimer because of low chemoselectivity (25 % yield, see the Supporting Information). Other functionalized alkynes including propargylamine and ester-functionalized alkynes such as diethyl(3-phenyl-2-propynyl)amine and ethyl phenylpropiolate could not participate in the reaction. These results indicate that the use of an unsymmetrical internal alkyne possessing an ether group is essential for the effective three-component cross-trimerization of alkynes. The use of electron-donating p-, m-, o-methyl- or p-methoxy-substituted aryl alkynes also afforded cross-trimer **4** with high regioselectivities in good to high yields (Table 2, entries 4–7), and the presence of an electron-withdrawing trifluoromethyl-substituted alkyne resulted in the formation of cross-trimer **4ha** with good regioselectivity, albeit in a moderate yield (Table 2, entry 8). In spite of the low-valent nickel catalyst, the p-chloro-substituted aryl alkyne **2i** reacted to selectively afford the corresponding cross-trimer **4ia** in high yield (Table 2, entry 9). Reactions of **2j** and **2k**, which possess heteroaryl groups, also proceeded to form the products **4ja** and **4ka** in high yields, albeit the regioselectivity of **4ka** is lower than that of **4ja** (Table 2, entries 10 and 11).



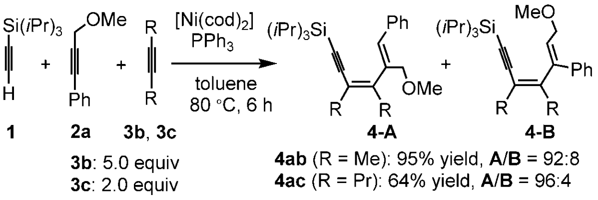
(2)

In addition to the arylacetylenes, cyclohexyl-substituted asymmetrical acetylene **2m** was also effective in affording the corresponding cross-trimer **4ma** with excellent regioselectivity and in good yield [Eq. (3)]. However, replacement of the cyclohexyl group with a n-hexyl group resulted in a complex mixture.



(3)

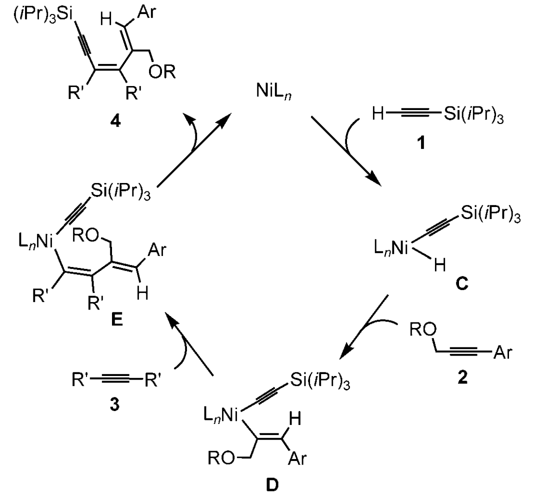
Furthermore, two more symmetrical internal alkyl alkynes, 2-butyne (**3b**) or 4-octyne (**3c**), were also shown to proceed with high regioselectivities and high or good yields [Eq. (4)].



(4)

As shown in the proposed mechanism of the three-component cross-trimerization (Scheme 1), the reaction presumably proceeds through a reaction mechanism similar to that of the two-component cross-trimerization reactions[3d] and the nickel-catalyzed dimerization of alkynes.[9] First, the oxidative addition of the C–H bond of triisopropylsilylacetylene onto nickel(0) forms the nickel(II)–alkynyl hydride intermediate **C**.[10] Next, the selective insertion of alkyne **2** into the Ni–H bond of intermediate **C** results in the formation of intermediate **D** (**C**→**D**), in which the chemoselectivity of the insertion reaction may be accelerated by the ligation of the oxygen atom to the nickel center.[11] The regioselectivity can be attributed to the restriction of the insertion direction of alkyne **2** to avoid the steric hindrance between the nickel fragment and the aryl or cyclohexyl group. Next, internal alkyne **3** bearing a small substituent is inserted into the Ni–C bond of sterically hindered intermediate **D** (**D**→**E**).[12] Lastly, the formation of **4** is achieved by C–C reductive coupling.

In summary, we have demonstrated the first chemoselective three-component cross-trimerization of three distinct alkynes leading to 1,3-dien-5-ynes by combining triisopropylsilylacetylene, an ether-functionalized unsymmetrical



Scheme 1. Possible pathway for the three-component cross-trimerization of alkynes.

internal alkyne, and a symmetrical internal alkyne and using [Ni(cod)$_2$]/PPh$_3$ as the catalyst. Moreover, our highly chemo-, regio-, and stereoselective reaction is applicable for various internal alkynes.

Experimental Section

Representative procedure (Table 2, entry 1): A mixture of [Ni(cod)$_2$] (28 mg, 0.10 mmol), toluene (3 mL), triphenylphosphine (52 mg, 0.20 mmol), triisopropylsilylacetylene (**1**) (0.22 mL, 1.0 mmol), **2a** (146 mg, 1.0 mmol) and 3-hexyne (**3**) (0.24 mL, 2.0 mmol) was charged in Schlenk tube under nitrogen atmosphere. After stirring for 6 h at 80°C, the solution was filtered though a small amount of silica gel. The residue was purified by silica gel preparative TLC (ether/*n*-hexane 1:5), which furnished **4aa** (378 mg, 0.92 mmol, 92% yield) as a pale-yellow oil. ^{1}H NMR (CDCl$_3$, 300 MHz): $\delta = 1.0$–1.2 (m, 27 H, Si*i*Pr$_3$, Et-CH$_3$), 2.2–2.4 (m, 4 H, Et-CH$_2$), 3.33 (s, 3 H, OMe), 4.21 (s, 2 H, OCH$_2$), 6.70 (s, 1 H, C=CH), 7.2–7.4 ppm (m, 5 H, Ph); OCH$_2$ and C=CH protons of minor isomer **4aa-B**; $\delta = 3.89$ (d, $J = 7.0$ Hz, 2 H, OCH$_2$), 5.87 ppm (t, $J = 7.0$ Hz, C=CH); ^{13}C NMR (CDCl$_3$, 75 MHz): $\delta = 11.3$ (s, Si*i*Pr$_3$-CH), 12.9, 13.5 (s, Et), 18.6 (s, Si*i*Pr$_3$-CH$_3$), 24.4, 25.7 (s, Et), 58.0, 70.0 (s, OMe, OCH$_2$), 92.3, 108.2 (s, C≡C), 120.7, 126.8, 127.8, 129.0, 133.6, 136.9, 139.7, 151.0 ppm (s, C=C, Ph); HRMS (ESI) calcd for C$_{27}$H$_{42}$OSi $[M+\text{Na}]^+$ 433.2903, found 433.2938.

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[6] NOESY spectra of **3aa-A** and **3ga-A** are shown in the Supporting Information.

[7] A homodimer of **1** ((*E*)-1,4-bis(triisopropylsilyl)but-1-en-3-yne) was obtained in 60% yield.

[8] The corresponding three-component cross-trimer was obtained in 40% yield (**A**/**B** = 86:14) using [Ni(cod)$_2$]/PPh$_3$ as a catalyst.

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