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Highly Chemoselective Nickel-Catalyzed Three-Component Cross-Trimerization between Two Distinct Terminal Alkynes and an Internal Alkyne

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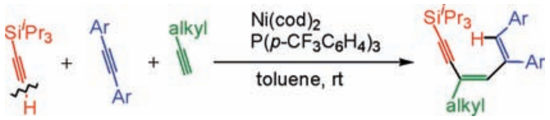
ABSTRACT



The highly chemo-, regio-, and stereoselective three-component cross-trimerization reaction between triisopropylsilylacetylene, diarylacetylene, and a terminal alkyne was achieved by Ni(cod)$_2$/P(p-CF$_3$C$_6$H$_4$)$_3$ catalyst at room temperature via selective C−H oxidative addition of the terminal silylacetylene. The reaction is applicable for various diarylacetylenes and terminal alkynes to yield the corresponding 1,3-diene-5-yne compounds.

The transition metal-catalyzed addition of an alkyne C−H bond onto an unsaturated C−C bond is an effective and highly atom economical method for construction of new C−C bonds.[1,2] Recently, investigations of this reaction have been extended to involve bulky silyl-substituted terminal alkynes. Using a bulky silylacetylene, a successful hydroalkynylation onto an unsaturated C−C bond has been reported.[2,3] The majority of the reports within this category are cross-dimerizations of alkynes resulting from the addition of a terminal silylacetylene C−H bond onto C−C triple bonds of other alkyne molecules.[2] In addition to cross-dimerizations of alkynes, some examples of cross-trimerizations of alkynes involving terminal silylacetylene and internal alkynes leading to 1,3-diene-5-ynes have been reported.[4] We have recently reported highly selective 1:2 and 1:1:1 cross-trimerizations of alkynes between a terminal silylacetylene and two identical or distinct internal alkynes in the presence of Ni(cod)$_2$/phosphine catalyst.[4d,e] Although the 2:1 cross-trimerization involving two identical terminal silylacetylenes and an internal alkyne in the presence of a nickel catalyst has been reported,[4a,b] the three-component cross-trimerization involving two distinct terminal alkynes has yet to be studied. The 1:1:1 three-component cross-trimerization with two distinct terminal alkynes is more

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(1) For examples of cross-dimerization between terminal alkyne and an electron-deficient internal alkyne, see: (a) Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255. (b) Trost, B. M.; Frontier, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 11727. (c) Chen, L.; Li, C. *Tetrahedron Lett.* **2004**, *45*, 2771. (d) Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* **2005**, *347*, 872.

(2) For examples of cross-dimerization of alkynes involving bulky silylacetylene, see: (a) Katayama, H.; Yari, H.; Tanaka, M.; Ozawa, F. *Chem. Commun.* **2005**, 4336. (b) Nishimura, T.; Guo, X.-X.; Ohnishi, K.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2669. (c) Katagiri, T.; Tsurugi, H.; Funayama, A.; Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 830. (d) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919. (e) Katagiri, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Commun.* **2008**, 3405. (f) Ogata, K.; Oka, O.; Toyota, A.; Suzuki, N.; Fukuzawa, S.-i. *Synlett* **2008**, 2663. (g) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3576.

(3) Hydroalkynylation of bulky silylacetylene onto alkenes such as diene, styrene, methylenecyclopropane, and α,β-unsaturated ketone: (a) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (b) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (c) Shirakura, M.; Suginome, M. *Org. Lett.* **2009**, *11*, 523. (d) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060.

(4) (a) Ishikawa, M.; Ohshita, J.; Ito, Y.; Minato, A. *J. Chem. Soc., Chem. Commun.* **1988**, 804. (b) Matsuyama, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2008**, *350*, 2274. (c) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. (d) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (e) Ogata, K.; Sugasawa, J.; Fukuzawa, S.-i. *Angew. Chem., Int. Ed.* **2009**, *48*, 6078.

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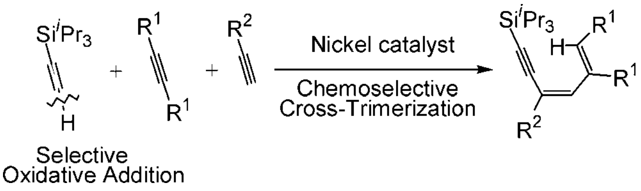
challenging than the 1:2 and 2:1 cross-trimerizations of alkynes involving terminal alkynes and internal alkynes because oxidative addition of each of the two kinds of terminal alkynes onto the metal center is competitive. Additionally, control of the chemoselectivity of the terminal alkynes is required.

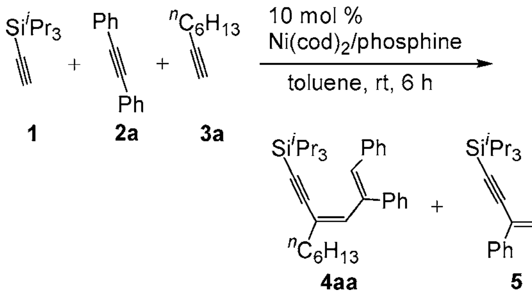
In this report, we demonstrate the first chemoselective three-component cross-trimerization between two distinct terminal alkynes and an internal alkyne by the combination of triisopropylsilylacetylene, diarylacetylene, and a terminal alkyl alkyne in the presence of nickel(0)/phosphine as a catalyst at room temperature (Scheme 1).

Scheme 1



First, several phosphines were screened in the three-component cross-trimerization reaction of triisopropylsilylacetylene (**1**), diphenylacetylene (**2a**), and 1-octyne (**3a**), as shown in Table 1. In the presence of Ni(cod)$_2$/2P(p-CF$_3$C$_6$H$_4$)$_3$, the three-component cross-trimerization reaction proceeded smoothly at room temperature to afford **4aa**, in high yield, and with complete regio- and stereoselectivities (entry 1).[5,6] This catalytic system was previously reported by Miura et al. in the 2:1 cross-trimerization reaction between 2 equiv of trimethylsilylacetylene and diarylacetylene.[4b] At a higher reaction temperature (80 °C), the reaction resulted in a lower yield of **4aa** (entry 2). Under those reaction conditions, the cross-dimeric product **5** resulting from the reaction between **1** and **2a** was also formed. The reaction with other arylphosphines such as P(p-MeOC$_6$H$_4$)$_3$, PPh$_3$, P(2-furyl)$_3$, and PMePh$_2$ resulted in lower yields of **4aa** (entries 3−6). Alkylphosphines such as P^{n}Pr$_3$ and PCy$_3$ were not effective in this reaction (entries 7 and 8). This screening of phosphine ligands revealed that the highest yield for the formation of the three-component cross-trimer **4** was achieved with P(p-CF$_3$C$_6$H$_4$)$_3$.

Table 1. Screening of Phosphine Ligands for the Three-Component Cross-Trimerization between **1**, **2a**, and **3a**[a]

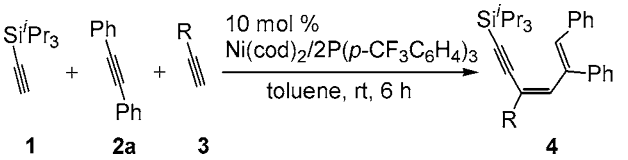


entry	phosphine	yield (%) of **4aa**[b]	yield (%) of **5**[b]
1	P(p-CF$_3$C$_6$H$_4$)$_3$	89	trace
2[c]	P(p-CF$_3$C$_6$H$_4$)$_3$	60	31
3	P(p-MeOC$_6$H$_4$)$_3$	66	10
4	PPh$_3$	88	5
5	P(2-furyl)$_3$	55	0
6	PMePh$_2$	51	5
7	P^{n}Pr$_3$	7	3
8	PCy$_3$	12	60

[a] Reaction conditions: Ni(cod)$_2$ (0.10 mmol), phosphine (0.20 mmol), **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), and toluene (3 mL) were employed. [b] GC yield. [c] Reaction was carried out at 80 °C

Using this optimized catalytic system, Ni(cod)$_2$/2P(p-CF$_3$C$_6$H$_4$)$_3$, the three-component cross-trimerization with several terminal alkynes **3** was examined, as shown in Table 2. In addition to n-alkyl alkyne, benzylacetylene **3b** also participated in this reaction to give the cross-trimer **4ab** in high yield (entry 2). A secondary alkyl alkyne such as cyclohexylacetylene **3c** furnished the corresponding product **4ac** in good yield (entry 3). The use of a bulky tertiary alkyl alkyne, *tert*-butylacetylene **3d**, also afforded cross-trimer **4ad** in good yield (entry 4). A functionalized alkyne possessing a silyl-protected alcohol **3e** also participated in this reaction (entry 5). In spite of the low-valent nickel catalyst, alkyl chloride-substituted alkyne **3f** selectively afforded the corresponding product **4af** (entry 6). Reaction of **3g**, which possesses an ester group, also proceeded to form product **4ag** in high yield (entry 7). Unfortunately, phenylacetylene

Table 2. Ni-Catalyzed Three-Component Cross-Trimerization between **1**, **2a**, and **3a−h**[a]



entry	3	R	4 (% yield)[b]
1	**3a**	n-Hex	**4aa** (89)
2	**3b**	CH$_2$Ph	**4ab** (88)
3	**3c**	Cy	**4ac** (61)
4	**3d**	^{t}Bu	**4ad** (67)
5	**3e**	CH$_2$CH$_2$OTBS	**4ae** (82)
6	**3f**	CH$_2$CH$_2$CH$_2$Cl	**4af** (70)
7	**3g**	CH$_2$CH$_2$CH$_2$COOCH$_3$	**4ag** (86)
8	**3h**	Ph	− (0)

[a] Reaction conditions: Ni(cod)$_2$ (0.10 mmol), P(p-CF$_3$C$_6$H$_4$)$_3$ (0.20 mmol), **1** (1.0 mmol), **2a** (1.0 mmol), **3** (1.0 mmol), and toluene (3 mL) were employed. [b] Isolated yield.

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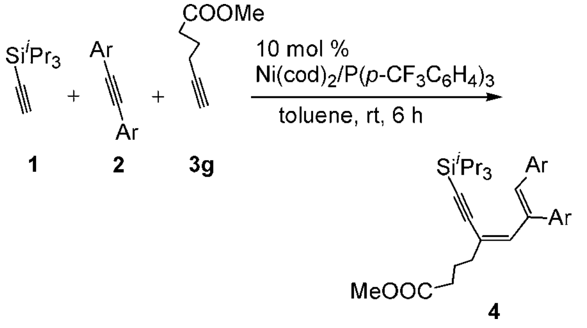
(5) Structure of **4** was confirmed by NOESY.

(6) The reaction with lower catalytic loading (5.0 mol %) resulted in lower yield of **4aa** (61% yield). Product **4aa** was not formed with palladium(0)/phosphine complex such as Pd$_2$(dba)$_3$/4P(p-CF$_3$C$_6$H$_4$). In this case, homodimer of **1** was confirmed as the main product by GC-MS.

did not participate in this reaction (entry 8).[7] Replacement of terminal alkyne with terminal 1,3-diyne such as 1,3-decadiyne resulted in a complex mixture.

After demonstrating the scope in substitution patterns of terminal alkynes, we next examined the scope tolerated in the internal alkyne partner (Table 3). The reaction with electron-donating *p*-methyl- and methoxy-substituted diarylalkynes also afforded cross-trimers **4** with high yields (entries 2 and 3), and the presence of electron-withdrawing *p*-trifluoromethyl- and *p*-chloro-substituted diarylalkynes resulted in the formation of cross-trimers **4** in high or good yields (entries 4 and 5). Sterically hindered diarylacetylene, which possesses *o*-fluorophenyl groups, also participated in the reaction (entry 6). Reaction of **2g** possessing thienyl groups also proceeded to form the product **4gg** in good yield (entry 7). However, replacement of the aryl groups with 2-pyridyl groups resulted in a complex mixture, and the corresponding cross-trimerization reaction did not proceed. In addition to the diarylacetylene, the cross-trimerization reaction with aryl propargyl ether **2h**, which participated in the cross-trimerization of an alkyne involving **1** and two distinct internal alkynes,[4e] was also shown to proceed, albeit with the formation of small amounts of regioisomers (Scheme 2).[8] In contrast, propargylamine could not participate in the reaction.

Table 3. Ni-Catalyzed Three-Component Cross-Trimerization between **1**, **2a−f**, and **3g**[a]

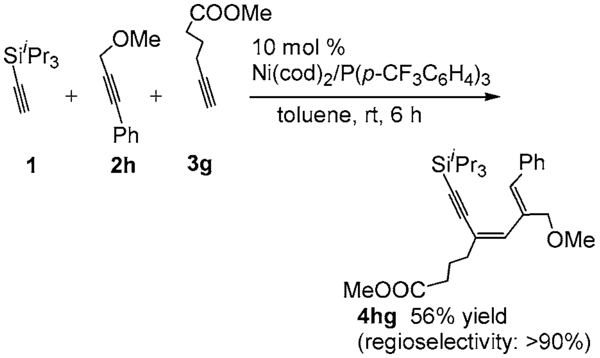


entry	2	Ar	4 (% yield)[b]
1	**2a**	Ph	**4ag** (89)
2	**2b**	*p*-$CH_3C_6H_4$	**4bg** (84)
3	**2c**	*p*-$CH_3OC_6H_4$	**4cg** (66)
4	**2d**	*p*-$CF_3C_6H_4$	**4dg** (80)
5	**2e**	*p*-ClC_6H_4	**4eg** (65)
6	**2f**	*o*-FC_6H_4	**4fg** (56)
7	**2g**	2-thienyl	**4gg** (63)

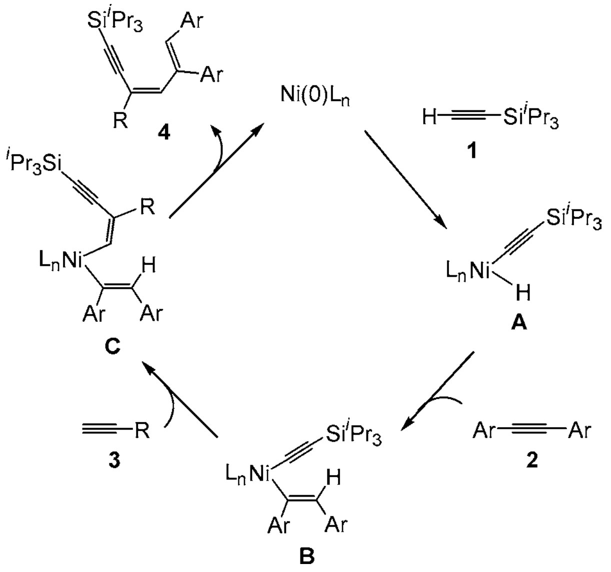
[a] Reaction conditions: Ni(cod)$_2$ (0.10 mmol), P(p-CF$_3$C$_6$H$_4$)$_3$ (0.20 mmol), **1** (1.0 mmol), **2** (1.0 mmol), **3g** (1.0 mmol), and toluene (3 mL) were employed. [b] Isolated yield.

A possible pathway for the three-component cross-trimerization is shown in Scheme 3. First, the chemoselective oxidative addition of the silylacetylene C−H bond to the nickel(0) metal affords nickel(II) hydride alkynyl intermediate **A**,[9] followed by insertion of diarylacetylene **2** into the Ni−H bond to give intermediate **B**. Next, terminal alkyne **3** is inserted into the Ni−C(acetylide) bond of intermediate **B**, resulting in the formation of intermediate **C**. In this step, insertion of **1** is probably prevented by the steric bulkiness of its triisopropyl group, and selective insertion of **3** is preferred.[10] The regioselective insertion of the terminal alkyne can be attributed to sterics as well, since the alkyl substituent of the terminal alkyne may prefer to be located far from the sterically hindered nickel center. Lastly, the formation of cross-trimer **4** is achieved by C−C reductive coupling.

Scheme 2



Scheme 3



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[7] In this case, [2 + 2 + 2] cycloaddition reaction of phenylacetylene was confirmed by GC-MS.

[8] Another regioisomer of **4hg** was confirmed by GC.

[9] The formation of a nickel(II)−hydride complex from Ni(cod)$_2$/phosphine by reaction with a terminal alkyne is usually postulated, See ref 2 and reference therein.

[10] In the reaction with trimethylsilylacetylene instead of triisopropylsilylacetylene, the selective three-component reaction did not proceed, and a 2:1 cross-trimerization product involving two molecules of trimethylsilylacetylenes and a diphenylacetylene was formed in 21% isolated yield. This two-component cross-trimerization product has been reported, ref 4b.

In summary, we have demonstrated the first chemoselective three-component cross-trimerization of two distinct terminal alkynes and an internal alkyne by combining triisopropylsilylacetylene, a diaryl alkyne, and a terminal alkyne. The reaction proceeded via selective oxidative addition of a terminal C−H bond of triisopropylsilylacetylene to the nickel metal center and selective insertion of another terminal alkyne and diaryl alkyne with $Ni(cod)_2/P(p\text{-}CF_3C_6H_4)_3$ as the catalyst.

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Supporting Information Available: Standard experimental procedure and characterization data for the new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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