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Nickel-Catalyzed Highly Chemo-, Regio-, and Stereoselective Three-Component Reaction of Norbornene with Two Alkynes

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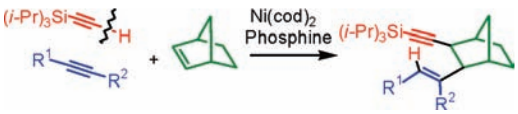
ABSTRACT



The first three-component reaction of norbornene with two alkynes leading to 1,5-enyne via C−H bond activation of terminal silylacetylene was achieved using a Ni(cod)$_2$/phosphine catalyst. This reaction is applicable for various internal alkynes and norbornene derivatives with high regio- and stereoselectivities.

The transition-metal-catalyzed addition of a C−H bond onto an unsaturated C−C bond has been widely employed for the effective construction of new C−C bonds. In particular, the addition reaction of a terminal alkyne C−H bond has allowed a convenient and simple method for the synthesis of functionalized alkynes. Although the majority of reports within this category are those of dimerization and cross-dimerization of alkynes,[1] addition onto C−C double bonds has also been reported for alkenes, such as norbornene,[2] norbornadiene,[3] cyclopropene,[4] allene,[5] diene,[6] styrene,[7] and methylenecyclopropane.[8] These reactions, however, are limited to simple hydroalkynylation of alkenes. The simultaneous construction of two C−C bonds via C−H bond activation of a terminal alkyne has yet to be reported.

We have recently reported on the synthesis of 1,3-diene-5-ynes via highly chemo-, regio-, and stereoselective two- and three-component cross-trimerization of alkynes involving triisopropylsilylacetylene, two internal alkynes, and Ni(cod)$_2$/phosphine as the catalyst.[9] Consequently, we decided to extend our methodology toward the reaction among two alkynes and an alkene for the simultaneous alkenylation and alkynylation of the alkene to afford the corresponding 1,5-enyne (Scheme 1). Such simultaneous introduction of alkenyl and alkynyl moieties onto an alkene by three-component reaction between an alkene with two alkynes has yet to be reported. The reaction is challenging because of the need to

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(1) For recent examples for cross-dimerization of alkynes: (a) Nishimura, T.; Guo, X.-X.; Ohnishi, K.; Hayashi, T. *Adv. Synth. Catal.* **2007**, *349*, 2669. (b) Katagiri, T.; Tsurugi, H.; Funayama, A.; Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 830. (c) Tsukada, N.; Ninomiya, S.; Aoyama, Y.; Inoue, Y. *Org. Lett.* **2007**, *9*, 2919. (d) Katagiri, T.; Tsurugi, H.; Satoh, T.; Miura, M. *Chem. Commun.* **2008**, 3405. (e) Ogata, K.; Oka, O.; Toyota, A.; Suzuki, N.; Fukuzawa, S.-i. *Synlett.* **2008**, 2663. (f) Matsuyama, N.; Tsurugi, H.; Satoh, T.; Miura, M. *Adv. Synth. Catal* **2008**, *350*, 2274. (g) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 3576.

(2) Kohno, K.; Nakagawa, K.; Yahagi, T.; Choi, J.-C.; Yasuda, H.; Sakakura, T. *J. Am. Chem. Soc.* **2009**, *131*, 2784.

(3) Tenaglia, A.; Giordano, L.; Buono, G. *Org. Lett.* **2006**, *8*, 4315.

(4) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632.

(5) (a) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816. (b) Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, *35*, 5689. (c) Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R. K.; Korn, S.; De La Cierva, C. O.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 8669. (d) Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D. J.; Gevorgyan, V. *J. Org. Chem.* **2003**, *68*, 6251.

(6) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410.

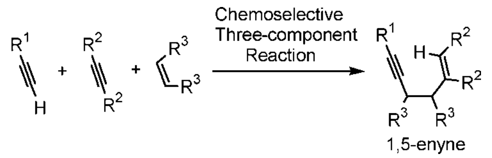
(7) Shirakura, M.; Suginome, M. *Org. Lett.* **2009**, *11*, 523.

(8) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 5060.

(9) (a) Ogata, K.; Murayama, H.; Sugasawa, J.; Suzuki, N.; Fukuzawa, S.-i. *J. Am. Chem. Soc.* **2009**, *131*, 3176. (b) Ogata, K.; Sugasawa, J.; Fukuzawa, S.-i. *Angew. Chem., Int. Ed.* **2009**, *48*, 6078.

10.1021/ol9025556

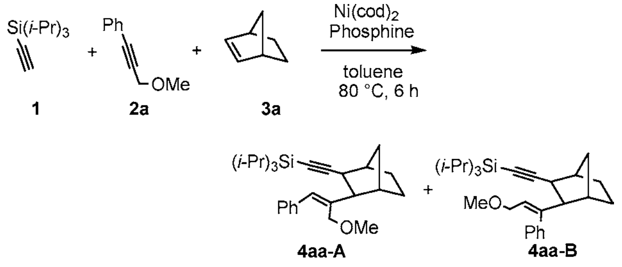
Scheme 1



control the chemoselectivity between alkene and two alkynes. Herein, we describe the first highly regio- and stereoselective three-component reaction of norbornene with two alkynes via C−H bond activation of a terminal silylacetylene using Ni catalyst.

First, several phosphines were screened in the cross-reaction of triisopropylsilylacetylene (**1**), internal alkyne **2a**, and norbornene **3a**, as shown in Table 1. In the presence of $Ni(cod)_2/2PMePh_2$, the three-component reaction proceeded smoothly at 80 °C to afford **4aa**, in a high yield, and with complete chemoselectivity (entry 1). On the basis of ^1H NMR analyses, the ratio between the regioisomers was determined as A/B = 88:12 by integrating the signals of the alkene proton for each isomer, whereas the stereochemistry of the alkynyl and alkenyl groups was determined to be exclusively in the *exo,exo* configurations.[10] Moreover, the use of other bulky silylacetylenes such as *tert*-butyldimethylsilylacetylene gave the corresponding 1,5-enyne **4** in lower yields.[11] Whereas the use of PEt_2Ph (entry 2) resulted in a slightly lower yield of **4aa**, the use of triarylphosphine or trialkylphosphine such as PPh_3, PEt_3, $P(n\text{-}Pr)_3$, $P(n\text{-}Bu)_3$, $P(i\text{-}Pr)_3$, and PCy_3 (entries 3−8), was significantly less effective. On the basis of the screen of the phosphine ligands, the highest yield of the 1,5-enyne **4aa** was achieved using $PMePh_2$.

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

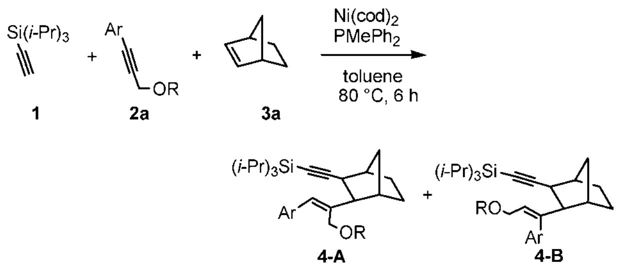


entry	phosphine	yield [%][b]	A/B[c]
1	$PMePh_2$	94	88:12
2	PEt_2Ph	73	85:15
3	PPh_3	61	93:7
4	PEt_3	49	84:16
5	$P(n\text{-}Pr)_3$	62	79:21
6	$P(n\text{-}Bu)_3$	73	79:21
7	$P(i\text{-}Pr)_3$	27	99:<1
8	PCy_3	22	99:<1

[a] $Ni(cod)_2$ (0.10 mmol), phosphine (0.20 mmol), **1** (1.0 mmol), **2a** (1.0 mmol), **3a** (3.0 mmol), and toluene (3 mL) were employed. [b] Isolated yield. [c] Determined by ^1H NMR.

Next, the $Ni(cod)_2/PMePh_2$-catalyzed three-component reaction was examined using aryl propargylic ethers **2**, as shown in Table 2. Ethoxy- and methoxymethyl (MOM)-substituted alkynes (**2b**, entry 2, and **2c**, entry 3, respectively) furnished the corresponding products (**4ba** and **4ca**, respectively) with high regioselectivities and in good yields. In contrast, replacement of the ether group with a methyl group (1-phenyl-1-propyne) resulted in a complex mixture of products, indicating the importance of the ether group for the selective three-component reaction. The use of electron-donating (*p*-, *m*-, *o*-methyl and *p*-methoxy-substituted) or electron-withdrawing (*p*-trifluoromethyl-substituted) aryl alkynes afforded product **4** with high regioselectivities in good to high yields (entries 4−8). In spite of the low-valent nickel catalyst, the *p*-chloro-substituted aryl alkyne **2i** selectively afforded the corresponding 1,5-enyne **4ia** (entry 9). Reactions of **2j** and **2k**, which possess heteroaryl groups, also proceeded to form products **4ja** and **4ka**, respectively,

Table 2. Ni-Catalyzed Three-Component Reaction between **1**, **2a**−**k**, and **3a**[a]



entry	2	R	Ar	4, yield [%][b]	A/B[c]
1[d]	**2a**	Me	Ph	**4aa** (94)	88:12
2	**2b**	Et	Ph	**4ba** (79)	89:11
3	**2c**	MOM	Ph	**4ca** (70)	88:12
4	**2d**	Me	$p\text{-}MeC_6H_4$	**4da** (84)	94:6
5	**2e**	Me	$m\text{-}MeC_6H_4$	**4ea** (80)	93:7
6	**2f**	Me	$o\text{-}MeC_6H_4$	**4fa** (74)	99:<1[e]
7	**2g**	Me	$p\text{-}MeOC_6H_4$	**4ga** (91)	98:2[e]
8	**2h**	Me	$p\text{-}CF_3C_6H_4$	**4ha** (66)	96:4[e]
9	**2i**	Me	$p\text{-}ClC_6H_4$	**4ia** (52)	87:13
10	**2j**	Me	3-pyridyl	**4ja** (64)	97:3
11	**2k**	Me	2-thiophenyl	**4ka** (64)	83:17

[a] $Ni(cod)_2$ (0.10 mmol), $PMePh_2$ (0.20 mmol), **1** (1.0 mmol), **2** (1.0 mmol), **3a** (2.0 mmol), and toluene (3 mL) were employed. [b] Isolated yield. [c] Determined by ^1H NMR. [d] **3a** (3.0 mmol). [e] Determined by GC.

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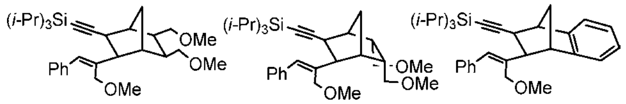
(10) The signal assigned to the alkenyl- and alkynyl-substituted *endo* proton was observed as a doublet due to the coupling with each other (ca. 9 Hz), and no coupling was observed with the bridgehead proton. These observations support the *exo,exo* structure of **4**. See: (a) Nishihara, Y.; Inoue, Y.; Itazaki, M.; Takagi, K. *Org. Lett.* **2005**, *7*, 2639. (b) Caltskan, R.; Ali, M. F.; Sahin, E.; Watson, W. H.; Balci, M. *J. Org. Chem.* **2007**, *72*, 3353.

(11) The corresponding 1,5-enyne which possesses a *tert*-butyldimethylsilyl group was obtained in 33% isolated yield (A/B = 93:7).

with high or good regioselectivities in good yields. In contrast, replacement of the aryl group with a cyclohexyl group resulted in a low yield of the corresponding 1,5-enyne product.[12]



4ab-A
51% yield
A/B = 87:13

4ac-A
44% yield
A/B = 94:6

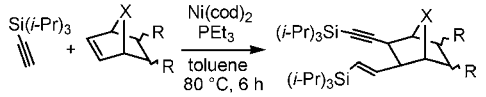
4ad-A
49% yield
A/B = 92:8

Figure 1. Products of three-component reaction between **1**, **2a**, and norborene derivatives **3b**−**d**.

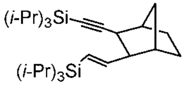
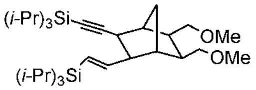
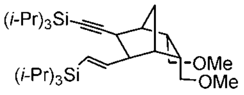
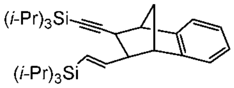
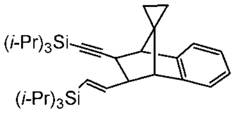
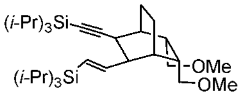
As depicted in Figure 1, *exo*-,*exo*- and *endo*-,*endo*-5,6-bis(methoxymethyl)-substituted norbornenes **3b** and **3c** and benzonorbornadiene **3d** were shown to successfully undergo the reaction to afford products **4ab**, **4ac**, and **4ad**, respectively, with good to high regioselectivities, albeit in moderate yields. In contrast, the reaction of norbornadiene was not detected.[13] Oxa- and azabenzonorbornadienes also could not participate in this reaction.

In addition to the reaction with two distinct alkynes, the reaction between two molecules of **1** and one molecule of norbornene **3a** also proceeded to yield 1,5-enyne **5a** with complete regio- and stereoselectivities using Ni(cod)$_2$/PEt$_3$ catalyst (Table 3, entry 1).[14] The use of *exo*-,*exo*- and *endo*-,*endo*-5,6-bis(methoxymethyl)-substituted norbornenes **3b** and **3c** also afforded 1,5-enyne **5b** and **5c** with high yields (entries 2 and 3), and the presence of benzonorbornadiene **3d** also resulted in the formation of **5d** in high yield (entry 4). The cyclopropyl-bridging bicyclo-alkene **3e** could also participate in the reaction (entry 5). In contrast, using ethylene-bridging bicyclo-alkene **3f** resulted in a low yield (entry 6).

Table 3. Ni-Catalyzed Three-Component Reaction between Two Molecules of **1** and **3a**−**f**[a]

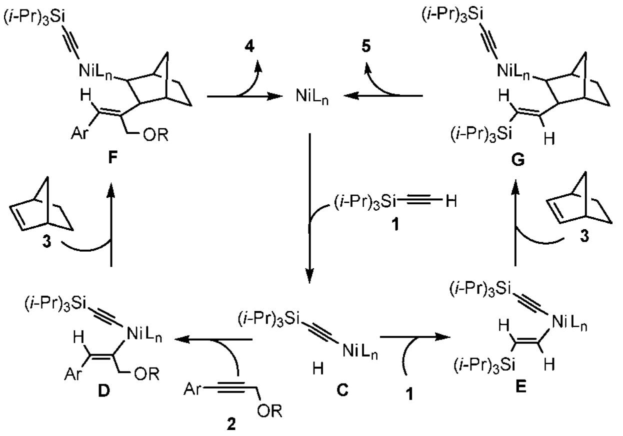


1 **3** **5**

entry	3	product	5, yield [%][b]
1	**3a**		**5a** (92)[c]
2	**3b**		**5b** (90)
3	**3c**		**5c** (99)
4	**3d**		**5d** (90)
5	**3e**		**5e** (63)
6	**3f**		**5f** (12)

[a] Ni(cod)$_2$ (0.10 mmol), PEt$_3$ (0.10 mmol), **1** (1.25 mmol), **3** (0.5 mmol), and toluene (3 mL) were employed. [b] Isolated yield. [c] Determined by ^{1}H NMR with 4-methoxybiphenyl as internal standard; ref 15.

Scheme 2



A possible pathway for the three-component reaction is shown in Scheme 2. First, the oxidative addition of a silylacetylene C−H bond to Ni(0) affords Ni(II) alkynyl hydride intermediate **C**,[16] in which the Ni−H bond undergoes regioselective insertion into internal alkyne **2** or triisopropylsilylacetylene **1** to give intermediate **D** or **E**. The regioselective insertion of these alkynes can be attributable to steric reasoning in which the Ni center may prefer to be located far from the sterically hindered group such as the aryl and triisopropylsilyl group. Finally, norbornene is inserted into the Ni−C (alkenyl) bond to yield intermediate **F** and **G**, followed by reductive C−C coupling to afford **4** and **5**, respectively.

While the use of the bulky silylacetylene is essential for preventing the homodimerization of the terminal alkynes, its use also offers the advantage of a readily removable silyl group that can be converted to other groups. The silyl group of **4aa** was readily removed by the reaction with tetrabutylammonium fluoride (TBAF), and resulting desilylated

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(12) Corresponding 1,5-enyne **4la** which possesses a cyclohexyl group was obtained in 28% isolated yield (A/B = 79:21).

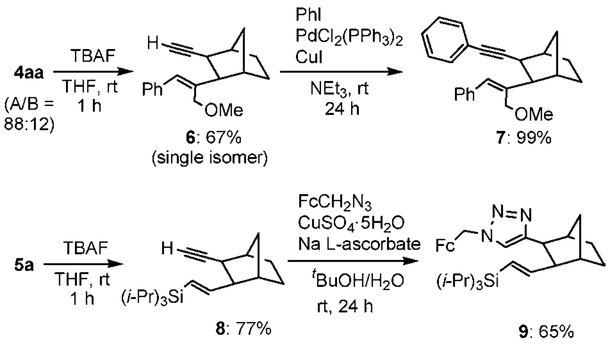
(13) In this reaction, the hydroalkynylation product of norbornadiene was obtained in 42% isolated yield.

(14) Phosphine screening results for reaction between two molecules of **1** and **3c** are shown in the Supporting Information.

(15) Yield of compound **5a** was determined by ^{1}H NMR because it is difficult to separate compound **5a** and small amounts of byproduct (homodimer of **1**).

(16) The formation of a nickel(II)−alkenyl hydride complex from Ni(cod)$_2$/phosphine by the reaction with terminal alkyne is usually postulated. See: Ogoshi, S.; Ueta, M.; Oka, M.; Kurosawa, H. *Chem. Commun.* **2004**, 2732, and refs 1f, 6−8, and 9.

Scheme 3



compound **6** was isolated as a single isomer (Scheme 3). Compound **6** can be easily transformed into a phenyl-substituted compound by the reaction with iodobenzene using Sonogashira coupling. The selective desilyation of terminal silyl moiety of **5a** by treatment with TBAF also proceeded to form desilylated compound **8** (Scheme 3). As another example of a synthetic application, **8** was subjected to a click reaction that has been widely used as a versatile method for the synthesis of 1,2,3-triazoles.[17] The reaction with ferrocenylmethyl azide furnished 4-substituted 1,2,3-triazole **9** in good yield. The structure of triazole **9** was confirmed by X-ray analysis.[18]

In summary, we have demonstrated the first three-component reaction of norbornene with two alkynes leading to 1,5-enyne via C−H activation of a terminal alkyne using a Ni(cod)$_2$/phosphine catalyst. Moreover, our highly chemo-, regio-, and stereoselective reaction is applicable for various internal alkynes and norbornene derivatives.

Supporting Information Available: Standard experimental procedure, characterization data for new compounds, and ORTEP drawing of **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51.

[18] The supplementary crystallographic data of **9** (CCDC number, 749875) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.