

Nickel-Catalyzed Highly Regio- and Stereoselective Cross-Trimerization between Triisopropylsilylacetylene and Internal Alkynes Leading to 1,3-Diene-5-yne

Kenichi Ogata,^{*,†} Hiroyuki Murayama,[†] Jun Sugawara,[†] Noriyuki Suzuki,[‡] and Shin-ichi Fukuzawa^{*,†}

Department of Applied Chemistry, Institute of Science and Engineering, Chuo University, 1-13-27 Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan, and Chemical Analysis Team, RIKEN Advanced Science Institute, Wako, Saitama 351-0198, Japan

Received January 8, 2009; E-mail: orgchem@kc.chuo-u.ac.jp

The transition-metal-catalyzed addition of C–H bonds to unsaturated carbon–carbon bonds has received much attention because of its highly atom-economical nature. Much research on the addition of terminal alkyne C–H bonds to unsaturated compounds has been reported.¹ The transition-metal-catalyzed coupling of alkynes through the addition of alkyne C–H bonds to carbon–carbon triple bonds is recognized as a versatile method for the synthesis of π -conjugated compounds.² Recently, the cross-dimerization of alkynes leading to enynes has also been achieved by several research groups using a bulky silyl-substituted terminal alkyne.³ On the other hand, the selective linear cross-trimerization of alkynes has scarcely been studied, and the substrates of such examples are very limited. Eisen and co-workers⁴ reported lanthanide-catalyzed unselective cross-trimerization between trimethylsilylacetylene and *tert*-butylacetylene. Ishikawa et al.^{5a} and Miura and co-workers^{5b} reported the 2:1 cross-trimerization between two molecules of terminal silylacetylene and limiting diarylacetylene, which provided a dienyne using a Ni catalyst. In the case of selective 1:2 cross-trimerization that consists of a terminal alkyne and two molecules of internal alkyne, only the cross-trimerization between phenylacetylene or propargyl alcohol and 1-phenylsulfonyl-1-propyne in the presence of a Pd catalyst has been reported by Trost et al.,⁶ the reaction was limited to these substrates. Effective cross-trimerization, especially 1:2 cross-trimerization, that can be utilized with various internal acetylenes has not been reported. In this report, we demonstrate the first effective 1:2 cross-trimerization between triisopropylsilylacetylene and two internal alkyne molecules, leading to 1,3-diene-5-yne compounds; this was achieved with high regio- and stereoselectivity by the use of a Ni(cod)₂/PⁿPr₃ catalyst (cod = 1,5-cyclooctadiene).

The effect of the phosphine was first investigated for the cross-trimerization reaction between triisopropylsilylacetylene (**1**) and 3-hexyne (**2a**), as shown in Table 1. In the presence of the Ni(cod)₂/2PⁿPr₃ catalyst, the 1:2 cross-trimerization reaction between **1** and **2a** proceeded successfully to afford **3a** as a single product in high yield by the slow addition of **1** into a solution of **2a** (2.5 equiv) and the Ni(cod)₂/2PⁿPr₃ catalyst at 80 °C (entry 1). On the other hand, for reaction between other bulky silylacetylenes, such as *tert*-butyldimethylsilylacetylene and 3-hexyne under these conditions, the corresponding 1:2 cross-trimer was obtained in low yield (19% isolated yield).⁷ When large excess amounts of **2a** were used, the selective cross-trimerization reaction also proceeded (entry 2). The reaction resulted in a lower yield of **3a** when not carried out by the slow addition of **1** (entry 3). Under those reaction conditions, small amounts of 2:1 cross-trimer **4a** and cross-dimer **5a** were also

Table 1. Screening of Reaction Conditions^a

entry	phosphine	% yield ^b		
		3a	4a	5a
1 ^d	P ⁿ Pr ₃	99 (82) ^c	0	0
2 ^{d,e}	P ⁿ Pr ₃	99	0	0
3	P ⁿ Pr ₃	35	6	11
4 ^f	P ⁿ Pr ₃	15	4	10
5	P ⁿ Bu ₃	17	6	11
6	P ⁿ Pr ₃	7	18	55
7	PCy ₃	13	10	50
8	PPh ₃	32	17	46
9 ^g	dppe	47	34	18
10 ^g	dppf	9	28	58

^a Ni(cod)₂ (0.10 mmol), phosphine (0.20 mmol), **1** (1.0 mmol), **2a** (2.5 mmol), and toluene (3 mL) were employed. ^b GC yield. ^c Isolated yield of **3a** is given in parentheses. ^d Slow addition of **1** for 30 min. ^e **2a** (10.0 mmol). ^f PⁿPr₃ (0.40 mmol). ^g Diphosphine (0.10 mmol).

formed. The reaction with the Ni(cod)₂/4PⁿPr₃ catalyst produced a lower yield of **3a** (entry 4). Other alkylphosphines, such as PⁿBu₃, PⁿPr₃, and PCy₃, were less effective (entries 5–7). The use of PPh₃ also resulted in a low yield and selectivity of **3a** (entry 8). Diphosphines, such as dppe and dppf, proved to be less selective (entries 9 and 10). Screening of phosphine ligands revealed that the highest yield and selectivity for the formation of cross-trimer **3** was achieved using PⁿPr₃. In this catalytic system, Ishikawa- and Miura-type 2:1 cross-trimers⁵ were not obtained even when the reaction between **1** (2.5 equiv) and **2a** (1 equiv) was carried out.⁸

Next, the cross-trimerization between **1** and various alkynes was examined in the presence of the Ni(cod)₂/2PⁿPr₃ catalyst, as shown in Table 2. The use of the symmetrical alkyl-substituted internal acetylenes 2-butyne (**2b**) and 4-octyne (**2c**) furnished **3b** and **3c**, respectively, in good yield (entries 2 and 3). The reaction with ether-functionalized alkynes also proceeded with good to high yield (entries 4–6). Although alkyne diols, such as 2-butyne-1,4-diol, failed to react with **1**, methoxymethyl (MOM)-protected alkyne **2g** participated in this reaction with good yield (entry 7). Not only symmetrical acetylenes but also asymmetrical internal acetylenes could participate in the reaction. It is interesting and synthetically useful that the cross-trimerization of **1** with ether-functionalized

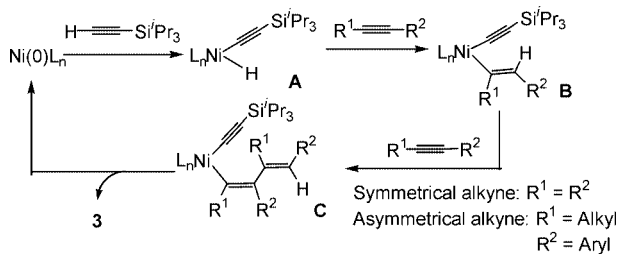
[†] Chuo University.

[‡] RIKEN.

Table 2. Ni-Catalyzed Cross-Trimerization between Triisopropylsilylacetylene (**1**) and Internal Alkynes (**2a–m**)^a

entry	2	R ¹	R ²	3 (% yield) ^b
1 ^c	2a	Et	Et	3a (82)
2 ^d	2b	Me	Me	3b (65)
3 ^{c,e}	2c	Pr	Pr	3c (96)
4	2d	CH ₂ OMe	CH ₂ OMe	3d (70)
5	2e	CH ₂ OEt	CH ₂ OEt	3e (90)
6	2f	CH ₂ O ⁿ Pr	CH ₂ O ⁿ Pr	3f (82)
7	2g	CH ₂ OMOM	CH ₂ OMOM	3g (79)
8	2h	CH ₂ OEt	Ph	3h (70)
9	2i	CH ₂ OEt	<i>p</i> -CH ₃ C ₆ H ₄	3i (70)
10	2j	CH ₂ OEt	<i>p</i> -CF ₃ C ₆ H ₄	3j (65)
11	2k	CH ₂ OMOM	Ph	3k (72) ^f
12	2l	Me	Ph	3l (68) ^f
13	2m	Ph	Ph	– (0) ^g

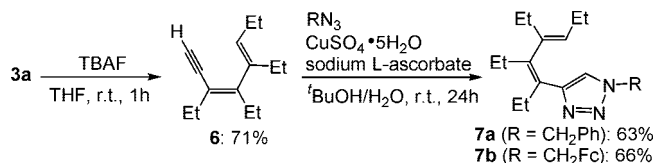
^a Ni(cod)₂ (0.10 mmol), P^rPr₃ (0.20 mmol), **1** (1.0 mmol), **2** (2.5 mmol), and toluene (3 mL) were employed. ^b Isolated yield. ^c Slow addition of **1** for 30 min. ^d The reaction was carried out in an autoclave; **2b** (10.0 mmol). ^e **2c** (5.0 mmol). ^f Other regioisomers were also confirmed by ¹H NMR and GC–MS (see ref 10). ^g Cross-dimerization product was formed.

Scheme 1. Possible Pathway for the Alkyne Cross-Trimerization

asymmetrical alkyne **2h** afforded **3h** as a single isomer in good yield (entry 8).⁹ The use of the other asymmetrical alkynes **2i** and **2j** also afforded the respective cross-trimers **3i** and **3j** in good yields with excellent regioselectivity (entries 9 and 10). The reaction with **2k** resulted in moderate selectivity (entry 11).¹⁰ The reaction involving 1-phenyl-1-propyne also proceeded to yield the **3l** cross-trimer with minor regioisomers,¹⁰ although diphenylacetylene could not participate in this reaction (entries 12 and 13).¹¹

The proposed mechanism for the formation of **3** is given in Scheme 1. The reaction probably proceeds by a reaction mechanism similar to that for the Ni-catalyzed dimerization of alkynes.¹² Oxidative addition of the triisopropylsilylacetylene C–H bond to Ni(0) affords the Ni(II) alkynyl hydride intermediate **A**. The formation of a Ni(II) hydride acetylide complex from the Ni(cod)₂/phosphine system by reaction with a terminal acetylene is usually postulated.^{1g,5,12} Alkyne insertion into the Ni–H bond (**A** → **B**) and insertion of a second alkyne into the Ni–C bond of intermediate **B** (**B** → **C**) then proceed.¹³ Finally, C–C coupling results in the formation of **3**. The regioselectivity in the reaction with the asymmetrical internal alkyne is derived from restriction of the insertion direction of the internal alkyne to avoid steric hindrance between the Ni fragment and the aryl substituent (R²).

The silyl group of **3a** was readily removed by treatment with tetrabutylammonium fluoride (TBAF) to afford **6** in good yield

Scheme 2. Synthetic Application of Compound **3**

(Scheme 2). As an example of a synthetic application, **6** was subjected to a click reaction that has been widely used as a versatile method for the synthesis of 1,2,3-triazoles.¹⁴ The reaction with benzyl or ferrocenylmethyl azide furnished 4-substituted 1,2,3-triazoles **7a** and **7b**, respectively, in good yield. Compound **6** can be also easily transformed into a phenyl-substituted diyne in 73% yield by the reaction with iodobenzene using Sonogashira coupling (see the Supporting Information).

In summary, we have demonstrated the first effective 1:2 cross-trimerization of alkynes, leading to silyl-substituted 1,3-diene-5-yne compounds, using a Ni(cod)₂/P^rPr₃ catalyst. The reaction could be applied to several symmetrical and asymmetrical internal alkynes with high regio- and stereoselectivity.

Acknowledgment. The authors are grateful to Dr. Yayoi Hongo and Dr. Takemichi Nakamura (RIKEN) for assistance with the high-resolution mass spectrometry analysis.

Supporting Information Available: Experimental procedures and new compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Yin, J.; Chisholm, J. D. *Chem. Commun.* **2006**, 632. (b) Tenaglia, A.; Giordano, L.; Buono, G. *Org. Lett.* **2006**, 8, 4315. (c) Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, 112, 2816. (d) Yamaguchi, M.; Omata, K.; Hirama, M. *Tetrahedron Lett.* **1994**, 35, 5689. (e) 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. (f) Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D. J.; Gevorgyan, V. *J. Org. Chem.* **2003**, 68, 6251. (g) Shirakura, M.; Sugimoto, M. *J. Am. Chem. Soc.* **2008**, 130, 5410. (h) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, 130, 1576.
- (2) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 259.
- (3) (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.
- (4) Haskel, A.; Straub, T.; Dash, A. K.; Eisen, M. S. *J. Am. Chem. Soc.* **1999**, 121, 3014.
- (5) (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.
- (6) Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühler, G. *J. Am. Chem. Soc.* **1997**, 119, 698.
- (7) In this reaction, 2:1 cross-trimer was also obtained in 15% isolated yield.
- (8) **3a** (12%), **4a**, (11%), and **5a** (12%) were obtained (GC yield).
- (9) The structure of **3h** was confirmed by a NOESY measurement.
- (10) Two other regioisomers of **3k** (24%, entry 11) and one regioisomer of **3l** (12%, entry 12) were also produced. On the basis of triplet (**3k**) and quartet (**3l**) signals observed at ~6 ppm by ¹H NMR spectroscopy, these regioisomers have the structures C=C(H)CH₂OMOM (**3k**) and C=C(H)CH₃ (**3l**).
- (11) Cross-dimer was obtained in 70% yield.
- (12) Ogoshi, S.; Ueta, M.; Oka, M.; Kurosawa, H. *Chem. Commun.* **2004**, 2732.
- (13) Alkyne insertion into the Ni–C(alkenyl) bond was reported in the case of the CpNi system. See: Malyshev, D. A.; Scott, N. M.; Marion, N.; Stevens, E. D.; Ananikov, V. P.; Beletskaya, I. P.; Nolan, S. P. *Organometallics* **2006**, 25, 4462.
- (14) (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.

JA900146U