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Palladium-Catalyzed Selective Cross-Addition of Triisopropylsilylacetylene to Internal and Terminal Unactivated Alkynes

Naofumi Tsukada,* Satoshi Ninomiya, Yoshimi Aoyama, and Yoshio Inoue*

Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan

tsukada@aporg.che.tohoku.ac.jp

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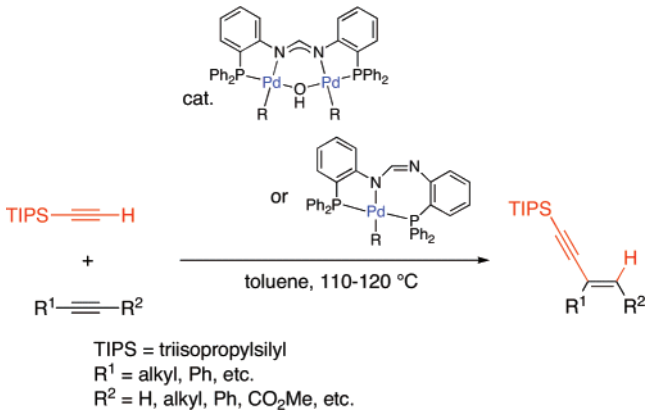
ABSTRACT



Dinuclear and mononuclear palladium complexes having *N,N′*-bis[2-(diphenylphosphino)phenyl]amidinate (DPFAM) as a ligand catalyzed the cross-addition of triisopropylsilylacetylene (TIPSA) to unactivated internal alkynes, giving enynes selectively. When palladium catalysts having PPh_3, TDMPP, dppe, or dppf were used, dimers of TIPSA were obtained as major products. The reactions of TIPSA with several terminal alkynes also gave cross-adducts selectively, although the yields were moderate.

The addition of terminal alkyne C−H bonds to other alkynes is a very simple and highly atom-economical method for forming enynes (eq 1),[1] which are important precursors in organic synthesis. Various transition metals can be used as catalysts for the addition reaction, and many papers have explored the method over the last few decades.[2] However, almost all of these studies have been limited to homodimerization of terminal alkynes, which cannot be extensively utilized for organic synthesis. The cross-addition of two different alkynes, which has greater synthetic scope, has been rather limited[3−7] because in these reactions it is difficult to prevent the homodimerization of alkynes. Several groups reported selective cross-dimerization of two terminal alkynes under mild conditions. Titanium-,[3] uranium-,[4] and palladium-catalyzed[6e] reactions proceed with high *gem*-selectivity, and

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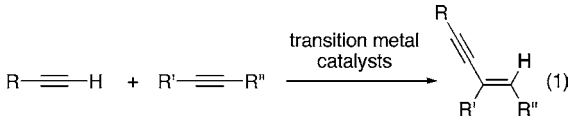
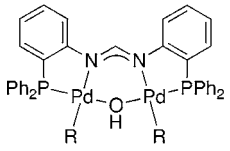
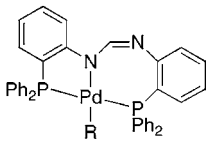
ruthenium-catalyzed reactions give (*Z*)-isomers selectively.[5] In these reports, however, the cross-addition of terminal alkynes to *internal alkynes* was not mentioned, except the palladium-catalyzed addition to alkynes having oxygen subsituents at propargylic positions. Insertion of internal alkynes to alkynylmetal intermedates would be impossible mechanistically[5] or require more drastic conditions than that of terminal alkynes, which induce homodimerization of terminal alkynes.[4] Trost reported that tris(2,6-dimethoxyphenyl)phosphine (TDMPP) was effective for the palladium-catalyzed cross-addition of terminal alkynes to internal *acceptor alkynes* activated by electron-withdrawing groups as well as for the homodimerization of alkynes.[6] Recently, rhodium-catalyzed addition to internal arylalkynes was also reported.[7] Regarding unactivated internal alkynes, there have been a few examples for the ruthenium-catalyzed reaction reported by Yi and Liu.[8] We report here the palladium-catalyzed selective cross-addition of a silylacetylene to *unactivated internal alkynes* along with the cross-addition to terminal alkynes.



We first investigated the cross-addition of various terminal alkynes to 3-hexyne in the presence of the dinuclear complex **1a**, which had been reported to serve as a catalyst for the addition reaction of aryl and alkenyl C−H bonds to unactivated alkynes.[9,10] While the reactions of *tert*-butylacetylene



1a (R = *p*-Tol)
1b (R = Me)



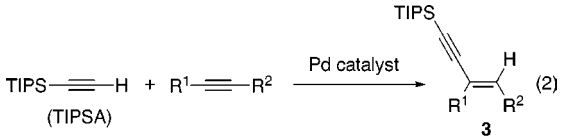
2a (R = *p*-Tol)
2b (R = Me)

and phenylacetylene with 3-hexyne gave only homodimers of terminal alkynes, the reaction of trimethylsilylacetylene with 3-hexyne afforded a small amount of a cross-addition product along with homodimers. To prevent homodimerization, silylacetylenes having bulky silyl groups were investigated. The use of triphenylsilyl or *tert*-butyldimethylsilyl groups did not significantly reduce dimerization of the terminal silylacetylenes. In contrast, in the reaction of triisopropylsilylacetylene (TIPSA) with 3-hexyne at 110 °C for 17 h, the cross-addition product **3a** was obtained in 82% yield, with the TIPSA dimers yield only 3% (Table 1, entry 1). Comparable results were also obtained by using the mononuclear complexes **2** having the same multidentate ligand, *N*,*N*′-bis[2-(diphenylphosphino)phenyl]amidinate (DPFAM) (entries 3 and 4). Thus, it does not seem likely that a bimetallic structure, or cooperation of the two palladium centers, is essential.[11] Reactions using palladium catalysts having monodentate phosphines, such as triphenylphosphine and TDMPP, selectively gave TIPSA homodimers (entries 5 and 6). Although using bidentate phosphines somewhat increased the yield of **3a**, the selectivity was largely inferior to that obtained when using **1** or **2** (entries 7 and 8). A tridentate ligand, *N*,*N*-bis[2-(diphenylphosphino)phenyl]amine,[12] completely inhibited both the cross-addition and homodimerization reactions.

Table 1. Palladium-Catalyzed Cross-Addition of TIPSA to 3-Hexyne[a]

			yield[b] (%)	
entry	catalyst (mol %)	*T* (°C)	**3a**	homodimers[c]
1	**1a** (2)	110	82	3
2	**1b** (2)	120	61	2
3	**2a** (2)	120	78	6
4	**2b** (2)	110	94	4
5	$Pd(PPh_3)_4$ (4)	120	2	35
6	$Pd(OAc)_2$ (4), TDMPP (4)	120	17	72
7	$Pd(OAc)_2$ (4), dppe (4)	120	36	39
8	$Pd(OAc)_2$ (4), dppf (4)	120	20	40

[a] A mixture of TIPSA (0.50 mmol), 3-hexyne (0.50 mmol), and catalyst in toluene (2.0 mL) was heated for 17 h. [b] GC yields. [c] A mixture of homodimers of TIPSA.



3a: $R^1 = R^2$ = Et
3b: $R^1 = R^2$ = Pr
3c: $R^1 = R^2$ = Ph
3d: $R^1 = R^2 = CH_2OMe$
3e: R^1 = Ph, R^2 = Me
3f: R^1 = Me, $R^2 = CH_2OH$
3f': $R^1 = CH_2OH$, R^2 = Me
3g: R^1 = Me, $R^2 = CO_2Me$
3g': $R^1 = CO_2Me$, R^2 = Me (*E*/*Z* mixture)
3h: R^1 = *n*-hexyl, R^2 = H
3i: R^1 = *n*-pentyl, R^2 = H
3j: R^1 = *n*-heptyl, R^2 = H
3k: R^1 = *t*-Bu, R^2 = H
3l: $R^1 = (CH_2)_4OH$, R^2 = H
3m: $R^1 = (CH_2)_3CO_2Me$, R^2 = H
3n: $R^1 = (CH_2)_3CN$, R^2 = H

Table 2 summarizes the results of cross-addition of TIPSA to various internal and terminal alkynes. The reactions of

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(7) Katagiri, T.; Tsurugi, H.; Funayama, A.; Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 830−831. A similar rhodium-catalyzed reaction was reported by another group: Nishimura, T.; Onishi, K.; Guo, X.-X.; Hayashi, T. The 87th National Meeting of the Chemical Society of Japan, Osaka, March 2007, Abstract 3D6 02.
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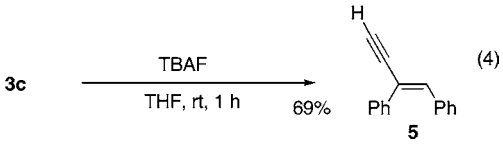
Table 2. Palladium-Catalyzed Cross-Addition of TIPSA to Various Alkynes[a]

	alkyne				
entry	R^1	R^2	time (h)	product	yield[b] (%)
1	Et	Et	20	**3a**	86[c]
2	*n*-Pr	*n*-Pr	67	**3b**	90
3	Ph	Ph	24	**3c**	82
4	CH_2OMe	CH_2OMe		**3d**	63
5	Ph	Me	43	**3e**	92
6[d]	Me	CH_2OH	27	**3f** + **3f′**[e]	71
7	Me	CO_2Me	17	**3g** + **3g′**[f]	68
8	*n*-hexyl	H	18	**3h**	65[c]
9[d]	*n*-hexyl	H	37	**3h**	60[c]
10	*n*-pentyl	H	17	**3i**	61
11	*n*-heptyl	H	30	**3j**	44
12[d]	*t*-Bu	H	19	**3k**	28
13	$(CH_2)_4OH$	H	19	**3l**	49
14	$(CH_2)_3CO_2Me$	H	20	**3m**	36
15	$(CH_2)_3CN$	H	16	**3n**	24

[a] A mixture of TIPSA (0.50 mmol), another alkyne (0.50 mmol), and **1a** (0.01 mmol) in toluene (2.0 mL) was heated at 110 °C. [b] Isolated yields. [c] GC yields. [d] **2b** was used as a catalyst. [e] **3f**:**3f′** = 58:42. [f] **3g**:**3g′** = 74:26.

dialkyl- and diphenylacetylenes gave enynes **3a**−**c** in high yields (entries 1−3). While the cross-addition to 1-phenyl-1-propyne afforded **3d** with high regioselectivity (entry 5), a hydroxyl substituent at the propargylic position[6e] did not control the regioselectivity (entry 6). While several regio- and stereoselective additions to activated alkynes have been reported,[3,5] the cross-addition of TIPSA to methyl tetrolate gave a mixture of isomers (entry 7). No product was obtained in the reaction with bis(trimethylsilyl)acetylene. The reactions of TIPSA with terminal alkynes also gave branched cross-adducts **3g**−**m** (entries 8−15). In all cases, no other regioisomers were observed, and the yield of TIPSA homodimers was less than 5%, although dimers of the other terminal alkyne were formed to some degree (less than 20%). The reactions of *n*-alkylacetylenes gave **3h**−**j** in good selectivities (entries 8−11). These results are complementary to the ruthenium-catalyzed reaction,[5] in which linear silyl enynes were selectively obtained and alkylacetylenes could not be used. A bulky *tert*-butyl group decreased the yield of **3k** (entry 12). Terminal alkynes having hydroxy, methoxycarbonyl and cyano groups could be used in the cross-addition, giving **3l**−**n** as major products, although the yields were not high. Activated alkynes such as phenylacetylene and methyl propiolate were not applicable to the cross-addition, with alkyne homodimers forming as major products in reactions with TIPSA. As with the cross-addition to 3-hexyne, the use of $Pd(PPh_3)_4$ as a catalyst did not give satisfactory results in cross-addition reactions with terminal alkynes. For example, the reaction of TIPSA with 1-octyne afforded a dimer of TIPSA (22%), a dimer of 1-octyne (16%), and isomers of **3h** (14%) along with **3h** (31%).

While the use of TIPSA, which has a bulky triisopropylsilyl group, is essential for the selective cross-addition, TIPSA has another advantage over other terminal alkynes in that the silyl group can be easily removed from enynes **3**, or converted to other groups. Using the Hiyama coupling reaction,[13,14] silyl enyne **3a** was transformed into phenyl enyne **4** (eq 3). Treatment of **3c** with TBAF in THF gave enyne **5** having an acetylenic terminus, to which various functional group can be further introduced (eq 4).



In both reactions using **1** and **2**, the corresponding triisopropylsilylethynyl complex of **2** would be a key intermediate, into which the other alkyne inserts. The bulkiness of the triisopropylsilyl group prevents insertion of TIPSA giving homodimers. The choice of ligand was also crucial for selectivity and reactivity of the cross-addition. Tridentate coordination of DPFAM and the lability of seven-memberd chelation in **2** could play an important role in the cross-addition.

In summary, we have found that the palladium complexes **1** and **2**, having the multidentate ligand DPFAM were effective as catalysts for the selective cross-addition of TIPSA to internal and terminal alkynes. Mechanistic study, in particular, the influence of ligand structure on selectivity between cross-addition and homodimerization, is in progress.

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Supporting Information Available: Experimental details and spectroscopic/analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Since disproportionation of mononuclear complexes **2** can give dinuclear complexes along with free DPFAM, the cooperation of two palladium in the cross-addition cannot be entirely ruled out.

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