

## Palladium-catalyzed cross-addition of triisopropylsilylacetylene to unactivated alkynes\*

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**Abstract:** Selective cross-addition of triisopropylsilylacetylene (TIPSA) to unactivated alkynes is catalyzed by dinuclear and mononuclear palladium complexes supported by a multidentate ligand, *N,N'*-bis[2-(diphenylphosphino)phenyl]formamidine (dpfamH). While the addition reactions of TIPSA to dialkylacetylenes using palladium catalysts supported by monodentate and bidentate ligands gives dimers of TIPSA as major products, the reactions with the palladium complexes supported by dpfam affords cross-adducts selectively, in which the yields of TIPSA dimers are less than 5%. The addition of TIPSA to monoalkylacetylenes also gives cross-adducts as major products, although the selectivity and yield are moderate.

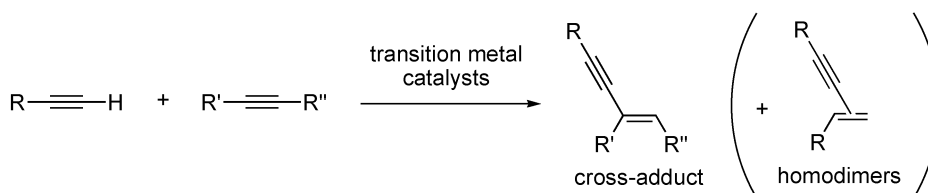
**Keywords:** palladium; alkyne; cross-addition; dimerization; dinuclear complex.

### INTRODUCTION

Homodimerization of terminal alkynes is an efficient and highly atom-economical method for forming enynes [1], which are important precursors in organic synthesis. Various transition-metal complexes can serve as catalyst for the homodimerization, and therefore many regio- and stereo-selective reactions have been reported over the last few decades [1b,2]. For extensive utilization of the enyne formation for organic synthesis, cross-addition of two different alkynes (Scheme 1) also has been desired. However, selective cross-addition has been rather limited [3–8] probably due to difficulty of prevention of the homodimerization of alkynes. Selective cross-addition reactions of two terminal alkynes were reported by several groups. Titanium-, uranium-, and palladium-catalyzed reactions proceed with high *gem*-selectivity [3,4,6e], and ruthenium-catalyzed reactions give *Z*-isomers selectively [5]. However, no examples for cross-addition to internal alkynes were reported in these papers. Selective cross-addition to internal alkynes was studied by Trost et al. [6]. They reported that palladium acetate and tris(2,6-dimethoxyphenyl)phosphine (TDMPP) were effective for the cross-addition of terminal alkynes to internal acceptor alkynes activated by electron-withdrawing groups. Very recently, rhodium-catalyzed addition to internal arylalkynes was reported [7]. Regarding the selective addition to unactivated internal alkynes, there are only two papers, in which a few example of cross-addition to dialkylacetylenes [8] or internal alkynes having oxygen-substituent at the propargylic position [6e] are reported [9]. Herein, we describe our recent findings for selective cross-addition of a silylacetylene to unactivated internal and terminal alkynes [10], and mechanistic consideration for the reaction.

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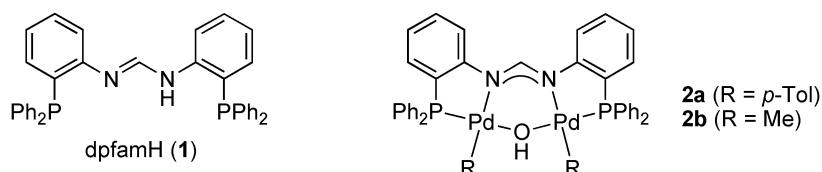
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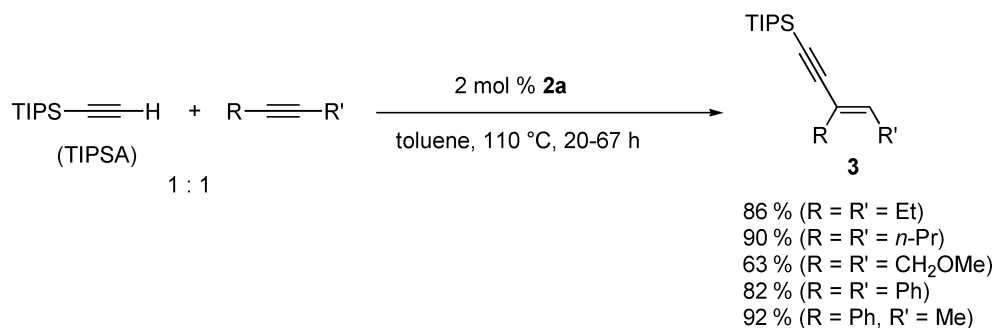
**Scheme 1** Transition-metal-catalyzed cross-addition of two alkynes.

### CROSS-ADDITION TO UNACTIVATED INTERNAL ALKYNES

During the course of our study on the reactivity of dinuclear complexes **2** supported by a multidentate ligand, *N,N'*-bis[2-(diphenylphosphino)phenyl]formamidine (dpfamH, **1**) [11], we reported that dinuclear complexes **2** served as catalyst for the addition of arene and alkene C–H bonds to unactivated alkynes, to which mononuclear palladium complexes were not effective (Fig. 1) [12]. Based on these findings, the addition of alkyne C–H bonds to unactivated alkynes was next investigated by using **2** as catalyst. As a result of screening of terminal alkynes in the addition to 3-hexyne, the reactions of monosilylacetylenes were found to give cross-adducts. While trimethylsilyl-, *tert*-butyldimethylsilyl-, and triphenylsilylacetylene did not afford satisfactory results, the reaction of triisopropylsilylacetylene (TIPSA) with several internal alkynes gave cross-adducts **3** with high stereoselectivity (Scheme 2). The addition of TIPSA to 1-phenyl-1-propyne proceeded with high regioselectivity, giving only one isomer.



**Fig. 1** New dinucleating ligand, dpfamH, and dinuclear palladium complexes.

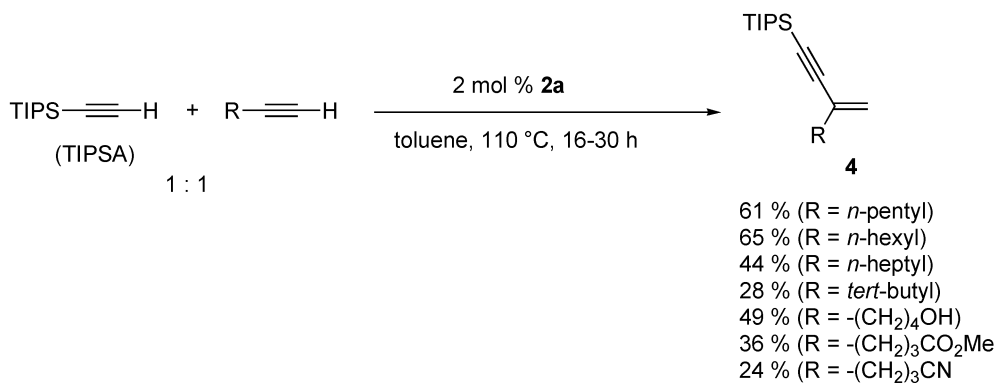


**Scheme 2** Cross-addition of TIPSA to unactivated internal alkynes.

### CROSS-ADDITION TO UNACTIVATED TERMINAL ALKYNES

The addition reaction using **2** and TIPSA can be applied to unactivated terminal alkynes. In all reactions, branched cross-adducts **4** were obtained as major products, and no regio- and stereoisomers were observed. The yields of TIPSA homodimers were less than 5 %, although dimers of the other terminal

alkynes were observed to some degree. The cross-addition is tolerant of several functional groups such as hydroxyl, cyano, and ester (Scheme 3).



**Scheme 3** Cross-addition of TIPSA to unactivated terminal alkynes.

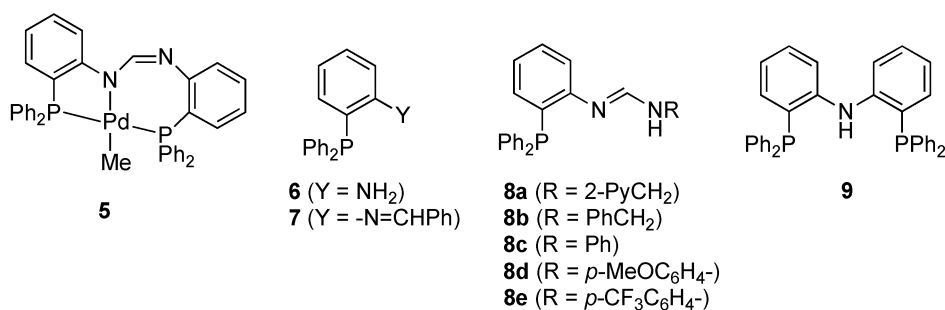
### ROLE OF THE MULTIDENTATE LIGAND dpfam

We started this study using dinuclear complexes **2** because the above-mentioned hydroarylation and hydroalkenylation of alkynes did not proceed with mononuclear palladium complexes. However, the cross-addition proceeded by using mononuclear complexes **5** as catalyst (Table 1, entry 1). The use of a mixture of **1** and  $\text{Pd}_2(\text{dba})_3$  gave a similar result (entry 2). In contrast, mononuclear palladium catalysts supported by mono- or bidentate phosphine ligands were not effective for the cross-addition reactions (entries 3–6). A special ligand such as **1** may be required for high selectivity. Various PN ligands **6–9** similar to **1** also did not give a satisfactory yield and selectivity (entries 7–14). These results show that both of two PN components in **1** are necessary.

**Table 1** Reaction of TIPSA with 3-hexyne in the presence of various palladium catalysts.<sup>a</sup>

Entry	Catalyst	Yield of <b>3</b> (%)	TIPSA dimers (%)
1	<b>5</b>	94	4
2	$\text{Pd}_2(\text{dba})_3 + \mathbf{1}$	73	2
3	$\text{Pd}(\text{PPh}_3)_4$	2	35
4	$\text{Pd}(\text{OAc})_2 + \text{TDMPP}$	17	72
5	$\text{Pd}(\text{OAc})_2 + \text{dppe}$	36	39
6	$\text{Pd}_2(\text{dba})_3 + \text{dppf}$	5	8
7	$\text{Pd}_2(\text{dba})_3 + \mathbf{6}$	2	4
8	$\text{Pd}_2(\text{dba})_3 + \mathbf{7}$	7	5
9	$\text{Pd}_2(\text{dba})_3 + \mathbf{8a}$	3	5
10	$\text{Pd}_2(\text{dba})_3 + \mathbf{8b}$	41	14
11	$\text{Pd}_2(\text{dba})_3 + \mathbf{8c}$	60	18
12	$\text{Pd}_2(\text{dba})_3 + \mathbf{8d}$	45	24
13	$\text{Pd}_2(\text{dba})_3 + \mathbf{8e}$	50	25
14	$\text{Pd}_2(\text{dba})_3 + \mathbf{9}$	1	0

<sup>a</sup>A mixture of TIPSA (0.5 mmol), 3-hexyne (0.5 mmol), and a catalyst (2 mol %) in toluene (2.0 mL) was heated at 110 °C.

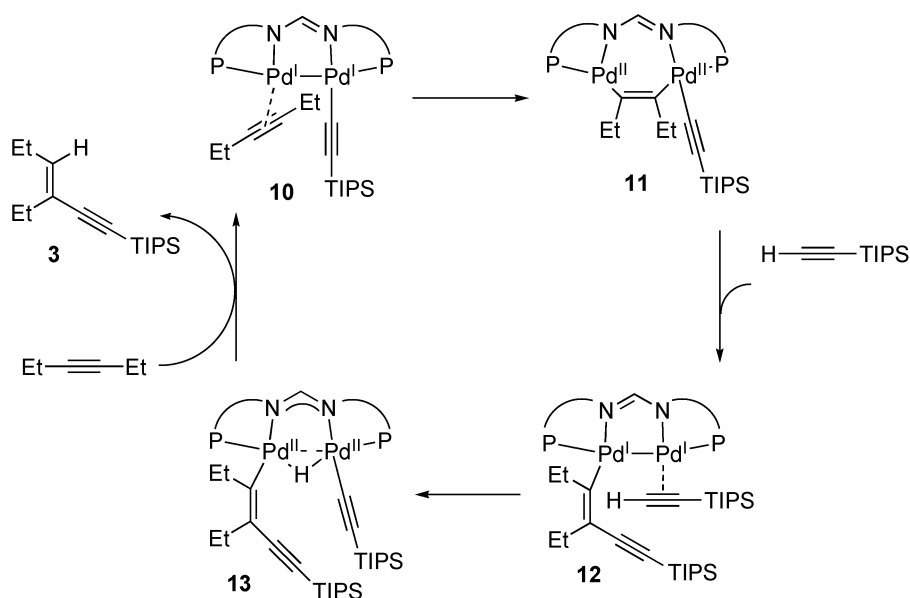


**Fig. 2** A mononuclear palladium complex having dpfam and various PN ligands.

It is conceivable that a real active species has a dinuclear structure in which each PN component holds one palladium atom even if mononuclear complex **5** is used as a catalyst. Disproportionation of two molecules of **5** can give a dinuclear complex. Actually, the disproportionation was observed in the reaction of **5** with excess TIPSAs. While the  $^{31}\text{P}$  NMR spectra of **5** exhibits two doublets (19.0 and 35.5 ppm), an unidentified complex obtained from the reaction of **5** with TIPSAs exhibits one singlet at 33.9 ppm, which means that the complex has a symmetrical dinuclear structure. Treatment of **2b** with excess TIPSAs at 110 °C also gave the same complex.

## PLAUSIBLE MECHANISMS

Although there is little evidence for the mechanistic aspects of the cross-addition reaction at the present time, one of the plausible reaction mechanisms for the addition of TIPSAs to 3-hexyne is described in Scheme 4 on the assumption that the reaction intermediates have dinuclear structures. In our previous study, we proposed a hydride-bridged dinuclear complex for an intermediate in the hydroarylation and hydroalkenylation of unactivated alkynes. Similarly, the hydroalkynylation would proceed via hydride-bridged intermediates, which would be generated from the above unidentified dinuclear complex.

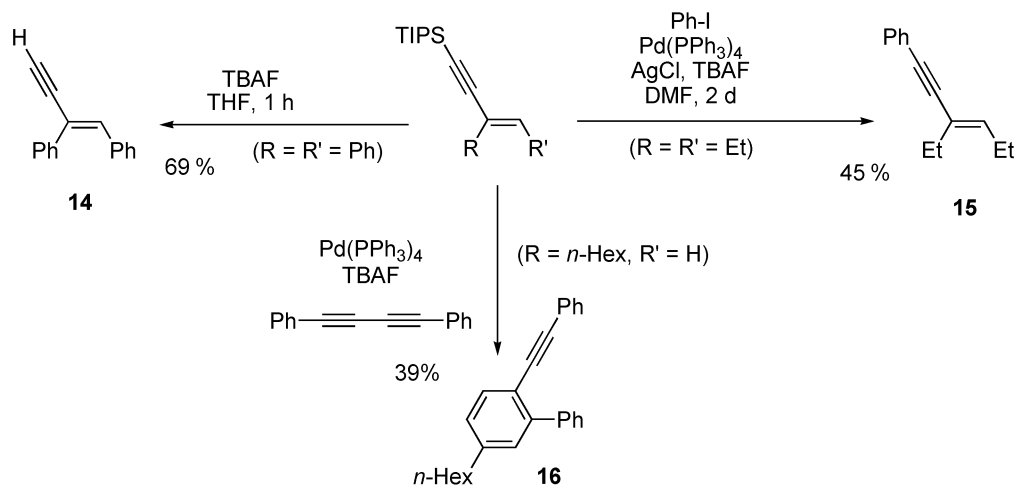


**Scheme 4** Plausible mechanism for the cross-addition catalyzed by dinuclear palladium complexes.

Reductive elimination of the hydride-bridged complexes would give low-valent palladium-complex **10**, which has a Pd–Pd bond. Insertion of 3-hexyne to the Pd–Pd bond of **10** and reductive elimination would afford alkenyl complex **12**. Oxidative addition of TIPS-A and reductive elimination of **3** from hydride-bridged intermediate **13** would regenerate **10**.

### TRANSFORMATION OF THE PRODUCTS

Since products **3** and **4** have a silyl group, various transformations are possible (Scheme 5). Desilylation by tetrabutylammonium fluoride (TBAF) is very easy, and the resulting terminal alkyne **14** can be further transformed by various reactions. Although arylalkynes cannot be used in the selective cross-addition, arylenyne **15** can be prepared by a palladium-catalyzed cross-coupling reaction. Cycloaddition with a diyne gives trisubstituted benzene **16**. Preparation of a benzene ring from three different alkynes has been achieved by the combination of the cross-addition and the cycloaddition. Thus, although the selective cross-addition is limited to the reaction of TIPS-A, the existence of a silyl group on TIPS-A has a certain advantage for organic synthesis.



**Scheme 5** Transformation of enynes formed by the cross-addition.

### SUMMARY

As described above, it has been found that the palladium complexes such as **2** and **5**, which are supported by dpfam, served as catalysts for the selective cross-addition of TIPS-A to various unactivated internal and terminal alkynes. The use of dpfam as a ligand is essential for high selectivity. Although mononuclear complex **5** can be used as a catalyst, it seems likely that real reaction intermediates have dinuclear structures bridged by dpfam. Precise mechanistic study is expected to reveal the activation of alkynes by two palladium centers.

### ACKNOWLEDGMENT

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