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A Single-Step Synthesis of Enynes: Pd-Catalyzed Arylalkynylation of Aryl Iodides, Internal Alkynes, and Alkynylsilanes

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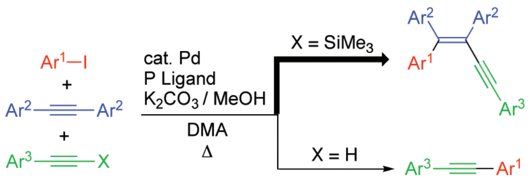
ABSTRACT



An unprecedented single-step synthesis of enyne derivatives through Pd-catalyzed arylalkynylation of aryl iodides, internal alkynes, and alkynylsilanes is described.

Conjugated enynes, especially 1,1,2-trisubstituted conjugated enynes, constitute basic units of naturally occurring compounds, related biologically active substances, and organic electronic materials.[1] A number of approaches for the synthesis of the enyne skeleton have been extensively studied.[2,3] Among these approaches, the Sonogashira-type coupling reaction of terminal alkynes with vinyl halides[4] and metal-catalyzed coupling reactions between various alkynylmetals containing B,[5] Mg,[6] Zn,[7] Si,[8] Sn,[9] Ag,[10] Au,[11] and In[12] and vinyl halides/triflates are most frequently used.[13] On the other hand, we have reported that $InBr_3$ functions as a cocatalyst in Sonogashira-type coupling reactions between aryl iodides and a terminal alkyne.[14] Our ongoing studies

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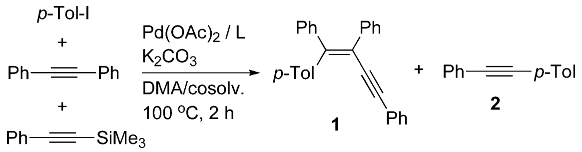
of metal-catalyzed coupling reactions that use the alkyne derivatives produced unique results. We found that employment of an alkynylsilane instead of a terminal alkyne as the coupling partner permits a three-component coupling reaction of an aryl iodide and two alkynylsilanes, producing an enyne skeleton. Use of alkynylsilanes is of considerable interest, owing to their commercial availability, relatively low toxicity, high tolerance to functional groups, and common utilization as a convenient reactant in previously described common organic reactions.[15] In this paper we report a palladium-catalyzed arylalkynylation of aryl iodides, internal alkynes, and alkynylsilanes, leading to the preparation of 1,1,2-trisubstituted enyne derivatives. To our knowledge, direct preparation of an enyne and a related alkene derivative through trapping of an in situ generated alkenylpalladium intermediate with organosilicon compounds has not been previously reported.[16]

Table 1. Optimization of Reaction Conditions



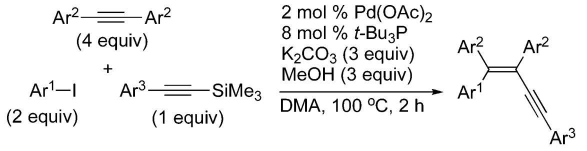
run	molar ratio[a]	ligand	cosolv[b]	yield (%)[c]	
				1	**2**
1	1:3:1.5			42	16
2	1:3:1.5	DPEPhos		53	20
3	1:3:1.5	Ph_3P		46	23
4	1:3:1.5	t-Bu_3P		60	26
5	1:3:1.5	t-Bu_3P	MeOH	67	24
6	2:3:1	t-Bu_3P	MeOH	68	18
7	2:4:1	t-Bu_3P	MeOH	(80)	(17)
8[d]	2:4:1	t-Bu_3P	MeOH	17	80

[a] Molar ratio = *p*-iodotoluene:diphenylacetylene:alkynylsilane. [b] DMA/MeOH = 99.5/0.5 (v/v). [c] NMR yield of runs 1−4 based on *p*-iodotoluene. NMR (Isolated) yield of runs 6−8 based on an alkynylsilane. [d] Reaction was carried out with phenylacetylene instead of alkynylsilane.

First, when the reaction of 4-iodotoluene, diphenylacetylene (3 equiv), and 1-phenyl-2-trimethylsilylacetylene (1.5 equiv) was conducted in dimethylacetamide (DMA) at 100 °C in the presence of 2 mol % of $Pd(OAc)_2$ and 3 equiv of K_2CO_3 as a model reaction, the 1,1,2-trisubstituted enyne derivative **1** was obtained in 42% yield along with the Sonogashira product **2** in 16% yield (run 1 in Table 1).[17] The geometric structure of **1** was determined from NOE and H−H COSY measurements.[18] To improve the yield and selectivity of the product **1**, the effects of several additives were examined. The phosphine ligand t-Bu_3P was highly effective for this reaction (runs 2−4). The addition of a cosolvent was also an important determinant of product yield. Thus, when MeOH (0.5% of solvent volume) was added, the reaction mixture was clean, and the yield increased to 67% (run 5). Moreover, examination of variation in the substrates molar ratio (aryl iodide:alkyne: alkynylsilane = 2:4:1) improved the selectivity and gave the highest yield of the desired enyne **1** (run 7). In contrast, use of phenylacetylene produced the Sonogashira-coupling product **2** as the major product in 80% yield without insertion of the alkyne (run 8).

To extend the generality of the coupling reaction, the reaction with alkynylsilanes, aryl iodides, and symmetrical internal alkynes was then carried out under the optimal conditions (Table 2). For example, when the reaction was run with alkynylsilanes derived from 1-(4-substituted-phenyl)-2-(trimethylsilyl)acetylene, the corresponding enyne de-

Table 2. Synthesis of Tetraarylsubstituted Enynes



entry	Ar^1	Ar^2	Ar^3	yield (%)[a]
1	Ph	Ph	Ph	**3**, 75
2	Ph	Ph	4-Me-C_6H_4	**4**, 60
3	Ph	Ph	4-MeO-C_6H_4	**5**, 70
4	Ph	Ph	4-F-C_6H_4	**6**, 62
5	Ph	Ph	3-pyridinyl	**7**, 60
6	Ph	Ph	2-thiopheyl	**8**, 62
7	4-F-C_6H_4	4-F-C_6H_4	4-F-C_6H_4	**9**, 80
8	4-F-C_6H_4	4-F-C_6H_4	Ph	**10**, 80
9	4-Me-C_6H_4	4-Me-C_6H_4	Ph	**11**, 40

[a] Isolated yield based on an alkynylsilane.

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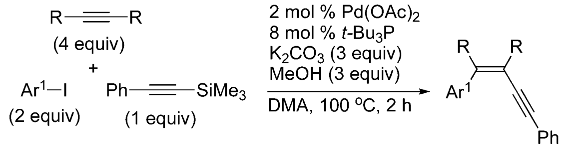
(17) See the experimental details in the Supporting Information.

(18) Correlation between two benzene rings derived from an internal alkyne was observed. See details in the Supporting Information.

rivatives **3**−**6** were obtained in practical yields. When alkynylsilanes containing a pyridine and thiophene ring were used, the heterocycle-containing enynes **7** and **8** were obtained in 60% and 62% yield. The electronic effect of the substituted group on the benzene ring may not affect the reactivity of the coupling reaction. Reactions with 4-fluorinated diphenylacetylene gave the corresponding enynes **9** and **10** in good yields. On the other hand, the use of an internal alkyne containing a methyl group reduced the yield of the desired product **11** to 40%.

Similar reactions were then performed with several aryl iodides under the optimal conditions (Table 3). Use of aryl iodides with an electron-donating group repressed the Sonogashira-type reaction to afford the corresponding triaryl-substituted enyne derivatives **13** and **15** in relatively good yields. Use of aryl iodides with an electron-withdrawing group gave the enyne derivative **14** and the Sonogashira-type product in 30% yield. When an aryl iodide with an ortho-substituted group was used, the product **12** was obtained in low yield due to steric hindrance by the methyl group.

Table 3. Synthesis of Tetrasubstituted Enynes

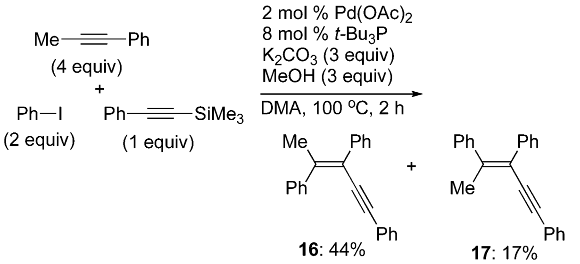


entry	Ar^1	R	yield (%)[a]
1	2-Me-C_6H_4	Ph	**12**, 36 (10)[b]
2	4-MeO-C_6H_4	Ph	**13**, 60 (E:Z = 2:5)[c]
3	4−F-C_6H_4	Ph	**14**, 50 (30)[b]
4	4-Me-C_6H_4	C_3H_7	**15**, 60

[a] Isolated yield based on an alkynylsilane. [b] Yield of the Sonogashira-type product is in parentheses. [c] Ratio of E:Z was determined by NOE and H−H COSY.

Moreover, to evaluate the regioselectivity of this type of coupling reaction, we attempted the reaction with the unsymmetrical alkyne 1-phenylpropyne. When the reaction was carried out under our standard conditions, the Z-adduct **16** and the E-adduct **17** were isolated in 44% and 17% yields, respectively, after standard purification (Scheme 1). The phenyl group from iodobenzene favored the less-hindered side (Me group) of the internal alkyne, and the alkynyl moiety favored the more-hindered end (Ph group) of the unsymmetrical alkyne. In addition, when a similar reaction was carried out with an internal alkyne with a strong electron-withdrawing group, the single coupling compound **18** with the stereostructure shown in Scheme 2 was obtained in 58% yield. Thus, the p-tolyl group was preferentially added to the more electron-deficient side of the alkyne. The regioselectivity of the reaction observed in the present study was consistent with the results reported by several groups.[16b,e] On the other hand, geometrical selectivity was not consistent with the previous reports.[16b,e,19] In Scheme 1, we observed formation of cis−trans geometrical isomers **16** and **17**, due to isomerization of the alkenylpalladium intermediate.[2]

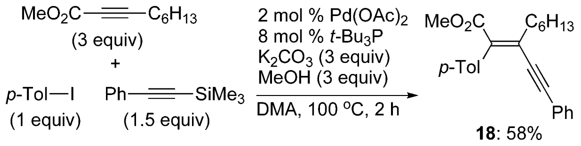
Scheme 1



16: 44%

17: 17%

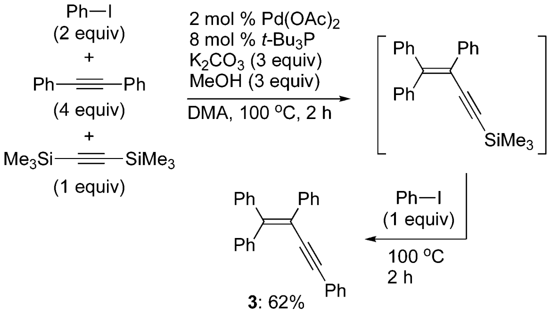
Scheme 2



18: 58%

When bis(trimethylsilylacetylene) was used under optimal conditions, a corresponding enyne product was produced, in which the other terminal trimethylsilyl group remained intact. Thus, when an excess of iodobenzene was added without isolation of the product and the reaction mixture was further heated at 100 °C for 2 h, the four-component coupling product **3** was obtained in 62% yield (Scheme 3).

Scheme 3



3: 62%

We then applied the present method for preparation of a 1,3-diene derivative using vinylsilane instead of alkynylsilane. When a similar reaction of 4-iodoanisole, dipheny-

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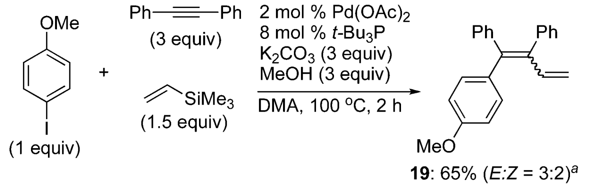
lacetylene, and vinylsilane was performed, the (*E*,*Z*)-diene[20] **19**, which is a Tamoxifen precursor, was directly obtained in 65% yield through a single step (Scheme 4).[16e,21]

Scheme 4[a]

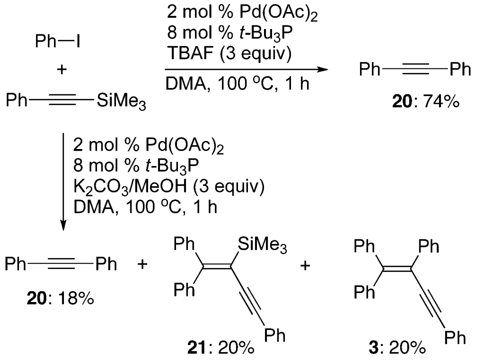


19: 65% (*E*:*Z* = 3:2)[a]

[a] Ratio of *E*:*Z* was determined by NOE and H−H COSY.

To understand the reaction path, we performed several control experiments. For instance, iodobenzene and alkynylsilane were used as reactants under the following reaction conditions: 2 mol % of $Pd(OAc)_2$, 8 mol % of t-Bu_3P, and 3 equiv of KF in DMA. As a result of this reaction, the Sonogashira-type product diphenylacetylene (**20**) was isolated in 74% yield (Scheme 5). In contrast, when a similar reaction was conducted under our standard conditions with K_2CO_3 and MeOH, diphenylacetylene (**20**) was obtained in only 18% yield and a mixture of two enyne derivatives **3** and **21** was simultaneously isolated. Thus, we assumed that use of an activating reagent that permits facile cleavage of a C−Si bond, such as fluoride ion, favors transmetalation of an acetylide ion over insertion of an internal alkyne on the Pd center, resulting in the formation of an internal alkyne derivative as well as the products obtained from a sila-Sonogashira-type (Hiyama-type) coupling reaction.[8]

Scheme 5



We demonstrated an unprecedented single-step synthesis of enyne derivatives through a Pd-catalyzed arylalkynylation of aryl iodides, internal alkynes, and alkynylsilanes. In particular, we found that when the coupling reaction was performed under relatively mild conditions, which consisted of a methanol solution containing K_2CO_3, the formation of an enyne derivative from an aryl iodide, an internal alkyne, and an alkynylsilane preferentially formed a Sonogashira-type product.

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Supporting Information Available: The experimental procedures, spectroscopic data for the prepared compounds, and ORTEP drawings of compounds **7**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[20] Because a trace amount of the byproduct involving a TMS group on the terminal carbon was isolated, this reaction may proceed through a Heck-type reaction path.

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