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Palladium-Catalyzed Cycloaddition of Alkynyl Aryl Ethers with Internal Alkynes via Selective Ortho C−H Activation

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Supporting Information

ABSTRACT: Alkynyl aryl ethers react with internal alkynes through selective ortho C−H activation by a palladium(0) catalyst to give substituted 2-methylidene-2*H*-chromenes. The alkynoxy group acts as a directing group to promote ortho C−H functionalization. Deuterium-labeling experiments indicated that the arylpalladium hydride complex is a key intermediate via oxidative addition. Various functional groups tolerate the present transformation to give the corresponding products.

Selective C−H bond functionalization by transition-metal complexes is recognized as an important process in synthetic organic chemistry.[1] To achieve this transformation, the use of a coordinating group (a so-called directing group) in the substrate is a promising approach for site-selective C−H bond functionalization. A variety of functional groups, such as carbonyl, imine, carboxyl, and pyridyl groups, are appropriate for this process. Since unsaturated C−C bonds can interact with metals through their π bonds to give η^2-metal complexes that undergo intramolecular hydroarylation with electron-rich aryl rings,[2] these unsaturated bonds have high synthetic potential. However, except for nitriles, they are seldom used as directing groups.[3] Other examples include rhodium-catalyzed intermolecular cyclization of 4-alkynals with alkynes, rhodium-catalyzed dimerization of styrene, and palladium-catalyzed intramolecular cyclization of *o*-alkynyl biaryls and alkynyl ketones.[4−7] Herein we report that palladium-catalyzed activation of an ortho C−H bond followed by cycloaddition of alkynoxyarenes (**1**) with internal alkynes (**2**) produces 2-methylidene-2 *H*-chromenes (2-methylidene-2*H*-1-benzopyrans, **3**). The presence of both oxygen and alkynyl moieties in **1** is essential for the success of the annulation. Chromenes are an important structural motif in medicinal and material chemistry.[8]

When the reaction of 4-$MeOC_6H_4OC{\equiv}CTIPS$ (**1a**; TIPS = triisopropylsilyl) with 4-octyne (**2a**) was performed in the presence of catalytic amounts of $Pd(OAc)_2$ (5 mol %), tricyclohexylphosphine (5 mol %), and Zn (5 mol %) in toluene at 90 °C for 6 h, it produced cyclic adduct **3a** in 86% yield after isolation by neutral silica-gel column chromatography and high-pressure liquid chromatography (HPLC) (Table 1, entry 1). The structure of **3a** was unambiguously determined by NMR spectroscopy.[9] No trace of the simple alkyne adduct **4**, benzoxepin **5**, or the [2 + 2 + 2] trimer of **1a** or **2a**[10] was observed. When the less bulky ligands PPh_3 and PBu_3 were used in the reaction, **3a** was produced in yields of 79 and 39% with 21 and 35% yields of homocycloadduct **6** (the dimer of **1a**) as regio- and stereoisomers, respectively.[9] These results indicate that the bulkiness of the ligand leads to the formation of **3a** in preference to **6**. The Zn reduces palladium(II) to palladium(0), as shown in entry 1. In the absence of Zn, no desired product **3a** was formed (entry 2). Use of $Pd(PCy_3)_2$ instead of $Pd(OAc)_2/PCy_3/Zn$ was equally effective (entry 3). Further co-use of $Zn(OAc)_2$ led to no improvement (entry 4). A reduced catalyst loading [0.5 mol % $Pd(PCy_3)_2$] was found to give **3a** in 85% yield (entry 5).

The cycloadditions of **1a** with various alkynes were examined, and the results are shown in Table 2. The reactions using diphenylacetylene (**2b**) and bis(trimethylsilyl)acetylene (**2c**) gave the corresponding adducts **3b** and **3c** in 92 and 23% yield, respectively (entries 1 and 2). In the case of **2c**, the main product generated was **6**, probably as a result of steric hindrance during the alkyne insertion event. When 1,4-bis(trimethylsilyl)-2-butyne (**2d**) was used, the corresponding adduct (**3d**) was obtained in 73% NMR yield (entry 3). However, attempted HPLC purification caused protodesilylation of the 4-methyl to give **3d′**. The reaction of **1a** with 1-phenyl-1-propyne (**2e**) occurred regioselectively to give **3e** in 70% yield with the phenyl group at the C4 position (entry 4). Annulation with sterically biased alkyne **2f** occurred highly regioselectively to give cyclic product **3f** with a bulkier substituent at the C3 position (entry 5). Unfortunately, the reaction with 1-octyne provided only the simple alkynyl−H adduct (*E*)-(4-$MeOC_6H_4O$)(HexC≡C)C=C(TIPS)(H) in 37% yield without any formation of the expected cycloadduct.[11]

Variously substituted alkynyl aryl ethers **1** were next applied to this reaction (Table 3). The substrate containing the *tert*-butyldimethylsilyl (TBDMS) group for R^4 underwent annulation with **2a** and **2b** (5 equiv) to form 2*H*-chromenes **3g** and **3h** in 44 and 67% yield, respectively (entries 1 and 2). The triethylsilyl (TES)- and *tert*-butyldiphenylsilyl (TBDPS)-protected alkynes **1c** and **1d** upon reaction with **2b** gave **3i** and **3j** in 56 and 85% yield, respectively (entries 3 and 4). The structure of **3j** was unambiguously determined by X-ray crystallographic analysis (Figure 1).[12] In contrast, the trimethylsilyl (TMS)-substituted alkynyl ether did not provide the desired product, indicating that a bulky silyl substituent at R^4 is key for achieving the present cycloaddition. Variously substituted phenyl groups bound to the alkynoxy group did not hamper the reaction with **2a** (entries 5−8). The reaction of *m*-methyl-substituted substrate **1g** provided product **3m** in 73%

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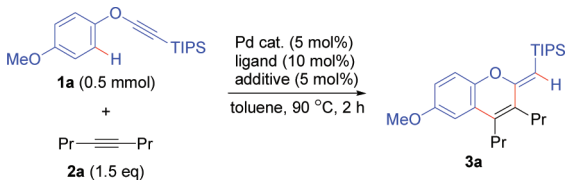
Table 1. Palladium-Catalyzed Cycloaddition of 1a with 4-Octyne (2a)



entry	Pd	ligand	additive	yield (%)[a]
1[b]	$Pd(OAc)_2$	PCy_3	Zn	94 (86[c])
2	$Pd(OAc)_2$	PCy_3	–	0
3	$Pd(PCy_3)_2$	–	–	93
4	$Pd(PCy_3)_2$	–	$Zn(OAc)_2$	94
5	$Pd(PCy_3)_2$[d]	–	–	85

TIPS = triisopropylsilyl. [a]NMR yields. [b]6 h. [c]isolated yield. [d]0.5 mol %.

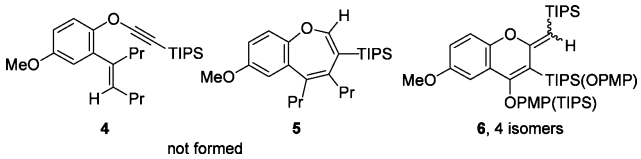
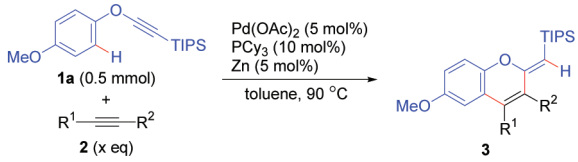


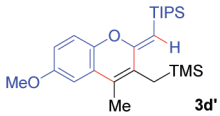
Table 2. Palladium-Catalyzed Cycloaddition of 1a with 2[a]



2b ($R^1 = R^2 = Ph$), **2c** ($R^1 = R^2 = TMS$), **2d** ($R^1 = R^2 = CH_2TMS$)
2e ($R^1 = Ph$, $R^2 = Me$), **2f** ($R^1 = Ph$, $R^2 = TMS$)

entry	2	x	time (h)	product	yield (%)[b]
1	**2b**	1.1	6	**3b** ($R^1 = R^2 = Ph$)	92
2	**2c**	5	13	**3c** ($R^1 = R^2 = TMS$)	23
3	**2d**	5	6	**3d** ($R^1 = R^2 = CH_2TMS$)	(73[c])
4	**2e**	1.1	6	**3e** ($R^1 = Ph$, $R^2 = Me$)	70
5	**2f**	1.1	6	**3f** ($R^1 = Ph$, $R^2 = TMS$)	60

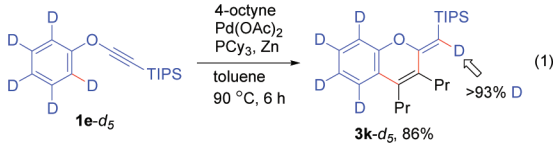
[a]Unless otherwise noted, a mixture of **1a** (0.5 mmol), **2**, $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol), Zn (0.025 mmol), and toluene (0.5 mL) was heated at 90 °C. TMS = trimethylsilyl. [b]Isolated yields. [c]NMR yield.



yield as a single isomer, indicating that annulation was completed at the less hindered ortho position (entry 7).

To gain insight into the mechanism, the following experiments were conducted. In contrast to the rhodium-catalyzed ortho-selective alkenylation of anisole with internal alkynes,[13] the reaction of 1,4-dimethoxybenzene with **2a** did not occur under the optimized conditions. In addition, 4-$MeOC_6H_4CH_2C{\equiv}CTIPS$ remained totally intact under similar conditions. These results indicated that sole ligation by the oxygen atom or by the C≡C bond to palladium(0) does not induce C−H cleavage. 4-$MeOC_6H_4C(O)C{\equiv}CTIPS$ gave no adduct, demonstrating that the carbonyl group is not appropriate for the cyclization. These results demonstrate that the presence of a highly polarized alkynyl ether group is crucial for successful annulation.

The reaction of **1e**-d_5 with **2a** in C_6D_6 resulted in the formation of **3k**-d_5, as shown by ^{1}H NMR analysis, demonstrating that the original *o*-deuterium was selectively shifted to the 2-methylidene position (eq 1). This result clearly shows that the sequential bimolecular insertion of two C≡C bonds into the ortho C−H bond is actually what occurs. This



result and the fact that the palladium(0) complex is the active catalyst strongly indicate that the C−H bond functionalization proceeds via oxidative addition to a palladium(0) complex to give the arylpalladium hydride complex. The kinetic isotope effect (KIE) was investigated by a competitive experiment between **1e** and **1e**-d_5 in C_6D_6 (eq 2), which revealed a high intermolecular KIE of 4.7. Accordingly, the C−H bond cleavage step is concluded to be turnover-limiting.

The triple bond of the *O*-alkynyl group may have a ketene-like polarized resonance structure (i) (Scheme 1).[14,15] The *α*-

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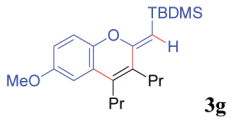
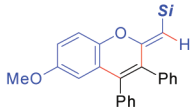
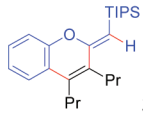
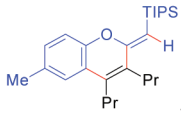
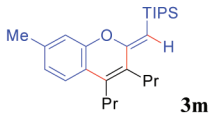
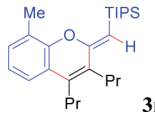
Table 3. Palladium-Catalyzed Cycloaddition of 1 with 2[a]

entry	1	2	x	product	yield (%)[b]
1	**1b**	**2a**	1.1	 **3g**	44
					
2	**1b**	**2b**	6	**3h** (R^4 = TBDMS)	67
3[c]	**1c**	**2b**	6	**3i** (R^4 = TES)	56
4	**1d**	**2b**	1.5	**3j** (R^4 = TBDPS)	85
5	**1e**	**2a**	1.1	 **3k**	82
6	**1f**	**2a**	1.1	 **3l**	90
7	**1g**	**2a**	1.1	 **3m**	73
8	**1h**	**2a**	1.1	 **3n**	60

[a]Unless otherwise noted, a mixture of **1** (0.5 mmol), **2**, $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol), Zn (0.025 mmol), and toluene (0.5 mL) was heated at 90 °C. TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TBDPS = *tert*-butyldiphenylsilyl. [b]Isolated yields. [c]3 h. [d]Toluene (2.0 mL).

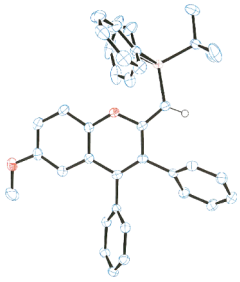
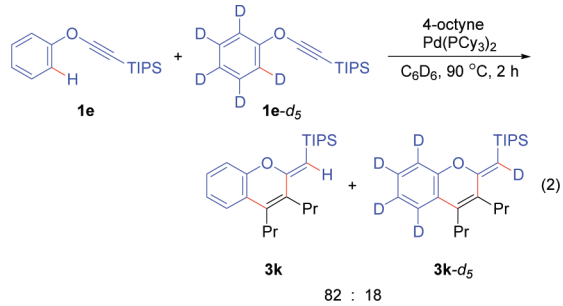
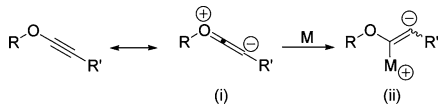


Figure 1. ORTEP diagram of **3j**.

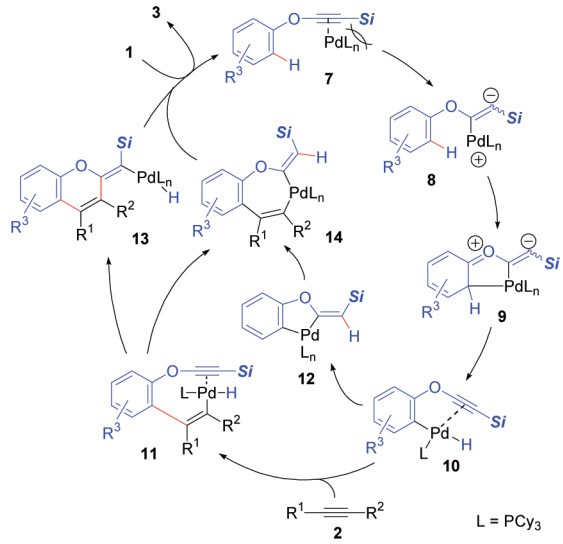
carbon in this structure may be effectively attacked by a nucleophilic low-valent transition-metal complex to give a cationic metal (ii). On the basis of this working hypothesis, a plausible mechanism is briefly described in Scheme 2. Initially, ligation of the C≡C bond in **1** to the palladium(0) complex forms η^2-complex **7**, which is converted into zwitterionic palladium complex **8**. The effect of bulky silyl groups can be



Scheme 1. Resonance Structure of Alkynyl Ether and Its Reaction with a Low-Valent Transition Metal



Scheme 2. Plausible Catalytic Cycle

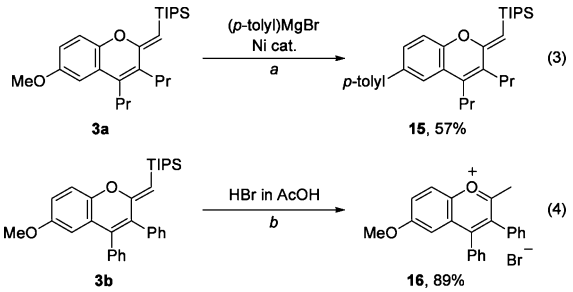


explained as follows: the formation of **8** is promoted by stabilization of the negative charge by silicon, which may push the η^2-palladium(0) complex to the electrophilic α-carbon because of steric repulsion. Subsequent formation of palladacycle **9** from **8** and a 1,2-hydrogen shift induce the oxidative addition to give palladium hydride complex **10**.[16,17] Insertion of alkyne **2** into the aryl−palladium bond of **10** gives alkynylpalladium **11**, which undergoes addition to the C≡C bond to give the intermediate alkenylpalladium hydride **13** or palladacycle **14**.[17] Subsequent reductive elimination of **3** from either **13** or **14** regenerates **7** and completes the catalytic cycle. An alternative insertion pathway could be also assumed: intramolecular insertion of the C≡C bond into the Pd−H bond in **10** could give five-membered palladacycle **12**, which could react with alkyne **2** to give **14**. The regioselectivity of **3e** with a phenyl group at R^1 is derived from a plausible π-stacking interaction between the two aryl rings in the coordination of **2e** to **10** or **12** followed by the arylpalladation. For sterically biased alkynes such as **2f**, the coordination takes place in the direction that avoids steric repulsion between the bulky R^2 group and the aryl group in **10** and **12**.

Synthetic transformations of the products are depicted in Scheme 3. Cross-coupling of the aryl−OMe bond in **3a** with (*p*-tolyl)MgBr under Dankwardt's conditions gave **15** in 57%

yield without cleavage of the cyclic aryl−O bond (eq 3).[18] Treatment of **3b** with hydrogen bromide in acetic acid

Scheme 3. Synthetic Transformations[a]



[a]Reagents and conditions; (a) **3a** (1.0 equiv), (*p*-tolyl)MgBr (6.0 equiv), $NiCl_2(PCy_3)_2$ (5 mol %), PCy_3 (10 mol %), $^iPr_2O$, 60 °C, 16 h. (b) **3b** (1.0 equiv), HBr in AcOH (2.5 eq, ca. 5.1 M), CH_2Cl_2, RT, 6 h.

produced benzopyrylium salt **16** in 89% yield via hydrodesilylation, hydrobromination of the resultant carbon−carbon double bond, and elimination of bromide ion (eq 4).[19]

In conclusion, the present study has demonstrated that the palladium-catalyzed cycloaddition of alkynyl aryl ethers with internal alkynes gives 2-methylidene-2*H*-chromenes via ortho C−H activation. The alkynoxy moiety as a directing group plays a key role in the present transformation. Synthetic applications of these reaction products have been accomplished. Current efforts are directed toward understanding the detailed reaction mechanism and developing similar cycloadditions.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data for new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) Crystal data for **3j**: space group $P2_1/c$ (No. 14); a = 18.911(6) Å, b = 9.338(3) Å, c = 19.236(5) Å, β = 116.261(3)°; Z = 4; ρ = 1.231 g/cm^3; R = 0.0557, R_w = 0.1178.

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