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Palladium-catalyzed Cycloaddition of Alkynyl Aryl Ethers to Allenes to Form a 2,3-Bismethylidene-2,3-dihydro-4*H*-1-benzopyran Framework

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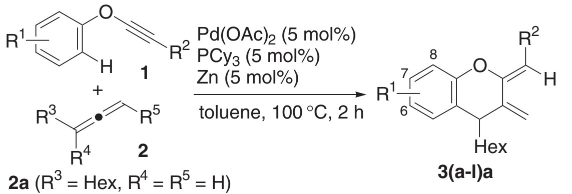
Palladium-catalyzed cycloaddition of alkynyl aryl ethers to allenes proceeds through *o*-C–H activation to give 2,3-dihydro-4*H*-1-benzopyran derivatives containing 2,3-exo-double bonds. These benzopyran derivatives further cycloadd stereoselectively to dienophiles to give condensed polycycles.

The Diels–Alder reaction of 1,2-bismethylidene carbocycles with dienophiles is a straightforward method to obtain polycyclic homologues, the synthetic method being the long-standing target of synthetic chemistry.[1] Thus, such a conjugated diene unit is a useful structural motif for polycyclic annulation. Representative preparative methods for 1,2-exomethylidene carbocycles are dehydrohalogenation of cyclic substrates having two adjacent halo- or pseudohalomethyl groups,[2] the Ramberg–Bäcklund reaction of in situ generated allylchloromethyl sulfones,[3] and metal-mediated and -catalyzed cyclizations of enynes as well as allenyl alkynes, diynes, and bisallenes.[4,5] Among these, metal-catalyzed cyclization appears to be ideal for the synthesis of multisubstituted 1,2-bismethylidene carbocycles with high atom-economy. This approach, however, is generally limited to unimolecular reactions, and its application to intermolecular cycloadditions remains a challenge.[6] In keeping with the goal of developing such reactions, regioselective insertion of allenes into C–H bonds of substrates having C–C triple bonds is a promising method.[7] In this respect, we recently found that an alkynoxy group (–OC≡CR)[8] works as a directing group for C–H activation and a cyclization partner as well.[9,10] Herein, we report the palladium-catalyzed activation of an *o*-C–H bond of alkynoxyarenes **1** followed by cycloaddition with allenes **2** to produce a wide range of 2,3-bismethylidene-2,3-dihydro-4*H*-1-benzopyrans **3**. The cycloadducts are extremely useful for the Diels–Alder reactions with dienophiles to give condensed cycles.

The reaction of 4-methoxyphenyl triisopropylsilylethynyl ether (**1a**) with 1,2-nonadiene (**2a**) gave 2,3-bismethylidenechromane derivative **3aa** in 81% yield as a single regioisomer in the presence of Pd(OAc)$_2$, PCy$_3$, and Zn (for in situ Pd(II) reduction) in toluene at 100 °C for 2 h (Table 1, Run 1). The structure of **3aa** was unambiguously determined by NMR spectroscopy. It should be noted that the internal double bond of **2a** readily underwent cycloaddition. The reaction of **1b** (R^2 = TBDPS), **1c** (R^2 = TES), and **1d** (R^2 = TBDMS) proceeded to afford **3ba**, **3ca**, and **3da** in moderate to excellent yields (Runs 2–4). In addition, the Me$_2$PhSi-substituted alkynyl ether **1e**, which was reluctant to cycloadd to alkynes, provided the desired product **3ea** in 40% yield (Run 5). The presence of a silyl substituent, however, is not essential for this reaction to occur: a bulky carbonaceous group also allows the substrate to undergo the transformation, as is evidenced by substrate **1f**, which despite the presence of the bulky substituent C(OMe)(–CH$_2$–)$_5$ produces **3fa** in 64% yield (Run 6). The reaction of 4-MeOC$_6$H$_4$OC≡CMe, however, resulted in a complex mixture of products. These results clearly demonstrate that a bulky R^2 group is crucial to the success of the reaction, and that silyl groups are the most effective. The fact that C$_6$H$_5$CH$_2$C≡CTIPS remained totally intact under similar conditions indicates that the sole ligation of the oxygen atom or C≡C bond to palladium(0) does not induce the C–H cleavage reaction. The substituent effect on the aryl groups was investigated next. Phenyl and 4-, 3-, and 2-tolyl groups did not hamper the cycloaddition (Runs 7–10). It is worth noting that the reaction of 3-tolyl substrate **1h** provided **3ha** in 73% yield as a single regioisomer (Run 8). Fluorine and trifluoromethyl group did not interfere with the reaction and gave cycloadducts **3ka** and **3la** in 52% and 66% yields, respectively (Runs 11 and 12).

Next, various allenes were applied to the cycloaddition reaction (Table 2). Alkyls with cyano (**2b**), oxycarbonyl (**2c**), silyloxy (**2d**), and cyclohexyl (**2e**) tolerated the reaction of either **1b** or **1m** to give the corresponding products (Runs 1–5). The reaction of **1c** with *p*-methoxyphenylallene (**2f**) took place to give **3cf** in 53% yield (Run 6). Internal allenes such as 4,5-nonadiene (**2g**) underwent the reaction with **1b** under these conditions, giving **3bg** in 71% yield as a mixture of stereo-

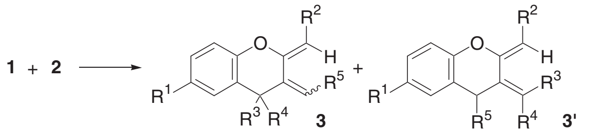
Table 1. Palladium-catalyzed cycloaddition of **1** with hexylallene **2a**[a]

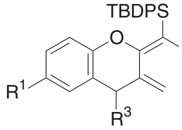
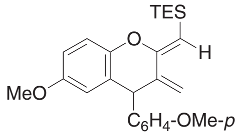
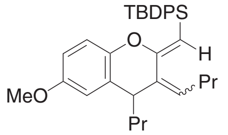
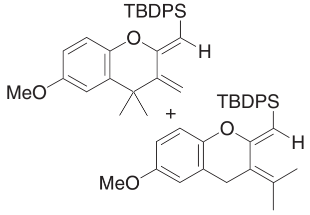


Run	1	R^1	R^2	3	R^1	Yield/%[b]
1	**1a**	4-MeO	TIPS	**3aa**	6-MeO	81
2	**1b**	4-MeO	TBDPS	**3ba**	6-MeO	>99
3	**1c**	4-MeO	TES	**3ca**	6-MeO	82
4	**1d**	4-MeO	TBDMS	**3da**	6-MeO	58
5	**1e**	4-MeO	SiMe$_2$Ph	**3ea**	6-MeO	40
6	**1f**	4-MeO	C(OMe)(–CH$_2$–)5	**3fa**	6-MeO	64
7	**1g**	4-Me	TIPS	**3ga**	6-Me	84
8	**1h**	3-Me	TIPS	**3ha**	7-Me	73
9	**1i**	2-Me	TIPS	**3ia**	8-Me	77
10	**1j**	H	TIPS	**3ja**	H	77
11	**1k**	4-F	TIPS	**3ka**	6-F	52
12	**1l**	4-CF$_3$	TIPS	**3la**	6-CF$_3$	66

[a]Unless otherwise noted, a mixture of **1** (0.5 mmol), **2a** (1.0–1.5 mmol), Pd(OAc)$_2$ (0.025 mmol), PCy$_3$ (0.025 mmol), Zn (0.025 mmol), and toluene (2.0 mL) was heated at 100 °C. [b]Isolated yields. TIPS: Si*i*-Pr$_3$, TBDPS: Si*t*-BuPh$_2$, TBDMS: Si*t*-BuMe$_2$, TES: SiEt$_3$.

Table 2. Palladium-catalyzed cycloaddition of **1** with **2**[a]



Run	1	2	Time/h	Product	Yield/%[b]
					
1	**1b**	**2b**	5	**3bb** (R^1 = MeO, R^3 = $(CH_2)_3CN$)	60
2	**1b**	**2c**	5	**3bc** (R^1 = MeO, R^3 = $(CH_2)_3CO_2Me$)	63
3	**1b**	**2d**	15	**3bd** (R^1 = MeO, R^3 = $(CH_2)_4OTBDPS$)	67
4	**1b**	**2e**	25	**3be** (R^1 = MeO, R^3 = c-C_6H_{11})	>99
5	**1m**	**2e**	5	**3me** (R^1 = H, R^3 = c-C_6H_{11})	95
6	**1c**	**2f**	26	 **3cf**	53
7	**1b**	**2g**	2	 **3bg**	71[c]
8	**1b**	**2h**	2	 **3bh** + **3'bh**	>99 (1.2:1)[d]

[a] Unless otherwise noted, a mixture of **1** (0.5 mmol), **2** (1.0–1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.025 mmol), Zn (0.025 mmol), and toluene (2.0 mL) was heated at 100 °C. [b] Isolated yields. [c] $E/Z = 25:75$. [d] Ratio of **3bh**/**3'bh**.

isomers (Run 7). 1,1-Dimethylallene (**2h**) upon reaction with **1b** also gave a mixture of **3bh** and **3'bh** (1.2:1 ratio) in quantitative yield (Run 8). These results show that sterically biased allenes tend to form the regioisomer **3'**, as a result of the reaction at the less-hindered terminal carbon.

The reaction with silylallenes gave a mixture of **3** and 3-silylmethylchromenes **4** (eq 1). For example, TES- and Me_2Ph-Si-substituted propa-1,2-dienes **2i** and **2j** reacted with **1b** to give **3bi** and **3bj** together with 3-silylmethylchromenes **4bi** and **4bj** in 60% (**3bi**:**4bi** = 80:20) and 84% (**3bj**:**4bj** = 60:40) yields, respectively. This indicates that the bulkier silyl substituents result in higher ratios of **4**. In the case of 3-triphenylsilyl-1,2-butadiene (**2k**), a mixture of **3bk**, **3'bk**, and **4bk** was obtained (36:22:42, >99% total yield). The structure of **4bk** was unambiguously determined by X-ray crystallographic analysis,[11] providing evidence that the triphenylsilyl group apparently migrated to the terminal carbon of allene **2k**. In view that **3bj** did not isomerize to **4bj** via a 1,3-silicon shift under the catalytic conditions, it is possible that the insertion of the internal double bond of allene **2k** into the Ar–Pd bond is followed by β-silyl elimination and silylpalladation of the less-hindered terminal double bond.[12]

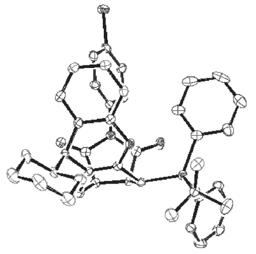
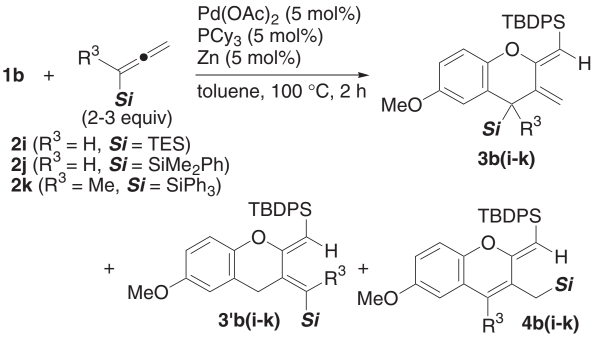


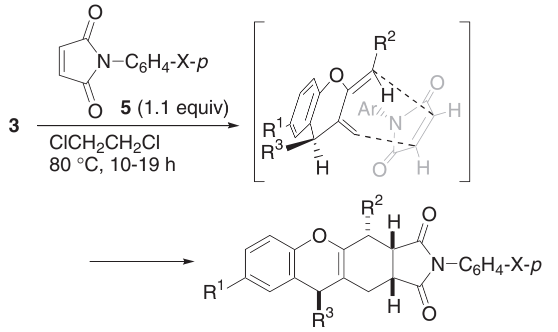
Figure 1. ORTEP diagram of **6d** (one isomer).



(1)

60% (**3bi** : **3'bi** : **4bi** = 80 : 0 : 20)
84% (**3bj** : **3'bj** : **4bj** = 60 : 0 : 40)
>99% (**3bk** : **3'bk** : **4bk** = 36 : 22 : 42)

The Diels–Alder reaction of **3** with *N*-arylmaleimide **5** was investigated (eq 2). The reaction of **3aa**, **3be**, and **3me** with *N*-phenylmaleimide (**5a**) (X = H) gave the *endo*-cyclic adducts **6a**, **6b**, and **6c** in 70–91% yields, respectively. Brominated derivative **5b** (X = Br) reacted with **3me** to provide **6d** in 87% yield. The structure and stereochemistry of **6d** were unambiguously determined by X-ray crystallographic analysis (Figure 1),[11] showing that the reaction proceeded selectively by approach from only one side, so as to minimize steric hindrance on R^3.



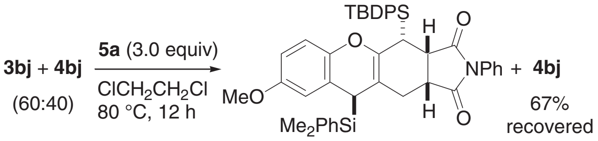
(2)

6a (R^1 = MeO, R^2 = TIPS, R^3 = Hex, X = H), 70%
6b (R^1 = MeO, R^2 = TBDPS, R^3 = c-C_6H_{11}, X = H), 78%
6c (R^1 = H, R^2 = TBDPS, R^3 = c-C_6H_{11}, X = H), 91%
6d (R^1 = H, R^2 = TBDPS, R^3 = c-C_6H_{11}, X = Br), 87%

The one-pot cycloaddition/Diels–Alder reaction sequence employing **1a**, **2a**, and **5a** can be carried out and **6a** was isolated in 74% overall yield (eq 3). In addition, when a 60:40 mixture of **3bj** and **4bj** was treated with **5a**, only **3bj** participated in the reaction to give **6e** in 86% yield, whereas most of **4bj** remained intact (eq 4).

To get an insight into the mechanism of the cycloaddition, we carried out the reaction of **1j**-***d*****$_5$** with **2c** and obtained the cycloadduct ***d*****-3jc**, whose structure was determined by ^{1}H NMR.

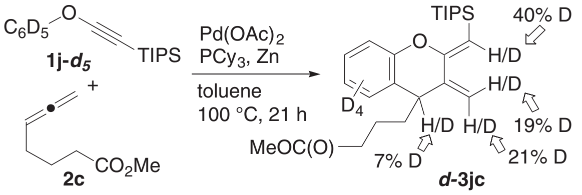
$$\mathbf{1a} \xrightarrow[\text{2) } \mathbf{5a} \text{ (3.0 equiv), 100 °C, 12 h}]{\text{1) } \mathbf{2a} \text{ (3.0 equiv), Pd(OAc)}_2 \text{ (5 mol\%), PCy}_3 \text{ (5 mol\%), Zn (5 mol\%), toluene, 100 °C, 2 h}} \underset{\text{74\% (one-pot)}}{\mathbf{6a}} \qquad (3)$$



(4)

6e, 86% (based on **3bj**)

The data showed that the original *o*-deuterium was distributed among four sites in the product: the C2-silylmethylidene (containing 40% D), C3-methylidene (19% and 21% D), and C4-methine (7% D) positions (eq 5). In control experiments, the reaction of **1a** with **2a** in the absence of Zn gave **3aa** in lower yields. Of note was the fact that [Pd(PCy$_3$)$_2$] and its combination with [Pd(dba)$_2$]/PCy$_3$ also showed catalytic activity. These facts indicate two reaction pathways. One, the *o*-C–H activation proceeds via the reaction with an active palladium(0) catalyst to give an aryl palladium hydride complex,[13] which then undergoes intermolecular insertion of the allene in a manner similar to reaction with alkynes.[9a] The deuterium-labeling experiment may support this mechanism. The incorporation of deuterium into three separate positions in addition to the C2-silylmethylidene site may be attributed to β-H elimination–reinsertion after the initial insertion into the Pd–H bond of the aryl palladium hydride complex (See the Supporting Information).[14] In the second mechanism, the π-allyl palladium complex may be formed via the nucleophilic attack of the α-carbon to the internal carbon of allenes ligating palladium catalysts, followed by the intramolecular attack of the *ortho*-carbon of oxyarenes on the allyl ligands.



(5)

In conclusion, we have demonstrated that the palladium-catalyzed cycloaddition of alkynyl aryl ethers with allenes is a viable approach for the synthesis of the benzopyran framework with 2,3-bismethylidene moieties through C–H activation. It should be noted that the alkynoxy group behaves both as a directing group and as the cycloaddition partner during the reaction. The Diels–Alder reaction of the diene moieties of the cycloadducts gave the linearly condensed tetracycles. Our continuing research is currently focusing on extending the present cycloaddition and understanding the detailed reaction mechanism.

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This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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