Synthetic Methods

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Synthesis of Substituted Tetrahydrocyclobuta[*b*]benzofurans by Palladium-Catalyzed Substitution/[2+2] Cycloaddition of Propargylic Carbonates with 2-Vinylphenols**

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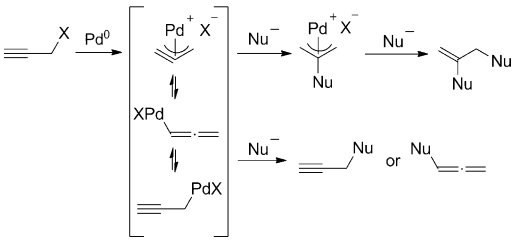
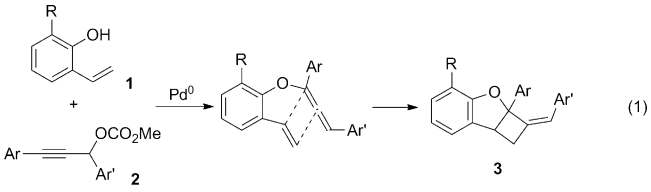
Propargylic compounds comprise useful synthetic intermediates in organic synthesis, and various reactions utilizing their properties have been reported.[1,2] For example, propargylic compounds containing an ester or a halide react with palladium complexes to form π-propargyl-, σ-propargyl-, and σ-allenylpalladium complexes,[3] which are subjected to the reaction with various reactants. In the case of soft nucleophiles, a nucleophile attacks the central carbon atom of the π-propargylpalladium, thus leading to a π-allylpalladium complex which further reacts with another nucleophile to afford disubstituted allylic compounds (Scheme 1).[4] A



Scheme 1. Palladium-catalyzed reaction of propargylic compounds with soft nucleophiles.

variety of the related reactions have been developed for propargylic substrates and nucleophiles.[2] In contrast, substitution of the soft nucleophiles at the terminal position of σ-propargyl- and σ-allenylpalladium complexes affords the corresponding propargylic and allenic products, but examples of the synthesis of allenes are limited to either intramolecular reactions or specific substrates.[5,6] During the course of our studies on the reaction of propargylic carbonates with soft nucleophiles in the presence of a palladium catalyst,[7] we unexpectedly found that nucleophilic substitution at the terminal position followed by [2+2] cycloaddition of the resulting phenoxyallene occurs when 2-vinylphenols (**1**) are used as nucleophiles [Eq. (1)]. Herein, we describe a novel

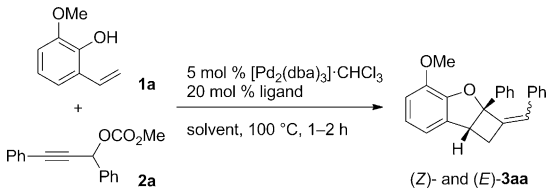


(1)

type of palladium-catalyzed domino reaction of propargylic carbonates (**2**) with 2-vinylphenols (**1**), in which substituted tetrahydrocyclobuta[*b*]benzofurans (**3**)[8] are produced in a stereoselective manner.

We began our studies using 2-methoxy-6-vinylphenol (**1a**) and 1,3-diphenylprop-2-ynyl methyl carbonate (**2a**). When **1a** and **2a** were subjected to a reaction with 5 mol% of $[Pd_2(dba)_3]\cdot CHCl_3$ and 20 mol% of dppf in DMSO at 100 °C for 1 hour, the tetrahydrocyclobuta[*b*]benzofurans (*Z*)-**3aa** and (*E*)-**3aa** were produced in a 4.5:1 ratio and 59% yield (Table 1, entry 1). The structures of (*Z*)- and (*E*)-**3aa** were

Table 1: Initial attempts for the reaction of **1a** with **2a**.



Entry	Ligand	Solvent	*Z*/*E*	Yield [%][a]
1	dppf	DMSO	4.5:1	59
2	dppb	DMSO	5.5:1	35
3	PPh_3	DMSO	2.9:1	62
4	P(*o*-tolyl)$_3$	DMSO	5.5:1	64
5	P(2-furyl)$_3$	DMSO	5.5:1	69
6	P(2-furyl)$_3$	toluene	3.4:1	67
7	P(2-furyl)$_3$	1,4-dioxane	3.5:1	85

[a] Yield is that of the isolated product. dba = dibenzylideneacetone.

confirmed by X-ray crystallographic analyses.[9] Attempts to employ various ligands revealed that the use of monodentate phosphine ligands enhanced the reactivity (entries 2–5), and the yield was increased to 69% in the case of P(2-furyl)$_3$ (entry 5). After experimenting with reaction solvents (entries 6 and 7), we found that (*Z*)- and (*E*)-**3aa** were produced in a 3.5:1 ratio and 85% yield when the reaction was carried out in 1,4-dioxane (entry 7).

Reactions of various substituted vinylphenols (**1b–g**) with **2a** are summarized in Table 2. When the methyl-substituted

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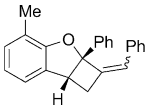
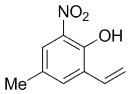
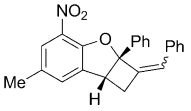
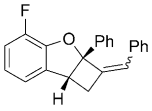
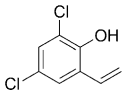
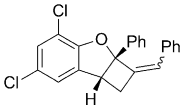
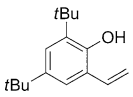
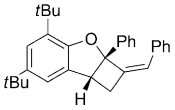
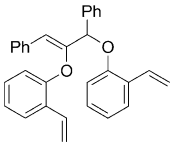
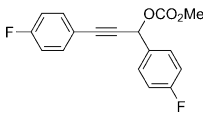
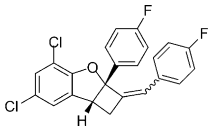
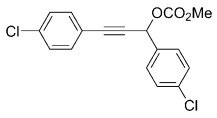
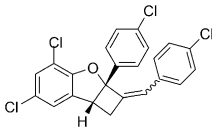
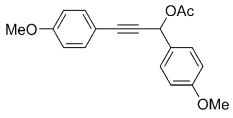
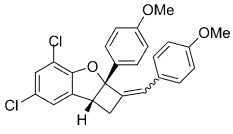
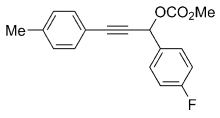
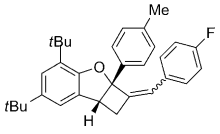
Table 2: Substrate scope of the reactions using various substituted vinylphenols **1b–g** with **2a**.[a]

Entry	Substrate **1**	Product **3**	Yield [%] *Z*/*E*
1			82 4.5:1
	1b	**3ba**	
2			78 4.5:1
	1c	**3ca**	
3[b]			70 4:1
	1d	**3da**	
4			92 4.4:1
	1e	**3ea**	
5			99 >20:1
	1f	**3fa**	
6			99
	1g	**4**	

[a] The reactions were carried out using **1** and **2a** in the presence of 5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 20 mol% P(2-furyl)$_3$ in 1,4-dioxane at 100°C for 1 h. [b] P(*o*-tolyl)$_3$ was used as the ligand.

Table 3: Substrate scope of the reactions using various substituted propargylic esters **2b–2e**.[a]

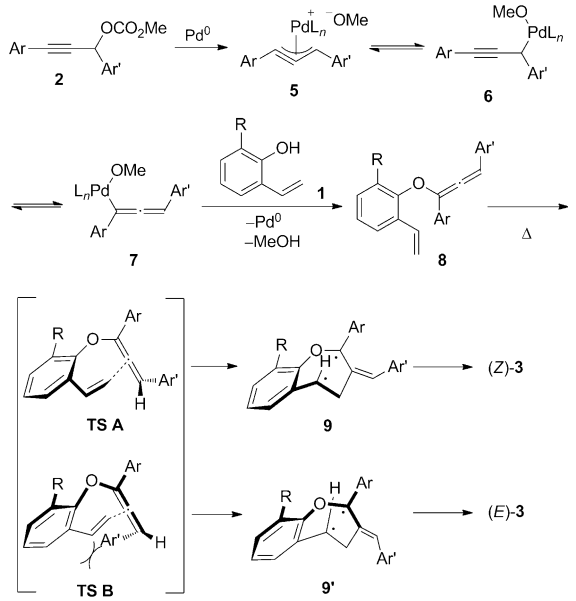
Entry	Propargylic ester **2**	Product **3**	Yield [%] *Z*/*E*
1			88 4.7:1
	2b	**3eb**	
2			89 5.9:1
	2c	**3ec**	
3[b]			72 10:1
	2d	**3ed**	
4[c]			99 4.8:1
	2e	**3fe**	

[a] The reactions were carried out using **1e** and **2** in the presence of 5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ and 20 mol% P(2-furyl)$_3$ in dioxane at 100°C for 1 h. [b] K_3PO_4 was added as a base. [c] Vinylphenol **1f** was used as the substrate.

substrate **1b** was exposed to the optimal reaction conditions, the oxatricyclic compounds (*Z*)- and (*E*)-**3ba** were produced in a 4.5:1 ratio and 82% yield (entry 1). The reaction using 4-methyl-2-nitro-6-vinylphenol (**1c**) also proceeded to give the corresponding products **3ca** in good yield and moderate selectivity (entry 2). The substrates **1d** and **1e**, having a fluoro and dichloro group, respectively, on the benzene ring successfully reacted with **2a** to afford the corresponding oxatricyclic compounds **3da** and **3ea** (entries 3 and 4). Interestingly, the corresponding product (*Z*)-**3fa** was obtained almost quantitatively as a sole product when the vinylphenol **1f**, containing two *tert*-butyl groups, was subjected to the reaction (entry 5). In contrast, the reaction of a nonsubstituted 2-vinylphenol (**1g**) did not give the tetrahydrocyclobuta[*b*]benzofurans, but instead gave the diphenoxy-substituted allylic compound **4** in 99% yield (entry 6).[10]

We next conducted the reactions using the propargylic esters **2b–e**, having a substituent at the *para* position of the phenyl groups (Table 3). The reaction of the substrates **2b** and **2c**, having a fluoro and a chloro group, respectively, with **1e** successfully proceeded to produce the corresponding tetrahydrocyclobuta[*b*]benzofurans **3eb** and **3ec** in good yields (entries 1 and 2). When the reaction of the propargylic acetate **2d** was carried out, the oxatricyclic products **3ed** were produced in a 10:1 ratio and 72% yield (entry 3). Furthermore, the corresponding products **3fe** were regioselectively produced in 99% yield when the substrate **2e** containing two different aryl groups was subjected to the reaction with **1f** (entry 4). The structure of (*Z*)-**3fe** was confirmed by X-ray crystallographic analysis.[9]

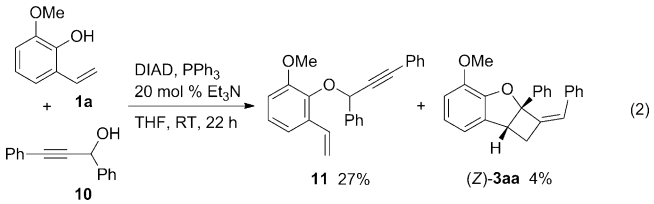
A plausible mechanism, which accounts for the observed stereo- and regioselective nature of this process, is shown in Scheme 2. By reacting with a palladium catalyst, the propargylic carbonate **2** undergoes decarboxylation to give the π-propargylpalladium complex **5**, σ-propargylpalladium **6**, and σ-allenylpalladium **7** as an equilibrium mixture. Then ligand exchange of the complex **7** between the methoxy group and **1** and subsequent reductive elimination of the palladium occurs to afford the phenoxy allene **8**.[11] The phenoxy allene **8** then undergoes the intramolecular [2+2] cycloaddition to produce the tetrahydrocyclobuta[*b*]benzofuran **3**. The thermal [2+2] cycloaddition of allenes is normally assumed to proceed in a stepwise fashion via the formation of a diradical intermediate.[12] Even in our process, it is expected that the cycloaddition could proceed via either the diradical intermediate **9** or **9′**, which arise from the initial attack of the terminal vinylic carbon onto the central carbon atom of the allene moiety. The observed stereoselectivity could be the result of steric factors which influence the relative energies of the competing transition states **TS A** and **TS B**. It is proposed



Scheme 2. Proposed reaction mechanism.

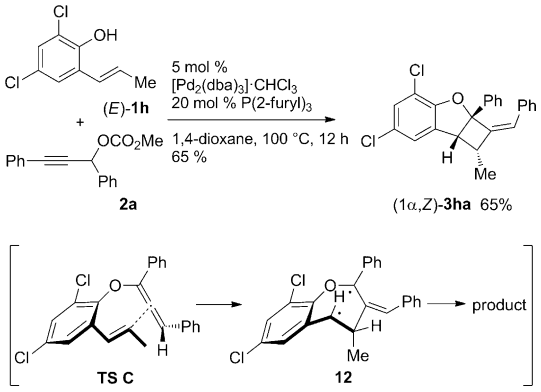
that the transition state **TS A**, leading to (*Z*)-**3** via **9**, is lower in energy because of the absence of the steric repulsion between Ar' and the vinyl groups, an interaction which exists in **TS B** and yields the stereoisomer (*E*)-**3** via **9′**. A reason for the formation of the diphenoxy-substituted allylic compound **4** in the case of vinylphenol **1g** (Table 1, entry 6) may be that nucleophilic attack of the phenolic oxygen atom on the central carbon atom of the π-propargylpalladium **5** would occur predominantly because the nucleophilicity is increased in the absence of the *ortho*-substituent. The results with the monodentate ligands were better than those with the bidentate ligands for the synthesis of **3** in Table 1, thus indicating that an equilibrium between the **5** and either **6** or **7** shifts to the latter in the presence of monodentate ligand.[3b,5b]

To confirm that **8** is actually generated as the reaction intermediate, Mitsunobu reaction of **1a** with the propargylic alcohol **10** was next conducted [Eq. (2); DIAD = diisopropyl



(2)

azodicarboxylate]. Treatment of **1a** and **10** with DIAD and PPh_3 led to the formation the tetrahydrocyclobuta[*b*]benzofuran (*Z*)-**3aa** in 4% yield along with the propargylphenol **11**. It is expected that the resulting (*Z*)-**3aa** was produced by the S_N2' substitution of **1a** with **10** followed by the [2+2] cycloaddition with **8**, and this result supports our reaction mechanism, including the substitution/[2+2] cycloaddition process as described in Scheme 2.



Scheme 3. Reaction using 2-propenyl-substituted phenol (*E*)-**1h** with **2a**.

We next attempted a reaction of (*E*)-**1h**, having a (*E*)-2-propenyl moiety in place of the vinyl group (Scheme 3). When the palladium-catalyzed reaction of **1h** with **2a** was carried out, the tetrahydrocyclobuta[*b*]benzofurans (1α,*Z*)-**3ha** was obtained in 65% yield as a single diastereomer. The structure of (1α,*Z*)-**3ha** was confirmed by X-ray crystallographic analysis.[9] The reaction should proceed via the favorable transition state **TS C** and formation of the diradical intermediate **12** along with the geometric stereoconversion of the propenyl group. This result demonstrates that the [2+2] cycloaddition proceeds by a two-step mechanism.

In conclusion, we have developed a novel methodology for the synthesis of substituted tetrahydrocyclobuta[*b*]benzofurans by a palladium-catalyzed domino reaction of propargylic carbonates with 2-vinylphenols. The reaction proceeds by the substitution of vinylphenols with propargylic carbonates and subsequent [2+2] cycloaddition of the resulting phenoxyallene. To the best of our knowledge, this is the first example in which a phenolic oxygen atom attacks at the terminal position of propargylmetal complexes. Further studies on the application of this reaction using other substrates are in progress.

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