Tandem Reactions

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Highly Regioselective Synthesis of Spirocyclic Compounds by a Palladium-Catalyzed Intermolecular Tandem Reaction**

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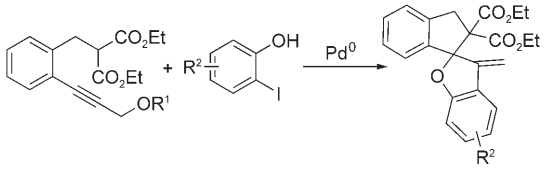
In the field of organic synthesis, it would be very desirable to facilitate two- or multi-step bond formation in one pot using a single catalyst to achieve economically useful transformations, which should minimize the chemicals used and the waste produced, as well as the reaction time.[1] As a result, great attention has been given to the development of tandem reactions.[2,3] A significant challenge with this process is that all the reagents are added at the beginning and the same reaction conditions are maintained throughout.

Although intramolecular tandem reactions are powerful methods for constructing complex organic molecules, the corresponding highly selective intermolecular reactions remain a challenge in synthetic organic chemistry. A range of strategies involving the sequential generation of radical and anionic species has been used for such intermolecular transformations.[4,5] However, only a limited effort has been made in applying transition-metal-catalyzed intermolecular tandem processes[6] to the synthesis of complex cyclic compounds.[7] Palladium-catalyzed cyclization of allenes with 2-halophenols, 2-haloanilines, and related reagents leading to the cyclized products have been reported.[8] To our knowledge, there are no reports of tandem reactions with allene formation and cyclization.

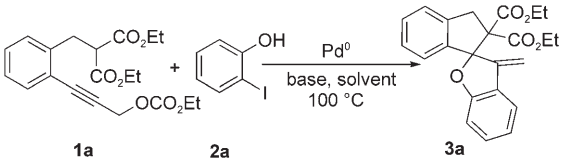
In connection with our research into the carboannulation reaction,[9] herein we report a novel palladium-catalyzed cyclization reaction of propargylic compounds with 2-halophenols to offer an efficient, direct route to a polycyclic framework having a unique aromatic spiro ring system in which benzo[*b*]furan and indene rings share one carbon atom. An alkene functional group is formed in the product which can be used in subsequent transformations (Scheme 1). The challenges in this case are 1) sequential regioselective formation of two carbon-carbon bonds and a carbon-oxygen bond; 2) control of the reaction sequence;[10] and 3) avoiding Heck coupling[11] of the in-situ-formed alkene moiety with aryl halides.



Scheme 1. Synthesis of the spiro compound.

We began with the reaction of **1a** (0.20 mmol), 1.5 equivalents of 2-iodophenol (**2a**), 5 mol% of $[Pd(PPh_3)_4]$ as the catalyst, and 2.0 equivalents of Cs_2CO_3 in DMF at 100°C under argon for 16 h. The desired product **3a** was isolated in a 68% yield with high regioselectivity (Table 1, entry 1). Na_2CO_3 and K_2CO_3 were also investigated as bases. Na_2CO_3 provided a slightly higher yield but longer reaction time than K_2CO_3 (Table 1, entries 2 and 3). Changing the solvent from DMF to DMSO did not enhance the yield of **3a** (Table 1, entry 4). However, the reaction gave a poor result in THF (Table 1, entry 5). Other palladium catalysts tested, such as $[Pd_2(dba)_3]$ (dba = dibenzylideneacetone) and $Pd(OAc)_2$/PPh_3, (OAc = acetate) were less effective (Table 1, entries 6 and 7).

Table 1: Optimization of the palladium-catalyzed cyclization of propargylic carbonate **1a** with **2a**.[a]



1a **2a** **3a**

Entry	Catalyst	Base	Solvent	*t* [h]	Yield of **3a**[b] [%]
1	$[Pd(PPh_3)_4]$	Cs_2CO_3	DMF	16	68
2	$[Pd(PPh_3)_4]$	Na_2CO_3	DMF	36	57
3	$[Pd(PPh_3)_4]$	K_2CO_3	DMF	16	45
4	$[Pd(PPh_3)_4]$	Cs_2CO_3	DMSO	24	41
5	$[Pd(PPh_3)_4]$	Cs_2CO_3	THF	24	trace
6	$[Pd_2(dba)_3]$	Cs_2CO_3	DMF	24	33
7	$[Pd(OAc)_2]$/PPh_3	Cs_2CO_3	DMF	24	58

[a] Reactions were carried out on a 0.2-mmol scale in 2.0 mL of solvent under argon at 100°C for the specified time with **1a** (1.0 equiv), **2a** (1.5 equiv), base (2.0 equiv), and [Pd] (0.05 equiv). [b] Yield of isolated product based on **1a**.

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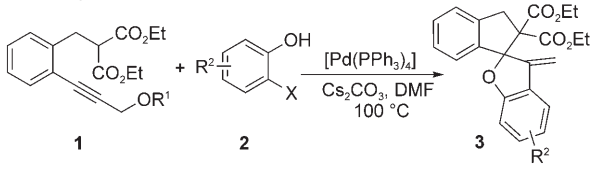
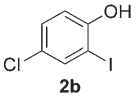
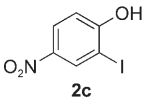
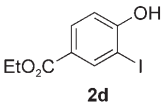
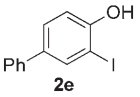
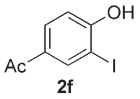
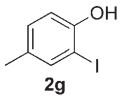
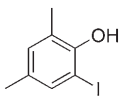
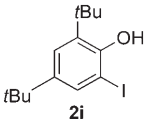
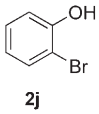
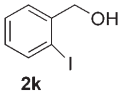
Using the optimized reaction conditions above, the reactions of **1a** with a variety of 2-iodophenols afforded the corresponding products **3** in moderate to good yields (Table 2, entries 1–7). 2-Iodophenols bearing an electron-withdrawing group in the *para* position resulted in an increase in both the yield and the velocity of the reaction. When **2h** was employed in the reaction, the spirocyclic product **3h** was isolated in a 35% yield (Table 2, entry 8). Nevertheless, **2i** produced a complex mixture of unidentified products, presumably arising from steric effects (Table 2, entry 9). The use of less-reactive 2-bromophenol (**2j**) also afforded the polycyclic product **3a** in a 43% yield. However, attempts to extend the range of substrates to (2-iodophenyl)methanol were unsuccessful (Table 2, entry 11). We have also investigated the reactions of substrates having various leaving groups. The reactions of propargyl carbonate **1b**, propargyl acetate **1c** and propargyl benzoate **1d** gave the desired products **3a** in moderate yields (Table 2, entries 12–14). In addition, propargyl phosphate **1e** also gave the product **3a** in a 62% yield and shorter reaction time was required (Table 2, entry 15).

Table 2: Palladium-catalyzed cyclization of propargylic compounds **1** with 2-halophenols **2**.[a]

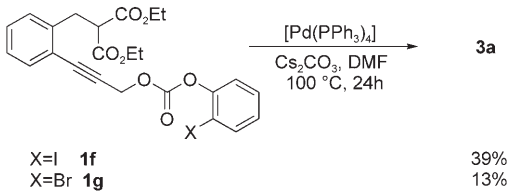


1 2 3

Entry	1	2	t [h]	3	Yield[b] [%]
1	**1a**[c]	 **2a**	16	**3a**	68
2	**1a**	 **2b**	16	**3b**	66
3	**1a**	 **2c**	12	**3c**	74
4	**1a**	 **2d**	12	**3d**	81
5	**1a**	 **2e**	16	**3e**	71
6	**1a**	 **2f**	12	**3f**	79
7	**1a**	 **2g**	24	**3g**	63
8	**1a**	 **2h**	24	**3h**	35
9	**1a**	 **2i**	24		
10	**1a**	 **2j**	24	**3a**	43
11	**1a**	 **2k**			
12	**1b**[d]	**2a**	16	**3a**	66
13	**1c**[e]	**2a**	16	**3a**	69
14	**1d**[f]	**2a**	16	**3a**	58
15	**1e**[g]	**2a**	13	**3a**	62

[a] All reactions were carried out under the optimal conditions reported in the text. [b] Yield of isolated product based on the propargylic compound **1**. [c] $R^1 = CO_2Et$. [d] $R^1 = CO_2Me$. [e] $R^1 = COMe$. [f] $R^1 = COPh$. [g] $R^1 = PO(OEt)_2$.

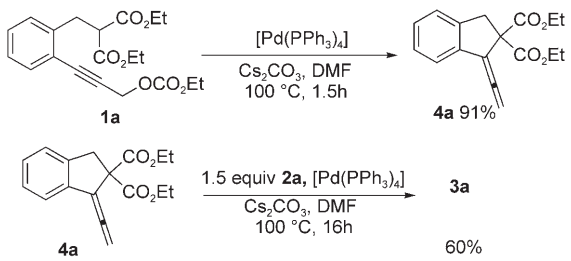
The reactions of **1f** and **1g**, containing latent 2-halophenols as a part of the carbonate leaving group, were also examined (Scheme 2). When **1f** and **1g** were subjected to the palladium-catalyzed reaction, the desired product **3a** was isolated in 39 and 13% yields, respectively. In this reaction, the substrate initially releases the phenoxide, which then acts as a substrate for the palladium-catalyzed cyclization reaction to produce the product.



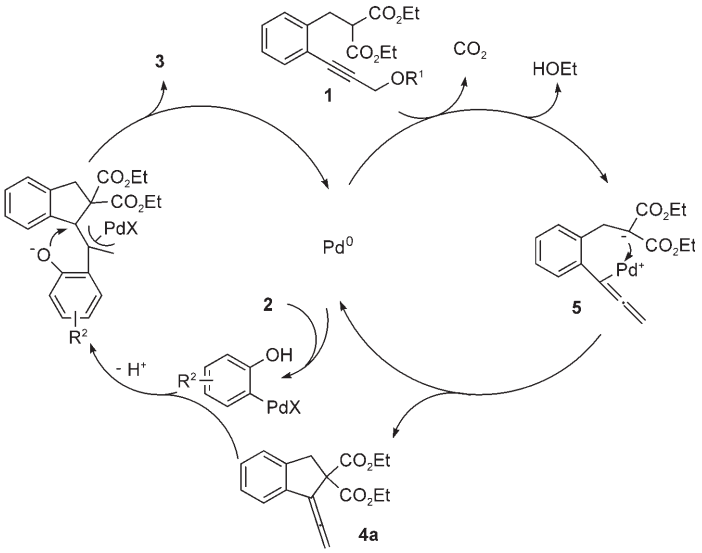
Scheme 2. The synthesis of compound **3a** from **1f** and **1g**.

To clarify the mechanism of this process, we examined the reaction of **1a** without 2-iodophenol, and allene **4a** was obtained in a 91% yield (Scheme 3). The reaction of purified **4a** with 2-iodophenol (**2a**) also afforded the corresponding product **3a** in 60% yield under the optimized reaction conditions above (Scheme 3).[12] In fact, **4a** was also observed in the one-pot reaction. However, it disappeared as the reaction progressed. This result confirmed that the tandem reaction proceeds via an allene intermediate.

The mechanism shown in Scheme 4 is proposed for this process. It consists of the following key steps: a) initial decarboxylation of propargylic compound **1** by palladium(0)



Scheme 3. Allene formation and cyclization.



Scheme 4. The proposed reaction pathway (see text for details).

to generate an allenylpalladium complex **5**;[13,14] b) regioselective intramolecular nucleophilic attack of the carbanion to form intermediate **4a**; c) oxidative addition of the aryl halide to the palladium(0) catalyst; d) the addition of arylpalladium compounds to 1,2-dienes produces π-allylpalladium compounds;[15] and e) regioselective intramolecular nucleophilic attack[14] at the more hindered site to afford products **3**.[16] The selectivity is presumably due to electronic effects[8a,9c] at the benzylic position.

In conclusion, we have developed a novel palladium-catalyzed intermolecular tandem reaction for the synthesis of tetracyclic compounds with sequential high regioselectivity and with reaction conditions compatible with sequential transformations of various functional groups of easily accessible substrates. It is noteworthy that the mechanism was verified by the isolation of a reaction intermediate. In addition, this process is one of the comparatively few examples in which a palladium(0) catalyst is simultaneously involved in two catalytic cycles.[2,3,6j]

Experimental Section

General procedure (Table 1, entry 1): Cs_2CO_3 (130.4 mg, 0.40 mmol) was added to a solution of 3-(2-(2,2-di(ethoxycarbonyl)ethyl)phenyl)prop-2-ynyl ethyl carbonate **1a** (75.2 mg, 0.20 mmol) in DMF (2.0 mL). The mixture was stirred for 5 min and $[Pd(PPh_3)_4]$ (11.5 mg, 0.01 mmol, 5 mol%), and 2-iodophenol **2a** (66.0 mg, 0.30 mmol) were added. The resulting mixture was then heated under an argon atmosphere at 100 °C. When the reaction was considered complete as determined by thin-layer chromatography, the reaction mixture was allowed to cool to room temperature and quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water and saturated brine. The organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel to afford **3a** 51.4 mg (68%) as an oil.

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