Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700978

Link to VoR: http://dx.doi.org/10.1002/adsc.201700978

10.1002/adsc.201700978

UPDATE

DOI: 10.1002/adsc.201

Palladium-catalyzed Oxa-[4+2] Annulation of *para*-Quinone Methides

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Received:

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract: A palladium-catalyzed oxa-[4+2] annulation of *para*-quinone methides with allyl carbonates bearing a nucleophilic alcohol side chain has been developed. This method provided an efficient strategy to the construction of 2-oxaspiro-cyclohexadienones via 1,6-conjugated addition-mediated allylation in moderate to good yields. Preliminary results on asymmetric derivatives promised potential in the synthesis of enantioenriched frameworks.

Keywords: palladium-catalyzed; *para*-quinone methides; spirocyclic compounds; oxa-[4+2] annulation; allylation

Spiro-cyclohexadienones are privileged structures existed in various natural products and pharmaceutical molecules with remarkable biological activities.[1] So that many efforts have been contributed to construct these skeletons. However, 2-oxaspiro[5.5]undeca-7,10-dien-9-one as a member of the spiro-cyclohexadienone family and the key skeleton of gymnothelignans (Figure 1), was rarely mentioned,[2] and only few examples related to their synthesis has been reported.[3] Thus, it is highly desirable to develop an effective synthetic method to synthesize them for chemists to comprehensively investigate their bioactivity and medicinal value.

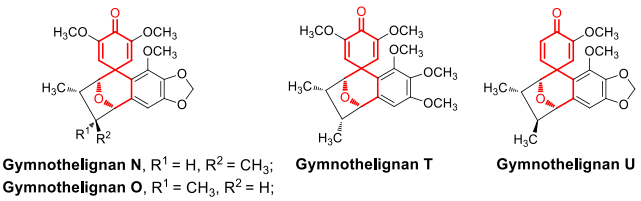
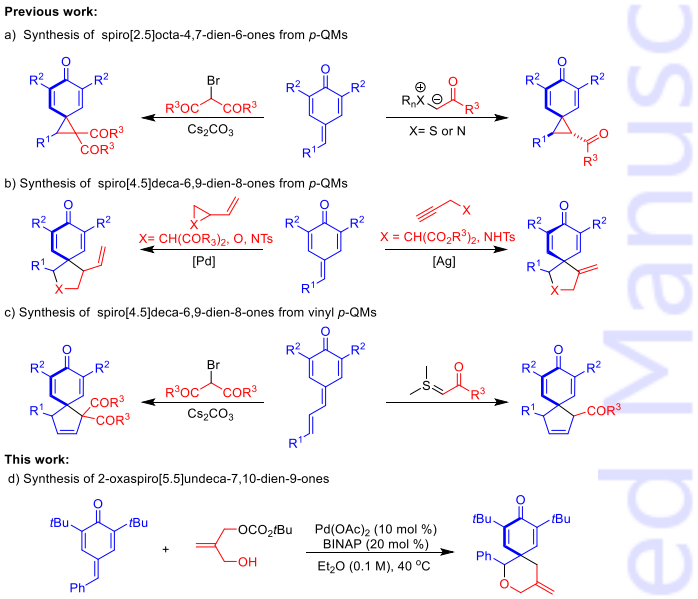


Figure 1. 2-Oxaspiro[5.5]undeca-7,10-dien-9-one existed in nature products.

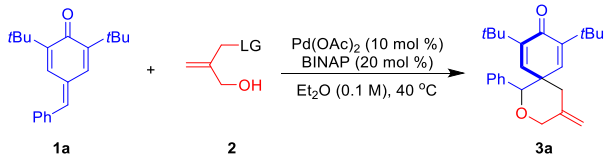


Scheme 1. Strategies to the synthesis of spiro-cyclohexadienones from *p*-QMs.

Recently, *para*-quinone methides (*p*-QMs)[4] as versatile synthons have been employed to construct varieties of spiro-cyclohexadienones. Since 2015, our group, Fan's group and Waser's group successively achieved spiro[2.5]octa-4,7-dien-6-ones from *p*-QMs via 1,6-addition-mediated [2+1] annulation with bromomalonates[5], sulfur ylides[6] and ammonium ylides[7] (Scheme 1a). In addition, our group and Zhao's group revealed that spiro[4.5]deca-6,9-dien-8-ones could be approached through palladium or silver-catalyzed 1,6-addition-mediated allylation[8] or alkenylation[9] of *p*-QMs (Scheme 1b). In 2017, our group and Fan's group simultaneously constructed spiro[4.5]deca-6,9-dien-8-ones again through cascade 1,6-addition/VCP rearrangement reactions of vinyl *p*-quinone methides (*p*-VQMs) with bromomalonates[10] or sulfur ylides[11] (Scheme 1c). To further strengthen our continuous interest in the synthesis of spiro-cyclohexadienones and characterizing the reactivity of *p*-QMs,[12] herein, we will describe our latest work

on palladium-catalyzed oxa-[4+2] annulation of *p*-QMs with allyl carbonates bearing a nucleophilic alcohol side chain[13] to achieve 2-oxaspiro[5.5]undeca-7,10-dien-9-ones. The process underwent tandem oxa-1,6-addition and palladium-catalyzed allylation dearomatization reactions (Scheme 1d).

Table 1. Investigation of the leaving groups.



Entry[a]	2	Leaving group	Yield[b]
1	**2a**	OCO_2Me	64
2	**2b**	OCO_2Et	70
3	**2c**	OCO_2iPr	92
4	**2d**	OCO_2tBu	94[c]
5	**2e**	OCO_2Bn	88
6	**2f**	OAc	NR
7	**2g**	$OPO(OPh)_2$	NR

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%) in Et_2O (1.0 mL) at 40 °C. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene.
[b] The yields were determined by ^1H NMR of crude reaction mixtures using CH_2Br_2 as internal standard. NR = No reaction.
[c] Isolated yield.

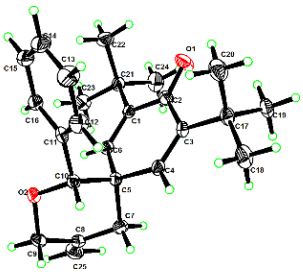
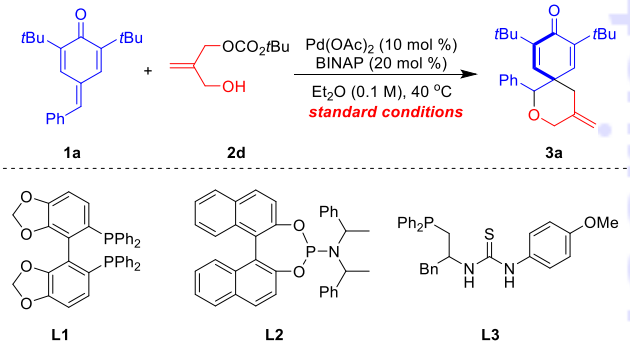


Figure 2. Single-crystal X-ray diffraction analysis of **3a**.

After evaluation of various leaving groups (Table 1), we found that the -OCO_2tBu group played as the most efficient one, giving the desired 2-oxaspiro-cyclohexadienone **3a** in 94% yield (Table 1, entry 4). The structure of **3a** was confirmed by ^1H and ^{13}C NMR spectra, mass spectrometry, and single-crystal X-ray diffraction analysis (Figure 2).[14] It is noteworthy that the carbonate ester is crucial for this reaction because no desired product was detected when other leaving groups were installed (Table 1, entries 6 and 7). No better result was obtained when employing other palladium salts to replace $Pd(OAc)_2$ as catalysts (Table 2, entries 2–5). The choice of bisphosphorus ligands is critical for a productive reaction for that other phosphoramidite, monophosphorus or phosphine oxide[15] ligands were ineffective (Table 2, entries 7–9). Among a variety of solvents, Et_2O emerged as the optimal one (Table 2, entries 10 and 11), which may stabilize both the reacting partners and intermediates well than other nonpolar solvents.[16] Carrying out the reaction at room temperature or 60 °C proved less efficiency (Table 2, entries 12 and 13). Further decreasing the catalyst loadings led to low yield (Table 2, entries 14 and 15).

Table 2. Effect of the reaction parameters.



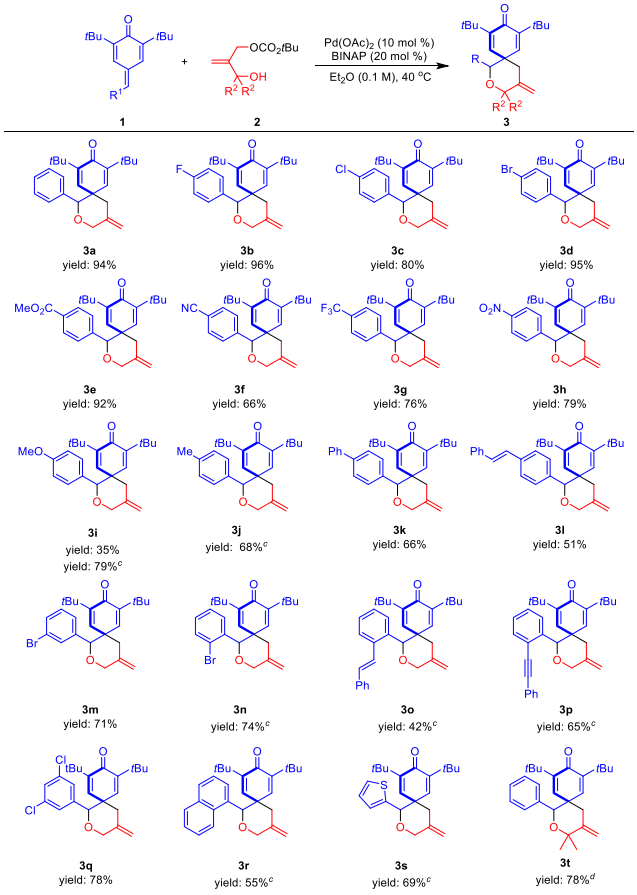
Entry[a]	Variation from the ***standard conditions***	Yield[b]
1	none	94[c]
2	$Pd_2(dba)_3{\cdot}CHCl_3$ instead of $Pd(OAc)_2$	44
3	$Pd_2(dba)_3$ instead of $Pd(OAc)_2$	32
4	$Pd(PPh_3)_4$ instead of $Pd(OAc)_2$	43
5	$PdCl_2$ instead of $Pd(OAc)_2$	NR
6	**L1** instead of BINAP	72
7	**L2** instead of BINAP	NR
8	**L3** instead of BINAP	NR
9	BINAPO instead of BINAP	NR
10	PhMe instead of Et_2O	47
11	CH_2Cl_2 instead of Et_2O	NR
12	room temperature instead of 40 °C	NR
13	60 °C instead of 40 °C	87
14	5 mol % $Pd(OAc)_2$ and 10 mol % BINAP were used	66
15	2.5 mol % $Pd(OAc)_2$ and 5 mol % BINAP were used	56

[a] Reaction conditions: **1a** (0.1 mmol), **2f** (0.2 mmol), [Pd] (10 mol%), ligand (20 mol%) in solvent (1.0 mL) at 40 °C. BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene. BINAPO = 1,1'-[1,1'-Binaphthalene]-2,2'-diylbis[1,1-diphenylphosphine oxide].
[b] The yields were determined by ^1H NMR of crude reaction mixtures using CH_2Br_2 as internal standard. NR = No reaction.
[c] Isolated yield.

With the optimized conditions in hand, we then examined the versatility of this palladium-catalyzed oxa-[4+2] annulation, and the results are summarized in Table 3. Halogen groups (-F, -Cl, -Br) and electron-withdrawing groups (-CO_2Me, -CN, -CF_3, -NO_2) at the *para*-position of phenyl ring of *p*-QMs led to the corresponding products **3b**–**3h** in moderate to good yields. When *p*-QMs containing *para*-methoxyl group was tested, **3i** was obtained in 35%

yield under the standard conditions. It is gratifying that changing the catalyst to $Pd_2(dba)_3{\cdot}CHCl_3$ and employing DPPF as the ligand in THF (Condition **B**), **3i** could be formed in 79% yield and **3j** was achieved in 68% yield.[17] For functionalized *p*-QMs with phenyl or alkenyl groups, the reactions proceeded smoothly to give **4k** and **4l** in 66% and 51% yields under the standard conditions. *p*-QMs with bromine group at the *meta*-position of phenyl ring gave **3m** in 71% yield. Condition B showed better performance when substrates with *ortho*-substituents at the phenyl ring were employed, delivering **3n**–**3p** in 42%–74% yields. Product **3q** with di-chlorine groups was obtained in 78% yield. In addition, naphthyl and heterocyclic-substituted substrates (**2q** and **2r**) were both tolerated well under condition B, which offered **3q** and **3r** in 55% and 69% yield, respectively. Moreover, product **3t** could be obtained in 78% yield from the substrate **2t** containing a tertiary alcohol with the reaction temperature increased to 60 °C. Limitations include incompatibility of non-terminal allylic carbonates, which were unreactive in this methodology. [18]

Table 3. Substrate scope. [a] [b]



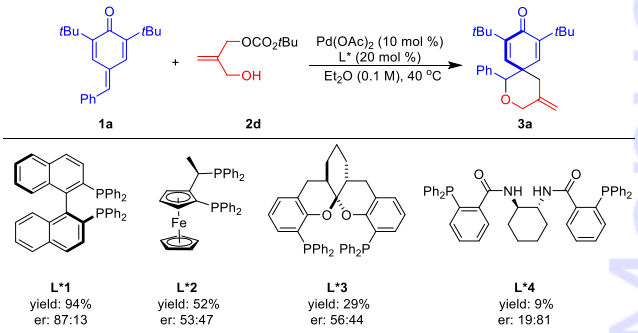
[a] Standard conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), BINAP (20 mol%) in Et_2O (1.0 mL) at 40 °C. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene.

[b] All yields refer to the isolated yields.

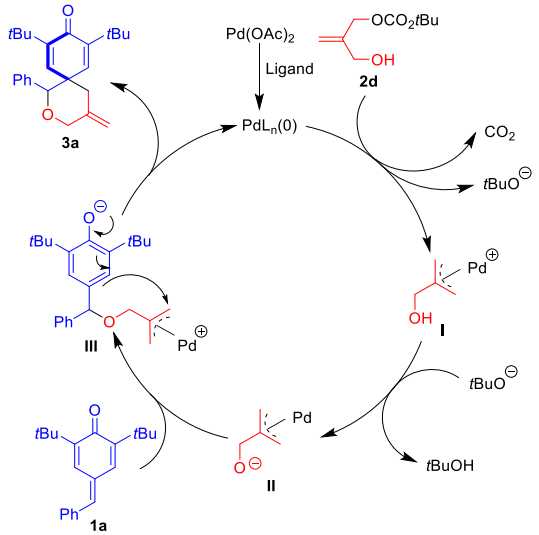
[c] Condition B: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol%), DPPF (20 mol%) in THF (1.0 mL) at 40 °C. DPPF = 1,1'-bis(diphenylphosphino)ferrocene.

[d] 60 °C.

To achieve optically active 2-oxaspiro[5.5]undeca-7,10-dien-9-ones, an expansion of the present system to an asymmetric oxa-[4+2] annulation reaction was also examined, and the preliminary results for the ligand screening with **1a** are shown in Scheme 2. After screening considerable reaction conditions,[19] **3a** could be achieved in 94% yield with 87:13 er value employing chiral (*S*)-BINAP (**L*1**) as ligand. The chiral ferrocene ligand **L*2**, chiral spiroketal-based diphosphine (SKP) ligand **L*3**, and chiral Trost ligand **L*4** were also tested. However, the optimization of ligands did not improve the er value of this transformation. Nevertheless, the result given by **L*1** showed promising reactivity and enantioselectivity of this palladium-catalyzed oxa-[4+2] annulation reaction of *p*-QMs.



Scheme 2. Preliminary results on asymmetric experiment.



Scheme 3. Plausible mechanism of palladium-catalyzed oxa-[4+2] annulation of *p*-QMs.

Finally, according to the previous mechanistic studies on allylic carbonates[20] and our previous work on *p*-QMs, a proposed mechanism of this oxa-[4+2] annulation is shown in Scheme 3. The reaction is initiated by the well-established palladium-mediated oxidative addition of allylic carbonate to Pd(0)

species formed from $Pd(OAc)_2$ and ligand, which leads to π-allyl-palladium intermediate **I**, *tert*-butoxy anion, as well as carbon dioxide. Next, the hydrogen atom of the hydroxyl group is deprotonated by the liberated *tert*-butoxy anion, forming an oxygen anion intermediate **II**. Then, 1,6-conjugated addition of the oxygen anion to *p*-QM **1a** provides intermediate **III**, followed by palladium-catalyzed allylation dearomatization ring closure to provide the product **3a** and regenerates the active palladium catalyst for the next catalytic cycle.

In conclusion, we have developed an unprecedented palladium-catalyzed oxa-[4+2] annulation of *p*-QMs with allyl carbonates bearing a nucleophilic alcohol side chain. This method offered various 2-oxaspiro[5.5]undeca-7,10-dien-9-ones in moderate to good yields with good functional group tolerance under mild conditions. Initial exploration on the synthesis of chiral products offered moderate enantioselectivity. Further investigations on synthesizing 2-oxaspiro-cyclohexadienones with higher enantioselectivity are currently underway in our laboratory.

Experimental Section

General procedure for the synthesis of 2-oxaspiro[5.5]undeca-7,10-dien-9-ones: A sealed tube was charged with *para*-quinone methides **1** (0.10 mmol, 1.0 equiv), allyl carbonate **2f** (0.20 mmol, 2.0 equiv), palladium catalyst (0.01 mmol, 10 mol%), and ligand (0.02 mmol, 20 mol%). The vial is thoroughly flushed with argon and solvent (1.0 mL) was added under argon. Then the reaction mixture was stirred at 40 ºC for 48 h. After the reaction vessel was cooled to room temperature, the solution was concentrated in *vacuo* and purified by careful chromatography on silica gel (EtOAc/petroleum ether = 1/200) to afford the desired products **3**.

Acknowledgements

Generous financial support from the National Natural Science Foundation of China (NSFC21502232 and NSFC 21572272), the Natural Science Foundation of Jiangsu Province (BK20140655), and the Foundation of State Key Laboratory of Natural Medicines (ZZYQ201605) is gratefully acknowledged.

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10.1002/adsc.201700978

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