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Bifunctional Organo/Metal Cooperatively Catalyzed [3 + 2] Annulation of *para*-Quinone Methides with Vinylcyclopropanes: Approach to Spiro[4.5]deca-6,9-diene-8-ones

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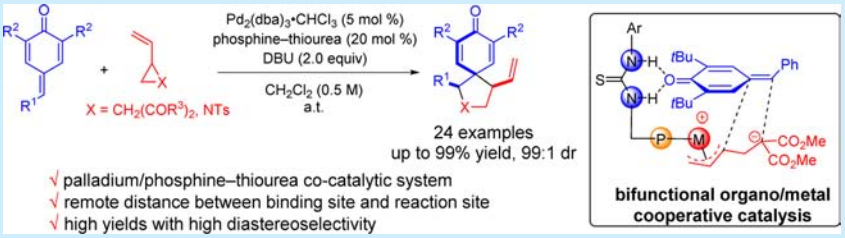
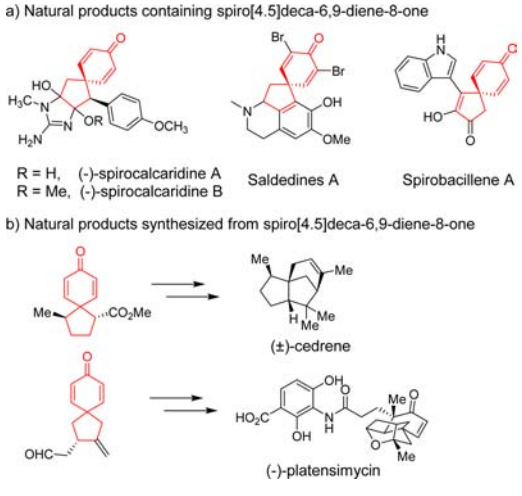
Supporting Information



ABSTRACT: A novel [3 + 2] annulation between *para*-quinone methides and vinylcyclopropanes for the synthesis of spiro[4.5]deca-6,9-diene-8-ones has been described. The palladium and phosphine−thiourea cooperative catalysis system played an important role in high yields and diastereoselectivities. The reaction exhibited good functional group tolerance and scalability.

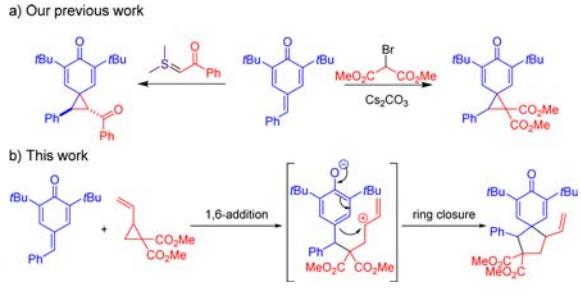
Spiro[4.5]deca-6,9-diene-8-one as a privileged structural motif was widely found in a variety of natural products and bioactive molecules (Scheme 1a).[1] Moreover, it also served as an important intermediate in natural products synthesis (Scheme 1b).[2] Consequently, a wide range of powerful synthetic methods have been developed to construct this framework, such as metal-catalyzed intramolecular dearomatization reactions[3] and rhodium-catalyzed enyne cycloisomerization of terminal alkynes.[4] However, common to these methods was that they were intramolecular reactions with well-designed substrates. An intermolecular strategy to versatile spiro[4.5]-deca-6,9-diene-8-ones from simple starting materials has rarely been reported to date.[5]

Scheme 1. Selected Examples of Spiro[4.5]deca-6,9-diene-8-ones in Natural Products and Application in Natural Products Synthesis



Recently, *para*-quinone methides (*p*-QMs), an important and readily available class of synthetic intermediates, have been applied to achieve diarylmethines through 1,6-addition.[6] Our group[7] and Fan's group[8] have achieved the 1,6-conjugate addition-mediated [2 + 1] annulations of *p*-QMs to afford spiro[2,5]octa-4,7-dien-6-ones (Scheme 2a). In continuation of our interest in synthesizing spiro compounds and characterizing the reactivity of *p*-QMs, we envisaged that the spiro[4.5]deca-6,9-diene-8-ones could be constructed through [3 + 2] annulation between *p*-QMs and donor−acceptor (D−A) reagents, such as vinylcyclopropanes. Predictable challenges of

Scheme 2. Our Strategies To Construct Spirocycles from *p*-QMs



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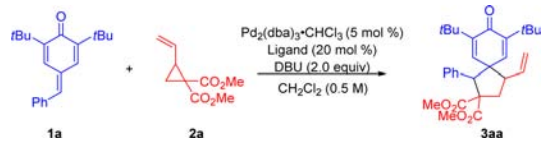
this design to be met are as follows: (1) whether the vinylcyclopropane could attack on *p*-QM through 1,6-conjugate addition after ring opening; (2) whether the carbon atom at the *para*-position of the phenolic hydroxyl still exhibits sufficient nucleophilicity to realize the ring closure process; (3) how to control the diastereoselectivity of this reaction (Scheme 2b).

To address the challenges mentioned above, a cooperative catalysis strategy has been taken into account, as it was considered a powerful strategy to improve the synthetic efficiency and selectivity in organic synthesis.[9] Previously, we have achieved remote controlled asymmetric 1,6-conjugate addition of *p*-QMs through intermolecular hydrogen-bond interaction between the bifunctional chiral phosphine−thiourea catalyst and the *p*-QMs.[6i] Coordination of metal and the organocatalyst through a covalent bond, forming a new bifunctional catalyst, could make full use of advantages of organocatalysts and metal catalysts, and this strategy has been well applied in organic synthesis recently.[10] Herein, we employ this strategy to construct spiro[4.5]deca-6,9-diene-8-ones through an intermolecular [3 + 2] annulation, and the reactivity and diastereoselectivities could be well controlled by palladium/phosphine−thiourea cooperative catalysis through activating vinylcyclopropanes and *p*-QMs simultaneously.

We commenced our research by attempting different phosphine−thiourea ligands with $[Pd_2(dba)_3]\cdot CHCl_3$ to verify our hypothesis. When phosphine−thiourea **L1** was tested, as we expected, **3aa** could be obtained in 81% yield with 94:6 dr (Table 1, entry 1). By fine-tuning the acidity of thiourea through changing the electronic property of the benzene ring (Table 1, entries 2−4), the yield of **3aa** increased to 88% when **L4** was used. Increasing the molar ratio of **2a** could further enhance the yield to 93% with 96:4 dr (Table 1, entry 5). When racemic ligand **L5** was employed, we found that **3aa** could be obtained in 86% yield with 94:6 dr, suggesting that the chirality of the ligand made no difference to the diastereoselectivity (Table 1, entry 6). Moreover, the chiral starting materials of the phosphine−thiourea ligands[11] were cheaper and more widely available than the racemic ones; thus, we decided to employ **L4** in the subsequent substrate scope investigation. In contrast, when simple monodentate (Table 1, entries 7−9) and bidentate phosphine ligands (Table 1, entries 10−14) were tested, the diastereoselectivities dramatically declined. These results verified the importance of a bifunctional organo/metal cooperatively catalyzed strategy to achieve high yields and diastereoselectivities in this reaction.

With the optimized conditions in hand, we then investigated the scope and generality of *p*-QMs and vinylcyclopropanes. The results are summarized in Scheme 3. Most *p*-QMs employed in the reaction provided the corresponding products in high yields and high diastereoselectivities. Methyl, methoxyl, halogen, or electron−deficient substituents (−CN, $-CF_3$, $-CO_2Me$) at the *para*-position of the benzene ring afforded **3ba**−**3ia** in 68−99% yields. Functionalized *p*-QMs with phenyl or alkenyl delivered **3ja** and **3ka** in 74% and 94% yields with 95:5 dr. *p*-QMs **1l** and **1m** bearing *m*-OMe or *o*-OMe groups gave the corresponding products **3la** and **3ma** in 95% and 70% yields, which indicated that the position of the substituent at the phenyl group remained important to the yield. By varying the phenyl group to naphthyl, thienyl, and *N*-methyl indolyl, **3na**−**3pa** were achieved in 83−98% yields. Methyl substituted *p*-QMs **1q** could also lead to the product **3qa** in 42% yield. When di-*tert*-butyl groups were replaced by di-isopropyl and dimethyl

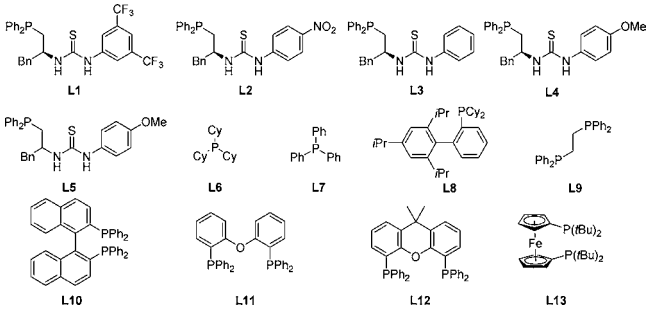
Table 1. Optimization of Reaction Conditions[a,b]



1a 2a 3aa

entry	ligand	yield (%)	dr
1	**L1**	81	94:6
2	**L2**	63	95:5
3	**L3**	56	97:3
4	**L4**	88	96:4
5[c]	**L4**	**93**[d]	**96:4**
6[c]	**L5**	86[d]	94:6
7[c]	**L6**	85	68:32
8[c]	**L7**	90	59:41
9[c]	**L8**	79	71:29
10[c]	**L9**	94	68:32
11[c]	**L10**	87	73:27
12[c]	**L11**	92	65:35
13[c]	**L12**	82	27:73
14[c]	**L13**	63	45:54

[a]All reactions were performed using **1a** (0.1 mmol), **2a** (0.1 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %), ligand (20 mol %), and DBU (0.2 mmol) in dichloromethane (0.20 mL) at ambient temperature for 24 h. [b]The yields and dr values were determined by ^1H NMR analysis with dibromomethane as an internal standard. [c]**2a** (0.12 mmol) was added. [d]Isolated yield.



groups, **3ra** and **3sa** were produced in moderate yields. By changing the methyl ester group to ethyl, isopropyl, and benzyl groups, **3ab**−**3ad** were produced in 77−99% yields. 2-Vinylspiro[cyclopropane-1,2′-indene]-1′,3′-dione **2e** delivered the corresponding product **3ae** in 61% yield with 93:7 dr. 1-Tosyl-2-vinylaziridine **3f** was also compatible in this reaction and afforded **3af** in 92% yield. The relative configurations of the products were determined according to the single-crystal X-ray diffraction analysis result of **3aa**.[12]

To gain insight into the utility of the reaction, the spiro[4.5]deca-6,9-diene-8-one **3aa** was synthesized in 3 mmol scale in 92% yield (1.32 g) with 93:7 dr when the palladium and phosphine−thiourea were reduced to 2.5 and 10 mol %, respectively. By further decreasing the palladium and phosphine−thiourea to 1.25 and 5 mol %, 3.23 g of **3aa** were synthesized in 8 mmol scale in 84% yield with 92:8 dr. Reduction of ester groups and the terminal olefin of **3aa** produced propylene glycol derivative **4** in 71% yield and ethylcyclopentane derivative **5** in 96% yield. A functional cross-coupling reaction, such as the Heck reaction, afforded styrene derivative **6** in 74% yield (Scheme 4).

Finally, according to previous mechanistic studies on vinylcyclopropane[13] and our previous work on *p*-QMs,[6i,7] a reasonable mechanism was proposed in Scheme 5. First, the

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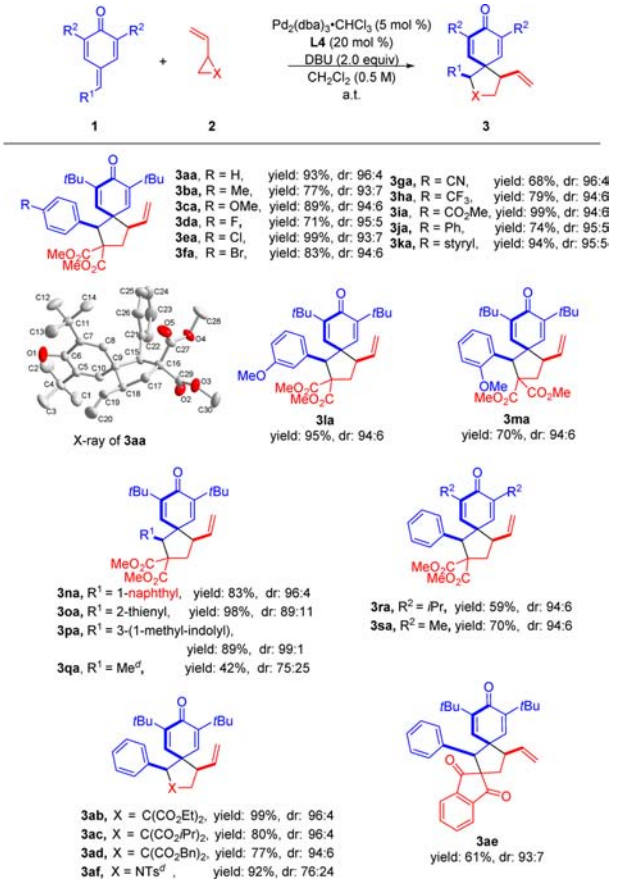
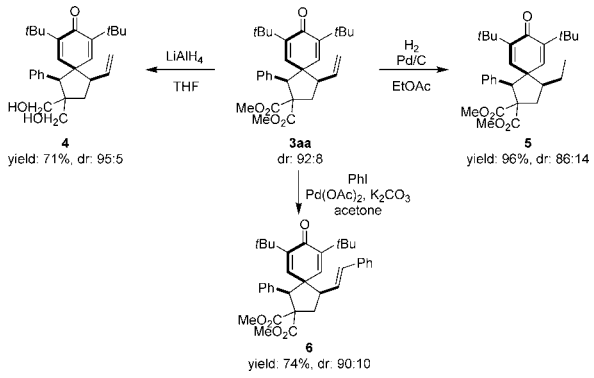
Scheme 3. Substrate Scope for the Reaction of *p*-QMs and Vinylcyclopropanes[a,b,c]



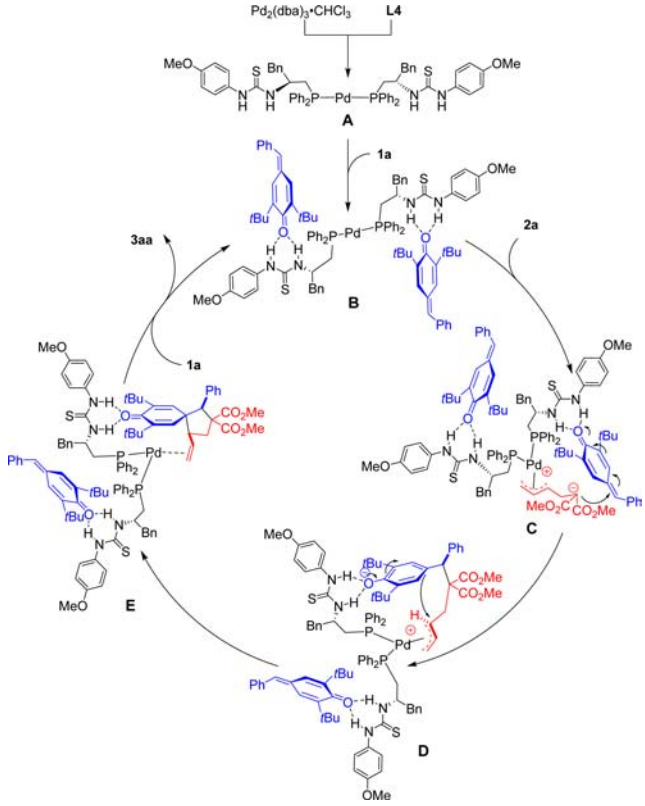
[a]All reactions were performed using **1a** (0.1 mmol), **2a** (0.12 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (5 mol %), **L4** (20 mol %), DBU (0.2 mmol) in dichloromethane (0.20 mL) at ambient temperature for 24 h. [b]Isolated yield. [c]dr values were determined by ^{1}H NMR analysis. [d]LiBr (0.2 mmol) was added.

Scheme 4. Transformations of 3aa



catalyst complex **A** was formed by the combination of palladium and phosphine−thiourea. Next, **1a** was activated by **A** through intermolecular hydrogen-bond interaction to form complex **B** which was detected on MS (ESI) analysis.[14] Subsequently, in the presence of **B**, cyclopropane **2a** led to an activated zwitterionic π-allyl-palladium intermediate **C**. Then, 1,6-conjugate addition of a carbon anion to *p*-QM provided intermediate **D**, followed by ring closure dearomatization to provide the complex **E**. Disassociation of complex **E** yielded the product **3aa** and regenerated the catalyst complex **B** for the next catalytic cycle.

Scheme 5. Plausible Mechanism of Palladium and Phosphine−Thiourea Cooperative Catalysis



In conclusion, we have described a novel intermolecular 1,6-conjugate addition-mediated [3 + 2] annulation between *p*-QMs and vinylcyclopropanes. Spiro[4.5]deca-6,9-diene-8-ones were efficiently synthesized in high yields with high diastereoselectivities on account of the cooperative catalysis by palladium and phosphine−thiourea through activating both *p*-QM and vinylcyclopropane simultaneously. The reaction exhibited good functional group tolerance and scalability. Further investigations on mechanism and asymmetric synthesis of this protocol are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01512.

Experimental procedures and full characterization for all compounds (PDF)

X-ray crystallographic data for **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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(12) Crystallographic data for **3aa** have been deposited with the Cambridge Crystallographic Data Centre as Deposition Numbers CCDC 1477219. Detailed information can be found in the Supporting Information.

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(14) See Supporting Information for details of MS analysis of intermediate **B**.

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