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Letter

Palladium-Catalyzed Asymmetric (2+3) Annulation of *p*-Quinone Methides with Trimethylenemethanes: Enantioselective Synthesis of Functionalized Chiral Spirocyclopentyl *p*-Dienones

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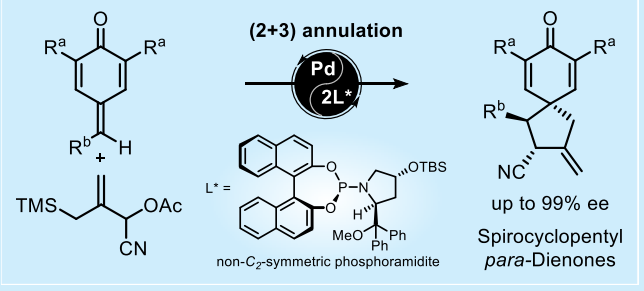
ABSTRACT: A novel asymmetric catalytic (2+3) annulation of *p*-quinone methides with CN-substituted trimethylenemethane is described under palladium catalysis, providing an alternative approach for the enantioselective construction of highly functionalized chiral spirocyclopentyl *p*-dienones. Driven by the significant improvement in the reactivity and enantioselectivity, a novel type of non-C_2-symmetric phosphoramidite ligand from the chirality-matched combination of (*S*)-BINOL and sterically demanding amine derived from L-hydroxyproline is evolved and explored for the protocol presented here.



The spirocyclopentyl *p*-dienone unit **A** (spiro[4.5]deca-6,9-dien-8-one), which is generally characterized by the spirocyclic 2,5-cyclohexadienone ring system, widely exists in biologically active natural products (Figure 1),[1] and its

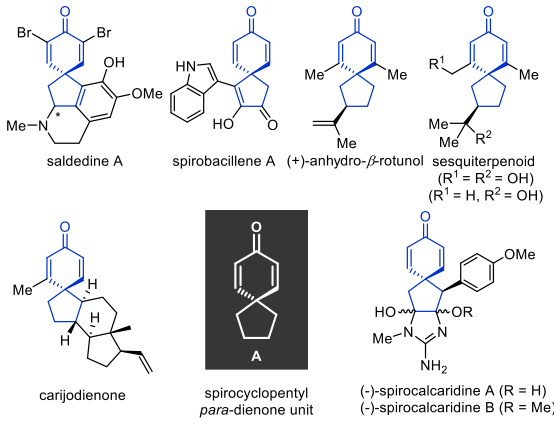
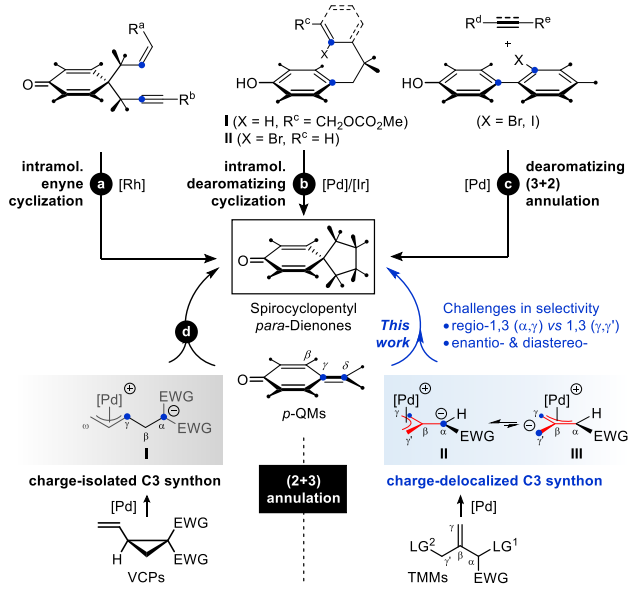


Figure 1. Selected natural products containing the spirocyclopentyl *p*-dienone unit.

functionalized building blocks also serve as versatile intermediates for natural product synthesis.[2] Due to its unique molecular architecture and considerable potential in organic synthesis, the catalytic asymmetric construction of such a structural unit has attracted significant interest from the synthetic community. As shown in Scheme 1, several elegant works on the enantioselective establishment of spirocyclopentyl unit **A** have been previously published, including Rh-

Scheme 1. Known Catalytic Asymmetric Approaches to Spirocyclopentyl *p*-Dienones and Our Design



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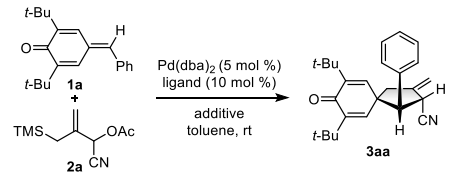
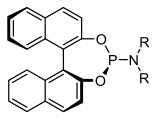
catalyzed intramolecular asymmetric enyne cyclization of substituted *p*-dienone precursors by Nicolaou (route a),[2] Pd- and Ir-catalyzed intramolecular asymmetric dearomatizing cyclization of phenol precursors by You,[3a] Hamada,[3c] and Buchwald[3b] (route b), Pd-catalyzed dearomatizing (3+2) annulation of biaryl precursors with alkynes or 1,3-dienes by Luan (route c),[4] and Pd-catalyzed asymmetric (2+3) annulation of *p*-quinone methides (*p*-QMs) with charged−isolated C3 synthon (**I**) generated *in situ* from vinyl cyclopropanes (VCPs) by Zhao (route d).[5] Despite much recent progress on this topic, the development of an alternative catalytic asymmetric methodology for the diversity-oriented synthesis of functionalized spirocyclopentyl *p*-dienones is still highly appealing.

The chemistry of *p*-quinone methides (*p*-QMs) featuring a unique bisvinylogous enone system has received a great deal of attention over the past decade in asymmetric catalysis.[6−10] Compared with its intensive investigations, mostly focusing on enantioselective 1,6-conjugate addition[9] and (4+2) annulation,[10] however, the design of catalytic asymmetric (3+2) annulation of *p*-QMs has been explored rarely.[5] In connection with our continuing interest in the chemistry of *p*-QMs,[8,11] together with the importance of structurally divergent functionalized spirocyclopentyl *p*-dienones, a strategically alternative regio- and stereoselective (2+3) annulation of *p*-QMs with a charged−delocalized C3 synthon [**II** and **III** (Scheme 1)] formed *in situ* from substituted trimethylenemethanes (TMMs)[12−16] has been developed under palladium catalysis, in which a novel type of non-C_2-symmetric chiral phosphoramidite ligands containing the BINOL backbone and hydroxyproline moiety has been produced to explore the pivotal stereoselectivities (enantio- and diastereo-) as well as the regioselectivity (α,γ vs γ,γ'). This novel annulation reaction provides an effective method for the diastereo- and enantioselective synthesis of multifunctionalized spirocyclopentyl *p*-dienones. Herein, we report our results on this subject.

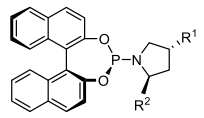
Initially, as shown in Table 1, the model reaction for the designed asymmetric (2+3) annulation was investigated by using *p*-QM **1a** as a two-carbon synthon and racemic cyano-substituted trimethylenemethane (CN-TMM) **2a**[17,18] as a three-carbon synthon in the presence of $Pd(dba)_2$ as a catalyst and toluene as a solvent[19] at room temperature. Compared with the inefficiency of (*R*)-BINAP as a typical bisphosphine ligand (entry 1), using C_2-symmetric (*S*)-BINOL-based phosphoramidite **L1** (entry 2) delivered the desired annulation adduct **3aa** with a promising stereoselectivity (75% ee, >20:1 dr), albeit in a modest yield of 13%. Interestingly, the employment of the monodentate phosphoramidite **L2** having a bulky (*S*)-CH(Me)Ph substituent (entry 3) led to a substantially increased yield (70%) and stereoselectivity (94% ee, >20:1 dr). Notably, phosphoramidite **L3** with a less bulky methyl group (entry 4) was ineffective in this model reaction. In addition to these phosphoramidite ligands with acyclic amino moieties (**L1**−**L3**), a series of phosphoramidites **L4**−**L9** having structurally modified cyclic pyrrolidinyl motifs were further investigated in this case. No reaction was observed when phosphoramidites **L4**−**L6** with a less sterically hindered pyrrolidinyl ring system were employed (entries 5−7, respectively). In contrast to the nonreactivity observed in the cases using L-proline-derived phosphoramidites **L5** (R^1 = H, R^2 = CO_2Me, entry 6) and **L6** (R^1 = H, R^2 = CH_2OMe, entry 7), it is noteworthy that the same chiral framework-based ligand

Table 1. Optimization of Reaction Conditions[a]





L1 (R = *n*-Pr)
L2 (R = (*S*)-CH(CH$_3$)Ph)
L3 (R = Me)



L4 (R^1 = R^2 = H)
L5 (R^1 = H, R^2 = CO_2Me)
L6 (R^1 = H, R^2 = CH_2OMe)
L7 (R^1 = H, R^2 = $C(Ph)_2OMe$)
L8 (R^1 = OTBS, R^2 = $C(Ph)_2OMe$)
L9 (R^1 = OTBDPS, R^2 = $C(Ph)_2OMe$)

entry	ligand	additive	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	(*R*)-BINAP		12	NR[e]	–	–
2	**L1**		12	13	>20:1	75
3	**L2**		1	70	>20:1	94
4	**L3**		12	NR[e]	–	–
5	**L4**		12	NR[e]	–	–
6	**L5**		12	NR[e]	–	–
7	**L6**		12	NR[e]	–	–
8	**L7**		1	69	>20:1	98
9	**L8**		0.5	72	>20:1	99
10	**L9**		1.2	50	>20:1	99
11	**L8**	Na_2CO_3	0.5	77	>20:1	99
12	**L8**	K_2CO_3	0.5	92	>20:1	99
13	**L8**	Cs_2CO_3	0.5	80	>20:1	99

[a]Unless otherwise noted, the reaction was performed with **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(dba)_2$ (0.005 mmol), and ligand (0.01 mmol) under an argon atmosphere in the presence of an additive (0.1 mmol) in toluene (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC analysis. [e]No reaction.

L7 [R^1 = H, R^2 = $C(Ph)_2OMe$, entry 8] bearing a sterically congested tertiary substituent gave a good yield (69%) and high stereoselectivity (98% ee, >20:1 dr), showing the somewhat increasing steric demand of the phosphoramidite ligand. Accordingly, two novel sterically enhanced phosphoramidites **L8** [R^1 = OTBS, R^2 = $C(Ph)_2OMe$, entry 9] and **L9** [R^1 = OTBDPS, R^2 = $C(Ph)_2OMe$, entry 10], which were derived from readily available L-hydroxyproline, were then evaluated, and gratifyingly, OTBS-substituted **L8** gave a better result (0.5 h, 72% yield, 99% ee, >20:1 dr) (entry 9). With an attempt to further improve the reaction reactivity, some inorganic bases were examined (entries 11−13). Among them, the model reaction utilizing K_2CO_3 as an additive in the presence of **L8** could deliver the optimal result in 92% yield with a 99% ee and a >20:1 dr (entry 12).

With the optimal conditions in hand, as shown in Scheme 2, the generality of the asymmetric catalytic (2+3) annulation reaction was explored by using a series of *p*-QMs bearing different aromatic R^b group at their δ position. In general, the desired spirocyclic products could be afforded in good yields (56−95%) with excellent stereoselectivities (>20:1 dr, 99% ee). For example, *p*-QMs with electron-deficient (**1b**−**1f** and **1i**), electron-rich (**1g**, **1h**, **1j**, **1k**, and **1n**), or electron-neutral (**1a**) aromatic R^b groups at the *meta* and *para* positions were well tolerated, and the corresponding spirocyclic products **3aa**−**3ka** and **3na** were obtained in excellent stereoselectivities

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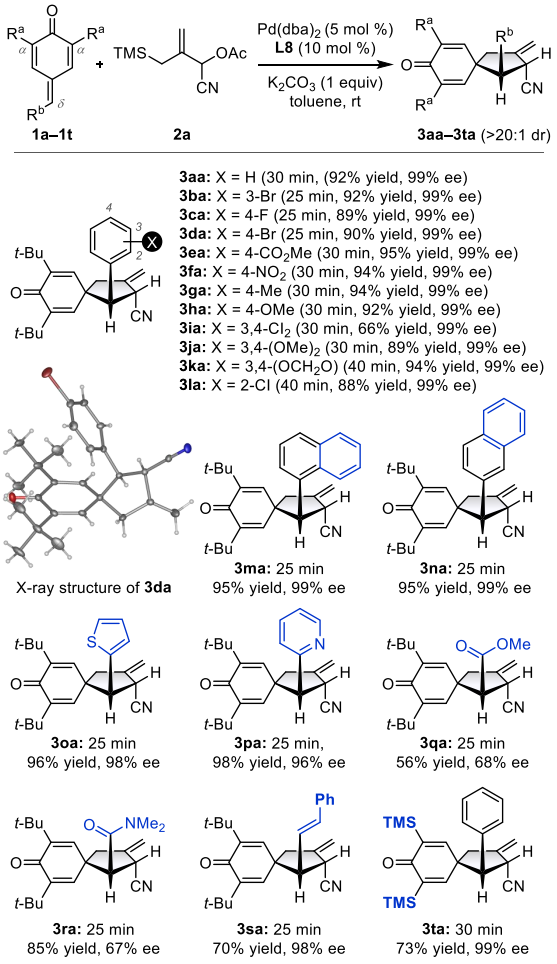
Scheme 2. Generality of the Asymmetric Catalytic (2+3) Annulation

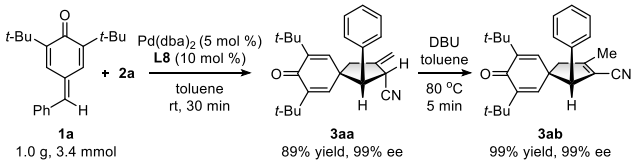


(>20:1 dr, 99% ee) and moderate to good yields (66−95%). In addition, the absolute configuration of **3da** was unambiguously established by X-ray crystallographic analysis.[20] While using *p*-QMs **1l** and **1m** with sterically bulky *ortho* substituents, notably the reactions proceeded smoothly to afford the expected products **3la** (88% yield, 99% ee) and **3ma** (95% yield, 99% ee), respectively.

In addition, the heteroaryl *p*-QMs **1o** (R^b = 2-furyl) and **1p** (R^b = 2-pyridinyl) were also exposed to the optimized conditions, smoothly giving the related annulation products **3oa** (96% yield, >20:1 dr, 98% ee) and **3pa** (98% yield, >20:1 dr, 96% ee). Moreover, the expansion of the ester- and amide-substituted *p*-QMs (**1q** and **1r**, respectively) to this spiroannulation was also conducted, and the formation of the desired carbonyl-functionalized products **3qa** (56% yield, >20:1 dr, 68% ee) and **3ra** (85% yield, >20:1 dr, 67% ee) was achieved, in which the decreased enantioselectivity might be due in part to the negative influence of the electron-withdrawing carbonyl group at its δ position on this Pd-catalyzed enantioselective annulation. Notably, vinylogous *p*-QM **1s** was an excellent partner in this transformation, and the structurally interesting product **3sa** was provided in 70% yield and excellent stereoselectivity (>20:1 dr, 98% ee). In addition, α,α'-TMS-substituted *p*-QM **1t** could smoothly react as well to give the desired product **3ta** in 73% yield with >20:1 dr and 99% ee.

To explore the practical utility of this protocol, as demonstrated in Scheme 3, the gram-scale reaction of **1a**

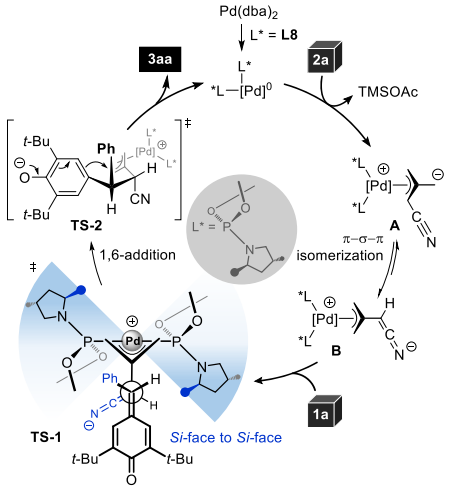
Scheme 3. Gram-Scale Reaction and Its Isomerization



and **2a** was performed under the standard conditions, and the desired spiroannulated product **3aa** was obtained in high yield (89%) and excellent stereoselectivity (>20:1 dr, 99% ee). In an attempt to increase the structural diversity of chiral spirocyclopentyl *p*-dienones, the treatment of **3aa** with DBU in toluene at 80 °C resulted in an effective isomerization of the exocyclic double bond to the thermodynamically stable endocyclic double bond, giving **3ab** in 99% yield and 99% ee.

According to the aforementioned experimental results and literature reports,[16b,17,21] a rational mechanism is proposed for the present Pd-catalyzed (2+3) annulation reaction of *p*-QM **1a** with CN-TMM precursor **2a** (Scheme 4). Initially, **2a** is

Scheme 4. Proposed Mechanism



activated by the complex resulting from $Pd(dba)_2$ and chiral phosphoramidite **L8**, rapidly generating Pd-TMM species **A**. Due to the electron-withdrawing property of the cyano group, **A** can readily isomerize to the thermodynamically stable species **B**. As graphically simplified in **TS-1**, the chiral phosphoramidite **L8** backbone, which is three-dimensionally distributed between the (*S*)-BINOL motif and the (2*S*,4*R*)-2-C(OMe)Ph_2-4-OTBS-pyrrolidinyl group, spatially renders the *si* face of the nucleophilic ketenimine moiety accessible. Because of the small steric effect of the linear ketenimine group, the enantiotopic facial discrimination of the *si* face of *p*-QM **1a** is analogously controlled by minimizing the steric hindrance resulting from interaction with the chiral phosphoramidite backbone. Accordingly, an asymmetric 1,6-addition of *p*-QM **1a** from the *si* face to the *si* face of the ketenimine moiety proceeds via favorable transition state **TS-1**. Following subsequent intramolecular dearomative cyclization through an S_N2' process in **TS-2**, the formation of desired spirocyclic

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product **3aa** is achieved with the regeneration of the palladium catalyst for the next cycle.

In conclusion, a highly regio- and stereoselective asymmetric catalytic (2+3) annulation of *p*-quinone methides with the charge-delocalized C3 synthon (CN-TMM) has been developed to forge a series of highly functionalized spirocyclopentyl *p*-dienone building blocks. Significantly, a novel type of non-C_2-symmetric phosphoramidite ligand consisting of an (*S*)-BINOL framework and L-hydroxyproline-derived amine units is designed and applied to the current annulation, to some extent manifesting the impact of phosphoramidites as chiral ligands in asymmetric catalysis. This reaction not only provides a strategically complementary enantioselective synthesis of functionalized chiral spirocyclopentyl *p*-dienones but also enriches the chemistry of *p*-QMs in the design of methodology for asymmetric catalytic (2+3) annulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01252.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1994600 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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