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Asymmetric Dearomative Hydrofunctionalization of Enyne-Tethered Biaryls Via Pd(0)/Chiral Phosphoric Acid Co-Catalysis

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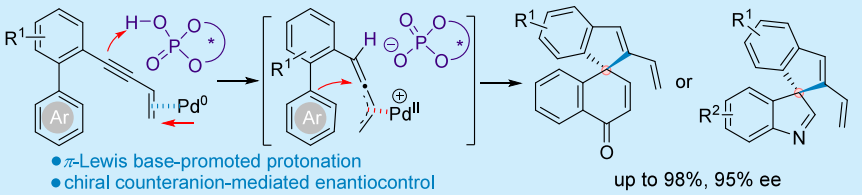

ABSTRACT: We report an asymmetric dearomatization reaction of enyne-tethered biaryls through Pd(0)/chiral phosphoric acid cocatalyzed intramolecular hydrofunctionalization, furnishing spirocyclic hexenones and indolenines with fair to excellent enantioselectivity. A Pd(0) π-Lewis base-promoted protonation may be involved, and chiral phosphate anion plays a key role in enantiocontrol.

Spirocyclic hexanones and indolenines are privileged scaffolds in organic synthesis and medicinal chemistry, exemplified by their presence in bioactive natural products such as spirobacilene A, stepharinine, and spirobacilene B (Figure 1).[1] However, their efficient synthesis remains fundamentally challenging due to the construction of the sterically congested quaternary spirocyclic center, which presents significant kinetic and thermodynamic barriers.[2]

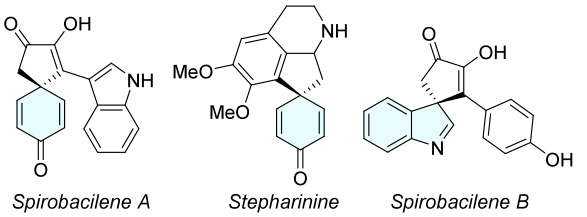

Figure 1. Selected bioactive spirocyclic molecules.

Catalytic asymmetric dearomatization (CADA) has emerged as a powerful strategy for furnishing three-dimensional, stereochemically rich spirocyclic scaffolds from readily available planar aromatic feedstocks.[3] Notably, the dearomatization of biaryl substrates through metal-catalyzed CADA represents an efficient and straightforward approach to accessing valuable spirocyclic hexenone and indolenine frameworks. In this context, Luan and co-workers developed a palladium-catalyzed dynamic kinetic asymmetric transformation of bromo-substituted naphthol derivatives with alkynes, which proceeded through an oxidative addition/migratory insertion/cyclization cascade to deliver the expected spirocycles (Scheme 1a, top).[4] Zhang and Jiao further extended this strategy to the indole analogues with remarkable efficiency, respectively.[5] Moreover, You and Shi independently uncovered asymmetric dearomatization of naphthols via transition metal-catalyzed C−H activation followed by similar reaction with alkynes (Scheme 1a, bottom).[6] While these methods achieved excellent efficiency and enantioselectivity, they inevitably required bromo-functionalized starting materials (leading to halogen loss) or stoichiometric oxidants, which compromises atom economy and limits functional-group tolerance.

Alternatively, metal-catalyzed asymmetric hydrofunctionalization of unsaturated hydrocarbons offers a more atom-economic strategy for molecular construction.[7] Our group has recently established a cooperative Pd(0)/Brønsted acid catalytic system that enabled asymmetric hydrofunctionalization of dienes and enynes, wherein Pd(0) served as a π-Lewis base to facilitate the protonation process.[8] Building on these works, we now disclose an asymmetric dearomatization process of enyne-tethered biaryls **1** through Pd(0)/chiral phosphoric acid (CPA)-catalyzed hydrofunctionalization (Scheme 1b). It was envisaged that 1,3-enynes **1** would undergo protonation with CPA via Pd(0) π-Lewis base activation, and the ene-π-allylpalladium complexes **I** would participate in an intramolecular C2-regioselective alkylation with the assistance of a chiral phosphoric anion, finally affording multifunctional spirocyclic hexenone derivatives via enantioselective dearoma-

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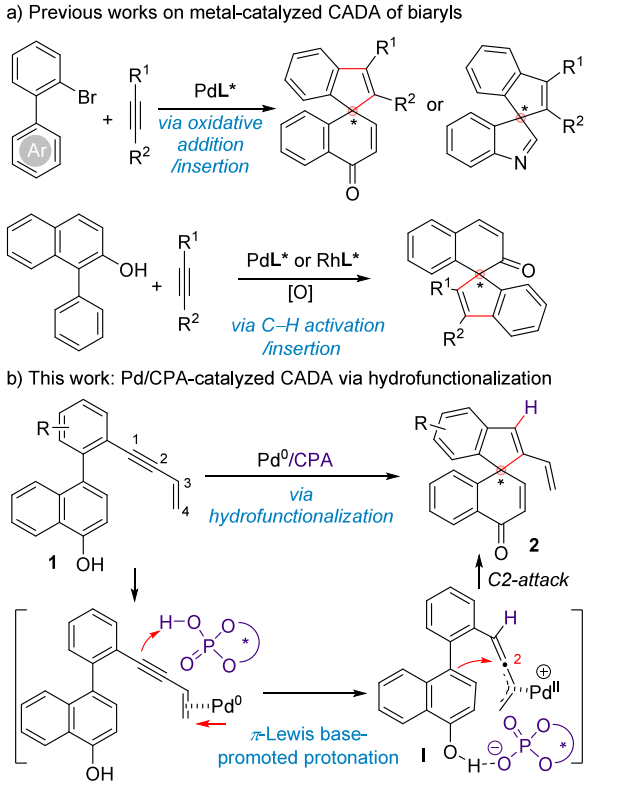
Scheme 1. Transition Metal-Catalyzed CADA of Biaryls



Scheme 2. Substrate Scope of the CADA for the Construction of Spirocyclic Hexenone Derivatives

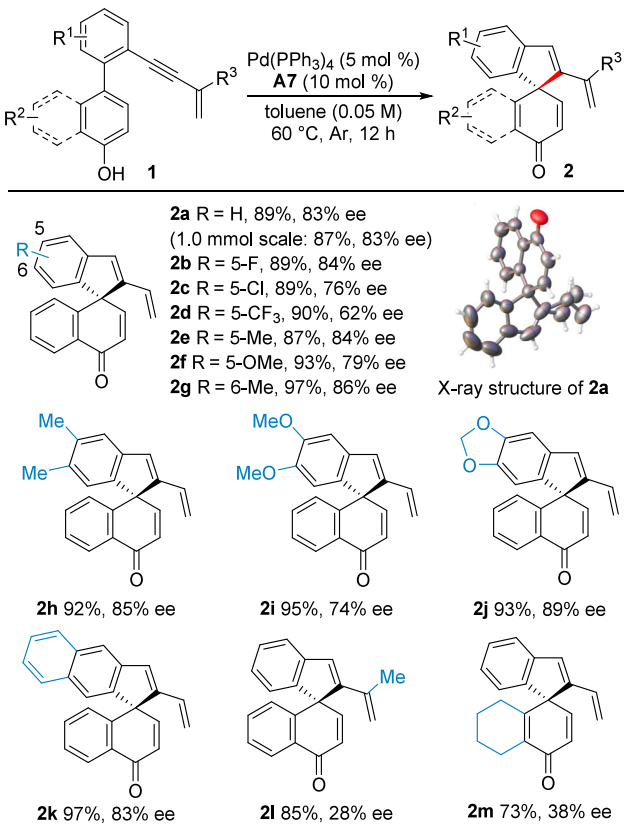
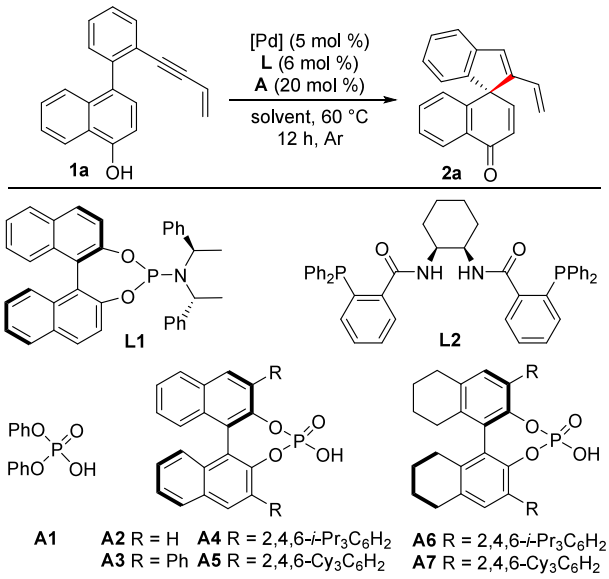


Table 1. Condition Optimizations of the Asymmetric Dearomatization of Substrate 1a[a]



entry	[Pd]	L	A	solvent	yield (%)[b]	ee (%)[c]
1	$Pd_2(dba)_3$	PPh_3	**A1**	toluene	83	/
2	$Pd_2(dba)_3$	**L1**	**A1**	toluene	28	−9
3	$Pd_2(dba)_3$	**L2**	**A1**	toluene	52	16
4	$Pd(PPh_3)_4$	/	**A2**	toluene	79	8
5	$Pd(PPh_3)_4$	/	**A3**	toluene	87	7
6	$Pd(PPh_3)_4$	/	**A4**	toluene	78	68
7	$Pd(PPh_3)_4$	/	**A5**	toluene	72	71
8	$Pd(PPh_3)_4$	/	**A6**	toluene	77	74
9	$Pd(PPh_3)_4$	/	**A7**	toluene	87	78
10	$Pd(PPh_3)_4$	/	**A7**	THF	76	20
11	$Pd(PPh_3)_4$	/	**A7**	DCM	80	77
12[d]	$Pd(PPh_3)_4$	/	**A7**	toluene	86	83
13[d,e]	$Pd(PPh_3)_4$	/	**A7**	toluene	90	83

[a]Unless noted otherwise, the reaction was performed with **1a** (0.05 mmol), [Pd] (5 mol %), **L** (6 mol %), and **A** (20 mol %) in solvent (0.5 mL) at 60 °C for 12 h under Ar. [b]Yield of the isolated product. [c]Determined by HPLC analysis on a chiral stationary phase. [d]In 1.0 mL of toluene. [e]With **A7** (10 mol %).

tization. In contrast to previous protocols, this oxidant-free Pd(0)/CPA system avoids halogen prefunctionalization, thereby improving atom economy and exhibiting broader functional group tolerance.

The intramolecular hydrofunctionalization of 1,3-enyne **1a** was initially investigated using $Pd_2(dba)_3/PPh_3$ and diphenyl phosphate (**A1**) as the catalysts in toluene at 60 °C, and the expected spirocyclic product **2a** was obtained in good yield (Table 1, entry 1). To establish an asymmetric variant, we first evaluated chiral phosphoramidite **L1** and phosphine **L2** as the ligands; however, they proved ineffective for enantiocontrol (entries 2 and 3).[9] Then we turned our attention to CPAs in combination with $Pd(PPh_3)_4$. It was found that BINOL-derived CPA **A2** and **A3** resulted in only low enantioselectivity (entries 4 and 5). Notably, introducing sterically demanding 3,3′-substituents on the BINOL scaffold (**A4** and **A5**) dramatically improved the enantioselectivity (entries 6 and 7), suggesting that the crowded environments were helpful for asymmetric induction. Further enhancement was achieved with H_8–BINOL derivatives **A6** and **A7** (entries 8 and 9).

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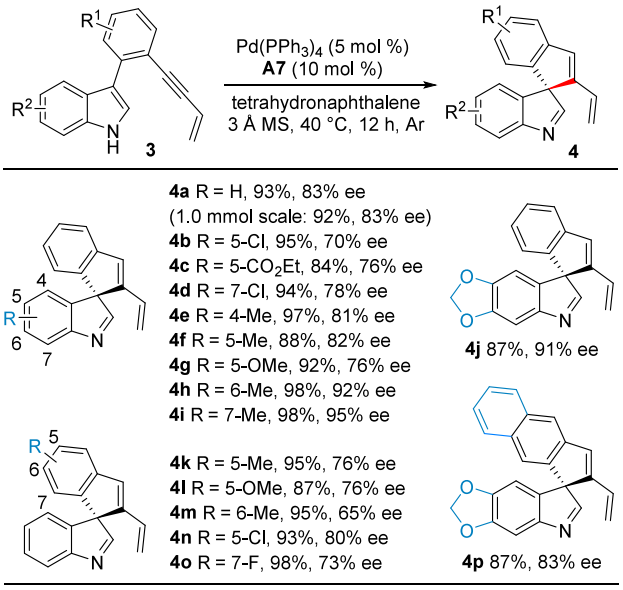
Scheme 3. Substrate Scope of the CADA for the Construction of Spirocyclic Indolenines



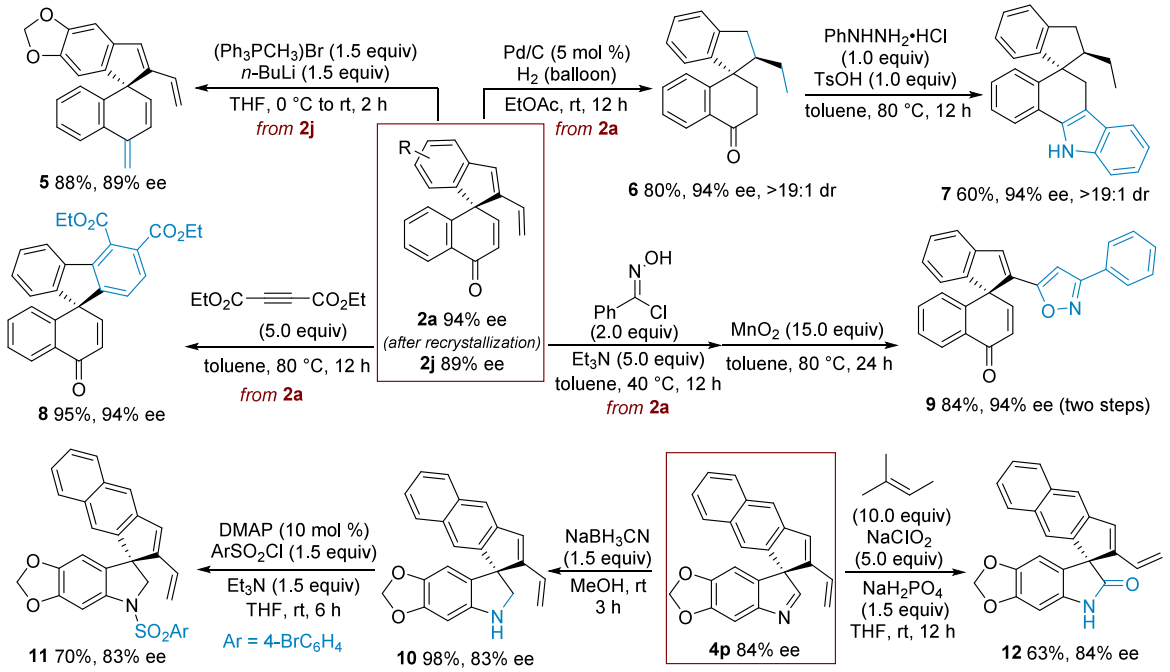
Subsequently, some commonly used solvents were tested, and toluene was still the optimal solvent (entries 10 and 11). Fine-tuning of the reaction parameters through decreasing concentration and loadings of **A7** further improved both yield and enantioselectivity, providing **2a** in an excellent yield with good enantioselectivity (entries 12 and 13).

With the optimized conditions established, we explored the substrate scope of the CADA reaction using 1,3-enyne-functionalized biaryls **1**. As shown in Scheme 2, the reaction proceeded well on a 0.1 mmol scale, and **2a** was obtained with comparable data. The absolute configuration of **2a** was unambiguously determined by X-ray crystallography analysis. In addition, various substituents on the phenyl ring of **1** were generally tolerated well, delivering products **2b–j** in high yields with moderate to good enantioselectivity, whereas the ee value of **2d** was slightly diminished, probably due to the strong electron-withdrawing effect of the trifluoromethyl group. The protocol also accommodated a naphthalene-based enyne, producing **2k** in excellent yield with similar enantiocontrol. An additional methyl group at the enyne moiety was also compatible, affording **2l** in a good yield albeit with low enantioselectivity, likely due to steric congestion that perturbs coordination and distorts the chiral pocket surrounding the ene-π-allylpalladium intermediate (**I**). Notably, replacing the naphthol moiety with a phenol group led to a dramatic reduction in enantioselectivity (**2m**), probably because the absence of the naphthol unit reduces favorable $\pi-\pi$ interactions between the substrate and the ligands.

Apart from naphthol-derived biaryls, we successfully applied asymmetric hydrofunctionalization to indole-derived substrates (**3**). The cooperative catalytic system of $Pd(PPh_3)_4$ and **A7** was effective for the CADA of **3a**,[9] delivering spirocyclic indolenine **4a** in an excellent yield with good enantioselectivity, even on a 1.0 mmol scale (Scheme 3). The reaction proved applicable to diversely functionalized enynes **3** bearing varied indole substituents, affording products **4b–j** in high yields with moderate to excellent enantioselectivity. Furthermore, substrates with different substituents on the phenyl ring were compatible, yielding **4k–p** with high efficiency and moderate to good enantiocontrol.

To demonstrate the synthetic versatility of these multifunctional products, we performed a series of structural elaborations (Scheme 4). The carbonyl group in **2j** was successfully transformed into an alkene via a Wittig reaction, affording compound **5** in a high yield. In addition, the multiple alkene groups in **2a** underwent complete hydrogenation to deliver **6** with excellent diastereoselectivity, which subsequently participated in a Fischer indolization with $PhNHNH_2$·HCl to construct fused indole derivative **7**.[10] The diene moiety

Scheme 4. Synthetic Transformations of the Products



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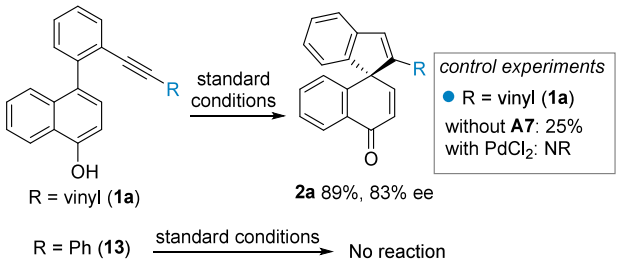
of **2a** proved reactive, enabling efficient construction of spirocycle **8** through a Diels–Alder reaction with diethyl but-2-ynedioate followed by oxidative aromatization. The *exo*-vinyl group also chemoselectively undertook a 1,3-dipolar cycloaddition reaction with in situ formed nitrile oxide, and isoxazole-containing product **9** was finally obtained in a good yield after oxidation.[11] Furthermore, reduction of the imine moiety in spirocyclic indolenine **4q** provided indoline **10**, which was then converted to sulfonamide **11**.[12] The absolute configuration of **11** was unambiguously confirmed by an X-ray crystallographic analysis. Moreover, oxindole **12** was yielded via Pinnick oxidation of **4q**, further highlighting the synthetic potential of these scaffolds.[13]

To elucidate the reaction mechanism, we performed several control experiments for the CADA reaction (Scheme 5).

Scheme 5. Control Experiments



Under the standard conditions, the asymmetric hydrofunctionalization of **1a** proceeded efficiently, whereas a significantly diminished yield was observed in the absence of **A7**. In addition, no reaction occurred when Pd(II) was used instead, clearly demonstrating that both the acid additive and Pd(0) species are essential for reactivity. Furthermore, biaryl **13** possessing a sole alkyne group proved inert under the standard catalytic conditions, highlighting the critical role of the conjugated vinyl group in the transformation. These experimental observations are consistent with a Pd(0) π-Lewis base-promoted vinylogous activation mechanism.[14]

In conclusion, we have developed an efficient catalytic asymmetric dearomatization process through Pd(0)/chiral phosphoric acid cooperative catalysis, rendering an atom-economical intramolecular hydrofunctionalization reaction of enyne-tethered biaryl substrates. This protocol provided efficient access to diverse spirocyclic hexenone and indolenine derivatives with fair to excellent enantioselectivity. The synthetic utility of these scaffolds was showcased through various transformations, affording enantioenriched frameworks with a higher molecular complex and skeletal diversity. The experiments supported a reaction mechanism involving Pd(0) π-Lewis base-mediated protonation, and chiral phosphate counteranion was essential for the enantiocontrol in the dearomative step, verifying such a dual catalytic system would be a powerful paradigm for expanding the hydrofunctionalization of more polyunsaturated substrates.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c03387.

Complete experimental procedures and characterization of new products, synthetic transformations of the products, NMR, HRMS spectra and HPLC chromatograms (PDF)

Accession Codes

Deposition Numbers 2479844–2479845 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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