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Palladium-Catalyzed Diastereo- and Enantioselective [3 + 2] Cycloaddition of Vinylcyclopropanes with Azadienes: Efficient Access to Chiral Spirocycles

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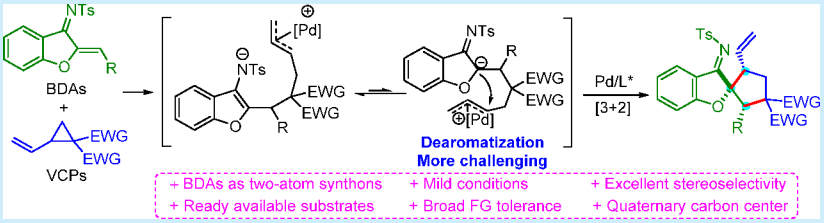

ABSTRACT: Benzofuran-derived azadienes (BDAs) have been widely used as four-atom synthons in transition-metal-mediated cycloaddition reactions, while the exploitation of their reactivity as a two-atom unit to construct spirocycles is still underdeveloped. Herein, we reported the first palladium(0)-catalyzed diastereo- and enantioselective [3 + 2] annulation of vinylcyclopropanes (VCPs) and BDAs. This transformation is featured with a broad substrate scope (31 examples), allowing for facile access to a variety of enantioenriched spirocycles bearing a quaternary stereogenic center in good yields with excellent regio-, diastereo-, and enantioselectivities (up to 93% yield, >20:1 dr, and mostly >99% ee) under mild reaction conditions. Moreover, the spirocyclic products could be efficiently converted to structurally complex tricyclo[8.3.0.0^{1,5}]-azatridecane and tricyclo[7.3.0.0^{1,5}]-azadodecane skeletons.

Spiro[benzofuran-cyclopentane] and related scaffolds are ubiquitous skeletons existing in a wide array of biologically active molecules, natural products, and pharmaceutical agents (Figure 1).[1] The three-dimensional and rigid structure of spirocycles and their resulting ability to achieve a better interaction between a ligand and binding site make them more suitable as core structures in the drug discovery process compared to planar ring systems.[2] Despite great success in spirocycle synthesis,[3] the development of asymmetric catalytic methods for the efficient construction of highly functionalized and enantioenriched spirocycles with a good control of regio-, diastereo-, and enantioselectivity, especially bearing a spirocyclic quaternary stereocenter, is still a highly desirable yet challenging subject.

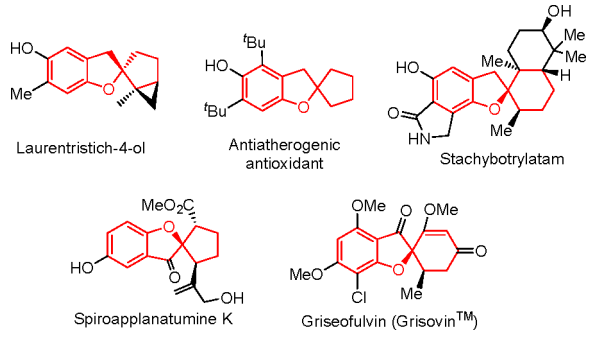

Figure 1. Representative bioactive molecules containing spiro[benzofuran-cyclopentane] and related scaffolds.

In recent years, benzofuran-derived azadienes (BDAs) have emerged as versatile building blocks for the efficient construction of a diverse range of cyclic compounds. In 2016, the Zhao group disclosed the first [4 + 2] cycloaddition of BDAs and aldehydes catalyzed by *N*-heterocyclic carbenes (NHCs) or chiral amines (Scheme 1a).[4a] Since then, BDAs have been thoroughly studied in a variety of [4 + *n*] cycloadditions (*n* = 2−6) by serving as four-atom synthons owing to their intrinsic driving force of aromatization (Scheme 1a).[4,5] Among them, Trost,[5a] Deng,[5b] Huang,[5c] Ye,[5d] and Chen[5e] prepared a series of benzofuran-fused medium-sized heterocycles via [4 + 3] cycloadditions of BDAs with trimethylenemethane (TMM) or Morita−Baylis−Hillman (MBH) carbonates or enals, respectively. In 2017, Lu and co-workers reported the first enantioselective phosphine-catalyzed [4 + 4] cycloaddition reaction between allene

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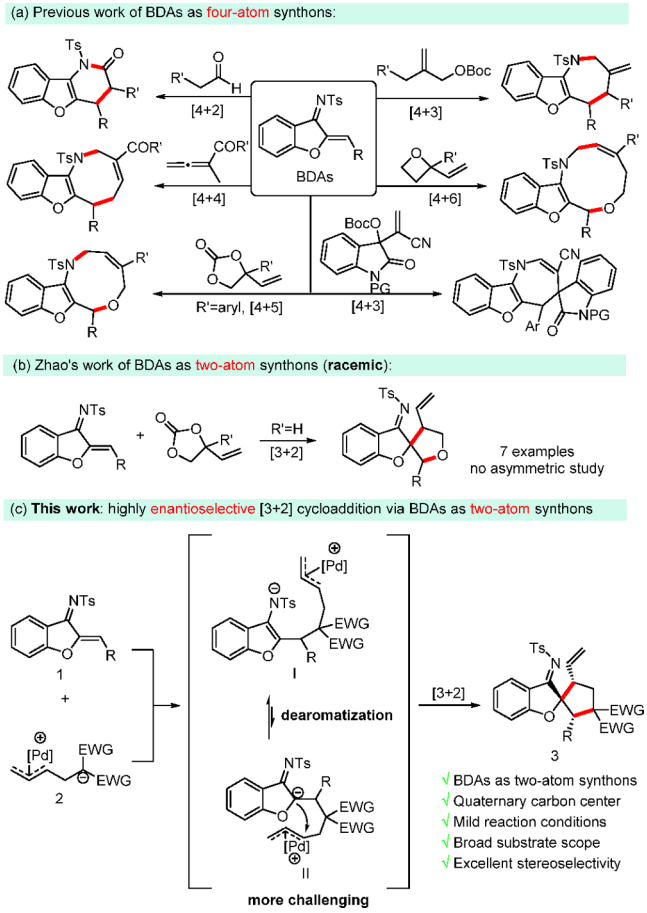
Scheme 1. Different Reaction Patterns of BDAs

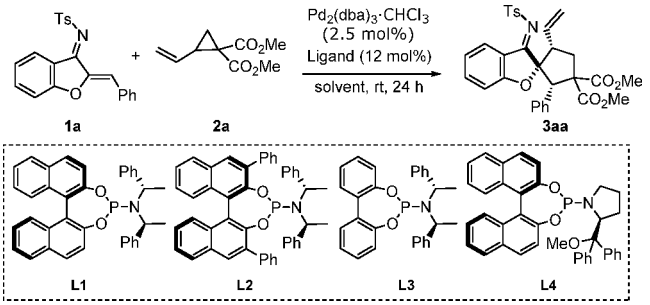


ketones and BDAs.[5f] Later, the Zhao group developed an asymmetric formal [4 + 6] annulation of BDAs with vinyl oxetanes to afford 10-membered heterocycles.[5g]

These strategies highlighted the power of using BDAs as four-atom synthons in cycloadditions, but BDAs acting as two-atom synthons, especially in asymmetric catalysis, is more challenging and still rare, as the strong driving force of aromatization to form the benzofuran skeleton after the addition of nucleophiles makes it energetically and sterically unfavorable to perform [2 + *n*] cycloadditions (Scheme 1c). In 2016, the Zhao group reported their seminal study describing a palladium(0)-catalyzed [2 + 3] annulation of BDAs with unsubstituted vinylethylene carbonates (VECs) to provide functionalized spirotetrahydrofurans with good results, albeit in a racemic version (Scheme 1b).[6a] In 2020, the Zhao group disclosed an efficient synthetic method using BDAs and bromomalonate to prepare spirocyclopropanes.[6b] To the best of our knowledge, the asymmetric cycloaddition involving BDAs as two-carbon synthons has not been disclosed yet. In conjunction with our interest in transition-metal-catalyzed cycloaddition reactions involving vinylcyclopropanes (VCPs),[7,8] herein, we report a stereoselective [3 + 2] cycloaddition reaction of VCPs and BDAs for the concise preparation of optically active spiro[benzofuran-cyclopentane] derivatives with multichiral centers including a spirocyclic quaternary carbon under mild reaction conditions (Scheme 1c).

We began our investigation by studying the coupling of azadiene **1a** with VCP **2a** as the model reaction (Table 1). To

Table 1. Optimization Process[a]



entry	ligand	solvent	yield[b]	ee[c]	dr[d]
1	**L1**	DCE	45%	46%	1:1
2	**L2**	DCE	38%	44%	4:1
3	**L3**	DCE	53%	73%	1:1
4	**L4**	DCE	78%	84%	2:1
5	**L4**	toluene	88%	97%	5:1
6	**L4**	THF	92%	80%	2:1
7[e]	**L4**	toluene	83%	>99%	7:1
8[e]	**L4**	*p*-xylene	82%	93%	6:1
9[e]	**L4**	mesitylene	67%	95%	6:1
10[e]	**L4**	ethylbenzene	77%	91%	5:1
11[f]	**L4**	toluene:HFB = 1:2	83%	>99%	18:1

[a]Conditions: all reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), and ligand (12 mol %) in the indicated solvent at room temperature under a nitrogen atmosphere. [b]Isolated yield of product **3aa**. [c]The ee was determined by HPLC. [d]The dr was determined by ^1H NMR crude. [e]The reaction was run at 0 °C. [f]The reaction was run at 4 °C. HFB: Hexafluorobenzene.

our delight, the expected [3 + 2] cycloaddition proceeded smoothly after careful evaluation of different reaction parameters, and the preliminary result showed that a combination of $Pd_2(dba)_3{\cdot}CHCl_3$ and chiral P-containing ligands exhibited optimal asymmetric induction in such an annulation process (more details in the Supporting Information).[9] The Feringa ligand **L1** afforded the desired product **3aa** in 45% yield with 46% ee and 1:1 dr (entry 1). Encouraged by this promising result, further examination of various chiral phosphoramidite ligands indicated that they showed a dramatic impact on both the cycloaddition reaction efficiency and selectivity. Among them, 3,3′-diphenyl-substituted BINOL ligand **L2** afforded the **3aa** in 44% ee with 4:1 dr (entry 2), whereas the biphenyl skeleton ligand **L3** improved the ee (73% ee, entry 3) albeit with a 1:1 dr. We then turned our attention to substitutions on the nitrogen moiety of phosphoramidite ligands. When the chiral methyl-protected diarylprolinol was employed,[10] the ligand **L4** was found to be the optimal ligand, providing the chiral cycloadduct **3aa** with a good result (78% yield, 2:1 dr, and 84% ee, entry 4). Further screening various solvents and decreasing the reaction temperature (entries 5−11) revealed that the mixed solvent of toluene and hexafluorobenzene (HFB) at a ratio of 1:2 was the best one in terms of cycloaddition reactivity and selectivity, affording cycloadduct **3aa** in 83% yield and >99% ee with 18:1 dr at 4 °C (entry 11). It should be noted that no [4 + 3] cycloaddition product was observed during the optimization process.

With optimized reaction conditions in hand, we proceeded to investigate the substrate scope of azadienes **1** for this asymmetric [3 + 2] cycloaddition reaction (Table 2). *N*-Sulfonyl substituents of azadienes did not affect this trans-

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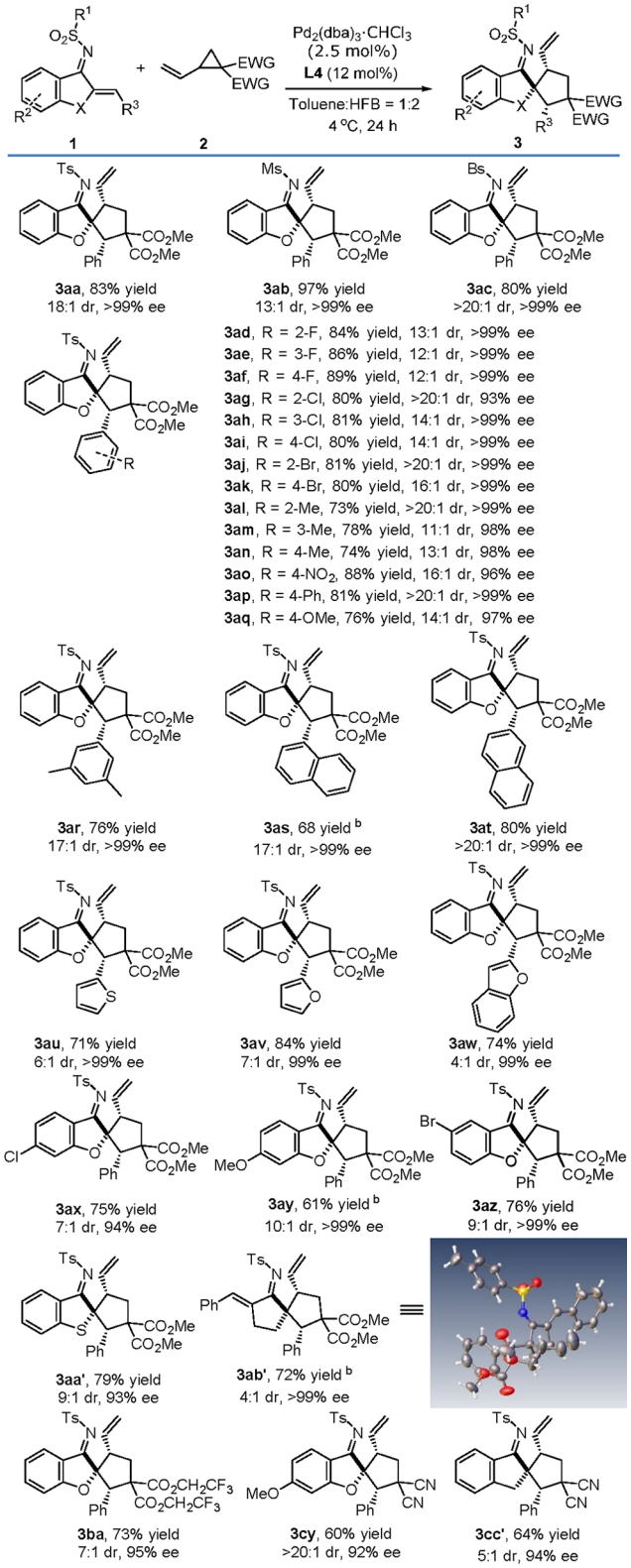
Table 2. Substrate Scope of [3 + 2] Cycloaddition[a]



[a]Conditions: all reactions were performed with **1** (0.1 mmol), **2** (0.1 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), and **L4** (12 mol %) in 1 mL of solvent toluene:HFB = 1:2) at 4 °C under a nitrogen atmosphere. Isolated yields. The ee values were determined by HPLC. The dr values were determined by ^{1}H NMR crude. [b]Chlorobenzene:toluene = 1:2 as the solvent at room temperature. HFB: Hexafluorobenzene.

formation, providing benzofuran-fused spirocycles **3aa**−**3ac** in good yields with excellent stereoselectivities. A series of *N*-tosyl azadienes bearing either electron-withdrawing or electron-donating groups at the R^3 position could participate in this cycloaddition efficiently, affording the corresponding spirocycles **3ad**−**3aq** in 73−89% yields, 11:1 to >20:1 dr, and mostly >99% ee. The cycloaddition reaction was applicable to a wide range of common functional groups, including fluorides (**3ad**−**3af**), chlorides (**3ag**−**3ai**), bromides (**3aj** and **3ak**), nitro (**3ao**), and ether (**3aq**), thus providing useful handles for further derivatization of cycloadducts. In addition, azadienes with *meta* substituents (e.g., 3,5-Me) on the aromatic ring, as well as 1- and 2-naphthyl-substituted substrates, all delivered the corresponding products with good results (**3ar**−**3at**), indicating that the steric nature of substituents has no influence on this transformation. Substrates containing heterocyclic moieties (**3au**−**3aw**, all 99% ee) could also undergo the cycloaddition efficiently.

Moreover, R^2 substitutions on **1** bearing halogens or a methoxy group at either the C5- or C6-position of the benzofuran ring were amenable to this cycloaddition, furnishing the enantiopure spirocycles **3ax**−**3az** with 94 to >99% ee. Notably, the substrates of this transformation were not limited to the benzofuran skeletons. Benzothiophene-substituted azadiene **1a′** could also react smoothly to yield **3aa′** with a good result. In addition, aliphatic-based *N*-tosyl azadiene **1b′** was examined for the formation of aliphatic-fused bicyclic spirocycles which are prevalent and invaluable skeletons in bioactive natural products.[11] To our delight, product **3ab′** was successfully generated in 72% yield with 4:1 dr and >99% ee with a slightly modified procedure. The absolute configuration of **3ab′** was unambiguously determined as 1R, 4S, 5S by X-ray analysis (CCDC 2047650).

Next, we began to explore the substrate scope of VCPs **2**. For example, trifluoroethyl-ester-substituted VCP was suitable for this stereoselective [3 + 2] cycloaddition, affording the corresponding spirocycle **3ba** in 73% yield with 7:1 dr and 95% ee. However, VCPs containing bulkier esters (e.g., *tert*-butyl ester) were incompatible in this reaction, presumably due to the steric hindrance of the ester group. We then studied this cycloaddition of azadienes with 1,1-dicyanocyclopropane **2c**.[12] Gratifyingly, substrate **1y** with a methoxy group on the benzofuran ring could undergo the cycloaddition with VCP **2c** efficiently, providing an important complement to the ubiquitous geminal diester VCPs. Further, indene-based azadiene **1c′** reacted smoothly, delivering cycloadduct **3 cm**$^{3'}$ in high enantioselectivity and moderate diastereoselectivity.

To further demonstrate the synthetic utility of our protocol, a scale-up cycloaddition reaction of substrates **1a** and **2a** was performed with reduced loadings of palladium catalyst (3.0 mol %) and **L4** (7.0 mol %), and the desired product **3aa** was isolated in an improved yield (93%) with the levels of diastereomeric and enantiomeric enrichment unchanged (Scheme 2a). In addition, various transformations of the cycloadduct **3aa** were performed. Hydrolysis of the *N*-sulfonyl derivatives offered the corresponding benzofuranone **4** in 81% yield, providing a facial method for the synthesis of the core structure of spiroapplanatumine K.[13] The secondary amine **5** could be diastereoselectively obtained via reduction in the presence of diisopropyl aluminum hydride (DIBAL-H). The synthetic utilization potential of this new enantioselective cycloaddition method was further illustrated via the transformation of intermediate **5**. Delightfully, electrophilic

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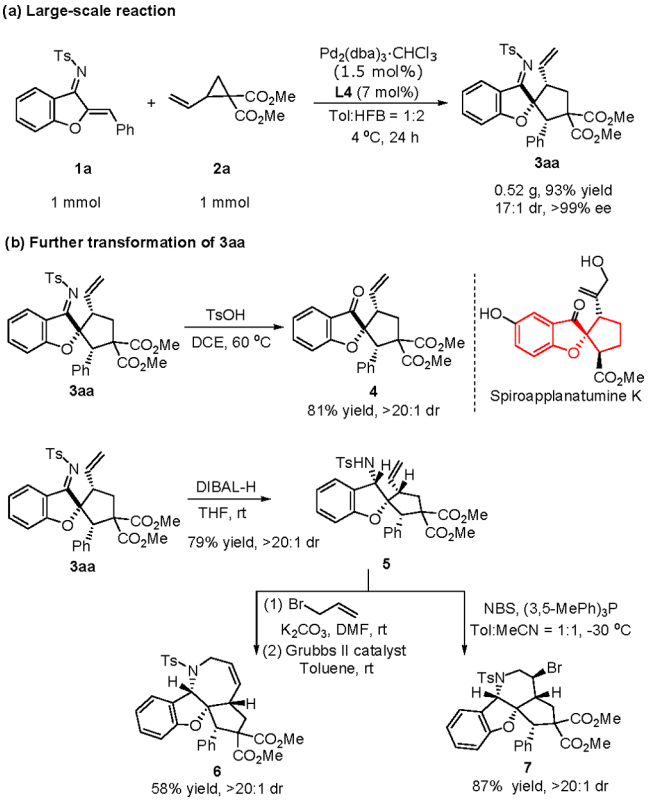
Scheme 2. Large-Scale Reaction and Further Transformation of 3aa



substitution of amine **5** with allyl bromide was followed by a ring-closing metathesis (RCM) reaction to generate the structurally more complex tricyclo[8.3.0.0^{1,5}]-azepine **6** in 58% yield over two steps. Moreover, highly diastereoselective bromocyclization of amine **5** to tricyclo[7.3.0.0^{1,5}]-piperidine **7** with four contiguous stereogenic centers was achieved in 87% yield.

In conclusion, we have developed the first palladium(0)-catalyzed, stereoselective [3 + 2] cycloaddition reaction of BDAs as two-atom synthons to provide a reliable strategy for the synthesis of highly functionalized spiro[benzofuran-cyclopentane] molecules bearing three continuous stereocenters from readily available VCPs in high efficiency. In addition, further transformation of the functionalized cycloadducts to a range of tricyclic skeletons was also demonstrated. We expect such a protocol to offer alternative and concise strategies for the synthesis of benzofuran-fused spirocycles and pharmaceutical molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04062.

Optimization tables, experimental procedures, products characterization, and spectral data (PDF)

Accession Codes

CCDC 2047650 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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