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Access to Chiral Polycyclic 1,4-Dihydropyridines via Organocatalytic Formal [3 + 3] Annulation of 2-(1-Alkynyl)-2-alken-1-ones with 3-Aminobenzofurans

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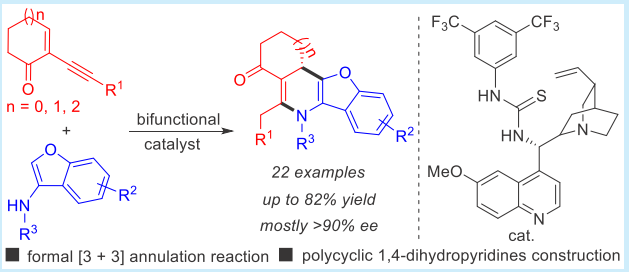
ABSTRACT: A rational designed tandem reaction of 2-(1-alkynyl)-2-alken-1-ones with 3-aminobenzofurans enabled by a chiral bifunctional catalyst is described, affording biologically significant polycyclic 1,4-dihydropyridines in moderate to good yields (43−82%) with good to excellent enantioselectivities (83−99%). This formal [3 + 3] annulation reaction reveals good practicality when conducted on a gram scale, and the cycloadduct has the capability for further elaborations.



1,4-Dihydropyridines (1,4-DHPs) represent a family of vital molecules that constitute the backbones of numerous pharmaceutical drugs, such as calcium channel modulators[1a−c] and antimicrobial,[1d] analgesic,[1e] antitumor,[1f] and antidiabetic agents.[1g] Notably, the stereochemistry at the C4 position of 1,4-DHPs plays a crucial role in determining their biological activities, and enantiomers of 1,4-DHPs may exhibit different or even opposite properties. For instance, (*S*)-amlodipine has about 2000-fold potency in an in vitro evaluation in the rat aorta compared with the corresponding (R) enantiomer.[2a] (*R*)-PN 202-791 is a calcium channel blocker, but (*S*)-PN 202-791 is a calcium channel agonist (Figure 1).[2b]

As a consequence, the preparation of enantioenriched 1,4-DHPs has drawn considerable attention from the chemical community.[3] To date, there are two main routes toward the catalytic asymmetric synthesis of such molecules. Route one is through various catalyst-mediated asymmetric three-component Hantzsch reactions and their variants (Scheme 1a).[4] Route two is through various catalyst-promoted stereoselective 1,4-additions of pyridinium salts (Scheme 1b).[5] However, despite the fact that a range of approaches following those two routes have been successfully created, there are still several limitations on the substrate scope and reaction generality. For route one, the substituents on the C4 chiral center are usually restricted to aryl groups, and the enantioselectivities of those multicomponent reactions are typically less satisfactory. For route two, a strong electron-withdrawing group must be installed at the C3 position of the pyridine ring to suppress the

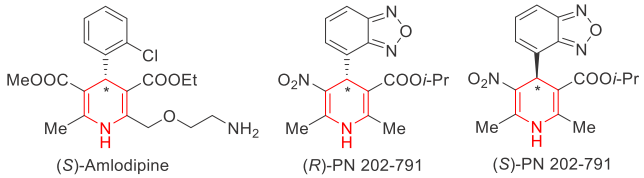
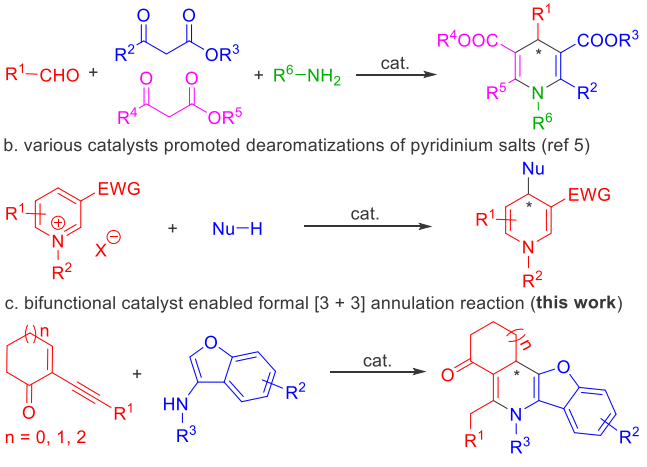


Figure 1. Representative examples of 1,4-dihydropyridine-based pharmaceuticals bearing stereocenters at the C4 position.

Scheme 1. Catalytic Asymmetric Preparation of 1,4-Dihydropyridine Derivatives



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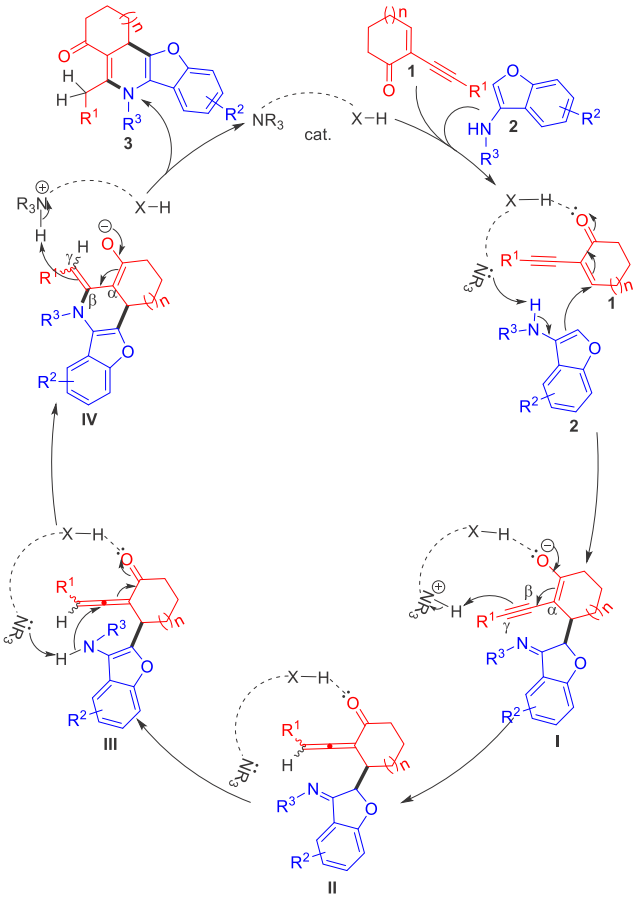
Scheme 2. Proposed Reaction Pathway

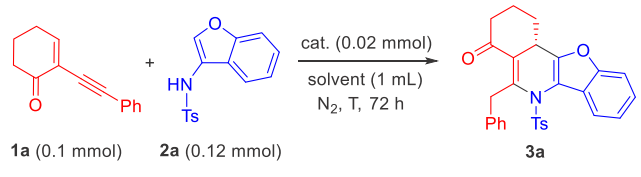


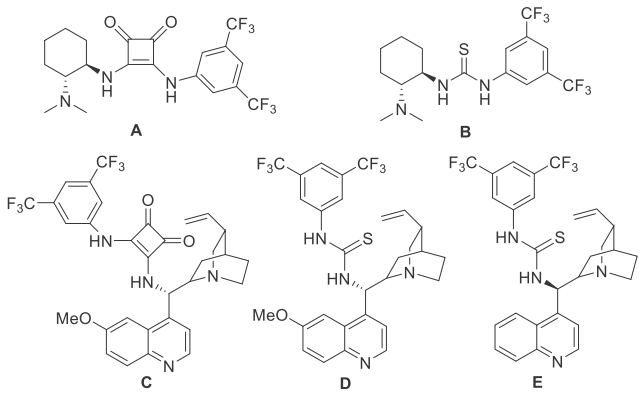
competitive 1,2-addition, and these dearomatization reactions can afford only partially substituted monocyclic 1,4-DHPs. In this context, the development of efficient strategies for the rapid construction of 1,4-DHPs with both optical purity and molecular complexity is highly desirable and urgently needed.

2-(1-Alkynyl)-2-alken-1-ones are known as versatile building blocks bearing multifunctional groups at the same molecule.[6] In the past decade, various protocols have been established for the preparation of chiral furans,[7a−g] 4*H*-pyrans,[7h] 2,3-dihydroisoxazoles,[7i] and pyranopyrazoles[7j] using 2-(1-alkynyl)-2-alken-1-ones as the key substrates. However, to the best of our knowledge, the participation of 2-(1-alkynyl)-2-alken-1-ones in the catalytic asymmetric synthesis of 1,4-DHPs has not yet been achieved. Our group is interested in developing potent strategies for the creation of valuable molecules via organocatalysis.[8] In 2021, we disclosed an N-heterocyclic-carbene-promoted formal [3 + 3] annulation reaction of 3-aminobenzofurans with *β*,*β*-disubstituted, *α*,*β*-unsaturated carboxylic esters to provide enantioenriched benzofuran-fused *δ*-lactams.[8j] Because 3-aminobenzofurans have recently emerged as a powerful bis-nucleophile in organic synthesis,[9] we envisioned that the combination of 2-(1-alkynyl)-2-alken-1-ones with 3-aminobenzofurans in the presence of a chiral bifunctional catalyst would furnish polycyclic 1,4-DHPs in an enantioselective manner (Scheme 1c).

Our reaction design is depicted in Scheme 2. The hydrogen-bonding donor of the bifunctional catalyst first activates the ketone group of 2-(1-alkynyl)-2-alken-1-one **1**; concurrently, the Brønsted base moiety of the bifunctional catalyst deprotonates 3-aminobenzofuran **2** to undergo a Michael

Table 1. Optimization of Reaction Conditions[a]





entry	cat.	solvent	*T* (°C)	yield of **3a** (%)[b]	ee of **3a** (%)[c]
1	**A**	DCE	60	35	45
2	**B**	DCE	60	29	80
3	**C**	DCE	60	63	25
4	**D**	DCE	60	58	95
5	**D**	THF	60	56	78
6	**D**	EtOAc	60	46	87
7	**D**	CH_3CN	60	16	74
8	**D**	$CHCl_3$	60	54	90
9	**D**	toluene	60	65	95
10	**D**	**toluene**	**40**	77	**95**
11	**D**	toluene	25	69	95
12	**E**	toluene	40	68	−93

[a]Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2a** (0.12 mmol), cat. (0.02 mmol), and solvent (1 mL) at a specific temperature under a nitrogen atmosphere for 72 h. [b]Isolated yield based on **1a**. [c]Enantiomeric excess of **3a** determined via chiral-phase high-performance liquid chromatography (HPLC) analysis.

addition reaction with **1** to form enolate intermediate **I**. Then, *γ*-protonation of intermediate **I** generates allenone intermediate **II**, which is next converted to intermediate **III** via proton transfer. Subsequent deprotonation followed by the intramolecular aza-Michael addition of intermediate **III** furnishes tetrahydropyridine intermediate **IV**. Finally, *γ*-protonation of intermediate **IV** offers polycyclic 1,4-DHP **3** as the desired product and releases the catalyst.

On the basis of our proposal, we first verified the feasibility of this tandem reaction by exploiting 2-(phenylethynyl)-cyclohex-2-en-1-one **1a** and *N*-Ts-protected 3-aminobenzofuran **2a** as the model substrate (Table 1). Gratifyingly, the use of *trans*-1,2-diaminocyclohexane-derived squaramide **A**[10] as the bifunctional catalyst straightforwardly led to the target molecule **3a** in 35% yield with 45% ee (entry 1). Replacing the squaramide unit in **A** with a thiourea motif (catalyst **B**[11]) afforded **3a** in 29% yield with 80% ee (entry 2), whereas the employment of two quinine-derived bifunctional catalysts (**C**[12] and **D**[13]) revealed that catalyst **D** could provide **3a** in 58% yield with 95% ee (entries 3 and 4). Encouraged by this result, we next chose **D** as the optimized catalyst and studied the solvent effect. A variety of polar and nonpolar solvents were

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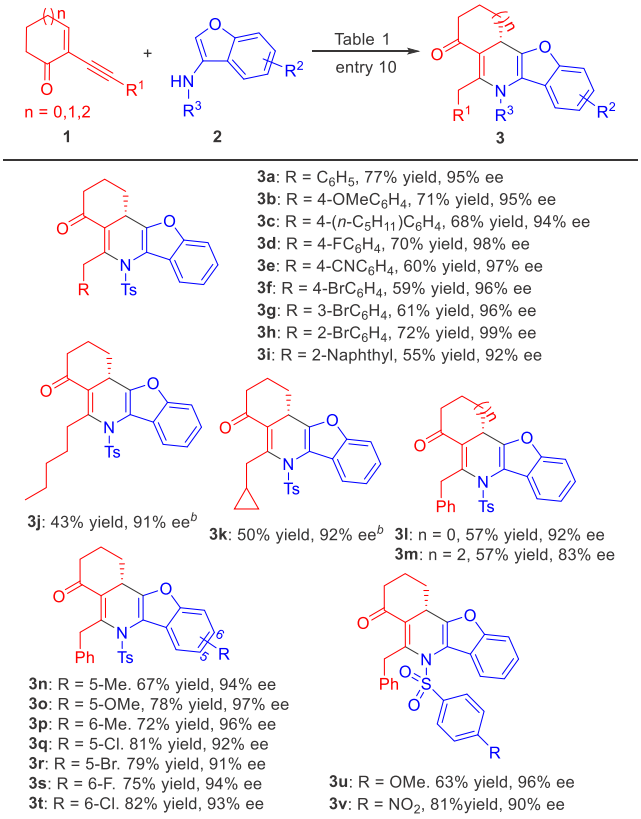
Scheme 3. Scope of Reactions[a]



[a]Reaction conditions unless otherwise specified: **1** (0.1 mmol), **2** (0.12 mmol), **D** (0.02 mmol), and toluene (1 mL) at 40 °C under a nitrogen atmosphere for 72 h. Isolated yields based on **1**. [b]These reactions were carried out at 60 °C for 72 h.

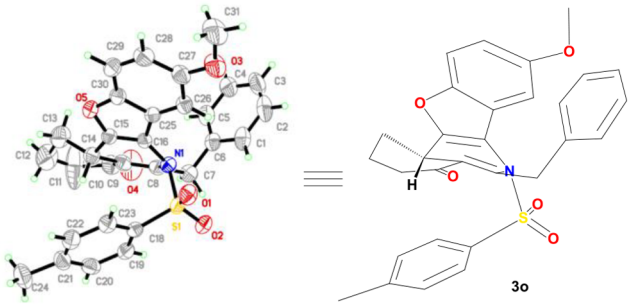
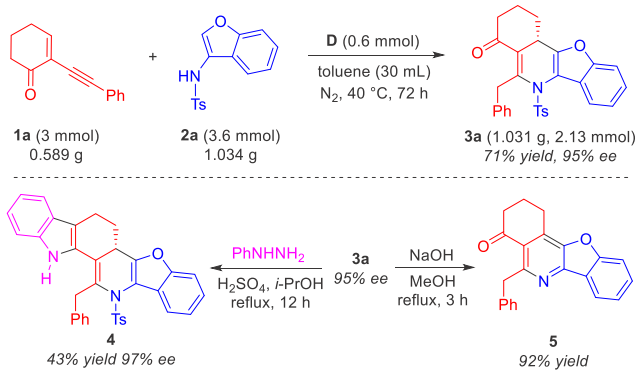


Figure 2. ORTEP diagram of **3o** (ellipsoid contour at 30% probability).

proven to be compatible with the current reaction, as they all smoothly delivered the corresponding product **3a** (entries 5–9). Among them, toluene showed the highest efficiency by forming **3a** in 65% yield with 95% ee. Moreover, with **D** as the catalyst and toluene as the solvent, we also evaluated the temperature influence. When the model reaction was performed at 40 °C, the yield of **3a** was enhanced to 77% without a loss of enantioselectivity (entry 10), but when the temperature was further lowered to 25 °C, a slight drop in yield was observed (entry 11). Finally, the use of cinchonine-derived thiourea catalyst **E**[14] furnished **3a** in 68% yield with −93% ee, indicating that in the current reaction, both of the enantiomeric series of the products were accessible (entry 12).

Scheme 4. Gram-Scale Preparation and Synthetic Utility of 3a



Having established an optimal protocol for this reaction (Table 1, entry 10), we then examined the substrate generality (Scheme 3). First, a number of 2-(1-alkynyl)-2-alken-1-ones **1** were investigated by reacting with **2a**. For the alkynyl moiety in substrate **1**, both electron-rich and electron-deficient substituted aromatic rings were accommodated, resulting in the anticipated products **3a–i** in good yields with excellent ee values. When aliphatic substituents such as *n*-butyl and cyclopropyl were incorporated, perhaps due to the low reactivity, a higher temperature (60 °C) had to be applied to achieve the full consumption of the starting materials (products **3j,k**). The ring size of substrate **1** can be modified. Under the standard reaction conditions, cyclopentenone- and cycloheptenone-derived 2-(1-alkynyl)-2-alken-1-ones furnished the corresponding 1,4-DHPs **3l** and **3m** in 57% yield with 92% ee and in 57% yield with 83% ee, respectively. Next, a series of 3-aminobenzofurans **2** were surveyed by reacting with **1a**. The use of 5-Me-, 5-OMe-, and 6-Me-substituted benzofurans in the reaction all proceeded smoothly, producing the desired products **3n–p** in good yields with excellent enantioselectivities. Halogen substituents (5-Cl, 5-Br, 6-F, and 6-Cl), which can be utilized for further derivatizations, were well tolerated in this reaction, as products **3q–t** were successfully obtained. The protecting group on the amine part was also probed. An electron-donating group such as a 4-OMe-substituted reactant gave product **3u** with similar ee, but when an electron-withdrawing group such as 4-NO_2 was employed, the ee value of product **3v** dropped to 90%.

To figure out the stereochemistry of the C4 position in the major enantiomer of compound **3o**, a single crystal was grown and tested. The X-ray crystallographic analysis of this crystal unequivocally confirmed that the absolute configuration of the newly formed stereocenter was S (Figure 2). The configurations of other chiral 1,4-DHPs were assigned on the assumption of a uniform mechanistic pathway.

The practicability of this formal [3 + 3] annulation reaction was displayed by gram-scale synthesis and further elaboration of 1,4-DHP **3a**. Under the optimal reaction conditions, simple amplification of the model reaction to the 3 mmol scale straightforwardly produced >1 g of **3a** without losing efficiency (Scheme 4, top). In the presence of a catalytic amount of sulfuric acid, **3a** directly underwent Fischer indole synthesis with phenylhydrazine to provide hexacyclic compound **4** (Scheme 4, bottom, left). The tosyl group was removed by treating **3a** with sodium hydroxide under reflux conditions to

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generate polycyclic pyridine **5** in 92% yield (Scheme 4, bottom, right).

In summary, we have developed a novel bifunctional catalyst-mediated cascade reaction of 2-(1-alkynyl)-2-alken-1-ones with 3-aminobenzofurans to deliver polycyclic 1,4-DHPs with a broad substrate scope and excellent enantioselectivities. This concise protocol has the potential to be applied in practical synthesis, and the products could be further transformed to architecturally complex molecules through simple operations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02211.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2085035 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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