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Chiral β-Keto Propargylamine Synthesis via Enantioselective Mannich Reaction of Enamides with C-Alkynyl N-Boc N,O-Acetals

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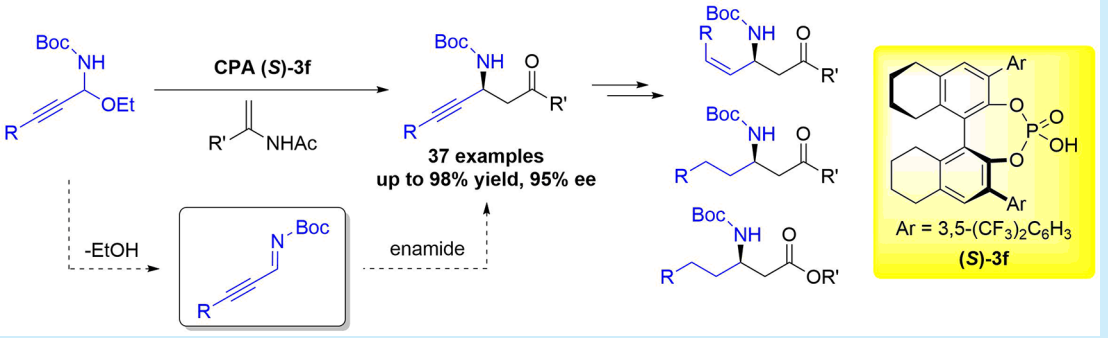
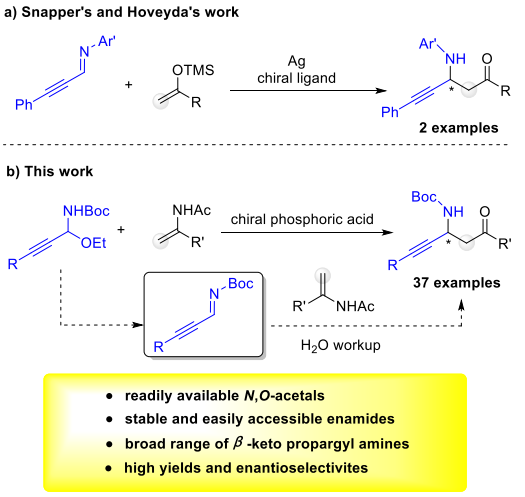
Supporting Information



ABSTRACT: Propargylamines are an important class of compounds in organic synthesis and drug discovery, yet the synthesis of chiral β-keto propargylamines remains underdeveloped. Herein, we describe a streamlined and general enantioselective Mannich reaction of enamides with C-alkynyl N-Boc N,O-acetals, which serve as readily available C-alkynyl imine precursors, to access a broad range of chiral β-keto N-Boc-propargylamines bearing single stereogenic centers in high yields (up to 98%) and in high enantioselectivities (up to 95% ee).

Propargylamines, particularly their chiral forms, are important structural motifs[1] and synthetic intermediates[2] of natural products and biologically active molecules. In particular, chiral keto-substituted propargylamines are an attractive class of functionalized propargylamines in organic synthesis owing to the potential transformations of both keto and alkynyl groups to multiple functionalities.[3] Over the past decades, a diverse set of functionalized chiral propargylamines have been accessed by employing the asymmetric additions of alkynyl nucleophiles to imines[4] as well as the asymmetric additions of nucleophilic substrates to C-alkynyl imine derivatives.[5−8] In this context, only one report by Snapper and Hoveyda et al. has presented the Ag-catalyzed asymmetric reaction between 3-phenylpropynyl N-arylimine and silyl vinyl ethers to obtain two examples of chiral β-keto propargylamines (Scheme 1a).[5b] On the other hand, enamides have been utilized as readily available and bench-stable carbon nucleophiles in organic synthesis, especially in asymmetric catalysis.[9] Recently, our group demonstrated the enantioselective addition of enamides to in situ generated cyclic ketimines to give a myriad of chiral β-keto amine derivatives.[10,11] Therefore, we envisioned that the asymmetric reaction of enamides with C-alkynyl N-Boc N,O-acetals recently introduced by the Shao group, which are a class of easily accessible C-alkynyl imine precursors in asymmetric catalysis,[7] would be viable, providing a general and complementary method to access enantioenriched β-keto propargylamines (Scheme 1b). Herein, we report our preliminary findings on this subject.

Scheme 1. Methods for Synthesis of β-Keto Propargylamines from Alkynyl Imine Derivatives



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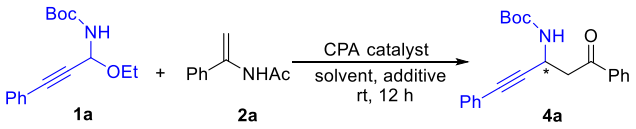
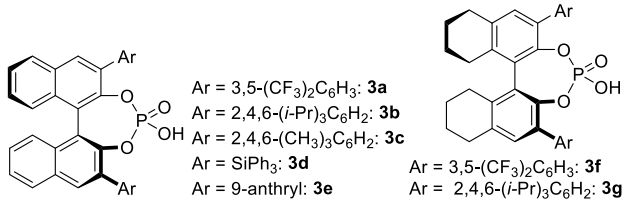
We commenced the study of the asymmetric synthesis of β-keto propargylamine **4a** using *C*-alkynyl *N*-Boc *N,O*-acetal **1a** and α-arylenamide **2a** as the model substrates (Table 1). Initial screening of organocatalysts (**3a**–**3g**, entries 1–7) indicated that BINOL-based chiral phosphoric acid (CPA) (*S*)-**3f** was the optimal catalyst to facilitate the reaction of **2a** (2 equiv) with **1a** (1 equiv) in CH_2Cl_2 solvent at ambient conditions, affording the desired product **4a** in 83% yield and in 86% enantiomeric excess (ee, entry 6). In addition, Na_2SO_4 was found to be the superior additive compared to 4 Å molecular sieves, further promoting the yield and ee to 86% and 88%, respectively (entries 8 and 9). In the presence of Na_2SO_4, the loading of **2a** could be reduced to 1.5 equiv without diminishment of yield and erosion of ee (entry 10). Based on this improved protocol, we subsequently screened various solvents (entries 11–15). The use of toluene as nonpolar solvent could enhance the enantioselectivity to 91% ee (entry 15). In order to further improve the enantioselectivity, the reaction temperature and catalyst loading were optimized (entries 16–18). By reducing the loading of (*S*)-**3f** to 5 mol %, **4a** was obtained in 86% yield and in 92% ee (entry 17). However, further reducing the loading of **2a** to 1 equiv resulted in the diminishment of product yield (entry 19).

The asymmetric reaction of *N,O*-acetals with enamides proved to be general (Scheme 2) under the optimized conditions (Table 1, entry 17). A wide range of β-keto 3-arylpropargyl amides (**4a**–**4n**) could be synthesized in high to excellent yields (78–95%) with high enantioselectivities (89–95% ee). Electron-neutral (**4a**), electron-rich (**4b**–**4g**), and electron-deficient aryl groups (**4h**–**4n**) were all compatible in the *N,O*-acetal reaction partners. Among these substrates, functional groups such as trifluoromethoxy (**4h**), trifluoromethyl (**4i**), fluoro (**4j**–**4l**), and chloro groups (**4m**, **4n**) were tolerated as well. Notably, the protocol allowed for the reactions with various *para*-, *meta*-, and *ortho*-substituted arylpropargylamines to afford the products in similar yields and ee. In addition, *N,O*-acetals bearing naphthyl (**4o**) and thienyl groups (**4p**) were also suitable electrophiles to afford the corresponding products in equally high yields with high ee values. On the other hand, 3-butyl- (**4q**) and 3-cyclohexylpropargylamines (**4r**) were formed in lower ee (70–

Table 1. Catalyst Screening and Reaction Optimization[a]

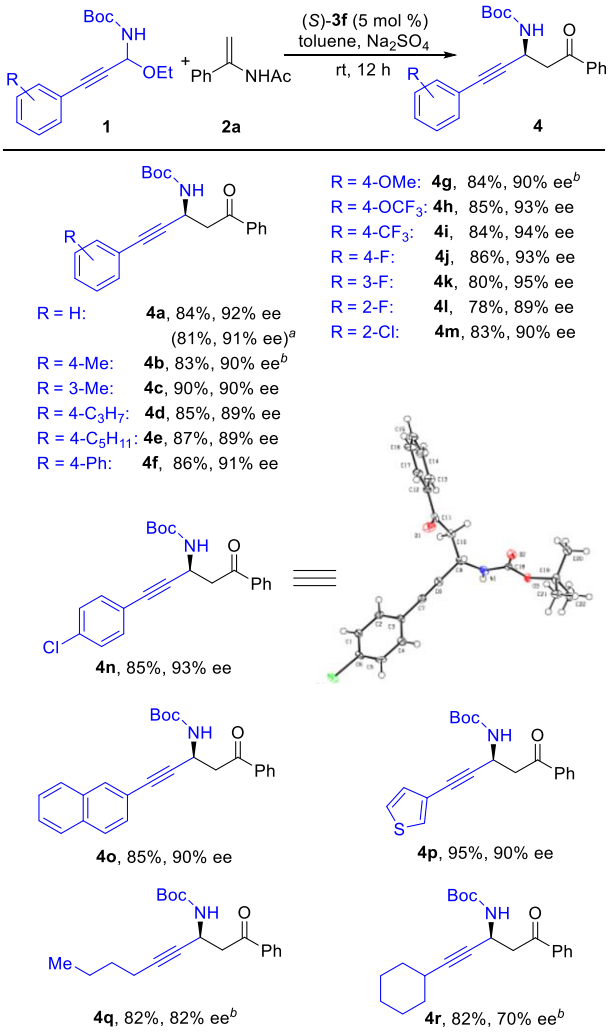




entry	catalyst (mol %)	2a (equiv)	solvent	yield[b] (%)	ee[c] (%)
1	(*S*)-**3a** (10)	2	CH_2Cl_2	80	81
2	(*S*)-**3b** (10)	2	CH_2Cl_2	70	0
3	(*S*)-**3c** (10)	2	CH_2Cl_2	72	58
4	(*S*)-**3d** (10)	2	CH_2Cl_2	68	30
5	(*S*)-**3e** (10)	2	CH_2Cl_2	69	55
6	(*S*)-**3f** (10)	2	CH_2Cl_2	83	86
7	(*S*)-**3g** (10)	2	CH_2Cl_2	75	49
8[d]	(*S*)-**3f** (10)	2	CH_2Cl_2	50	85
9[e]	(*S*)-**3f** (10)	2	CH_2Cl_2	86	88
10[e]	(*S*)-**3f** (10)	1.5	CH_2Cl_2	85	89
11[e]	(*S*)-**3f** (10)	1.5	THF	82	55
12[e]	(*S*)-**3f** (10)	1.5	CCl_4	80	84
13[e]	(*S*)-**3f** (10)	1.5	Et_2O	50	80
14[e]	(*S*)-**3f** (10)	1.5	MeCN	70	51
15[e]	(*S*)-**3f** (10)	1.5	toluene	83	91
16[e,f]	(*S*)-**3f** (10)	1.5	toluene	84	90
17[e]	(*S*)-**3f** (5)	1.5	toluene	86	92
18[e]	(*S*)-**3f** (1)	1.5	toluene	88	90
19[e]	(*S*)-**3f** (5)	1.0	toluene	75	88

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.2/0.3/0.4 mmol), chiral phosphoric acid (1–10 mol %), solvent (2 mL), and additive, rt, 12 h. [b]Isolated yield. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis. [d]50 mg of 4 Å molecular sieves was added. [e]50 mg of Na_2SO_4 was added. [f]Reaction was conducted at 0 °C.

Scheme 2. Substrate Scope of C-Alkynyl *N*-Boc *N,O*-Acetals*



*Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), CPA (*S*)-**3f** (5 mol %), Na_2SO_4 (50 mg), toluene (2 mL), rt, 12 h. [a]Based on 1.0 mmol of **1a**. [b]The reaction was conducted at 0 °C.

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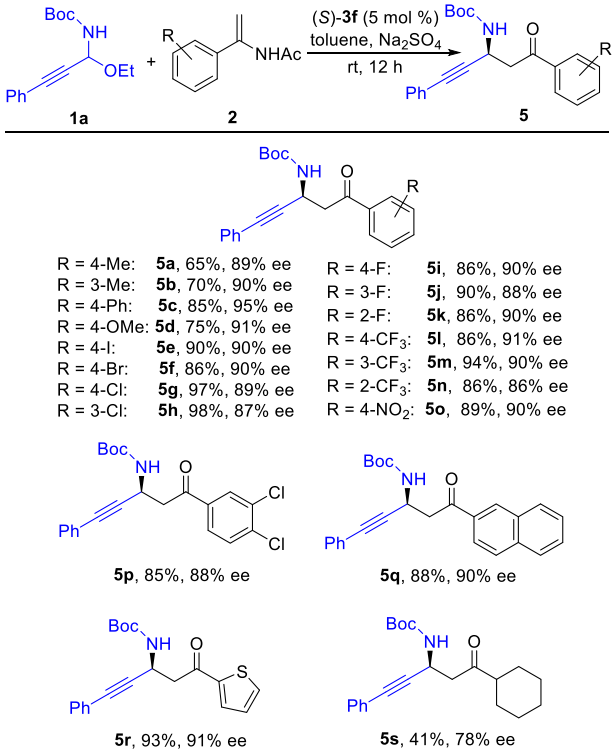
82%) despite the high product yields (82%). Large-scale reaction based on 1 mmol of *N,O*-acetal afforded the product **4a** without diminishment in yield and ee, suggesting that the reaction was scalable. The product **4n** could be isolated as a crystalline compound, and its structure was further characterized by X-ray crystallographic analysis. The absolute configuration of the stereogenic carbon center formed in the reaction was assigned as *S*-stereochemistry.

The protocol was also applicable to the chiral β-keto propargylamine synthesis with various enamides (Scheme 3).

Scheme 3. Substrate Scope of Enamides[a]

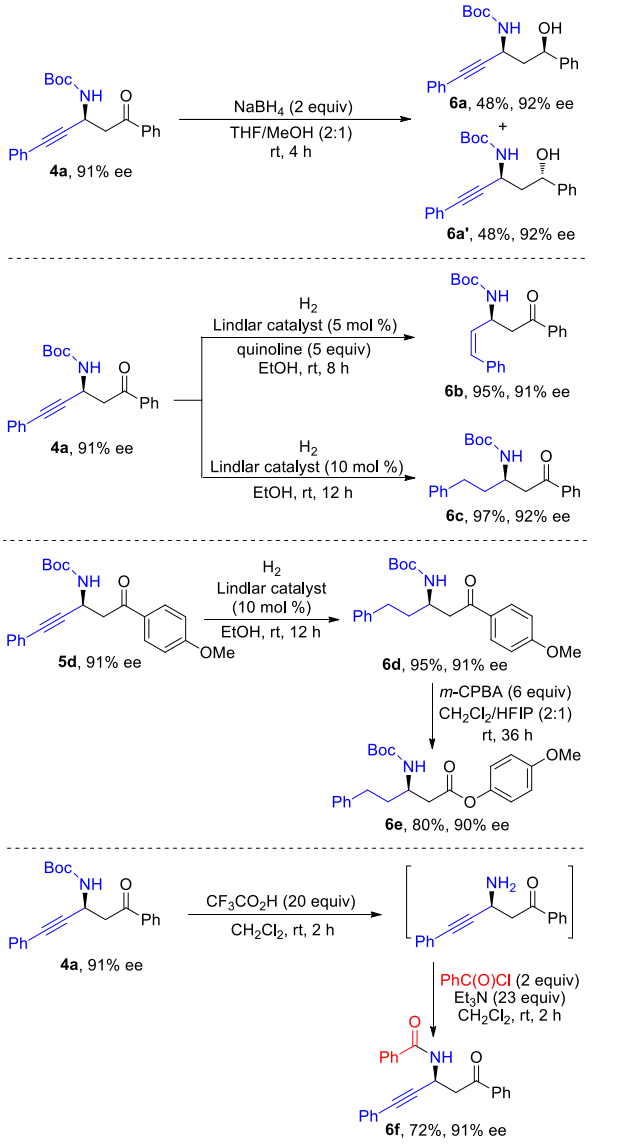


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), CPA (*S*)-**3f** (5 mol %), Na_2SO_4 (50 mg), toluene (2 mL), rt, 12 h.

A myriad of electron-rich (**5a**–**5d**) and electron-deficient α-arylenamides (**5e**–**5o**) could be utilized as carbon nucleophiles, delivering the desired products in good to excellent yields (65–98%) with high enantioselectivities (86–91%). Remarkably, a series of functional groups, including iodo (**5e**), bromo (**5f**), chloro (**5g, 5h**), fluoro (**5i**–**5k**), trifluoromethyl (**5l**–**5n**), and nitro groups (**5o**), were all tolerated in the enamide substrates. Furthermore, propargylamines containing 3,4-dichlorophenyl- (**5p**), naphthyl- (**5q**), and thienyl-substituted ketone moieties (**5r**) could be accessed under this protocol. In addition, propargylamine-bearing cyclohexyl-substituted ketone moieties (**5s**) were also synthesized in 41% yield and in 78% ee.

To demonstrate the synthetic utility of the chiral β-keto propargylamine products, several transformations were conducted (Scheme 4). β-Keto propargylamine **4a** could be selectively reduced by $NaBH_4$ to generate the β-hydroxy propargylamines **6a** and **6a′** in 1:1 diastereomeric ratio. On the other hand, the alkynyl moiety of **4a** could be partially reduced to alkenyl group (**6b**) or fully reduced to alkyl group (**6c**), respectively, via different Pd-catalyzed hydrogenation processes. Likewise, β-keto propargylamine **5d** was hydrogenated to deliver the β-amino ketone **6d**, which could be further converted to the corresponding β-amino ester **6e** under the Baeyer–Villiger oxidation conditions. Furthermore, the Boc group of **4a** can be removed under acidic medium to form the primary β-keto propargylamine with a free NH_2 group in situ, which could further react with benzoyl chloride under basic conditions to afford the corresponding β-keto propargyl amide **6f**. Importantly, all chemical transformations proceeded smoothly without the loss of enantioselectivity.

Scheme 4. Synthetic Transformations of Products



To gain mechanism insights of the asymmetric reaction between *N,O*-acetals and enamides, several control experiments were carried out (Scheme 5). By employing *N*-methyl enamide in place of enamide **2a** as nucleophile, no reaction occurred to give the β-keto propargylamine **4i** (Scheme 5a), suggesting that the N–H group of enamide substrate is necessary for the CPA-assisted activation of reaction substrates.[10] Moreover, the reaction did not proceed when acetophenone was employed instead of enamide **2a** (Scheme 5b), indicating that prior hydrolysis of enamide to

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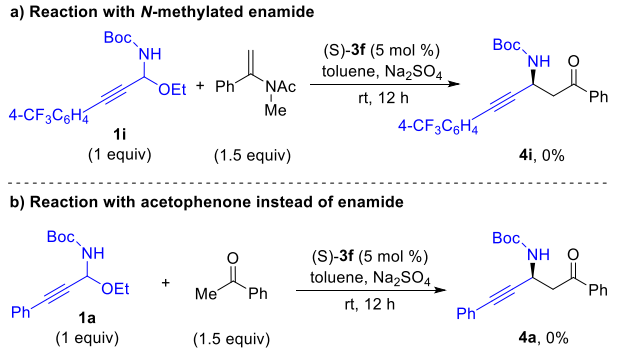
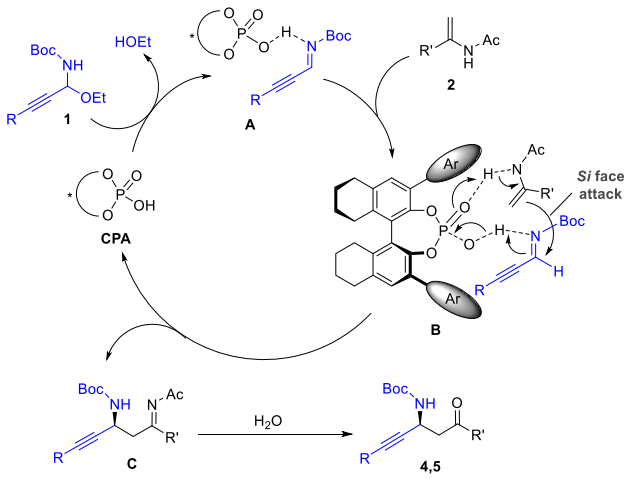
Scheme 5. Control Experiments for Mechanistic Elucidation



acetophenone as nucleophilic substrate is not involved for subsequent product formation.

On the basis of the control experiments as well as the related CPA-catalyzed reactions,[7,10] a plausible mechanism was proposed (Scheme 6). Initially, CPA catalyzes the elimination

Scheme 6. Proposed Mechanism and Transition-State Model



of ethanol from *N*,*O*-acetal **1** to form the *C*-alkynyl imine intermediate.[7a,b] Na_2SO_4 additive likely behaves as a scavenger of ethanol to promote its elimination from **1**. The OH group of CPA forms hydrogen bond with the nitrogen atom of *C*-alkynyl imine to form species **A**, enhancing the electrophilicity of imine group. Meanwhile, the nitrogen atom of enamide **2** forms hydrogen bond with the P═O bond of CPA to form species **B**, enhancing the nucleophilicity of *β*-carbon of **2**. At this point, enamide reacts with *C*-alkynyl imine via an aza-ene-like reaction pathway,[10] forming the chiral *β*-iminyl propargylamine **C** and regenerating the CPA for subsequent catalytic cycle. Finally, the hydrolysis of **C** upon water addition in the reaction workup provides the chiral *β*-keto propargylamine products **4** or **5**. Notably, the bifunctional nature of CPA allows the simultaneous activation of both *C*-alkynyl imine and enamide via the intermolecular hydrogen bondings.[7b] The chiral environment of the BINOL backbone facilitates the preferential nucleophilic attack of enamide to imine electrophile from the *Si* face, resulting in the formation of propargylamine product with (*S*)-configuration.

In conclusion, we have developed a streamlined and general method to prepare chiral *β*-keto propargylamines bearing single stereogenic centers in high yields (up to 98%) with high enantioselectivities (up to 95% ee). A wide range of readily available *C*-alkynyl *N*-Boc *N*,*O* acetals and enamides can be utilized as reaction substrates. The derivatizations of propargylamine products are accessible via various transformations. An aza-ene-type reaction mechanism is proposed, involving the cooperative activation of both *C*-alkynyl imine and enamide by chiral phosphoric acid via the hydrogen-bonding interaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03181.

Experimental details and spectral data of all the new compounds and HPLC analytical results (PDF)

Accession Codes

CCDC 1948170−1948171 contain 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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