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Organocatalytic Enantioselective Conjugate Alkynylation of β-Aminoenones: Access to Chiral β-Alkynyl-β-Amino Carbonyl Derivatives

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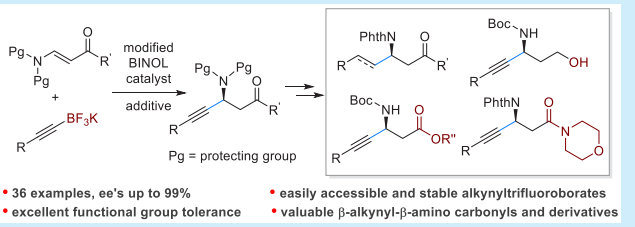
ABSTRACT: Readily available potassium alkynyltrifluoroborates were used for organocatalytic asymmetric conjugate alkynylation of β-enaminones. The interception of a modified binaphthol catalyst and in situ generated organodifluoroboranes proved important to access functionalized β-alkynyl-β-amino carbonyls and derivatives with improved chemo-reactivity and enantio-induction. Mechanistic studies revealed the impact of molecular sieves on efficiency and stereocontrol. The products undergo additional functionalization to yield a diverse set of valuable β-alkynyl-β-amino carbonyl scaffolds.



Chiral β-alkynyl-β-amino carbonyls constitute a special class of α-substituted propargyl amines[1] that are required for the preparation of biologically active natural products and pharmaceutically important compounds, such as xemilofiban[2] and the GpIIb/IIIa antagonist FR184764.[3] While the prevailing strategy relies on the diastereoselective addition of Reformatsky-type reagents to imines using stoichiometric amounts of chiral auxiliaries,[4] only few attempts have successfully accessed chiral β-alkynyl-β-amino carbonyls through asymmetric catalysis (Scheme 1a). Several efforts have been made to carry out the asymmetric Mannich reaction of C-alkynyl imines[5] or their precursors[6] with enolates or enolizable carbonyl compounds or transition-metal-catalyzed alkynylation of imines;[7] however, challenges related to substrate generality and functional group tolerance have not been effectively addressed.[5−7] In this respect, an asymmetric catalytic assembly that allows the construction of functionalized β-alkynyl-β-amino carbonyls and derivatives remains an important unmet challenge.

β-Amino α,β-unsaturated carbonyl substrates[8,9] allow privileged access to chiral β-substituted β-amino ketone derivatives. Pioneering work by Sibi[9e,f] et al. and Hayashi[9g] et al. highlighted the use of organomagnesium amides and arylboronic acids to achieve high levels of stereocontrol in the metal-catalyzed 1,4-addition of β-dehydroamino esters (Scheme 1b). The major obstacle is represented by the deamination process, which leads to the formation of undesired β-substituted β-carbonyl products.[10] Moreover, no attempts have been made to catalyze asymmetric conjugate addition of alkynyl nucleophiles to the corresponding precursors.

The enantioselective organocatalytic conjugate addition of organoboron nucleophiles has emerged as a valuable means of stereoselective C−C bond construction.[11−16] The first organocatalytic enantioselective conjugate addition of alkynylboronic esters by Chong and co-workers[12a,b] provided a unique opportunity to selectively introduce alkynyl substituents into the β-position of α,β-unsaturated enones. The main limitation of this approach, however, is the high sensitivity of alkynylboronic esters toward nucleophilic compounds, air, and moisture.

To address the aforementioned challenges, we hypothesized that an efficient binaphthol could catalyze the enantioselective conjugate addition of stable alkynylborate nucleophiles using *N*-phthaloyl-β-enaminones as potential precursors, thus facilitating the generation of optically enriched β-alkynyl-β-amino carbonyls. Potassium alkynyltrifluoroborate and its derivatives are attractive owing to the elevated tolerance of their functional groups, ease of access, and convenient handling.[17,18] In situ generation of highly reactive organodifluoroboranes from alkynyltrifluoroborates[19] hinders the ability to directly control substrate interception in a stereoselective manner, in contrast to the more controllable, but slower, reactivity of achiral alkynylboronates.[12a,c] In this context, we report the identification of efficient bisphenol catalysts and additives that enabled enantioselective conjugate alkynylation of potassium trifluoroborates to β-enaminones and delivered highly functionalized β-alkynyl-β-amino carbonyl scaffolds with excellent enantioselectivities (Scheme 1c). Additionally, acylimidazole and benzoyl moieties incorporated into the propargyl amide framework served as versatile handles for further trans-

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Scheme 1. Enantioselective Synthesis of *β*-Alkynyl-*β*-amino Carbonyls via Asymmetric Catalysis

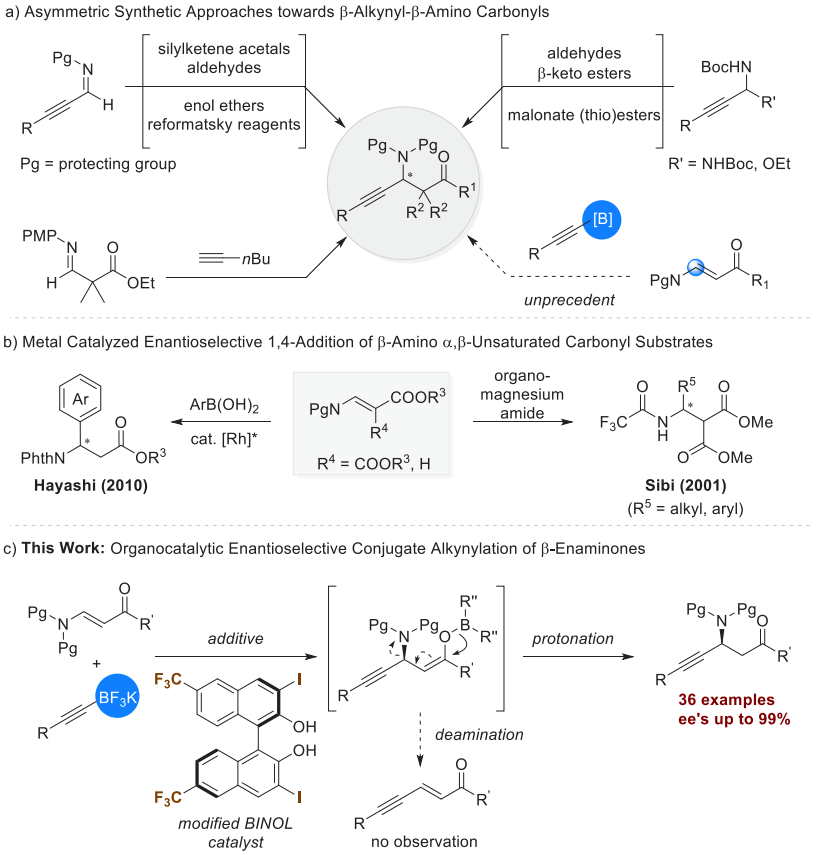
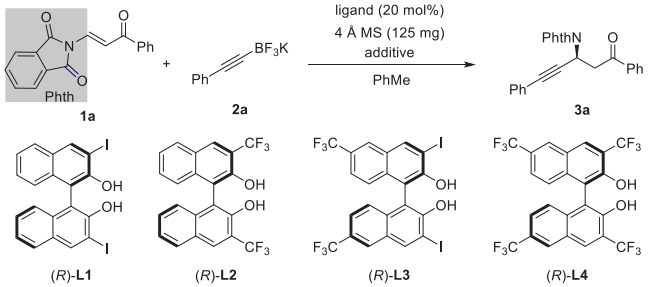


Table 1. Selected Optimization Strategies[a]



entry	ligand	additive	T (°C)	t (h)	yield[b] (%)	ee[c] (%)
1	(*R*)-**L1**	none	80	12		
2	(*R*)-**L1**	$BF_3{\cdot}Et_2O$	rt	2	87	41
3	(*R*)-**L1**	$BF_3{\cdot}Et_2O$	−35	10	90	86
4	(*R*)-**L2**	$BF_3{\cdot}Et_2O$	−35	10	89	82
5	(*R*)-**L3**	$BF_3{\cdot}Et_2O$	−35	7	93	91
6	(*R*)-**L4**	$BF_3{\cdot}Et_2O$	−35	7	92	91
7[d]	(*R*)-**L3**	$BF_3{\cdot}Et_2O$	−35	9	92	92
8[e]	(*R*)-**L3**	$BF_3{\cdot}Et_2O$	−35	2	94	88
9[d,f]	(*R*)-**L3**	LiBr	35	5	95	84
10[d,g]	(*R*)-**L3**	LiI	35	24	70	80

[a]The standard reaction was carried out using **1a** (0.1 mmol, 1.0 equiv), **2a** (0.3 mmol, 3.0 equiv), 4 Å molecular sieves (MS) (125 mg), $BF_3{\cdot}Et_2O$ (1.0 equiv), and catalyst (20 mol %) in PhMe (2.0 mL), unless otherwise noted. [b]Yields refer to isolated products. [c]Enantiomeric excess (ee) was determined by chiral HPLC analysis. Absolute stereochemistry was assigned by correlation. [d]**2a** (2.0 equiv). [e]The reaction was conducted using 1.0 mmol of **1a**. [f]LiBr (3.0 equiv). [g]LiI (3.0 equiv). rt = room temperature.

formations, leading to the formation of *β*-alkynyl-*β*-amino esters and derivatives.

Our investigation began by reacting *β*-enaminone **1a** with potassium alkynyltrifluoroborate **2a** in the presence of 4 Å molecular sieves (MS) at a moderately elevated temperature of 80 °C (Table 1, entry 1). Although zeolite-based sieves affect fluoride dissociation,[15c] we speculated that the reactivity of potassium alkynyltrifluoroborate **2a** would be further enhanced in the presence of Lewis acid, which would speed up difluoroalkynylborane formation.[19] Indeed, an equimolar amount of $BF_3{\cdot}Et_2O$ along with 4 Å MS resulted in a significant rate enhancement and moderate enantioselectivity (41% ee). The low level of enantioinduction was likely due to spurious additions, suggesting that competing pathways involving difluoroalkynylborane addition prevailed over the anticipated asymmetric alkynylation. Optimization revealed that 3,3′,6,6′-$(CF_3)_4$-BINOL ((*R*)-**L3**) was an effective catalyst, with a slightly better result (92% yield and 92% ee) (Table 1, entry 7). Conjugate addition could be scaled up 10 times with only a slight decrease in enantioselectivity (Table 1, entry 8). Substituting $BF_3{\cdot}Et_2O$ with lithium salts promoted the reaction efficiency, with reduced enantioselectivity (Table 1, entries 9 and 10). It is noteworthy that the additive selected markedly influenced both yield and stereoselectivity during enantioselective conjugate addition.

As depicted in Scheme 2, the scope of potassium alkynyltrifluoroborates was explored using *N*-phthaloyl *β*-enaminone **1a**. A number of halogen-substituted (**3b**−**d**) and trifluoromethylated benzenetrifluoroborates (**3e**) generated alkynylated products with excellent yields and enantioselectivities. Reactions with *o*-methoxy-, *p*-methoxy-, and 2-naphthyl-

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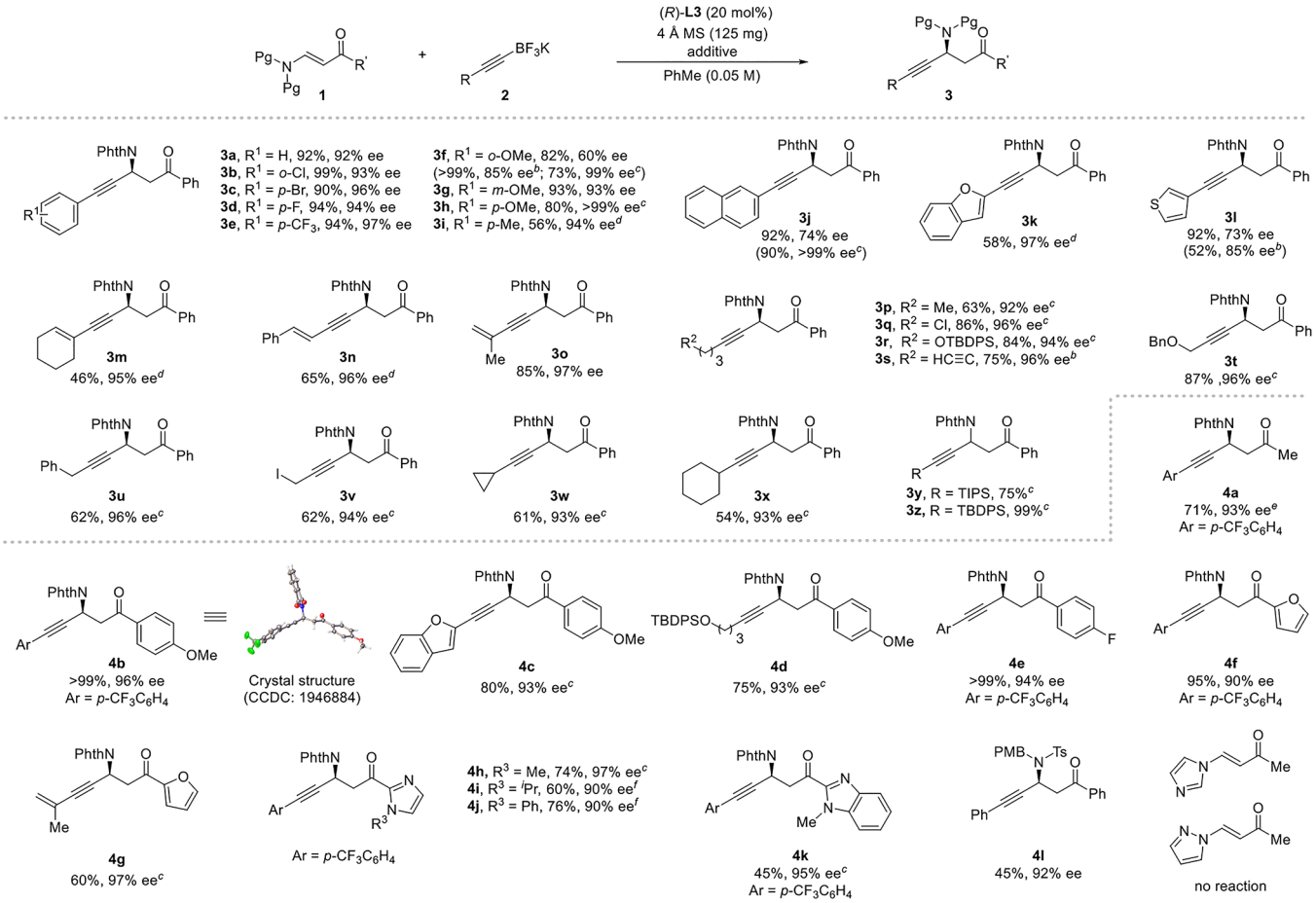
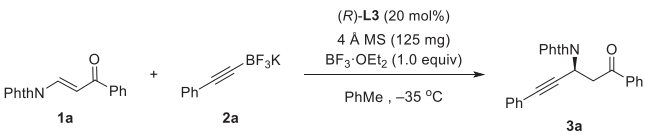
Scheme 2. Application of Potassium Alkynyltrifluoroborates for Enantioselective Conjugate Alkynylation of β-Enaminones[a]



[a]Unless otherwise noted, reactions were run under the following conditions: **1a** (0.1 mmol, 1.0 equiv), **2** (0.2 mmol, 2.0 equiv), (*R*)-**L3** (20 mol %), 4 Å MS (125 mg), $BF_3{\cdot}Et_2O$ (1.0 equiv), toluene (2.0 mL), −35 °C. Yields refer to isolated products. Enantiomeric excess (ee) was determined by chiral HPLC analysis. Absolute stereochemistry was assigned by correlation. [b]LiBr (3.0 equiv), 35 °C. [c]LiI (3.0 equiv), 35 °C. [d]Without $BF_3{\cdot}Et_2O$, 60 °C [e]Reaction run at 0 °C. [f]LiI (3.0 equiv), 60 °C.

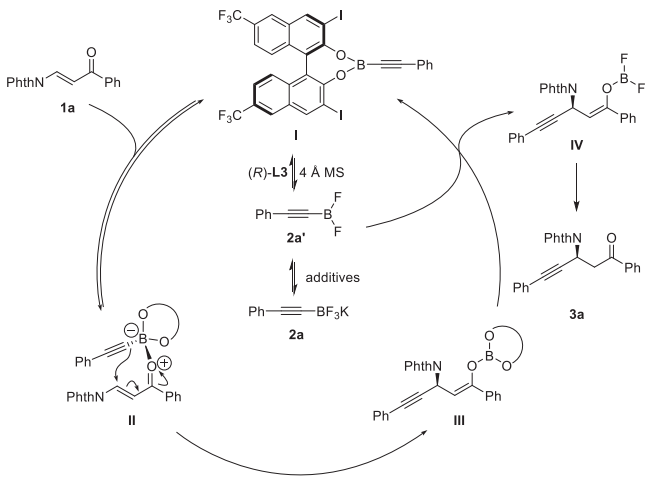
Table 2. Control Experiments



entry	deviation from standard conditions	*t* (h)	yield[a] (%)	ee[b] (%)
1	none	9	92	92
2	diisopropyl (phenylethynyl)boronate instead of **2a**	24	0	
3	no (*R*)-**L3**	2	85	0
4	no $BF_3{\cdot}OEt_2$	12	0	
5	no 4 Å MS	12	90	24

[a]Yields refer to isolated products. [b]Enantiomeric excess (ee) determined by chiral HPLC analysis.

Scheme 3. Proposed Catalytic Cycle



substituted trifluoroborates yielded alkynylation products **3f**, **3h**, and **3j**, respectively, with lower asymmetric induction. Significant improvements in enantioselectivity were achieved at ambient temperature when the additive was switched from $BF_3{\cdot}Et_2O$ to LiI. Alkynylation could be readily achieved only in the presence of 4 Å MS, efficiently delivering products **3i** and **3k**, with comparable yields and selectivities. The use of LiBr as a promoter has been previously demonstrated by the successful conversion of 3-thienyl-substituted trifluoroborate, although a slight decrease in enantioselectivity was observed.[15c,20]

Alkynyltrifluoroborates bearing conjugated enynes proved to be viable nucleophiles for generating the desired products with 95−97% ee (**3m**−**o**). A number of alkynyltrifluoroborates substituted with an acyclic hydrocarbon chain, including alkyl

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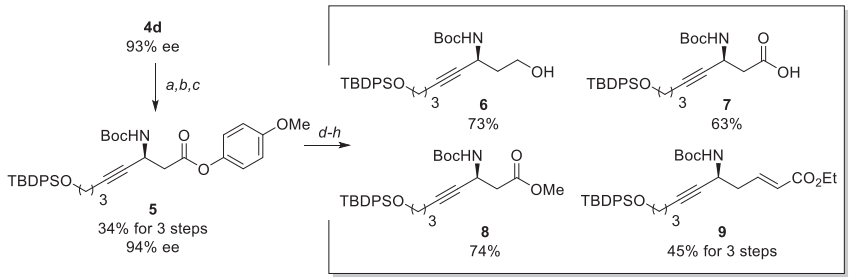
Scheme 4. Enantioselective Synthesis of β-Alkynyl-β-Amino Ester and Derivatives



[a]$H_2N(CH_2)_2OH$ in EtOAc. [b]Boc_2O, Et_3N in CH_2Cl_2. [c]$NaHCO_3$, *m*-CPBA in CH_2Cl_2. [d]$LiBH_4$ in MeOH. [e]KOH in THF/H_2O = 3:1. [f]KOH in MeOH. [g]DIBAL-H in PhMe. [h]Ph_3P = $CHCO_2Et$ in CH_2Cl_2.

halide, silyl ether, alkyne, benzyl ether, and benzylic methylene, were all compatible with the reaction conditions, as demonstrated by the alkynylation products **3p**−**u**. Alkynylation by **2** bearing a tosylate proceeded smoothly, although product **3v** resulted from a concomitant S_N2 displacement of tosylate by iodide in the presence of iodonium salt. Similarly, the reaction with cycloalkyl-substituted trifluoroborates resulted in alkynylated products **3w** and **3x**, with moderate yields and excellent selectivities. Crucially, selection of an appropriate fluoride-abstracting agent overcame the shortcomings resulting from the different reactivities of potassium alkynyltrifluoroborates. We also studied the application of silyl-substituted alkynyltrifluoroborates; however, only racemic products **3y** and **3z** were obtained. It seems that a facile uncatalyzed background reaction proceeded without participation of the chiral ligand, thereby impeding efficient enantioselective control in the conjugate alkynylation (see the SI for details).[4b]

Next, a collection of β-enaminone substrates was investigated. Either a methyl group or different substituted aromatics attached to the carbonyl carbon of the β-enaminone were well tolerated, allowing for high efficiency and stereoselectivity (Scheme 2, **4a**−**e**).[21] Importantly, the heteroaryl-derived substrates were compatible with organoborate salts, enabling the formation of alkynylation products, with good results (**4f**−**k**). The enantiodiscrimination of furan-derived substrate remained excellent, although different additives were required for the formation of compounds **4f** and **4g**. We were attracted to the use of acyl imidazoles as ester surrogates along with their tunability to control yield and selectivity.[22] *N*-Methylimidazole led to the production of the 1,4-adduct **4h**, with 70% yield and 97% ee. *N*-Substitution in the imidazole core achieved full conversion, albeit with a slight decrease in stereoselectivity (**4i** and **4j**). Replacement of the acylimidazole fragment with *N*-methylbenzimidazole resulted in a lower yield (45%), but the high enantioselectivity (95% ee) remained unchanged. Interestingly, catalytic transformation with *para*-methoxybenzyl-protected enesulfonamide resulted in product **4l**, with 45% yield and 92% ee. In contrast, reaction of the substrates with the imidazolyl or pyrazolyl groups instead of the *N*-phthaloyl moiety did not result in the expected products.

A series of control experiments were carried out to provide insight into the exact role of the additive (Table 2). Alkynylboronate was unreactive toward β-enaminone **1a** under control conditions (Table 2, entry 2). The omission of ligand resulted in full conversion even at lower temperatures, indicating a strong background reaction. Product **3a** was not observed in the absence of $BF_3{\cdot}Et_2O$, clearly demonstrating its requirement for the conversion (Table 2, entry 4). However, the reaction yielded the desired product in low enantiomeric excess even in the absence of 4 Å MS (Table 2, entry 5). We hypothesized that controlled release of binaphthyl alkynylboronate intermediates could be achieved by the addition of MS to maintain a low concentration of difluoroalkynylborane and thus inhibit the background reaction. This idea was supported by ^1H NMR spectroscopic findings at −30 °C in d_8-toluene (for details, see the SI). In the reaction of **2a** and $BF_3{\cdot}Et_2O$ along with ligand (*R*)-**L3**, difluoroalkynylborane was generated, and resonance at 5.26 ppm was assigned to the hydroxyl group of the ligand.[13a] Subsequent addition of 4 Å MS led to the formation of new species corresponding to binaphthyl alkynylboronate complex.

A possible reaction pathway is proposed in Scheme 3. In accordance with prior studies,[23] the precomplexation step involving the mixing of potassium phenyltrifluoroborate and $BF_3{\cdot}Et_2O$ resulted in the formation of phenyldifluoroborane **2a′** and its corresponding etherate after the consumption of $BF_3{\cdot}Et_2O$. Transesterification of **2a′** with ligand (*R*)-**L3** produces more reactive binaphthyl-derived alkynylboronate **I**. This reaction is accelerated by the addition of MS, as suggested by the fact that their omission led to significant loss of stereoselectivity. The ligated enolate **III** is generated where the alkyne group is attached to the β-enaminone **1a** in a conjugate fashion, presumably activated by coordination to the boron center through a six-member transition state. Exchange of ligands with phenyldifluoroborane regenerates the chiral alkynylboronate **I**, producing the difluoroboron enolate **IV**. Finally, formation of product **3a** is achieved by the protonation of **IV**.

The synthetic utilities of this practical method were demonstrated by subsequent derivatizations of the products bearing the alkyne moiety and the acyl imidazole motif (for details, see the SI). Replacement of *N*-phthalimide with a *tert*-butyloxycarbonyl (Boc) group followed by Baeyer−Villiger oxidation generated the densely functionalized phenyl ester **5**, with 34% yield and 94% ee, in three steps (Scheme 4). Attempts to reduce ester **5** led to the formation of 1,3-amino alcohol **6**. The enantioenriched β-alkynyl-β-amino acid **7** was obtained with 63% yield through base-catalyzed hydrolysis of the phenyl ester. Exposure of ester **5** to potassium hydroxide in methanol enabled its transesterification into product **8**, with 63% yield. Functionalization with an additional α,β-unsaturated ester was successfully completed in the form of α-substituted propargyl amine **9** via reduction of diisobutylaluminum hydride and treatment with Wittig reagent.[6e]

In summary, for the first time, we successfully achieved organocatalytic enantioselective conjugate alkynylation of β-

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enaminones with potassium alkynyltrifluoroborates. The process offers a novel approach for synthesizing optically active β-alkynyl-β-amino carbonyls. The possible mechanism of action was explored on the basis of experimental observations and ^{1}H NMR studies, which pointed to the important role of MS. Subsequent functionalization of adducts proved their widespread utility for the synthesis of enantioenriched β-alkynyl-β-amino carbonyl derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02394.

Full experimental details, characterization data, and copies of ^{1}H and ^{13}C spectra and HRMS data for all products; X-ray structures and data for **4b** (PDF)

Accession Codes

CCDC 1946884 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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