OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Asymmetric Organocatalytic Synthesis of 2,3-Allenamides from Hydrogen-Bond-Stabilized Enynamides

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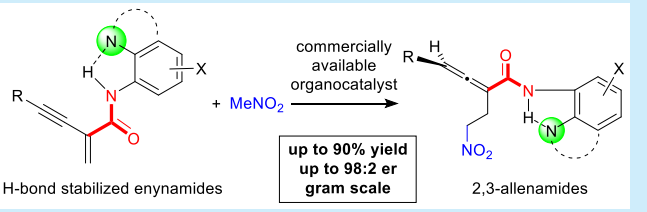
Supporting Information

ABSTRACT: Asymmetric catalytic synthesis of 2,3-allenamides from hydrogen-bond-stabilized enynamides in the presence of quinine-based bifunctional squaramide organocatalysts is described. This protocol forms a variety of 2,3-allenamides in high yields and excellent stereoselectivities, in which the elaborated introduction of intramolecular H-bonds within the *N*,*N*-bidentate amide group constitutes one of the keys to this highly enantioselective transformation. The synthetic practicality of this reaction has been demonstrated by the axis-to-center chirality transfer of allenamides to furnish enantiomerically enriched building blocks.



Allenes featuring two perpendicular cumulated carbon−carbon double bonds consist of one class of structurally unique molecules in organic chemistry, and importantly the allene units are widely distributed in natural products, pharmaceuticals, and functional materials.[1] Chiral allenes are highly useful building blocks in organic synthesis and are even designed as ligands/catalysts.[2] Accordingly, the asymmetric synthesis of multisubstituted allenes has received significant research interest. Classical approaches mostly rely on the resolution of preformed racemic allenes and chirality transfer from enantiomerically enriched propargylic alcohols or amine derivatives.[3] Recently, some progress has been made in catalyst-controlled stereoselective synthesis of functionalized allenes from achiral precursors based on metal catalysis and organocatalysis.[4]

As functionalized allenes, chiral 2,3-allenyl carbonyl derivatives are important subsets that have a myriad of applications.[1−4] However, catalytic synthesis of these compounds is rarely reported. Since Hayashi pioneered a metal-catalyzed 1,4-addition to enynes for the synthesis of chiral allenes and Tang subsequently developed an enantioselective organic-catalyst-promoted intramolecular reaction, the 1,4-addition for the preparation of allenes has made great progress.[5] In this context, the asymmetric 1,4-addition of nucleophiles to conjugated enyne−carbonyl compounds has become one of the most efficient approaches to generate allenyl−carbonyl compounds (Scheme 1). In 2013, Zhang and Sun first reported a quinoline thiourea-catalyzed enantioselective 1,4-addition of nitroalkanes to activated enynes for the direct preparation of 2,3-allenoates.[6] In 2016, Feng and Liu reported a highly efficient asymmetric 1,4-conjugate addition of malonic esters to enynes with the assistance of an *N*,*N*′-dioxide/scandium(III) complex, affording 2,3-allenyl ketones.[7] Very recently, Jørgensen presented a prolinol silyl ether promoted either aldehyde or α,β-unsaturated aldehyde addition to alkynyl-substituted enones to yield chiral 2,3-allenic ketones.[8]

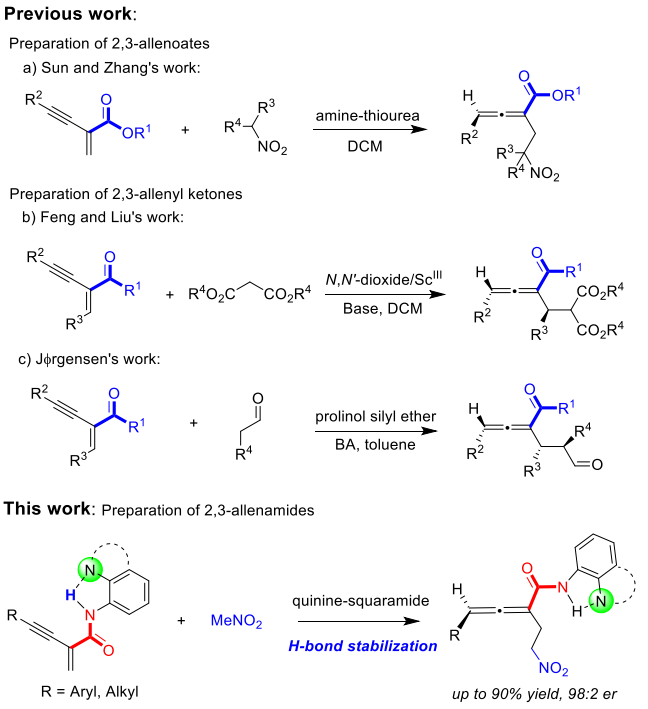
However, as a nontrivial extension of these elegant works, the catalytic 1,4-addition for asymmetric construction of 2,3-allenamides remains elusive and unreported. Chiral allenamides are attractive intermediates for the construction of multisubstituted azo-compounds and other interesting structures.[4l,9,16] In this study, we present an effective methodology for the direct asymmetric catalytic synthesis of 2,3-allenamides from newly designed hydrogen-bond-stabilized enynamides in combination with squaramide bifunctional catalysis.

Inspired by the pioneering asymmetric Michael addition/isomerization reaction for the synthesis of 2,3-allenoates,[6] we originally envisioned that it might be possible to generate chiral 2,3-allenamides by the cascade 1,4-addition/isomerization reaction of nitromethane to enynamides by applying bifunctional organocatalysis. In our initial experiments, only 1,4-addition products were detected when *N*,*N*-disubstituted enynamides were employed (**1ab** and **1ac**) (Scheme 2, eq 1).

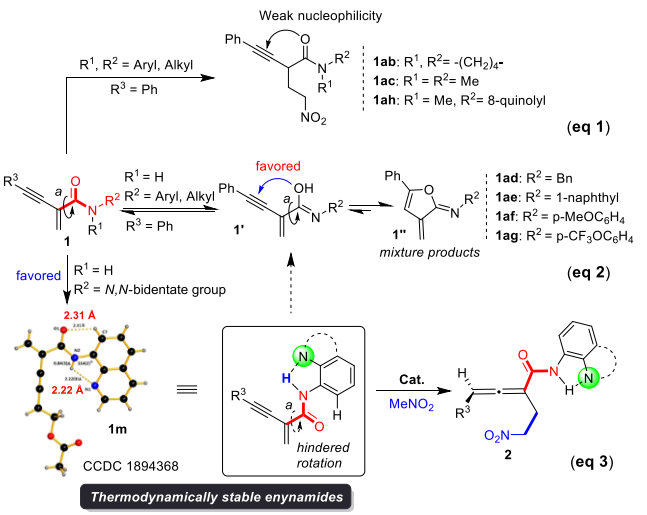
Received: March 7, 2019

DOI: 10.1021/acs.orglett.9b00839
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Catalytic Asymmetric 1,4-Addition for the Synthesis of Allenes



Scheme 2. Preliminary Experiment and Our Design



This result was presumably because of the inertia and rigidity of amide derivatives so that the 1,4-addition products could not isomerize to allenes.[10] *N*-Alkyl and different electronic *N*-aryl-substituted enynamides were more reactive but unstable. The isolation of a pure such enynamide was complicated by its decomposition during silica gel chromatography or concentration and led to the presence of various byproducts, for instance, the cyclization products obtained through the nucleophilic attack of enol/enolate oxygen to the alkyne moiety (**1ad**−**1ag**) (Scheme 2, eq 2).[11] Although the desired allene was not obtained, this result inspired us that the allenamide might be synthesized from stabilized enynamide. The enynamide might be stabilized by the regulation of its molecular conformation and increased the barrier to rotation of the C−C bond *a*, so that the nucleophilic attack of the oxygen atom was unfavored. Based on our previous research about the *N*-quinolone amide,[12] this hypothesis might be achieved with *N*-quinolone enynamides as the substrate due to the interaction of its intramolecular H-bonds (Scheme 2, eq 3).[13] This assumption was indeed supported by the H-bonds (N−H···N and C−H···O) and approximately plane conformation of enyamide **1m** observed in the X-ray crystal structure (see SI), in which the oxygen and alkynyl group were on the opposite side of the C−C single bond *a*. These H-bonds would not only reduce the nucleophilicity of the oxygen atom but also make the conformation of enynamides **1** unfavored for the nucleophilic attack of the oxygen. Moreover, the intramolecular H-bonds might also intervene in the interaction between the substrate and catalyst, according to previous reports.[14]

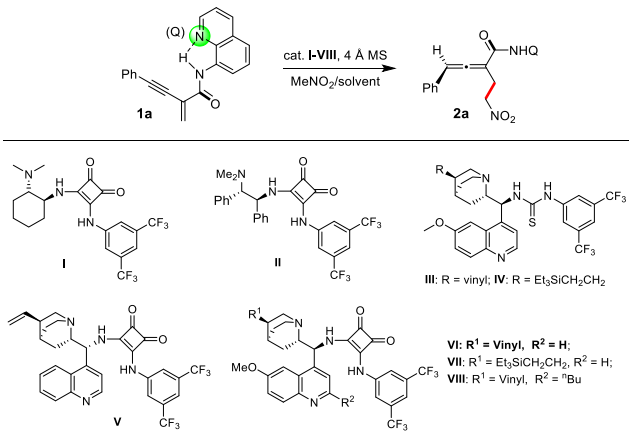
Fortunately, the desired allene product **2a** was unambiguously obtained with *N*-quinolone enynamide **1a** as the substrate. Furthermore, the *N*-methyl-*N*-quinolone enynamide **1ah** was proven to be unstable when we attempted to prepare it (Scheme 2, eq 1). This result confirmed the stabilization effect of H-bonds. Employing bifunctional amine-thiourea or squaramides as the organocatalyst, we quickly identified **VI** as the best catalyst, which furnished product **2a** in high yield and excellent enantioselectivity (Table 1, entries 1−6). Notably, the thiourea catalyst **IV**, which had excellent performance in addition/isomerization synthesis of allenoates, afforded only 70:30 er (entry 4).[6] Further modifications of the catalyst structure offered no improvement (entries 7 and 8).[15] Assessment of the solvents identified *o*-xylene, which gave the product in an enhanced 75% yield and 98:2 er (entries 9−12). Finally, evaluation of the temperature and the ratio of $MeNO_2$/*o*-xylene did not improve the reaction results (entries 13−16).

With the optimized procedure in hand, we turned our attention to examining the reaction scopes (Scheme 3). Different aryl substitutions on the triple bond of enyne amides were first studied. The substituents on the aromatic ring were tolerated well, giving corresponding allenamides with moderate to high yields. The electronic nature had little effect on the enantioselective. Enynamides with an electron-rich methoxy or tertiary butyl group gave the product **2** in similar or slightly higher er than those with electron-deficient groups (F, Cl). 2-Naphthyl (**2i**) and heteroarenes, 3-thienyl (**2j**) and 2-thienyl (**2k**), did not hinder the reaction and furnished the desired allenes **2** in moderate yields and high optical purities. The lower yield for **2k** could be ascribed to the instability of the 2-thienyl enyne amide **1k**. Encouraged by the successful synthesis of chiral aryl-substituted allenamides, this methodology was applied to alkyl-substituted starting materials. Gratifyingly, enyne amides bearing alkyl groups with different steric and electronic properties were also applicable (**2l**, **2m**, and **2n**).

To further confirm the stabilization of the intramolecular hydrogen bonds, the focus was switched to other *N*-aryl eneynamides containing intramolecular hydrogen bonds. As expected, the corresponding products **2** were afforded in high yields and excellent enantiomeric excess (**2o** and **2p**). This result highlighted the stabilization and facilitation effect of H-bonds in our 1,4-addition/isomerization reaction for asymmetric synthesis of 2,3-allenamides. In addition to nitromethane, nitrocyclopentane was examined as the nucleophile under optimized reaction conditions (**2q**). The reaction can also proceed with comparable yield but diminished enantio-

DOI: 10.1021/acs.orglett.9b00839
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Condition Optimization[a]



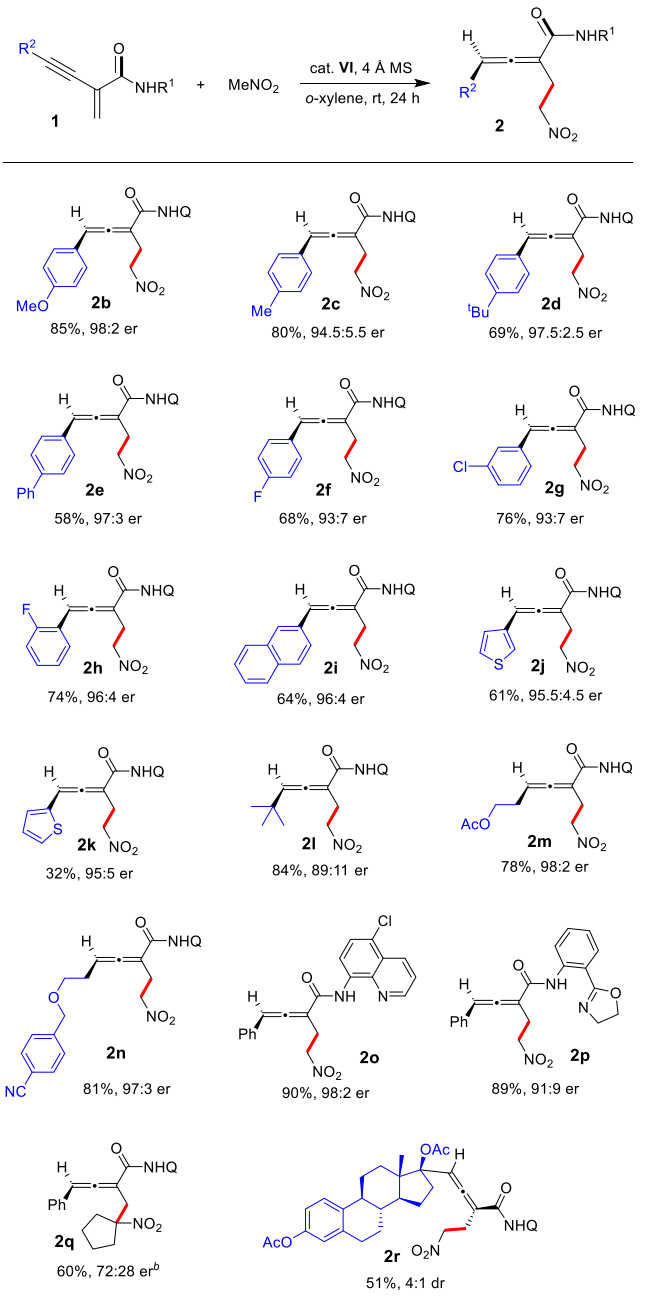
entry	conditions	yield (%)[b]	er (%)[c]
1	**I**, DCE, rt	63	87.5:12.5
2	**II**, DCE, rt	43	25.5:74.5
3	**III**, DCE, rt	50	77.5:22.5
4	**IV**, DCE, rt	68	70:30
5	**V**, DCE, rt	53	8.5:91.5
6	**VI**, DCE, rt	73	97:3
7	**VII**, DCE, rt	43	91.5:8.5
8	**VIII**, DCE, rt	60	91:9
9	**VI**, toluene, rt	80	97:3
10	**VI**, MeCN, rt	72	94:6
11	**VI**, THF, rt	65	95.5:4.5
12	**VI**, ***o*-xylene, rt**	**75**	**98:2**
13	**VI**, *o*-xylene, 0 °C	58	98:2
14[d]	**VI**, *o*-xylene, rt	68	97:3
15[e]	**VI**, *o*-xylene, rt	71	96.5:3.5
16[f]	**VI**, $MeNO_2$, rt	76	96:4

[a]Reaction conditions: **1a** (0.2 mmol), 4 Å molecular sieve (MS) and organocatalyst (10 mol %) in $MeNO_2$/solvent (2.0 mL, 1:1) stirred at the indicated temperature for 24 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]*o*-Xylene/$MeNO_2$ (4:1). [e]*o*-Xylene/$MeNO_2$ (1:4). [f]Only $MeNO_2$ was used as the solvent.

selectivity (60% yield, 72:28 er). Finally, this protocol was applied to the late-stage combination of a chiral allene unit with bioactive steroids, affording **2r** in 51% yield and 4:1 dr under standard conditions, regardless of the steric hindrance introduced by the steroids. These results demonstrated the good functional group compatibility of our method and the potent bioapplication of our allenamides as imaging units.

To demonstrate the application of our method (Scheme 4), the 1,4-addition/isomerization reaction was performed on a gram scale (1.04 g, 3.5 mmol of **1a**), and product **2a** was obtained without compromising the yield (82%) or optical purity (98:2 er) (eq 1). Additionally, the resulting axially chiral allene was transformed to densely functionalized compounds with central chirality. As illustrated in Scheme 4, the Diels–Alder reaction of chiral **2a** with freshly distilled cyclopentadiene at 80 °C in toluene led to the formation of a mixture of adducts (endo:exo = 3.7:1), in which good chirality transfer was observed in both the favored endoproduct **3b** (95:5 er) and exoproduct **3b′** (96:4 er) (eq 2).[16] Finally, the chiral allenamide **2a** was submitted to a palladium-catalyzed [3 + 2] cycloaddition reaction with vinyl epoxides.[17] The resulting tetrahydrofuran **3c** bearing two vicinal quaternary stereocenters was obtained with maintained enantioselectivity

Scheme 3. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), 4 Å MS (40 mg), and **VI** (10 mol %) in $MeNO_2$/*o*-xylene (2.0 mL, 1:1) stirred at room temperature for 24 h. [b]Run with 10 equiv of nitrocyclopentane for 4 days.

(97:3 er) in high yield (80%) and good diastereoselectivity (9:1) (eq 3). These transformations of the resulting allenes into highly functionalized compounds with axial chirality being entirely converted to point chirality demonstrated that our allenamides are conceivably important chiral intermediates in organic synthesis.

A plausible reaction pathway was proposed in Scheme 5. The reaction is believed to begin with deprotonation of the nitromethane by the quinuclidine tertiary amine (**TS1**). Afterward, formation of the carbon–carbon bond between the nitrate anion and the electrophile was facilitated by the protonated catalyst through multiple hydrogen bonds. Once

DOI: 10.1021/acs.orglett.9b00839
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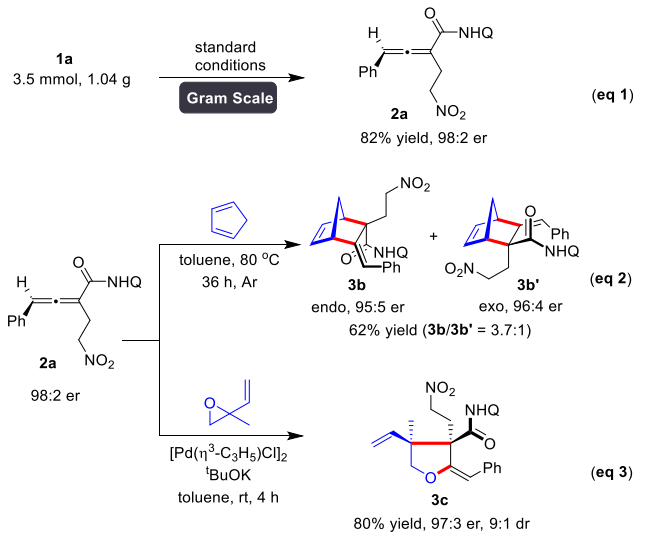
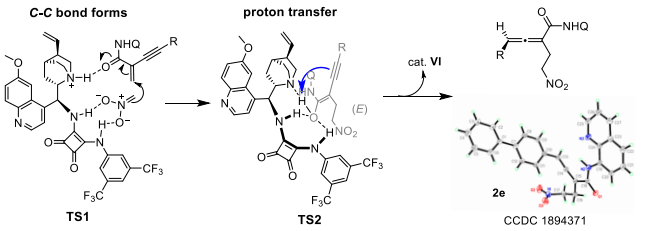
Scheme 4. Synthetic Applicability



Scheme 5. Proposed Approaching Models for the Addition and Protonation Steps



the adduct formed, the negative charge was located not in the nitro moiety but in the enol/enolate site. Thus, the H-bonds between nitryl and protonated quinuclidine weakened, and several hydrogen bonds between the quinolone moiety and enol/enolate formed. Finally, the enol/enolate intermediate was highly ordered by multiple hydrogen bonds, as shown in **TS2**, so that the front face proton transfer would deliver either directly from the conjugate acid of the catalyst or mediated by a proton-shuttle mechanism. Therefore, the configuration of the adduct was controlled by the highly ordered transition state.[6,18] This rationale is consistent with the absolute configuration (*Ra*) of product **2e** determined by X-ray crystal structural analysis (see SI).

In summary, we have developed the first enantioselective synthesis of 2,3-allenamides using a 1,4-addition/isomerization methodology from hydrogen-bond-stabilized enynamides with commercially available organocatalysts. The intramolecular hydrogen bond of enynamides plays an important role in our reaction, and the chemical versatility of thus-obtained allenes is also illustrated. Gram-scale synthesis of the product and its good axis-to-center chirality transfer demonstrated the potential practicality of our methodology. This H-bond stabilization strategy opens a door for chiral 2,3-allenamide synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00839.

Experimental procedures and characterization data of all new compounds (PDF)

Accession Codes

CCDC 1894368 and 1894371 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.

■ ACKNOWLEDGMENTS

This work was supported by the "Thousand Youth Talents Plan", NSFC (21672145 and 51733007), Shanghai Science and Technology Committee (17JC1403700), the Drug Innovation Major Project of the Ministry of Science and Technology of China (2018ZX09711001-005-002), and Shanghai Sailing Program (17YF1409000). We thank Prof. Hong-Liang Zhong (Shanghai Jiao Tong University) for helpful discussion and Dr. Ling−Ling Li (Shanghai Jiao Tong University) for assistance with X-ray diffraction and intramolecular H-bonds analysis.

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DOI: 10.1021/acs.orglett.9b00839
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