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Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes

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Supporting Information

ABSTRACT: The first efficient intermolecular addition of nitroalkanes to activated enynes for asymmetric synthesis of 2,3-allenoates is described. It is a new addition to the limited available strategies for catalytic asymmetric synthesis of allenoates. Enabled by a new bifunctional catalyst, a range of trisubstituted allenoates can be obtained in excellent chemical and optical purity. These allenoate products with a pendant 2-nitroethyl α-substituent are useful chiral building blocks.

Asymmetric synthesis is fundamentally important in organic chemistry in view of the wide applications of enantioenriched materials.[1] Over the past few decades, there has been significant progress in establishing central chirality and two-point axial chirality (e.g., BINAP). In sharp contrast, efficient generation of three-point axial chirality, such as that in allenes, has met with very limited success and still remains challenging today.[2] On the other hand, enantioenriched allenes are tremendously important not only because of their wide occurrence in natural products and biologically active compounds as well as functional materials but also due to their versatility in organic synthesis as chiral building blocks and even chiral ligands/catalysts.[3−6]

2,3-Allenoates represent a particularly useful subset of allenes with demonstrated utility.[2−5] In the past two decades, substantial efforts have been paid to the asymmetric synthesis of 2,3-allenoates. However, for a long time, successful methods were largely limited to the use of enantioenriched substrates or stoichiometric amounts of chiral promoters/auxiliaries.[7] Truly catalytic asymmetric synthesis of 2,3-allenoates has not been realized until recently.[8,9] Early examples include isomerization of alkynoates catalyzed by a chiral base (Tan and Takemoto)[8a−c] and kinetic resolution of racemic allenoates (Gong).[8d] During the preparation of our manuscript, Maruoka, Frantz, and Ma independently reported three efficient protocols: phase-transfer-catalyzed deprotonation of doubly activated allenoates followed by substitution,[8e] asymmetric β-hydride elimination of enol triflates,[8f] and asymmetric carbonylation of propargylic carbonates,[8g] respectively. Herein we report a new synthesis of trisubstituted 2,3-allenoates with bifunctional catalysis.

Catalytic synthesis of chiral electron-rich and normal allenes by metal-catalyzed enyne addition was pioneered by Hayashi.[9a−e] Tang also reported an intramolecular enyne addition for the asymmetric synthesis of bromoallenes.[9f] Recently, racemic synthesis of allenoates from activated enynes has been realized by us.[10a−c] In continuation of our effort in asymmetric allenoate synthesis,[10d] we envisioned that a stereocontrolled intermolecular nucleophilic addition to activated enynes can afford enantioenriched allenes, provided that a suitable chiral bifunctional catalyst could activate both the nucleophile and the electrophile. Our initial attempt was focused on the use of nitroalkanes as the nucleophile in view of their wide success in stereoselective nucleophilic addition reactions.[11]

We started to evaluate our hypothesis with enyne **1a**. Nitromethane was initially employed as nucleophile as well as cosolvent (Table 1). Preliminary evaluation of some chiral base catalysts, such as cinchona-based amines **Q1**−**3** and chiral guanidine **G1**,[8a] indicated that the desired allenoate **3a** could indeed be obtained in moderate yield but with good enantioselectivity when bifunctional amine-thiourea catalyst **Q3** was used (entries 1−4).[12] The reaction also gave byproduct alkynoate **4a** as a result of direct conjugate addition. Such alkynoates are common byproducts for the synthesis of allenoates, and base-catalyzed isomerization of alkynoates to allenoates has been reported.[8a−c,10d] However, it is worth mentioning that the previously reported catalyst of choice (**G1**) for such isomerization was not capable of catalyzing the present intermolecular addition reaction (entry 3), emphasizing the importance of the bifunctional nature of **Q3**. Subsequent modifications of the catalyst structure aiming at improving the reaction efficiency and enantioselectivity have been tedious. Selected results are shown (entries 4−11). Removing the methoxy group in the quinioline moiety (**Q4**) resulted in both decreased yield and diminished ratio of **3a**/**4a**. Replacing the thiourea unit by a guanidine (**Q5**) proved inferior. Tuning the electronic property of the aryl group did not improve the results (**Q6**−**7**). Replacing the thiourea moiety with a squaramide (**Q8**) resulted in decreased enantioselectivity. After considerable effort, we were pleased to find that saturation of the terminal olefin unit in the cinchona backbone can improve both chemical efficiency and stereoselectivity. Particularly, the reaction with the new catalyst **Q10**, where a silyl group was incorporated, gave both good product yield and enantioselectivity (91% ee and 84% yield, entry 11). Brief examination of other reaction parameters, such as solvent and temperature as well as cosolvent ratio, identified the best conditions (**Q10**, DCM/**2a** = 4:1, 0 °C, entry 18).

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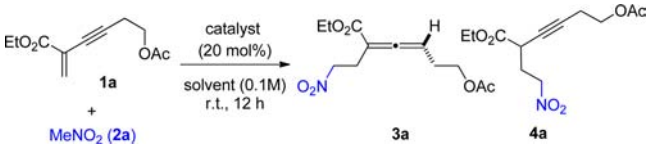
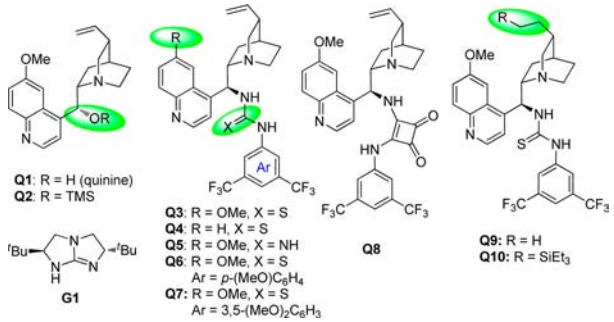
Table 1. Condition Optimization



entry	catalyst	solvent/**2a** (v/v)	yield (**3a**)[a]	ee (**3a**)[b]	**3a**/**4a**[c]
1	**Q1**		10%	−24%	2.5:1
2[d]	**Q2**		<5%	0%	–
3[d]	**G1**		<5%	–	–
4	**Q3**		36%	84%	1.3:1
5	**Q4**		24%	84%	0.8:1
6	**Q5**		17%	67%	0.3:1
7	**Q6**		42%	47%	0.8:1
8	**Q7**	DCM/**2a** (1:1)	51%	5%	6:1
9	**Q8**		60%	78%	3.0:1
10	**Q9**		53%	91%	2.3:1
11	**Q10**		84%	91%	10:1
12	**Q10**	THF/**2a** (1:1)	46%	83%	5.3:1
13	**Q10**	Et_2O/**2a** (1:1)	74%	87%	5.6:1
14	**Q10**	toluene/**2a** (1:1)	60%	88%	6.7:1
15	**Q10**	**2a** only	44%	84%	3.8:1
16	**Q10**	DCM/**2a** (4:1)	87%	90%	10:1
17	**Q10**	DCM/**2a** (9:1)	67%	91%	11:1
18[e]	**Q10**	DCM/**2a** (4:1)	89%[f]	96%	8.4:1

[a]The reaction was run with **1a** (0.1 mmol), catalyst (0.02 mmol), and solvent (1.0 mL) for 12 h. The yield was determined by GC analysis with *n*-decane as an internal standard. [b]The ee value was determined by HPLC. [c]The ratio was determined by ^{1}H NMR of the crude mixture. [d]Low conversion. [e]Run at 0 °C. [f]Isolated combined yield of **3a** and **4a**.



In order to know the possible interconversion of **3a** and **4a**, we monitored the reaction progress by GC (Figure 1). Under

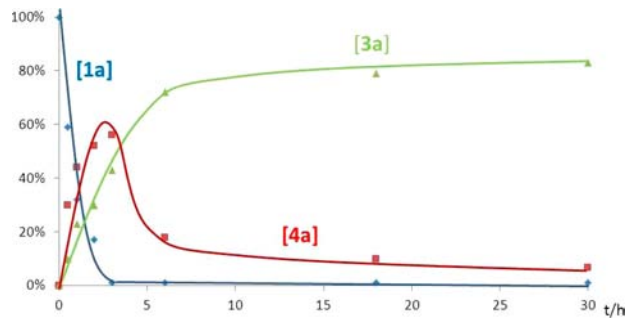
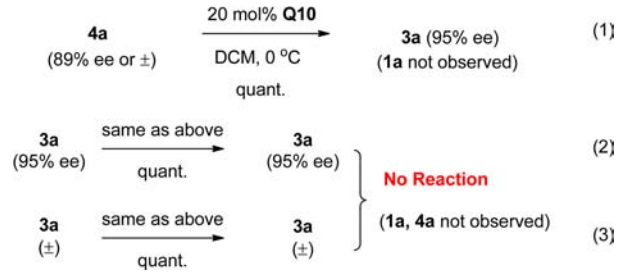


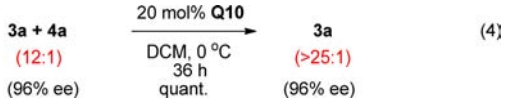
Figure 1. Reaction progress monitored by GC analysis with ndecane as the internal standard.

the standard conditions (Table 1, entry 18), the reaction reached full conversion within 5 h, producing alkynoate **4a** initially as the major product. It is obvious that **4a** was subsequently converted to allenoate **3a**. It is worth mentioning that the alkynoate **4a** was obtained in enantioenriched form, and the ee values of both **3a** and **4a** remained constant during the reaction progress (95 ± 1% ee and 90 ± 1% ee, respectively). To further probe the nature of the isomerization between **3a** and **4a**, we treated pure **3a** and **4a**, respectively, with **Q10** (20 mol %, DCM, 0 °C). As shown in eq 1, both racemic and enantioenriched **4a** could be quantitatively isomerized to allenoate **3a** with the same enantioselectivity. In contrast, **3a** remained untouched under the same conditions (eqs 2−3). Particularly noteworthy is the



unchanged optical purity of racemic **3a**, indicating the isomerization is irreversible. The failure to observe any starting **1a** in these reactions (eq 1−3) suggests that the first step (nitroalkane addition) is also irreversible. Thus, catalyst **Q10** is capable of catalyzing both the addition and the isomerization.

Inspired by the above results, we were curious about the possibility of improving the product purity (allenoate/alkynoate ratio). Thus, we subjected the isolated product mixture of **3a**/**4a** (12:1 ratio) to the isomerization conditions (eq 4). To our delight, **3a** was obtained in essentially pure form without



erosion in its optical purity. We have confirmed that this isomerization step can be retarded by the presence of nitromethane, which explains the slow and/or incomplete isomerization under the standard one-pot conditions.

With the established reaction conditions and the option to further improve the product purity by isomerization (eq 4), we next examined the reaction scope. As shown in Table 2, a wide range of enynes and nitroalkanes can participate smoothly in the efficient process to form the desired trisubstituted allenoates **3** (mostly in pure form) with excellent efficiency and enantioselectivity. Allenoates with different ester groups, such as alkyl and aryl groups with different steric and electronic properties, can all be synthesized efficiently (**3a**−**f**). Enynes with different substituents on the triple bond, including aryl and bulky alkyl groups, are suitable substrates. The mild conditions can tolerate a variety of functional groups, such as esters, mesylates, amides, ethers, nitriles, etc. In addition to nitromethane, other nitroalkanes with α-hydrogen are also excellent nucleophiles for this process (**3q**−**v**). It is worth mentioning that with a reduced catalyst loading (e.g., 10 mol %), the reaction can also proceed with comparable efficiency and enantioselectivity, except that the initially obtained **3**/**4** ratio is lower but can be enhanced by isomerization. With a reduced

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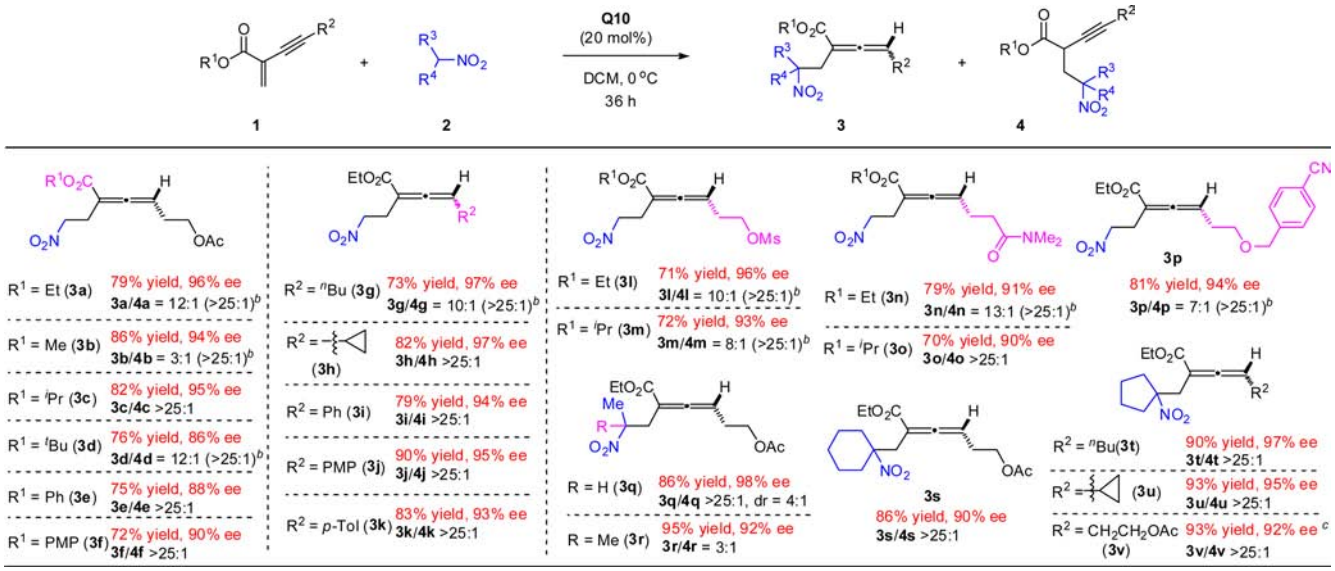
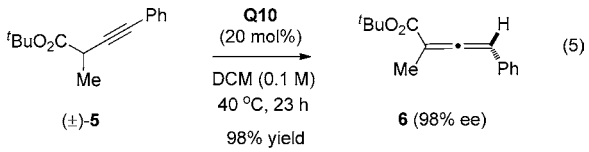
Table 2. Reaction Scope[a]



[a]The reaction was run with 0.5 mmol of enyne **1**. The loading of nitroalkane: 35 equiv for $MeNO_2$ and 9 equiv for other nitroalkanes. [b]The ratio in the parentheses is after isomerization with **Q10**, as shown in eq 4. [c]This entry has also been run with 1.2 equiv of nitroalkane. It was incomplete after 66 h. More nitroalkane (additional 1.8 equiv) was added. After additional 20 h: **3v**/**4v** >25:1, 83% yield, 94% ee.

loading of the nitroalkane, the reaction could also give comparable results, although an extended reaction time is required (Table 2, footnote for **3v**). Finally, the catalyst **Q10** used in our reaction has all been recovered in excellent yield by silica gel chromatography, and the recovered catalyst was proved to be equally effective.

To further confirm the competence of **Q10** as an excellent isomerization catalyst for enantioselective synthesis of allenoates from racemic alkynoates, we have separately synthesized racemic alkynoate **5** and tested its isomerization. As shown in eq 5, in the presence of **Q10**, the asymmetric isomerization proceeded smoothly at 40 °C to afford allenoate **6** with both excellent efficiency and enantioselectivity.[8a−c]



We have proposed two transition states to rationalize the reaction mechanism and the origin of the observed absolute stereochemistry (Figure 2). We believe that the reaction begins with deprotonation of the nitroalkane by the quinuclidine nitrogen. As shown in **TS1**, the resulting conjugate acid of the catalyst has multiple interactions with the nucleophile and electrophile: (1) the double hydrogen bonding between the thiourea moiety and the nitro anion; (2) the ammonium unit can also activate the electrophile by hydrogen bonding with the carbonyl group. Thus, this highly ordered transition state, in which both of the reaction partners are oriented by the catalyst, facilitates the C−C bond formation with a low-activation barrier. The initially formed enol/enolate intermediate is planner and achiral. Thus, the following proton shift determines the product stereochemistry. As shown in **TS2**, the planar enol intermediate is oriented by multiple hydrogen bonds so that the proton from the thiourea N−H is delivered to the front face of the γ-position to form the desired allenoate product, in which the catalyst serves as a chiral proton shuttle.[13,14] Overall, the bifunctional feature of the catalyst is not only important for lowering the activation barrier in the first C−C bond formation step but also crucial to the second stereocontrolled protonation step. The rationale is consistent with the observed product absolute stereochemistry as well as the incompetence of some monofunctional catalysts during catalyst screening.

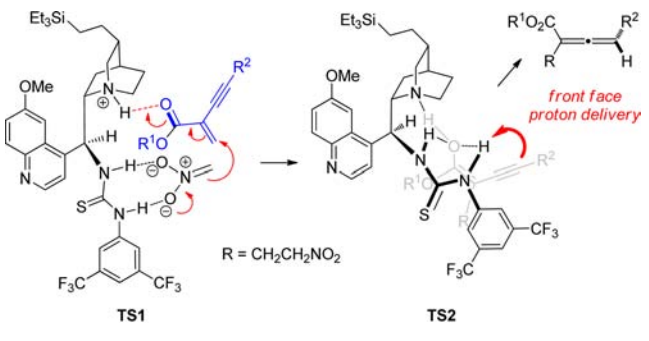
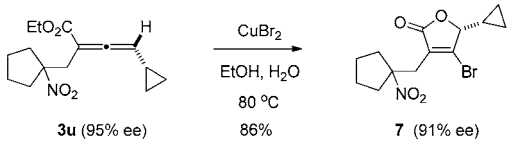


Figure 2. Plausible transition states.

We have carried out some derivatizations to demonstrate the utility of the allenoate products. For example, in the presence of $CuBr_2$ as the promoter, the enantioenriched allenoate **3u** underwent efficient cyclization to form the highly substituted lactone **7**. Particularly notable is the excellent axial-to-central chirality transfer (eq 6).[15] Additionally, nucleophilic γ-additions of allenoates have been well-explored.[16] It is also noteworthy



that the allenoates synthesized in our reaction have a 2-nitroethyl substituent at the α position, which can serve as an intramolecular nucleophile to add to the γ-position (see SI). Such allenoates have never been efficiently synthesized before, even in racemic form.

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In summary, we have developed the first intermolecular asymmetric synthesis of 2,3-allenoates by bifunctional catalysis. It is a new addition to the small family of catalytic asymmetric syntheses of allenoates without using stoichiometric amounts of chiral reagents or starting materials. Enabled by the new bifunctional catalyst, the reactions between various nitroalkanes and activated enynes proceed efficiently under mild conditions with good functional group compatibility, and these trisubstituted allenoates were mostly obtained in excellent optical as well as chemical purity (without contamination by alkynoates). The cinchona-based thiourea catalyst is crucial to the success because it not only provides a highly ordered transition state to promote the first C−C bond formation but also serves as an excellent proton shuttle in the second enantioselectivity-determining step. Moreover, it can also function as an excellent isomerization catalyst for the conversion from racemic alkynoates to highly enantioenriched allenoates. These trisubstituted allenoates with a pendant 2-nitroethyl α-substituent have been synthesized for the first time, and they are versatile synthetic intermediates toward other useful building blocks.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) Although the *Z*-enol form is depicted in **TS2**, it is reasonable to propose an *E*-enol form. However, in the *E*-enol form, the γ-position is remote to a proton (not shown), resulting in relatively slow (unfavorable) proton delivery. Overall, the equilibrium will shift towards the favored **TS2** to form the desired product.

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