Access to Allene-Containing Molecules via Enantioselective Reactions of Azolium Cumulenolate Intermediates

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Abstract: Azolium cumulenolates are a special type of intermediates in N-heterocyclic carbene catalysis. They contain elongated linear structures with three contiguous C=C bonds and sterically unhindered α-carbon. These structure features make it difficult to develop enantioselective reactions for these intermediates. Here we disclose the first carbene-catalyzed highly enantioselective addition reactions of azolium cumulenolates. The reaction starts with alkynals as the precursors for azolium cumulenolate intermediates that undergo enantioselective addition to activated ketones. From the same set of substrates, both allene and spirooxindole products can be obtained with high yields and excellent enantioselectivities. The allene moieties in our optically enriched products carry rich reactivities and can be transformed to diverse molecules. The spirooxindole scaffolds in our products are important structural motifs in natural products and medicines.

Allenes are a special class of molecules with unique reactivity patterns and have found certain presence in natural products and synthetic bioactive molecules such as medicines (Figure 1). [1, 2] For example, acalycixeniolides E is an allene-containing natural product isolated from corals of the *Acalycigorgia* species with antitumor activity.[3a] Enprostil is a medicine for the treatment of gastric and duodenal ulcers; the allenic unit in this molecule is a critical structural motif for the observed bioactivity.[3b] Allene-containing molecules have also found impressive applications as ligands for metal complexes and organic catalysts in asymmetric catalysis.[4] In chemical synthesis, the allene moiety itself is commonly used to prepare biologically-relevant heterocyclic molecules.[5] Both axial and central chiralities can be installed to these allene substrates for subsequent chiral inductions and transformations.[6] In recent years, asymmetric catalysis enabled by either transition metals[7] or organic catalysts[8, 9] have been developed to prepare allene-containing molecules. Among these approaches, the use of cumulenolate and alkynlenolate intermediates or their analogues under transition metal-free catalysis received considerable attentions.[9] Miller designed peptide-based catalysts for enantioselective reactions between allenoates and acylimines.[9a, 9b] Maruoka reported the use of chiral ammonium phase-transfer catalyst to mediate asymmetric addition of cumulenolate intermediates to imines to prepare fully substituted allenes with high optical purities.[9c] List employed chiral Brønsted acid to catalyze reaction of alkynyl-substituted ketene acetals and aldehydes to prepare chrial allenes.[9d] A number of other organic catalysts, such as guanidines and cinchona alkaloid derivatives, have also been studied for this class of reactions, as reported by Tan, Lu, Guo, and others. [9e-9j]

We're interested in designing new activation modes and asymmetric reactions by using N-heterocyclic carbene (NHC) as a key catalyst.[10] Azolium cumulenolate intermediates can be obtained by reacting alkynal derivatives with NHC catalysts, as disclosed by Sun and Wang (Figure 1b).[11a, 11b] These NHC-

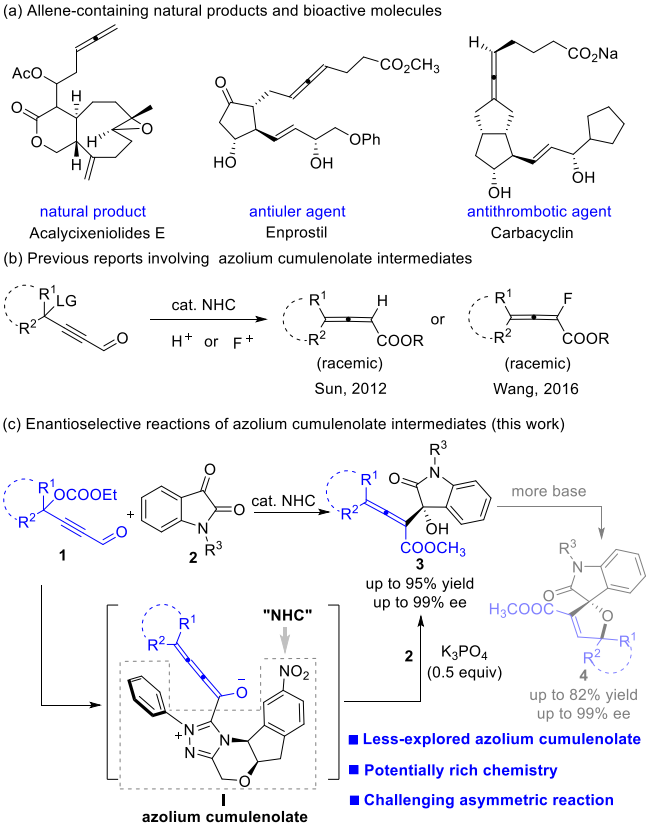

Figure 1. Allene-containing molecules and preparation via azolium cumulenolate intermediates

azolium cumulenolate intermediates bear multiple reactive sites and can in principle offer rich reactivity patterns and provide

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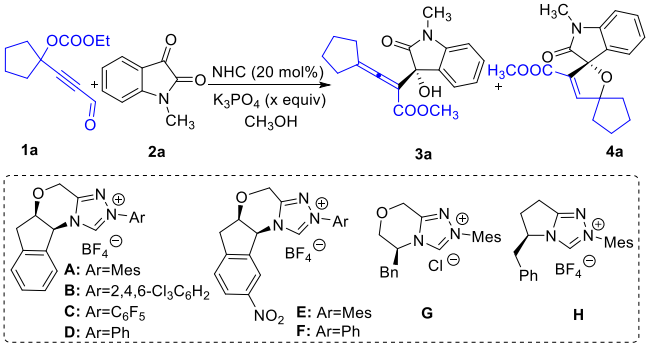
functional molecules containing allene scaffolds. Unfortunately, till to date the potentials of azolium cumulenolate intermediates remain largely undeveloped; the only two reports dealt with racemic versions.[11] The elongated linear structures with three contiguous C=C bonds (and two sp-hybridized carbons) in azolium cumulenolates pose special challenges with respect to both reactivities and stereoselectivities. The asymmetric reaction involving NHC-bounded cumulenolates remains challenging likely due to the less sterically-hindered *α*-position and the generation of mixture of *E*/*Z* isomer for cumulenolates.[11] In Maruoka's study, the cumulenolate intermediates derived from bulky di-tert-butyl allenic esters offered better enantioselectivities than those from less bulky substrates.[9c] In part inspired by this study, we envisioned that sterically hindered and highly reactive electrophiles such as activated ketones (rather than proton[11a] or fluorine reagent[11b]) can potentially react with azolium cumulenolates in a highly enantioselective manner. Here we disclose the first highly enantioselective addition of azolium cumulenolates to isatins under NHC catalysis (Figure 1c). The reaction starts with addition of a NHC catalyst to alkynal **1** to eventually form azolium cumulenolate intermediate **I**. Asymmetric addition of the α-carbon of **I** to isatin **2** furnishes the allene product **3** with regeneration of the NHC catalyst. Interestingly, these allene products could be readily converted to spirooxindole **4** by simply introducing additional bases to the same reaction mixture. We expect this study to encourage further exploration of NHC-bounded azolium cumulenolate intermediates for asymmetric reactions. The rich reactivities installed with the allene moieties[5] of our enantiomerically enriched products shall also find applications in organic synthesis.

We initiated our studies by using alkynal **1a** bearing a leaving group at *γ*-position and isatin **2a** as model substrates to search for suitable conditions, with key results summarized in Table 1. When 0.5 equivalent of K_3PO_4 was used, aminoindanol-derived precatalysts with a *N*-mesityl unit (**A**)[12] gave the desired allene product **3a** in 90% yield and 66% ee (Table1, entry 1). Replacing the *N*-mesityl unit with electron-deficient groups such as trichlorophenyl (**B**)[13] or pentafluorophenyl (**C**)[14] group, provided only trace amount of the desired product (entries 2-3). When precatalyst **D**[15] with a phenyl group was used, the allene product formed in excellent enantioselectivity, albeit with moderate yield (entry 4). In general, installing a NO_2 group on the indane moiety of the catalyst will lead to a better asymmetric control likely due to increased steric hindrance.[16] To our delight, installing a NO_2 group on the indane moiety of the precatalyst **A** (to get precatalyst **E**) [16] led to the formation of allene product in 99% yield and 92% ee (entry 5). Installing a NO_2 group on the indane moiety of the precatalyst **D** (to get precatalyst **F**)[17] resulted in decreased yield and extremely high enantioselectivity (entry 6). Futher investigation of the NHC precatalyst **G**[18] and **H**[19] could not give better results (entries 7-8). Decreasing the reaction temperature to 0 °C led to **3a** in 90% isolated yield and 96% ee (entry 9). In addition, the NHC catalyst loading could be reduced to 10 mol% with the formation of **3a** in 81% yield without loss of the enantioselectivity (entry 10). Surprisingly, we found that the use of excess amount of base (2.5 equiv) at room temperature



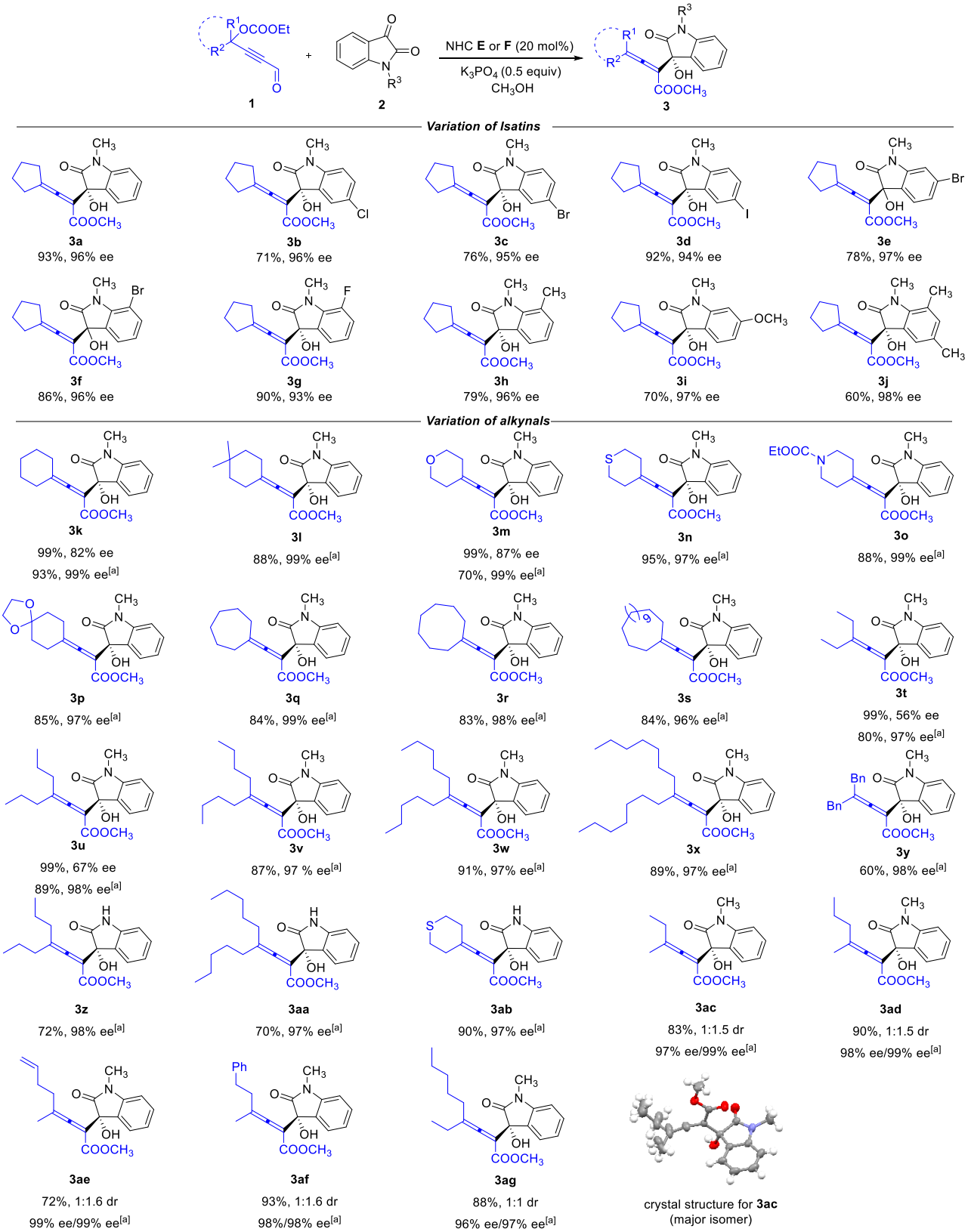
entry	NHC	K_3PO_4 (x equiv)	**3a** Yield [%][b]	ee [%][c]	**4a** Yield [%][b]	ee [%][c]
1	**A**	0.5	90	66	-	-
2	**B**	0.5	trace	-	-	-
3	**C**	0.5	trace	-	-	-
4	**D**	0.5	42	95	-	-
5	**E**	0.5	99	92	-	-
6	**F**	0.5	21	99	-	-
7	**G**	0.5	98	78	-	-
8	**H**	0.5	97	50		
9[d]	**E**	0.5	**91 (90)**	**96**		
10[d, e]	**E**	0.5	81	96		
11	**E**	2.5	-	-	61	90
12[d]	**E**	2.5	85	96	trace	-
13[f]	**E**	2.5	-	-	**73 (70)**	**96**

Table 1. Optimization of the Reaction Conditions.[a]

[a] Reaction conditions: **1a** (0.075 mmol), **2a** (0.05 mmol), and NHC (20 mol%) in CH_3OH (0.5 mL) at rt for 16 h; [b] Yield was determined by ^1H NMR using CH_2Br_2 as the internal standard; The data in parenthesis is isolated yield; [c] Determined via chiral HPLC; [d] Performed at 0 °C; [e] 10 mol% of catalyst loading; [f] K_3PO_4 (0.5 equiv), 0 °C for 16 h, then 2.0 equiv K_3PO_4 was added again and stirred at 60 °C for 0.5 h.

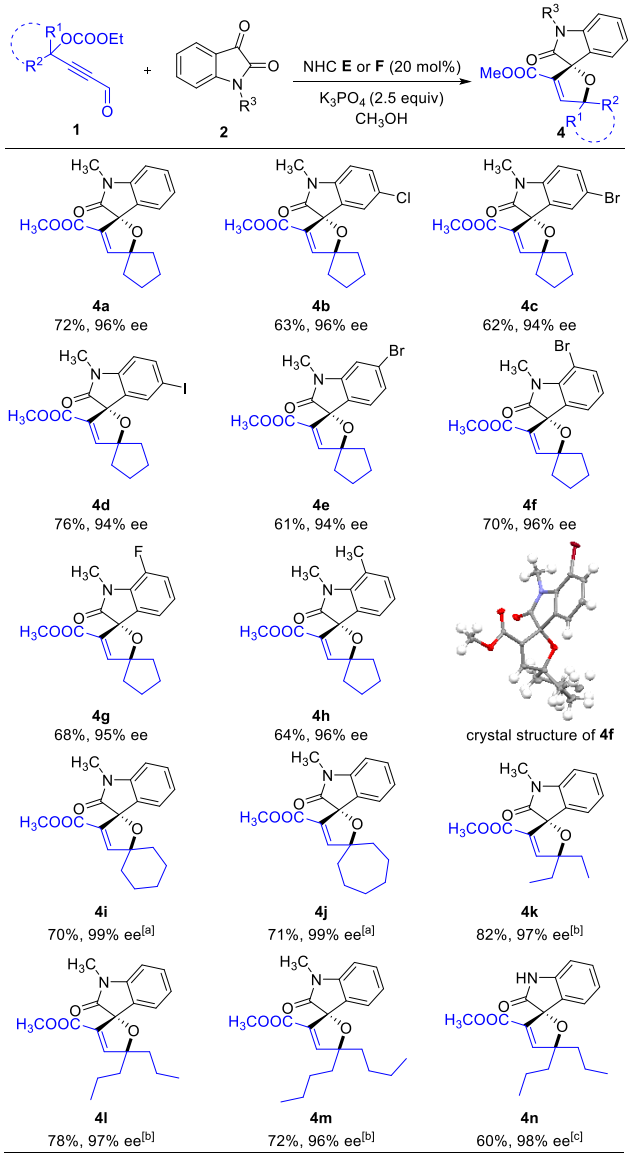
generated only the spirooxindole dihydrofuran product **4a** in 61% yield and 90% ee (entry 11). Trace amount of the cyclization product was observed and only allene product formed when carrying out the reaction at 0 °C (entry 12). Performing the reaction at 0 °C in the presence of 0.5 equiv of K_3PO_4 for 16 h, then adding additional 2.0 equiv of K_3PO_4 and stirring at 60 °C for 0.5 h, furnished only the cyclization product in 70% isolated yield and 96% ee (entry 13).

With the optimal reaction conditions in hand, we examined the scope of both alkynals (**1**) and isatins (**2**) for access to various



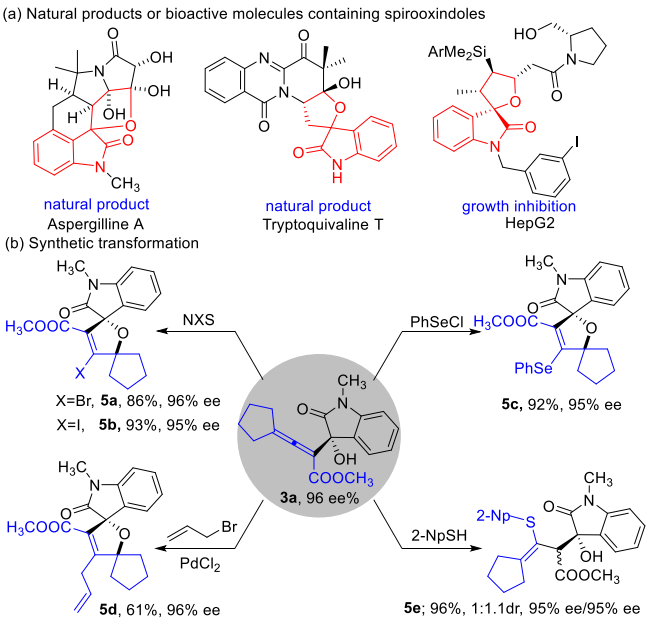
Scheme 1. Scope of NHC-catalyzed enantioselective reaction of azolium cumulenolate intermediates for synthesis of allenes. Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), and NHC **E** (20 mol%) in CH_3OH (1 mL) at 0 °C for 16 h; [a] NHC **F** (20 mol%) was used.

allenes (Scheme 1). At first, we investigate the generality of an array of isatins (**2**) by varying substituents on the phenyl ring of isatins (**3a** to **3j**). Both electron-withdrawing groups (**3b** to **3g**) and electron-donating groups (**3h** to **3j**) were well compatible in this reaction, providing the desired allene products in good yields and excellent ee values (**3b to 3j**). Functional groups such as chloro (**3b**), bromo (**3c**), iodo (**3d**), fluoro (**3g**), methyl (**3h**) and methoxy (**3i**) were demonstrated to be well tolerated. Substituents at different positions had no strong impact on the reaction (**3c**, **3e** and **3f**). Moreover, disubstituted isatin also worked under the optimal conditions, affording 60% yield and 98% ee (**3j**). Next, we examined the scope of alkynals. Six-membered cyclic alkynals with less ring strain exhibited excellent efficiency but just provided 82% and 87% ee (**3k** and **3m**) under the optimal conditions. We reasoned that the release of ring strain for alkynal substrates has a negative effect on the enantioselectivities. This was further



Scheme 2. Scope of NHC-catalyzed enantioselective reaction of azolium cumulenolate intermediates for synthesis of spirooxindolo dihydrofurans. Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), and NHC **E** (20 mol%) in CH_3OH (1 mL) at 0 °C for 16 h, then 2.0 equiv K_3PO_4 was added again and stirred at 60 °C for 0.5 h; [a] NHC **F** (20 mol%) was used; [b] NHC **F** (20 mol%) was used and stirred at 60 °C for 2 h; [c] NHC F (20 mol%) was used and stirred at 60 °C for 12 h.

demonstrated by the use of the acyclic alkynals (di-ethyl or -propyl substituted alkylnals), which underwent the reaction under the optimal conditions to give allene products **3t** and **3u** with excellent yields but sharp decreased ee values (56% and 67% ee). To our delight, we found that NHC pre-catalyst **F** is a better choice for these less strained cyclic substrates or acyclic substrates. When we used NHC pre-catalyst **F** for less strained cyclic substrates or acyclic substrates, significant improvement of yields was observed compared with the five-membered cyclic alkynal **1a** (Table1, entry 6). The approximated trends we observed is that substrates with less ring strains gave much higher yields than those with higher ring strains (regardless of the catalyst structure). The possible reason can lie on the stability and reactivity of the cumulenolate intermediates in matching with the other reaction partner (isatins). The exact reason and interactions remain unclear at this point. Based on newly established reaction condition, we continue to investigate the scope of the alkynal substrates. The current method was applicable to various cyclic substrates with different ring size (6- to 15-membered rings; **3k**, **3q**, **3r** and **3s**). Besides, alkynals containing *O*-heterocycle (**3m**), *S*-heterocycle (**3n**) and *N*-heterocycle (**3o**) were also well tolerated in this reaction, providing the corresponding products in 70-95% yields and over 97% ee. Cyclic *γ*-disubstituted alkynals modified by introducing methyl (**3l**), ester (**3o**) or acetal (**3p**) groups, also worked well in the reaction. Acyclic alkynals bearing different length of alkyl chains did not have large effect on the current reaction, providing the corresponding products in 80-91% yields and over 97% ee (**3t** to **3x**). In addition, this reaction system was also suitable for di-benzyl substituted substrate (**3y**). Notably, the *N*-unprotected isatin could also react well with various alkynals to provide the corresponding allenes in 70-90% yields and excellent ee values (**3z** to **3ab**). To obtain allenes with axial chirality and central chirality, we turned our attention to examine the scope of unsymmetric *γ*-disubstituted alkynals. The reaction of unsymmetric alkynals led to the chiral allene products in good yields with excellent enantioselectivities and 1:1 to 1:1.6 dr values (**3ac** to **3ag**). Notably, the diastereoisomers in these reactions can be easily separated via silica gel column chromatography. The



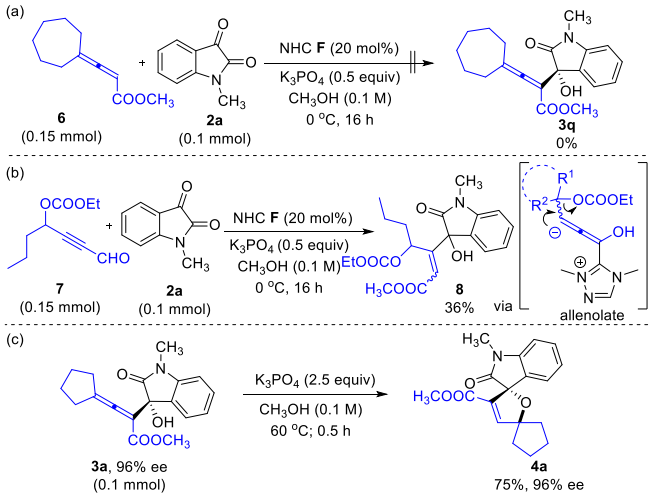
Scheme 3. Synthetic transformations of our allene products.

absolute configuration of **3ac** (major isomer) was confirmed by X-ray analysis.[20]

We then set out to investigate the generality of NHC-catalyzed enantioselective reaction of azolium cumulenolate intermediates for synthesis of spirooxindolo dihydrofurans (Scheme 2). The substituents on the isatins had little effect on the yields and enantioselectivies, providing the corresponding products in 61% to 76% yield and excellent ee values (**4a** to **4h**). The absolute configuration of **4f** was confirmed by X-ray analysis.[21] Moreover, six- and seven-membered cyclic alkynals (**4i**, **4j**) and acyclic alkynals (**4k** to **4m**) were also amenable to this approach. Notably, the isatin without a *N*-substituent (**4n**) was also found to be suitable partner and afforded the corresponding product in 60% yield and 98% ee.

Spirooxindole is a unique structural scaffold in natural products and biologically active compounds (Scheme 3a).[22] The chiral allenes from our catalytic reactions could be readily transformed to spirooxindole units (Scheme 3b). For example, in the presence of NBS or NIS, the enantioenriched allene **3a** underwent efficient cyclization to deliver highly substituted spirooxindole dihydrofuran scaffolds (**5a** and **5b**).[9e] Treatment of allene **3a** with PhSeCl gave the phenylselenenyl-substituted spirooxindole dihydrofuran scaffold in 92% yield and 95% ee (**5c**). Allyl substituted spirooxindole dihydrofuran **5d** could be obtained when the allene **3a** was submitted to a palladium-catalyzed cyclizaton and allylation reaction.[23] It should be noted that the spirooxindole dihydrofurans prepared in our reaction have several functional groups such as carbon-carbon double bond, ester and halogens, which offer opportunities for further structural manipulations to obtain different kinds of bioactive spirooxindole dihydrofurans.[22] In addition, the sulfa-Michael addition of 2-naphthyl thiol to compound **3a** afforded product **5e** in 96% yield and around 1:1.1 dr value almost without any loss of enantiopurity.

Several control experiments were carried out to gain insights into the reaction mechanism (Scheme 4). When allenoate **6** was subjected to the standard conditions, no desired product **3q** was observed (Scheme 4a). This result rules out the possibility of NHC-catalyzed Morita-Baylis-Hillman reaction of allenoate,[24] which is likely formed via protonation of cumulenolates in our reaction systems.[11a] Besides, the *γ*-monosubstituted alkynal **7** could not undergo the reaction to give the desired allene product;



Scheme 4. Control experiments.

Instead, side product **8** was obtained (Scheme 4b). This observation suggests the presence of allenolate intermediate (see Supporting Information for detailed reaction mechanism, Table S4). Under the standard conditions for the cyclization reaction in the absence of carbene catalyst, allene **3a** could be converted to the corresponding spirooxindole dihydrofuran **4a**, which indicates that the cyclization step is promoted by the base (Scheme 4c).

In summary, we have developed the first enantioselective carbon-carbon bond forming reactions of NHC-bound azolium cumulenolates. The reactions use readily available alkynals and isatins as the substrates and generate allene-containing molecules with high optical purities. When additional base is added to the same reaction mixture, the allene product efficiently converts spirooxindole dihydrofurans with excellent yield and enantiomeric excess. Further exploration on the reactivity of azolium cumulenolates and their synthetic applications for medicinal molecules are currently in progress in our laboratories.

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Layout 2:

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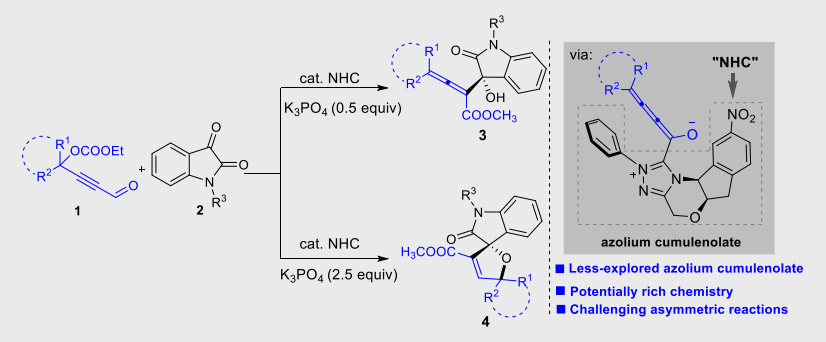

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Access to Allene-Containing Molecules via Enantioselective Reactions of Azolium Cumulenolate Intermediates

The first carbene-catalyzed highly enantioselective addition involving cumulenolates is disclosed. Both allene and spirooxindole products could be accessed with high yields and excellent enantioselectivities by varying the amount of the base.