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NHC-Catalyzed Aldol-Like Reactions of Allenoates with Isatins: Regiospecific Syntheses of γ-Functionalized Allenoates

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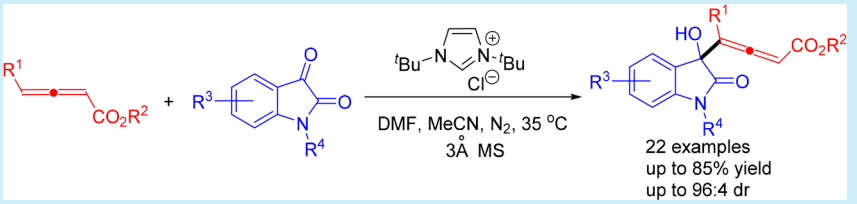
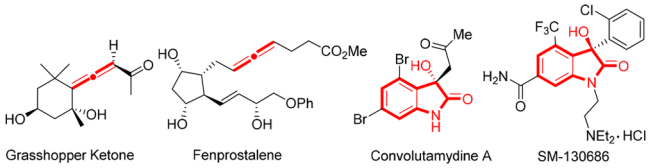
Supporting Information



ABSTRACT: An N-heterocyclic carbene (NHC) catalyzed γ-specific aldol-like reaction between allenoates and isatins has been achieved under mild conditions, giving trisubstituted allene derivatives bearing isatin moiety in moderate to good yields with high diastereoselectivity and excellent atom efficiency. The DFT computations indicated that the formation of the γ-adduct was more energetically favorable than that of the α-adduct. The result reported herein opens a new route for NHC-promoted allenoate-involved reaction.

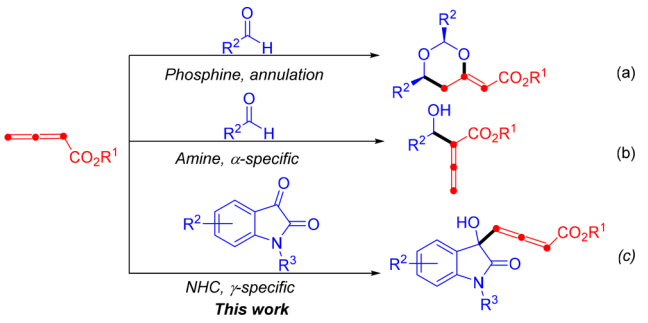
The allene moiety was found in a number of natural products and pharmaceuticals, thus it is an important unit in the discovery of medicine and other new chemical entities with specific functions (Scheme 1).[1] Moreover, 3-hydroxyoxindole is a crucial structural motif that represents a privileged pharmacophore in biologically active natural products and synthetic compounds (Scheme 1).[2] For instance, convolutamydine A shows potential antinociceptive activity, and SM-130688 is a new orally active growth hormone secretagogue (Scheme 1).[3] Inspired by the intriguing biological activities of many allenic and 3-hydroxyoxindole-based natural products, substantial efforts have been devoted toward embedding the allene and 3-hydroxyoxindole framework in the designed molecules for the development of functional compounds.[4]

Scheme 1. Selected Natural Products and Pharmaceutical Compounds Bearing Allene or a 3-Hydroxyoxindole Unit



Besides, the unique reactivity (a higher reactivity than noncumulated C=C bonds) of allenes renders them versatile building blocks in organic synthesis.[5] Ever since Lu's pioneering work[6,26a] on [3 + 2] annulation of allenoates and activated alkenes, the allene-related reactions received enormous attention and were widely explored for the erection of cyclic scaffolds or syntheses of allene-containing compounds.[1f,7] For instance, nucleophilic catalysts such as popular phosphine or amine have become powerful promoters in allene chemistry owing to their high versatility, operational simplicity, and low cost.[8] For example, Kwon and co-workers reported a phosphine-catalyzed [2 + 2 + 2] annulation of allenoates with aldehydes, which revealed that phosphine could be used as a Lewis base to facilitate the cyclization of aldehydes and allenoates (Scheme 2a) for the first time.[9] Furthermore, a

Scheme 2. Reactions of Allenoates with Carbonyl Compounds



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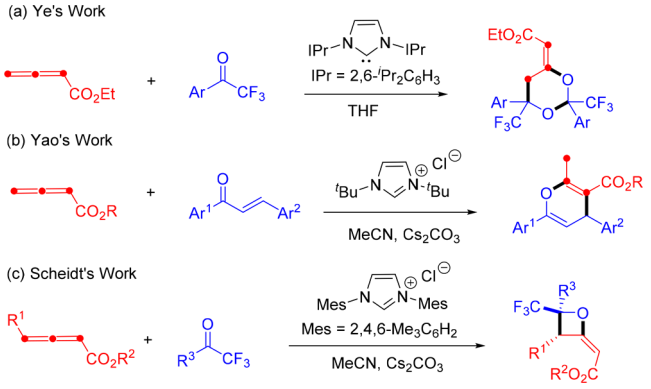
DABCO-catalyzed α-specific aldol condensation of allenoates with aldehydes was disclosed by Tsuboi's group at an earlier time (Scheme 2b).[10] Therefore, it can be concluded safely that the structure of the products and the reaction selectivity are mainly dependent on the catalysts in the conversions involving allenoates and aldehydes.

As a number of the most important nucleophilic organic molecular catalysts, N-heterocyclic carbenes (NHCs) have attracted increasing attention for the efficient construction of carbon−carbon and carbon−heteroatom bonds.[11] Early exploration of NHC catalysis was primarily focused on the biomimetic Breslow intermediates, an umpolung acyl anion equivalent formed by the nucleophilic attack of NHC on aldehyde.[12] In recent years, research efforts were more concentrated on uncovering hidden activation of NHC for functional groups beyond aldehyde carbonyls.[13] Recent studies demonstrated that NHC can react with other highly electrophilic carbonyl substrates such as ketenes[14] and acid chlorides.[15] Above and beyond, activation of less reactive esters[16] and acids[17] was also realized under corresponding reaction conditions.

To this point, the key step of NHC catalysis was the nucleophilic attack of the catalyst to an electrophilic carbon of the carbonyls to form a strong, covalent bond. However, compared to the well-established NHC-catalyzed reactions of C−X (X = O, N) bonds, the NHC-catalyzed activations of C−C unsaturated bonds are far less developed due to the high stability of NHC−substrate adduct,[18] and there were only a few examples of NHC-promoted reaction of allene substrates. The first study on the annulation variation was reported by Ye et al., where the imidazonium-based NHC was used to catalyze the [2 + 2 + 2] annulation reaction of allenoate with two molecules of trifluoromethylketone (Scheme 3a),[19] providing a

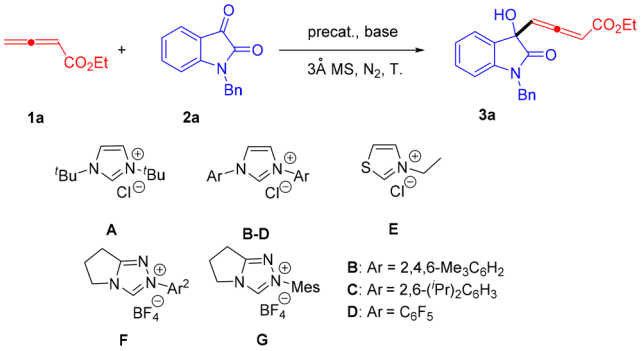
Scheme 3. NHC-Catalyzed Reactions Employing Allenoate



six-membered cycloadduct distinctly different from the corresponding [3 + 2] and [2 + 2] cycloadditions catalyzed by phosphines and amines, respectively.[20] More recently, our group also reported a [4 + 2] cyclization of chalcone with allenoate in the presence of imidazolium salt to construct the pyran scaffold successfully (Scheme 3b).[21] Subsequently, Scheidt's group developed an NHC-catalyzed formal [2 + 2] annulation of γ-substituted allenoates with trifluoromethyl ketones for the diastereoselective assembly of oxetane (Scheme 3c).[22] As mentioned above, the reaction selectivity of allenoate-involved reactions could be tuned by the modification of catalysts. Moreover, the organocatalytic γ-aldol reactions between allenoates and carbonyl compounds are less developed and remain a challenge. To continue our work on NHC-catalyzed reactions, we shall report herein an unknown example of NHC-promoted γ-specific diastereoselective aldol-like addition of allenic esters to isatins (Scheme 2c). This strategy also provided a shortcut to 2,3-allenol derivatives, which served as not only the platform intermediates for the syntheses of the natural products including (+)-Furanomycin, Liatrin, Capsochrom, and so on[23] but also the precursors to construct cyclic skeletons such as lactones, lactams, and benzene.[24]

To test our hypothesis, the study began using 2,3-butadienoic acid, ethyl ester (**1a**), and 1-benzylindoline-2,3-dione (**2a**) as the model substrates to optimize the reaction conditions, and the results were summarized in Table 1. First,

Table 1. Optimization of the Reaction Conditions[a]



entry	precat.	base	solvent	yield (%)[b]	dr[c]
1	**A**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	MeCN	62	52:48
2	**B**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	MeCN	trace	ND
3	**C**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	MeCN	43	50:50
4	**D−G**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	MeCN	0	ND
5	**A**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	MTBE	45	55:45
6	**A**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	DCM	56	57:43
7	**A**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	DCE	53	55:45
8	**A**	$(^t\mathrm{BuO})_2\mathrm{Mg}$	THF	46	57:43
9	**A**	K_2CO_3	MeCN	18	ND
10	**A**	^{t}BuOK	MeCN	51	56:44
11	**A**	Cs_2CO_3	MeCN	39	ND
12	**A**	DABCO	MeCN	trace	ND
13	**A**	DMF	MeCN	65	51:49
14[d]	**A**	**DMF**	**MeCN**	**72**	**58:42**
15[e]	**A**	DMF	MeCN	60	56:44
16[f]	**A**	DMF	MeCN	23	51:49

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.1 mmol), NHC (20 mol %), base (0.05 mmol), 3 Å MS (50 mg), solvent (2.0 mL) at 25 °C. [b]Isolated yields. [c]Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product. [d]Reaction was performed at 35 °C. [e]Reaction performed at 45 °C. [f]Reaction without 3 Å MS. ND = not determined.

several different NHC precatalysts were examined in MeCN in the presence of $(^t\mathrm{BuO})_2\mathrm{Mg}$ as a base. Imidazolium salts **A** and **C** furnished the desired product **3a** in 62% and 46% yields, while the use of imidazolium **B** as precatalyst led to poor results, and only a trace of desired compound was detected. In the contrast, thiazolium catalyst **E** and triazolium salts **F** and **G** were ineffective for the system (entries 1−4, Table 1). After a careful screening of the solvents and bases, compound **3a** was obtained in 65% yield with enhanced diastereoselectivity in the presence of DMF in MeCN (entry 13). Gratifyingly, further

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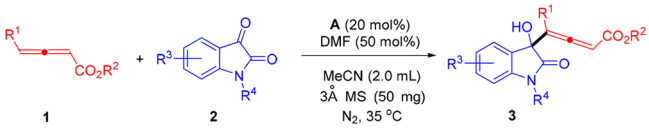
assessment on reaction temperature revealed both the reaction yield and diastereoselectivity were slightly improved by further changing the temperature to 35 °C, which was finally established as the optimal reaction conditions (entry 14). It should be worth mentioning that the unemployment of 3 Å MS led to a dramatic decrease in yield (entry 16, Table 1).

With the optimized conditions in hand, the substrate scope of the reaction was evaluated (Table 2). Initially, it was found

Table 2. Exploration of Substrate Scope



1 2 3

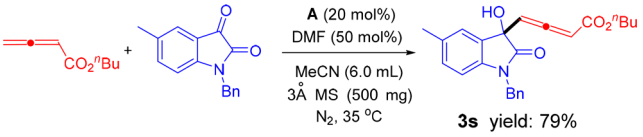
entry	R^1/R^2	R^3/R^4	product	yield (%)[a]	dr[b]
1	H/Et	H/Bn	**3a**	72	58:42
2	H/Et	5-Me/Bn	**3b**	79	85:15
3	H/Et	5-MeO/Bn	**3c**	75	55:45
4	H/Et	7-Me/Bn	**3d**	63	60:40
5	H/Et	5-Me/4-$FC_6H_4CH_2$	**3e**	65	96:4
6	H/Et	5-Me/4-$BrC_6H_4CH_2$	**3f**	60	70:30
7	H/Et	5-Me/4-$MeC_6H_4CH_2$	**3g**	76	57:43
8	H/Et	5-MeO/4-$ClC_6H_4CH_2$	**3h**	70	55:45
9	H/Et	5-MeO/4-$BrC_6H_4CH_2$	**3i**	58	84:16
10	H/Et	5-MeO/4-$MeC_6H_4CH_2$	**3j**	73	56:44
11	H/Et	7-Me/4-$MeC_6H_4CH_2$	**3k**	61	55:45
12	H/Et	H/4-$FC_6H_4CH_2$	**3l**	61	57:43
13	H/Et	H/4-$ClC_6H_4CH_2$	**3m**	64	52:48
14	H/Et	H/4-$BrC_6H_4CH_2$	**3n**	74	90:10
15	H/Et	H/4-$MeC_6H_4CH_2$	**3o**	68	50:50
16	H/Et	H/Me	**3p**	54	51:49
17	H/Et	H/Allyl	**3q**	62	50:50
18	H/^{i}Pr	5-Me/Bn	**3r**	80	56:44
19	H/^{n}Bu	5-Me/Bn	**3s**	85	65:35
20	H/Bn	5-Me/Bn	**3t**	73	87:13
21	H/Bn	H/Allyl	**3u**	62	52:48
22	Me/Et	5-Me/Bn	**3v**	83	56:44

[a]Isolated yields. [b]Diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product.

that a broad range of isatins **2** were compatible with the reaction conditions. Incorporating different electron-donating groups (such as Me, MeO) at positions C5 or C7 of the phenyl ring in isatins did not affect the efficiency of reaction (**3b**−**3d** in Table 2). On the other hand, the variation of the N-protecting groups in isatins was also investigated to explore the generality of the strategy. It showed that the benzyl group with different substituents on the phenyl rings was suitable for the reaction; products **3e**−**3q** were obtained in moderate yields with good diastereoselectivities. However, isatins with with electron-withdrawing substituents could not take part in this reaction system. Subsequently, the allenoate scope was probed, and we found that the allenoates possessing bulkier ester substituents such as ^{i}Pr and ^{n}Bu gave the products in higher yields (**3b** vs **3r** and **3s** in Table 2). In addition, the γ-specific aldol-like reaction between γ-substituted allenoate and isatin went smoothly and gave the product in 83% yield (Table 2, **3v**). These results highlighted the broad substrate scope of the NHC-catalyzed γ-specific aldol-like reactions of allenoates and isatins.

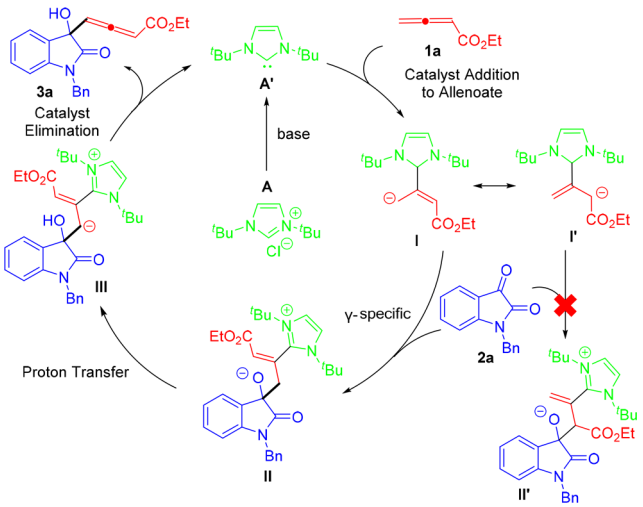
To exhibit the potential utility of our method, we performed a 1 mmol scale synthesis of **3s**. The desired product was obtained in 79% yield, validating that the reaction is scalable (Scheme 4).

Scheme 4. Reaction on 1 mmol Scale



Substrate **3a** was employed to illustrate the reaction process, and the plausible catalytic cycle for this reaction was depicted in Scheme 5. The deprotonation of NHC salt **A** occurred with

Scheme 5. Proposed Mechanism



a base-generated free carbene **A**′ initially, which then added to the allenoate **1a** to form intermediate **I** or **I**′. Due to the steric effect and electron nature, intermediate **I** may prefer a γ-selective addition to isatin to give intermediate **II**, which underwent a proton transfer to provide intermediate **III**. **III** then transformed into the desired product **3a** with the releasing of catalyst. Moreover, to shed some light on the proposed reaction pathway, DFT calculations, which have been performed widely to rationalize the NHC organocatalysis,[25] were carried out to account for the structural conversion from **I** and **2a** to **III** (or **III**′). It should be noted that the proton media-assisted [1,3]-proton transfer pathways have been studied based on the model pioneered by Yu.[26] The calculated results indicated that the pathway associated with intermediate **III** is more energetically favorable than the route connected with intermediate **III**′ in thermodynamics, which is in agreement with the experimental observations (see SI).

In conclusion, an NHC-catalyzed γ-specific aldol-like reaction between allenoates and isatins has been developed, providing indole derivatives bearing a trisubstituted allene moiety in moderate to good yields with broad substrate scope, high diastereoselectivity, and excellent atom economy.[27] Further studies on the application of this protocol are underway in our lab.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04082.

Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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