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Carbene-Catalyzed [4 + 2] Annulation of 2*H*-Azirine-2-carboxaldehydes with Ketones via Azolium Aza-Dienolate Intermediate

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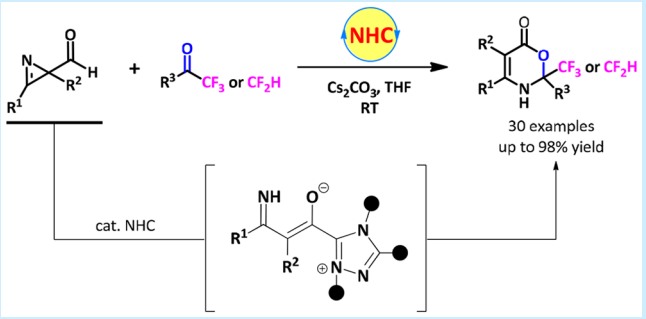
Supporting Information

ABSTRACT: A new carbene-catalyzed [4 + 2] annulation of 2*H*-azirine-2-carbaldehydes with ketones was developed, thus providing the 2,3-dihydro-6*H*-1,3-oxazin-6-one core structures with broad scope and good to excellent yields. Notably, the azolium aza-dienolates generated from the addition of NHCs to 2*H*-azirines are first uncovered.



Over the past decade, N-heterocyclic carbenes (NHC)-catalyzed organic reactions have attracted considerable attention from the synthetic community.[1] Within this context, protocols exploring the C_α- or C_β-position's chemical reactivity of the NHC-bound intermediates have been well investigated.[2] However, the chemical reactivity of the remote position of the NHC-bound intermediates (i.e., azolium dienolates) has gained very little attention.[3] For example, Ye and co-workers first utilized the easily prepared α,β-unsaturated acid chlorides as substrates to form azolium dienolate intermediates.[4] Shortly thereafter, Chi's group reported an elegant example of using β-methyl enals to produce vinyl enolate intermediates.[5] Setting up a leaving group at the α-position or γ-position of carbonyls had been identified as an efficient strategy to obtain azolium dienolates (Scheme 1a-ii).[6,7] In 2013, Chi et al. disclosed another efficient route to make azolium dienolates via the first use of activated esters as precursors (Scheme 1a-i).[8] Meanwhile, the same group found that the cyclobutenones can be practical precursors in the preparation of azolium dienolates (Scheme 1a-iii).[9] When azolium dienolates have a heteroatom at the remote position, these intermediates will lead to the formation of new functionalized heterocyclic molecules. The sole case is the in situ generation of azolium oxy-dienolate intermediates reported by Chi and co-workers recently.[10]

Building upon our sustainable interests in NHC organocatalysis,[11] we herein report the unprecedented route to diversely synthesize azolium aza-dienolate intermediates by first utilizing 2*H*-azirines as substrates. A novel carbene-catalyzed [4 + 2] annulation was proposed. To complete the task, two major challenges have to be overcome: (1) to control the competitive reaction sites, C_γ vs [C_α, C_β] and (2) to find suitable substrates to prepare azolium aza-dienolates. 2*H*-Azirines, as one of the smallest unsaturated nitrogen-containing heterocycles, have proven to be useful building blocks[12] and have attracted our considerable attention recently. For example, our group has successfully demonstrated that the Breslow intermediates could stereoselectively attack 2*H*-azirines to produce chiral aziridines.[13] Inspired by this finding, we speculated whether we can utilize NHC catalysts to activate 2*H*-azirine-2-carbaldehyde substrates to generate aza-azolium dienolates followed by nucleophilic addition to fluorinated ketones to yield [4 + 2] adducts (Scheme 1b). 1,3-Oxazin-6-ones as core structures are widely found in natural products and bioactive molecules, such as discoipyrroles A, B, and D, spinoxazines A and B, and Cetilistat[14] (Scheme 1c). Moreover, drugs bearing fluorinated motifs have shown unique ADMET properties.[15] Therefore, this strategy would be an important and supplementary protocol for natural product synthesis and lead compound optimization.

We commenced our study with the model reaction of 3-phenyl-2*H*-azirine-2-carbaldehyde (**1a**) with 2,2,2-trifluoro-1-phenylethan-1-one (**2a**). Under the initial conditions of catalyst **A** (15 mol %), Cs_2CO_3 (30 mol %), and DCM as solvent, the desired formal [4 + 2] annulation occurred and provided the corresponding product **3a** in 25% yield (Table 1, entry 1). Catalysts **B** and **C**, bearing *N*-2,4,6-$(Br)_3C_6H_2$ or *N*-C_6F_5 substituents, respectively, exhibited almost no reactivity (Table 1, entries 2 and 3). The morpholine-derived triazolium catalyst **D** afforded **3a** in good yield (Table 1, entry 4, 70%). The imidazole-derived catalyst **F** or thiazole catalyst **G** failed to promote this process (Table 1, entries 5 and 6). Further investment of solvent and bases indicated that THF and Cs_2CO_3

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Scheme 1. Strategies for the Generation of Azolium Dienolates

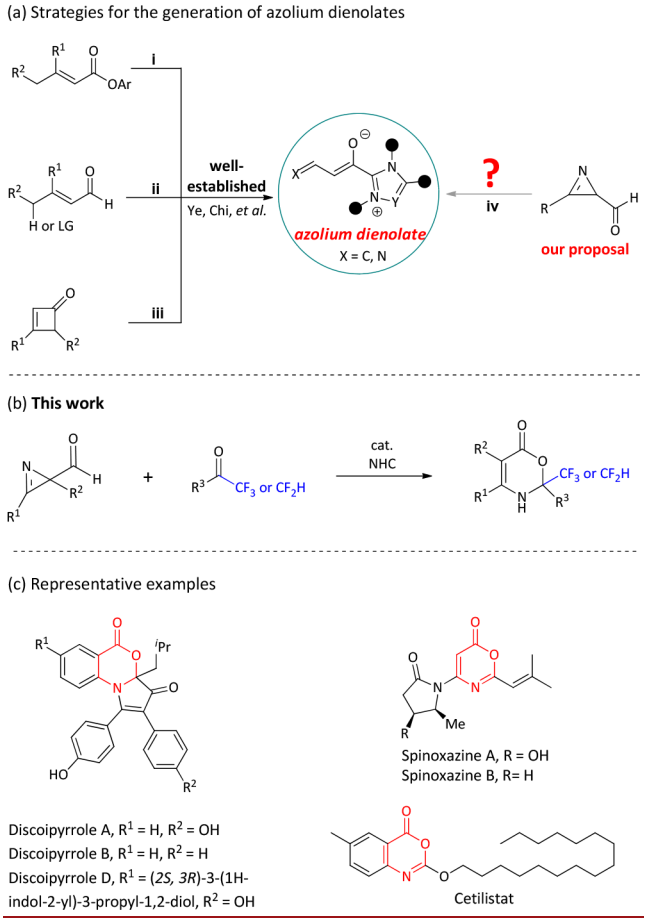
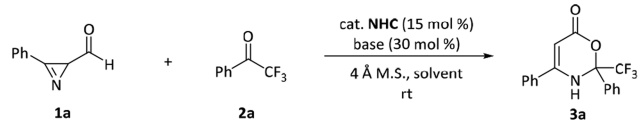
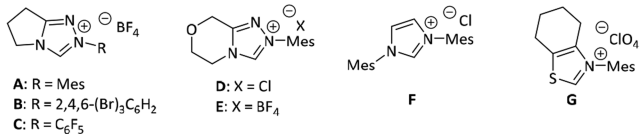


Table 1. Optimization of the Reaction Conditions[a]

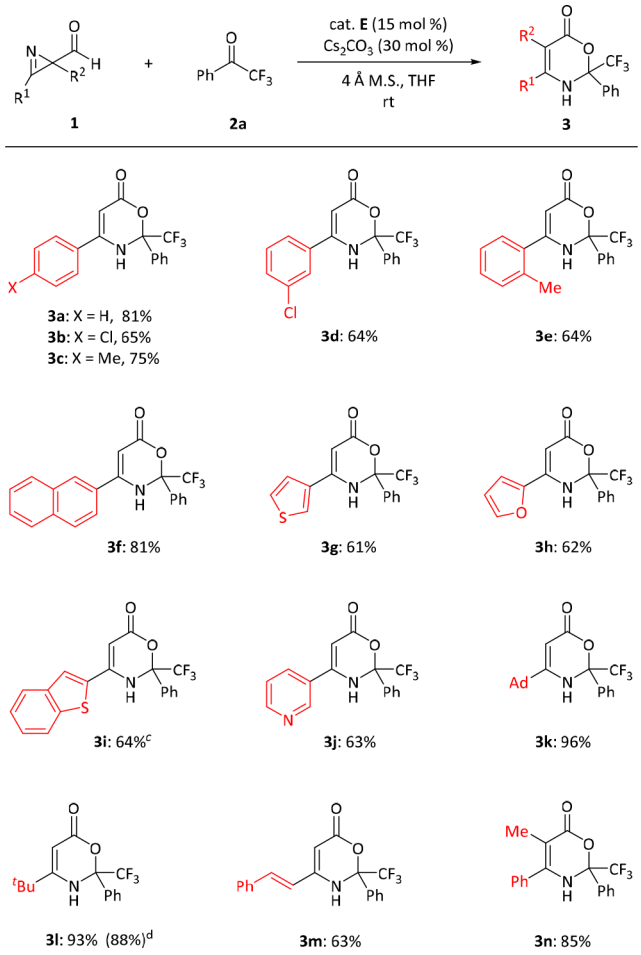




entry	cat.	solvent	base	yield (%)[b]
1	**A**	DCM	Cs_2CO_3	25
2	**B**	DCM	Cs_2CO_3	trace
3	**C**	DCM	Cs_2CO_3	nr[d]
4	**D**	DCM	Cs_2CO_3	70
5	**F**	DCM	Cs_2CO_3	trace
6	**G**	DCM	Cs_2CO_3	nr[d]
7	**D**	THF	Cs_2CO_3	79
8	**D**	$CHCl_3$	Cs_2CO_3	59
9	**D**	toluene	Cs_2CO_3	23
10	**D**	THF	^{t}BuOK	51
11	**D**	THF	^{t}BuOLi	29
12	**D**	THF	K_3PO_4	25
13	**E**	**THF**	**Cs_2CO_3**	**89**
14[c]	**E**	THF	Cs_2CO_3	79

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), cat. NHC (15 mol %), 4 Å MS (25 mg), base (0.03 mmol), solvent (1 mL), 20 h, room temperature. [b]Yield was determined by ^{1}H NMR based on the use of 1,3,5-trimethoxybenzene as internal standard. [c]Catalyst **E** (10 mol %), Cs_2CO_3 (20 mol %), 28 h. [d]No reaction.

Scheme 2. Scope of 2*H*-Azirine-2-carbaldehyde 1[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), cat. **E** (15 mol %), 4 Å MS (25 mg), Cs_2CO_3 (0.03 mmol), THF (1 mL), room temperature. [b]Isolated yield after flash column chromatography. [c]At 0 °C. [d]Performed on 1 mmol scale.

have proven to be an ideal medium and organic base, respectively (Table 1, entries 7−12). Gratifyingly, when the morpholine-derived triazolium catalyst **E** replaced catalyst **D** in the model reaction, a higher yield was obtained regularly (Table 1, entry 13, 89%). Moreover, 10 mol % of catalyst **E** also provided a good yield but bore a prolonged time (Table 1, entry 14, 28 h).

With the optimized reaction conditions in hand, we examined the scope of 2*H*-azirine-2-carbaldehydes. As shown in Scheme 2, electronic effects or substituted patterns have limited influence on reactivity (**3a−e**). The naphthalene ring was compatible in the system and provided the corresponding **3f** in 81%. It is noteworthy that a set of heteroaromatic rings (e.g., furan, thiophene, pyridine, and benzothiophene) were tolerated and offered the desired products **3g−j** in moderate yields. Then we turned our attention to the alkyl substituents. The results showed that they both furnished the corresponding **3k−l** in excellent yields. Additionally, when 2*H*-azirine-2-carbaldehyde bears an alkenyl group, the reaction also occurred smoothly (**3m**). Even with a sterically hindered group located at the 2-position of 2*H*-azirine-2-carbaldehyde, a good yield could still be achieved (**3n**). The relative configuration of **3a** was determined by X-ray crystallography, and other products were assigned by analogy (see the Supporting Information, SI).

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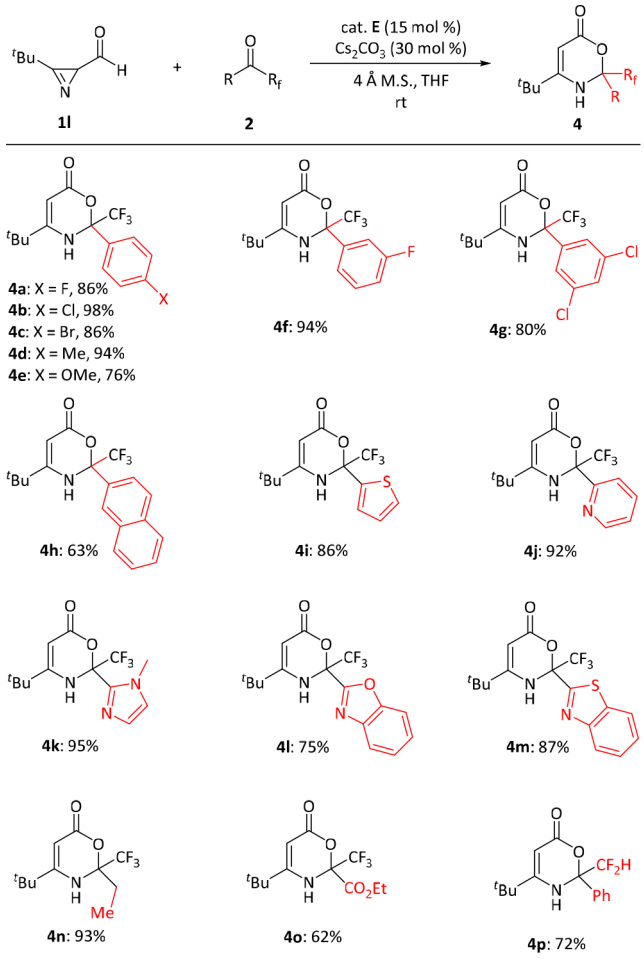
Scheme 3. Scope of Ketones[a,b]

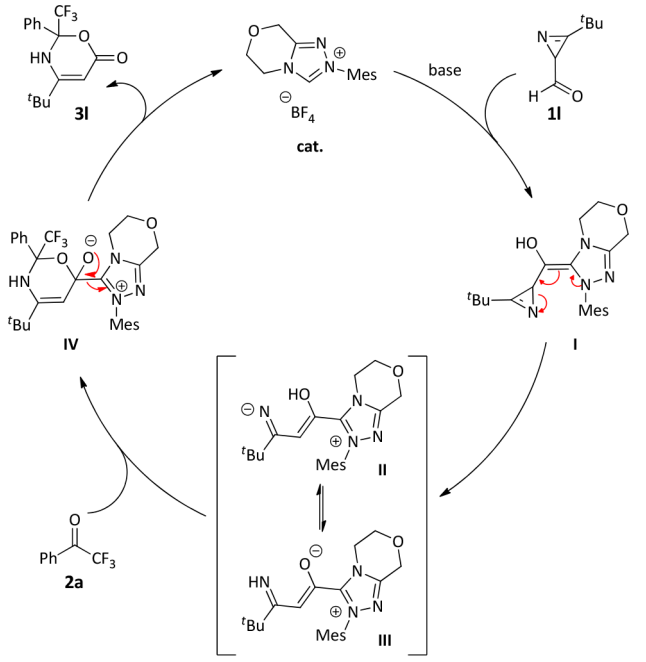


[a]Reaction conditions: **1l** (0.1 mmol), **2** (0.12 mmol), cat. **E** (15 mol %), 4 Å MS (25 mg), Cs_2CO_3 (0.03 mmol), THF (1 mL), room temperature. [b]Isolated yield.

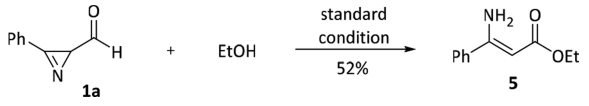
Further investigation on the scope of ketones was conducted (Scheme 3). The aromatic ketones, whether bearing halides, methyl, or methoxy groups, afforded the desired products in good to excellent yields (**4a**−**g**). The ketones having naphthyl or heterocyclic motifs gave the corresponding products in good to high yields (**4h**−**m**), as well. Likewise, the ketone bearing an alkyl substituent performed well in the reaction (**4n**). In addition, α-ketoester and difluoromethyl ketone also successfully delivered their corresponding **4o** and **4p**, respectively.

Our mechanistic studies mainly concentrated on identifying the key intermediate. To capture the azolium aza-dienolate intermediate, the reaction of **1a** with EtOH catalyzed by catalyst **E** was conducted and afforded the desired 3-amino-3-phenylacrylate **5** in 52% (Scheme 5). This experimental result partially proved the feasible existence of the azolium aza-dienolate intermediate **II** or **III** (Scheme 4). To our delight, the ^{19}F NMR spectra exhibited a peak at −85.10 ppm (see the SI), which may be assigned to intermediate **IV** despite the absence of HRMS or ^{1}H NMR. Building upon this transformation, we want to realize its asymmetric version. Unfortunately, we still have not found an effective chiral NHC catalyst to achieve a high enantioselective control of this reaction (see the SI). Further investigation on an asymmetric version of this process is in process in our laboratory.

Scheme 4. Postulated Mechanism



Scheme 5. Mechanistic Experiments



Based on the above mechanistic studies, we postulated a reaction pathway. The NHC catalyst reacts with 2*H*-azirine-2-carbaldehyde **1l** to form Breslow intermediate **I**.[16] Intermediate **I** breaks the azirine ring to generate intermediate **II**. Intermediate **II** can quickly convert to intermediate **III** after proton transfer. Intermediate **II** or **III** attacks **2a** to form intermediate **IV** followed by regenerating NHC catalyst and affording target product **3l**.

In conclusion, we have developed a new carbene-catalyzed [4 + 2] annulation of 2*H*-azirine-2-carbaldehydes with ketones, thus enabling the efficient assembly of various 2,3-dihydro-6*H*-1,3-oxazin-6-one structures from simple and available starting substrates under mild conditions. It should be noted that the azolium aza-dienolates made from 2*H*-azirines catalyzed by NHCs are first uncovered. Further exploration based on the azolium aza-dienolate intermediates is in process in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03378.

Experimental procedures, product characterization, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1873117 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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