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A Route to Polysubstituted Aziridines from Carbenes and Imines through a Nondiazo Approach

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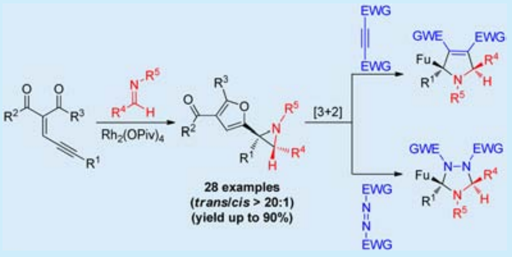
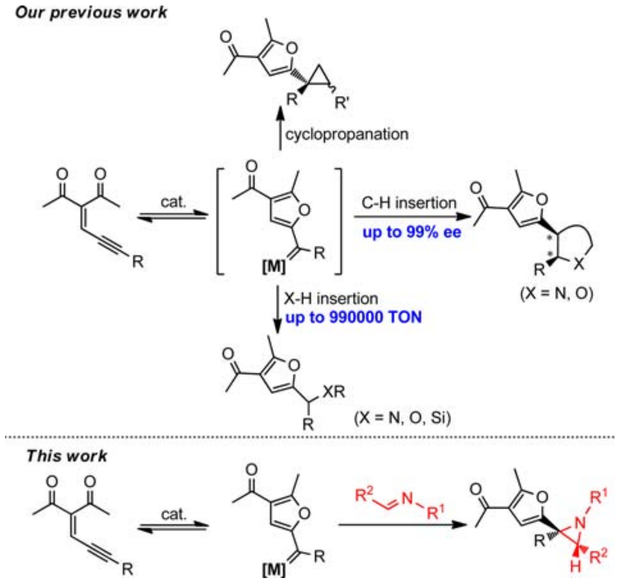
Supporting Information

ABSTRACT: An efficient method for the synthesis of polysubstituted aziridines utilizing enynones and imines is described. This transformation is achieved through the reaction of imines with donor/donor carbene intermediates, which were generated in situ from the cyclization of enynones. Furthermore, the resulted aziridines were good 1,3-dipoles, which could be efficiently trapped by dipolarophiles to give five-membered heterocycles. The obvious advantages of wide substrate scopes, mild reaction conditions, and high atom efficiency make this system highly appealing for construction of polysubstituted aziridines, 2,5-dihydropyroles, and 1,2,4-triazolidines.



Aziridines are useful synthetic intermediates in organic synthesis and are structural units of many natural products and drugs.[1] Various synthetic methods of aziridines,[2] including several asymmetric versions,[3] have been reported in the past decades. Synthetic methodologies for the preparation of aziridines[4] include nitrene addition to olefins, carbene and ylide addition to imines, Lewis acid catalyzed diazo compounds addition to imines, and cyclization of 1,2-amino alcohols,[4f] 1,2-amino halides,[4g] and 1,2-azido alcohols.[4h] The addition of metal–carbenoids to imines or Lewis acid catalyzed addition of diazo compounds to imines are most attractive pathways because of their mild reaction conditions, good selectivities, and well-established catalytic systems.[5] However, the substrates containing the highly energetic diazo moiety are often unstable, explosive, and toxic, particularly for those donor or donor/donor diazo compounds. These disadvantages severely limit the application of these methodologies.[6]

Scheme 1. Carbene-Transfer Reaction with Enynone as Carbene Source



Recently, enynal/enynone has emerged as one of the most reliable and safe donor or donor/donor–carbene precusors, which have been widely applied in classic carbene-transfer reactions such as cyclopropanation and C–H/X–H insertion reactions.[7,8] As part of our continuous efforts to develop new tandem reactions based on enynal/enynone,[8e,f,s,9] we have successfully applied enynal/enynone as the donor or donor/donor carbene precursors for the carbene-transfer reactions. For example, we developed a highly efficient NHC-AuCl/Selectfluor-catalyzed carbene-transfer reaction based on enynal/enynone chemistry with turnover numbers (TONs) up to 990000.[8s] Furthermore, we also developed the first enantioselective intramolecular C–H insertion of donor and donor/donor carbenes by an enynal/enynone approach, with ee values up to 99% (Scheme 1).[8e] Inspired and encouraged by the above results, we envisaged that this method might be further extended to the synthesis of polysubstituted aziridines, which would provide an attractive alternative to the traditional addition of donor/donor metal–carbenoids to imines based on a diazo approach or Lewis acid catalyzed addition of donor/donor diazo compounds to imines due to obvious safety concerns.

Herein, we report the first aziridination from the reaction of enynones and imines. Initially, enynone **1a** and imine **2a** were chosen as the model substrates for this investigation. As shown in Table 1, the reactions were conducted in CH_2Cl_2 at 60 °C.

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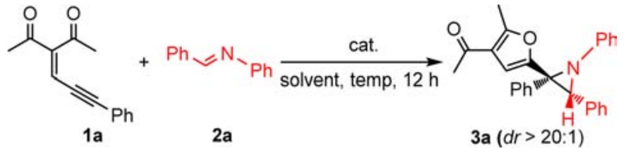
Table 1. Optimization of Reaction Conditions[a]



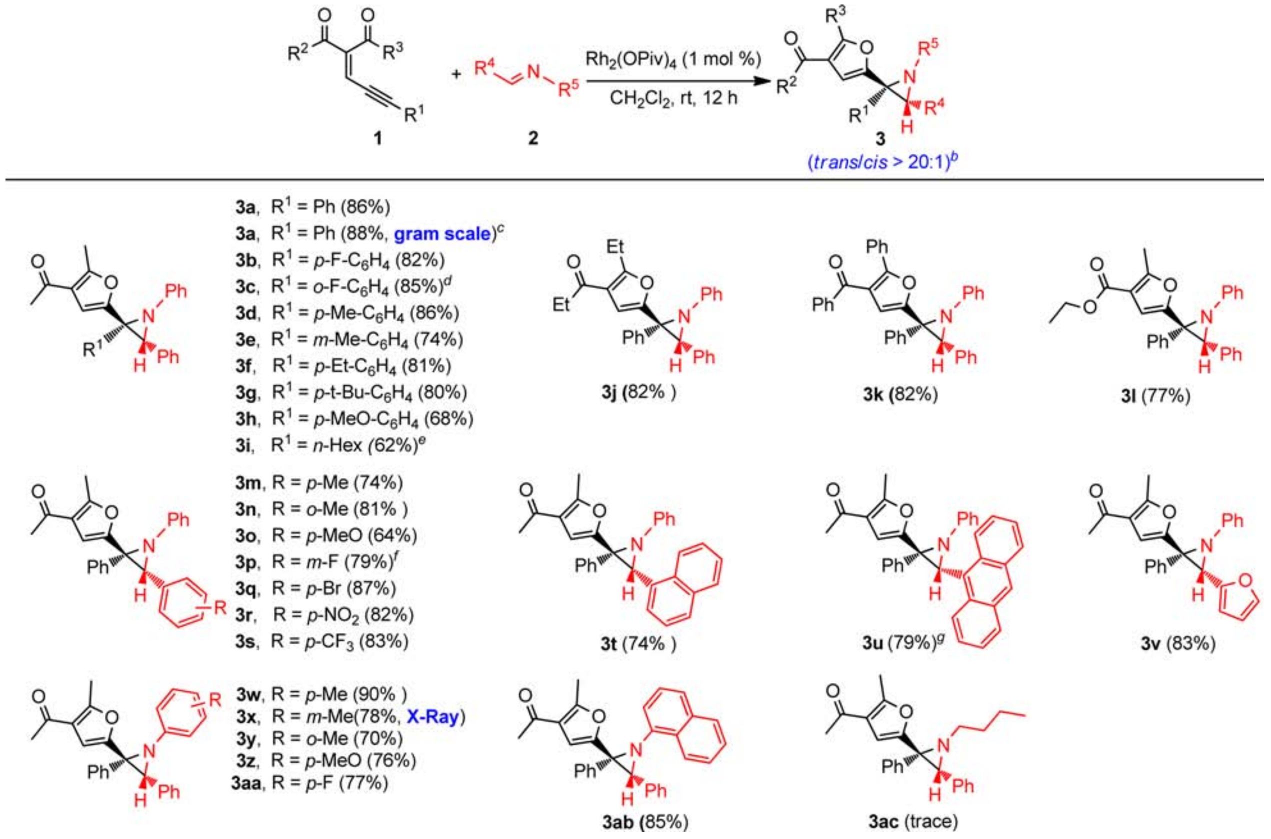
entry	cat. (mol %)	temp (°C)	solvent	3a (%)
1	$AgNTf_2$ (5)	60	CH_2Cl_2	ND
2	$Ph_3PAuNTf_2$ (5)	60	CH_2Cl_2	ND
3	$Cu(OTf)_2$ (5)	60	CH_2Cl_2	ND
4	CuBr (5)	60	CH_2Cl_2	ND
5	$ZnCl_2$ (5)	60	CH_2Cl_2	ND
6	$Rh_2(OAc)_4$ (1)	60	CH_2Cl_2	76
7	$Rh_2(OPiv)_4$ (1)	60	CH_2Cl_2	85
8	**$Rh_2(OPiv)_4$ (1)**	**rt**	**CH_2Cl_2**	**86**[b]
9	$Rh_2(OPiv)_4$ (1)	rt	DCE	72
10	$Rh_2(OPiv)_4$ (1)	rt	toluene	70
11	$Rh_2(OPiv)_4$ (1)	rt	THF	36
12		rt	CH_2Cl_2	ND

[a] **1a** (0.2 mmol), **2a** (0.4 mmol), [**1a**] = 0.2 M. The yield was determined by ^{1}H NMR using CH_3NO_2 as an internal standard. dr value was estimated by ^{1}H NMR. [b] Isolated yield.

Different transition metals were tested for this transformation. The coinage metal salts, which were typically good catalysts for enynones,[8h−m] were ineffective for this transformation; no desired product **3a** was detected (Table 1, entries 1−4). $ZnCl_2$, another important catalyst in the literature,[8b−d] could not catalyze this reaction either (Table 1, entry 5). Gratifyingly, the desired aziridine **3a** could be successfully obtained in 76% and 85% yields when $Rh_2(OAc)_4$ and $Rh_2(OPiv)_4$ were applied as the catalysts (Table 1, entries 6 and 7). The reaction yield remained unchanged when the reaction was conducted at room temperature (Table 1, entry 8). Other solvents, such as DCE, toluene, and THF, gave inferior results (Table 1, entries 9−11). Further control experiments indicated that the reaction did not occur without catalyst (Table 1, entry 12). It is noted that excellent diastereoselectivities of aziridine **3a** (dr >20:1) were observed for the rhodium-catalyzed conditions in Table 1, which could be attributed to the $\pi-\pi$ stacking interactions of two *cis*-phenyl groups.

With the optimized reaction conditions (Table 1, entry 8) in hand, the substrate scope was then examined (Scheme 2). First, the reaction could be conducted on a gram scale and gave the product **3a** in 88% yield. Second, this catalytic system could be successfully applied to a variety of enynones **1** and imines **2** as well. For example, in addition to enynone **1a**, various enynone derivatives tethered with aryl groups (R^1 = aryl) could be effectively reacted with imine **2a**, giving the desired aziridines **3a−h** in 68−88% yields. The reaction was not sensitive to the electronic properties of enynones **1**, the enynones with both electron-withdrawing and -donating substituents at the aryl groups of R^1 could be utilized as good substrates for this reaction. Alkyl enynone (R^1 = *n*-hexyl) transferred to the corresponding aziridine **3i** in 62% yield. The reactions for propionyl-, benzoyl-, and ethoxycarbonyl-substituted enynones proceeded equally well, leading to the desired products **3j−l** in

Scheme 2. Substrate Scope of Aziridination[a]

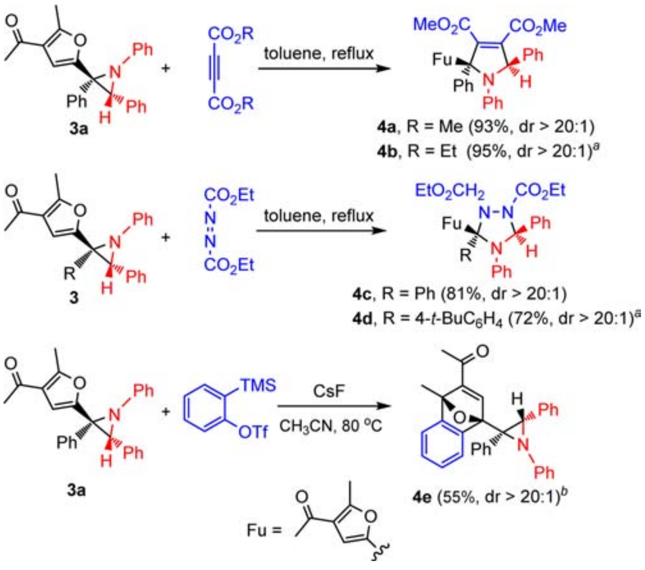


[a] $Rh_2(OPiv)_4$ (1 mol %), **1** (0.2 mmol), **2** (0.4 mmol), [**1**] = 0.2 M, 3−12 h, isolated yield. [b] Estimated by ^{1}HNMR. [c] **1a** (5 mmol). [d] *trans/cis* = 5:1. [e] *trans/cis* = 3:1. [f] *trans/cis* = 10:1. [g] *trans/cis* = 4:1.

77–82% yields. In addition to the enynones, we also investigated different imines. As shown in Scheme 2, the reactions were not sensitive to the electronic and steric properties of the imines. For example, the imines with different electronic properties and steric hindrance on both R^4 and R^5 groups could serve as good substrates for this transformation, furnishing the desired aziridines **3m–ab** in 64–90% yields. Steric bulky imines could be aziridinated smoothly, leading to the desired products **3t**, **3u**, and **3ab** in 74–85% yields. Furthermore, the imine derived from furan-2-carbaldehyde was also an efficient substrate, affording the aziridine **3v** in 83% yield. The imine from aliphatic amine was not an effective substrate for this reaction, and only a trace of the desired product **3ac** could be detected. The structure and stereochemistry of the product were confirmed by the X-ray diffraction analysis of compound **3x** (see the Supporting Information).

With aziridines **3** substituted with three different aryl groups in hand, we were very curious about the reactivity of these electron-rich aziridines. Electron-rich aziridines were often regarded as effective precursors of azomethine ylides, which are good 1,3-dipoles in [3 + 2]-cycloadditions.[10] Therefore, several electron-deficient dipolarophiles, dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate, and diethyl azodicarboxylate were then tested for the [3 + 2]-cycloadditions. As shown in Scheme 3, simply refluxing the solution of aziridines **3** and dipolarophiles smoothly furnished the desired 2,5-dihydropyrroles and 1,2,4-triazolidines in good to excellent yields (**4a–d**, 72–95%). The furan ring of aziridine **3a** could be used as the 4π-component to react with benzyne through the [4 + 2]-cycloaddition reaction, giving the product **4e** in 55% yield. The structure and stereochemistry of 2,5-dihydropyrole and 1,2,4-triazolidine were further confirmed by the X-ray diffraction analysis of compounds **4b** and **4d** (see the Supporting Information).

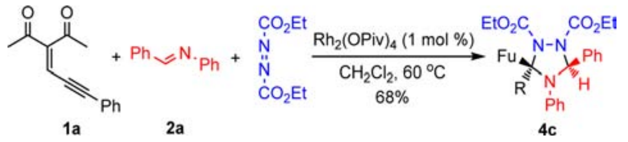
Scheme 3. Chemical Transformation of Aziridines 3



[a]The stereochemistry was determined by X-ray diffraction analysis. [b]The stereochemistry was determined by NOE.

Furthermore, 1,2,4-triazolidine **4c** could also be obtained in a one-pot manner from the reaction of enynone **1a**, imine **2a**, and diethyl azodicarboxylate in the presence of 1 mol % of $Rh_2(OPiv)_4$ (Scheme 4).

Scheme 4. Three-Component Reaction[a]

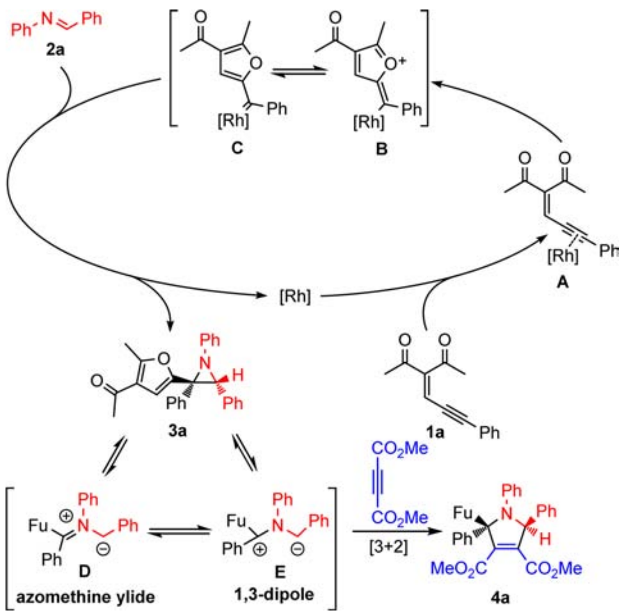


[a]The reaction was conducted in a sealed tube.

Interestingly, the relative stereochemistry has been reversed during the cycloaddition process. Two phenyl groups situated *cis* to each other in azirindines **3a** and **3g** but *trans* in the adducts **4a–d** (Scheme 3). These results indicated that the [3 + 2]-cycloaddition of the aziridine **3** and dipolarophile is a stepwise process.

With the above results, a plausible mechanism was then proposed (Scheme 5).[8s]

Scheme 5. Proposed Reaction Mechanism



Taking aziridine **3a**, for example, the coordination of the triple bond of the enynone **1a** to rhodium catalyst enhanced the electrophilicity of the alkyne, and subsequent intramolecular nucleophilic attack of the carbonyl oxygen atom to the electron-deficient alkyne would form the intermediate **B**, which was in equilibrium with the carbene intermediate **C**. In the presence of imine **2a**, the carbene intermediate was then trapped to form the aziridine **3a**. The electron-rich aziridine **3a** was a good precursor of azomethine ylide **D** or 1,3-dipole **E**,[10] which could further react with the electron-deficient dipolarophile, such as DMAD, to produce the desired adduct **4a**.

In summary, we have developed an efficient method for the synthesis of polysubstituted aziridines from enynones and imines. This transformation is achieved through a reaction of imines with donor/donor carbene intermediates, which were generated in situ from the cyclization of enynones. Furthermore, the resulting aziridines were good 1,3-dipoles which could be efficiently trapped by electron-deficient

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dipolarophiles to give five-membered heterocycles. The obvious advantages of wide substrate scopes, mild reaction conditions, and high stereoselectivity and atom efficiency make this reaction highly appealing for construction of polysubstituted aziridines, 2,5-dihydropyroles, and 1,2,4-triazolidines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02429.

Typical experimental procedure and characterization for all products (PDF)
Crystallographic data for **3x** (CIF)
Crystallographic data for **4b** (CIF)
Crystallographic data for **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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