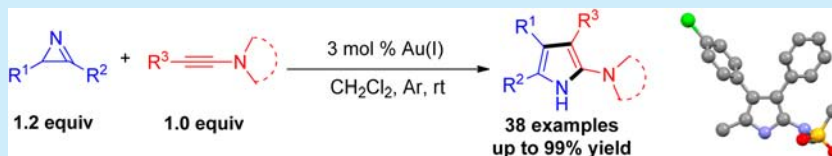


Gold-Catalyzed Intermolecular Nitrene Transfer from 2*H*-Azirines to Ynamides: A Direct Approach to Polysubstituted PyrrolesLei Zhu,[†] Yinghua Yu,[†] Zhifeng Mao, and Xueliang Huang*

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Supporting Information



ABSTRACT: An effective gold-catalyzed intermolecular nitrene transfer by the reaction of 2*H*-azirines and ynamides is reported, which provides highly substituted pyrroles in a straightforward manner. This transformation proceeds under mild conditions and gives the polysubstituted pyrroles in good-to-excellent yields. Preliminary results indicate that a nongold carbenoid pathway is preferred for current pyrrole synthesis.

Polysubstituted pyrrole derivatives have found broad application in organic synthesis and material science. In addition, they exhibit diverse biological and therapeutic activities (Figure 1).¹ The most frequently used method to synthesize

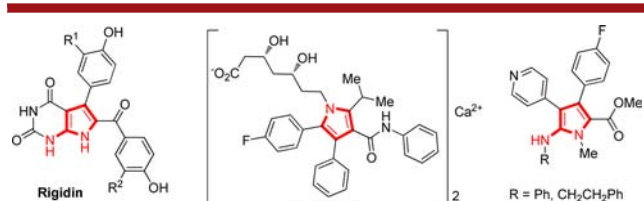
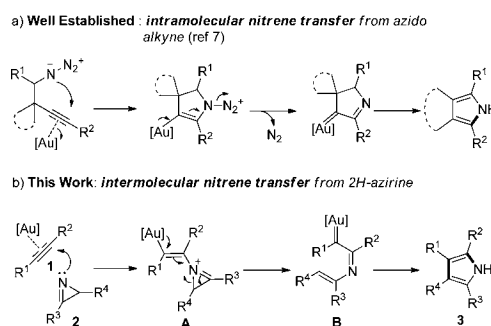


Figure 1. Examples of biologically and therapeutically active molecules containing pyrrole scaffold.

pyrrole units relies on the classical Hantzsch, Paal–Knorr procedure. Although a variety of methods have been recently developed for the synthesis of functionalized pyrrole derivatives,^{2,3} direct access to polyfunctionalized pyrroles from readily available feedstocks, especially in an atom and step economic manner, still remains challenging and highly desirable.

Recently, homogeneous gold-catalyzed reactions of alkynes with nucleophiles have been recognized as one of the most powerful and useful tools in organic synthesis.^{4,5} In particular, the discovery of the formation of α -carbonyl gold carbenoids through oxygen transfer has led to the development of numerous useful synthetic transformations.⁶ Compared with the generation of α -Oxo gold carbenoids, gold-catalyzed nitrene transfer is still far from being fully explored. Intramolecular gold-catalyzed nitrene transfer reactions of alkynes with tethered azide moieties have been achieved by the research groups of Toste (Scheme 1a),⁷ Zhang,⁸ and Gagosz.⁹ For the intermolecular nitrene transfer, only a few examples on gold-catalyzed intermolecular reactions of iminopyridium ylides with activated alkynes were

Scheme 1. Pyrrole Synthesis via Gold-Catalyzed Nitrene Transfer



reported recently, which release 1 equiv of pyridine as a byproduct.^{10,11–13}

2*H*-Azirine, which can be readily prepared by Neber reaction or elimination of dinitrogen from vinyl azide, has been widely applied in *N*-heterocycles synthesis.^{14,15} Compared with azide, 2*H*-azirine is sufficiently stable, easy to handle, and thus could be considered as a better reagent for nitrene transfer. It possesses high ring strain, and the nitrogen atom in imino moiety is mildly nucleophilic. So, treatment of 2*H*-azirine **2** with an activated alkyne **1** may lead to formation of zwitterion intermediate **A** (Scheme 1b). More importantly, the potential side reaction azide–alkyne Huisgen cycloaddition can be avoided. In this context, we envisioned that treatment of alkyne **1** with 2*H*-azirine **2** in the presence of a proper gold catalyst would afford multisubstituted pyrrole **3** in an atom economic manner, as all atoms are fused into **3** during the nitrene transfer process (**A** → **B** → **3**). Recently, Gagosz et al. reported a gold-catalyzed pyridine

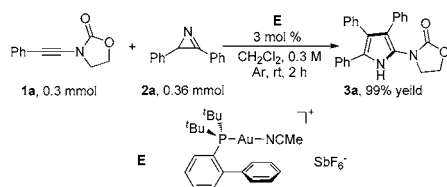
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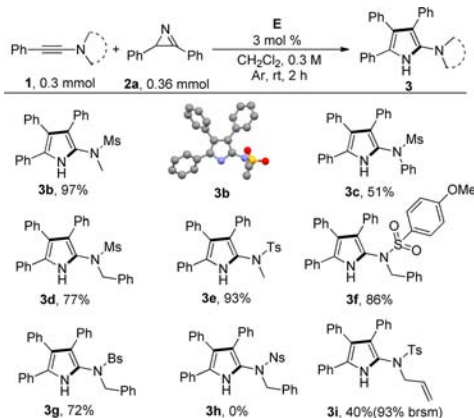
synthesis from 2-propargyl-2*H*-azirine.¹⁶ Herein we describe a facile approach to another important one-ring heterocycle, pyrrole, by gold-catalyzed intermolecular [3 + 2] cycloaddition of 2*H*-azirine and ynamide under mild conditions. It is worthwhile to mention that our hypothesis is mechanistically distinct from previously reported procedures for multiply substituted pyrrole synthesis from 2*H*-azirines and activated ketones (*vide infra*).^{15a–c}

After initial investigation and evaluation of reaction parameters,¹⁷ we found that the reaction of ynamide **1a** and 2*H*-azirine **2a**, conducted with 3 mol % of gold complex **E** in CH₂Cl₂ at rt, afforded the desired pyrrole **3a** in nearly quantitative yield (Scheme 2). Consequently the effects of the amide moiety were

Scheme 2. Gold Complex E Catalyzed Formal [3 + 2] Cycloaddition of 2*H*-Azirine **2a** and Ynamide **1a**



Scheme 3. Scope of the Ynamides Bearing Different Amides Groups^a

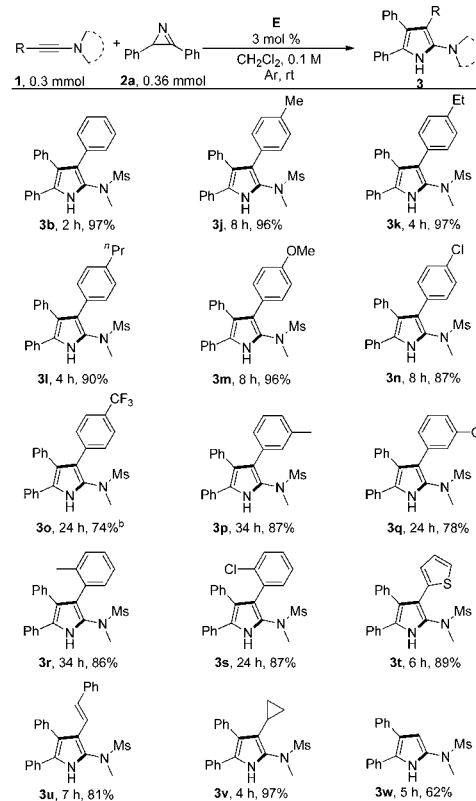


^aYields reported are for pure, isolated compounds.

evaluated (Scheme 3). In general, the reactions of ynamides bearing a variety of protecting groups proceeded well, giving the desired products (**3b**–**3g**) in moderate to high yields. The ynamide possessing an Ns (*p*-NO₂C₆H₄SO₂, **1h**) is not compatible with current reaction conditions. The structure of **3b** was confirmed by single-crystal X-ray analysis. Notably, according to our mechanistic hypothesis (Scheme 1b), the allylic group in ynamide **1i** should be able to intercept the carbenoid intermediate. In contrast, pyrrole **3i** was solely obtained, with no observation of the expected cyclopropane,²⁰ which might suggest a different mechanistic perspective as depicted in Scheme 1b (*vide infra*).

The current protocol for pyrrole synthesis is efficient, as a wide array of ynamides undergo formal [2 + 3] cycloaddition with 2*H*-azirine **2a** at ambient temperature using **E** as the catalyst in DCM (Scheme 4). Both electron-donating (products **3j**–**3m**) and -withdrawing substituents (products **3n** and **3o**) at the *para* position of the aryl ring were tolerated. The ynamides containing

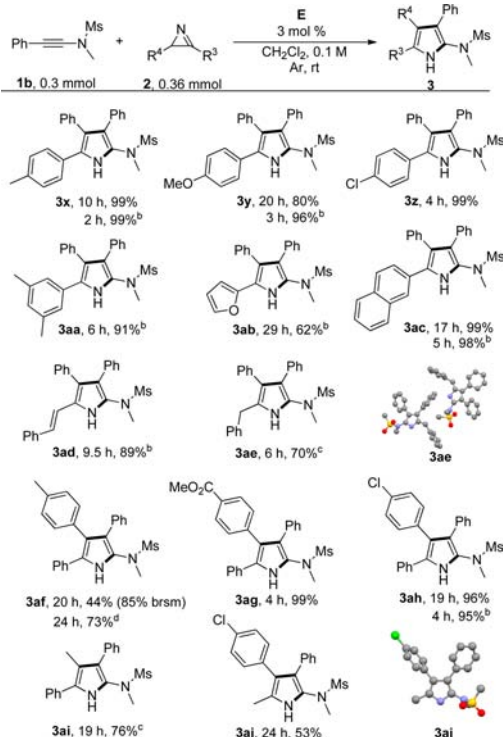
Scheme 4. Reaction Scope of Ynamides with 2*H*-Azirine **2a**^a



^aYields reported are for pure, isolated compounds. ^b5 mol % **E** was employed.

a methyl or chloro group at the *meta* position of the phenyl ring reacted well with **2a**, giving the corresponding pyrroles (**3p** and **3q**) in high yields. Of note, ynamides possessing *ortho* substituents were well tolerated in the reactions; pyrroles **3r** and **3s** were isolated in 87% and 89% yields, respectively. In addition, the reaction also worked well for thiophenyl substituted ynamide, furnishing pyrrole **3t** in high yield. Interestingly, replacement of the aryl ynamide with styryl or cyclopropyl ynamide had no significant influence on the reaction (**3u** and **3v**). When the ynamide bearing a trimethylsilyl group at the terminal position of the triple bond was employed for this reaction, an in situ desilylation took place, and pyrrole **3w** was obtained in 62% yield.

With the ynamide **1b** as the model electrophile, we studied the scope of 2*H*-azirines for this reaction and the results are listed in Scheme 5. The reaction was first examined by variation of R³ on the C=N double bond moiety. Introducing an electron-donating (**3x**, **3y**, and **3aa**) or electron-withdrawing (**3z**) group on the phenyl ring had no significant influence, and the corresponding pyrroles were obtained in excellent yields (up to 99%). Furyl, naphthyl, and alkenyl groups were tolerated as well, affording pyrroles **3ab**, **3ac**, and **3ad** in good to excellent yields. Replacement of the aryl group with an alkyl substituent also led to the effective formation of the corresponding pyrrole by carrying out the reaction at elevated temperature (**3ae**). In contrast, the reaction was sensitive to the electronic nature of substituent R⁴. With electron-withdrawing groups (e.g., ester, chloro) at the *para* position of the phenyl ring, high efficiencies of the reactions were maintained (**3ag** and **3ah**). When a methyl group was placed at the *para* position of the phenyl ring, the reaction was significantly slow (**3af**), presumably due to the

Scheme 5. Reaction Scope of 2*H*-Azirine with Ynamides 1b^a

^aYields reported are for pure, isolated compounds. ^bThe concentration is 0.3 M. ^cThe reaction was run in toluene at 110 °C. ^d5 mol % E was employed.

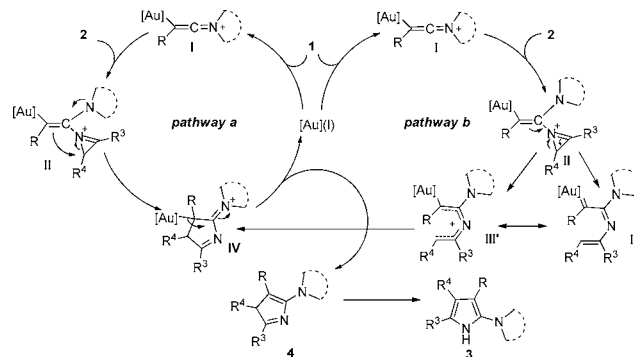
enhanced stability of intermediate A (Scheme 1b) and thus resulted in a slower ring expansion of the 2*H*-azirine core. Similarly, when R⁴ is an alkyl group (R⁴ = Me, 3ai), higher reaction temperature was required to reach full conversion in a reasonable reaction time. Unambiguous evidence of the regioselectivity was established by single-crystal X-ray analysis of pyrroles 3ae and 3aj,²¹ which ruled out the mechanistic pathway related to previous reports (*vide supra*).^{15a-c,22}

To gain more information on the mechanism, ynamide 1x was prepared and subjected to the current transformation (eq 1).



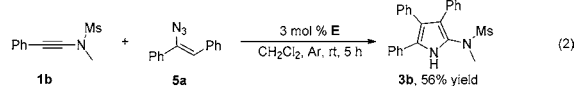
Pyrrole 3ak was obtained in 39% isolated yield. Combining the results we obtained from the reactions of ynamides 1i and 1v (cf. products 3i and 3v), a plausible mechanistic rationale²² for current pyrrole synthesis is depicted in Scheme 6. The reaction is initiated by gold(I) activation of an ynamide, generating highly electrophilic keteniminium intermediate I, which reacts with 2*H*-azirine 2 to afford zwitterion intermediate II. At this stage, an intramolecular nucleophilic addition of an enamine to the azirine moiety would lead to the formation of a pyrrole core (IV) (pathway a). Alternatively, ring opening of the three-member ring may lead to the formation of a gold-carbenoid III which is in equilibrium with cationic intermediate III'. Similarly, direct ring opening of II also gives III'. Cyclization of III' would afford IV (pathway b). No observation of cyclopropane (cf. the reaction of ynamide 1i)^{20,23} may be due to a rapid ring closure from III' to IV. When R⁴ is more electron-donating, intermediate II is more stable, thus leading to a slower formation of intermediate IV.

Scheme 6. Mechanistic Rationale for the Pyrrole Synthesis



This electronic stabilization accounts for the slow reaction rates of azirines 2ae, 2af, and 2ai. Elimination of the cationic gold(I) catalyst and liberation of 3*H*-pyrrole 4 complete the catalytic cycle.

Because vinyl azide has been widely used for the synthesis of multiply functionalized pyrrole²⁴ and it is a precursor of 2*H*-azirine, we also studied the reaction of vinyl azide 5a with ynamide 1b in the presence of catalyst E (3 mol %) at rt. This reaction afforded pyrrole 3b in only moderate yield (eq 2). Although less efficient, to the best of our knowledge, this represents the first example of gold-catalyzed intermolecular nitrene transfer from an organic azide to an alkyne.



In summary, we have reported a gold-catalyzed formal [3 + 2] cycloaddition of 2*H*-azirines with ynamides, which provides a straightforward approach to fully substituted pyrroles in good to excellent yields. The current transformation features mild reaction conditions, low catalyst loadings, a broad substrate scope, and atom economy.²⁵ Additional studies to elucidate the mechanism and to distinguish the reactivities between vinyl azide and 2*H*-azirine are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and data; NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

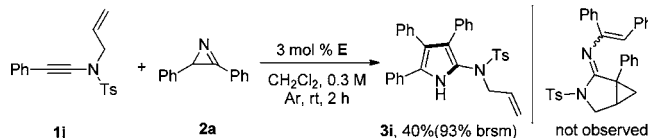
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