Organic LETTERS

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Gold-Catalyzed Intermolecular Ynamide Amination-Initiated Aza-Nazarov Cyclization: Access to Functionalized 2-Aminopyrroles

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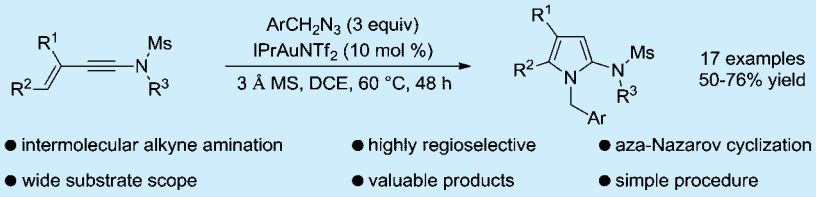
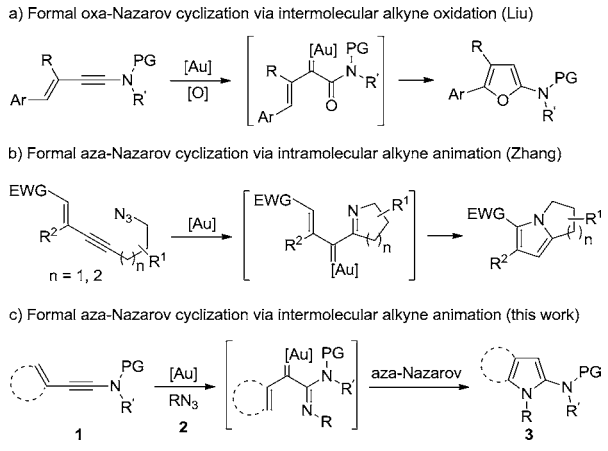
Supporting Information



ABSTRACT: A novel gold-catalyzed intermolecular ynamide amination-initiated aza-Nazarov cyclization has been developed, allowing the facile and efficient synthesis of various 2-aminopyrroles in moderate to good yields. Furthermore, a mechanistic rationale for this tandem sequence, especially for the observed high regioselectivity, is also well supported by DFT (density functional theory) computations. The high flexibility, broad substrate scope, and mild nature of this reaction render it a viable alternative for the construction of 2-aminopyrroles.

The Nazarov cyclization is a stereospecific 4π-electrocyclization that, in its typical manifestation, converts divinyl ketones into cyclopentenones via a conrotatory cyclization. In the past decades, this cyclization has been proven to be a powerful method for the synthesis of five-membered carbo- or heterocycles;[1] however, metal carbene involved Nazarov-type cyclization is less explored.[2] Recent rapid development in homogeneous gold catalysis offers a highly attractive approach for accessing this cyclization. For example, Liu et al. reported a gold-catalyzed formal [4 + 1] cycloaddition between 3-en-1-ynamides and quinoline oxide via oxa-Nazarov cyclization to afford various 2-aminofurans in 2012 (Scheme 1a).[3] Simultaneously, Zhang et al. also demonstrated an elegant protocol for the efficient synthesis of substituted 2,3-dihydro-1*H*-pyrrolizines through gold-catalyzed aza-Nazarov cyclization of linear azidoenynes, but requiring electron-withdrawing groups in the 5-position (Scheme 1b).[4] Despite these significant achievements, it is still highly desirable to explore new reactions based on such a gold carbene[5] involved Nazarov cyclization, especially in an intermolecular and atom-economic way. In our recent study on the ynamide chemistry,[6−8] we first disclosed that benzyl azides could serve as efficient nitrene transfer reagents to react with ynamides to intermolecularly generate the α-imino gold carbenes,[9,10] allowing the site-selective synthesis of versatile 2-aminoindoles and 3-amino-β-carbolines.[8b] Inspired by these results, we envisioned that the gold-catalyzed intermolecular ynamide amination-initiated formal aza-Nazarov cyclization might be achieved by reaction of benzyl azides with 3-en-1-ynamides (Scheme 1c). Herein, we describe the realization of such a formal aza-Nazarov cyclization, thus leading to the highly regioselective synthesis of various 2-aminopyrroles, which are common structural motifs found in a variety of bioactive molecules (Figure 1).[11] Moreover, a mechanistic rationale for this tandem reaction, especially for the observed high regioselectivity, is also supported by DFT (density functional theory) calculations.

Scheme 1. Gold-Catalyzed Nazarov-Type Cyclization



At the outset, 3-en-1-ynamide **1a** was chosen as a model substrate for our initial study, and some of the results are outlined in Table 1. To our delight, the expected 2-

Received: May 24, 2016
Published: June 22, 2016

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DOI: 10.1021/acs.orglett.6b01503
Org. Lett. 2016, 18, 3254−3257

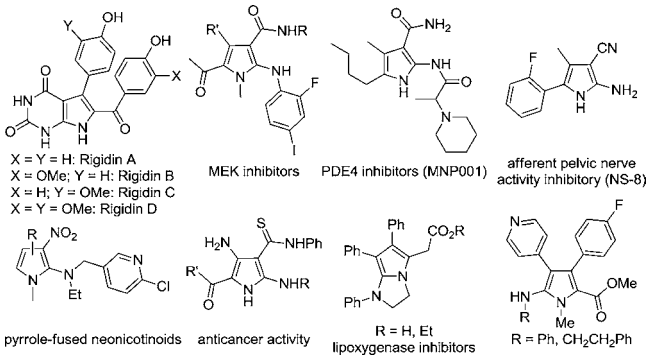
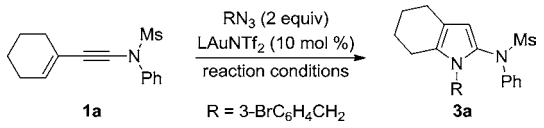


Figure 1. Selected examples of bioactive 2-aminopyrroles.

Table 1. Optimization of Reaction Conditions[a]



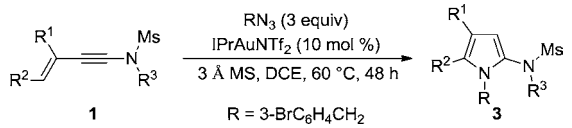
entry	gold catalyst	conditions	yield (%)[b]
1	$IPrAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	65
2	$SIPrAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	60
3	$Me_3PAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	<5
4	$Ph_3PAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	<5
5	$XPhosAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	<5
6	$BrettPhosAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	<5
7	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	4 Å MS, DCE, 80 °C, 30 h	6
8	$IPrAuNTf_2$	4 Å MS, DCE, 60 °C, 48 h	69
9	$IPrAuNTf_2$	3 Å MS, DCE, 60 °C, 48 h	74
10[c]	$IPrAuNTf_2$	3 Å MS, DCE, 60 °C, 48 h	80

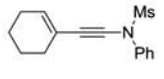
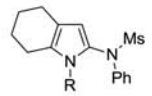
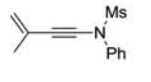
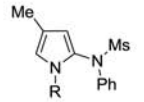
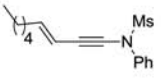
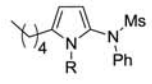
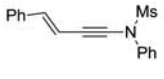
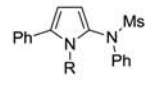
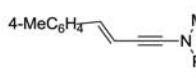
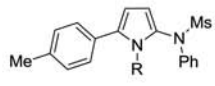
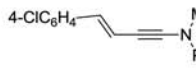
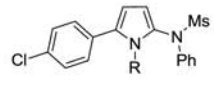
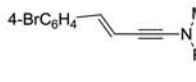
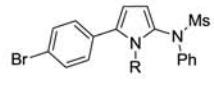
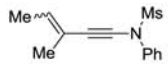
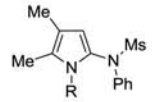
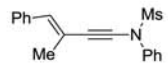
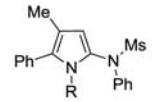
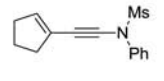
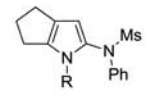
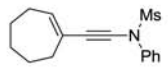
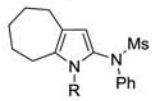
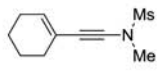
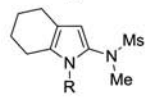
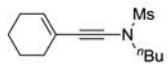
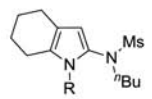
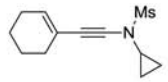
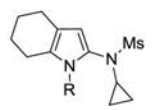
[a]Reaction conditions: [**1a**] = 0.1 M; DCE: 1,2-dichloroethane. [b]Estimated by ^1H NMR using diethyl phthalate as internal reference. [c]3 equiv of **2a** were used.

aminopyrrole **3a** was indeed formed in 65% ^1H NMR yield under our previously developed conditions ($IPrANTf_2$, 4 Å MS, DCE)[8b] by using 3-bromobenzyl azide **2a** as a nitrene transfer reagent (Table 1, entry 1). Importantly, this tandem reaction is highly regioselective and no 2-aminoindole formation was observed.[8b] Then, various typical gold catalysts with a range of electronic and steric characteristics were screened, and it was found that they failed to give an improved yield (Table 1, entries 2−7). The reaction yield could be slightly improved at 60 °C albeit with a long reaction time (Table 1, entry 8). Gratifyingly, a 74% yield was obtained by replacing 4 Å MS with 3 Å MS (Table 1, entry 9). In addition, it was found that the yield could be further improved to 80% by employing 3 equiv of **2a** (Table 1, entry 10). Finally, it should be mentioned that other typical transition metals such as $PtCl_2$, $AgNTf_2$, and $Zn(OTf)_2$ were not effective in promoting this reaction (<5%).[12]

Under the optimal reaction conditions, the generality of this novel formal [4 + 1] cycloaddition was then evaluated with a variety of 3-en-1-ynamide derivatives **1**. As shown in Table 2, various ynamides with aromatic or aliphatic substituents at the α or β position were first investigated, and it was found that the reaction could work smoothly to produce the expected 2-aminopyrroles **3b**−**3g** in 60−72% yields (Table 2, entries 2−7). In addition, the reaction was also compatible with ynamides bearing substituents at both the α and β positions, affording the corresponding pyrroles **3h**−**3i** in good yields (Table 2, entries 8−9). To our satisfaction, cyclopentenyl and cycloheptenyl substituted ynamides **1j** and **1k** were also suitable substrates for this reaction, thus delivering the desired fused 2-aminopyrroles

Table 2. Reaction Scope Study[a]



entry	substrate	1	product	3	yield (%)
1		1a		3a	76
2		1b		3b	71
3		1c		3c	64
4		1d		3d	72
5		1e		3e	60
6		1f		3f	68
7		1g		3g	70
8		1h		3h	70
9		1i		3i	71
10		1j		3j	74
11[b]		1k		3k	50
12[b]		1l		3l	72
13[b]		1m		3m	65
14		1n		3n	70

[a]Reactions run in vials; [**1**] = 0.1 M; isolated yields are reported. [b]Reaction time: 72 h.

DOI: 10.1021/acs.orglett.6b01503
Org. Lett. 2016, 18, 3254−3257

3j and **3k** in 74% and 50% yield, respectively (Table 2, entries 10−11). Notably, this tandem reaction is highly regioselective and no 2-aminoindole formation was observed in all these cases. Ynamides with different R^3 were also effective substrates and provided the desired products **3l**−**3n** in 65−72% yields (Table 2, entries 12−14). Finally, it should be mentioned that a longer reaction time was needed in some cases (Table 2, entries 11−13). The molecular structure of **3d** was further confirmed by X-ray crystallography (Figure 2). Thus, this protocol

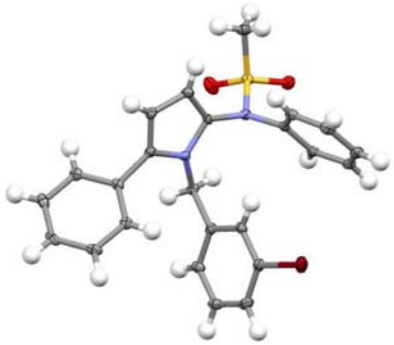
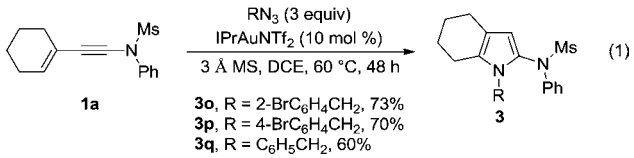


Figure 2. X-ray structure of **3d**.

provides a highly convenient and efficient route for the preparation of synthetically useful 2-aminopyrroles. To our disappointment, attempts to expand this chemistry to tosyl-protected ynamide were not successful.[12]

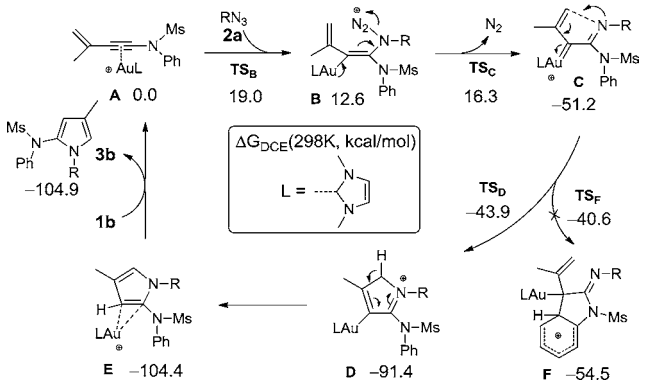
Besides 3-bromobenzyl azide **2a**, it was found that other bromo-substituted benzyl azides **2b**−**2c** also worked well to afford the desired 2-aminopyrroles **3o**−**3p** in good yields (eq 1). Similar to our previous protocol,[8b] benzyl azide **2d** gave a



decreased yield (eq 1) and the reaction proceeded with low efficiency (<30%) when the benzyl azides were substituted with electron-donating groups such as methyl and methoxyl.

A possible mechanism to rationalize the formation of **3b** was presented in Scheme 2 along with the relative free energies of key intermediates and transition states predicted by DFT

Scheme 2. M06(SMD, DCE)/6-31G(d,p)/SDD-Computed Relative Free Energies for the Reaction of 1b with 2a



computations.[12] The benzyl azide **2a** first attacked Au-activated alkyne **A**, leading to the generation of Au-substituted alkene **B** by overcoming a moderate free-energy barrier of 19.0 kcal/mol. Departure of N_2 readily gave the imine-containing gold−carbene intermediate **C**. Intramolecular cyclization occurred preferentially between the imine and terminal alkene, rather than between the gold−carbene and *N*-phenyl group. Finally, the as-formed intermediate **D** underwent proton transfer[8b] and ligand exchange to furnish product **3b**. The whole process was highly exothermic with free-energy release of 104.9 kcal/mol.

In summary, we have developed a convenient and viable alternative for the synthesis of structurally diverse 2-amino-pyrroles through gold-catalyzed intermolecular formal [4 + 1] cycloaddition of 3-en-1-ynamides with azides. Compared with the relevant intramolecular alkyne amination,[4] where an electron-deficient alkene is required to be conjugated with the alkyne, this intermolecular protocol demonstrates more flexibility and a wider substrate scope. Moreover, the mechanistic rationale for this novel intermolecular amination reaction, especially for the observed unique regioselectivity, is also strongly supported by DFT calculations. Further investigations into the synthetic applications of the current reaction are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01503.

Experimental procedures and spectral data for all new compounds (PDF)

X-ray crystallographic data for **3d** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Nos. 21272191, 21273177, and 21572186), the Natural Science Foundation of Fujian Province for Distinguished Young Scholars (No. 2015J06003), the President Research Funds from Xiamen University (No. 20720150045), NFFTBS (No. J1310024), and XMU Undergraduate Innovation and Entrepreneurship Training Programs (201510384008).

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(2) For recent selected examples, see: (a) Chen, M.; Sun, N.; Xu, W.; Zhao, J.; Wang, G.; Liu, Y. *Chem. - Eur. J.* **2015**, *21*, 18571. (b) Alford,

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