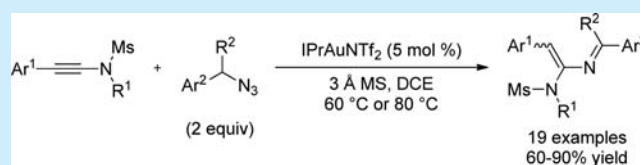


## Synthesis of 2-Aza-1,3-butadienes through Gold-Catalyzed Intermolecular Ynamide Amination/C–H Functionalization

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## S Supporting Information

**ABSTRACT:** A novel gold-catalyzed tandem intermolecular ynamide amination/C–H functionalization has been developed. A variety of highly functionalized 2-aza-1,3-butadienes can be obtained readily by utilizing this strategy. In addition,  $\alpha$ -imino gold carbene intermediates are proposed in this amination reaction and with support by DFT (density functional theory) calculations.

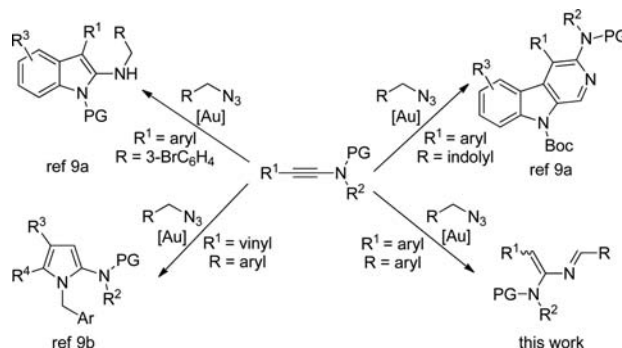


Functionalized 2-aza-1,3-butadienes have proved to be a very fundamental class of compounds.<sup>1,2</sup> For example, they have been widely used as key building blocks in the synthesis of nitrogen heterocycles,<sup>1,2</sup> which are common structural motifs found in a very large number of bioactive natural and non-natural molecules. It is surprising, however, that only a few preparative methods have been reported.<sup>3</sup> Therefore, novel approaches, especially those with high flexibility, efficiency, and good modularity, are in high demand to access this important structural motif.

Recently, the generation of  $\alpha$ -imino gold carbenes<sup>4</sup> through gold-catalyzed alkyne amination has received considerable attention, as this chemistry would offer great potential to build structurally complex nitrogen-containing molecules, especially the nitrogen heterocycles.<sup>5,6</sup> In 2015, our group demonstrated for the first time that benzyl or indolyl azides could serve as efficient nitrene-transfer reagents to react with ynamides<sup>7,8</sup> for the intermolecular generation of  $\alpha$ -imino gold carbenes, thus leading to the efficient synthesis of versatile 2-aminoindoles and 3-amino- $\beta$ -carboline skeletons (Scheme 1).<sup>9a</sup> On the basis of this work, we very recently developed the gold-catalyzed intermolecular ynamide amination initiated aza-Nazarov cyclization reaction, which afforded highly functionalized 2-aminopyrroles (Scheme 1).<sup>9b</sup> In this paper, we describe herein the realization of such an Au-catalyzed amination-initiated C–H functionalization, allowing the facile and efficient synthesis of various 2-aza-1,3-butadienes in generally moderate to good yields. In addition, relevant DFT (density functional theory) computations were also carried out to elucidate the reaction mechanism, especially for the observed high regioselectivity.

In our previous work, the formation of 2-aza-1,3-butadiene could be observed when the benzyl azides were substituted with electron-donating groups as nitrene-transfer reagents to react with ynamides.<sup>9a</sup> Inspired by this result, we began our

## Scheme 1. Gold-Catalyzed Intermolecular Reaction of Ynamides with Azides



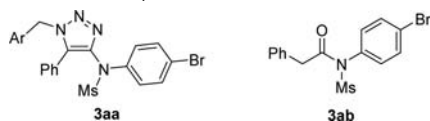
study by using ynamide **1a** bearing electron-deficient aryl group and *p*-methylbenzyl azide **2a** as the model substrates so as to inhibit the background 2-aminoindole formation. To our delight, the desired tandem ynamide amination/C–H functionalization proceeded well, affording the corresponding 2-aza-1,3-butadiene **3a** in 90% yield albeit with poor *Z/E* selectivity under the previously optimized reaction conditions (Table 1, entry 1).<sup>9a</sup> Importantly, neither triazole nor 2-aminoindole formation was detected in this case.<sup>10</sup> Then, various typical gold catalysts with different electronic and steric characteristics were investigated but failed to improve the reaction (entries 2–5). In addition, the yield was slightly improved by replacing 4 Å MS with 3 Å MS (entry 6). Gratifyingly, excellent *Z/E* selectivity was achieved when the reaction was performed at a reduced temperature (entry 7). Further screening of other solvents such as toluene and PhCl led to a significantly decreased yield (entries 8 and 9). Finally,

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Table 1. Optimization of Reaction Conditions<sup>a</sup>

$\text{Ph}-\text{C}\equiv\text{N}-\text{N}(\text{Ms})-\text{Ar} + \text{Ar}-\text{CH}_2-\text{N}_3 \xrightarrow[\text{reaction conditions}]{\text{catalyst (5 mol \%)}} \text{Ph}-\text{CH}=\text{N}-\text{N}(\text{Ms})-\text{CH}=\text{Ar}$				
entry	catalyst	conditions	yield (%) <sup>b</sup>	Z/E <sup>c</sup>
1	IPrAuNTf <sub>2</sub>	4 Å MS, DCE, 80 °C, 15 h	90	2.2:1
2	SIPrAuNTf <sub>2</sub>	4 Å MS, DCE, 80 °C, 15 h	88	2.0:1
3 <sup>d</sup>	Ph <sub>3</sub> PAuNTf <sub>2</sub>	4 Å MS, DCE, 80 °C, 15 h	11	>20:1
4	Cy-JohnPhosNTf <sub>2</sub>	4 Å MS, DCE, 80 °C, 15 h	80	1.2:1
5 <sup>e</sup>	BrettPhosAuNTf <sub>2</sub>	4 Å MS, DCE, 80 °C, 15 h	14	1.5:1
6	IPrAuNTf <sub>2</sub>	3 Å MS, DCE, 80 °C, 15 h	94	2.3:1
7	IPrAuNTf <sub>2</sub>	3 Å MS, DCE, 60 °C, 24 h	95	>20:1
8	IPrAuNTf <sub>2</sub>	3 Å MS, toluene, 80 °C, 15 h	60	1.3:1
9 <sup>f</sup>	IPrAuNTf <sub>2</sub>	3 Å MS, PhCl, 80 °C, 15 h	<1	
10 <sup>f</sup>	AgNTf <sub>2</sub>	3 Å MS, DCE, 80 °C, 15 h	<1	
11 <sup>g</sup>	PtCl <sub>2</sub>	3 Å MS, DCE, 80 °C, 30 h	<1	
12 <sup>h</sup>	Zn(OTf) <sub>2</sub>	3 Å MS, DCE, 80 °C, 15 h	<1	
13 <sup>f</sup>		3 Å MS, DCE, 80 °C, 15 h	<1	

<sup>a</sup>Reaction conditions: [1a] = 0.05 M. DCE: 1,2-dichloroethane.<sup>b</sup>Estimated by <sup>1</sup>H NMR using diethyl phthalate as internal reference.<sup>c</sup>Determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures.<sup>d</sup>71% of 1a remained unreacted. <sup>e</sup>84% of 1a remained unreacted.<sup>f</sup>>95% of 1a remained unreacted. <sup>g</sup>65% of 1a remained unreacted, and 3aa was obtained in 30% yield. <sup>h</sup>3ab was obtained in 75% yield.

it was found that other typical transition metals such as AgNTf<sub>2</sub>, PtCl<sub>2</sub>, and Zn(OTf)<sub>2</sub> were not effective in promoting this reaction (entries 10–12), and no 2-azabutadiene was formed in the absence of gold catalyst (entry 13). Of note, triazole 3aa was obtained as the main product by employing PtCl<sub>2</sub> as catalyst (entry 11).<sup>10</sup>

With the optimized reaction conditions in hand, we then explored the substrate scope with various ynamides (1a–m) and azides (2a–d). The reaction was found to be quite general as illustrated in Table 2. Besides ynamide 1a, the reaction also worked for ynamides with other phenyl substituents such as fluoro and chloro, affording the desired products 3b,c in excellent yields with excellent Z/E selectivity (entries 2 and 3). Notably, when ynamide 1d was employed, 2-aminoindole 3da could be formed in 21% yield (entry 4). Then, various alkyl-substituted ynamides were investigated, and the reaction furnished the corresponding 2-azabutadienes 3e–h in 60–85% yields with good to excellent Z/E selectivity (entries 5–8). In addition, ynamides bearing different Ar<sup>1</sup> groups were also suitable substrates for this reaction to deliver the desired products 3i–m in moderate to good yields with good to excellent Z/E selectivity (entries 9–13). Attempts to

extend the reaction to alkyl-substituted and terminal ynamides only gave a complicated mixture of products, and no desired 2-azabutadienes were detected.<sup>11</sup> Besides 4-methylbenzyl azide 2a, it was found that other arylmethyl azides 2b–d also worked well to produce the desired 2-azabutadienes 3n–q in good yields (entries 14–17). Of note, higher temperature and longer reaction time were needed in some cases (entries 8–13 and 15–17). The molecular structure of 3n was further confirmed by X-ray crystallography (Figure 1). Finally, it

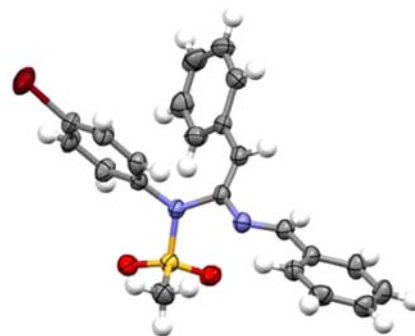
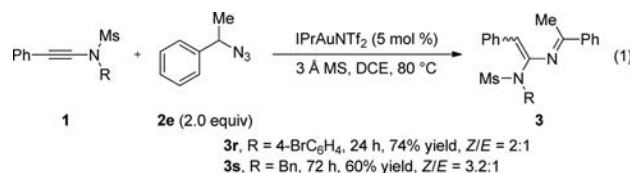


Figure 1. X-ray structure of 3n.

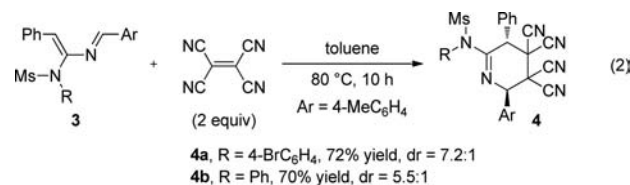
should be mentioned that no triazole formation was observed in any case. Thus, this protocol provides a facile, efficient, and viable alternative for the synthesis of valuable 2-azabutadienes.

In addition, we also tested whether sterically hindered (1-azidoethyl)benzene 2e could serve as the nitrene-transfer reagent. As shown in eq 1, the reaction of ynamides 1a and



1h with azide 2e proceeded smoothly under the optimal reaction conditions, affording the corresponding 2-azabutadienes 3r and 3s in 74% and 60% yield, respectively.

Further chemical transformation of the as-synthesized 2-aza-1,3-butadienes was also explored, as depicted in eq 2. For



example, aza-Diels–Alder reaction of 2-azabutadienes 3 with tetracyanoethylene in toluene could furnish the corresponding adducts 4 in good yields with good diastereoselectivity.<sup>12</sup>

A plausible mechanism to rationalize the formation of 3a is presented in Scheme 2 along with the relative free energies of key intermediates and transition states on the basis of DFT calculations.<sup>11</sup> First, azide 2a attacked the Au-activated alkyne A, forming the Au-substituted alkene B by overcoming a free energy barrier of 17.5 kcal/mol. Subsequent departure of N<sub>2</sub> from B with a small barrier of 4.1 kcal/mol gave the gold carbene intermediate C. Intermediate C underwent preferentially a concerted deprotonation/protodeauration process to

Table 2. Reaction Scope Study<sup>a</sup>

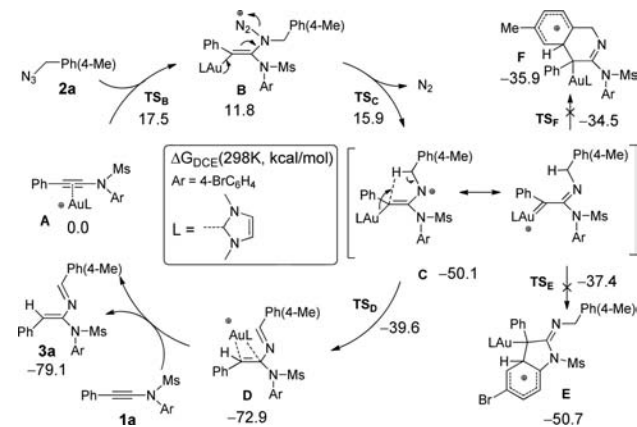
$$\text{Ar}^1\text{---}\text{N}(\text{Ms})\text{---}\text{R} + \text{Ar}^2\text{---}\text{N}_3 \xrightarrow[3 \text{ \AA MS, DCE, 60 }^\circ\text{C, 24 h}]{\text{IPrAuNTf}_2 (5 \text{ mol } \%)} \text{Ar}^1\text{---}\text{N}(\text{Ms})\text{---}\text{C}(\text{R})\text{=N---Ar}^2$$

1                      2 (2 equiv)                      2a, Ar<sup>2</sup> = 4-MeC<sub>6</sub>H<sub>4</sub>; 2b, Ar<sup>2</sup> = Ph  
2c, Ar<sup>2</sup> = 4-ClC<sub>6</sub>H<sub>4</sub>; 2d, Ar<sup>2</sup> = 4-BrC<sub>6</sub>H<sub>4</sub>                      3

entry	substrate	1	product	3	yield (%) Z/E
1	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 4-BrC <sub>6</sub> H <sub>4</sub>	1a	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ 4-BrC <sub>6</sub> H <sub>4</sub>	3a	90 >20:1
2	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 4-ClC <sub>6</sub> H <sub>4</sub>	1b	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ 4-ClC <sub>6</sub> H <sub>4</sub>	3b	88 14:1
3	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 4-FC <sub>6</sub> H <sub>4</sub>	1c	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ 4-FC <sub>6</sub> H <sub>4</sub>	3c	85 16:1
4 <sup>b</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Ph	1d	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Ph	3d	70 20:1
5 <sup>c</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Me	1e	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Me	3e	60 12:1
6 <sup>c</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 3	1f	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ 3	3f	70 >20:1
7	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 3	1g	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ 3	3g	72 >20:1
8 <sup>d</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1h	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3h	85 10/1
9 <sup>c</sup>	4-FC <sub>6</sub> H <sub>4</sub> $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1i	4-FC <sub>6</sub> H <sub>4</sub> $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3i	75 16/1
10 <sup>c</sup>	4-ClC <sub>6</sub> H <sub>4</sub> $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1j	4-ClC <sub>6</sub> H <sub>4</sub> $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3j	83 >20:1
11 <sup>c</sup>	4-BrC <sub>6</sub> H <sub>4</sub> $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1k	4-BrC <sub>6</sub> H <sub>4</sub> $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3k	79 >20:1
12 <sup>d</sup>	4-MeC <sub>6</sub> H <sub>4</sub> $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1l	4-MeC <sub>6</sub> H <sub>4</sub> $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3l	72 8.5:1
13 <sup>d</sup>	4-MeOC <sub>6</sub> H <sub>4</sub> $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1m	4-MeOC <sub>6</sub> H <sub>4</sub> $\text{---}$ C $\text{=}$ N $\text{---}$ Ar Ms-N $\text{---}$ Bn	3m	63 11:1
14 <sup>e</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ 4-BrC <sub>6</sub> H <sub>4</sub>	1a	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ph Ms-N $\text{---}$ 4-BrC <sub>6</sub> H <sub>4</sub>	3n	81 >20:1
15 <sup>d,e</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1h	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ Ph Ms-N $\text{---}$ Bn	3o	70 10:1
16 <sup>d,f</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1h	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ 4-ClC <sub>6</sub> H <sub>4</sub> Ms-N $\text{---}$ Bn	3p	72 17:1
17 <sup>d,g</sup>	Ph $\equiv$ N $\text{---}$ N(Ms) $\text{---}$ Bn	1h	Ph $\text{---}$ C $\text{=}$ N $\text{---}$ 4-BrC <sub>6</sub> H <sub>4</sub> Ms-N $\text{---}$ Bn	3q	71 18:1

<sup>a</sup>Reactions run in vials; [1] = 0.05 M; isolated yields (combined yields of Z and E) are reported; Z/E was determined by <sup>1</sup>H NMR spectroscopy of the crude reaction mixtures. <sup>b</sup>21% of 2-aminoindole 3da was isolated. <sup>c</sup>Reaction time: 72 h. <sup>d</sup>Reaction run at 80 °C, 72 h. <sup>e</sup>2b was used. <sup>f</sup>2c was used. <sup>g</sup>2d was used.

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



form intermediate **D** with a barrier of 10.5 kcal/mol, rather than the previously observed<sup>9a</sup> intramolecular cycloaddition of the gold carbene moiety to either 4-Br-phenyl or 4-Me-phenyl to form, respectively, intermediate **E** or **F**. Finally, ligand exchange with ynamide **1a** delivered product **3a** along with

regeneration of intermediate **A**. The whole process was highly exothermic with free energy release up to 79.1 kcal/mol.

In summary, we have developed an efficient, flexible, and viable alternative strategy for the preparation of synthetically useful 2-aza-1,3-butadienes through gold-catalyzed intermolecular ynamide amination/C–H functionalization reaction of ynamides with azides. Other notable features of this method include widespread availability of the substrates, compatibility with broad functional groups, simple procedure, mild reaction conditions, and in particular, no need to exclude moisture or air (“open flask”). Moreover, the mechanistic rationale for this novel intermolecular amination reaction, especially for the observed high regioselectivity, is also well supported by theoretical calculations. Further investigations into the synthetic applications of the current reaction are ongoing in our group.

## ■ ASSOCIATED CONTENT

### § Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02267.



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

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

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### Notes

The authors declare no competing financial interest.

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