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Gold-Catalyzed Formal [3 + 2] Cycloaddition of Ynamides with 4,5-Dihydro-1,2,4-oxadiazoles: Synthesis of Functionalized 4-Aminoimidazoles

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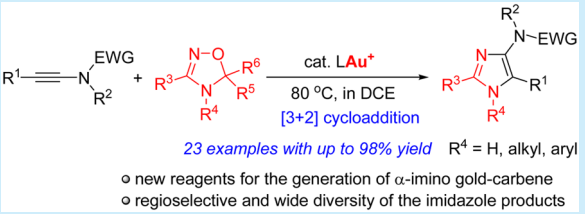
Supporting Information

ABSTRACT: A gold-catalyzed formal [3 + 2] cycloaddition of ynamides with 4,5-dihydro-1,2,4-oxadiazoles has been developed. The reaction provides a concise and regioselective access to highly functionalized 4-aminoimidazoles likely via the formation of an α-imino gold carbene intermediate followed by cyclization. 4,5-Dihydro-1,2,4-oxadiazole was found to act as an efficient *N*-iminonitrene equivalent in these reactions.



Imidazole rings constitute core structures of a wide range of biologically active substances, natural products, and synthetic organic compounds.[1] They have also found many applications in marketed drugs,[2] ionic liquids,[3] agrochemical industries,[4] coordination chemistry as unique ligands,[5] and functional materials.[6] 4-Aminoimidazoles are highly attractive due to their significant biological activities. For example, 1-methyl-4-amino-imidazole derivative **A** is a novel Jak2 inhibitor, which might be used for the treatment of myeloproliferative neoplasms (MPNs).[7] Imidazole **B** with a 4-[(2-sulfobenzoyl)amino] group represents a novel class of potent nonpeptide angiotensin II receptor antagonists, which may serve as a useful therapeutic agents for the treatment of hypertension.[8] 4-Pyridin-2(1*H*)-one-linkered imidazole **C** was discovered to be a potent inhibitor of human cytomegalovirus (HCMV).[9] In addition, 4-amino-imidazole **D** with a cyclobutyl ring was found to be an inhibitor of cyclin-dependent kinase 5/p25 for the treatment of Alzheimer's disease[10] (Figure 1). Although a large number of imidazole syntheses have been developed in recent years, few of these procedures are capable of being used for the synthesis of 4-aminoimidazoles.[11] These compounds are usually synthesized via reduction of 4-nitroimidazoles or cyclization of nitrile derivatives such as aminoacetonitrile with the thioiminoether hydrochloride salts.[11d] However, these methods usually suffer from limited substrate scope. Therefore, the development of highly efficient methods for the synthesis of 4-aminoimidazoles from easily available starting materials under mild reaction conditions is highly desirable.

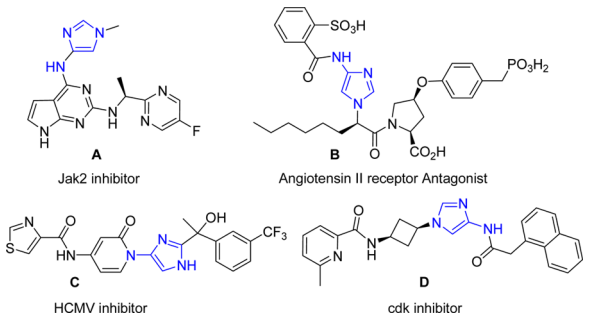


Figure 1. Biologically active 4-aminoimidazole derivatives.

On the other hand, gold-catalyzed cyclization or cycloaddition reactions involving α-imino gold carbenes as the key synthetic intermediates have gained much attention due to their high efficiency for the synthesis of nitrogen-containing heterocycles.[12] A series of nitrene-transfer reagents such as azides,[13a] 2*H*-azirines,[13b] *N*-iminopyridium ylides,[13c] isoxazoles,[13d] benzoisoxazoles,[13e] and triazapentalene[13f] have been developed to induce the generation of these highly reactive α-imino gold−carbene species. Recently, we discovered that 1,4,2-dioxazoles can be used as an efficient *N*-acylnitrene equivalent to trigger a facile generation of α-imino gold−carbene intermediate in gold-catalyzed nitrene-transfer reactions to ynamides.[14] The reaction offers a novel approach to highly functionalized oxazoles under mild reaction conditions (Scheme 1, A). Inspired by this work and our continuous interests on the chemistry of ynamides,[14,15] we envisioned that 4,5-dihydro-1,2,4-oxadiazoles might act as a new type of nitrene-transfer reagent because these substrates might also undergo the N−O bond cleavage reactions under the appropriate reaction conditions. For example, the N−O bond in 4,5-dihydro-1,2,4-oxadiazoles can be reductively cleaved through H_2/Raney nickel or under basic conditions.[16] The development of such transformations would be of great interest for the synthesis of functionalized 4-aminoimidazoles from ynamides and easily available heterocyclic substrates (Scheme 1, B). To date, transformations of 4,5-dihydro-1,2,4-oxadiazoles in catalysis are quite rare. During the preparation of our manuscript,

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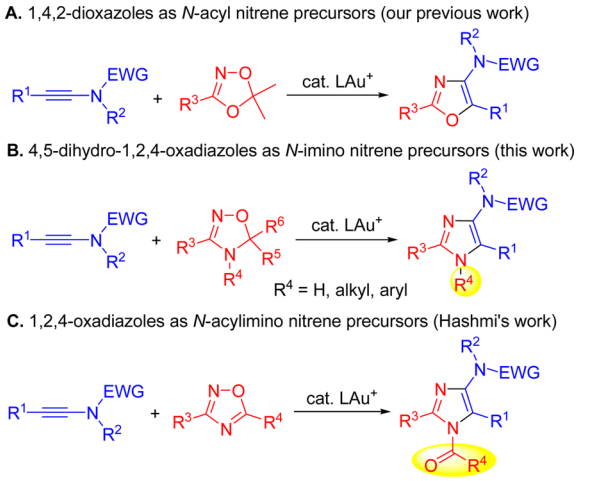
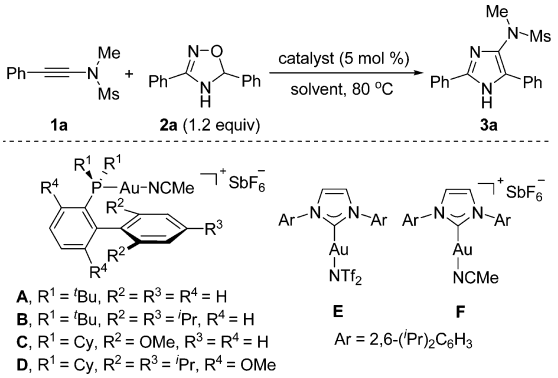
Scheme 1. Gold-catalyzed [3 + 2] Cycloaddition of Ynamides with Nitrene Precursors



Hashmi et al. reported an elegant gold-catalyzed cyclization of ynamides with saturated 1,2,4-oxadiazoles to *N*-acyl-substituted 4-aminoimidazoles (Scheme 1, C).[17] Compared with this work, our method utilizes 4,5-dihydro-1,2,4-oxadiazole, an unsaturated heterocycle, as the nucleophilic nitrene equivalent, which allows the access to *N*-H-, alkyl-, and aryl-substituted 4-amino-imidazoles. The method serves as a highly attractive complement to Hashmi's work for the synthesis of a wider diversity of 4-aminoimidazoles.

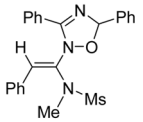
To test the feasibility of our hypothesis, we initially investigated the cyclization reaction of mesylamide-derived ynamide **1a** with 3,5-diphenyl-4,5-dihydro-1,2,4-oxadiazole **2a** bearing a free *N*-H moiety (Table 1). We anticipated that the 4-aminoimidazole **3a** with a free *N*-H group would result, which can be readily functionalized via *N*-substitution reactions. To our delight, the expected product **3a** was formed in 66% yield in the presence of 5 mol % of Johnphos(MeCN)AuSbF$_6$ (catalyst **A**) in DCE at 80 °C for 6 h (Table 1, entry 1). The results implied that the desired [3 + 2] cycloaddition of ynamide with 4,5-dihydro-1,2,4-oxadiazole could proceed with concomitant elimination of benzaldehyde. Since the steric and electronic effects of the ligands could have a large influence on the selectivity and efficiency of the reactions, we expected that the yield of **3a** might be improved through variation of the different ligands on gold catalyst. Then the effects of phosphine ligands on gold catalysts were examined (entries 2−4). Gratifyingly, it was found that gold catalyst **B** with a bulky ^{t}BuXphos as the ligand was highly efficient for this transformation, leading to **3a** in 98% yield (entry 2). In addition, benzaldehyde was formed quantatively according to ^{1}H NMR analysis of the crude reaction mixture. BrettPhosAu(MeCN)SbF$_6$ (catalyst **D**) with a highly crowded biphenyl ligand also afforded **3a** in a good yield of 85% (entry 4). The use of *N*-heterocyclic carbene gold(I) complex **E** (IPrAuNTf$_2$) or **F** (IPrAu(MeCN)SbF$_6$) (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene) as the catalysts only afforded moderate yields of **3a** (entries 5 and 6). PPh$_3$-ligated gold catalysts led to **3a** in 64−65% yields (entries 7 and 8). A gold(III) complex such as PicAuCl$_2$ or AuCl$_3$ could also catalyze the reaction, furnishing **3a** in 56% and 83% yield, respectively (entries 9 and 10). When the reactions were carried out in other solvents such as THF, DCM, MeCN, or toluene, **3a** was formed in lower yields of 30−68% (entries 11−14). Decreasing the amount of **2a** to 1.0 equiv gave a lower yield of **3a** (78%, entry 15). The use of ^{t}BuXphosAuCl as the catalyst afforded only 10% of **3a** (entry 16). Employing AgSbF$_6$, TfOH, or HNTf$_2$ as the catalyst afforded enamine **4a** as the major product derived from the attack of imino nitrogen of **2a** to the ynamide (entries 17−19). Increasing the amount of HNTf$_2$ to 1.0 equiv resulted in the formation of the complex reaction mixture.[18]

Table 1. Optimization of the Reaction Conditions



entry	catalyst	solvent	time (h)	yield (%)[a]
1	**A**	DCE	6	66
2	**B**	DCE	6.5	98[b]
3	**C**	DCE	17	68
4	**D**	DCE	12	85
5	**E**	DCE	6	68
6	**F**	DCE	9	61
7	PPh$_3$AuCl/AgSbF$_6$	DCE	5	64
8	PPh$_3$AuNTf$_2$	DCE	5	65
9	PicAuCl$_2$	DCE	5.5	56
10	AuCl$_3$	DCE	3.5	83
11	**B**	THF	4	41[c]
12	**B**	DCM	13	30[c]
13	**B**	MeCN	3	68
14	**B**	toluene	4	67
15	**B**	DCE	9	78[d]
16	^{t}BuXPhosAuCl	DCE	18	10
17	AgSbF$_6$	DCE	8.5	5[e]
18	TfOH	DCE	4	3[f]
19	HNTf$_2$	DCE	2.5	4[g]

[a]Isolated yields. [b]Benzaldehyde was formed in 97% NMR yield after stirring for 7 h as determined by ^{1}H NMR of the crude reaction mixture. [c]In a sealed Schlenk tube. [d]1 equiv **2a** was used. [e]48% **4a** was also isolated. [f]10 mol % TfOH was used. 50% **4a** was also isolated. [g]15 mol % HNTf$_2$ was used. 45% **4a** was also isolated.



4a

Having established an effective catalytic system for this novel cascade annulation reaction, we turned our attention to investigate the generality of this reaction. The scope of ynamides **1** was first studied using **2a** as the reaction partner under the reaction conditions given in Table 1, entry 2. As illustrated in Scheme 2, a wide variety of ynamides **1** participated well in the target reaction. The effects of the electron-withdrawing groups on nitrogen were examined. Compared with mesyl-protected substrate **1a**, tosyl-protected substrate **1b** afforded **3b** in a much lower yield of 70% with a longer reaction time. The results reveal that *N*-alkyl ynamides bearing mesyl protecting group display higher reactivity for this transformation. In addition, *N*-aryl-substituted ynamides, whenever bearing a mesyl or tosyl group on nitrogen, resulted in lower products yields and longer reaction time (**3c** and **3d**). Next, we examined the effects of the R^1 group on the alkyne terminus. When R^1 was an aryl group, generally, both electron-donating (*p*-Me, *p*-OMe) and electron-withdrawing substituents (*p*-F, *p*-CO$_2$Et) on the aryl rings were well compatible, leading to **3e**−**h** in 79−91% yields. Ynamide

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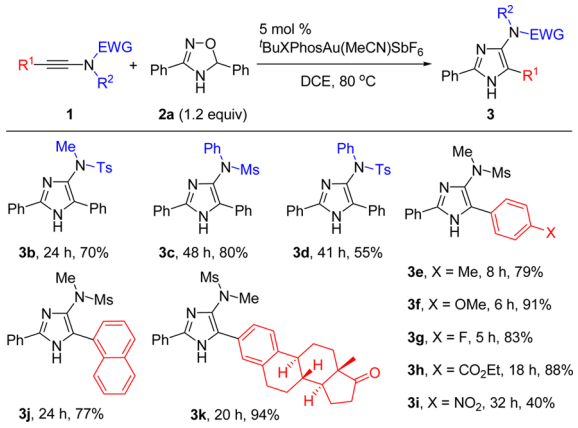
Scheme 2. Scope of Ynamides[a]

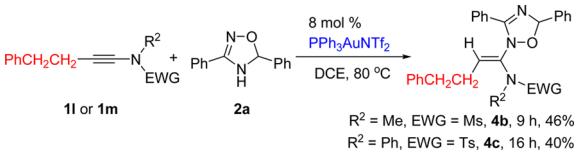


[a]Isolated yields.

bearing a NO_2-substituted aryl ring could also undergo the desired cyclization, albeit with a lower product yield (**3i**, 40%). A sterically demanding 1-naphthyl group was well suited, furnishing **3j** in 77% yield. Interestingly, ynamide with an 1,3,5(10)-estratrien-3-ol-17-one derivative also reacted efficiently to afford **3k** in 94% yield.

The reactivity of alkyl-substituted ynamides were also evaluated (Scheme 3). Interestingly, the reaction of phenethyl-

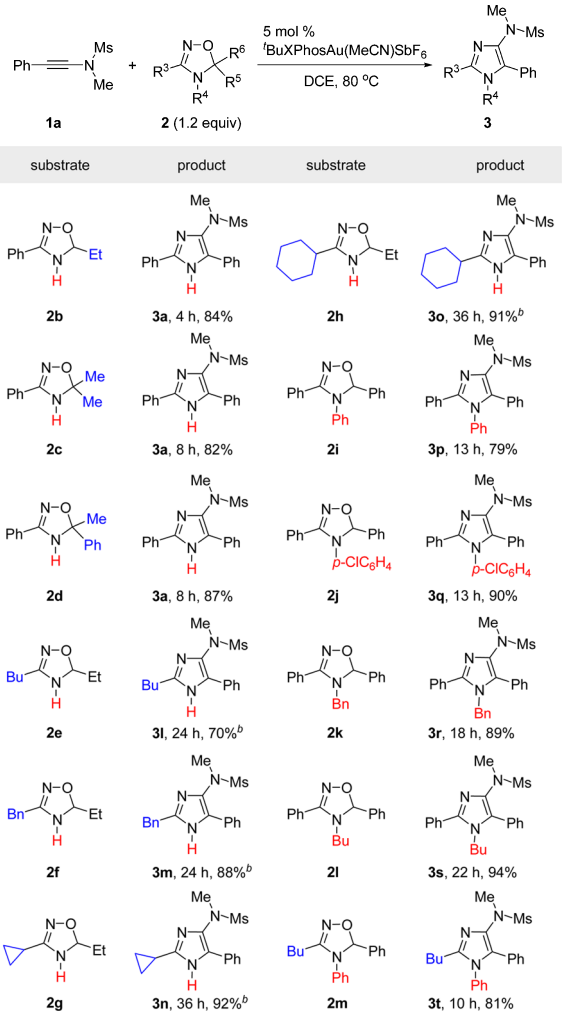
Scheme 3. Reactions of Alkyl-Substituted Ynamides with 2a



substituted ynamide **1l** with **2a** afforded enamine **4b** in 17% yield with high *Z*-stereoselectivity catalyzed by 5 mol % of catalyst **B**. The yield of **4b** could be improved to 46% using PPh_3AuNTf_2 as the catalyst. Under these conditions, *N*-tosylynamide **1m** afforded **4c** in 40% yield. It was likely that *Z*-**4b** was formed by gold-catalyzed isomerization of the initially generated *E*-**4b** or from the reaction of **2a** with keteniminium ion intermediate **5′** (vide infra) directly. The results indicate that the imino nitrogen attacks the ynamide preferentially, and ring-opening of 4,5-dihydro-1,2,4-oxadiazole does not occur in these cases, possibly due to the lower stability of the gold−carbene intermediate formed in the fragmentation step. These results also strongly supported our assumption that a vinyl gold intermediate was formed during the process. The structures of 4-aminoimidazole **3f** and **4a**, **4c** were unambiguously confirmed by X-ray crystallography.[19]

We next investigated the scope of 4,5-dihydro-1,2,4-oxadiazoles **2** using ynamide **1a** as the reaction partner (Table 2). To our delight, both of the *N*-H- and *N*-substituted[20] 4,5-dihydro-1,2,4-oxadiazoles **2** worked very well under the standard reaction conditions, furnishing the corresponding 4-amino-imidazoles in generally good to excellent yields (70−94%). In the cases of substrates **2b−d** with a free *N*-H group, the reaction efficiency was not affected by the nature of leaving groups (R^5COR^6): R^5 = Et, R^6 = H (**3a**, 84%) $R^5 = R^6$ = Me (**3a**, 82%), R^5 = Ph, R^6 = Me (**3a**, 87%). Alkyl (R^3)-substituted 4,5-dihydro-1,2,4-oxadiazoles such as butyl-, benzyl-, cyclopropyl-, or

Table 2. Scope of the 4,5-Dihydro-1,2,4-oxadiazoles[a]

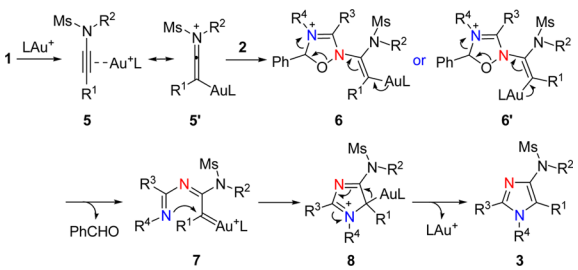


[a]Isolated yields. [b]1.8 equiv of 4,5-dihydro-1,2,4-oxadiazole was used.

cyclohexyl-substituted ones were also well suited for this reaction, furnishing **3l−o** in 70−92% yields. The effects of *N*-substituents R^4 were also investigated. *N*-Aryl-, benzyl-, and butyl-substituted substrates **2i−l** also turned out to be perfect substrates, leading to **3p−s** with a phenyl group as R^3 in high yields of 79−94%. *N*-Phenyl-substituted 4,5-dihydro-1,2,4-oxadiazole **2m** with an alkyl substituent as R^3 worked also efficiently (**3t**). These results further demonstrated the diversity and flexibility of this method.

On the basis of the above results and our previous work, a possible reaction mechanism is given in Scheme 4. Initially, the imino nitrogen attacks on the gold-coordinated ynamide **5** or

Scheme 4. Possible Reaction Mechanism



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keteniminium ion intermediate **5′** regioselectively due to the polarity of the ynamide to afford vinyl gold intermediate **6** or **6′** with an iminium ion moiety. Intermediate **6**/**6′** fragmentizes into the α-imino gold carbene **7** and benzaldehyde via N−O and C−N bond cleavage reaction. Nucleophilic attack of the imino nitrogen in **7** to gold−carbene followed by elimination of the gold catalyst leads to the products **3**.

In conclusion, we have developed a gold-catalyzed formal [3 + 2] cycloaddition of ynamides with 4,5-dihydro-1,2,4-oxadiazoles. The reaction provides a concise and regioselective access to highly functionalized 4-aminoimidazoles likely via the formation of an α-imino gold carbene intermediate followed by cyclization. 4,5-Dihydro-1,2,4-oxadiazole was found to act as an efficient *N*-imino nitrene equivalent in these reactions. The method offers several advantages such as easily accessible starting materials, high efficiency, and wide functional group tolerance. Further extensions of this reaction to the synthesis of other heterocycles such as sulfur-containing heterocycles are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01469.

Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallographic data for compounds **3f**, **4a**, and **4c** (PDF)

X-ray crystallographic data for compound **3f** (CIF)

X-ray crystallographic data for compound **4a** (CIF)

X-ray crystallographic data for compound **4c** (CIF)

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Notes

The authors declare no competing financial interest.

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(18) Very recently, Wan et al. reported that $HNTf_2$ could catalyze the [3 + 2] cycloaddition of ynamides with dioxazoles or *N*-alkyl-substituted oxadiazolones to oxazoles or 4-aminoimidazoles, respectively. See: (a) Zhao, Y.; Hu, Y.; Wang, C.; Li, X.; Wan, B. *J. Org. Chem.* **2017**, *82*, 3935. (b) Zhao, Y.; Hu, Y.; Li, X.; Wan, B. *Org. Biomol. Chem.* **2017**, *15*, 3413. However, in their work, when free *N*-H oxadiazolone was employed, only *N*-vinylimidazole derived from [3 + 2] cycloaddition followed by the addition with ynamide was obtained in low yield (ref 18b.). Our results indicated that the use of $HNTf_2$ as the catalyst only afforded a trace amount of the desired imidazole **3** when substrate **2** with a *N*-H group was employed. In addition, **3a** was not observed by treatment of **4a** with 5 mol % of catalyst **B** at 80 °C, indicating that our reaction does not proceed via **4a**. When **4a** was treated with 10 mol % of $HNTf_2$ at 80 °C, only a trace amount of **3a** was observed. A good yield of the imidazole product could be observed in the presence of 1.0 equiv of $HNTf_2$ when the substrate **2** with a *N*-R group was used. See ref 20.

(19) See the Supporting Information.

(20) The reaction of **1a** with **2j** bearing an *N*-R group was also investigated in the presence of $HNTf_2$. The yields of the desired **3q** were obtained in 28% and 69% at 80 °C in DCE using 15 mol % or 1.0 equiv of $HNTf_2$, respectively.

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