α-Imino Gold Carbenes from 1,2,4-Oxadiazoles: Atom-Economical Access to Fully Substituted 4-Aminoimidazoles

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Supporting Information

ABSTRACT: A novel and atom-economical synthesis of fully substituted 4-aminoimidazoles via gold-catalyzed selective [3 + 2] annulation of 1,2,4-oxadiazoles with ynamides is reported. This protocol represents a new strategy to access α-imino gold carbenes, which corresponds to an unprecedented intermolecular transfer of N-acylimino nitrenes to ynamides. Moreover, the reaction proceeds with 100% atom economy, exhibits good functional group tolerance, and can be conducted in gram scale.

As one fundamental framework, imidazole motifs frequently exist in a large number of natural products, pharmaceuticals, ionic liquids, and precursors of N-heterocyclic carbenes. In this family, fully substituted 4-oximidazole derivatives are core structures of some bioactive compounds and also serve as versatile building blocks (Figure 1). However, in contrast with the wealth of imidazole syntheses, few routes can allow direct access to fully substituted 4-oximidazoles. Hence, the development of general and practical methods for the construction of highly functionalized 4-oximidazole scaffolds is meaningful to synthetic and medicinal chemistry.

Recently, we and other groups verified that highly reactive α-imino gold carbenes generated in situ from various nucleophilic nitrenoid equivalents, such as azides, N-iminopyridinium ylides, 2H-azirines, and very recently developed isoxazoles, anthranils, triazapentalenes, dioxaazoles, and pyrido[1,2-b]indazoles, provided a powerful platform to construct an array of structurally diverse aza-heterocycles. Notwithstanding the recent advance attained, the exploration of α-imino gold carbene chemistry with less sensitive nitrene-transfer reagents, especially in an atom-economical and selective manner, is highly desirable.

1,2,4-Oxadiazole is an appealing candidate due to its stability, structural diversity, and simple handling. To date, the further transformations of 1,2,4-oxadiazoles were still surprisingly scarce. One representative work is the photoinduced rearrangement of 1,2,4-oxadiazoles to form N-acylimino nitrene intermediates which were subsequently trapped by different nucleophiles (Scheme 1a). Inspired by our previous work on gold carbenes, we considered the possibility of using 1,2,4-oxadiazoles as formal nitrene equivalents to form α-imino gold carbene intermediates via regioselective addition to gold-activated ynamides. Based on their high electrophilicity, subsequent intramolecular chemoselective trapping completed a [3 + 2] annulation, affording fully substituted 4-oximidazoles (Scheme 1b). If successful, this process would open

Figure 1. Representative bioactive compounds with fully substituted 4-oximidazole frameworks (in red).
a new window for the reaction pattern of 1,2,4-oxadiazoles and also complement the existing strategies for the synthesis of polysubstituted 4-aminoimidazole derivatives. Herein, we disclose a new route to α-imino gold carbenes from 1,2,4-oxadiazoles and ynamides, enabling the convergent and atom-economic synthesis of fully substituted 4-aminoimidazoles.

To evaluate the feasibility, ynamide 1a and 1,2,4-oxadiazole 2a were initially chosen for the model reaction (Table 1).

Gratifyingly, employing 5 mol % of IPrAuCl/AgNTf₂ as a catalyst at 80 °C can afford the desired product 3a in 95% NMR yield (entry 1). Control experiments without any catalyst or silver salt alone showed no conversion (entries 2 and 3). Other gold catalysts, PPh₃AuNTf₂, (2,4-tBu₂PhO)₃PAuCl/AgNTf₂, SPhosAuNTf₂, and KAuBr₄, were much less efficient, leading to 3a in lower yields (entries 4−7). Switching the counteranion from NTf₂ to OTf led to a significantly decreased yield (95% versus 67%, entries 1 and 8). In addition, other solvents such as DCE and toluene could not improve the reaction efficiency (entries 9 and 10). Decreasing the reaction temperature from 90 to 60 °C delivered 3a in moderate yield (entry 11).

Under the optimized reaction conditions, the scope of this novel transformation was investigated (Figure 2). First, with 1,2,4-oxadiazole 2a as the reaction partner, diverse ynamides bearing different protecting groups (Ms, Ts and Bs) and substituents on nitrogen tolerated the reaction conditions well, furnishing 3a−f in satisfying yields. We then examined the influence of the R₁ group on the alkyne terminus. Aryl-substituted ynamides with various substituents on the phenyl ring uniformly afforded the desired products 3g−m in 71−91% yields, regardless of their electronic and positional properties. An array of functional groups, including chloride, bromide, fluoride, ether, and ester, remained intact, offering opportunities for further modification at these positions (3h−m, p, w).

When thiophene-yl-substituted ynamide was subjected to standard conditions, imidazole 3n was obtained in high yield. With regard to the scope of 3,5-diaryl-1,2,4-oxadiazoles, it was found that electron-donating, electron-withdrawing, and neutral substituents on the aromatic ring were all compatible (3e−r).

Encouraged by these results, we further broaden the scope of this reaction by using a series of 1,2,4-oxadiazoles bearing one alkyl group on the parent ring (Figure 3). However, the use of 5 equiv of 1,2,4-oxadiazole 2a was necessary to obtain the desired products 3a in 95% NMR yield (entry 1). Control experiments without any catalyst or silver salt alone showed no conversion (entries 2 and 3). Other gold catalysts, PPh₃AuNTf₂, (2,4-tBu₂PhO)₃PAuCl/AgNTf₂, SPhosAuNTf₂, and KAuBr₄, were much less efficient, leading to 3a in lower yields (entries 4−7). Switching the counteranion from NTf₂ to OTf led to a significantly decreased yield (95% versus 67%, entries 1 and 8). In addition, other solvents such as DCE and toluene could not improve the reaction efficiency (entries 9 and 10). Decreasing the reaction temperature from 90 to 60 °C delivered 4-aminoimidazole 3a in a good yield of 80%.
In conclusion, we have demonstrated that 1,2,4-oxadiazoles could serve as novel nucleophilic nitrenoid equivalents for the generation of α-imo gold carbenes, corresponding to an intermolecular transfer of N-acyliminonitrenes to ynamides. This protocol offers a new reaction pattern of 1,2,4-oxadiazoles and opens up a novel and atom-economical strategy for the synthesis of valuable fully substituted 4-aminoimidazoles. The present reaction proceeds with 100% atom economy, displays good functional group compatibility, and can be conducted in gram-scale synthesis. Further applications of 1,2,4-oxadiazoles in other organic syntheses are ongoing in our group.

**REFERENCES**


**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00001.

Experimental procedures and spectroscopic characterization data (PDF)

X-ray data for 3v (CIF)

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**Notes**

The authors declare no competing financial interest.

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Figure 3. Reaction scope for 3,5-disubstituted 1,2,4-oxadiazoles. Reaction conditions: 1 (0.2 mmol), 2 (1 mmol), IPrAuCl/AgNTf2 (5 mol %), PhCF3 (1 mL), 80 °C. Isolated yields.

Scheme 2. Gram-Scale Synthesis

In conclusion, we have demonstrated that 1,2,4-oxadiazoles could serve as novel nucleophilic nitrenoid equivalents for the generation of α-imo gold carbenes, corresponding to an intermolecular transfer of N-acyliminonitrenes to ynamides. This protocol offers a new reaction pattern of 1,2,4-oxadiazoles and opens up a novel and atom-economical strategy for the synthesis of valuable fully substituted 4-aminoimidazoles. The present reaction proceeds with 100% atom economy, displays good functional group compatibility, and can be conducted in gram-scale synthesis. Further applications of 1,2,4-oxadiazoles in other organic syntheses are ongoing in our group.


