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Gold-Catalyzed Intermolecular Oxidative Diyne Cyclizations via 1,6-Carbene Transfer

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Abstract. A vinyl/ α -oxo carbene is generated *via* an α -oxo carbene formation and subsequently transferred across the second alkyne. These highly active species can react with nitriles in an intermolecular fashion to provide substituted oxazoles. This methodology goes through 1,6-carbene shift and offers a range of valuable products.

Keywords: gold catalysis; gold carbene; *N*-oxides; diyne; carbene transfer

demonstrated that the final electrophilic vinyl carbenoids can be exploited for further transformations like sp^3 -C-H insertions^[10] or alkyl-migrations^[11] (Scheme 1A). Based on the carbene shift strategy with *N*-oxides, we assumed that an *inter*molecularly offered reagent could also react with the final gold carbene which would significantly expand the applications of diynes in combination with *N*-oxides (Scheme 1B).

Homogeneous gold catalysis has attracted great attention in the field of organic synthesis in the last nineteen years.^[1] Chemists found that gold complexes as powerful soft Lewis acids are able to activate alkynes.[A. S. K. Hashmi, Gold Bull. 2003, 36, 3-9.] If appropriate precursors are used, gold carbenes are generated, which enable the design of many useful transformations.^[2] Recently, carbene to carbene transformations to obtain vinyl gold carbenes^[3] or benzyl gold carbenes^[4] were reported. Frist, an alkyne can be activated via π -coordination, then an 1,2migration/oxidation generates gold carbenes. This highly reactive intermediate can be transferred over a second tethered alkyne that enable a range of fruitful transformations. This interesting carbene transfer procedure was founded via Rh catalyzed diazo substrates^[5] and the first gold carbene transfer was demonstrated by Toste's group who also used a diazo compound as carbene precursor.^[6]

Our group has contributed the gold-catalyzed syntheses of naphthalene derivatives *via* 1,7-carbene shifts.^[7] That work demonstrated that an tethered alkyne can capture gold carbenes which were generated *via* 1,2-migration. In 2013, we found an unexpected reaction pathway to obtain gold carbene by using *N*-oxides in diyne systems.^[8] *N*-oxides can be used instead of diazo compounds to access α -oxo gold carbene shift of a initially formed α -oxo gold carbene generated by oxygen transfer from *N*-oxides which was transferred over a tethered alkyne. We also



Scheme 1. 1,6-carbene Transfer.

To test this assumption, we chose diyne substrates bearing one terminal alkyne and one alkyne conjugated to a carbonyl group. We assumed that nitriles could serve as reacting partners finally leading to oxazole substructures. As initial reaction we selected diyne **1a** in combination with acetonitrile and various N-oxides. To our delight the desired product **3a** was obtained in 13% yield by using IPrAuCl and AgNTf₂ (IPr 1,3-bis(2,6diisopropylphenyl)imidazol-2-ylidene, Tf trifluoromethylsulfonyl) in combination with 2,6dibromopyridine N-oxide as oxidant. The obtained structure was additionally confirmed by an X-ray single crystal structure analysis (Figure 1).^[12] The solid state molecular structure proved that both oxygen transfer and intermolecular attack occurred during the reaction.



Figure 1. Solid-state molecular structure of 3a.

Encouraged by this result, we started to optimize the reaction conditions (Table 1). Initially, we tested several *N*-oxides but no obvious increase in yield was observed (entries 2 and 3). Without N-oxides we only detected decomposition of the substrate. After that we investigated the effect of different ligands (entries 4-8). Among a series of different phosphane ligands Me_4 ^{BuXPhoxAuCl} turned out to be the best candidate, leading to 46% yield (entry 8). The role of the counter anion was significant and replacing AgNTf₂ with AgOTf led to the best result in combination with the optimized ligand Me₄ 'BuXPhos (entries 9-10). Under these conditions the desired product **3a** was obtained in 75% yield while with AgOTf alone no product was formed (entry 11).

Table 1. Optimization of the reaction conditions^{a,b}



^{a)} All reactions were carried out on a 0.2 mmol scale in 1 mL CH₃CN in presence of 1.2 equiv. *N*-oxide at 60 °C for 1 h. b) The yield was determined by GC with *n*-dodecane as internal standard. c) 5 mol% AgSbF₆ was used. d) 5 mol% AgOTf was used. e) Isolated yield is in the parenthesis.



Table 2. Scope with respect to the substrate^{a,b}



^{a)} Reaction conditions: **1** (0.2 mmol), **2a** (1 mL) Me₄^tBuXPhosAuCl (5 mol%), AgOTf (5 mol%) in presence of 1.2 equiv. 8-Ethylquinoline *N*-oxide at 60 °C. ^{b)} Isolated yield.

With the best reaction conditions in hand, we began to explore the substrate scope of the reaction (Table 2). At first, we synthesized a series of substrates containing differently substituted aromatic backbones (1b-1j). Electron-donating methyl or methoxy groups in para- or meta-position to the terminal alkyne at the arene moiety were tolerated well and the corresponding products were obtained in 72% and 64%, respectively (entries 2 and 3). Electronwithdrawing substituents further increased the yield. Halogen substituents including -F and -Cl afforded the products in good yields (entries 4 and 5). The same was the case for a CF₃-containing product **3f** that was obtained in 80% yield (entry 6). A decrease of the yield was observed with dimethoxy substituted 1g that was obtained in only 44% yield (entries 7). A longer alkyl chain on the carbonyl group also reacted well (70%, entry 8). The same was the case for aromatic substituted keto compound 1i that formed the corresponding product in 53% yield (entry 9). If an aldehyde was used instead of the ketone, no product was formed which might be attributed to the decreased nucleophilicity of the oxygen atom.



^{a)} All reactions were carried out on a 0.2 mmol scale in 1 mL nitriles in presence of 1.2 eq N-oxide, at 60 °C.

To further expand the scope, several nitriles were investigated. Propionitrile and isobutyronitrile proved to be suitable reaction solvents as well (Table 3, entries 11 and 12). Besides, benzonitrile also reacted with the diyne leading to 4c in moderate yield (entriy 13). If the amount of of nitrile was reduced to 10 eq. of acetonitrile in toluene as solvent after 8h **3a** was obtained in an acceptable yield of 57% yield (eqs 1). However, 5 eq. of benzonitrile led to a poor yield of less than 20% (eqs 2) which can be attributed to the reduced nucleophilicity of the nitrile.



Scheme 2. Control experiments.

According to our previous work and the work of Zhang,^[13,8] a proposed reaction mechanism is shown in Scheme 3. The first step starts with π -activation of the terminal alkyne in the presence of the gold catalysts. An α -oxo gold carbene **II** is then generated through oxygen transfer under selective oxidation of the alkynes by the N-oxides. It is worth noting that Noxides do not play the role of base like in the case of the dual activation reactions.^[14] Subsequently, the α oxo gold carbene II can undergo an intramolecular cyclopropenation to form intermediate III.^[15] Then a gold-mediated ring opening takes and a vinyl/ α -oxo carbene V is generated after ring opening of the cyclopropene. This stablized carbene V can be captured by the intermoleculary offered nitrile to obtain a cation intermediate VI. Intramolecular cyclization then delivers the desired product.



Scheme 3. Proposed reaction mechanism.

In conclusion, we demonstrated that gold carbenes generated by a 1,6-carbene shift can be trapped by an intermoleculary offered reagent. By following this strategy highly substituted oxazoles could b synthesized in good efficiency and broad scope. Further studies on the intermolecular capture of rearranged carbenoids are ongoing in our laboratories.^[16]

Experimental Section

General procedure for the synthesis of 3-(2,5dimethyloxazol-4-yl)-1H-inden-1-one (3a): To a Schlenk tube were added 4-(2-ethynylphenyl)but-3-yn-2-one(0.2 mmol), [Me₄ 'BuXPhosAuCl]/AgOTf (0.01 mmol), 8ethylquinoline *N*-oxide (0.24 mmol) in CH₃CN (1 mL). The resulting mixture was stirred at 60 °C for 1h. Then the solvent was removed under vacuum to give a residue, which was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) to yield the corresponding product **3a**.

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