Gold-Catalyzed Carbocyclization/C–N Bond Formation Cascade of Alkyne-Tethered Diazo Compounds with Benzo[c]isoxazoles for the Assembly of 4-Iminonaphthalenones and Indenes

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Abstract: A gold-catalyzed carbocyclization/C–N bond formation cascade reaction has been developed for the synthesis of polyfunctionalized 4-iminonaphthalenones and indenes in good to high yields under mild reaction conditions. The reaction goes through 5/6-endo-dig diazo-yne carbocyclization to form the endocyclic vinyl carbene species from corresponding alkyne-tethered diazo compounds, followed by electrophilic addition/N–O bond cleavage/aromatization sequence with benzo[c]isoxazoles, which features a C=N bond formation process. In addition, the resulting products could be converted into multi-substituted 2-naphthol derivatives in high yields.

Keywords: Gold-Catalysis; Alkyne Carbocyclization; Endocyclic Vinyl Carbone; Benzo[c]isoxazoles; 4-Iminonaphthalenones

Introduction

The 4-iminonaphthalenone motif is a unique and valuable skeleton found in a variety of natural products and bioactive molecules. During the past decade, a variety of catalytic approaches have been reported for construction of 4-iminonaphthalenones, such as condensation of quinone with arylamine, naphthol oxidation and aromatic electrophilic substitution with nitrosoarenes. Nevertheless, most of these methods are less efficient for the synthesis of multi-substituted analogous. Therefore, the development of effective and novel synthetic methods for the assembly of highly substituted 4-iminonaphthalenone frameworks with readily available substrates under mild conditions would certainly be in demand.

In the last two decades, the homogeneous gold catalysis comprises one of the most effective methods for the alkyne functionalization. In particular, the gold-catalyzed transformations of alkynes that involve carbene intermediates are of particular interest due to the divers possibilities for the effective construction of C–C and C–X bonds through metal carbene transformations, including C–H/X–H insertion, cycloaddition, cyclization, ylide interception, oxidation, rearrangement, and many others (Scheme 1a).

On the other hand, instead of using oxidative reagents to form α-carbonyl or α-imino carbene species, the catalytic transformations of diazo group embodied alkynes via carbene-alkyne metathesis (CAM) process, which in situ lead to the vinyl carbene intermediates, has provided a complemental approach in this area (Scheme 1b). Recently, our group has been focused on the catalytic diazo-yne carbocyclization for direct construction of a variety of carbocyclic frameworks. For example, the gold-catalyzed 6-endo-dig carbocyclization of alkynes with the pendent diazo unit in situ led to endocyclic vinyl carbene intermediates, providing practical approaches for the synthesis of multi-functionalized naphthalene derivatives with corresponding nucleophilic species (Scheme 1c, path a and path b). Inspired by these advances and as our ongoing interest in catalytic alkyne functionalization, we envisioned that a general approach for the construction of 4-iminonaphthalenone frameworks could be realized by...
interception of the endocyclic vinyl carbene intermediates with N-nucleophiles to form the C=N bond.\textsuperscript{[20]}

Herein, we report our recent results on this direction, a gold-catalyzed 6-endo-dig diazo-yne carbocyclization of diazo compounds 1, followed by a stepwise C=N bond formation cascade with benzo[c]isoxazoles, providing an expeditious synthesis of poly-functionalized 4-iminonaphthalenone and indene derivatives from corresponding diazo compounds (n = 0 or 1) in good to high yields under mild conditions. (Scheme 1c, path c).\textsuperscript{[21]}

Results and Discussion

Initially, the alkyne tethered diazo compound 1a and benzo[c]isoxazole 2a were used as the model substrates (Table 1). A variety of gold-complexes, which are potent π-acids and could selectively activate the alkynes,\textsuperscript{[7,18]} were investigated in dichloroethane (DCE) at 60 °C or 80 °C to ensure the complete conversion (entries 1–7). Among them, JohnPhosAuSbF$_6$ showed best results at 60 °C in term of yield and selectivity, providing the iminonaphthalenone 3a in 88% yield (entry 7). Encouraged by these results, other different metal catalysts were studied (entries 8–11). In the cases with Rh$_2$(OAc)$_4$, Cu(MeCN)$_2$PF$_6$, or AgSbF$_6$ as the catalyst, the tricyclic product 4a was obtained selectively in 67%, 88%, and 53% yields, respectively (entries 8–10).\textsuperscript{[22]} This product was generated via CAM process followed by formal [3+2]-cyclization.\textsuperscript{[15–17]} Whereas, the ZnCl$_2$ (20 mol%) led to the naphthalene-1,4-diol 5a in 65% yield, which was derived from addition of endocyclic vinyl carbene intermediate with unintentionally contaminated with water (entry 11).\textsuperscript{[18,23]}

With the optimal reaction conditions established, the substrate scope with respect to the diazo compounds was investigated (Table 2). A variety of substituents on the different positions of terminal aryl ring were all well tolerated, delivering the 4-iminonaphthalenone products 3a–3h in 63–95% yields. The 1-naphthyl, 1-thienyl, and cyclopropyl substituted alkynes also underwent the reaction smoothly, leading to the corresponding products 3i–3k in good to high yields. The impact of the ester part was then evaluated. It was found that the reaction could be applied to benzyl, 3-phenylallyl, diphenylmethyl, and alkyl esters without a noticeable yield deterioration (3l–3o, 71%–94% yields). Notably, L-menthol and citronellol derived esters were also effective, providing product 3p and 3q in 78% and 75% yields, respectively. Diazo compounds with substituents on the aryl linkage were suitable substrates, affording the corresponding products 3r–3t in 50%–89% yields. The structure of product 3g was confirmed by single-crystal X-ray
diffraction analysis, and other products were assigned by analogy.²⁴

The reaction scope with respect to benzo[c]isoxazoles was then examined under standard conditions (Table 3). The reaction with benzo[c]isoxazoles containing an electron-donating or electron-withdrawing group at the 5- or 6-position of aryl ring proceeded smoothly to afford the corresponding products 6a–6h in 80–93% yields. Moreover, the cascade reaction also occurred well with alkyl or phenyl substitution at the 3-position of benzo[c]isoxazoles, forming 6i and 6j in 50% and 82% yields, respectively.

Furthermore, this method could be extended to donor-acceptor type of diazo compounds 7. After a brief optimization (see Table S1 in SI for details), the best results were obtained by using BrettPhosAuNTf₂ (5.0 mol%) as the catalyst in DCE at 60 °C for 24 hours (Table S1, entry 4). The substrate scope was then examined under these optimal reaction conditions. As shown in Table 4, the reaction occurred smoothly with benzo[c]isoxazoles that have various substitutions on the different positions of aryl ring, including electron-neutral, electron-withdrawing, and electron-donating groups, leading to 8a–8i in good to high yields. Moreover, comparable high yields were obtained in the cases with 3-methyl and 3-phenyl substituted ones, finishing 8j and 8k in 55% and 85% yields, respectively. The structure of these generated indenes was confirmed by single-crystal X-ray diffraction analysis of its bromo-derivative 8l (90% yield).²⁴

To gain insight into the reaction mechanism, control experiments with alkynes 9 or 11, which did not have the diazo unit, with benzo[c]isoxazole 2a were conducted under standard conditions (Scheme 2).

Both of these reactions only led to the cyclization products 10 and 12 in 90% and 85% yields,
respectively; and no reaction with benzo[c]isoxazole 2a was occurred. These results implied that this reaction might go through intramolecular 6-endo-dig carbocyclization to form the endocyclic vinyl carbene species initially, rather than intermolecular electrophilic addition with 2a which is well known for the formation of α-imino carbene. Based on these results and previously reported work, a proposed mechanistic pathway has been illustrated in Scheme 3. Initially, the gold catalyst coordinates the π-bond of alkyne to form a gold π-complex I, followed by a 6-endo-dig cyclization with the nucleophilic carbon on the diazo group to generate the vinyl gold carbene II which might also existing as a cationic form II'. Both of these species, II and II', could be terminated by an electrophilic addition/ring-opening/ aromatization sequence with benzo[c]isoxazole 2a to form the 4-iminonaphthalenone product 3a via III with E-geometry. The formation of indenes 8 could go through an analogous process involving a 5-endo-dig carbocyclization. In the cases with Rh, Cu or Ag catalysts, the formation of carbene intermediate IV would occur preferentially, and the tricyclic product 4a was generated predominantly via carbene/alkyne mathesis process. Moreover, the intermolecular O–H insertion/aromatization of the vinyl carbene II would lead to the formation of naphthalene-1,4-diol 5a in the presence of ZnCl₂.

To demonstrate the synthetic utility of current method, we performed the reaction on a gram scale to provide 2.1 g 3d in 90% yield. Then, the generated products were subjected to further transformation (Scheme 4). The epoxidation product 13 was isolated as a single isomer in 90% yield after treating 3d with H₂O₂ in acetone. The 2,3-disubstituted naphthoquinone 14 was afforded in the presence of CF₃CO₂H in 80% yield. Moreover, the reduction product 15 could be obtained smoothly by treating 6f with NaBH₄ at 0°C in 90% yield. These postsynthetic modifications enhanced the potential value of this method for the expeditious synthesis of naphthalene derivatives with structural diversity.

### Conclusion
In summary, we have reported a gold-catalyzed diazo-yne carbocyclization/C=N bond formation cascade of alkynyl-tethered diazo compounds with benzo[c]isoxazoles that provides an expeditious synthesis of polyfunctionalized 4-iminonaphthalenones and indenes.
derivatives in good to high yields with broad substrate generality. In comparison with these reported works via initial addition of benzo[c]isoxazole with gold activated alkyne, this cascade reaction features a 6-endo-dig diazo-yne carbocyclization followed by addition sequence. Moreover, the products could be smoothly converted into naphthalene derivatives in good to excellent yields with structural diversity.

Experimental Section

General Procedure for the Synthesis of 4-iminonaphthalenones 3 and 6 (Table 2 and 3)

To a 10-mL oven-dried vial with a magnetic stirring bar, JohnPhosAuSbF$_5$ (3.9 mg, 5.0 mol%), 1 (0.1 mmol), 2 (0.12 mmol, 1.2 equiv.) and DCE (2.0 mL) was added in sequence at 30 °C under argon atmosphere, and the reaction mixture was stirred for 24 h under these conditions. When the reaction was completed (monitored by TLC), the crude reaction mixture was purified by flash column chromatography on silica gel (Hexanes:EtOAc = 20:1 to 15:1) to give the pure products 3 or 6 in 50%–95% yields.

General Procedure for the Synthesis of Indenes 8 (Table 4)

To a 10-mL oven-dried vial with a magnetic stirring bar, BrettPhosAuSbF$_5$ (5.0 mg, 5.0 mol%), 7 (0.1 mmol), 2 (0.12 mmol, 1.2 equiv.) and DCE (2.0 mL) was added in sequence at 30 °C under argon atmosphere, and the reaction mixture was stirred for 24 h under these conditions. When the reaction was completed (monitored by TLC), the crude reaction mixture was purified by flash column chromatography on silica gel (Hexanes:EtOAc = 20:1 to 15:1) to give the pure products 8 in 55%–95% yields.

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