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Gold-Catalyzed Stereoselective Dearomatization/Metal-Free Aerobic Oxidation: Access to 3-Substituted Indolines/Oxindoles

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unprecedented dearomatization of indoles with An diazoesters has been developed via cationic gold(I) catalysis. The functionalization selectively occurs at C3-position to deliver methylene indole derivatives in good yields with excellent Z-selectivity, demonstrating unusual reactivity and selectivity compared with other noble metal catalysis. Importantly, simply followed by silica gel adsorption, an unprecedented metal-free aerobic oxidation occurs for indoles bearing N-electronic donating substituents, providing a novel and efficient approach towards 3-substituted indolin-2-ones with newly formed quaternary stereocenter in excellent stereoselectivity. Notably, these processes afford directly and selectively access to a variety of valuable intermediates from abundant feedstock chemicals.

Introduction

Transition-metal-catalyzed carbene transfer from diazo compounds represents a powerful tool in modern organic synthesis, allowing rapidly assembling a range of valuable structures which can't be easily achieved by other methodologies.¹ Particularly, different metal-carbenes often exhibit distinct reactivity and selectivity toward the same reaction precursors, which increased molecular complexity. A noble example is the reaction of diazoesters with 2,3-nonsubstituted indoles, which often leads to two principals of products, namely cyclopropane derivatives (Scheme 1a)² and formal $C(sp^2)$ -H insertion products (Scheme 1b).³⁻⁷ Indeed, for the addition reaction, the use of rhodium,³ copper,⁴ iron⁵ and palladium⁶ complexes selectively afforded C3-alkylation products. In contrast, C2-alkylation has been observed for 1H-indoles when exposing to a ruthenium catalyst.⁷ Additionally, the annulation⁸ and N-H insertion reaction⁹ have also been reported.

On the other hand, recent literature disclosed that the reactivity and chemoselectivity of gold-carbene highly depended on the electronic and steric properties of ligand ancillary to the gold center,^{10,11} as well as the choice of counterion.¹² Variation of the gold catalysts has

recently shown to even allow the formation of gold(III) intermediates from gold(I) precursors.¹³ In 2014, Shi and

a) Metal-catalyzed cyclopropanation



Scheme 1 Functionalization of indoles by metal-carbene transfer from diazo compounds: previous reports and our discovery

co-workers described a ligand-controlled gold-catalyzed addition of arenes to α -aryl diazoesters.¹⁴ They mentioned one example of indole C3-alkylation in the presence of electron-deficient phosphite-gold catalyst, which exhibited similar chemo- and site-selectivity to rhodium and copper catalysis (Scheme 1b). However, we recently found that N-heterocyclic carbene (NHC) gold complexes displayed inverse chemoselectivity to phosphite gold catalysts even for the same substrates.^{15b} Thus, we envisioned that, when exposing to different gold catalysts, the reaction of indoles with diazo compounds would probably result in distinct reaction pathways. In continuation with our interests in gold-carbene chemistry,¹⁵ also as anticipated but out of expectation, we report herein the

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unprecedented stereoselective dearomatization of indoles with diazoesters under cationic gold(I) catalysis (Scheme 1c). Furthermore, when N-electron-donating substituted indoles have been utilized, an unprecedented metal-free aerobic oxidation occurs after the initial dearomatization.

Results and discussion

Table 1 Optimization of the reaction conditions^a



142aIPrAu(PhCN)BArFDCE-65152aIPrAu(PhCN)BArFTHF-50"Reaction conditions: To a solution of 5 mol% gold catalyst in 2 mL of
solvent was added 1a or 2a (0.2 mmol) and 3a (0.3 mmol) in 2 mL solvent
via a syringe pump under argon for 2 h. The mixture was stirred at rt for
another 2h. For 6a, silica gel (5 g) adsorption of crude products was
performed and has been put under air for 12 h at rt. ^bIsolated yields. (ArO) =
(2,4-di-tert-butylphenyl).Sch

At the outset, we employed N-boc indole 1a, N-benzyl indole 2a and phenyl diazoacetate 3a as model substrates to investigate the reaction (Table 1). The use of $Ph_3PAuCl/AgSbF_6$ (5 mol%) in dichloromethane at room temperature afforded C3-insertion product 5a in 70% yield (entry 1), while JohnPhosAuCl/AgSbF₆ gave 16% yield of 5a (entry 2). When *t*-BuXPhosAuCl was used, 10% yield of 4a was obtained although 5a still was the major product (entry 3). Not surprisingly, electron-deficient phosphite gold complex only gave 5a as single product (entry 4). Gratifyingly, the use of IPrAuCl/AgSbF₆ provided 4a in 70% yield (entry 5). We therefore start to survey other NHC gold complexes as well as to try different counterions. To our delight, the yield of **4a** was improved to 79% by IPrAu(PhCN)SbF₆ (entry 6), and was further increased to 81% by IPrAu(PhCN)BAr_F¹⁶ (entry 7). A screen of solvents revealed (entries 8 to 11) chloroform was the best one, providing **4a** in 87% yield (entry 9), and no significant side products were detected. The structure of **4a** was confirmed by NMR spectra and was further identified by X-ray analysis.¹⁷ Notably, when N-benzyl indole **2a** was subjected to this reaction, the corresponding 3-methyleneindoline was not obtained instead of the isolation of 3-substituted indolin-2-one **6a** in 77% yield (entry 12, see Supporting Information for details), indicating an aerobic oxidation occurred. Variation of the solvents didn't improve the reaction (entries 13 to 15).



Scheme 2. Substrate scope: Reaction conditions: To a solution of 5 mol% of IPrAu(PhCN)BAr_F in CHCl₃ (2 mL) was added a solution of **1** (0.2 mmol) and **3** (0.3 mmol) in 2 mL CHCl₃ at rt for 2h via a syringe pump under argon. The resulting mixture was stirred at rt for another 2h. Isolated yields were listed. 4 equiv of diazo substrate was used for the preparation of **4g**.

We then started to explore the substrate scope for the first dearomatization (Scheme 2). The reaction of indole 1a with a variety of diazoesters was firstly examined. It was observed that methyl phenyl diazoacetate gave the corresponding product in better yield than other esters (4a to 4d). Aromatic diazoesters with different substituents were employed, providing the corresponding 3-methyleneindolines in moderate to excellent yields (4e to 4k). In

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general, electron-deficient aromatic diazoesters furnished the products (4e to 4i) in higher yields than electron-rich substrates (4j to 4k). Next, the scope of indoles was investigated. Gratifyingly, C5-, C6- and C7-substituted N-boc indoles bearing either electronwithdrawing or electron-donating groups were all tolerated, furnishing the corresponding indolines in moderate to excellent vields (41 to 4p). Furthermore, different N-substituted indoles were also examined. The protecting groups such as tosyl (Ts), benzyloxycarbonyl (Cbz), benzoyl (Bz) and acetyl (Ac) were all amenable to the reaction and the corresponding products were obtained in acceptable yields (4g to 4t). This protocol was also amenable to pyrroles. The desired dearomatization products were isolated in good yields (4u to 4x). The structure of 4x was further confirmed by single-crystal X-ray crystallography.17 It should be noted all of the methylene derivatives were isolated in single Zconfiguration.



Scheme 3 Tandem reaction of dearomatization and aerobic oxidation. Reaction conditions: $IPrAu(PhCN)BAr_F$ (5 mol%), 2 (0.2 mmol) and 3 (0.3 mmol) in 4 mL CHCl₃ at rt for 4h. Then SiO₂ (5 g) adsorption, under air at rt for 12 to 24 h. Isolated yields

Next, we investigated the substrate scope of tandem reaction towards the formation of 3-substituted indolin-2-ones (Scheme 3). Generally, the reaction of 2a with aromatic diazoesters either bearing electron-donating or electron-withdrawing substituents all proceeded smoothly to afford the corresponding products in moderate to good yields (6a to 6h). Longer oxidation time (24 h) is needed for 6e to 6h. Afterwards, indoles bearing various substituents were examined. The use of N-benzyl 5-methoxy and 5-bromo indoles provided 6i and 6j in 81% and 74% yield, while 6-chloro and 6-methyl delivered the corresponding products in 75% and 78% yield, respectively. 7methoxy N-benzyl indole was also examined, and 6m was isolated in 53% yield. Finally, N-methyl and N-phenyl indoles were tested and the corresponding products (**6n** and **6o**) were obtained in moderate yields. The structure of **6a** and **6l** was confirmed by X-ray analysis.

Deuterium labeling and control experiments were conducted to understand the reaction mechanism (Scheme 4). First, 4a can't be converted to 5a under standard reaction conditions (Scheme 4a), which ruled out the possibility of preferential formation of 5 then followed by isomerization and vice versa. Next, the reaction of D-1a with 3a yielded D-4a. The high deuterium incorporation at the 2position might indicate a 1.2-hydrogen shift is likely involved in the reaction (Scheme 4b). Since there is significant loss of deuterium, we suspected that the reaction may be interfered by adventitious water present in the reaction mixture. Thus, a control reaction with 3 equivalents of D₂O was run. Indeed, significant deuterium incorporation in the product was observed (Scheme 4c), suggesting there is D/H exchange with adventitious proton source during the reaction progress. A study on the kinetic isotope effect (KIE) using intermolecular competition between 1a and D-1a indicated a KIE value of 3.35 (Scheme 4d), which is consistent with the 1,2hydrogen shift being the rate-determining step. Furthermore, compound 7 was separately prepared and subjected to the standard reaction conditions. Unfortunately, no reaction was observed. The chemical incompetence of 7 rules out its possible role as an intermediated in this process (Scheme 4e).



Scheme 4 Mechanistic studies on the dearomatization reaction

Next, mechanistic studies for the aerobic oxidation were carried out (Scheme 5). First, the reaction of **D-2a** with **3a** gave **D-6a** in 73% yield with low ratio of deuterium labeling (Scheme 5a). Moreover, the ¹⁸O-labeled product **6a'** was obtained in 78% yield under an ¹⁸O₂ atmosphere, indicating the oxygen atom in **6** came from air (Scheme 5b). Using TBHP (*tert*-Butyl hydroperoxide) instead of air as oxidant, the reaction was messy although **6a** could still be detected by GC/MS (Scheme 5c). To determine the role of silica gel, *p*-toluene sulfonic acid was added and the C-3 alkylation product **8**

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was obtained in high yield (Scheme 5d). Moreover, replacing silica gel with anhydrous MgSO₄, 6a was isolated in 68% yield upon exposure to air for 12 h (Scheme 5d). Therefore, the acidic property of silica gel may not be critically important for this transformation. Its role is presumably to facilitate the aerobic oxidation by increasing the contact surface of the olefin intermediate with oxygen. Just recently, López and co-workers reported gold-catalyzed formal insertion of arvl diazoesters to ferrocene to generate functionalized metallocenes.¹⁸ They also found silica gel promoted aerobic oxidation leading to tertiary-substituted ferrocenyl alcohols. In that case, they believed the aerobic oxidation might proceed through initial electron-transfer from iron to molecular oxygen, which triggered the radical sequence to give the target product. Thus, to determine the reactive intermediate for this oxidation process, the C3-alkylation product 8 was subjected to silica gel under air, however, no reaction occurred (Scheme 5d). Gratifyingly, although the reaction intermediates are extremely unstable, we successfully isolated intermediate 9 after carefully checking all of the reaction listed in Scheme 3. Furthermore, treatment of 9 with silica gel under air provided 6h in 73% yield (Scheme 5e). This result indicated that gold catalyst didn't work during the aerobic oxidation. Without silica gel adsorption, 6h can't be obtained either. Different from López's report, this aerobic oxidation does not involve metal participation.

this moment, the plausible ones have been proposed (Scheme 6). In view of the unique formation of Z-olefins, the carboxylate group may assist the olefin selectivity. Partially analogous to Fox's description on rhodium-catalyzed C-3 alkylation of indoles with diazoesters^{3d} and density functional theory (DFT) calculations reported by Xie et al,^{3f} the reaction of **3a** with cationic gold catalyst first generates gold carbene species IA or IB, which is followed by nucleophilic attack with indole to produce vlide III via transition state II. Then this ylide intermediate would undergo 1,2-hydrogen shift to give the final dearomatization intermediate IV, together with catalyst regeneration. The assistant of the ester carbonyl group explains the Z-configuration of the observed product. Next, silica gel-assisted aerobic oxidation occurs. The reaction of IV with molecular oxygen generates intermediate V via Schenck ene reaction.²¹ Owning to the high oxidation ability of the peroxide motif and electron-rich nature of the indole ring, subsequent internal epoxidation can rapidly take place via either VI and VII. Finally, semi-pinacol rearrangement of VI²² or rearrangement of the amino epoxide motif in VII^{23} leads to the observed amide 6. Considering the high reactivity of the peroxide V, the epoxidation step occurs on the same face of the indole plane once it is formed (C-C bond rotation is thus discouraged). In this scenario, the stereochemistry integrity determines the high diastereoselectivity observed in the final product.





Till now, several reaction mechanisms have been proposed for indole functionalization with diazo compounds in the presence of rhodium, copper or other metal complexes.²⁻⁸ Clearly, this gold-catalyzed dearomatization is quite different from these known processes.¹⁹ Although the exact reaction mechanism is not clear at

Scheme 6 Proposed reaction mechanism

Conclusions

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In summary, we have developed an unprecedented goldcatalyzed stereoselective dearomatization of indoles with diazoesters, providing 3-methyleneindolines in good to excellent yields with unique Z-configuration. Moreover, when N-donating substituents indoles were subjected to the reaction, a tandem reaction sequence occurred including the initial dearomatization and sequential metal-free aerobic oxidation to produce 3-substituted indolin-2-ones. As a result, molecular oxygen has been successfully inlaid into the final structure. Notably, the use of cationic gold(I) catalyst IPrAu(PhCN)BAr_F is crucial to the whole processes.

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Unprecedented gold-catalyzed dearomatization and metal-free aerobic oxidation have been developed.

