Acyl Migration versus Epoxidation in Gold Catalysis: Facile, Switchable, and Atom-Economic Synthesis of Acylindoles and Quinoline Derivatives

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Abstract: We report a switchable synthesis of acylindoles and quinoline derivatives via gold-catalyzed annihilations of anthranils and ynamides. α-Imino gold carbenes, generated in situ from anthranils and an N,O-coordinated gold(III) catalyst, undergo electrophilic attack to the aryl π-bond, followed by unexpected and highly selective 1,4- or 1,3-acyl migrations to form 6-acylindoles or 5-acylindoles. With the (2-biphenyl)di-tert-butylphosphine (JohnPhos) ligand, gold(I) carbenes experienced carbene/carbonyl additions to deliver quinoline oxides. Some of these epoxides are valuable substrates for the preparation of 3-hydroxyquinolines, quinolin-3(4H)-ones, and polycyclic compounds via facile in situ rearrangements. The reaction can be efficiently conducted on a gram scale and the obtained products are valuable substrates for preparing other potentially useful compounds. A computational study explained the unexpected selectivities and the dependency of the reaction pathway on the oxidation state and ligands of gold. With gold(III) the barrier for the formation of the strained oxirane ring is too high; whereas with gold(I) this transition state becomes accessible. Furthermore, energetic barriers to migration of the substituents on the intermediate sigmatropic complexes support the observed substitution pattern in the final product.

Introduction

Acyl groups are moieties of fundamental importance in organic chemistry. In contrast to classic Friedel–Crafts acylation reactions,[1] the migration of an acyl group is an atom-economic technique for preparing aryl aldehydes and ketones. In gold catalysis, propargylic esters undergo 1,2- or 1,3-acyloxy migration by nucleophilic attack of the carbonyl oxygen atom at the gold-activated C≡C triple bond, affording a gold carbene or an allene, which are both highly reactive for subsequent functionalization, and enable the generation of structural complexity.[2] A gold-triggered 1,3-acyloxy shift and 1,5-acyl shift cascade for preparing δ-diketones was devised using more complex propargylic esters.[3] Our group developed a gold-catalyzed tandem 1,3-acyloxy/1,5-acyloxy migration for the synthesis of pyrrolidin-2-ones.[4] 1,2-Acyl migrations for the synthesis of azeppino[3,4-b]indol-1-ones and dihydro-γ-carbolines were also explored by our group[5a] and the group of Liu et al.[5b] To date, although gold-catalyzed 1,2- and 1,5-acyl, as well 1,3- and 1,5-acyloxy, migrations have been studied well, neither a 1,4- nor a 1,3-acyl migration on a benzene ring has been described to the best of our knowledge.

The development of efficient synthetic methods through α-imino gold carbene intermediates has become an important tool for the construction of heterocycles. Gold-promoted nitrene transfer from nucleophilic nitrene equivalents, such as pyridine-basedaza-ylides,[6a] azides,[7] 2H-azirines,[8] isoxazole derivatives,[9] and sulfinimines[10] to alkynes, generates α-imino gold carbenes. These can efficiently undergo nucleophilic attack, C–H insertion, or cyclopropanation. However, no carbene/carbonyl additions of these gold carbenes to form epoxides have been reported in the literature. In 2015, the group of Ye et al.[9a] reported a formal [3+2] annulation of isoxazoles and ynamides for the synthesis of acylpyrroles (R = H, Scheme 1, entry 1). When R ≠ H, deacylated products are formed. Subsequently, diverse aza-heterocycles have been prepared from isoxazole derivatives by labile N–O bond cleavage.[9b–f] Anthranils, readily available and useful nitrene-transfer reagents, have attracted considerable interest over the last three years. Either an attack at the nitrogen atom forms α-imino gold carbenes and subsequent C–H insertions gives 7-acylindoles (Scheme 1, entry 2),[9g] or this versatile reagent undergoes oxygen attack to give quinoline oxides through seven-membered ring intermediates (Scheme 1, entry 3).[9h] Inspired by previous reports[9i–11] we herein report...
the unprecedented site-selective trapping of such α-imo

gold carbenes for a divergent synthesis of acyindoles or
epoxides via selective acyl shifts and epoxidations (Scheme 1,
entry 4).

Results and Discussion

We initially envisioned the synthesis of 2-aminooindole

from 7-methylanthranil 1a and N-phenylnamide 2ac

through a [3+2] C–H annulation (Scheme 2, path a). How-
ever, a quinoline oxide 5b (confirmed by X-ray crystallog-
raphy) was formed instead via a carbene-complex-mediated
epoxidation (Scheme 2, path b). An optimization of the
reaction conditions was conducted with 7-methylanthranil 1a
and N-methylamide 2a in the presence of various catalysts
LaUCl/AgX and solvents (Table 1). At room temperature
and in toluene, IPrauCl/AgNTf2 produced quinoline oxide 5a
in 20% yield, along with the unexpected 6-acylindole 3a
(13% yield) via an unprecedented 1,4-acyl migration
(Table 1, entry 1). When PPh3 was replaced by (2-biphenyl)-
di-tert-butylphosphine (JohnPhos), the conversion of 1a
was higher than 80% and the ratios of 5a/3a increased
dramatically (Table 1, entries 2–5). A change of the silver
activators (AgX; X = OTs, OTf, BF4, SbF6) delivered 5a/3a
with high selectivity (Table 1, entries 6–9), and John-
PhosAuCl/AgSbF6 performed best (Table 1, entry 9). Solvent

Table 1: Optimization of the reaction conditions.

| Entry | Catalyst | Solvent | Conversion 1a [%] | Yield 3a [%] | Yield 5a [%] |
|-------|----------|---------|-------------------|-------------|-------------|
| 1     | IPrauCl/AgNTf2 | toluene | 34               | 13          | 20          |
| 2     | Ph3PauCl/AgNTf2 | toluene | 81               | 8           | 39          |
| 3     | L1AuCl/AgNTf2  | toluene | 87               | 11          | 50          |
| 4     | L2AuCl/AgNTf2  | toluene | 90               | <5          | 29          |
| 5     | L3AuCl/AgNTf2  | toluene | 80               | <5          | 51          |
| 6     | L3AuCl/AgOtfs | toluene | 52               | <5          | 26          |
| 7     | L3AuCl/AgOTf    | toluene | 83               | <5          | 64          |
| 8     | L3AuCl/AgBF4    | toluene | 84               | <5          | 42          |
| 9     | L3AuCl/AgSbF6   | toluene | 87               | <5          | 75          |
| 10    | L2AuCl/AgSbF6   | toluene | 75               | <5          | 56          |
| 11    | L3AuCl/AgSbF6   | MeCN   | 97               | <5          | 77          |
| 12    | L3AuCl/AgSbF6   | CH2Cl2 | >99              | <5          | 95 (88)     |
| 13    | NaAuCl2·2H2O   | toluene | 92               | 69          | <5          |
| 14    | PicAuCl2        | toluene | >99              | 78          | 9           |
| 15    | PicAuCl2        | THF     | >99              | 42          | 16          |
| 16    | PicAuCl2        | MeCN    | >99              | 61          | 20          |
| 17    | PicAuCl2        | DCE     | >99              | 54          | <5          |
| 18    | PicAuCl2        | CH2Cl2  | >99              | 91 (87)     |
| 19    | AuBr3           | CH2Cl2  | 86               | 60          | 16          |

Acetonitrile (MeCN), 1,2-dichloroethane (DCE), tetrahydrofuran (THF), tosylate (OTs), triflate (OTf), bis(trifluoromethyl)sulfonylimide (NTf2).

Scheme 1. Gold-catalyzed annulations of alkynes and isoxazole deriva-
tives by N–O bond cleavage.

Scheme 2. The initial design and the unexpected result.
screening revealed CH$_2$Cl$_2$ as the optimal choice (Table 1, entries 10–12), affording 5a in 95% NMR yield (88% isolated yield on a 0.2 mmol scale). Interestingly, gold(III) catalysts precipitously reversed the reaction to give the totally unexpected 6-acetylindole 3a as a major product (Table 1, entries 13–18). Best among the gold(III) catalysts and solvents was PicAuCl$_2$ [13] giving 3a in 91% NMR yield (87% isolated yield on a 0.2 mmol scale) in CH$_2$Cl$_2$ (Table 1, entry 18). Alkyl-substituted substrates only afforded products of a 1,2-H shift.

The scope for the synthesis of acylindoles was first investigated under the optimized reaction conditions (Table 1, entry 18). As shown in Scheme 3, anthranil 1a reacted smoothly with a range of N-sulfonyl ynamides 2a–d at room temperature, affording the corresponding 6-acetylindoles 3a–d in 87–94% yields. While N-aryl ynamides 2j–n gave the desired products 3j–n in moderate yields, N-alkyl ynamides 2e–i showed higher efficiency. Yields of 50–99% were achieved with different ynamides 2o–x bearing a wide range of functionalities (Me, iBu, OEt, F, Cl, Br, or CF$_3$) at the ortho-, meta-, or para-positions on the arene rings. Dimethoxy ynamide 2y also underwent the transformation efficiently [12]. Compared to phenyl-substituted substrates, alkyl-substituted substrates only afforded the products of a 1,2-H shift; for example, the ynamide 2ac gave the unsaturated amidine 8.

The oxazolidinone-derived ynamide 2ab was well tolerated to produce 3ab (66%). 7-Methoxyl- and 7-chloroanthranils are appropriate substrates for this reaction. Disubstituted anthranils 1d and 1e were converted into the targets 3ae and 3af with 99% yields. Unexpectedly, by blocking the 6-position of anthranils, 1,3-acyl migrations proceeded and yielded 5-acetylindoles 4a–c [12] in 74–99% yields. Acetyl also migrated successfully and 5-acetylindole 4d was obtained in 42% yield. Notably the tricyclic product 4e was delivered in 99% yield.

We then explored the scope for the synthesis of quinoline derivatives by using JohnPhosAuCl/AgSbF$_6$ as the best catalyst (Scheme 4). In the case of ynamides 2, electronically diverse aromatic and aliphatic substituents at the R$_1$ position, and different protecting groups, were tolerated well to afford 5a, 5c–e, and 6a–e in 56–79% yields. Some of these quinoline oxides 5 underwent facile rearrangements [14] to 3-hydroxyquinolines 6a–e [13]. The polycyclic compound 10 was formed by an intramolecular nucleophilic ring opening reaction of epoxide 5d (Scheme 5). Ynamides containing either an electron-withdrawing group (F, CF$_3$, or Cl) or an electron-donating group (CH$_3$, or OCH$_3$CH$_2$) on the arene ring (R$_2$ = Ar) were easily converted to epoxides 5f–j and rearranged products 6f–h. The epoxidation reaction was applied to phenyl ynamides (R$_2$ = phenyl) and heterocyclic ynamide (R$_2$ = thiophen-3-yl), and the terminal ynamide (R$_2$ = H) also reacted well (89% of 3-hydroxyquinoline 6j). An alkyl ynamide delivered unsaturated amidine 8 in 47% yield instead of the desired quinoline product. Various anthranils were then examined. Anthranil 1j, without any

**Scheme 3.** Scope for the synthesis of acylindoles. [a] Reaction conditions: 1 (0.20 mmol, 1.0 equiv), PicAuCl$_2$ (3.9 mg, 5 mol%), CH$_2$Cl$_2$ (2 mL, 0.1 M). [b] Yield of isolated product. [c] 4-nitrophenylsulfonyl (Ns). [d] Reaction temperature = 50°C. Key: protecting group (PG), tosly (Ts), mesityl (Ms), nosyl (Ns).

**Scheme 4.** Scope for the synthesis of quinoline derivatives. [a] General procedure: 1 (0.24 mmol, 1.2 equiv) and 2 (0.20 mmol, 1.0 equiv) were added to a well-stirred mixture of JohnPhosAuCl$_2$ (5.3 mg, 5 mol%), and AgSbF$_6$ (3.4 mg, 5 mol%) in CH$_2$Cl$_2$ (2 mL, 0.1 M). [b] Yield of isolated product. [c] Catalyst (10 mol%), reaction temperature = 50°C. [d] The yield when using 5 mol% PicAuCl$_2$ is shown in parentheses.
substituents, gave epoxide 5k in moderate yield. 7-Chloro- and 7-bromoanthranils led to the corresponding products 5l (98%) and 5m (80%). 3-Methyl-substituted anthranils 1i and 1g delivered quinolin-3(4H)-ones 7a and 7b through epoxidations and subsequent rearrangements (Scheme 5).

Non-polarized alkynes were also tested (Scheme 6). At higher temperatures, both PicAuCl and JohnPhosAuCl/AgSbF6 were able to catalyze the annulation of 1a and phenylacetylene to 3-hydroxylquinoline 6k in 30% yield in slow reaction. 10 mol% Methanesulfonic acid (MsOH) was beneficial for substrate conversion and product formation. Diphenylacetylene also afforded 6l in 60% yield.

The gram-scale reaction between 1a and 2a (using only 2 mol% gold catalyst) gave 3a in 83% yield (Scheme 7). Even more useful compounds can be prepared from the obtained acylindoles and quinoline oxides. The NaBH4-mediated reduction of 3a afforded 6-hydroxymethylindole 3a’ in excellent yield, LiAlH4 reduced 3a to 6,7-dimethylindole 3a” in 74% yield at higher temperature. The acyl group of 3a could be converted to an alkynyl group through a Seyer–Gilbert homologation. Treatment of quinoline oxide 5b with 3 equiv of LiAlH4 provided facile access to tetrahydroquinolin-3-ol 9 via reduction/deamination processes.

To gain more insight into the reaction mechanism, we conducted two crossover experiments (Scheme 8). For the 1,3-acyl migration process, the experiment employed a mixture containing an equimolar amount of [D]-1k and 1f in the reaction with ynamide 2a. A 1H NMR spectroscopy and mass spectrometry study of the obtained products [D]-3a, 3ae, 4a, and [D]-4e showed no scrambling of deuterium; both of these two acyl migration processes are intramolecular.

Finally, we conducted a detailed computational study of the reaction mechanism at the M06-D3/def2-TZVP//M06/LANL2DZ,6-31G(d) level in CH2Cl2. We commenced our DFT-based mechanistic study by investigating which coordinating atom of the ligand on complex i is involved in the substitution reaction—a question that has not been studied in the many applications of i in catalysis. To this end, four trigonal bipyramidal transition structures TSi–TSiv were calculated for which the potential energies are reported underneath each structure in Figure 1. Our calculations indicate that TSi is lower in energy than the other three transition states, suggesting that the substitution reaction should mostly occur through TSi to give intermediate iii (Figure 2) from which the remainder of the catalytic reaction proceeds. Once structure iii is formed, it is subjected to a nucleophilic attack by substrate iv to afford v through transition structure TSi-v, which lies only 6.8 kcal mol⁻¹ above iii. The ensuing intermediate then undergoes N–O bond cleavage via transition structure TSii-v with an overall activation free energy of 14.4 kcal mol⁻¹, leading to exergic formation of intermediate vi.

**Scheme 5.** Synthesis of polycyclic compound 10 and quinolin-3(4H)-ones 7.[a,b] Reaction conditions: 1 (0.24 mmol, 1.2 equiv), 2 (0.20 mmol, 1.0 equiv), JohnPhosAuCl (5.3 mg, 5 mol%), AgSbF6 (3.4 mg, 5 mol%), CH2Cl2 (2 mL, 0.1 M). [b] Yield of isolated product. [c] Catalyst (10 mol%), reaction temperature = 50°C.

**Scheme 6.** Tests with non-polarized alkynes.[a] Yield of isolated products.

The gram-scale reaction between 1a and 2a (using only 2 mol% gold catalyst) gave 3a in 83% yield (Scheme 7). Even more useful compounds can be prepared from the obtained acylindoles and quinoline oxides. The NaBH₄-mediated reduction of 3a afforded 6-hydroxymethylindole 3a’ in excellent yield, LiAlH₄ reduced 3a to 6,7-dimethylindole 3a” in 74% yield at higher temperature. The acyl group of 3a could be converted to an alkynyl group through a Seyer–Gilbert homologation. Treatment of quinoline oxide 5b with 3 equiv of LiAlH₄ provided facile access to tetrahydroquinolin-3-ol 9 via reduction/deamination processes.

To gain more insight into the reaction mechanism,[¹⁵] we conducted two crossover experiments (Scheme 8). With respect to the 1,4-acyl migration, we conducted a crossover experiment using [D]-1a and 1d reacting with 2a. For the 1,3-acyl migration process, the experiment employed a mixture containing an equimolar amount of [D]-1k and 1f in the reaction with ynamide 2a. A 1H NMR spectroscopy and mass spectrometry study of the obtained products [D]-3a, 3ae, 4a, and [D]-4e showed no scrambling of deuterium; both of these two acyl migration processes are intramolecular.

Finally, we conducted a detailed computational study of the reaction mechanism at the M06-D3/def2-TZVP/M06/LANL2DZ,6-31G(d) level in CH₂Cl₂. We commenced our DFT-based mechanistic study by investigating which coordinating atom of the ligand on complex i is involved in the substitution reaction—a question that has not been studied in the many applications of i in catalysis. To this end, four trigonal bipyramidal transition structures TSᵢ–TSᵣᵢ were calculated for which the potential energies are reported underneath each structure in Figure 1. Our calculations indicate that TSᵢ is lower in energy than the other three transition states, suggesting that the substitution reaction should mostly occur through TSᵢ to give intermediate iii (Figure 2) from which the remainder of the catalytic reaction proceeds. Once structure iii is formed, it is subjected to a nucleophilic attack by substrate iv to afford v through transition structure TSᵢ-v, which lies only 6.8 kcal mol⁻¹ above iii. The ensuing intermediate then undergoes N–O bond cleavage via transition structure TSᵢᵢᵢ-v with an overall activation free energy of 14.4 kcal mol⁻¹, leading to exergic formation of intermediate vi.
Intermediate vi is a branching point for two pathways (Figure 3) as follows: 1) nucleophilic attack of the carbonyl group followed by deauration reaction via TS$_{vii}$ (pathway A) and 2) nucleophilic attack of the aryl ring to afford intermediate ix (pathway B). Our calculations show that the carbonyl group is a better nucleophile than the aryl ring but formation of vii is a dead end, from which the deauration process is very energy consuming with $\Delta G^* > 30$ kcal mol$^{-1}$. This low reactivity toward C–C coupling (deauration with formation of a strained three-membered oxirane ring) is ascribed to the high electrophilicity of the Au$^{III}$ center. Thus, although formation of vii is feasible during the reaction, it undergoes a reverse reaction to give vi from which ix is formed via transition structure TS$_{vi-ix}$.

Attempts to locate transition structure TS$_{vii}$ were unsuccessful. Thus, the energy of this transition structure was estimated by the scan of the potential energy surface, as illustrated in Figure 4.

Intermediate ix is a branching point for two competitive pathways (Figure 5). The formyl group can migrate along either the anticlockwise (pathway C) or clockwise (pathway D) direction. Pathway C was calculated to be about 4.4 kcal mol$^{-1}$ higher in energy than pathway D, implying that the formyl migration preferably takes place via pathway D. A potentially competing methyl shift would have a much higher barrier TS$_{xi-xii}$ to provide xii'. The preference for pathway D over C can be easily explained by the natural population analysis (NPA) of intermediate ix (Figure 5). The analysis shows that the partial charge of the carbon atom bonded to the sp$^2$ nitrogen is much more electron deficient than other centers, resulting in the formyl group preferentially migrating along the clockwise direction.
Once xii is formed, it can be consumed in two ways (Figure 6). It can be involved in another formyl migration (pathway E) or in a deprotonation process assisted by a base-like substrate iv (pathway F). In agreement with the experiment, pathway F was determined to be more favorable. Indeed, this pathway is preceded by protodeauration (proton transfer from xiii to the sp² nitrogen atom of xiv in a barrierless reaction) and finally produces the experimentally observed product. Based on these findings, we proposed a catalytic cycle for the acyl migration processes (Figure 7).

At this juncture, we are interested in understanding why the gold(I) complex mainly gives the epoxide product, which contrasts with the behavior of the gold(III) complex. This difference stems from the fact that the gold(I) complex contains a less electrophilic center compared with the gold(III) complex. As a consequence, the deauration reaction that starts from intermediate xix, and proceeds via C–C coupling, takes place more easily. Our calculations support this claim by showing that the energies of TSxviii–xix and TSxvii–xviii are com-
parable, resulting in both pathways A’ and B’ being competitive (Figure 8).

Conclusion

In summary, catalyst-controlled, tunable acyl migrations and epoxidations were discovered that occur via α-imo gold carbene intermediates. This efficient, scalable, atom-economic reaction shows high regioselectivity and broad scope, and it operates under mild conditions with easily available substrates. The method opens novel and concise routes to complicated acylindoles, quinoline oxide derivatives, poly cyclic compounds, and related compounds—all of which are potentially useful in medicinal chemistry and drug discovery. A computational study fully supported the observed chemoselectivity for gold(III), as well as the selectivity switch when using gold(I) catalysts. The effects explaining these selectivities and selectivity switches will be inspiring for further research in the field.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acyl migrations · anthranils · epoxidations · gold carbenes · gold catalysis

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Figure 8. Free energy profile for competition between two pathways A’ and B’ where gold(I) is used as the catalyst. Gibbs free energies (potential energies) are in kcal mol⁻¹.
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