Highly Stereoselective Synthesis of Polycyclic Indoles through Rearrangement/[4+2] Cycloaddition under Sequential Catalysis

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The indole moiety is a privileged structural motif in many biologically active and medicinally valuable molecules.[1] Polycyclic frameworks lead to relatively rigid structures that could be expected to show substantial selectivity in their interactions with enzymes or receptors.[2] Construction of polycyclic indoles usually requires multistep approaches.[3] The preparation of polyfunctional indoles is therefore an important research field.[4]

Sequential catalysis involving a binary catalytic system often reduces labor and waste and therefore has attracted much attention recently.[5] Homogeneous catalysis by gold complex has also received considerable attention in recent years.[6] The combination of mechanistically distinct organocatalysis and transition-metal catalysis, especially gold catalysis, has enabled novel transformations beyond those possible with single catalytic systems.[7–9] During our ongoing investigation on the nitrogen- or phosphine-containing Lewis base-catalyzed chemical transformation, we found that nitrogen-containing Lewis bases are efficient catalysts for highly regioselective and stereochemical active and medicinally valuable molecules.[1] Polycyclic frameworks lead to relatively rigid structures that could be expected to show substantial selectivity in their interactions with enzymes or receptors.[2] Construction of polycyclic indoles usually requires multistep approaches.[3] The preparation of polyfunctional indoles is therefore an important research field.[4]

In 2010, Gagosz’s group reported a novel gold-catalyzed rearrangement of propargyl benzyl ethers that allows for rapid preparation of variously substituted allenes (Scheme 1 A).[13] As for isatin-derived propargyl benzyl ether 1a, the α,β-unsaturated ketone 2a could be formed in 20% yield along with the release of HOBn (determined by GC analysis) rather than the allene product in wet dichloromethane (Scheme 1 B). Herein, we wish to report an interesting rearrangement/cycloaddition based on sequential catalysis of gold complex and a nitrogen-containing Lewis base to construct polycyclic indoles.

In order to clarify the effect of water on the rearrangement of benzyl ether 1a, we first carried out the reaction in freshly distilled dichloromethane containing various concentrations of water. The results are summarized in Table 1, and as can be seen the concentration of water has an obvious effect on this reaction: 1.0 equiv of water is enough to give 2a in good yield.

| Table 1. Effect of different water concentrations for the gold(I)-catalyzed rearrangement.[4] |
|-----------------------------------------------|
| H2O [equiv] | Yield 2a [%] | Yield 3a [%] |
| 0.5          | 30          | 5           |
| 1.0          | 41          | 5           |
| 1.5          | 36          | 20          |
| 2.0          | 33          | 35          |

[a] Reagents and conditions: a) [Ph3P]AuCl/AgOTf (5 mol%), CH2Cl2, RT, 2–10 h.

Next, we used propargyl benzyl ether 1a (0.1 mmol) as the substrate to optimize the reaction conditions. The results are summarized in Table 2. Examination of solvent effects revealed that chloroform was the solvent of choice giving 2a in 67% yield, whereas, in other organic solvents such as 1,2-dichloroethane, toluene, acetonitrile or 1,4-dioxane, 2a was formed in lower yield (Table 2, Entries 1–5). Carrying out the reaction in the presence of [(Bu3P)AuCl] or [(Me3P)AuCl] (5 mol%) afforded the desired product 2a in 40% and 52% yields, respectively (Table 2, Entries 6 and 7). Using [AuCl] or [AuCl3] instead of [(Bu3P)AuCl] as the gold catalyst gave 2a in 46% and 42% yields, respectively, and [Ph3PAu]OBF4 as well as [(BuXPhos)Au(NCMe)]SbF6 were not effective gold catalysts in this reaction (Table 2, Entries 8–11). Changing silver salt to
AgSbF$_6$ or AgBF$_4$ did not improve the reaction outcomes (Table 2, Entries 12 and 13). Moreover, adding [(Ph$_3$P)AuCl]/AgOTf or AgOTf (5 mol %) as the catalyst in the presence of water (1.0 equiv) did not promote the reaction (Table 2, Entry 14). Control experiments indicated that using [(Ph$_3$P)AuCl]/AgOTf alone as the catalyst did not promote the reaction (Table 2, Entries 15 and 16). Therefore, optimal reaction conditions were found when the reactions were carried out in chloroform at room temperature using [(Ph$_3$P)AuCl]/AgOTf (5 mol %) as the catalyst in the presence of water (1.0 equiv).

We subsequently examined the substrate scope of the reaction catalyzed by gold under the optimized conditions, and the results are shown in Table 3. As can be seen, for N-Bn protected substrates 1b–1d having an alkyl group at the terminus of the alkyne moiety (R$^1$), α,β-unsaturated ketones 2b–2d could be afforded in 45–50% yields (Table 3, Entries 1–3). Regardless of whether electron-withdrawing or electron-donating groups at the 5-, 6- or 7-position of the benzene ring of N-Bn protected isatins 1e–1o were employed, the reactions proceeded smoothly to give the corresponding products 2e–2o in moderate yields (up to 61% yield; Table 3, Entries 4–14). In the case of other substrates 1p–1s bearing different N-protecting groups, the reaction also produced the desired products 2p–2s in 34–55% yields (Table 3, Entries 15–18). It should be mentioned here that 10–25% of benzyl ether 3 were formed in all cases. Moreover, as for propargylic acetate 1t, the corresponding enone 2a was afforded only in 15% yield under the standard conditions (Scheme 2). The structure of compound 2i was confirmed by NMR spectroscopy and X-ray crystal structure analysis.[14] The ORTEP drawing of 2i is shown in Figure 1. The structures of products 2b–2s were determined by NMR, MS, and HRMS (for details, see the Supporting Information).

Next, we utilized α,β-unsaturated ketone 2a (0.1 mmol) and ethyl 2,3-butadienoate 4a (1.5 equiv) as the substrates to investigate their cyclization behavior in the presence of nitrogen-containing Lewis bases. The results are summarized in Table 4. We found that an interesting dihydropyran derivative 5a was formed in 80% yield using 1,4-diazabicyclo[2.2.2]octane (DABCO; 20 mol%) as the catalyst in chloroform at room temperature for 10 h (Table 4, Entry 1). Examination of solvent effects revealed that tetrahydrofuran was the solvent of choice giving 5a in 83% yield, while in other organic sol-

Table 2. Optimization of the reaction conditions for the gold(I)-catalyzed rearrangement.[4,12]

| Entry | Catalyst | Solvent | t [h] | Yield [%] |
|-------|----------|---------|-------|----------|
| 1     | [(Ph$_3$P)AuCl]/AgOTf | DCE     | 2     | 21       |
| 2     | [(Ph$_3$P)AuCl]/AgOTf | Toluene | 2     | 37       |
| 3     | [(Ph$_3$P)AuCl]/AgOTf | CH$_2$CN | 10    | NR       |
| 4     | [(Ph$_3$P)AuCl]/AgOTf | 1,4-Dioxane | 15    | 41       |
| 5     | [(Ph$_3$P)AuCl]/AgOTf | CHCl$_2$ | 2     | 67       |
| 6     | [(Bu$_3$P)AuCl]/AgOTf | CHCl$_2$ | 2     | 40       |
| 7     | [Me$_3$P$_2$Au]/AgOTf | CHCl$_2$ | 2     | 52       |
| 8     | [AuCl$_3$/AgOTf | CHCl$_2$ | 2     | 46       |
| 9     | [AuCl$_3$/AgOTf | CHCl$_2$ | 2     | 42       |
| 10    | [Ph$_3$PAu$_3$OBF$_4$ | CHCl$_3$ | 23    | 8        |
| 11    | [(Bu$_3$P)AuCl]/AgBF$_4$ | CHCl$_3$ | 22    | 7        |
| 12    | [(Ph$_3$P)AuCl]/AgBF$_4$ | CHCl$_3$ | 22    | 4        |
| 13    | [(Ph$_3$P)AuCl]/AgOTf | CHCl$_3$ | 24    | 0        |
| 14    | [(Ph$_3$P)AuCl]/AgBF$_4$ | CHCl$_3$ | 24    | 15       |
| 15    | AgOTf | CH$_2$Cl$_2$ | 10    | NR       |
| 16    | [(Ph$_3$P)AuCl] | CHCl$_2$ | 10    | NR       |

[a] Reagents and conditions: a) 1a (0.1 mmol), H$_2$O (1.0 equiv), catalyst (5 mol%), solvent (2.0 mL), RT, unless otherwise specified. [b] 10–20% of benzyl ether 3 was formed in the reaction. [c] Yield of isolated product. [d] 10 mol % catalyst was used. NR = no reaction; Bn = benzyl; DCE = 1,2-dichloroethane.

Table 3. Substrate scope of the gold(I)-catalyzed rearrangement.[4,14]

| Entry | Compd | R$^1$ | R$^2$ | PG | Product | Yield [%] |
|-------|-------|-------|-------|-----|---------|-----------|
| 1     | 1b    | Cyclohexyl | H | Bn | 2b     | 50        |
| 2     | 1c    | Me    | H | Bn | 2c     | 45        |
| 3     | 1d    | nBu   | H | Bn | 2d     | 46        |
| 4     | 1e    | Cyclopropyl | 5-Br | Bn | 2e     | 60        |
| 5     | 1f    | Cyclopropyl | 5-Cl | Bn | 2f     | 57        |
| 6     | 1g    | Cyclopropyl | 5-F  |     | 2g     | 48        |
| 7     | 1h    | Cyclopropyl | 5-Me | Bn | 2h     | 58        |
| 8     | 1i    | Cyclopropyl | 5-MeO| Bn | 2i     | 61        |
| 9     | 1j    | Cyclopropyl | 6-Br | Bn | 2j     | 58        |
| 10    | 1k    | Cyclopropyl | 6-Cl | Bn | 2k     | 53        |
| 11    | 1l    | Cyclopropyl | 6-Me | Bn | 2l     | 59        |
| 12    | 1m    | Cyclopropyl | 7-Br | Bn | 2m     | 47        |
| 13    | 1n    | Cyclopropyl | 7-Cl | Bn | 2n     | 44        |
| 14    | 1o    | Cyclopropyl | 7-F  | Bn | 2o     | 45        |
| 15    | 1p    | Cyclopropyl | H   | Ally | 2p | 52        |
| 16    | 1q    | Cyclopropyl | H   | Anthracen-9-ylmethyl | 2q | 34        |
| 17    | 1r    | Cyclopropyl | H   | Me  | 2r     | 55        |
| 18    | 1s    | Cyclopropyl | 5-Br | CPh$_3$ | 2s | 39        |

[a] Reagents and conditions: a) 1 (0.2 mmol), H$_2$O (1.0 equiv), [(Ph$_3$P)AuCl]/AgOTf (5 mol %), CHCl$_3$ (2.0 mL), RT, 3–10 h. [b] 10–25% benzyl ether 3 was formed during the reaction. [c] Yield of isolated product. PG = protecting group; Bn = benzyl.
vents such as acetonitrile, diethyl ether, 1,4-dioxane or toluene, 5a was afforded in lower yields (Table 4, Entries 2–6). Using 4-N,N-dimethylpyridine (DMAP), 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) or triethylamine instead of DABCO as the catalyst did not give 5a under otherwise identical conditions (Table 4, Entries 7–9). In the presence of K2CO3 or triphenylphosphane, 5a could not be obtained (Table 4, Entries 10 and 11). Increasing the employed amount of 4a to 2.0 equiv gave 5a in 86% yield (Table 4, Entry 12).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of the [4+2] cycloaddition reaction catalyzed by DABCO. As shown in Table 5, for N-Bn protected substrates 2b–2d in which R1 was an alkyl group, polycyclic indoles 5b–5d could be afforded in 70–83% yields (Table 5, Entries 1–3). Regardless of whether electron-withdrawing or electron-donating groups at the 5-, 6- or 7-position of the benzene ring of N-Bn protected isatins 2e–2o were employed, the corresponding products 5e–5o could be formed in 63–85% yield (Table 5, Entries 4–14). In the case of other α,β-unsaturated ketones 2p–2s bearing different N-protecting groups, the reaction also proceeded smoothly to give the desired cycloadducts 5p–5s in 74–89% yields (Table 5, Entries 15–18). Employing α-allenic ester 4b (R1 = Bn) instead of 4a gave corresponding polycyclic indoles 5t and 5u in 82% and 86% yields, respectively (Table 5, Entries 19 and 20). Further examination of 4c (R1 = tBu) revealed that dihydropyran derivative 5v could be obtained in 49% yield at reflux temperature, and 43% of 2a was recovered, indicating a broad substrate scope of this reaction (Table 5, Entry 21). The structure of compound 5f was confirmed by NMR spectroscopy and X-ray crystal structure analysis.[15] The ORTEP drawing of 5f is shown in Figure 2. The structures of products 5b–5v were determined by NMR, MS, and HRMS (for details, see the Supporting Information).

Figure 1. ORTEP drawing of 2i.

Figure 2. ORTEP drawing of 5f.
On the other hand, a convenient one-pot synthesis of polycyclic indoles from propargyl benzyl ether 1 is also possible and is described in Scheme 3. As for substrates 1a (R1 = cyclopropyl) and 1b (R1 = cyclohexyl), polycyclic indoles 5a and 5b could be afforded in 52% and 41% yields, respectively. Whether electron-withdrawing (R2 = 5-Br) or electron-donating groups (R2 = 6-Me) present on the benzene ring, the reaction proceeded smoothly in both cases to give the desired cycloaducts 5e and 5l in 45–48% yields.

To elucidate the rearrangement mechanism, an isotopic-labeling experiment has been performed (Scheme 4A). Carrying out the reaction in the presence of H218O (1.0 equiv) led to the formation of the corresponding product 2a in 32% yield (60% 18O) along with 3a in 27% yield (40% 18O; determined by ESI-MS analysis). Moreover, benzyl ether 3a could not be transformed to α,β-unsaturated ketone 2a under the standard conditions (Scheme 4B).

On the basis of above results, a plausible mechanism for these reactions is outlined in Scheme 5. In cycle L, coordination of gold(I) complex A to the alkene forms intermediate B, which is attacked by water to form enol D. The tautomerization and hydrolysis of intermediate D produces benzyl ether 3a. Alternatively, nucleophilic attack of water on the alkene moiety of intermediate B can also afford allenol C along with the release of HOBn, and which can further tautomerize to the corresponding conjugated enone 2a and regenerating the gold(I) complex A. In cycle R, DABCO reacts with the allenic ester 4a to generate a zwitterionic intermediate F, which undergoes intramolecular Michael addition with enone 2a to produce intermediate G. Enolization of G forms oxo-anionic intermediate H, followed by an intramolecular nucleophilic attack to give 2,3-dihydropyran I. Subsequently, the facile single bond rotation affords the sterically favored intermediate J, and then the elimination takes place to give the polycyclic indole 5a along with the regeneration of the catalyst E.

In conclusion, we have developed an efficient procedure for the sequential catalysis of rearrangement and [4+2] cycloadition to construct the polycyclic indoles in good yields with high stereoselectivities from isatin derivatives and allenic esters. This transformation is rapid and practical. It can be performed under very mild conditions bearing various substituents at many positions. Further applications of this chemistry and more detailed mechanistic investigation are under way in our laboratory.

**Experimental Section**

General procedure for gold(I)-catalyzed rearrangement of propargyl benzyl ethers under the standard reaction conditions:
Under ambient atmosphere, propargyl benzyl ethers 1 (0.2 mmol) and H$_2$O (1.0 equiv) were dissolved in CHCl$_3$ (2.0 mL) in a Schlenk tube, and [(Ph$_3$P)AuCl]/AgOTf (5 mol %) were added. The reaction mixture was stirred at RT until the reaction completed (determined using thin-layer chromatography). The solvent was removed in vacuo, and the residue was purified using flash column chromatography (SiO$_2$) to give corresponding products 2 in moderate yields.

General procedure for DABCO-catalyzed [4+2] cycloaddition of isatin-derived α,β-unsaturated ketones with α-allenic ester under standard reaction conditions: Under argon atmosphere, α,β-unsaturated ketones 2 (0.2 mmol) and 1,4-diazabicyclo[2.2.2]octane (DABCO; 20 mol %) were dissolved in tetrahydrofuran (THF; 2.0 mL) in a Schlenk tube, α-allenic ester 4 was added. The reaction mixture was stirred at RT until the reaction completed (determined using thin-layer chromatography). The solvent was removed in vacuo, and the residue was purified by flash column chromatography (SiO$_2$) to give corresponding products 5 in good yields.

Experimental procedures and spectral data for all new compounds are available in the Supporting Information.

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Scheme 4. A) Isotopic-labeling experiment. Reagents and conditions: a) [(Ph$_3$P)AuCl]/AgOTf (5 mol %), H$_2$^{18}O (1.0 equiv), CH$_2$Cl$_2$, RT, 2 h. B) Benzyl ether 3a did not react to α,β-unsaturated ketone 2a under the standard conditions. Reagents and conditions: b) [(Ph$_3$P)AuCl]/AgOTf (5 mol %), CHCl$_3$, RT, no reaction.

Scheme 5. A plausible reaction mechanism for the rearrangement/[4+2] cycloaddition under sequential catalysis.

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