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# Gold(I)-Catalyzed Dearomative Rautenstrauch Rearrangement: Enantioselective Access to Cyclopenta[*b*]indoles

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Supporting Information

**ABSTRACT:** A highly enantioselective dearomative Rautenstrauch rearrangement catalyzed by cationic (*S*)-DTBM-Segphosgold(I) is reported. This reaction provides a straightforward method to prepare enantioenriched cyclopenta[*b*]indoles. These studies show vast difference in enantioselectivity in the reactions of propargyl acetates and propargyl acetals in the chiral ligand-controlled Rautenstrauch reaction.

Since its first report in 1984, the Rautenstrauch rearrangement[1a] and related reactions have received attention as efficient approaches for the assembly of substituted carbocyclic compounds. Although earlier studies utilized palladium-based catalysts, other transition metals (Pt, Ru, Au) were subsequently found to catalyze this transformation through analogous mechanisms involving the 2,3-acyloxy migration of propargyl esters.[1,2] Generally, vinylogous metal carbenoid species have been proposed as intermediates in the reaction (Figure 1a).[3a,b] However, our group reported excellent chirality transfer in a gold-catalyzed Rautenstrauch rearrangement, which is inconsistent with an achiral carbenoid intermediate.[1g] Experimental and computational studies have supported a mechanism in which chirality transfer occurs through a transition state with helical chirality (Figure 1b).[3c] Although this asymmetric transformation provided a route to enantioenriched cyclopentenones from readily obtained chiral secondary propargyl alcohols, the lack of straightforward methods for the preparation of tertiary propargyl alcohols limited the scope of this process. Meanwhile, an enantioselective Rautenstrauch rearrangement of racemic propargyl esters is still an unresolved challenge for transition-metal catalysis.[4]

Indolines with a fused five-membered ring at the C2 and C3 positions (cyclopenta[*b*]indoles) represent a key structural motif of a number of natural products which exhibit a wide range of biological activities.[5] A number of methods have been developed to prepare this skeleton, but enantioselective variants are limited.[6] In 2005, Sarpong et al. reported a platinum-catalyzed Rautenstrauch-like rearrangement of indole-derived substrates,[1c] showing reactivity that was consistent with that of vinylogous carbenoid intermediate (Figure 1c, path a). In contrast, we rationalized that the presence of a cation-stabilizing amino group suggested that the intermediate might be best represented by taking into account the delocalized cationic resonance form.[7] As an alternative mechanism, we envisioned

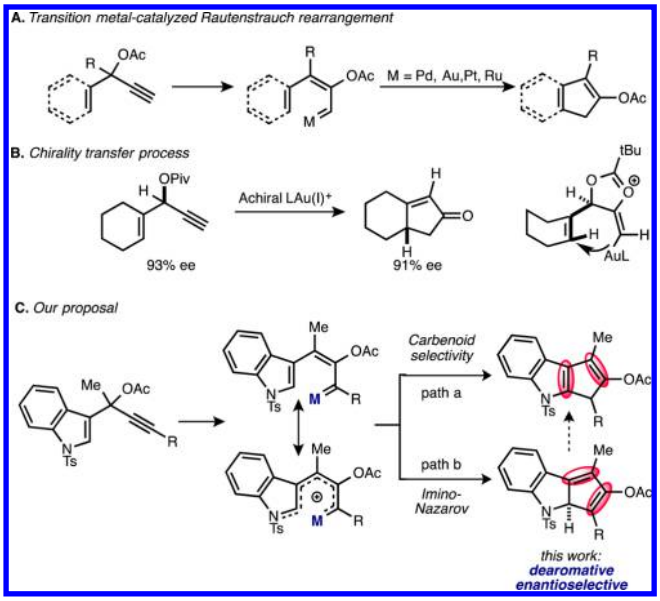


**Figure 1.** Mechanistic background for proposed studies.

this 1-aminopentadienyl intermediate would be subject to an imino-Nazarov rearrangement[8,9] providing a chiral dearomatized indole product, which could subsequently isomerize to the indole product.[10] Moreover, we posited that, in contrast to our previously report of chirality transfer,[1g,3c] the achiral gold carbenoid intermediate incorporated in the transformation might allow for a ligand controlled enantioselective Rautenstrauch rearrangement.

Initial studies revealed that, in the presence of cationic gold catalyst, indole-derived propargyl acetate **1a** indeed rearranged to deliver the proposed dearomative Rautenstrauch reaction product **2a** (Scheme 1). This result prompted us to examine chiral phosphine ligands to potentially render this transformation enantioselective.[11] However, low enantioselectivity was obtained even when sterically demanding ligands were employed. Efforts to improve the enantioselectivity by tuning the reaction conditions were uniformly unsuccessful. We hypothesized that reaction might be proceeding through a cyclic intermediate (A, Scheme 2) rather than a 1-aminopentadienyl carbenoid species, hence a chirality transfer process

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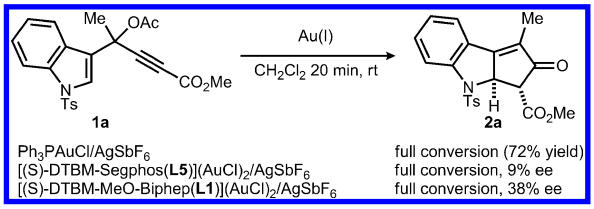
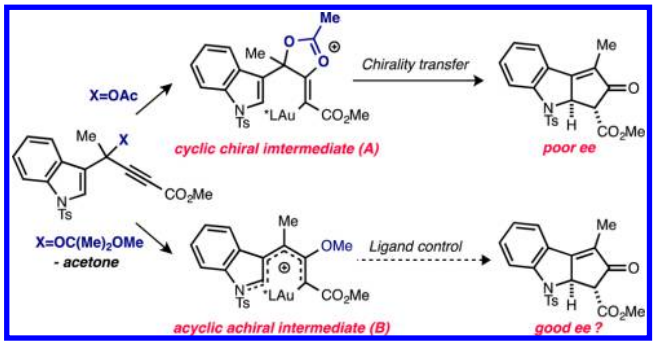
**Scheme 1. Preliminary Results**



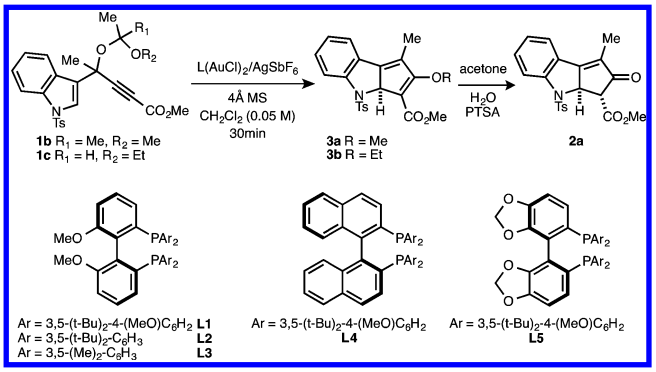

**Scheme 2. Mechanistic Hypothesis**




dominated instead of the desired ligand-controlled cyclization. In analogy to our previous carboalkoxylation,[12] we reasoned that the use of a ketal[13] in place of the acetoxy group in **1a** might lead to fully planar and achiral intermediate (B) that could undergo cyclization in a ligand-controlled manner.

To this end, we prepared propargyl ketal **1b** and subjected it to our previously developed conditions. In the presence of (*S*)-DTBM-MeO-Biphep$(AuCl)_2/AgSbF_6$ in dichloromethane, **1b** furnished the corresponding dearomatized indole in significantly improved ee, compared to substrate **1a** (Table 1, entry1). Different ligands based on the bisphosphine backbone

**Table 1. Optimization of the Reaction Conditions**




| entry[a] | substrate | ligand | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **1b** | **L1** | 72 | 87 |
| 2 | **1b** | **L2** | 69 | 92 |
| 3 | **1b** | **L3** | 62 | 40 |
| 4 | **1b** | **L4** | 54 | 83 |
| 5 | **1b** | **L5** | 63 | 91 |
| 6 | **1c** | **L2** | 74 | 92 |
| 7[d] | **1c** | **L5** | 75 | 95 |

[a]Reaction conditions: (1) 5 mol % gold catalyst, 10 mol % $AgSbF_6$, 0.05 mmol substrate, 10 mg 4 Å molecular sieves, 1 mL $CH_2Cl_2$. (2) 5 mg PTSA·$H_2O$, 1 mL acetone, 0.1 mL $H_2O$. [b]Isolated yields after two steps. [c]ee was determined by chiral HPLC analysis of the crude product.[16] [d]0.1 mmol scale, $c$ = 0.1 M, 20 min.

were evaluated and among them, DTB-MeO-Biphep (entry 2) and DTBM-Segphos (entry 5) gave the highest ee but the yield was moderate. Replacing the ketal moiety with a less hindered acetal (substrate **1c**) improved the yield to 74% without loss of enantioselectivity (entry 6 vs entry 2). Finally, both yield and enantioselectivity improved when the reaction was performed at higher concentration (75 yield, 95% ee, entry 7).

With these optimized conditions in hand, the substrate scope of this transformation was explored (Table 2). The substituents on the indole ring were first investigated. Substrates with an electron-withdrawing group (Br, F) or an electron-donating group (MeO, Me) at the C5 position were well-tolerated (entries 2−5). Substitution on the C6 and C7 position provided satisfactory results as well (entries 7−9). However, a substrate with substitution at the C4 position (entry 6) gave diminished enantioselectivity (66% yield, 81% ee), possibly as a consequence of restricted rotation of the indole ring resulting from the steric interaction between the C4 substituent and R2. Similarly, diminished enantioselectivities were observed for substrates bearing bulkier R2 substituents (compare entries 5, 10 and 11). Changing the ester group from a methyl ester to an ethyl ester had no obvious effect to the enantioselectivity and yield. An allylic ester was also investigated, giving the desired $\beta$-keto allylic ester in 78% yield with 94% ee (entry 13). Interestingly, no alkene cyclopropanation product was observed in this case. Reactions for substrates with other electron-withdrawing R3 groups were also examined. The reaction for the benzoyl substrate proceeded to give the product with acceptable enantioselectivity; however, moderate ee was obtained when the less bulky acetyl was employed (entries 14 and 15). Finally, a pyrrole-based substrate was tested under the standard reaction conditions. The reaction was complete in 1 min and the corresponding bicyclic product isolated in a moderate yield but still excellent ee (entry 16). Finally, to explore the scalability of the process, substrate **1a** was subjected to standard reaction conditions on a 1 mmol scale, employing 1 mol % catalyst. Under these conditions, the desired product **1a** was isolated in 67% yield, without affecting the enantioselectivity (entry 17).[14]

Given the propensity of the dearomatized adducts to racemize and isomerize to the indole product (see Supporting Information), we sought methods for their derivatization to stereochemically stable compounds.[16] As shown in Scheme 3, reduction of the Rautenstrauch reaction product furnished products with high yield and diastereoselectivity. Reduction of the ketone under Luche conditions gave the corresponding alcohol **4** in 53% combined yield from **1c** with 97% ee. Further catalytic hydrogenation of the alkene in **4** led to multi-substituted cyclopenta[*b*]indoles **5** in nearly quantitative yield with excellent diastereoselectivity. X-ray structure of **5** revealed that both the Luche reduction and the palladium-catalyzed hydrogenation occurred with approach from the convex face.

A proposed mechanism is shown in Scheme 4 using **1c** as a representative example. Upon initial coordination of the alkyne moiety in **6**, *anti* attack of the ethoxy ether of the acetal leads to the formation of oxonium species **7**. Rapid cleavage of the C−O bond in **7** generates acyclic oxocarbenium **8**, which extrudes acetaldehyde to give gold-substituted 1-aminopentadienyl intermediate **9** (which could also be represented by carbenoid resonance structure **9′**). Enantiodetermining C−C bond formation occurs through a chiral phosphinegold-controlled imino-Nazarov cyclization of **9** to afford **10**. Decomplexation of


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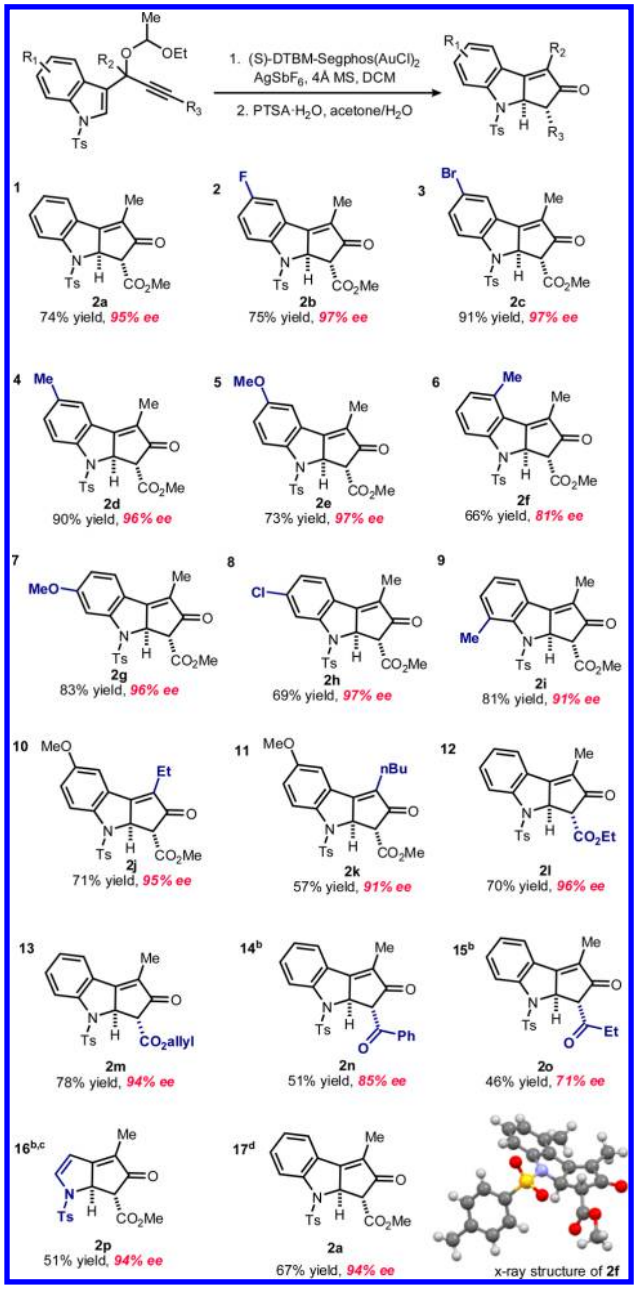
**Table 2. Substrate Scope**[a]

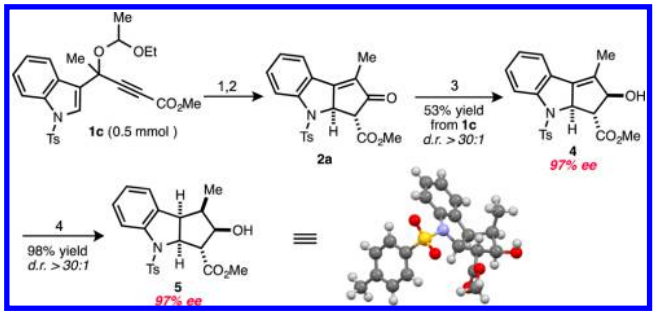



[a](a) Reaction conditions: (1) 5 mol % (*S*)-DTBM-Segphos(AuCl)$_2$, 10 mol % AgSbF$_6$, 0.1 mmol substrate, 20 mg 4 Å molecular sieve, 1 mL $CH_2Cl_2$, 20 min. (2) 10 mg PTSA·$H_2O$, 1 mL acetone, 0.1 mL $H_2O$, 3 min. See Supporting Information for details. (b) Isolated yields after two steps; ee was determined by chiral HPLC analysis of the crude product.[16]. (c) Absolute stereochemistry assigned by analogy to **2f**. [b]2.5 mol % (*S*)-DTBM-Segphos(AuCl)$_2$, 5 mol % AgSbF$_6$ was used. [c]Reaction was performed at 0 °C for 1 min. [d]1.0 mmol scale, 1 mol % (*S*)-DTBM-Segphos(AuCl)$_2$, 2 mol % AgSbF$_6$, 40 mg 4 Å molecular sieve, 3 mL $CH_2Cl_2$, 1 h.

cationic gold(I) furnishes the product **3b** which is subsequently hydrolyzed to **2a**.

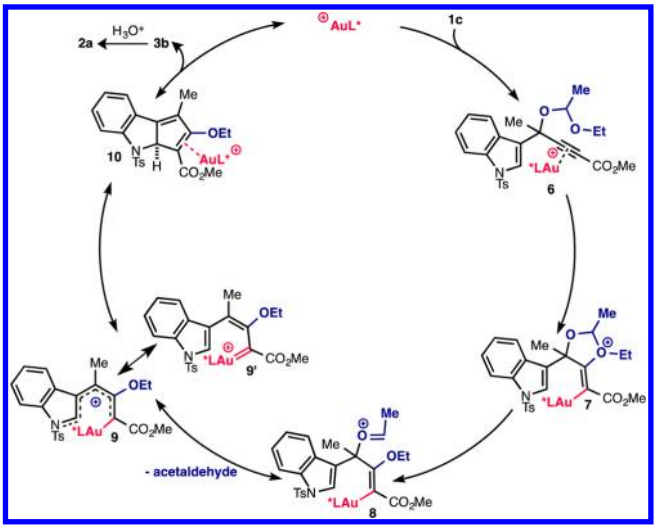
In conclusion, we have developed the first gold-catalyzed dearomative Rautenstrauch rearrangement. The (*S*)-DTBM-Segphos(AuCl)$_2$/AgSbF$_6$-catalyzed reactions provides access to cyclopenta[*b*]indoles with excellent enantioselectivities. The work highlights the divergent transformations achievable with

**Scheme 3. Synthetic Transformations**[a]




[a](a) Reaction conditions: (1) 2.5 mol % (*S*)-DTBM-Segphos(AuCl)$_2$, 5 mol % AgSbF$_6$, 0.5 mmol **1c**, 50 mg 4 Å molecular sieve, 2.5 mL $CH_2Cl_2$, 20 min. (2) 10 mg PTSA·$H_2O$, 2 mL acetone, 0.2 mL $H_2O$, 3 min. (3) $CeCl_3·7H_2O$, $NaBH_4$, DCM/EtOH, −78 to 0 °C. (4) 20 atm $H_2$, EtOH/EtOAc. (b) Isolated yields. d.r. were determined by $^1$H NMR analysis of the crude product. ee was determined by chiral HPLC.

**Scheme 4. Proposed Catalytic Cycle**




of electrophilic platinum and gold catalysis. In this case, these differences in product selectivity can, in part, be attributed to the milder reaction conditions of the gold-catalyzed reaction allowing isolation on the initially formed dearomatization adduct. While carbenoid intermediates generated by 1,2-propargyl shifts are often treated as identical, profoundly different selectivity was observed through vinylgold-carbenoid intermediates generated from propargyl acetals and esters.[15] Utilizing acetal-based substrates, the Rautenstrauch reaction proceeds through a planar and achiral intermediate and thus allows the cyclization proceed in a ligand-controlled manner.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.



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(16) The ees in Tables 1 and 2 were obtained before purification since the products were optically unstable during chromatography. See Supporting Information for details.



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