Gold(I) Catalysis Applied to the Stereoselective Synthesis of Indeno[2,1-b]thiochromene Derivatives and Seleno Analogues

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ABSTRACT: A gold(I)-catalyzed cascade reaction for the stereoselective synthesis of sulfur- or selenium-containing indeno[1,2-b]chromene derivatives from o-(alkynyl)styrenes substituted at the triple bond with a thio- or seleno-aryl group is described. The reaction involves a double cyclization process through a proposed key gold−cyclopropyl carbene intermediate that evolves by the intramolecular addition of an aromatic to the cyclopropane ring, affording polycyclic structures. The enantioselective version was studied using gold(I) complexes bearing chiral ligands.

S- and Se-containing heterocyclic compounds have received increased attention due to their unique chemical, physical, and biological properties. The presence of these heteroatoms results in substantial alterations of the cyclic structure. Moreover, their size and electronegativity and the availability of unshared electrons lead to heterocycles with particular characteristics that find applications in fields such as medicine and materials science. On the other hand, gold catalysis has become one of the most valuable tools for the straightforward synthesis of (hetero)cyclic compounds. Thus, the π-activation of alkynes by gold complexes toward intramolecular attack by nucleophiles is nowadays a common strategy for constructing cyclic molecules from acyclic compounds. In particular, the use of olefins as the internal nucleophiles has been extensively considered and therefore a wide number of synthetically useful Au-catalyzed cycloisomerization reactions of enyne derivatives have been described. In this context, we have reported practical methods for the synthesis of 1H-indenes and benzofulvenes from appropriately substituted o-(alkynyl)-styrenes. These reactions proceed through the initial activation of the alkyne by the coordination of the gold catalyst. The subsequent reaction of the alkene with the activated alkyne through a S-endo-dig pathway leads to a cyclopropyl gold carbene derivative, which can also be represented as a gold-containing indene derivative with an exocyclic carbocation. This species evolves in the presence of an external nucleophile to give the final 1H-indene derivatives (Scheme 1a).

Although the Au-catalyzed reaction of o-(alkynyl)styrenes with external nucleophiles has been studied extensively, investigations of the intramolecular version where the cyclopropyl gold carbene intermediate reacts with an internal nucleophile are scarce. In fact, the intramolecular reaction with C-based nucleophiles was not considered before. With all this in mind, we envisioned that unique S- or Se-containing heterocyclic compounds could be obtained from o-(alkynyl)-styrenes substituted at the triple bond with a thio- or seleno-aryl group, respectively (Scheme 1b). The importance of S- and Se-heterocycles along with the easy availability of the starting materials encouraged us to attempt the synthesis of potentially useful indeno[1,2-b]thiochromene derivatives, or

Scheme 1. Previous Results in the Au(I)-Catalyzed Reaction of o-(Alkynyl)styrenes and Present Work

a) Previous work

b) Our proposal. Synthesis of S or Se indeno[1,2-b]chromenes

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their seleno-analogues, through a gold-catalyzed reaction. This unprecedented reaction would proceed through a cascade process involving enyne cycloisomerization and subsequent intramolecular Friel–Crafts-type cyclization. Apart from proving the reactivity of the cyclopropyl gold carbene intermediate with an internal nucleophile, the intriguing stereochemical issues of the proposal were another motivation to work on the project.

As noted above, the starting materials necessary to test our hypothesis are readily available. For example, we prepared α-(alkynyl)styrene 3a, functionalized with a thiaryl group at the terminal position of the alkene, from readily available 2-(trimethylsilyl)benzaldehyde (1a) by a straightforward sequence involving a Wadsworth–Emmons reaction followed by the deprotection of the alkene, to give enyne derivative 2a, and further thiolation to provide 3a (Scheme 2).10

With α-(alkynyl)stylene (E)-3a in hand, we tried our planned reaction. Gratifyingly, when 3a was treated with different gold complexes (2.5 mol%) in DCM at room temperature, the desired indeno[1,2-b]thiochromene 4a was obtained in a high yield after a short reaction time (30 min, Table 1). Interestingly, the final product was obtained as a single isomer in all attempts. As IPrAuNTf₂ is a stable, easy-to-handle complex that does not require a silver salt cocatalyst, it was selected for the subsequent experiments.

![Scheme 2. Preparation of (E)-3a](image)

Table 1. Gold-Catalyzed Synthesis of Dihydroindeno[2,1-b]thiochromene 4a from (E)-3a

| entry | catalyst [Au] | yield (%) |
|-------|---------------|-----------|
| 1     | [3,5-(I-Bu)_2C_6H_3],PdCl2/AgNTf₂ | 83        |
| 2     | IPrAuCl/AgSBF₄ | 84        |
| 3     | IPrAuCl/AgNTf₂ | 85        |
| 4     | Ph₂PdAuNTf₂  | 71        |
| 5     | XPhosAuNTf₂  | 76        |
| 6     | IPrAuNTf₂   | 89 (81)   |

“Reaction conditions are as follows: 3a (0.1 mmol) and catalyst (2.5 mol %) in DCM (0.4 mL) at rt for 30 min. XPhos = dicyclohexyl[2’,4’,6’-tris(propan-2-yl)-1,1’-biphenyl]-2-yl]phosphine. IPr = 1,3-bis(2,6-disopropylphenyl)imidazol-2-ylidene. Determined by 1H NMR analysis of the crude mixture using CH₃Br (1 M) as an internal standard. Isolated yield is shown in parentheses.”

To evaluate the scope of the process, a representative set of S- and Se-substituted α-(alkynyl)styrnes 3 and 5 was subjected to the optimized reaction conditions (Table 2). As shown, the expected indeno[1,2-b]thiochromene derivatives 4 were isolated in high yields and as single diastereoisomers in all cases. Different aryl substituents were allowed at the alkene moiety (R). Regarding the aromatic ring on the S or Se atom (Ar), nonfunctionalized rings (entries 1–7), aryl groups substituted with electron-donating groups (entries 8 and 9), and halogen-substituted aryl groups (entries 10–14) were allowed. The reaction was also performed with α-(alkynyl)styrnes substituted at the aromatic ring core (entries 15–17). Interestingly, the Se-containing products 6 (entries 18–21) were obtained as efficiently as their S-analogues. The structures and relative configurations of the stereogenic centers of these compounds were determined by NMR experiments and unambiguously confirmed by X-ray analysis of 4m.11

Apart from these reactions conducted with α-(alkynyl)styrnes 3 with the E-configuration at the C=C bond, we also performed some experiments from starting materials with the Z-configuration, i.e., (Z)-3 (Table 3). These reactions worked perfectly, and the corresponding products 4 were obtained in high yields; surprisingly, however, mixtures of the two possible diastereoisomers (4/diast-4) were observed. Only when the aromatic ring at the alkene (Ar) was electronically rich (p-methoxyphenyl) was a single diastereoisomer (4c) observed (entry 4). Interestingly, the structure of this isomer matches that of the product previously obtained with (E)-3c (see Table 2, entry 3).12

We also performed some experiments with α-(alkynyl)styrnes 3r–w, which were fully substituted at the terminal position of the alkene (Scheme 3). As shown, when the alkene was substituted with two phenyl groups (3r–t), the expected products 4r–t were isolated in high yields. Next, we tried the reaction with 3u and 3w bearing two methyl groups. Thus, when the aromatic ring linked to the sulfur atom (Ar) was a simple phenyl group (3u), we only isolated the indene 7u.1c However, the formation of the expected indeno[1,2-b]thiochromene derivative occurred when an electronically richer aromatic ring was used (3v, Ar = 3,5-(MeO)₂C₆H₄), although even in this case indene 7v was isolated along with the major product 4v. Finally, we carried out the reaction with α-(alkynyl)stylene 3w containing a phenyl group and a methyl group at the terminal position of the alkene. In this case, we observed the exclusive formation of the indeno[1,2-b]thiochromene 4w in a high yield. It should be noted that although the starting material was a 2:1 mixture of E/Z isomers, the final product 4w was obtained as a single diastereoisomer. The structure and relative configuration of the stereogenic centers of this compound were unambiguously determined by X-ray analysis.11

Finally, the enantioselective version of this new cascade reaction was attempted (Table 4).10 When the reaction was performed with the gold(I) complex containing (S)-DMSEGPHOS as a chiral ligand in DCE at −10 °C, the corresponding final indeno[1,2-b]thiochromenes 4 were isolated in high yields with moderate to high enantioselectivities.

A plausible mechanism that explains the formation of indeno[1,2-b]thiochromene derivatives 4 from α-(alkynyl)styrnes 3 is shown in Scheme 4a (for simplicity, the reaction of 3a is taken as model). Thus, the initial coordination of the catalyst to the alkyno generates the first intermediate I. This coordination favors the reaction with the alkene through a S-endo-dig pathway to form the cyclopropyl gold carbene derivative II in a stereospecific manner. The addition of the electron-rich phenylthio group to the cyclopropyl ring and the subsequent ring opening of the cyclopropane yield the cationic species III. This intermediate evolves through a rearomatiza-
Table 2. Synthesis of Dihydroindeno[2,1-b]thiochromenes 4 and Dihydroindeno[2,1-b]selenochromenes 6 from o-(Alkynyl)styrenes (E)-3 and (E)-S

| entry | 3 or 5 | R¹ | R² | R³ | Ar | 4 or 6 | yield (%) |
|-------|-------|----|----|----|----|--------|-----------|
| 1     | 3a    | H  | H  | Ph | Ph | 4a     | 81        |
| 2     | 3b    | H  | H  | 4-MeC₆H₄ | Ph | 4b     | 82        |
| 3     | 3c    | H  | H  | 4-(MeO)C₆H₄ | Ph | 4c     | 88        |
| 4     | 3d    | H  | H  | 4-ClC₆H₄ | Ph | 4d     | 80        |
| 5     | 3e    | H  | H  | 2,6-F₂C₆H₄ | Ph | 4e     | 87        |
| 6     | 3f    | H  | H  | Ph | Ph | 4-MeC₆H₄ | 4f    | 85        |
| 7     | 3g    | H  | H  | Ph | 1-naphthyl | 4g | 83        |
| 8     | 3h    | H  | H  | 4-(MeO)C₆H₄ | Ph | 4h     | 87        |
| 9     | 3i    | H  | H  | 3-(MeO)C₆H₄ | Ph | 4i     | 77        |
| 10    | 3j    | H  | H  | Ph | Ph | 4-ClC₆H₄ | 4j | 82        |
| 11    | 3k    | H  | H  | Ph | Ph | 4-BrC₆H₄ | 4k | 88        |
| 12    | 3l    | H  | H  | Ph | Ph | 2-ClC₆H₄ | 4l | 83        |
| 13    | 3m    | H  | H  | Ph | Ph | 2-FC₆H₄ | 4m | 78        |
| 14    | 3n    | H  | H  | Ph | Ph | 4-FC₆H₄ | 4n | 79        |
| 15    | 3o    | F  | H  | Ph | Ph | Ph      | 4o     | 77        |
| 16    | 3p    | -OCH₂O− | Ph | Ph | Ph | 4p | 80        |
| 17    | 3q    | -OCH₂O− | Ph | Ph | 4-ClC₆H₄ | 4q | 76        |
| 18    | 5a    | H  | H  | Ph | Ph | Ph | 6a | 86        |
| 19    | 5b    | H  | H  | 4-MeC₆H₄ | Ph | 6b | 79        |
| 20    | 5c    | H  | H  | 4-(MeO)C₆H₄ | Ph | 6c | 88        |
| 21    | 5d    | H  | H  | 4-ClC₆H₄ | Ph | 6d | 70        |

*Reaction conditions are as follows: 3 or 5 (0.3 mmol) and IPrAuNf² (2.5 mol%) in DCM (1.2 mL) at rt for 30 min. †Isolated yield referred to the corresponding starting o-(alkynyl)styrene 3 or 5. ‡Obtained as a 6:1 mixture of regioisomers.

Table 3. Synthesis of Dihydroindeno[2,1-b]thiochromenes 4 and diast-4 from (Z)-3

| entry | 3 or 5 | Ar | product | dr | yield (%) |
|-------|-------|----|---------|----|-----------|
| 1     | 3a    | Ph | 4a/diast-4 | 1:2 | 83        |
| 2*    | 3e    | 2,6-F₂C₆H₄ | 4f/diast-4 | 1:1.6 | 73        |
| 3*    | 3d    | 4-ClC₆H₄ | 4d/diast-4 | 4:1 | 75        |
| 4     | 3c    | 4-MeOC₆H₄ | 4c | >20:1 | 88        |

*Reaction conditions are as follows: 3 (0.3 mmol) and IPrAuNf² (2.5 mol%) in DCM (1.2 mL) at rt for 30 min. †Diastereoisomeric ratio of 4 determined by 1H NMR analysis of the crude reaction mixture. ‡Isolated yield refers to the corresponding starting o-(alkynyl)styrene 3. ‡‡Reaction time of 10 min.

Scheme 3. Cycloisomerization of β,β-Disubstituted o-(Alkynyl)styrenes 3r–w

| 3r: Ar = 4-MeC₆H₄ | 4r (84%); 4s (82%); 4t (70%) |
|-------------------|--------------------------------|
| 3s: Ar = 4-ClC₆H₄ | 4u (0%); 4v (52%) |
| 3t: Ar = 2-FC₂H₄ | 4w (79%); dr >20:1 |

atom (with its ligand) is placed. The ring opening of the sterically less crowded cyclopropyl gold carbene IV is the precursor of II, which is the precursor of 4. It seems that in those cases where the aromatic ring at the terminal position of the alkene (Ar in Scheme 4b) is electronically rich (for example, in (Z)-3c with a 4-methoxyphenyl group), the interconversion of diast-II to II is fast and, finally, a single diastereoisomer (4c) is obtained. In
Table 4. Gold(I)-Catalyzed Enantioselective Synthesis of Dihydroindeno[2,1-b]thiochromenes 4 from (E)-3

| entry | 3     | R¹  | R²  | R³  | Ar     | 4     | yield (%) | er² |
|-------|-------|-----|-----|-----|--------|-------|-----------|-----|
| 1     | 3a    | H   | H   | Ph  | 4a     | 89    | 90:10     |
| 2     | 3b    | H   | H   | 4-MeC₆H₄| 4b    | 84    | 86:14     |
| 3     | 3d    | H   | H   | 4-CIC₆H₄| 4d    | 85    | 78:22     |
| 4     | 3j    | H   | H   | Ph  | 4j     | 87    | 88:12     |
| 5     | 3o    | F   | H   | Ph  | 4o     | 74    | 72:28     |
| 6     | 3p    | −OCH₂O− |     | Ph  | 4p     | 88    | 84:16     |

Reactions conditions are as follows: 3 (0.3 mmol), (S)-DM-SEGPHOS(AuCl)₂ (2.5 mol%), and AgOTf (5 mol%) in DCE (1.2 mL) at −10 °C for 16 h. Yield of isolated 4 based on 3. Determined by HPLC on a chiral stationary phase using a Chiralpak AD-H column (n-hexane/i-PrOH eluent).

Scheme 4. Mechanistic Proposal

a) Mechanistic proposal:

b) Proposed evolution of styrene derivatives 3 with Z-configuration:

(Z)-3 = [Au]⁺ SPh

[c) Proposed evolution of styrene derivatives 3 with methyl groups:

3u,v = [Au]⁺ Me

In conclusion, we have reported a simple method for the synthesis of S- or Se-containing indeno[1,2-b]chromene derivatives from readily available starting materials that involves a double-cyclization process. More precisely, we have found that simple ω-(alkynyl)styrenes substituted at the triple bond with a thio- or seleno-aryl group react in the presence of a gold(I) catalyst through a cascade process that involves the initial formation of a cyclopropyl gold carbene intermediate, followed by a cyclopropane ring opening promoted by the intramolecular addition of the arene from the thio- or seleno-aryl group. The stereoselectivity of the process is determined by a key gold–cyclopropyl carbene intermediate, which controls the attack of the aromatic ring. This work further expands the utility of gold catalysis to access unusual complex heterocyclic compounds from easily available starting materials. The possibility of performing the reaction in an enantioselective way using a chiral gold(I) catalyst is demonstrated.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03411.

Experimental details, characterization data, X-ray crystallographic data for 4m and 4w, and copies of NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds (E)-2a–e, (E)-2o, (E)-2p, (Z)-2a, (Z)-2d, (Z)-2e, 2r, 2u, 2w, (E)-3a–q, (Z)-3a, (Z)-3c–e, 3r–t, 3v–w, 4a–t, 4v–w, diast-4d, (E)-5a–d, and 6a–d (ZIP)

Accession Codes

CCDC 2168642 and 2168644 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(10) See the Supporting Information for further details.

(11) CCDC2168644 (4m) and CCDC2168642 (4w) contain the crystallographic data for this paper.

(12) To know if the formation of 4 and diast-4 was a consequence of isomerization between them, solutions of isolated 4a and mixtures of 4a/diast-4a were stirred under the reaction conditions for 1 h, but no isomerization occurred. No interconversion between 4a and diast-4a took place in CDCl₃ for a week.