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# Oxyacylation of Iodoalkynes: Gold(I)-Catalyzed Expeditious Access to Benzofurans

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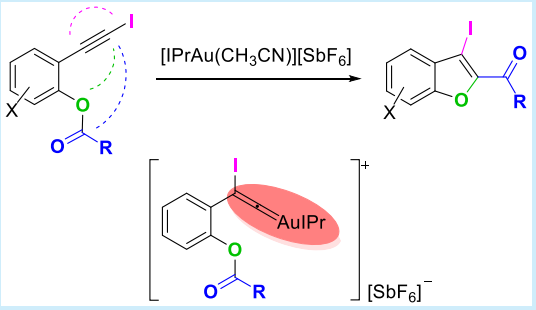
Supporting Information

**ABSTRACT:** (Acetonitrile)[1,3-bis(2,6-diisopropylphenyl)-imidazole-2-ylidene] gold(I) catalyzes the cycloisomerization of 2-(iodoethynyl)-aryl esters to give 3-iodo-2-acyl benzofurans. This catalytic transformation is the result of an unprecedented selective synthetic event, which comprises a [1,2]-iodine shift, a C−O ring-closure step, and a C−C bond-formation that installs the ketone functionality into the new ring. Experimental evidence supports the involvement of a $\beta$-iodo-substituted gold vinylidene as the intermediate species. The reaction tolerates different substitution patterns at the phenol moiety and a wide diversity of groups at the carboxylic fragment, including not only alkyl but also alkenyl, aryl, and heteroaryl groups.

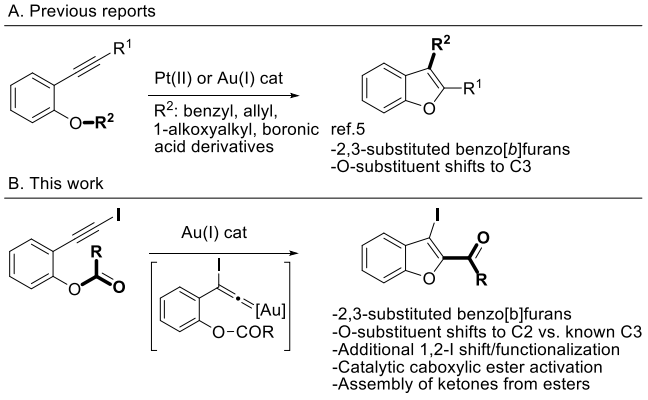





Organic synthesis contributes to the welfare of modern society, providing access to crucial chemicals. Thus, identifying new reactions is of prime interest. For this purpose, alternative catalytic protocols for the generation of intermediate species such as metal vinylidenes play a main role in contemporary synthetic methodology.[1] Gold vinylidenes are relatively new players in the field, but increasingly gaining significance.[2,3] Now, we are reporting an unprecedented catalytic transformation furnishing 2-acyl-3-iodobenzo[*b*]furan cores and evolving through a gold vinylidene intermediate. At the same time, it reveals a distinctive cyclization pattern for coinage-metal-catalyzed isomerization reactions of related precursors, adding interest to this process (Scheme 1A).[4,5]

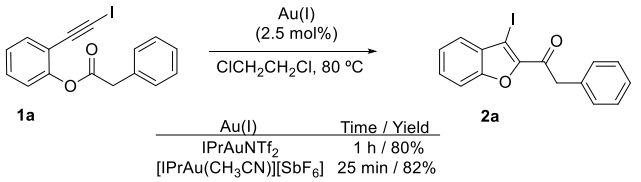
Thus, catalytic reactions giving C-3-substituted benzo[*b*]-furans as the result of a selective transfer of the oxygen substituent to the C-3 position of the assembled heterocycle are known, but the related transformation involving a selective migration to C-2 is missing (Scheme 1B).

**Scheme 1. Catalytic Isomerizations to 2,3-Benzo[*b*]furans**




Readily available esters derived from phenols containing the *o*-iodoethynyl fragment were chosen as substrates. According with early observations on accessing gold vinylidene complexes from iodoalkynes [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene] [bis(trifluoromethanesulfonyl)imide]gold(I) ($IPrAuNTf_2$) was chosen as catalyst.[6] Heating *o*-(iodoethynyl) 2-phenylacetate **1a** (0.1 M solution in 1,2-dichloroethane) with 2.5 mol % of the gold catalyst at 80 °C furnishes 1-(3-iodobenzofuran-2-yl)-2-phenyl ethanone **2a**, in 80% yield (Scheme 2). The influence of the counteranion over the reaction was tested. A faster reaction was observed for (acetonitrile)[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)hexafluoroantimoniate $[IPrAu(CH_3CN)][SbF_6]$, giving **2a** in virtually the same isolated yield.[7]

**Scheme 2. Gold(I)-Catalyzed Deep Rearrangement**




Overall, three bonds were formed along the catalytic event, namely the C($sp^2$)−I and new C($sp^2$)−O and C($sp^2$)−C($sp^2$) bonds. The C−I bond suggests interest for building-block diversification. Interestingly, the ester moiety catalytically turns

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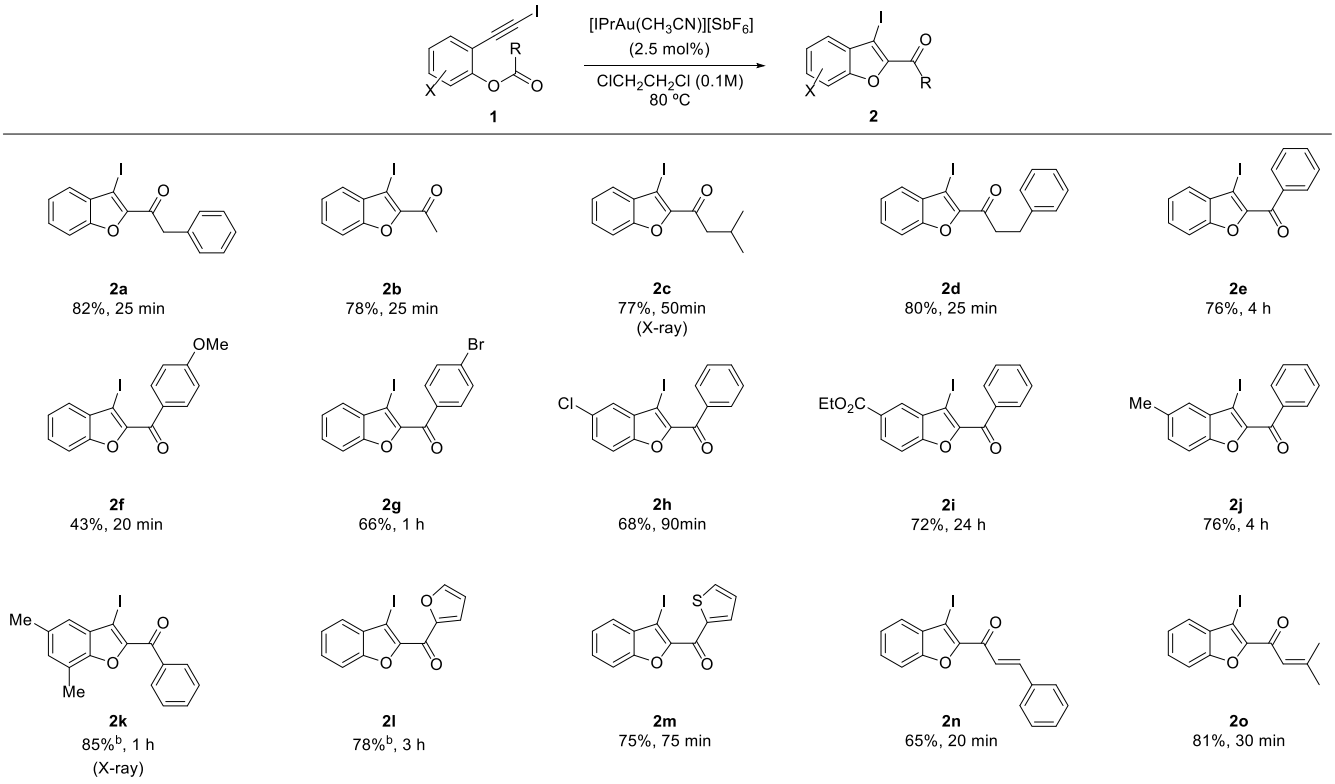
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 3. Scope of the Catalytic Isomerization**[a]




[a]Reactions were conducted on 0.2 mmol scale. Yields refer to the isolated product after purification. [b]Five mol % added catalyst.

into a ketone selectively attached at the elusive C2-position. Metal-catalyzed 1,1-oxyacylation reactions are scarce[8] and unprecedented using gold catalysis.

With these preliminary results in hand, and taking into account the biological prevalence[9] and the interest in the preparation of this heterocyclic motif,[10] the scope of the reaction was investigated, using $[IPrAu(CH_3CN)][SbF_6]$ as the catalyst (Scheme 3). Besides, $IPrAuNTf_2$ was tested over some additional substrate, giving rise always to the corresponding product **2** in lower yield, even after extended reaction time.

Using as precursors esters derived from carboxylic acids having other alkyl chains, the conversion was completed in <1 h for 2.5 mol % catalyst loading, affording compounds **2b−d** in synthetically useful isolated yields. The assigned structures for compounds **2** are based on their characterization data, including extensive NMR studies. Single-crystal X-ray diffraction analysis of **2c** nicely endorses the proposed structure.[11]

Esters based on *o*-(iodoethynyl)phenol and different aryl carboxylic acids were subjected to the conditions described above. Ester **1f**, derived from an electron-rich arene carboxylic acid, was rapidly consumed; however, side reactions partly limited the formation of **2f**, which was isolated only in moderate yield. On the contrary, esters **1e** and **1g** derived, respectively, from benzoic acid and the related *p*-bromophenyl motif reacted slower but more efficiently in terms of giving the target benzofuranyl ketones **2e** and **2g**. The reaction tolerates substituents at the phenol moiety in **1**. The process transformed **1h** and **1j**, bearing modestly deactivated or activated substituents (4-Cl or 4-Me) at the *para*-position, into the compounds **2h** and **2j**. It also performs nicely if a more electron-withdrawing group is present at the *para*-position, which gives **2i** in fair isolated yield, though after an extended reaction time.

The presence of a substituent at the *ortho*-position is also compatible with this catalytic cyclization, as noticed in the cyclization yielding **2k**, as confirmed by X-ray diffraction analysis. The possibility of using this reaction to obtain bis(heteroaryl) ketones was tested for esters obtained from heteroaromatic carboxylic acids. Precursors **1l** and **1m**, obtained from 2-furan and 2-thiophene carboxylic acids, gave **2l** and **2m**, respectively. This catalytic cyclization also yields *α*,*β*-unsaturated ketones. Remarkably, the reaction is also efficient on a gram-scale basis. Thus, 1.45 g of **2o** was prepared on comparable 78% yield to that reported for the smaller scale.

The fact that the process relies on a simple ester preparation brings interest to this catalytic cycloisomerization for a late stage modification of bioactive molecules. Naproxen, a known nonsteroidal anti-inflammatory (NAISD) drug with the structure of (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid,[12] was chosen for this purpose. A commercial sample of this bioactive molecule (purity (HPLC) ≥ 97.5%) was converted to ester **1p** (Scheme 4). Partial erosion of the enantiomeric purity occurred at this stage (er: 89:11). Next, enantioenriched **1p** was exposed to gold(I) catalysis and led to the new hybrid structure **2p**. Interestingly, the integrity of the stereocenter (er: 87:13) was virtually preserved along the catalytic transformation.

In order to postulate a reaction mechanism, additional experimental work was conducted. The outcome of a potential crossover experiment was tested (Scheme 5). A 1:1 mixture of **1h** and **1m** was subjected to the standard reaction conditions and the crude reaction mixture monitored by $^1H$ NMR ($CH_2Br_2$ added as internal standard). Only formation of **2h** and **2m** was noticed. The absence of crossover products is compatible with an intramolecular process. However, it does not support in full



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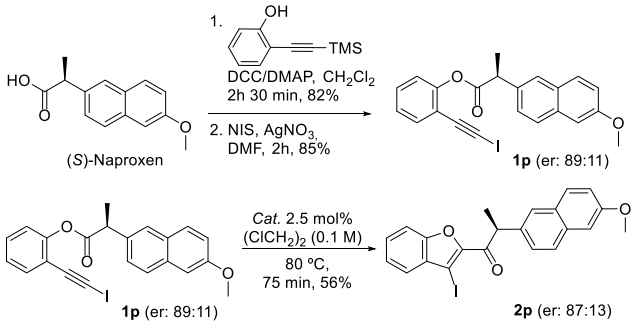
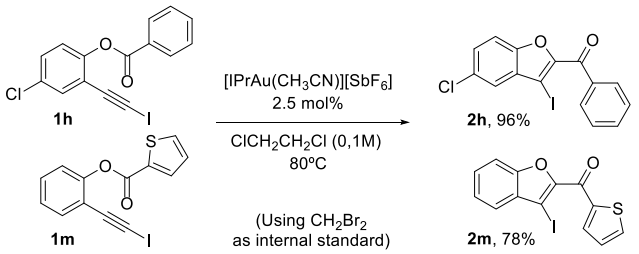
**Scheme 4. Late Stage Functionalization of (*S*)-Naproxen**



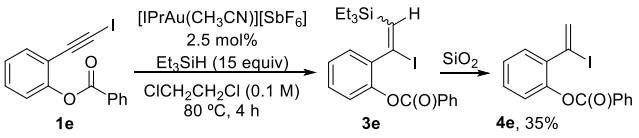

**Scheme 5. Crossover Experiment**




an alternative initial O-cyclization path followed by the release into the solution of the acyl cation.[13]

Interestingly, when **1e** was exposed to the gold(I) catalyst in the presence of an excess of triethylsilane, the cyclization leading to **2e** was inhibited. Conversely, the analysis of the crude reaction mixture by NMR revealed the formation of the product **3e**, which reasonably arises from an alternative trapping of the intermediate gold vinylidene species by insertion into the silane, leading to the hydrosilylation product. Along the purification step (column chromatography over silica gel, eluting with mixtures of hexanes and ethyl acetate), an easy proto-desilylation took place, and a clean generation of **4e** was noticed (Scheme 6).

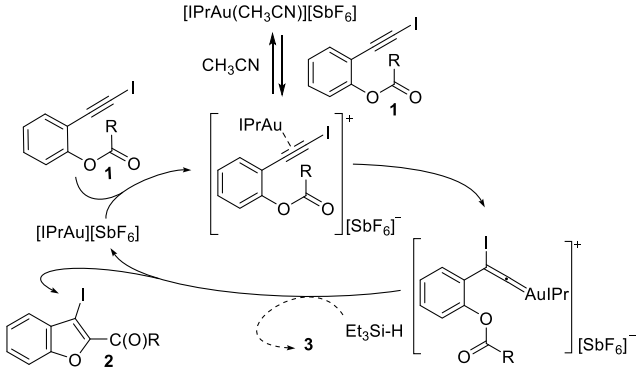
**Scheme 6. Trapping Intermediate Gold Vinylidene Species**




On this basis, a mechanistic proposal is depicted in Scheme 7. Coordination of gold(I) to **1** would release the nitrile and activate the alkyne. Then, a 1,2-iodine migration facilitated by the donor ability of the ligand at gold would furnish the key gold vinylidene intermediate, which is supported by the above given trapping experiment with silane affording **3**.[14] Insertion of the *O*-acyl bond into this reactive species would account for the assembly of **2**,[15] without forming scrambled products in the attempted crossover experiment, while at the time preserving the stereochemical integrity.

In short, a new gold(I)-catalyzed cycloisomerization reaction of practical utility is presented. The ketone that is formed at the time of elaborating the benzo[*b*]furan core is of significance. The accessibility of an ester as the tether bringing together the two main fragments conveniently enables a catalytic increasing of molecular complexity in a simple and straightforward manner, which can be implemented for a late stage diversification of

**Scheme 7. Mechanistic Proposal**




bioactive compounds. The process encodes a new cyclization mode in the context of coinage metal-catalyzed reactions of derivatives of *o*-alkynylphenols. Now, the original substituent onto oxygen gets selectively attached at the C-2 position of the assembled benzo[*b*]furan. Mechanistic insights are provided supporting the involvement of an intermediate gold vinylidene. A number of products were obtained via a new reaction comprising the selective migration of both iodine and the acyl moiety at the time of elaborating the heterocyclic scaffold.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02551.

Experimental procedures, compound characterization, and NMR spectra (PDF)

### Accession Codes

CCDC 1917876−1917877 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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