Gold catalysis for organic synthesis II

Edited by F. Dean Toste
Two years have now passed since the publication of the first Thematic Series on gold catalysis for organic synthesis in the Beilstein Journal of Organic Chemistry. In the intervening time, the pace of progress and discovery in the field has continued unabated. Many of these advancements are exemplified in the more than twenty contributions that have been collected in this second Thematic Series.

Many of the early examples of homogeneous gold-catalysis focused on the ability of cationic gold complexes to activate π-bonds towards attack of nucleophiles. This reactivity platform, examples of which can be found in this Thematic Series, continues to provide a fruitful basis for the discovery of important new transformations. This includes the development of a tandem or domino process that can be employed for the synthesis of complex polycyclic structures. These articles demonstrate the power of gold catalysis for the construction of complex structures, including the development of tandem processes, the expedient synthesis of heterocyclic structures, and applications to the synthesis of complex natural products.

The field has also witnessed growth through the discovery of other modes of reactivity. For example, gold-catalyzed cycloaddition reactions, examples of which are found in this Thematic Series, have featured prominently. Additionally, enantioselective catalysis with gold has seen notable advancements and is highlighted in several articles. The remarkable breakthroughs in oxidative transformations catalyzed by gold complexes, including those employing N-oxides as stoichiometric oxidants, have featured prominently in many recent innovations. Taken together, these articles present an outstanding overview of the state of the field from many of its top practitioners. They foreshadow the many additional reactions, reactivity modes, and catalysts based on gold that remain to be uncovered. I am grateful to the authors for their excellent contribution and making this second Thematic Series as successful as the first.

F. Dean Toste

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Gold-catalyzed oxycyclization of allenic carbamates: expeditious synthesis of 1,3-oxazin-2-ones
Benito Alcaide*1, Pedro Almendros*2, M. Teresa Quirós1 and Israel Fernández3

Abstract
A combined experimental and computational study on regioselective gold-catalyzed synthetic routes to 1,3-oxazinan-2-ones (kinetically controlled products) and 1,3-oxazin-2-one derivatives (thermodynamically favored) from easily accessible allenic carbamates has been carried out.

Introduction
The search for new synthetic routes to 1,3-oxazin-2-one derivatives [1] is of interest because of the biological activity of these molecules [2-7]. Carretero and colleagues have published the Au(I)-catalyzed cyclization of N-Boc-3-butyn-1-amines to afford six-membered 2-oxazinones, namely, 6-methylene-1,3-oxazinan-2-ones involving a 6-exo-dig cyclization [1]. This interesting method avoids complicated prefunctionalization of starting materials and minimizes the formation of byproducts; however, it is used just for the preparation of four simple examples. 1,3-Oxazin-2-ones are also used as valuable intermediates in organic synthesis [8-14]. Recently, allenes have attracted much attention as they have been used for the preparation of both biologically relevant drugs as well as advanced materials [15-27]. However, regioselectivity problems are significant (endo-trig versus endo-dig versus exo-dig versus exo-trig cyclization). Great effort is currently being made in the search for a variety of reactions promoted by gold salts due to their impressive catalytic properties [28-41]. The Boc protective group has been widely used in allene chemistry, being an inert and recommended partner in gold- and palladium-catalyzed
aminoacyclizations of allenes [42]. On the other hand, reports of gold-catalyzed cyclizations leading to heterocycles that contain more than one heteroatom are rare [43-48]. Besides, it has been reported very recently that the Au(I)-catalyzed cyclization of a N-phenethyl-N-Boc-protected allenamide failed [49]. Despite the above precedents, but in continuation of our interest in heterocyclic and allene chemistry [50-55], we decided to examine the gold-catalyzed cyclization of N-Boc-allenenes with the aim of establishing a protocol for the synthesis of 1,3-oxazin-2-one derivatives in which the carbamate group should serve as the source of CO₂.

Results and Discussion

To explore the effects of various substrates on gold-catalyzed oxycyclization reactions, a number of new allenic carbamates were synthesized as shown in Scheme 1. Starting materials, tert-butyl (prop-2-ynyl)carbamates 1a–j, were obtained both in the racemic form and in optically pure form by using standard methodologies. Thus, alkylnycarbamates 1a–g were prepared through reductive amination of the appropriate aldehyde with propargylamine, followed by Boc₂O treatment of the corresponding N-substituted prop-2-yn-1-amine. Alkynylcarbamate 1h was prepared from Garner’s aldehyde following a literature report [56,57]. Alkynylcarbamate 1i was readily accessed from (S)-prolinol by using a modified known procedure [58]. Alkynylcarbamate 1j was achieved through the reaction of 3-bromo-1H-indole-2-carbaldehyde with the Ohira–Bestmann reagent followed by the addition of Boc₂O. Terminal alkynes 1 were conveniently converted into allenic carbamates 2 by treatment with paraformaldehyde in the presence of disopropylamine and copper(I) bromide (Crabbé reaction) [59,60].

We employed three different gold salts in our initial screening of catalysts for the model system, allenic carbamate 2a. Initially, the use of AuCl₃ and AuCl were tested, but both failed to catalyze the reaction. Fortunately, we found that [AuClPPh₃]/AgOTf was an excellent catalyst for our purpose. To our delight, the reaction of allenic carbamate 2a at room temperature afforded 3-benzyl-6-methylene-1,3-oxazinan-2-one (3a) bearing an exocyclic double bond as the sole product (Scheme 2). Adding a catalytic amount of Brønsted acid (PTSA) into the reaction system did slightly improve the yield of 3a. Solvent screening demonstrated that dichloromethane was the best choice in the reaction.

As revealed in Scheme 2, a variety of allenic carbamates 2 were also suitable for such heterocyclization reactions to afford 1,3-oxazinan-2-ones 3. To increase the molecular diversity by incorporating more 1,3-oxazin-2-ones in the molecule, compound 2g having two allenic carbamate units was used. Notably, bis(allenic carbamate) 2g also undergoes this interesting transformation to give bis(6-methylene-1,3-oxazinan-2-one) 3g through a two-fold cyclization. This product particularly underlines the power of the present cyclization reaction, as none of the conventional methods would allow its synthesis with such great ease.

Interestingly, as a first try, we were pleased to notice that the reaction of allenyl derivative 2a in dichloromethane at 90 °C, afforded 1,3-oxazin-2-one 4a bearing an endocyclic double bond as the major component, and 1,3-oxazinan-2-one 3a was also isolated as a minor component. Notably, starting from allenic carbamates 2a–j and performing the reaction in dichloromethane at 130 °C, a series of 6-methyl-3-substituted 3,4-dihydro-2H-1,3-oxazin-2-ones 4a–j were exclusively formed (Scheme 2) [61-68]. The observed regioselectivity is worthy of note, because under our reaction conditions only 1,3-oxazinan-2-ones 3 (arising from 6-endodig cyclization) or 3,4-dihydro-2H-1,3-oxazin-2-ones 4 (arising from 6-exo-dig cyclization) were achieved, with the nucleophilic oxygen attacking the central allene carbon atom in each case. This is an interesting result, because the available examples on related metal-catalyzed allene heterocyclizations usually lead to 5-exotrig cyclization [69,70]; only Hashmi et al. have recently reported an attack at the central position of the allene in allenylamides [44].

Thus, it is possible to suppress the formation of the 1,3-oxazinan-2-one ring by performing the reaction at higher temperature, yielding the 1,3-oxazin-2-one as the exclusive product. A general trend can be deduced on the basis of these results: heterocycle 4 is the thermodynamically controlled product while heterocycle 3 is the kinetically controlled product [71-73]. Probably, double-bond migration in compounds 3 results in the formation of the 1,3-oxazin-2-one 4. In order to verify the role of the Au(I) catalyst in the double-bond migration process, we set up two experiments. Heating a mixture of 3a with Au(OTf)₂PPh₃ at a loading of 2.5 mol % in dichloromethane for 1.5 h at 130 °C resulted in full conversion into 4a. Running the same reaction in the absence of any catalyst resulted in 30% conversion after two days, as determined by ¹H NMR. Treatment of 1,3-oxazinan-2-one 3a with 5 mol % TIOH in CH₂Cl₂ at room temperature did not proceed to give an appreciable amount of 3,4-dihydro-2H-1,3-oxazin-2-one 4a after 2 h. This indicates that the Au(I) catalyst might participate in the double-bond migration process; being a possible intermediate, the π-allyl complex 5 is depicted in Scheme 3 [74]. Despite that, the isomerization process can be also viewed as an intramolecular 1,3-H shift assisted by gold.

A possible pathway for the gold-catalyzed achievement of heterocycles 3 from allenyl-tethered carbamates 2 may initially
Scheme 1: Preparation of allenic carbamates 2a–j. Reagents and conditions: (i) Propargylamine, MgSO$_4$, CH$_2$Cl$_2$, rt, 15 h. (ii) NaBH$_4$, MeOH, rt, 0.5 h. (iii) Boc$_2$O, Et$_3$N, CH$_2$Cl$_2$, rt, 2–15 h. (iv) (CH$_2$O)$_n$, iPr$_2$NH, CuBr, 1,4-dioxane, reflux, 1 h. (v) Ohira–Bestmann reagent, K$_2$CO$_3$, MeOH, rt, 15 h. (vi) Boc$_2$O, DMAP, CH$_3$CN, rt, 2 h. (vii) Dess–Martin periodinane, CH$_2$Cl$_2$, rt. PMP = 4-MeOC$_6$H$_4$.
Scheme 2: Controlled oxycyclization reactions of allenic carbamates 2 to 1,3-oxazinan-2-ones 3 and 1,3-oxazin-2-ones 4 under selective gold-catalyzed conditions. Reagents and conditions: (i) 2.5 mol % [AuClPPh_3], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, rt, 3a: 6 h; 3b: 7 h; 3c: 6 h; 3d: 8 h; 3e: 7 h; 3f: 5.5 h; 3g: 5.5 h; 3h: 5 h; 3i: 7 h; 3j: 2 h. (ii) 2.5 mol % [AuClPPh_3], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, sealed tube, 130 °C, 4a: 1.5 h; 4b: 2 h; 4c: 4 h; 4d: 6 h; 4e: 4 h; 4f: 0.5 h; 4g: 5.5 h; 4i: 2 h. (iii) 2.5 mol % [AuClPPh_3], 2.5 mol % AgOTf, 10 mol % PTSA, CH_2Cl_2, sealed tube, 80 °C, 4j: 2 h. PMP = 4-MeOC_6H_4.
involve the formation of a complex 6 through coordination of the gold salt to the proximal allenic double bond. Next, chemo- 
and regioselective 6-endo-dig oxyauration of the carbamate car- 
bonyl moiety forms species 7. Attack of the carbamate carbon- 
yl group occurs as a result of the stability of the intermediate ammonium cation type 7. Loss of proton linked to 2-methyl- 
prop-1-ene release [75-78], generates neutral species 8, which 
followed by protonolysis of the carbon–gold bond affords 6-methylene-1,3-oxazinan-2-ones 3 with concurrent regenera-
tion of the gold catalyst (Scheme 4, left catalytic cycle). In line 
with the above mechanistic proposal, the easy breakage of the tert-buty1 group at species 7 is essential for the formation of 1,3-oxazinan-2-ones 3. Besides, the replacement of the tert-buty1 group in allenic carbamates 2 by other alkyl functions, 
such as methyl, did not allow the preparation of heterocycles 3. 
In addition to the double-bond isomerization that transforms 
products 3 into the thermodynamically more favored compounds 4, a mechanistic scenario involving the initial coordina-
tion of the gold to the distal allenic double bond leading to com-
plex 9, followed by a 6-exo-dig oxyauration is likely for the achievement of 1,3-oxazin-2-ones 4 from allenic carbamates 2 (Scheme 4, right-hand catalytic cycle).

Density functional theory (DFT) calculations (see Supporting 
Information File 1) have been carried out at the PCM-M06/ 
def2-SVP/B3LYP/def2-SVP level to gain more insight into the 
reaction mechanism of the above discussed gold-catalyzed 
divergent oxycyclization reaction. The corresponding computed 
reaction profiles of the model allene 1M with the model gold 
catalyst AuPMe3(OTf) are shown in Figure 1, which gathers the 
respective free energies (computed at 298 K) in CH2Cl2 solu-
tion.
As initially envisaged, two different coordination modes of the metal fragment to the allenic double bond of \( 1M \), i.e., distal versus proximal, are possible. Our calculations indicate that the distal coordination leading to \( \text{INT1-B} \) is favored over the proximal coordination mode, which forms \( \text{INT1-A} \) (\( \Delta\Delta G = 3.8 \text{ kcal/mol} \)). This is mainly due to the presence of a two-electron stabilizing interaction established by donation of electronic density from the lone pair of the oxygen atom of the carbonyl moiety to a vacant \( d \) atomic orbital of the gold atom in \( \text{INT1-B} \) [79]. Both complexes can undergo the corresponding oxoauration cyclization reaction. Thus, \( \text{INT1-A} \) is converted into \( \text{INT2-A} \) in a slightly exergonic process (\( \Delta G_{R,298} = -0.4 \text{ kcal/mol} \)) through the saddle point \( \text{TS1-A} \), which is associated with the 6-endo-dig cyclization. Similarly, \( \text{INT1-B} \) is transformed into \( \text{INT2-B} \) in a slightly endergonic process (\( \Delta G_{R,298} = +0.9 \text{ kcal/mol} \)) via \( \text{TS1-B} \), associated with the 6-exo-dig cyclization reaction.

From the data in Figure 1, it becomes obvious that the 6-endo-dig transformation is kinetically favored over the 6-exo-dig reaction in view of the computed lower activation barrier of the former process (\( \Delta\Delta G_{298} = +7.4 \text{ kcal/mol} \)). However, the cyclic reaction product \( \text{INT2-B} \) is thermodynamically more stable than the counterpart \( \text{INT2-A} \) (\( \Delta G = 2.5 \text{ kcal/mol} \)), which is in agreement with the experimental findings (see above). The next step of the process involves the TiO\(^+\) promoted elimination of isobutene to form the corresponding \( \text{INT3} \) complexes. The driving force of this process is clearly related to the thermodynamically favored release of isobutene (\( \Delta G_{R,298} = -1.9 \) and \(-5.2 \text{ kcal/mol} \) from \( \text{INT3-A} \) and \( \text{INT3-B} \), respectively). Finally, the protonolysis reaction of the carbon–gold bond by TiOH renders the final products \( 3M \) and \( 4M \) regenerating the catalyst. This step occurs through the transition states \( \text{TS2-A} \) and \( \text{TS2-B} \), respectively, in an exergonic transformation (\( \Delta G_{R,298} = -4.5 \) and \(-3.0 \text{ kcal/mol} \) from \( \text{INT3-A} \) and \( \text{INT3-B} \), respectively). Again, the data in Figure 1 indicate that the final product \( 4M \) is thermodynamically more stable than \( 3M \), which is in line with the experimentally observed conversion of \( 3a \) into \( 4a \) by heating in the presence and also in the absence of the gold-catalyst. From the computed reaction profile, it can be concluded that the observed divergent cyclization finds its origin in the initial 6-endo versus 6-exo oxoauration reaction steps, with the former being kinetically favored whereas the

Figure 1: Computed reaction profile for the reaction of \( \text{AuPMe}_3^+ \) and \( 1M \). Numbers indicate the corresponding PCM-corrected \( \Delta G_{298} \) energies (in kcal/mol) using dichloromethane as solvent. Bond distances are given in angstroms. All data have been computed at the PCM-M06/def2-SVP//B3LYP/def2-SVP level.
latter is thermodynamically favored. At this point, it cannot be safely discarded that the formation of the thermodynamically more stable 6-exo-dig products is the result of the simple thermally promoted isomerization of the less stable 6-endo-dig species.

Conclusion

In conclusion, efficient gold-catalyzed synthetic routes to 1,3-oxazinan-2-one and 1,3-oxazin-2-one derivatives from easily accessible allenic carbamates under mild conditions have been reported. The oxycyclization reactions were found to proceed with complete control of regioselectivity. The mechanism of these processes has additionally been investigated by a computational study showing that heterocycles 3 are the kinetically controlled products whereas heterocycles 4 are thermodynamically favored.

Experimental

General Information

$^1$H NMR and $^{13}$C NMR spectra were recorded on 700, 500, 300, or 200 MHz spectrometers. NMR spectra were recorded in CDCl$_3$ solutions, except were otherwise stated. Chemical shifts are given in parts per million relative to TMS ($^1$H, 0.0 ppm) or CDCl$_3$ ($^{13}$C, 7.26 ppm). Low- and high-resolution mass spectra were taken on a QTOF LC–MS spectrometer using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation [α]$_D$ is given in 10$^{-1}$ deg cm$^2$ g$^{-1}$ at 20 °C, and the concentration (c) is expressed in grams per 100 mL. All commercially available compounds were used without further purification.

Typical procedure for the Au(I)-catalyzed preparation of 1,3-oxazin-2-ones, 4

[AuClPPh$_3$]$_2$ (0.00475 mmol), AgOTf (0.00475 mmol), and p-toluenesulfonic acid (0.019 mmol) were sequentially added to a stirred solution of the allenic carbamate 2a (50 mg, 0.19 mmol) in dichloromethane (1.9 mL). The resulting mixture was heated in a sealed tube at 130 °C until disappearance of the starting material (TLC, 1.5 h). The reaction was allowed to cool to room temperature and filtered through a pack of celite. The filtrate was extracted with dichloromethane (3 × 5 mL), and the combined extracts were washed twice with brine. The organic layer was dried (MgSO$_4$), concentrated under reduced pressure, and purified by flash column chromatography on silica gel (hexanes/ethyl acetate 4:1) to afford product 4a (27 mg, 70%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$, 25 °C) $\delta$ 3.73 (m, 2H), 4.76 (m, 1H), 4.58 (s, 2H), 3.68 (dq, J = 3.2, 1.9 Hz, 2H), 1.86 (td, J = 1.9, 1.2 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$, 25 °C) $\delta$ 150.9, 148.1, 135.6, 128.7, 128.2, 127.9, 94.4, 52.1, 44.6, 18.3; IR (CHCl$_3$): $\nu$ 1685 cm$^{-1}$; HRMS–ES (m/z): [M]$^+$ calcd for C$_9$H$_{12}$N$_2$O$_2$, 203.0946; found, 203.0952.

Supporting Information

Supporting Information File 1

Experimental details, analytical data of new compounds, copies of $^1$H NMR and $^{13}$C NMR spectra and computational details.

[http://www.beilstein-journals.org/bjc/2013/9/s1.pdf]

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References


See for the synthesis of oxazinones from N-Boc-(3-butenyl)-1-amines.


See for a review.
68. Except for fused 6-methylene-1,3-oxazinan-2-one, 3j, heterocycles 3 or 4 were exclusively obtained. Surprisingly, the exposure of tert-butyl allenic carbamate 2j to the gold-catalyzed conditions at room temperature afforded the 1,3-oxazin-2-one 4j as the major adduct, with the corresponding 1,3-oxazinan-2-one adduct 3j being the minor component.


See for the isolation of an allylic gold complex.

75. H NMR of the reaction mixtures revealed the presence of 2-methylprop-1-ene, which is likely formed from the tert-butyl fragmentation. For pioneering work on the introduction of tert-butyl carbonates as a cation-trapping group in gold catalysis, see references [76-78].


79. The corresponding second-order perturbation energy from the NBO method associated with this LP(0) → d(Au) delocalization was computed to be ca. −5 kcal/mol.
Gold-catalyzed intermolecular hydroamination of allenes with sulfonamides
Chen Zhang*1, Shao-Qiao Zhang1, Hua-Jun Cai2 and Dong-Mei Cui*2

Abstract
A co-catalyst of (PPh3)AuCl/AgOTf for the intermolecular hydroamination of allenes with sulfonamides is shown. The reaction proceeded smoothly under mild conditions for differently substituted allenes giving N-allylic sulfonamides in good yields with high regio- and stereoselectivity.

Introduction
Hydroamination of an N–H bond across a C–C unsaturated bond represents one of the most effective and atom-economical methods to prepare amine derivatives [1-5]. In the case of using allenes, this reaction can lead to allylamines, which are invaluable precursors for the synthesis of natural products and other potentially biologically relevant substances [6]. In the literature, a wide range of catalytic intramolecular hydroaminations of allenes are known, but only a small number of intermolecular hydroamination reactions are reported [7-15]. More recently, Au(I), Au(III), Pt(II) and Rh(I) have been used for the intermolecular hydroamination of allenes with secondary alkylamines, ammonia, or carboxamide [7,16-24]. Although some of these advances have been efficiently made in hydroamination, many require extreme and extended reaction conditions. Thus, development of these reactions is still needed. Recently, Yamamoto and co-workers reported the Pd(0)-catalyzed intermolecular hydroamination of allenes with sulfonamides [25]. In this paper, we wish to develop a gold(I)-complex-catalyzed addition of sulfonamides as the amine partner to allenes to synthesize N-allylic sulfonamides with high regio- and stereoselectivity.

Results and Discussion
As part of our ongoing studies on metal-catalyzed reactions, we have reported the hydroalkoxylation of allenes with alcohols and hydroamination of alkynes with sulfonamides in the presence of gold catalysts [26-28]. On the basis of these studies, in
an initial experiment, 1-phenyl-1,2-propadiene (1a) (1.5 mmol) was treated with 4-methylbenzenesulfonamide (2a) (0.5 mmol) in the presence of 2 mol % of (PPh₃)AuCl and 8 mol % of AgOTf in dioxane at 70 °C efficiently to form linear adduct 3a in 43% yield (Table 1, entry 1). Different solvents were screened, and dioxane was found to be the most suitable one (Table 1, entries 2–4). Decreasing the amount of AgOTf resulted in lower yields (Table 1, entry 7). We were pleased to find that efficient hydroamination was realized at rt and led to a 91% yield of 3a with good regioselectivity and high E-selectivity (Table 1, entry 6). Other possible isomers could not be detected. As Ag catalysts, other salts were also screened, AgBF₄ was ineffective. With AgSbF₆ or AgNTf₂, the reaction took place and gave adducts in 33% and 47% yield (Table 1, entries 8 and 9). The use of the gold alone gave a lower yield, and the reaction did not proceed in the absence of gold or through the use of TfOH (entries 11–14). Finally, we determined the optimal conditions as 5 mol % of (PPh₃)AuCl and 8 mol % of AgOTf in dioxane at rt (Table 1, entry 6).

To further assess the scope of this process, we first examined the hydroamination of 1a with several sulfonamides. Benzene-sulfonamides containing p-Br or p-Cl groups on the benzene ring were tolerated for the reaction, obtaining the corresponding adducts 3d and 3e in 54 and 72% yields, respectively (Table 2, entries 4–5). Under the same reaction conditions, the hydroamination of aliphatic sulfonamides took place smoothly to afford the corresponding N-allylic sulfonamide 3f with 56% yield (Table 2, entry 6). We also used N-substituted sulfonamide 2g as the amine partner. Although drastic conditions are required, the addition occurred to provide linear adduct 3g in good yield (Table 2, entry 7). In all cases, the adduct was obtained with high selectivity.

Various allenes were then examined, and aromatic rings of phenyllallenes with either an electron-donating or an electron-withdrawing group gave good isolated yields of the corresponding adducts (Table 3, entries 1 and 2). Whereas hydroamination of the monosubstituted heteroaromatic allene 1d also lead to the conversion into the expected addition product 3j, hydroamination of the monoalkyl-substituted aliphatic allene 1e formed a 71:29 mixture of linear product (3ka) and branch product (3kb) under the same conditions (Table 3, entry 4). Furthermore, disubstituted allenes also worked well. Differentially 1,1-disubstituted allene 1f reacted with sulfonamide to afford trans-adducts 3l with high selectivity (Table 3, entry 5). Single crystals of the compound 3l suitable for X-ray crystallographic analysis were also obtained (Figure 1). This shows that 3l is the E isomer, the sulfonamide carbon link being trans to the phenyl group (Figure 1). As for differentially 1,3- disubstituted allene 1g, hydroamination took place with exclusive attack of sulfonamide at the more electron-rich allene terminus to afford the corresponding adduct 3m with 68% yield and with high E-selectivity (Table 3, entry 6). In addition, hydroamination of trisubstituted allene 1h took place to afford a different product (Table 3, entry 7). Single crystals of the compound 3n

### Table 1: Catalytic hydroamination of 1a and 2a.²

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<tr>
<th>Entry</th>
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<th>[Ag] (mol %)</th>
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<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)²</th>
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<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>TfOH (8)</td>
<td>dioxane</td>
<td>16</td>
<td>rt</td>
<td>0</td>
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</tbody>
</table>

²All reactions were performed with 0.8 mmol of 1a, 0.4 mmol of 2a, 0–5 mol % of (PPh₃)AuCl, and 0–8 mol % of AgOTf. — Isolated yields.
Table 2: Hydroamination of 1a with sulfonamide 2.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfonamide</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TsNH₂</td>
<td>2a</td>
<td>3a  91</td>
</tr>
<tr>
<td>2</td>
<td>PhSO₂NH₂</td>
<td>2b</td>
<td>3b  76</td>
</tr>
<tr>
<td>3</td>
<td>o-Me-C₆H₄SO₂NH₂</td>
<td>2c</td>
<td>3c  60</td>
</tr>
<tr>
<td>4</td>
<td>p-Br-C₆H₄SO₂NH₂</td>
<td>2d</td>
<td>3d  54</td>
</tr>
<tr>
<td>5</td>
<td>p-Cl-C₆H₄SO₂NH₂</td>
<td>2e</td>
<td>3e  72</td>
</tr>
<tr>
<td>6</td>
<td>MeSO₂NH₂</td>
<td>2f</td>
<td>3f  56</td>
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<tr>
<td>7(^c)</td>
<td>n-BuNHTs</td>
<td>2g</td>
<td>3g  79</td>
</tr>
</tbody>
</table>

\(^a\)The reactions were performed with 0.8 mmol of allene 1a, 0.4 mmol of 2, 5 mol % of (Ph₃P)AuCl and 8 mol % of AgOTf in 2 mL of dioxane at rt for 16 h. \(^b\)Isolated yield. \(^c\)At 100 °C for 8 h.

Table 3: Hydroamination of allenes 1 with 2a.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allene</th>
<th>Product</th>
<th>Yield (%)</th>
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</thead>
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<tr>
<td>1</td>
<td><img src="image" alt="" /> 1b</td>
<td><img src="image" alt="" /> 3h</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="" /> n-C₄H₆</td>
<td><img src="image" alt="" /> 1c</td>
<td><img src="image" alt="" /> 3i</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="" /> 1d</td>
<td><img src="image" alt="" /> 1d</td>
<td><img src="image" alt="" /> 3j</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="" /> n-C₄H₇</td>
<td><img src="image" alt="" /> 1e</td>
<td><img src="image" alt="" /> 3ka</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="" /> 1f</td>
<td><img src="image" alt="" /> 1f</td>
<td><img src="image" alt="" /> 3l</td>
</tr>
</tbody>
</table>
Table 3: Hydroamination of allenes 1 with 2a. (continued)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Allene</th>
<th>Sulfonamide</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Ph-(\equiv\ng{\cdot}C_3H_7)</td>
<td>1g</td>
<td>n-C_3H_7</td>
</tr>
<tr>
<td>7</td>
<td>Ph-(\equiv\nC\text{Ph}_2)</td>
<td>1h</td>
<td>Ph-NHTs</td>
</tr>
</tbody>
</table>

\[^a\]The reactions were performed with 0.8 mmol of allene 1, 0.4 mmol of 2a, 5 mol % of (Ph_3P)AuCl and 8 mol % of AgOTf in 2 mL of dioxane at rt for 16 h. \[^b\]Isolated yield. \[^c\]3ka/3kb \(\approx 71:29\).

suitable for X-ray crystallographic analysis were also obtained (Figure 2). This showed that 3n is the E isomer, the sulfonamide being trans to the diphenylmethyl groups (Figure 2).

The proposed mechanism of the gold-catalyzed hydroamination of allenes is shown in Scheme 1 [2,7,29-36]. The gold cation coordinated with allene to form cationic Au(I)-allene complex A, and this leads to cationic gold(I) complex B. The sulfonamide attacks at the less-substituted terminus of intermediate B to form C. Protonolysis of the Au–C bond of B yields the allylic sulfonamide 3, regenerating the gold complex. On the other hand, in comparison with phenyl-substituted allenes, for alkyl-substituted allene 1e, a mixture of 3ka and 3kb was produced; although the details are unclear, perhaps due to electronic factors, the addition of sulfonamide also occurred at the more-hindered position of intermediate B to give 3ka and 3kb.

Figure 1: The X-ray structure of 3l.

Figure 2: The X-ray structure of 3n.

Scheme 1: Proposed mechanism for the hydroamination of allenes.

Conclusion

In conclusion, we have successfully employed (PPh_3)AuCl/AgOTf catalyzed intermolecular hydroamination of allenes with sulfonamides to produce \(N\)-allylic sulfonamide. This reaction takes place under mild conditions with effective and high regio- and stereoselectivity. Monosubstituted, 1,1- and 1,3-disubstituted, and trisubstituted allenes were well tolerated in the reaction.
Experimental

General Information: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Allenes were prepared by procedures in the literature [37-39]. Thin-layer chromatography (TLC) was performed on glass plates coated with silica gel 60 F254 and visualized by UV light (254 nm). Column chromatography was performed with silica gel (mesh 300–400). Infrared (IR) spectra were obtained on a 370 FTIR spectrometer; absorptions are reported in cm⁻¹. Mass spectra were obtained in the electron impact (EI) mode, and high-resolution mass spectra were measured on a high-resolution mass spectrometer (GCT Premier).

General Procedure: To a mixture of sulfonamide (0.4 mmol), PPh₃AuCl (0.02 mmol), and AgOTf (0.032 mmol) in anhydrous 1,4-dioxane (2 mL) was added allene (0.8 mmol). The mixture was then sealed and stirred at room temperature until the starting sulfonamide was consumed as judged by TLC. The mixture was then quenched with a saturated solution of NaHCO₃ and then extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to yield the product in an analytically pure form.

Supporting Information

Supporting Information File 1
Analytical and spectroscopic data for compounds 3a–3j, 3ka, 3kb and 3l–3n. [http://www.beilstein-journals.org/bjoc/content/supporting/1860-5397-9-117-S1.pdf]

Acknowledgements

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References


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A$^3$-Coupling catalyzed by robust Au nanoparticles covalently bonded to HS-functionalized cellulose nanocrystalline films

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Full Research Paper

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Keywords:
A$^3$-coupling reaction; cellulose nanocrystallites (CNCs) films; gold catalysis; water or without solvent

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Abstract

We decorated HS-functionalized cellulose nanocrystallite (CNC) films with monodisperse Au nanoparticles (AuNPs) to form a novel nanocomposite catalyst AuNPs@HS-CNC. The uniform, fine AuNPs were made by the reduction of HAuCl$_4$ solution with thiol (HS-) group-functionalized CNC films. The AuNPs@HS-CNC nanocomposites were examined by X-ray photoelectron spectroscopy (XPS), TEM, ATR-IR and solid-state NMR. Characterizations suggested that the size of the AuNPs was about 2–3 nm and they were evenly distributed onto the surface of CNC films. Furthermore, the unique nanocomposite Au@HS-CNC catalyst displayed high catalytic efficiency in promoting three-component coupling of an aldehyde, an alkyne, and an amine (A$^3$-coupling) either in water or without solvent. Most importantly, the catalyst could be used repetitively more than 11 times without significant deactivation. Our strategy also promotes the use of naturally renewable cellulose to prepare reusable nanocomposite catalysts for organic synthesis.

Introduction

Organic synthesis is usually performed in organic solvents; however, from a green chemistry perspective, evaporation and discharge of organic solvents not only generates chemical waste but also causes environmental pollution [1,2]. In the past few decades, aqueous-phase organic reactions have achieved great success [3-5]. The classic examples include the Grignard-type reactions [6,7], transition-metal catalyzed C–C bond formations [8,9] and cross-dehydrogenative coupling (CDC) reactions [10-13]. In addition, the three-component aldehyde–alkyne–amine (A$^3$) coupling and asymmetric aldehyde–alkyne–amine (AA$^3$) coupling reactions have received increasing attention due to the easy formation of high-value
product propargylamines [14-16]. Notably, the A^3 coupling reaction has also been achieved in aqueous media or without solvent by gold catalysis [17-19]. However, up until now, most of the reactions are conducted by using homogenous organometallic catalysts. They usually show the high catalytic activity and selectivity [20]; however, homogeneous catalysts are difficult to adopt in large-scale industrial settings because of challenges associated with recovery and reuse of the catalysts from the reaction system, which may also increase the cost and cause environmental pollution by metallic ions. Heterogeneous catalysts could overcome the above problems [21]; however, they usually show lower catalytic activities compared with homogeneous catalysts, which may be caused by blocking the diffusion and adsorption of organic reactant molecules and products or the poor dispersion of active sites [22,23].

Cellulose nanocrystals (CNCs) have emerged as a new class of nanomaterials owing to their renewable, environmentally benign, naturally abundant, biodegradable and biocompatible nature, as well as their excellent mechanical properties and anticipated low cost [24-26]. CNCs are obtained from semicrystalline cellulose derived from wood fibers and plants. Potential applications for CNCs include nanocomposite formulation, polymer reinforcement, drug delivery [27], enzyme immobilization [28], biomedical applications [29] and as templates for the synthesis of nanomaterials [30]. The deposition of metal nanoparticles onto the surface of CNCs can lead to new nano-heterogeneous catalysts for organic synthesis. Recently, CNCs have been used as an effective support for Pd nanoparticles [31], AuNPs [32], SeNPs [33], NiNPs [34] and Au–Ag alloy NPs [35] for greener organic synthesis. However, to date, studies on combining the surface chemistry of CNCs with metal nanoparticles in catalysts are still very limited.

This paper describes the use of HS-functionalized CNCs decorated with gold nanoparticles as a novel class of heterogeneous catalysts for greener organic reactions. AuNPs were formed and deposited on the surface of HS-functionalized CNCs by coordination with the free HS-ligands. The as-prepared Au@HS-CNC catalyst displays high catalytic efficiency in A^3-coupling reactions performed in either aqueous media or without solvent. More importantly, it can be used repetitively up to 11 times without significant loss of catalytic efficiency.

Results and Discussion

Preparation and characterizations of nanocomposite Au@HS-CNC catalyst

Scheme 1 briefly illustrates the preparation of the Au@HS-CNC catalyst. First, the HS-CNC composite was prepared by using a modified procedure reported by MacLachlan et al [30]. In a typical procedure, 30 mL of a 2.1% aqueous CNC suspension was sonicated for 10 min (see Methods for details of CNC preparation in Supporting Information File 1) and pH adjusted to 2.9 with AcOH. 3-Mercaptopropyltrimethoxysilane (1.0 mL, 4.5 mmol) was added to the CNC suspension and the mixture was stirred at 25 °C until a homogeneous mixture was obtained (typically about 4 h). This solution was cooled to room temperature, and then dried on a polystyrene Petri dish. After slow evaporation at room temperature, the nanocomposite films of the HS-CNC materials were dried at 120 °C for 2 h. Then, the films were successively Soxhlet extracted with EtOH for 6 h and filtered. Finally, the HS-CNC films were added into 0.12 M HAuCl_4 ethanol solution and kept under stirring at room temperature for 24 h (during this step, the Au^{3+} was reduced to Au^{0} by the HS-groups attached on CNC), then filtered and dried at 40 °C overnight. Alternatively, the Au@HS-CNC was also synthesized by using a modified procedure reported by Tingaut et al. Only the method of thiol functionalized CNC support (HS-CNC) is different from that reported by MacLachlan et al. (see Methods for the details about the catalyst preparation).

Structure characterizations

The XPS spectra (Figure 1) demonstrated that the binding energy of the Au species in the Au@HS-CNC (4.4 mol %) sample was 84.8 eV for the Au^{4f7/2} level corresponding to zero-valent Au, according to reference data reported by Li et al. [17], and no other peak was observed. This indicated that metal ions (Au^{3+}) have been reduced to their metallic states (Au^{0}). TEM
pictures in Figure 2 further confirm this result. The HRTEM images in Figure S1 clearly show the size (2–3 nm) and lattice of the Au nanoparticles on the surface of the Au@HS-CNC (4.4 mol %) catalyst. The S species were mainly present in −2 states, corresponding to HS-groups with the binding energy around 163.5 in the S$_{2p}$ level. Thermogravimetric analysis (Figure 3) showed that the deposition of AuNPs onto CNC apparently enhanced the thermal stability of the Au@HS-CNC (4.4 mol %) films, which might be due to a composite of the saline reagent (3-mercaptopropyltrimethoxysilane). The Au@HS-CNC (4.4 mol %) decomposed at above 250 °C under an inert atmosphere, making them an attractive catalyst for catalytic reactions. The FT-IR spectra of CNC, HS-CNC and Au@HS-CNC (4.4 mol %) (Figure 4) showed absorbance bands around 2920 cm$^{-1}$ due to the stretching vibration of the C–H bond in the HS–CH$_2$–CH$_2$–CH$_2$–group. The peaks at 600–1180 cm$^{-1}$ were designated to the v$_{Si-O-Si}$ and v$_{Si-C-Si}$...
vibrations [36]. In comparison with the pure CNC, the HS-CNC and the Au@HS-CNC (4.4 mol %) catalysts exhibited an additional peak at 2546 cm\(^{-1}\) corresponding to the vibration of the HS-group [37]. However, the Au@HS-CNC (4.4 mol %) catalyst showed a weaker signal of the HS-group than the HS-CNC sample due to the coordination of the HS-ligand with the AuNPs. The solid-state \(^{13}\text{C}\) NMR spectra (Figure 5) further confirmed the presence of SH-groups in the Au@HS-CNC (4.4 mol %). In comparison with the pure CNCs, the Au@HS-CNC (4.4 mol %) catalyst clearly displayed two strong peaks at around 17 and 25 ppm owing to the C atoms connected with the S atoms in the HS–CH\(_2–\)CH\(_2–\)CH\(_2\) group [38]. The other peaks at around 65–80, and 105 ppm could be assigned to carbon atoms in the cellulose framework.

![Figure 5: Solid-state \(^{13}\text{C}\) NMR spectra of the CNC and Au@HS-CNC (4.4 mol %) catalyst.](image)

**Catalytic performances**

The A\(^3\)-coupling reaction of benzaldehyde, piperidine, and phenylacetylene was selected as the probe reaction to examine the catalytic activity of the Au@HS-CNC catalyst. Table 1 summarizes the catalytic performances of the catalyst with different Au-loadings, which were measured by inductively coupled plasma (ICP) analytical techniques. Both the HS-CNC and the Au sponge were inactive, implying that the Au is the active site and that the controlling of Au nanoparticle size is essential for the present reactions. The catalytic activity first increased with the increase of the Au loading up to 4.4 mol %. However, the activity slightly decreased with further increases in Au-loading up to 5.2 and 6.3 mol %. This decrease might be due to both the poor distribution of the Au active sites and the aggregation of the nanoparticles (See Figure S2, Supporting Information File 1). We determined the optimal Au-loading to be 4.4 mol %. Besides the Au-loading, we also investigated the effects of reaction solvents, temperature and reaction time on the catalytic efficiency. As shown in Table 1, one could conclude from the influence of the reaction time on the activity that the A\(^3\)-coupling reaction reaches completion after 24 h under the present conditions. At a lower reaction temperature (25 °C), the Au@HS-CNC (4.4 mol %) showed lower conversion due to an incomplete reaction. We obtained the best conversion at a higher reaction temperature (above 80 °C). Solvent-free conditions proved to be the most effective for the A\(^3\)-coupling reaction (Table 1, entry 23) and the conversion was comparable to that of the homogeneous catalyst (Table 1, entry 3). We obtained slightly lower conversions when using water or toluene as the solvent (Table 1, entries 14 and 15). Ethanol, acetonitrile, dichloromethane, tetrahydrofuran (THF), ethyl acetate (EA), dimethyl sulfoxide (DMSO), and N,N-dimethylformamide (DMF) afforded the products in moderate or low conversions (Table 1, entries 16–22). The optimized reaction conditions include 1.0 equiv of aldehyde, 1.2 equiv of amine, 1.5 equiv of alkyne, and 4.4 mol % of Au nanoparticles at 80 °C, solvent-free in air.

To expand the scope of this A\(^3\)-coupling, we used various aldehydes and amines as substrates under the optimized reaction conditions, and the results are summarized in Table 2. Both aromatic and aliphatic aldehydes provided the desired products in good to moderate yields (Table 2, entries 1–8). However, long chain aldehydes had a lower activity, giving lower yields (Table 1, entries 9, 10). We also observed good to moderate yields when the cyclic dialkylamines such as pyrrolidine, morpholine and azepane were used (Table 2, entries 11–19).

**Catalyst recycling**

In order to determine the recycling ability of the catalysts, the following experiments were conducted. After completion of the reaction, the mixture was diluted with 0.5 mL deuterated chloroform (CDCl\(_3\)) and filtered, and then the solid Au@HS-CNC (4.4 mol %) catalyst was washed 3 times with CDCl\(_3\), dried in vacuum, and then reused with a fresh charge of reactants for a subsequent run of reactions under identical conditions. Figure 6 demonstrates that the catalyst could be used repetitively more than 11 times without significant deactivation, suggesting its good reusability in solvent-free A\(^3\)-coupling of formaldehyde, piperidine, and phenylacetylene. It is important to verify that the actual catalytic process is heterogeneous and not homogeneous [39]. For this reason, we did the following experiment: the solid catalyst was removed by filtering when the conversion was up to 45% in A\(^3\)-coupling reactions, and then the solution reaction was continued under the same conditions. The conversion of the formaldehyde did not significantly increase, which strongly suggested that this catalytic process was a heterogeneous process.
Table 1: Three-component coupling of benzaldehyde, piperidine, and phenylacetylene catalyzed by Au-based catalysts.\(^{a}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>solvent/temp (°C)/time (h)</th>
<th>conversion (%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HS-CNC (0)</td>
<td>H(_2)O/80/24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Au(^{0}) sponge (4.0)</td>
<td>H(_2)O/80/24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>HAuCl(_4) (1.0)</td>
<td>H(_2)O/80/24</td>
<td>&gt;99</td>
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<tr>
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<td>Au@SH-CNC (2.9)</td>
<td>H(_2)O/80/24</td>
<td>61</td>
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<td>Au@SH-CNC (4.4)</td>
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<td>8</td>
<td>Au@SH-CNC(^{c}) (4.4)</td>
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<td>56</td>
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<td>EA/80/24</td>
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</tr>
<tr>
<td>23</td>
<td>Au@SH-CNC (4.4)</td>
<td>neat/80/24</td>
<td>100</td>
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</table>

\(^{a}\)All reactions were carried out with benzaldehyde (0.2 mmol), piperidine (0.24 mmol), phenylacetylene (0.3 mmol), 0.2 mL solvent in a sealed well tube. \(^{b}\)Conversions were determined by \(^{1}\)H NMR of the crude reaction mixture. \(^{c}\)Catalyst was prepared by using a modified procedure reported by Tingaut et al.

Table 2: Three-component coupling of aldehyde, amine, and phenylacetylene catalyzed by Au@SH-CNC catalysts in solvent-free conditions.\(^{a}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>amine</th>
<th>product</th>
<th>yield (%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>formaldehyde</td>
<td>piperidine</td>
<td></td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>benzaldehyde</td>
<td>piperidine</td>
<td></td>
<td>93</td>
</tr>
</tbody>
</table>

\(^{a}\)All reactions were carried out with benzaldehyde (0.2 mmol), piperidine (0.24 mmol), phenylacetylene (0.3 mmol), 0.2 mL solvent in a sealed well tube. \(^{b}\)Conversions were determined by \(^{1}\)H NMR of the crude reaction mixture.
Table 2: Three-component coupling of aldehyde, amine, and phenylacetylene catalyzed by Au@SH-CNC catalysts in solvent-free conditions.\textsuperscript{a}

(continued)

<table>
<thead>
<tr>
<th></th>
<th>Aldehyde</th>
<th>Amine</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ethylbutyraldehyde</td>
<td>piperidine</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>isobutyraldehyde</td>
<td>piperidine</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>1-naphthaldehyde</td>
<td>piperidine</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>2-methylbutyraldehyde</td>
<td>piperidine</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>cyclohexanecarboxaldehyde</td>
<td>piperidine</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>hydrocinnamaldehyde</td>
<td>piperidine</td>
<td>51</td>
</tr>
<tr>
<td>9</td>
<td>decanal</td>
<td>piperidine</td>
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<tr>
<td>10</td>
<td>valeraldehyde</td>
<td>piperidine</td>
<td>36</td>
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<tr>
<td>11</td>
<td>benzaldehyde</td>
<td>morpholine</td>
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</table>
Table 2: Three-component coupling of aldehyde, amine, and phenylacetylene catalyzed by Au@SH-CNC catalysts in solvent-free conditions.\textsuperscript{a}

(continued)

<table>
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<tr>
<th></th>
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<tr>
<td></td>
<td>benzaldehyde</td>
<td>pyrrolidine</td>
<td>benzaldehyde</td>
<td>azepane</td>
<td>formaldehyde</td>
<td>morpholine</td>
<td>formaldehyde</td>
<td>ppyrrolidine</td>
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<tr>
<td>a</td>
<td>All reactions were carried out with aldehyde (0.2 mmol), amine (0.24 mmol), phenylacetylene (0.3 mmol), and catalyst containing Au (4.4 mol %) in a sealed well tube, at 80 °C (oil bath) for 24 h. \textsuperscript{b}Yields were determined by \textsuperscript{1}H NMR of the crude reaction mixture.</td>
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</table>
Conclusion

In summary, this work developed a new approach to design Au nanoparticles immobilized on the HS-functionalized CNCs. The novel Au@HS-CNC nanocomposite catalyst exhibited an excellent catalytic activity in the three-component coupling reaction of aldehyde-alkyne-amine (A3-coupling) either in water or without solvent, and could be used repetitively, which could reduce the cost and diminish the environmental impact of such reactions. Other immobilized metallic nanoparticle catalysts could also be designed based on the present method, which offered more opportunities for greener organic synthesis.

Supporting Information

Detailed experimental procedures for the synthesis of CNCs and Au@HS-CNCs using a modified procedure reported by Tingaut et al. and the HRTEM images of the Au@HS-CNC (4.4 mol%) catalysts. TEM images of the (A) Au@HS-CNC (2.9 mol %), (B) Au@HS-CNC (5.2 mol %) and (C) Au@HS-CNC (6.3 mol %) catalysts and the analysis procedure of the product.

Supporting Information File 1

File Format PDF.

Experimental procedures, HRTEM images and analysis procedure.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-155-S1.pdf]

Acknowledgements

The work was supported by a team grant from Fonds de recherche sur la nature et les technologies Québec. We thank Dr. X. D. Liu, of the Facility for Electron Microscopy (FEMR) for TEM imaging.

References


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Gold-catalyzed intermolecular coupling of sulfonylacetylene with allyl ethers: [3,3]- and [1,3]-rearrangements

Jungho Jun, Hyu-Suk Yeom, Jun-Hyun An and Seunghoon Shin

Abstract
Gold-catalyzed intermolecular couplings of sulfonylacetylenes with allyl ethers are reported. A cooperative polarization of alkynes both by a gold catalyst and a sulfonyl substituent resulted in an efficient intermolecular tandem carboalkoxylation. Reactions of linear allyl ethers are consistent with the [3,3]-sigmatropic rearrangement mechanism, while those of branched allyl ethers provided [3,3]- and [1,3]-rearrangement products through the formation of a tight ion–dipole pair.

Introduction
Homogeneous gold catalysis has been established during the last decade as a prominent tool in organic chemistry, mediating a variety of C–C and C–X (heteroatom) bond formations, various tandem reactions and rearrangements [1]. Despite these significant advances, overcoming entropic penalty in intermolecular coupling of alkenes with alkynes is still a major challenge in gold catalysis, reflected by the scarcity of such examples [2-5]. Earlier examples in this vein include intermolecular reactions of electron-rich arenes and heteroarenes [2,3]. More recently, relatively polarized 1,1-disubstituted olefins were also found to react intermolecularly with phenylacetylenes or propiolic acids [4,5].

Recently, strategies capitalizing upon donor- or acceptor-polarized alkynes have been introduced, perhaps to enhance the charge interaction and thus to facilitate the intermolecular reactivity (Figure 1). For example, Liu and co-workers have utilized ynamides for intermolecular [4 + 2] and [2 + 2 + 2] reactions with alkynes [6]. On the other hand, Shin and co-workers have adopted propiolic acids and alkynyl sulfones...
for formal enyne cross metathesis (f-EYCM) [5]. These examples allow for an effective alkyne-alkene coupling under mild reaction conditions (rt) with as little as 1.5–2 equiv of an excess component.

Expanding upon the intermolecular coupling reactions of readily available alkenes with alkynes would significantly enhance the synthetic utility of gold catalysis and therefore should find fruitful applications. While it has been known for a long time that allyl alcohols undergo intermolecular alkylation-[3,3]-sigmatropic rearrangement under Ag(I) or Au(I) catalysis [7,8], allyl ethers that are less nucleophilic due to steric reasons react more slowly and have not been known to undergo similar reactions until recently. In our previous work [9], it was shown that ester-substituted alkynes underwent an efficient intermolecular carboalkoxylation with allyl ethers via a tandem conjugate addition and a [3,3]-sigmatropic rearrangement [10-12]. Preliminary results in the above studies [5,9] have demonstrated that a polarizing effect of the sulfonyl substituent on the alkyne is highly effective in promoting the reaction under a mild condition with relatively low amount of excess reactants. We report herein the details of our investigation on the intermolecular reactions of alkynyl sulfones with allyl ethers aimed at definition of the substrate scope and at elucidation of the competitive [1,3]- and [3,3]-rearrangement pathways and their respective mechanisms.

Results and Discussion

At the outset, the effect of ligand, counter-anion and solvent in the Au-catalyzed coupling of p-toluenesulfonylacetylene (1) with an allyl ether 2 was examined (Table 1). When Au(L)SbF$_6$ ($L = \text{di-i-butyl-o-biphenylphosphine, JohnPhos}$) formed in situ was used as catalyst, the reaction was more efficient in chlorinated solvents rather than polar aprotic or aromatic hydrocarbon solvents (Table 1, entries 1–7). Contrary to the previous [4 + 2] cycloaddition, formal enyne cross metathesis or [2 + 2] cycloaddition [4,5] where JohnPhos ligand showed the best performance, the optimal ligand for the current carboalkoxylation was different. While the role of electron density of the ligand was less obvious, the steric bulk on the ligand clearly seemed to retard the reaction and a less bulky PPh$_3$ was chosen as the optimal ligand (Table 1, entries 8–13). Further optimization with regard to reactants stoichiometry was conducted. An increased rate was observed when the amount of allyl ethers increased up to 3 equivalents. However, an increase in the amount of sulfonylethylene (1) was less effective (Table 1, entries 14–18). Finally, SbF$_6$ turned out to be an optimal counter-anion for cationic [Au(PPh$_3$)$_2$]$^+$ (Table 1, entries 19–21). A control experiment with AgSbF$_6$ as the only catalyst led to no reaction (Table 1, entry 22). Apparently, unlike allyl alcohols, sterically bulkier allyl ethers do not undergo O-attack on the alkyne in the presence of Ag-catalyst [7].

With the above optimized conditions in hand, the scope of the carboalkoxylation of sulfonylethylene was examined (Table 2). The alkoxy group in the ethers 2 had an impact on the efficiency of the current tandem carboalkoxylation. The reaction of methyl ether 2a was accompanied by a side product 4 ($R^1 = \text{Me}$) resulting from a premature dissociation of the allyl cation fragment before the rearrangement, decreasing the yield of desired 3a (Table 2, entry 1). However, 2b having sterically bulky secondary (IPr) or primary alkoxy groups underwent smooth reactions (Table 2, entries 2 and 3). It is reasonable to assume that a bulky group $R^1$ would decelerate the initial O-attack on the alkyne. However, once the Au-bound oxonium ion (A in Scheme 1) is formed, the resulting rearrangement seems to be facilitated by the presence of a bulky substituent at $R^1$.

The substituents on the allyl unit also affected the reaction significantly. A cyclohexyl group as $\gamma$-substituent ($R^2$) led to a slower reaction, delivering 3d only in 54% yield, with a concomitant decrease in the ratio of [3,3]- versus [1,3]-rearrangement products, while primary allyl groups as $R^2$ were well accommodated (Table 2, entries 4–6). These indicated that a steric crowding in the proposed [3,3]-sigmatropic rearrangement transition state (Path A in Scheme 1) resulted in a sluggish reaction, but affected the competitive [1,3]-rearrangement less severely. It is noteworthy that an unsubstituted ($R^2, R^3 = $ H) allyl ether 2g afforded 3g in a good yield (Table 2, entry 7), unlike the reactions with propiolates [9] where only ~21% of carboalkoxylation product was obtained. However, a competition experiment using 3h having two different allyl groups showed that the more electron-rich allyl unit migrated exclusively (Table 2, entry 8), clearly indicating that an electron-rich $R^2$ substituent accelerated the [3,3]-sigmatropic rearrangement. In the presence of $R^3$ ($\alpha$-substituent (2i–k)), however, both the rate and the yield of the reaction was significantly compromised and the reaction was accompanied by the extensive formation of either 4 or 5 (Table 2, entries 9–13). It is interesting to note that the ratio of [3,3]- versus [1,3]-rearrangement prod-
Table 1: Optimization of the reaction conditions.\(^a\)

\[
\begin{array}{cccccc}
\text{Entry} & \text{Ligand} & \text{AgX} & \text{Solvent} & \text{Yield} \\
1 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 32 \\
2 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{DCM} & 30 \\
3 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{DCE} & 23 \\
4 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{CH}_3\text{NO}_2 & 20 \\
5 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{CH}_3\text{CN} & 0 \\
6 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{THF} & 0 \\
7 & \text{JohnPhos} & \text{AgSbF}_6 & 1:1.2 & \text{PhH} & 3 \\
8 & \text{P(OC}_6\text{H}_5)_3 & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 36 \\
9 & \text{PPPh}_3 & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 48 \\
10 & \text{IMes} & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 22 \\
11 & \text{IPr} & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 19 \\
12 & \text{P(C}_6\text{F}_5)_3 & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 10 \\
13 & \text{PtBu}_3 & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 7 \\
14 & \text{PPPh}_3 & \text{AgSbF}_6 & 1:1.2 & \text{CHCl}_3 & 40 \\
15 & \text{PPPh}_3 & \text{AgSbF}_6 & 1:2 & \text{CHCl}_3 & 68 \\
16 & \text{PPPh}_3 & \text{AgSbF}_6 & 1:3 & \text{CHCl}_3 & 77 \\
17 & \text{PPPh}_3 & \text{AgSbF}_6 & 1:5 & \text{CHCl}_3 & 74 \\
18 & \text{PPPh}_3 & \text{AgSbF}_6 & 5:1 & \text{CHCl}_3 & 53 \\
19 & \text{PPPh}_3 & \text{AgOTf} & 1:3 & \text{CHCl}_3 & 48 \\
20 & \text{PPPh}_3 & \text{AgNTf}_2 & 1:3 & \text{CHCl}_3 & 44 \\
21 & \text{PPPh}_3 & \text{AgBF}_4 & 1:3 & \text{CHCl}_3 & 22 \\
22 & \text{AgSbF}_6 & 1:3 & \text{CHCl}_3 & 0 \\
\end{array}
\]

\(^a\)Conditions: in situ formed catalyst from Au(L)Cl and AgX (5 mol % each); rt, 1 h. \(^b\)Crude yield based on the internal reference (N,N-dimethylacetamide). \(^c\)IMes = 1,3-dimesitylimidazol-2-ylidene. \(^d\)IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. \(^e\)In the absence of Au(L)Cl.

Table 2: Scope of the carboalkoxylation of sulfonyl acetylene (1).\(^a\)

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}^1 & \text{R}^2 & \text{R}^3 & \text{Product} & \text{Yield}^b (\%) & [3,3]/[1,3] \\
1 & \text{Me} & \text{n-Pr} & \text{H} & \text{H} & \text{3a} & 53 \\
2 & \text{IPr} & \text{n-Pr} & \text{H} & \text{H} & \text{3b} & 67 \\
3 & \text{(CH}_2\text{)}_2\text{Ph} & \text{n-Pr} & \text{H} & \text{H} & \text{3c} & 72 \\
4 & \text{(CH}_2\text{)}_2\text{Ph} & \text{Cy} & \text{H} & \text{H} & \text{3d} & 54 \\
5 & \text{(CH}_2\text{)}_2\text{Ph} & \text{(CH}_2\text{)}_2\text{Ph} & \text{H} & \text{H} & \text{3e} & 75 \\
6 & \text{(CH}_2\text{)}_2\text{Ph} & \text{Me} & \text{H} & \text{H} & \text{3f} & 75 \\
7 & \text{(CH}_2\text{)}_2\text{Ph} & \text{H} & \text{H} & \text{H} & \text{3g} & 74 \\
8 & \text{Allyl} & \text{n-Pr} & \text{H} & \text{H} & \text{3h} & 60 \\
9 & \text{Me} & \text{n-Pr} & \text{Me} & \text{H} & \text{3i} & 40 \\
10 & \text{(CH}_2\text{)}_2\text{Ph} & \text{(CH}_2\text{)}_3 & \text{H} & \text{3j} & 23 \\
\end{array}
\]

\(^a\)Conditions: \[\text{Ts} + \text{R}^{1}\text{R}^{2}\text{R}^{3}\rightarrow \text{Ts} + \text{R}^{1}\text{R}^{2}\text{R}^{3}\]

\[^{[3,3]}\] [\text{3a}~\text{[1,3]}]

\[^{[3,3]}\] [\text{3a}~\text{[1,3]}]
products reversed dramatically in these cases in favor of [1,3]-rearrangement (Table 2, entries 9 and 11), most probably because of a facile ionization of the C–O bond leading to an allyl cation and C (Path C, Scheme 1). Intriguingly, 2l having an α-Me substituent and no γ-substituent provided an exclusive formation of an apparent [3,3]-rearrangement product 3l (Table 2, entry 11). These experiments indicated that for those having an α-substituent, the steric nature of R\textsubscript{2} and R\textsubscript{3} substituents determined the ratio of [3,3]- versus [1,3]-products. Finally, R\textsuperscript{4} substituent at the allyl group (2n) retarded the transformation severely, indicating an unfavorable steric interaction. Unlike previous intramolecular [3,3]-sigmatropic rearrangements [13,14], the γ,γ-disubstituted allyl ethers derived from geraniol or nerol were completely inactive, most probably due to steric reasons as in the case of 2d.

The proposed mechanism accounting for the above reactivity profile is depicted in Scheme 1. Having a stronger acceptor (Ts), I requires less amount of an excess reactant for the formation of the key intermediate A than propiolates and allows for the migration of even less electron-rich allyl group as in 2g [9]. A key mechanistic difference is the facile cleavage of the allyl C–O bond in A induced by the stronger polarizing effect of the tosyl group to give C and allyl cation, which evolves into 4 and a mixture of dienes. This was especially severe for substrates having an α-substituent (2i–l) where the stability of the resulting allyl cation further facilitates the ionization. The combination of the resulting intermediate C and the allyl cation occurred at the sterically less hindered allyl end, leading to preferential formation of the [1,3]-rearrangement product for 2i and 2k and an apparent [3,3]-rearrangement product for 2l. For those without α-substituents, the negative influence of steric bulk at the R\textsuperscript{2} (2d) and R\textsuperscript{4} (2n) indicates a compact transition state in the concerted [3,3]-sigmatropic rearrangement (Path A) where repulsion between R\textsuperscript{2} and Au(L) and between R\textsuperscript{4} and Ts decelerates the reaction, respectively.

### Table 2: Scope of the carboalkoxylation of sulfonyl acetylene \(^{(1)}\)\(^{\text{a}}\) (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsubscript{1}</th>
<th>R\textsubscript{2}</th>
<th>R\textsubscript{3}</th>
<th>Yield</th>
<th>Ratio</th>
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<tr>
<td>11</td>
<td>nC\textsubscript{8}H\textsubscript{17}</td>
<td>n-Pr</td>
<td>Me</td>
<td>H</td>
<td>3k</td>
</tr>
<tr>
<td>12</td>
<td>nC\textsubscript{8}H\textsubscript{17}</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>3l</td>
</tr>
<tr>
<td>13</td>
<td>(CH\textsubscript{2})\textsubscript{2}Ph</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>3m</td>
</tr>
<tr>
<td>14</td>
<td>(CH\textsubscript{2})\textsubscript{2}Ph</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>3n</td>
</tr>
</tbody>
</table>

\(^{a}\)Conditions: Allyl ether (3.0 equiv) and I (1 equiv) in the presence of in situ formed [Au(PPh\textsubscript{3})\textsubscript{3}]SbF\textsubscript{6} (5 mol %) in CHCl\textsubscript{3} from −15 °C to rt, 2.5 h.

\(^{b}\)Isolated yield after chromatography.

\(^{c}\)Characterization data have been previously provided ([9]).

\(^{d}\)15% of 4 (R\textsubscript{1} = Me) was observed for the reaction of 3i.

\(^{e}\)10% of 4 and 43% of 5 (R\textsubscript{1} = (CH\textsubscript{2})\textsubscript{2}Ph) was observed for the reaction of 3j.

\(^{f}\)20% of 4 (R\textsubscript{1} = n-H\textsubscript{17}) was observed for the reaction of 3k.

\(^{g}\)3% of 4 (R\textsubscript{1} = n-H\textsubscript{17}) was observed for the reaction of 3i.

**Scheme 1:** Proposed mechanism of the [3,3]- and [1,3]-rearrangement.
To examine the possible role of 4 in the carboalkoxylation, 4 (R₁ = Me) was added in a reaction mixture of 2c in the presence of the Au-catalyst. No product resulting from a combination of 4 with the allyl fragment in 2c was observed (Scheme 2, reaction 1), eliminating the role of 4 as the nucleophilic component along the Path C to B/B’. Furthermore, in a cross-over experiment with an equimolar mixture of 2a and 2d in the presence of the Au-catalyst, no cross-over product was observed by GC–MS and NMR spectrometry, indicating the [3,3]- and [1,3]-rearrangement occurred intramolecularly (Scheme 2, reaction 2). This was further confirmed by the cross-over experiment employing 2i and 2m, two α-substituted allyl ethers [9]. The absence of cross-over in the latter experiment strongly indicated that the formation of a tight ion-dipole pair between C and the allyl cation in the reactions of α-substituted allyl ethers (Path C). A concerted [1,3]-sigmatropic rearrangement (Path B) seems less likely because such a rearrangement should occur through antarafacial selectivity due to the orbital symmetry.

Conclusion
Gold catalyzed intermolecular coupling of allyl ethers with sulfonylacetylene has been reported. The strong polarizing effect of the sulfonyl group induced an effective intermolecular tandem carboalkoxylation with a lower amount of the excess reactant. However, it is accompanied by a significant amount of byproduct(s) such as 4 and 5, resulting from the dissociation of the allyl C–O cleavage. While the linear allyl ethers preferred [3,3]-sigmatropic rearrangements, the presence of an α-substituent led to a facile dissociation of the allyl C–O bond leading to [1,3]- or [3,3]-rearrangement products depending on the substituents. For both [3,3]- and [1,3]-rearrangements, control experiments confirmed the intramolecular mechanism of the allyl migration. Our current efforts are aimed at the elucidation of the exact nature of the [1,3]-rearrangement pathway with its stereochemical consequences and at the synthetic applications of the resulting products.

Supporting Information
Supporting Information File 1
Characterization of starting materials, general procedure for the carboalkoxylation, characterization of products, and 1H and 13C NMR spectra of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-198-S1.pdf]

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Gold-catalyzed cyclization of allenyl acetal derivatives

Dhananjayan Vasu, Samir Kundlik Pawar and Rai-Shung Liu*

Abstract
The gold-catalyzed transformation of allenyl acetals into 5-alkylidenecyclopent-2-en-1-ones is described. The outcome of our deuterium labeling experiments supports a 1,4-hydride shift of the resulting allyl cationic intermediates because a complete deuterium transfer is observed. We tested the reaction on various acetol substrates bearing a propargyl acetate, giving 4-methoxy-5-alkylidenecyclopent-2-en-1-ones via a degradation of the acetate group at the allyl cation intermediate.

Introduction
Gold-catalyzed cyclization/cycloaddition reactions [1-5] are useful synthetic methods to construct complicated carbo- and oxacyclic frameworks. Such cascade reactions have been well studied on various difunctionalized molecules including oxoalkynes [6-13], oxoallenes [14], oxoalkenes [15] and allenyl acetals [16-18]. In this cascade sequence, two new rings and three chemical bonds are generated in a one-pot procedure. We previously reported gold-catalyzed reactions of allenyl acetals with suitable dipolarophiles such as 1,3-diones to chemoselectively produce the cycloaddition product 2 [17] (Scheme 1). Similar reactions with nitrones stereoselectively delivered distinct formal cycloadducts 3 [18]. We postulate that compounds 2 arise from the attack of 1,3-diones at initially generated allyl cation intermediates I. In the case of electrophilic nitrones, allylic cations I release a proton to form reactive 1-methoxyfulvenes II to achieve a [3 + 2]-nitrene cycloaddition. The versatility of cationic intermediates I encourages us to understand their behavior in the absence of a dipolarophile. This work reports gold-catalyzed intramolecular cyclizations of these allenyl acetals [19].

Results and Discussion
We first tested the intramolecular cyclizations of allenyl acetal 1a with PPh₃AuCl/AgSbF₆ (5 mol %), which was shown to be an active catalyst in the two cascade reactions, as depicted in Scheme 1 [17,18]. As shown in Table 1, the treatment of com-
pound 1a with this gold catalyst (5 mol %) in dichloromethane (DCM, 28 °C, 0.5 h) afforded 5-isopropylidenecyclopent-2-en-1-one derivative 4a in 65% yield (Table 1, entry 1). With a change of the counter anion as in PPh₃AuCl/AgOTf, the product yield increased to 89% (Table 1, entry 2). PPh₃AuCl/AgNTf₂ was also active to give the same product in 83% yield (Table 1, entry 3). Under the same conditions, AgOTf alone gave the desired 4a in 48% yield (Table 1, entry 4). AuCl₃ and PtCl₂ enabled a complete consumption of the starting material 1a, but the yields of compound 4a were 51% and 30%, respectively (Table 1, entries 5 and 6).

Table 1: Catalyst screening over various acid catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh₃AuCl/AgSbF₆</td>
<td>0.5</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>PPh₃AuCl/AgOTf</td>
<td>0.5</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃AuCl/AgNTf₂</td>
<td>0.5</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>2.0</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>AuCl₃/CO</td>
<td>1.5</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>PtCl₂/CO</td>
<td>1.5</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2 shows the substrate scope including additional allenyl acetals 1b–1h. The reactions were catalyzed by PPh₃AuCl/AgNTf₂ (5 mol %) in DCM. As shown in entries 1–3, this cyclization was applicable to allenyl acetals 1b–1d bearing a cyclopentyl bridge. The resulting products 4b–4d were produced with satisfactory yields (68–82%). We also tested the reaction on acyclic allenyl acetal 1e (E/Z = 3:1), and afforded the desired product 4e in 52% yield according to initial E-configured 1e. The structure of compound 4e was determined by ¹H NMR NOE spectra. The reaction was still operable with 1f, bearing a 1,2-disubstituted allene, giving the desired 4f in moderate yield (49%). Its E-configuration was determined by NOE measurements, and assignable to other products including 4g and 4h. The reaction worked well with substrates bearing a different trisubstituted allenes, giving the desired cyclopentenone 4g and 4h in 82–83% yields.

The preceding cyclization is mechanistically interesting because it involves a cleavage of the C–H bond of the acetal group. We prepared d₁-1a bearing a deuterium (>98%, Scheme 2, reaction 1) at its acetal group. The resulting product d₁-4a has almost one full deuterium (X = 0.98 D) at one of the methylene protons according to DEPT ¹³C NMR analysis. In the presence of added D₂O, undeuterated 1a gave the product without deuterium content (Scheme 2, reaction 2). The results of these labeling experiments reveal a 1,4-hydrogen shift [20-22] in the d₁-1a → d₁-4a transformation.

Scheme 1: Reported cascade reactions on allenyl acetals.

Scheme 2: Gold-catalyzed cyclization of deuterated d₁-1a.
Table 2: Gold-catalyzed cyclization of allenyl acetals.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Time/min</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>15</td>
<td>4b (82%)</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>10</td>
<td>4c (68%)</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>10</td>
<td>4d (70%)</td>
</tr>
<tr>
<td>4c</td>
<td>1e</td>
<td>30</td>
<td>4e (52%)</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>30</td>
<td>4f (49%)</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>30</td>
<td>4g (82%)</td>
</tr>
<tr>
<td>7</td>
<td>1h</td>
<td>10</td>
<td>4h (83%)</td>
</tr>
</tbody>
</table>

*Substrates: 5 mol % AuClPPh$_3$/AgOTf, [1] = 0.1 M, 25 °C, DCM.
*Isolated yield.
*10 mol % of gold catalyst.

Scheme 3 shows a plausible mechanism to rationalize the transformation of the allenyl acetal 1e into the observed cyclopentenone 4e. The deuterium labeling experiment of the 1a→1e transformation (Scheme 2, reaction 1) indicates that one methylene proton of 4a is derived from the original acetal group. Accordingly, we postulate a 1,4-hydride shift [21,22] for the intermediate transformation B→C. We excluded an alternative route involving the protonation of the fulvene intermediate D because this route would water as a proton source. The formation of the fulvene intermediate D from allyl
cation B is assisted by a weak base like nitrone [18]. We envisage that a 1,2-hydrogen shift for the allyl cation B fails to explain a complete deuterium transfer for the d1-1a→d1-4a transformation because its resulting cyclopent-3-en-1-one derivative became isomerized to the final product 4a with a loss of deuterium content.

We also prepared the substrate 5a bearing a propargyl acetate moiety because this functionality can be transferred to the allenyl acetate 5a* by a gold catalyst [23,24]. As shown in Scheme 4, the treatment of species 5a with PPh3AuOTf (5 mol %) in dichloromethane (28 °C, 5 min) gave 4-methoxy-5-isopropylidenecyclopent-2-en-1-one 6a in 76% yield. The structure of compound 6a was determined by an X-ray diffraction study (crystallographic data are provided in Supporting Information File 1). Formation of this product is postulated to arise from the attack of the methoxy anion at the acetyl group of the corresponding allyl cation E, a process not involving a 1,4-hydride shift. This alternative pathway highlights the diversified mechanism of such oxidative cyclizations.

We prepared the additional substrates 5b–5g bearing an acetate group to examine the scope of the reaction, results are shown in Table 3. This gold-catalyzed cyclization was applicable to compound 5b bearing a cyclopentyl bridge, giving the desired 6b in 96% yield. The reaction worked also with 5c and 5d bearing a cyclohexyl bridge, delivering the desired products 6c and 6d in 78% and 72% yields, respectively (Table 3, entries 2 and 3). We tested the reaction with the benzenoid substrates 5e–5g, giving the corresponding enones 6e–6g in 63–78% yields.

Conclusion

In summary, we report a gold-catalyzed transformation of allenyl acetals 1 into 5-alkylidenecyclopent-2-en-1-ones 4. Our deuterium labeling experiments support a 1,4-hydride shift for the resulting allyl cation because of a complete deuterium transfer. This observation excludes the pathway involving the protonation of a 1-methoxyfulvene species. We tested the reactions of acetal substrates 5 bearing a propargyl acetate to afford 4-methoxy-5-alkylidenecyclopent-2-en-1-ones 6. The formation mechanism involves a degradation of the acetate group at the corresponding allyl cation.

Experimental

General procedure for the gold-catalyzed carbocyclization

General procedure for the gold(I)-catalyzed carbocyclization of vinyllallenyl acetals: A two-necked flask was charged with chloro(triphenylphosphine)gold(I) (11.1 mg, 0.022 mmol) and silver triflate (5.8 mg, 0.022 mmol), and to this mixture CH2Cl2 (2.0 mL) was added. The resulting solution was stirred at room temperature for 10 min. To this mixture CH2Cl2 (2.0 mL) was added. The reaction was kept stirring at 25 °C for 30 min before it was filtered over a short silica bed. The solvent was evaporated under reduced pressure. The crude product was eluted through a short silica bed.
Table 3: Gold-catalyzed carbocyclization of propargylic esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Time/min</th>
<th>Product (yield)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Structure 5b" /></td>
<td>5</td>
<td><img src="image2" alt="Structure 6b" /> (96%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Structure 5c" /></td>
<td>5</td>
<td><img src="image4" alt="Structure 6c" /> (78%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Structure 5d" /></td>
<td>5</td>
<td><img src="image6" alt="Structure 6d" /> (72%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Structure 5e" /></td>
<td>10</td>
<td><img src="image8" alt="Structure 6e" /> (78%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Structure 5f" /></td>
<td>10</td>
<td><img src="image10" alt="Structure 6f" /> (68%)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Structure 5g" /></td>
<td>10</td>
<td><img src="image12" alt="Structure 6g" /> (63%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>5 mol % AuCl<sub>3</sub>PPh<sub>3</sub>/ AgOTf, [5] = 0.1 M, 25 °C, DCM.  
<sup>b</sup>Isolated yield.

column (3% ethyl acetate in hexane) to afford the desired ketone 4a (70.6 mg, 0.40 mmol, 89%) as a pale yellow oil.

**General procedure for the gold(I)-catalyzed carbocyclization of propargylic ester acetals:** Chloro(triphenylphosphine)gold(I) (8.0 mg, 0.016 mmol) and silver triflate (4.2 mg, 0.016 mmol) were added to a dried Schlenk tube under an N<sub>2</sub> atmosphere, and freshly distilled CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was introduced by a syringe. The resulting mixture was stirred at room temperature for 10 minutes before the addition of propargylic ester acetal 5a (100 mg, 0.32 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2.2 mL). The reaction mixture was stirred for additional 5 minutes at 25 °C.
After the completion of reaction, the brown suspension was filtered through a short bed of silica gel. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography to afford the desired ketone 6a (58 mg, 0.25 mmol, 76%) as a dark yellow oil.

Supporting Information

Supporting Information File 1
Experimental details.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-202-S1.pdf]

Acknowledgements
We thank the National Science Council, Taiwan, for financial support of this work.

References

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The definitive version of this article is the electronic one which can be found at: doi:10.3762/bjoc.9.202
Abstract
The direct alkynylation of benzofurans was achieved for the first time using the hypervalent iodine reagent 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX) based on the cooperative effect between a gold catalyst and a zinc Lewis acid. High selectivity was observed for C2-alkynylation of benzofurans substituted with alkyl, aryl, halogen and ether groups. The reaction was also successful in the case of the more complex drug 8-methoxypsoralen (8-MOP).

Introduction
Benzofurans are important heterocycles frequently encountered in both bioactive compounds and organic materials (Figure 1). For example, members of the furocoumarin class of natural products including psoralen (1), 8-methoxypsoralen (2) and angelicin (3) can cross-link with DNA upon light irradiation. They have consequently been used for the treatment of skin diseases such as cancer or psoriasis [1-4]. The natural product coumestrol (4) is found especially in soy beans and has estrogenic activity [5]. Synthetic bioactive compounds containing benzofurans are also important, as exemplified by amiodarone (5), as antiarrhythmic drug [6,7]. Finally, benzofurans have also emerged recently as important structural elements for organic materials, such as the organic transistor 6 [8].

Due to the importance of benzofurans, the discovery of new efficient methods for their synthesis and functionalization is an intensive field of research [9-11]. Especially interesting would be methods allowing the direct and regioselective C–H functionalization of benzofurans [12]. In this context, the introduction of an alkyne would be particularly useful, as acetylenes are important building blocks in synthetic chemistry, chemical biology and materials science [13]. Nevertheless, to the best of our knowledge, the direct alkynylation of benzofurans is still an unknown process.

Since 2009, our group has developed a mild gold-catalyzed [14-17] method for the alkynylation of electron-rich aryls such as...
indoles and pyrroles [18], thiophenes [19], anilines [20] and furans [21]. Key for success was the use of ethynylbenziodoxolones, which are cyclic hypervalent iodine reagents [22,23]. Nevertheless, the conditions we have used for other heterocycles gave only very low yields in the case of benzofurans. Herein, we would like to report the first catalytic direct C2-alkynylation of benzofurans based on a cooperative effect between a gold catalyst and a zinc Lewis acid using 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1H)-one (TIPS-EBX, 8) as reagent (Scheme 1). The reaction proceeded under mild conditions (60 °C under air) and could also be used to alkynylate the more complex polycyclic natural product 8-methoxy-psoralen (2).

Findings

Benzofuran (7a) is less reactive than furans and indeed no product was observed under the conditions optimized for the latter [21] at room temperature or at 60 °C using the commercially available electrophilic alkynylation reagent TIPS-EBX (8) (Table 1, entries 1 and 2) [24-27]. Fortunately, benzofuran (7a) was also more stable in the presence of acidic additives, and co-activation became possible, whereas Zn(OTf)2 was superior to trifluoroacetic acid (TFA) at 60 °C (Table 1, entries 3 and 4) [19,28]. No product was observed in the absence of AuCl, demonstrating the cooperative effect of the two metals (Table 1, entry 5). Lower or higher temperatures did not increase the yield (Table 1, entries 6 and 7). Finally, using a larger excess of TIPS-EBX (8) and Zn(OTf)2 gave 75% yield of alkynylation product 9a (Table 1, entry 8). The use of Zn(OTf)2 in catalytic amount led to a lower yield (Table 1, entry 9), and a larger excess resulted in decomposition of the starting material only (Table 1, entry 10). Although other Lewis acids could also be used (Table 1, entries 11 and 12) [29], no better results than with Zn(OTf)2 were obtained (Table 1, entry 7). Importantly, in contrast to our previous work with benzothiophenes [19], high selectivity for C2 alkynylation was observed.

Table 1: Optimization of the alkynylation of benzofuran (7a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv 8</th>
<th>Additive</th>
<th>T [°C]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>–</td>
<td>23</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>–</td>
<td>60</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>TFA</td>
<td>60</td>
<td>42%</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>Zn(OTf)2</td>
<td>60</td>
<td>56%</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>Zn(OTf)2c</td>
<td>60</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>Zn(OTf)2</td>
<td>40</td>
<td>48%</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>Zn(OTf)2</td>
<td>82</td>
<td>36%</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>Zn(OTf)2</td>
<td>60</td>
<td>75%</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>Zn(OTf)2d</td>
<td>60</td>
<td>37%</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>Zn(OTf)2</td>
<td>60</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>Zn(NTf)2</td>
<td>60</td>
<td>57%</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>Yb(OTf)3</td>
<td>60</td>
<td>62%</td>
</tr>
</tbody>
</table>

*Reaction conditions: 7a (0.20 mmol) and AuCl (0.01 mmol) in acetonitrile (0.8 mL) under air for 26 h, isolated yield; †same amount as 8; ‡without gold catalyst; §0.2 equiv; ω4.0 equiv.

Scheme 1: Zinc–gold catalyzed C2-alkynylation of benzofurans.
The scope of the reaction was then investigated (Scheme 2). Substitution by diverse functional groups was first examined on the C5 position. An electron-rich methoxy group was well tolerated, giving the desired alkynylation product 9b in 73% yield. The reaction was also successful with a bromide substituent (product 9c), making the method orthogonal to classical cross-coupling chemistry [30]. In presence of an aryl or an alkyl substituent, alkynylation was also obtained in 72% and 50% respectively (products 9d and 9e). Benzofurans substituted at the C7 position could also be used, as demonstrated by the efficient formation of alkynes 9f and 9g. In contrast, when 7-methoxybenzofuran (7j) was used, no C2 alkynylation product could be isolated. Instead, a mixture of C4 and C6 alkynylated benzofurans 9j and 9j' was obtained (Scheme 3) [31]. Substitution on the furan ring was also possible at the C3 position (product 9h), but the use of 2-methylbenzofuran (7i) led to very a low yield in the alkynylation reaction.

Finally, we wondered if the alkynylation method could also be successful in the case of more complex benzofuran-containing natural products and drugs. We were pleased to see that the alkynylation of 8-methoxypsoralen (2) was indeed possible. The major product 10 bearing the acetylene group at the C5' position was obtained in 37% yield (Scheme 4) [32]. Although the yield was still moderate, this was one of the first examples of direct alkynylation of a marketed drug. It also gave access in a single step to an interesting furocoumarin derivative with an extended chromophore, which could be important for phototherapy.

Mechanistically, the reaction could proceed either via π-activation of the triple bond by the gold catalyst followed by conjugate addition of the benzofuran, α-elimination and 1,2-shift, or oxidative addition of TIPS-EBX (8) onto the gold catalyst (either at the Au(I) or Au(0) oxidation level) followed by elec-
trophic auration and reductive elimination [33]. The role of the zinc Lewis acid is not completely clear at this stage, but it may act by complexing the carboxylate group of the hypervalent iodine reagent, enhancing its electrophilic reactivity [19,34]. In fact, a complete shift of the $^1$H NMR signals of TIPS-EBX (8) was observed when Zn(OTf)$_2$ was added, whereas no signal shift was observed when mixing the Lewis acid and benzofuran (7a) [35].

In conclusion, the first direct alkynylation method of benzofurans has been developed. Key for success was a cooperative effect between a gold catalyst and a zinc Lewis acid, together with the use of the hypervalent iodine reagent TIPS-EBX (8). Preliminary results obtained with 8-methoxypsoralen (2) demonstrated that the reaction could also be applied to more complex furocoumarin natural products.

Experimental
General procedure for the alkynylation of benzofurans: TIPS-EBX (8, 342 mg, 0.800 mmol, 2.0 equiv), AuCl (4.6 mg, 0.020 mmol, 0.050 equiv), Zn(OTf)$_2$ (289 mg, 0.800 mmol, 2.0 equiv), and benzofuran 7 (0.40 mmol, 1.0 equiv) were added into CH$_3$CN (2.0 mL) under air. The mixture was stirred for 26 hours at 60 °C. Then the mixture was concentrated in presence of silica gel and purified directly by column chromatography.

Supporting Information
Supporting Information File 1
Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-204-S1.pdf]

Acknowledgements
The EPFL and F. Hoffmann-La Roche Ltd are acknowledged for financial support.

References
   See for a review on electrophilic alkynylation.
   See for a recent example of cooperative gold-zinc catalysis.
30. No product was obtained with strongly electron-withdrawing substituents, such as cyanide.
31. A 5:1 mixture of non-separable products was obtained, which prevented complete assignment of the structure of the major regioisomer.
32. The regiochemistry of the alkylation was determined by 2D NMR experiments after removal of the silyl protecting group on alkyne 10. One other non-identified isomer was observed in the crude mixture by 1H NMR (yield < 5%).
33. See Supporting Information for a full list of tested Lewis acids.
35. See Figure S1 in the Supporting Information File 1.

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Gold(I)-catalyzed formation of furans from \(\gamma\)-acyloxyalkynyl ketones

Marie Hoffmann, Solène Miaskiewicz, Jean-Marc Weibel, Patrick Pale* and Aurélien Blanc*

Abstract
Various \(\gamma\)-acyloxyalkynyl ketones were efficiently converted into highly substituted furans with 2.5 mol % of triflimide (triphenylphosphine)gold(I) as a catalyst in dichloroethane at 70 °C.

Introduction
Furans are an important class of aromatic compounds. They are found in many natural products, in pharmaceutical and agrochemical compounds as well as in flavor and fragrance industries [1]. Furans are also routinely used as building blocks in organic synthesis [2,3]. Therefore, a large number of synthetic methods has been developed to construct the furan motif [4,5]. Among them, late transition metal-catalyzed intra- or intermolecular cyclizations of oxygenated functionalities on unsaturated carbon–carbon bonds proved to be powerful synthetic methods due to their mildness, efficiency and diversity [6,7]. In the last decade, gold catalysts with their carbophilic character have emerged as a new tool for furan preparation. As summarized in Scheme 1, furans could now be obtained by either gold(I) or gold(III) catalysis from various types of substrates such as allenyl ketones [8-14], enynes or diynes [15-17], alkynes and sulfur ylides [18,19], alkynyl oxiranes [20-26], alkynyl ketones [27-35], alkynyl alcohols [36-46], and alkynyl ethers [47,48]. Very recently, a three-component coupling reaction toward furans catalyzed by gold(III) has been reported starting from terminal alkenes, glyoxal derivatives and secondary amines [49].

In this emerging research area, we have been focusing our effort on the development of furan motifs from alkynyl epoxides [21,22,50,51] and new precursors, i.e. \(\gamma\)-acyloxyalkynyl ketones. The latter have already been described to rearrange into furans by using copper catalysts. Indeed, Gevorgyan et al. showed that the combination of copper(I) chloride and triethyl-
amine catalyzed the 1,2-migration/cycloisomerization of \( \gamma \)-acyloxyalkynyl ketones in dimethylacetamide (DMA) at 130 °C (Scheme 2) within 1–46 h [31,52,53]. Despite the relative harsh reaction conditions, furans could be obtained in good to excellent yields. However, one major limitation was ascribed to the types of the employed ketones (\( R^3 \) in Scheme 2), as only phenyl and tert-butyl alkynyl ketones were able to furnish acceptable yields.

We herein report that gold(I) can overcome these limitations, providing a general, fast and very efficient transformation of \( \gamma \)-acyloxyalkynyl ketones into trisubstituted and functionalized furans.

**Results and Discussion**

In order to find the most appropriate conditions, we applied various gold catalysts in different solvents at different tempera-
tures to the easily available ynone 1a (Table 1), which has been reported to afford furan 2a in 86% yield under Gevorgyan’s conditions (Table 1, entry 1). We started our catalyst screening by using the classical combination of Ph₃PAuCl/AgSbF₆ and the Gagosz’s catalyst [54], i.e. (triphenylphosphine)gold(I) triflimide, in dichloroethane at room temperature. In both cases, a fast consumption of the starting material 1a was observed compared to the copper(I) catalysis, but lower yields of furans, 44% and 65% respectively, were obtained mostly due to the formation of the hydration product 3 (Table 1, entries 2 and 3 versus entry 5). We then verified that the hydrate product was not a transient intermediate in this rearrangement by subjecting pure compound 3 to the latter reaction conditions and, even after 3 h at 70 °C, no trace of furan 2a could be detected by ¹H NMR analysis. Interestingly, decreasing the catalytic loading from 5 to 1 mol % still provided the furan in less than 1 h and in high yields (Table 1, entries 2 and 3 versus entries 4 and 5). However, hydration started to compete again at low loading, as evidenced by tiny amounts of 3 in the NMR spectrum of the crude (Table 1, entry 7). Control experiments revealed that other triflimide salts of coinage metals were not suited for this transformation. Indeed, silver(I) triflimide resulted mainly in degradation (Table 1, entry 8) and tetrakis(acetonitrile)copper(I) triflimide furnished the furan 2a in only modest yield even after prolonged reaction time (Table 1, entry 9).

With these conditions in hand (Table 1, entry 6), we started investigating the scope of the reaction by preparing various acyloxyalkynyl ketones (Table 2). As for the phenyl alkynyl ketone 1a, the corresponding tert-buty1 alkynyl ketone 1b turned out to be a good substrate for this transformation confirming Gevorgyan’s results (Table 2, entry 1 versus entry 2). Despite its bulkiness, full conversion was achieved within 30 min and 2.5 mol % of Ph₃PAuNTf₂, affording furan 2b in 93% yield. We also evaluated the influence of the alkynyl substitution by increasing the size of the R¹ group. To implement this, we introduced secondary and tertiary carbon centers next to the acyloxy function by preparing compounds 1c (R¹ = 2-decyl) and 1d (R¹ = tert-buty1). Compound 1c, similar to 1a, rearranged under these conditions, furnishing the furan 2c in 90% yield (Table 2, entry 3). However, the presence of the sterically demanding tert-buty1 group in 1d drastically affected the reaction (Table 2, entry 1 and 3 versus entry 4). Even running the reaction with 5 mol % of catalyst to avoid the hydration product, the reaction took 6 h to reach almost full conversion. Beside the expected furan 2d, its corresponding regioisomer 2d’ arising from 1,3-migration of the pivaloyl group is formed in this reaction and both products were obtained in a combined yield of 68% (Table 2, entry 4). We next varied the nature of the migratory acyloxy group. We synthesized similar substrates 1e–1h bearing pivaloyl, benzoyl, acetyl and 2-phenylacetyl groups, respectively. These compounds were engaged in the gold-catalyzed process affording the furans 2e–2h in the same range of yields (70–80%), suggesting that the nature of the acyloxy group had no crucial influence on the rearrangement.

Indeed, the slight differences in terms of yield could be ascribed to the formation of hydration products (5–15%), and the reac-
tion times of each reaction were inferior or equal to 1 h (Table 2, entries 5–8). We then turned our attention to the problematic R$_3$ position in which only phenyl and tert-butyl substituents adjacent to the ketone, i.e. without enolizable position, were tolerated under copper(I)-catalyzed reaction conditions. We were pleased to observe that various other

### Table 2: Scope of the gold(I)-catalyzed formation of furans from γ-acyloxyalkynyl ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates 1</th>
<th>Time (h)</th>
<th>Furans 2</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>0.5</td>
<td>2a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>0.5</td>
<td>2b</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>0.75</td>
<td>2c</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>6</td>
<td>2d / 2d'</td>
<td>68$^a$</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>1</td>
<td>2e</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>0.5</td>
<td>2f</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>0.75</td>
<td>2g</td>
<td>70</td>
</tr>
</tbody>
</table>

$^a$Reaction time for entries 5–8 was 1 h.

substituents, such as methyl, propyl, 2-phenylethyl, 3-benzylxloxypropyl (Table 2, entries 9–12), were fully compatible with our gold-catalysis giving furans 2i–l in good yields.

Two different mechanistic hypotheses could be envisaged in the rearrangement of γ-acyloxyalkynyl ketones into furans based on multifaceted gold-catalyst properties, i.e. the ability of gold cations to act as π or σ Lewis acids (Scheme 3) [21,55,56]. Intramolecular [1,4]-addition of the acyloxy function by oxophilic activation of γ-acyloxyalkynyl ketones could lead to the formation of gold allenolate A, which is in equilibrium with both Z or E vinylgold B and C [57]. Intermediate B, which could also be generated by carbophilic gold activation followed by nucleophilic addition of the acyloxy part, could evolve into the gold carbened species D [31]. Intermediate C, possessing the correct stereochemistry, and D might then cyclize by an attack of the carbonyl function on the carbon bearing the R substituent to afford the oxygenated five-membered ring E. Furan would finally be formed after tautomerization and protodemetalation of intermediate E.

**Conclusion**

We have reported an efficient, very general and regioselective preparation of functionalized furans through a gold(I)-catalyzed rearrangement of γ-acyloxyalkynyl ketones under mild conditions. Further work is currently underway in our laboratory to fully understand this novel rearrangement.

**Experimental**

**General procedure for gold(I)-catalyzed formation of furans from γ-acyloxyalkynyl ketones.** In an oven-dried flask, γ-acyloxyalkynyl ketone (0.4 mmol) was dissolved in dry
dichloroethane (0.1 M) and heated to 70 °C under an argon atmosphere. Ph₃PAuNTf₂ (2.5 mol %) was then added to the stirred solution at 70 °C. The reaction was monitored by thin-layer chromatography until completion. The solvent was then removed in vacuo, and the crude residue was purified by silica gel flash chromatography (pentane/Et₂O).

**Supporting Information**

**Supporting Information File 1**

General procedures, characterization data and NMR spectra for compounds 1a–l, 2a–l and 3.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-206-S1.pdf]

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**References**


Gold(I)-catalysed one-pot synthesis of chromans using allylic alcohols and phenols

Eloi Coutant, Paul C. Young, Graeme Barker and Ai-Lan Lee

Abstract
A gold(I)-catalysed reaction of allylic alcohols and phenols produces chromans regioselectively via a one-pot Friedel–Crafts allylation/intramolecular hydroalkoxylation sequence. The reaction is mild, practical and tolerant of a wide variety of substituents on the phenol.

Introduction
Chromans (dihydrobenzopyrans) are important and ubiquitous structural motifs found in a variety of important biologically active natural products such as vitamin E and flavanoids [1-5]. One approach towards chromans [6-12], which is biosynthetically inspired, is the Friedel–Crafts alkylation [13] of phenols followed by cyclisation of the allylated phenol intermediate (via hydroalkoxylation). Initially, traditional alkylation reagents such as allylic acetates were employed in Friedel–Crafts alkylations [14], but more recently, there has been a distinct drive towards utilising more environmentally benign allylic alcohols (via a direct dehydrative coupling strategy) [15,16]. To this end, the use of molybdenum catalyst CpMoCl(CO)3 together with an oxidant, o-chloranil, has been documented to catalyse the reaction of allylic alcohols with phenols to form chromans [17,18]. Strong and superacids have also been utilised in the synthesis of chroman-containing targets [19-21]. Nevertheless, there are still a few drawbacks with these methods, for example, they usually require a large excess of substrate (e.g. ~30-fold excess), and in the case of acid catalysis, also poor yields when the phenol is not para-substituted. Therefore, it would be desirable to have a milder method which is compatible with a wide range of substituted phenols.

As part of our continued interest in developing new gold-catalysed [22-41] reactions [42-51], we have recently shown that gold(I) can catalyse a direct allylic etherification [52-59] of unactivated alcohols 2 with unactivated allylic alcohols 1 (Scheme 1, reaction 1) [60,61]. The reaction is mild, regiose-
lective, and produces only water as a byproduct. During our studies, a wide range of primary, secondary and tertiary alcohols were successfully employed as nucleophiles [61-72], but our one attempt employing a phenol 5 as a nucleophile surprisingly produced chroman 6 instead (Scheme 1, reaction 2). Although gold(III)-catalysed Friedel–Crafts allylation of phenols has been reported by Chan and co-workers [73], there have been no reports on the direct synthesis of chromans [74] using gold catalysis [75] with phenols and allylic alcohols prior to our example shown in Scheme 1.

Since the reaction is very practical: distilled solvents and inert air atmosphere are not required, and the chroman is formed directly in a mild one-pot procedure with only water as the byproduct, we decided to investigate the chroman-forming reaction in more detail, beyond the sole example previously reported (Scheme 1, reaction 2). In this paper, we present our further studies on this one-pot chroman synthesis: improving the yield of the desired chroman and exploring the substrate scope.

Results and Discussion

To commence our studies, we first investigated the possibility of lowering the reaction temperature and used equivalents of phenol nucleophile. Suspecting that the moderate yield of 6 in Scheme 1 is due to the slight volatility of 6, an allylic alcohol 7 with a higher molecular weight was chosen as the model substrate in order to avoid any issues of volatility with the chroman products. As shown in Table 1, the standard conditions (50 °C, 5 equiv phenol 5) pleasingly provide a good 65% yield of the desired chroman 8 (Table 1, entry 1). Reducing the temperature is unfortunately detrimental to the formation of chroman: 40 °C gives a lower 59% yield of 8, as well as Friedel–Crafts allylation products 9 and 10, whereas 30 °C provides no chroman 8 at all, instead yielding only Friedel–Crafts products 9 and 10 (Table 1, entries 2 and 3). The ortho- and para-Friedel–Crafts products 9 and 10 are formed via formal S\(_{N2}'\) regioselectivity and 9 is presumably the intermediate towards chroman 8 (vide infra). Thus, the higher
Table 2: Phenol nucleophile scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv 5</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Phenol 5</th>
<th>Product</th>
<th>Yield (%)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>50</td>
<td>19</td>
<td>5a</td>
<td>8a</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>50</td>
<td>64</td>
<td>5b</td>
<td>9b</td>
<td>N/D^b</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>60</td>
<td>18</td>
<td>5b</td>
<td>8b</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>60</td>
<td>17</td>
<td>5c</td>
<td>8c and 8c'</td>
<td>71 (~1:1 8c:8c')</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>60</td>
<td>18</td>
<td>5d</td>
<td>8d</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>60</td>
<td>17</td>
<td>5e</td>
<td>8e</td>
<td>63</td>
</tr>
</tbody>
</table>

temperature is clearly necessary to force the in situ cyclisation of 9 to 8.

Next, lower equivalents of phenol 5 were investigated. Unfortunately, dropping the equivalents of phenol also appears to be detrimental to chroman formation: only Friedel–Crafts products 9 and 10 are observed with 2 or 1 equivalents of phenol (Table 1, entries 4 and 5). Pleasingly however, lower equivalents of phenol are tolerated if the temperature is increased to 60 °C (Table 1, entries 6 and 7).

In order to ascertain if the gold(I) catalyst is really necessary for the formation of chroman 8, several control reactions were carried out (Table 1, entries 8–10). Firstly, no reaction is observed in the absence of a catalyst (Table 1, entry 8). The Brønsted acid catalyst HNTf$_2$ does form chroman 8, but in a poorer isolated yield (21%, Table 1, entry 9) and the silver salt [76] AgNTf$_2$ as a catalyst does not provide any 8, yielding only 9 and 10 (Table 1, entry 10). The former is consistent with literature reports that Brønsted acid-catalysed reactions give poor yields when the phenol is not para-substituted [19]. Therefore, it seems that the gold(I) catalyst is most efficient in catalysing the one-pot formation of chroman 8.

With these results in hand, a phenol screen was carried out next (Table 2). Initially, the same conditions that were best for the
formation of 8a were used (50 °C, 5 equiv 5a, Table 2, entry 1) with p-cresol (5b), but these conditions only produced the Friedel–Crafts intermediate 9b (Table 2, entry 2). Pleasingly, when the temperature was raised to 60 °C, the desired chroman 8b is successfully formed in 57% yield (Table 2, entry 3). Therefore, 60 °C was adopted as the new general conditions temperature. Additionally, it was found that the equivalents of phenol 5 can be lowered to 2 equivalents in some cases at this higher temperature (Table 2, entries 4, 7, 8 and 10). In contrast to the Brønsted acid procedure [19], the substitution position has limited effect on the efficiency of the gold-catalysed reaction, with p-cresol (5b), m-cresol (5c) and o-cresol (5d) all forming the desired chromans 8b–d in decent to good yields (Table 2, entries 3–5). The regioselectivity of the meta isomer is unsurprisingly poor (1:1 of 8c:8c'), and when both meta-positions are substituted (5e) the reaction proceeds to 8e well (Table 2, entry 6). A phenol with an electron-donating substituent 5f provides 8f in a good 71% yield (Table 2, entry 7) and one with an electron-withdrawing substituent 5g pleasingly also produces chroman 8g in a reasonable 54% yield (Table 2, entry 8). p-Bromo-substituted phenol 5h successfully yields chroman 8h which provides a handle for further functionalisation (Table 2, entry 9).

Next, the effect of a larger substituent was probed (Table 2, entries 10 and 11). More hindered 2,4-di-tert-butylphenol (5j, Table 2, entry 11) requires a higher temperature (70 °C) and twice the reaction time (43 h) to go to completion compared to 4-tert-buylphenol (5i, Table 2, entry 10). Although phenol 5j exhibits the slowest reactivity of the phenols screened, it was chosen as the model phenol in the next allylic alcohol substrate screen (Table 3) since the extra molecular weight from the t-Bu substituents should reduce any volatility issues with the chroman products [77].
At this point, we observed that the general procedure does not work if the phenol reactant is insoluble in toluene, such as 5k. However, a simple change of solvent from toluene to dioxane provides the desired chroman 8k (Table 2, entry 12), although slightly higher temperatures (70–80 °C) and a longer reaction time (65 h) are required in this polar solvent to push the reaction to completion.

Finally, to show the synthetic utility of this procedure, a hydroquinone (trimethylhydroquinone TMHQ (5l)) was also evaluated, as TMHQ is commonly used towards the synthesis of vitamin E and its analogues [17,21]. For solubility issues, dioxane is used as the solvent. Initially, an oxidised side product 11 (Figure 1, formed by auto-oxidation of the Friedel–Crafts intermediate) is observed in 35% yield if the reaction is carried out in air (80 °C), resulting in a low 45% yield of 8l. When the reaction vessel is flushed with argon, the yield of 8l improves to 69%, but ultimately carrying out the reaction at 90 °C in a sealed tube provides a much better yield of 83% (Table 2, entry 13).

Next, the allylic alcohol scope was investigated (Table 3). Firstly, going from more hindered Cy substituents (7) to less hindered n-hexyl substituents (12) allows the reaction to work smoothly at a lower temperature of 60 °C (Table 3, entries 1 and 2). Hindered 4 works equally well but requires extended reaction times (67 h) to achieve a good 83% yield (Table 3, entry 3). Less hindered 13 as well as 14 work smoothly to form 8o and spirocyclic chroman 8p (Table 3, entries 4 and 5). An aromatic substituent is also well tolerated (Table 3, entry 6). Next, the effect of substitution along the alkene was investigated (Table 3, entries 7–10). Substitution at the γ-position (16 and 17) seems to be tolerated, forming chromans 8r and 8s respectively albeit in moderate yields (Table 3, entries 7 and 8). Substitution at the β-position, however, is not tolerated: the

Table 3: Allylic alcohol scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Allylic alcohol</th>
<th>Product</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43</td>
<td>70</td>
<td>7</td>
<td>8j</td>
<td>83</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>60</td>
<td>12</td>
<td>8m</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>60</td>
<td>4</td>
<td>8n</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>60</td>
<td>13</td>
<td>8o</td>
<td>64</td>
</tr>
</tbody>
</table>

\(^a\) Yield determined by 

\[ \text{PPh}_3\text{AuNTf}_2 \] (5 mol %) toluene
reaction stops at the Friedel–Crafts stage (9t), and is reluctant to undergo further cyclisation to the desired chroman (Table 3, entry 9). Having investigated a series of tertiary allylic alcohols in entries 1–9, we next looked at selected primary and secondary allylic alcohols (Table 3, entries 10–12). The γ,γ-disubstituted primary allylic alcohol 19 forms the chroman 8o efficiently (Table 3, entry 10), which is the same product as from the tertiary allylic alcohol substrate 13 in entry 4. This implies that 19 undergoes the Friedel–Crafts allylation via opposite regioselectivity (a formal S_N2 instead of S_N2' observed in all other examples so far in Table 2 and Table 3) to form 9, followed by cyclisation to form the observed 8o. Using a γ,γ-
disubstituted secondary allylic alcohol 20 also forms chroman 8a via an initial S\textsubscript{N}2 Friedel–Crafts regioselectivity, thus \(\gamma,\gamma\)-disubstitution on the alkene appears to be responsible for the switch in regioselectivity (Table 3, entry 11). This implies that the initial Friedel–Crafts allylation goes via Markovnikov selectivity. The unsubstituted secondary allylic alcohol 21, however, produces only the Friedel–Crafts allylation product 9v and is reluctant to undergo cyclisation to the chroman (Table 3, entry 12) even under more forcing conditions (80 °C, 65 h).

Since 9 is always observed as a precursor towards 8 (i.e. at lower temperatures, shorter reactions times or when the reaction is analysed before completion), the most likely mechanism is the expected gold(I)-catalysed Friedel–Crafts allylation of the phenol (via Markovnikov regioselectivity), with allylic alcohol [15,73], followed by cyclisation of the intermediate 9 via hydroalkoxylation to form chroman 8 (Scheme 2) [13,15,16]. Chan and co-workers have previously proposed that the Friedel–Crafts mechanism could involve the activation of the allylic alcohol by the gold catalyst to turn the hydroxy group into a better leaving group [73]. The observed regioselectivities is then due to the subsequent attack at the less hindered position of this presumed activated intermediate [73,78].

Our subsequent investigations with the Friedel–Crafts intermediate 9a suggests that the second hydroalkoxylation step is not (or not solely) gold catalysed (Scheme 3). When isolated 9a is resubjected to the reaction conditions with or without additional phenol (5a), no cyclisation to the chroman 8a occurs (Scheme 3). Thus, the second cyclisation step is most likely Brønsted acid catalysed (or acid and gold(I) co-catalysed) [79], where the \(H^+\) required is being released in situ during the first Friedel–Crafts step to form 9. This would explain why 9 readily cyclises to chroman 8 in situ, but is reluctant to do so when it is isolated before being resubjected to more gold(I) catalyst, as in Scheme 3. Nevertheless, simply using the equivalent Brønsted acid \(\text{HNTf}_2\) is not as efficient as using gold(I), as shown in Table 1, entry 9.

If the hydroalkoxylation step is indeed \(H^+\) catalysed, addition of a Brønsted acid co-catalyst could force the chroman formation from substrates such as 21, which do not undergo the second hydroalkoxylation step under just gold(I)-catalysed conditions (Table 3, entry 12). Indeed, the reaction of 21 with 5j successfully produces the desired chroman 8v in 52% yield when \(\text{HNTf}_2\) is added as a co-catalyst (Scheme 4), further suggesting that the hydroalkoxylation step is most likely Brønsted acid catalysed or co-catalysed.

The suggested mechanism is presented in Scheme 5. Gold(I) catalysts are known to coordinate to alcohols [80], in this case turning the hydroxy group into a better leaving group (I), as previously suggested by Chan [73]. Attack at the less hindered position could occur either directly on I [S\textsubscript{N}2' shown, but in the case of \(\gamma,\gamma\)-disubstituted substrates (e.g. 19 and 20), this will occur via S\textsubscript{N}2] or via an allylic cation intermediate II. The intermediate 9 subsequently undergoes an acid-catalysed hydroalkoxylation to produce the desired chroman 8. Active catalyst LAu\(^+\) is presumably regenerated by protonolysis of LAuOH [81].

**Conclusion**

In conclusion, a simple one-pot procedure towards chromans is described via gold(I)-catalysed reaction of readily accessible phenols with allylic alcohols. This one-pot procedure involves a regioselective Friedel–Crafts allylation followed by cyclisation.
via hydroalkoxylation to form the chromans in good yields. At
lower temperatures or shorter reaction times, the Friedel–Crafts
allylation intermediates are usually observed. The reaction
works with ortho-, meta- and para-substituents as well as elec-
tron donating and withdrawing substituents on the phenol, and
hydroquinones (Table 2). A variety of allylic alcohol substrates
work well, although substitution on the alkene is only tolerated
at the γ-position, and not the β-position (Table 3). The proce-
dure is mild, practically simple and regioselective. We
therefore believe that it should find utility as a convenient
method towards the synthesis of chroman targets.

Experimental

General procedure: The gold-catalysed reactions were all
carried out in 1 dram screw-cap vials without the need for
distilled solvents or inert atmosphere, unless otherwise stated.
PPh₃AuNTf₂ (5 mol %) was added to a toluene solution
(0.386 M) of allylic alcohol (1 equiv) and phenol (2 or 5 equiv).
The reaction mixture was allowed to stir at 50–70 °C until the
reaction is complete (16–67 h). The reaction was then filtered
through a plug of silica (eluent: neat diethyl ether). The filtrate
was concentrated under reduced pressure, and
¹H NMR analysis
of the crude mixture was used to determine the conversion to
chroman 8. The crude material was then purified by flash
column chromatography. [Note: If the starting materials are
insoluble in toluene, dioxane is used as the solvent instead and
the reaction temperature increased to 70–80 °C.]

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was acquired at the EPSRC UK National Mass Spectrometry
Facility at Swansea University.

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triflate-mediated cyclisation of phenols with 1,3-dienes. Using these
methods, chromans and/or coumarans are obtained, depending on the
structure of the 1,3-diene used. For selected recent examples, see
references [7-10].
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doi:10.1021/ol0607692
doi:10.3762/bjoc.6.6

Supporting Information

Supporting Information File 1
Full experimental procedures, characterisation for all new
compounds and copies of ¹H and ¹³C NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-209-S1.pdf]
62. For an independent report using NHS gold(i) complexes, see reference [61]. For related reactions with N-nucleophiles instead, see references [63–67].
77. We have noted that the formation of chromans 8a–8j from 7 is also accompanied by the formation of a rearrangement side-product in approximately 15–25% yields (see Supporting Information File 1 for details). The formation of this rearrangement side product is only ever observed with cyclohexyl substituents (i.e. 7) and is not detected in any of the other allylic alcohols screened in Table 3. We have previously observed unusual behaviour in other substrates containing bis-cyclohexyl substituents in gold(I)-catalysed reactions, see reference [48].

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Gold-catalyzed regioselective oxidation of propargylic carboxylates: a reliable access to α-carboxy-α,β-unsaturated ketones/aldehydes

Kegong Ji, Jonathan Nelson and Liming Zhang*

Abstract
Gold-catalyzed intermolecular oxidation of carboxylates of primary or secondary propargylic alcohols are realized with excellent regioselectivity, which is ascribed to inductive polarization of the C–C triple bond by the electron-withdrawing carboxy group. The gold carbene intermediates thus generated undergo selective 1,2-acyloxy migration over a 1,2-C–H insertion, and the selectivities could be dramatically improved by the use of a P,S-bidentate ligand, which is proposed to enable the formation of tris-coordinated and hence less electrophilic gold carbene species. α-Carboxy α,β-unsaturated ketones/aldehydes can be obtained with fair to excellent yields.

Introduction
We reported in 2010 [1] that α-oxo gold carbenes could be conveniently generated as reactive intermediates in gold-catalyzed intermolecular oxidation of alkynes. By using pyridine N-oxides [1] and later 8-substituted quinoline N-oxides [2] as the external oxidants, this approach permits a safe and efficient access to α-oxo gold carbenes without resorting to the dediazotization strategy [3-5] using hazardous and potentially explosive diazo substrates (Scheme 1). Since then an array of versatile synthetic methods has been developed based on the general approach by us [2,6-12] and other researchers [13-20], thus making it an exciting area for further advancing gold chemistry.

Among various types of alkynes examined, internal alkynes, while without incident in the generation of the gold carbene intermediates, present an additional challenge, namely how to control the regioselectivity of the oxidation. We reported previously that synthetically useful regioselectivity could be
achieved if the two ends of the C–C triple bond are biased by a steric bulk and/or via conjugation (Scheme 2). In our continued effort to reveal regioselectivities of this oxidation with different types of internal alkynes, we examined propargylic carboxylates, which have served as a versatile platform for the development of a diverse range of gold catalysis [21]. Herein we report our findings and the development of a reliable synthesis of α-carboxy α,β-unsaturated ketones/aldehydes.

Results and Discussion

We began by subjecting the propargylic acetate 4a to the suitable conditions developed in our previous study, namely IPrAuNTf$_2$ (5 mol %) and 8-methylquinoline N-oxide (3, 1.5 equiv) in 1,2-dichloroethane at ambient temperature. To our delight, the reaction proceeded efficiently, yielding the α-acetoxyenone 5a-OAc (Z/E >50:1) and the isomeric β-acetoxyenone 5a-H in an excellent combined 92% yield along with a minute amount of the enone 6 (<0.5%, Scheme 3); moreover, 5a-OAc is favored over 5a-H by a ratio of ~7:1. Of particular importance is that the anticipated isomer 5a', accessible via the gold carbene B' from a regioisomeric alkyne oxidation, was not positively detected due to the trace amount (<0.5%), thereby revealing an exceptional level of regioselectivity in the oxidation of this type of internal alkynes. The formations of 5a-OAc and 5a-H are rationalized as the results of divergent transformations of the α-oxo gold carbene B: the former is formed via a two-step 2,3-acetoxy migration [22,23], and the latter most likely via a concerted carbene 1,2-C–H insertion[2]. The selective formation of the Z isomer of 5a-OAc can be attributed to that B adopts a preferred conformation, as detailed in Scheme 3, in order to avoid steric interaction between Me and the acyl moiety. It needs to be noted that a related intramolecular version of this reaction has been previously reported [24].

An alternative mechanism for the formation of 5a-OAc is also shown in Scheme 3 (the top half). Instead of initially undergoing oxidative gold carbene formation, a gold-promoted 1,2-acetoxy migration [25] would generate a vinyl gold carbene intermediate (i.e., C), which can then be oxidized by 3 to yield the product. However, this scenario is deemed unlikely by the following observations and considerations: a) propargylic carboxylates of type 4a with an internal C–C triple bond typically undergo facile 3,3-rearrangements [26-30] instead of 1,2-acloxy migrations. The former process would eventually lead to the formation of the enones 6 [31]. Due to hydrolysis, only under thermal and anhydrous conditions products derived from the latter processes can be predominantly formed [32]; under our conditions (at ambient temperature and without exclusion of moisture), the enone 6 was indeed detected but in a minute amount, suggesting that the 1,2-acloxy migration might be an even less meaningful event in the reaction; b) it is known that the gold carbenes of type B can be readily oxidized by Ph$_2$S=O [33], which, however, is an inefficient oxidant for generating α-oxo gold carbenes of type A via alkyne oxidation [34,35]; when the N-oxide 3 is replaced by the sulfoxide, 5a-OAc was formed in only 5% yield even at 60 °C after 12 h (Scheme 4); moreover, the major product in the reaction was the expected
enone 6 (56% yield, 88% conversion) due to a dominant gold-catalyzed 3,3-rearrangement; c) this alternative could not rationalize the formation of 5a-H.

The fact that in the presence of the oxidant 3 the previously observed facile transformations of propargylic carboxylates (i.e., 3,3-rearrangement and 1,2-acyloxy migration) are no longer competitive with the oxidative catalysis is surprising and suggests that this oxidation process could divert substrates from other well established, facile gold catalysis to the formation of distinctively different functional products in the presence of oxidants.

The relatively low selectivity (i.e., ~7:1) of 5a-OAc over 5a-H was drastically improved upon catalyst screening. It was eventually found that the ratio could reach >200:1 by using the gold(I) catalyst derived from our previously developed bulky P,S-bidentate ligand L1 (Figure 1) [11]. A similarly high selectivity was also achieved by using the P,N-bidentate ligand MorDalPhos [36,37]. However, the Z/E ratios of 5a-OAc in the former case is ~13:1, better than ~7:1 in the latter case, albeit both lower than that by IPrAuNTf$_2$ (>50:1, see Scheme 3). The enhanced preference of AcO migration en route to the formation of 5a-OAc over the 1,2-C-H insertion is attributed to attenuation of the electrophilicity of the gold carbene moiety via the formation of a tris-coordinated gold complex (i.e., D) [11].

Figure 1: The impact of ligands on the ratio of 5a-OAc and 5a-H in the gold-catalyzed oxidation of 4a (reaction conditions: 5 mol % gold catalyst, 1.5 equiv of 3, DCE, rt, 3 h).

Scheme 3: Gold-catalyzed oxidation of the propargylic acetate 4a and the mechanistic rationale.

Scheme 4: A drastically different outcome by using diphenyl sulfoxide as the oxidant.
The scope of this alkyne oxidation/acyloxy migration reaction is outlined in Table 1. Acetates derived from primary/secondary propargylic alcohols with various substitution patterns and containing different functional groups were all allowed, although the tertiary counterpart underwent gold-catalyzed 3,3-rearrangement preferentially [21] and hence was not a viable substrate. Except entry 7, the gold-catalyzed oxidations proceeded with excellent regioselectivities (>25:1), and the desired α-acyloxy α,β-unsaturated ketones/aldehyde were isolated with fair to excellent yields. While the bulky catalyst Me₄t-BuXPhosAuNTf₂ [38] was used in entry 1 to obtain a better oxidation regioselectivity (28:1), it did not lead to a good ratio in the case of 4h (entry 7), where the oxidation regiosomer of type 5a' was formed in 23% yield. This outcome is rationalized in the next paragraph. In the case of pivalate 3c with a terminal alkyne (entry 2), the use of this bulky acyl group instead of acetyl is to curtail the hydrolytic formation of the corresponding α-ketoaldehyde. In many cases the ratios of

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**Table 1: Reaction scope studies for the formation of α-acyloxyenones from propargyl acetates.**

<table>
<thead>
<tr>
<th>entry</th>
<th>4</th>
<th>5</th>
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<th>ratio</th>
<th>time</th>
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</thead>
<tbody>
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<td>1d</td>
<td>OAc</td>
<td>OAc</td>
<td>80%</td>
<td>14/1</td>
<td>3 h</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Ph</td>
<td>74%</td>
<td>&gt;100/1</td>
<td>2.5 h</td>
</tr>
<tr>
<td>3</td>
<td>Me₄t</td>
<td>Me₄t</td>
<td>86%</td>
<td>&gt;50/1</td>
<td>12 h</td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>Bn</td>
<td>85%</td>
<td>&gt;50/1</td>
<td>9 h</td>
</tr>
<tr>
<td>5f,g</td>
<td>Me₄t</td>
<td>Me₄t</td>
<td>75%</td>
<td>&gt;200/1</td>
<td>2.5 h</td>
</tr>
<tr>
<td>6</td>
<td>Me₄t</td>
<td>Me₄t</td>
<td>76%</td>
<td>33/1</td>
<td>7 h</td>
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<table>
<thead>
<tr>
<th>entry</th>
<th>4</th>
<th>5</th>
<th>yieldᵦ</th>
<th>ratio</th>
<th>time</th>
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<tbody>
<tr>
<td>7d</td>
<td>OAc</td>
<td>OAc</td>
<td>62%</td>
<td>21/1</td>
<td>5 h</td>
</tr>
<tr>
<td>8l</td>
<td>OAc</td>
<td>OAc</td>
<td>60%</td>
<td>&gt;200/1</td>
<td>6.5 h</td>
</tr>
<tr>
<td>9f</td>
<td>OAc</td>
<td>OAc</td>
<td>75%</td>
<td>&gt;100/1</td>
<td>2.5 h</td>
</tr>
<tr>
<td>10</td>
<td>OAc</td>
<td>OAc</td>
<td>90%</td>
<td>&gt;20/1</td>
<td>10 h</td>
</tr>
<tr>
<td>11</td>
<td>OAc</td>
<td>OAc</td>
<td>84%</td>
<td>&gt;35/1</td>
<td>5 h</td>
</tr>
</tbody>
</table>

*a = 0.05 M. bIsolated yield of 5-OAc 5a-OAc/5-H. cMe₄t-BuXPhosAuNTf₂ was used as the catalyst. dIPrAuNTf₂ as the catalyst, 3,5-dichloropyridine N-oxide (2 equiv) as the oxidant, and DCM as the solvent. eL1AuCl/AgNTf₂ used as catalyst. f10 mol % catalyst. gThe oxidation regiosomer of type 5a' was formed in a 23% yield.
5-OAc and 5-H were high with IPrAuNTf₂ as the catalyst; for the ones with low selectivities, LI AuNTf₂ offered again dramatic improvements (entries 5, 8 and 9) although at the expense of the geometric selectivities of the major product.

The excellent regioselectivities of gold-catalyzed oxidations of propargylic carboxylates, albeit unexpected, could be readily rationalized by invoking inductive polarization of the C–C triple bond by the electron withdrawing carbonyl group. Such polarization could be revealed by calculated natural charges via natural population analysis [39] and corroborated by experimentally detectable properties such as $pK_a$ [40] and $^{13}$C NMR [41]. We calculated the natural charges at the sp-hybridized carbons using the Density Functional Theory (B3LYP/6-31G*, Spartan06). The NC is 0.230 for the C(sp) distal to the carboxy group and −0.081 for the proximal C(sp), revealing a strong inductive effect that leads to a more electron-deficient distal alkyn end (Figure 2). This revelation is consistent with the $^{13}$C NMR chemical shifts of the alkynyl carbons. The observed regioselectivity can be ascribed to a selective attack of the nucleophilic oxidant to the more electrophilic distal C(sp). Notably, a recently published Pt-catalyzed hydrosilylation on a similar substrate showed a 3.7:1 regioselectivity [42]. This unexpectedly high selectivity with gold catalysis is attributed to the synergistic effect of the steric bias [2].

While a previous Pd catalysis [43] could also accomplish this transformation, the demonstrated scope is much limited, and the catalyst loading is 20%. With this oxidative gold catalysis, the propargylic esters, except those derived from tertiary alcohols, can be reliably converted into α-acyloxy α,β-unsaturated ketones/aldoxdehydes.

Conclusion

We have realized a gold-catalyzed, highly regioselective oxidation of carboxylates of primary and secondary propargylic alcohols by utilizing inductive polarization of the C–C triple bond by the electron-withdrawing carboxy moiety. The α-oxo gold carbene intermediates generated can selectively undergo 1,2-acyloxy migrations over 1,2-C–H insertion. This inherent selectivity can be much enhanced by the use of our previously developed P,S-bidentate ligand, which enables the generation of tri-coordinated and less electrophilic gold carbene species. α-Acyloxy α,β-unsaturated ketones/aldoxdehydes can be obtained with fair to excellent yields.

Supporting Information

Supporting Information File 1
Experimental procedure, compound characterization, and NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-227-S1.pdf]

Acknowledgements

The authors are grateful for the financial support from NSF (CHE-1301343).

References


Figure 2: Natural charges at and the $^{13}$C chemical shifts of the alkynyl carbons in 4a.

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An approach towards azafuranomycin analogs by gold-catalyzed cycloisomerization of allenes: synthesis of \((\alpha S,2R)-(2,5\text{-dihydro-}1H\text{-pyrrol-2-yl})\text{glycine}\)

Jörg Erdsack and Norbert Krause*

Full Research Paper

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* Corresponding author

Keywords:
allenes; amino acids; cuprates; furanomycin; gold catalysis

Abstract

The synthesis of \((\alpha S,2R)-(2,5\text{-dihydro-}1H\text{-pyrrol-2-yl})\text{glycine}\) \((22\), normethylazafuranomycin\) by the gold-catalyzed cycloisomeration of \(\alpha\)-aminoallene \(17\) is described. The target molecule was synthesized in 13 linear steps from Cbz-protected Garner aldehyde \((R)\)-2 in an overall yield of 2.4%. The approach was first examined in model studies, which afforded the alkylated azafuranomycin derivative \(13a\) in 2.9% yield over 12 steps.

Introduction

In 1967, Katagiri et al. reported the isolation of a novel antibiotic from the culture broth of the fungus *Streptomyces threomyceticus* [1]. The compound acts as a competitive antagonist for isoleucine in vitro and hampers the growth of several microorganisms, including the *E. coli*, *S. aureus* and *M. tuberculosis*. \((+)-\text{Furanomycin (1a, Figure 1, X = O)}\) was identified as a non-proteinogenic amino acid bearing a characteristic 2,5-dihydrofuran ring. The correct \((\alpha S,2R,5S)\)-stereochemistry was established in 1980 by the first total synthesis by Joullié and co-workers [2] and the X-ray analysis of the \(N\)-acetyl derivative of the natural product by Shiro et al. [3]. \((+)-\text{Furanomycin belongs to the smallest natural antibiotics [4]. Therefore, the compound found considerable interest in synthetic chemistry. Until today, five total syntheses were published [2,5-8] as well as numerous reports dedicated to derivatives and stereoisomers [9-20]. Examination of structure–activity relationship (SAR) revealed a loss of antibiotic activity upon shifting of the methyl group to different positions, removal of the double bond, or change of the relative configuration [14,16]. Likewise, carba-furanomycin \((1b)\) showed insufficient biological activity [17].
In 2007, we reported a synthesis of furanomycin derivatives by gold-catalyzed endo-selective cycloisomerization of α-hydroxyallenes [19]. This method opens an efficient stereoselective access to chiral 2,5-dihydrofurans by axis-to-center chirality transfer (Scheme 1) [21-32] and was applied to the total synthesis of various natural products [29-37]. Likewise, the corresponding gold-catalyzed cycloisomerization of various protected or unprotected α-aminoallenes affords 2,5-dihydropyrroles [29-32,38,39]. Due to the difference in biological activity of furanomycin (1a) and carbafuranomycin (1b), we became interested in the synthesis of derivatives of the (so far unknown) azafuranomycin (1c). Here, we describe the first results of this study.

Results and Discussion

Since Boc-protected intermediates tend to decompose during late-stage oxidation to the carboxylic acid [19], we selected the Cbz-protected Garner aldehyde 2 as starting material instead of the commonly used Boc-protected analog [40,41]. We prepared aldehyde (S)/(R)-2 on a multigram scale in three steps starting from commercial available (S)/(R)-serine methylester hydrochloride by treatment with Cbz-Cl [42], acetalization with dimethoxypropane [43], and ester reduction with DIBAL-H [44]. In our hands, this pathway was most effective as only for the reduction step Schlenk technique was necessary. Addition of lithiated tert-butyldimethylprop-2-ynyloxysilane 3 [45] to (S)-2 in THF at –78 °C in the presence of HMPA afforded alcohol 4 [46-50] in 74% yield and high anti-selectivity (>95:5; Scheme 2). Only traces of the syn-isomer were detected by TLC. Conversion of 4 into tosylate 5a and acetate 5b by standard conditions (p-TsCl/cat. DMAP in pyridine and acetic anhydride/cat. DMAP/triethylamine, respectively) proceeded in 81 and 88% yield, respectively. In contrast, treatment of alcohol 4 with diethyl chlorophosphate and n-BuLi or cat. DMAP in pyridine gave the phosphate 5c in low yield. Here, direct quenching of the acetylide formed from (S)-2 and lithiated 3 with diethyl chlorophosphate was more effective and afforded phosphate 5e in 54% yield. With these propargylic electrophiles in hand, we studied the allen synthesis by copper-mediated S_N2'-substitution [51] (Table 1, see below).

In order to establish suitable reaction conditions, we first examined the synthesis of the butyl-substituted model substrate 6a. Treatment of propargyl tosylate 5a with the organocopper reagent formed in situ from n-BuMgCl, CuBr·SMe_2, and LiBr [32] afforded allene 6a with up to 74% yield (Table 1, entries 1–3). In order to achieve complete conversion, a large excess of the nucleophile is required. The yield could be raised further by using the cyanocuprate n-BuCu(CN)MgBr [53-55] or the heterocuprate n-BuC(SPh)Li [56] (Table 1, entries 4 and 5). In the latter case, no formal reduction product (6, R^2 = H) was observed which might have been formed by hydrolysis of a stable copper(III) intermediate [51,56]. As expected, all S_N2'-substitutions proceeded with excellent anti-stereoselectivity [51]. With propargyl acetate 5b as starting material, allene 6a was obtained in 85% yield using n-BuCu(CN)MgBr·2LiCl as nucleophile (Table 1, entry 6). In contrast, use of the heterocuprate n-BuC(SPh)Li led to decomposition (Table 1, entry 7). Propargyl phosphate 5e is also a suitable precursor of allene 6a (Table 1, entries 8 and 9).
Table 1: Copper-promoted $S_{N}2'$-substitution of propargylic electrophiles 5 to afford allenes 6.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>6</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 equiv n-BuCuMgBr₂·LiCl, THF, –60 → 0 °C, 90 min</td>
<td>6a</td>
<td>—b</td>
</tr>
<tr>
<td>2</td>
<td>8 equiv n-BuCuMgBr₂·LiCl, THF, –60 → 0 °C, 90 min</td>
<td>6a</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>10 equiv n-BuCuMgBr₂·LiCl, THF, –60 → 0 °C, 90 min</td>
<td>6a</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>10 equiv n-BuCu(CN)MgBr·2LiCl, THF, –78 °C, 30 min</td>
<td>6a</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>4 equiv n-BuCu(SPh)Li, Et₂O, –78 °C, 30 min</td>
<td>6a</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>10 equiv n-BuCu(CN)MgBr·2LiCl, THF, –78 °C → rt, 12 h</td>
<td>6a</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>4 equiv n-BuCu(SPh)Li, Et₂O, –78 °C, 30 min</td>
<td>6a</td>
<td>—b</td>
</tr>
<tr>
<td>8</td>
<td>10 equiv n-BuCuMgBr₂·LiCl, THF, –78 °C, 60 min</td>
<td>6a</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>10 equiv n-BuCu(CN)MgBr·2LiCl, THF, –78 °C, 3 h</td>
<td>6a</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>6 equiv LiCuBr₂·THF, reflux, 12 h</td>
<td>6b</td>
<td>68</td>
</tr>
<tr>
<td>11</td>
<td>1.2 equiv (PhMe₂Si)₂CuCNLi₂, THF, –78 °C, 30 min</td>
<td>6c</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>1.2 equiv (PhMe₂Si)₂CuCNLi₂, THF, –78 °C, 30 min</td>
<td>6c</td>
<td>—b</td>
</tr>
</tbody>
</table>

*Incomplete conversion. b Decomposition.*

After these successful model studies, we introduced substituents into the allene which can be removed at a later stage. Treatment of propargyl tosylate 5a with lithium dibromocuprate [57-59] or the silylcuprate (PhMe₂Si)₂CuCNLi₂ [60,61] afforded the allenes 6b and 6c with 68% and 77% yield, respectively (Table 1, entries 10 and 11). Also these $S_{N}2'$-substitution took place with complete anti-stereoselectivity. In contrast, decomposition occurred when propargyl acetate 5b was treated with the silylcuprate (Table 1, entry 12).

The next steps towards the substrates of the gold-catalyzed cycloisomerization proceeded uneventfully (Scheme 3). Disilylation of allenes 6a and 6b with tetrabutylammonium fluoride trihydrate afforded the α-hydroxyallenes 7a/b in high yield, and these were converted into the aminoallenes 8a/b under standard Mitsunobu conditions (DEAD, PPh₃, phthalimide; then hydrazine monohydrate) [38,39,62]. Unfortunately, fluoride-mediated desilylation of allene 6c caused complete epimerization of the allenic chirality axis. Therefore, the silylallene was not used in further studies.

The results of the gold-catalyzed cycloisomerization of the allenes 7 and 8 to the five-membered heterocycles 9/10 are summarized in Table 2. Treatment of the α-hydroxyallene 7a with 1 mol % AuCl₃ in THF [21-23] afforded the desired 2,5-dihydrofuran 9a with 84% yield (Table 2, entry 1). The temperature was decreased to 5 °C to avoid acetal cleavage by the Lewis-acidic gold catalyst [19]. For the corresponding cyclization of the bromoallene 7b, the temperature had to be raised to 50°C in order to achieve complete conversion (Table 2, entry 2). Only traces of the acetal cleavage product were detected by TLC. However, the cycloisomerization was accompanied by partial epimerization of the allene, so that dihydrofuran 9b was isolated as a 4:1-mixture of diastereomers.

Scheme 3: Synthesis of α-hydroxyallenes 7 and α-aminoallenes 8.
Table 2: Gold-catalyzed cycloisomerization of allenes 7 and 8.

<table>
<thead>
<tr>
<th>Entry</th>
<th>7/8</th>
<th>Conditions</th>
<th>9/10</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>1 mol % AuCl₃, THF, 5 °C, 12 h</td>
<td>9a</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>7b</td>
<td>2 mol % AuCl₃, THF, 50 °C, 5 h</td>
<td>9b</td>
<td>77a</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>10 mol % AuCl, 10 mol % imidazole, DCE, 80 °C, 12 h</td>
<td>10a</td>
<td>66b</td>
</tr>
<tr>
<td>4</td>
<td>8a</td>
<td>10 mol % AuCl, 10 mol % imidazole, toluene, 80 °C, 12 h</td>
<td>10a</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>8b</td>
<td>7 mol % Ph₃PAuCl, 7 mol % AgBF₄, 7 mol % imidazole, toluene, 100 °C, 12 h</td>
<td>10b</td>
<td>47c</td>
</tr>
</tbody>
</table>

a\(\text{dr} = 4:1\). bThe \(N\)-chloroethylated dihydropyrrole was formed as side product (29% yield). cYield of the twofold protected dihydropyrrole 11b obtained by treatment of 10b with CbzCl and DMAP; 2'-epi-11b was obtained as minor product (4% yield).

As expected, the cycloisomerization of allenes 8 bearing an unprotected amino group is much slower [38,39] and requires rather forcing conditions. For a complete conversion of \(\alpha\)-aminoallene 8a, 10 mol % of AuCl [38,39], 10 mol % of imidazole as stabilizing ligand and an elevated temperature (80 °C) are necessary. With dichloroethane as solvent, dihydropyrrole 10a was obtained in 66% yield (Table 2, entry 3); however, this was accompanied by 29% of the corresponding \(N\)-chloroethylated product. This undesired side product could be avoided by using toluene as the solvent (Table 2, entry 4). Application of these conditions to the brominated \(\alpha\)-aminoallene 8b gave incomplete conversion. Full conversion was achieved with 7 mol % each of Ph₃PAuCl, AgBF₄ and imidazole in toluene at 100 °C (Table 2, entry 5). The dihydropyrrole 10b thus formed could not purified completely even after repeated column chromatography. Therefore, the crude product was treated with CbzCl and DMAP [63] to give the twofold protected dihydropyrrole 11b (formula not shown) with 47% yield over two steps. Additionally, we isolated the epimeric compound 2'-epi-11b in 4% yield, indicating a minimal epimerization of bromoallene 8b during the gold-catalyzed cyclization.

The synthesis of azafuranomycin analogs was continued with the twofold Cbz-protected heterocycle 11a which was obtained with 79% yield by treatment of 10a with CbzCl and DMAP [63] (Scheme 4). This protection step was carried out in order to avoid dehydrogenation or chlorination of the secondary amine in the subsequent oxidation steps [64,65]. Acetal cleavage under
mild protic conditions furnished the hydroxycarbamate, which underwent two-step oxidation with Dess–Martin periodinane [66,67] and sodium chlorite in buffered solution [68] in the presence of resorcinol [19]. The carboxylic acid 12a was isolated in 65% yield. Finally, the protecting groups were removed with trifluoroacetic acid in the presence of thioanisole [69] to afford the azafuranomycin analog 13a with 31% yield. Later, we found that a higher excess of thioanisole, which captures benzylic cations in the deprotection step, affords higher yields of the amino acid (Scheme 5).

After successful conclusion of the model studies, the synthesis of (αS,2R)-(2,5-dihydro-1H-pyrrol-2-yl)glycine (22, normethyl-azafuranomycin) was carried out (Scheme 5). The aldehyde (R)-2, which was prepared from D-serine [42-44], underwent chelation-controlled nucleophilic addition of metallated alkyne 3 [45] to give the propargyl alcohol 14 in 84% yield and a syn-diastereoselectivity of >95:5 [7,46,47]. After tosylation of 14 (85% yield), synthesis of the bromoaellene 15 with lithium dibromocuprate resulted in an unexpected epimerization of the allene moiety to afford an inseparable 2:1-mixture of diastereomers in 66% yield. Addition of stabilizing ligands ([(n-Bu)3P or (n-BuO)3P) did not affect this loss of stereoselectivity. Fortunately, the correct stereoisomer was enriched at the stage of the dihydropyrrole 18 due to several purification steps.

Desilylation of 15 with tetrabutylammonium fluoride trihydrate (94% yield) and conversion of 16 into the α-aminoallene 17 under Mitsunobu conditions (45% yield) [38,39,62] set the stage for the gold-catalyzed cycloisomerization. This was carried out with 10 mol % each of AuCl and imidazole in toluene at 100 °C to give the desired dihydropyrrole 18 in ca. 67% yield. Similar to the diastereomer 10b, compound 18 could not be purified in a sufficient manner even after repeated column chromatography. Treatment of 18 with CbzCl/DMAP [63] gave the fully protected heterocycle 19 in 42% yield over two steps from 17. The spectroscopic data are identical with those of 2’-epi-11b, except for the sign of the optical rotation \{19: [α]19D +37.9 (c 1.27, CHCl3); 2’-epi-11b: [α]20D –47.0 (c 0.10, CHCl3)\}.

For the debromination of dihydropyrrole 19, we first tested radical conditions ((n-Bu)3SnH/AIBN), but these led to complete decomposition. This is surprising since carbamates are known to be stable under radical conditions [70]. Indeed, treatment of diastereomer 11b with (n-Bu)3SnH/AIBN afforded the desired dehalogenated dihydropyrrole with 66% yield (formula not shown). For the conversion of 19 to 20, we applied a bromine–lithium exchange with 2 equivalents of t-BuLi in diethyl ether at –90 °C [71], followed by hydrolysis. Even though oxazolidines are known to be sensitive towards organo-
lithium compounds [19,72–74], dehalogenated dihydroxypyrrole 20 was obtained in 60% yield, together with 22% of reisolated 19. The remaining steps towards azafuranomycin analog 22 followed those established for 13a: acetal cleavage (71% yield), two-step oxidation which afforded protected amino acid 21 with 72% yield [19.66–68], and final deprotection according to the procedure of Kiso et al. (50 equiv thiouisole and 270 equiv TFA per Cbz-group) [69] gave the target molecule 22 with 66% yield after purification by ion exchange chromatography (DOWEX 50W X8).

Conclusion
We have developed the first synthesis of the azafuranomycin analog (aS, 2R)-(2,5-dihydro-1H-pyrr-2-yl)glycine (22) in 13 linear steps with an overall yield of 2.4% starting from the Cbz-protected Garner aldehyde (7)-2. The sequence was first tested in model studies catalyzed cycloisomerization of 17 to dihydroxypyrrole 18. The sequence was first tested in model studies which afforded butyl-substituted azafuranomycin derivative 13a in 12 linear step with an overall yield of 2.9% starting from (S)-2.

Supporting Information
Supporting Information File 1
Experimental part.

References
Gold-catalyzed reaction of oxabicyclic alkenes with electron-deficient terminal alkynes to produce acrylate derivatives

Yin-wei Sun¹, Qin Xu*¹ and Min Shi*¹,²,§

Abstract
Oxabicyclic alkenes can react with electron-deficient terminal alkynes in the presence of a gold catalyst under mild conditions, affording the corresponding addition products in moderate yields. When using alkynyl esters as substrates, the (Z)-acrylate derivatives are obtained. Using but-3-yn-2-one (ethynyl ketone) as a substrate, the corresponding addition product is obtained with (E)-configuration. The proposed mechanism of these reactions is also discussed.

Introduction
Oxabicyclic alkenes are common intermediates in organic synthesis since these compounds can be easily prepared and have a high reactivity for further transformations [1-8]. For example, they are often used to construct substituted tetrahydroanaphthalene skeletons in the presence of metal catalysts such as Pd [9,10], Ir [11-15], Rh [16-21] and Cu [22]. However, their reactivity in the presence of gold catalysts has been rarely reported [23]. It is well known that gold catalysts have different catalytic abilities compared with other transition metals [24]. Moreover, gold-catalyzed chemical transformations have made significant progress during the last 5 years [25-56]. Many gold complexes have been proved to be efficient catalysts in C–C [33-48] bond or C–X (X = heteroatom) [49-56] bond forming reactions. Our group has a long-standing interest in gold-catalyzed C–C [57-61] or C–X bond [62-67] formation reactions. So far, we have reported a variety of gold-catalyzed intramolecular rearrangements with highly strained small rings for C–C or C–X bond formations [57-59,62-68]. Based on these...
previous findings, we envisaged that oxabicyclic alkenes could also react with electron-deficient alkynes in the presence of gold catalysts to generate a new C–C or C–O bond thereby releasing the oxabicyclic alkenes of their ring strain. In this paper, we report the formation of (Z)-acrylate derivatives in the gold catalyzed intermolecular reaction of oxabicyclic alkenes with electron-deficient terminal alkynes under mild conditions [69-76] (Scheme 1).

**Results and Discussion**

To generate a new C–O bond in the reaction of oxabicyclic alkenes 1a with electron-deficient terminal alkyne 2a, we first used PPh₃AuCl as a catalyst, AgSbF₆ as an additive, and toluene as a solvent to examine the reaction outcome. Acrylate derivative 3a was formed with (Z)-configuration in 11% yield (Table 1, entry 1). In this reaction, naphthalen-1-ol was also obtained with 44% yield as the major product. The usage of

**Scheme 1**: Gold-catalyzed reactions of oxabicyclic alkenes with electron-deficient terminal alkyne.

![Scheme 1](image-url)

**Table 1**: Initial screening of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Au cat.</th>
<th>Ag salt</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₃PPh₃Cl</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>IPrAuCl</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>dppb(AuCl)₂</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>(p-FC₆H₄)₃PAuCl</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>DPE-phos(AuCl)₂</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>N.R.</td>
</tr>
<tr>
<td>6</td>
<td>Me₃PAuCl</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>N.R.</td>
</tr>
<tr>
<td>7</td>
<td>Cy₃PAuCl</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>6</td>
<td>AgSbF₆</td>
<td>toluene</td>
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<td>9</td>
<td>6</td>
<td>–</td>
<td>toluene</td>
<td>N.R.</td>
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<tr>
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<td>None</td>
<td>AgSbF₆</td>
<td>toluene</td>
<td>trace</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>AgNTf₂</td>
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<td>12</td>
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<td>AgOTs</td>
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<tr>
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<td>6</td>
<td>CF₃COOAg</td>
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<tr>
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<td>10</td>
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</table>

*The reaction was carried out on a 0.2 mmol scale in solvent (1.0 mL). The ratio of 1a:2a was 1:2. Yield determined by ¹H NMR by using 1-ido-2-methoxybenzene (4) as an internal standard. Naphthalen-1-ol (5) was the major product. 50 mg of 4 Å MS was added to the reaction system.
IPrAuCl, dpbb(AuCl)$_2$, (p-FC$_6$H$_4$)$_3$PAuCl, DPE-phos(AuCl)$_2$, Me$_3$PAuCl and Cy$_3$PAuCl as gold catalysts did not significantly improve the yield of 3a (Table 1, entries 2–7). In these cases, the maximum yield of 3a was 34% when the gold complex Cy$_3$PAuCl coordinated by an electron-rich phosphine ligand was used as a catalyst (Table 1, entry 7). In order to further improve the yield of 3a, we employed gold complex 6 (Figure 1) coordinated by a sterically bulky and electron-rich biaryl phosphine-type ligand as a catalyst, affording 3a in 40% yield (Table 1, entry 8). In the absence of AgSbF$_6$, no reaction occurred (Table 1, entry 9). The usage of AgSbF$_6$ as a catalyst produced naphthalen-1-ol (5) as the major product (Table 1, entry 10). Next, we further screened the reaction conditions with gold complex 6 as a catalyst. When using AgOTs or CF$_3$CO$_2$Ag as a silver additive, we did not obtain any of the desired products (Table 1, entries 12 and 13), whereas the usage of AgNTf$_2$ as a silver additive afforded 3a in 32% yield (Table 1, entry 11). AgOTf was not an effective silver additive, giving 3a in 20% yield (Table 1, entry 14). Utilization of the already prepared electrophillic cationic phosphinogold(I) complexes XPhosAuNTf$_2$ and XPhosAu(MeCN)SbF$_6$ as gold catalysts slightly increased the yield of 3a to 33% and 45% yields, respectively (Table 1, entries 15 and 16). The examination of solvent effects revealed that toluene was the best solvent (Table 1, entries 17–22). Adding 4 Å MS into the reaction system, 3a was obtained in only 10% yield (Table 1, entry 23).

Since the yield of 3a was still low, we next tried to improve the yield of 3a by deploying different ligands, Ag salts, solvents and temperature. The results are summarized in Table 2. At first, we examined many other gold(I) phosphane complexes with dialkylbiarylphosphane ligands (Figure 1) by using AgSbF$_6$ as an additive and toluene as a solvent. No reaction occurred when gold(I) phosphane complexes 8–10 (Figure 1) were used as catalysts under identical conditions (Table 2, entries 2–4). Furthermore, the usage of gold(I) phosphane complexes 7, 11, 13 and 14 (Figure 1) as catalysts gave 3a in 10–29% yields (Table 2, entries 1, 5, 7 and 8). Gold complex 12 (Figure 1) with an electron-rich biphenylphosphine ligand was identified as the best catalyst, giving 3a in 67% yield (Table 2, entry 6). We attempted to further optimize the reaction conditions by using SPhosAuCl 12 as a catalyst and AgNTf$_2$ or AgSbF$_6$ as an additive and obtained 3a in 66% and 67% yields, respectively (Table 2, entries 6 and 9). However, the use of AgOTf or AgBF$_4$ as an additive afforded 3a in 37% and 11% yields, respectively (Table 2, entries 10 and 11). Employment of the prepared electrophillic cationic phosphinogold(I) complex SPhosAu(MeCN)SbF$_6$ as a catalyst gave 3a in 78% NMR based
Table 2: Further screening of the reaction conditions.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Au cat.</th>
<th>Ag salt</th>
<th>solvent</th>
<th>T (°C)</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; (%) 3a</th>
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<tr>
<td>1&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>toluene</td>
<td>rt</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>AgSbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>toluene</td>
<td>rt</td>
<td>N.R.</td>
</tr>
<tr>
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<td>9</td>
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<td>toluene</td>
<td>rt</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
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<td>toluene</td>
<td>rt</td>
<td>10</td>
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<tr>
<td>5</td>
<td>11</td>
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<td>toluene</td>
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<td>67</td>
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<td>toluene</td>
<td>rt</td>
<td>20</td>
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<tr>
<td>7</td>
<td>13</td>
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<td>toluene</td>
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<td>rt</td>
<td>66 (59)&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>toluene</td>
<td>rt</td>
<td>78 (67)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
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<td>toluene</td>
<td>rt</td>
<td>53</td>
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<td>–</td>
<td>DCM</td>
<td>rt</td>
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<td>SPhosAu(MeCN)SbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>–</td>
<td>DCE</td>
<td>rt</td>
<td>55</td>
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<td>–</td>
<td>CHCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>rt</td>
<td>45</td>
</tr>
<tr>
<td>17&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>50</td>
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<td>30</td>
<td>70</td>
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</table>

<sup>a</sup>The reaction was carried out on a 0.2 mmol scale in solvent (1.0 mL) and the ratio of 1a/2a was 1/2.
<sup>b</sup>Yield determined by <sup>1</sup>H NMR by using 1-iodo-2-methoxybenzene as an internal standard.
<sup>c</sup>Isolated yield in parentheses.

yield and 67% isolated yield (Table 2, entry 12). The phosphinogold(I) complex SPhosAuNTf<sub>2</sub> produced 3a in 53% yield under the standard conditions (Table 2, entry 13). The examination of solvent effects disclosed that toluene was the best solvent (Table 2, entries 14–16). Either increasing or decreasing the reaction temperature did not further improve the reaction outcome (Table 2, entries 17–20). Careful screening of the reaction conditions led to the conclusion that the reaction should be carried out in toluene at room temperature with SPhosAu(MeCN)SbF<sub>6</sub> as the catalyst (Table 2, entry 12).

Having identified the optimal conditions, we next examined the substrate scope of this reaction. We found that only the usage of ethynylbenzene and dimethyl but-2-yne-2-dioate as substrates did not afford any of the desired products (Table 3, entries 6 and 9). In all other cases, the reactions proceeded smoothly to give the desired products in moderate to good yields (Table 2, entries 1–5, 7 and 8). The introduction of electron-donating substituents on the benzene ring impaired the reaction outcome (Table 3, entries 1 and 7). Increasing the steric hindrance of the ester group improved the yields of 3 (Table 3, entries 4 and 5). The usage of but-3-yne-2-one (terminal alkyne ketone) 2i as a substrate gave the corresponding 3i with (E)-configuration in 48% yield (Scheme 2).

Since naphthalene-1-ol (5) was obtained in this reaction, we used naphthalene-1-ol (5) as a substrate and carried out the reaction under the optimal conditions to clarify whether the reaction proceeded through naphthalene-1-ol. The formation of 3a could not be observed, suggesting that naphthalene-1-ol is not the intermediate in this reaction (Scheme 3).

Based on the previously established mechanistic model [23,77], we propose the following pathway for the formation of acrylate derivatives 3a and 3i (Scheme 4). In the presence of cationic phosphinogold(I) complex, a cationic intermediate A is formed by a regioselective opening of the oxygen bridge in substrate 1a. Intermediate A releases a proton to afford intermediate B. Intermediate B attacks methyl propiolate, which is activated by the gold catalyst, to generate gold vinyl complex C. In inter-
Table 3: Substrate scope of the reactions with SPhosAu(MeCN)SbF$_6$ as a catalyst.

<table>
<thead>
<tr>
<th>entry</th>
<th>R$^1$</th>
<th>R$^2$, R$^3$</th>
<th>Yield$^b$ (%)</th>
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<td>COOMe, H</td>
<td>3b, 42</td>
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<td>F</td>
<td>COOMe, H</td>
<td>3c, 66</td>
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<td>Br</td>
<td>COOMe, H</td>
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</tr>
<tr>
<td>4</td>
<td>H</td>
<td>COOEt, H</td>
<td>3e, 54</td>
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<td>H</td>
<td>COO-t-Bu, H</td>
<td>3f, 84</td>
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<td>6</td>
<td>H</td>
<td>Ph, H</td>
<td>trace</td>
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<td>Me</td>
<td>COO-t-Bu, H</td>
<td>3g, 58</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>COO-t-Bu, H</td>
<td>3h, 72</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>COOMe, COOMe</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

$^a$The reaction was carried out on a 0.2 mmol scale in solvent (1.0 mL). The ratio of 1/2 was 1/2. $^b$Isolated yield.

Scheme 2: The reaction with terminal alkyne 2i as a substrate.

Scheme 3: The reaction with naphthalen-1-ol (5) as a substrate.

mediate C, the ester group and the naphthalene ring are on the same side, yielding the final product 3a with (Z)-configuration via protodeauration. The alkyne ketone 3i is more electron-deficient and more reactive than methyl propiolate and it is more difficult to coordinate by the gold complex. Therefore, with alkyne ketone 2i as a substrate, intermediate B attacks non-coordinated alkyne ketone 2i in a cis-addition manner to generate gold vinyl complex D. In intermediate D, the carbonyl group and the naphthalene ring are on opposite sides, affording product 3i with (E)-configuration by protodeauration.

Conclusion

In summary, we have developed a novel method to synthesize acrylate derivatives from oxabicyclic alkenes and electron-deficient terminal alkynes in toluene in moderate to good yields in the presence of the gold catalyst SPhosAu(MeCN)SbF$_6$ under mild conditions. Efforts are in progress to elucidate the mechanistic details of this reaction and to disclose its scope and limitations.

Experimental

General remarks

Dichloromethane was freshly distilled from calcium hydride; THF and toluene were distilled from sodium under an argon atmosphere. $^1$H NMR, $^{13}$C NMR and $^{19}$F NMR spectra were recorded on a Bruker AM-400 spectrometer. Infrared spectra were recorded on a Perkin-Elmer PE-983 spectrometer with absorption in cm$^{-1}$. Flash column chromatography was performed by using 300–400 mesh silica gel. For thin-layer
chromatography (TLC), silica gel plates (Huanghai GF254) were used. Mass spectra were recorded by ESI, and HRMS were measured on a HP-5989 instrument.

General procedure for the reaction catalyzed by Au(I) catalysts
Into an oven-dried reaction flask under Ar gas protection was added oxabicyclic alkene (0.2 mmol), Au catalyst (0.001 mmol), methyl propiolate (0.4 mmol) and toluene (1.0 mL). The reaction mixture was stirred at room temperature normally overnight. After complete consumption of the starting materials, monitored by TLC, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography.

Supporting Information
Supporting Information File 1
Experimental procedures and characterization data of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-233-S1.pdf]

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References

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Abstract
A range of arylgold compounds have been synthesized and investigated as single-component catalysts for the hydrophenoxylation of unactivated internal alkynes. Both carbene and phosphine-ligated compounds were screened as part of this work, and the most efficient catalysts contained either JohnPhos or IPr/SIPr. Phenols bearing either electron-withdrawing or electron-donating groups were efficiently added using these catalysts. No silver salts, acids, or solvents were needed for the catalysis, and either microwave or conventional heating afforded moderate to excellent yields of the vinyl ethers.

Introduction
The use of gold compounds to promote hydroelementation reactions has grown tremendously over the past few years [1-5]. Using this approach, a host of different organic substrates have been successfully functionalized. Despite the intense interest in this chemistry the addition of phenols to internal alkenes has rarely been investigated [1,5]. Recently, Sahoo reported the hydrophenoxylation of alkynes using a multicomponent catalyst comprised of AuCl3, JohnPhos as the supporting ligand, and various silver/potassium salts as promoters [1]. He found that moderate to excellent yields of the vinyl ethers could be obtained upon heating the reaction mixtures (dichloromethane or THF solutions) to 100 °C for 24–146 hours. Given the current interest in the synthetic community regarding the development of sustainable transformations [6-10] that are practical and operationally straightforward, we decided to attempt to generate the active gold species in situ from a single-component precursor. Furthermore, one of the current goals of developing sustainable and “greener” organic reactions is focused on the elimination of solvents and additives from the synthetic methodology [10]. Thus, the design of gold catalyzed reactions
that proceed under solvent-free conditions and without the addition of silver salts or acidic promoters would be of interest to those charged with designing sustainable organic reactions.

From the standpoint of the gold catalyst, there are several ways to generate an active species. One of the first reports on this type of catalysis entailed the use of strong acids to remove the methyl group from a methylgold compound and generate a (LAu⁺) species that promoted the addition reaction [11]. Additionally, these cationic gold species can be generated through the reaction of chlorogold compounds with silver salts [1-4]. Recently, there has been growing interest in developing approaches that generate a catalytically active species under acid-free and silver-free conditions [12,13]. To this end, we have synthesized and investigated a series of arylgold compounds as single-component catalysts for hydroelementation reactions under acid, silver, and solvent-free conditions.

We recently reported the synthesis of arylgold compounds using a focused microwave reactor (Scheme 1) [14]. Although microwave-assisted reactions are legion in organic chemistry, they are rare in organometallic synthesis [15-21]. Our initial report on this chemistry was focused on gold compounds bearing Buchwald-type phosphine ligands such as JohnPhos and t-BuXPhos. These bulky ligands were selected since they were found to inhibit dynamic phosphine exchange between gold complexes [22]. The chemistry was operationally straightforward, and simply heating the reagents in the microwave for 20–30 minutes afforded high yields of the arylgold compounds. In this report, we extend the chemistry to the synthesis of arylgold compounds containing carbene ligands.

Results and Discussion

The synthesis of the carbene-ligated arylgold compounds was accomplished using (NHC)AuCl (NHC = IMes, SIMes, IPr, SIPr) precursors. For the initial screening runs, (IMes)AuCl and 4-tert-butylphenylboronic acid were chosen as representative substrates. The same protocol that was successful for the synthesis of arylgold compounds from (JohnPhos)AuCl or (t-BuXPhos)AuCl afforded incomplete conversion and the formation of an intractable mixture of gold compounds when (IMes)AuCl was used. After some experimentation with the reaction conditions and different mineral bases, the key issue appeared to be the use of THF as the solvent. Changing from THF to iPrOH afforded high yields of (IMes)Au(C₆H₄t-Bu) after heating at 50 °C for 20 minutes. Once a successful protocol was determined for the model system, the chemistry was extended to other (NHC)AuCl compounds (Figure 1). It was anticipated that incorporating electron-donating groups into the aryl fragments on the gold would facilitate the cleavage of the organic group from the gold center through protodeauration; thus, –C₆H₄t-Bu and –C₆H₄OMe were selected as substituents. In general, the use of 4-tert-butylphenylboronic acid gave higher yields of the arylgold compounds than 4-methoxyphenylboronic acid. Once isolated by column chromatography (basic alumina), the arylgold compounds were relatively stable white solids. The IMes and SIMes examples (4–6) were the least stable of the group, and although no decomposition was noted when stored in the solid state under nitrogen (6 months) they begin to decompose within 24 hours in solution (THF). In contrast, the IPr and SIPr examples were quite stable in both solution and the solid state.

Once the arylgold compounds were isolated, the efficacy of both phosphine and carbene-ligated species in hydrophenoxyla-

tion reactions was investigated (Table 1). For these screening reactions, 4-nitrophenol, diphenylacetylene, and 5-decyne served as representative substrates. These alkynes were selected since unactivated internal alkynes remain some of the most challenging substrates to functionalize through hydroelementation reactions. Initially, we selected compound 1 as the gold catalyst and used a focused microwave reactor to heat the reactions. After some experimentation, we discovered that heating the phenol and alkyne with gold catalyst in the absence of solvent to 130 °C for 20 minutes generated excellent yields of the vinyl ethers. Control reactions revealed that the arylgold compound was essential to the success of the reaction as its removal lead to quantitative recovery of starting materials. The
Figure 1: Synthesis of arylgold compounds\textsuperscript{a,b}. \textsuperscript{a}Chlorogold precursor (0.32–0.37 mmol), 2 equiv arylboronic acid, 2 equiv Cs\textsubscript{2}CO\textsubscript{3}, 50 °C, 20 min, iPrOH (1.5 mL), microwave irradiation. \textsuperscript{b}Isolated yields. \textsuperscript{c}THF was used as the solvent.

Table 1: Hydrophenoxylation of unactivated internal alkynes.\textsuperscript{a}

<table>
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<tr>
<th>Entry</th>
<th>Gold catalyst</th>
<th>Comp.\textsuperscript{b}</th>
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</tr>
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<td>3</td>
<td>(t-BuXPhos)AuCl</td>
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<td>0</td>
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<tr>
<td>4</td>
<td>(IMes)AuCl</td>
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</tbody>
</table>

\textsuperscript{a}Diphenylacetylene or 5-decyne (0.28 mmol), 4-nitrophenol (0.56 mmol), catalyst (14.0 μmol, 5%), 130 °C, 20 min, no solvent, microwave irradiation. \textsuperscript{b}Based upon \textsuperscript{1}H NMR spectroscopy using anisole as an internal standard.

generation of the active gold catalyst in these reactions is proposed to occur through a protodeauration reaction between the arylgold compounds and the phenols. The observation of tert-butylbenzene in the reaction mixture supports this proposal. Furthermore, to probe whether or not simple chlorogold-coordination compounds could promote this reaction, JohnPhosAuCl and other gold compounds were investigated under the same reaction conditions (Table 1, entries 2–7). In all cases, the chlorogold compounds were unable to catalyze the addition reaction and analysis of the crude reaction mixtures revealed only starting materials. Conventional heating was also investi-
gated during the screening phase of the project. Plunging a reactor vial containing 1, 4-nitrophenol, and either internal alkyne into a preheated oil bath (130 °C, 20 min) followed by rapid cooling also afforded high yields of the vinyl ether (Table 1, entry 18).

The effectiveness of different gold catalysts on the addition reaction was also studied (Table 1). While 1 was effective at promoting the addition reaction, an arylgold compound bearing a bulkier Buchwald ligand (2) afforded lower yields of the vinyl ether. Adding an additional equivalent of t-BuXPhos increased the yield slightly; however, 1 was still a superior catalyst. Increasing the electron-donating ability of the substituent on the aromatic group attached to the gold center in the t-BuXPhos based catalyst 3 slightly increased the yield of the vinyl ether.

To investigate the effectiveness of carbene-ligated gold compounds on the addition reaction, catalysts 4–9 were screened (Table 1). When IMes or SIMes based catalysts 4, 5, or 6 were used, lower yields of the vinyl ethers were observed. Examining the reaction vessels when 4, 5, and 6 were used revealed the formation of a significant amount of metallic gold. These metallic deposits were not observed when using phosphine ligated gold compounds 1–3. This observed decomposition/reduction to elemental gold could be a rationale for the lower conversions observed with these catalysts. Furthermore, changing to conventional heating did not prevent the decomposition of 4, 5, and 6 during the addition reaction. In contrast, the complexes bearing IPr and SIPr carbene ligands 7–9 afforded high yields of the vinyl ethers. Examination of the reaction vessels from these reactions did not reveal the formation of metallic gold. There was little difference between the saturated (SIPr) and unsaturated (IPr) carbene ligands, and there was only slight difference between catalysts bearing –C₆H₄-t-Bu and –C₆H₄OMe aryl groups (8,9).

Building on the results from the screening reactions, the scope of the hydrophenoxylation reaction was investigated using a range of phenols with diphenylacetylene and 5-decyne serving as representative internal alkynes (Figure 2). Microwave and conventional heating were used in these reactions. Based upon the initial studies, the phosphine ligated catalyst 1, as well as NHC ligated catalysts 7–9 afforded high yields of the vinyl ethers. After a bit of experimentation, it was observed that 1 afforded the highest conversions in microwave-assisted reactions, while 7 generated the highest yields in conventionally heated reactions. The addition reaction was tolerant of both electron-withdrawing and electron-donating groups, and the ortho-substituted substrate 2-nitrophenol was also successfully used in the addition reactions. The resulting vinyl ethers were

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Figure 2: Hydrophenoxylation of alkynesabcd. aAlkyne (0.28 mmol), phenol (0.56 mmol), 130 °C, 20 min, no solvent. bIsolated yields. cMicrowave heating with 1 as the catalyst (14.0 μmol, 5%). dConventional heating with 7 as the catalyst (14.0 μmol, 5%).
purified by column chromatography and isolated as powders or viscous oils.

The regioselectivity of the addition reaction was investigated using 1-phenyl-1-hexyne as a representative unsymmetrical alkene, 4-nitrophenol as the model phenol, and 1 and 7 as catalysts. As shown in Scheme 2, both catalysts generated the addition product in excellent yields. Catalyst I gave a slightly higher yield of the addition product, but 7 was more selective. The regioselectivity of the reaction using our arylgold precatalysts is the opposite of what Sahoo found using his catalyst system [1] and is similar to the regioselectivity found by Nolan using his hydroxide bridged precatalysts [5].

**Conclusion**

In summary, we have synthesized several carbene-ligated arylgold compounds and investigated the efficacy of both phosphine and carbene-based gold catalysts towards the hydrophenoxylation of unactivated internal alkynes. Using these single component catalysts, a range of phenols have been successfully added to unactivated internal alkynes. No silver salts, acids, or solvents were needed for the catalysis, and either microwave or conventional heating and afforded moderate to excellent yields of the vinyl ethers.

**Experimental**

**General considerations:** Unless specified, all solvents were dried using a Grubbs-type solvent purification system. (JohnPhos)AuCl and (t-BuXPhos)AuCl, were prepared by displacement of dimethyl sulfide from Me₂SAuCl by JohnPhos or t-BuXPhos [23,24]. The (NHC)AuCl (NHC = SiMes, IMes, SIPr, IPr) [19,25] precursors as well as arylgold compounds 1–3 [14] were prepared following literature procedures. The arylboronic acids, alkynes, phenols, and Cs₂CO₃ (powder) were obtained from Aldrich and used as received. NMR spectra were collected on a Varian DirectDrive 600 MHz NMR spectrometer (¹H: 599.77 MHz and ¹³C: 150.81 MHz) ¹H and ¹³C{¹H} chemical shifts were determined by reference to residual non-deuterated solvent resonances. The alkene geometry was determined using ¹H–¹H NOESY experiments. All coupling constants are listed in Hertz. Microwave-assisted reactions were carried out in sealed vessels using a CEM Discover equipped with an external IR (surface) temperature sensor. The PowerMax setting on the Discover was off. Conventionally heated reactions were carried out in an oil bath. HRMS data were obtained on a Thermo Scientific Exactive Plus LC–MS system (ESI).

**General method for the arylation reactions: general procedure A:** For a typical reaction, (NHC)AuCl, 2 equiv of the arylboronic acid, 2 equiv of Cs₂CO₃, and a magnetic stirring bar were added to a 10 mL reactor vial. After exchanging the air for nitrogen, isopropanol was added by syringe, the mixtures were triturated on a stirring plate for 3 minutes, and irradiated. The following settings were used for each experiment: Temperature = 50 °C, time = 20 min, initial power level = 25 W. The initial power setting listed for each reaction was maintained until the desired temperature was reached. The power was then reduced for the remainder of the reaction to maintain the temperature. The reaction time listed is the total irradiation time (no ramping periods). Note: High initial high levels of microwave power (to rapidly heat the sample) lead to significant decomposition (gold metal). After cooling to room temperature, the volatiles were removed, and the title compounds were purified by column chromatography (basic alumina). The arylgold compounds were dissolved in CH₂Cl₂ and dried over molecular sieves. After filtration, they were dried under vacuum to afford white powders.

**Preparation of (IMes)Au(4-C₆H₄t-Bu) (4):** General procedure A was followed with (IMes)AuCl (0.20 g, 0.37 mmol), 4-tert-butylphenylboronic acid (0.135 g, 0.76 mmol), cesium carbonate (0.24 g, 0.74 mmol), and isopropanol (1.5 mL). Chromatography: basic alumina (37.5 g), gradient hexane/THF.
(90:10–50:50), \(R_f\) 0.60 (hexane/THF 50:50), yield = 0.18 g of a white powder (76.1%). HRMS: [M + Na]\(^+\) calecd for \(C_{17}H_{37}Au_{2}Na\), 657.2520; found, 657.2509. Spectral data: \(^1H\) NMR (CDCl\(_3\), 25 °C) \(\delta\) 7.07 (s, 4H, Ar-H), 7.04 (s, 2H, =CH), 6.98 (br s, 4H, Ar-H), 2.34 (s, 6H, -Me), 2.16 (s, 12H, -Me), 1.19 (s, 9H, -Me); \(^13C\) \(\delta\) 196.0 (s, quat), 150.0 (s, =CH), 139.0 (s, quat), 135.4 (s, quat), 134.9 (s, quat), 129.2 (s, Ar-CH), 123.6 (s, Ar-CH), 121.7 (s, =CH), 34.0 (s, quat), 31.4 (s, -CMe\(_2\)), 21.1 (s, -Me), 18.0 (s, -Me).

General method for the catalyst screening reactions: microwave and conventional heating; general procedure B: A reactor vial (10 mL) was charged with the LAuAr species \(1\)–\(7\) (0.014 mmol), alkene (0.28 mmol), phenol (0.56 mmol), and a magnetic stirring bar. After exchanging the air for nitrogen, the samples were irradiated in a focused microwave reactor or heated in an oil bath. For the reactions carried out in the microwave reactor, the initial power setting was determined until the desired temperature was reached. No ramping periods were used in these reactions; thus, the reaction time listed is the total irradiation time (not the time at the desired temperature). After cooling, CDCl\(_3\) was added to the reaction mixtures until homogeneous solutions were obtained (<2 mL). Anisole (internal standard, 0.28 mmol) was added to the solutions and the extent of each reaction was determined by \(^1H\) NMR spectroscopy.

Isolation of the vinyl ethers: The synthesis of the vinyl ethers was carried out following the same general procedure from the catalyst screening reactions using either \(1\) or \(7\) as the catalyst. Once cooled, the vinyl ethers were purified by column chromatography, dried using molecular sieves (hexane/EtOAc solution), and isolated as oils or powders following removal of the volatiles.

Preparation of 4-{[(1Z)-1-buty1-1-hexen-1-yl(oxy)nitrobenzene (16): General procedure B was followed (microwave heating) with \(1\) (0.0088 g, 0.014 mmol), 5-deceny (50.6 µL, 0.28 mmol), and 4-nitrophenol (0.078 g, 0.56 mmol), \(25\) °C, 20 min, initial power level = 50 W. Chromatography: silica gel (19.1 g), column chromatography, dried using molecular sieves (hexane/EtOAc solution), and isolated as oils or powders following removal of the volatiles.

\(1\) C_{24}H_{37}NO_{3}S; found, 278.1748. Spectral data: \(^1H\) NMR (CDCl\(_3\), 25 °C) \(\delta\) 8.19 (AA’BB’, 2H, Ar-H), 6.99 (AA’BB’, 2H, Ar-H), 5.12 (t, \(J = 7.2\) Hz, -CH\(_2\)), 2.15 (t, \(J = 7.8\) Hz, -CH\(_2\)), 1.93 (q, \(J = 7.2\) Hz, -CH\(_2\)), 1.47 (m, 2H, -CH\(_2\)), 1.34–1.25 (m, 6H, -CH\(_2\)), 0.84 (t, \(J = 6.8\) Hz, -Me), -CMe\(_2\)); \(^13C\) \(\delta\) 162.3 (s, quat), 150.0 (s, quat), 141.9 (s, quat), 126.0 (s, Ar-CH), 117.5 (s, =CH-), 115.5 (s, Ar-CH), 32.2 (s, -CH\(_2\)), 31.3 (s, -CH\(_2\)), 28.9 (s, -CH\(_2\)), 24.9 (s, -CH\(_2\)), 22.3 (s, -CH\(_2\)), 22.1 (s, -CH\(_2\)), 13.8 (s, -Me).

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Total synthesis of (−)-epimyrtine by a gold-catalyzed hydroamination approach

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Abstract

A new approach to the total synthesis of (−)-epimyrtine has been developed from D-alanine. The key step to access the enantiopure pyridone intermediate was achieved by a gold-mediated cyclization. Finally, various transformations afforded the natural product in a few steps and good overall yield.

Findings

(−)-Epimyrtine, isolated from Vaccinium myrtillus (Ericaceae) [1,2], is a quinolizidine alkaloid. This alkaloid family exhibits potential pharmacological properties such as anticancer, antibacterial, antiviral and anti-inflammation activities [3-5]. This alkaloid has been a target of interest for synthetic chemists because of its structural simplicity among the family of quinolizidine structures. Since it has been isolated, numerous total syntheses of this alkaloid in racemic form have been reported in the literature. However, only a few asymmetric syntheses of (−)-epimyrtine have been described to date including the intramolecular allylsilane N-acyliminium ion cyclization [6], the organocatalytic aza-Michael reaction [7], the intramolecular Mannich reaction [8], and the iminium ion cascade reaction [9,10]. More efficient, convenient and highly stereoselective synthetic routes are still being sought after. In the past decades, gold catalysis has emerged as an important tool in a plethora of fields of synthetic organic chemistry, and after methodological investigations [11-16], the good functional group compatibility of gold catalysts renders gold catalysis a straightforward protocol in the realm of the synthesis of natural products [17,18].

Herein we report a short total synthesis of (−)-epimyrtine employing an alternative strategy by using a gold(I)-catalyzed...
hydroamination of a β-aminonone as the key step. Actually, cyclization of enantiopure α and β-aminonones was successfully used in our group to access pyrrolidinone and pyridone heterocycles via a gold-mediated approach [19,20]. The use of β-aminonone intermediates for the synthesis of 2,3-dihydropyridones was recently developed by Georg [21] (Scheme 1). This strategy involves the in situ deprotection of the amine function to permit the cyclization by Michael addition. However, in some instances partial racemization of the reaction products was observed [22].

Here, one major advantage of gold catalysis is the use of very mild conditions for the cyclization, thereby avoiding any racemization and obtaining N-protected compounds which may be useful for further transformations. In order to illustrate the efficiency of our method, we were interested in extending this methodology to quinolizidine privileged structures.

Our retrosynthetic analysis is shown in Scheme 2. We expected that the good side-chain functionality tolerance of the gold catalyst could easily provide chiral dihydropyridone from the corresponding β-aminonone in a 6-endo-dig selective cyclization process. The β-aminonone could be stereoselectively prepared in two steps from N-Boc-D-alanine.

Preparation of the β-aminonone 2 began with the Arndt–Eistert homologation [23] of N-Boc-protected D-alanine (Scheme 3). Thus, the N-Boc-D-alanine was treated with isobutyl chloroformate at 0 °C in THF/diethyl ether followed by the addition of diazomethane to afford the corresponding diazoketone. The Wolff rearrangement was then carried out by using silver nitrate in THF to give the intermediate ketene which was trapped with N,N-dimethylhydroxylamine to provide the corresponding Weinreb amide 1 in 84% yield over two steps. In the next step, the Weinreb amide 1 was added to a solution of O-protected 1-hexynol lithium acetylide to furnish the β-aminonone 2 with a yield of 71%. With this key building block in hand, efforts were directed toward the gold-mediated intramolecular hydroamination for the construction of the chiral pyridone intermediate 3. For this, PPh₃AuSbF₆ generated in situ from a 5 mol % mixture of PPh₃AuCl and AgSbF₆, in 1,2-dichloroethane afforded the desired pyridone 3. These conditions, selected in our previous work, represent a good compromise in terms of reaction time, yield and cost of the catalyst. As an example, lower catalyst loading (1 mol %) does not affect the yield but lowers the reaction speed of the cyclization. A 5-exo-dig product was not observed, presumably as a result of electronic strain. The reaction was completed in 2 hours at 40 °C to afford 3 in good yield (78%).

Reduction and deprotection of 3 by means of H₂ (1 atm) in the presence of Pd/C for 48 h afforded stereospecifically the corresponding piperidone 4 in 80% yield. Subsequent bromination with CBr₄ in the presence of PPh₃ (Appel reaction) gave 5 in 84% yield. Finally, deprotection with 1 M SnCl₄ in dichloromethane then neutralization by using K₂CO₃ afforded the final product (−)-epimyrtine in a 80% yield.

N-Cbz compound was also tested. In this case, the cyclization occurred in similar conditions as described for the N-Boc-

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**Scheme 1:** Previously reported approach from β-aminonones for the synthesis of pyridones.

**Scheme 2:** Retrosynthetic analysis of (−)-epimyrtine.
protected compound and resulted in a good yield (81%). Yet, under the catalytic hydrogenolytic conditions as described above (H₂, 1 atm, 10% Pd/C, rt, 48 h) only deprotection of the nitrogen occurred, while the desired benzyl ether cleavage and pyridine reduction were unsuccessful. Increase of the pressure to 5 atm or replacement of Pd/C with Pd(OH)₂ (Pearlman's catalyst) did also not result in the obtainment of the desired product.

The natural product (-)-epimyrtine was thus obtained over 6 steps in a 25% overall yield starting from N-Boc-D-alanine. The spectroscopic data and optical rotation are in agreement with the literature [6].

Conclusion
In conclusion, we have achieved the asymmetric total synthesis of (-)-epimyrtine in six steps and with a good overall yield. We have demonstrated in this work that this natural product is easily accessible from D-alanine by a gold-mediated intramolecular hydroamination in a unique 6-endo-dig process. The approach provides a straightforward tool for synthetic applications toward quinolizidines and indolizidines.

Experimental
All reagents of high quality were purchased from commercial suppliers and used without further purification. All reactions requiring anhydrous conditions were performed under an argon atmosphere by using oven-dried glassware. 1,2-DCE and THF were distilled from CaH₂ and Na/benzophenone, respectively. ¹H and ¹³C NMR were recorded at 500 or 300 and 125 or 75 MHz respectively, by using CDCl₃ (and TMS as internal standard). Chemical shifts, δ values are given in parts per million (ppm), coupling constants (J) are given in Hertz (Hz), and multiplicity of signals are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; app, apparent. Thin-layer chromatography was performed by using pre-coated silica gel plates (0.2 mm thickness).
To a solution of 6-benzoxyhex-1-yne (2.44 g, 12.9 mmol, 4 equiv) in 10 mL of dry THF was added dropwise a solution of n-BuLi (5 mL, 12.5 mmol, 3.8 equiv) at −78 °C under argon atmosphere. The reaction mixture was stirred for 45 min at −78 °C. Then, a solution of Weinreb amide 1 (800 mg, 3.3 mmol, 1 equiv) in 8 mL of dry THF was added dropwise at −78 °C. The reaction was stirred for 1 h. The reaction was warmed to −20 °C and stirred for 2 h. The reaction was quenched with a solution of 1 M NaH₂PO₄ (50 mL). The aqueous layer was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄, concentrated under reduced pressure, and purified by silica gel column chromatography by using petroleum ether/ethyl acetate (9:1) as an eluent to give pure 2 as a yellow oil (250 mg, 71%). Rf 0.3 (petroleum ether/ethyl acetate, 8:2). [α]D²⁵ +2.3 (c 1.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.20 (d, J = 6.8 Hz, 3H), 1.43 (s, 9H), 1.69–1.74 (m, 4H), 2.40 (t, J = 6.7 Hz, 2H), 2.66 (ABX system, J = 16.2 Hz, J = 5.8 Hz, 2H), 3.50 (t, J = 5.8 Hz, 2H), 4.05–4.14 (m, 1H), 4.50 (s, 2H), 4.74 (brs, 1H), 7.29–7.35 (m, 2H), 7.30–7.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 186.0, 155.0, 138.3, 128.3, 127.5, 106.4, 94.8, 81.1, 72.9, 69.4, 51.3, 43.3, 28.8, 28.3, 24.5, 18.7; HRMS–ESI⁺ (m/z): [M + Na]⁺ calcd for C₂₂H₃₁NO₄Na, 396.2151; found, 396.2153.

To a solution of 2 (838 mg, 2.2 mmol, 1 equiv) in 15 mL of anhydrous 1,2-dichloroethane was added PPh₃AuCl (55 mg, 0.11 mmol, 5 mol %) and AgSbF₆ (38 mg, 0.11 mmol, 5 mol %) under argon atmosphere. The mixture was stirred for 2 h at 40 °C. The reaction was cooled to room temperature and diluted with ether. The organic phase was filtered through a pad of Celite®, concentrated under reduced pressure, purified by silica gel column chromatography, and eluted with petroleum ether/ethyl acetate (5:5) as an eluent to give 3 as a yellow oil (78%). Rf 0.25 (petroleum ether/ethyl acetate, 8:2). [α]D²⁵ +226.9 (c 1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.25 (d, J = 6.8 Hz, 3H), 1.52 (s, 9H), 1.55–1.67 (m, 4H), 2.23 (dt, J = 16.9 Hz, J = 1.5 Hz, 1H), 2.31 (ddd, J = 14.7 Hz, J = 8.5 Hz, J = 6.0 Hz, 1H), 2.81 (ddd, J = 16.9 Hz, J = 6.2 Hz, 1H), 3.07 (ddd, J = 14.6 Hz, J = 9.3 Hz, J = 5.2 Hz, 1H), 3.47 (t, J = 6.2 Hz, 2H), 4.49 (s, 2H), 4.78 (app quintd, J = 6.6 Hz, J = 1.4 Hz, 1H), 5.36 (s, 1H), 7.30–7.36 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 193.7, 158.3, 152.1, 138.5, 128.4, 127.6, 111.1, 82.9, 72.9, 69.8, 52.1, 42.7, 35.8, 29.4, 28.1, 24.7, 16.5; HRMS–ESI⁺ (m/z): [M + Na]⁺ calcd for C₂₂H₃₁NO₄Na, 396.2151; found, 396.2153.

Pd/C (45 wt %) was added to a solution of 3 (585.7 mg, 1.57 mmol, 1 equiv) in 12 mL of MeOH, and the mixture was stirred under hydrogen atmosphere (1 atm) for 48 h at room temperature. The mixture was filtered through a pad of celite®, concentrated and purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate to give 4 as a yellow oil (360 mg, 80%). Rf 0.25 (petroleum ether/ethyl acetate, 5:5). [α]D²⁵ +21.9 (c 1.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.28 (d, J = 5.0 Hz, 3H), 1.35–1.42 (m, 3H), 1.49 (s, 9H), 1.57–1.62 (m, 4H) 2.28 (ddd, J = 14.9 Hz, J = 3.8 Hz, J = 1.6 Hz, 1H), 2.34 (dd, J = 15.0 Hz, J = 7.6 Hz, 1H), 2.72 (dd, J = 14.9 Hz, J = 7.5 Hz, 1H), 3.46 (3H, 2H), 4.61–4.62 (m, 1H), 4.70 (3H, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 208.7, 154.9, 80.3, 62.6, 52.5, 48.4, 45.5, 43.8, 36.6, 32.2, 28.4, 23.0, 22.7; HRMS–ESI⁺ (m/z): [M + Na]⁺ calcd for C₁₅H₃₂NO₄Na, 308.1838, found, 308.1838.

32.2, 28.4, 25.5, 22.7; HRMS-ESI$^+$ (m/z): [M + Na]$^+$ calcd for C$_{15}$H$_{26}$NO$_3$BrNa, 370.0994; found, 370.0990.

To a solution of 5 (263 mg, 0.75 mmol, 1 equiv) in 5 mL of CH$_2$Cl$_2$ under argon atmosphere was added a solution of 1 M SnCl$_4$ in CH$_2$Cl$_2$ (3.8 mL, 5.0 equiv). The reaction was stirred at room temperature for 3 h. The solvent was removed under reduced pressure. Then 25 mL of THF and 40 mL of an aqueous saturated solution of K$_2$CO$_3$ were added. The mixture was stirred for 12 h at room temperature. The aqueous phase was extracted with CH$_2$Cl$_2$, the combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The crude residue was purifled by silica gel column chromatography eluting with dichloromethane/MeOH (9:1) to give (−)-epimyrtine as a yellow oil (102 mg, yield 80%).

Supporting Information

Supporting Information File 1
Spectra of new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-242-S1.pdf]

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Gold(I)-catalyzed hydroarylation reaction of aryl (3-iodoprop-2-yn-1-yl) ethers: synthesis of 3-iodo-2H-chromene derivatives

Pablo Morán-Poladura, Eduardo Rubio and José M. González*

Abstract
An efficient entry to the preparation of elusive 4-unsubstituted-3-iodo-2H-chromenes has been accomplished as result of a catalytic cyclization. Thus, upon exposition of [(3-iodoprop-2-yn-1-yl)oxy]arenes to IPrAuNTf₂ (3 mol %), in 1,4-dioxane at 100 °C, the desired heterocyclic motif is readily assembled. This process nicely tolerates a variety of functional groups and, interestingly, it is compatible with the presence of strong electron-withdrawing groups attached to the arene. The overall transformation can be termed as a new example of a migratory cycloisomerization and, formally, it involves well-blended 1,2-iodine shift and hydroarylation steps.

Introduction
The structure of 2H-chromene embodies a relevant heterocyclic motif, which is present in naturally occurring compounds [1-6] and encodes interesting properties that renders it attractive for functional applications. Thus, for instance, this molecular frame has been associated with photochromic crystals [7], photochromic organogelators [8], selective cyclooxygenase-2 inhibitors [9,10], antifungal [11] and antitrypanocidal activity [12], transforming growth factor-β receptors [13] and with potential novel termiticides [14], among other remarkable applications. On this basis, new approaches to access this relevant heterocyclic scaffold are the subject of ongoing synthetic interest [15-22].

In connection with synthetic efforts searching for new Hsp90 inhibitors [23], the metal-catalyzed coupling reaction of nitrogen-containing nucleophiles with 3-halo-substituted chromenes has been recognized as a convenient synthetic tool, which provides smooth access to potentially useful candidates [24]. The required halogen containing building-blocks can be prepared from aryl propargyl ethers following either metal-free
iodinating [25,26] or a palladium-catalyzed brominating [27] approach that yield the required halogenated regioisomer at the time of assembling the target heterocyclic skeleton. These strategies are quite general to give 3-halo-4-substituted-2H-chromenes (see Scheme 1, entries a and b, respectively). However, they fail to produce simple 3-halo-4-unsubstituted derivatives. This synthetic context suggests a timely opportunity for devising new protocols to access the latter class of 3-halo-2H-chromene scaffolds from readily available precursors. Although a stepwise selective modification of the preassembled heterocycle has been recently developed (Scheme 1 entry c) [28], a de novo elaboration of 3-halo-2H-chromenes giving straight access to the desired regioisomer is yet to be accomplished. A desirable approach would also consider the generation of an increase in the molecular diversity, offering a suitable strategy intended for library discovery.

On the other hand, migratory cycloisomerization are important processes in contemporary catalysis [41]. In this context, our group is interested in C–H functionalization reactions of arenes involving propargylic derivatives [42]. Furthermore, the influence of different gold(I) catalysts over the outcome of the cyclization of N-(3-iodoprop-2-ynyl)-N-tosylanilines has been noticed [43]. For the latter reaction, conditions to modulate the relative amount of each of the possible regioisomeric cyclization products formed, with or without iodine shift, were outlined. Tuning the ligand at the gold atom [44] was used to accomplish a reaction manifold earlier recognized in the synthesis of regioisomeric halogenated phenanthrenes, but they are using two different metals [45]. Catalytic cycloisomerization reactions of heteroatom-substituted alkynes that take place without heteroatom migration are known [46-48].

On this ground, we were curious about the attractive possibility of combining known reaction profiles in an attempt to execute an efficient entry into the elusive 4-unsubstituted-3-iodo-2H-chromene derivatives. We hypothesize that this specific heterocyclic motif can be conveniently prepared from cyclization of aryl (3-iodoprop-2-yn-1-yl) ethers relying on the power of gold(I) catalysis, as depicted in Scheme 1 entry d. Herein, we report a new strategy to carry out this transformation.

**Results and Discussion**

In a previous work on gold-catalyzed cyclization reactions of N-(3-iodoprop-2-ynyl)-N-tosylanilines, the influence of the ancillary ligand and the arene over the cyclization products was recognized [43]. The catalyst based on the N-heterocyclic carbene ligand IPr [49] (IPr: 1,3-bis(2,6-diisopropyl)phenyl-imidazol-2-ylidene), was identified as suitable controller to favor the formation of the product arising from the migratory cyclization against that deriving from a straight iodoalkyne arylation reaction. As for the substituents on the amine ring, more electron-donating ones gave rise to the formation of the heterocycle featuring a distribution of regioisomers that indicates less iodine shift. In this context, switching from NTs to O as the linker is, intrinsically, a demanding process attempting to access 3-iodo-2H-chromene cores, as migration is less favorable for more electron-donating groups. So, the application of this cyclization and concomitant iodine migration strategy to synthesize the target chromenes is challenging.

On this basis, we started to investigate the feasibility of the intended synthetic approach to the target chromene scaffold exploring the reactivity of 1-chloro-4-[(3-iodoprop-2-yn-1-yl)oxy]benzene (1a) as model compound. For the catalyst, the gold(I) complex with the IPr ligand was systematically tested. As for the counter anion to gold, bis(trifluoromethane-
sulfonylimidate (NTf₂) was chosen which, as early pointed out by Gagosz, renders very active catalysts [50].

An initial screening for experimental conditions showed that heating the reaction mixture at 100 °C in 1,4-dioxane provides a good result for the synthesis of the desired 6-chloro-3-iodo-2H-chromene (2a), using 3 mol % of IPrAuNTf₂ as catalyst. Representative data concerning the selection of the solvent and the identification of convenient values for the reaction temperature and time are summarized in Table 1.

For the solvent, weakly coordinating polar ethers offer a fair balance for conversion and regioselectivity. In this regard, reaction in 1,4-dioxane at 100 °C were identified as the best experimental conditions to approach the cyclization leading to the desired 3-iodochromene 2a. Thus, the conditions outlined in Table 1 entry 7 were chosen to broach the potential of this 1,2-iodine migration–hydroarylation process using different iodinated propargyl aryl ethers. The results are summarized in Table 2.

Interestingly, as no further additives are required, heating the corresponding aryl propargyl ether in dioxane under the sole influence of a relatively low catalyst loading furnishes, consistently, a significant variety of differently substituted chromenes. The selectivity in favor of the 3-iodo-substituted chromene is in all cases of practical significance. In some cases, exclusive formation of the desired 3-iodo-2H-chromene is noticed upon inspection of the crude reaction mixture; see, for instance, Table 2 entries 5 and 8. The structure of the prepared compounds 2 was established from their characterization data (see Supporting Information File 1). The recorded data nicely endorse the assigned structure, which was further corroborated by an X-ray analysis of 2f (Figure 1).

![Figure 1: X-ray molecular structure of 2f.](image)

The assembled collection of 4-unsubstituted iodinated heterocycles is relevant, both in terms of functional group tolerance and also for the purpose of further molecular diversification. A gram-scale reaction was conducted on the multi-halogen-containing precursor 1f. The process is robust and 8-chloro-6-

### Table 1: Screening for conditions for the hydroarylation of 4-chlorophenyl (3-iodoprop-2-yn-1-yl) ether.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>t (h)</th>
<th>% conversion&lt;sup&gt;a&lt;/sup&gt;</th>
<th>2a:3a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ClCH₂CH₂Cl</td>
<td>rt</td>
<td>14</td>
<td>70</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>Et₂O</td>
<td>rt</td>
<td>24</td>
<td>34</td>
<td>4:3:1</td>
</tr>
<tr>
<td>3</td>
<td>Et₂O</td>
<td>40</td>
<td>24</td>
<td>62</td>
<td>4.5:1</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOMe</td>
<td>56</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>dioxane</td>
<td>rt</td>
<td>24</td>
<td>40</td>
<td>5.2:1</td>
</tr>
<tr>
<td>6</td>
<td>dioxane</td>
<td>40</td>
<td>24</td>
<td>68</td>
<td>5.3:1</td>
</tr>
<tr>
<td>7</td>
<td>dioxane</td>
<td>100</td>
<td>2.25</td>
<td>98</td>
<td>5:1</td>
</tr>
<tr>
<td>8</td>
<td>CH₃NO₂</td>
<td>rt</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>CH₃NO₂</td>
<td>40</td>
<td>24</td>
<td>71</td>
<td>2.3:1</td>
</tr>
<tr>
<td>10</td>
<td>DMSO</td>
<td>80</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>DMF</td>
<td>80</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>ClCH₂CH₂Cl/CH₃CN (1:1)</td>
<td>80</td>
<td>24</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup>Conversion determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.
Table 2: Synthesis of 3-iodo-2H-chromenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>t (h)</th>
<th>Yield (%)(^a)</th>
<th>2-3(^b)</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>6</td>
<td></td>
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<td></td>
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<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield (mixture of regioisomers). \(^b\)Determined from the crude of reaction.

fluoro-3-iodo-2H-chromene (2f) was readily obtained (1.5 g, 97% yield) after purification by column chromatography from the reaction of 5 mmol of If (1.55 g) (Scheme 2). Also, another practical issue that was addressed was the proof of the configurational stability of a chiral center in the vicinity of the alkyne. For this purpose, optically active 1j was prepared.
As next step, its reactivity in the gold(I)-catalyzed hydroarylation study was investigated (Scheme 3).

Though the regioselectivity was lower and requires further optimization, this experiment nicely reveals that chirality installed at the propargylic position in the starting material can be successfully delivered to the cyclization product, as the result of this hydroarylation with concomitant 1,2-iodine shift process.

Although this work deals mainly with preparative aspects for the title compounds, a preliminary mechanistic proposal to justify the obtained results could reasonably involve the generation of gold–vinylidene as key intermediate behind the formation of the corresponding 3-iodo-2H-chromenes (Scheme 4).

Gold–vinylidenes have been proposed to mediate related hydroarylation reactions affording halogenated phenanthrenes and 3-iodo-N-tosyl-1,2-dihydroquinoline derivatives. Recent studies have provided strong evidence for their existence, and have demonstrated their powerful reactivity, identifying them as key players in ongoing activity developing the exciting notion of dual activation using gold catalysts.

As outlined in Scheme 4, after an initial π-activation of the iodoalkyne, gold might trigger the generation of the β-iodo-substituted vinylidene, in a process that might take place in competition with a direct Friedel–Crafts-type cyclization reaction yielding 3. In previous work dealing with the cyclization of N-(3-iodoprop-2-ynyl)-N-tosylanilines to give related 1,2-dihydroquinolines (Scheme 4A, X = NTs), we documented for a phosphite-based gold-catalyst, which render a more electrophilic metal center, an increase of the relative amount of the
cycloisomerization product 3 (4-iodo-substituted, X = NTs) at the expenses of the formation of the one with concomitant iodine shift, product 2 (3-iodo-substituted, X = NTs). On the contrary, under related conditions, a gold catalyst based on the electron-rich and neutral donor IPr ligand favors the latter cyclization against the former.

On this ground, a change in the tethering element switching the linker from NTs to oxygen (Scheme 4A, X = O) results in more activated rings towards aromatic electrophilic substitution processes. To this respect, two facts are of mechanistic significance. First, the 2:3 ratio for a given R substituent (Scheme 4A, R = 4-Cl) can be compared for the two linkers. For the nitrogen-containing tether (X = NTs, Scheme 4A), almost exclusive formation of 2 was noticed (reaction in 1,2-dichloroethane, at rt for 24 h, [43]). However, for the case of X = O, the corresponding value for the 2:3 ratio is 5:1 (Table 1, entry 7). Next, as depicted in Table 2, the herein reported cyclization takes place satisfactorily when additional electron-withdrawing groups are attached to the aromatic ring, the yield typically ranging on or above the nineties. At the same time, the selectivity of the process is dependent on the nature of the substituent R in Scheme 4A. Remarkably, the more electron-withdrawing group (R = NO2, Table 2, entry 4) gives similar yield and higher 2:3 ratio than the aldehyde (R = CHO, Table 2 entry 2). For less electron-withdrawing substituents such as halogens an increase in selectivity was noticed as function of their number and nature. This is shown for the cyclization of 1a (Table 1, entry 7) in comparison with the cyclization of 1f and 1i (Table 2, entries 5 and 8). These results nicely match the proposed process competition scenario. The noticed scope endorses an active involvement for a highly reactive gold–vinylidene intermediate as responsible for the selectivity of the eventual cyclization step, in agreement with the tentative mechanistic rationale depicted in Scheme 4A.

Though the substitution pattern is not the one commonly associated with conventional electrophilic aromatic substitution reactions, other mechanism should not be disregarded on the basis of the structure of the final product. So, the alternative mechanistic description summarized in Scheme 4B cannot be firmly rejected, at the moment. In this case, a demanding electrophilic substitution must occur and should produce very efficiently the 3-aurated-4-ido-2H-chromene C and one equivalent of acid. Next, gold-assisted protonation at C-4 should afford D [57], an intermediate featuring a gold-carbene at C-3, that would require a subsequent and selective 1,2-iodine shift to furnish compounds 2 and regenerate the catalyst.

In this context, on the basis of the information gathered so far, and taking into account the precedents in the literature, we favor the mechanism outlined in Scheme 4A as the most likely one.

Conclusion
In short, the reported gold-catalyzed cyclization opens up a versatile approach to the synthesis of elusive 4-unsubstituted-3-iodo-2H-chromenes. This transformation uses common starting materials. The resulting protocol is compatible with a significant variety of functional groups and can be easily conducted on a gram-scale.

Experimental
All the reactions were carried out using oven dried glassware under nitrogen (99,99%) or argon (99,99%) atmosphere. Dioxane was distilled before used from sodium. Flash chromatography was performed on silica gel 60 (230–400) mesh. The solvents used in flash chromatography, hexane and ethyl acetate, were obtained from commercial suppliers and used without further purification. Cyclization reactions were performed in a RR98030 12 place Carousel Reaction Station™ from Radleys Discovery Technologies, equipped with gas-tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. All common reagents and solvents were obtained from commercial suppliers and used without any further purification unless otherwise noted. 1H NMR (300, 400 MHz) and 13C NMR (75.5, 100 MHz) spectra were measured in CDCl3, CD2Cl2 or DMSO at room temperature on a Bruker DPX-300, or Bruker AVANCE-300 MHz and 400 MHz instruments, with CHCl3 (δ = 7.26, 1H NMR; δ = 77.16, 13C NMR), CH2Cl2 (δ = 5.33, 1H NMR; δ = 54.84, 13C NMR) or DMSO (δ = 2.50, 1H NMR; δ = 39.52, 13C NMR) as internal standards. Data are reported as follows: chemical shift, multiplicity (s: singlet, bs: broad singlet, d: doublet, t: triplet, q: quartet, m: multiplet), coupling constants (J in Hz) and integration. Carbon multiplicities were assigned by DEPT and HSQC techniques. Melting points (mp) were measured on a Büchi–Totoli apparatus and are uncorrected.

Synthesis of starting materials
Starting materials 1 were obtained from the corresponding phenols through a two steps synthetic route.

General procedure for the propargylation of phenols

To a suspension or solution of the corresponding phenol (1 equiv; 5 mmol) in DMF (20 mL), potassium carbonate was added (2 equiv; 10 mmol) followed by a solution of propargyl bromide (commercial source: 80% in toluene) (1.5 equiv; 7.5 mmol). The reaction was controlled by TLC and when it
was finished, it was diluted with Et₂O (30 mL) and then brine was added. The organic layer was washed in a separation funnel with brine to extract all the DMF (5 times, 15 mL), dried over Na₂SO₄, filtered and evaporated to afford the corresponding crude mixture which, in most cases, was pure enough to use in the next step without further purification.

Iodination of terminal alkynes

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{AgNO}_3 (10 \text{ mol %}) \\
\text{NIS} \\
\text{acetone, rt} \\
\end{array}
\]

The starting alkyne (1 equiv; 2 mmol) was dissolved in acetone (10 mL). Then, silver nitrate (0.1 equiv; 0.2 mmol) and N-iodosuccinimide (NIS) (1.15 equiv; 2.30 mmol) were added successively. After three hours, the reaction mixture was cooled to 0 °C and filtered. The resulting crude was subjected to flash chromatography to obtain compounds 1 substantially pure.

Preparation of ethers from phenols and chiral non-racemic propargylic alcohols

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{HO} \\
\text{DEAD/PPPh₃} \\
\text{THF, 0 °C to rt} \\
\end{array}
\]

(S)(−)-3-butyn-2-ol (5 mmol; commercially available, 464007 Sigma-Aldrich) was dissolved in THF (25 mL) in a flame dried round bottom flask, under nitrogen atmosphere, and the corresponding phenol (1.05 equiv, 5.25 mmol) and triphenylphosphine (1.1 equiv, 5.5 mmol) are added successively. The solution was cooled to 0 °C and diethyl azodicarboxylate (1.2 equiv, 6 mmol) was added dropwise. The ice bath was removed and the reaction was stirred overnight. The solvents were removed under reduced pressure and the resulting crude was subjected to flash chromatography to give substantially pure and optically active terminal alkynes with (R)-configuration.

Cycloisomerization to give 3-iodo-2H-chromenes

\[
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{IPrAuNTf₂ (3 mol %)} \\
\text{dioxane, 100 °C, 5 h} \\
\end{array}
\]

To a solution of the corresponding starting material 1 (1 equiv; 0.3 mmol) in dioxane (2 mL), under argon atmosphere, IPrAuNTf₂ was added (0.03 equiv; 0.009 mmol) and the reaction mixture was heated at 100 °C. The reaction progress was monitored by TLC and, upon completion, solvents were removed under vacuum and the resulting crude was subjected to flash chromatography to afford the products (see specific conditions for each substrate).

Scaled-up cycloisomerization of 2-chloro-4-fluoro-1-[(3-iodoprop-2-yn-1-yl)oxy]benzene (1f)

5 mmol of 1f (1.55 g) were disposed in a flame-dried 250 mL Schlenk flask under argon and dissolved with 35 mL of dry dioxane. After complete solution of the starting material, 0.15 mmol of the catalyst (3 mol %; 0.130 g) were added and the reaction was heated at 100 °C. After 5 h, when the reaction was finished, solvents were removed in vacuum and the solid residue was purified by flash chromatography using n-hexane as eluent furnishing 2f with >99:1 regioselectivity (2:3) and in 97% yield (1.50 g).

Supporting Information

Supporting Information File 1
Characterization data for compounds 1a–j and 2a–j; ¹H and ¹³C NMR spectra for compounds 1a–j and 2a–j; X-ray molecular structure for 2f; HPLC chromatograms for 1j and 2j and structural assignment for compounds 3.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-249-S1.pdf]

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References


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Gold-catalyzed glycosidation for the synthesis of trisaccharides by applying the armed–disarmed strategy

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Full Research Paper

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Abstract

The synthesis of oligosaccharides is still a challenging task as there is no universal glycosyl donor for the synthesis of all oligosaccharides. The gold catalysis for glycosidation reactions, in which alkylnlated glycosides are used, has emerged as one of the versatile options in this regard. A cleavage of the interglycosidic bond that was thought to be due to the higher reaction temperature and the acidic medium was observed during the synthesis of trisaccharides. In addition, a very little percentage of deprotection of benzyl protecting groups at the C-6 position was observed and no deprotection of benzyl ethers in aliphatic molecules was noticed. In order to overcome this fact, a collection of leaving groups that contain an alkynyl moiety were screened. It was found that 1-ethynylcyclohexanyl (Ech) glycosides are suitable for carrying out the glycosidation at 25 °C in the presence of 5 mol % each of AuCl₃ and AgSbF₆. Subsequently, Ech-glycosides were observed to be suitable for the synthesis of trisaccharides under gold catalysis conditions.

Introduction

Observations that gold(III) has a great affinity for alkynes placed the chemistry of gold in an enviable situation that culminated into the total synthesis of several natural products, in which gold-mediated reactions are a key step [1-7]. Over the last two decades, chemistry with gold complexes has gained immense significance and thus been investigated for a variety of organic transformations in homogeneous and heterogeneous reaction media [8-14]. The use of gold catalysts in carbohydrate chemistry was first reported for the oxidation of alcohols [11-16]. However, until recently these catalysts were scarcely applied. Glycosidation is one of the key reactions in chemistry of carbohydrates, in which a nucleophile attaches to a saccharide to form a glycoside. In this process, the saccharide unit that is donating its glycon is called a glycosyl donor,
whereas the saccharide that is accepting the glycon is referred to as glycosyl acceptor or aglycon. The synthesis of oligosaccharides is still a formidable task in spite of the development of various methods. There is still no universal glycosyl donor \[17,18\], although the first glycoside was reported by Emil Fischer more than a century ago.

A series of observations in our laboratory led to the identification of a gold(III)-catalyzed glycosidation reaction that uses alkynyl glycosides as glycosyl donors \[19-21\]. The salient features of this glycosidation reaction are the requirement of a catalytic amount of gold salts, good reaction yields and mild reaction conditions \[22\]. The alkynophilicity of gold(III) salts has been found to be beneficial for the synthesis of 1,2-trans-glycosides \[23\], amino acid glycoconjugates \[24\], carbohydrate epitopes present on the cell surface of infectious bacteria \[25\], glycopolypeptides \[26\], glycopolyacrylates \[27\], and glycomimetics \[28\]. The remarkable reactivity and chemoselectivity have also attracted other groups to investigate gold catalysts for glycosidation \[29-34\].

Esters at the C-2 position of the saccharide are known to impede the glycoside formation whereas ethers (–OBn) facilitate the reaction. Fraser-Reid applied the terms disarmed to deactivated glycosyl donors [e.g., esters], and armed to the activated donors [e.g., ethers] \[35,36\]. During the synthesis of oligosaccharides by sequentially adding saccharides, armed–disarmed effects can effectively be utilized to tune the reactivity of the glycosyl donors by placing appropriate protecting groups at the C-2 position. Similar armed and disarmed effects were noticed during several gold-catalyzed glycosidations \[22-28\]. Propargyl mannosides as glycosyl donors are ideal for investigating armed–disarmed strategies for the synthesis of oligosaccharides, because the gold-catalyzed glycosidation proceeds in a highly 1,2-trans diastereoselective fashion \[22\]. Accordingly, the armed mannosyl donor 1 was allowed to react with the disarmed aglycon 2, under the standard conditions for a gold-catalyzed glycosidation (AuBr3, CH3CN, 70 °C), to observe the formation of disaccharide 3, in which the propargyl substitution is disarmed due to the presence of benzoates. Subsequently, the disarmed disaccharide 3 was transformed into an armed glycosyl donor 4 by simple saponification followed by etherification. The reaction between armed donor 4 and disarmed aglycon 2, which was carried out under the aforementioned conditions did not result in the formation of desired trisaccharide. Instead, disaccharide 3 (53%) and 1,6-anhydro sugar 5 (20%) were isolated as major products \[37\]. Interestingly, propargyl mannoside 1 (12%) along with benzyl glycoside 6 and lactol 7 were noticed in 5% and 4% yield, respectively (Scheme 1).

The Brønsted acid (HBr) released from AuBr3 in the presence of the aglycon can protonate the exocyclic oxygen present in the

![Scheme 1: Gold-catalyzed synthesis of a disaccharide.](image-url)
disaccharide 4. The protonation of the exocyclic oxygen and subsequent cleavage could give rise to oxocarbenium ion intermediates A and B as shown in Scheme 2. The formation of 1,6-anhydro sugar 5 can be easily envisioned by the intramolecular attack of C-6-OH on the intermediate A. The surprising cleavage of the interglycosidic linkage leads to intermediate B, which can be trapped by various nucleophiles that are present in the reaction mixture. The trapping of the intermediate B by propargyl alcohol gives propargyl mannoside 1 (12%), the addition of OH$^{-}$ due to moisture results in lactol 7 (4%), the addition of aglycon 2 gives rise to disaccharide 3. The formation of benzyl mannoside 6 (5%) can be explained by the attack of BnO$^{-}$ on the intermediate B. The presence of BnO$^{-}$ could be explained due to the hydrolysis of the primary benzyl ether.

**Results and Discussion**

In order to further understand the cleavage of the C-6 benzyl ether, the model propargyl mannoside 8 was treated with 5 mol % of AuBr$_3$ under aforementioned conditions. LC–MS analysis of the reaction mixture showed the formation of anhydro sugar 4 (13%), p-methylbenzyl mannoside 9 (9%) and lactol 10 (6%), which indicated the hydrolysis of the primary benzyl ether. The gold-catalyzed hydrolysis of benzyl ethers was not observed in the case of non-carbohydrate benzyl ether 11 (Scheme 3). For example, per-O-benzylated glycerol 11 did not show any benzyl deprotection, whereas the more acid-sensitive p-methoxybenzyl derivative 12 underwent deprotection of the p-methoxybenzyl moiety to give alcohol 13 with 88% yield. The deprotection of the p-methoxybenzyl moiety can be utilized for the one-pot synthesis of glycerol mannosides from mannosyl...
donor 1 and compound 12 in 67% yield under gold-catalysis conditions (Scheme 3). Importantly, the hydrolysis of benzyl ethers was not observed when the gold catalysis reactions were performed at room temperature [23-28,38].

From the above observations, the high temperature (70 °C) of the glycosidation and the oxophilicity of gold salts were observed to be major impediments for the synthesis of oligosaccharides. In order to overcome this problem, a systematic investigation of various leaving groups that bear an alkynyl moiety was carried out. The aim was to find a better leaving group, which would facilitate the glycosidation at ambient temperature. Accordingly, a panel of alkynylated glycosyl donors (15a–j) was synthesized and subjected to the glycosidation with three widely available gold salts, namely AuBr3, AuCl3 and HAuCl4, at 25 °C for 12 h in acetonitrile (Table 1).

<table>
<thead>
<tr>
<th>LG</th>
<th>% yield of disaccharide 17 with catalyst</th>
<th>LG</th>
<th>% yield of disaccharide 17 with catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AuCl3</td>
<td>AuBr3</td>
<td>HAuCl4</td>
</tr>
<tr>
<td>15a</td>
<td>8</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>15b</td>
<td>17</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>15c</td>
<td>12</td>
<td>0</td>
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<tr>
<td>15d</td>
<td>15</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>15e</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
</tbody>
</table>
Substitutions at the terminal alkyne carbon (15b–e) were not tolerated. The \textit{gem}-dimethyl alkyne 15g showed a substantial improvement of the performance at 25 °C compared to the other alkylnyl donors 15a–f (Table 1). However, the \textit{gem}-dimethyl donor 15g was not preferred due to the shorter shelf life. The alicyclic derivatives 15h–j gave comparable yields to 15g and were observed to be much more stable. Furthermore, 15h needs to be prepared from cyclohexanone, while 15i is costly compared to 15j. Thus, further studies were performed with 15j only. The alkyne moiety is really essential for the transglycosylation reaction as only very little formation of the desired product was noticed in the case of the donors 15k and 15l. Subsequently, it was found that the addition of 5 mol % of AgSbF$_6$ along with AuCl$_3$ would increase the yield of disaccharide 17 to 96%. However, the disaccharide formation was not observed with AgSbF$_6$ alone [38].

In addition, armed mannosyl donor 15j reacted with aglycon 19 in the presence of 5 mol % each of AuCl$_3$/AgSbF$_6$ in CH$_2$CN/CH$_3$Cl$_2$ (1:1) at 25 °C for 4 h to give 1,2-trans menthyl mannoside 20. The leaving group 21 could be removed easily by applying high vacuum. Disarmed donors 18a and 18b failed to react with menthol (19) under aforementioned modified gold-catalysis conditions (Scheme 4).

The strong armed–disarmed effects that were observed for the Ech-donors at 25 °C encouraged us to continue the use of the armed–disarmed strategy for the trisaccharide synthesis. Accordingly, the armed mannosyl donor 15j was allowed to react with disarmed aglycon 22 in the presence of AuCl$_3$ (5 mol %)/AgSbF$_6$ (5 mol %) in CH$_2$CN/CH$_3$Cl$_2$ (1:1) at 25 °C for 4 h to obtain the disaccharide 23 in 85% yield. Further, the armed disaccharide 24 was synthesized from 23 by saponification followed by the etherification in 84% over two steps. The glycosylation between disaccharide 24 and disarmed aglycon 16 was performed under aforementioned conditions for a gold-catalyzed transglycosidation. Purification by conventional silica gel column chromatography enabled us to characterize the anticipated trisaccharide 25 (21%) along with disaccharide 17 and anhydro sugar 5 (Scheme 5). In trisaccharide 25, three anomeric protons were noticed at δ 4.88 (d, $J = 1.6$ Hz, 1H), 4.91 (d, $J = 1.6$ Hz, 1H), 5.61 (dd, $J = 1.6$, 3.2 Hz, 1H) ppm. The $^{13}$C NMR spectrum revealed that there are three mannose residues with 1,2-trans configuration as their anomeric carbon atoms were noticed at δ 98.1, 98.2 and 98.5 ppm and the molecular weight was found to be 1483.586 ([M + 23]$^+$ for the Na adduct). The rest of the resonances in the spectrum were completely in agreement with the assigned structure of trisaccharide 25. Formation of disaccharide 17 (34%) and anhydro sugar 5 (16%) can be rationalized on the basis of an interglycosidic bond cleavage.

The hydrolysis of the interglycosidic bond during the gold-catalyzed transglycosidation reaction depends on the nature of interglycosidic linkage. Generally the glycosyl donors with axial hydroxy groups are considered to be more reactive than the glycosyl donors without axial hydroxy group. For example, β-D-glucose is less reactive than α-D-glucose or α-D-mannose. In order to verify the effect of the differences in reactivity on the cleavage of the interglycosidic bond, armed disaccharide 26 was prepared and allowed to react with menthol (19) under aforementioned conditions for 6 h to obtain the anticipated methyl glycoside (27) in 32% yield. Similarly, the reactions with 4-penten-1-ol (28) and methyl 2,3,4-tri-O-benzyl α-D-glucopyranoside (30) gave the corresponding transglycosides 29 and 31 in 37% and 23% yield, respectively (Scheme 6).

Finally, the gold-catalyzed transglycosidation reaction between disaccharide 32 and aglycon 16 gave the corresponding trisaccharide 33 in 76% yield. A cleavage of the interglycosidic bond was not observed, which shows the importance of the protecting groups in gold-catalyzed glycosidation reactions (Scheme 7).

![Scheme 4: Armed–disarmed effect in Ech-glycosides during gold-catalyzed reactions.](image-url)
Scheme 5: Gold-catalyzed glycosidation at ambient temperature for the synthesis of trimannoside 25.

Scheme 6: Gold-catalyzed glycosidation at ambient temperature for the synthesis of higher saccharides.
Conclusion

In conclusion, the armed–disarmed effect in propargyl glycosides in the presence of a catalytic amount of gold salts is studied. The high temperature of the glycosidation was found to be partially responsible for the cleavage of the interglycosidic bond along with side reactions like benzyl deprotection. These observations were then successfully applied for PMB deprotection and one-pot glycosidation. Subsequent experiments proved the significance of the alkyne moiety. It was also observed that the addition of the silver salt AgSbF6 during the gold-mediated transglycosidation reaction helps in reducing the reaction temperature to 25 °C. This was successfully utilized for activating 1-ethynylcyclohexanyl donors at 25 °C. Trisaccharides were synthesized under identified conditions in moderate yields.

Experimental

All the reactions were performed under argon atmosphere. Products obtained as solids or syrups were dried under high vacuum. Gold and silver salts were purchased from Sigma–Aldrich. Analytical thin-layer chromatography was performed on pre-coated Merck silica plates (F254, 0.25 mm thickness); compounds were visualized by UV light or by staining with anisaldehyde spray. Optical rotations were measured on a JASCO P-1020 or Rudolph polarimeter. NMR spectra were recorded either on a Bruker AC 200, AV 400, AV 500 or JEOL ECX 400 or Bruker Avance 500 with CDCl3 as the solvent and tetramethylsilane as internal standard. High resolution mass spectroscopy (HRMS) was performed on ABI–MALDI–TOF using TiO2 as the solid matrix.

Compound characterization data

Characterization data for compound 15 [38]: [α]D25 +28.2 (CHCl3, c 1.00); 1H NMR (200.13 MHz, CDCl3) δ 1.10–2.15 (m, 10H), 2.40 (s, 1H), 3.65–4.12 (m, 6H), 4.59 (s, 2H), 4.60 (ABq, J = 12.6 Hz, 2H), 4.71 (ABq, J = 10.6 Hz, 2H), 4.76 (s, 2H), 5.56 (d, J = 1.8 Hz, 1H), 7.13–7.42 (m, 20H); 13C NMR (50.32 MHz, CDCl3) δ 22.7, 22.7, 25.0, 37.6, 38.2, 69.3, 71.9, 72.1, 72.3, 73.3, 74.1, 75.0, 75.2, 75.5, 80.0, 84.6, 94.0, 127.3–128.3, 138.4, 138.5, 138.5, 138.5; HRMS (MALDI–TOF, m/z): [M + Na]+ calcd for C42H46NaO6, 669.3192; found, 669.3173.

Characterization data for compound 25: [α]D25 +10.6 (CHCl3, c 1.00); 1H NMR (500.13 MHz, CDCl3) δ 3.42 (s, 3H), 3.51–3.69 (m, 8H), 3.80 (dd, J = 3.9, 11.6 Hz, 1H), 3.84–3.88 (m, 4H), 3.95 (dt, J = 9.4, 25.7 Hz, 2H), 4.14 (dt, J = 4.2, 9.6 Hz, 1H), 4.35–4.62 (m, 8H), 4.41 (ABq, J = 11.0 Hz, 2H), 4.61 (s, 2H), 4.84 (ABq, J = 11.0 Hz, 2H), 4.88 (d, J = 1.5 Hz, 1H), 4.90 (d, J = 1.5 Hz, 1H), 5.03 (t, J = 10.0 Hz, 1H), 5.06 (d, J = 1.3 Hz, 1H), 5.84 (dd, J = 3.3, 10.2 Hz, 1H), 7.11–7.51 (m, 44H), 7.81–8.08 (m, 6H); 13C NMR (125.76 MHz, CDCl3) δ 55.4, 65.6, 66.6, 69.0, 69.1, 69.8, 70.6, 71.3, 71.7, 71.7, 71.7, 72.2, 72.7, 73.2, 74.2, 74.6, 74.8, 74.9, 74.9, 75.0, 79.2, 80.2, 98.1, 98.2, 98.4, 127.2–129.8, 133.1, 133.3, 133.5, 138.3, 138.3, 138.4, 138.4, 138.6, 138.6, 138.7, 165.3, 165.4, 165.5; HRMS (MALDI–TOF, m/z): [M + Na]+ calcd for C88H88NaO19, 1483.5818; found, 1483.5837.

Characterization data for compound 29: [α]D25 +18.4 (CHCl3, c 1.00); 1H NMR (399.78 MHz, CDCl3) δ 1.54 (t, J = 7.2 Hz, 2H), 1.59 (s, 2H), 1.99 (m, 2H), 3.26–3.98 (m, 12H), 4.25–5.06 (m, 18H), 5.73 (m, 1H), 7.15–7.37 (m, 35H); 13C NMR (100.53 MHz, CDCl3) δ 28.4, 30.2, 66.8, 68.9, 69.0, 71.3, 72.0, 72.6, 73.4, 74.7, 74.7, 74.9, 74.9, 74.9, 75.0, 75.7, 77.8, 80.2, 82.0, 84.6, 97.7, 104.0, 114.8, 126.9–128.5, 137.9, 138.1, 138.2, 138.3, 138.5, 138.5, 138.6; HRMS (MALDI–TOF, m/z): [M + Na]+ calcd for C66H72NaO11, 1063.4972; found, 1063.4994.

Abstract
A flexible, efficient and straightforward methodology for the synthesis of N-heterocyclic carbene gold(I)–amide complexes is reported. Reaction of the versatile building block [Au(OH)(IPr)] (1) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) with a series of commercially available (hetero)aromatic amines leads to the synthesis of several [Au(NRR')(IPr)] complexes in good yields and with water as the sole byproduct. Interestingly, these complexes present luminescence properties. UV–vis and fluorescence measurements have allowed the identification of their excitation and emission wavelengths (λmax). These studies revealed that by selecting the appropriate amine ligand the emission can be easily tuned to achieve a variety of colors, from violet to green.

Introduction
The synthesis of organogold complexes has recently attracted wide attention due to their considerable range of applications, in areas such as materials and medicinal chemistry, as well as their potential role as reaction intermediates or new catalysts in gold-catalyzed processes [1-7]. This has led several research groups to investigate general, green and straightforward methodologies for the synthesis of organogold complexes. We have focused on the synthesis and study of transition metal complexes bearing N-heterocyclic carbene (NHC) ligands [8-10]. Recently, we have been very active in the synthesis and characterization of new gold(I)–NHC complexes and the study of their reactivity, with a special focus on the development of straightforward methodologies [11,12]. As a result of our investigations, we have recently reported the synthesis of [AuX(NHC)] (X = Cl, Br, I) complexes, directly from imidazolium and imidazolium salts and a suitable gold source, such as [AuCl(SMe2)], using K2CO3 as a base [13]. Moreover, we have also reported the synthesis of the first mononuclear gold(I) hydroxide species,
Scheme 1: Straightforward synthesis of organogold complexes via deprotonation reactions, using 1.

Results and Discussion

Synthesis and characterization of gold(I)--amide complexes

We began our studies by exposing hydroxide 1 to a series of alkyl- and arylamines. While no reaction was observed with either morpholine or isopropylamine, the use of 1 equiv of aniline or 2-aminopyridine led to the isolation of complexes 2 and 3 respectively, in good yields after overnight reaction at room temperature. These results are consistent with the known pKₐ of [Au(OH)(IPr)] (30.3) [26]; the scope of this preparative route is, as with other deprotonation reactions with this building block, limited to substrates with a pKₐ lower than 30.

Encouraged by these exploratory reactions, a series of (hetero)aromatic amines were employed to prepare the corresponding gold(I)--amide complexes. The desired complexes were obtained by reaction of [Au(OH)(IPr)] (1) with each (hetero)aromatic amine in THF at room temperature for 20 h. A range of aromatic amines were employed, including aniline, diphenylamine, pyridines, a pyrimidine and one isoquinoline. The corresponding complexes were obtained in analytically pure form and in good yields as yellow or white microcrystalline powders after a simple work-up (Scheme 2). All complexes were found to display the expected two-coordinate linear geometry around the metal center, with all C–Au–N angles in the range 173–179°. There was no evidence of any interactions between the gold center and the heteroatoms in complexes 3, 7, 8, 10 or 11. However, for 3, 7, 8, 10 and 11 there is an intermolecular contact between the aromatic nitrogen atom and the NHC ligand backbone proton (d_N-H = 2.27 Å–2.34 Å). All gold–carbon bond lengths were in the range 1.95 Å (8) to 2.02 Å (2), while gold–nitrogen bond lengths varied from 1.98 Å (8) to 2.06 Å (2).

During the characterization of the gold–NHC amide complexes we observed that some of the complexes possessed luminescent
A number of luminescent organogold complexes have been reported in the literature, often demonstrating interesting properties that may lead to their application in materials science and the preparation of optical materials [28-34]. Amongst these, NHC-bearing gold complexes have been shown by several research groups to be very useful luminescent materials [19,35-39], and have attracted industrial interest [40-42]. Thus, we decided to explore the potential of these gold amide species as luminescent materials.

We began our luminescence studies by recording the UV–vis spectra of the aforementioned gold–amide complexes using a dilute (ca. 0.2 mmol/L) CH$_2$Cl$_2$ solution. The wavelengths of the absorption maxima on the UV–vis spectra were in the range of 250–350 nm for most complexes, with the exception of 2-amino-5-nitropyridine derived 9 and 3-aminoisooquinoline-derived 10, which exhibited absorption maxima at ca. 430 nm.
Figure 1: X-ray crystal structures of complexes 2, 3, 7, 8, 10, 11 and 12. Hydrogen atoms are omitted for clarity.

Figure 2: Selected examples of gold–NHC amide complexes under UV light (λ = 366 nm).
Figure 3: Excitation (blue) and emission (pink) data for complex 3, bearing a 2-pyridine ligand (see inset).

Figure 4: (a) LUMO, (b) HOMO and (c) HOMO-1 of complex 3.
Table 1: Fluorescence measurement data.\textsuperscript{a}

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\textsuperscript{a}At ca. 4 mmol/L in CH$_2$Cl$_2$ solution.

Centered predominantly on the amide ligand, the LUMO is localized on the aryl ring of the NHC ligand; we propose that the fluorescence behavior is due to a HOMO-to-LUMO transition. Therefore, the use of different NHC ligands should also allow access to different fluorescence behavior.

**Conclusion**

A novel series of NHC-bearing gold(I)–amide complexes have been prepared using a simple, straightforward synthetic route that can be conducted using reagent-grade materials on the laboratory bench in air. The resulting species have been charac-
terized using a number of methods, including NMR spectroscopy and X-ray crystal diffraction. These new species have been shown to be fluorescent, and their absorbance and emission maxima have been determined. Notably, there are key trends in the fluorescence behavior of these materials, with more electron-rich 2-pyridine derivatives showing strong emission, and isoquinoline-derived complexes showing the strongest fluorescence. While the present study has been conducted using commercial reagent-grade amines, there is significant scope to prepare a much wider range of gold(I)–amide complexes, including those prepared using designed aromatic amines. Further work is underway in our group to explore both the potential of gold(I)–NHC amide complexes, and further applications of gold(I) hydroxides as building blocks and catalysts.

Supporting Information
Supporting Information File 1
Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-260-S1.pdf]

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Synthesis of axially chiral gold complexes and their applications in asymmetric catalyses

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Full Research Paper

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Keywords:
asymmetric gold catalysis; chiral Au catalysts; gold–π interaction; NHC gold complex

Abstract
Several novel chiral N-heterocyclic carbene and phosphine ligands were prepared from (S)-BINOL. Moreover, their ligated Au complexes were also successfully synthesized and characterized by X-ray crystal diffraction. A weak gold–π interaction between the Au atom and the aromatic ring in these gold complexes was identified. Furthermore, we confirmed the formation of a pair of diastereomeric isomers in NHC gold complexes bearing an axially chiral binaphthyl moiety derived from the hindered rotation around C–C and C–N bonds. In the asymmetric intramolecular hydroamination reaction most of these chiral Au(I) complexes showed good catalytic activities towards olefins tethered with a NHTs functional group to give the corresponding product in moderate yields and up to 29% ee.

Introduction
After the long-held assumption of the non-reactivity of gold complexes, numerous reactions catalyzed by gold complexes have emerged in the last 2 decades [1-9]. In the past few years, reports on gold-catalyzed organic transformations have increased substantially [10-29]. Homogeneous gold catalysis has proven to be a powerful tool in organic synthesis. However, chiral gold complexes [30-45], especially chiral NHC–gold complex-catalyzed asymmetric reactions [46-53] are still uncommon. Very few efficient chiral NHC–gold catalysts have been known up to the year of 2013. So far, several axially chiral NHC–gold catalysts based on binaphthyl skeleton such as 1 and 2 [46,49] have been reported with good to excellent chiral inductions in asymmetric gold catalysis (Figure 1). Encouraged by these results, we attempted to develop novel types of axially chiral NHC–gold catalysts based on the binaphthyl skeleton.
Very recently, Echavarren’s group has reported a very important gold–arene interaction in dialkylbiarylphosphane gold complexes, which is very useful in gold catalysis [54]. It has been disclosed that there was a weak gold-π interaction between the gold atom and the aromatic ring in catalysts 1 [46]. On the basis of this finding, we envisaged that if an aryl group is introduced near the ligated gold atom, the gold–arene interaction may affect the catalytic efficiency in gold catalysis (Figure 1).

Results and Discussion

Synthesis of the carbene–Au(I) complexes. The synthesis of compound 9 was reported by Slaughter and co-workers (Scheme 1) [49]. The usage of (S)-BINOL as the starting material to react with trifluoromethanesulfonic anhydride in the presence of DIPEA afforded at 0 °C in dichloromethane the corresponding product (S)-2'-hydroxy-1,1'-binaphthyl-2-yl trifluoromethanesulfonate (5) in good yield. The crude product and NiCl₂(dppe) (10 mol %) was dissolved in toluene under argon. To this solution was added dropwise a 1.0 M THF solution of 3,5-bis(trifluoromethyl)phenylmagnesium bromide, which afforded (S)-6 in 33% yield in two steps under reflux [55]. Then, (S)-7 was obtained by treatment of (S)-6 with Tf₂O and pyridine in DCM in 99% yield. The usage of dimethylbis(diphenylphosphino)xanthene (XantPhos) as a ligand and Pd₂(dbazu)₃ as a catalyst in the presence of Cs₂CO₃, facilitated the reaction of (S)-7 with benzylamine in toluene to give the desired compound (S)-8 in 57% yield [49]. Reduction of (S)-8 by using Pd/C and H₂ in MeOH produced the desired compound (S)-9 in 95% yield.

The preparation of chiral benzimidazolium salt (S)-13 is shown in Scheme 2. Based on our previous work [52], the coupling reaction between compound (S)-9 and 1-bromo-2-nitrobenzene was carried out by using Pd₂(dbazu)₃ as the catalyst in the presence of bis[2-(diphenylphosphino)phenyl] ether (DPEphos) and Cs₂CO₃, affording the desired compound (S)-10 in 94% yield [51]. Reduction of (S)-10 was performed under H₂ (1.0 atm) atmosphere by using Pd/C as a catalyst, giving the desired compound (S)-11 in 95% yield. The subsequent cyclization of (S)-11 with triethyl orthoformate was carried out at 100 °C in the presence of p-toluenesulfonic acid, affording the desired product (S)-12 in 89% yield. The corresponding benzimidazolium salt (S)-13 was obtained in quantitative yield upon treating the benzimidazole ring of (S)-12 with methyl iodide in acetonitrile.
under reflux (Scheme 2). Moreover, treatment of the benzimidazole ring of (S)-12 by using benzyl bromide upon heating in dioxane could produce the corresponding benzimidazolium salt (S)-14 also in quantitative yield (Scheme 3).

With these NHC precursor salts (S)-13 and (S)-14 in hand, their coordination pattern with Au was examined. Benzimidazolium salts (S)-13 and (S)-14 were treated with AuCl·S(Me)\(_2\) in acetonitrile in the presence of NaOAc under reflux, giving the corresponding Au complexes (S)-15 [two diastereomers: (S)-15a in 46% yield and (S)-15b in 37% yield] and (S)-16 in 75% total yield [the two diastereomers: (S)-16a and (S)-16b can not be separated by silica gel column chromatography] as a white solid after purification with silica gel column chromatography (Scheme 4). The ratio of (S)-16a and (S)-16b was identified as 1:2 on the basis of \(^1\)H NMR spectroscopic data. After recrystallization from the mixed solvent of DCM and pentane, the single crystals of diastereomers (S)-15a and (S)-15b were obtained and their structures were confirmed by the X-ray crystal structure diffraction (Figure 2 and Figure 3). The distance between the center of the aromatic ring in one naphthyl moiety (C20–C25) and the Au atom in (S)-15a was only 3.7 Å (Figure 2). The distance from the Au atom to the center of the bis(trifluoromethyl)phenyl ring (C29–C34) in (S)-15b was 3.5 Å (Figure 3). Thus, their X-ray crystal structures clearly revealed the presence of a weak gold–π interaction between the Au atom and the aromatic rings in these gold complexes. Because of the gold–π interaction, the C–N bond could not rotate freely, giving two diastereomeric rotamers (S)-15a and (S)-15b. Slaughter and co-workers have also found two rotamers in gold complexes 1 caused by the handicap of C–N bond rotation on the basis of X-ray diffraction and named them as “out” rotamer and “in” rotamer \[49\] (Scheme 5). Their energy barrier has been also disclosed by DFT calculations.

**Synthesis of the P–Au(I) complexes.** The synthesis of the Au complexes (S)-18 and (S)-22 is shown in Scheme 6. Compounds (S)-17 and (S)-19 were prepared according to published literature procedures \[56\]. Compound (S)-17 was treated with AuCl·S(Me)\(_2\) in acetonitrile at room temperature to give the corresponding Au complex (S)-18 in 88% yield as a white solid after purification with silica gel column chromatography. The
Scheme 4: Synthesis of carbene Au complexes.

Figure 2: The crystal data of gold complex (S)-15a was deposited in the CCDC with the number 883917. Empirical formula: C_{36}H_{22}AuF_6N_2; formula weight: 920.42; crystal color, colorless; crystal dimensions: 0.321 × 0.212 × 0.143 mm; crystal system: orthorhombic; lattice parameters: a = 9.6909(5) Å, b = 18.5814(9) Å, c = 36.0427(18) Å; α = 90°, β = 90°, γ = 90°, V = 6490.2(6) Å³; space group: P2(1)2(1)2(1); Z = 8; D_{calc} = 1.884 g/cm³; F_{000} = 3504; final R indices [I > 2σ(I)]: R1 = 0.0421; wR2 = 0.0793.

The structure of (S)-18 was confirmed by the X-ray crystal structure diffraction (Figure 4). The distance from the Au atom to the center of the aromatic ring (C11, C12 and C17–C20) in one naphthyl moiety was 3.3 Å.

Figure 3: The crystal data of gold complex (S)-15b was deposited in the CCDC with the number 883916. Empirical formula: C_{36}H_{22}AuF_6N_2; formula weight: 920.42; crystal color, colorless; crystal dimensions: 0.265 × 0.211 × 0.147 mm; crystal system: orthorhombic; lattice parameters: a = 7.6103(5) Å, b = 12.6408(8) Å, c = 34.029(2) Å; α = 90°, β = 90°, γ = 90°, V = 3273.6(4) Å³; space group: P2(1)2(1)2(1); Z = 4; D_{calc} = 1.868 g/cm³; F_{000} = 1752; final R indices [I > 2σ(I)]: R1 = 0.0482; wR2 = 0.0972.

The compound (S)-19 and NiCl₂(dppe) (10 mol %) were dissolved in toluene under argon. To this solution was added dropwise a 1.0 M THF solution of phenylmagnesium bromide and the desired compound (S)-20 was afforded in 21% yield.

Then, the obtained compound (S)-20 was treated with SiHCl₃ in the presence of triethylamine in toluene at 120 °C, giving (S)-diphenyl(2’-phenyl-1,1’-binaphthyl-2-yl)phosphine (21) in 81% yield. The corresponding gold complex (S)-22 was obtained in 91% yield upon treating (S)-21 with the same method as the gold complex (S)-18. The structure of (S)-22 was confirmed by
Scheme 5: Rotamers of 1a and 1b by DFT calculation reported by Slaughter’s group.

Scheme 6: The synthesis of P–Au complexes.

X-ray crystal structure diffraction (Figure 5). The crystal structure of (S)-22 (Figure 5) revealed that the distance from the Au atom to the center of the phenyl ring (C21–C26) was 4.5 Å. During the process of the preparation of (S)-21, we found a small amount of naphtho[1,2-g]chrysene (23), presumably derived from a cross coupling of compound (S)-19 with PhMgBr. Its structure was also confirmed by the X-ray crystal structure diffraction (Figure SI-1 in Supporting Information File 1).

The catalytic activities of these gold complexes were examined by the gold-catalyzed asymmetric intramolecular hydroamination of allenes by using a variety of chiral phosphine–Au(I) complexes [57-63]. On the other hand, the intramolecular hydroamination of olefins is a more important reaction in organic synthesis and has been widely reported [64-68]. Recently, the enantioselective intramolecular hydroamination of olefins has also been significantly improved by using various transition metal complexes or other metal complexes [69-77]. However, to the best of our knowledge, the enantioselective intramolecular hydroamination of olefins catalyzed by gold complexes has not been reported yet. We therefore applied our Au complexes to the asymmetric catalysis of the intramolecular hydroamination of olefin 24 tethered with a NHTs functional group.

Intramolecular hydroamination reaction catalyzed by Au(I) complexes. We synthesized a variety of Au complexes both neutral and cationic and subsequently used these complexes as catalysts in a variety of reactions. High enantioselectivities were achieved in the asymmetric intramolecular hydroamination of allenes by using a variety of chiral phosphine–Au(I) complexes [57-63]. On the other hand, the intramolecular hydroamination of olefins is a more important reaction in organic synthesis and has been widely reported [64-68]. Recently, the enantioselective intramolecular hydroamination of olefins has also been significantly improved by using various transition metal complexes or other metal complexes [69-77]. However, to the best of our knowledge, the enantioselective intramolecular hydroamination of olefins catalyzed by gold complexes has not been reported yet. We therefore applied our Au complexes to the asymmetric catalysis of the intramolecular hydroamination of olefin 24 tethered with a NHTs functional group.

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Treatment of olefin 24 with the axially chiral gold complex (S)-22 and AgOTf (5 mol %) in toluene at 85 °C for 36 h afforded pyrrolidine derivative 25 in 46% yield and 17% ee. While using AgSbF6 or AgNTf2 as additives, only trace amounts of 25 were formed. Further screening of silver salts revealed that AgOTs showed the best catalytic activity in this reaction, giving 25 in 72% yield and 27% ee (Table 1, entries 1–6). The usage of other solvents such as DCE, CH3CN and THF, decreased significantly the yield (Table 1, entries 7–9). The employment
of other axially chiral Au complexes in this reaction led to similar results, affording 25 in 42–65% yields and 7–27% ee (Table 1, entries 10–13). The control experiment indicated that no reaction occurred in the absence of a Au catalyst (Table 1, entry 14).

Conclusion
Axially chiral Au(I) complexes exhibiting a binaphthyl scaffold with NHC or phosphine gold complexes on one side and an arene moiety on another side were prepared starting from axially chiral BINOL. A weak gold–π interaction between the Au atom and the aromatic ring in these gold complexes was identified. These axially chiral Au(I) complexes showed moderate catalytic activities along with low chiral inductions in the asymmetric intramolecular hydroamination reaction of olefin 24 tethered with a functional group of NHT.

Experimental
Synthesis of NHC–Au(I) complexes (S)-15a and (S)-15b
The compound (S)-13 (145 mg, 0.2 mmol) and AuCl-S(Me)$_2$ (59 mg, 0.2 mmol), NaOAc (33 mg, 0.4 mmol) were heated under reflux in CH$_3$CN (2 mL) overnight. The volatiles were then removed under reduced pressure and the residue was purified by a silica gel flash column chromatography to afford gold-complexes (S)-15a (84 mg) in 46% yield and (S)-15b (68 mg) in 37% yield. A single crystal grown from complex (S)-15a or (S)-15b in a saturated solution of CH$_2$Cl$_2$/pentane was suitable for X-ray crystal analysis. (S)-15a: white solid; [α]$_D^{20} = -64.7$ (c 0.10, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$, TMS) δ 8.17–8.13 (m, 2H, ArH), 7.90–7.78 (m, 2H, ArH), 7.74–7.70 (m, 1H, ArH), 7.66–7.59 (m, 3H, ArH), 7.56–7.50 (m, 2H, ArH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 7.34–7.28 (m, 4H, ArH), 7.06 (s, 2H, ArH), 6.86–6.82 (m, 2H, ArH), 5.60 (d, $J = 8.4$ Hz, 1H, ArH), 3.78 (s, 3H, CH$_3$); $^{19}$F NMR (376 MHz, CDCl$_3$); CFC$_3$) δ −63.096; $^{13}$C NMR (100 MHz, CDCl$_3$; δ 141.5, 140.8, 134.9, 134.5, 133.4, 132.9, 132.6, 131.3, 131.0, 130.9, 130.7, 129.9, 129.2, 129.1, 129.0, 128.5, 128.41, 128.37, 128.79, 127.6, 126.9, 126.8, 126.4, 123.7, 123.4, 121.0, 120.6, 113.2, 111.4, 34.8; IR (CH$_2$Cl$_2$); v: 3059, 2926, 1594, 1346, 1277, 1182, 897, 820, 745, 713 cm$^{-1}$; HRMS–ESI: [M + NH$_4$]$^+$ calculated for C$_{36}$H$_{26}$AuF$_3$N$_2$, 938.0736; found, 938.0728. (S)-15b: white solid; [α]$_D^{20} = -66.1$ (c 1.45, CH$_2$Cl$_2$); $^1$H NMR (400 MHz, CDCl$_3$, TMS) δ 8.17 (d, $J = 8.4$ Hz, 1H, ArH), 8.13 (d, $J = 8.0$ Hz, 1H, ArH), 7.85 (d, $J = 8.0$ Hz, 1H, ArH), 7.79–7.69 (m, 4H, ArH), 7.63 (d, $J = 8.0$ Hz, 1H, ArH), 7.59–7.54 (m, 3H, ArH), 7.50–7.46 (m, 1H, ArH), 7.23 (d, $J = 8.8$ Hz, 2H, ArH), 7.17 (s, 2H, ArH), 7.08–7.04 (m, 1H, ArH), 6.47–6.42 (m, 2H, ArH), 3.94 (s, 3H, CH$_3$).

Table 1: Asymmetric intramolecular hydroamination catalyzed by Au complexes.

<table>
<thead>
<tr>
<th>entry</th>
<th>Au cat.</th>
<th>Ag salt</th>
<th>solvent</th>
<th>yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>AgOTf</td>
<td>toluene</td>
<td>46</td>
<td>17</td>
</tr>
</tbody>
</table>
| 2     | 22      | AgSbF$_6$ | toluene | trace     | _d_
| 3     | 22      | CF$_3$COOAg | toluene | 69        | 11     |
| 4     | 22      | AgOTs  | toluene | 72        | 27     |
| 5     | 22      | AgBF$_4$ | toluene | 15        | 10     |
| 6     | 22      | AgNTf$_2$ | toluene | 48        | 0      |
| 7     | 22      | AgOTs  | CH$_2$CN | 12        | 27     |
| 8     | 22      | AgOTs  | DCE     | 11        | 29     |
| 9     | 22      | AgOTs  | THF     | N.R.      | _d_
| 10    | 18      | AgOTs  | toluene | 58        | 24     |
| 11    | 16      | AgOTs  | toluene | 65        | 27     |
| 12    | 15a     | AgOTs  | toluene | 42        | 7      |
| 13    | 15b     | AgOTs  | toluene | 51        | 10     |
| 14    | none    | AgOTs  | toluene | N.R.      | _d_

*The reaction was carried out on a 0.1 mmol scale in solvents (1.0 mL). $^b$Isolated yield. $^c$Measured by chira HPLC. $^d$Not determined.
CH₃); ¹³C NMR (376 MHz, CDCl₃, CFC₁₃) δ -62.451; ¹²C NMR (100 MHz, CDCl₃) δ 134.6, 134.5, 134.1, 134.0, 133.6, 131.4, 131.27, 129.1, 129.0, 128.8, 128.7, 128.66, 128.58, 128.5, 128.3, 128.2, 127.8, 126.9, 126.5, 124.1, 123.4, 118.6, 31.9; IR (CH₂Cl₂) v: 2923, 2851, 1726, 1465, 1387, 1277, 1181, 1131, 894, 823, 743, 712, 681 cm⁻¹; HRMS–ESI: [M + NH₄]⁺ calcd for C₃₈H₅₆AuClNOP, 764.1543; found, 764.1532.

Synthesis of chiral P–Au(I) complexes (S)-18 and (S)-22

The compound (S)-17 (454 mg, 1.0 mmol) and AuCl₂(SMe₂) (294 mg, 1.0 mmol) were stirred in CH₂CN (10 mL) overnight. The volatiles were then removed under reduced pressure and the residue was purified by silica gel flash column chromatography to afford gold-complex (S)-18 (603 mg) in 88% yield. A single crystal grown from complex (S)-18 in a saturated solution of CH₂Cl₂/pentane was suitable for X-ray crystal analysis. (S)-18: white solid; [α]D²⁰ -35.4 (c 0.20, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, TMS) δ 7.99–7.93 (m, 3H, ArH), 7.80 (d, J = 8.4 Hz, 1H, ArH), 7.60–7.56 (m, 1H, ArH), 7.50–7.45 (m, 3H, ArH), 7.42–7.17 (m, 12H, ArH), 6.86–6.82 (m, 1H, ArH), 6.45 (d, J = 8.4 Hz, 1H, ArH), 5.17 (br, 1H, OH); ³¹P NMR (162 MHz, CDCl₃, 85% H₃PO₄) δ 26.116; ¹³C NMR (100 MHz, CDCl₃) δ 141.8, 136.5, 134.4, 133.7, 133.24, 133.22, 133.1, 132.39, 132.35, 130.5, 130.2, 129.8, 129.9, 128.9, 128.6, 128.4, 127.6, 127.3, 127.2, 127.1, 127.0, 126.6, 124.2, 123.7, 123.0, 112.6, 110.4; IR (CH₂Cl₂) v: 3559, 3055, 2924, 1623, 1513, 1435, 1269, 1098, 972, 937, 814, 743, 692 cm⁻¹; HRMS–ESI: [M + NH₄]⁺ calcd for C₂₃H₂₇AuClNOP, 704.1179; found, 704.1170.

Gold complex (S)-22 has been prepared by the same reaction procedure as gold complex (S)-18 in 91% yield. A single crystal grown from complex (S)-22 in a saturated solution of CH₂Cl₂/pentane was suitable for X-ray crystal analysis. white solid; [α]D²⁰ -80.7 (c 0.95, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.27 (d, J = 8.8 Hz, 1H, ArH), 8.05 (d, J = 8.4 Hz, 1H, ArH), 7.90 (d, J = 8.0 Hz, 1H, ArH), 7.84 (d, J = 8.4 Hz, 1H, ArH), 7.67 (t, J = 8.4 Hz, 1H, ArH), 7.62–7.57 (m, 1H, ArH), 7.47 (t, J = 7.6 Hz, 1H, ArH), 7.40–7.35 (m, 4H, ArH), 7.28–7.24 (m, 2H, ArH), 7.22–7.12 (m, 6H, ArH), 6.97 (d, J = 7.6 Hz, 2H, ArH), 6.92 (t, J = 7.2 Hz, 2H, ArH), 6.88 (d, J = 7.6 Hz, 1H, ArH), 6.84 (d, J = 8.8 Hz, 1H, ArH), 6.77 (t, J = 7.6 Hz, 2H, ArH); ³¹P NMR (162 MHz, CDCl₃, 85% H₃PO₄) δ 22.898, 22.825, 22.751, 22.679; ¹³C NMR (100 MHz, CDCl₃) δ 151.4, 134.6, 134.4, 134.1, 133.9, 133.7, 133.5, 133.2, 133.1, 131.5, 131.44, 131.37, 131.35, 131.25, 129.9, 129.3, 129.04, 128.98, 128.92, 128.89, 128.87, 128.85, 128.84, 128.7, 128.64, 128.59, 128.51, 128.5, 128.3, 128.2, 127.8, 127.5, 126.81, 126.80, 126.6, 126.5, 126.47, 126.1, 126.0, 124.1, 123.4; IR (CH₂Cl₂) v: 3054, 1589, 1494, 1480, 1436, 1306, 1265, 1098, 1027, 819, 763, 744, 698 cm⁻¹; HRMS–ESI: [M + NH₄]⁺ calcd for C₃₈H₃₂AuClNOP, 764.1543; found, 764.1532.

General procedure for the intramolecular hydroamination reaction catalyzed by Au(I) complexes

In a similar way as described in reference [51], a mixture of Au catalyst (5 mol %) and AgX (5 mol %) in solvent (0.5 mL) was stirred at room temperature for 5 min under argon, then a solution of compound 24 (39.1 mg, 0.10 mmol) in solvent (0.5 mL) was added into the resulting solution. The resulting suspension was stirred at 85 °C for 36 h. Column chromatography of the reaction mixture gave the desired product. The enantiomeric purity of the product was determined by chiral HPLC analysis.

Supporting Information

Supporting Information File 1
Experimental procedures and characterization data of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-261-S1.pdf]

Supporting Information File 2
Chemical information file of compound (S)-15a.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-261-S2.cif]

Supporting Information File 3
Chemical information file of compound (S)-15b.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-261-S3.cif]

Supporting Information File 4
Chemical information file of compound (S)-18.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-261-S4.cif]

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Gold(I)-catalyzed 6-endo hydroxycyclization of 7-substituted-1,6-enynes

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Full Research Paper

Abstract

The cyclization of o-(alkynyl)-3-(methylbut-2-enyl)benzenes, 1,6-enynes having a condensed aromatic ring at C3–C4 positions, has been studied under the catalysis of cationic gold(I) complexes. The selective 6-endo-dig mode of cyclization observed for the 7-substituted substrates in the presence of water or methanol giving rise to hydroxy(methoxy)-functionalized dihydronaphthalene derivatives is highly remarkable in the context of the observed reaction pathways for the cycloisomerizations of 1,6-enynes bearing a trisubstituted olefin.

Introduction

The cycloisomerization reactions of enynes catalyzed by gold complexes are a powerful tool for accessing complex products from rather simple starting materials under soft and straightforward conditions [1-4]. In this context, 1,6-enynes have been extensively studied, mainly by Echavarren and co-workers, as substrates in the identification of new reactivities catalyzed by gold and other transition metal complexes [5-13]. Cyclopropyl metal carbenes II are usually formed by exo-dig processes from enynes I bearing a terminal alkyne, which in the absence of external nucleophiles undergo skeletal rearrangements to afford products such as III (single cleavage) [14]. However, reactions of II with alcohols or water give the corresponding products of alkoxy(hydroxy)cyclization IV [15-17] (Scheme 1). The less common 6-endo cyclization via metal carbenes V was also observed in particular cases affording methylenecyclohexene derivatives like VI [14]. On the other hand, 1,6-enynes VII, bearing an aryl substituent at the alkyne, undergo a formal intramolecular [4 + 2] cycloaddition through an initial 5-exo cyclization followed by a Friedel–Crafts-type reaction to cyclo-penta[b]naphthalenes VIII or, alternatively, a 6-endo cyclization to bicyclo[4.1.0]hept-4-enes like IX [18,19] (Scheme 1). In the case that MeOH is present a 5-exo methoxycyclization is observed, e.g., in the formation of X resembling the behaviour of I [16,20]. In addition, the gold-catalyzed reaction of 7-phe-
Scheme 1: Gold(I)-catalyzed reactions of 1,6-enynes.

Despite the numerous studies about the metal-catalyzed transformations of 1,6-enynes, \( o-(\text{alkynyl})-(3\text{-methylbut}-2\text{-enyl})\text{benzenes} \) that are also 1,6-enynes bearing an attached aryl ring at the C3–C4 positions, have been scarcely studied. Only Liu and co-workers have reported the behaviour of terminal substrates \( I (R = H) \) under ruthenium catalysis, which afford the corresponding metathesis-type product \( XI \) (Scheme 2). More recently, the same authors have described the gold-catalyzed [2 + 2 + 3] cycloaddition reaction of these compounds with nitrones giving rise to functionalized 1,2-oxazepane derivatives \( XIII \). This cascade process takes place through the interception of the 1,4-dipole equivalent \( XII \) generated by an initial 5-exo cyclization, although with some gold catalysts minor amounts of \( XI \) were also obtained (Scheme 2). Following our interest in the development of new gold-catalyzed reactions [24-31], in this context we thought that it could be interesting to study if the cyclization of easily available compounds \( I \) bearing an internal acetylene moiety would take place through an initial 5-exo cyclization that in the case of aryl-substituted enynes \( (R = \text{Ar}) \) would give rise to a formal \( [4 + 2] \) cycloaddition product \( XIV \) [18,19], or alternatively, through a relatively less common 6-endodig pathway via gold species \( XV \), which could be represented as two resonance structures highlighting both the carbocation or carbenoid nature of this intermediate (Scheme 2).

Results and Discussion
As established in Scheme 2, we were intrigued by the possibility that \( o-(\text{alkynyl})-(3\text{-methylbut}-2\text{-enyl})\text{benzenes} \) could undergo a 6-endodig cyclization in the presence of cationic gold(I) complexes instead of the usually more favoured 5-exo-dig pathway. So, we initially prepared a variety of these \( o\)-disubstituted benzene derivatives \( I \) by two approaches (see Supporting Information File 1) (Scheme 3). First, \( o\)-(bromo)-3-(methylbut-2-enyl)benzene was prepared by the reaction of commercially available 2-methyl-1-propenylmagnesium bro-
mide with 2-bromobenzyl bromide in the presence of CuI and 2,2′-bipyridyl [32]. This aryl bromide could be coupled with selected terminal alkynes by using cesium carbonate as a base and PdCl2(MeCN)2/XPhos as a catalytic system [33]. Alternatively, several o-(alkynyl)bromobenzenes [34] could be transformed into the corresponding derivatives 1 by bromine–lithium exchange and further treatment with 3,3-dimethylallyl bromide in the presence of TMEDA [23].

We selected 1-(2-(2-(3-methylbut-2-enyl)phenyl)ethynyl)benzene (1a) as model substrate for the initial experiments (Scheme 4). Its reaction with (Ph3P)AuNTf2, reported by Gagosz and co-workers as a very active catalyst for the cycloisomerization of closely related 7-aryl-1,6-enynes [35], gave rise to a ca. 3:1 mixture of dihydronaphthalene derivative 2a and tetracyclic compound 3a along with some other unidentified minor products. The two major products resulted to be inseparable by column chromatography and were isolated in 68% overall yield. It is remarkable that compound 2a, derived from a 6-endo cyclization and further proton elimination from intermediate resonance structures 4a and 4a‘, is generated in preference to 3a which would be the expected product derived from a formal [4 + 2] cycloaddition initiated by a 5-exo cyclization followed by a Friedel–Crafts-type process in intermediate 5a or 5a‘, as described by Echavarren and co-workers [18,19].

Prompted by this result and taking into account the reported results about the 5-endo hydroxy- and alkoxycyclization of 1,5-enynes [36], as well as our recent report about the alkoxycyclization of 1,3-dien-5-yynes [31], we wondered if the presence of an external protic nucleophile, such as methanol or water, could have an important influence on controlling the selectivity of the reaction. Encouragingly, when we treated model substrate 1a with (Ph3P)AuNTf2 in a 10:1 mixture of CH2Cl2 and MeOH as the solvent, the methoxoalkyl-substituted derivative 6a was obtained as the major product along with minor amounts of 3a (ca. 6:1 ratio) (Scheme 5) [37]. Moreover, the use of H2O (20 equiv) also led to a high yield of the hydroxyalkyl-substituted dihydronaphthalene derivative 7a, whose structure was further confirmed by X-ray analysis [38]. In both cases the high selectivity (>5:1) of these reactions for the 6-endo-type cyclization should be noted and only minor amounts (10–15%) of 3a were also formed.

Due to the unexpected 6-endo-favored pathway found for substrate 1a [39], we attempted to further improve this selectivity in the hydroxycyclization process (Table 1). Switching the ligand from Ph3P to XPhos or N-heterocyclic carbene (IPr) slightly decreases the selectivity for the 6-endo cyclization (Table 1, entry 1 vs entries 2 and 3). However, when the cationic gold complex (JohnPhos)(NCMe)AuSbF6, developed by Echavarren and co-workers [40], was employed as a catalyst a moderate increase in the ratio of 7a vs 3a was observed (Table 1, entry 4). Both cationic gold complexes (Ph3P)AuNTf2 and (JohnPhos)(NCMe)AuSbF6 gave rise to a similar yield of isolated alcohol 7a. Changing the solvent from CH2Cl2 to a mixture containing other more polar solvent such as acetone or dioxane (Table 1, entries 5 and 6) did not have a significant influence on the selectivity but led to the formation of minor amounts of alcohol 8a, derived from a 5-exo hydroxycyclization reaction. With a 1:1 mixture of CH2Cl2/dioxane the effect of the selected catalytic systems was checked (Table 1, entries 7–10). We found that the use of JohnPhos as a ligand and SbF6 as a counter ion (Table 1, entries 9 and 10) resulted in a slightly better selectivity, although trace amounts of alcohol 8a were
also generated, which make the isolation of 7a more difficult. Overall, we concluded that both commercially available gold complexes (Ph3P)AuNTf2 and (JohnPhos)(NMe)AuSbF6 lead to comparable good results in the 6-endo hydroxycyclization of 1a. The type of products derived from the 5-exo pathway (3a and 8a) depends on the solvent: in CH2Cl2 3a is mainly obtained, whereas the alcohol 8a appears when a more polar mixture of solvents was used.

Once we have selected the best conditions to favor the 6-endo hydroxycyclization reaction, a selection of substrates 1a–k, bearing different groups at the triple bond, were reacted under the established conditions (Table 2). When aromatic or alkanyl groups are present as the substituents of the alkyne (Table 2, entries 1–7) the 6-endo cyclization takes place in selective or almost exclusively fashion allowing the isolation of 2-(1,2-dihydro-3-substituted naphthalen-2-yl)propan-2-ol derivatives 7 in usually high yields. Interestingly, we have also observed that when starting with enynes possessing an electron-rich aromatic ring or an alkanyl group at the C7-position of the 1,6-enzyme the cyclization results almost completely selective via the 6-endo mode (Table 2, entries 2, 3 and entries 6, 7). However, in the case of halogen-containing aromatic substituents at C7 the formation of the corresponding products 3 or 8, derived from an initial 5-exo cyclization, becomes more competitive (Table 2, entries 4 and 5). Then, we turned our attention to alkyl-substituted alkenes (Table 2, entries 8 and 9), which could not undergo the formal [4 + 2] cycloaddition leading to 3. In these cases, and after some optimization studies, we surprisingly found that the solvent has an important role on the selectivity of the cyclization. When a 1:1 mixture of CH2Cl2/dioxane was used the 5-exo hydroxycyclization that gives rise to alcohols 8 was competitive with the 6-endo process (3:1 for 1h and 1.7:1 for 1i), allowing the isolation of the corresponding methyleneindene derivatives 8h and 8i in 21% and 30% yield, respectively [41]. Gratifyingly, we found that when the same reactions were performed in CH2Cl2 the 6-endo cyclization was completely selective leading to the corresponding alcohols 7 in high yields (Table 2, entries 8 and 9). On the other hand, the reaction of trimethylsilyl-substituted enyne 1j did not proceed at all (Table 2, entry 10), whereas the presence of a phenylthio group as an R substituent mainly afforded the corresponding 6-endo product 7k although the reaction was significantly slower (Table 2, entry 11). As expected [10–12] the terminal enyne 1l (R = H) underwent exclusively the 5-exo cyclization leading to the corresponding alcohol 8l in 55% yield (Table 2, entry 12).
Table 2: Synthesis of 2-(1,2-dihydro-3-substituted-naphthalen-2-yl)propan-2-ol derivatives 7 by gold-catalyzed 6-endo hydroxycyclization of enynes 1.a

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Product</th>
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<td>1</td>
<td>1a Ph</td>
<td>7a</td>
<td>77 (12)c</td>
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<tr>
<td>2</td>
<td>1b 4-MeOC₆Η₄</td>
<td>7b</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>1c 2,4,5-(Me)₃C₆H₂</td>
<td>7c</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>1d 3-ClC₆H₄</td>
<td>7d</td>
<td>63 (22)d</td>
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<tr>
<td>5</td>
<td>1e 2,4-(F)₂C₆H₃</td>
<td>7e</td>
<td>75e</td>
</tr>
<tr>
<td>6</td>
<td>1f thiophen-3-yl</td>
<td>7f</td>
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<td>7</td>
<td>1g c-C₆H₉</td>
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<td>11h</td>
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<td>12</td>
<td>1l H</td>
<td>8l</td>
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aData reactions were carried out by treatment of 1 (0.3 mmol) with H₂O (22 equiv, 0.12 mL) in 1.2 mL of solvent until complete consumption of the starting material, as judged by GC–MS and/or TLC analysis (overnight). bIsolated yield of compounds 7 after column chromatography. cYield of 3a which could not be isolated in pure form. dIsolated yield of 3d which was obtained as a mixture of regioisomers with respect to the chlorine atom position. eIsolated along with ≈10% of 8e. f10% of 2e is also observed. fCarried out with (Ph₃P)AuNTf₂. Slightly lower yield (ca. 5%) was obtained with (JohnPhos)(NCMe)AuSbF₆. gStarting material was recovered. hReaction time: 48 h.

At this point we wondered if the cyclization would be diastereoselective, so we prepared enynes 1m by reacting 2-(phenylethynyl)phenyllithium with geranyl bromide and 1n by two Wittig reactions from 2’-(phenylethynyl)acetophenone (see Supporting Information File 1). First, the hydroxycyclization of 1m, as a pure E isomer, under the previously established conditions afforded the dihydro(naphthalene derivative 7m as a single isomer (Scheme 6), whose relative configuration was
assigned by analogy with previously related results reported by Gagosz and co-workers [37]. On the other hand, the reaction of 1n afforded a ca. 2.5:1 mixture of alcohol 7n [42] and the tetracyclic product 3n, derived from an initial 5-exo cyclization and subsequent Friedel–Crafts reaction (Scheme 6). Both compounds were isolated as single stereoisomers with a high overall yield [43]. In this case, the 5-exo pathway was more competitive compared to the result of model substrate 1a, probably due to the Thorpe–Ingold-type effect caused by the methyl group at the allylic position. To account for the stereoselectivity of these reactions we proposed the generation of a stabilized gold–carbenoid intermediate such as A that undergoes stereoselective attack by water (Scheme 6).

Furthermore, we have also carried out the methoxycyclization of selected 1,6-enynes 1 by their treatment with catalytic amounts of (JohnPhos)(NCMe)AuSbF6 in a 30:1 mixture of CH2Cl2 and MeOH as the solvent (Scheme 7) [44]. The corresponding methoxy-functionalized dihydronaphthalene derivatives 6 were obtained in high yields although the corresponding minor isomer derived from a 5-exo cyclization could not be separated in the case of 6a and 6h.

Finally, to support the proposed intermediacy of gold–carbenoid intermediate 4 or 4' (Scheme 4), we treated enyne 1b with D2O instead of water and under the same catalytic conditions we observed the exclusive formation of the deuterated compound [D]-7b in 75% yield (>90% deuterium incorporation at C4). The generation of that compound could be explained by deuterodemetallation of the vinylgold species B generated by an attack of the nucleophile on intermediate 4b or 4b' (Scheme 8).

Conclusion

We described an efficient gold(I)-catalyzed 6-end0 hydroxycyclization of 7-substituted 1,6-enynes bearing a condensed aromatic ring at the C3–C4 position of the enyne. This type of cyclization has not been previously observed for 1,6-enynes bearing trisubstituted olefins and represents a new addition to the observed reaction topologies in the gold-catalyzed cycloisomerization of these substrates. The new oxygen-functionalized dihydronaphthalene derivatives have been synthesized in high yields.

Supporting Information

Experimental procedures and spectroscopic data for all new compounds. Copies of 1H NMR and 13C NMR spectra for new compounds.

Supporting Information File 1
Experimental and analytical data. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-263-S1.pdf]

Supporting Information File 2
NMR spectra. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-263-S2.pdf]

Acknowledgements

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References

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However, 6a was isolated with trace amounts of a by-product that could be the corresponding methoxyalkyl-substituted product derived from a 5-exo-cyclization.

CCDC-945504 contains the supplementary crystallographic data for compound 7a. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif.

Condensed furnishing the best results in terms of selectivity and chemical yield.

In the methoxycyclization of 1h the 6-exo methoxy ether 6h and its 5-membered isomer derived from the 5-exo cyclization were obtained approximately in a 4:1 ratio (80% overall yield). For 1a only trace amounts of the 5-membered ring were observed.
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Gold(I)-catalyzed enantioselective cycloaddition reactions

Fernando López*1,§ and José L. Mascareñas*2,¶

Abstract

In recent years there have been extraordinary developments of gold(I)-catalyzed enantioselective processes. This includes progress in the area of cycloaddition reactions, which are of particular interest due to their potential for the rapid construction of optically active cyclic products. In this article we will summarize some of the most remarkable examples, emphasizing reaction mechanisms and key intermediates involved in the processes.

Introduction

In the past decade, there have been extraordinary advances in the development of novel stereoselective gold(I)-catalyzed transformations [1-10]. In this context, enantioselective gold catalysis has been identified as a particularly challenging goal because the linear two-coordination mode of gold(I) complexes and the out-sphere π-activation usually associated to carbophilic gold catalysts [11] places ligands far from the reacting centers, thus limiting the capacity to transfer asymmetry [12]. A number of strategies to tackle this problem have been developed, most of them based on the use of a new type of chiral gold complexes. This resulted in a number of gold-catalyzed enantioselective transformations in the past years, including hydrogenations, aldol reactions, 1,3-dipolar cycloadditions, and cyclizations [13-15]. Other gold-promoted asymmetric induction strategies rely on the use of chiral counterions. Indeed, it has been shown that a tight chiral ion pair with the gold cation
is able to induce excellent levels of asymmetry in certain cyclizations [16].

Cycloaddition reactions are very important synthetic processes that allow the transformation of simple acyclic precursors into complex cyclic or polycyclic adducts in a rapid and efficient way [17,18], usually providing a rapid increase in skeletal and stereochemical complexity. Moreover, cycloadditions are atom economical, and usually take place with high levels of regio- and stereocontrol. Especially relevant in terms of synthetic practicality are cycloadditions which are catalyzed by transition metal complexes [19-23]. In particular, gold(I) complexes, owing to their high carbophilicity, low oxophilicity and high oxidation potential between gold(I) and gold(III) have shown a unique potential to unveil novel types of chemoselective and stereoselective cycloadditions involving alkynes, allenes or alkenes [24-26].

A lot of interest has been directed to the development of these cycloaddition processes in an enantioselective manner, so that the resulting cyclic products could be obtained in an optically pure fashion [27]. Herein, we describe the most relevant types of enantioselective cycloaddition reactions based on the use of carbophilic gold(I) complexes. We do not consider cycloaddition reactions in which the gold complex acts more like a conventional Lewis acid rather than by activating \( \pi \)-bonds [28-32]. The reactions included in this review are classified according to the type of key reactive gold intermediates that formally participate in the cycloaddition. Thus, we will present cycloaddition processes (i) with a gold–carbene intermediate, (ii) involving an allene activation to generate a gold–allyl cationic intermediate and, (iii) in which the proposed key reactant is a vinylgold zwitterionic species.

Review
Cycloadditions involving gold–carbene intermediates

Gold–carbene species are frequent intermediates in gold-catalyzed reactions, in particular those involving alkynes [33-37]. Gold(I) catalysts bind chemoselectively to \( \pi \)-C–C triple bonds, promoting the attack of different types of nucleophiles on these electrophilic species. Depending on the particular system, the resulting vinylgold intermediates can be externally trapped or evolve to reactive carbene species. This is the case for propargyl esters (Figure 1), as these systems usually undergo 1,2 or 1,3-acyloxy migrations in the presence of gold catalysts. Such migrations proceed via a nucleophilic intramolecular attack of the carboxy moiety on the activated alkyne. 1,2-Migration of the ester affording a gold–carbene of type A is usually preferred when a terminal alkyne is used [38-40].

Based on this concept, several groups have shown that the resulting carbenoid intermediates of type A can engage in different types of cycloaddition reactions with diverse \( \pi \)-unsaturated systems. Here, we discuss the systems for which an enantioselective variant has been developed.

In 2005, Toste and coworkers described one of the first gold-catalyzed enantioselective processes that could be formally categorized as a [2 + 1] cycloaddition. In particular, they showed that it is possible to trap the intermediate gold–carbenes resulting from a 1,2-acyloxy migration in propargyl esters such as 1, with external alkenes (e.g. vinylarenes), to give cyclopropane products [41]. The racemic variant of the method, which employs \( \text{Ph}_3\text{PAuCl/AgSbF}_6 \) as a catalyst, predominantly affords \( \text{cis} \)-cyclopropane adducts of type 2, and tolerates a wide range of olefin substituents. Importantly, the authors demonstrated that the process could also be rendered enantioselective by using a chiral bisgold complex derived from DTBM-Segphos (Au1). High or even very high levels of enantioselectivity could be achieved when the propargyl system features sterically demanding esters such as pivaloates, or the alkene component presents large aromatic substituents. In all these cases the reaction afforded the \( \text{cis} \) isomer with high diastereoselectivity. Moreover, the enantioselective cyclopropanation was not limited to arylated olefins (e.g. styrenes), but allyltrimethylsilane also participated in the process, producing the corresponding silylmethyl cyclopropane as a 5:1 mixture of \( \text{cis:trans} \) isomers with a good 78% ee (Scheme 1).

In 2009, the same group extended the utility of this asymmetric cyclopropanation reaction to an intramolecular process that allows the enantioselective synthesis of polycarbocyclic products embedding seven or eight-membered rings [42]. Curiously, the catalytic system based on DTBM-Segphos, which was particularly successful in the abovementioned intermolecular cases, only provided good enantioselectivities in the case of systems affording products with seven-membered rings (3, \( n = 0 \), Scheme 2). For the eight-membered counterparts, the authors found that a related bisphosphine-gold catalyst, Xylyl-Binap(AuCl)\( _2/\text{AgSbF}_6 \) was more efficient, facilitating good yields of the corresponding products and enantioselectivities.
between 75 and 92%. In these cases, the bulky pivaloate at the propargylic position led to lower enantioselectivities than a less congested acetate group, showcasing that a fine-tuning of the catalyst and substrate is required to achieve excellent enantioselectivities.

More recently, Nevado and co-workers have shown that propargyl acetates \textsuperscript{4} react with 1,3-dienes in the presence of a gold catalyst to give good yields of cycloheptadiene products of type \textsuperscript{5}; thus the process could be formally considered as a \([4 + 3]\) annulation. A possible mechanism would involve a gold-mediated 1,2-acyloxy migration of the propargyl ester to generate a gold–carbene species \textsuperscript{III} which cyclopropanates a C–C double bond of the diene to form a \textit{cis}-cyclopropane intermediate \textsuperscript{IV}. A subsequent gold-catalyzed Cope rearrangement through a boat-like transition state would deliver the \textit{cis}-2,3-disubstituted cycloheptenyl acetates of type \textsuperscript{5} (Scheme 3) \textsuperscript{[43]}.

Although the process was essentially developed in a racemic fashion, by using \textbf{Au3}/AgSbF\textsubscript{6} \textsubscript{6} or a combination of \textbf{Au4} and (PhO)\textsubscript{3}PAuSbF\textsubscript{6} (Scheme 3), the authors also demonstrated the feasibility of an enantioselective variant. Thus, treatment of pivaloate \textsuperscript{4a} with 6,6-dimethyl-1-vinylcyclohexene in the
Scheme 3: Gold-catalyzed cyclohepta-annulation cascade.

Scheme 4: Application to the formal synthesis of frondosin A.

presence of the chiral gold catalyst (S)-MeO-DTBM-Biphep(AuCl)_2/AgSbF_6, followed by in situ hydrolysis, allowed the construction of the basic bicarbocyclic core of frondosins (for example, 5a), in 68% yield and 90% ee (Scheme 4). Since this bicyclic enone was previously elaborated into frondosin A and B, the approach represented a streamlined formal enantioselective synthesis of both molecules.

Analogous to other transition metals from groups eight to eleven, gold has also demonstrated to be an efficient promoter of intermolecular carbene transfer reactions from diazo compounds to unsaturated systems such as alkenes or alkynes, resulting in cyclopropanation processes [44,45]. The development of an enantioselective variant of this type of reactions remained elusive until very recently, when Davies and co-workers reported a highly enantioselective cyclopropenation of internal alkynes 6 with aryl diazoacetates 7 [46]. In some cases the complex DTBM-Segphos(AuCl)_2 (12%)/AgSbF_6 (10%) provided the best performance. For most of the substrates, however, the chiral digold cationic complex Xyllyl-Binap(AuCl)_2/AgSbF_6 provided higher enantiomeric excesses and better yields of the desired cyclopropanes 8 (Scheme 5).

In 2013, Zhou and co-workers reported another example of a highly enantioselective gold-catalyzed cyclopropanation reaction by using diazo compounds as a source of gold carbenes. In
particular, the authors demonstrated that the chiral bisgold complex Au6, derived from the spiroketal bisphosphine ligand, was a very efficient promoter of the cyclopropanation between donor–acceptor diazooxindoles such as 9 and a broad range of alkenes (Scheme 6) [47]. The resulting spirocyclopropyloxindoles 10, which are obtained in excellent yields and enantioselectivities, are appealing structures from a medicinal point of view. The scope of the alkene is quite remarkable, since not only monosubstituted and 1,1-disubstituted olefins participated in the cyclopropanation, but also 1,2-disubstituted alkenes (cis or trans), which previously failed with other chiral transition metal catalysts, providing excellent yields and very good levels of enantioselectivity.

Cycloadditions initiated by activation of allenes

Gold(I) catalysts can efficiently activate allenes in a highly chemoselective way, triggering the formation of allenylation species. Different structures have been proposed to represent these gold-activated allene complexes, including η2-complexes.
Scheme 7: Gold-catalyzed enantioselective [2 + 2] cycloadditions of allenes.

In 2007, Toste and coworkers described an intramolecular [2 + 2] cycloaddition of allenes by using gold catalysts [49]. The proposed mechanism is based on the generation of a gold(I)-activated allene, which undergoes a cyclization to give a new carbocationic species of type VI (Scheme 7) [50,51]. A subsequent ring closure provides the observed bicyclo[3.2.0] systems of type 12, featuring a four-membered carbocycle. These reactions, which are efficiently promoted by Ph₃PAuBF₄ in their racemic variants, could be performed in a highly enantioselective manner with gold catalysts containing a DTBM-Segphos ligand. Enantioselectivities ranged from 54 to 96%, and seem to be highly dependent on the tether that links the allene and the alkene moieties. Thus, the reaction proved to be efficient for substrates containing tethers with geminal diesters, whereas those containing N-tosyl-based tethers led to significantly lower enantioselectivities. However, the same group more recently demonstrated that a chiral phosphoramidite-gold complex, such as Au7, could eventually solve this limitation, leading to a complementary reactivity to that exhibited by DTBM-Segphos(AuCl)₂/AgBF₄ in terms of substrate scope, and affording enantioselectivities up to 97% (Scheme 6) [51]. Additionally, Fürstner and co-workers have also demonstrated that a phosphoramidite-gold complex like Au8, containing an acyclic Taddol-based backbone, was also an excellent catalyst to perform the same type of [2 + 2] cycloadditions of allenes 11 [52,53]. This catalyst performs equally...
well with carbon-based and nitrogen-based tethers, and excellent levels of asymmetric induction were obtained from a set of representative examples, including those with structural modifications at the allene and alkene sites (Scheme 7).

Early in 2008, our group demonstrated the possibility of using gold-activated allenes as allyl cation surrogates capable of participating in concerted [4C(4π) + 3C(2π)] cycloadditions with conjugated dienes [54], a process related to the classical oxyallyl cation [4 + 3] cycloadditions [55-57]. An initial screening demonstrated that PtCl₂ was a good catalyst for promoting these intramolecular [4C + 3C] cycloadditions [54]. Further studies revealed that the scope of the methodology could be significantly broadened by using a gold catalyst such as Au₉/AgSbF₆ [58]. In general, the reactions are completely diastereoselective, affording bicyclo[5.3.0]decanec products (14 and/or 14') that result from an exo-like approach of the allyl cation to the diene. Curiously, by using a gold(I) catalyst bearing a π-acceptor phosphite ligand, such as Au₁₀/AgSbF₆, allenedienes disubstituted at the distal position of the allene lead to products formally arising from a [4 + 2] cycloaddition process (Scheme 8, b) [59,60]. Several experimental data as well as theoretical calculations suggested that both cycloadducts, 14 and 15, arise from the same intermediate, the cycloheptanyl metal–carbene species VIII, which might evolve through a 1,2-hydrogen shift to give the seven-membered carbocycles 14 (Scheme 8, a), or by a ring-contraction process to give the cyclohexenyl products (Scheme 8, b) [60-64]. Therefore, the ligand at gold, as well as the type of substituents at the allene terminus, determine the fate of this carbene and hence the formation of the [4 + 3] (14) or [4 + 2] (15) cycloadducts.

The development of enantioselective versions of these two cycloadditions was actively pursued by several groups. The electronic similarity between phosphites and phosphoramidites suggested that chiral gold complexes of these highly modular monodentate ligands [65] could be good candidates to promote enantioselective variants of the [4 + 2] cycloaddition (Scheme 9, R¹, R² = alkyl groups). This turned out to be the case and, gratifyingly, we showed that it is possible to perform highly enantioselective allenediene [4 + 2] cycloadditions by using gold complexes derived from a bulky phosphoramidite equipped with anthracenyl substituents at the Binol ortho-positions (Au₁₁, Scheme 9) [60]. Independently, Toste and co-workers reported that the related phosphoramidite–gold complex Au₁₂, and the chiral gold catalyst Au₁₃, derived from a C₃-symmetric phosphite [66], were also able to induce excellent enantioselectivities in these [4 + 2] cycloadditions [67]. Moreover, Fürstner and co-workers also showed that the Taddol-based phosphoramidite–gold complex Au₈, which was effective in the [2 + 2] cycloadditions of allenes, was also able to induce good enantioselectivities in these higher order annulations (Scheme 9) [52].

Although π-acceptor ligands, such as phosphites or phosphoramidites favor the formation of the [4 + 2] adduct of type 15,
Scheme 9: Gold-catalyzed enantioselective [4 + 2] cycloadditions of allenedienes.

DFT calculations indicated that the activation barriers for the ring-contraction process leading to these six-membered systems, and the 1,2-H shifts that retain that seven-membered ring, are quite similar [60]. Therefore, it seemed plausible that this type of chiral catalysts could also provide an enantioselective entry to the seven-membered adducts of type 14, provided that the ring-contraction route could be slightly deactivated. The viability of this hypothesis was validated by Mascareñas, López and co-workers, demonstrating that terminally monosubstituted allenes, which provide carbene intermediates that are less prone to undergo a ring contraction (VIII, Scheme 8), react with phosphoramidite–gold catalyst Au11/AgSbF6 to afford optically active, synthetically relevant bicyclo[5.3.0]decadiene and bicyclo[5.4.0]undecadiene skeletons 14 with good yields, complete diastereocontrol and excellent enantioselectivities (Scheme 10) [68]. The scope of this method, which constituted the first highly enantioselective intramolecular [4C + 3C] cycloaddition promoted by a transition metal complex, encompasses internally monosubstituted allenes, as well as disubstituted counterparts, offering a direct entry to 5,7 bicyclic systems including those with all-carbon quaternary stereocenters at the ring fusion.

In contrast to the intramolecular counterpart, gold-catalyzed intermolecular cycloadditions of allenes have been scarcely studied. However, significant progress has been made in the last 4 years. While the development of an intermolecular [4 + 3] cycloaddition between allenes and dienes remains elusive, neither in a racemic nor enantioselective fashion [69], it has been shown that allenamides [70] or allenyl ethers [71] participate as two-carbon atom components in several gold-catalyzed [4 + 2] cycloadditions with dienes. The racemic version of the reaction between allenamides and dienes, which is efficiently promoted by AuCl or the cationic gold catalyst Au9/AgSbF6, was translated into a enantioselective version by using a novel chiral gold complex Au14, featuring a triazole unit embedded in a rigid axially chiral cyclic frame (Scheme 11) [72]. The catalyst generated from Au14 and AgNTf2 was able to promote the [4 + 2] cycloaddition between allenamides 16 and conjugated dienes 17 with total regio- and stereoselectivity and excellent enantioselectivity. The method provides a versatile and practical approach to a variety of optically active cyclohexene products like 18. Importantly, the scope of the asymmetric process is even wider than that of the racemic reaction [70], allowing the construction of six-membered adducts with up to three new
stereogenic centers with complete diastereoselectivity and enantioselectivities of up to 91% ee (R\textsubscript{1}, R\textsubscript{2} = Me, R\textsubscript{4} = Ph, Scheme 11). With regard to the mechanism, it has been proposed that the activation of the allenamide by the gold catalyst provides a gold–allyl cationic species of type IX, which is the species undergoing the cycloaddition process with the diene [73].

Simple alkenes do also react with gold-activated allenamides to provide cyclobutane products, formally resulting from a [2 + 2] cycloaddition. Thus, independent investigations by the groups of Mascareñas, González and Chen revealed that the gold-catalyzed cycloaddition between an allenamide and an appropriate alkene (e.g., enamide, enol ether or vinylarene) provides a variety of cyclobutanic systems in excellent yields. The optimum catalysts for the racemic processes include a phosphite–gold complex Au\textsubscript{10} and a biaryl-di-tert-butylphosphine–gold complex (Au\textsubscript{3}) [74-76]. More recently, González and co-workers accomplished the enantioselective version of these annulations between sulfonyl allenamides and...
vinylarenes, providing a straightforward entry into optically active cyclobutanes [77]. Several chiral phosphoramidite–gold complexes, such as (S,R,R)-Au7, (S,R,R)-Au15 and (R,R,R)-Au16, derived from Siphos, Binol and Vanol, respectively, provided excellent enantioselectivities, displaying useful complementarity in some of the cases. Importantly, the method also allowed the preparation of cyclobutanes containing challenging quaternary carbon centers (Scheme 12).

From a mechanistic point of view, these [2 + 2] cycloadditions, either in racemic or asymmetric versions, have been proposed to proceed through a stepwise cationic pathway consisting of an initial activation of the allene to provide an Au–allyl cationic species, followed by a regioselective interception by the alkene to give a second cationic intermediate (X, Scheme 13) [73]. The substituent at the alkene (R1, Scheme 13), either an aryl, nitrogen or oxygen-group, plays a key role in the stabilization of this intermediate and therefore facilitates the overall process. Finally, a ring-closing process through attack of the vinylgold species to the stabilized carbocation yields the cyclobutane system and regenerates the catalyst.

In view of this mechanistic proposal, Mascareñas and López recently developed a gold-catalyzed cascade cycloaddition between allenamides and carbonyl-tethered alkenes, including an enantioselective variant, that provides synthetically appealing oxa-bridged seven, eight and even nine-membered rings (22, Scheme 14) [78]. The cascade process relies on the interception of intermediates of type X by an intramolecular carbonyl group, followed by the ring closing of the resulting oxonium intermediate XI. The reaction occurs at low temperatures by using only 1 mol % of a phosphite-based gold catalyst. The enantioselective version, which is catalyzed by the DTBM-Segphos complex Au1/AgNTf2, or the phosphoramidite–gold complex (S,R,R)-Au16/AgNTf2, provides the corresponding cycloadducts with good or high enantioselectivities (Scheme 14). The method constituted the first direct catalytic and enantioselective entry to oxygen-bridged eight-membered carbocycles and one of the few methods that affords optically active cyclooctanes by means of a catalytic enantioselective process.

Also recently, Chen and co-workers demonstrated that gold-activated allenamide species can participate in [3 + 2] cycloadditions with azomethine imines or nitrones under catalysis with Ph3PAuCl/AgOTf or Ph3PAuCl/AgNTf2 [79,80]. Moreover, for the latter cycloaddition with nitrones, the authors reported an enantioselective variant by using chiral phosphoramidite–gold complexes. In these cases, the binol-derived complexes, with aryl substituents at the 3 and 3’ positions, turned out to be the optimal systems, providing the corresponding 4-alkylideneoxazolidine derivatives in high yields and excellent enantioselectivities. The highest enantioselectivities were obtained with (R,R,R)-Au17 and (R,S,S)-Au18, which include 9-phenanthryl or 4-biphenyl units in these binol ortho-positions, respectively (Scheme 15). Further derivatization of the products led to enantio-enriched 1,3-aminoalcohols.
Other reactions involving zwitterionic alkenyl-gold intermediates

The gold-bound allyl cation species generated from allenes could be formally viewed as 1,2 or 1,3-zwitterionic cycloaddition components. In a recent paper, Liu and co-workers demonstrated that 1,6-enynes like 24 when treated with appropriated gold complexes lead to related 1,4-zwitterionic homologs that can be efficiently intercepted by nitrones in a formal [4 + 3] cycloaddition.
Enantioselective formal [4 + 3] cycloadditions leading to 1,2-oxazepane derivatives.

The resulting 1,2-oxazepane derivatives are isolated as single diastereoisomers with high enantioselectivities (84–95% ee) [81]. Optimal conditions for the enantioselective variant of the process involved the use of the chiral gold complex Au5 (3.8 mol %), derived from MeO-DTBM-Biphep, in combination with AgOTf. The requirement of equimolar amounts of the silver salt and the bisgold complex suggests that only one Au–Cl bond remains intact in the gold catalyst (Scheme 16). From a mechanistic point of view, the authors proposed that the intermediate species can be viewed as either a cyclopropylgold carbene XII or as a zwitterionic alkenylgold derivative XII', the latter being the species that participates in the cycloaddition to the nitrone, probably in a concerted pathway, and thus providing the corresponding products with high levels of stereoselectivity [82,83].

Previously, in 2009, J. Zhang had reported a gold(I)-catalyzed 1,3-dipolar [3 + 3] cycloaddition between 2-(1-alkynyl)-2-alken-1-ones and nitrones. The reactions provide fused heterobicyclic oxazine derivatives of type 27 with good yields and excellent regio- and diastereoselectivities. The racemic series, promoted by Ph3PAuCl/AgOTf as a catalyst [84], was translated into an enantioselective version by using any of the chiral bisgold complexes derived from (R)-C1-Tunephos (Au19) or (R)-MeO-DTBM-Biphep (Au5) (Scheme 17) [85]. From a mechanistic point of view, the authors proposed the generation of a zwitterionic furanylgold complex of type XIII by a gold-promoted intramolecular cyclization process. This key intermediate is then trapped by the nitrone to afford XIV, which eventually evolves to the product by an intramolecular cyclization (Scheme 17).

Finally, the same group recently reported a related reaction of 1-(1-alkynyl)cyclopropyl ketones such as 28, by means of a gold(I)-catalyzed asymmetric [4 + 3] cycloaddition. In this article, the authors demonstrated that a chiral gold catalyst generated from MeO-DTBM-Biphep was able to promote the [4 + 3] cycloaddition between ketone 28 and the nitrone 29, to afford the corresponding 5,7-fused bicyclic furo[3,4-d][1,2]oxazepine 30 in good yield, high diastereoselectivity (dr 11:1) and excellent 91% ee (Scheme 18) [86-88]. However, the extension of this method to 1-(1-alkynyl)cyclopropyl ketones and nitrones others than 28 and 29 remains to be demonstrated.

**Conclusion**

In the last years there have been remarkable advances in the development of enantioselective gold(I)-catalyzed cycloadditions. Although the area is still in its infancy, there is enough evidence to predict that the number of examples will steadily increase in the near future. It would be highly desirable to have more information on the precise factors that govern the enantioselectivity process, as this will facilitate the design of new asymmetric processes.
Scheme 17: Enantioselective gold(I)-catalyzed 1,3-dipolar [3 + 3] cycloaddition between 2-(1-alkynyl)-2-alken-1-ones and nitrones.

Scheme 18: Enantioselective [4 + 3] cycloaddition leading to 5,7-fused bicyclic fur[3,4-d][1,2]oxazepines.

**Acknowledgements**

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**References**

See for a review covering transition metal catalyzed enantioselective cycloadditions.

Recent theoretical computations indicate that the intermediate of type VI could be better described as VI', where the gold center establishes carbocations.

Many Au-carbene species can also be understood as Au-stabilized carbocations.

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50. Recent theoretical computations indicate that the intermediate of type VI, could be better described as VI', where the gold center establishes a stabilizing electrostatic interaction with the benzyl carbocation. See reference [51].
84. Two isolated examples for related intramolecular enantioselective [4 + 2] cycloadditions.
88. For the racemic versions of the previous cycloadditions (reference [86]).

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Synthetic scope and DFT analysis of the chiral binap–gold(I) complex-catalyzed 1,3-dipolar cycloaddition of azlactones with alkenes

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Abstract

The 1,3-dipolar cycloaddition between glycine-derived azlactones with maleimides is efficiently catalyzed by the dimeric chiral complex [(S₅)-Binap·AuTFA]₂. The alanine-derived oxazolone only reacts with tert-butyl acrylate giving anomalous regiochemistry, which is explained and supported by Natural Resonance Theory and Nucleus Independent Chemical Shifts calculations. The origin of the high enantiodiscrimination observed with maleimides and tert-butyl acrylate is analyzed using DFT computed at M06/Lanl2dz//ONIOM(b3lyp/Lanl2dz:UFF) level. Several applications of these cycloadducts in the synthesis of new proline derivatives with a 2,5-trans-arrangement and in the preparation of complex fused polycyclic molecules are described.

Introduction

The synthesis of α-amino acids employing an α-amino carbonyl template constitutes the most straightforward route to introduce the α-side chain [1]. As a valid example, oxazol-5-(4H)-ones (azlactones) are suitable heterocycles to perform this C–C bond generation based strategy affording both quaternized and non quaternized α-amino acid derivatives [2-5]. The preparation of azlactones is very simple and their reactivity is very diverse due to their functional groups [2-5]. Many enantiose-
lective and/or diastereoselective processes have been focussed on the elaboration of enantiomerically enriched new non-proteinogenic \(\alpha\)-amino acids, such as Michael-type additions \([6,7]\), transition metal-catalyzed allylations \([8]\), Mannich-type additions \([9]\), aldol-type reactions \([10]\), and for other different purposes \([11-17]\). These substrates can be easily transformed in \(\text{m"unchnrones}\), which are potential 1,3-dipoles, after deprotonation and imine-activation with a chiral Lewis acid. Despite of the easy access to this mesoiinic heterocycles their enantioselective cycloadditions with electrophilic alkenes have not been exploited. Toste’s group published an efficient 1,3-dipolar cycloaddition \((1,3-\text{DC})\) between alanine, phenylalanine and allylglycine derived azlactones with maleimides and acrylates employing dimetallic \((S)\)-Cy-Segphos(AuOBz)\(_2\) complex 1 as a catalyst \((2 \text{ mol} \%)\) in the absence of base (Figure 1) \([18,19]\).

This catalytic system was very effective but the reactions performed with \((R)\)-Binap(AuOBz)\(_2\) (Figure 1) as catalyst offered a very low enantioselection, for example, a 8% ee was achieved in the 1,3-DC of alanine derived azlactone and \(N\)-phenylmaleimide (NPM).

Numerous gold-catalyzed transformations employing mild reaction conditions appeared during the last twelve years \([20-22]\). Initially, coordination arrangements of chiral gold complexes avoided high enantiodiscriminations but, recently, it has been demonstrated that chiral bis-gold complexes type 2 (Figure 1) are very efficient in asymmetric catalysis \([23,24]\). The high amount of gold per mole of catalyst and the chiral ligand itself make these processes somehow expensive.

The relative lower cost of chiral privileged ligand Binap (versus Cy-Segphos) and the good results obtained in the 1,3-DC of \(\alpha\)-imino esters and electrophilic alkenes using the bis-gold(I) complex 3 (where the gold atom:ligand ratio is 1:1, Figure 1) \([25-27]\) inspired us to test it in this azlactone involved cycloaddition. Previous experience in the 1,3-DC between imino esters and electrophilic alkenes revealed that the dimeric chiral gold complex 3 resulted to be unique efficient catalyst in terms of enantioselection rather than the bis-gold complex 4 \([25-27]\). This data is in a clear contrast to the previously mentioned result for the reactivity of azlactones \([18,19]\). In this work we describe a more extended study than the analogous one described in a preliminary communication \([28]\) concerning the catalytic activity of complexes 3 and 4 in the 1,3-DC of oxazolones with electrophilic alkenes. Here, a deep DFT analysis and the application of other computational experiments (NRT, NICS) were compared to the experimentally observed results in order to clarify the enantio- and anomalous regioselectivity.

**Results and Discussion**

Initially, the synthesis of oxazolones 5 was accomplished under mild reaction conditions by mixing \(N\)-acyl-\(\alpha\)-amino acid derivatives in the presence of dehydrating agents such as carbodiimides \([2-5]\). Gold(I) complexes 3 and 4, identified and characterized by Puddephatt’s group \([X = \text{trifluoroacetate (TFA)}]\) \([29-31]\), were obtained from NaAuCl\(_4\) and dimethyl sulfide and the corresponding amount of the chiral Binap ligand. Finally, the anion interchange was promoted by the addition of an equivalent amount of silver(I) salt. These complexes were used immediately after filtration through a celite path. Particularly, complexes 3 and 4 \((X = \text{TFA})\) could be isolated in 96 and 89% yield, respectively, but other gold(I) complexes (see Table 1) with different anions were generated in situ and used as catalysts in the same solution.

Oxazolone derived from glycine 5a was allowed to react with \(N\)-phenylmaleimide (NPM) at room temperature \((25 \degree C \text{ approx.})\) using 5 mol % of the chiral catalytic complex and 5 mol % of base (Scheme 1). After completion, a large excess of trimethylsilyldiazomethane was added to obtain the methyl ester of intermediate carboxylic acid 6a (30 min). Compound 7aa was obtained diastereoselectively \((\text{>98.2, by } ^{1}H \text{ NMR spectroscopy})\) after purification and its absolute configuration was established according to the retention times of signals observed after HPLC analysis employing chiral columns and by comparison with the previously reported data \([18,19]\).
Scheme 1: 1,3-DC of azlactone 5a and NPM.

Using this model reaction (Scheme 1), we tested the dimeric gold complex [(Sₐ)-Binap·AuTFA]₂ according to the previous experience obtained in the 1,3-DC involving imino esters and electrophilic alkenes and the reaction conditions employed by Toste’s group [18,19]. The use of fluorobenzene as solvent or co-solvent did not afford neither good conversions nor enantioselectivities, even working with the dimetallic complex 4 (X = TFA) (Table 1, entries 1–4). After the evaluation of the influence of the solvent, we concluded that toluene was the most appropriate solvent for these reactions (Table 1, entries 5–9), being the chemical yield high (90%) and the enantiodiscrimination excellent (99% ee). The presence of triethylamine as base is crucial for this transformation, it ensures both of the high conversions and enantioselections (Table 1, entries 11–14). Other different bases such as DBU, and DIPEA did not improve the result achieved by the analogous reaction carried out with triethylamine (Table 1, entries 12 and 13). Again, the presence of the chiral catalytic complex 4 (X = TFA) did not give the expected results (Table 1, entries 6 and 10). The enantiomerically pure form of 7aa with opposite absolute configuration was isolated by working in the presence of [(Rₐ)-Binap·AuTFA]₂ complex (Table 1, entry 11). Surprisingly, no reaction was observed in the presence of silver(I) complex (Sₐ)-Binap·AgTFA (Table 1, entry 15). In this section the effect of

**Table 1: Optimization of the 1,3-dipolar cycloaddition of 5a and NPM using chiral complexes.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/X²</th>
<th>Solvent</th>
<th>Base</th>
<th>Yield¹ (%)</th>
<th>ee² (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Sₐ)-3/TFA</td>
<td>PhF</td>
<td>Et₃N</td>
<td>&lt;50</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>(Sₐ)-4/TFA</td>
<td>PhF</td>
<td>Et₃N</td>
<td>___d</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>(Sₐ)-3/TFA</td>
<td>PhF-THF</td>
<td>Et₃N</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>4</td>
<td>(Sₐ)-4/TFA</td>
<td>ThF</td>
<td>Et₃N</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>5</td>
<td>(Sₐ)-3/TFA</td>
<td>ThF</td>
<td>Et₃N</td>
<td>76</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>(Sₐ)-4/TFA</td>
<td>DCM</td>
<td>Et₃N</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td>(Sₐ)-3/TFA</td>
<td>Et₂O</td>
<td>Et₃N</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>(Sₐ)-4/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>10</td>
<td>(Rₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>90</td>
<td>-99</td>
</tr>
<tr>
<td>11</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>DBU</td>
<td>70⁹</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>DIPEA</td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>none</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>14</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>15</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>90</td>
<td>64</td>
</tr>
<tr>
<td>16</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>___d</td>
<td>___d</td>
</tr>
<tr>
<td>17</td>
<td>(Sₐ)-3/TFA</td>
<td>PhMe</td>
<td>Et₃N</td>
<td>91</td>
<td>74</td>
</tr>
</tbody>
</table>

¹The gold catalysts were freshly generated in situ. ²After flash chromatography (silica gel). The observed exo:endo ratio was always >98:2 (¹H NMR). ³Determined by using analytical chiral HPLC columns (Daicel, Chiralpak AS). ⁴Not determined.
different anions of the metal complex was studied as well. In contrast with the negligible reaction observed when poor basic anion, such as perchlorate, was essayed (Table 1, entry 16), anions with basic character such as acetate or benzoate, incorporated to the chemical structure of the gold(I) catalyst, promoted the enantioselective reaction although with lower efficiency (Table 1, entries 17 and 18) [32].

The scope of the reaction was next surveyed. Firstly, azlactone 5a was allowed to react with several maleimides (Scheme 2, and Table 2, entries 1–10). NPM and 4-acetoxyphenylmaleimide were the best entries of this series affording almost enantiomerically pure bicyclic products 7aa and 7ae, respectively (Table 2, entries 1 and 8). N-Substituted methyl, ethyl and benzylmaleimides did not afford compounds 7 with so high enantioselections. Then, a lower temperature (−20 °C) was attempted but the increment of ee for N-methyl- and N-ethyl-maleimides was not very noticeable (Table 2, entries 2, 3 and 4, 5, respectively). Nevertheless, a gap of 21 units of ee was achieved in the case of the reaction involving N-benzylmaleimide (Table 2, compare entries 6 and 7). In the case of N-(4-bromophenyl)maleimide a good enantioselection was observed when the reaction was run at −20 °C furnishing enantiomerically pure 7af in good chemical yields (Table 2, entries 9 and 10). The variation of the arene substituent of the azlactones promoted also excellent to good enantioselectioens in compounds 7ba and 7ca (Table 2, entries 11 and 12). Even working with an heteroaromatic substituent, such as 2-thienyl, compound 7da was isolated in 95% ee (Table 2, entry 13).

When benzyamine was employed as alternative quenching reagent to trimethylsilyldiazomethane, the generation of the corresponding N-benzylamide in 76% yield and 96% ee was achieved after 17 h at 25 °C (Scheme 3) [18,19].

The study of the key points of the enantiodiscrimination step and mechanism for the 1,3-DC of azlactone 7aa and NPM can be originated by the presence of a more active homochiral dimer catalyst (S_S)-3 (X = TFA) with a lower TS energy with all the reaction components, rather than the corresponding heterochiral ones and even lower than homochiral dimer catalyst (R_R)-3 (X = TFA). The clear positive non-linear effects (NLE) described in Figure 2 supported this hypothesis [33].

![Scheme 2: General 1,3-DC between azlactones 5 with maleimides.](image)

**Table 2**: 1,3-Dipolar cycloaddition of azlactones 5a with maleimides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar, 5a</th>
<th>R</th>
<th>Product 7</th>
<th>Yieldb (%)</th>
<th>eec (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph, 5a</td>
<td>Ph</td>
<td>7aa</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Ph, 5a</td>
<td>Me</td>
<td>7ab</td>
<td>90</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Ph, 5a</td>
<td>Me</td>
<td>7ab</td>
<td>79</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Ph, 5a</td>
<td>Et</td>
<td>7ac</td>
<td>87</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>Ph, 5a</td>
<td>Et</td>
<td>7ac</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>Ph, 5a</td>
<td>Bn</td>
<td>7ad</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>Ph, 5a</td>
<td>Bn</td>
<td>7ad</td>
<td>83</td>
<td>71</td>
</tr>
<tr>
<td>8</td>
<td>Ph, 5a</td>
<td>4-(AcO)C6H4</td>
<td>7ae</td>
<td>90</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>Ph, 5a</td>
<td>4-BrC6H4</td>
<td>7af</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>Ph, 5a</td>
<td>4-BrC6H4</td>
<td>7af</td>
<td>84</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC6H4, 5b</td>
<td>Ph</td>
<td>7ba</td>
<td>78</td>
<td>99</td>
</tr>
<tr>
<td>12</td>
<td>4-ClC6H4, 5c</td>
<td>Ph</td>
<td>7ca</td>
<td>83</td>
<td>98</td>
</tr>
<tr>
<td>13</td>
<td>2-Thienyl, 5d</td>
<td>Ph</td>
<td>7da</td>
<td>80</td>
<td>95</td>
</tr>
</tbody>
</table>

aThe gold catalyst was freshly generated in situ. bAfter flash chromatography (silica gel). The observed exo:endo ratio was always >98:2 (1H NMR).

cDetermined by using analytical chiral HPLC columns (Daicel, Chiralpak AS). dReaction run at −20 °C.
Next, we studied the reaction between the oxazolone 5aa and NPM catalyzed by [(Sa)-Binap-AuTFA]2. In previous works, we have demonstrated that the stereoselectivity of the 1,3-DC employing chiral metallic Lewis acids arises from the blockage of one of the prochiral faces [34]. Starting from this selected conformation of the catalyst, our results show that the (2R,5R) prochiral face is less hindered than the other prochiral face in the most stable conformation of [(Sa)-Binap-Au]2-5aa complex (Figure 3). As expected, the existence of dimeric gold units is crucial in the blockage of one of the prochiral faces, and therefore, in the stereochemical outcome of the final cycloadducts [26,27].

Refined computational results showed the exo-approach [35] is the preferred one. In this analysis, only that approach was considered. The less energetic computed TS are depicted on
Figure 4 (see Supporting Information File 1 for further information of additional TS’s).

The computed transition structures correspond to concerted but highly asynchronous cycloadditions (Figure 4). Our calculations show that there is a different overlap between the accessible-solvent surface of the catalyst and the one of the incoming dipolarophile. That implies an increase of the 4e− Pauli repulsion between the reactives in TS_{NPM}^{down} compared to TS_{NPM}^{up}, and thus an increase of the activation barrier. Moreover, lower energy to deform the initial ylide (strain energy) is required in the latter TS. With that energetic difference, the computed ee is about 99%, in good agreement with the experimental results (Table 2, entry 1).

The complete reaction path of the cycloaddition process is shown in Scheme 4. We do not study computationally the second synthetic step, namely the ring-opening of the tricyclic-cycloadduct, because that step has no relevance in the stereochemical outcome of the reaction.

**Figure 4**: Main geometrical features and relative Gibbs free energies (in kcal mol\(^{-1}\)) of the less energetic transition states associated with the 1,3-DC of 5aa and NPM catalyzed by (S\(_a\))-Binap gold dimers computed at M06/Lanl2dz//ONIOM(b3lyp/Lanl2dz:UFF) level of theory. High-level and low level layers are represented as ball and stick and wireframe models, respectively. Distances are in Å. Blue and purple surfaces represent the solvent-accessible surface of the catalyst and NPM with a probe radius of 1.9 Å.

**Scheme 4**: Reaction Gibbs free energy associated with the 1,3-DC of 5aa and NPM catalyzed by (S\(_a\))-Binap gold dimers computed at M06/Lanl2dz//ONIOM(b3lyp/Lanl2dz:UFF) level of theory.
We also studied the last step of the catalytic cycle that ensures the recovery of the catalyst obtaining a favourable Gibbs energy of $-55.3$ kcal mol$^{-1}$ (Scheme 5).

No chemical reaction occurred when 5a was combined with other dipolarophiles such as fumarates, maleates, vinyl phenyl sulfone, trans-1,2-bis(phenylsulfonyl)ethylene, chalcone, crotonaldehyde and cinnamaldehyde at the same reaction conditions [36]. Another drawback was the poor reactivity observed when $\alpha$-substituted azlactones were used as starting material in the named reaction with NPM. However, the alanine-derived 4-methyloxazole-5-one 10, surprisingly, reacted at 25 and at 0 °C with tert-butyl acrylate yielding cycloadduct 11 in good yields and moderate to good enantioselections (Scheme 6).

If we compare this result with previous ones obtained using $\alpha$-imino esters, this last diastereoselective cycloaddition exhibited an opposite regioselection. Besides, the resulting relative configuration of $\Delta^1$-pyrroline 11 is equivalent to the exo-approach of the dipolarophile when an endo-transition state was the most favourable in the gold(I)-catalyzed 1,3-DC with $\alpha$-imino esters and alkenes [37].

To gain more insight into the unexpected regioselectivity of the 1,3-DC depicted in Scheme 6, calculations within the DFT framework were performed. In the accepted mechanism of the metal catalyzed 1,3-DC of azomethine ylides and acrylates, the $\alpha$-carbon atom of the azomethine ylide (C2 in Figure 5) reacts with the $\beta$-carbon of the acrylate moiety, independently of the mechanism (concerted fashion or via Michael-like transition state followed by a Mannich-like ring closure in a stepwise mechanism yields the same cycloadduct) [38]. This fact is assumed to be a consequence of the unsymmetrical electron density in the 1,3-dipole moiety, being higher in the carbon in $\alpha$-position to the carboxy group (C2).

![Figure 5](image_url)  
Figure 5: (A) Schematic representation of the model gold(I) ylides. (B) HOMO of the ylides and expansion orbital coefficient values of carbon atoms 2 and 5 computed at HF/Lanl2dz level of theory. Hydrogen atoms are omitted for clarity. (C) Most stable Lewis structures of the ylides obtained with the Natural Resonance Theory (NRT) analysis.
Initially, a model azomethine ylide derived from oxazolone 10 was considered (Figure 5). Moreover, an acyclic w-shaped ylide analogue (Ylide-II) was also studied as a reference. We chose this latter 1,3-dipole because it is known that with this kind of reactive species, the reaction yields cycloadducts possessing a standard regioselectivity in 1,3-DC with acrylates [38]. Since our goal was to understand the origins of the unusual regioselectivity observed in the reaction between dipoles of type Ylide-I with acrylates, trimethylphosphine was coordinated directly to the gold(I) atom in our model (Figure 5).

Analysis of atomic expansion coefficients of the HOMO of Ylide I reveal no significant difference between the azomethine ylides reported in Figure 5. However, Natural Resonance Theory Analysis (NRT) [39-41] shows that the negative charge in the Lewis structure of Ylide I is mainly placed on C5. In the case of Ylide II, this negative charge is placed on the oxygen of the carboxy group instead. The importance of these electronic distributions was verified by Nucleus Independent Chemical Shifts (NICS) calculations in the ring point of the oxazoline [42]. The NICS value of −7.3 ppm pointed to the aromaticity of that ring in Ylide I. These results explain the existence of different regioselectivities for both ylides.

Following the same calculation patterns previously shown for the reaction with NPM, the results of the main geometrical features an relative Gibbs free energies were determined for the approach of the gold(I) complex-azlactone 10 to tert-butyl acrylate (Figure 6).

In order to have a complete view of the reaction mechanism, all transition structures corresponding to the endo- or exo-approaches of the acrylate moiety as well as possible regiochemistry of the selected 1,3-DC, were considered. The main geometrical features of the less energetic transition structures are depicted in Figure 7.

Our calculations show that the less energetic transition structure associated with the 1,3-DC of 10 and tert-butyl acrylate is TS₁₁exo (Figure 7), is in good agreement with the experimental results in which a high ee of the corresponding stereoisomer was observed. The formation of the enantiomer (TS₁₁endo) was found to have an activation barrier of 4.5 kcal mol⁻¹ higher in energy. That difference can be a consequence of the higher strain energy necessary to deform the initial ylide. Our calculations also pointed out the stabilizing interaction of the carboxy group of the incoming acrylate and the gold atom closest to the ylide moiety, despite the long distance (dAu-C=O = 2.8 Å). In fact, the exo-approach is ca. 11 kcal mol⁻¹ lower in energy than the endo analogue (TS₁₁exo vs TS₁₁endo in Figure 7). Moreover, the a priori expected regiochemistry of the cycloaduct, in which C2–Cβ and C5–Cα are new bonds (12), was considered. In this case, TS₁₂ is 12.1 kcal mol⁻¹ higher in energy than TS₁₁exo. It is noticeable that transition structures associated with the forma-
tion of C2–Cα and C5–Cβ bonds (TS\textsubscript{11exo}, TS\textsubscript{11ent} and TS\textsubscript{11endo}) correspond to concerted but highly asynchronous cycloadditions. On the other hand, TS\textsubscript{12} is associated with a stepwise mechanism.

As possible applications of the resulting pyrrolines 7aa, it was submitted to different transformations. For example, it could be reduced to the corresponding pyrrolidines employing sodium cyanoborohydride in acidic media. In this reaction, a 1:1 mixture of 2,5-cis-pyrrolidine 13 and its 5-epimer 14 (2,5-trans) was isolated in good chemical yield (71%) (Scheme 7, reaction a). Fortunately, 5-epimer 14 (2,5-trans) was diastereoselectively generated through a 10% Pd/C-catalyzed hydrogenation using 4 atmospheres of hydrogen during three days at 25 °C.
Scheme 7: Reduction of heterocycle 7aa under different conditions.

(Scheme 7, reaction b). This trans- arrangement in molecule 14 is not very easy to built because several steps were needed using other synthetic strategies [43].

Pyrrolines also possess a typical 1,3-dipole precursor structure (azomethine ylide), so a second cycloaddition was attempted with a new equivalent of N-methylmaleimide. The reaction took place under microwave assisted heating (1 h, 75 W) using triethylamine as base and toluene as solvent at 120 °C. Polycyclic compound 15 was finally obtained in 50% yield as single diastereoisomer (Scheme 8). Despite being a solid product it was not possible to perform an X-ray diffraction analysis. Positive (CH derived from NPM with the CH derived from NMM) nOe experiments supported the drawn absolute configuration of 15.

Other different dipolarophiles were attempted to react with starting 7aa obtaining very complex mixtures including decomposed materials. In the most cases, reactions had to be refluxed for 24 h (110 °C, toluene) because microwave assisted irradiation was not as effective as occurred in the reaction with NMM. For example, the purification of the crude reaction mixture of the cycloaddition of 7aa with β-nitrostyrene afforded an overall poor yield (~28%) of a complex 4:15:10 mixture of three compounds (16, 17, and 18) (Scheme 9) [44]. The desired compound 16 was identified (almost as unique diastereoisomer) in low chemical yield (~5%) together with two pyrrole derivatives 17 (only one stereoisomer), and 18. The last compound was formed by a retro-cycloaddition of the pyrrole 7aa with elimination of NMM, which was favoured by a prolonged heating [45].

Conclusion

In this work it has been demonstrated the efficiency of the chiral [BinapAuTFA]_2 complexes in the enantioselective 1,3-DC between azlactone derived from glycine and maleimides, especially those containing a N-aromatic substituent, and between alanine derived oxazolone with tert-butyl acrylate. In the last example the regiochemistry was totally opposite to the common trend of these cycloadditions. This behaviour has been explained for the first time using NRT, NICS, whilst DFT calculations served to justify the elevated enantioselection observed in the 1,3-DC between azlactones and maleimides. The general scope is not very wide but enantioselections
obtained are quite good. Very interesting pyrrolidines with a trans-arrangement were obtained after hydrogenation of the pyrrole precursor.

Supporting Information
Description of all procedures and characterization of all new compounds, as well as computational details and coordinate tables are reported in the Supporting Information.

Supporting Information File 1
Experimental and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-280-S1.pdf]

Acknowledgements
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References
in ref. [18] and [19] the same result was obtained, but no explanation to this anomalous addition was given.

In ref. [18] and [19] the same result was obtained, but no explanation to this anomalous addition was given.

The published [4 + 2] cycloaddition of azlactones to \( \beta, \gamma \)-unsaturated \( \alpha \)-ketoesters was unsuccessfully attempted. Only a low yield of \( \alpha \)-alkylation addition product to the ketone group was detected.

The exo descriptor is referred to the approach of the two reaction components where the tert-butyl ester and carbonyl group of the azlactone are placed in oposite direction.

See for a regioselective synthesis of tetrasubstituted pyrroles by 1,3-DC from azlactones and spontaneous decarboxylation.

See for retro 1,3-DC, that has also been observed in many thermal processes.

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Abstract

Gold-catalyzed O-vinylation of cyclic 1,3-diketones has been achieved for the first time, which provides direct access to various vinyl ethers. A catalytic amount of copper triflate was identified as the significant additive in promoting this transformation. Both aromatic and aliphatic alkynes are suitable substrates with good to excellent yields.

Introduction

The past decade has witnessed the fast growth of homogeneous gold catalysis as one of the important branches in transition-metal chemistry [1-9]. The utility of cationic gold(I) complexes as π-carbophilic acids toward alkyne and allene activation renders them as essential tools in organic synthesis. Generally with the unique reactivity and mild reaction conditions, this type of transformation has found widespread applications in complex molecule synthesis [10,11]. Among those reactions, the gold-catalyzed hydration of alkynes is regarded as one of the signature reactions in the field (known as Teles hydration) [12]. This reaction usually utilized the combination of methanol and water, wherein methanol served as the nucleophile to attack the triple bond, forming the vinyl ether intermediate. This vinyl ether then collapsed to give a ketone as the final product [13-17].

A vinyl ether is a common and versatile building block in organic synthesis as well as polymer chemistry. Typical methods for the preparation of a vinyl ether involve elimination, olefination of esters, addition of alcohols to alkynes, as well as transition metal-mediated cross-coupling reactions [18]. Based on the π-carbophilicity of gold(I), the addition of alcohol to alkyne should provide direct access to the corresponding vinyl ether. However, most of the reported gold-catalyzed O-nucleophile additions to alkynes are intramolecular reactions. No general protocol for vinyl ether synthesis using gold has been
reported to date [17]. Nevertheless, there have been examples regarding the intermolecular addition of carboxylic acids [19,20], phenols [21,22] as well as phosphoric acids [23-25] to alkynes. In this context, we report a gold(I)-catalyzed O-vinylolation of 1,3-diketones with unactivated alkynes at ambient temperature.

Results and Discussion

As indicated in Scheme 1, the main challenge for the intermolecular O-nucleophile addition to alkynes is the competitive hydration side reaction. Although, theoretically, strictly anhydrous conditions shall prevent the water addition, new effective catalytic systems that can avoid the “precautionary” treatment of solvents and substrates are much more practical and highly desirable.

From literature reported examples, a gold activated water intermediate, [L-Au-(H$_2$O)]$^+$, has been proposed in helping the water addition to the alkyne besides the typical π-acid activation [12-17]. Our group has developed the 1,2,3-triazole coordinated gold complexes (TA-Au) as stable catalysts for alkyne activation in the past several years [26-30]. Considering that TA-Au complexes might have different binding ability toward water activation, we wondered whether the intermolecular O-addition could be achieved through ligand tuning. In this report, we focus on the cyclic 1,3-diketone nucleophiles due to A) the transformation is challenging and has never been reported in the past, B) vinyl ether products are highly functional materials, which can be easily extended to complex molecules through simple transformations.

1,3-Cyclohexanedione and phenylacetylene were used as the model substrates for the evaluation of various gold catalysts. As shown in Table 1, the use of Ph$_3$PAuCl/AgOTf (5%) gave an acceptable yield (59%) of the desired vinyl addition product 3a. Thermally-stable Ph$_3$PAu(TA)OTf (TA-Au, 5%) slightly improved the performance, yielding 63% of the desired product and less hydration byproduct 4. When changing the primary ligand from triphenylphosphine to a NHC, the yield slightly decreased. However, the corresponding TA-Au complexes indicated significantly improved selectivity towards the diketone addition over the hydration (Table 1, entry 4). Finally, the application of the XPhos ligand and the corresponding TA-Au complex largely promoted this reaction, giving 3a in 85% yield with

---

Table 1: Screening of gold catalysts.$^{a,b}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Au] cat.</th>
<th>2a (equiv)</th>
<th>Loading</th>
<th>Time (h)</th>
<th>Conversion of 2a (%)</th>
<th>Yield of 3a (%)</th>
<th>Yield of 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPh$_3$AuCl/AgOTf</td>
<td>1.0</td>
<td>5%</td>
<td>17</td>
<td>81</td>
<td>59</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>PPh$_3$Au(TA)OTf</td>
<td>1.0</td>
<td>5%</td>
<td>17</td>
<td>82</td>
<td>63</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>IPrAuCl/AgOTf</td>
<td>1.0</td>
<td>5%</td>
<td>17</td>
<td>100</td>
<td>55</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>IPrAu(TA)OTf</td>
<td>1.0</td>
<td>5%</td>
<td>17</td>
<td>64</td>
<td>50</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>XPhosAuCl/AgOTf</td>
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<td>5%</td>
<td>10</td>
<td>100</td>
<td>76</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>XPhosAu(TA)OTf</td>
<td>1.0</td>
<td>5%</td>
<td>10</td>
<td>100</td>
<td>85</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>XPhosAu(TA)OTf</td>
<td>1.2</td>
<td>5%</td>
<td>10</td>
<td>100</td>
<td>99</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>XPhosAu(TA)OTf</td>
<td>1.2</td>
<td>3%</td>
<td>17</td>
<td>100</td>
<td>99</td>
<td>n.d.</td>
</tr>
<tr>
<td>9</td>
<td>XPhosAu(TA)OTf</td>
<td>1.2</td>
<td>1%</td>
<td>20</td>
<td>100</td>
<td>98 (95)</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

$^a$General conditions: 1 (0.2 mmol), 2a (1 or 1.2 equiv), and catalyst in CDCl$_3$ (0.4 mL), rt. $^b$Yield and conversion are determined by using 1,3,5-trimethoxybenzene as the internal standard. Isolated yield is given in parenthesis.
12% hydration byproduct. Notably, the reaction occurred at room temperature with no need for “careful” condition control (open to the air and untreated solvent). The fact that TA-Au complexes generally gave improved selectivity of diketone addition over hydration (compared with the corresponding [L-Au]⁺ complexes) supported our hypothesis and made the TA-Au catalysts important for this transformation. Slightly increasing the ratio of alkyne to 1.2 equivalents (relative to the nucleophile) increased the formation of the desired vinyl ester to a near quantitative yield (98% NMR yield, 95% isolated yield), even with only 1% catalyst loading.

Given the encouraging results associated with the XPhosAu-TA catalysts, we explored the reaction scope. However, surprisingly, significantly slower reaction was observed when conducting the reaction in dichloromethane (DCM) or 1,2-dichloroethane (DCE), though selectivity for the diketone addition over hydration was maintained as shown in Table 1. Solvent screening shown in Scheme 2 proved that the trace amount of acid from chloroform decomposition was crucial for the optimal performance, which likely helped the protodeauration. Other Lewis acids have also been screened and the Cu(OTf)₂ was identified [31] as the optimal choice due to the practical reasons (easy to weigh and less hygroscopic) and excellent reactivity. Cu(OTf)₂ and HOTf itself could not catalyze the reaction, suggesting that it is indeed a gold-catalyzed process. Finally, it is worth noting that the use of 1 mol % Echavarren catalyst t-BuXPhosAu(MeCN)SbF₆ gave a slightly lower yield (71%), and the combination of 1 mol % t-BuXPhosAu(MeCN)SbF₆ and 1 mol % Cu(OTf)₂ gave 86% yield (under otherwise identical conditions). This result highlights the synthetic utility of TA-Au catalyst in the transformation.

With this optimal conditions in hand, we embarked on the evaluation of the substrate scope for this transformation. A variety of aromatic alkynes were initially tested as summarized in Table 2.

![Scheme 2: Acid as the critical additive for optimal performance.](image-url)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>3a</td>
<td>95%</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>3b</td>
<td>88%</td>
</tr>
</tbody>
</table>

Table 2: Reaction scope of alkynes

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2539
Table 2: Reaction scope of alkynes.\textsuperscript{a} (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>(\text{F}_3\text{C}C\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3c</td>
<td>89%</td>
</tr>
<tr>
<td>4</td>
<td>F(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3d</td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td>Cl(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3e</td>
<td>59%</td>
</tr>
<tr>
<td>6</td>
<td>Me(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3f</td>
<td>68%</td>
</tr>
<tr>
<td>7</td>
<td>(\text{S}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3g</td>
<td>86%</td>
</tr>
<tr>
<td>8\textsuperscript{c}</td>
<td>Fe(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>3h</td>
<td>70%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}General conditions: 1 (0.4 mmol), 2 (1.2 equiv), 1 mol % \text{XPhosAu(TA)OTf} and 1 mol % Cu(OTf)\textsubscript{2} in dry DCM (0.8 mL), rt. \textsuperscript{b}Isolated yield. \textsuperscript{c}1 (0.4 mmol), 2 (2 equiv), 3 mol % \text{XPhosAu(TA)OTf} and 3 mol % Cu(OTf)\textsubscript{2}.

This reaction tolerated both electron-rich (2b) and electron-deficient (2c) alkynes. Aromatic alkynes with substituents at meta (2e) and ortho (2f) positions also worked well, although giving slightly lower yields. Electron-rich heterocycle-containing alkynes (2g) were also suitable substrates for this transformation. However, electron-poor alkynes, such as 2- and 3-pyridylacetylenes, did not undergo the reaction, likely caused by the low reactivity of the C–C triple bonds. Interestingly, the addition to the ethynylferrocene gave the corresponding vinyl ether in good yield, which highlighted the mild conditions of this catalytic system and potential applications of this gold catalyst in other metal containing compound syntheses. A series of aliphatic alkynes were also tested for this reaction. Alkynes containing 6-, 5- and 3-membered rings worked well, giving good to excellent yields (Table 3). Notably, the cyclopropylacetylene formed the direct O-addition adduct (6c) with no ring opening product observed. In addition, the conjugate enyne could undergo this reaction, giving the interesting electron-rich...

Table 3: Reaction scope with aliphatic alkynes.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>5a</td>
<td>89%</td>
</tr>
<tr>
<td>2\textsuperscript{c}</td>
<td>(\text{C}\equiv\text{C}\equiv\text{C}\equiv)</td>
<td>5b</td>
<td>80%</td>
</tr>
</tbody>
</table>
Table 3: Reaction scope with aliphatic alkynes.\textsuperscript{a} (continued)

<p>| | | | | | |</p>
<table>
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<tr>
<td>3</td>
<td>5c</td>
<td>6c</td>
<td>86%</td>
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<tr>
<td>4</td>
<td>5d</td>
<td>6d</td>
<td>86%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>5e</td>
<td>6e</td>
<td>67%</td>
<td></td>
<td></td>
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</table>

\textsuperscript{a}General conditions: 1 (0.4 mmol), 5 (2 equiv), 1 mol % XPhosAu(TA)OTf and 1 mol % Cu(OTf)\textsubscript{2} in dry DCM (0.8 mL), rt. \textsuperscript{b}Isolated yield. \textsuperscript{c}A ratio of 1:0.4 is observed for terminal/internal alkene mixtures. Combined yield.

conjugated diene (6d). In some cases, thermodynamically more stable internal alkenes were also observed along with the kinetic product terminal alkene, likely through olefin isomerization [22].

The internal alkyne (1-phenyl-1-propyne), which was usually much less reactive than the terminal alkyne, was also tested. As expected, no reaction occurred at room temperature under the optimal conditions. To our delight, the desired products 8 were obtained while refluxing at 60 °C for 48 h, though in low yield. Two regioisomers were isolated, which were assigned as 8a and 8b (Scheme 3A). Diphenylacetylene gave trace amounts of the desired product under the identical conditions.

\begin{center}
\textbf{Scheme 3}: Reactions of internal alkyne and other O-nucleophiles. Isolated yields are given in paranthesis. \textsuperscript{a}A ratio of 1:2.6 is observed for terminal/ internal alkene mixtures. Combined yield.
\end{center}
Several diketones were tested to explore the scope of nucleophiles. The 1,3-cyclohexanedione derivative worked well, giving the vinyl ether 10a in good yield. The five-membered diketone, 1,3-cyclopentadione could also yield the desired O-vinylation product (10b–10d) in excellent yield, under similar conditions. Elevated temperature (50 °C) was required for good results due to the poor solubility of 1,3-cyclopentadione in DCM at room temperature. Finally and notably, all tested acyclic 1,3-diketones as well as 1,2-diketones gave no O-addition products under the current reaction conditions, likely caused by the intramolecular H-bonding.

Conclusion

In this letter, we report the first successful gold(I)-catalyzed intermolecular O-vinylation of cyclic 1,3-diketones with unactivated alkenes. The reaction tolerates a large scope of alkenes, giving the desired O-addition products in good to excellent yields. The triazole coordinated gold catalysts gave improved reactivity compared with the typical [I–Au]⁺ by overcoming the undesired hydration. This discovery will likely benefit many future developments that currently suffer from the common hydration side reaction. The application of copper(II) triflate as the effective additive not only improves the reactivity, but also provides another example for plausible bimetallic catalysis, which is a very active research area in the gold catalysis community. Evaluation of distinct O-nucleophiles toward intermolecular addition to alkenes is currently underway in our group.

Supporting Information

Supporting Information File 1
General methods, characterization data and NMR spectra of synthesized compounds.

Acknowledgements

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References

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New developments in gold-catalyzed manipulation of inactivated alkenes

Michel Chiarucci and Marco Bandini*

Abstract
Over the recent years, the nucleophilic manipulation of inactivated carbon–carbon double bonds has gained remarkable credit in the chemical community. As a matter of fact, despite lower reactivity with respect to alkynyl and allenyl counterparts, chemical functionalization of isolated alkenes, via carbon- as well as hetero atom-based nucleophiles, would provide direct access to theoretically unlimited added value of molecular motifs. In this context, homogeneous [Au(I)] and [Au(III)] catalysis continues to inspire developments within organic synthesis, providing reliable responses to this interrogative, by combining crucial aspects such as chemical selectivity/efficiency with mild reaction parameters. This review intends to summarize the recent progresses in the field, with particular emphasis on mechanistic details.

Review
1 Introduction
Homogeneous gold catalysis is emerged as one of the most powerful means for the activation of C–C multiple bonds toward a number of complexity-oriented transformations. In this segment, gold-catalyzed addition of carbon- and heteroatom-based nucleophiles to inactivated alkenes are widely recognized as “capricious” transformations due to alkyne and allene counterparts [1-5]. However, over the past few years, tremendous developments were made, and some of the major contributes will be summarized in the present review.

Mechanistically, it is generally accepted that the gold-catalyzed nucleophilic addition to alkenes proceeds through three elementary steps: i) activation of the C–C double bond by gold coordination. ii) anti-Nucleophilic attack with formation of an alkyl-gold intermediate (outer-sphere pathway). iii) Protodeauration with formation of the product and catalyst regeneration (Figure 1).

The simplified mechanistic sketch depicted in Figure 1 accounts also for the lower reactivity of alkenes with respect to different
π-systems. In particular, the intrinsic inertness of alkylgold intermediate 1 (i.e. Csp³-Au bond) towards protodeauration (path a, Figure 2) determines the scarce reactivity of alkenes in nucleophilic addition reactions [6].

The use of allylic alcohols as C=C surrogates opens an eliminative pathway for the cleavage of the C–Au bond in the intermediate 1 (Figure 2, path b). This reaction channel is accessible under mild conditions and without external activation when proper gold catalysts are employed [7,8].

Furthermore, in recent years, advances in the gold-catalyzed functionalization of alkenes rely on the use of “oxidative strategies” exploiting the [Au(I)/Au(III)] or [Au(I)Au(I)/Au(II)Au(II)] catalytic couples that can be accessed through the use of a suitable exogenous oxidant (Figure 2, path c) [9].

Last but not least, the potential role of Brønsted acid co-catalysis should always be considered when metal triflates are employed [10,11]. Indeed, it was demonstrated that catalytic amounts of TfOH could catalyze some specific additions of oxygen- and nitrogen-based nucleophiles to simple alkenes with comparable efficiency/selectivity as much as some metal triflates [12,13].

In this review some selected examples of gold-catalyzed nucleophilic additions to inactivated alkenes will be discussed with particular emphasis on the corresponding reaction machinery. In the context of this review, allylic alcohols will be treated as inactivated olefins, considering that normally activated equivalents, like halides, acetates, carbonates and phosphates are employed in metal-catalyzed Tsuji–Trost type alkylation [14,15].

2 Formation of C–O bonds
2.1 Mechanistic considerations

The addition of oxygen-based nucleophiles to C–C multiple bonds is an effective and atom-economical process for the formation of new C–O bonds. In this direction numerous examples of metal and Brønsted-acid catalyzed condensations of alcohols, phenols and carboxylic acids to inactivated olefins have been reported [16].

Interestingly, He and co-workers compared the catalytic attitude of TfOH and PPh₃AuOTf in the addition of various nucleophiles to alkenes, demonstrating how the gold complex and triflic acid can exhibit complementary efficiency [17]. This finding suggests that although Brønsted acid co-catalysis is a possible competing process, under suitable conditions the gold-catalyzed pathway is still the dominating process. For example by adopting the addition of p-NO₂- and p-MeO-phenol to aryl and alkyl olefins as a model process, it emerged that TfOH was an effective catalyst at room temperature and led to decomposition of the starting material at higher temperatures. On the contrary, cationic [Au(I)] species exhibited comparable activity to TfOH at 85 °C (Table 1).
**Table 1:** Comparison of the catalytic activity of TfOH and PPh₃AuOTf in the addition of phenols to alkenes.

<table>
<thead>
<tr>
<th>Entry</th>
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<th>R²</th>
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<td></td>
<td>NO₂</td>
<td></td>
<td>93</td>
<td>Ph₃PAuOTf</td>
</tr>
<tr>
<td></td>
<td>rt</td>
<td>85</td>
<td>trace</td>
<td>--</td>
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<tr>
<td></td>
<td>MeO</td>
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<td>57</td>
<td>Ph₃PAuOTf</td>
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<td>trace</td>
<td>58</td>
</tr>
</tbody>
</table>

This complementary behavior can be ascribed to different activation modes of the double bond. Computational investigations on the [H⁺]-catalyzed reaction predicted a transition state with significant carbocation character [18,19], therefore more easily subjected to substrate isomerization or degradation. Notwithstanding, gold activation was shown to occur through the formation of a η²-complex [20-24].

An important contribution to this scenario, was also provided by Ujaque and co-workers, who performed a theoretical investigation on the Me₃PAuOTf catalyzed addition of phenol to ethylene [25]. The proposed catalytic cycle initiated with the exchange of the TfO⁻ ion with the alkene reveals that the poorly coordinating anion seems to form a “loose” ion pair lying far from the metal center (Figure 3). This step was energetically favorable and the activation of the alkene by the gold cation was confirmed by elongation of the C–C double bond [26]. After an exhaustive survey of plausible reaction channels, it turned out that the phenol is involved in assisting the concerted addition/protodeauration machinery. The presence of a second molecule of phenol, acting as a proton shuttle, considerably lowered the energetic barrier for the protodeauration (i.e. rate limiting step of the overall process), which takes place through a more favorable 6-membered cyclic transition state. Analogous calculations indicate that also water is a potential proton transfer agent in the protodeauration event of the catalytic cycle.

### 2.2 Selected examples

Initial reports dealing with the gold-catalyzed addition of oxygen-based nucleophiles to isolated olefins required the use of relatively acidic nucleophiles. In their seminal works, Yang and He reported on the Ph₃PAuOTf assisted Markovnikov-like addition of phenols and carboxylic acids to C=C under mild reaction conditions (Scheme 1) [27]. Electron-rich and electron-poor phenols reacted smoothly in toluene (85 °C) with only 1 mol % of catalyst loading (Scheme 1a). Contrarily, carboxylic acids required a higher loading of catalyst (5 mol %), but an acceptable yield was obtained even when sterically demanding 2-methylpropionic acid was employed as the nucleophile (Scheme 1b).

Li and co-workers exploited the [Au(III)]-catalyzed addition of phenols and naphthols to conjugated dienes realizing an efficient synthesis of dihydrobenzofuran derivatives 3 (Scheme 2a) [28]. The protocol was assumed to proceed via a two-step
mechanism: involving an initial hydroarylation of the double bond followed by an intramolecular phenol addition (Scheme 2b).

Shortly after, Zhang and Corma considerably expanded the scope of this transformation to aliphatic alcohols (Scheme 3) [29]. Under these conditions, the addition of primary and secondary alcohols to aryl and alkyl olefins 4 took place efficiently, with good yield and regioselectivity. However, poor diastereoselectivity was recorded in the presence of secondary alcohols.

The efficiency of the process relied on the stabilization of cationic [Au(III)] species by using a catalytic amount CuCl2 (16 mol %), which prevented gold deactivation via parasitic reductive side reactions [30,31].

Moreover, recent advances in the alkoxylation of olefins enabled the use of simple dimethyl acetals 6 in the carboalkoxylation of alkenes (Scheme 4) [32]. A 1:2 mixture of [picAuCl2] (7) and AgNTf2 efficiently catalyzed the double functionalization of aryl alkenes 4 in good yields and mild conditions. Dialkyl substituted olefins afforded the product only in moderate yields whereas monoalkyl olefins were completely unreactive under the optimized conditions. Although an activation of the acetals by the gold catalyst cannot be ruled out, a reaction pathway involving gold activation of the alkene, followed by addition of the alkyl gold intermediate 10 to the activated carbonyl compound 9 was also hypothesized (Scheme 4b).

3 Hydroamination of olefins
3.1 Mechanistic considerations
Due to the ubiquity of the C–N bond in organic compounds the development of efficient catalytic systems for the hydroamination of olefins is of particular significance from a practical point of view [33]. Although many metal and Brønsted acid assisted processes have been documented the high functional group
tolerance of gold complexes combined with their high efficiency in the electrophilic activation of C–C multiple bonds have made gold catalysis an important tool for the hydroamination of alkenes. Detailed computational studies on the addition of benzyl carbamate to dienes revealed the protodeauration as the rate-determining step of the reaction [34]. Mechanistically, the initial stage was determined dealing with the energetically favourable substitution of the TfO$^-$ ligand from the gold coordination sphere with the diene (Figure 4). Preferred coordination geometry is the $\eta^2$-type, with the gold cation coordinating to a single double bond. Either direct coordination of the nucleophile to the gold cation, or reaction of the PH$_3$AuOTf with the carbamate to deliver TfOH and PH$_3$AuNHCOOBn [35] were ruled out by experimental and computational observations. Differently, addition of the nucleophile to the gold activated double bond took place with Markovnikov regioselectivity affording the intermediate 11. At this point many possible reaction pathways were evaluated to shed light on the real mechanism of the protodeauration step. Interestingly the reaction profile with the lowest activation energy was distinguished in the TfO$^-$ promoted tautomerization of 11 to form 12 followed by direct proton transfer to afford the product 13 and regeneration of the catalyst.
Intermediates of type 11 were isolated by Toste in the intramolecular hydroamination of alkenyl urea 14 with a stoichiometric amount of phosphine–gold complex \([\text{PPh}_3\text{Au}]_3\text{O}\)BF_4 (Scheme 5a) [2]. The reaction proceeded at room temperature and was found being favoured by electron-withdrawing ligands. Finally, the use of the deuterated compounds 14a, b permitted to confirm the anti-diastereoselective hydroamination of the double bond. (Scheme 5b). Interestingly, although 14 represents a likely intermediate of the reaction course, when it was treated with various Brønsted and Lewis acids, the expected product 16 was not observed and the elimination reaction to reform the starting material was the dominant process (Scheme 5c). Only reductive conditions afforded 16 in good yield (81%, Scheme 5d). This experimental evidence contributed substantially at the definition of the complex reaction machinery, with direct implication also in the correlated gold-catalyzed oxidative heteroarylation of unsaturated olefins (see section 6).

### 3.2 Selected examples

Initial reports on the gold-catalyzed hydroamination of olefins were presented by He [36] and Widenhoefer [37], independently. He and Brouwer disclosed the intermolecular addition of carbamates, sulfonamides and imidazolidinones to linear and cyclic dienes 17 in the presence of catalytic amounts of PPh_3AuOTf (Scheme 6). The method featured excellent 1,2-regioselectivity and high chemoselectivity, providing protected allylamines 18, in good yields, using nearly equimolar amounts of the diene and nitrogen-based nucleophile.

Analogously, Widenhoefer and Han developed the intramolecular addition of carbamates to terminal alkenes affording...
N-protected pyrrolidines and piperidines 21 (Scheme 7). Best conditions involved the use of a 1:1 mixture of [Au(I)] complex 20a and AgOTf [38]. Although prolonged reaction times were required (up to 68 h in refluxing dioxane), remarkable tolerance in terms of carbamate protecting groups (Scheme 7a) and substituents at the carbon chain was recorded (Scheme 7b, c). Soon after the same team disclosed that the titled transformation could be extended to amide-based nucleophiles exploiting similar operational conditions [39].

<table>
<thead>
<tr>
<th>19a R = Cbz</th>
<th>19b R = Boc</th>
<th>19c R = Fmoc</th>
<th>19d R = p-MeO-Ph-CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>21a-d, Yield: 93–97%</td>
<td></td>
<td></td>
<td></td>
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</table>

**Scheme 7:** Intramolecular [Au(I)]-catalyzed hydroamination of alkenes with carboxamides.

After these seminal works the scope of gold-catalyzed hydroamination of olefins was extend to other classes of nitrogen nucleophiles. Sulfonamides were successfully employed in the intra- and intermolecular hydroamination of alkenes catalyzed by Ph3PAuOTf (toluene, 85 °C, Scheme 8) [40]. In particular, primary and secondary sulfonamides reacted smoothly with mono and substituted alkenes delivering nitrogen compounds 22 and 23 with Markovnikov regioselectivity (Scheme 8a). Moreover, N-protected pyrrolidines 24 and 25 were accessed by intramolecular addition in excellent yields (Scheme 8b).

The combined use of more electrophilic phosphite-gold complexes [41,42] and enabling techniques such as microwave irradiation [43] led to consistent improvement in efficiency of the catalytic system. In particular when (Ph3O)PAuOTf was employed under microwave irradiation as low as 0.05 mol %, the condensation of TsNH2 to norbornene was realized in quantitative yield.

In addition, the introduction of carbene ligands [44] allowed performing the intramolecular hydroamination of N-alkenyl ureas, efficiently (Scheme 9) [45]. When PtAuCl (27) and AgOTf were mixed together in 1:1 ratio, the intramolecular exo-addition of N'-alkyl and N'-aryleura to primary or secondary olefins took place smoothly at room temperature to afford the variously substituted pyrrolidines 28 and piperidines 30 (Scheme 9a, b). Even unsubstituted substrate 31 afforded the corresponding product 32 in excellent yield although more forcing conditions were necessary (Scheme 9c). Monosubstitution at carbon C1 or C2 of the chain led to the formation of the product 2,4-cis or 2,5-cis-32 with diastereomeric ratios up to 5:1.

Enantioselective variant of this transformation was recently reported by Mikami and co-workers [46]. The protocol focuses on the use of a gold complex comprising the racemic 2,2'-bis(diphenylphosphino)-1,1'-biphenyl digold(I) complex 33 which, in combination with enantiopure silver phosphate 34, afforded the diastereopure complex 35. Interestingly, the strong [Au(I)]–[Au(I)] aurophilic interaction in 35 prevented racemization even if chiral anions were removed (Scheme 10a). (S)-33 found application in the intramolecular hydroamination of 36, delivering 37 in quantitative yield (98%) and moderate enantioselectivity (ee up to 48%, Scheme 10b). The efficiency of 33 was ascribed to double activation of the substrate by the binuclear gold complex 38.

The synthetic versatility of alkenyl ureas was further demonstrated by Widenhoefer employing slightly different substrates, namely N-allyl-N'-aryleuras. When 39 was treated with a 1:1 mixture of 20a and AgPF6, imidazolidin-2-ones 40 were obtained in high yields under mild reaction conditions (Scheme 11a) [47]. Analogously, substituted N-allyureas 41 provided 42 with high trans diastereoselectivity (dr = 50:1, Scheme 11b). Surprisingly, inversion of diastereoselection (i.e. cis stereoisomer as the major product) was recorded in the case of hydroxymethyl derivative 43.
The challenging task of direct hydroamination with simple amines was faced, by means of in situ protection of the basic functionality as an ammonium salt (Scheme 12) [48]. The best catalyst for the titled reaction turned out to be the complex 20b bearing an electron-rich phosphinic ligand. When 20b was mixed with AgOTf (1:1 ratio) the intramolecular hydroamination of alkenyl ammonium salts 45/47 took place at 80–100 °C affording pyrrolidines and piperidines 46/48 in moderate to good yields.

In 2009 Widenhoefer reported the first example of enantioselective gold-catalyzed intermolecular hydroamination of simple olefins. Firstly, the authors demonstrated that functionalization of ethylene derivatives could be conveniently accessed by using cyclic ureas 49 as nucleophiles in combination with phosphine gold complexes. Starting from this consideration a protocol for the enantioselective addition of cyclic ureas to simple alkenes 4 was developed (Scheme 13) [49]. In spite of the forcing conditions (100 °C for 48 hours) the use of the chiral binuclear gold complex (S)-50(AuCl)2 ensured enantioselectivity up to 78% for the products 51.

A considerable enhancement of enantioselectivity was recently obtained by Toste’s group in the [Au(I)]-catalyzed intramolecular addition of sulfonamides to dienes (Table 2) [50]. The authors observed that, when the binuclear gold complex based on (R)-DTBM-segphos ligand 53 and AgBF₄ was used in combination with alcoholic additives, the rate of the intramolecular hydroamination of 52 increased considerably, leading to the concomitant formation of 55 in combination with the expected product 54. A screening of various chiral alcohols and kinetic studies established that the use of 2.0 equivalents of (−)-menthol led to an increase in both the yield and ee of 55 leaving unaffected the formation of 54.

This observation found adequate rationale with the presence of two different competing mechanisms for the formation of the products. In particular, while 54 was formed via a standard
Scheme 9: Intramolecular hydroamination of N-alkenylureas catalyzed by gold(I) carbene complex.

Scheme 10: Enantioselective hydroamination of alkenyl ureas with biphenyl tropos ligand and chiral silver phosphate.
Scheme 11: Intramolecular [Au(I)]-catalyzed hydroamination of N-allyl-N’-aryl ureas. (PNP = pNO$_2$C$_6$H$_4$, PMP = pMeO-C$_6$H$_4$).

Scheme 12: [Au(I)]-catalyzed hydroamination of alkenes with ammonium salts.

hydroamination reaction (Scheme 14, path a), compound 55 was formed via Brønsted acid catalysis because of the enhancement of alcohol acidity due to gold coordination (Scheme 14, path b). Under these conditions various pyrrolidines and piperidines were obtained in excellent yields and high enantioselectivity (Table 2).

4 Formation of C–C bonds

Besides heteroatoms, the electrophilic activation of alkenes by gold catalysts can be exploited also to form new C–C bonds. Early achievements relied on the use of active methylene compounds or electron rich arenes as carbon nucleophiles.

4.1 Alkylation of active methylene compounds

Hydroalkylation of styrenes, indene and norbornene with 1,3-diketones was firstly reported in 2004 by using AuCl$_3$ and AgOTf in 1:3 ratio as the catalyst (Scheme 15) [51]. The addition took place with Markovnikov selectivity in good yields, however optimal conditions suffered from severe limitations on 1,3-diketones as nucleophiles and unfunctionalized olefins. The same catalytic system was then employed with cyclic enols, dienes and trienes although lower yields were recorded [52].

Remarkably, the intramolecular [Au(I)]-catalyzed addition of β-keto amides to inactivated alkenes was also exploited for the synthesis of highly substituted lactams 59, also in a preparative scale [53]. When alkenyl β-keto amides 60 were reacted with a 1:1 mixture of phosphine-gold complex 20a and AgOTf (toluene, 50–90 °C), exo-trig hydroalkylation of the C–C double bond took place, affording 5-, 6-membered lactams and spiro-lactams 61 in excellent yields and high trans diastereoselectivity (Scheme 16).

Scheme 13: Enantioselective [Au(I)]-catalyzed intermolecular hydroamination of alkenes with cyclic ureas.

Table 2: Cooperative [Au(I)]/menthol catalysis for the enantioselective intramolecular hydroamination of dienes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt; (54:55)</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>95 (1:6.3)</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>91 (1:6.1)</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>93 (1:3.5)</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>99 (1:5.0)</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>80 (1:8.0)</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>77 (1:12.1)</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>42 (1:3.2)</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>99 (1:1.5)</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>67 (1:7.6)</td>
<td>91</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mbs = p-MeO-benzenesulfonyl.<sup>b</sup>Combined yield of 54 and 55.<sup>c</sup>The ee values are referred to (E)-55.

4.2 The hydroarylation reaction
In addition to methylene active compounds, electron-rich benzenes and heteroaromatics can be added to gold activated alkenes under suitable conditions. In this context, in situ made [Ph<sub>3</sub>P[AuOTf] was found to be an efficient catalyst for the addition of indoles 62 to styrenes and aryldienes in toluene at 85 °C.
Scheme 14: Mechanistic proposal for the cooperative [Au(I)]/menthol catalysis for the enantioselective intramolecular hydroamination of dienes.

Scheme 15: [Au(III)]-catalyzed addition of 1,3-diketones to alkenes.

Scheme 16: [Au(I)]-catalyzed intramolecular addition of β-keto amides to alkenes.

(Scheme 17a,b). Less reactive aliphatic alkenes required harsher reaction conditions, however the corresponding hydroarylation products 66 were obtained from moderate to good yields under microwave irradiation (DCE, Scheme 17c) [54].

Additionally, the stronger Lewis acid AuCl₃/AgSbF₆ was documented to catalyze the Markovnikov selective hydroarylation of aryl- and alkyl olefins with less-nucleophilic benzene derivatives and thiophene in good yields (Scheme 18, DCE, 50 °C) [55]. To be underlined that despite of efficiency, isomerization of the C=C was found competing with the desired Friedel–Crafts-type alkylation under the optimized reaction conditions.

Analogously, [Au(III)] catalysis was employed in the intramolecular hydroarylation of olefins. It is worth mentioning, that a 1:1 mixture of AuCl₃ and AgOTf promoted the ring-closing processes of arenes 68, delivering the corresponding dihydrobenzopyrans, tetralins and tetrahydroquinolines 69 in good yields (Scheme 19a). Experimental controls with deuterium labelled compounds suggested the step-wise mechanism described in Scheme 19b. In detail, initial gold activation of the
olefin would trigger the outer-sphere attack of the aryl ring to the double bond followed by protodeauration of the alkyl–gold compound [56].

4.3 Latest developments

Recent advances in the field of C–C bond forming processes through gold activated olefins allowed expanding the scope of the reaction to other carbon nucleophiles. For examples Che and co-workers reported on the hydroalkylation of alkenes with simple ketones [57]. Reaction of alkenyl ketones with IPrAuCl/AgClO$_4$ (5 mol %) afforded functionalized cyclopentyl and cyclohexyl derivatives in excellent yields and good trans diastereoselectivity, via exo-trig cyclization (Scheme 20a–c).

The proposed mechanism involved activation of the C–C double bond by the carbene-based cationic gold species to form the intermediate 76 which underwent gold-promoted tautomerization affording the enol 77. Nucleophilic attack of the enol on the gold activated alkenes led to a new C–C bond with subsequent releasing of the product 71 (Scheme 21).

This protocol was also extended to an intermolecular variant (i.e. one-pot N-Michael addition/hydroalkylation). The use of [PPh$_3$AuCl/AgClO$_4$] (5/15 mol %) furnished corresponding functionalized pyrrolidines in good yields and moderate stereoselectivity (Scheme 22) [58].

The preferred alkene activation versus allenes was recently observed in the cascade 1,3-migration/[2 + 2] cycloaddition of 1,7-enzyme benzoates (Scheme 23) [59]. When 83 was heated in presence of the silver free gold complex 20c a variety of highly substituted azabicyclo[4.2.0]oct-5-enes 84 was obtained in good
Scheme 19: a) Intramolecular [Au(III)]-catalyzed hydroarylation of alkenes. b) A S_{EAr}-type mechanism was hypothesized by the authors.

Scheme 20: Intramolecular [Au(I)]-catalyzed hydroalkylation of alkenes with simple ketones.
yields as a single regio- and diastereoisomer. The protocol displayed excellent functional group compatibility and efficient transfer of chirality was observed with enantiopure substrates. The proposed mechanism proceeded through 3,3-migration of the propargylic ester to form the allenate 87. The expected activation of the allene was probably unfavoured for steric reasons, therefore gold activation of the alkene moiety triggered attack of the more nucleophilic double bound of the
allene, forming the intermediate 88. Finally, condensation of the alkylgold 88 onto the carbonyl group led to the bicyclic product 84 (Scheme 23).

An interesting example of gold-catalyzed intramolecular cyclopropanation of olefins was recently documented by Maulide and coworkers [60]. In particular, a range of densely functionalized heterobicyclic and carbocycles 90 were readily accessible in high yields and high stereoselectivity starting from properly functionalized sulfonium ylides 89 (Scheme 24). Computational and experimental investigations suggested the initial 20d-based electrophilic activation of the C=C, with consequent nucleophilic attack by the ylidal carbon onto the internal carbon of the double bond. Finally, the intermediate lactone 92 underwent cyclopropanation, delivering SPh$_2$ as a leaving group (Scheme 24b).
5 Addition to allylic alcohols

The use of simple allylic alcohols as alkylating agents, in place of more activated analogues (i.e. halides, acetates, carbonates and phosphates) is highly desirable from a synthetic, environmental and economic point of view [61]. Late transition metal catalysts demonstrated efficiency in addressing the poor reactivity of these substrates [62]. Due to the ability of gold complexes to act as σ- and π-acids, gold catalysis gained a prominent role in the activation of allylic alcohols, delivering of water as the side-product. As the topic has been recently extensively reviewed by Aponick and Biannic [7], only the most recent examples of gold-catalyzed manipulation of inactivated allylic alcohols will be discussed here [63,64].

5.1 Mechanistic considerations

Very recently Ess and Aponick reported a detailed mechanistic study on the intramolecular hydroalkoxylation of hydroxy allylic alcohols 94, pointing out the key role of intramolecular hydrogen bond (H-bond) interactions for both reactivity and stereoselectivity [65]. Theoretical calculations and experimental evidences ruled out the S_N1 reaction mechanism via allylic carbocation. Experiments with stereodefined hydroxy allylic alcohols revealed that the reaction was stereospecific: alcohols with the same configuration of the secondary carbinol atom, but different geometry of the double bond, afforded the cyclized product 95 with the opposite absolute configuration of the stereocenter, but the olefin had E configuration in both cases (Scheme 25).

Whereas concerted S_N2’ pathway was judged energetically unfavourable, two possible mechanistic channels were supposed to account for the observed stereoselectivity: anti addition followed by anti-elimination or syn addition followed by syn-elimination. Calculations showed that the former pathway was energetically favoured. Interestingly, a strong hydrogen bond was established during the catalytic cycle between the hydroxy groups. The H-bond turned out to be a key interaction for the high reactivity of 94 toward cyclization, leading to an intramolecular proton transfer resulting into a better leaving group. Furthermore, as the H-bond was conserved during the entire course of the reaction, it also determined the E geometry of the newly formed C–C double bond (Scheme 26).
The importance of the H-bond network in gold-catalyzed enantioselective transformations of allylic alcohols has been recently highlighted also by Bandini and Miscione [66-68] that documented on the intramolecular enantioselective allylic alkylation of indoles. Combined computational and experimental studies revealed the presence of a complex H-bond network between the indole ring, the counterion (i.e. OTf\(^-\)) and the leaving OH group along all the reaction profile (Scheme 27). Multiple functions were recognized in these interactions. Firstly, all the strong H-bonds conferred a constrained conformation to the substrate (U-fold) placing the two reacting moieties in close proximity (101). Secondly, after nucleophilic attack of the indole ring, the counterion facilitated the elimination of water (103) by shuttling one proton atom, from the indolyl ring to the leaving hydroxy group. The proposed catalytic cycle accounted also for the observed stereochemistry of the product 100 (R) when the chiral binuclear gold complex (R)-DTBM-MeO-biphep 50 was employed.

5.2 Recent advances
Latest advances in gold-catalyzed transformations of allylic alcohols mainly concern the development of stereoselective processes. In particular, mild conditions allowed a more efficient development of enantioselective protocols and the scope of the process can be widen to more functionalized substrates, efficiently.

For examples Robertson and co-workers reported on the synthesis of (+)-isoaltholactone, by adopting an intramolecular stereoselective Ph\(^3\)PAuOTf-catalyzed 5-exo alkoxylation of allylic alcohols, to form tetrahydrofuran rings (Scheme 28) [69]. Experiments with configurationally defined hydroxy allylic alcohols 105b,c demonstrated the stereospecificity of the process. Due to the complexity of the substrates, the stereocchemical model proposed by Aponick [65] could only partially account for the stereocchemical outcome of the reaction, since the importance of the configuration of the carbon bearing the nucleophilic OH group was not considered.

In this segment, Widenhoefer has recently documented on the enantioselective dehydrative amination of allylic alcohols with carbamates [70,71]. Pyrrolidines and piperidines 109 were obtained with enantiomeric excesses up to 94% by using a chiral gold complex based on \((S)\)-DTBM-MeO-biphep (Scheme 29). Mechanistic investigation highlighted complete catalyst control on the configuration of the newly formed stereocenter. On the contrary, studies on stereocchemically defined secondary allylic alcohols revealed that the configuration of the allylic carbon atom affected the configuration of the newly formed C–C double bond. The \(E\) configuration of the starting material turned out to be fundamental to achieve high enantioselectivity. Also in this case, a mechanism sketch consisting on anti-aminoauration followed by anti-elimination was invoked to account for the observed experimental outcome (Scheme 29d).

A complementary approach for the enantioselective synthesis of 3,4-disubstituted pyrrolidines was recently reported by Bandini and co-workers [72]. Intramolecular hydroalkylation of allylic alcohols with aldehydes was performed under synergistic activation of the substrate by gold catalyst 20c and organocatalyst 116 (Scheme 30). The 5-membered hetero- and carbocycles 115...
Scheme 28: Synthesis of (+)-isoaltholactone via stereospecific intramolecular [Au(I)]-catalyzed alkoxylation of allylic alcohols.

Scheme 29: Intramolecular enantioselective dehydrative amination of allylic alcohols catalyzed by chiral [Au(I)]-complexes.
were obtained in moderate to good yield and interesting level of diastereo- and enantioselectivity, supporting the perfect compatibility between the amino-catalyst and the electrophilic gold complex. Experiments on chiral enriched secondary alcohols suggested the anti-attack of the in situ formed enamine 117 on gold activated allylic alcohol followed by anti-elimination of water.

6 Double functionalization of olefins by oxidative strategies

Differently from many transition metals, usually gold is not subjected to redox processes during the catalytic cycles. However, in recent years it has been demonstrated that both \([\text{Au(I)}/\text{Au(III)}]\) (i.e. monometallic catalytic systems) and \([\text{Au(I)Au(I)}/\text{Au(II)Au(II)}]\) (i.e. bimetallic catalytic systems) redox couples could be accessed using external stoichiometric oxidants (i.e. Selectfluor or hypervalent iodine compounds) [73]. As schematically shown in Figure 1 this approach allows a double functionalization of simple alkenes with subsequent formation of new C–X and C–C bonds in a single catalytic process.

In 2009 Muñiz and coworkers reported on the diamination of alkenes catalyzed by \(\text{PPh}_3\text{PAuOAc}\) in presence of \(\text{PhI(OAc)}_2\) (Scheme 31) [74]. The process led to the formation of two new C–N bonds under mild conditions with excellent yields. A mechanistic rationale was also provided dealing with initial \([\text{Au(I)}]\)-promoted anti-amination with formation of alkylgold intermediate 121, followed by oxidation to \([\text{Au(III)}]\) species 122 by means of \(\text{PhI(OAc)}_2\). A final ring-closing step will provide product 120 (Scheme 31).

Exploiting a similar strategy, Nevado developed a flexible protocol for the gold-assisted aminoxygenation of alkenes,
intercepting the hydroamination intermediate with various nucleophiles (i.e. alcohols, ethers and esters, Scheme 32a) [75]. A remarkable variety of products could be accessed with minimal variation of the reaction conditions. For instance, by using nitriles as solvents and only 2 equivalents of water, a nucleophilic attack of the nitrile itself on the hydroamination intermediate took place, affording the corresponding aminoamidation product 127 in moderate to good yields (Scheme 32b). In absence of external nucleophiles, the phenyl rings of the substrate backbone could intercept the hydroamination intermediate affording tricyclic 3-benzazepines 129 (Scheme 32c).

In the same field, Zhang reported the carboamination, carboalkoxylation and carbolactonization of terminal alkenes with arylboronic acids. Under best conditions, oxidative gold catalysis provided expedient access to various substituted N- or O-heterocycles in high yields (Scheme 33) [76]. Deuterium labeling experiments unambiguously demonstrated the anti-functionalization of the double bond and the use of neutral gold complexes suggested that [Au(I)] oxidation took place prior of C–X bond formation.

The same team also reported on the efficiency of gold catalysis in the functionalization of C–H bonds [77]. In particular, N-aryl-N’-allylureas 136 were selectively transformed into tricyclic indolines 137 in good yields. The reaction proceeded through the regioselective 5-exo anti-aminoauration of the C–C double bond (139) followed by oxidative coupling of the formed alkylgold moiety with the ortho C–H bond of the tethered phenyl group. Compound 137 was finally obtained via reductive elimination of intermediate 141 (Scheme 34). The formal [3 + 2] annulation between the aniline moiety and the C–C double bond constitutes the first example of C–H functionalization by alkylgold intermediates. The optimized conditions required the use of the electrophilic complex [(p-CF₃Ph)₃PAuNTf₂] and 30 equivalents of water, in order to increase the solubility of Selectfluor in THF.
Scheme 32: Gold-catalyzed aminooxygenation and aminoarylation of alkenes.

Scheme 33: Gold-catalyzed carboamination, carboalkoxylation and carbolactonization of terminal alkenes with arylboronic acids.
Heteroarylation of alkenes with arylboronic acids under the assistance of redox gold catalysis was also elegantly investigated by Toste’s group. In particular, aminoarylation of terminal olefins was documented in the presence of catalytic amounts of \([\text{dpmm(AuBr)}_2]\) (3 mol %) and Selectfluor as the stoichiometric oxidant \([78]\). Despite the undoubted synthetic interest relying on the synthetic approach (a wide range of densely functionalized nitrogen-based heterocyclic cores (143) were readily accessible) (Scheme 35), intriguing mechanistic insights derived from a detailed investigation based on experimental and computational observations \([79]\).

In particular, the inability of [Au(I)] halide complexes in promoting the aminoauration of the double bond suggested the
oxidation of the [Au(I)] complex as the first step of the catalytic cycle (Scheme 36 i). This hypothesis was further supported by the failure recorded when an isolated alkylgold compound was reacted with Selectfluor and PhB(OH)$_2$ (ii). Moreover, Ph$_3$PAuCl and PhB(OH)$_2$ were mixed together, no formation of Ph$_3$PAuPh was detected ruling out the transmetallation as initial stage of the catalytic cycle (iii). In addition, Ph$_3$PAuPh proved to be a competent catalyst of the process but only in the presence of arylboronic acid (iv and v). The latter evidence prompted the authors to conclude that the aryl group was transferred from the boronic acid and not from the gold complex (i.e. the phenyl group on the in situ formed PPh$_3$AuPh complex acts as a spectator in the process).

Based on such observations, the mechanistic cycle depicted in the Scheme 37 was proposed. Oxidation of the bimetallic [dppm(Au$_2$Br$_2$)] complex by Selectfluor led to the preferred formation of the cationic [Au(II)Br$_2$-Au(II)F]$^+$ complex 144 also due to the instauration of a strong aurophilic interaction (σ-bond) between the two gold atoms. Then, intramolecular aminoarylation of the C=C occurred via an anti-stereochemical reaction profile, leading to intermediate 145. Finally, arylation of 145 was supposed to occur via a concerted bimolecular elimination (146), in which the F–B bond assisted the formation of the new C–C bond (Scheme 37) [80].

It should be emphasized that the latter step of the proposed reaction machinery referred as “redox synergy” is in clear conflict with the commonly reported alternative invoking trans-
metalation/reductive elimination steps (see Schemes 33 and 34). The catalytic superiority of bimetallic systems with respect to PPh₃AuOTf in the aminoarylation is clearly explainable by the latter mechanistic proposal, that found solid validations/analogies in the “Pd--Pd” cooperative catalysis [81].

The same catalytic system was also utilized in the three-component oxyarylation of olefins (Scheme 38) [82]. The reaction took place under mild conditions and exhibited a wide substrate scope, being highly tolerant towards a number of olefins, aryloboronic acids and nucleophiles. In particular, primary, secondary, tertiary alcohols and even water could be employed as nucleophiles, affording the corresponding ethers and alcohols in moderate to good yields (up to 90%, Scheme 38a,c). Differently, although carboxylic acids were suitable nucleophiles as well, the corresponding products were isolated in lower extent (Scheme 38b).

Furthermore, the present strategy was extended to arylsilanes, enabling the use of oxygen- and nitrogen-containing coupling partners [83,84]. Interestingly, due to the employment of Selectfluor as a stoichiometric exogenous oxidant, the addition of basic activators for silane reagents were not required. The ready availability of silane precursors, with respect to boronic acid counterparts, allowed an intermolecular variant to be successfully developed (Scheme 39a).

Scheme 38: Oxyarylation of terminal olefins via redox gold catalysis.

Scheme 39: a) Intramolecular gold-catalyzed oxidative coupling reactions with arytrimethylsilanes. b) Oxyarylation of alkenes catalyzed by gold in presence of iodine-(III) compound IBA as an external oxidant.
A slight modification of the reaction conditions enabled to expand the oxidative coupling to a wider range of olefins. In particular the use of IBA (153) as the oxidant allowed substrates incompatible with Selectfluor, (i.e. styrene and gem-disubstituted olefins) to be efficiently employed (Scheme 39b) [85].

An innovative approach to the double functionalization of olefins was developed by Glorius and co-workers, very recently. The authors reported on the use of visible light-mediated photoredox catalysis to access the [Au(I)]/[Au(III)] redox couple during the intramolecular oxy- and aminoarylation of alkenes (Scheme 40) [86].

Optimal conditions for the reaction involved the use of Ph$_3$PAuNTf$_2$ in presence of [Ru(bpy)$_3$]$^{2+}$ as redox photocatalyst and aryl diazonium salts 157. In the proposed tandem catalytic cycle, the initial anti oxy-auration of the double bond led to the alkylgold intermediate 159, that was oxidized to [Au(II)] 160 via a SET process by the aryl radical formed in the photoredox catalytic cycle. The highly reactive species 160 was promptly oxidized by [Ru(III)(bpy)$_3$]$^{3+}$ affording the [Au(III)] intermediate 161 and regenerating the [Ru(II)(bpy)$_3$]$^{2+}$ photocatalyst. Finally, arylated tetrahydrofuran 158 was obtained by reductive elimination with concomitant regeneration of the [Au(I)] catalyst.

**Conclusion**

Metal catalyzed electrophilic activation of isolated alkenes is by far considered among the most challenging metal-assisted nucleophilic manipulation of inactivated unsaturated hydrocarbons. Relative inertness of C=C with respect to alkynes or allenes accounts for this trend. In this scenario [Au(I)] and
[Au(III)] catalysis is playing a major role leading to tremendous developments spanning from C-/hetero-nucleophilic manipulations, mono-/difunctionalizations, intra-/intermolecular transformations and regio-/stereoselective methodologies. In this chemistry, it should be mentioned that concomitant catalytic activity exerted by Brønsted acidity can not be ruled out a priori and it should not be underestimated. Therefore, practitioners should carefully determine the real role of gold complexes during the reaction course, with respect to [H⁺] sources, from time to time. Experimental controls would certainly contribute to unambiguously clarify the intrinsic mechanistic aspects of the process but they would also concur to a better optimization/rationalization of optical outcomes deriving from stereoselective transformations. Despite the apparent interchangeability between cationic gold(I) species and [H⁺] sources, a major breakthrough introduced by [Au(I)] complexes in the nucleophilic manipulation of inactivated alkenes relies on enantioselective processes, that still represent an unsolved issues in metal-free catalysis [87].

Acknowledgements

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References

81. For a study on the reactivity of alkyl [Au(III)]-F complexes. See for a study on the reactivity of alkyl [Au(III)]-F complexes.
83. And reference therein. For a study on the reactivity of alkyl [Au(III)]-F complexes. See for a study on the reactivity of alkyl [Au(III)]-F complexes.
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Gold(I)-catalyzed domino cyclization for the synthesis of polyaromatic heterocycles

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Full Research Paper

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Abstract
Gold(I) complexes have emerged as powerful and useful catalysts for the formation of new C–C, C–O and C–N bonds. Taking advantage of the specificity of [IPrAuNCMe][SbF$_6$] complexes to favor the 5-exo-dig cyclization over the 6-endo-dig pathway, we report a high yielding and efficient method to generate substituted polyaromatic heterocycles under remarkably mild reaction conditions.

Introduction
In the last decade, phosphino and NHC–gold complexes have become prominent catalysts for the addition of nucleophiles to alkenes, alkynes and allenes [1-11]. Owing to the high affinity of gold(I) complexes to C–C π-systems in the presence of other functional groups combined by its predictable reactivity pattern, the gold(I)-catalyzed reaction provides tremendous opportunities for the discovery of new and useful reactions [12]. Recently, we [13] and other groups [14-17] reported that divergent pathway can be obtained by modulating the steric and electronic properties of the gold(I) catalyst (Scheme 1). The ancillary ligand plays a direct role in the regioselectivity for the first bond formation rather than via a common intermediate created after an initial bond formation [18]. Indeed, the cyclization of cyclic enol ether 1 using σ-donor ligands such as IPr (L1) [19] was exceptionally selective for the 5-exo-dig pathway (1 → 2) whereas bulky Me$_4$XPhos (L2) [12] gave mainly 6-endo-dig-cyclized product 3.

Results and Discussion
During the course of our investigation, we examined the cyclization of non-cyclic enol ethers. As expected, the cyclization of enol ether 4 using [L2AuNCMe][SbF$_6$] in dichloromethane afforded the cyclohexene 5 in 79% yield (Scheme 2). However, the anticipated 5-exo-dig product 6 was
not observed when the catalyst [L1AuNCMe][SbF6] was utilized. Instead, the benzothiophene 7 was isolated in 89% yield. The formation of this unforeseen product can be explained by the proposed mechanism illustrated in Scheme 2. The gold(I) complexation of alkyne 4 triggers the 5-exo-dig cyclization to produce intermediate 9. At this point, a nucleophilic addition of the thiophene unit to the carboxonium provides the sulfonium 10 which upon protodeauration and aromatization gives 7 [20-25]. Other polar solvents such as acetone and dichloromethane were employed without much success. One might consider that the high polarity of nitromethane helps to alleviate the charge build-up at the cationic cyclization transition state.

Substituted aromatic compounds have a fundamental importance in organic and medicinal chemistry as well as in materials. Although there are many methods to functionalize aromatic rings, one can recognize that the above transformation represents an attractive and complementary approach for the synthesis of substituted aromatic rings. Taking advantage of the high regiospecificity of [L1AuNCMe][SbF6] associated with alkyne activation, we examined the scope of the reaction using
various substituted alkynes (Scheme 3). Gold(I)-catalyzed cyclizations of the enol ether 11a (R1 = p-BrC6H4, R2 = H) gave the corresponding benzothiophene 12a in 83% yield. The use of electron-poor silyl enol ether 11b (R1 = p-NO2C6H4, R2 = H) gave the desired product 12b, albeit in lower yield of 63%. Di- and trisubstituted silyl enol ethers 11c (R1 and R2 = H) and 11d (R1 = H and R2 = Me) were converted to benzothiophenes 12c and 12d in 82% and 95% yield, respectively. The synthesis of substituted hydridened 12e was also achieved in 85% yield from monosubstituted enyne 11e (R1 = Ph, R2 = H). Substituted enynes bearing heterocycles such as indole 11f (R1 and R2 = H) and furan 11g (R1 = Ph and R2 = H) were effectively transformed to the desired carbazole 12f and benzofuran 12g in 95% yields. It can be noticed that large substituents at R1 and R2 did not affect the efficiency of the reaction. The gold(I)-catalyzed cyclization of 11h (R1 = R2 = Ph) and 11i (R1 = Ph and R2 = Me) provided the corresponding benzoazepines 12h and 12i in 91% and 87% yield, respectively.

**Conclusion**

In summary, we have developed a mild and efficient gold(I)-catalyzed 5-exo-dig polycyclization cascade to prepare an array of substituted aromatic compounds such as benzofuran, benzothiophene, carbazole and hydridene in high yields. The use of σ-donor ligands such as iPr (L1) was exceptionally selective for the 5-exo-dig pathway. This Au(I)-catalyzed cyclization occurring in cascade provides a direct access to synthetically useful motifs commonly found in natural products and important medicinally compounds. The application of this method in the total syntheses of senequidolide (13) [26] and ellipticine (14) [27,28] are currently underway and will be reported in due course (Figure 1).

**Experimental**

**General experimental procedure for the Au(I)-catalyzed cyclization:** In a flask equipped with a magnetic stirrer was added the silyl enol ether 11 (0.101 mmol) followed by nitromethane (1 mL) and [L1AuNCMe][SbF6] (0.005 mmol). After stirring overnight, the reaction mixture was concentrated in vacuo and the crude mixture was purified by flash chromatography (1–5% ethyl acetate/hexanes) to give the desired cyclized product 12.

**Scheme 3:** Gold-catalyzed 5-exo-dig carbocyclization cascade.
Supporting Information

Supporting Information File 1
Materials and methods, experimental procedures for 4 and \(11a-i\), characterization data for \(5, 7\) and \(12a-i\), \(^1\text{H}\) and \(^{13}\text{C}\) NMR spectra for all cyclized compounds.

[http://www.beilstein-journals.org/bjoc/content.Supplementary/1860-5397-9-297-S1.pdf]

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Aminofluorination of 2-alkynylanilines: 
a Au-catalyzed entry to fluorinated indoles

Antonio Arcadi¹, Emanuela Pietropaolo¹, Antonello Alvino² and Véronique Michelet*³

Abstract
The scope and limitations of gold-catalyzed tandem cycloisomerization/fluorination reactions of unprotected 2-alkynylanilines to have access to 3,3-difluoro-2-aryl-3H-indoles and 3-fluoro-2-arylindoles are described. An unprecedented aminoauration/oxidation/fluorination cascade reaction of 2-alkynylanilines bearing a linear alkyl group on the terminal triple bond is reported.

Introduction
Introducing fluorine atoms into organic molecules still faces challenges in organic synthesis [1]. Organofluorine compounds found growing use in various areas including pharmaceuticals, agrochemicals, and materials [2]. A significant proportion of pharmaceuticals are fluorinated derivatives because the inclusion of fluorine into organic compounds has been shown to improve properties such as solubility, bioavailability and metabolic stability, which are of great importance for the development of a large number of viable drug candidates [3]. Finding original methodologies for the selective preparation of fluorinated heterocyclic compounds is therefore still highly challenging [4,5]. The variation of the indole structure has been a field of high interest for a long time, considering the importance of this skeleton as a ubiquitous skeleton of pharmaceuticals and bioactive natural products [6-11]. The synthesis of 3-substituted 3-fluoroindoles has been described in the presence of Selectfluor as a commercial source of F⁺, starting from 3-substituted indoles, in acetonitrile/water. These derivatives have been used as key adducts for the indole biosynthesis mechanism as well as synthetic target for the development of novel medicinal agents [12]. Recently, 7-fluoroindole has been proposed as a potential candidate for the use in an antivirulence
approach against persistent Pseudomonas aeruginosa infections [13]. Fluorine introduction in the benzene moiety of respective indoles was accomplished through a variety of methods [14]. 4-Fluoroindole derivatives have been prepared through nucleophilic attack on intermediate 4-iodoindium salts [15]. The regioselective fluorination of the benzene ring of indole to give the important neurochemicals 4-fluoroserotonin and 4-fluoromelatonin was accomplished by means of a lithiation/fluorination sequence [16]. The validity of this latter strategy was also demonstrated for the fluorination at the 2-position of N-protected indoles by electrophilic fluorinating agents. Our literature search revealed that the access to C-3 fluorinated indole derivatives was less investigated. Fluorination of triarylstannyliodole derivatives with cesium fluoroxy sulfate or Selectfluor was investigated for the synthesis of the corresponding 3-fluoroindoles [17]. A borane-tetrahydrofuran complex has been used to study the reduction of 3,3-difluoro-2-oxindoles to give the corresponding 3,3-difluoroindolones when electron-withdrawing groups were present as substituents in the benzene nucleus. The 3,3-difluoro-2-oxindoles were prepared by the reaction of appropriately substituted isatin derivatives with DAST [18]. Anodic fluorination of various N-acetyl-3-substituted indoles was successfully carried out to provide trans-2,3-difluoro-2,3-dihydroindoles which upon treatment with a base gave monofluoroindolone derivatives or monofluoro-3H-indoles depending on the substituents at the 3-position [19]. More recently, the indole ring was difluorinated highly regioselectively at the C-3 carbon site with Selectfluor [20]. The C-3 monofluorinated indole derivatives were supposed to serve as intermediates in the transformation and can be isolated under suitable reaction conditions [21]. We envisaged that the aminofluorination of the readily available o-alkynylaniline derivatives should provide a viable alternative to the desired C-3 fluorinated indoles. Catalytic aminofluorination of alkenes and alkynes is receiving growing attention as efficient way to construct fluorinated heterocycles [22,23]. In particular, Au-catalyzed fluorination strategies by using Selectfluor as an electrophilic source of fluorine [24-31] can provide a powerful tool for building up nitrogen heterocycle derivatives. Fluorinated pyrrolidines [32] and fluorinated pyrazoles [33] have been synthesized from 1,ω-N-protected aminoalkynes and alkynyl phenylhydrazones, respectively. Propargyl amidines were converted into 5-fluoromethylimidazoles in the presence of Selectfluor under gold(I) catalysis [34-36] through a cascade cyclization/fluorination process [37]. Following our previous work on gold catalysts (Scheme 1) [38], we wish to report herein a comprehensive study on gold-catalyzed tandem cycloisomerization/fluorination reactions to access 3,3-difluoro-2-aryl-3H-indoles and 3-fluoro-2-arylindoles, putting the stress on the scope and limitations of such systems.

Results and Discussion
Optimization of the catalytic system
The substrate 2-[[4-(methoxy)phenyl]ethyl]aniline (1a) was selected as a model substrate and was subjected to various conditions in the presence of Selectfluor as the electrophilic fluorine source. The results are compiled in Table 1. When the reaction of 1a was carried out at room temperature with an excess of Selectfluor and water in CH3CN in the absence of any catalyst (Table 1, entry 1), no desired fluorinated indole was detected and degradation of the starting N-unprotected 2-alkynylaniline 1a was observed, which excludes a fluorocyclization according to a direct electrophilic process [39]. When the same reaction was performed in the presence of [bis(trifluoromethanesulfonylimidate)(triphenylphosphine)gold (I) catalyst [40] (5 mol %), the formation of the difluorinated 3H-indole 2a was observed although in low overall yield (Table 1, entry 2). No traces of C–C bond formation, a competitive pathway in the presence of gold catalysts and Selectfluor [41-43] were observed. The yield of 2a was increased to 35% when the reaction was carried out in the presence of 10 mol % of the gold catalyst (Table 1, entry 3). Various other parameters were modified to increase the reaction efficiency. The amount of water played a determinant role in CH3CN as the reaction medium (Table 1, entries 3–5). The presence of water is considered important both as a reagent and for helping the dissolution of Selectfluor in CH3CN. One of the most notable limitations on the use of Selectfluor is indeed its relative insolubility in commonly used organic solvents. Even in MeCN, the solvent of choice for many reactions with Selectfluor, its solubility is undesirably low and presents a limitation in its overall use as a fluorinating agent. The presence of a minimal amount of water has previously been reported to increase the yield of fluorination in the 5-position of mono- and nonbrominated 2-acylpyroles with Selectfluor under microwave conditions [44]. The presence of larger amounts of water may nevertheless
speed up the protodeauration of the indolylgold species derived from the gold-catalyzed aminoauration of 1a to give the 2-substituted indole [39]. The reaction of 1a was also evaluated in various solvents and proceeded nicely in EtOH compared to MeCN, 1,4-dioxane, and acetone (Table 1, entries 9, 11, and 12).

In the presence of EtOH, we were pleased to find that the desired adduct 2a was isolated in 75% yield (Table 1, entry 9). The addition of NaHCO₃ [20,33] as a base to the reaction mixture failed to give 2a, whereas it was successful for the preparation of fluorinated pyrazole, via the gold(I)-catalyzed tandem aminofluorination of 1-phenyl-2-(4-phenylbut-3-yn-2-ylidene)hydrazine. Other gold catalysts such as gold(III) species presented interesting results for the reaction beside lower yield than gold(I) catalyst (Table 1, entries 14–16 vs entries 9 and 13). Other transition metal catalysts such as PdCl₂, PtCl₂, CuCl₂·2H₂O, RuCl₃·2H₂O, or AgNTf₂ were also tested, but did not give the desired difluorinated 3H-indole (Table 1, entries 17–21). We selected the PPh₃AuNTf₂ catalyst as a highly efficient complex and the cheaper NaAuCl₄·2H₂O catalyst and decided to confront their reactivity to various substrates.

We selected some derivatives (1a–e, 1g, 1i and 4a,b) from literature [38,39,45-51] and synthesized them together with new functionalized 2-alkynylanilines to evaluate the efficiency of the gold catalytic system.

### Scope and limitations of the catalytic system

The prepared 2-substituted anilines were then engaged in the cycloisomerization/fluorination process in the presence of the Au(I) cationic catalyst or the Au(III) catalyst (Table 2, conditions A and B). The anilines 1b–1f were subjected to conditions A and B at room temperature or refluxing ethanol. Under conditions A, the NaAuCl₄·2H₂O catalyst operated smoothly and Selectfluor (3 equiv) was added when full conversion of the
Table 2: Cycloisomerization/fluorination reaction of 2-substituted anilines.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aniline</th>
<th>t [h]</th>
<th>Cond.</th>
<th>T</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>1</td>
<td>A</td>
<td>reflux</td>
<td><img src="image" alt="Product 2b" /></td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>0.75</td>
<td>B</td>
<td>reflux</td>
<td><img src="image" alt="Product 2b" /></td>
<td>74</td>
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<tr>
<td>3</td>
<td>1c</td>
<td>24</td>
<td>A</td>
<td>rt</td>
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<td>83</td>
</tr>
<tr>
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<td>1c</td>
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<td>B</td>
<td>rt</td>
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<td>57</td>
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<td>5</td>
<td>1d</td>
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<td>A</td>
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<td>76</td>
</tr>
<tr>
<td>6</td>
<td>1d</td>
<td>0.75</td>
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<td>reflux</td>
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<td>85</td>
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<tr>
<td>7</td>
<td>1e</td>
<td>24</td>
<td>A</td>
<td>rt</td>
<td><img src="image" alt="Product 2e" /></td>
<td>67</td>
</tr>
</tbody>
</table>

Conditions: A) 5 mol % NaAuCu₂·2H₂O, EtOH/H₂O, rt or reflux. b) Selectfluor (3 equiv).
Conditions B: 10 mol % PPh₃AuNTf₂, Selectfluor (3 equiv), EtOH/H₂O, rt or reflux.
Table 2: Cycloisomerization/fluorination reaction of 2-substituted anilines. (continued)

<table>
<thead>
<tr>
<th>No.</th>
<th>Substrate</th>
<th>Condition</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1e</td>
<td>B reflux</td>
<td>2e</td>
<td>40</td>
</tr>
<tr>
<td>9</td>
<td>1f</td>
<td>A reflux</td>
<td>2f</td>
<td>61</td>
</tr>
<tr>
<td>10</td>
<td>1f</td>
<td>B reflux</td>
<td>2f</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>1g</td>
<td>24 A reflux</td>
<td>2g</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>1g</td>
<td>1 B reflux</td>
<td>2g</td>
<td>–</td>
</tr>
</tbody>
</table>

*Isolated yield.

gold(III)-catalyzed cyclization of 1 was observed. The use of the cationic PPh₃AuNTf₂ complex allowed in situ addition of Selectfluor. Both catalytic systems were efficient and depending on the substrate higher yields were obtained either in the presence of the Au(III) or Au(I) catalyst. The difluoro derivatives 2b–f were isolated in moderate to very good yields. In the case of substrates 2b or 2d bearing an o-substituent group in the aryl moiety, better yields of these desired cyclized and functionalized derivatives were observed in ethanol at reflux (Table 2, entries 1/2 and comparison of 5 vs 6). The reaction conditions were compatible with a halogen substituent such as in 2e (Table 2, entries 7 and 8), which was obtained in up to 67% yield. Gratifyingly the presence of 4-substituted 1H-pyrazole allowed the clean formation of the corresponding difluoroadduct 2f in good isolated yields (Table 2, entries 9 and 10). One limitation was found when 2-substituted pyridylalkyne 1g was subjected to conditions A (Table 2, entry 11). No reaction occurred and the starting material was recovered. A complex reaction mixture was obtained by reacting 1g in EtOH at reflux for 1 h with an excess of Selectfluor (3 equiv) in the presence of PPh₃PAuNTf₂ catalyst (Table 2, entry 12).

The case of aniline 1h was particularly interesting as it showed that ethanol was not a fully inert solvent (Scheme 2, reaction 1). Indeed, when reacting aniline 1h substituted with electron-withdrawing groups on both the aniline and the aryl moiety under Au(III) conditions, the desired product 2h was accompanied by the hemiaminal difluoroadduct 3h, which was isolated in 56% yield. The isolated 3h spontaneously decomposed to give quantitatively 2h. A similar trend was observed in the case of tosyl-protected aniline 4a (Scheme 2, reaction 2). The reaction of the latter compound led to the formation of difluoro hemiaminal 5a in 42% yield. Interestingly a novel derivative 6a was also isolated in 14% yield. We also tested the reactivity of
Scheme 2: Synthesis of hemiaminal derivatives.

trifluoroacetyl-protected aniline 4b, but no cyclization occurred and the starting material was recovered. In the case of the tolyl-substituted alkyne 4c, the difluorinated product 5c was the only isolated derivative in moderate 54% yield (Scheme 2, reaction 3).

We also envisaged evaluating the influence of the alkynyl substituent of the aniline moiety. For this purpose, the Au(III)-catalyzed cycloisomerization/fluorination process was tested on n-alkyl-substituted derivative 1i (Scheme 3). The reaction conducted at room temperature led to the (E)-2-(1-fluorohexylidene)indolin-3-one (7), whose structure and stereochemistry was confirmed by 1H NMR and NOESY experiments (see Supporting Information File 1), in 39% yield. Pleasingly, the monofluoro derivative 8i was isolated in 25% yield by conducting the same reaction at 50 °C and in the presence of a lower amount of Selectfluor.

The mechanism for the formation of 7 (Scheme 4) may imply amino-auration of the alkyne 1i to generate the indolyl–Au complex 1 according to the results observed in the tandem aminopalladation/oxidation process of azidoalkynes [52]. Then the C–Au bond is oxidized by Selectfluor [53-57] and would give the 2-hexyl-3H-indol-3-one (9). The formation of this latter derivative by the oxidation of 2-hexyl-1H-indole [58-62] or 3-fluoro-2-hexyl-1H-indole (8i) [63] cannot be ruled out. The

Scheme 3: Reaction on n-hexyl-substituted derivative 1i.
following fluorination [64-67] of 9 led to 2-(1-fluorohexyl)-3H-indol-3-one (10), which tautomerizes to accomplish the stereo-selective formation of 7.

Considering the reactivity of anilines 1a–1i in the presence of NaAuCl₄·H₂O complex in ethanol and the formation of 8 in the presence of 1 equivalent of Selectfluor, we decided to modify our initial procedure to selectively prepare 3-fluoro-2-arylindoles. We found that the cyclization of various unprotected anilines in acetonitrile followed by one-pot addition of Selectfluor in DMSO allowed the clean formation of monofluorinated derivatives and results are collected in Table 3.

With the optimal reaction conditions in hand, the substrate scope was examined. In the presence of the electron-rich aromatic groups on the terminal triple bond the desired prod-
ucts were isolated in moderate yields (Table 3, entries 1–3). In the presence of the 1H-pyrazolyl moiety the difluorination prevailed over the monofluorination process (Table 3, entry 4). With the 2-alkynylanilines bearing a linear alkyl group on the terminal triple bond, better results were observed in the presence of electron withdrawing groups in the aromatic ring of the aniline framework (Table 3, compare entry 5 with entry 6). It’s noteworthy that the preparation of 3-fluoroindoles is quite challenging. Because of overoxidation, the isolation of 3-fluoroindoles from 2-alkynylanilines has been reported to fail to occur [52] using previously developed silver catalysts [68]. In our cases, the fluorination reactions were conducted at 0 °C to avoid overoxidation processes.

**Conclusion**

In conclusion, we have contributed to the development of one-pot gold-catalyzed aminofluorination of unprotected 2-alkynylanilines. The combination of a Au(I) or Au(III) complex associated to Selectfluor promotes the cycloisomerization/fluorination of non-protected aryl-substituted anilines at room temperature or refluxing ethanol. The reactions were found to be highly substrate- and solvent-dependent as different outcomes occur in ethanol or acetonitrile/DMSO mixture. The functionalized fluorinated indoles were isolated in moderate to very good yields. An unusual aminoauration/oxidation/fluorination cascade reaction was observed with 2-alkynylanilines bearing a linear alkyl group on the terminal triple bond. Further studies are in progress aimed to the selectivity control of the sequential gold-catalyzed oxidative cycloamination process of 2-alkynylanilines.

### Supporting Information

**Supporting Information File 1**

Experimental.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-42-S1.pdf]

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**References**


And references cited therein.


See for the formation of analogues of 9 during Pd- and Au-catalyzed cycloisomerization reactions of nitro-alkyne derivatives.


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