

Digest paper

Merging gold catalysis and haloethynyl frames: Emphasis on halide-shift processes



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ABSTRACT

Haloalkynes can enter a wide variety of metal-catalyzed transformation giving rise to the formation of products with or without showing halide-shift. This article offers an overall view of the reactivity of these substrates under gold catalysis. Particular attention is devoted to intramolecular reactions that involve a concomitant halide-shift process for the case of alkynyl iodides as starting materials.

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Introduction

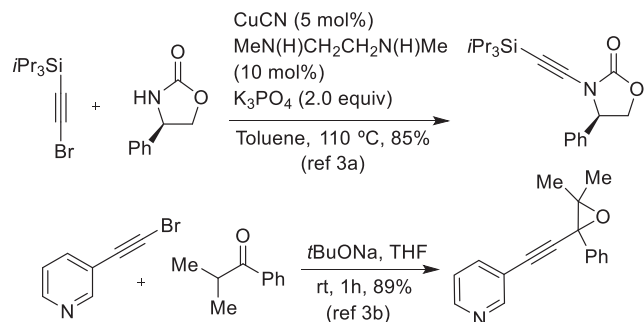
Haloalkynes are unique acetylene derivatives [1]. They are of significance for the preparation of carbon-rich materials [2] and as intermediates for developing synthetic methodology, particularly through a variety of halide substitution processes (Scheme 1) [3].

They are valuable partners in cross-coupling reactions [4], and are useful reagents for an array of innovative catalytic processes involving selective C–H functionalization reactions (Scheme 2) [5].

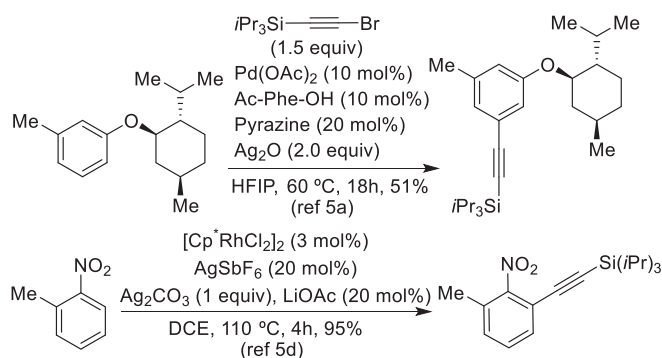
Furthermore, catalytic C–C bond-forming transformations of halogen-masked terminal alkyne derivatives affording products showing halogen retention are known. The dimerization reaction of alkynyl halides offers interesting examples based on the consideration of complementary strategies. Selective head-to-tail dimerization of aryl-substituted iodoalkynes can be catalytically accomplished using a proper source of iodonium ions through a cationic process. The substitution pattern onto the aryl ring dic-

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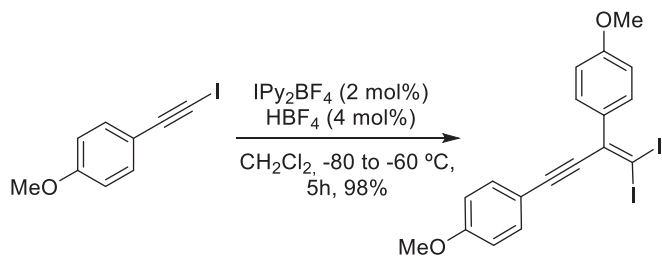
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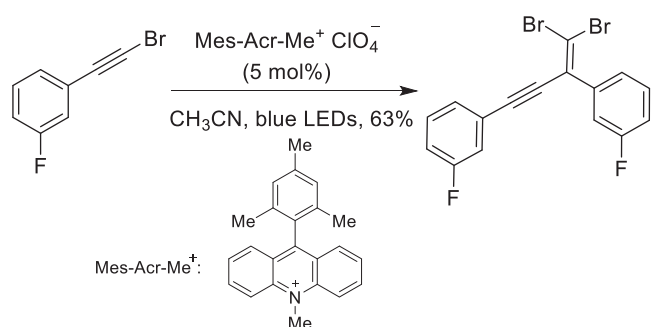
Scheme 1. Synthetic methodology from haloalkynes: formal halide displacement reactions.



Scheme 2. Some recent cross-coupling processes involving alkynyl halides.



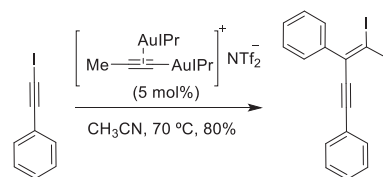
Scheme 3. Iodonium-catalyzed iodoalkyne dimerization reaction.



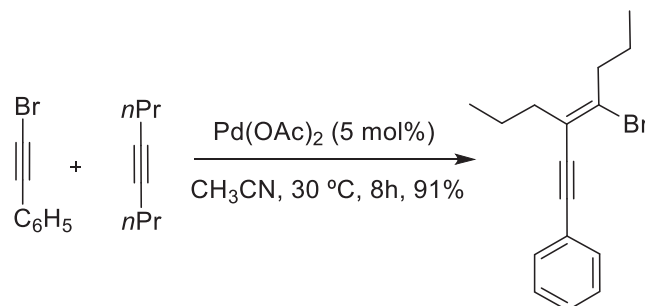
Scheme 4. Photocatalyzed self-coupling of bromoalkynes.

tates the efficiency of the overall transformation, with electron donor substituents affording better results (Scheme 3) [6].

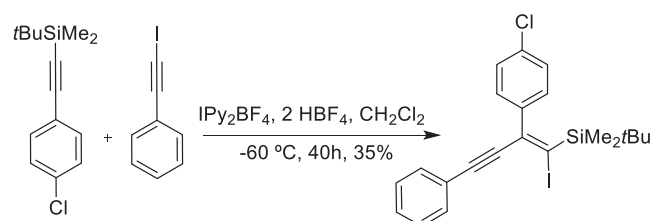
A related photocatalytic coupling reaction of aryl-substituted bromoalkynes was recently disclosed, and yields the head-to-tail dimer in an efficient and selective manner (Scheme 4) [7].



Scheme 5. Gold-catalyzed head-to-tail coupling of iodoalkynes.



Scheme 6. Palladium-catalyzed bromoalkynylation of alkynes.



Scheme 7. Iodonium mediated cross-dimerization of an iodoalkyne and a silyl-substituted alkyne.

Mechanistically, an energy transfer pathway promoted by visible-light photocatalysis resulting in the formation of bromine and arylacetylene radicals was proposed.

Also recently, gold(I) complexes were identified as valuable catalysts to give the corresponding 1,1-diodo-1-en-3-yne from the parent (iodoethynyl)arene precursor. So, when different iodoalkynes were treated in acetonitrile with a catalytic amount of a σ,π -dinuclear propyne-gold acetylide (dual activation catalyst) the corresponding head-to-tail dimerization products were selectively assembled (Scheme 5) [8].

Interestingly, this reaction also allows the dimerization of alkyl-substituted iodoalkynes, expanding the scope previously described for this transformation. This observation is in line with the noticed reactivity of this type of catalyst for the dimerization of aliphatic terminal alkynes [9].

The bromoalkynylation of internal alkynes with bromoalkynes is another synthetically useful halogen-retentive transformation. Jiang showed that palladium acetate is an efficient catalyst to accomplish this demanding task. The C—C bond-making reaction nicely takes place at 30 °C, in acetonitrile as solvent (Scheme 6) [10].

The reaction can be also conducted using an iodoalkyne but in lower yield. So the iodine-containing analogue of the enyne depicted in Scheme 6 was prepared in a related manner from (iodoethynyl)benzene in 48% yield.

In the context of the study of iodonium-promoted self-coupling reactions of (*tert*-butyldimethylsilyl)alkynes to furnish the corresponding head-to-tail dimerization product, it was also reported that iodoalkynes can add across the related TBDMS-substituted

acetylenes to afford the corresponding heterodimer, a process that was not further optimized (Scheme 7) [11].

All those reactions highlight some aspects of the rich chemistry of haloalkynes. This contribution deals with the utility of this class of heteroatom-substituted alkynes to establish new transformations with incorporation of the halogen atom into the structure of the product, in particular through transformations that, reasonably, might be rationalized assuming the intermediacy of metal vinylidene species. Main attention will be devoted to the growing number of gold-catalyzed processes fulfilling this condition. Accordingly, this brief account will be arranged according to the discussion of the main following topics:

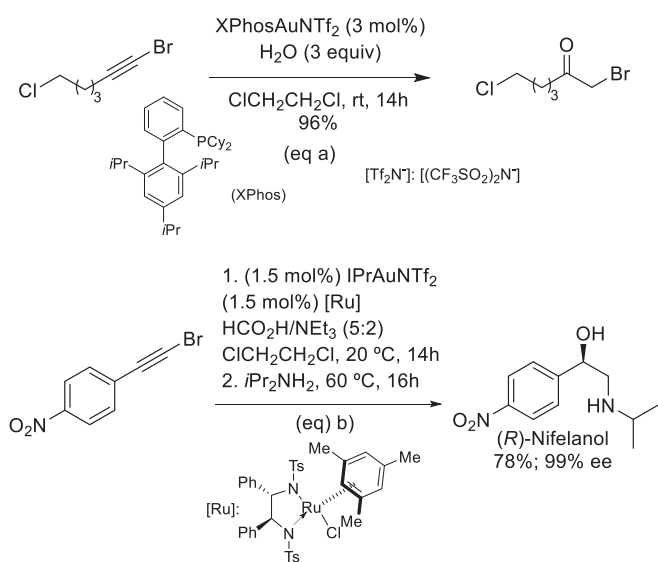
- Gold-catalyzed direct addition reactions to haloalkynes.
- Metal-vinylidenes in organic synthesis.
- Gold vinylidenes: structure and synthetic utility.
- Haloalkynes as a potential source for gold vinylidenes.
- Gold-catalyzed reactions of haloalkynes involving halogen shifting: selective alkyne-alkyne and alkyne-alkene couplings.

In this context we will briefly outline our work in this field, as well as recent contributions from other authors that, though evolving though differentiate reaction mechanisms, contribute to shape and develop another growing hot area for gold catalysis.

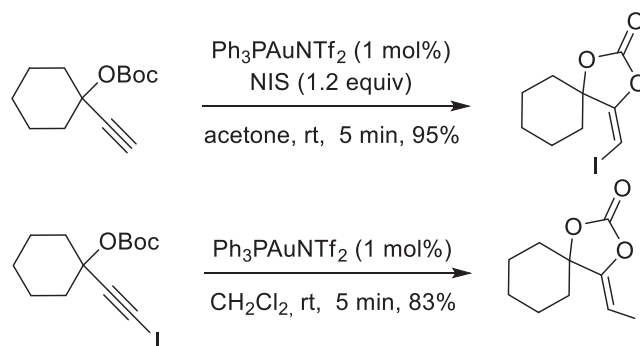
Gold-catalyzed direct addition reactions to haloalkynes.

The above presented transformations are a personal selection of representative reactions that contribute to highlight some significant aspects of the chemistry of haloalkynes. Interestingly, along the two past decades a plethora of gold-catalyzed new synthetic processes and a number of distinctive structural features were documented [12], with alkynes proving to be unique partners for gold [13]. In this scenario, gold-catalyzed hydrofunctionalization reactions of unsaturated C–C multiple bonds were rapidly developed [14]. These processes have an impact onto haloalkyne chemistry, which was put into context in another recent review [15].

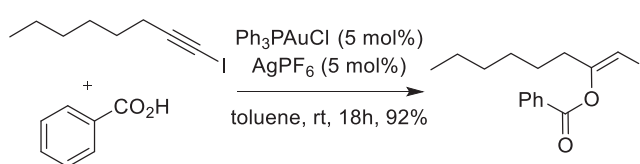
The search for efficient alternatives to the use of mercury salts as catalysts in the addition reaction of water to alkynes offered a useful transformation for catalysts development. It has been an active research arena from the early days of the study of the



Scheme 8. Gold-catalyzed addition of water to bromoalkynes and its subsequent synthetic application.



Scheme 9. Stereoselective synthesis of vinyl iodides from gold(I)-catalyzed cyclization reaction of propargyl carbonates.



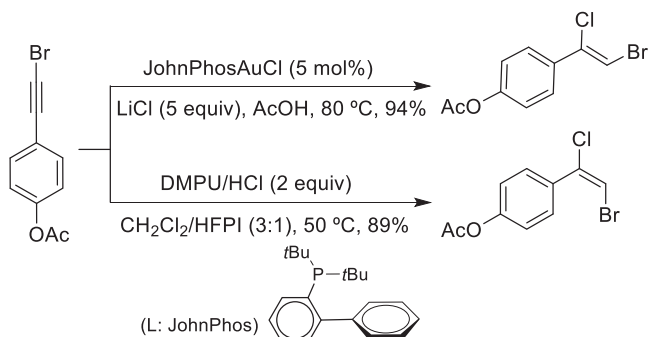
Scheme 10. (Z)-β-iodoenol esters by catalytic intermolecular addition reaction of carboxylic acids to iodoalkynes.

synthetic utility of different gold species [16]. The merit of gold catalysis to access α-halomethylketones upon reaction of haloalkynes with water was proved (Scheme 8, eq a) [17].

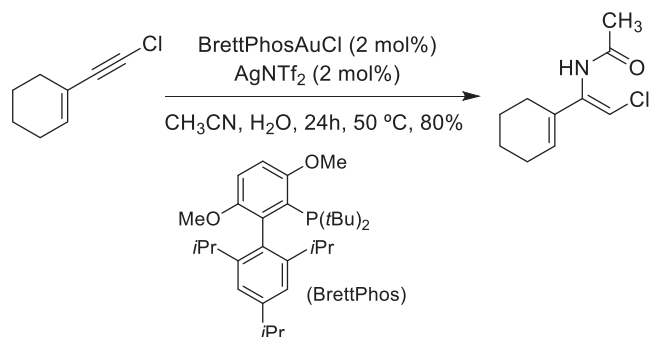
A related regioselective hydration reaction of halo-substituted propargyl carboxylates under gold(I) catalysis was reported to produce valuable synthetic intermediates having the structure of α-acyloxy α'-halo ketones [18]. Interestingly, the gold-catalyzed alkyne hydration can be also coupled with a ruthenium-catalyzed asymmetric transfer hydrogenation reaction to furnish chiral β-adrenergic receptor blockers, in a new one-pot cascade, as shown in Scheme 8, eq b for a selective synthesis of (R)-Nifelanol [19].

Furthermore, α-halomethyl ketones can be directly accessed from terminal alkynes conducting the gold-catalyzed hydration reaction in the presence of N-halosuccinimides [20].

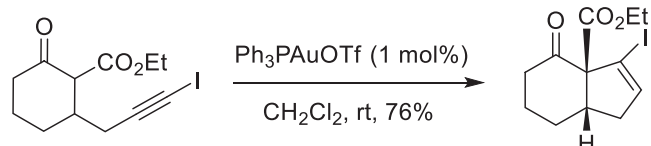
In connection with the iodination reaction of terminal alkynes, Gagosz was the first to demonstrate the nice stereochemical complementarity of gold(I)-catalyzed cyclization reactions of terminal propargyl *tert*-butylcarbonates to prepare cyclic carbonates. To this end, both, the activation of a terminal alkyne under iodination conditions and, alternatively, the related hydro-functionalization process starting from the parent iodoalkyne were developed (Scheme 9) [21].



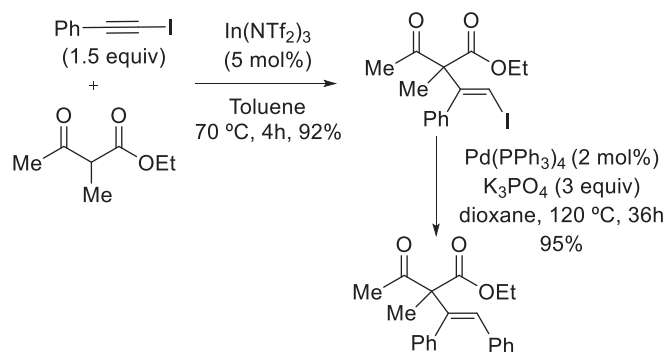
Scheme 11. Catalytic hydrochlorinations of bromoalkynes.



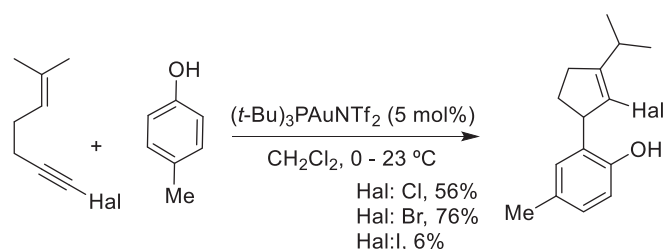
Scheme 12. Gold(I)-catalyzed Ritter reaction of haloalkynes.



Scheme 13. Catalytic Conia-ene cyclization of an iodoalkyne.



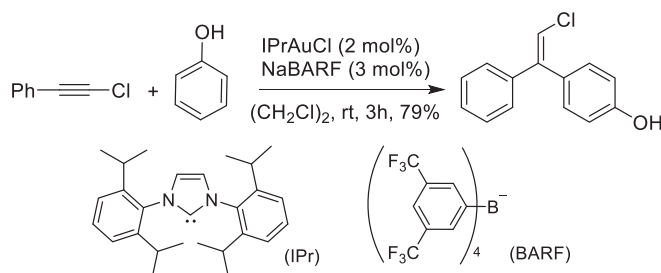
Scheme 14. Indium-catalyzed C-addition to iodoalkynes.



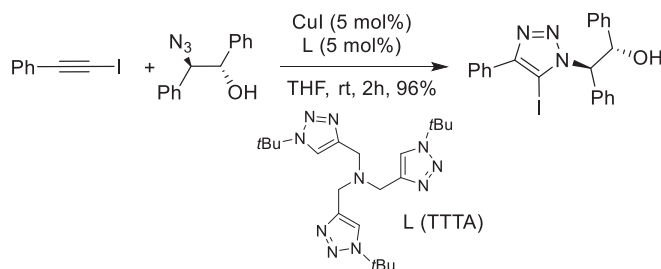
Scheme 15. Catalytic reaction: 1-halo-1,5-enyne and phenols.

Interestingly, Cadierno, García-Garrido and their team reported a synthetically valuable intermolecular addition reaction of carboxylic acids to iodoalkynes, which resulted in the selective formation of (*Z*)- β -iodoenol esters, which were then elaborated into (*Z*)-enynyl esters by palladium-catalyzed Sonogashira cross-coupling reaction with terminal acetylenes (Scheme 10) [22].

Besides oxygen-based nucleophiles, other heteroatoms add across haloalkynes under gold catalysis. Stereoselective hydrochlorination reactions of haloalkynes are known. Catalysis based on both hydrogen-bonding-assisted Brønsted acid and on gold species were applied to this purpose. For instance, 4-(bromoethynyl)phenyl acetate can be selectively diversified into the (*Z*) and (*E*) isomers of 4-(2-bromo-1-chlorovinyl)phenyl acetate applying alternative catalytic conditions (Scheme 11) [23].



Scheme 16. Selective addition of phenols to haloalkynes.



Scheme 17. Iodoalkynes in the CuAAC reaction.

A gold(I) catalyzed Ritter-type process giving (*Z*)- β -halogenated enamides from the reaction of nitriles and water with bromo- or chloroalkynes was recently disclosed (Scheme 12) [24].

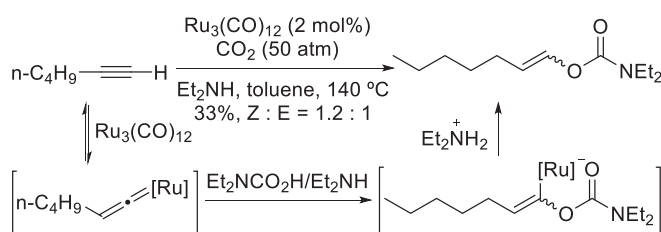
Moreover, new carbon-carbon bond-forming events resulting from direct addition of C-based nucleophiles to haloalkynes are also known. Thus, the iodoalkyne carbocyclization reaction depicted in Scheme 13 represents an early example, which results in a synthetically valuable gold-catalyzed 5-*endo*-dig cyclization of internal alkynes, including both C- and halo-substituted precursors [25].

In some cases, In(III) demonstrated capability to complement Au(I) catalysis promoting addition reactions of C-based nucleophiles to C-C multiple bonds. Thus, Nakamura documented a valuable *syn*-addition of 1,3-dicarbonyl compounds to iodoalkynes. The resulting *E*-alkenyl iodides are partners for further derivatization to assemble trisubstituted alkenes with defined stereochemistry as depicted in Scheme 14 [26].

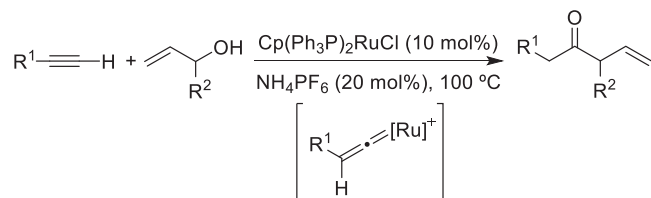
The catalytic reaction of phenols with 1-bromo-1,5-enynes gives 2-(halocyclopent-2-en-1-yl)phenols through a domino process (Scheme 15) [27]. The reaction also works for chloro enynes but fails for the related iodine-modified enynes.

A chemo- and regioselective C-H bond-functionalization of phenols by reaction with haloalkynes under gold catalysis was documented, and gave aryl-substituted alkenes bearing a phenol substituent (Scheme 16). [28].

Moreover, 1-iodoalkynes are particularly reactive substrates towards organic azides in the copper-catalyzed azide-alkyne cycloaddition chemistry (CuAAC), affording 5-iodo-1,2,3-triazoles



Scheme 18. Catalysis by *in-situ* generated vinylidene species.



Scheme 19. Ruthenium-catalyzed reconstructive condensation of terminal acetylenes and allylic alcohols.

in a selective manner, under mild catalytic reaction conditions (Scheme 17) [29]. In this synthetic scenario, the reactivity of this type of internal alkynes exceeds that of terminal alkynes.

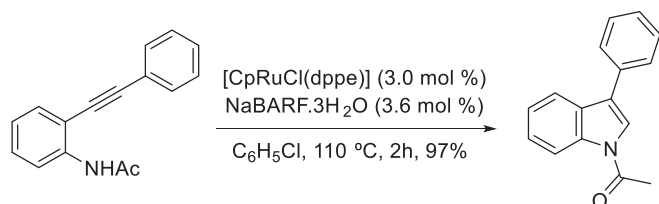
Metal vinylidenes from terminal and internal alkynes: generalities and applications in organic synthesis

Different reaction pathways and precursors are available to access alkenylidene carbene (for short vinylidene) intermediate species [30]. The generation of vinylidene reactive species by isomerization of terminal alkynes attracted much interest over the years [31]. Transition metal vinylidene compounds allow for a fine tuning of the reactivity of these types of reaction intermediates, enabling unique catalytic applications in organic synthesis [32]. Seminal discoveries from Dixneuf resulted in the assembly of vinyl carbamates from ruthenium-catalyzed reactions of terminal alkynes, CO₂ and diethylamine (Scheme 18) [33].

First, polynuclear ruthenium complexes were used as the catalyst source [33s]. Conditions were then identified using mononuclear complexes [33b]. Ruthenium-vinylidene intermediates resulting from the initial interaction of terminal alkynes with the metal were proposed as the catalytic active species [33c]. Also very early, Trost disclosed a ruthenium-catalyzed addition of allylic alcohols to terminal alkynes affording β,γ-unsaturated ketones. Mechanistic studies support the participation of a ruthenium vinylidene complex as the reaction intermediate (Scheme 19) [34].

Merlic presented a ruthenium-catalyzed cyclization reaction of dienylnalkynes based on this principle. A variety of fused carbo- and heterocyclic structures were prepared in a catalytic manner [35]. Ruthenium catalysis greatly contributed to develop the synthetic potential associated with the terminal alkyne to metal vinylidene equilibria [36]. Nonetheless catalytic systems based on other metals were also documented [37–40]. The terminal alkyne to vinylidene isomerization at a metal center keeps on drawing much attention from the chemical community [41].

In addition to the potential associated with the use of terminal alkynes as substrates to access reactive metal vinylidene species, structural studies proving that internal alkynes can also generate metal vinylidene are known. Thus, the thermal reaction of a cyclotriphosphato ruthenium complex with an internal alkyne gave rise to the isolation and characterization, both in solution and in the solid state, of ruthenium-vinylidene complexes [42].



Scheme 20. Indoles upon Ru-catalyzed 1,2-carbon shift.

Besides disclosing the synthesis of additional cationic iron and ruthenium vinylidene complexes from isomerization reactions of diarylacetylene derivatives [43], as well as computational studies on this rearrangement process [44], Mutoh and Ishii reported catalytic applications for this elusive entry to vinylidene complexes [45–47]. Thus, based on the 1,2-carbon migration, a ruthenium-catalyzed *N*-[2-(arylethynyl)aryl]acetamide cycloisomerization leading to *N*-acyl-3-arylindoles was presented (Scheme 20) [48].

Metoxycarbonyl [49] and acyl [50] substituted alkynes are also proper sources of carbon-based groups that enter this alkyne to vinylidene isomerization step, at a transition metal center.

Far from the above discussed C-substituted internal acetylene derivatives, heteroatom-substituted ones encode a wide set of differentiate classes of precursors. They found utility to assemble metal vinylidene complexes at transition metal centers, which keeps on expanding the borders of this field. Among them, structural studies on the complexes resulting from the 1,2-migration of elements belonging to group 14 other than carbon, as silicon [51] and tin [52], and group 16, as sulfur [53] and selenium [54], were early reported and conquered attention. More recently, the use of phosphorous-substituted alkynyl derivatives to access vinylidene species was also proved. [55].

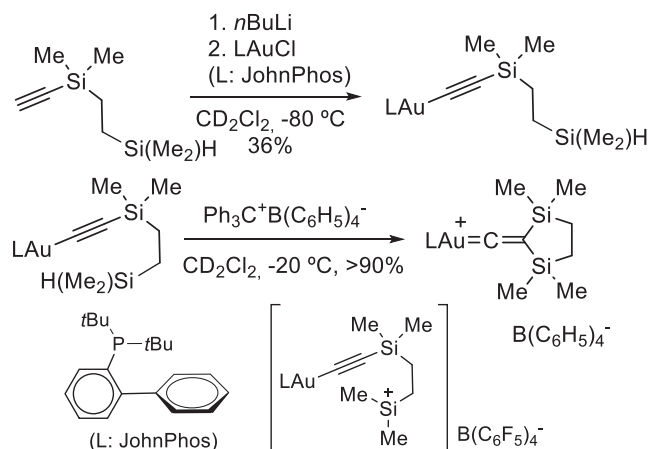
Gold vinylidenes from terminal alkynes: structural features and synthetic utility

Along the past two decades, research efforts aimed to promote the catalytic activation of alkynes by means of gold complexes underwent enormous advances [13,56]. Compared with significant discoveries of complex reaction settings based on gold-catalyzed activation of alkynes through an intermediate gold carbene, the number of studies and the progresses accomplished dealing with related vinylidene intermediates are scant and more recent [57].

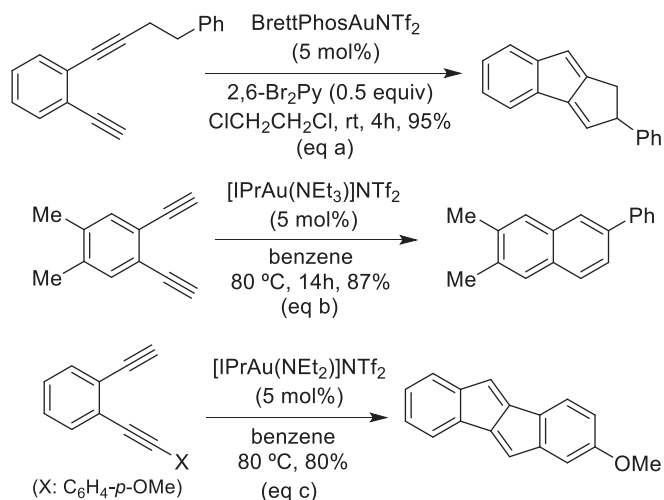
From the structural point of view Widenhoefer revealed useful insights into the nature of this elusive intermediate species, characterizing the first gold vinylidene complex (Scheme 21) [58].

At present, the most advanced and practiced approach that exploits the potential of gold vinylidenes to move forward the field of organic synthesis relies on the notion of dual activation catalysis. Remarks on gold acetylides [59], and key findings in late 2011 independently accomplished by the groups of Zhang and Hashmi contributed to develop this notion (Scheme 22).

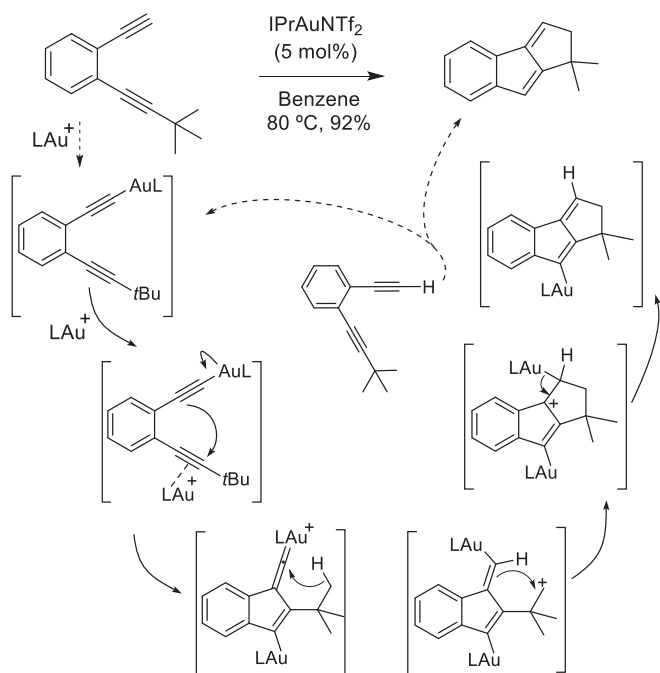
Zhang documented a BrettPhosAuNTf₂-catalyzed isomerization of (2-ethynylphenyl)alkynes to tricyclic indenes (Scheme 22, eq a) [60]. Mechanistic and computational studies support the involvement of gold vinylidenes as key intermediates. Almost simultane-



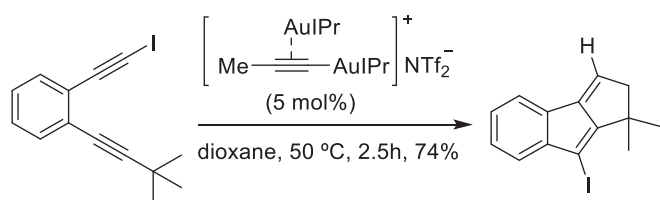
Scheme 21. Gold vinylidene synthesis and characterization.



Scheme 22. Bases for the dual gold catalysis approach to catalytic gold vinylidene generation and synthetic applications. [IPr: 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene].



Scheme 23. Dual gold-catalyzed approach to benzofulvenes.



Scheme 24. Dual gold-catalysis involving an iodoalkyne.

ously, studies by Hashmi proposed a key role for gold vinylidene intermediates to explain the unexpected formation of β -arylated naphthalene regioisomers in cyclization-hydroarylation reactions of 1,2-dialkynylarenes with benzene, using IPrAuNTf₂ as catalyst (Scheme 22, eq b) [61]. Hashmi also reported the synthesis of

dibenzopentalenes from arene-1,2-diynes featuring an aryl-substituted and a terminal acetylene fragments (Scheme 22, eq c) [62–64]. A dual activation mode of the two alkyne fragments was invoked. The involvement of gold vinylidene intermediate was crucial to rationalize this result.

A detailed mechanistic picture of the events involved in the catalytic dual-activation mode was disclosed by Hashmi and his team (Scheme 23) [65], including the eventual catalyst transfer-step and the equilibrium between the active monogold species involved in such operation and the *gem*-diaurated species.

The notion of dual gold catalysis rapidly matured and the resulting synthetic methodology was soon put into context and reviewed [66]. Besides, Hashmi and his group further reported relevant new transformations [67] and careful studies on the detection of intermediate species operating in the dual-gold-catalyzed activation of 1,5-diynes towards benzene, providing support to the conceptual basis behind the strategy [68].

Early, this group also recognized the merit of the dual gold-catalysis to get iodofulvenes from catalytic cycloisomerization reactions of 1-(3,3-dimethylbut-1-yn-1-yl)-2-(iodoethynyl)arenes (Scheme 24) [69]. The catalytic cycle comprises the generation of a gold acetylide. Subsequently a gold vinylidene results out of the dual activation mode and evolves through different species to render a vinyl gold intermediate, which yields the iodo-containing fulvene via an unprecedented iodine/gold exchange.

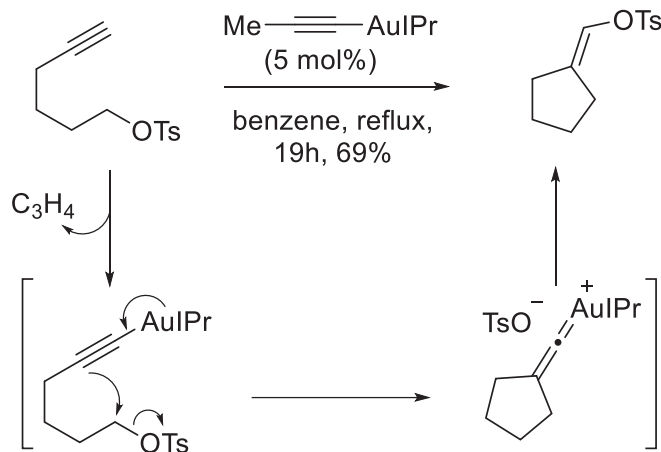
Nowadays, the dual gold-catalysis activation mode is a fairly active research arena and several groups are contributing to its further development. Additional intramolecular elaboration of diyne frames into synthetically useful products were reported [70–72].

Apart from dual gold-catalysis, Hashmi and his group reported a catalytic strategy for the cyclization of α,ω -alkynyl tosylates to cycloalkylenemethyl tosylates, which is proposed to involve as intermediate a gold-vinylidene (Scheme 25) [73]. The yield was optimized by fine tuning the NHC ligand. Replacing the 2,6-diisopropylphenyl unit attached to one of the nitrogens by a cyclopentadecyl group, increases the yield from 69% up 92%.

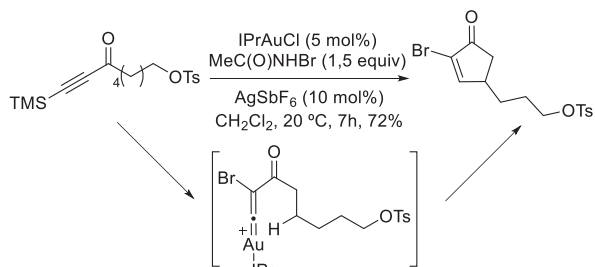
Gold(I) acetylides offered additional alternative entries to gold vinylidenes. Zhang showed that the catalytic reaction of conjugated enynones with gold(I) in the presence of a bromonium donor renders cyclopentenone frames (Scheme 26) [74].

Fürstner also recognized a gold vinylidene as intermediate in the reaction of TBSOTf with the 2'-substituted IPr-gold acetylide derived from [1,1'-biphenyl]-2-carbaldehyde (Scheme 27) [75].

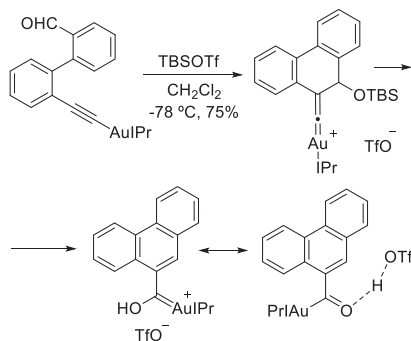
As shown in the previous section, several metals react with terminal alkynes to give vinylidene complexes via 1,2-hydrogen shift. Using gold catalysis, Gevorgyan and his group reported



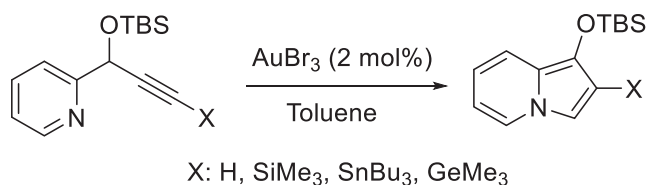
Scheme 25. Leaving group approach to gold vinylidenes.



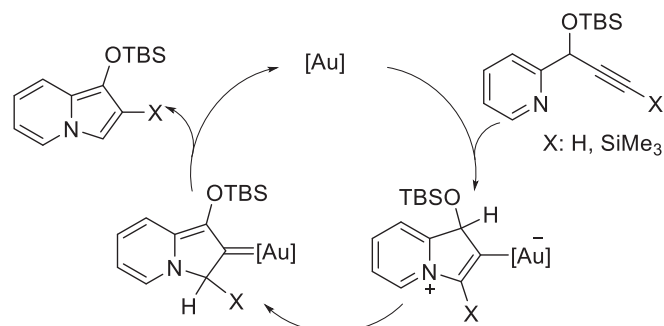
Scheme 26. Gold vinylidenes by intermolecular electrophilic activation of acetylides.



Scheme 27. Gold vinylidenes by intramolecular electrophilic activation of acetylides.



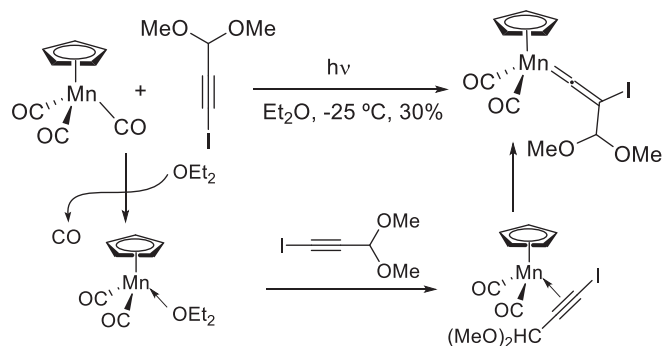
Scheme 28. Gold(III)-catalyzed cycloisomerization involving 1,2-hydrogen shift.



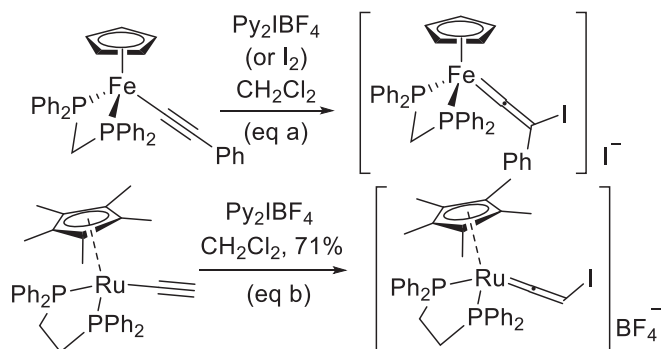
Scheme 29. Catalytic isomerization of propargylpyridines.

gold(III)-catalyzed cycloisomerization reactions of propargylic derivatives from *N*-containing heterocycles (Scheme 28) [76].

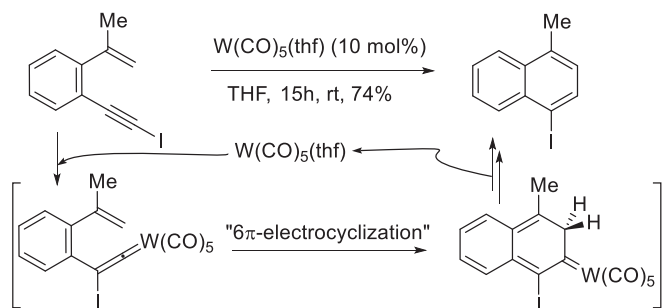
It features a 1,2-H shift from a terminal alkyne, as well as 1,2-migrations of silyl, stannyl and germly groups from the corresponding heteroatom-masked acetylene precursors. Based on the structure of the products and some control experiments, it was initially assumed that the reaction involves a gold vinylidene as intermediate. Subsequent, theoretical calculations fully supported an alternative mechanism (Scheme 29) [77].



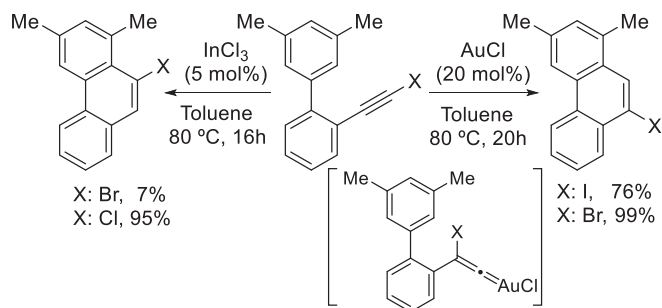
Scheme 30. 1,2-I shift to give β -iodo Mn-vinylidene complex.



Scheme 31. Metal-vinylidene complex upon reaction of metal-acetylides with iodonium donors.



Scheme 32. Catalytic elaboration and reactivity of an iodo-substituted tungsten vinylidene complex.



Scheme 33. Pioneering work on 1,2-halogen migration from gold-catalyzed haloalkyne activation reactions.

Haloalkynes as precursors for metal vinylidene complexes

Several transition metal complexes undergo oxidative addition processes in the presence of alkynyl halides, thus limiting the

applicability of these heteroatom-substituted alkynes to furnish vinylidene complexes. Even though, some examples are known, virtually involving iodo-substituted acetylene derivatives.

Early observations using other metals than gold.

Berke prepared and characterized by X-ray diffraction a manganese vinylidene complex upon irradiation of a iodoalkyne and cyclopentadienyl manganese tricarbonyl (Scheme 30) [78].

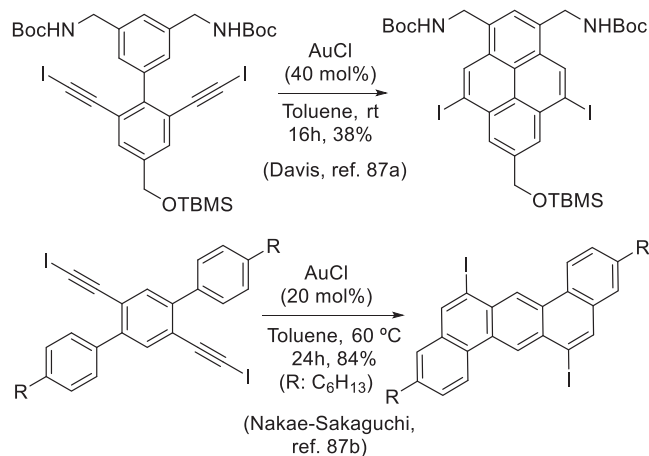
An opposite entry to forge vinylidene complexes at transition metal centers is based on the reaction of transition metal acetylides with a proper halogen source of the electrophile, a process that selectively takes place at the β -carbon of the parent alkynyl complex (Scheme 31, eq a [79] and b [80]).

The number of synthetic reports based on a catalytic 1,2-halogen rearrangement is limited. Iwasawa documented a catalytic isomerization of *o*-(iodoethynyl)styrenes into the corresponding iodo-substituted naphthalene derivatives featuring this iodine-migration process (Scheme 32) [81].

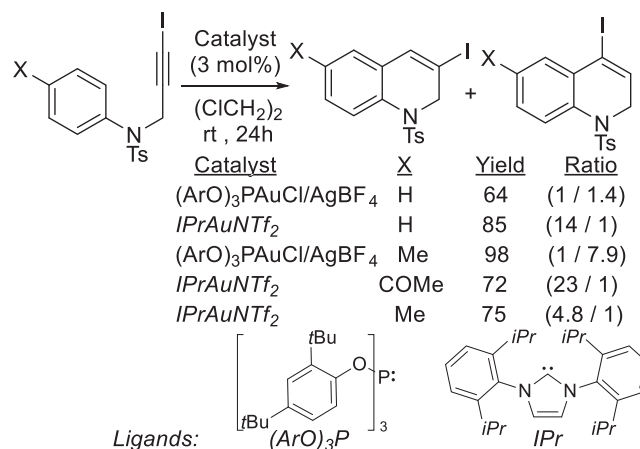
1,2-Halogen shift events in catalytic gold-activation of heteroatom-substituted alkynes: gold vinylidenes as likely reaction intermediates

Fürstner discovered the 1,2-halogen shift reaction in gold-catalyzed cyclization reactions of *o*-alkynyl-substituted biphenyl derivatives (Scheme 33) [82]. Interestingly, within the general context of a search to obtain phenanthrenes, haloalkynes provide a complementary synthetic manifold, which is selectively driven by the catalyst. Thus, after testing different catalyst, InCl_3 successfully afforded the target 10-halophenanthrene derivatives. Moreover, adding AuCl as catalyst, the 9-halo-substituted regioisomer was exclusively formed [83].

This alternative process was explained assuming the formation of a gold vinylidene as the reactive species resulting from a 1,2-halogen migration. Then, different groups reported DFT calculations on the mechanism of these transformations. The reached conclusions from these theoretical studies depend on the accuracy of the chosen functional. Thus, for the gold(I) catalyzed process, relying on B3LYP/6-31G* (LANL2DZ) calculations, an initial gold complexation to the haloalkyne, followed by the 1,2-halide shift to the vinylidene complex and subsequent 6-*endo-dig* electrocyclization and then a 1,2-H shift were identified as the steps outlining the energetically most favorable reaction pathway [84]. Then, years later, subsequent M06/6-31+G* (LANL2DZ) calculations originated a different sequence of events to explain the cycloisomerization leading to 9-halophenanthrenes under gold(I) catalysis



Scheme 34. Polycyclic aromatics from migration-cyclization.



Scheme 35. Catalytic assembly of regioisomeric heterocyclic frames.

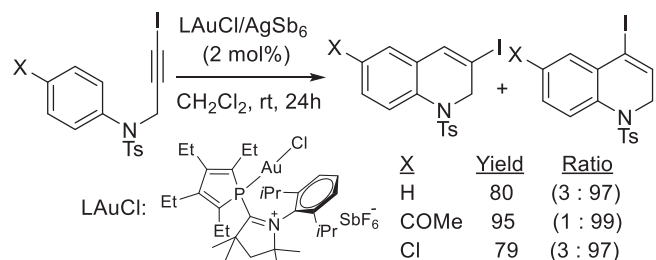
[85]. Now, the outcome of the gold-catalyzed electrophilic hydroarylation results from an initial 6-*endo-dig* cyclization that renders the Wheland-type intermediate, which evolves through a 1,2 migration of H, followed by a kinetically favored 1,2-Br shift [86].

Anyway, the number of reports on C–C bond-formation based on gold-catalyzed reactions of haloalkynes via a 1,2-halogen shift is limited. In all the cases, the haloalkyne unit was bounded to the arene ring and the strategy was focused on its application to the synthesis of pyrene, picene and dibenzo[*a,h*]anthracene cores through catalytic events involving double migration-cyclization processes (Scheme 34) [87].

Considering the attention payed by our laboratory to establish different hydroarylation strategies, including iodonium-promoted and metal-catalyzed arylation reactions of different unsaturated motifs [88–90], we became interested in broaching the synthetic potential of that halogen-dancing cyclization mode under gold catalysis. Moreover, gold-catalyzed hydroarylation reactions of terminal *N*-propargyl aniline and phenol derivatives usually require the presence of additional activating substituent at the arene platform to be of synthetic utility [91]. On this ground, we first tested the merit of the process to assemble common heterocyclic frames with distinguishable regiocontrol. Also, we were attracted by the possibility of doing so on the basis of using as catalysts only gold-based complexes. Furthermore, exploring the outcome of the reaction when additional electron-withdrawing substituents are present at the arene platform is another attractive task to consider. On this ground, the reaction of *N*-(3-iodoprop-2-ynyl)-*N*-tosylanilines with different gold(I) complexes was tested, and some representative examples are depicted in below (Scheme 35) [92].

The intended points were validated proving that the nature of the ancillary ligand on gold is an essential element of control. Thus, the regular hydroarylation is the main cyclization pathway if the catalyst is based on a phosphite ligand. The performance of this electrophilic system based on a π -acceptor ligand attached to gold and a tetrafluoroborate anion can be additionally tuned by the substitution at the arene fragment of the propargyl aniline derivative. In fact, the introduction of a modest donor substituent enhances the efficiency and the regioselectivity of the cyclization. Just switching from H to Me-substitution at the *para*-position of the starting material renders a preparative useful transformation. Thus, affording a regioselective synthesis of the *N*-tosyl-4-iodo-6-methyl-1,2-dihydroquinoline from a common hydroarylation pathway.

The use as catalyst of IPrAuNTf_2 furnishes as main product the opposite regioisomer (Scheme 35, see X = H). In this case, the IPr is a strong σ -donating NHC ligand and induces a 1,2-I shift prior



Scheme 36. Normal hydroarylation pathway for iodoalkynes catalyzed by gold(I) complexes with α -cationic phospholes.

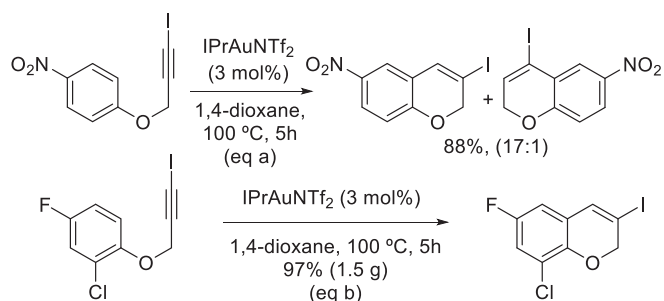
to the cyclization event. Again, the additional substituents at the aniline fragment modulate the intensity of this behavior. Interestingly, an electron-withdrawing substituent at the *para*-position disfavors the normal path and magnifies the formation of the cyclization product with concomitant 1,2-I-shift. For the case of a more electron-rich precursor the IPrAuNTf₂-catalyzed reaction still gives the dihydroquinoline with the associated iodine shift as the main regioisomer from this cyclization event, as shown in [Scheme 35](#) for the *p*-anisidine derivative (X = Me).

Those examples evidence the strong control over the selectivity exerted by the ancillary ligand and the additional tuning over the selectivity dictated by the nature of the aryl moiety. Thus, the combination of a σ -donor ligand with an arene moiety decorated with electron-withdrawing substituents is optimal to afford hydroarylated products showing additional 1,2-iodine dancing. On the contrary, a π -acceptor ligand acting in conjunction with electron-rich substituents at the arene ring tends to favor the formation of a normal hydroarylation product of the parent iodoalkyne.

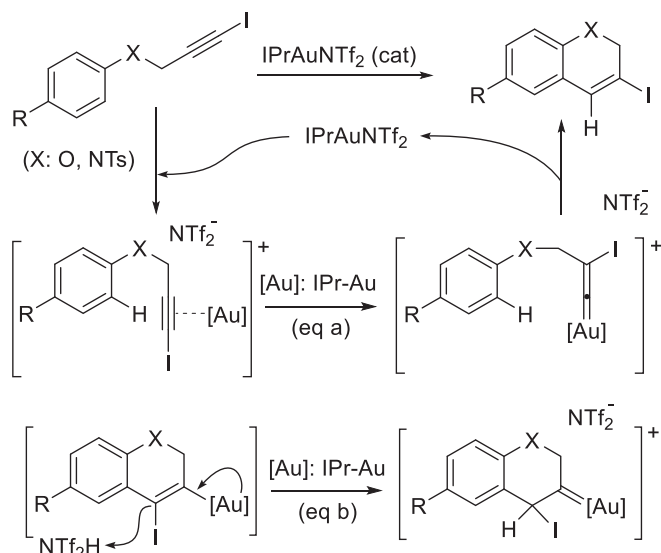
In a recent paper dealing with the design and preparation of strong π -acceptor ligands, Alcarazo showed the unique properties of α -cationic phosphole gold(I) complexes as ancillary ligands to access the normal cyclization, which provides strong support to the previously formulated hypothesis. The new ligand allows a nice discrimination among the two competing cyclization paths, favoring the normal hydroarylation outcome with outstanding selectivity ([Scheme 36](#)) [93].

The resulting gold catalyst targets the preparation of 4-iodo-2,3-dihydroquinolines from intramolecular hydroarylation of iodoalkynes with exquisite selectivity, without showing the previously noticed dependence on the presence of additional activating substituents at the arene.

As we were interested in the less commonly reported pathway leading to cyclization with a concomitant halogen shift, it was challenging to target the synthesis of related 3-iodo-2*H*-chromene derivatives using this type of cyclization. At the same time, it is a demanding process as the tethering ether functional group is a more activating unit than the already studied sulfonamide precursor.



Scheme 37. 1,2-Iodo-shift in the hydroarylation reaction of iodoalkynes catalyzed by a gold(I)-complex with a NHC-ligand.



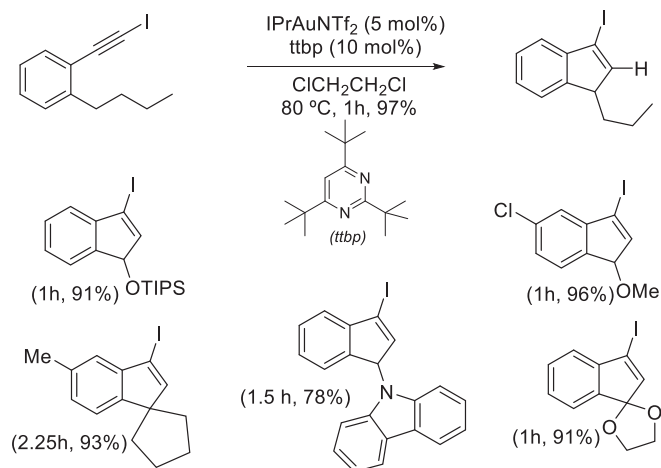
Scheme 38. Mechanistic rationale for the 1,2-iodine shifting iodoalkyne hydroarylation reaction.

Thus, on the basis of the previously gathered knowledge, the gold complex with the powerful σ -donor IPr ligand was selected from the onset. Besides, phenolic moieties containing electron-poor substituents were chosen to conduct this study, searching for a rarely examined substitution pattern in alkyne hydroarylation processes.

Aryl (3-iodoprop-2-yn-1-yl) ethers were cyclized using this approach. Among others, derivatives of phenol precursors substituted at the *para*-position by groups as: CN, CHO, CO₂Et and NO₂ ([Scheme 37](#)) [94].

In all cases, the iodo-shifting process was the major reaction pathway, defining a highly regioselective entry to the catalytic synthesis of 6-substituted 3-iodo-2*H*-chromenes.

The reaction of a substrate containing chiral information at the propargylic position renders the corresponding 1,2-iodo-shifted cyclized product without eroding the stereochemical information, highlighting an additional attractive feature associated with this elaboration of 3-iodo-2*H*-chromene scaffolds. The formation of this type of product was rationalized according to the mechanistic scenario depicted in the equation a, in [Scheme 38](#).



Scheme 39. Intramolecular C–H activation by gold-catalyzed activation of iodoalkynes.

The π -complex formed from the interaction of the iodoalkyne with the electrophilic gold triggers the alkyne activation to yield, upon the 1,2-iodine shift, the reactive gold-vinylidene species that could ultimately be responsible for the noted C—H functionalization. The differentiated nature of this intermediate in comparison to that involved in a straight electrophilic substitution processes might account for the noticed enlarged scope in terms of the tolerated functional decoration present at the arene unit. An alternative reaction path is outlined in equation b. There, a reactive carbene would arise from Au/Pr-assisted protonation of the formed vinyl-gold intermediate resulting from aromatic substitution at the arene by electrophilic attack of the initial gold-alkyne complex. A selective 1,2-iodine migration could be justified in terms of previous related studies [77]. However, the easiness of the initial electrophilic substitution step using arenes bearing additional strong-withdrawing substituents represents an unusual trend for this key step, and a main drawback for considering this alternative reaction path.

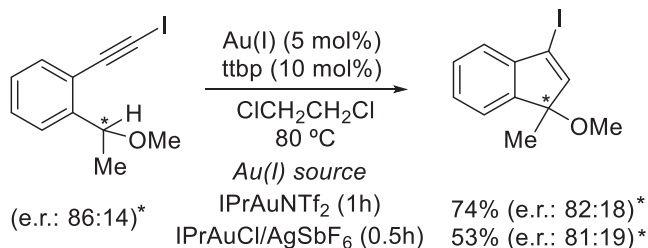
Interestingly, this intended entry to gold-vinylidenes enables the catalytic C(sp³)-H functionalization of benzylic positions [95]. Thus, various 3-iodo-1*H*-indenes were prepared from gold(I)-catalyzed cycloisomerization reactions of the proper parent iodoalkyne, as depicted in Scheme 39 for the assembly of 3-iodo-1-propyl-1*H*-indene from 1-butyl-2-(iodoethyl)benzene [96].

The structure of some representative additional compounds synthesized following this novel approach is also shown. The added tertiary hindered base (ttbp, see Scheme 39) provides a robust catalytic system and offers reproducible reaction conditions, although it takes slightly longer reaction times. In the absence of ttbp the cyclization occurs but, in many cases, the resulting product was found labile under the reaction conditions.

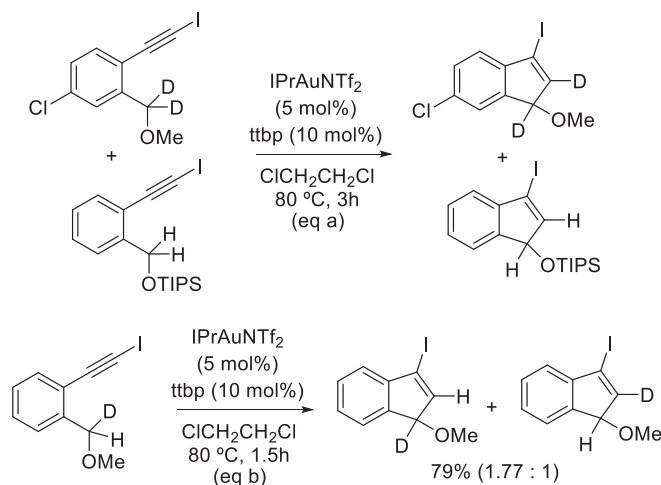
Different control experiments were performed and support the likely involvement of a gold vinylidene as the species responsible for the ring-closing step, via a C—H activation process. In particular, the preservation of the stereochemical integrity noticed for the cycloisomerization of an *enantio*-enriched benzylic chiral precursor offers valuable information concerning the timing of the C—H bond-breaking and C—C bond-making events. The influence of the anion over the stereochemistry was negligible and it reasonably seems to rule out a stepwise transformation involving strong ion pairing (Scheme 40).

Moreover, the lack of formation of cross-over products for the catalytic cyclization of an equimolar mixture of 4-chloro-1-(iodoethyl)-2-(methoxymethyl-*d*₂)benzene and {[2-(iodoethyl)benzyloxy]triisopropyl}silane speaks in favor for an intramolecular nature of the observed process (Scheme 41, eq a).

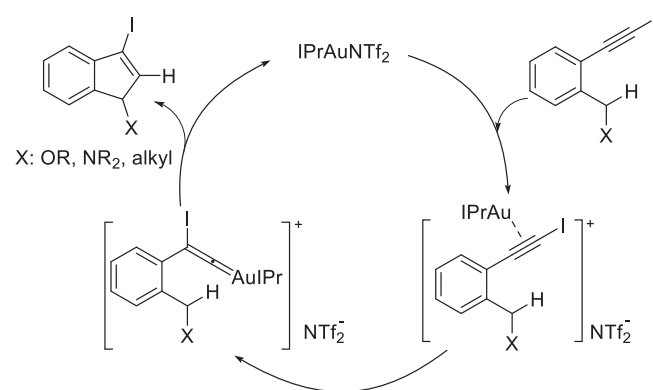
Besides, a figure for the primary kinetic isotopic effect was recorded from an intramolecular competition experiment (Scheme 41, eq b). The figure obtained is in agreement with data early reported in the literature for related 1,5 insertion reactions of C—H bonds in alkylidenecarbenes to generate cyclopentene derivatives [97].



Scheme 40. Stereochemistry for the catalytic intramolecular 1,1-addition of the benzylic C—H bond across an iodoalkyne.



Scheme 41. Studies using deuterium-labelled substrates.



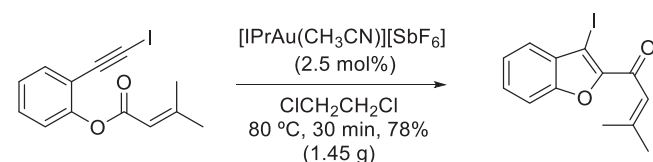
Scheme 42. Proposed C—H insertion reaction into the gold-vinylidene species.

On this ground, the following mechanistic rationale was proposed. The initially formed complex upon interaction of the gold catalyst with the alkyne could evolve to generate a gold vinylidene intermediate by 1,2-iodine shift. Eventually, it could then furnish the 3-iodo-1*H*-indene scaffold via C—H activation, which would occur through an insertion process (Scheme 42).

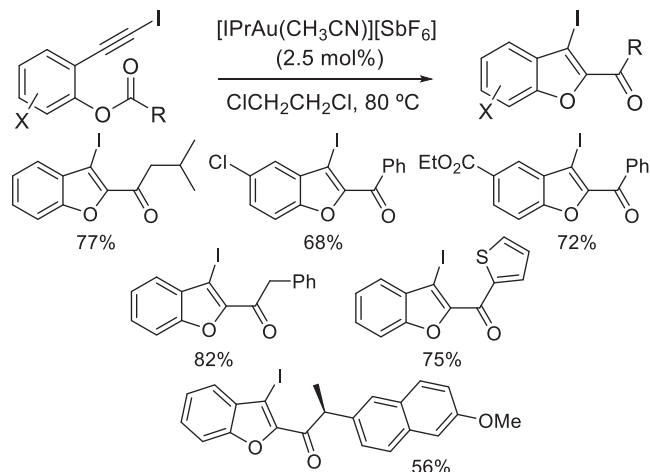
An alternative mechanistic proposal, involving a hydride transfer to the initially formed alkyne-gold complex, followed by ring-closing via nucleophilic attack of the vinyl gold species to the resulting benzylic cation fails to accommodate the noticed results for the assayed stereochemical probes [98].

Recently, in the context of a report on the catalytic activity of in situ generated rhenium-carbene species, the ability of [ReBr(CO)(thf)₂] to cycloisomerize this class of iodoalkynes to 3-iodoindenes was established, and a rhenium-vinylidene was also proposed as key reaction intermediate [99].

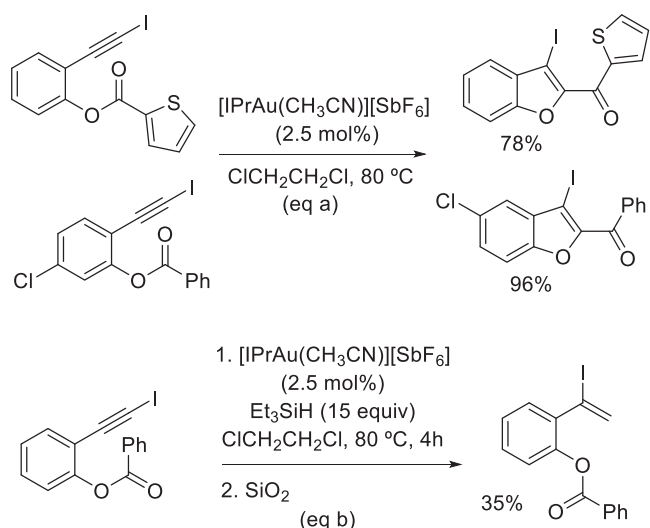
The intramolecular activation of the *O*-acyl moiety of an ester by the species generated from the interaction of the gold catalyst



Scheme 43. Intramolecular ester activation triggered by gold-catalyzed reaction of an iodoalkyne moiety.



Scheme 44. Gold(I)-catalyzed cycloisomerization reactions of acylated o-iodoethynyl phenol derivatives furnishing ketones.

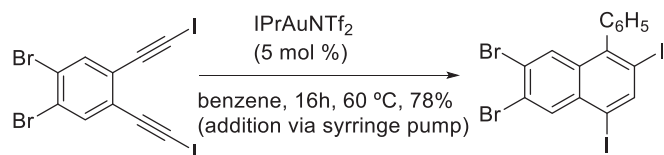


Scheme 45. Additional insights on the cyclization.

with an iodoalkyne represents another attractive and interesting target to further test the reactivity of the proposed β -iodo-substituted gold-vinylidene intermediate. Gratifyingly, this new target was accomplished and resulted in an efficient and catalytic cycloisomerization of acyl-capped phenols into different (3-iodobenzofuran-2-yl) ketone derivatives [100].

The reaction performs nicely using a cationic gold complex, as highlighted for the gram scale conversion of 2-(iodoethynyl)phenyl 3-methylbut-2-enoate to 1-(3-iodobenzofuran-2-yl)-3-methyl-2-en-1-one (Scheme 43.).

The nature of the migrating acyl fragment includes a set of representative patterns, featuring alkyl, alkenyl, aryl and heteroaryl fragments. Some examples, including a late stage modification of



Scheme 46. Gold-catalyzed conversion of 1,5-diiododiyne into diiodinated naphthalene derivatives upon trapping benzene.

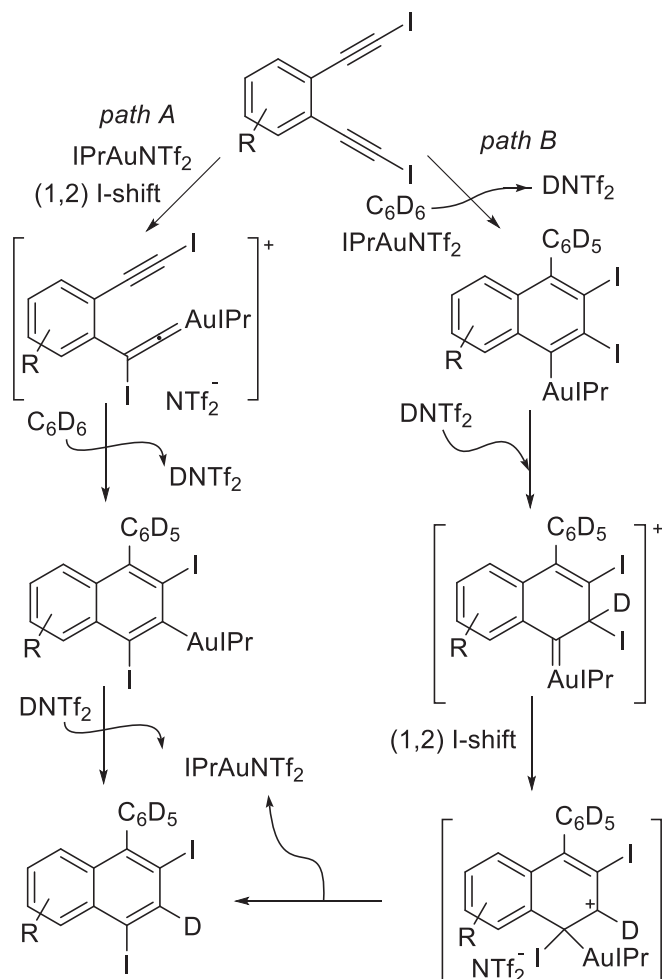
the non-steroidal anti-inflammatory drug (*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid, commercially known as Naproxen, are collected within the Scheme 44. Besides the stereochemical integrity associated with the formation of the ketone resulting from modification of Naproxen, additional information concerning the evolution of the reaction was gathered.

Only the products corresponding to an intramolecular process were found when the outcome of a potential crossover experiment was tested (Scheme 45, eq a). Besides, conducting the reaction in the presence of an excess of triethylsilane inhibited the cyclization. Isolation after chromatographic purification of the product likely arising from the alternative trapping of the intermediate upon silane insertion, followed by protodesilylation was noticed (Scheme 45, eq b).

These experiments are compatible with the involvement of gold vinylidene reactive intermediate species for this catalytic unusual oxy-acylation reaction of iodoalkynes [101].

Hashmi reported that 1,2-bis(2-iodoethynyl)arenes (Scheme 46) [102] enter a cyclization mode different than other classes of 1,5-diyne previously investigated (see previous Schemes 22 and 24).

This new behavior was rationalized considering a different mechanistic frame to that previously described for the formation of iodofulvenes in a dual gold catalysis scenario. However, now for the assembly of the diiodinated naphthalene derivatives, an initial 1,2-I shift leading to a gold-vinylidene was proposed, as outlined in Scheme 47 (path A), for the reaction with perdeuterated benzene.



Scheme 47. Mechanistic evaluation of the catalytic assembly of diiodonaphthalenes from 1,5-diyne and deuterated benzene.

In the presence of the aromatic solvent, the electrophilicity of the vinylidene species promotes the cyclization event and the liberation of a proton/deuterium, which ultimately would be the responsible of closing the catalytic cycle by protodeauration of the C–Au bond, regenerating the catalyst and releasing the assembled naphthalene frame. The D-labelled scaffold (around 80% deuterium incorporation) is fully consistent with this model.

An alternative mechanistic picture was also safely evaluated (path B), though it was considered less likely bearing in mind the position at which the deuterium label was exclusively incorporated. This alternative model is also depicted. It follows the guiding principle already analyzed as a potential carbene approach in the previously discussed hydroarylation reaction of iodinated propargylic *N*-tosyl aniline and phenol derivatives (Scheme 38), though it cannot be firmly ruled out, at this point.

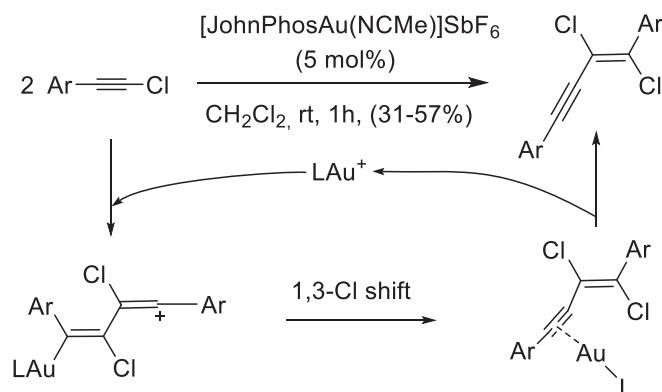
Other types of gold-catalyzed reactions of haloalkynes involving halogen-shifting: selective alkyne-alkyne and alkyne-alkene couplings

After Hashmi's discovery on dual gold-catalyzed head-to-tail coupling reactions involving haloalkynes [8] (Scheme 5), attention has been devoted to unveil the potential offered by haloalkynes to devise new gold-catalyzed coupling processes of synthetic significance. The role played by cationic halogen rearrangement reactions in those reactions was clarified and contribute to outline a differentiate challenging synthetic arena, which further highlight the significance of haloalkynes in the context of gold catalysis. Though evolving through alternative reaction intermediates, as shown by pertinent experimental and theoretical work, these transformations are formally related to the main issue being discussed in this digest paper and, consequently, key results are also briefly summarized within this section.

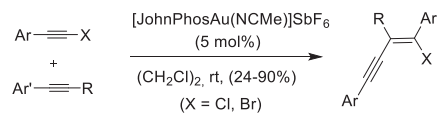
In a combined theoretical and experimental study, Haberhauer identified alternative conditions to access the elusive head-to-head process of chloroacetylenes via gold catalysis, a reaction that selectively affords *E*-dimerization products (Scheme 48) [103].

Interestingly, an unusual 1,3-chlorine shift was initially proposed as the key step in the reaction. An early computational analysis of the mechanism suggested that the intermediate vinyl cation leading to the branched head-to tail dimer is more stable than the corresponding linear head-to-head cationic vinylic species. However, without the presence of an additional nucleophile, the former pathway should be reversible. The low activation barrier for the evolution of the linear head-to-head vinyl cation might drive the formation of the noticed product via a facile 1,3-chlorine shift.

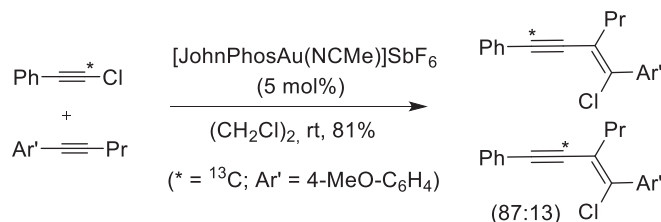
Next, Haberhauer et al. documented a selective gold-catalyzed haloalkynylation reaction of aryl alkynes that furnishes bromo or chloro-substituted conjugated enynes (Scheme 49) [104].



Scheme 48. Head-to-head catalytic coupling of chloroalkynes.



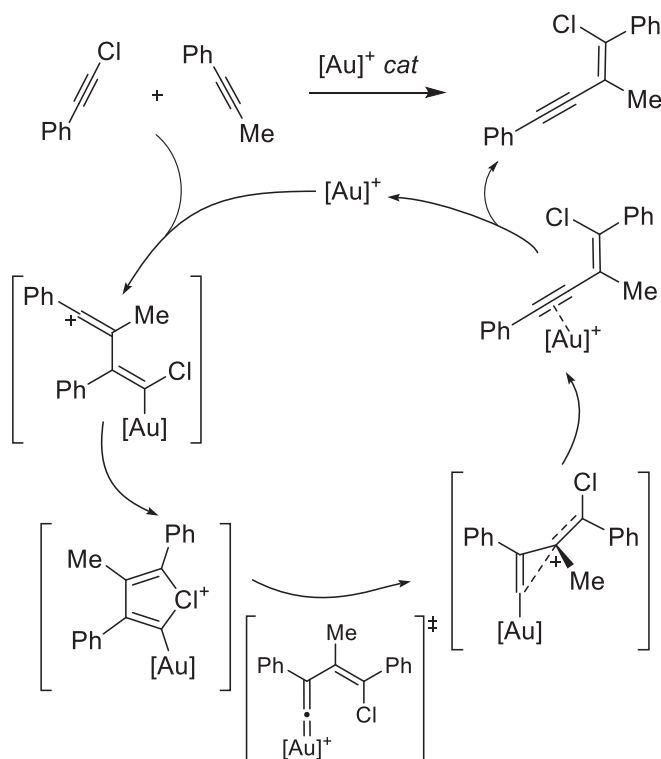
Scheme 49. Catalytic haloalkynylation of aryl alkynes.



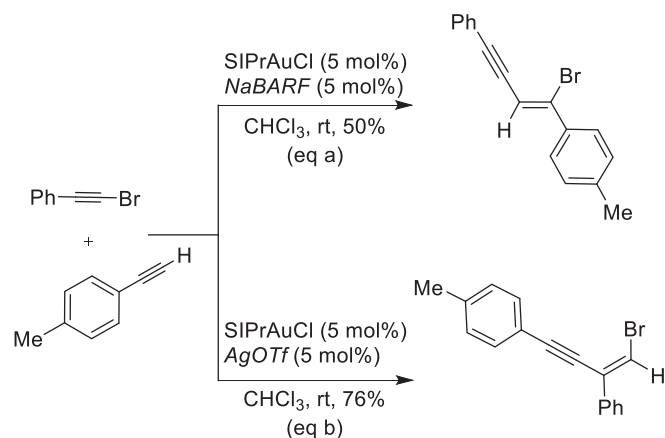
Scheme 50. Gold-catalyzed reaction of pent-1-yn-1-yl-arene with ^{13}C -labelled (chloroethynyl)benzene.

The yield of the process performs typically in the 70–90% range. Higher figures are obtained for the combination of electron-poor aryl-substituted haloalkynes in conjunction with electron-rich aryl-substituted internal alkynes. Experiments using a ^{13}C -labelled chloroalkyne at the outer acetylenic carbon atom showed that enriched ^{13}C signals are present in both acetylenic carbons for the assembled conjugated enyne system (Scheme 50).

This experiment was useful to ascertain the mechanistic rationale behind the C–C bond-making step. Early computational studies suggested the enyne product can be formed through two complementary reaction paths arising from the attack of the internal alkyne to either C1 or C2 at the complex of the chloroalkyne with the catalyst. Differentiate evolution pathways would be eventually responsible for the noticed distribution of the informative ^{13}C label within the products. Subsequent additional labelling



Scheme 51. Gold-catalyzed 1,2-chloroalkynylation of internal alkynes: cyclopropenylmethyl cation as reaction intermediate.



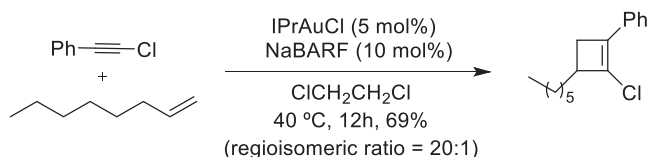
Scheme 52. Coupling reactions of alkynes with haloalkynes [SIPr: 1,3-bis(2,6-diisopropylphenyl)imidazolidene].

experiments using haloalkynes showed label scrambling to be a general feature for these alkyne-alkyne coupling reactions. As a consequence, the implication of the cyclopropenylmethyl cation in those reactions was discovered and its significance as reaction intermediate highlighted [105]. Computational studies revealed that the products derived from an initial coupling involving a head-to-tail addition mode, while the subsequent formation of the adducts results from a more complex event. A detailed evolution for the coupling of prop-1-yn-1-ylbenzene with (chloroethyl)benzene is outlined in Scheme 51.

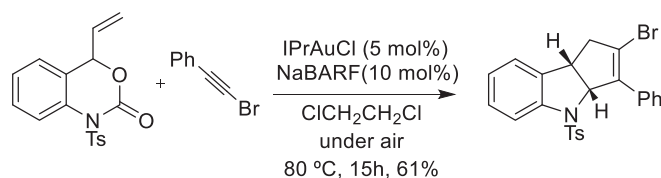
The coupling product arises from a reaction course that involves a cyclopropenylmethyl cation intermediate. Noteworthy, for the case of vinyl-substituted species, this intermediate is more stable than the well-recognized vinylidene cation that, alternatively, accounts for the transition state of its generation.

The reaction of terminal alkynes with haloalkynes gave additional breakthroughs, as the discovery of the gold-catalyzed divergent cross-coupling of these substrates (Scheme 52) [106].

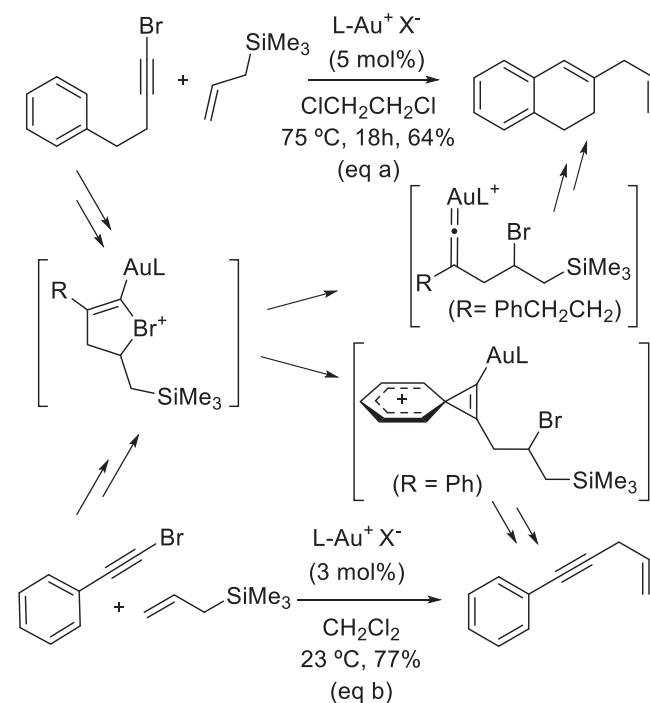
At room temperature, using chloroform as solvent, two different aryl acetylene moieties, one being a terminal alkyne and the second a bromoalkyne, can be selectively cross-coupled using gold(I) catalysis. A valuable reaction manifold was accomplished, just switching the nature of the anion to furnish two different and well-defined bromo-substituted enyne scaffolds. Díez, Gómez-Bengoa, Fernández, Lassaletta and coworkers showed that the reaction of a gold catalyst with a strongly basic NHC-type ligand and a non-coordinating anion, as tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, affords the product resulting from *cis* addition of the C-Br bond of the haloalkyne across the terminal alkyne (eq a). The reaction also works for related iodo or chloro-substituted alkynes. Interestingly, replacing the anion by a triflate determines an entirely different process. This time, the formed adduct results from selective *trans* addition of the terminal alkyne across the bromoalkyne (eq b) [107]. Pertinent experimental and mechanistic studies were conducted and the key role of the weakly coordinating triflate anion revealed.



Scheme 53. Regioselective [2+2] cycloaddition between a chloroalkyne and a monosubstituted unactivated alkene.



Scheme 54. Elaboration of tetrahydrocyclopenta[b]indoles.



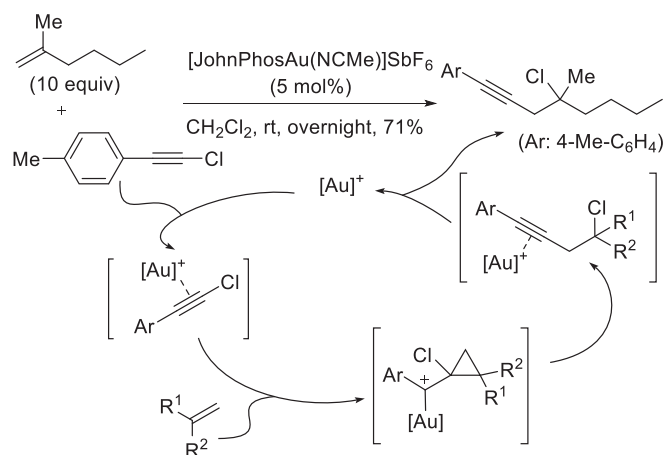
Scheme 55. Gold-catalyzed synthesis of 1,4-enynes.

Haloalkynes react with other unsaturated systems, particularly alkenes. Zhang and his group identified conditions to promote gold (I)-catalyzed [2+2] cycloaddition reactions between chloroalkynes and unactivated alkenes. The reaction did not involve an associated noticeable halogen-rearrangement process (Scheme 53) [108]. As depicted, it works well for monosubstituted unactivated alkenes, with outstanding regioselectivity. For the case of 1,2-disubstituted alkenes, the reaction was basically stereospecific.

Bromoalkynes also enter gold-catalyzed rearrangement reactions with alkenes without involving a halogen-shift. *Syn*-tetrahydro-cyclopenta[b]indoles were assembled using gold catalysis under air from the reaction of vinylbenzoxazinones with aryl-substituted bromoalkynes, as depicted in Scheme 54 [109].

The reaction of the unactivated alkene and the haloalkyne evolves via [2+2] cycloaddition followed by a decarboxylative rearrangement cascade. Also worth nothing, replacing the terminal alkene by an activated alkene as that in 1-azadienes allows for the synthesis of benzofuro[3,2-*b*]pyridines under related experimental conditions.

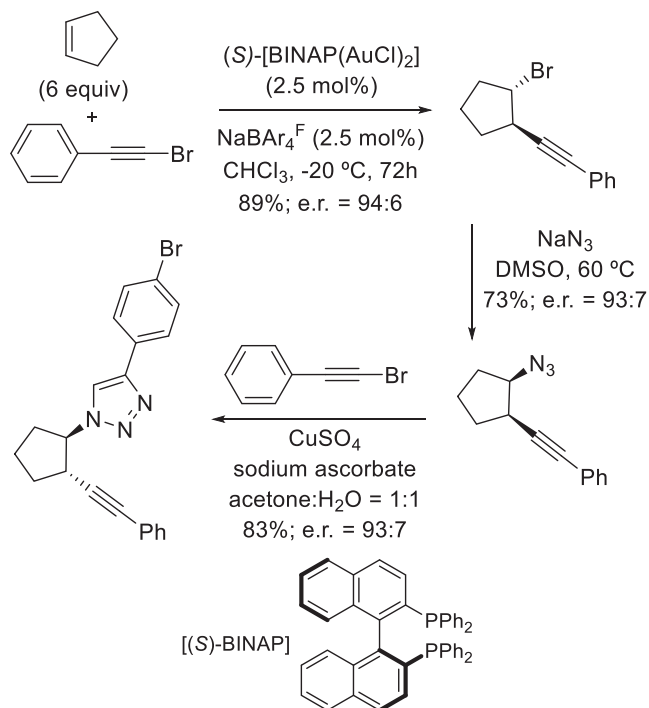
Echavarren and his group early discovered the gold(I)-catalyzed coupling reaction of bromoalkynes with allylsilanes leading to the selective formation of 1,4-enynes, a process that can be also conducted in the presence of indium bromide (Scheme 55) [110].



Scheme 56. Chloroalkynylation of 1,1-disubstituted alkenes.

The mechanism reveals differential features depending on the alkyne. After the initial formation of a bromonium ion with the structure of a five-membered-ring the reaction will move forward through a gold(I) vinylidene species for the case of an sp^3 -substituted alkyne (eq a), which then triggers additional synthetic cascades. For the case of aryl-substituted alkynes, the five-membered bromonium ion gives rise to a vinylidenephonium cation that, after 1,2-aryl migration and gold-promoted bromodesilylation steps, leads to the noticed 1,4-enynes (eq b). This new chemistry paves the way for the catalytic assembly of 1,4-enynes, which are current subject of synthetic interest [111].

For simple alkenes, independent work from Haberhaur and Fernández and Lassaletta set the basis for the gold-catalyzed haloalkynylation process. Haberhaur and Kreuzahler showed that the reaction of aryl-substituted chloroalkynes with 1,1-disubstituted alkenes can be catalyzed by gold(I) complexes, as shown



Scheme 57. Enantioselective gold-catalyzed alkene haloalkynylation and subsequent synthetic elaborations.

below for the coupling of 1-(chloroethynyl)-4-methyl benzene with an excess of 2-methylhex-1-ene (Scheme 56) [112].

On the basis of experimental work and quantum chemical calculations the authors proposed that the reaction involves an initial coordination of the electrophilic gold(I) to the alkyne. Nucleophilic attack of the alkene to the assembled cationic π -complex affords a cyclopropyl methyl cation stabilized by the gold(I) frame. This intermediate evolves through a reaction path involving ring-opening followed by a 1,3-chlorine shift, which releases the product upon transferring the active gold(I) to another chloroalkyne.

On the other hand, Díez, Fernández, Lassaletta and coworkers devised an alternative approach based on distinctive ligands to accomplish the gold(I)-catalyzed haloalkynylation reaction of a variety of alkenes. This process shows nice generality with respect to both, the structure of the unsaturation (cyclic *gem*-disubstituted and monosubstituted alkenes react efficiently) and the nature of the halogen (bromo- and chloroalkynes are proper partners for this transformation). Interestingly, they also reported preliminary results on the demanding enantioselective version of the process using cyclopentene as the alkene (Scheme 57) [113].

Further synthetic transformations highlighted the potential that the C–C bond forming strategy via catalytic haloalkynylation of alkenes offers for a subsequent *enantio*-enriched building-block elaboration.

Perspective

The gathered collection of reactions involving gold-catalyzed transformations of haloalkynyl fragments visibly points towards a rapidly evolving research arena. Moreover, together with a variety of synthetically useful catalytic addition reactions of a wide set of nucleophiles to this class of functionalized alkynes, the interaction of the haloethynyl moiety with the gold catalyst can be used to trigger further innovative catalytic transformations involving an additional halogen-shift. Remarkably, for this type of gold-catalyzed processes, the haloalkyne fragment do unveil differentiate chemistry in comparison to that known for the parent terminal alkyne. Furthermore, in this gold scenario, the catalytic reactivity of the haloethynyl fragment enables distinctive transformation to be accomplished, in particular regarding the activation of otherwise elusive structural motifs. In this regard, future advances concerning the activation of strong bonds promoted by the unique reaction coordinates resulting upon gold activation of haloethynyl moieties can be foreseen.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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